

Dichlorolissoclimide from *Lissoclinum voeltzkowi* Michaelson (Urochordata): Crystal Structure and Absolute Stereochemistry

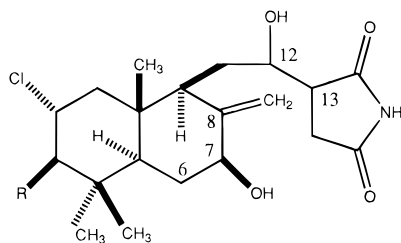
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The structures of the cytotoxic lissoclimides isolated from the New Caledonian ascidian *Lissoclinum voeltzkowi* Michaelson were originally determined on the basis of spectroscopic methods. X-ray analysis has now been performed to determine definitively the absolute stereochemistry of dichlorolissoclimide, and as a result the original assignment of one hydroxyl group must be inverted.

In earlier papers the structure and relative configuration of chlorolissoclimide (**1**) and dichlorolissoclimide (**2**), two labdane diterpenes isolated from the New Caledonian tunicate *Lissoclinum voeltzkowi*, were determined.^{1,2} The biological activity of these products³ and of some derivatives prompted us to initiate their total synthesis. A method for the preparation of the diequatorial dichlorinated trimethyldecalin derivatives, analogues of the AB rings of dichlorolissoclimide, has recently been described.⁴ However, knowledge of the absolute configuration of **1** and **2** is essential to complete their synthesis.



(1) R = H Chlorolissoclimide
(2) R = Cl Dichlorolissoclimide

The absolute configuration of dichlorolissoclimide (**2**) was thus determined by X-ray crystallography as described in the Experimental Section. This analysis resulted in the unambiguous assignment of the configuration shown (Figure 1). In comparison with the previous papers,^{1–3} the absolute configurations of the carbon atoms 12 and 13 are, respectively, *S* and *R*. As a result, the previous assignment of the hydroxyl group on C7 is in error and must be revised to an equatorial position as shown. This position is in agreement with the observed NMR coupling constant of 4.9 Hz observed between H-7 and C-OH.⁵

Experimental Section

X-ray Analysis of Compound 2. Crystals were obtained by very slow evaporation (15 days) of a dichloromethane:ethanol (90:10) solution of dichlorolis-

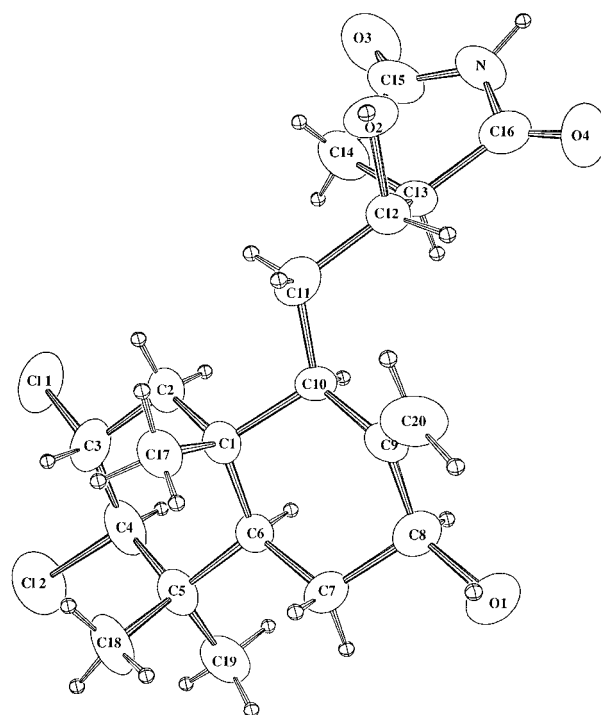


Figure 1. ORTEP diagram of dichlorolissoclimide (**2**) (X-ray numbering).

soclimide and submitted to X-ray structure determination. The sample (0.25 × 0.25 × 0.45 mm) was analyzed on a CAD4 ENRAF-NONIUS automatic diffractometer with graphite-monochromatized Mo K α radiation. The cell parameters were obtained by least-squares analysis of a set of 25 high- θ reflections. Data collection was carried out with $2\theta_{\max} = 50^\circ$, scan $\omega/2\theta = 1$, $t_{\max} = 60$ s, and range hkl : $h - 2, 9, k - 6, 15, l - 11, 23$. Intensity controls were made without appreciable decay (0.4%). A total of 5499 reflections were collected from which 3030 were independent and observed with $I > 3\sigma(I)$. Compound **2** had the following properties: C₂₀H₂₉NO₁₄Cl₂, FW = 418.36, orthorhombic, $P2_12_12_1$, $a = 9.238(3)$ Å, $b = 13.230(2)$ Å, $c = 19.682(3)$ Å, $V = 2145.1(8)$ Å³, $Z = 4$, $\rho_c = 1.295$ Mg·m⁻³, $\lambda(\text{Mo K}\alpha) = 0.70926$ Å, $\mu = 3.25$ cm⁻¹, $F(000) = 888$, $T = 293$ K.

After Lorenz and polarization corrections, the structure was solved via direct methods that revealed all non-hydrogen atoms in the structure. After isotropic ($R = 0.082$), then anisotropic refinement ($R = 0.063$), all the

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hydrogen atoms were found with a difference-Fourier map between 0.34 and 0.15 e \cdot \AA^{-3} . The whole structure was refined by full-matrix least-squares techniques (use of F magnitude; x, y, z, β_{ij} for Cl, O, N, and C atoms and x, y, z for H atoms; 332 variables and 3030 observations; $w=1/\sigma(F_o)^2 = [\sigma^2(J) + (0.04F_o^2)^2]^{-1/2}$) with the resulting $R = 0.0288$, $R_w = 0.0318$, and $S_w = 1.077$ (residual $\Delta\rho = 0.20$ e \cdot \AA^{-3}). Absolute stereochemistry was assigned via application of the η parameter,⁶ which refined to 1.00(2). As a check, a refinement on the structure with the opposite absolute stereochemistry gave $R = 0.0301$, $R_w = 0.0327$, and $S_w = 1.106$. Atomic scattering factors were taken from the *International Tables for X-ray Crystallography*.⁷ The calculations were performed on a Hewlett-Packard 9000-710 for structure determination⁸ and on a Digital MicroVAX 3100 computer with the MOLEN package⁹ for refinement and ORTEP calculations.^{10,11}

Dichlorolissoclimide (3-[2-(decahydro-6,7-dichloro-3-hydroxy-2-methylene-5,5,8a-trimethyl-1-naphthalenyl)-1-hydroxyethyl]succinimide (**2**): colorless crystals; C₂₀H₂₉NO₄Cl₂; mp 210–210 °C; $[\alpha]^{20}_D +30^\circ$ ($c = 0.2$, MeOH); UV (EtOH) λ_{max} 242 nm (ϵ 76); IR (KBr) 3400, 2950, 710, 1180, 900, 770 cm⁻¹; ¹H and ¹³C NMR and FABMS, see ref 2.

References and Notes

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