

Marine Natural Products XII Isolation of a Family of Multihalogenated
Gamma-Methylene Lactones from the Red Seaweed Delisea fimbriata¹

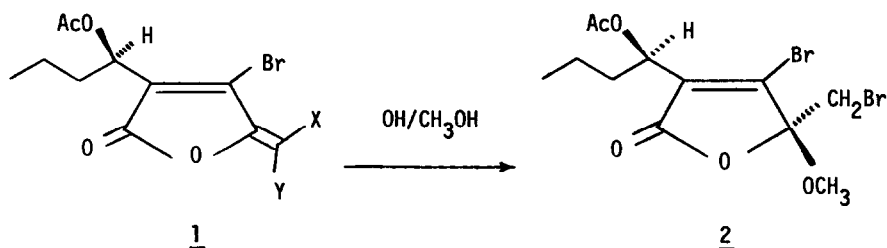
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The thallus of Delisea fimbriata (Lamour.) Mont. collected near Palmer Station, Antarctic Peninsula is unique because it is remarkably free of the normal organisms (micro and macro) which colonize other algae in the immediate area. Our investigation of the organic extract of D. fimbriata has resulted in the isolation of a series of lactones, acetoxyfimbrolides a-f, which have antimicrobial activity. The compounds represent new structural types with high halogen content as is shown by structures 1a-f.



% dry wt.		X	Y	$[\alpha]_D^{25}$ CHCl ₃	mp	$[\alpha]_D^{25}$ CHCl ₃
0.075	<u>1a</u>	Br	H	-4.1° c=1.3	80-80.5	47° c=0.24
0.20	<u>b</u>	H	Br	29° c=5.8		
0.020	<u>c</u>	I	H			
0.049	<u>d</u>	H	I	26° c=1.4		
0.007	<u>e</u>	H	Cl			
0.002	<u>f</u>	Br	Br			

The lactones 1a-f were separated from a methylene chloride extract of the air dried alga by open column silica gel chromatography followed by high pressure liquid chromatography. The major compound isolated was 1b, which, by high resolution mass spectrometry, was shown to be $C_{11}H_{12}Br_2O_4$. Its ultra-violet spectrum (CH_3OH) showed λ_{max} 291 (ϵ 8900). The infrared spectrum ($CHCl_3$) gave evidence for a conjugated 5-ring lactone structure with strong bands at 5.58, 5.72, 6.08 and 6.20 μ . The proton nmr spectrum (100 MHz, CCl_4 , δ) of 1b indicated a substituted *n*-butyl side chain (CH_3 , 0.97 t; CH_2 , 1.39 m; CH_2 , 1.86 m; $CHOAc$, 5.44 dd, $J = 7.4, 6.3$) an acetate methyl (2.01 s) and an olefinic hydrogen ($=CHBr$, 6.24 s). The ^{13}C spectrum (CFT-20, $CDCl_3$, ppm) gave further evidence for acetate (170 s) and lactone (162, s) carbonyls, a tetra-substituted (149,131) double bond and a trisubstituted, enolic double bond (130,92); other peaks were at 68 d, 33 t, 21 q, 19 t, 14 q.

Under basic conditions, the lactone 1b added methanol to give two diastereomers of 2 which were separated by hplc. One of these was crystalline. Its structure and absolute configuration was established by X-ray diffraction.

Our assignment of stereochemistry about the exocyclic double bond in 1a-d is based on the observation that on heating 1a and 1c converted respectively to 1b and 1d. The corresponding alcohols underwent the conversion spontaneously. This change took place with or without solvent or light. From molecular models it appears that the two halogen atoms in the molecules 1a and 1c would crowd each other and that no such crowding is evident in 1b and 1d. We propose that the configuration of the double bond is E in 1a and 1c and Z in 1b and 1d.

Slow cooling of a hexane solution of derivative 2 gave triclinic needles. One which had overall dimensions of .1 x .3 x .1 mm was mounted onto the long axis (b) for a single crystal diffraction study. The space group was established to be P_1 by successful solution of the structure.

The cell constants determined from least squares refinement of 12 carefully centered reflections ($MoK\alpha_1 = 0.70926A$) with $31^\circ < 2\theta < 38^\circ$ were $a_0 = 8.158(4)$, $\alpha = 72.97(3)^\circ$, $\beta = 111.25(3)^\circ$ and $\gamma = 115.42(2)^\circ$. One formula unit was contained in the cell, and the intensities of 805 reflections out to $\sin \theta / \lambda = 0.48$ were collected on a computer controlled diffractometer using a θ - 2θ scan of 1.8° and $MoK\alpha$ radiation made monochromatic by Bragg reflection from a graphite crystal. These reflections were remeasured once every 49 scans and the entire data

set was normalized to compensate for a random 1.6% fluctuation in the standard reflection intensities. Following the Lorentz-polarization corrections, 713 unique reflections whose intensities exceeded background by at least 1.5 were retained.

The structure was solved² by the heavy atom method and a final R factor of 0.057 (based on F) was achieved for a model³ in which only the two bromines were refined anisotropically and the real and imaginary corrections for anomalous dispersion by bromine was made.

Since the R factor for the enantiomer is 6.1%, the absolute configuration is established⁴ to be that shown in the figure. The five atom cyclic ether ring is quite flat (RMS deviation = .03A), and the bond from C3 to BR1 is unusually short (1.76(3)A). Otherwise, all the molecular parameters are well within normal limits.⁵

Previous work on the genera *Asparagopsis*⁶ and *Bonnemaisonia*⁷ of the red algal family Bonnemaisoniaceae has shown the presence of C₃, C₄ and C₇ ketones that appear unrelated to the compounds reported here. *Delisea fimbriata* does contain small amounts of, at present, unknown volatile ketones which we are investigating.

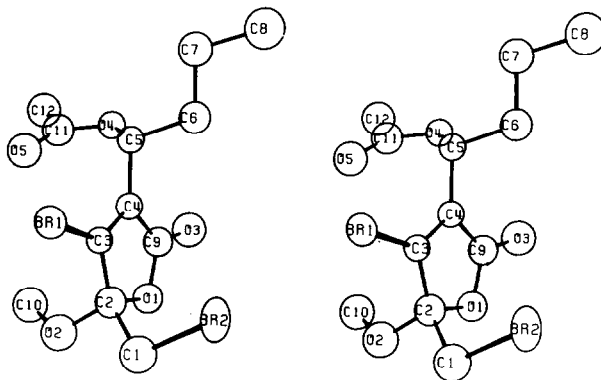


Figure: A stereo view of 2

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