A comparison of the ring conformational properties of two derivatives prepared from the same diene diacetate precursor

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Results of single-crystal X-ray experiments performed for the title compounds, (1S,2R,3S,4R,5R)-4-benzyloxy-2-[1-(benzyloxy)allyl]-5-hydroxymethyl-2,3,4,5-tetrahydrofuran-3-ol, $C_{22}H_{26}O_5$, (I), and (3R,5S,6S,7S,8S)-3,6-bis(benzyloxy)-5-iodomethyl-2,3,4,5-tetrahydrofuro[3,2-b]furan-2-one, $C_{21}H_{21}IO_5$, (II), demonstrate that the tetrahydrofuran ring that is common to both structures adopts a different conformation in each molecule. Structural analyses of (I) and (II), which were prepared from the same precursor, indicate that their different conformations are caused by hydrogen-bonding interactions in the case of (I) and the presence of a fused bicyclic ring system in the case of (II). Density functional theory calculations on simplified analogs of (I) and (II) are also presented.

Comment

The chiral molecules (1S,2R,3S,4R,5R)-4-benzyloxy-2-[1-(benzyloxy)allyl]-5-hydroxymethyl-2,3,4,5-tetrahydrofuran-3-ol, (I), and (3R,5S,6S,7S,8S)-3,6-bis(benzyloxy)-5-iodomethyl-2,3,4,5-tetrahydrofuro[3,2-b]furan-2-one, (II), have been prepared from the same precursor, namely (3S,4R,5R,6S)-3,6-bis(benzyloxy)octa-1,7-diene-4,5-diol, (III), and structurally characterized during the course of our work toward the synthesis of natural products related to marine sponge extracts. Dienediol (III) was also used to prepare a conduritol E derivative that we have reported previously (Clark *et al.*, 2001). We compare here the conformational properties of the two tetrahydrofuran-ring-bearing compounds (I) and (II) (Figs. 1 and 2).

The absolute stereochemical assignment of (I) [R (C1), S (C2), R (C3), R (C4) and S (C5)] is based solely on knowledge of the synthesis, while the chiral centers in (II) were unequivocally assigned as S (C1), S (C2), S (C3), S (C4) and R (C5)

from the crystallographic data. Crystallographic studies verify the expectation that the five-membered O1/C1–C4 heterocycles in the two structures have the same relative stereochemistry, with all substituents in a *cis* arrangement with respect to one another. In the case of (II), this all-*cis* arrangement forces the substituents on atoms C3, C4 and C5 to be directed toward the concave face of the bicyclic ring system.
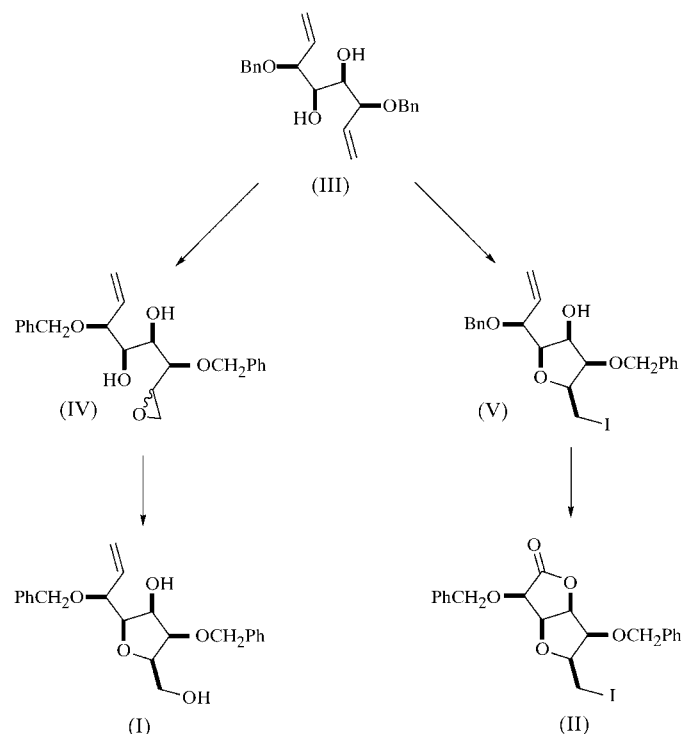
Although the bond distances in (I) and (II) are typical, several bond angles of the O1/C1–C4 ring system in (I) exhibit appreciable differences from the corresponding parameters in (II). The C3—C2—C1 [99.4 (2)°], O1—C4—C3 [105.25 (18)°] and C1—O1—C4 [108.91 (17)°] angles in (I) differ significantly from the related C3—C2—C1 [104.6 (4)°], O1—C4—C3 [107.0 (3)°] and C1—O1—C4 [110.1 (3)°] angles in (II). The presence of a second ring in (II), which is fused to the tetrahydrofuran ring of interest at the C1- and C2-atom positions, causes widening of these bond angles, with concomitant reduction of the C5—C1—C2 and C1—C2—O2 angles.

The stereochemical properties of the O1/C1–C4 heterocycles of (I) and (II) were further characterized by conformational analysis according to Cremer & Pople (1975), using the program *RING*5 (Guzei, 2003). The conformation of the O1/C1–C4 ring system in (I) is characterized by a puckering amplitude, q_2, of 0.410 Å and a phase angle, φ_2, of 63.36°. The latter value indicates that the ring conformation is intermediate between twisted $^3T_2$ and envelope ^3E, in which atom C2 would be the flap atom. A similar conformation intermediate between twisted $^4T_3$ and envelope ^4E is observed for the O2—C6—C5—C1—C2 ring in (II), which is characterized by a q_2 value of 0.296 Å and a phase angle of 279.61°. This ring

does not deviate quite as much from planarity, as revealed by the puckering amplitude. The other five-membered ring in (II), O1/C1–C4, has an envelope conformation, E_2, with atom C1 occupying the flap position [$q_2 = 0.295$ Å and $\varphi_2 = 37.96°$].

The primary contributors to the adopted conformations of the O1/C1–C4 rings of the two structures are the presence of hydrogen-bonding interactions in (I) and a bicyclic ring system in (II). In (I), an intramolecular O3—H3···O5 hydrogen bond is observed (Table 1). The mean $D···A$ distance and $D—H···A$ angle for 155 compounds with 192 similar hydrogen bonds reported to the Cambridge Structural Database (CSD; Allen, 2002) are 2.73 (8) Å and 161 (6)°. This distance is indicative of a reasonably strong hydrogen bond that could affect the bond angles and ring conformation mentioned earlier. In the crystal lattice of (I), intermolecular O5—H5···O1($x + \frac{1}{2}, -y + \frac{3}{2}, -z$) hydrogen-bonding interactions form a series of one-dimensional chains in the a direction (Table 1). The mean $D···A$ distance and $D—H···A$ angle for 398 compounds with 429 similar hydrogen bonds are 2.82 (6) Å and 166 (8)° (CSD). Both types of hydrogen-bonding interactions may influence the positioning of flap atom C2 in (I). In contrast, (II) does not contain hydrogen bonds but instead contains a bicyclic ring system. Steric repulsion and torsional strain of the adjoined rings in (II) are probably minimized when atom C1 is the flap atom of the O1/C1–C4 heterocycle.
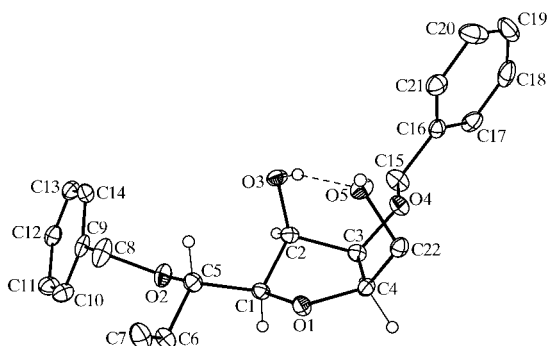

Figure 1
The molecular structure of (I). Displacement ellipsoids are shown at the 30% probability level and the intramolecular hydrogen bond is shown as a dashed line.
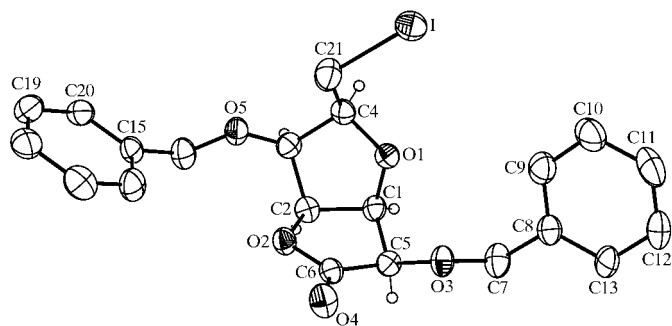

Figure 2
The molecular structure of (II). Displacement ellipsoids are shown at the 30% probability level.

In order to compare the observed ring conformations with theoretical data, density functional theory calculations were performed on simplified analogs of (I) and (II), referred to as (Ia) and (IIa). In both molecules, the phenyl rings were replaced by methyl groups, and the I atom was replaced with an H atom in (IIa), in order to reduce computational time. The geometry optimizations were performed at the B3LYP/6-311++G** level (GAUSSIAN98; Frisch et al., 1998). The calculated C—O bond distances agree with experimental data within 0.006 Å in (I) and 0.01 Å in (II), while the calculated C—C distances for both molecules differ by up to 0.026 Å from the experimental parameters. The puckering coordinates for the O1/C1–C4 ring in (Ia) ($q_2 = 0.391$ Å and $\varphi_2 = 66.14°$) are in excellent agreement with the experimental data producing a similar conformation, i.e. intermediate between $^3T_2$ and ^3E, with atom C2 in the flap position of the envelope configuration.

The results of conformational analysis of (IIa) differ considerably from those obtained for (II), apparently because of the influence of the I atom on the packing. While the energy required to affect torsion angles in the lattice may not exceed several kcal mol^{-1}, it is instructive to appreciate the changes that a large atom can introduce. Thus, ring O1/C1–C4 in (IIa) ($q_2 = 0.374$ Å and $\varphi_2 = 345.84°$) has a twisted conformation, $^1T_5$, and ring O2—C6—C5—C1—C2 ($q_2 = 0.203$ Å and $\varphi_2 = 83.55°$) adopts a conformation intermediate between ^3E and $^3T_4$, with atom C5 in the flap position. For the two rings, both the conformations and the amplitudes are very different from the corresponding values in the parent compound, (III) (see above), indicating that the lattice forces in the solid-state structure of (II) play a significant role and considerably affect the molecular configuration.

Experimental

For the preparation of (I), dienediol (III) was treated with meta-chloroperoxybenzoic acid in CH$_2$Cl$_2$ at room temperature for 36 h, giving the monoepoxide (IV) in 43% yield as a ~1:1 mixture of stereoisomers, along with 40% of unreacted (III). Subjection of (IV) to MeONa in MeOH at reflux for 3 h then provided the crystalline alcohol (I) in 38% yield (m.p. 393–396 K). ^{1}H NMR (CDCl$_3$, 300 MHz): δ 3.68 (dd, J = 7.9, 2.8 Hz, 1H), 3.73 (AB*X, J_{AB} = 12.6 Hz, J_{BX} = 2.1 Hz, 1H), 3.78 (A*BX, J_{AB} = 12.6 Hz, J_{AX} = 8.1 Hz, 1H), 4.17 (ABX*, ddd, J = 8.1, 3.0, 2.1 Hz, 1H), 4.22 (br d, J = 7.2 Hz, 1H), 4.29 (dd, J = 8.2, 4.5 Hz, 1H), 4.37 (dd, J = 4.5, 2.8 Hz, 1H), 4.49 (d, J = 11 Hz, 1H), 4.50 (d, J = 11 Hz, 1H), 4.64 (d, J = 11 Hz, 1H), 4.80 (d, J = 11 Hz, 1H), 5.41 (m, 2H), 5.92 (m, 1H). For the preparation of (II), dienediol (III) was treated with I$_2$ and NaHCO$_3$ in CH$_2$Cl$_2$ at 273 K for 1 h, providing the iodoetherification product (V) in 35% yield, along with 60% of unreacted (III). Ozonolysis of (V) at 195 K followed by oxidation of the resulting hemiacetal with tetra-n-propylammonium perruthenate and N-methylmorpholine N-oxide provided the crystalline lactone (II) in 53% yield in two steps (m.p. 389 K). ^{1}H NMR (CDCl$_3$, 300 MHz): δ 3.21 (dd, J = 10.2, 7.1 Hz, 1H), 3.45 (dd, J = 10.2, 6.4 Hz, 1H), 4.21 (d, J = 5.0 Hz, 1H), 4.22 (dd, J = 6.3, 4.8 Hz, 1H), 4.38 (aq, J = 6.9 Hz, 1H), 4.50 (dd, J = 5.0, 4.0 Hz, 1H), 4.54 (d, J = 11 Hz, 1H), 4.76 (d, J = 11 Hz, 1H), 4.85 (dd, J = 4.5, 4.0 Hz, 1H), 4.91 (ABq, J = 11 Hz, 2H).

Compound (I)

Crystal data

$C_{22}H_{26}O_5$
$M_r = 370.43$
Orthorhombic, $P2_12_12_1$
$a = 5.5273\ (5)$ Å
$b = 13.4315\ (13)$ Å
$c = 26.074\ (2)$ Å
$V = 1935.7\ (3)$ Å^3
$Z = 4$
$D_x = 1.271$ Mg m^{-3}

Mo $K\alpha$ radiation
Cell parameters from 3927
    reflections
$\theta = 2.0–50.0°$
$\mu = 0.09$ mm^{-1}
$T = 173\ (2)$ K
Needle, colorless
$0.50 \times 0.30 \times 0.30$ mm

Data collection

Bruker CCD1000 area-detector
    diffractometer
φ and ω scans
Absorption correction: empirical
    (SADABS; Blessing, 1995)
    $T_{min} = 0.933$, $T_{max} = 0.974$
10 541 measured reflections

2262 independent reflections
1973 reflections with $I > 2\sigma(I)$
$R_{int} = 0.045$
$\theta_{max} = 26.4°$
$h = 0 \rightarrow 6$
$k = 0 \rightarrow 16$
$l = 0 \rightarrow 31$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.050$
$wR(F^2) = 0.135$
$S = 1.00$
2262 reflections
234 parameters

H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.1041P)^2]$
    where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.34$ e Å^{-3}
$\Delta\rho_{min} = -0.20$ e Å^{-3}

Table 1
Hydrogen-bonding geometry (Å, °) for (I).

$D—H\cdots A$	$D—H$	$H\cdots A$	$D\cdots A$	$D—H\cdots A$
O3—H3$\cdots$O5	0.84	1.93	2.741 (3)	163
O5—H5$\cdots$O1^i	0.84	1.94	2.754 (3)	162

Symmetry code: (i) $\frac{1}{2} + x, \frac{3}{2} - y, -z$.

Compound (II)

Crystal data

$C_{21}H_{21}IO_5$
$M_r = 480.28$
Monoclinic, $P2_1$
$a = 6.0077\ (7)$ Å
$b = 15.4106\ (14)$ Å
$c = 11.0654\ (13)$ Å
$\beta = 96.066\ (2)°$
$V = 1018.72\ (19)$ Å^3
$Z = 2$

$D_x = 1.566$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 2146
    reflections
$\theta = 2.0–50.0°$
$\mu = 1.60$ mm^{-1}
$T = 296\ (2)$ K
Needle, colorless
$0.40 \times 0.30 \times 0.30$ mm

Data collection

Bruker CCD1000 area-detector
    diffractometer
φ and ω scans
Absorption correction: empirical
    (SADABS; Blessing, 1995)
    $T_{min} = 0.567$, $T_{max} = 0.645$
4977 measured reflections

2969 independent reflections
2480 reflections with $I > 2\sigma(I)$
$R_{int} = 0.018$
$\theta_{max} = 26.3°$
$h = -6 \rightarrow 7$
$k = -8 \rightarrow 18$
$l = -13 \rightarrow 13$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.028$
$wR(F^2) = 0.065$
$S = 1.03$
2969 reflections
244 parameters
H-atom parameters constrained

$w = 1/[\sigma^2(F_o^2) + (0.0326P)^2]$
    where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.52$ e Å^{-3}
$\Delta\rho_{min} = -0.27$ e Å^{-3}
Absolute structure: Flack (1983)
Flack parameter = $-0.02\ (2)$

Hydroxy H atoms were constrained to an ideal geometry [with $U_{iso}(H) = 1.5U_{eq}(O)$] and allowed to rotate freely about their C—O bonds. All other H atoms were constrained and allowed to ride on their parent C atoms [with $U_{iso}(H) = 1.2U_{eq}(C)$]. In (I), atoms C16, C17, C18, C19, C20 and C21 were fitted to a regular hexagon.

For both compounds, data collection: *SMART* (Bruker, 2000–2003); cell refinement: *SMART*; data reduction: *SAINT* (Bruker, 2002–2003) and *SHELXTL* (Bruker, 2000–2003); program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1990); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *SHELXTL*; software used to prepare material for publication: *SHELXTL*.

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