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MARINE NATURAL PRODUCTS

DEODACTOL, ANTINEOPLASTIC SESQUITERPENOID FROM THE SEA HARE *APLYSIA DACTYLOMELA*[1]

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Abstract—Deodactol, a halogenated bisabolene-type sesquiterpene alcohol, has been isolated from the sea hare *Aplysia dactylomela*, and its structure and absolute configuration have been determined by X-ray diffraction. The compound crystallizes in the monoclinic system with the following crystal data: a = 6.723(2), b = 11.838(1), c = 10.962(2) Å, $\beta = 99.41(2)°$, V = 860.7; $\rho_x = 1.669\ g\ cm^{-3}$ at $-135 \pm 2°C$; space group $P2_1$. The structure was solved by the heavy-atom method from 3-dimensional diffractometer data collected at $-135 \pm 2°C$ using CuK_α radiation. The final R factor for 1854 reflections is 0.029. The absolute configuration of the molecule was determined by the "R Method" of Hamilton. Deodactol has a strong intramolecular OH···O hydrogen bond bridging its tetrahydropyranyl and cyclohexanol rings. The alcohol shows moderate cytotoxic activity. The absolute configuration of deodactol corresponds to that of several halogenated chamigrenes and supports the proposed biogenetic hypothesis linking halogenated bisabolenes and chamigrenes.

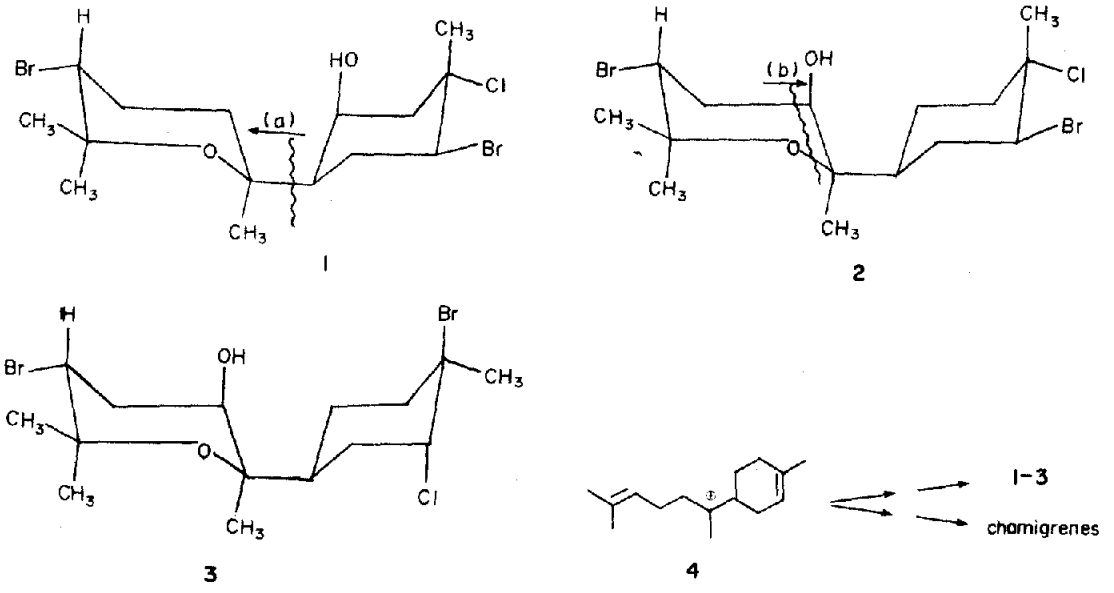
Interest in the chemistry of sea hares arises in part from the reputation for toxicity they hold in folklore.[2] Chemical studies of these molluscs have revealed that they are rich sources of natural products,[3–11] but only a few of these have actually been proven to be toxic.[5] Comparative biochemical studies[6] have shown that the products isolated from sea hares are algal metabolites that are concentrated in the animal's digestive gland.

We initiated chemical studies on the sea hare *Aplysia dactylomela* because of a report[12] that extracts of this animal showed *in vivo* tumor-inhibitory activity. Incidental to the search for the antineoplastic active agent(s) we have discovered a variety of novel natural products, one of which shows interesting pharmacological activity,[13] but until now antineoplastic active components have eluded us. We wish to report herein the isolation of a new halogenated sesquiterpene alcohol, deodactol (1) which shows moderate *in vitro* antineoplastic activity. Extracts of other sea hares also have yielded antineoplastic active substances.[4,14]

Deodactol (1) was isolated from an isopropyl alcohol extract of the digestive gland of *A. dactylomela*. The concentrated extracts, after dilution with water, were extracted with dichloromethane; and the organic solubles were partitioned between hexane and 10% aqueous methanol. The hexane fraction was distilled at 5 microns until the volatile components (b.p. 35–45°/5 μ) were mostly removed. The residue was chromatographed on Sephadex LH-20 in chloroform–methanol (1:1), and the fraction rich in dactylol[10] was chromatographed on silica gel. Fractions containing dactylol were combined and resolved by high pressure liquid chromatography using a micro-particle silica gel column. In addition to dactylol, this chromatography afforded the new alcohol deodactol (1), m.p. 134–135°, $[\alpha]_D = +40$.

A molecular formula for deodactol (1) of $C_{15}H_{25}O_2Br_2Cl$ was indicated by mass spectrometry [*m/e* 421, 419, 417, 415 ($M^+ - 15$); high resolution *m/e* 414.971 ($C_{14}H_{22}O_2\ ^{79}Br_2\ ^{35}Cl$ requires: 414.968), 353.073 ($C_{15}H_{25}O_2\ ^{81}Br\ ^{35}Cl$ requires: 353.071)]. The presence of a single alcohol group in 1 was established by IR ($3400\ cm^{-1}$) and ^1H NMR data (one exchangeable proton at δ 3.89). The 100 MHz ^1H NMR spectrum exhibited signals for four quaternary Me groups (δ 1.35, 1.37, 1.44 and 1.85) and three protons deshielded by heteroatoms, δ 3.89 (dd, J = 11, 5 Hz), 4.24 (dd, J = 12, 5 Hz) and 4.32 (bs, W 1/2 8 Hz; –CH(OH)–).

Definitive elucidation of the structure was carried out by single crystal X-ray diffraction since very little material was isolated. The resulting structure, including absolute configuration, is depicted in 1. A stereoview of a single molecule of deodactol is shown in Fig. 1. Final coordinates are listed in Table 1. Bond distances for non-H atoms are shown in Fig. 2; corresponding angles are given in Table 2. Torsion angles are listed in Table 3. Deodactol is a bicyclic compound containing cyclohexane and tetrahydropyran rings. One novel aspect of the molecular structure of deodactol (1) is the presence of a strong intramolecular H-bond between the OH group and the heterocyclic O atom. The relevant H-bond dimensions are: O(1)–H = 0.89 Å, O(1)–O(2) = 2.67 Å, H–O(2) = 1.87 Å and O(1)–H–O(2) = 147°. Such H-bonding necessitates a relative rotation of the rings about the C(6)–C(7) bond, and as a result, the two rings are nearly perpendicular to each other. The interplanar angle between the least-squares planes through the two rings is 80°. The relative position of the two rings is such that the torsion angle C(5)–C(6)–C(7)–C(14) is exactly 180°. Both the rings are in a chair conformation maintaining approximately regular staggered geometry at all parts of the



molecule. This is indicated by the torsion angles (Table 3) which do not vary too widely from ± 60°.

Bond lengths and angles are normal with few exceptions. The two bond lengths, C(2)–C(3) = 1.509(7) Å and C(9)–C(10) = 1.505(7) Å, are significantly shorter than the average C–C distance. It is interesting to note that both involve C atoms attached to bromine. The two Br–C distances are equal, 1.975(5) Å each. Both these bond lengths and the Cl–C length of 1.825(5) Å observed in this structure are significantly longer than the normally expected values (Br–C = 1.937 Å and Cl–C = 1.767 Å).[15] However, elongation of exocyclic carbon–halogen distances has been observed previously.[16] The bond C(6)–C(7) which bridges the two rings shows expected lengthening (1.560 Å).

Deodactol is isomeric with caespitol (2)[17] and isocaespitol (3),[18] metabolites of the red alga *Laurencia caespitosa*. The parent skeleton of all these compounds was first observed in deodarone, a plant sesquiterpenoid.[19] In 1 the axial OH group is located on carbocyclic ring rather than on the tetrahydropyran ring as in 2 and 3, and this causes a downfield shift of the C-3 Me ^{1}H NMR signal (δ 1.85) relative to that in 3 (1.67). As expected, in pyridine-d_5 the C-3 Me signal of 1 is shifted downfield (δ 2.22).[20] The low field position of the C-5 proton absorption in 1 (δ 4.32) relative to that in 2 and 3 (δ 3.57, 3.47 respectively) may be due to deshielding by the lone pair electrons of the ether oxygen. As might be anticipated the position of the OH group in the isomeric compounds causes significant differences in their mass

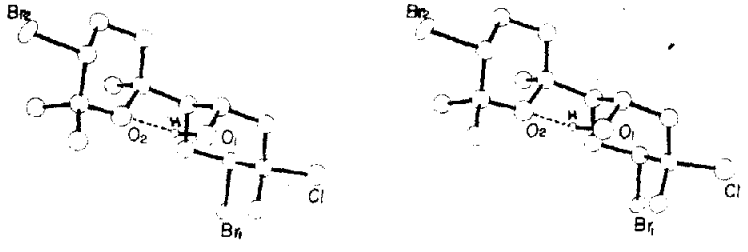


Fig. 1. Stereoview of the single molecule of deodactol. Hydrogen bond is shown by dashed line.

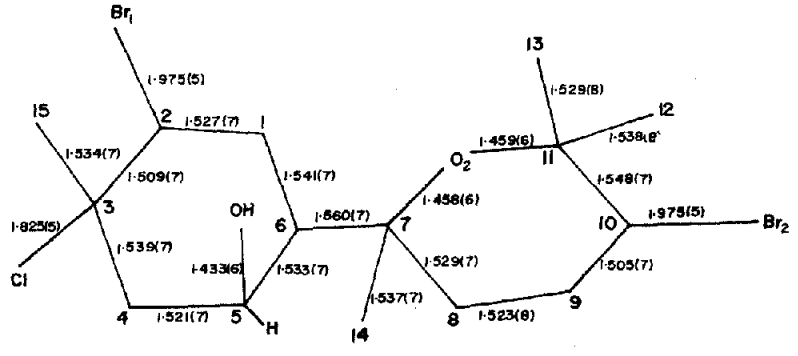


Fig. 2. Bond lengths involving non-hydrogen atoms.

Table 1. Final atomic parameters for deodactol. Standard deviation of last digit is in parentheses

Atoms	x/a·10⁴	y/b·10⁴	z/c·10⁴
Br (1)	10428 (1)	-32 (1)	846 (1)
Br (2)	803 (1)	-4072 (1)	-5406 (1)
Cl (1)	8239 (2)	-1273 (1)	3112 (1)
O (1)	5497 (6)	-3404 (3)	-429 (3)
O (2)	4941 (5)	-2470 (3)	-2676 (3)
C (1)	6998 (7)	-987 (4)	-685 (4)
C (2)	7728 (7)	-728 (4)	680 (4)
C (3)	7668 (8)	-1742 (4)	1507 (4)
C (4)	5475 (8)	-2166 (4)	1305 (4)
C (5)	4577 (7)	-2406 (4)	-36 (5)
C (6)	4784 (7)	-1379 (4)	-858 (4)
C (7)	3843 (7)	-1527 (4)	-2247 (4)
C (8)	1593 (7)	-1798 (5)	-2387 (5)
C (9)	746 (8)	-2280 (5)	-3653 (5)
C (10)	1963 (7)	-3312 (4)	-3847 (4)
C (11)	4218 (8)	-3042 (4)	-3842 (4)
C (12)	5475 (8)	-4125 (5)	-3744 (5)
C (13)	4627 (9)	-2341 (5)	-4955 (5)
C (14)	4146 (9)	-443 (4)	-2966 (5)
C (15)	9213 (9)	-2665 (4)	1363 (4)

Atoms	x/a·10³	y/b·10³	z/c·10³	B (Å²)
H (1)	542 (10)	-337 (6)	-125 (6)	2.4 (1.4)
H (11)	718 (9)	-31 (5)	-118 (5)	1.1 (1.1)
H (12)	783 (9)	-159 (5)	-104 (5)	1.8 (1.3)
H (21)	720 (8)	-24 (5)	94 (5)	1.0 (1.1)
H (41)	481 (11)	-158 (6)	164 (6)	2.5 (1.4)
H (42)	531 (10)	-276 (6)	178 (6)	2.4 (1.4)
H (51)	293 (10)	-252 (5)	0 (6)	1.8 (1.3)
H (61)	425 (11)	-81 (7)	-54 (6)	3.1 (1.6)
H (81)	132 (12)	-229 (6)	-177 (7)	3.5 (1.7)
H (82)	121 (13)	-114 (7)	-212 (7)	4.2 (1.9)
H (91)	109 (11)	-164 (6)	-433 (6)	2.6 (1.4)
H (92)	-80 (10)	-244 (5)	-360 (5)	1.5 (1.2)
H (101)	169 (10)	-401 (6)	-322 (6)	2.0 (1.3)
H (121)	695 (13)	-402 (8)	-369 (8)	4.5 (1.9)
H (122)	534 (10)	-463 (5)	-299 (6)	2.1 (1.3)
H (123)	501 (9)	-468 (5)	-449 (5)	1.2 (1.1)
H (131)	600 (12)	-207 (7)	-471 (8)	4.1 (1.9)
H (132)	471 (11)	-294 (7)	-574 (6)	2.8 (1.6)
H (133)	336 (15)	-177 (8)	-523 (9)	6.7 (2.6)
H (141)	395 (10)	19 (5)	-240 (6)	2.0 (1.3)
H (142)	539 (8)	-40 (4)	-307 (5)	0.8 (1.0)
H (143)	295 (13)	-49 (7)	-388 (7)	4.0 (1.9)
H (151)	1045 (9)	-242 (5)	169 (5)	1.5 (1.2)
H (152)	924 (16)	-293 (10)	50 (9)	7.0 (2.9)
H (153)	910 (14)	-340 (7)	189 (8)	5.3 (2.2)

spectra: the base peak in **1** occurs at 205, 207 corresponding to fragment (a), while in **2** and **3** the base peak corresponds to fragment (b), $m/e = 253, 255, 257$ (see formulas).

Deodactol likely arises by the biosynthetic pathway proposed[21] for **2** and **3** and a group of halogenated chamigrene derivatives isolated from algae of the genus *Laurencia*. This hypothesis envisages a common bisabolonium ion intermediate, e.g. **4**, as a precursor for all these compounds. A recent elaboration of the scheme by Gonzalez *et al.*[21a] predicts that all the compounds in this group having the vicinal *trans*-diequatorial bromochloro substitution will have the same absolute configuration. All such halogenated chamigrene derivatives of known configuration isolated to date from *Laurencia* do conform to this prediction.[21a] Of the three closely related halogenated bisabolenes, **1–3**, deodactol (**1**) is the first for which the absolute configuration has been determined; and indeed it has the same absolute configuration as do the chamigrenes possessing a *trans*-diequatorial bromochloro system.

An alternative pathway for cyclization of farnesol that accounts for another group of algal metabolites is the monocyclofarnesol route.[21b,c] This biosynthetic scheme rationalizes the genesis of the sesquiterpene ethers dactyloxene-A, -B, -C and dactyloxenol,[9,11] all of which have been isolated earlier by us from *A. dactylomela*. Other members of this skeletal group are α- and β-snyderol,[22] nidifidienol,[23] and 3β-bromo-8-epicaparrapi oxide.[24]

Deodactol exhibits an effective dose (50% inhibition) in the LE cell line of 12 μg/ml.[25] To date insufficient material has been available for *in vivo* testing.

EXPERIMENTAL[26]

Isolation of deodactol (**1**). Sea hares were collected at Bimini, Bahamas in May 1975. The digestive glands were excised and macerated in isopropyl alcohol. The alcohol was decanted, filtered, and concentrated at reduced pressure. The concentrate was suspended in water (final volume 1200 ml) and extracted with CH_2Cl_2 continuously for 24 hr. Evaporation of the CH_2Cl_2 yielded a dark green oil (388 g). The dry weight of the digestive glands after exhaustive extraction with CH_2Cl_2 and MeOH was 459 g.

A 100 g portion of the CH_2Cl_2 extract was dissolved in 1500 ml of MeOH–water (9:1) and extracted with hexane three times (1500, 2 × 700 ml). Evaporation of the combined hexane extracts gave a dark, viscous residue (77.5 g).

A 33 g portion of the hexane extract was distilled at 5 μ pressure (pot. temp., 60–70°) to yield 9.1 g of an orange distillate (b.p. 35–45°) and 23.8 g of residue. A 10.0 g portion of the residue

Table 2. Bond angles in deodactol

C(2) - C(1) - C (6)	109.3(4)°
C(1) - C(2) - C (3)	113.2(4)
C(1) - C(2) - Br(1)	108.5(3)
C(3) - C(2) - Br(1)	113.0(3)
C(2) - C(3) - C (4)	107.0(4)
C(2) - C(3) - C (15)	114.8(4)
C(2) - C(3) - Cl	108.4(3)
C(4) - C(3) - C (15)	113.7(4)
C(4) - C(3) - Cl	106.5(3)
C(15) - C(3) - Cl	106.1(3)
C(3) - C(4) - C (5)	114.8(4)
C(4) - C(5) - C (6)	111.1(4)
C(4) - C(5) - O (1)	108.8(4)
C(6) - C(5) - O (1)	113.1(4)
C(5) - C(6) - C (1)	110.2(4)
C(5) - C(6) - C (7)	115.1(4)
C(1) - C(6) - C (7)	112.6(4)
C(6) - C(7) - C (8)	111.0(4)
C(6) - C(7) - O (2)	104.8(4)
C(6) - C(7) - C (14)	109.9(4)
C(8) - C(7) - C (14)	109.6(4)
C(14) - C(7) - O (2)	110.9(4)
C(8) - C(7) - O (2)	110.6(4)
C(7) - C(8) - C (9)	112.7(4)
C(8) - C(9) - C (10)	107.6(4)
C(9) - C(10) - C (11)	112.8(4)
C(9) - C(10) - Br(2)	110.2(3)
C(11) - C(10) - Br(2)	110.1(3)
C(10) - C(11) - O (2)	106.5(4)
C(10) - C(11) - C (12)	110.9(4)
C(10) - C(11) - C (13)	114.3(4)
C(12) - C(11) - C (13)	109.9(4)
C(12) - C(11) - O (2)	103.1(4)
C(13) - C(11) - O (2)	111.5(4)
C(7) - O(2) - C (11)	121.7(4)

Table 3. Torsion angles in deodactol

C(1) - C(2) - C(3) - C(4)	-57.8°
C(2) - C(3) - C(4) - C(5)	+54.1°
C(3) - C(4) - C(5) - C(6)	-53.6°
C(4) - C(5) - C(6) - C(1)	+53.4°
C(5) - C(6) - C(1) - C(2)	-56.8°
C(6) - C(1) - C(2) - C(3)	+61.4°
C(7) - C(8) - C(9) - C(10)	+56.6°
C(8) - C(9) - C(10) - C(11)	-61.7°
C(9) - C(10) - C(11) - O(2)	+55.5°
C(10) - C(11) - O(2) - C(7)	-48.8°
C(11) - O(2) - C(7) - C(8)	+46.1°
O(2) - C(7) - C(8) - C(9)	-47.5°
C(5) - C(6) - C(7) - C(8)	+58.5°
C(5) - C(6) - C(7) - O(2)	-61.0°
C(5) - C(6) - C(7) - C(14)	180.0°

was chromatographed on a column of Sephadex LH-20 (450 g) in $CHCl_3$–MeOH (1:1). The fraction (PS = 25)[25] found by tlc analysis to contain dactylol[10] was chromatographed on a column of Silicar CC-7 (50 g) using toluene as eluant. Fractions containing dactylol were combined (173 mg) and subjected to HPLC separation on microparticle silica gel using hexane–THF (9:1). There was obtained in addition to pure dactylol (36 mg) a second major fraction (63 mg, PS = 6.8). A 38 mg portion of this was rechromatographed in like manner to yield deodactol (7.6 mg), m.p. 134–135°, after recrystallization from hexane; $[\alpha]_D^{25} + 40°$ (*c*, 0.2, EtOH); IR (KBr) 3400 (sharp), 1445, 1390, 1125, 1115, 1095, 990, 965, 750 cm^{-1}; 100 MHz PMR (CCl_4) 1.27–1.33 (2H, m, C-8), 1.35, 1.37, 1.44, 1.85 (3H ea, s, C-12, 13, 14, 15), 2.00–2.48 (6H, m), 2.63 (1H, dd, J = 14, 3 Hz, C-4 eq H), 3.88 (1H, s; shifts to 4.3 upon addition of D_2O), 3.89 (1H, dd, J = 11, 5 Hz, C-10 H), 4.24 (1H, dd, J = 12, 5 Hz, C-2 H), 4.32 (1H, bs, $W_{1/2}$ 8 Hz, C-5 H); Mass spectrum *m/e* (%) 421(1), 419(6), 417(8), 415(3), 268(13), 266(11), 207(99), 205(100), 186(16), 169(15), 151(21), 133(20), 125(64), 109(32), 107(60), 105(20); high resolution *m/e*, see text.

Large platy crystals of the compound were obtained from hexane–benzene. A crystal of dimensions 0.25 × 0.24 × 0.03 mm was cut from one of the larger plates for X-ray diffraction studies. The entire X-ray investigation was carried out on a Nonius CAD-4 automatic diffractometer controlled by PDP8/e computer and fitted with a low-temperature apparatus. The crystal data of the compound are: $C_{15}H_{25}Br_2ClO_2$; Mol. wt. 432.6; monoclinic; a = 6.723(2), b = 11.838(1), c = 10.962(2) Å, β = 99.41(2)°; V = 860.7; Z = 2, ρ_x = 1.669 g cm^{-3}; space group $P2_1$, $\mu(CuK_\alpha)$ = 79.8 cm^{-1}.

The unit cell parameters were determined by a least-squares fit to the $+2\theta$ and -2θ of 28 reflections distributed throughout the reciprocal lattice, and measured at $-135 \pm 2°$ with nickel filtered CuK_{α_1} (λ = 1.5405 Å) radiation. A total of 1854 intensity data, comprising all unique reflection with $2\theta \leq 150°$, were measured using nickel filtered $CuK_{\bar{\alpha}}$ radiation (λ = 1.5418 Å) on the above-mentioned diffractometer at $-135 \pm 2°$.

The data were collected using θ–2θ scan techniques with variable scan width of $(1.0 + 0.10 \tan\theta)°$ for each reflection. A receiving aperture with variable width of $(4.0 + 0.86 \tan\theta)$ mm and a constant height of 6 mm was located 173 mm from the crystal. A reflection was scanned for a maximum time of 50 s with 2/3 of that time spent scanning the peak (P) and 1/6 of the time spent scanning each of the left and right backgrounds (LB and RB). The unscaled intensity I is calculated as, I = P-2 (RB + LB). During the intensity measurements, the intensity of a standard reflection ($05\bar{3}$) was monitored after every 25 measurements. Three orientation control reflections were centered after every 100 measurements, and in case of any angular change greater than 0.1°, a new orientation matrix was automatically determined from a list of 11 reflections. Out of the total, 56 reflections with $I < 2\sigma(I)$ were considered unobserved and were assigned an intensity equal to $1.4\,T^{1/2}$, where T = P + 2(LB + RB), for the purpose of least-squares refinement.

A Gaussian method[27] was employed to make the absorption correction by using 216 sampling points. The transmission coefficient ranged from 0.2140 to 0.7950. Each structure factor was assigned a weight by $W_F = 1/\sigma_F^2$, where σ_F is defined as

$$\sigma_F = 1/2\left[\frac{\sigma^2 + (0.04\,I\nu)^2}{(LP)(I\nu)}\right]^{1/2}$$

$\sigma = (T^{1/2})\nu$, ν is a scan speed, and LP is the Lorentz-Polarization factors.

The positions of the two Br atoms were located from a 3-dimensional sharpened Patterson map. The bromine parameters were refined anisotropically to an R-factor $(R = \Sigma||KFo| - |Fc||/\Sigma|KFo|$ of 0.267. The rest of the non-hydrogen atoms were obtained from successive difference Fourier maps. All the atom positions were refined first isotropically and later with anisotropic thermal parameters. After several cycles of least-squares refinement, the R factor was 0.038 for 1792 reflections included into least-squares calculations and 0.040 for all 1854 reflections. From a difference Fourier map calculated at this stage all the hydrogen atoms were located. The hydrogen peaks ranged from 0.3 $eÅ^{-3}$ to 0.7 $eÅ^{-3}$. All hydrogen parameters were refined isotropically. All least-squares refinements were carried out by using a block-diagonal least-squares program[28] in which the quantity $\Sigma W_F(|KFo| - |Fc|)^2$ was minimized. The scattering factors for Br, Cl, O and C atoms were taken from the *International Tables for X-ray Crystallography*[29] and those for hydrogen atoms from Stewart, Davidson and Simpson.[30] Refinement was terminated when maximum parameter shift was less than 1/3 of its corresponding

standard deviation. The final R factor is 0.029 for all 1854 reflections. At the final stage of refinements, anomalous dispersion effects of both bromine and chlorine atoms were included in least-squares calculations. $\Delta f'$ and $\Delta f''$ for both bromine and chlorine were taken from *International Tables for X-ray Crystallography*.[31]

The absolute configuration of the molecule was ascertained by "R method" of Hamilton.[32] The R-factor for the enantiomer was 0.031 which indicated that this enantiomer can be rejected at better than the 0.005 level.

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Supplementary materials are available from the authors: Listings of the anisotropic thermal parameters and structure factor amplitudes.

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[26]The m.p. is uncorrected. The IR spectrum was taken on a Beckman Acculab 3 spectrophotometer. NMR spectra were acquired on a Varian XL-100 instrument; signals are reported in ppm (δ) downfield from internal TMS. Mass spectra were obtained on Hitachi RMU-7 and CEC (Dupont, Monrovia, Calif.) 110 mass spectrometers. A Perkin–Elmer Model 141 polarimeter was used for obtaining the optical rotation. Chromatographic adsorbents used were Mallinckrodt, silic AR CC-7 and Whatman Inc., 10 μ micro-particulate silica gel (Partisil 10).

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