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Bromocyclococanol, a halogenated sesquiterpene with a novel carbon skeleton from the red alga *Laurencia obtusa*

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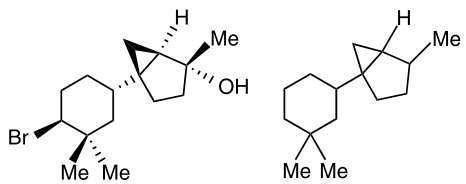
Abstract—A bromo sesquiterpene, bromocyclococanol **1**, containing fused cyclopropane–cyclopentane rings leading a novel carbon skeleton has been isolated from the red alga *Laurencia obtusa*. The structure and stereochemistry were established by spectroscopic evidence and biogenetic considerations. A biogenetic route for this compound has also been proposed

Species of algae from the genus *Laurencia* (Ceramiales, Rhodomelaceae) are found throughout the world, mostly in tropical and subtropical habitats and have been the subject of intensive research[1] since Irie's pioneering[2] investigations on *Laurencia*. Most of the halogenated sesquiterpenes described occur in various species of *Laurencia*[3] and although diterpenes, triterpenes and especially C-15 acetogenins have also been found,[4,5] the sesquiterpene metabolites with a chamigrene skeleton appear to be the most generalized in the genus. Sometime ago, we reported[6] on the chemical analysis of *L. obtusa* and we believed it of interest to compare the chemical content of *L. obtusa* from Cuba with previous studies of this species from the Canary Islands. In this work we report a minor interesting sesquiterpene, bromocyclococanol **1**, isolated from *L. obtusa* collected in Cayo Coco, with a novel skeleton for which we proposed the trivial name cyclococane **2**.



1 **2**

Bromocyclococanol **1** was obtained[7] as a colorless oil from the hexane–ethyl acetate (90:10) of the vacuum flash chromatography fraction of the dichloromethane extract of *L. obtusa* followed by gel filtration and purification by recycling-HPLC. The EIMS spectrum showed peaks at m/z 300/302 $[M]^+$, with relative intensities suggestive of a bromine atom which correspond to the empirical formula $C_{15}H_{25}BrO$ $[M]^+$ (HRMS). The IR spectrum showed absorption for a hydroxyl group at ν_{max} 3460 cm^{-1}. Since the IR spectrum revealed no absorptions for unsaturations, the molecule is tricyclic.

The ^{13}C NMR spectrum of **1** (Table 1) displayed signals for 15 carbons. Multiplicities of the carbon signals were determined from the DEPT spectrum: three methyls, six methylenes, three methines (one bearing a heteroatom), and three non-protonated carbons. In the ^1H and ^{13}C NMR spectra, both proton- and carbon-bearing heteroatoms showed a chemical shift at $\delta_{H\text{-}10}$ 3.87 and $\delta_{C\text{-}10}$ 66.2, unusual for a bromine or hydroxyl substituent. However, the presence of a signal for a non protonated carbon at δ_C 78.9 in the ^{13}C NMR spectrum and for a methyl group at δ_H 1.29 in the ^1H NMR suggested that the oxygen of the molecular formula should take the form of a methyl carbinol (H_3-15). This, together with the fact that the alcoholic function does not react with acetic anhydride and pyridine, suggested that the substituent of the methine carbon bearing heteroatom was a bromine atom.

In addition to the methyl carbinol at δ 1.29, the ^1H NMR spectrum showed high-field signals for two tertiary methyl groups at δ 1.03 (3H, s), δ 0.97 (3H, s) and also for protons of a cyclopropane ring at δ 0.64 (1H)

Keywords: marine sesquiterpene; fused cyclopropane–cyclopentane rings; novel skeleton; algae; *Laurencia*.

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and δ 0.26 (1H). In the absence of another heteroatom or unsaturation, the presence of only three methyl groups suggested that the four-methyl group corresponding to a sesquiterpene skeleton must form a part of a ring.

Chemical shift arguments and ^1H–^1H COSY correlations supported by MS data allowed the assignment of fragments **a**–**c** as shown in Fig. 1 (**I**). From the ^1H–^1H COSY NMR spectrum it was possible to differentiate one discrete spin system and part of another spin system due to the complex overlapping signals of most of the methines and methylene protons.

The coupling of both protons at δ 0.64 and δ 0.26 of the methylene of the cyclopropane with a methine at δ 1.05 established the connectivity of the H-4–H-5 fragment **a**. The H-10 geminal to a bromine atom at δ 3.87 is coupled to H_2-9 methylene protons at δ 2.13 and δ 1.93 and, in turn, one of them at δ 1.93 showed coupling with a proton at δ 1.20 of a methylene H_2-8 indicating the connectivity of the H-8–H-10 fragment **b**.

Table 1. ^1H, ^{13}C and HMBC data of compound **1** [500 MHz, δ ppm, (J) Hz, chloroform-*d*]

No.	H	C	HMBC
1	1.58 m	25.8	C_3, C_5, C_6
2	1.49 m, 1.24 m	35.8	C_1, C_3, C_4, C_6, Me-15
3		78.9	
4	1.05 dd (3.8, 8.1)	33.1	C_2
5	*endo*: 0.64 t (4.3, 4.7) *exo*: 0.26 dd (5.2, 8.1)	11.2	C_1, C_3, C_6,C_7
6		31.3	
7	1.20 m	37.3	C_6, C_8, C_{14}
8	1.56 m, 1.20 m	30.9	C_{10}
9	α: 2.13 ddd (3.4, 3.3, 12.3) β: 1.93 ddd (8.9, 12.4, 12.9)	34.0	
10	3.87 dd (4.3, 12.9)	66.2	
11		36.4	
12	1.03 s	31.6	C_{10}, C_{11}, C_{14}, Me-13
13	0.97 s	20.3	C_{10}, C_{11}, C_{14}, Me-12
14	α: 1.10 ddd (2.8, 11.4, 12.4), β: 1.60 m	43.7	C_{10}, C_{11}, Me-13
15	1.29 s	27.9	C_2, C_3, C_4

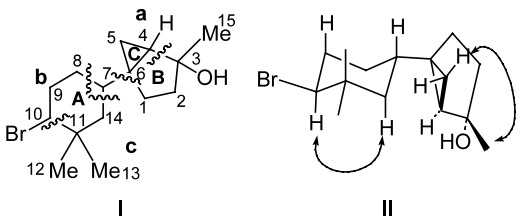
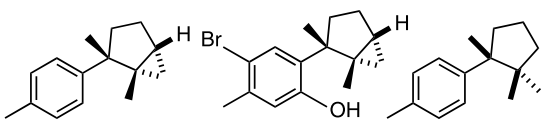


Figure 1. Partial structure and configuration of bromocyclococanol.

HMBC showed connectivities for a C-12–C-13 *gem*-dimethyl group. Both methyl groups showed long-range correlations to H_{10} and to a methylene H_{14} establishing the linkage of the fragment **b**/**c**. The simultaneous correlation between a *gem*-dimethyl group with a methine bearing a heteroatom and a methylene is uncommon in marine sesquiterpene skeletons, which leads us to suspect that the missing methyl group could be involved as a methylene in a ring, suggesting a subunit **A**.

Biogenetic considerations, together with the HMBC long-range correlation observed between the H-5 cyclopropane methylene protons of fragment **a** with a C-4 methine and the quaternary carbinol C-3 as well as the long-range correlation between the methyl carbinol group H_3-15 with a C-2 methylene and the C-4 methine of the cyclopropane allowed us to define subunit **B**/**C**. This was supported by MS which showed a base peak fragment at m/z 93 for C_7H_9 (HRMS) consistent with a dehydrated subunit **B**/**C**. Both ring **A** and the fused **B**/**C** rings account for all 15 carbons of the molecule. The C-6/C-7 linkage between **A** and **B**/**C** was supported by the correlation of H-5 with C-7 and H-7 with C-6, suggesting the overall planar structure **I** for bromocyclococanol with the requisite three degrees of unsaturation.

The relative configurations for C-10, C-3 and C-4 chiral centers of **1**, Fig. 1 (**II**), were assigned by studying the coupling constants of the scarcely non-overlapped protons and NOESY experiments. The disposition for the bromine atom on ring **A** was established as equatorial on the basis of the J values (4.3 and 12.9 Hz), typical of an axial proton, H-10. The linkage of the **B/C** unit to the cyclohexane ring was assigned as equatorial due to the NOE observed between $H_{\alpha ax}$-10 and a proton at δ 1.1 of the H_2-14 methylene allowed us to assign an axial configuration to this proton, and the large J-coupling (dd 11.4, 12.4) between $H_{\alpha ax}$-14 and the adjacent H-7 methine indicates they are *trans*-diaxial. Hence the bicyclic substituent at C-7 was equatorial. On the other hand, the NOE observed between H_{endo}-5 and Me-15 suggested a *cis*-relationship and allowed us to propose the relative configuration represented in **II** for bromocyclococanol.



3 **4** **5**

Many sesquiterpenes isolated from *Laurencia* species have five-membered rings and also fused three- and five-membered rings (e.g. cyclolaurene **3**, laurinterol **4**, cuparene **5**, and others[3]). These rings come biogenetically from the rearrangement and aromatization of ring **A** of a chamigrene[3,5] skeleton. Contrarily, the C-3/C-5 fused rings of bromocyclococanol **1** come from ring closure and rearrangement of a monocyclo nerolidylol-derivative precursor **III**, shown in Fig. 2. An array of

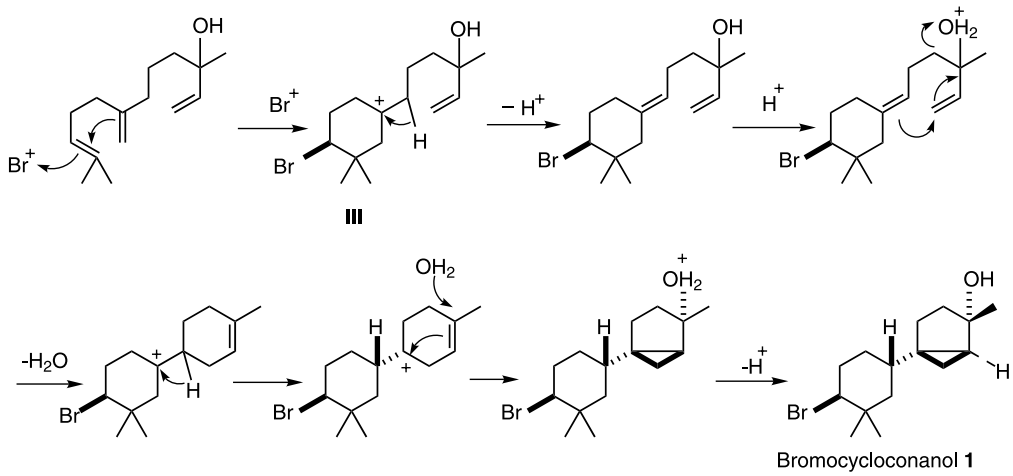


Figure 2. Possible biogenetic pathway for bromocyclococanol.

possible new metabolites generated from this novel metabolic pathway, should be expected.

Acknowledgements

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7. Bromocyclococanol **1**. Colourless oil; $[\alpha]_D^{25}=+7.3$ (*c*, 0.2, $CHCl_3$); IR ν_{max} 3460 cm^{-1}; ^1H and ^{13}C NMR data, see Table 1; EI-MS *m*/*z* (%) 300/302 $[M]^+$ (1, 1), 282/284 $[M-H_2O]^+$ (19, 19), 203 $[M-H_2O-Br]^+$ (10), 109 (59), 93 $[C_7H_9]$ (100); HREIMS $[M]^+$ 300.1101 (Calcd for $C_{15}H_{25}{}^{79}BrO$, 300.1089), $[M-H_2O]^+$ 282.0973 (Calcd for $C_{15}H_{23}{}^{79}Br$, 282.0983), $[C_7H_9]$ 93.0712 (Calcd for C_7H_9, 93.0704).