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J. Nat. Prod., **1991**, 54 (2), 460-465• DOI: 10.1021/np50074a017 • Publication Date (Web): 01 July 2004

Journal of Natural Products
Vol. 54, No. 2, pp. 460-465, Mar-Apr 1991

NEW SESQUITERPENES FROM *XANTHIUM CATHARTICUM*[1,2]

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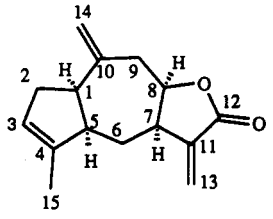
ABSTRACT.—A new daucane ester, lasidiol *p*-methoxybenzoate [**2**], and the known guaianolide ziniolide [**1**] were isolated from the roots of *Xanthium catharticum*. The MeOH extract of the aerial part afforded three new xanthanolides, 11α,13-dihydro-8-*epi*-xanthatin [**5**] and the corresponding 1β,5β- and 1α,5α-epoxides, **7** and **8**, respectively. The structures were elucidated by highfield nmr techniques. Cytotoxic and antitumor activities were found for ziniolide [**1**].

The genus *Xanthium* (family Compositae, tribe Heliantheae) is represented by a relatively limited number of species, distributed worldwide. The chemistry of this well studied genus is quite homogeneous, xanthanolides being detected in all cases (1–3). In this paper we have studied, for the first time, *Xanthium catharticum* H.B.K., a small, spiny plant, well known in Ecuador with the Quechua name Cashamarucha ("spiny chrysalis"). The plant grows on the lowlands of the Sierra region, and in the local folk medicine it is used as diuretic, emetic, and purgative and against prostate diseases (4). An MeOH extract of the roots and a CH_2Cl_2 extract of the aerial parts (see Experimental) showed weak antibacterial activity (plate diffusion method) against *Bacillus subtilis* and *Staphylococcus aureus* and antifungal activity against *Candida albicans*.

RESULTS AND DISCUSSION

MeOH extraction of *X. catharticum* was carried out separately on the roots and on the aerial parts, as preliminary tests showed a rather different composition of the two



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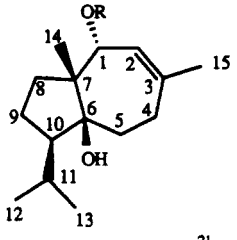
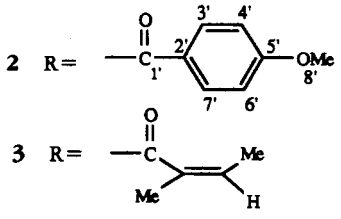




2 R=

3 R=

4 R=H

[1]Part 4 in the series "Metabolites of Medicinal Plants." For Part 3 see M. De Bernardi, G. Vidari, P. Vita-Finzi, S. Abdo, G. Marinoni, and G. Mellerio, *Rev. Latinoam. Quim.*, in press.

[2]Part of this work was reported, as a poster communication, at the Symposium "Ecological Chemistry and Biochemistry of Plant Terpenoids," Murcia, Spain, 13–15 September, 1989.

extracts. The extract of the roots contained very few compounds, among them sitosterol and, as the most abundant constituent, the known sesquiterpene guaianolide ziniolide [**1**] (5). They were identified by comparison of their ^{1}H-nmr, mass, and ir spectra with those reported in the literature. For completeness, the ^{13}C-nmr data of ziniolide [**1**], $[\alpha]^{21}D$ +159.8° (*c* = 2.1, CH_2Cl_2) [lit. (6) +140.2° (*c* = 1.6, $CHCl_3$)], never reported before, are included in Table 1. The ir spectrum of the new daucane ester **2** indicated the presence of an aromatic ester (1708, 1605, 1580, 1509, and 1256 cm^{-1}) and hydroxyl groups, the latter being tertiary as indicated by the failure of acetylation with Ac_2O/pyridine. The ^{13}C-nmr data (Table 1) also indicated the presence of an aromatic acyl moiety, a tertiary OH, and a total of eight degrees of unsaturation, including a trisubstituted double bond. Based on eims and ^{13}C-nmr data, compound **2** must be a bicyclic sesquiterpene ester with a composition of $C_{23}H_{32}O_4$. The ^{1}H-nmr spectrum of **2** showed, in addition to the *p*-$MeOC_6H_4CO$- side chain signals, the presence of a tertiary methyl signal at 1.06, two isopropyl methyl doublets at δ 1.04 and 0.95, and an acyl geminal proton doublet at δ 5.29. The latter signal was coupled to only a broad vinylic proton doublet at δ 5.52, which showed allylic coupling with a vinylic methyl signal located at δ 1.68. In addition, 2D homonuclear COSY experiments revealed the presence of two isolated vicinal methylene carbons and provided a partial structure of R-CH_2-CH_2-CH(R)-isopropyl (R = nonprotonated carbon atom). Therefore, as all the proton and carbon signals were thus assigned, the bicyclic structure of compound **2** should be a condensed five- and seven-membered ring system.

On the basis of the above spectral data, **2** is 6-hydroxy-1-*p*-methoxybenzoyloxydauc-2-ene. The relative configuration could be assigned with confidence to the sterogenic centers, as shown in the formula, on the basis of the close similarity of the ^{1}H- and ^{13}C-nmr data of **2** with those of lasidiol angelate [**3**] (6), fercomin (8-

TABLE 1. ^{13}C-nmr Spectral Data for Compounds **1**, **2**, **5**, **7**, and **8**.[a,b]

Carbon	Compound									
	1[c]		**2**[c,d]		**5**		**7**		**8**	
C-1	50.9[e]	(1)	77.9	(1)	143.2	(0)	63.0	(0)	64.0	(0)
C-2	51.6	(2)	121.7	(1)	146.8	(1)	146.6	(1)	144.2	(1)
C-3	123.8	(1)	143.0	(0)	125.8	(1)	129.0	(1)	128.6	(1)
C-4	141.4[e]	(0)	30.3	(2)	198.6	(0)	197.5	(0)	198.0	(0)
C-5	35.8	(1)	35.6	(2)	136.5	(1)	66.1	(1)	63.8	(1)
C-6	31.9	(2)	83.3	(0)	22.9	(2)	22.1	(2)	23.6	(2)
C-7	42.3	(1)	53.6	(0)	38.1	(1)	38.7	(1)	37.7	(1)
C-8	79.9	(1)	24.8	(2)	79.9	(1)	79.5	(1)	80.1	(1)
C-9	34.7	(2)	36.1	(2)	36.4	(2)	31.1	(2)	34.0	(2)
C-10	142.8[e]	(0)	56.8	(1)	31.3	(1)	30.4	(1)	31.8	(1)
C-11	143.6[e]	(0)	26.6	(1)	40.3	(1)	39.7	(1)	40.2	(1)
C-12	170.0	(0)	21.3[e]	(3)	179.1	(0)	177.7	(0)	178.4	(0)
C-13	122.0	(2)	24.6[e]	(3)	12.2	(3)	10.2	(3)	10.2	(3)
C-14	115.6	(2)	22.9	(3)	21.6	(3)	19.2	(3)	18.6	(3)
C-15	15.0	(3)	25.8	(3)	27.6	(3)	28.2	(3)	28.0	(3)

[a]75.47 MHz. Values in ppm, relative to δ = 0.00 for TMS in $CDCl_3$ solutions.

[b]The number in parentheses indicates the number of hydrogens attached to the corresponding carbon and was determined from DEPT experiments.

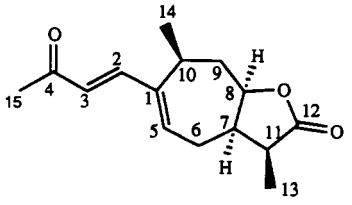
[c]Assignments are based on ^{1}H-^{13}C chemical shift correlated 2D nmr spectroscopy.

[d]-O_2CAr signals: δ 165.91 (1′), 163.31 (5′), 131.5 (3′ and 7′), 123.1 (2′), 113.6 (4′ and 6′), 55.5 (8′).

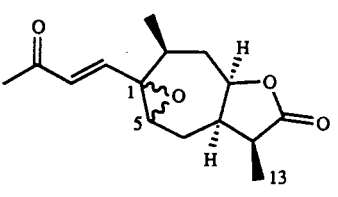
[e]Assignments in the same vertical column may be interchanged.

ketolasidiol *p*-anisate) (7,8), and lasidiol [**4**], a compound whose stereochemistry is well established by total synthesis (6).

Compounds **1** and **2** were virtually absent in the CH_2Cl_2-soluble fraction of the MeOH extract of the aerial parts of *X. catharticum* (see Experimental). Three sesquiterpene lactone xanthanolides were isolated instead. The most abundant compound was 11α,13-dihydro-8-*epi*-xanthatin [**5**], accompanied by minor amounts of the corresponding 1,5-epoxides **7** and **8**. The structure of **5** was deduced from the following evidence. The ^{13}C-nmr spectrum and the molecular ion $[M]^+$ ($C_{15}H_{20}O_3$) required a bicyclic compound, as only signals for one disubstituted and one trisubstituted double bond, one unsaturated keto group (δ 198.6), and one lactone group (δ 179.1) were present. The ir band at 1765 cm^{-1} indicated that the latter was part of a γ-lactone moiety, whereas ir bands at 1687, 1605, 1595 cm^{-1} and uv λ max 277.2 nm clearly showed the presence of an α,β,γ,δ-unsaturated dienone system. In the ^{1}H-nmr spectrum of **5**, in addition to a methyl singlet (δ 2.27) of an acetyl group, two methyl doublets on saturated carbons (δ 1.18 and 1.22) were visible. ^{1}H-^{1}H decoupling experiments in $CDCl_3$ allowed the assignment of all hydrogens and the resulting sequences indicated the position of the lactone ring and the substituents. On the basis of these data and ^{13}C-nmr data for the remaining carbons, the gross structure of the molecule was thus assigned as **5**. The double bond *E* geometry and the relative stereochemistry at C-7, C-8, and C-10 were determined by analysis of the coupling constants for the ring protons (Table 2). They also indicated that the cycloheptene ring must exist predominantly in a distorted boat conformation carrying a pseudoequatorially oriented methyl group at C-10. No conclusive supporting evidence was obtained for the relative stereochemistry at C-11 from the coupling $J_{7,11}$ (9). In fact, the complex multiplets of H-7, H-10, and H-11 could not adequately be separated in order to carry out selective spin decoupling experiments. However, in the ^{13}C nmr of **5** (Table 1) reciprocal shielding γ effects were observed due to the small dihedral angle (10) between C-13 and C-6, thus suggesting the β-methyl configuration of C-11. Furthermore, the ^{1}H-nmr data of **5** (Table 2), particularly the chemical shift of H-11, agree with those of 11α,13-dihydrotomentosin [**6**] (9) better than with the corresponding 11β epimer (9,11). Therefore **5** is 11α,13-dihydro-8-*epi*-xanthatin. The stereoisomeric structures of **7** and **8** followed from the molecular ion $[M]^+$ ($C_{15}H_{20}O_4$) at *m/z* 264 and the nmr spectral data (Tables 1 and 2) which were similar to each other and to those of compound **5**. However, a few signals were characteristically different. In particular the presence of a 1,5-epoxide, instead of the double bond present in **5**, was clearly indicated by the upfield shift of the H-5 signal, which moved from δ 6.15 for **5** to δ 2.99 for **7** and δ 2.89 for **8**. Consistently, the ^{13}C-nmr spectra of **7** and **8** contained two additional ether carbons instead of the signals of the trisubstituted double bond of **5**. ^{1}H-^{1}H decoupling experiments allowed the assignments of all hydrogens. The relative configuration at C-7, C-8, C-10, and C-11 was dictated by the values of vicinal *J*'s for the ring protons and the results of difference nOe experiments. The flexibility of the seven-membered ring did not allow a clear assign-



5
6 2,3-dihydro



7 1β,5β-epoxide
8 1α,5α-epoxide

TABLE 2. ^{1}H-nmr spectral data for Compounds **5**, **7**, and **8** (300 MHz).

Proton	Compound				*J* (Hz)	Compound		
	5[a]	**7**[a]	**8**[a]	**8**[b]		**5**[a]	**7**[a]	**8**[b]
H-1	—	—	—	—	2,3	16.2	15.5	15.5
H-2	6.98 d	6.74 d	6.94 d	6.75 d	5,6β	5.0	4.0	$J_{5,6\alpha}+J_{5,6\beta}=8.0$
H-3	6.10 d	6.24 d	6.23 d	6.30 d	5,6α	9.5	8.2	
H-4	—	—	—	—	6α,6β	14.5	15.0	[f]
H-5	6.15 dd	2.99 dd	2.89 dd	2.35 dd	6β,7	13.5	13.5	$J_{6\alpha,7}+J_{6\beta,7}=14.9$
H-6β	2.53 dt	~1.7 m	[c]	[d]	6α,7	3.0	2.0	
H-6α	2.13 ddd	2.07 ddd	[c]	[d]	7,11	[f]	7.5	7.3
H-7	~2.85 m	2.62 m	2.69 m	1.85 m	7,8	7.0	5.6	4.9
H-8	4.62 ddd	4.51 dt	4.51 dt	3.62 m	8,9β	11.0	11.3	$J_{8,9\alpha}+J_{8,9\beta}=12.0$
H-9α	2.20 ddd	1.84 ddd	[c]	[d]	8,9α	3.5	5.6	
H-9β	2.04 dt	~1.7 m	[c]	[d]	9α,9β	14.2	14.0	[f]
H-10	~2.8 m	2.24 m	[c]	1.68 m	9β,10	11.2	11.5	$J_{9\alpha,10}+J_{9\beta,10}=11.5$
H-11	~2.8 m	2.85 qu[e]	2.84 qu[e]	2.02 qu[e]	9α,10	5.5	1.0	
H-12	—	—	—	—	10,14	7.0	6.9	7.2
H-13	1.22 d[f]	1.16 d	1.19 d	0.82 d	11,13	7.0	7.3	7.2
H-14	1.18 d[f]	1.08 d	1.18 d	0.79 d				
H-15	2.27 s	2.24 s	2.25 s	1.84 s				

[a]δ_H values in ppm, relative to $\delta_H = 0.00$ for TMS in $CDCl_3$ solutions.
[b]δ_H values in ppm, relative to $\delta_H = 0.00$ for TMS in C_6D_6 solutions.
[c]Highly overlapped multiplets between δ 1.95 and 2.20.
[d]Highly overlapped multiplets between δ 1.25 and 1.60.
[e]qu = quintet.
[f]Undetermined.

ment of the stereochemistry at C-5, though inspection of models favored a β-epoxide for **7** and an α-epoxide for **8**, if the couplings $J_{5,6}$ were considered. This assignment received further support by considering the chemical shift of C-9, in the ^{13}C-nmr spectra of compounds **7** and **8**, with respect to the corresponding signal of **5**. It was shown, in fact, that the introduction of an epoxide into a six-membered unsaturated ring causes the homoallylic-positioned carbon atom, bearing an axial proton cis to the oxygenated function, to undergo an upfield shift of 4–6 ppm (12,13). In principle this γ effect should exert the same influence also on the homoallylic carbon shifts of epoxides in rings other than six-membered, provided that the local conformation, near the oxygen, is the same as in epoxycyclohexanes. Inspection of the models of **7** and **8** showed that in the former H-9β is properly oriented with respect to the oxirane ring, whereas in the latter no γ-gauche interaction (13) is suffered by the homoallylic carbon. Therefore, the larger shielding effect exhibited by C-9 of **7**, compared with the corresponding signal of **8** (Table 1), is consistent with the proposed stereochemistry. Epoxides **7** and **8** are obtained by partial epoxidation of **5** with *m*CPBA or, more simply, by exposure of **5** to the air. In view of the easy oxidizability of **5** one cannot exclude that **7** and **8** are formed, at least in part, during the extraction and isolation steps.

Following the *Index Kewensis*, *X. catharticum* should be identical with *Xanthium spinosum*, which also contains xanthanolides but with the opposite configuration at C-8 and a C-11–C-13 double bond (14). *X. catharticum*, therefore, is probably a variety. Ziniolide [**1**] has also been isolated from *Xanthium canadense* (15) and from *Xanthium occidentale* (1). Daucane esters, such as **2**, have never been found before in other *Xanthium* species. Ziniolide [**1**] showed weak antibacterial activity against *B. subtilis* and *S. aureus*, while **5** was inactive. Moreover, **1** showed interesting cytotoxic and antitumor ac-

tivities. A value of LC_{50} (ppm) 14.0 was found in the brine shrimp lethality assay (16), and a 49% inhibition was found in the potato disc assay (17).

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Ir spectra were recorded with a Perkin-Elmer Model 881 spectrophotometer; nmr spectra were determined with a Bruker CPX 300 instrument. Ms spectra were determined with a Finnigan MAT 8222 mass spectrometer at 70 eV using a direct inlet system. Specific optical rotations were determined with a Perkin-Elmer model 141 automatic polarimeter. Neutral Al_2O_3 (Woelm, activity III), Merck Kieselgel 60 (0.043–0.060 mm) and Si gel RP-18 (25–40 μm) were used for cc. A Miniprep 100 (Jobin Yvon) instrument was employed for medium pressure liquid chromatography (mplc). Tlc was carried out on Si gel plates (GF_{254} Merck, 0.25 mm) and RP-18 Si gel plates (F_{254}, 0.25 mm). The spots were visualized by spraying the plates with an ethanolic H_2SO_4/vanillin solution and then heating at 120° for 5 min.

PLANT MATERIAL.—Samples of *X. catharticum* were collected from the Calpi area, near Riobamba, Ecuador, in February and September 1987, for the extraction of the aerial parts and the roots, respectively. The plant was identified by Dr. Francisco Latorre and Ing. Alberto Ortega (Universidad Central, Quito). A voucher specimen is deposited in the Departamento de Quimica, Facultad de Ciencias, ESPOCH.

EXTRACTION AND ISOLATION OF TERPENOIDS.—Air-dried and coarsely powdered roots (0.5 kg) were extracted with MeOH at room temperature and gave 21 g of viscous oil. Part of the extract (8.3 g) was roughly fractioned into nine fractions by mplc (Si gel, 240 g) using CH_2Cl_2 with an increasing amount of MeOH. From fraction 3 (0.42 g), 0.19 g was again separated by mplc (Si gel RP-18, 20 g) using MeOH-H_2O (8:2), which gave 120 mg of **1**. Fraction 7 (0.2 g) could be separated by three consecutive cc's [A: Si gel RP-18, MeOH-H_2O (8:2→9:1); B: Si gel, CH_2Cl_2; C: Si gel, hexane/Et_2O] and gave 20 mg of **2** and 12 mg of sitosterol.

Air-dried aerial parts of *X. catharticum* (2.6 kg) were extracted with MeOH (12 liters) at room temperature and gave 65 g of viscous oil. Part of the extract (6 g) was roughly divided into polar and nonpolar fractions by dissolving in MeOH-H_2O (4:1) and partitioning first with hexane and then with CH_2Cl_2. The hexane layer contained mainly chlorophylls, carotenes, and waxes. Residue from the CH_2Cl_2 layer (2.2 g) was fractionated into eight fractions by cc (Al_2O_3, 30 g) using hexane with increasing amounts of EtOAc. After chromatography of fraction 6 (2 g) in Si gel cc (hexane/EtOAc gradient elution), one band could be crystallized from Et_2O to afford 80 mg of **5**. The mother liquors were combined with fractions 7 and 8 of the first column and again separated by mplc (Si gel), employing a hexane/Me_2CO gradient elution, to give a further amount (100 mg) of **5** and a mixture (86 mg) of **7** and **8**. The latter fraction could be separated by three consecutive mplc's [A: Si gel, hexane-EtOAc (1:1); B and C: RP-18, MeOH-H_2O (1:1)] and afforded 45 mg of **7** and 10 mg of **8**.

Lasidiol p-*methoxybenzoate* [**2**].—$[\alpha]^{21}D$ −123.1° (*c* = 0.8, CH_2Cl_2); ir ν max (film) cm^{-1} 3538, 2953, 1708, 1605, 1509, 1256, 1166, 1101, 847, 769; ^1H nmr (300 MHz, $CDCl_3$, TMS as internal standard) δ 7.98 (2H, d, *J* = 9 Hz, H-3′, -7′), 6.92 (2H, d, *J* = 9 Hz, H-4′, -6′), 5.52 (1H, br d, *J* = 6.5 Hz, H-2), 5.29 (1H, d, *J* = 6.5 Hz, H-1), 3.86 (3H, s, H-8′), 2.0–2.5 (2H, m, H-4), 2.0–2.35 (2H, m, H-5), 1.86 (1H, m, H-11), 1.72 (1H, m, H-10), 1.68 (3H, br s, H-15), 1.5–1.7 (2H, m, H-8), 1.35–1.8 (2H, m, H-9), 1.06 (3H, s, H-14), 1.04 (3H, d, *J* = 6.5 Hz, H-13), 0.95 (3H, d, *J* = 6.5 Hz, H-12); ^{13}C nmr see Table 1; ms *m/z* (% rel. int.) $[M]^+$ 372 (16), $[M-H_2O]^+$ 354 (3), $[M-ArCO_2H]^+$ 220 (12), $[M-ArCO_2H-H_2O]^+$ 202 (45), $[220-C_3H_7]^+$ 177 (25), $[202-C_3H_7]^+$ 159 (56), 150 (11), 137 (15), $[ArCO]^+$ 135 (100), 132 (28), 121 (12), 109 (15), 107 (22), 97 (13), 95 (12), 93 (15), 81 (19), 77 (21), 69 (21), 55 (18), 43 (15), 41 (24).

11α,13-Dihydro-8-epi-*xanthatin* [**5**].—Mp 76°; $[\alpha]^{21}D$ +46.2° (*c* = 0.3, EtOH); uv λ max (ε) (EtOH) 277.2 nm (15073); ir ν max (KBr) cm^{-1} 1765, 1687, 1605, 1595, 1362, 1288, 1200, 1183, 995, 965; ^1H nmr see Table 2; ^{13}C nmr see Table 1; ms *m/z* (% rel. int.) $[M]^+$ 248 (20), $[M-Me]^+$ 233 (5), 148 (15), 147 (14), 135 (100), 123 (17), 109 (24), 105 (16), 97 (17), 95 (18), 91 (23), 83 (16), 81 (16), 79 (16), 77 (15), 71 (22), 69 (20), 57 (33), 55 (34), 43 (71), 41 (29).

1β,5β-Epoxy-1,5,11α,13-tetrahydro-8-epi-*xanthatin* [**7**].—Mp 90–95°; $[\alpha]^{21}D$ −24.3° (*c* = 1.3, CH_2Cl_2); uv λ max (ε) (EtOH) 229.4 nm (14860); ir ν max (KBr) cm^{-1} 3060, 1771, 1676, 1628, 1379, 1358, 1267, 1196, 1161, 966; ^1H nmr see Table 2; ^{13}C nmr see Table 1; ms *m/z* (% rel. int.) $[M]^+$ 264 (3), $[M-MeCO]^+$ 221 (1), 135 (9), 123 (8), 109 (100), 97 (17), 95 (23), 83 (16), 81 (16), 77 (14), 71 (15), 69 (25), 67 (15), 57 (23), 55 (27), 43 (56), 41 (23).

1α,5α-Epoxy-1,5,11α,13-tetrahydro-8-epi-*xanthatin* [**8**].—Uv λ max (EtOH) 227.1 nm; ir ν max

(film) cm^{-1} 2969, 2937, 1762, 1671, 1628, 1456, 1419, 1380, 1358, 1262, 1178, 1123, 1006, 983, 954, 821, 792, 738; ^1H nmr see Table 2; ^{13}C nmr see Table 1; ms *m/z* (% rel. int.) $[M]^+$ 264 (13), $[M-MeCO]^+$ 221 (16), 151 (21), 135 (20), 127 (11), 125 (11), 123 (16), 121 (12), 109 (100), 97 (26), 95 (43), 91 (14), 83 (22), 81 (29), 79 (18), 77 (14), 69 (20), 67 (25), 57 (17), 55 (41), 43 (94), 41 (57).

ACKNOWLEDGMENTS

The authors express their gratitude to prof. G. Fronza (Politecnico di Milano, Italy) and Dr. G. Mellerio (CGS, Università di Pavia, Italy) for measuring the nmr and ms spectra, respectively; Dr. D.F. Wiemer (University of Iowa) for a copy of ^1H-nmr and ^{13}C-nmr spectra of lasidiol and lasidiol angelate; Dr. A. De Giulio (I.C.M.I.B., CNR, Napoli, Italy) for performing the potato disc assay; CONUEP, CNR (Progetto bilaterale Italia-Ecuador) and MURST (grant 60%) for financially supporting this work.

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Received 31 July 1990