Terpenoids from *Croton regelianus*

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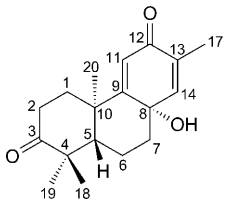
Two new terpenoids, the bisnorditerpene *rel*-(5β,8α,10α)-8-hydroxy-13-methylpodocarpa-9(11),13-diene-3,12-dione (**1**) and the guaiane sesquiterpene *rel*-(1*R*,4*S*,6*R*,7*S*,8a*R*)-decahydro-1-(hydroxymethyl)-4,9,9-trimethyl-4,7-(epoxymethano)azulen-6-ol (**2**), together with seven known compounds, were isolated from *Croton regelianus* var. *matosii*. The structures of the isolated compounds were determined by HR-ESI-TOF and a combination of 1D- and 2D-NMR experiments.

Introduction. – The genus *Croton* (Euphorbiaceae), represented by trees, shrubs, and herbs which are in general odoriferous, comprises *ca.* 1,300 species disperse in tropical and subtropical regions of the world [1]. 'Caatinga', the main biome of the Northeast region of Brazil, represents 18.3% of the Brazilian national territory. The 'caatinga' is an exclusive Brazilian biome and its vegetation consists of a wide variety of semi-desert and dry deciduous forest formations, ranging from savanna dominated by cacti to thorn scrub and gallery forest with trees up to 15 m high. This region possesses a large diversity of *Croton* species, many of which are used in traditional medicine [2–5], including *Croton regelianus* var. *matosii*, popularly known as 'velame de cheiro'. The leaf infusion of this plant is used to treat rheumatism, malignant tumors, and stomachache [6][7]. In a previous work, the chemical composition of the leaf essential oil of *C. regelianus* was reported, as well as the evaluation of its biological properties, such as larvicidal and nematicidal properties [8]. More recently, some of us investigated the *in vitro* and *in vivo* antitumor properties of the essential oil, including ascaridole, the main component of the oil [9].

In the present article, we describe the structural characterization of two new terpenoids, a bisnorditerpene, **1**, and a guaiane sesquiterpene, **2**, including the acetylated derivative of **2** (**2a**).

Results and Discussion. – The phytochemical investigation of the extracts of *C. regelianus* afforded the known compounds triacontanol [10], phytol [11], β-sitosterol [12], (3*R*,4*R*,6*S*)-3,6-dihydroxymenth-1-ene [13], β-sitosterol glycoside [12], 6α-hydroxycampest-4-en-3-one, 6β-hydroxycampest-4-en-3-one [14], and cleomiscosine A [15], as well as two new terpenoids, the bisnorditerpene *rel*-(5β,8α,10α)-8-hydroxy-13-methylpodocarpa-9(1),13-diene-3,12-dione (**1**), and the sesquiterpene *rel*-

(1*R*,4*S*,6*R*,7*S*,8a*R*)-decahydro-1-(hydroxymethyl)-4,9,9-trimethyl-(epoxymethano)azulen-6-ol (**2**).



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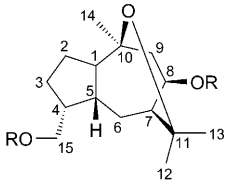


2 R = H
2a R = Ac

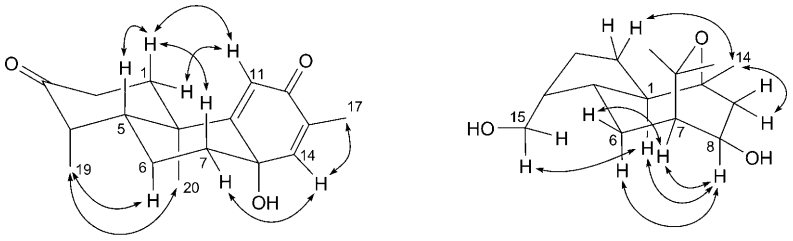
Compound **1** was isolated as a yellowish resin. The IR spectrum exhibited a broad band at 3412 cm^{-1} typical for OH groups, bands at 1727 and 1710 cm^{-1} for CO groups, and 1638 cm^{-1} for C=C bonds. The molecular formula $C_{18}H_{25}O_3$ was established by HR-ESI-TOF from the *quasi*-molecular ion peak at *m/z* 289.1798 ($[M+H]^+$, calc. 289.1803), and supported by the NMR data (*Table 1*). The ^{1}H-NMR spectrum showed signals for four Me groups at δ(H) 1.12 (*s*, Me(18)), 1.16 (*s*, Me(19)), 1.59 (*s*, Me(20)), and 1.88 (br. *s*, Me(17)), two olefinic H-atom signals at δ(H) 6.04 (*s*, H–C(11)) and 6.53 (br. *s*, H–C(14)), and a set of signals in the range of δ(H) 1.43 to 2.83 due to CH_2 and CH H-atoms. The ^{13}C-NMR (DEPT-135 and APT) spectra exhibited signals for seven non-hydrogenated C-atoms, including two CO groups at δ(C) 215.4 (C(3)) and 189.2 (C(12)) for a non-conjugated and a conjugated ketone, respectively; two sp^2 C-atoms at δ(C) 167.5 (C(9)) and 133.1 (C(13)) and a sp^3 O-bearing C-atom at δ(C) 69.2

Table 1. *^{13}C- and ^{1}H-NMR Data of Compound* **1**[a])

	δ(C)	δ(H)	HMBC (H → C)
CH_2(1)	32.3	1.90–192 (*m*), 2.08–2.06 (*m*)	
CH_2(2)	34.4	2.51–253 (*m*), 2.81–283 (*m*)	C(3)
C(3)	215.4	–	
C(4)	48.2	–	
H–C(5)	54.3	1.42–1.44 (*m*)	C(6)
CH_2(6)	18.6	1.66–1.67 (*m*), 2.15–2.18 (*m*)	C(5)
CH_2(7)	39.1	1.44–1.46 (*m*), 2.13–2.15 (*m*)	C(6)
C(8)	69.2	–	
C(9)	167.5	–	
C(10)	40.8	–	
H–C(11)	122.6	6.04 (*s*)	C(8), C(9), C(13)
C(12)	189.2	–	
C(13)	133.1	–	
H–C(14)	148.2	6.53 (br. *s*)	C(8), C(12), C(17)
Me(17)	15.1	1.88 (br. *s*)	C(17)
Me(18)	26.2	1.12 (*s*)	C(3), C(4) C(5)
Me(19)	22.2	1.16 (*s*)	C(3), C(4), C(5)
Me(20)	19.7	1.59 (*s*)	C(1), C(5), C(10)

[a]) Measured in $CDCl_3$; chemical shifts (δ) in ppm; coupling constants (J) in Hz; assignments determined by a combination of 1D- and 2D- (COSY, HSQC, and HMBC) NMR experiments.

(C(8)); three CH groups, two of which olefinic at δ(C) 148.2 (C(14)) and 122.6 (C(11)); four CH_2 and four Me groups, one of them linked to an olefinic C-atom (*Table 1*). A detailed analysis of COSY, HSQC, and HMBC spectra allowed the construction of two partial structures, a 1,4-quinoid moiety and a decalin-type system containing a CO and three angular Me groups. Further, the HMBC spectrum showed correlations between H–C(11) and C(9) and C(8). Additionally, the HMBC for H–C(14) with C(8), C(12), and C(17) supported the quinoid moiety on the *C* ring of a diterpene sub-structure. Search in the literature for model compounds revealed two examples, including a bisnorditerpene, yunnannin A [16], and the 8β-hydroxyabieta-9(11),13-dien-12-one [17]. Unfortunately, either the α or β configuration for the OH group at C(8) present in both examples gave approximately the same chemical shift for that C-atom, thus not allowing any further speculation about the relative configuration at C(8). However, the relative configuration of **1** was determined by a NOESY experiment. Correlations for H_β–C(1)/H_β–C(5), H_α–C(6)/Me(19), and Me(19)/Me(20), as depicted in the *Figure*, and, particularly, the NOE correlation between H–C(11)/CH_2(1) supported the configuration inferred for the OH group. Based on the above data, the structure of **1** was established as *rel*-(5β,8α,10α)-8-hydroxy-13-methylpodocarpa-9(11),13-diene-3,12-dione, a new bisnorditerpenoid that can be derived biosynthetically from a cleistanthane precursor. Cleistanthane-type diterpenes have been previously isolated from *C. moritibensis* [18] and *C. sonderianus* [19], the latter an endemic Brazilian plant widespread in northeastern Brazil.



1 **2**

Figure. *Relative configuration and key NOESY correlations for compounds* **1** *and* **2**

Compound **2** was isolated as colorless crystals. The IR spectrum exhibited a broad band at 3334 cm^{-1} typical for OH groups and bands at 1235 to 1050 cm^{-1} characteristic for single C–O bonds. The molecular formula $C_{15}H_{26}O_3$ was established by HR-ESI-TOF-MS from the *pseudo*-molecular ion at *m*/*z* 277.1774 ($[M+Na]^+$, calc. 277.1779). The ^{1}H-NMR showed three Me groups at δ(H) 1.13 (*s*, Me(14)), 1.27 (*s*, Me(13)), and 1.38 (*s*, Me(12)), an O-bearing H–C group at δ(H) 4.15 (*t*, $J=8.8$, H–C(8)), and two diastereotopic H-atoms of a O–CH_2 group at δ(H) 3.58 (*dd*, $J=10.6$, 4.9, H_a–C(15)) and 3.42 (*dd*, $J=10.6$, 6.8, H_b–C(15)). In addition, the ^{1}H-NMR spectrum exhibited a series of signals ascribable to four CH and four CH_2 H-atoms as deduced from the HSQC spectrum (*Table 2*). The ^{13}C-NMR and DEPT spectra of **2** showed signals for 15 C-atoms: three Me and five CH_2 groups, one of them O-bearing δ(C) 66.9 (C(15)), five CH groups, including an O-bearing one δ(C) 72.8 (C(8)), and two quaternary C-atoms,

Table 2. *^{13}C- and ^{1}H- NMR Data*[a]) *of Compounds* **2**[b]) *and* **2a**[c])

	2			**2a**		
	δ(C)	δ(H)	HMBC (H → C)	δ(C)	δ(H)	HMBC (H → C)
1	55.6	1.69–1.71 (*m*)	C(4)	54.6	1.69–1.71 (*m*)	
2	28.3	1.37–1.39 (*m*), 1.53–1.55 (*m*)	C(4), C(5)	27.3	1.41–1.42 (*m*), 1.54–1.55 (*m*)	
3	27.4	1.32–1.34 (*m*), 2.28–2.30 (*m*)	C(1), C(2), C(15)	26.3	1.41–1.42 (*m*), 1.76–1.78 (*m*)	
4	43.7	1.71–1.73 (*m*)	C(1), C(6), C(15)	42.7	1.73–1.74 (*m*)	C(5)
5	48.3	1.62–1.64 (*m*)	C(4)	43.5	1.81–1.83 (*m*)	
6	35.8	1.32–1.34 (*m*), 2.28–2.30 (*m*)	C(1), C(4), C(5), C(7)	34.1	2.28 (*dt*, *J* = 14.1, 6.7, 1.5)	C(1), C(7)
7	47.8	1.66 (br. *d*, *J* = 5.9)	C(6), C(7), C(8), C(9)	47.8	1.73–1.74 (*m*)	C(8)
8	72.8	4.15 (*t*, *J* = 8.8)	C(6), C(7), C(9), C(11)	74.8	5.08 (*t*, *J* = 8.9)	C(6), C(7), C(10), C(11), AcO–C(8)
9	46.0	2.15 (*dd*, *J* = 13.7, 9.4), 1.95 (*dd*, *J* = 13.7, 8.8)	C(1), C(7), C(8), C(14)	42.1	2.18 (*dd*, *J* = 13.8, 9.7), 1.94 (*dd*, *J* = 13.8, 8.4)	C(1), C(10), C(11)
10	75.0	–		72.9	–	
11	77.6	–		75.4	–	
12	32.6	1.38 (*s*)	C(7), C(11)	32.0	1.34 (*s*)	C(7), C(11)
13	29.3	1.27 (*s*)	C(7), C(11)	28.7	1.25 (*s*)	C(7), C(11)
14	27.9	1.13 (*s*)	C(1), C(9), C(10)	27.7	1.16 (*s*)	C(1), C(9)
15	66.9	3.58 (*dd*, *J* = 10.6, 4.9), 3.42 (*dd*, *J* = 10.6, 6.8)	C(3), C(4), C(5)	67.8	4.04 (*d*, *J* = 4.1)	C(3), AcO–C(15)
Me*C*O–C(8)	–	–	–	170.8	–	
Me*C*O–C(15)	–	–	–	170.2	–	
*Me*CO–C(8)	–	–	–	21.7	2.05 (*s*)	AcO–C(8)
*Me*CO–C(15)	–	–	–	21.2	2.04 (*s*)	AcO–C(15)

[a]) Chemical shifts (δ) in ppm; coupling constants (*J*) in Hz; assignments determined by a combination of 1D- and 2D- (COSY, HSQC, and HMBC) NMR experiments. [b]) Measured in CD_3OD. [c]) Measured in $CDCl_3$.

both linked to an O-atom δ(C) 75.0 (C(10)) and 77.6 (C(11)). An accurate analysis of the ^{1}H,^{1}H-COSY, HSQC, and HMBC spectra showed that **2** is an O-bearing sesquiterpene possessing a guaiane skeleton. The position of the HO–CH_2 and OH groups at C(4) and C(8), respectively, were defined by the HMBC analysis. The key correlations were from CH_2(15) to C(3), C(4) and C(5), from H–C(4) to C(1), C(6), and C(15), and from H–C(8) to C(6), C(7), C(9), and C(11). The HMBCs from Me(14) to C(1), C(9), and C(10), and from Me(12)/Me(13) to C(7) and C(11) supported the ether bridge between C(10) and C(11). The relative configuration established for the stereogenic centers was deduced by NOESY experiments. The NOE correlations of H–C(1)/H–C(8) and H_α–C(6)/H–C(8) indicated that HO–C(8) was β-oriented, while the correlation of H–C(1)/CH_2(15) suggested that the O–CH_2 group was α-oriented (*Fig.*). The observed correlations between H–C(7)/H–C(8) and H–C(7)/H_β–C(6) supported the configuration inferred for the ether moiety.

Acetylation of compound **2** yielded the diacetyl derivative **2a**, which exhibited in the ^{1}H-NMR spectrum two additional signals at δ(H) 2.04 (*s*) and 2.05 (*s*) compatible with two Me groups of AcO moieties. In addition, the H-atom signals of H–C(8) (δ(H) 5.08, *t*, *J* = 8.9) and of CH_2(15) (δ(H) 4.04, *d*, *J* = 4.1) of **2a** were shifted downfield when compared with those ascribed for **2**. The ^{13}C-NMR spectrum also showed signals for AcO groups at δ(C) 170.8/21.7 (AcO–C(8)) and 170.2/21.2 (AcO–C(15)). As expected, the remainder H- and C-atom signals were similar to those of **2** (*Table 2*). Therefore, the structure of **2** was established as *rel*-(1*R*,4*S*,6*R*,7*S*,8a*R*)-decahydro-1-(hydroxymethyl)-4,9,9-trimethyl-4,7-(epoxymethano)azulen-6-ol, a new guaiane sesquiterpene.

This work was supported by the national Brazilian agencies CNPq, CAPES, FUNCAP, and PRONEX. The authors are greatful to Prof. *Edson P. Nunes* for the plant identification and Prof. *Noberto L. Peporine* for the HR mass spectra.

Experimental Part

General. Semiprep. HPLC: *LC-10Atvp* (*SHIMADZU*). Column chromatography (CC): silica gel *60* (SiO_2; 70–230 mesh, *Vetec*, or 230–400 mesh, *Merck*). TLC: precoated SiO_2 Al sheets (*Kieselgel 60 F_{254}*, 0.20 mm, *Merck*); fractions and pure compounds were monitored by TLC, and the spots were visualized by heating (100°) the SiO_2 plates sprayed with vanillin/perchloric acid/EtOH soln. M.p.: digital *Mettler Toledo FP90* apparatus. Optical rotations: *Perkin-Elmer 341* digital polarimeter. IR Spectra (KBr): *Perkin-Elmer FT-IR 1000* spectrometer. ^{1}H- (500 MHz) and ^{13}C-NMR (125 MHz) spectra: *Bruker DRX-500* spectrometer. MS Spectra: MS system quadrupole time-of-flight instrument, *UltrOTOF-Q*, *Bruker Daltonics*, Billerica, equipped with an ESI source.

Plant Material. Ground leaves and stalks of *C. regelianus* were collected during the flowering stage, in July 2006, from Viçosa County, State of Ceará, Brazil. The plant material was authenticated by Prof. *Edson P. Nunes* of the Departamento de Biologia, Universidade Federal do Ceará. A voucher specimen (No. 24460) has been deposited with the Herbário Prisco Bezerra (EAC) of the Universidade Federal do Ceará.

Extraction and Isolation. The leaves (0.7 kg) and stalks (1.7 kg) of *C. regelianus* were extracted with hexane, followed by EtOH (3 × each) at r.t. The hexane and EtOH solns. were concentrated under reduced pressure to give the respective crude extracts (leaves: 13.7 and 40.0 g; stems: 9.8 and 53.0 g, resp.). The leaf hexane extract (13.7 g) was subjected to SiO_2 CC and eluted with hexane, CH_2Cl_2, AcOEt, and MeOH. The CH_2Cl_2 fraction (7.5 g), after successive gravitational columns over SiO_2 using increasing amounts of hexane/CH_2Cl_2, yielded triacontanol (49.6 mg; m.p. 81.2–82.4°), phytol

(16.9 mg), and sitosterol (143.7 mg; m.p. 121.8–122.6°). The AcOEt fraction (2.7 g) was chromatographed over SiO_2, using a step-wise gradient of CH_2Cl_2/AcOEt. The CH_2Cl_2/AcOEt 6:4 fraction (610 mg) was rechromatographed employing a solvent system of CH_2Cl_2/AcOEt (8:2 to 2:8), followed by AcOEt. The compound (3*R*,4*R*,6*S*)-3,6-dihydroxy-1-menthene (47.8 mg; m.p. 166.0–168.0°) was isolated from the CH_2Cl_2/AcOEt 6:4 fraction. The leaf EtOH extract (40.0 g) was dissolved in MeOH/H_2O 7:3 and partitioned with hexane, CH_2Cl_2, and AcOEt. The CH_2Cl_2-soluble fraction (10.2 g), after repeated CC on SiO_2, yielded sitosterol glucoside (17 mg; m.p. 293.0–294.1°). The hexane extract from the stems (9.8 g) was fractionated over SiO_2 eluting with hexane/CH_2Cl_2 8:2, CH_2Cl_2, AcOEt, and AcOEt/MeOH 1:1. The AcOEt fraction (4.4 g) was subjected to further CC using a binary mixture of CH_2Cl_2/AcOEt. The CH_2Cl_2/AcOEt 8:2 fraction (1.5 g) was rechromatographed using ^{i}PrOH (1%) in hexane to afford 53 fractions of 8 ml each, which were analyzed by TLC resulting in 12 sub-fractions. The sub-fraction *6–8* (362.3 mg) was subjected to fractionation using semiprep. HPLC (*Supercosil* 250 × 10 mm; UV detector; hexane/AcOEt 75:25; flow rate 2 ml/min) to give the steroidal mixture of 6*β*-hydroxycampest-4-en-3-one and 6*β*-hydroxystigmast-4-en-3-one (6.9 mg). The sub-fraction *14–20* (218.5 mg) was also subjected to semiprep. HPLC using hexane/AcOEt (92:8) to give compound **1** (6.8 mg). The EtOH extract from the stems (53.0 g) was dissolved in MeOH/H_2O 7:3 and partitioned with CH_2Cl_2 and AcOEt. The CH_2Cl_2-soluble fraction (18.1 g) was subjected to CC over SiO_2 and eluted with hexane/AcOEt (8:2; 6:4; 4:6; 2:8), AcOEt, AcOEt/MeOH 8:2, and MeOH. The fractions 4:6 and 2:8, after TLC analysis, were combined (2.1 g) and subjected to flash CC using hexane/AcOEt 4:6 as eluent to yield 75 fractions of 8 ml. The fraction *32–63* (750 mg) was rechromatograped through flash CC and eluted with CH_2Cl_2/AcOEt 6:4 to give 99 sub-fractions of 8 ml. From the sub-fraction *13–20* (72 mg), colorless crystals formed, which were filtered and washed with hexane/AcOEt 1:1 to give cleomiscosine A (15 mg; m.p. 246.0–247°). Flash CC of sub-fraction *36–47* (71 mg), using CH_2Cl_2/AcOEt 1:1, yielded compound **2** (12.2 mg).

rel-*(5β,8α,10α)-8-Hydroxy-13-methylpodocarpa-9(11),13-diene-3,12-dione* (**1**). Yellowish resin. $[\alpha]_D^{20} = +49$ ($c = 0.1$, $CHCl_3$). IR (KBr): 3412, 2932, 2867, 1727, 1710, 1638, 1460, 1372. ^{1}H- (500 MHz, $CDCl_3$) and ^{13}C-NMR (125 MHz, $CDCl_3$): *Table 1*. HR-ESI-TOF: 289.1798 ($[M+H]^+$, $C_{18}H_{26}O_3^+$; calc. 289.1803).

rel-*(1*R*,4*S*,6*R*,7*S*,8a*R*)-Decahydro-1-(hydroxymethyl)-4,9,9-trimethyl-4,7-(epoxymethano)azulen-6-ol* (**2**). Colorless crystals. M.p. 90–91°. $[\alpha]_D^{20} = +37$ ($c = 0.05$, MeOH). IR (KBr): 3334, 2918, 2860, 1450, 1374, 1235, 1050. ^{1}H- (500 MHz, CD_3OD) and ^{13}C-NMR (125 MHz, CD_3OD): *Table 2*. HR-ESI-TOF: 277.1774 ($[M+Na]^+$, $C_{15}H_{26}NaO_3^+$; calc. 277.1779).

Acetylation of Compound **2**. To a soln. of compound **2** (6.0 mg) in pyridine (0.5 ml) was added Ac_2O (1 ml). The mixture was stirred overnight at r.t. for 12 h and after usual workup afforded compound **2a** (6.6 mg): colorless crystals. M.p. 79–80°. $[\alpha]_D^{20} = +52$ ($c = 0.1$, $CHCl_3$). IR (KBr): 2939, 2871, 1738, 1454, 1367, 1243, 1125, 1091, 1028. ^{1}H- (500 MHz, $CDCl_3$) and ^{13}C-NMR (125 MHz, $CDCl_3$): *Table 2*.

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Received May 28, 2009