C2A—C1A—C3A	58.7 (2)	C2B—C1B—C3B	59.1 (2)
C1A—C2A—C3A	59.2 (2)	C1B—C2B—C3B	59.3 (2)
C1A—C3A—C2A	62.1 (2)	C1B—C3B—C2B	61.6 (2)
O1A—C4A—O2A	123.7 (2)	O1B—C4B—C1B	116.9 (3)
O1A—C4A—C1A	115.6 (2)	O1B—C4B—O2B	124.0 (2)
O2A—C4A—C1A	120.6 (2)	C1B—C4B—O2B	119.2 (3)

Table 2. *Hydrogen-bonding geometry (Å, °)*

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O1A—H4A···O2B	1.15 (4)	1.49 (4)	2.637 (2)	177 (5)
O1B—H4B···O2A	1.10 (4)	1.53 (4)	2.623 (2)	176 (6)

Fourier difference methods were used to locate the initial H-atom positions. In later stages of the refinement, the benzene ring H atoms were made canonical with a C—H distance 0.98 Å and $U_{iso} = 1.2U_{eq}$ of the associated C atom. All other H atoms were refined isotropically.

Data collection: *MSC/AFC Diffractometer Control Software* (Molecular Structure Corporation, 1992). Cell refinement: *MSC/AFC Diffractometer Control Software*. Data reduction: *TEXSAN* (Molecular Structure Corporation, 1995). Program(s) used to solve structure: *SHELXS86* (Sheldrick, 1985). Program(s) used to refine structure: *TEXSAN*. Molecular graphics: *ORTEP*II (Johnson, 1976). Software used to prepare material for publication: *TEXSAN*.

I thank Dr Gordon Renkes for assistance with the polarimetry and Dr J. C. Gallucci for help of various sorts. The diffractometer was purchased with funds provided in part by an NIH grant.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: FG1312). Services for accessing these data are described at the back of the journal.

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Intermediates in the Synthesis of Cembrane Diterpenes. I

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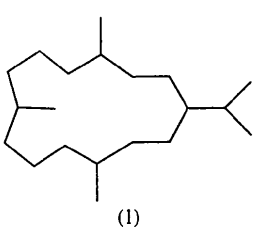
Abstract

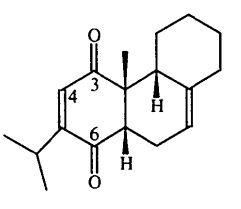
The molecular structure of *rac*-(1*R*,2*R*,3*S*,7*S*)-3-hydroxy-5-isopropyl-2-methyltricyclo[8.4.0.0^{2,7}]tetradeca-4,9-dien-6-one, $C_{18}H_{26}O_2$, has an all-*cis* ring-fusion tricyclic structure, with an overall distorted hemispherical conformation (the hydroxyl group is opposite the other substituents). The cyclohexenone ring is in a half-chair conformation, the cyclohexene ring is in a distorted half-chair conformation and the cyclohexane ring adopts an almost ideal chair conformation. The molecules are linked through a hydrogen bond.

Comment

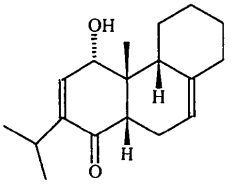
In our synthetic endeavors towards the cembrane diterpenes [carbon skeleton (1)], we have envisaged the construction of tricyclic intermediates by way of recently developed Diels–Alder reactions and further functional modifications preceding key fragmentation reactions (Brocksom *et al.*, 1994). The success of this reaction sequence depends mainly on the generation of key intermediates with the correct functionality and relative stereochemistry for C—C bond fragmentation, which is basically an antiperiplanar process. Therefore, unambiguous stereostructure determination of the intermediates is required.



(1)



(2)



(3)

The previously reported cyclo-adduct (2) (Zukerman-Schpector, Caracelli, Silva & Brocksom, 1996) was reduced with sodium borohydride in ethanol at 273 K for 20 min. Several possible chemical reductions of the enedione function of (2) are possible and include reduction at the 3- and/or 6-carbonyl groups (both in two stereodirections), and mixed 1,4-reductions involving the central conjugated C=C double bond. As a result, many structures are possible for the major (75%) reduction product, (3), which was therefore crystallized from a hexane–ethyl acetate (8:2) mixture and its stereostructure determined.

It was found that the major reduction compound corresponds to the 3-α-hydroxy derivative, (3), obtained by hydride addition at the 3-carbonyl group from the convex or outer face. Cremer & Pople (1975) puckering parameters show that the cyclohexenone ring is in a half-chair conformation [Q = 0.448 (3) Å, θ = 44.6 (4) and φ = 331.3 (6)°], the cyclohexene ring is in a half-chair, distorted towards a half-boat, conformation [Q = 0.464 (3) Å, θ = 48.0 (4) and φ = 82.1 (6)°] and the cyclohexane ring is in a chair conformation [Q = 0.578 (4) Å, θ = 174.9 (4) and φ = 191 (4)°]. The molecules are joined through a hydrogen bond: O1···O2^{i} = 2.866 (3), HO1···O2^{i} = 2.05 Å, O1—HO1···O2^{i} = 174° [symmetry code: (i) x, $\frac{1}{2}-y$, $-\frac{1}{2}+z$].

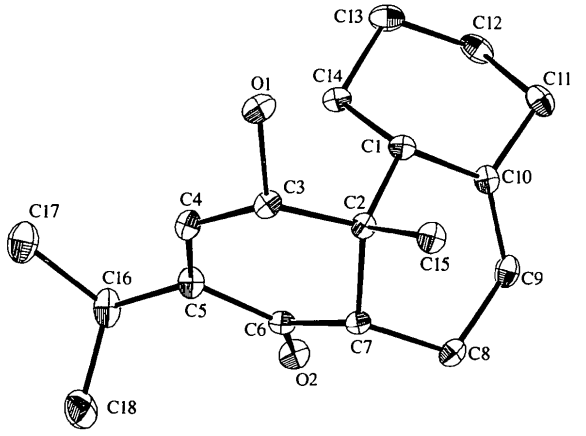


Fig. 1. The molecular structure of (3) showing the atom-labeling scheme. Displacement ellipsoids are drawn at the 50% probability level.

Experimental

Crystals were obtained by slow evaporation from a hexane–ethyl acetate (8:2) mixture.

Crystal data

$C_{18}H_{26}O_2$
M_r = 274.402
Monoclinic
$P2_1/c$
a = 9.7510 (10) Å
b = 12.1330 (2) Å
c = 13.9205 (9) Å
β = 105.654 (8)°
V = 1585.8 (3) Å^3
Z = 4
D_x = 1.1493 Mg m^{-3}
D_m not measured
Mo $K\alpha$ radiation
λ = 0.71073 Å
Cell parameters from 25 reflections
θ = 10.10–18.97°
μ = 0.073 mm^{-1}
T = 293 K
Irregular
0.45 × 0.35 × 0.30 mm
Colorless

Data collection

Enraf–Nonius CAD-4 diffractometer
ω–2θ scans
Absorption correction: none
2915 measured reflections
2789 independent reflections
1648 reflections with $F^2 > 2\sigma(F^2)$
R_{int} = 0.022
θ_{max} = 25°
$h = -11 \rightarrow 11$
$k = -14 \rightarrow 0$
$l = 0 \rightarrow 16$
2 standard reflections
frequency: 60 min
intensity decay: 0.7%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.057
$wR(F^2)$ = 0.182
S = 1.100
2789 reflections
185 parameters
H atoms constrained
$w = 1/[\sigma^2(F_o^2) + (0.0792P)^2 + 0.7299P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.281 e Å^{-3}
$\Delta\rho_{min}$ = −0.222 e Å^{-3}
Extinction correction: none
Scattering factors from *International Tables for Crystallography* (Vol. C)

Table 1. *Selected geometric parameters (Å, °)*

O1—C3	1.428 (4)	C5—C6	1.477 (4)
O2—C6	1.228 (3)	C8—C9	1.487 (4)
C3—C4	1.491 (4)	C9—C10	1.325 (4)
C4—C5	1.333 (4)		
O1—C3—C4	107.9 (2)	O2—C6—C5	121.0 (3)
O1—C3—C2	112.7 (2)	O2—C6—C7	121.9 (3)
C4—C3—C2	114.7 (2)	C5—C6—C7	117.1 (2)
C5—C4—C3	125.6 (3)	C10—C9—C8	125.3 (3)
C4—C5—C6	118.3 (3)	C9—C10—C11	123.8 (3)
C4—C5—C16	124.3 (3)	C9—C10—C1	122.4 (3)
C6—C5—C16	117.4 (3)		

H atoms were refined with fixed geometry (O—H 0.82 and C—H 0.93–0.98 Å), each riding on a carrier atom, with a fixed isotropic displacement parameter 1.5 (for methyl H atoms) or 1.2 (for all other H atoms) times the value of the equivalent isotropic displacement parameter of the atom to which they were attached.

Data collection: *CAD-4 Software* (Enraf–Nonius, 1989). Cell refinement: *CAD-4 Software*. Data reduction: *MolEN* (Fair, 1990). Program(s) used to solve structure: *SHELXS86* (Sheldrick, 1985). Program(s) used to refine structure: *SHELXL93* (Sheldrick, 1993). Molecular graphics: *ZORTEP* (Zsolnai, 1994). Software used to prepare material for publication: *SHELXL93*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: FG1311). Services for accessing these data are described at the back of the journal.

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(–)-Galanthaminium Bromide†

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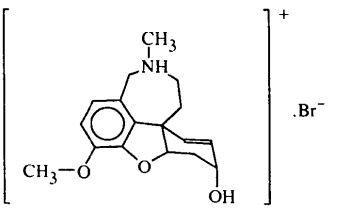
Abstract

The crystal structure and absolute configuration of the title compound, $C_{17}H_{22}NO_3^+.Br^-$, the hydrobromide salt of the alkaloid galanthamine, is reported. The tetrahydroazepine ring is in a chair conformation, the dihydrofuran ring in an envelope conformation and the cyclohexene ring between an envelope and a half-chair conformation. The axial hydroxy group forms an intramolecular hydrogen bond with the O atom of the dihydrofuran ring. The *N*-methyl group is in an axial position, while in galanthamine it is in an equatorial position.

† Internal code of the Janssen Research Foundation: R113675.

Comment

Galanthamine, a tertiary alkaloid extracted from several species of Amaryllidaceae, is an established competitive cholinesterase inhibitor. Although galanthamine has been used in the past as a treatment for a variety of neurological disorders, it nowadays attracts attention as a possible agent in the treatment of Alzheimer's disease (Thomson & Kelwitz, 1990). The three-dimensional structure and absolute configuration of the alkaloid galanthamine were first obtained from the crystal structure determination of the derivative galanthamine methiodide by Williams & Rogers (1964) and were later confirmed by Carroll, Furst, Han & Joullié (1990). The latter authors also reported the crystal structure of galanthamine itself. We report here the crystal structure of the title compound, (I).



(I)

Bond lengths and angles are not outstanding. The seven-membered tetrahydroazepine ring is in a chair conformation [puckering parameters q_2 = 0.208 (4), q_3 = 0.611 (4), Q_T = 0.645 (4) Å, φ_2 = 162 (1), φ_3 = 2.6 (3) and θ_2 = 18.8 (3)°, for the sequence C10—N11—C12—C12a—C3b—C8a—C9] with a pseudosymmetry plane through C10 [asymmetry parameter ΔC_s(C10) = 0.039 (1)]. The cyclohexene ring is in a conformation halfway between an envelope and a half-chair, with major puckering at C5. The dihydrofuran ring is in an envelope conformation with the flap at C4a. Two intramolecular hydrogen bonds are present in the structure, one between the axial hydroxy group and the O atom of the dihydrofuran ring [O6···O4 = 2.870 (4), H6*a*···O4 = 2.25 Å and O6—H6*a*···O4 = 134°] and the other between the protonated N atom and the Br^- anion [N11···Br = 3.185 (3), H11···Br = 2.29 Å and N11—H11···Br = 169°]. R.m.s. fits (Hypercube, 1993) of the four-ring system of (I) with galanthamine, norgalanthamine (Roques & Lapasset, 1976), norgalanthaminium chloride (Roques, Rossi, Declercq & Germain, 1980), galanthamine methiodide and (–)-*N*-(chloromethyl)galanthaminium chloride (Matusch, Kreh & Müller, 1994) give r.m.s. error values of 0.077, 0.064, 0.065, 0.035 and 0.092 Å, respectively. This indicates that the four-ring system has a rigid conformation in the crystal structures. The largest difference occurs between the C6 positions due to the presence of an intramolecular or intermolecular hydrogen bond of the hydroxy group. The most striking difference between