Cacalolides from *Senecio madagascariensis*

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Received May 24, 2000

14-Isovaleryloxy-*O*-methyl-1,2-dehydrocacalol (**1**) and cycloart-23-ene-3,25-diol, *β*-sitosterol, and stigmasterol, along with five new cacalolides, 1-hydroxy-2-methoxy-1,2,3,4-dehydro-6-dehydroxycacalone (**2**), 1-hydroxy-2-methoxy-1,2,3,4-dehydrocacalone (**3**), 1,2-dimethoxy-1,2,3,4-dehydro-6-dehydroxycacalone (**4**), 1,2-dimethoxy-1,2,3,4-dehydrocacalone (**5**), and 2-methoxy-*O*-methyl-1-oxo-2,3-dehydrocacalol (**6**), were isolated from *Senecio madagascariensis* collected from Colombia. The structures of the new compounds were determined using one- and two-dimensional NMR techniques. In addition, the structure of **2** was corroborated by derivatizations and single-crystal X-ray diffraction studies.

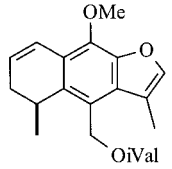
Cacalolides are biogenetic Wagner−Meerwein rearrangement products[1] derived from furoeremophylanes[2] and derive their name from cacalol, a sesquiterpenoid we isolated from the antihyperglycemic species *Cacalia decomposita*[3] also referred to as *Psacalium decompositum* and *Odontorichum decompositum*.[4]

Interest in the chemical study *of Senecio* species[5] is stimulated by the observation that in many agricultural countries, ingestion of these plants is responsible for more deaths to livestock than from all other poisonous plants together.[6] The toxic metabolites are thought to be pyrrole derivatives of the pyrrolizidine alkaloids. However, recently some furoeremophylanes have also been described as toxic compounds.[7]

Senecio madagascariensis Poir. (Compositae, Senecioneae), known as fireweed, is a plant of South African origin,[8] and many efforts have been made to control its infestation level in pastures.[9] This species has migrated to South America and is currently found in countries such as Argentina[10] and Colombia. We report herein the chemical study of the petroleum ether−ethyl ether extracts of Colombian whole plants, from which new cacalolides **2**−**6** were isolated.

A petroleum ether−diethyl ether extract of the whole plants of Colombian *S. madagascariensis* collected in September 1998 was subjected to column chromatography using hexane with increasing amounts of EtOAc as eluent. From the less polar fractions 14-isovaleryl-*O*-methyl-1,2-dehydrocacalol (**1**),[11] cycloart-23-ene-3,25-diol,[12] and a mixture of *β*-sitosterol and stigmasterol[13] were obtained. These compounds were identified by comparison of their NMR spectral data with those described. The ^{13}C NMR data of 14-isovaleryloxy-*O*-methyl-1,2-dehydrocacalol (**1**) (see Experimental Section) were assigned by NMR experiments including one-bond heteronuclear C−H correlations (HETCOR) and long-range C−H correlations obtained using the pulse sequence known as FLOCK.[14]

From the intermediate polarity fractions, **2**, **3**, and **4** were isolated. The positive-ion HRFABMS of **2** showed a quasimolecular ion peak $[M + H]^+$ at *m*/*z* 273.1112 (calcd for $C_{16}H_{17}O_4$, 273.1127 $[M + H]^+$), corresponding to the molecular formula $C_{16}H_{16}O_4$. The ^1H NMR spectrum of **2** shows an intramolecularly bonded hydroxyl group signal at *δ* 13.06, which was exchangeable with D_2O. In addition,



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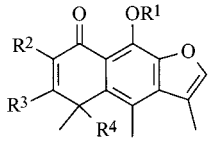
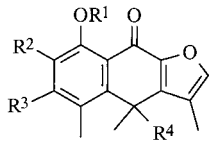
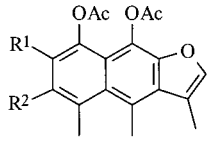


	R1	R2	R3	R4
6	Me	OMe	H	OH
7	H	H	OMe	H



	R1	R2	R3	R4
2	H	OMe	H	H
3	H	OMe	H	OH
4	Me	OMe	H	H
5	Me	OMe	H	OH
8	H	H	OMe	H
10	Ac	OMe	H	H
12	H	OMe	H	OAc



	R1	R2
9	OMe	H
11	H	OMe

signals for an aromatic proton at *δ* 6.86 (s), a proton on a furane ring at *δ* 7.49 (q, *J* = 1.2 Hz) coupled to a methyl group at *δ* 2.15 (d, *J* = 1.2 Hz, CH_3), a methoxyl group at *δ* 3.89 (OMe), an aromatic methyl group at *δ* 2.39 (s, CH_3), and an aliphatic methyl group at *δ* 1.33 (d, *J* = 7.1 Hz, CH_3) coupled to a downfield shifted proton at *δ* 4.09 (q, *J* = 7.1 Hz) were observed. All of these spectral data were almost identical to those described[5a] for **7**, the structure of which was reassigned as **8** some years later[15] on the basis of UV, IR, MS, and ^1H NMR spectral data. However, for the compound in our hands, the ^1H-coupled ^{13}C NMR spectrum shows the carbonyl group signal (C-9) at *δ* 178.6 as a singlet with no long-range coupling. In addition, the signals at *δ* 146.1 (C-12) and 119.0 (C-3) appear as double quartets (*J* = 201.5, 6.0 Hz, and *J* = 155.2, 5.2 Hz, respectively) since these two CH carbons are three-bond-coupled to methyl groups. The large heteronuclear coupling constant observed for the signal at *δ* 146.1 (C-12) is in agreement with the characteristic coupling constant for a CH-α in a furane ring.[16] Furthermore, a FLOCK contour plot showed correlation of the signal at *δ* 19.0 (C-15), in

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10.1021/np000257a CCC: $20.00
Published on Web 03/15/2001

Table 1. ^{1}H NMR Data for **2**−**6**, **9**, **10**, and **12** in $CDCl_3$ (mult., *J* in Hz)[a]

position	2	3	4	5	6[b]	9[c]	10	12
1	13.06 (s, OH)	13.17 (s, OH)	3.90 (s, OMe)	3.77 (s, OMe)			2.48 (s, OAc)	13.40 (s, OH)
2	3.89 (s, OMe)	3.72 (s, OMe)	3.88 (s, OMe)	3.75 (s, OMe)	3.70 (s, OMe)	3.90 (s, OMe)	3.87 (s, OMe)	3.89 (s, OMe)
3	6.86 (s)	6.69 (s)	6.96 (s)	6.72 (s)	5.76 (s)	7.05 (s)	7.05 (s)	6.80 (s)
6	4.09 (q, 7.1)	2.83 (br s, OH)	4.12 (q, 6.9)	3.40 (br s, OH)			4.15 (q, 6.9)	2.10 (s, OAc)
12	7.49 (q, 1.2)	7.46 (q, 1.1)	7.44 (q, 1.2)	7.34 (q, 1.1)	7.38 (q, 1.2)	7.32 (q, 1.2)	7.45 (q, 1.1)	7.49 (q, 1.1)
13	2.15 (d, 1.2)	2.30 (d, 1.1)	2.15 (d, 1.2)	2.29 (d, 1.1)	2.37 (d, 1.2)	2.42 (d, 1.2)	2.16 (d, 1.1)	2.16 (d, 1.1)
14	1.33 (d, 7.1)	1.78 (s)	1.37 (d, 6.9)	1.74 (s)	2.95 (s)	3.07 (s)	1.41 (d, 6.9)	1.86 (s)
15	2.39 (s)	2.69 (s)	2.49 (s)	2.73 (s)	1.71 (s)	2.93 (s)	2.53 (s)	2.51 (s)

[a] At 300 MHz, using TMS as the internal reference (δ 0). [b] 4-OH: 2.98 (br s), 9-OMe: 4.01 (s). [c] 1-OAc and 9-OAc: 2.39 and 2.44 (s each).

Table 2. ^{13}C NMR Data for **2**−**6**, **9**, **10**, and **12** in $CDCl_3$ [a]

C	2	3	4[b]	5[c]	6[d]	9[e]	10[f]	12[g]
1	151.8	151.6	149.4	147.7	180.1	130.3	138.5	152.8
2	146.4	147.0	152.0	152.0	148.0	146.5	150.2	147.6
3	119.0	120.7	119.0	120.1	120.7	116.5	118.5	120.4
4	125.1	128.0	131.2	134.1	70.9	135.5	125.2	124.3
5	135.7	136.3	137.9	138.4	138.4	128.0	133.8	133.8
6	30.9	71.3	30.7	70.8	127.1	127.6	30.6	76.7
7	143.6	144.2	139.6	140.8	134.2	128.8	140.5	141.1
8	145.1	143.1	147.3	144.7	147.1	145.9	146.7	144.1
9	178.6	178.5	173.4	172.7	144.1	125.7	172.4	178.4
10	116.1	114.5	126.7	125.0	119.3	121.4	137.5	115.2
11	120.6	121.6	119.6	120.6	117.6	116.7	119.8	119.3
12	146.1	146.8	144.7	145.1	144.6	143.8	145.1	146.8
13	8.0	8.9	8.0	9.0	11.5	12.1	7.9	8.6
14	21.9	27.3	22.7	27.7	17.3	20.0	22.3	27.5
15	19.0	21.3	19.8	22.3	29.8	27.3	19.8	20.9
2-OMe	56.2	55.7	56.3	55.5	55.0	56.7	56.2	56.0

[a] At 75.4 MHz, using TMS as the internal reference (δ 0). [b] 1-OMe: 61.4. [c] 1-OMe: 61.1. [d] 9-OMe: 61.7. [e] 1-OAc and 9-OAc: 168.9, 169.3, 20.8, 20.7. [f] 1-OAc: 169.7, 20.9. [g] 6-OAc: 168.1, 20.4.

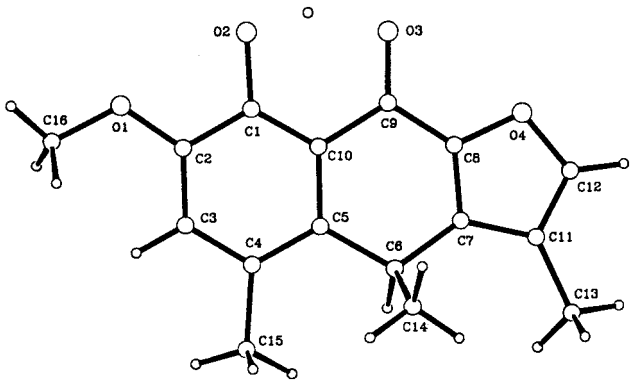

Figure 1. Perspective view of the molecular structure of **2**. The circle between O2 and O3 represents the hydroxyl group hydrogen atom.

the ^{13}C domain, with the signal at δ 6.86 (H-3), in the ^{1}H domain. These facts were inconsistent with either structure **7** or **8**, but in full agreement with structure **2**. The remaining ^{1}H NMR and ^{13}C NMR assignments (Tables 1 and 2, respectively) were also made from the HETCOR and FLOCK experiments.

The structure of **2** was independently confirmed by single-crystal X-ray diffraction studies[17] (Figure 1). As evidenced from the C(3)−C(4)−C(5)−C(6) (176.4°) and C(6)−C(7)−C(8)−O(4) (175.9°) torsion angles, the three-ring system was almost coplanar, and the methoxyl group was in the same plane, C(1)−C(2)−O(1)−C(16) (177.9°). The hydroxyl group hydrogen atom was located on the difference map between O(2) and O(3).

Further structural support for **2** was evident after performing acetylation reactions. Thus, reaction of **2** with acetic anhydride catalyzed by 4-dimethylaminopyridine[18] afforded **9** and **10** in 67 and 11% yield, respectively, while treating **2** with acetic anhydride in pyridine afforded **9** and **10** in 8 and 58% yield, respectively.

On the basis of its positive-ion HRFABMS, the molecular formula of **9** was determined to be $C_{20}H_{20}O_6$. The ^{1}H NMR spectrum of **9** shows acetyl group signals at δ 2.39 and 2.44 and signals at δ 7.05 (s), 7.32 (q, J = 1.2 Hz), and 2.42 (d, J = 1.2 Hz) assigned to H-3, H-12, and CH_3-13, respectively. The methyl group signals at δ 3.07 (s) and 2.93 (s) were assigned to CH_3-14 and CH_3-15, respectively, after detailed inspection of heteronuclear contour plots. The ^{1}H NMR chemical shifts for **9** (Table 1) are very similar to those described for **11**.[5a] However, the ^{1}H-coupled ^{13}C NMR spectrum of **9** shows the C-3 signal at δ 116.5 as a double quartet (J = 158.6, 6.4 Hz) due to heteronuclear scalar coupling with H-3 and CH_3-15, respectively. In addition, from the FLOCK experiment, a correlation between the signals at δ 27.3 (C-15) and 7.05 (H-3) was observed. These data are in agreement with structure **9** and in clear disagreement with structure **11**. The remaining ^{13}C NMR assignments were made as before, except for the signals at δ 125.7 and 121.4, which were assigned to C-9 and C-10, respectively, on the basis of their chemical shifts. In turn, the molecular formula of **10** was determined by a positive-ion HRFABMS to be $C_{18}H_{19}O_5$. The ^{1}H NMR spectrum of **10** (Table 1) shows an acetyl group signal at δ 2.48, while the remaining signals are similar to those of **2**. The ^{13}C NMR data (Table 2) were assigned as above.

The diacetate **9** offers the possibility to explore the structural preference of molecules of type **2** in comparison with the tautomerism represented by molecules of type **6**. Therefore, it was of interest to hydrolyze **9**, which afforded **2** as the principal product (48% yield) and **3** as the minor product (19% yield).

It is well known that oxidation of substituted phenols using $Pb(OAc)_4$ [19] leads to *o*- or *p*-quinol acetates. To gain evidence about the behavior of **2** when subjected to this type of reaction, a benzene solution of **2** was treated with $Pb(OAc)_4$. After workup and purification by TLC, **12** was obtained in 29% yield. The positive-ion HRFABMS of **12** indicated a molecular formula of $C_{18}H_{18}O_6$. Its structure followed after comparing its ^{1}H NMR spectrum (Table 1) with that of **2**. The presence of an acetyl group signal at δ 2.10 instead of the signal for H-6 at δ 4.09, along with a downfield-shifted methyl group (s, 1.86, CH_3-14), indicated that an acetyloxy group was placed on C-6. The complete ^{13}C NMR assignment (Table 2) further supported the structure of **12**.

The positive-ion HRFABMS of **3** showed a quasimolecular ion peak $[M + H]^+$ at *m/z* 289.1097, corresponding to the molecular formula $C_{16}H_{16}O_5$. The ^{1}H NMR spectrum of **3** (Table 1) shows two hydroxyl group protons at δ 13.17 (1-OH) and 2.83 (6-OH), which are exchangeable with D_2O, while the remaining signals are similar to those of **12** except for the absence of the acetyl group signal. The ^{1}H-coupled ^{13}C NMR spectrum of **3** shows the carbonyl group at δ 178.5 (C-9) as a singlet with no long-range coupling, while the signals at δ 146.8 (C-12) and 120.7 (C-3) are observed as double quartets (J = 201.9, 6.1 Hz, and J = 155.0, 5.2 Hz, respectively) due to one- and three-bond

heteronuclear couplings. In addition, a FLOCK experiment showed correlation of the signal at δ 147.0 (C-2) and the signal at δ 3.72 (2-OMe), indicating that the methoxyl group is placed on C-2.

The positive-ion HRFABMS of **4** indicated a molecular formula of $C_{17}H_{18}O_4$. The ^{1}H NMR spectrum of **4** (Table 1) shows no hydroxyl group signal, but an additional methoxyl group signal at δ 3.90 is observed. The remaining signals are similar to those of **2**. The distinction of the ^{1}H NMR signals for the methoxyl groups and the assignment of CH_3-15 were achieved by irradiation at δ 6.96 (s, H-3), which caused 11 and 19% NOE effects on the signals at δ 3.88 and 2.49, respectively, allowing assignment of those signals to 2-OMe and CH_3-15, respectively. Consequently, the signal at δ 3.90 could be assigned to the methoxyl group at C-1. The remaining ^{1}H NMR and ^{13}C NMR assignments were made as before.

From the more polar fractions, **5** and **6** were obtained. On the basis of its positive-ion HRFABMS, the molecular formula of **5** was determined to be $C_{17}H_{18}O_5$. The ^{1}H NMR spectrum of **5** (Table 1) shows a methoxyl group signal at δ 3.77 instead of the intramolecularly bonded hydroxyl group signal at δ 13.17 in **3**, while the remaining signals are similar to those of **3**. Assignment of the individual methoxyl groups was achieved as in the case of **4**.

The ^{1}H NMR spectrum of **6** (Table 1), the only compound isolated from *S. madagascariensis* in which C-1 is a carbonyl group, shows a vinyl proton signal at δ 5.76 (H-3) as a singlet, a non-intramolecularly bonded hydroxyl group signal at δ 2.98 (4-OH), and the characteristic signal for the furane ring proton at δ 7.38 as a quartet (J = 1.2 Hz, H-12) due to coupling with CH_3-13 (δ 2.37, d, J = 1.2 Hz). Two methoxyl group signals at δ 3.70 and 4.01 were also observed and assigned to 2-OMe and 9-OMe, respectively, since irradiation at δ 5.76 (H-3) affected only the signal at δ 3.70 (16% NOE effect). These assignments were confirmed after detailed inspection of a FLOCK experiment, since the signals at δ 3.70 (2-OMe) and 4.01 (9-OMe) showed correlation with the signals at δ 148.0 (C-2) and 144.1 (C-9), respectively. In addition, a COSY experiment showed correlation between the signal at δ 3.70 (2-OMe) and the signal at δ 5.76 (s, H-3). The remaining methyl group signals at δ 2.95 (s) and 1.71 (s) were assigned to CH_3-14 and CH_3-15, respectively, on the basis of their chemical shifts. The carbonyl group on C-1 (δ 180.1) was evident from the ^{1}H-coupled ^{13}C NMR spectrum, in which it appeared as a doublet (J = 6.8 Hz) due to heteronuclear scalar coupling with H-3. The signals at δ 144.6 and 120.7 were observed as double quartets (J = 201.1, 7.0 Hz, and J = 159.8, 3.4 Hz, respectively) since these two CH carbons are three-bond-coupled to methyl groups. All these data were in agreement with structure **6**.

Experimental Section

General Experimental Procedures. Melting points were obtained on a Fisher-Johns melting point apparatus and are uncorrected. The lack of optical activity was verified on a Perkin-Elmer 241 polarimeter. UV/vis spectra were determined on a Perkin-Elmer UV/vis Lambda 12 spectrophotometer. IR spectra were recorded on a Perkin-Elmer 16F PC FT-IR spectrophotometer. NMR spectra were recorded on Varian XL-300GS and Mercury 300 spectrometers. HRFABMS were obtained on a JEOL JMS SX 1021 spectrometer operated at an accelerating voltage of 10 kV. Samples were desorbed from a nitrobenzyl alcohol matrix using 6 kV positive xenon ions. Mass measurements were performed at a resolution of 10 000 using electric field scans and poly(ethylene glycol) ions as reference material. The electron ionization mass spectra (EIMS) were obtained on a Hewlett-Packard 5989-A spectrometer at 20 eV. For column chromatography (CC), Si gel Merck 230−400 mesh ASTM was used. The single-crystal X-ray diffraction analysis for **2** was performed on a Nicolet P3m four-circle diffractometer interfaced to a DEC VAXstation 4000−60.

Plant Material. Whole plants of *S. madagascariensis* were collected in September 1998 at the parking lot of the Department of Botany, Universidad Nacional de Colombia, in Bogotá, Colombia. A voucher specimen (S. Díaz no. 4339) is deposited at the Herbario Nacional Colombiano, Instituto de Ciencias Naturales, Universidad Nacional de Colombia, Bogotá, Colombia.

Extraction and Isolation. Dried and powdered whole plants of *S. madagascariensis* (200 g) were exhaustively extracted with mixtures of petroleum ether−ethyl ether (2:1) at room temperature. The solvent was evaporated and the crude extract defatted by precipitation with MeOH. The extract (3.6 g, 1.8%) was chromatographed over Si gel eluting with hexane and hexane−EtOAc mixtures. The fractions eluted with hexane−EtOAc (24:1) afforded 14-isovaleryloxy-*O*-methyl-1,2-dehydrocacalol[11] (**1**) (555 mg) as colorless oil, while those fractions eluted with hexane−EtOAc (4:1) were further purified by CC using hexane−EtOAc (9:1) as eluent to give cycloart-23-ene-3,25-diol[12] (9 mg) and a mixture of β-sitosterol and stigmasterol[13] (34 mg). The fractions eluted with hexane−EtOAc (7:3) were further purified by column chromatography using hexane−EtOAc (9:1, 4:1, and 7:1) to give **2** (21 mg), **3** (17 mg), and **4** (12 mg), respectively. The fractions eluted with hexane−EtOAc (3:2) were rechromatographed on CC using hexane−EtOAc (2:1) to yield **5** (25 mg). Finally, the fractions eluted with EtOAc were rechromatographed using hexane−EtOAc (1:1) to afford **6** (25 mg).

14-Isovaleryloxy-*O*-methyl-1,2-dehydrocacalol (1):[11] ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 145.6 (s, C-8), 142.2 (d, C-12), 141.0 (s, C-9), 137.3 (s, C-5), 129.4 (s, C-7), 124.9 (d, C-2), 121.1 (d, C-1), 120.9 (s, C-10), 118.5 (s, C-6), 116.1 (s, C-11), 60.8 (q, 9-OCH_3), 59.2 (t, C-14), 30.5 (t, C-3), 27.9 (d, C-4), 20.8 (q, C-15), 10.3 (q, C-13). δ 173.1 (s), 43.5 (t), 25.7 (d), 22.4 (q) ($OCOCH_2CH(CH_3)_2$).

1-Hydroxy-2-methoxy-1,2,3,4-dehydro-6-dehydroxycacalone (2): yellow prisms; mp 122−124 °C (EtOAc−hexane); IR ($CHCl_3$) ν_{max} 3520, 1648, 1598, 1584, 1540, 1464 cm^{-1}; UV (EtOH) λ_{max} (log ϵ) 233 (4.1), 268 (3.80), 278 (3.8), 319 (4.2), 383 (3.6) nm; EIMS m/z (rel int) 272 $[M]^+$ (8), 257 (100), 229 (41), 214 (25); HRFABMS m/z 273.1112 (calcd for $C_{16}H_{17}O_4$, 273.1127); ^{1}H and ^{13}C NMR, see Tables 1 and 2, respectively.

X-ray Crystallographic Analysis of 2.[17] Suitable crystals were grown by slow evaporation of EtOAc−hexane solutions. A yellow crystal measuring 0.26 × 0.40 × 0.50 mm was mounted on a Nicolet P3m four-circle diffractometer interfaced to a DEC VAXstation 4000-60 operated with Crystal Logic, Inc. (Los Angeles, CA) software. The diffractometer was operated using Cu Kα graphite-monochromated radiation with λ = 1.54178 Å. The final unit-cell parameters for a monoclinic crystal of molecular formula $C_{16}H_{16}O_4$, MW = 272.30, Z = 8, calculated density = 1.33 g cm^{-3}, were obtained by least-squares on the setting angles for 23 reflections as a = 11.347(4) Å, b = 12.185(3) Å, and c = 19.820(7) Å, β = 97.54(2)°, V = 2716(1) Å^3, and F(000) = 1152 e$^-$. The crystal data were collected at 298 K in the θ:2θ scan mode using a scan speed of 3.0 deg min^{-1}, a scan width of 1.3° below Kα_1 and of 1.6° above Kα_2 in the 3−110° range to obtain 3987 reflections during a 55.9 h period. From these, 1706 reflections were unique and 1226 were considered as observed using the $I \geq 3\sigma(I)$ criterion. The intensity of two standard reflections measured every 98 reflections throughout the data collection showed no significant variation, and therefore the data were corrected for background, Lorentz, and polarization effects, but not for crystal decay. The absorption coefficient μ = 7.45 cm^{-1} precluded the need of absorption corrections. The systematic absences of the observed reflections were consistent with the *C*2/*c* space group, and the structure was solved by direct methods using the SHELX86 software package provided by Crystal Logic, Inc. For the structural refinements the non-hydrogen atoms were treated anisotropically, and the hydrogen atoms bonded to

carbons in calculated positions with C−H = 1.00 Å were refined isotropically. After removal of redundant reflections, a few reflections were excluded from the final refinement calculations to improve the fit. The 990 reflections used for the final refinement of 181 parameters gave $R = 5.8\%$ and $R_w = 6.8\%$. A final difference map showed a maximum residual electron density of 0.16 e Å^{-3}.

1-Hydroxy-2-methoxy-1,2,3,4-dehydrocacalone (3): yellow prisms; mp 198−200 °C (EtOAc−hexane); IR ($CHCl_3$) ν_{max} 3490, 1652, 1598, 1582, 1534, 1460 cm^{-1}; UV (EtOH) λ_{max} (log ϵ) 233 (4.0), 260 (3.7), 330 (4.0) nm; EIMS *m*/*z* (rel int) 288 $[M]^+$ (29), 273 (100), 245 (21), 230 (24); HRFABMS *m*/*z* 289.1097 (calcd for $C_{16}H_{17}O_5$, 289.1078); ^{1}H and ^{13}C NMR, see Tables 1 and 2, respectively.

1,2-Dimethoxy-1,2,3,4-dehydro-6-dehydroxycacalone (4): yellow plates; mp 209−211 °C (CH_2Cl_2−hexane); IR ($CHCl_3$) ν_{max} 1658, 1588, 1542, 1474 cm^{-1}; UV (EtOH) λ_{max} (log ϵ) 228 (4.2), 310 (4.1) nm; EIMS *m*/*z* (rel int) 286 $[M]^+$ (10), 271 (100), 256 (17), 238 (19), 228 (28), 128 (26); HRFABMS *m*/*z* 287.1282 (calcd for $C_{17}H_{19}O_4$, 287.1283); ^{1}H and ^{13}C NMR, see Tables 1 and 2, respectively.

1,2-Dimethoxy-1,2,3,4-dehydrocacalone (5): pale yellow plates; mp 175−177 °C (EtOAc−hexane); IR ($CHCl_3$) ν_{max} 3444, 1666, 1586, 1542, 1472 cm^{-1}; UV (EtOH) λ_{max} (log ϵ) 228 (4.18), 314 (4.12) nm; EIMS *m*/*z* (rel int) 302 $[M]^+$ (2), 287 (100), 272 (14); HRFABMS *m*/*z* 303.1242 (calcd for $C_{17}H_{19}O_5$, 303.1232); ^{1}H and ^{13}C NMR, see Tables 1 and 2, respectively.

2-Methoxy-*O*-methyl-1-oxo-2,3-dehydrocacalol (6): pale yellow prisms; mp 170 °C decomp (EtOAc−hexane); IR ($CHCl_3$) ν_{max} 3456, 1656, 1584, 1464 cm^{-1}; UV (EtOH) λ_{max} (log ϵ) 215 (4.3), 242 (4.0), 281 (3.7), 315 (3.8) nm; EIMS *m*/*z* (rel int) 302 $[M]^+$ (39), 287 (100), 271 (30), 259 (46), 255 (49), 203 (35); ^{1}H and ^{13}C NMR, see Tables 1 and 2, respectively.

Acetylation of 2. A solution of **2** (40 mg, 0.15 mmol) and 4-dimethylaminopyridine (75 mg, 0.62 mmol) in acetic anhydride (6 mL) was heated at 70 °C for 1 h. The anhydride was removed with a nitrogen stream and the residue dissolved in $CHCl_3$, washed with water, dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness. The residue was crystallized from $CHCl_3$−hexane to afford **9** (35 mg, 67%). The filtrate was evaporated and chromatographed over Si gel, eluting with gradually more polar hexane−EtOAc mixtures to yield **10** (5 mg, 11%).

A solution of **2** (60 mg, 0.22 mmol) in pyridine (3 mL) was added to acetic anhydride (3 mL) and left to stand for 3 days. After this time the reaction mixture was poured over ice−water and the product extracted with EtOAc. The organic layer was washed with water, 10% HCl solution, and water, dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness. The residue was chromatographed over Si gel, eluting with a hexane−CH_2Cl_2−EtOAc (5:4:1) mixture to afford **9** (6 mg, 8%) and **10** (40 mg, 58%).

Hydrolysis of 9. To a solution of **9** (19 mg) in EtOH (4 mL) was added a solution of $KHCO_3$ (35 mg) in H_2O (1 mL). The mixture was refluxed for 3 h. The solvent was removed with a nitrogen stream and the residue dissolved in EtOAc, washed with water, dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness. The reaction product was purified by TLC, eluting with hexane−EtOAc (2:1), to afford 7 mg of **2** (48%) and 3 mg (19%) of **3**.

Oxidation of 2 with Pb(OAc)$_4$. To a solution of **2** (31 mg, 0.11 mmol) in benzene (4 mL) was added $Pb(OAc)_4$ (58 mg, 0.13 mmol), and the reaction mixture was stirred at room temperature for 7 h. The lead(II) acetate formed was filtered on Celite and washed with benzene. Excess of reagent was reduced by the addition of 2 mL of ethylene glycol. The organic layer was washed with water, dried over anhydrous Na_2SO_4, and filtered, and the solvent was eliminated. The crude product was purified by TLC using a hexane−EtOAc mixture (2:1) as eluent to afford **12** (11 mg, 29%).

***O*-Acetyl-1-acetyloxy-2-methoxy-1,2,3,4-dehydrocacalol (9):** colorless needles; mp 243−246 °C ($CHCl_3$−hexane); IR ($CHCl_3$) ν_{max} 1760, 1620, 1476, 1360 cm^{-1}; UV (EtOH) λ_{max} (log ϵ) 255 (4.7), 333 (4.1), 357 (4.0) nm; EIMS *m*/*z* (rel int) 356 $[M]^+$ (24), 314 (16), 272, (100), 257 (31); HRFABMS *m*/*z* 357.1352 (calcd for $C_{20}H_{21}O_6$, 357.1340); ^{1}H and ^{13}C NMR, see Tables 1 and 2, respectively.

1-Acetyloxy-2-methoxy-1,2,3,4-dehydro-6-dehydroxycacalone (10): pale yellow prisms; mp 202−204 °C decomp ($CHCl_3$-hexane); IR ($CHCl_3$) ν_{max} 1762, 1662,; 1598, 1542, 1476, 1362 cm^{-1}; UV (EtOH) λ_{max} (log ϵ) 225 (4.3), 257 (3.7), 308 (4.2) nm; EIMS *m*/*z* (rel int) 314 $[M]^+$ (1), 272 (76), 257 (100), 229 (29); HRFABMS *m*/*z* 315.1223 (calcd for $C_{18}H_{19}O_5$, 315.1232); ^{1}H and ^{13}C NMR, see Tables 1 and 2, respectively.

***O*-Acetyl-1-hydroxy-2-methoxy-1,2,3,4-dehydrocacalone (12):** yellow plates; mp 140−142 °C (EtOAc−hexane); IR ($CHCl_3$) ν_{max} 3532, 1742, 1652, 1600, 1586, 1460, 1372 cm^{-1}; UV (EtOH) λ_{max} (log ϵ) 234 (4.1), 282 (3.8), 328(4.1), 389(3.6) nm; EIMS *m*/*z* (rel int) 270 $[M - CH_3COOH]^+$ (100), 255 (37), 241 (55), 227 (30), 224 (22), 119 (30); HRFABMS *m*/*z* 331.1194 (calcd for $C_{18}H_{19}O_6$, 331.1182); ^{1}H and ^{13}C NMR, see Tables 1 and 2, respectively.

Acknowledgment. The stimulating support of CONACYT (México) and CYTED (Spain) is acknowledged. We thank Prof. Santiago Díaz-Piedrahita (Universidad Nacional de Colombia) for pointing our attention to the study of this plant material, and I. Q. Luis Velasco (Instituto de Química, University of Mexico) for HRFABMS measurements.

Supporting Information Available: Table of experimentally refined final fractional atomic coordinates (×10^4) of compound **2**, and ^{1}H and ^{13}C NMR spectra of **2**−**6**, **9**, **10**, and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) (a) Ruiz, R. M.; Correa, J.; Maldonado, L. A. *Bull. Soc. Chim. Fr.* **1969**, *10*, 3612−3614. (b) Terabe, M.; Tada, M.; Takahashi, T. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 661−662, and references therein.
(2) Rodríguez-Hahn, L.; Guzmán, A.; Romo, J. *Tetrahedron* **1968**, *24*, 477−483.
(3) (a) Romo, J.; Joseph-Nathan, P. *Tetrahedron* **1964**, *20*, 2331−2337. (b) Joseph-Nathan, P.; Morales, J. J.; Romo, J. *Tetrahedron* **1966**, *22*, 301−307.
(4) (a) Inman, W. D.; Luo, J.; Jolad, S. D.; King, S. R.; Cooper, R. *J. Nat. Prod.* **1999**, *62*, 1088−1092. (b) Garofalo, A. W.; Litvak, J.; Wang, L.; Dubenko, L. G.; Cooper, R.; Bierer, D. E. *J. Org. Chem.* **1999**, *64*, 3369−3372.
(5) (a) Bohlmann, F.; Knoll, K. H.; Zdero, C.; Mahanta, P. K.; Grenz, M.; Suwita, A.; Ehlers, D.; Le Van, N.; Abraham, W. R.; Natu, A. A. *Phytochemistry* **1977**, *16*, 965−985. (b) Pérez-Castorena, A. L.; Arciniegas, A.; Pérez, R.; Gutierrez, H.; Toscano, R. A.; Villaseñor, J. L.; Romo de Vivar, A. *J. Nat. Prod.* **1999**, *62*, 1039−1043.
(6) Robins, D. J. In *The Biology and Chemistry of the Compositae*; Heywood, V. H., Harborne, J. B., Turner, B. L., Ed.; Academic Press: New York, 1977; Vol. 2, Chapter 30, pp 831−850.
(7) Pomilio, A. B.; Jares, E. A. *Int. J. Pharmacogn.* **1997**, *35*, 207−211.
(8) (a) Humbert, H. *Les Composées de Madagascar*; Lanier, E.: Caen, 1923; p 134. (b) Scott, L. J.; Congdon, B. C.; Playford, J. *Plant Syst. Evol.* **1998**, *213*, 251−257.
(9) (a) Sindel, B. M.; Michael, P. W. *Weed Res.* **1992**, *32*, 399−406; *Chem. Abstr.* **1993**, *118*, 21605w. (b) Anderson, T. M. D.; Panetta, F. D. *Plant Prot. Q.* **1995**, *10*, 152−153; *Chem. Abstr.* **1996**, *124*, 168191r.
(10) Cabrera, A. L.; Zardini, E. M. *Manual de la Flora de los Alrededores de Buenos Aires*; Acme S.A.C.I.: Buenos Aires, 1978; pp 680−682.
(11) Bohlmann, F.; Zdero, C. *Phytochemistry* **1978**, *17*, 1161−1164.
(12) Greca, M. D.; Fiorentino, A.; Monaco, P.; Previtera, L. *Phytochemistry* **1994**, *35*, 1017−1022.
(13) Rubinstein, I.; Goad, L. J.; Clague, A. D. H.; Mulheirn L. J. *Phytochemistry* **1976**, *15*, 195−200.
(14) Reynolds, W. F.; McLean, S.; Perpick-Dumont, M.; Enriquez, R. G. *Magn. Reson. Chem.* **1989**, *27*, 162−169.
(15) Torres, P.; Chinchilla, R.; Asensi, M. C.; Grande, M. *Phytochemistry* **1989**, *28*, 3093−3095.
(16) Pretsch, E.; Seibl, J.; Simon, W. *Tables of Spectral Data for Structure Determination of Organic Compounds*; Springer-Verlag: New York, 1989; p C220.
(17) Tables of fractional atomic coordinates, complete bond lengths and angles, anisotropic temperature factors, hydrogen coordinates with temperature factors, torsion angles, and a listing of observed and calculated structure factors are in deposit with the Cambridge Crystallographic Data Center, University Chemical Laboratory, 12 Union Road, Cambridge, CB2 1EZ, U.K.
(18) Steglich, W.; Höfle, G. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 981.
(19) Criegee, R. In *Oxidations in Organic Chemistry*; Wiberg, K. B., Ed.; Academic Press: New York, 1965; Part A, pp 288−292.

NP000257A