Chemical Constituents from *Croton insularis*

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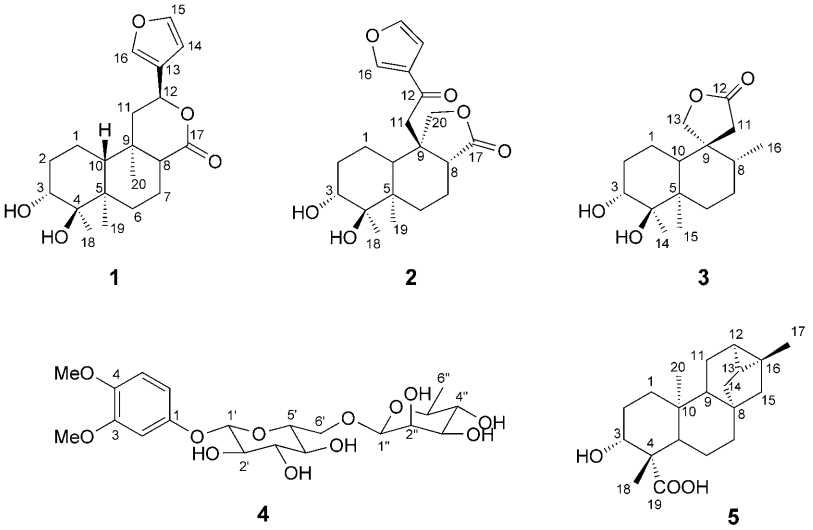
Three new clerodane-type terpenoids, furocrotinsulolide A (**1**), furocrotinsulolide B (**2**), and crotinsulactone (**3**), as well as a new phenolic disaccharide (**4**) have been isolated from the aerial parts of *Croton insularis*, together with eight known compounds. Their structures were established by in-depth 1D- and 2D-NMR spectroscopy, mass spectroscopy, and quantum-mechanical calculations.

Introduction. – The genus *Croton* L. (Euphorbiaceae), which includes *ca.* 750 species from the tropical and temperate regions, is a rich source of biologically active diterpenes, possessing, *e.g.*, anti-ulcer [1], antitumor [2], or co-carcinogenic [3] properties. *Croton insularis* BAILLON is a small tree widespread in New Caledonia, growing to *ca.* 15 m, and characterized by the silvery-white color of its branchlets and under-leaf surface [4]. Upon screening of a number of 90 higher plants from the rainforests of Australia, the bark crude extract of *C. insularis* has been reported to be moderately cytotoxic towards human cancer cells, and to exhibit weak antimicrobial activity [5]. Our previous work on this species has resulted in the isolation of six *ent*-trachylobane and two clerodane diterpenes [6].

The present paper describes the isolation of three new clerodane terpenoids, furocrotinsulolide A (**1**), furocrotinsulolide B (**2**), and crotinsulactone (**3**), the new phenolic disaccharide **4**, as well as the known compound 3β-hydroxy-*ent*-trachyloban-19-oic acid (**5**). Compound **5** has been isolated before from *Trachylobium verrucosum* [7], but its full NMR data are reported herein for the first time. In addition, the known compounds 3α,4β-dihydroxy-15,16-epoxy-12-oxoclerodan-13(16),14-dien-9-al [8], 1-(α-L-rhamnosyl-(1 $\rightarrow$ 6)-β-D-glucopyranosyloxy)-3,4,5-trimethoxybenzene [9], 1-(β-D-apiofuranosyl-(1 $\rightarrow$ 6)-β-D-glucopyranosyloxy)-3,4,5-trimethoxybenzene [10], isokaempferide [11], ferulic acid [12], and vanillic acid [13] were isolated. The structures of these compounds were established by means of in-depth NMR and MS experiments, and by comparison with literature data.

Results and Discussion. – Furocrotinsulolide A[1]) (**1**) was obtained as a colorless, amorphous solid. HR-ESI-MS Experiments indicated the molecular formula

[1]) For systematic names, see the *Exper. Part*.



$C_{20}H_{28}O_5$. The UV spectrum of **1** displayed typical absorption maxima at 257 and 214 nm, associated with a furan chromophore [14][15]. In the IR spectrum, a strong band at 3457 cm^{-1} indicated the presence of OH groups, a band at 1725 cm^{-1} was assigned to a δ-lactone, and those at 3028, 1462 and 872 cm^{-1} were due to a furyl moiety [14] [16].

The ^{13}C-NMR spectrum of **1** (*Table 1*) exhibited 20 signals, which were assigned by HMQC and DEPT-135° experiments as the resonances of five quaternary C-atoms, seven CH, five CH_2, and three Me groups. The lactone C=O group appeared at δ(C) 176.2. The ^{1}H-NMR spectrum (*Table 2*) showed two broad *singlet*s at δ(H) 7.46 and 6.52, and a third *singlet* at δ(H) 7.56, characteristic of a β-substituted furan ring. A secondary alcoholic group gave rise to a broad *singlet* at δ(H) 3.47. Three Me groups were identified from *singlet*s at δ(H) 1.20, 1.15, and 1.03.

The ^{1}H- and ^{13}C-NMR data of **1** showed general features very similar to those previously reported for the *A*-ring of the clerodane diterpene crotinsularin [6], and of the *B*- and *C*-rings of the clerodane diterpene 12-*epi*-methyl barbascoate [16]. Of particular interest was the H–C(12) lactone resonance appearing as a double *doublet* (J = 11.0 and 5.5 Hz) at δ (H) 5.53, which suggested the same configuration at this center as that of 12-*epi*-methyl barbascoate, and different from that of methyl barbascoate [15]. In good agreement with this assumption, strong NOE cross-peaks were observed between the signals of H–C(12) and Me(20), which indicated a furan ring in equatorial position. From an NOE between H–C(3) and both H-atoms of CH_2(2), the 3-OH group was deduced to be axial (α-position). NOESY Cross-peaks between Me(19) and Me(18) as well as Me(20) corroborated that these three Me groups were on the same side of the molecular plane, *i.e.*, opposite to the 4-OH group. A cross-peak between H–C(8) and H–C(10), and the lack of any NOE between the signals of H–C(8) or H–C(10) with Me(20) or Me(19), allowed us, together with the above data, to deduce the relative configuration of **1**.

Furocrotinsulolide B (**2**) was obtained as colorless needles from CH_2Cl_2. Its formula was established by ESI-MS as $C_{20}H_{26}O_6$. The UV spectrum of **2** showed characteristic absorption maxima at 255 and 215 nm due to a conjugated furan chromophore [14][15]. The IR band at 3684 cm^{-1} was assigned to OH groups, that at 1770 cm^{-1} to

Table 1. *^{13}C-NMR Data of Compounds* **1**–**3**. At 50 MHz in CD_3OD; δ in ppm. Arbitrary atom numbering[1]).

Position	**1**	**2**	**3**
1	18.3	19.3	19.1
2	31.5	32.2	31.5
3	77.2	77.6	77.2
4	77.5	77.6	77.1
5	42.4	42.8	43.1
6	33.1	31.3	33.8
7	19.3	22.7	28.0
8	52.4	46.2	44.3
9	38.3	47.1	47.5
10	49.0	41.1	44.3
11	45.8	49.5	41.3
12	74.3	197.0	180.7
13	127.9	133.0	71.4
14	110.2	110.2	21.6
15	145.5	147.1	17.4
16	141.6	151.3	17.4
17	176.2	183.6	–
18	21.5	22.0	–
19	18.1	17.5	–
20	15.4	76.2	–

Table 2. *^{1}H-NMR Data of Compounds* **1**–**3**. At 400 MHz in CD_3OD; δ in ppm, J in Hz. Arbitrary atom numbering[1]).

Position	**1**	**2**	**3**
1	1.74–1.53 (*m*)[a])	1.65–1.55 (*m*)[a])	1.48 (br. *d*, *J* = 13.4)
	1.37 (*dd*, *J* = 12.5, 4.0)	1.48–1.42 (*m*)[a])	1.77–1.62 (*m*)[a])
2	1.98 (br. *t*, *J* = 4.0)	1.89–1.78 (*m*)	2.05 (br. *t*, *J* = 14.0)
	1.74–1.53 (*m*)[a])	1.65–1.55 (*m*)[a])	1.77–1.62 (*m*)[a])
3	3.47 (br. *s*)	3.47 (br. *s*)	3.50 (br. *s*)
6	1.74–1.53 (*m*)[a])	1.65–1.72 (*m*)[a])	1.77–1.62 (*m*)[a])
	1.48 (br. *d*, *J* = 12.1)	1.48–1.42 (*m*)[a])	1.52–1.36 (*m*)[a])
7	1.91 (*dd*, *J* = 13.7, 3.1)	1.99–1.90 (*m*)	1.52–1.36 (*m*)[a])
	1.58 (br. *t*, *J* = 13.7)	1.65–1.72 (*m*)[a])	1.52–1.36 (*m*)[a])
8	2.19 (*dd*, *J* = 11.7, 2.7)	3.00 (*dd*, *J* = 11.2, 7.8)	1.52–1.36 (*m*)
10	1.78 (br. *d*, *J* = 12.1)	2.28 (*dd*, *J* = 12.2, 2.5)	1.93 (br. *d*, *J* = 12.1)
11	2.36 (*dd*, *J* = 13.7, 5.5)	3.17 (*d*, *J* = 15.2)	2.87 (*d*, *J* = 18.5)
	1.68 (*dd*, *J* = 13.7, 11.0)	2.88 (*d*, *J* = 15.2)	2.15 (*d*, *J* = 18.5)
12	5.53 (*dd*, *J* = 11.0, 5.5)	–	–
13	–	–	4.25 (*d*, *J* = 10.0)
			4.19 (*d*, *J* = 10.0)
14	6.52 (br. *s*)	6.78 (br. *s*)	1.19 (*s*)
15	7.46 (br. *s*)	7.60 (br. *s*)	0.94 (*s*)
16	7.56 (*s*)	8.42 (*s*)	0.92 (*d*, *J* = 6.0)
18	1.20 (*s*)	1.20 (*s*)	–
19	1.15 (*s*)	1.22 (*s*)	–
20	1.03 (*s*)	4.56 (*d*, *J* = 9.8)	–
		4.13 (*d*, *J* = 9.8)	

[a]) Assignment confirmed by COSY and HMQC experiments.

a γ-lactone, the one at 1660 cm^{-1} indicated an α,β-unsaturated C=O group, and those at 1596 and 873 cm^{-1} pointed to a furyl moiety [8][17].

The ^{13}C-NMR spectrum of **2** (*Table 1*) exhibited 20 signals, which were assigned by HMQC and DEPT-135° experiments as the resonances of six quaternary C-atoms, six CH, six CH_2, and two Me groups. The presence of a lactone C=O group was confirmed by a signal at δ(C) 183.6, and a keto C=O group was found at δ(C) 197.0. The ^{1}H-NMR spectrum of **2** (*Table 2*) showed two broad *singlet*s at δ(H) 7.60 and 6.78, and a further *singlet* at δ(H) 8.42, characteristic of a β-substituted furan ring [8]. A secondary alcoholic group gave rise to a broad *singlet* at δ(H) 3.47. Two *singlet*s at δ(H) 1.22 and 1.20 demonstrated the presence of two Me groups located at quaternary C-atoms. The two *doublet*s at δ(H) 4.56 and 4.13 corresponded to a CH_2 group attached to an oxygenated C-atom, and the two *doublet*s at δ(H) 3.17 and 2.88 were due to a CH_2 group next to a C=O group, as deduced from HMBC experiments. In addition, HMBC correlations of H–C(8) at δ(H) 3.00 and H–C(11) at δ(H) 3.17/2.88 with C(20) at δ(C) 76.2 confirmed the presence of a lactone ring fused in positions 8 and 9. A *trans*-fused decalin ring was identified from the Me(19) resonance at δ(C) 17.5 in the ^{13}C-NMR spectrum. In the NOESY spectrum, strong cross-peaks were observed between H–C(8) and H–C(10), so that both of them had to be on the same side. The lack of any NOE between H–C(10) and Me(19) corroborated the *trans*-fusion of the decalin. Finally, from a cross-peak between Me(19) and CH_2(20), which indicated their spatial proximity, and from the observation that H–C(8) exhibited strong NOE effects with both H-atoms of CH_2(7), and based upon the above data, the relative configuration of **2** could be established. If the configuration at C(8) was opposite to that shown, no cross-peaks between Me(19) and H–C(20), and between H–C(10) and H–C(8), would have been present. In addition, a correlation between Me(19) and H–C(11) should have been observed, which was not the case.

We observed unusual ^{1}H-NMR coupling constants in the case of **2**, with J(7a,8) = 7.8 and J(7b,8) = 11.2 Hz. To rationalize this effect, a conformational analysis based on molecular mechanics was performed. The Low Mode/Monte Carlo [18] search protocol, as implemented in the Macromodel 6.5 software [19], was used. After a 5000-step search, all structures lying within 50 kJ/mol of the global minimum were saved and minimized. The coupling constants were calculated by means of the NMR module of Macromodel based on the equation of *Altona et al.* [20]. The lowest-energy conformation of ring *B* of **2** was similar to most of the structures recovered from the search (*Figure*). The calculated values for J(7a,8) and J(7b,8) were 6.6 and 10.4 Hz, respectively, in fair agreement with the experimental values (see above).

Crotinsulactone (**3**) was obtained as a colorless, amorphous solid. Its formula was established by ESI-MS as $C_{16}H_{26}O_4$. Typical IR bands at 3428 and 1771 cm^{-1} indicated OH and γ-lactone functionalities, respectively [17].

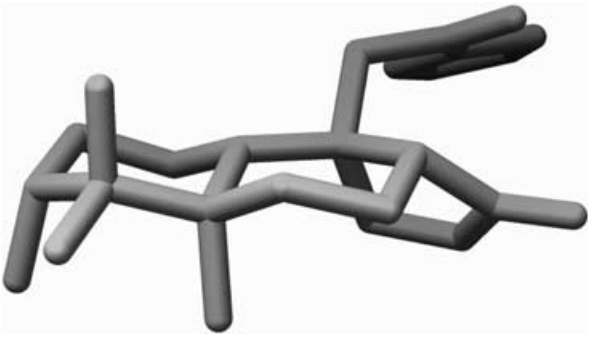


Figure. *Calculated lowest-energy conformation of* **2**

The ^{13}C-NMR spectrum of **3** (*Table 1*) displayed 16 signals, which were assigned by HMQC and DEPT-135° experiments as the resonances of four quaternary C-atoms, three CH, six CH_2, and three Me groups. The presence of a C=O group was confirmed by a signal at δ(C) 180.7. The ^{1}H-NMR spectrum (*Table 2*) showed two *singlet*s at δ(H) 1.19 and 0.94, and a *doublet* at δ(H) 0.92, accounting for three Me groups. The presence of an *AB* spin system at δ(H) 4.25/4.19 (*d*, J = 10.0 Hz) and a broad *singlet* at δ(H) 3.50 were similar to the corresponding signals for crotinsularin [6]. The major differences were the presence of an additional *AB* system at δ(H) 2.87/2.15 (*d*, J = 18.5 Hz), which corresponds to a CH_2 group next to a C=O group, instead of a *singlet* at δ(H) 4.62, corresponding to an olefinic H-atom in crotinsularin. Another difference was a C=O resonance at δ(C) 180.7, which showed ^3J correlations with the CH_2 H-atoms at δ(H) 4.25/4.19, as confirmed from a HMBC experiment, instead of furan-ring resonances, as present in crotinsularin. From these data, a *trans*-fused decalin ring [8] linked to a furanolactone was evident. The *trans*-decalin was confirmed by the lack of an NOE between H–C(10) and Me(15). Instead, strong cross-peaks were observed between H–C(8) and H–C(10), which, thus, had to be on the same side of the molecular plane. Moreover, an NOE signal between Me(15) and both H-atoms of CH_2(13) indicated their spatial proximity.

Compound **4** was obtained as a colorless, amorphous solid, with the molecular formula $C_{20}H_{30}O_{12}$, as established by ESI-MS. The UV spectrum of **4** showed absorption maxima at 278 and 222 nm.

The ^{1}H-NMR data of **4** (*Table 3*) indicated two MeO groups at δ(H) 3.81 and 3.78, two anomeric H-atoms at δ(H) 4.75 (*d*, J = 7.8) and 4.71 (*d*, J = 1.2 Hz), respectively, and three aromatic H-atoms at δ(H) 6.88 (*d*, J = 8.0), 6.78 (*d*, J = 2.0), and 6.68 (*dd*, J = 8.0, 2.0 Hz), corresponding to an *ABX* spin system. Overlapping *multiplet*s corresponding to sugar moieties were observed at δ(H) 4.10–3.35, and one Me group was identified from the signal at δ(H) 1.25 (*d*, J = 6.4 Hz). The ^{13}C-NMR spectrum of **4** (*Table 3*) displayed signals of two MeO groups at δ(C) 57.1 and 56.5, six aromatic signals (three CH and three oxygenated quaternary C-atoms), as well as characteristics signals of glucose (Glc) and rhamnose (Rha) [9]. HMBC Correlations indicated that the anomeric center of Glc (H–C(1′) at δ(H) 4.75) was attached to a trisubstituted phenol (C(1) at δ(C) 153.8), and that the anomeric center of Rha, H–C1″ at δ(H) 4.71, was connected with C(6′) of Glc at δ(C) 68.0.

Table 3. *^{1}H- and ^{13}C-NMR Data of Compound* **4**. At 400/50 MHz, resp., in $CDCl_3$; δ in ppm, J in Hz. Arbitrary atom numbering[1]).

Position	^{1}H	^{13}C	Position	^{1}H	^{13}C
1	–	153.8	6′	4.02 (*d*, J = 12.0)	68.0
2	6.78 (*d*, J = 2.0)	104.2		3.69–3.60 (*m*)[a])	
3	–	151.0	1″	4.71 (*d*, J = 1.2)	102.2
4	–	146.1	2″	3.82 (*dd*, J = 9.9, 1.2)	72.2
5	6.88 (*d*, J = 8.0)	113.9	3″	3.69–3.60 (*m*)[a])	69.8
6	6.68 (*dd*, J = 8.0, 2.0)	109.3	4″	3.45–3.32 (*m*)[a])	74.0
1′	4.75 (*d*, J = 7.8)	103.4	5″	3.69–3.60 (*m*)[a])	72.4
2′	3.45–3.32 (*m*)[a])	74.9	6″	1.25 (*d*, J = 6.4)	17.9
3′	3.45–3.32 (*m*)	78.0	3-MeO	3.81 (*s*)	57.1
4′	3.45–3.32 (*m*)[a])	71.5	4-MeO	3.78 (*s*)	56.5
5′	3.60–3.49 (*m*)[a])	76.9			

[a]) Assignment confirmed by COSY and HMQC experiments.

Experimental Part

General. Column chromatography (CC) was carried out with silica gel *60* (0.015–0.040 mm; *Merck*). Prep. TLC was carried out on glass-precoated silica gel *60 F_{254}* plates (*Merck*). Melting points (m.p.) were determined on a *Büchi* apparatus; uncorrected. UV Spectra were recorded on a *Shimadzu UV-160A* apparatus; λ_{max} (log ε). Optical rotations were measured on a *Perkin-Elmer 341* polarimeter. IR Spectra were obtained on a *Perkin-*

Elmer Paragon-500 instrument; in cm^{-1}. ^{1}H- (400 MHz) and ^{13}C-NMR (50 MHz) Spectra were recorded on a *Bruker DRX-400* and on a *Bruker AC-200* spectrometer, resp., with Me_4Si as internal standard; δ in ppm, J in Hz. COSY, HMQC, HMBC and NOESY (mixing time 950 ms) NMR data were performed using standard *Bruker* micro programs. Electrospray-ionization mass spectra (ESI-MS) were obtained in the pos. mode on a *Q-Tof-1 Micromass* mass spectrometer equipped with a standard Z-spray source; in m/z.

Molecular-Mechanics Calculations. The MM2* force field was used. All stereogenic centers were kept constrained during the search. The *Polak–Ribiere* conjugate-gradient algorithm was used for the energy minimization, with a convergence criterion of 0.05 kJ $Å^{-1}$ mol^{-1}. All calculations were performed on an *O_2 Silicon Graphics* workstation.

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

Extraction and Isolation. The powdered, air-dried leaves (4.5 kg) were 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 afford 121, 310, and 815 g of residue, resp. The MeOH extract was subjected to CC (SiO_2; cyclohexane/CH_2Cl_2 and CH_2Cl_2/MeOH step gradients): 29 fractions (Fr.). *Fr. 7*, eluted with CH_2Cl_2/MeOH 98:2, was re-chromatographed to provide a mixture, which was separated by prep. TLC to afford **1** (5.6 mg), **2** (86.8 mg), and **5** (8.9 mg), *Fr. 8*, eluted with CH_2Cl_2/MeOH 98:2, was re-chromatographed to afford a mixture of ferulic and vanillic acid (12.7 mg), isokaempferide (3.5 mg), and **3** (79.2 mg). *Fr. 21*, eluted with CH_2Cl_2/MeOH 85:15, was subjected to MPLC (*RP-18* column) to afford **4** (10.8 mg) and a mixture of 1-(α-L-rhamnosyl-(1→6)-β-D-glucopyranosyloxy)-3,4,5-trimethoxybenzene and 1-(β-D-apiofuranosyl-(1 → 6)-β-D-glucopyranosyloxy)-3,4,5-trimethoxybenzene.

Furocrotinsulolide A (=*(2*S**,4a*R**,6a*R**,7*R**,8*R**,10b*R**)-2-(Furan-3-yl)dodecahydro-7,8-dihydroxy-6a,7,10b-trimethyl-4*H*-naphtho[2,1-c]pyran-4-one*; **1**). Amorphous solid. M.p. 207–209°. UV (MeOH): 257 (1.12), 214 (1.90). $[\alpha]_D^{20} = +6.80$ ($c = 2.3$, MeOH). IR ($CHCl_3$): 3457, 3028, 1725, 1462, 872. ^{1}H- and ^{13}C-NMR: see *Tables 2* and *1*, resp. ESI-MS: 387 ($[M+K]^+$), 371 ($[M+Na]^+$). HR-ESI-MS: 371.1836 ($[M+Na]^+$, $C_{20}H_{28}NaO_5^+$; calc. 371.1834).

Furocrotinsulolide B (=*(3a*R**,5a*R**,6*R**,7*R**,9a*R**,9b*S**)-9b-[2-(Furan-3-yl)-2-oxoethyl]-decahydro-6,7-dihydroxy-5a,6-dimethylnaphtho[1,2-c]furan-3(1*H*)-one*; **2**). Colorless needles. M.p. 212–213°. UV (MeOH): 255 (1.35), 215 (2.02). $[\alpha]_D^{20} = -3.60$ ($c = 2.5$, MeOH). IR ($CHCl_3$): 3684, 1770, 1660, 1596, 873. ^{1}H- and ^{13}C-NMR: see *Tables 2* and *1*, resp. ESI-MS: 401 ($[M+K]^+$), 385 ($[M+Na]^+$). HR-ESI-MS: 385.1627 ($[M+Na]^+$), $C_{20}H_{26}NaO_6^+$; calc. 385.1626).

Crotinsulactone (=*(2′*R**,3*R**,4a′*R**,5′*R**,6′*R**,8a′*R*)-Octahydro-5′,6′-dihydroxy-2′,4a′,5′-trimethyl-2′*H*-spiro[furan-3,1′-naphthalen]-5(4*H*)-one*; **3**). Amorphous solid. M.p. 190–192°. UV (MeOH): 216 (1.99). $[\alpha]_D^{20} = -3.12$ ($c = 1.6$, MeOH). IR ($CHCl_3$): 3428, 1771. ^{1}H- and ^{13}C-NMR: see *Tables 2* and *1*, resp. ESI-MS: 321 ($[M+K]^+$), 305 ($[M+Na]^+$), 283 ($[M+H]^+$). HR-ESI-MS: 305.1725 ($[M+Na]^+$, $C_{16}H_{26}NaO_4^+$; calc. 305.1728).

*3,4-Dimethoxyphenyl 6-*O*-(α-L-Rhamnopyranosyl)-β-D-glucopyranoside* (**4**). Amorphous solid. M.p. 111–112°. $[\alpha]_D^{20} = -56.8$ ($c = 1.2$, MeOH). ^{1}H- and ^{13}C-NMR: see *Table 3*. ESI-MS: 501 ($[M+K]^+$), 485 ($[M+Na]^+$). HR-ESI-MS: 485.1638 ($[M+Na]^+$, $C_{20}H_{30}NaO_{12}^+$; calc. 485.1634).

3β-Hydroxy-ent-*trachyloban-19-oic Acid* (**5**). Amorphous solid. M.p. 263–265°. $[\alpha]_D^{25} = -72$ ($c = 0.6$, EtOH) [7]. ^{1}H-NMR (400 MHz, $CDCl_3$): 3.10 (*dd*, $J = 12.1$, 4.4, H–C(3)); 2.00 (*d*, $J = 11.4$, H_a–C(14)); 1.94–1.84 (*m*, H_a–C(11)); 1.75–1.62 (*m*, H–CH_2(2), CH_2(6), H_a–C(7), H_b–C(11)); 1.55–1.46 (*m*, H_a–C(15)); 1.50–1.40 (*m*, H_a–C(1)); 1.42 (*s*, Me(18)); 1.34–1.24 (*m*, H_b–C(1)); 1.24–1.17 (*m*, H_b–C(15)); 1.20 (*d*, $J = 11.4$, H_b–C(14)); 1.12 (*s*, Me(17)); 1.08–1.00 (*m*, H–C(9)); 0.96 (br. *s*, H–C(5)); 0.95–0.90 (*m*, H_b–C(7)); 0.89 (*s*, Me(20)); 0.85–0.80 (*m*, H–C(13)); 0.58 (br. *d*, $J = 7.7$, H–C(12)). ^{13}C-NMR (50 MHz, $CDCl_3$): 183.0 (C(19)); 78.1 (C(3)); 56.4 (C(5)); 52.5 (C(9)); 50.0 (C(15)); 43.9 (C(4)); 40.4 (C(8)); 38.9 (C(1)); 38.5 (C(10)); 38.0 (C(7)); 33.0 (C(14)); 27.7 (C(2)); 24.1 (C(18)); 23.9 (C(13)); 22.4 (C(16)); 21.6 (C(6)); 20.5 (C(12) and C(17)); 19.7 (C(11)); 12.5 (C(20)).

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