

OBTUSIN, A UNIQUE BROMINE-CONTAINING POLYCYCLIC KETAL
FROM THE RED MARINE ALGA LAURENCIA OBTUSA

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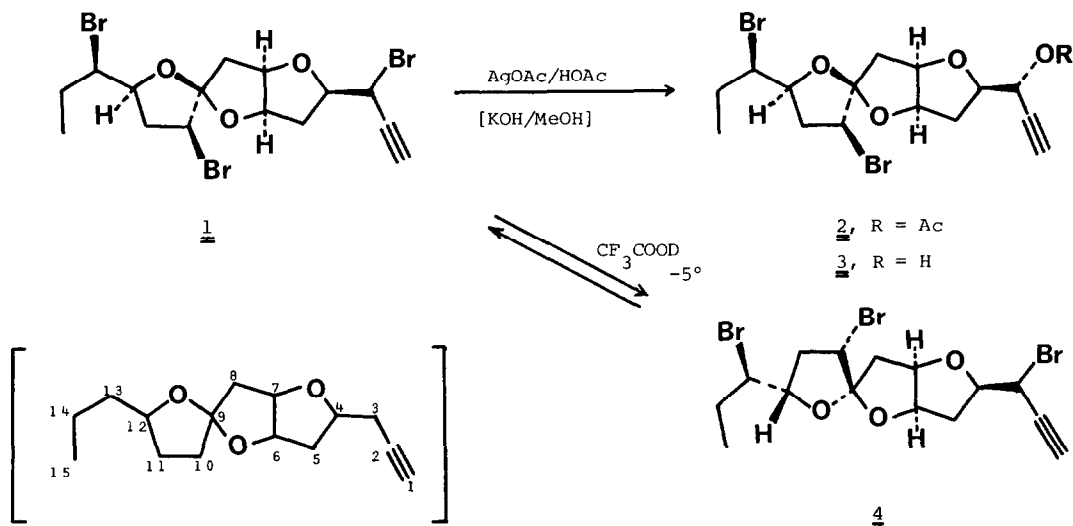
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Summary: The structure of a unique bromine-containing ketal, obtusin (1), has been determined by spectral and X-ray crystallographic techniques. 1 Obtusin is a natural component of the Mediterranean red alga Laurencia obtusa.

Bromine and chlorine-containing C₁₅ nonterpenoid compounds are common metabolites of several species of the marine red algae Laurencia.¹ These compounds usually possess terminal pentenyne functionalities, and they appear to be derived from the acyclic precursor, laurediol, which was also isolated from this source.² From extracts of the Mediterranean alga Laurencia obtusa,³ we have isolated an interesting modification of the Laurencia-derived acetylenes, obtusin(1), and we wish to report here the structure of this unusual metabolite. Obtusin contains bicyclic ketal and propargylic bromide functionalities which are unique features not yet observed in this group of compounds.

Open column silica gel chromatography of the chloroform:methanol (1:1) extract of L. obtusa yielded obtusin (1), [α]_D -65.8° (c 2.5, CHCl₃), as a colorless oil (10% of extract) on benzene elution. Mass spectral analysis of 1 showed an intense M⁺-X fragment at 404.9701, which indicated the composition C₁₅H₁₉⁷⁹Br₂O₃ (calc. 404.9702). Elemental analysis secured a final composition of C₁₅H₁₉Br₃O₃, which calculates for five degrees of unsaturation. The infrared spectrum of 1 indicated that obtusin contains the terminal acetylene group ($\nu_{C-H} = 3300 \text{ cm}^{-1}$), and further illustrated the absence of hydroxyl and ketone functionalities. The ¹H NMR spectrum of obtusin showed the absence of olefinic protons, and the presence of the terminal acetylenic proton at δ 2.55. This latter signal was observed as a doublet (J=2 Hz) which was coupled to a doublet of doublets (J=10,2 Hz) centered at δ 4.82, hence placing an ether or bromine substituent at C-3. The remainder of the spectrum consists of the following bands: δ 4.73 (1H, m), 4.61 (1H, m), 4.32



1H, ddd, $J=10,10,3$ Hz), 4.07 (1H, m), 3.91 (1H, dd, $J=12,7$ Hz), 3.70 (1H, m), 2.77 (1H, m), 2.55 (1H, d, $J=2$ Hz), 2.0 - 2.5 (6H, m), 1.70 (1H, m), and 1.13 (3H, t, $J=7$ Hz).

Treatment of obtusin with excess silver acetate in glacial acetic acid at 25° for 2 hr. resulted in the clean conversion to the acetate 2. A comparison of the ^{13}C NMR features of 1 and 2 (Table 1) illustrated that no major structural transformations had occurred.⁴

Table 1.

 ^{13}C NMR Spectra of 1 and 2 (C_6D_6)

<u>1</u>	<u>2</u>
-	169.9 (s)OAc
115.5 (s)	115.2 (s)
86.8 (d)	86.4 (d)
84.5 (d)	84.5 (d)
84.1 (d)	81.5 (d)
80.8 (d)	80.7 (d)
80.5 (d)	79.7 (s)
76.1 (d)	74.6 (d)
61.8 (d)	67.7 (d)
50.9 (d)	62.8 (d)
40.5 (d)	50.7 (d)
40.3 (t)	40.1 (t)
39.2 (t)	39.7 (t)
37.5 (t)	37.3 (t)
29.4 (t)	29.4 (t)
-	20.4 (q)OAc
11.9 (q)	12.1 (q)

Mild saponification of 2 with 2% KOH in methanol gave the crystalline alcohol, obtusinol (3), the structure of which was secured by X-ray crystallographic techniques. Stout needles of obtusinol were grown from petroleum ether-diethyl ether solution (1:1). Preliminary X-ray photographs showed obtusinol to belong to the orthorhombic crystal class. Accurate cell constants, determined by least-squares fit of fifteen diffractometer measured 2θ -values, were $a = 10.162(3)$, $b = 11.1161(3)$, and $c = 31.450(11)$. A measured and calculated ($z = 8$) density of 1.59 g/cc indicated eight molecules of composition $\text{C}_{15}\text{H}_{20}\text{Br}_2\text{O}_4$ per unit cell. The systematic extinctions uniquely indicated space group $\text{P}2_12_12_1$, and thus two molecules formed the asymmetric unit. All unique diffraction maxima with $2\theta \leq 50^\circ$ were collected on a computer controlled four-circle diffractometer using graphite monochromated MoK α

(0.71069 Å) radiation and a variable speed ω -scan technique. A total of 3576 reflections were surveyed in this manner, and after correction for Lorentz, polarization and background effects, 1981 (55%) were judged observed ($F_o \geq 3\sigma(F_o)$). The four independent bromine atoms were located by deconvoluting the Patterson synthesis, and all remaining nonhydrogen atoms were visible on a Br-phased electron density synthesis.⁵ Hydrogens were located on difference electron density syntheses following partial refinement. Full matrix least squares refinements, with anisotropic temperature factors for the nonhydrogen atoms, isotropic hydrogens, and anomalous scattering corrections for the bromines, have converged to a current crystallographic residual of 0.089.⁶ The enantiomeric structure had a significantly higher residual.

A computer-generated perspective drawing of the final X-ray model is shown in Figure 1. The two independent molecules in the asymmetric unit have the same configuration and conformation within experimental error, so only one is displayed. The absolute configurations of the chiral centers are 3(R), 4(R), 6(R), 7(R), 9(R), 10(S), 12(S), and 13(R).

In an attempt to produce the corresponding ketone at C-9, obtusin was treated under a variety of hydrolysis conditions. None were found to cleanly yield the ketone, but generally led to complex mixtures. Treatment of obtusin with anhydrous CF_3COOD at -5° , however, led to interesting results. The reaction yielded a 7:3 equilibrium mixture of obtusin and its C-9 epimer isoobtusin (4).⁷ Purification of isoobtusin, and subjection to the same conditions as above, led to the identical 7:3 mixture. These results indicate that epimerization occurs by protonation of 1 to yield either of the ions a and b (or both), and since deuterium is not incorporated from CF_3COOD , olefinic intermediates produced by deprotonation at C-8 or C-10 appear precluded.

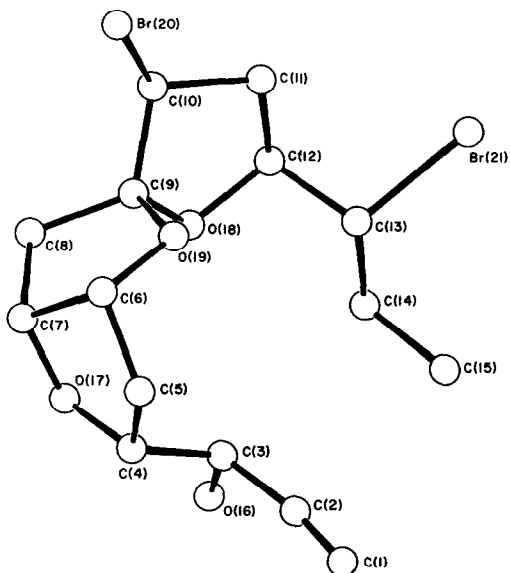
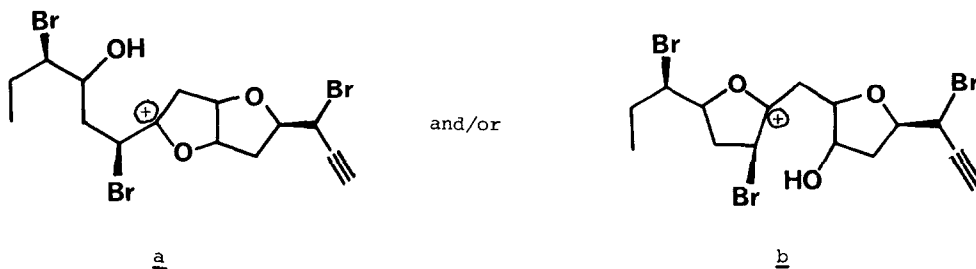


Figure 1. X-ray Drawing of Obtusinol(3).

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ACKNOWLEDGEMENTS

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2. E. Kurosawa, A. Fukuzawa, and T. Irie, *Tetrahedron Lett.*, 1091 (1965).
3. Collected at Tossa de Mar, Spain, May, 1975. Previous studies of the chemistry of *Laurencia obtusa* are: a) A. G. Gonzalez, J. D. Fourneron, J. D. Martin, and C. Perez, *Tetrahedron Lett.*, 3051 (1976), b) B. M. Howard, and W. Fenical, *Tetrahedron Lett.*, 41 (1976), c) D. J. Faulkner, *Phytochemistry*, 15, 1993 (1976), d) B. M. Howard, and W. Fenical, *Tetrahedron Lett.*, 2453 (1978).
4. This reaction yields a single crystallographically pure compound, 3, rather than the diastereomeric mixture expected considering the solvolytic nature of the silver acetate in acetic acid reaction. In the ^1H NMR spectrum of 1, the C-3 methine proton is observed at δ 4.82 as a doublet of doublets with coupling constants of 10 and 2 Hz. In 2, this proton appears at δ 5.52 as a doublet of doublets also showing coupling constants of 10 and 2 Hz. These data suggest the conversion of 1 to 2 occurs with retention of configuration at C-3, and hence, that obtusin also possesses the C-3 = R absolute configuration.
5. All crystallographic calculations were done on a Prime 400 computer, operated by the Materials Science Center, Cornell University. The principal programs used were: REDUCE and UNIQUE, data reduction programs, M. E. Leonowicz, Cornell University, 1978; BLS, block diagonal least squares refinement, K. Hirotsu, Cornell University, 1978; ORFLS (modified), full matrix least squares, W. R. Busing, K. O. Martin, and H. S. Levy, Oak Ridge, ORNL-TM305; ORTEP, crystallographic illustration program, C. Johnson, Oak Ridge, ORNL-3794, BOND, structural parameters and errors, K. Hirotsu, Cornell University, 1978; MULTAN-76, direct methods and fast fourier transform, G. Germain, P. Main, and M. Woolfson, University of York.
6. Tables of fractional coordinates, thermal parameters, bond distances, bond angles, and observed and calculated structure factors, are available from JC.
7. Spectral data for isoobtusin (4): ^1H NMR (CCl_4 , 220 MHz) δ 4.73 (1H, m), 4.58 (1H, m), 4.41 (1H, dd, J=8, 2 Hz), 4.24 (1H, dd, J=7, 1 Hz), 4.16 (2H, m), 4.05 (1H, m), 3.00 (1H, ddd, J=17, 7.6 Hz), 2.64 (1H, dd, J=16, 2 Hz), 2.50 (1H, d, J=2 Hz), 1.8 - 2.4 (5H, m), 1.73 (1H, m), and 1.07 (3H, t, J=7 Hz); ^{13}C NMR (C_6D_6): 119.2, 84.5, 84.2, 83.3, 79.9, 76.4, 60.5, 51.4, 42.4, 40.6, 38.3, 36.2, 28.5, 11.5, (only 14 carbons were resolved).

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