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MARINE NATURAL PRODUCTS XI[1] COSTATONE AND COSTATOLIDE, NEW HALOGENATED MONOTERPENES FROM THE RED SEAWEED, PLOCAMIUM COSTATUM.

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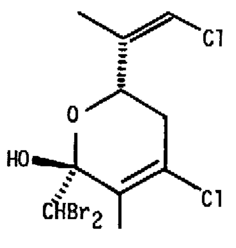
Polyhalogenated monoterpenes[2] have been reported from several species of the genus Plocamium[3-6] and from an unrelated genus Chondrococcus[7,8]. Our examination of Plocamium costatum (C. Ag.) Hook and Harv., collected from Robe, South Australia, has revealed two new oxygenated polyhalomonoterpenes, costatone, 1, and the related costatolide, 2,. Both compounds were isolated from the hexane extract of the air dried alga by silica gel chromatography.

Costatone, 1, (2% dry wt.) a stable, cyclic hemiketal, mp 70-70.5, $[\alpha]_D = -54.0$ (c = 1.02 $CHCl_3$) was shown to have the formula $C_{10}H_{12}Br_2Cl_2O_2$ by high resolution mass spectrometry. This formula requires three sites of unsaturation. The presence of a hydroxy group and double bond(s) was shown by appropriate bands in the ir spectrum. The pmr spectrum (60 MHz, $CDCl_3$) contained two methyl multiplets at 1.90 δ both showing small long range coupling, a methylene multiplet at 2.4 δ which was coupled to a methine proton at 5.22 δ (X of ABX J = 5, 10 Hz), a singlet at 3.03 δ (OH), a sharp, one proton singlet at 5.80 δ ($CHBr_2$) and a multiplet at 5.92 δ (=C-H). The ^{13}C nmr spectrum indicated four olefinic carbons atoms (137.2, s; 132.0, s; 125.7, s; 113.4, d; ppm), a ketal carbon (97.0, s), and five additional carbons at 67.6 (d), 51.6 (d), 35.0 (t), 16.0 (q), 13.8 (q).



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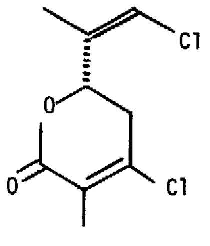

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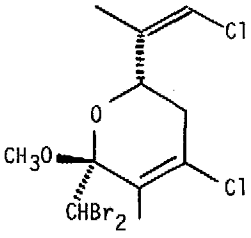
Treatment of 1 with HCl in methanol gave the ketal 3. Permanganate oxidation of 1 with purple benzene followed by diazomethane esterification produced methyl dibromoacetate. Room temperature reaction of 1 with NaOH in MeOH/H_2O for ten minutes followed by acidic work up yielded the aldehyde 4. Ozonolysis in CH_2Cl_2 gave selective cleavage of the trisubstituted double bond giving rise to 5. In analogy to the iodoform test for methyl ketones, the reaction of 1 with DBU in ether produced the lactone 2. Consideration of the chemical and spectral data led to proposal of structure 1 for the ketal.



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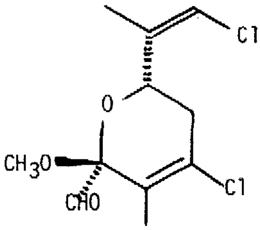

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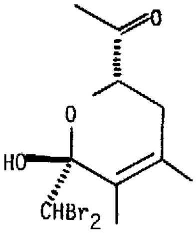

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The lactone 2 was isolated from the crude extract as an oil $[\alpha]_D = -152°$ (C = 0.87, $CHCl_3$). The α,β unsaturated lactone was suggested by the ir (1720 cm^{-1}) and UV ($\lambda_{max}^{MeOH} = 233$, $\varepsilon = 12000$). The pmr spectrum (60 MHz, $CDCl_3$) showed peaks at δ 1.90, d, 3H, J∿2Hz; 2.05, t, 3H, J∿2Hz; 2.75, m, 2H; 5.50, X of ABX, 1H. J = 5; 10 Hz; 6.00, m, 1H. The ^{13}C nmr spectrum revealed the lactone carbonyl (163.4, s), a tetrasubstituted double bond (145.6, s; 134.5, s), a trisubstituted double bond (125.0, s; 115.3, d), a carbon bearing oxygen (73.6, d) a CH_2 (34.9, t) and two methyls (16.1, q; 13.8, q).

The structure of 1 was confirmed and the conformation and absolute configuration established by a single crystal x-ray diffraction study. Slow cooling of a pentane solution gave monoclinic crystals with the space group $P2_1$ and cell constants of $a_o = 13.688(16)$ Å, $b_o = 7.122(6)$ Å, $c_o = 7.247\ (6)$ Å, $\alpha_o = \gamma = 90°$ and $\beta = 105.9(1)°$. The unit cell contained two symmetry related molecules and the intensities of 945 reflections out to sin $\theta/\lambda = 0.54$ were collected on a computer controlled diffractometer using a θ -2θ scan of 1.8° and MoK_α radiation made monochromatic by Bragg reflection from a graphite crystal. Three reflections were monitored after every 49 measurements and the entire data set was normalized to compensate for the random fluctuation of 2.7% in standard reflection intensities. Following the Lorentz-polarization corrections, only those 906 reflections which exceeded their own standard error by a factor of at least 1.5 were retained. The structure was readily solved[9] by the heavy atom method. A final R factor of .082 based on F was achieved for a model[10] in which only the Br and Cl atoms were refined anisotropically, the real and imaginary part of the anomalous dispersion for Br and Cl was made and the H atoms were included but not refined.

Since the R factor for the enantioner is .085, the absolute configuration is established[11] to be that form shown in the figure. The final weighted R was .095 and Chi Square was 3.45. All bond lengths and angles are within normal limits[12,13]. Only atom C6 of the six membered ring lies appreciably (0.62 Å) out of the best plane through C2, C3, C4, C5, C9, and Cl_2[14].

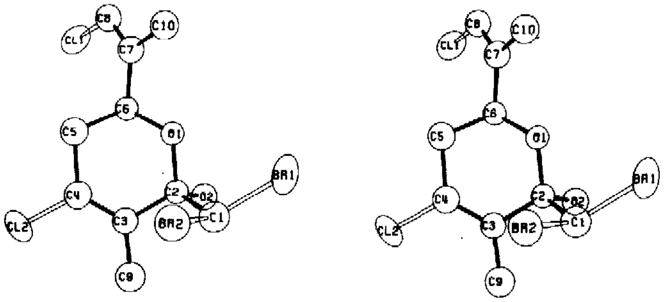

FIGURE: Stereo-pair drawing of Costatone, <u>1</u>.

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9. Calculations were done on the time shared HP-3000 computer in the U.C. Riverside Instrumentation Network using Zalkin's FORDAP for fouriers and Spark and Gantzel's BDLSQ for refinement. Several cycles of full matrix refinement were done on our IBM360-50 using Busing, Martin, and Levy's ORFLS.

10. Scattering powers for valence C and neutral O, H, Br, and Cl were taken from the International Tables for X-ray Crystallography (1962) Vol. III pp 202-206 Birmingham: Kynoch Press. Anomalous dispersion corrections were taken from table 3.3.2.C on pg 215 of the same publication.

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13. A list of structure factors and atom coordinates for this structure can be obtained from RMW.

14. A related metabolite isolated from this alga is discussed in the accompanying communication by R. Kazlauskas, *et al*. We are grateful to Dr. R. J. Wells for prior communication of these results and for agreeing to joint publication.