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New 3,4-*Seco-ent*-kaurene Dimers from *Croton micans*

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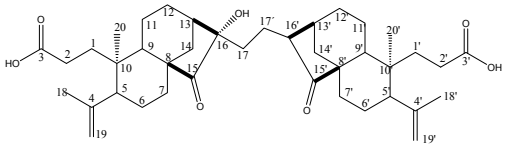
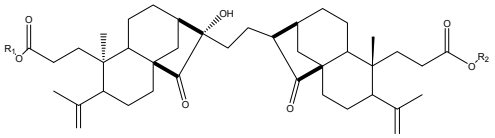
From the stems of *Croton micans* Sw., five new 3,4-*seco*-*ent*-kaurene dimers: micansinoic acid (**1**), isomicansinoic acid (**2**), and the dimethyl (**3**), monomethyl (**4**) and monoethyl ester (**5**) of micansinoic acid were isolated. The structures of the new compounds were elucidated by spectroscopic data interpretation, mainly 1D and 2D NMR experiments and MS. These compounds are the first 3,4-*seco*-*ent*-kaurene dimers from a *Croton* species.

Keywords: *Croton micans*, *seco*-*ent*-Kaurene, Dimers, Euphorbiaceae.

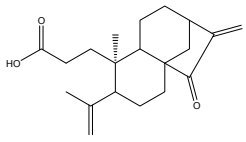
Croton, family Euphorbiaceae, is one of the largest genera of flowering plants and its species are distributed throughout tropical and subtropical regions of the world [1]. *Croton* species have been reported as rich sources of terpenoids, phenolic and peptide metabolites [2-4]. A great variety of structurally diverse diterpenes, such as those with abietane [5], neo-clerodane [6,7], labdane [8] and *ent*-kaurene [9] skeletons, are frequently found in *Croton* species. Many species have been shown to possess pharmacological activities [10,11]. *C. micans* Sw. is a shrub occurring in northern Venezuela and in other South American and Caribbean countries. No common name for this plant has been documented [12]. As part of our studies on potential bioactive metabolites from Venezuelan *Croton* species [13,14], we have undertaken phytochemical and pharmacological studies of *C. micans*. In a previous communication we reported the isolation of two 3,4-*seco*-*ent*-kaurenes, caracasine acid (**6**) and its methyl ester, from flowers of *C. micans* (which was misidentified as *C. caracasana* [15]). These two seco-entkaurenes exhibited good cytotoxic activity against a number of human tumor cells [16]. The chemical composition of the essential oils of *C. micans* has also been reported by us [17], showing them to be a rich source of several sesquiterpenes, of which fenchyl acetate was the main component. Continuing our studies on *C. micans*, herein we report the isolation and structural elucidation of dimers **1**, **2**, **3**, **4** and **5**, along with their precursor caracasine acid (**6**), from the stems of *C. micans*. The structural elucidation of these new compounds was achieved by spectroscopic and spectrometric measurements including two-dimensional NMR experiments and by comparison of the data with those of related compounds reported in the literature [18-23]. The 3,4-*seco*-entkaurene dimers: micansinoic (**1**), isomicansinoic (**2**) dimethyl (**3**), mono-methyl (**4**) and monoethyl ester of micansinoic acid (**5**), were isolated from the non-polar extracts of the stems. Previously reported compounds such as caracasine acid, caracasine, stigmastenone, stigmasterol, spathulenol, caryophyllene oxide, tiliroside, 3,7-dimethyl-1,5-octadien-3,7-diol, 16α, 17β-entkaurene diol, kaurenal and kaurenol were also isolated.



Micansinoic acid (**1**)



R1 = R_2 = H, Isomicansinoic acid (**2**)
R1 = R_2 = CH_3, Dimethyl ester (**3**)
R1 = H, R_2 = CH_3, Monomethyl ester (**4**)
R1 = H, R_2 = Et, Monoethyl ester (**5**)



Caracasine acid **(6)**

Figure 1: Chemical structures of the *seco*-*ent*-kaurenes from *C. micans*.

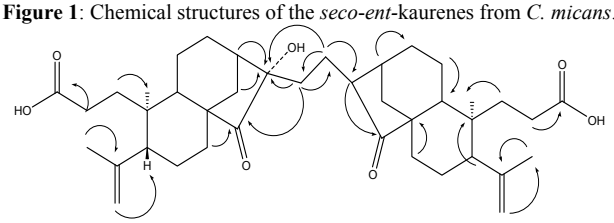


Figure 2: Key correlations in the HMBC spectrum of micansinoic acid.

Micansinoic acid was obtained as a yellow amorphous solid, mp 155-157°C, and assigned the structure **1** on the basis of the spectroscopic evidence. A molecular formula $C_{40}H_{58}O_7$ was inferred

Table 1: ^{13}C NMR spectroscopic data of compounds **1-2** and **6** in $CDCl_3$.

	1	2	6		1	2
C-1	33.4	33.4	33.4	**C-1´**	33.5	33.1
C-2	28.3	28.4	28.2	**C-2´**	25.0	27.1
C-3	179.4	179.3	179.5	**C-3´**	179.3	179.1
C-4	146.5	146.7	146.8	**C-4´**	146.7	146.2
C-5	49.7	49.6	49.7	**C-5´**	49.7	49.6
C-6	24.8	24.8	24.6	**C-6´**	24.9	22.7
C-7	33.5	31.6	31.9	**C-7´**	33.3	33.8
C-8	52.6	52.5	51.9	**C-8´**	52.0	52.0
C-9	43.3	43.9	43.3	**C-9´**	43.0	43.2
C-10	41.2	41.2	41.2	**C-10´**	41.1	41.3
C-11	18.8	18.6	18.2	**C-11´**	18.6	18.9
C-12	33.0	32.7	32.1	**C-12´**	33.1	33.1
C-13	39.4	39.3	37.9	**C-13´**	33.6	33.6
C-14	37.2	37.1	36.3	**C-14´**	37.2	35.2
C-15	221.7	221.3	210.5	**C-15´**	224.2	224.6
C-16	79.1	79.2	149.2	**C-16´**	53.6	53.7
C-17	29.7	29.7	114.8	**C-17´**	19.6	19.4
C-18	23.4	23.4	23.4	**C-18´**	23.3	23.3
C-19	114.2	114.0	114.0	**C-19´**	114.0	114.0
C-20	21.7	21.7	21.6	**C-20´**	21.8	14.2

from HRESIMS, which showed a molecular ion at *m/z* 673.7669 $[M + Na]^+$, suggesting a diterpene dimeric structure. Like **6,** the IR spectrum exhibited strong bands at 1730 and 1635 cm^{-1} for carboxy and carbonyl groups, while the ^1H NMR spectrum showed signals for quaternary methyl groups (δ 1.03, s) and isopropenyl moieties (δ 1.73, 4.66 and 4.87). ^{13}C NMR signals are reported in Table **1**, and are the result of the ^{13}C NMR spectrum, DEPT-135 experiments, and bidimensional spectra, such as HMQC for protonated and HMBC for quaternary carbons. By comparison of the data for **1**, signals corresponding to C-1 through C-12 are duplicates of those for C-1´ through C-12´, and are identical to those for caracasine acid (**6**). The same occurs for C-18 and C-19 with respect to C-18´ and C-19´. These findings support both the dimeric nature of **1** and the similarity with **6** for this part of the molecule. Significant differences may be found for the C-15 (δ 221.3) and C-15´ (δ 224.6) carbonyl groups with respect to C-15 (δ 210.5) of **6**. The downfield shifts of the keto groups agree with the lost conjugation of the carbonyl presented by **6**.

More drastic differences may be observed for the C-16 and C-17 signals, which are found at δ 79.2 (a quaternary carbynol) and δ 29.4 (a methylene), which replace the exocyclic methylene in **6**. In the HMBC spectrum (Figure 2), the quaternary carbynol (δ 79.2) correlates with both methylenes at δ 29.7 (C-17) and at δ 19.4 (C-17´), indicating that the bond between the monomers involves these methylenes. One compound with similar connectivity as that proposed by us was reported from *Isodon rubescens* (Lamiaceae) [20] and by comparison with this compound, we propose the stereochemistry of C-16. For further support for structure **1**, other long range correlations are reported in Figure **2**.

Compound **2** (mp 166-169ºC) was also obtained as amorphous powder with the same molecular formula $C_{40}H_{58}O_7$, deduced by a molecular ion at *m/z* 673.7234 $[M + Na]^+$ in the HRESIMS. IR and ^1H NMR spectra (see Experimental) had the same fingerprint, save for the presence in the latter spectrum of two quaternary methyls, now occurring at δ 1.10 (Me-20) and δ 1.02 (Me-20´). The same single difference may be observed in the ^{13}C NMR spectrum (Table **1**); therefore, isomicansinoic (**2**) and micansinoic acids (**1**) may be regarded as diasteromeric compounds.

Compound **3,** a yellow oil, with a molecular formula of $C_{42}H_{62}O_7$, $[M + Na]^+$ 701.5632, proved to be the dimethyl ester of micansinoic acid (**1**). In agreement, NMR spectroscopic data are the same as **1**, with an additional signal attributed to a methoxy group in the ^1H NMR (δ 3.57, singlet, 6H) and ^{13}C NMR spectra (δ 51.7, OCH_3), while the C-3 and C-3´ signals are shifted to δ 174.4. By similar analysis of the NMR and MS data compounds **4** and **5** were characterized as the monomethyl (**4**) and monoethyl (**5**) esters of micansinoic acid.

Several *seco*-labdanes [24] and *seco*-*ent*-kaurenes [25] have been isolated from *Croton* species, but, until now, compounds like **1-5** have not been reported in any species of *Croton*.

Experimental

General experimental procedures: Melting points were measured on a Kofler hot-stage melting point instrument and are uncorrected. Specific rotations were acquired with an ATAGO Polax-2L polarimeter. IR spectra were recorded on a Shidmazu 470, and HREIMS with a Finnigan Trace mass spectrometer. NMR spectra were measured on a JEOL 270 MHz. Chemical shifts are given in ppm referenced to the residual non-deuterated solvent signal ($CDCl_3$ 7.24 and 77.0 ppm). Column chromato-graphy (CC) was performed using Si gel (70-230 mesh) from Scharlau. TLC analysis was carried out using plastic precoated plates (Merck, Si gel plates $GF_{254,}$ 0.2 mm); the spots were visualized either using a UV lamp λ = 254 nm or by spraying with *p*-anisaldehyde. All solvents used were of analytical grade.

Plant material: *Croton micans* Sw. was collected flowering in June 2006 from Ocumare de la Costa, Aragua State, Venezuela. The specimen was identified and authenticated by one of us (R.R). A voucher specimen, MYF-26701, was deposited at the Herbarium Dr Víctor Manuel Ovalles (MYF) of the Faculty of Pharmacy, Universidad Central de Venezuela, Caracas, Venezuela.

Extraction and isolation: The freshly collected whole plant material was air dried and powdered. A portion (350 g) was macerated 3 times with methanol for 24 h. The solvent was evaporated under reduced pressure to give a total of 37 g raw extract. This was dissolved in a mixture of methanol/water (1:1) and partitioned successively with *n*-hexane (5.33 g), CH_2Cl_2 (4.34 g) and EtOAc (6.28 g). The *n*-hexane fraction (3.00 g) was subjected to CC over silica gel eluting with *n*-hexane/CH_2Cl_2, CH_2Cl_2 and dichloromethane/EtOAc in increasing order of polarity to afford 10 fractions, which were combined according to TLC (silica gel, *n*-hexane/ethyl acetate, 7:3; spots detected with UV light and *p*-anisaldehyde). Fraction 3 was further rechromatographed on silica gel with a $CHCl_3$/*n*-hexane gradient system, and 3 subfractions were collected to give ethylisomicansinoic acid (**5**) (23 mg), methylisomicansinoic acid (**4**) (16.5 mg), and the dimethyl ester of isomicansinoic acid (**3**) (104.2 mg). Fraction 5 was also chromatographed on a silica gel column with $CHCl_3$/EtOAC/MeOH (5/4.5/0.5) to afford 4 subfractions, which gave micansinoic acid (**1**) (34 mg) and isomicansinoic acid (**2**) (21 mg), and with them, caracasine acid (**6**) (55 mg). The compounds were also isolated from the dichloromethane extract subjected to CC.

Micansinoic acid (**1**)
MP: 155-157ºC.
$[\alpha]_D$: -56.60 (*c* 1.00, $CHCl_3$).
Rf: 0.46 ($CHCl_2$-MeOH, 5:1).
IR (KBr): 3431, 2928, 1730, 1635, 1444, 970 cm^{-1}.
^1H NMR (270 MHz, $CDCl_3$): 1.60-1.62 (4H, m, H-1,1'), 2.04-2.05 (4H, m, H-2,2'), 2.06 (2H, brs, H-5,5'), 1.49 (4H, m, H-6,6'), 1.26 (4H, m, H-7,7'), 1.35(2H, d, *J* = 8.3 Hz, H-9,9'), 1.65 (4H, m, H-11,11'), 1.86 (4H, m, H-12, 12'), 2.65 (2H, m, H-13,13'), 2.56-2.58 (4H, m, H-14,14'), 3.17(4H, m, H-17, 17'), 1.73 (6H, s, H-18, 18'), 4.66 (H, s, H-19a), 4.87 (H, s, H-19b), 1.02 (6H, s, H-20,20').

^{13}C NMR (64.5 MHz $CDCl_3$): Table 1
HRESIMS: *m/z* [M + Na^+] calcd for $C_{40}H_{58}O_7$: 673.7411; found: 673.7669.

Isomicansinoic acid (**2**)
MP: 166-169ºC.
$[\alpha]_D$: -120.60 (*c* 1.00, $CHCl_3$).
Rf: 0.56 ($CHCl_3$-EtOAc, 4:1).
IR (KBr): 3433, 2933, 1729, 1635, 1450, 995 cm^{-1}.
^{1}H NMR (270 MHz, $CDCl_3$): 1.60-1.62 (4H, m, H-1,1'), 2.04-2.05 (4H, m, H-2,2'), 2.06 (2H, brs, H-5,5'), 1.47 (4H, m, H-6,6'), 1.28 (4H, m, H-7,7'). 1.35(2H, d, *J* = 8.3 Hz, H-9,9'), 1.66 (4H, m, H-11,11'), 1.85 (4H, m, H-12, 12'), 2.64 (2H, m, H-13,13'), 2.55-2.60 (4H, m, H-14,14'), 3.16 (4H, m, H-17,17'), 1.73 (6H, s, H-18,18'), 4.66 (H, s, H-19a), 4.87 (H, s, H-19b), 1.02 (3H, s, H-20), 1.10 (3H, s, H-20').
^{13}C NMR (64.5 MHz $CDCl_3$): Table 1
HRESIMS: *m/z* [M + Na^+] calcd for $C_{40}H_{58}O_7$: 673.7431 found: 673.7234.

Dimethylester of micansinoic (**3**)
Yellow oil.
$[\alpha]_D$: -112.50 (*c* 1.00, $CHCl_3$).
Rf: 0.57 (CH_2Cl_2-EtOAc. 9:1).
IR (KBr): 3403, 2033, 3110, 1736, 1637, 1474, 995 cm^{-1}.
^{1}H NMR (270 MHz, $CDCl_3$): 1.60-1.62 (4H, m, H-1,1'), 2.04-2.05 (4H, m, H-2,2'), 2.06 (2H, brs, H-5,5'), 1.47 (4H, m, H-6,6'), 1.28 (4H, m, H-7,7'). 1.35(2H, d, *J* = 8.3 Hz, H-9,9'), 1.66 (4H, m, H-11,11'), 1.85 (4H, m, H-12, 12'), 2.64 (2H, m, H-13,13'), 2.55-2.60 (4H, m, H-14,14'), 3.16 (4H, m, H-17,17'), 1.73 (6H, s, H-18,18'), 4.66 (H, s, H-19a), 4.87 (H, s, H-19b), 0.99 (6H, s, H-20, H-20'), 3.60 (6H, s, H-21, H-21')
HRESIMS: *m/z* [M + Na^+] calcd for $C_{42}H_{62}O_7$: 701.9350; found: 701.5632.

Methyl-micansinoic acid (**4**)
Rf: 0.55 (*n*-Hex-EtOAc, 6:4).
IR (KBr): 3403, 2033, 3110, 1736, 1637, 1474, 995 cm^{-1}.
^{1}H NMR (270 MHz, $CDCl_3$): 1.60-1.62 (4H, m, H-1,1'), 2.04-2.05 (4H, m, H-2,2'), 2.06 (2H, brs, H-5,5'), 1.47 (4H, m, H-6,6'), 1.28 (4H, m, H-7,7'). 1.35(2H, d, J = 8.35, H-9,9'), 1.66 (4H, m, H-11,11'), 1.85 (4H, m, H-12, 12'), 2.64 (2H, m, H-13,13'), 2.55-2.60 (4H, m, H-14,14'), 3.16 (4H, m, H-17,17'), 1.73 (6H, s, H-18,18'), 4.66 (H, s, H-19a), 4.87 (H, s, H-19b), 1.02 (6H, s, H-20, H-20'), 3.63 (3H, s, H-21).
HRESIMS: *m/z* [M + Na^+] calcd for $C_{41}H_{60}O_7$: 687.9007; found: 688.0234.

Ethyl-micansinoic acid (**5**)
$[\alpha]_D$: -89.13 (*c* 1.00, $CHCl_3$).
Rf: 0.49 ($CHCl_2$-EtOAc, 5:1).
IR (KBr): 3433, 2932, 1732, 1637, 1449, 896 cm^{-1}.
^{1}H NMR (270 MHz, $CDCl_3$): 1.60-1.62 (4H, m, H-1,1'), 2.04-2.05 (4H, m, H-2,2'), 2.06 (2H, brs, H-5,5'), 1.47 (4H, m, H-6,6'), 1.28 (4H, m, H-7,7'). 1.35(2H, d, *J* = 8.35, H-9,9'), 1.66 (4H, m, H-11,11'), 1.85 (4H, m, H-12, 12'), 2.64 (2H, m, H-13,13'), 2.55-2.60 (4H, m, H-14,14'), 3.16 (4H, m, H-17,17'), 1.73 (6H, s, H-18,18'), 4.66 (H, s, H-19a), 4.87 (H,s, H-19b), 1.17 (6H, s, H-20, H-20'), 0.85 (3H, t, *J* = 7.23, H-21'), 4.04 (2H, q, *J* = 7.23, H-22').
HRESIMS: *m/z* [M + Na^+] calcd for $C_{42}H_{62}O_7$: 701.9407; found: 702.1751.

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