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A NEW HALOETHER FROM LAURENCIA POSSESSING A LAUROXACYCLODODECANE RING. STRUCTURAL AND CONFORMATIONAL STUDIES

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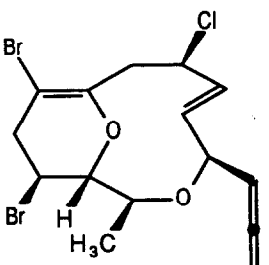
Summary: 10-Bromo-obtusallene **1**, a new haloether possessing a lauroxacyclododecane ring, has been isolated from the red alga **Laurencia obtusa**. Its structure has been established by spectroscopical methods. Likewise, its conformation in solution, as well as that of the related metabolite obtusallene **2**, has been studied by molecular mechanics calculations.

Research on secondary metabolisms from marine organisms has produced a host of compounds with unique structural features as well as promising biological activities[1]. Compounds having a polyether moiety are prime examples of the role of marine natural products bioactivity. Thus, the metabolites produced by dinoflagellates associated with red tide phenomena, such as the brevetoxins[2-4], okadaic acid and derivatives[5-7] and ciguatoxin[8], are well-known examples of trans-fused cyclic ether compounds. Moreover, red algae of the genus **Laurencia** are characterized not only by the production of interesting types of halogenated sesquiterpenes and diterpenes, but also by the production of squalene polyether derivatives and a great variety of haloether nonterpenoid C-15 compounds which arise from fatty acid metabolism[9].

We have focused our attention on this last type of compounds during our continuing research into the secondary metabolites of Laurencia species. Thus, we have reported recently the isolation of several compounds with lauroxocane, lauroxixane and lauroxolane ring systems[10], these heterocyclic ring sizes being



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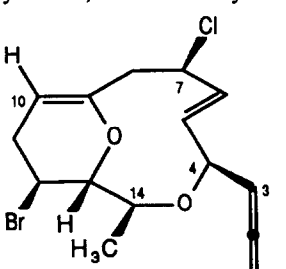

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the most frequently found. However, only a few examples of 12-membered ether rings have previously been isolated[11-12]. We wish to report in this paper on the isolation of a new example of this type of compounds, bromo-obtusallene 1 , as well as the spectroscopical and conformational studies of 1 and the previously reported obtusallene 2.

The compounds were isolated from samples of **Laurencia obtusa** collected at Kas (Turkey) in 1988. The air-dried alga was extracted with a mixture of $CHCl_3$:MeOH (2:1) and the solvent evaporated. The chloroform soluble fraction from this extract was chromatographed on silica gel yielding obtusallene 2, and bromo-obtusallene 1, together with other minor compounds. The structure of compound 1 was established as follows. The molecular formula $C_{15}H_{16}O_2ClBr_3$ was established on the basis of its HRMS. The existence of the bromoallene side chain was indicated by its IR, MS, ^1H and ^{13}C-NMR spectra. Since the IR spectrum of 1 showed the absence of hydroxyl and carbonyl groups, the oxygen atoms were assumed to be involved as ether linkages. Furthermore, through the correlations observed in the homonuclear COSY experiment, we could place in the ring the heteroatom positions at the carbons C-1, C-4, C-7, C-12, C-13, and C-14. The nature of these heteroatoms was easily established by correlation of the assigned proton signals to carbons in the heteronuclear COSY experiment, showing that compound 1 has an identical substitution pattern at these carbons with that observed for obtusallene 2. In order to compare the NMR spectral data of both compounds, we have previously assigned the NMR chemical shifts of obtusallene 2, which was solved by X-ray analysis, by using homo- and heteronuclear-NMR experiments (Table 1). Thus, the main differences observed with respect to 2 in the ^1H-NMR spectrum of 1 were the absence of the H-10 proton signal together with the shift to lower field for the H-11 signals, which agree with the presence of a vinylic bromine atom at C-10. This was confirmed by the ^{13}C-NMR chemical shifts observed for the carbons C-9 and C-10. Furthermore, the similarity observed for the ^1H-NMR coupling constants values led us to conclude that both compounds posses the same relative configuration. Likewise, the absolute configurations of the bromoallene moieties were established as R by application of Lowe's rule[13].

Table 1. NMR Spectral data of compounds 1 and 2.

C	1	2	H	1	2
1	74.3	74.0	1	6.09 dd,1.9;5.9	6.08 dd,1.9;5.9
2	201.3	202.2			
3	99.83	101.81	3	5.55 t,5.9	5.56 t,5.9
4	69.87	69.9	4	4.50 ddd,1.9;5.9;5.9	4.48 ddd,1.9;5.9;6
5	129.39	128.9	5	5.98 dd,5.9;15.8	5.93 dd,6;15.9
6	140.32	139.8	6	6.21 dd,10.3;15.8	6.28 dd,10.5;15.9
7	56.5	59.4	7	4.41 ddd,5.7;10.3;10.3	4.25 ddd,6.3;10.5;10.5
8	42.67	43.4	8	3.37 dd,5.7;13.1	2.82 dd,6.3;13.3
			8'	2.45 dd,10.3;13.1	2.46 dd,10.5;13.3
9	145.0	147.8			
10	112.0	95.0			4.60 dd,1.5;5.1
11	36.7	27.1	11	2.90 dd,5.2;18.8	2.47 ddd,1.5;5.1;19.1
			11'	2.68 dd,1.5;18.8	2.33 ddd,1.5;5.1;19.1
12	41.9	41.5	12	4.20 ddd,1.5;1.5;5.2	4.20 ddd,1.5;1.7;5.1
13	81.99	81.99	13	4.00 dd,1.5;9.3	3.98 dd,1.7;9.3
14	68.3	68.4	14	3.62 dq,6.4;9.3	3.63 dq,6.5;9.3
15	16.6	16.4	15	1.13 d,6.4	1.11 d,6.5

Chemical shifts are reported in ppm relative to TMS, 2D NMR methods data support the proton and carbon assignments.

One of the most intriguing aspects of this kind of compounds is to know their stereostructure. We have therefore carried out a conformational analysis of compounds **1** and **2**, which were performed by MMX molecular mechanics calculations[14]. These analyses revealed two energy minima conformers for each compound 1A - 1B and 2A - 2B, respectively. The symmetry of the polar map for the 7 chloro-1,4 dioxacyclodec-8(E)-ene systems of conformers 1A and 2A (Fig. 1) agrees for the more stable one and, it is worthy of note that these compounds showed in solution the same conformation as that obtained in solid state by X-ray analysis of obtusallene. A good correlation was also observed between the theoretical vicinal ^{1}H-NMR coupling constants values for compounds **1** and **2** and those observed in their spectra, as shown in Table 2.

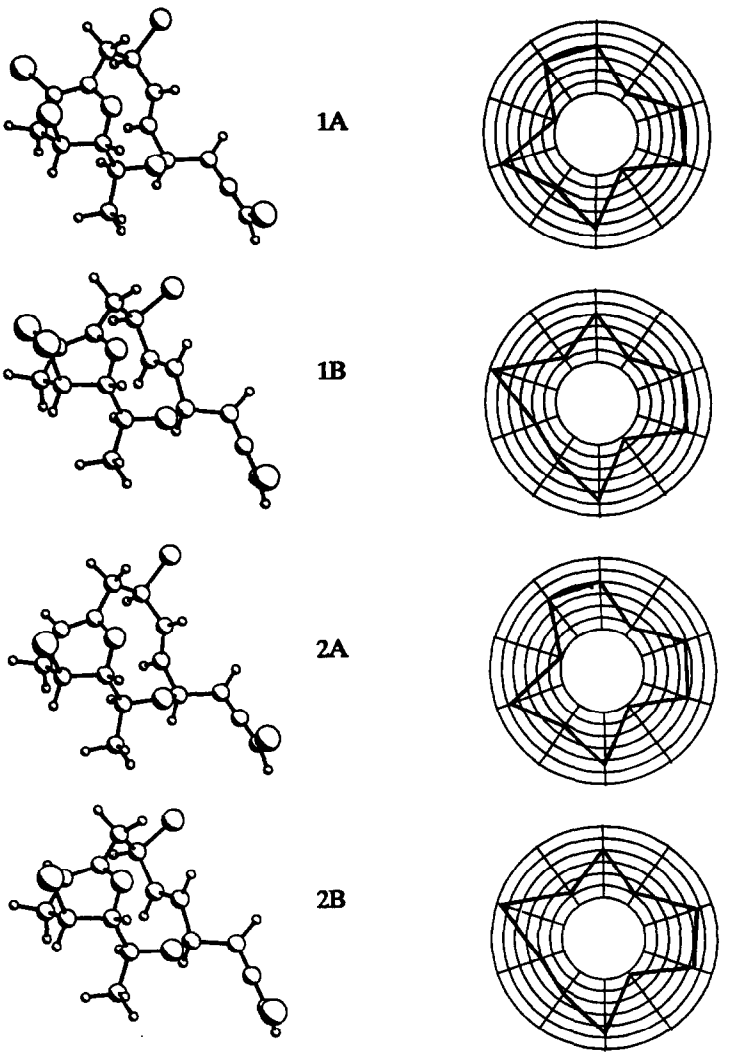

Figura 1. Lowest Energy Conformations of 10-Bromo-Obtusallene **1**, and Obtusallene **2**.

Table 2. Theorical and experimental coupling constants for compounds 1 and 2.

Conformer		$J_{3,4}$	$J_{4,5}$	$J_{6,7}$	$J_{7,8}$	$J_{7,8'}$	$J_{10,11}$	$J_{10,11'}$	$J_{11,12}$	$J_{11',12}$	$J_{12,13}$	$J_{13,14}$	$J_{14,15}$
1	Calculat.	5.16	6.59	11.56	4.98	11.04			4.15	2.43	1.64	8.96	5.95
	Experim.	5.90	5.90	10.30	5.70	10.30			5.20	1.50	1.50	9.30	6.40
	Differen.	-0.74	0.69	1.26	-0.72	0.74			-1.05	0.93	0.14	-0.34	-0.45
2	Calculat.	4.78	6.59	11.57	5.59	10.86	4.90	2.86	4.18	2.29	1.60	8.98	5.95
	Experim.	5.90	6.00	10.50	6.30	10.50	5.10	1.50	5.10	1.50	1.70	9.30	6.50
	Differen.	-1.12	0.59	1.07	-0.71	0.36	-0.20	1.36	-0.92	0.79	-0.10	-0.32	-0.55

EXPERIMENTAL PART

^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker Mod. WP 200 SY (200 MHz), chemical shifts are reported relative to Me_4Si (δ,0) and the coupling constants are given in hertz. The 2D-NMR spectra were obtained using Bruker's microprograms. Infrared spectra were recorded on a Perkin-Elmer Mod. 257. Optical rotations were determined for solutions in chloroform with a Perkin-Elmer Mod. 241. Mps were determined on a Büchi Mod. 535. Low and high resolutions mass spectra were obtained from a VG Micromass ZAB-2F. Sephadex LH-20 obtained from Pharmacia was used for gel filtration chromatography. Preparative HPLC purifications were carried out on LKB apparatus equipped with μ-PORASIL column and rapid spectral detector LKB Mod. 2140. Silica gel chromatography was performed on tlc obtained from Merck products. The tlc plates were developed by spraying with 6N sulphuric acid and heating. All solvents were purified by standard techniques.

Collections, extractions and chromatograhic separations

Laurencia obtusa was collected in October 1988 at Kaş, near Antalya, Mediterranean Sea, Turkey. The air-dried alga (0.2 kg) was extracted with $CHCl_3$:MeOH (2:1), and the solvent was evaporated in vacuo to afford 6.6 gr of crude extract. This extract was chromatographed on a Sephadex LH-20 column with chloroform:methanol:n-hexane 1:1:2 and 6 fractions were collected. Fraction 5 was chromatograhed on HPLC using a μ-PORASIL column eluted with n-hexane/ethyl acetate 4:1 affording pure 1 (6 mg) and 2 (17 mg).

Compound 1: oil, $[\alpha]_D^{25}$= -240° (c 0.19, $CHCl_3$). IR ν_{max} ($CHCl_3$): 3045, 2980, 2920, 2840, 1965, 1670, 1460, 1200, 1080, 998 and 965 cm^{-1}. UV λ_{max} ($CHCl_3$): 243 nm (ϵ =2566). ^{1}H and ^{13}C-NMR see Table 1. HRMS: M^+ at m/z: $C_{15}H_{16}O_2{}^{79}Br_2{}^{81}Br^{35}Cl$ 501.8383 (Calc. 501.83677). M.S.(E.I.) m/z(Rel. intentsity): 500, 502, 504, 506, 508 (8, 26, 31, 15, 3); 465, 467, 469, 471 (2, 5, 5, 2); 421, 423, 425, 427 (4, 9, 5, 2); 377, 379, 381, 383 (25, 55, 42, 9); 341, 343, 345 (5, 9, 4).

Compound 2: m.p. 165-167°, $[\alpha]_D^{25}$= -246° (c 1.26, $CHCl_3$). IR ν_{max} (KBr): 3040, 2987, 2838, 1953, 1681, 1368, 1200, 1167 1130 and 1074 cm^{-1}. UV λ_{max}($CHCl_3$): 243 nm (ϵ = 1300). ^{1}H and ^{13}C- NMR see Table 1.

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