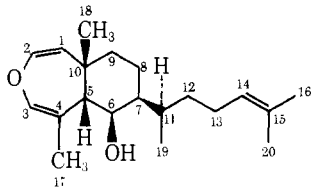
Dictyoxepin and Dictyolene, Two New Diterpenes from the Marine Alga *Dictyota acutiloba* (Phaeophyta)

Sir:

Diterpenoids have recently been isolated from brown algae in the genera *Pachydictyon* and *Dictyota*[1] and from *Dolabella* and *Aplysia* sea hares.[2] We have examined the antibiotic extracts of *Dictyota acutiloba* and have characterized two new and unusual diterpenoids, dictyoxepin (**1**) and dictyolene (**2**).



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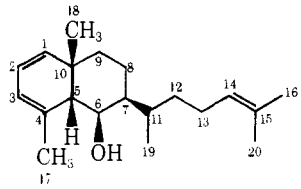

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The alga was collected off the Kahala and Ala Moana Reefs, Oahu, Hawaii, during the summer of 1973. Extraction of the fresh material gave an ether soluble portion, which, after extensive chromatography, afforded **1** and **2**, 2.4 and 0.6%, respectively, of the crude extract.

Dictyoxepin (**1**) analyzed for $C_{20}H_{32}O_2$ by mass spectrometry. Its IR (CCl_4) showed alcohol and vinyl ether functionalities (3600, 1670, 1650, 1290, 1240, 1195, 1110, and 1040 cm^{-1}). The ^1H NMR and ^{13}C NMR spectra supported the presence of a trisubstituted divinyl ether moiety (4.27, dd, $J_{1,2}$ = 8, $J_{1,5}$ = 2 Hz; 6.15, d, $J_{1,2}$ = 8 Hz; 6.37, m, $J_{3,17}$ = 1 Hz) (114.1, 119.5, 139.4, 140.7), an additional trisubstituted double bond (5.26, br m) (125.4, 131.0), a secondary alcohol (4.22, dd, $J_{5,6}$ = 11, $J_{6,7}$ = 4 Hz) (75.0), a secondary methyl (0.96, d, $J_{11,19}$ = 6 Hz), a tertiary methyl (1.20, s), and three vinyl methyl groups (1.67, s; 1.73, s; 1.80, d, $J_{3,17}$ = 1 Hz).

Catalytic hydrogenation of **1** proceeded in three stages, and all three compounds could be isolated.[3] The order of hydrogenation of the double bonds in **1** is 14,15 > 1,2 > 3,4. Oxidation of **1** with Jones reagent afforded the corresponding ketone[3] and acetylation the acetate.[3]

Because of the limited availability and stability of dictyoxepin (**1**) and failure to correlate its skeletal structure with any known diterpenoids, an x-ray crystallographic study was done on its *p*-bromophenylurethane derivative.

Crystals of $C_{27}H_{36}O_3NBr$ belonged to the hexagonal crystal class with $a = b = 14.238$ (3) Å and $c = 23.306$ (3) Å. A calculated density indicated $Z = 6$ and the systematic extinctions, $00l$ (absent if $l \neq 6n$) indicated space group $P6_1$ ($P6_5$). All unique data with $\theta \leq 57°$ were collected on a Syntex $P2_1$ diffractometer using monochromated Cu Kα radiation. After correction for Lorentz, polarization, and background effects, 1369 (74%) of the reflections were judged observed ($F_o^2 \geq 3\sigma(F_o^2)$). The bromine atom was located using a three-dimensional Patterson synthesis and the nonhydrogen atoms were located on a subsequent Br-phased electron density synthesis.[4] Hydrogen atoms were located on a subsequent difference synthesis. Full-matrix least-squares refinement with anisotropic temperature factors for the nonhydrogen atoms, isotropic temperature factors for the hydrogens, and anomalous dispersion corrections for Br converged to a standard crystallographic residual of 0.054. The enantiomeric structure refined to 0.053, a statistically significant lower residual.[5] Careful remeasurement of the 16 most enantiomorph sensitive Friedel pairs confirmed this choice of enantiomers.

A drawing of the final x-ray model is given in Figure 1. The ring junction is cis with the bridgehead methyl (C(18)) being equatorial and the bridgehead H being axial. The six-membered ring adopts a chair conformation with the -OR group

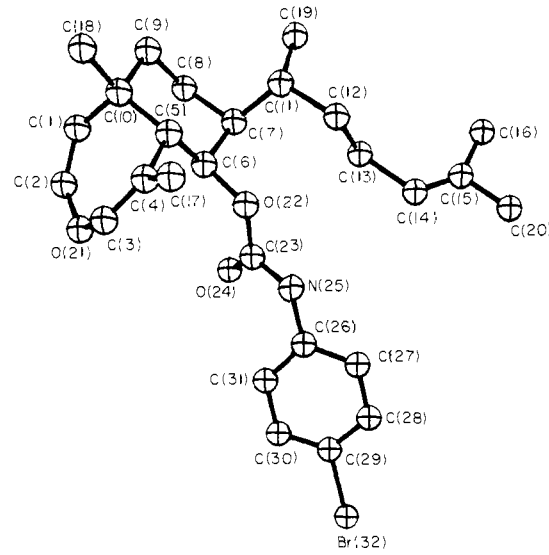
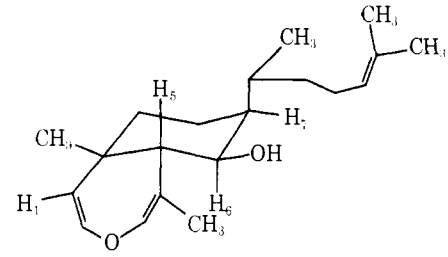


Figure 1. A computer generated perspective drawing of the *p*-bromophenylurethane of dictyoxepin (**1**). Hydrogens have been omitted for clarity.

equatorial and the side chain axial. The absolute configuration is 5(*S*), 6(*R*), 7(*S*), 10(*S*), and 11(*R*) for the chiral centers. Bond distances and bond angles agree well with generally accepted values although large thermal motions in the side chain make accurate assessment of these bond lengths difficult. Additional crystallographic details are included in the supplemental material; see paragraph at end of paper regarding supplementary material.



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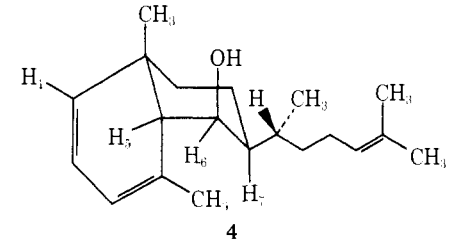

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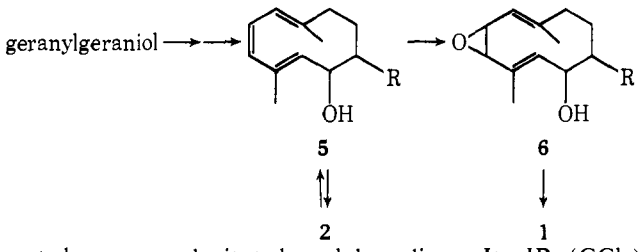
The conformation shown by x-ray for the *p*-bromophenylurethane of **1** is apparently the same conformation the free alcohol adopts in solution. Thus, the ^1H NMR spectrum of **1** indicates that H(6) must be axial as it displays axial-axial (11 Hz) and axial-equatorial (4 Hz) coupling to neighboring protons. That H(5) is the axial neighbor is shown by its long range coupling to H(1) of 2 Hz. Only in conformation **3** can H(1) and H(5) achieve a coplanar W arrangement necessary for such coupling.[6] The ^1H NMR of the *p*-bromophenylurethane of **1** showed no changes upon heating at 100 °C for several hours other than a reversible shift of the NH proton.

The 4,5-dihydrooxepin system of **1** is quite rare in the terpenoids[7] but has been reported in the sesquiterpenoids occidenol[8] and miscandenin.[9,10]

Dictyolene (**2**) analyzed for $C_{20}H_{32}O$ by mass spectrometry. Its UV (λ_{max}^{EtOH} 209 nm, ϵ 4200 and 269 nm, ϵ 4000) sug-

Scheme I



gested a monosubstituted cyclohexadiene. Its IR (CCl_4) showed vinylic (3030, 1650, 1630, and 1600 cm^{-1}) and alcoholic (3600 cm^{-1}) groups. The ^1H NMR and ^{13}C NMR indicated a secondary methyl (0.95, d, $J_{11,19}$ = 6 Hz) a tertiary methyl (1.07, s), three vinyl methyls (1.64, s; 1.73, s; 1.90, s), a secondary alcohol (4.09, br s) (72.0), a monosubstituted hexadiene system (5.29, d, $J_{1,2}$ = 9.5 Hz; 5.73, dd, $J_{1,2}$ = 9.5, $J_{2,3}$ = 5 Hz; 5.66, br. m) (135.6, 119.1, 121.9), and an additional trisubstituted double bond (5.15, br t, J = 6 Hz) (125.0).

Hydrogenation of **2** afforded two isolable compounds,[3] a tetrahydro derivative with the 3,4 double bond intact, and the completely saturated hexahydro derivative. Oxidation of **2** with Jones reagent gave the corresponding ketone.[3]

With the structure of **1** in hand, that for dictyolene can be written as **2.** The cis ring junction is established by a measurable (11%) NOE between the bridgehead methyl hydrogens (C(18)) and the proton on C(5). Further assignments of stereochemistry are made on the basis of conformer **4.** The lack of any long range W-coupling between H(1) and H(5) indicates that the latter is equatorially oriented. Further, in the ketone derived from dictyolene H(5) experiences a small downfield shift (δ 2.74 vs. 2.81) when the ^1H NMR solvent is changed from $CDCl_3$ to benzene-d_6, while the C(18) methyl hydrogens experience an upfield shift (δ 1.08 vs. 0.98) indicative of an equatorial H(5) and an axial C(18).[11] The stereochemistry at C(6) is established by the observation of an NOE (12%) between the vinyl methyl hydrogens of C(17) and H(6) which can only be achieved if H(6) is equatorially oriented.

In addition, H(6) displays no axial-axial coupling and cannot be axially oriented if it has an axial neighbor. The stereochemistry of the chiral centers at C(7) and C(11) cannot be assigned on the basis of any chemical or spectral evidence presented here. However, since dictyolene almost certainly is derived from the same biogenetic precursor as dictyoxepin, the configurations at C(7) and C(11) may be safely assumed to be that shown in conformer **4.**[12]

The 1,3 diene *cis*-decalin system of dictyolene (**2**) as well as this skeletal class appear to be unknown in the diterpenoid series. However, the sesquiterpenoid occidentalol[13-15] and the norsesquiterpenoid dehydrochamaecynenes[16] are of this structural type.

A plausible biogenesis of dictyoxepin (**1**) and dictyolene (**2**) parallels an earlier suggestion[8,9,13,17] for their sesquiterpenoid analogues (Scheme I). Cyclization and oxidation of geranylgeraniol gives trans,cis,trans-cyclodecatriene (**5**) and its corresponding epoxide **6.** A thermally allowed disrotatory ring closure[18] of **5** affords dictyolene (**2**) while a [3,3]sigmatropic shift[19] in the epoxide (**6**) yields dictyoxepin (**1**).

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Supplementary Material Available: A list of NMR spectral data, fractional coordinates and temperature factors, bond distances, bond angles and observed and calculated structure factors (12 pages). Ordering information is given on any current masthead page.

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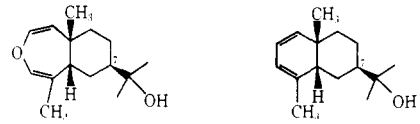
(12) Note that occidenol (i) prefers the conformation with its C(7) substituent axial,[8] while its diene analogue, 7-epioccidentalol (ii), assumes the alternate conformation with its C(7) group equatorial.[13] The structure shown for 7-eipoccidentalol (ii) is the enantiomer of the naturally occurring material.



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