

Absolute Stereochemistry of Ibhayinol from a South African Sea Hare

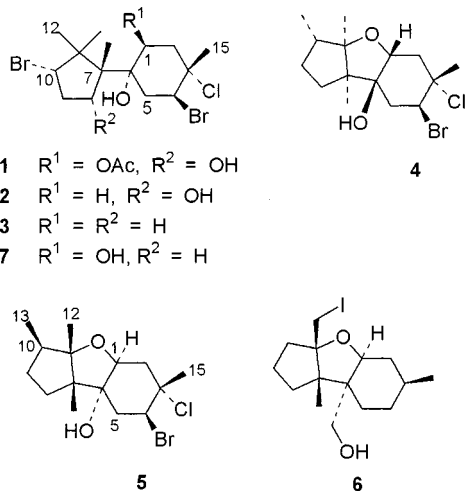
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The absolute stereochemistry of the tricyclic, sesquiterpene ibhayinol (**5**) extracted from the sea hare *Aplysia dactylomela*, collected in Algoa Bay, South Africa, was established as 1*S*, 3*S*, 4*S*, 6*R*, 7*S*, 10*R*, 11*S* from a single-crystal X-ray diffraction experiment. The structure of ibhayinol suggested that 8-dehydroxy-1-deacetylalgaone (**7**) might be a biosynthetic precursor of this compound.

Extracts of southern African specimens of the circum-tropical sea hare *Aplysia dactylomela*, collected in Algoa Bay, South Africa, yielded four new halogenated sesquiterpenes: algaone (**1**), 1-deacetoxyalgaone (**2**), 1-deacetoxy-8-deoxyalgaone (**3**), and ibhayinol (**4**).¹ Initially, we considered the tricyclic structure of ibhayinol to be unrelated to the bicyclic algaone series of compounds. Our assumption was based on the relative stereochemistry of **4**, proposed from a combination of NMR and molecular modeling data. However, the X-ray diffraction data of ibhayinol presented here have revealed that the proposed relative stereochemistry at five of the seven chiral centers in **4** was incorrect and that the structure of ibhayinol must be revised to **5** with a 1*S*, 3*S*, 4*S*, 6*R*, 7*S*, 10*R*, 11*S* absolute stereochemistry.



The single-crystal X-ray diffraction study showed ibhayinol to crystallize in the infrequently observed space group *I*222, with the asymmetric unit containing a single molecule of the compound (Table 1, Figure 1). The absolute configuration was unambiguously determined from the experiment. The six-membered ring adopts a chair conformation. Both five-membered rings have envelope conformations, with the flap atoms being C1 and C9. This

Table 1. Atomic Coordinates and Equivalent Isotropic Atomic Displacement Parameters (Å²) for **5**

	<i>x/a</i>	<i>y/b</i>	<i>z/c</i>	<i>U</i> (eq) ^a
C1	0.19698(19)	0.34645(19)	0.47899(12)	0.0264(5)
C2	0.15829(19)	0.3226(2)	0.54730(12)	0.0309(5)
C3	0.1909(2)	0.2147(2)	0.57408(13)	0.0349(6)
C4	0.3112(2)	0.1999(2)	0.56167(13)	0.0337(6)
C5	0.3382(2)	0.2081(2)	0.49004(14)	0.0340(6)
C6	0.3143(2)	0.3182(2)	0.46420(13)	0.0308(5)
C7	0.3167(2)	0.3254(2)	0.38917(13)	0.0321(5)
C8	0.3311(2)	0.4400(3)	0.36495(14)	0.0438(6)
C9	0.2550(3)	0.4492(3)	0.30768(15)	0.0455(7)
C10	0.1548(3)	0.3917(2)	0.33054(13)	0.0393(6)
C11	0.1974(2)	0.2963(2)	0.37022(12)	0.0304(5)
C12	0.1822(3)	0.1913(2)	0.33702(14)	0.0404(6)
C13	0.0766(3)	0.3671(3)	0.27605(16)	0.0545(9)
C14	0.4024(3)	0.2574(3)	0.35697(16)	0.0450(7)
C15	0.1197(3)	0.1263(2)	0.54993(15)	0.0425(7)
O1	0.13908(15)	0.28827(14)	0.43173(8)	0.0285(3)
O2	0.38600(18)	0.38934(18)	0.49632(11)	0.0432(5)
Cl	0.17206(7)	0.22285(7)	0.66135(4)	0.0507(2)
Br	0.36594(3)	0.06540(2)	0.594315(16)	0.04860(10)

^a *U*(eq) is defined as one-third of the trace of the orthogonalized *U*_{*ij*} tensor.

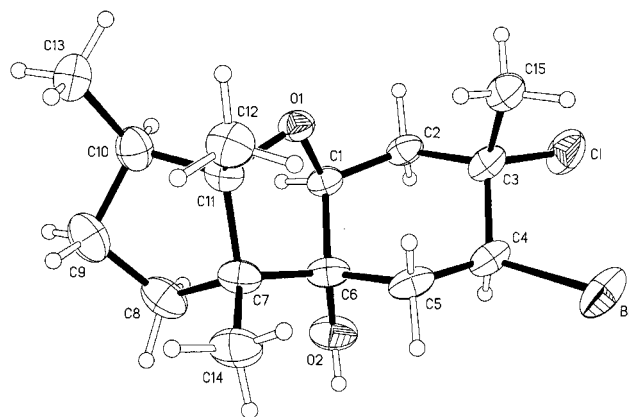


Figure 1. View of a molecule of ibhayinol from the crystal structure showing the numbering scheme employed. Anisotropic atomic displacement ellipsoids for the non-hydrogen atoms are shown at the 50% probability level. Only one component of a hydroxyl group disorder is shown. Hydrogen atoms are displayed with an arbitrarily small radius.

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arrangement is very similar to that reported previously by Gilbert and Selliah for the synthetic intermediate (**6**) containing the same fused tricyclic system.² A least-squares fit of the ring atoms for the two compounds has an rms

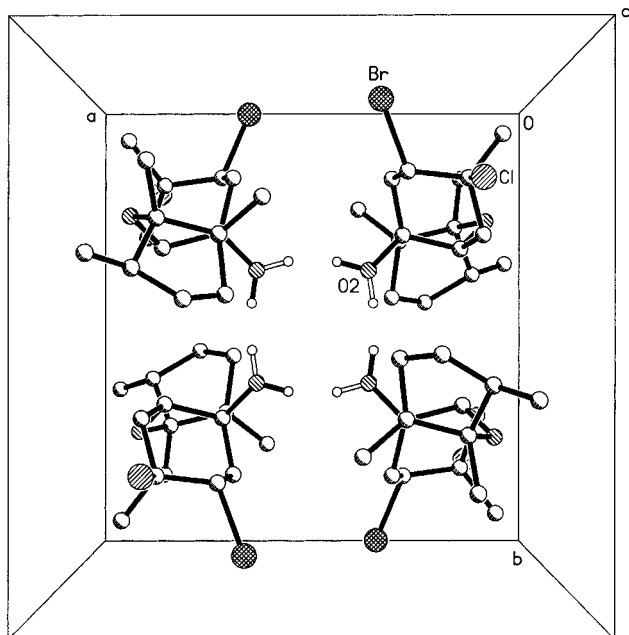


Figure 2. Arrangement of four molecules of ibhayinol about the center of the unit cell. For each molecule, both positions of the disordered hydroxyl hydrogen atom are shown. Hydrogen bonding can take place in either direction around the square of hydroxyl groups, and solid and open O–H bond types are used to emphasize this point. For clarity, all other hydrogen atoms have been omitted.

deviation of just 0.086 Å. Considering the crystal packing, the hydroxyl groups of four neighboring molecules are arranged in a square, centered about the point of intersection of three crystallographic 2-fold axes. This symmetry requires the hydroxyl hydrogen atom to be disordered over two equally probable positions (Figure 2). The disorder is easily rationalized since hydrogen bonding within the tetrameric unit can take place in either of two possible directions.

A reanalysis of the ^1H NMR and molecular modeling data, which led to the incorrect stereochemistry of proposed structure **4**, revealed an initial error in the assignment of an axial H-1 for the molecular modeling studies. The ^1H NMR signal for H-1 (br t, $J_{1,2} = 4$ Hz, $J_{1,2'} = 2.5$ Hz) required this proton to be in an equatorial or pseudo-equatorial position as per the analogous equatorial proton in **6**, which exhibited comparable signal broadening in its ^1H NMR spectrum.² Further confirmation of the equatorial orientation of H-1 was provided by the COSY spectrum of ibhayinol, in which a W -coupling cross-peak between H-1 and the equatorial methylene proton at C-5 was evident. A second error emerged from a simplistic interpretation of the splitting pattern for the H₂-5 and H-4 protons (doublet and quintet, respectively). The very small pair of outer, or satellite, peaks (indicative of virtual coupling in an ABX system where J_{ax} or J_{bx} is small, J_{ab} is large, and the difference in chemical shift between A and B is very small)³ had been missed in the former multiplet and misinterpreted in the latter. Computer-aided simulation⁴ (Figure 3) of the splitting patterns confirmed the H-4, H₂-5 coupling constants ($J_{5ax,5eq} = 13$ Hz, $J_{4,5ax} = 12.5$ Hz, and $J_{4,5eq} = 5.3$ Hz), which are consistent with similar sesquiterpene systems that possess an equatorial bromine at C-4.⁵ The corrected ^1H NMR data for **5** are presented in Table 2.

The revised structure of ibhayinol supported a possible biosynthetic link between **5** and the algoane series of compounds through a hypothetical algoane-type precursor, 8-dehydroxy-1-deacetoxyalgoane (**7**).⁶ An initial carbocation

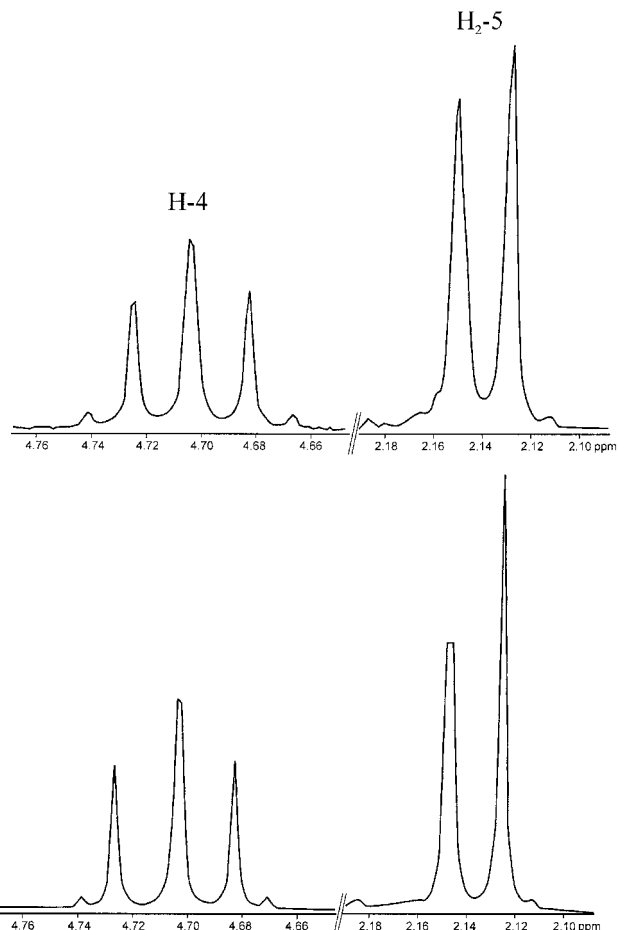


Figure 3. Observed (upper) and simulated (lower) ^1H NMR (400 MHz, CDCl_3) splitting patterns of the H-4 and H₂-5 protons of ibhayinol.

Table 2. ^1H NMR Data (400 MHz, CDCl_3) for Compound **5**

atom no.	δ_{H} ppm (mult., J/Hz)
1	3.74 (bt, 2.5)
2	2.41 (dd, 15, 4)
	2.64 (dd, 15, 2.5)
3	
4	4.70 (m, 12.5, 5.3)
5	2.138 (m, 13, 12.5)
	2.142 (m, 13, 5.3)
6	
7	
8	1.23 (m)
	1.77 (m)
9	1.11 (m)
	1.75 (m)
10	1.95 (m)
11	
12	1.05 (s)
13	0.94 (d, 7)
14	0.92 (s)
15	1.80 (s)
OH	1.39 (s)

rearrangement, generated by the loss of the equatorial bromine at C-10, followed by a 1,2 shift of the axial methyl group at C-11, would provide an opportunity for closure of the cyclic ether ring through nucleophilic attack of the C-1 hydroxyl moiety with *si* facial selectivity.

Experimental Section

X-ray Analysis of 5. Crystals of ibhayinol were grown via the slow evaporation of an ethyl acetate/hexane solution. A colorless plate of appropriate dimensions was mounted on a

glass fiber using paratone oil and flash frozen in a stream of N₂ gas to 150(2) K. All measurements were made using a BRUKER AXS SMART 6000 diffractometer with graphite-monochromated Cu K α radiation ($\lambda = 1.54178 \text{ \AA}$) from a normal focus sealed tube. The crystal–detector distance was 5.0 cm. Final lattice parameters were determined from 395 reflections with $67.92^\circ \leq 2\theta \leq 79.94^\circ$. In total, 6790 frames were collected with the detector set in two different positions of 2θ . The exposure time was 10.0 and 40.0 s for the low and high 2θ detector positions, respectively. Each frame covered 0.20° in ω . Of the 12 419 reflections collected with $8.16^\circ \leq 2\theta \leq 146.06^\circ$, 3207 were independent ($R_{\text{int}} = 0.0503$). This represents 98.9% of the unique data to the maximum value of 2θ . Data were corrected for Lorentz and polarization effects, and a Gaussian absorption correction was applied (transmission = 0.8597–0.5834). The structure was solved using the SHELXTL package.⁷ Atomic coordinates and anisotropic displacement parameters were refined for the non-hydrogen atoms. Coordinates were refined for the two positions of the hydroxyl hydrogen atom, with the O–H distances being restrained to 0.84(1) \AA . The remaining hydrogen atoms were included in idealized positions, either riding on the carbon atoms to which they were attached or, for the methyl hydrogen atoms, being treated as rigid, rotating groups. For all hydrogen atoms, isotropic displacement parameters were assigned as an appropriate multiple (either 1.2 or 1.5) of $U(\text{eq})$ for the atom to which they were bonded. The full-matrix least-squares refinement (on F^2) of 183 variables gave values of the conventional crystallographic residuals $R1 = 0.0296$ ($wR2 = 0.0664$) for 2948 observed data with $I \geq 2\sigma(I)$ and $R1 = 0.0327$ ($wR2 = 0.0674$) for all data. The goodness-of-fit was 0.997. The function minimized was $\sum w(F_o^2 - F_c^2)^2$. Weights, w , were assigned to the data as $w = 1/[\sigma^2(F_o^2) + (0.0346P)^2]$, where $P = [\max(F_o^2, 0) + 2F_c^2]/3$. A final difference Fourier map showed residual density between -0.395 and 0.446 e \AA^{-3} . The absolute configuration was assigned on the basis of the absolute

structure parameter,⁹ which refined to a value of 0.000(17). Values of the neutral atom scattering factors and real and imaginary dispersion corrections were taken from the *International Tables for X-ray Crystallography*.⁸

Crystal data:¹⁰ C₁₅H₂₄BrClO₂; fw 351.70; colorless plate; 0.13 \times 0.12 \times 0.03 mm; orthorhombic; space group *I*222 (No. 23); unit cell dimensions $a = 12.4352(14) \text{ \AA}$, $b = 12.7135(14) \text{ \AA}$, $c = 20.648(2) \text{ \AA}$, $V = 3264.3(11) \text{ \AA}^3$; $Z = 8$; $d_{\text{calc}} = 1.431 \text{ Mg m}^{-3}$; μ (Cu K α , $\lambda = 1.54178 \text{ \AA}$) = 4.905 mm^{-1} .

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Supporting Information Available: Details of crystal data for 5. This material is available free of charge via the Internet at <http://pubs.acs.org>.

References and Notes

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- (10) Crystallographic data for the structure reported in this paper has been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge, CB21EZ, UK (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

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