

The lack of C₂ molecular symmetry in (1*R*,2*R*,3*S*,6*S*)-3,6-dibenzyloxycyclohex-4-ene-1,2-diol

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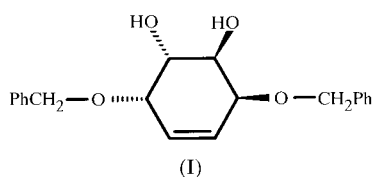
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The results of a single-crystal X-ray experiment and density functional theory calculations performed for the title compound, C₂₀H₂₂O₄, demonstrate that the lowest energy conformation of this molecule does not contain C₂ molecular symmetry.

Comment

We have synthesized the chiral title molecule, (I), during the course of our work on the synthesis of natural products related to marine sponge extracts. We report herein the structure of (I), discuss its molecular symmetry and present the results of density functional theory (DFT) calculations (Schrödinger Inc., 1998; all geometry optimizations were performed with the B3LYP hybrid functional and Pople basis set 6-3116(**)).



The absolute stereochemistries of the chiral centers were assigned as 1*R*, 2*R*, 3*S* and 6*S* from knowledge of the synthesis. The benzyloxy groups occupy pseudo-equatorial positions while the hydroxyl substituents are located in axial positions. Unfavorable steric interactions are minimized when the bulky substituents occupy pseudo-equatorial positions and this feature is similarly observed in the related compounds 3,5-dicyano-6-(2-methoxy-1,1,2-trimethylpropyl)cyclohexene, (II), *cis*-1,3-dicyano-4-(2-methoxy-1,1,2-trimethylpropyl)cyclohexene and *cis*-1,5-dicyano-4-(2-methoxy-1,1,2-trimethylpropyl)cyclohexene (Borg *et al.*, 1984).

The conformation of the cyclohexene ring in (I) is a half-chair. Atoms C1, C2, C3 and C6 are planar within 0.02 Å. Atoms C4 and C5 are located 0.372 (4) and 0.388 (4) Å above and below this plane, respectively. The C2—C1—C6—C5 and C1—C2—C3—C4 torsion angles are 18.7 (3)° and 18.1 (3)°,

respectively. Relevant torsion angles in the related structures (II), 5-*n*-butyl-3-hydroxymethyl-6-methylcyclohexene-4-ol (Batey *et al.*, 1999), (+)-(1*S*,2*S*,3*S*,6*R*,1'*S*)-methyl-2-(1-hydroxyethyl)-3-hydroxymethyl-6-methyl-4-cyclohexene-1-carboxylate and (+)-(1*S*,2*S*,3*S*,6*R*,1'*S*,1''*R*)-methyl-2,3-bis(1-hydroxyethyl)-6-methyl-4-cyclohexene-1-carboxylate (Ainsworth *et al.*, 1995) range from 5.9 to 25.4°. Notably, the DFT-calculated torsion angles C2—C1—C6—C5 (13.9°) and C1—C2—C3—C4 (13.9°) of cyclohexene, (III), fall in the middle of this range.

Several statistically significant differences are observed in the chemically equivalent bond lengths and torsion angles of (I). The O2—C4 distance [1.428 (2) Å] is 0.010 Å longer than the related O3—C5 distance [1.418 (2) Å]. In 4574 relevant compounds containing 8321 Csp³—OH bonds reported to the Cambridge Structural Database (CSD; Allen & Kennard, 1993), the corresponding values averaged 1.424 (15) Å. Additionally, the O4—C14 distance [1.430 (2) Å] is 0.016 Å longer than O1—C7 [1.414 (2) Å], and the torsion angles O1—C7—C8—C13 [−31.6 (3)°] and O4—C14—C15—C16 [−56.5 (3)°] are substantially different. To account for these discrepancies, several DFT geometry optimizations were performed on (I) and (III). The results of calculations for one molecule of (III) verify its optimal geometry to be C₂ symmetric. However, this is not observed in the case of (I). The DFT-calculated molecular parameters of (I) are in close agreement with the experimentally observed values. One exception to this is that the calculated O1—C7—C8—C13 and O4—C14—C15—C16 torsion angles are 41.0 and 69.4°, respectively. Although π -stacking interactions are not observed, other crystal-packing forces likely contribute to this difference. To test the hypothesis that the C₂-symmetric geometry of (I) is not the lowest in energy, DFT calculations were carried out for (I) starting from the symmetrical conformation and consecutively lifting all of the symmetry constraints. In the progress of optimization, the molecule departed from the symmetrical conformation. Additionally, DFT calculations were performed on (I) with two additional water molecules fixed at the observed O3...O2(1 − *x*, *y* + $\frac{1}{2}$, $\frac{1}{2}$ − *z*) and O2...O3(1 − *x*, *y* + $\frac{1}{2}$, $\frac{1}{2}$ − *z*) distances to simulate possible hydrogen bonding in the structure. This structure optimization did not fully converge. [The maximum displacement (2.13 × 10^{−2}) and r.m.s. displacement (7.88 × 10^{−3}) values were above the standard threshold values of 1.8 × 10^{−3} and 1.2 × 10^{−3}, respectively, which in turn is indicative of a flat minimum on the potential energy surface.] Consequently, it is concluded that hydrogen bonding probably does not contribute significantly to this symmetry lowering.

Weak hydrogen-bonding interactions between the hydroxyl substituents of symmetry-related molecules in the lattice of (I) are likely. An intermolecular hydrogen-bonding interaction is observed between donor atom O3 and acceptor atom O2(1 − *x*, *y* + $\frac{1}{2}$, $\frac{1}{2}$ − *z*) (Table 2). The corresponding distances and angles for 2222 compounds with 3998 similar hydrogen bonds in structures reported in the CSD were 2.79 (9) Å and 166 (7)°. The longer O...O separation in (I) is indicative of a weaker hydrogen bond. Interestingly, the chemically equivalent intermolecular O2...H—O3 hydrogen-bonding interac-

tion is not observed and also confirms the lack of C2 molecular symmetry. Results of this study demonstrate that the C1 molecular symmetry of (I) is determined by its conformational stability rather than by packing forces alone.

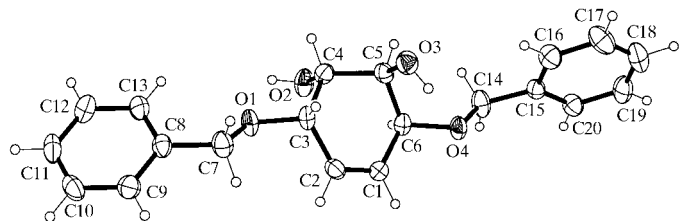


Figure 1

The molecular structure of (I) with displacement ellipsoids shown at the 50% probability level.

Experimental

Compound (I) was synthesized from L-diethyl tartrate, (IV), in seven steps. Conversion of (IV) to its acetonide followed by reduction with diisobutylaluminium hydride and addition of vinylmagnesium bromide gave a bis(allylic alcohol), (V), as a 71:23:6 mixture of diastereomers in a 72% yield. Benzylation of (V) was followed by hydrolysis of the isopropylidene ketal to give the diol in a 92% yield, which was then acetylated with acetic anhydride to provide the bis(acetate), (VI). Separation of the three stereoisomers was possible at this stage by chromatography on silica gel, providing the desired isomer in 55% yield along with 35% of the two undesired isomers. Subjection of diene (VI) to ring-closing metathesis with 3 mol% of a 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene-substituted second-generation Grubbs' catalyst (Scholl *et al.*, 1999) in refluxing benzene gave the (+)-conduritol E derivative in 93% yield along with 3% of unreacted starting material. Cleavage of the acetate esters in basic methanol then provided the title compound, (I), in 96% yield. The overall yield of the seven-step synthesis was 36%.

Crystal data

$C_{20}H_{22}O_4$
 $M_r = 326.38$
 Orthorhombic, $P2_12_12_1$
 $a = 8.5979$ (9) Å
 $b = 10.1090$ (10) Å
 $c = 18.9828$ (18) Å
 $V = 1649.9$ (3) Å³
 $Z = 4$
 $D_x = 1.314$ Mg m⁻³

Mo $K\alpha$ radiation
 Cell parameters from 1921 reflections
 $\theta = 2.0$ – 50.0°
 $\mu = 0.09$ mm⁻¹
 $T = 173$ (2) K
 Block, colorless
 $0.62 \times 0.62 \times 0.40$ mm

Data collection

Bruker CCD-1000 area-detector diffractometer
 φ and ω scans
 Absorption correction: empirical (SADABS; Blessing, 1995)
 $T_{\min} = 0.946$, $T_{\max} = 0.965$
 3184 measured reflections

1869 independent reflections
 1625 reflections with $I > 2\sigma(I)$
 $R_{\text{int}} = 0.018$
 $\theta_{\max} = 26.4^\circ$
 $h = -10 \rightarrow 10$
 $k = 0 \rightarrow 12$
 $l = 0 \rightarrow 22$

Refinement

Refinement on F^2
 $R[F^2 > 2\sigma(F^2)] = 0.033$
 $wR(F^2) = 0.079$
 $S = 1.00$
 1869 reflections
 219 parameters

H-atom parameters constrained
 $w = 1/[\sigma^2(F_o^2) + (0.0473P)^2]$
 where $P = (F_o^2 + 2F_c^2)/3$
 $(\Delta/\sigma)_{\max} < 0.001$
 $\Delta\rho_{\max} = 0.16$ e Å⁻³
 $\Delta\rho_{\min} = -0.14$ e Å⁻³

Table 1

Selected geometric parameters (Å, °).

O1—C7	1.414 (2)	O3—C5	1.418 (2)
O2—C4	1.428 (2)	O4—C14	1.430 (2)
C1—C2—C3—C4	18.1 (3)	O1—C7—C8—C13	−31.6 (3)
C2—C1—C6—C5	18.7 (3)	O4—C14—C15—C16	−56.5 (3)

Table 2

Hydrogen-bonding geometry (Å, °).

$D-H \cdots A$	$D-H$	$H \cdots A$	$D \cdots A$	$D-H \cdots A$
O3—H3 $\cdots$ O2 ⁱ	0.84	2.12	2.920 (2)	160

Symmetry code: (i) $1 - x, y - \frac{1}{2}, \frac{1}{2} - z$.

Hydroxyl H atoms were constrained to an ideal geometry with $U_{\text{iso}}(\text{H}) = 1.5U_{\text{eq}}(\text{O})$ and allowed to rotate freely about their C—O bonds. All other H atoms were constrained and allowed to ride on their C atoms with $U_{\text{iso}}(\text{H}) = 1.2U_{\text{eq}}(\text{C})$.

Data collection: *SMART* (Siemens, 1996); cell refinement: *SMART*; data reduction: *SHELXTL* (Sheldrick, 1997a); program(s) used to solve structure: *SHELXS97* (Sheldrick, 1990); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997b); molecular graphics: *SHELXTL*; software used to prepare material for publication: *SHELXTL*.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: FG1630). Services for accessing these data are described at the back of the journal.

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