New Diterpenes from *Croton insularis*

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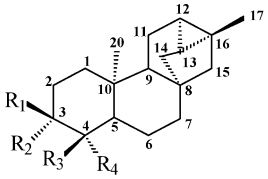
Two new diterpenes (**1** and **2**) have been isolated from the aerial parts of *Croton insularis*. Their structures have been established by NMR and mass spectral data, and the absolute configuration of **1** and related trachylobane diterpenes was determined through a series of chemical correlations.

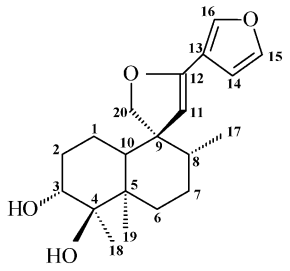
The genus *Croton* L., which includes some 750 species from the tropical and warm regions of the world, is a rich source of bioactive diterpenes, possessing for instance antiulcer,[1] antitumor,[2] or co-carcinogenic[3] properties. A recent report[4] of cytotoxic activity of a crude extract of *Croton insularis* Baillon toward human cancer cell lines prompted our study of this species.

Croton insularis is a small tree widespread in New Caledonia,[5] growing to ca. 15 m and characterized by the silvery white color of its branchlets and under-leaf surface. Fractionation of an extract of the aerial parts resulted in the isolation of two novel diterpenes, *ent*-trachyloban-3-one (**1**) and crotinsularin (**2**). Six known compounds were also isolated and identified as *ent*-13-*epi*-manoyl oxide,[6] 3α,4*β*-dihydroxy-15,16-epoxy-12-oxoclerodan-13(16),14-diene (**3**),[7,8] *ent*-trachyloban-19-oic acid (**4**),[9−11] 3α,19-dihydroxy-*ent*-trachylobane (**5**),[12] *ent*-trachyloban-3*β*-ol (**6**),[13] and 19-acetoxy-*ent*-trachylobane (**1**). The latter had been previously described only from an acetylated fraction of a fruit extract of *Xylopia aromatica* Lam.[14] The absolute configuration of **1** was deduced from chemical correlations, which also permitted us to determine those of **6** and **7**, which had not been previously unambiguously established.

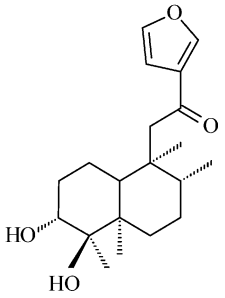
Compound **1** was obtained as a colorless gum and showed no UV absorption at 254 and 366 nm. Its empirical formula was established by HRESIMS as $C_{20}H_{30}O$. A strong band at 1717 cm^{-1} in the IR spectrum was indicative of a keto group. The ^{13}C NMR spectrum (Table 1) displayed 20 carbon signals, which were assigned by HMQC and DEPT 135° experiments as the resonances of five quaternary, four methine, seven methylene, and four methyl carbon atoms. The presence of a carbonyl group was also confirmed by a signal at *δ* 218.0. The ^1H NMR spectrum (Table 1) showed the presence of four methyl groups (*δ* 1.13, 1.10, 1.04, and 1.01) and two signals (a broad doublet and a multiplet) at *δ* 0.59 and 0.81 characteristic of the cyclopropane ring of a trachylobane diterpene. The ^1H and ^{13}C NMR data of this compound demonstrated general features very similar to those of *ent*-trachyloban-3*β*-ol (**6**). The main significant differences between **1** and **6** were the absence of the H-3 signal and replacement of the methine C-3 by a carbonyl group in **1**. The C-3 carbonyl was confirmed by the downfield shifts of H-2a and H-2b at *δ* 2.28 and 2.56, respectively, and by the strong cross-peaks observed in the HMBC spectrum, between C-3 and H-18, H-19 (^3J) and H-2 (^2J). Thus, the structure of compound **1** was established as *ent*-trachyloban-3-one.



1. $R_1, R_2 = O, R_3 = R_4 = CH_3$
4. $R_1 = R_2 = H, R_3 = CH_3, R_4 = COOH$
5. $R_1 = H, R_2 = OH, R_3 = CH_3, R_4 = CH_2OH$
6. $R_1 = H, R_2 = OH, R_3 = R_4 = CH_3$
7. $R_1 = R_2 = H, R_3 = CH_3, R_4 = CH_2OCOCH_3$



2



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The absolute configuration of **1** was determined through a series of chemical correlations (Scheme 1), starting from *ent*-trachyloban-19-oic acid (**4**), previously demonstrated by X-ray studies to belong to the *enantio* series.[11] Reduction[15] of **4** with $LiAlH_4$ afforded the primary alcohol **8**, which was treated with tosyl chloride in pyridine[16] to yield the corresponding ester **9**. Finally treatment of the latter by NaI and Zn[17] yielded *ent*-trachylobane (**10**). Compound **10** was also obtained by radical deoxygenation (Bu_3SnH/

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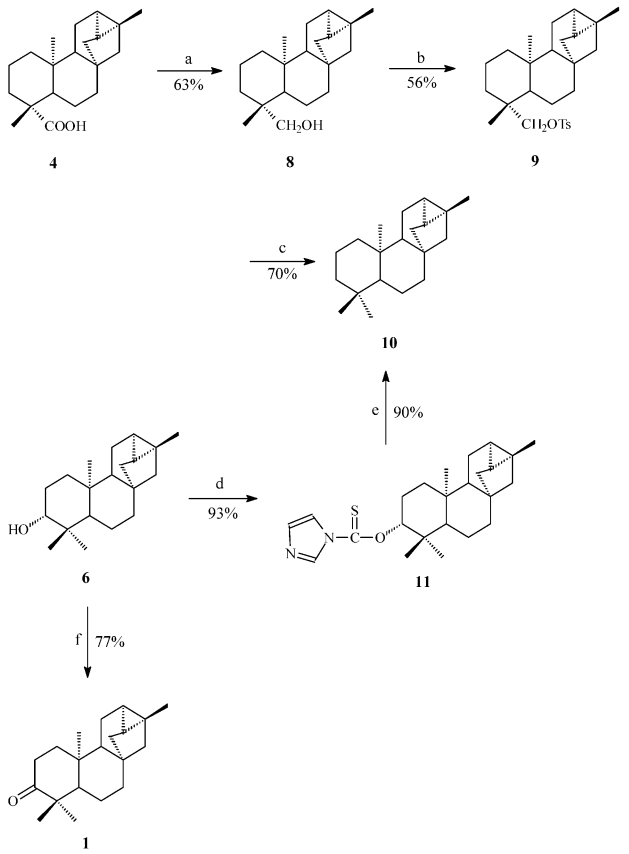
Table 1. ^{1}H and ^{13}C NMR Data of Compounds **1** and **2** (in $CDCl_3$)

	1			**2**		
	^{1}H NMR[a]		^{13}C NMR[a]	^{1}H NMR[a]		^{13}C NMR[a]
position	δ (mult)	J	δ (mult)	δ (mult)	J	δ (mult)
1	1.28 (m)		38.3	1.61−1.53 (m)		19.9
	1.77 (ddd)	13.5/7.1/3.5				
2	2.28 (ddd)	15.8/5.9/3.2	34.1	1.69 (m)		30.7
	2.56 (ddd)	15.8/12.3/6.8		2.06 (m)		
3			218.0	3.61 (brs)		77.0
4			42.1			78.3
5	1.22 (m)		55.5			41.4
6	1.18 (m)		21.1	1.66 (m)		32.6
	1.44 (m)			1.40 (m)		
7	1.19 (m)		38.0	1.33 (m)		26.8
	1.48 (m)			1.51 (m)		
8			40.4	1.35 (m)		40.8
9	1.12 (m)		52.4			56.0
10			37.7	1.90 (dd)	12.2/3.0	45.3
11	1.69 (ddd)	14.4/7.4/3.4	19.6	4.62 (s)		106.4
	1.90 (ddd)	14.4/11.2/3.0				
12	0.59 (brd)	11.8	20.4			147.9
13	0.81 (m)		24.1			118.0
14	1.21 (m)		33.2	6.48 (brs)		108.9
	2.06 (d)	11.8				
15	1.23 (d)	12.0	50.1	7.38 (brs)		143.7
	1.43 (d)	12.0				
16			22.5	7.52 (s)		140.1
17	1.13 (s)		20.4	0.88 (d)	6.0	17.1
18	1.01 (s)		26.0	1.26 (s)		22.0
19	1.04 (s)		21.5	0.94 (s)		16.5
20	1.10 (s)		14.1	4.18 (d)	9.2	70.9
				4.21 (d)	9.2	

[a] Assignments confirmed by DEPT, COSY, HMQC, and HMBC experiments.

Scheme 1[a]



[a] (a) $LiAlH_4$, Et_2O(anh), reflux; (b) TsCl, pyridine, 80 °C; (c) NaI, Zn, HMPA, 110 °C; (d) thiocarbonyldiimidazole, CH_2Cl_2(anh), pyridine, RT; (e) Bu_3SnH, AIBN, toluene(anh), 80 °C; (f) PCC, CH_2Cl_2(anh), RT.

AIBN)[18] of the ester **11**, which was prepared by treatment of compound **6** with *N*,*N*′-thiocarbonyldiimidazole. Thus compound **6** was proved to belong to the *enantio* series. The fact that compound **6**, on one hand, was oxidized with pyridinium chlorochromate (PCC)[19] to compound **1**, and compound **8**, on the other hand, was acetylated with excess Ac_2O to the corresponding ester **7** proved that compounds **1** and **7** also belong to the *enantio* series.

Compound **2** was obtained as a colorless gum. Accurate mass measurement of the molecular ion of **2** indicated a molecular formula $C_{20}H_{30}O_4$. The UV spectrum displayed absorption suggestive of a conjugated furan chromophore.[20] The IR spectrum showed hydroxyl absorptions at 3616 and 3471 cm^{-1}, and peaks at 3011, 1456, and 874 suggested the presence of a furan ring system.[21] From the ^{1}H and ^{13}C NMR spectral data, which were assigned by COSY, HMQC, and DEPT 135° experiments, it was obvious that **2** was a clerodane-type diterpene. The ^{1}H NMR spectrum showed two broad singlet peaks at δ 7.38 and 6.48 and a singlet at δ 7.52 characteristic of a β-substituted furan ring. Singlets at δ 1.26, 0.94 and a doublet at δ 0.88 demonstrated the presence of three methyl groups, two of them located at quaternary carbons. A secondary alcoholic group gave rise to a broad singlet at δ 3.61. These findings were similar to those present in the ^{1}H NMR spectrum of compound **3**. The major differences in **2** were the presence of only three methyl groups, of an AB system at δ 4.18, 4.21 instead of a similar system at δ 2.80, 2.65 in the case of compound **3**, and of a singlet at δ 4.62 corresponding to an olefinic proton of a trisubstituted double bond. The latter was confirmed by resonances at 106.4 and 147.9 in the ^{13}C NMR spectrum. These observations were consistent with a dihydrofuran ring as part of the structure of compound **2**. Furthermore, the ^{13}C NMR data revealed this compound has a *trans*-fused decalin ring system, as concluded from the methyl resonance δ 16.5, attributed to C-19.[8] More information on the structure of **2** was obtained from the HMBC spectrum. The ^3J correlation between the tertiary

Table 2. Cytotoxic Activity (IC_{50} values in μM) of Compounds **1**−**6** against Two Tumor Cell Lines[a]

compound	cell type	
	HeLa	L1210
1	131 (±16)	103 (±27)
2	148 (±7)	128 (±36)
3	*b*	98 (±1)
4	99 (±14)	99 (±5)
5	97 (±9)	91 (±7)
6	*b*	133 (±18)

[a] For protocols used, see ref 22. [b] In these cases IC_{50} was higher than the highest concentration tested (i.e., 200 μM).

carbon atom of the furan ring at δ 118.0 and the proton of the trisubstituted double bond at δ 4.62 showed that the furan and dihydrofuran rings were linked to each other. Furthermore, a ^3J correlation between the C-8 at δ 40.8 and the protons of the AB system at δ 4.18 and 4.21 revealed that the latter of the two above-mentioned rings was attached to the decalin system. Thus, **2** is a new clerodane, for which we propose the trivial name crotinsularin.

The relative configuration was deduced from the data of the NOESY spectrum. A strong cross-peak observed between H-20 (methylene group) and H-19/H-17 (methyl groups) suggested that these protons are oriented on the same side of the molecule. The lack of any NOE between H-10 and H-19 (methyl group) and the occurrence of a NOE between H-10 and H-11 was in accordance with the presence of a *trans*-fused decalin ring system.

Crotinsularin has a rearranged clerodane-type carbon skeleton, which includes a dihydrofuran attached at C-9. To the best of our knowledge, this ring system is described here for the first time in a natural product. From a biogenetic point of view, crotinsularin should be considered to arise from the oxidation of the C-20 methyl group of **1** to a primary alcohol, followed by cyclization onto the carbonyl oxygen at C-12.

The natural products (**1**−**6**) were tested against human cervical carcinoma (HeLa) and mouse leukemia (L1210) cell types for cytotoxic activity, and all showed moderate activity (Table 2).

Experimental Section

General Experimental Procedures. High-resolution electrospray ionization mass spectra (HRESIMS) were obtained in positive mode on a Q-Tof 1 Micromass mass spectrometer equipped with a standard Z-spray source. ^{1}H NMR (400 MHz) and ^{13}C NMR (50 MHz) data were recorded on a Bruker DRX-400 spectrometer and on a Bruker AC200 spectrometer, respectively (using TMS as an internal standard). COSY, HMQC, HMBC, and NOESY (mixing time 950 ms) NMR data were performed using standard Bruker micro programs. Optical rotations were measured on a Perkin-Elmer 341 polarimeter. IR spectra were obtained on a Perkin-Elmer Paragon 500 instrument. Column chromatography was carried out using silica gel 60 (Merck, 0.015−0.040 mm). Preparative TLC was carried out on glass precoated silica gel $60F_{254}$ plates (Merck).

Plant Material. The aerial parts of *Croton insularis* were collected in Tiébaghi (New Caledonia) in January 1997 and identified by one of us (M.L.). A voucher sample (LIT226) has been deposited at the herbarium of Institut de Recherche pour le Développement (IRD) at Nouméa (New Caledonia).

Extraction and Isolation. The air-dried leaves were powdered (4.5 kg) and extracted with cyclohexane (2 × 8 L), CH_2Cl_2 (2 × 8 L), and MeOH (3 × 8 L). The extracts were concentrated under reduced pressure to give 121, 310, and 815 g of residues, respectively. The cyclohexane extract (5 g), which was subjected to column chromatography on silica gel (0.015−0.040 mm) eluted with cyclohexane/CH_2Cl_2 and CH_2Cl_2/MeOH step gradients, yielded 27 fractions. Fraction 7 was deduced as *ent*-13-*epi*-manoyl oxide (14 mg) and fraction 12 as compound **1** (11.7 mg). Compound **4** (5.4 mg) was obtained from fraction 14 by preparative TLC. Fractions 15 and 16 were rechromatographed to give compounds **7** (3.1 mg) and compound **6** (28.9 mg), respectively. After crystallization from CH_2Cl_2, fraction 21 gave 3β-acetoxyfriedoolean-14-ene-28-oic acid (5.5 mg). The MeOH extract chromatographed by the same step gradient yielded 29 fractions. Fraction 6 was chromatographed to afford compounds **3** (6.5 mg), **2** (59.2 mg), and **5** (34.4 mg). Fraction 18, which was chromatographed by MPLC on a RP-18 column, afforded catechin, epi-catechin, and vomifoliol-3′*O*-β-D-glucopyranoside.

Cell Culture and Assessment of Cytotoxicity. The compounds **1**−**6** were tested for their cytotoxic activity on the following solid tumor cell lines: human cervical carcinoma (HeLa) and mouse leukemia (L1210) according to a previously described method.[22]

***ent*-Trachyloban-3-one (1):** amorphous solid; $[\alpha]^{20}_D$ −32° (*c* 0.40, $CHCl_3$); IR ($CHCl_3$) ν_{max} 2935, 1702, 1466, 1387 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) and ^{13}C NMR ($CDCl_3$, 50 MHz), see Table 1; HRESIMS *m*/*z* 287.2387 (calcd for $[M + H]^+$, 287.2381).

Crotinsularin (2): amorphous solid; $[\alpha]^{20}_D$ −17° (*c* 1.0, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 248 (3.70); IR ($CHCl_3$) ν_{max} 3470, 3011, 2935, 2873, 1677, 1456, 1373, 1161, 1108, 1052, 975, 874 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) and ^{13}C NMR ($CDCl_3$, 50 MHz), see Table 1; HRESIMS *m*/*z* 333.2052 (calcd for $[M + H]^+$, 333.2046).

Lithium Aluminum Hydride Reduction of Compound 4. $LiAlH_4$ (37 mg) was added to a solution of **4** (60 mg, 0.198 mmol) in anhydrous Et_2O (15 mL). The mixture was refluxed for 2 h, and MeOH was then added. The organic solvent was evaporated, and the residue was dissolved in EtOAc and extracted with H_2O. The organic layer was separated and evaporated under reduced pressure. Compound **8** (36 mg, 0.124 mmol, 63.1%) was purified by preparative TLC (CH_2Cl_2).

***ent*-Trachyloban-19-ol (8):** $[\alpha]^{20}_D$ −42° (*c* 0.5, $CHCl_3$); ^{1}H NMR, see ref 23.

Tosylation of Compound 8. A solution of alcohol **8** (30 mg) in dry pyridine (3 mL) was treated with TsCl (150 mg) at 80 °C for 2 h. The mixture was purified by column chromatography (cyclohexane/CH_2Cl_2, 80:20) to afford pure compound **9** (25.0 mg, 0.056 mmol, 54.4%).

19-*p*-Toluolosulfonyloxy-*ent*-trachylobane (9): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.57 (1H, brd, J = 11.5 Hz, H-12), 0.67 (1H, td, J = 13.0, 4.6 Hz, H-1a), 0.77 (1H, m, H-5), 0.79 (3H, s, H-18), 0.89 (3H, s, H-20), 0.90 (1H, m, H-13), 1.05−1.15 (5H, m, H-9, H-14a, H-17), 1.18 (1H, d, J = 11.4 Hz, H-15a), 1.21−1.26 (3H, m, H-2a, H-6a, H-7a), 1.32 (1H, d, J = 11.4 Hz, H-15b), 1.36−1.42 (3H, m, H-2b, H-6b, H-7b), 1.46 (1H, brd, J = 13.0 Hz, H-1b), 1.56 (1H, ddd, J = 14.6, 7.0, 2.4 Hz, H-11a), 1.63 (1H, brd, J = 13.7 Hz, H-3b), 1.82 (1H, ddd, J = 14.6, 11.4, 3.2 Hz, H-11b), 1.92 (1H, d, J = 11.5 Hz, H-14b), 2.43 (3H, s, Me-Ts), 3.75 (1H, d, J = 9 Hz, H-19b), 4.12 (1H, d, J = 9 Hz, H-19a), 7.32 (2H, d, J = 8 Hz, Ts-H), 7.75 (2H, d, J = 8 Hz, Ts-H).

Detosylation of Compound 9. NaI (300 mg) and Zn (260 mg) were added to a solution of the tosylate **9** (25.0 mg, 0.056 mmol) in hexamethylphosphoramide (5 mL). The mixture was stirred for 12 h at 110 °C. The resulting mixture was filtered on Celite, and the filtrate was evaporated. The residue was dissolved in Et_2O and extracted with H_2O. The organic layer was separated, dried (Na_2SO_4), and evaporated under reduced pressure. Compound **10** (11.5 mg, 0.043 mmol, 70%) was purified by column chromatography (cyclohexane).

***ent*-Trachylobane (10):** $[\alpha]^{20}_D$ −40° (*c* 1.0, $CHCl_3$); ^{1}H NMR, see ref 9.

Preparation of Compound 11. To a solution of compound **6** (10 mg, 0.034 mmol) in dry CH_2Cl_2 (2 mL) and dry pyridine (2 drops) was added thiocarbonyldiimidazole (25 mg). The mixture was stirred at room temperature for 12 h. Compound

11 (12.5 mg, 0.031 mmol, 92.6%) was purified by column chromatography (CH_2Cl_2).

3-Imidazolothiocarbonyloxy-*ent*-trachylobane (11): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.57 (1H, d, J = 7.8 Hz, H-12), 0.73−0.85 (2H, m, H-5, H-7b), 0.90 (1H, m, H-13), 0.92 (3H, s, H-20), 0.97 (3H, s, H-19), 0.99 (3H, s, H-18), 1.08 (1H, m, H-9), 1.11 (3H, s, H-17), 1.16 (1H, brd, J = 11.3 Hz, H-14a), 1.22 (1H, d, J = 11.4 Hz, H-15a), 1.29−1.52 (6H, m, H-1a, H-1b, H-6a, H-6b, H-7b, H-15b), 1.55−1.67 (3H, m, H-11a, H-2a, H-2b), 1.89 (1H, m, H-11b), 2.02 (1H, d, J = 11.3 Hz, H-14b), 5.17 (1H, dd, J = 11.7, 4.7 Hz, H-3), 7.01 (1H, s, =CH-N), 7.59 (1H, s, =CH-N), 8.31 (1H, s, N-CH=N).

Reduction of 11. Compound **11** (12.5 mg, 0.031 mmol) was dissolved in dry toluene (2 mL) and was treated with tributyltin hydride (0.1 mL) and α,α′-azoisobutyronitrile (15 mg) at 80 °C for 12 h. Purification of the mixture by column chromatography (CH_2Cl_2) afforded pure **10** (7.5 mg, 0.028 mmol, 89.6%) (^{1}H NMR data are reported by Pyrek).[9]

Acetylation of 8. Compound **8** (4 mg, 0.014 mmol) was dissolved in Ac_2O (1 mL) and C_5H_5N (1 mL). The mixture was stirred overnight at room temperature to obtain corresponding acetylated compound **7** (4.1 mg, 0.012 mmol, 88.7%).

19-Acetoxy-*ent*-trachylobane (7): $[\alpha]^{20}_D$ −20° (*c* 0.05, $CHCl_3$); ^{1}H NMR, see ref 9.

Pyridinium Chlorochromate Oxidation of Compound 6. PCC (10 mg) was added to an ice-cold suspension of compound **6** (10 mg, 0.034 mmol) in CH_2Cl_2 (2 mL). After 2 h at room temperature the mixture was purified by column chromatography (CH_2Cl_2) to afford **1** (7.5 mg, 0.026 mmol, 77.1%) (^{1}H NMR data, see Table 1).

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