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POITEDIENE A NEW METABOLITE FROM THE MARINE RED ALGA <u>LAURENCIA</u> <u>POITEI</u>

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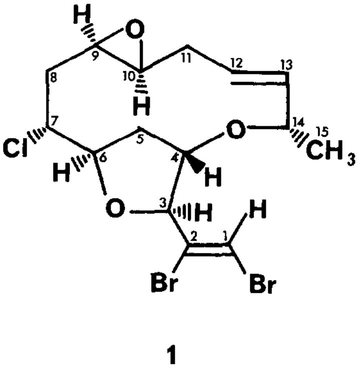
Abstract: The structure of a new, 15-carbon nonterpenoid compound, Poitediene 1, having the previously unobserved twelve membered ring system and dibromo olefin functionality has been determined by spectral and X-ray crystallographic methods.

Seaweeds of the red algal genus <u>Laurencia</u> are known to be a source of sesquiterpene[1] and nonterpenoid[2] halogenated compounds. The red alga <u>Laurencia</u> <u>poitei</u> collected at Boca Grande Key, Florida, was air dried and extracted by soxhlet with hexanes. Subsequent flash chromatography[3] (silica gel H) of the concentrated hexane extract, yielded 70 mg (0.008% by weight of the dried alga) of a colorless crystalline solid, m.p. 140-140.5 °C[4]. Chemical ionization mass spectral analysis gave a molecular formula of $C_{15}H_{19}O_3Br_2Cl$ (m/z 441/443/445/447 M^{+}+H). The highest molecular weight ion observed in the electron impact mass spectrum is m/z 405/407/409 due to loss of chlorine from the molecular ion.



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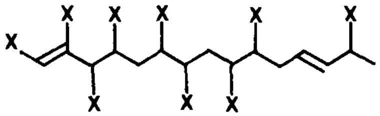
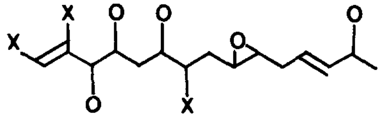


2 X = Br, Cl or O



3 X = Br,Cl

The presence of four olefinic resonances in the ^{13}C NMR spectrum allows for the assignment of two of the five sites of unsaturation required by the molecular formula. The infrared spectrum has absorptions attributable to carbon-carbon double bonds at 1615 cm^{-1} and ether linkages at 1100 cm^{-1}, but lacks those of hydroxyl, carbonyl or further unsaturation. This suggests that all three oxygen atoms are involved in ether linkages and that poitediene is tricyclic.

Analysis of the ^1H NMR spectrum including extensive decoupling experiments allowed for unambiguous assignment of all protons and gave the hydrocarbon backbone 2. The low field doublet at 7.04 ppm (J=1.6 Hz) in the ^1H NMR spectrum correlates by single frequency on-resonance ^1H-^{13}C decoupling to the trisubstituted olefin with ^{13}C NMR resonances at 110.0 ppm (d $^1J_{CH}$=197.7 Hz) and 129.9 ppm (s). The large ^1H-^{13}C one bond coupling constant is indicative of an olefinic carbon bearing halogen[5b]. As the chemical shift difference between the two olefinic carbon resonances is not large enough to be assigned to a highly polarized double bond such as a vinyl ether, the dihetero-substituted olefin must have two halogen substituents[6a,b].

Single frequency on-resonance ^1H-^{13}C decoupling experiments allowed for the assignment of the remaining halogen and oxygen functionality in backbone 2. The carbon NMR resonances at 56.0 ppm (d $^1J_{CH}$=180.6 Hz) and 52.5 ppm (d $^1J_{CH}$=175.7 Hz) correlate with the proton NMR shifts at 3.37 ppm (ddd J=10.3, 4.6 and 3.9 Hz) and 3.58 ppm (dd J=9.7, 3.9 Hz) respectively, suggesting the presence of an epoxide moiety at carbons 9 and 10 of backbone 2[5a]. The third halogen can be assigned to carbon 7 of backbone 2 by correlation of the proton resonance at 4.16 ppm (ddd J=10.9, 4.4 and 2.1 Hz) to the carbon resonance at 59.6 ppm (d $^1J_{CH}$=158.6 Hz). Oxygen substituents can be assigned to carbons 3,4,6, and 14 by correlation of the carbon NMR resonances at 89.4 ppm (d $^1J_{CH}$=156.2 Hz), 83.5 ppm (d $^1J_{CH}$=158.7 Hz), 79.1 ppm (d $^1J_{CH}$=148.9 Hz) and 76.4 ppm (d $^1J_{CH}$=144.0 Hz) with the proton NMR shifts at 4.54 ppm (bs), 4.45 ppm (d J=3.1 Hz), 4.36 ppm (dt J=2.3, 10.9 Hz) and 3.95 ppm (m) respectively.

Assignment of these functionalities gives carbon backbone 3 for which three tricyclic structures can be constructed, one of which can be immediately discarded as there is no evidence for the existence of a second epoxide functionality. To distinguish between the two remaining structures, to characterize the halogens and to determine the absolute configuration of poitediene an X-ray diffraction experiment was carried out.

Platelets suitable for X-ray diffraction were obtained from a solution of 1 in methanol/dichloromethane/water by slow evaporation. Poitediene crystallizes in the monoclinic system, space group C2, two molecules per asymmetric unit with cell constants: a=21.265 Å, b=8.246 Å, c=21.560 Å, β=112.57°, ρcalc=1.684 g/ml and ρobs=1.655 g/ml. 1665 intensities ($I>3\sigma I$) were collected on an Enraf-Nonius CAD4 diffractometer in the range $1<\Theta<25$. (Mo Kα radiation λ=0.71073).

Careful deconvolution of the Patterson function allowed for the assignment of two unique bromine atoms (MULTAN 11/82 failed to give any clue to the structure)[7]. Full matrix least square refinement of these two atoms followed by generation of a diffference Fourier map allowed for the assignment of the two remaining bromine atom positions. The structure was then solved by the heavy atom method utilizing full matrix least square refinement. Poitediene (Figure 1) has structure 1. All hydrogen atom positions except the C-15 methyl group hydrogens were located in a difference Fourier map, but were not refined. All nonhydrogen atoms were refined (halogens anisotropically) using calculated positions for the hydrogen atoms to yield a final unweighted R value of 0.042 ($R_{weighted}$=0.053). Oxygen atoms were identified by taking account of isotropic temperature factors as well as interatomic distances. The absolute configuration of poitediene was determined by using the anomalous dispersion of bromine atoms for Mo Kα radiation. The R ratio for the structure in Figure 1 and its optical antipode is 1.086 which allows for rejection of the latter at the 99.5% confidence level.

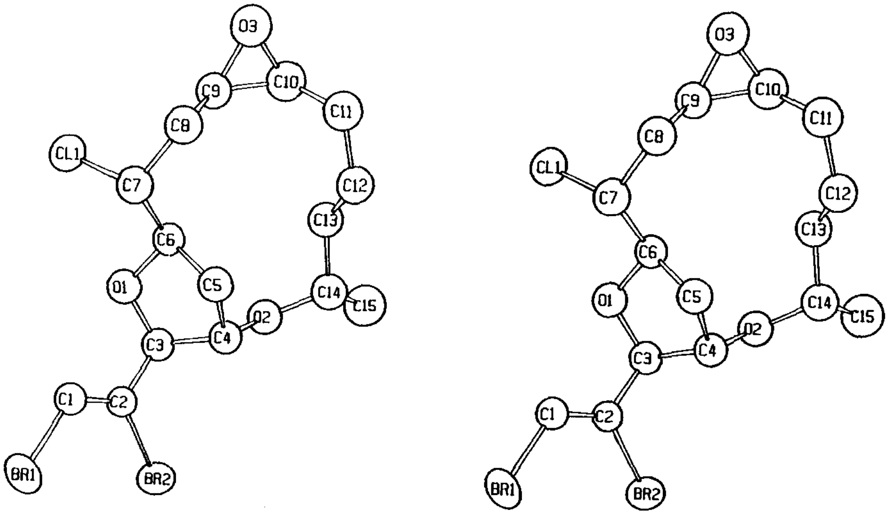


Figure 1. Stereo pair drawing of Poitediene.

Table I

^1H and ^{13}C Chemical Shifts and Multiplicities

C#	^{13}C Chemical Shift	$^1J_{CH}$(Hz)	^1H Chemical Shift	J_{HH} (Hz)[8]
1	110.0	d (197.7)	7.04	d (1.6)
2	129.9	s		
3	89.4	d (156.2)	4.54	bs*
4	83.5	d (158.7)	4.45	d (3.1)*
5	29.3	t (129.3)	3.14	dd (13.2, 1.5)*
			1.18	m*
6	79.1	d (148.9 CD_2Cl_2)	4.36	dt (2.3, 10.9)
7	59.6	d (158.6)	4.16	ddd (10.9, 4.4, 2.1)
8	30.8	t (126.9)	1.58	ddd (14.9, 9.7, 2.1)*
			2.43	dd (14.9, 4.4)*
9	52.5	d (175.7)	3.58	dd (9.7, 3.9)*
10	56.0	d (180.6)	3.37	ddd (10.3, 4.6, 3.9)*
11	33.5	t (129.3)	1.72	m*
			2.95	dd (17.8, 4.6)*
12	127.0	d (153.8)	5.73	m*
13	137.0	d (153.8)	5.73	m*
14	76.4	d (144.0 CD_2Cl_2)	3.95	m*
15	22.3	q (127.0)	1.27	d (6.4)

Two features previously unobserved in this class of compound are the terminal cis-dibromo olefin and the twelve membered ring. Attempts to prepare the more commonly observed terminal acetylene by debromination (activated Zn; Zn/acetic acid; various temperatures and solvents) resulted in no reaction of the olefin. Therefore, it is likely that a dibromo olefin such as poitediene is not a biosynthetic precursor to the vinyl acetylene class of *Laurencia* metabolites but rather results from further functionalization of an acetylene. The twelve membered ring of poitediene is the largest ring observed to date in this class of *Laurencia* metabolites. Note that the large ring allows the trans nature of the C12-C13 olefin of the proposed biosynthetic precursor laurediol[9] to be retained in poitediene.

References

1. J. D. Martín and J. Darius In "Marine Natural Products. Chemical and Biological Perspectives"; P. J. Scheuer Ed.; Academic Press: New York, Vol.1, 1978, 125-173.
2. R. E. Moore In "Marine Natural Products. Chemical and Biological Perspectives"; P. J. Scheuer Ed.; Academic Press: New York, Vol. 1, 1978, 43-59.
3. M. R. Brennan and K. L. Erickson *J. Org. Chem.* *1982*, *47*, 3917-3921.
4. Poitediene was later isolated from the digestive glands of the marine opisthobranch *Aplysia dactylomela* collected at the same location.
5. a) Large ^{1}H-^{13}C one bond coupling constants are observed for small ring compounds. See E. Breitmaier and W. Voelter, "Monographs in Modern Chemistry, Vol. 5, ^{13}C NMR Spectroscopy. Methods and Applications"; Verlag-Chemie: 1974, 93. b) ibid., 91-95.
6. a) Typical vinyl ether cmr chemical shifts are 150 and 85 ppm for the olefinic carbons. See J. B. Stothers "Carbon-^{13} NMR Spectroscopy": Academic Press: New York, 1972, 184. b) The chemical shift calculated for the proton on a cis dibromo olefin is 6.87 ppm. See A. J. Gordon and R. A. Ford, "The Chemist's Companion"; John Wiley and Sons: New York, 1972, 268-269.
7. The space group is pseudo C2/c. Only 9% of the h0l reflections disobey the C glide extinction rule, and the four unique bromine atoms are related in pairs by a pseudo glide mirror except for an origin discrepancy of 0.12 along y between the two pairs. Thus it is not surprising that no enantiomorph fixing reflection was ever found. MULTAN 11/82. P. Main, S. J. Fiske, S. E. Hull, L. Lessinger, G. Germain, J-P. Declercq, M. M. Woolfson; Dept of Physics, University of York, York, England. July 1982. This program is part of the Enraf-Nonius Structure Determination Package.
8. The proton-proton coupling constants reported are the apparent "first order" coupling constants at 200 MHz in CDCl$_3$ solution. The resonances denoted with an asterisk are not first order and small couplings which were detected through homonuclear decoupling which result in minor peak shape deformation of the totally coupled spectrum are not reported.
9. E. Kurosawa, A. Fukuzawa and T. Irie, *Tetrahedron Letters* *1972*, 2121-2124.
10. Poitediene: Colorless needles m.p. 140-140.5°C (CCl$_4$); $[\alpha]_D$=60.3° (c 0.055mM, CH$_2$Cl$_2$); UV: λmax EtOH=214 nm (6,671); IR: ν cm^{-1}(CHCl$_3$) 2950, 1610, 1440, 1100, 1055, 1045, 990, 978, 923. CIMS isobutane m/z 497/499/501/503 (M$^+$+t-Bu), 441/443/445/447 (M$^+$+H), 423/425/427/429 (M$^+$+H-H$_2$O), 405/407/409 (M$^+$-HCl), 387/389/391 (M$^+$-HCl-H$_2$O), 373/375/377/379, 361/363 (M$^+$-HBr). For ^{1}H (200 MHz, CDCl$_3$) and ^{13}C (50 MHz, CDCl$_3$) NMR data see Table I.

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