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An unusual twist conformation of 2-*O*-methyl-1,3,4,5-tetrakis-*O*-*tert*-butyldiphenylsilyl-*myo*-inositol

Hidetoshi Yamada,[a,*] Kotaro Okajima,[a] Hiroshi Imagawa,[b] Yusuke Nagata[a] and Mugio Nishizawa[b]

[a]*School of Science and Technology, Kwansei Gakuin University, 2-1 Gakuen, Sanda 669-1337, Japan*
[b]*Faculty of Pharmaceutical Sciences, Tokushima Bunri University, 180 Nishihamaboji, Tokushima 770-8514, Japan*

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Abstract—The ring conformation of 2-*O*-methyl-1,3,4,5-tetrakis-*O*-*tert*-butyldiphenylsilyl-*myo*-inositol was in a twist form both in solid state and in solution. This is the first observation of a stable twist conformer induced by the introduction of bulky silyl protecting groups.

The introduction of bulky trialkylsilyl or alkyldiarylsilyl groups into an adjacent diol on a six-membered ring sometimes changes the ring conformation from a chair form with more equatorial substituents (the equatorial-rich chair form) into another chair form, which has more axial substituents (the axial-rich chair form). Such conformational changes have been observed on the rings of substituted tetrahydropyranes and cyclohexanes.[1,2] However, none of the other conformers has been manifested except for the chair–chair interconversion.[3] Here, we would like to report the first stable twist conformer of a substituted cyclohexane ring induced by the introduction of bulky silyloxy groups.

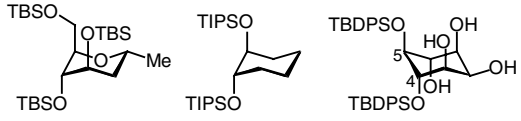
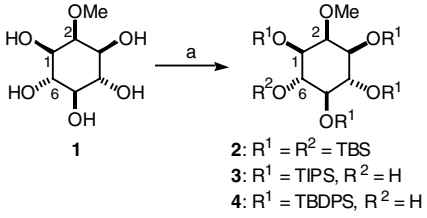


Figure 1. Examples of stable conformers in the axial-rich chair form.[1a,2]

During our investigation of the ring conformation of *myo*-inositol derivatives possessing bulky silyl protecting groups,[2b] we attempted to introduce five *tert*-butyldimethylsilyl (TBS), triisopropylsilyl (TIPS), or *tert*-butyldiphenylsilyl (TBDPS) groups into 2-*O*-methyl-*myo*-inositol (**1**).[4] Introduction of the five TBS groups was possible using TBSOTf at 130 °C to give **2** (Scheme 1). On the contrary, only four TIPS or TBDPS groups could be introduced providing the racemic **3** and **4**, respectively. The hydroxy group at the C-6 remained unprotected, and the ethanol solution of the accidentally derived **4** afforded single crystals.



Scheme 1. Reagents and conditions: (a) TBSOTf, 2,6-lutidine, 130 °C, 4 h, 87% to **2**; TIPSOTf, 2,6-lutidine, THF, reflux, 56 h, 44% for **3**; TBDPSOTf, 2,6-lutidine, 130 °C, 33 h, 57% for **4**.

The structure of **4** was determined by X-ray crystallographic analysis and the cyclohexane ring was in the twist form (Fig. 2).[5] The resulting crystallographic data indicated that the dihedral angle of the O-3–C-3–C-4–O-4 was as large as 177.5°. The other dihedral angles of the vicinal *trans*-C–O bonds, that is, O-4–C-4–C-5–O-5, O-5–C-5–C-6–O-6, and O-6–C-6–C-1–O-1, were 137.0°, 75.8°, and 47.9°, respectively. The dihedral angles of the vicinal *cis*-C–O bonds were small; the respective angles

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* Corresponding author. Tel.: +81-79-565-8342/47; fax: +81-79-565-9077; e-mail: hidetosh@kwansei.ac.jp

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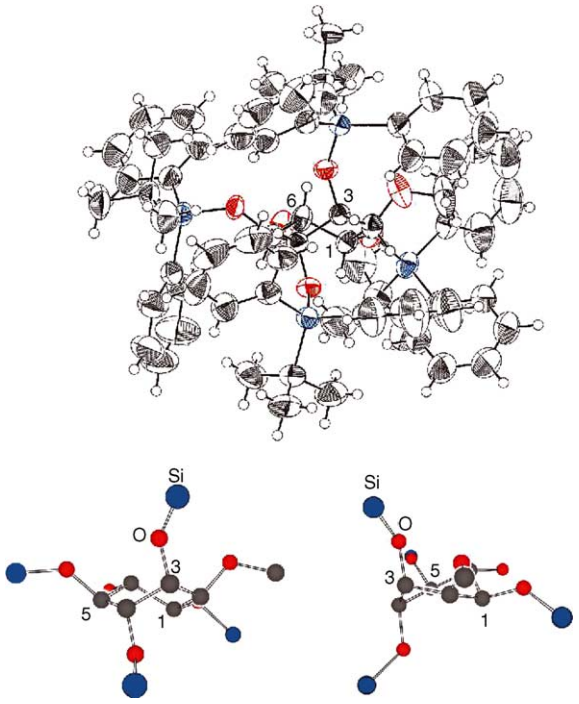

Figure 2. ORTEP drawing and Chem-3D models based on the X-ray diffraction study of **4**. In the models, the substituents on the silicon atoms are omitted for clarity. The right model is a view from another side.

of O-1–C-1–C-2–O-2 and O-2–C-2–C-3–O-3 were 30.5° and 36.7°. Thus, **4** was in the twist form possessing two axial C–O bonds at the 3- and 4-positions in the solid state, and this is the first observation of a stable twist form induced by the bulky silyloxy groups.

The ring conformations of **2**–**4** were also investigated in solution based on the coupling constants due to the vicinal protons on the cyclohexane rings ($^3J_{HH}$) in the ^{1}H NMR spectra. Table 1 shows the coupling constants observed in **2**–**4** at room temperature as well as the dihedral angles of the adjacent C–H bonds calculated by the modified Karplus equation.[6] Although the solution of the Karplus equation has two values for a given coupling constant, the six-membered cyclic structure limits the possible dihedral angles of the vicinal C–H bonds on the ring. For example, if the angle of a pair of 1,2-*trans*-C–H bonds in *myo*-inositol would be extremely less than 60°, the C–O bonds at the place would turn inside the six-membered ring increasing the strain energy. The calculated values were confirmed for their validity by assembling molecular models. The data of **1**, the nonsilylated compound which is obviously in the equatorial-rich chair form, are also listed for comparison.

In solution, the rings were recognized as the axial-rich chair form for **2**, the equatorial-rich chair form for **3**, and the twist form for **4** (Fig. 3). Because the dihedral angles of the pentakis(TBS)-protected **2** were in the range of 55–76°, the conformation was the axial-rich chair form. Long-range w-couplings due to H-3 and H-5 (0.3 Hz) and due to H-5 and H-1 (0.3 Hz) of **2** were particularly characteristic. Comparison of the coupling constants of the tetrakis(TIPS)-protected **3** to those of the nonsilylated **1** showed that the values at H-3–H-4, H-4–H-5, and H-5–H-6 decreased by the introduction of the TIPS groups. The molecular model assembled based on the calculated dihedral angles indicated that the ring of **3** was close to the half-chair form, but it was still in the range of the equatorial-rich chair form as illustrated

Table 1. ^{1}H NMR coupling constants and calculated dihedral angles of **1**–**4**

Compound	$^3J_{HH}$ (Hz) [calculated dihedral angle (°)][a]					
	H-1–H-2 [H-1–C-1–C-2–H-2]	H-2–H-3 [H-2–C-2–C-3–H-3]	H-3–H-4 [H-3–C-3–C-4–H-4]	H-4–H-5 [H-4–C-4–C-5–H-5]	H-5–H-6 [H-5–C-5–C-6–H-6]	H-6–H-1 [H-6–C-6–C-1–H-1]
1[b]	2.7 [61]	2.7 [61]	9.8 [166]	9.3 [160]	9.3 [160]	9.8 [166]
2[c]	3.3 [55]	3.3 [55]	2.9 [59]	1.6 [76]	1.6 [76]	2.9 [59]
3[c]	3.2 [56]	3.2 [56]	6.1 [135]	5.4 [131]	7.1 [142]	9.3 [160]
4[c]	5.6 [36]	4.0 [49]	2.0 [69]	2.0 [102]	6.8 [140]	8.8 [155]

[a] In absolute value.
[b] In CD_3OD.
[c] In $CDCl_3$.

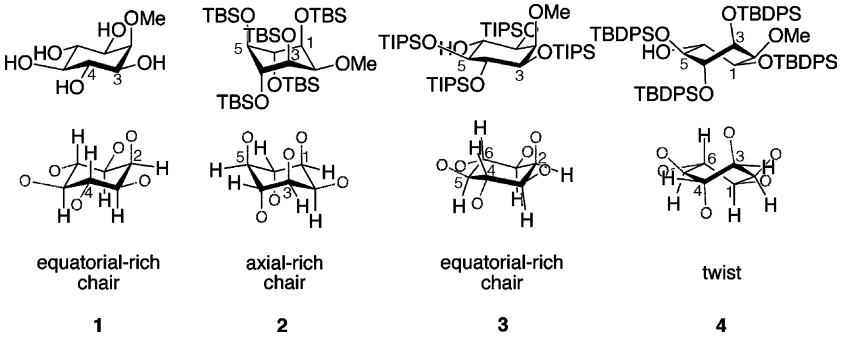

Figure 3. Stable conformers of **1**–**4**. The lower drawings are for the conspicuousness of the C–H bonds on the cyclohexane rings.

in Figure 3. The coupling constants of the tetrakis(TBDPS)-protected **4** were small at H-3–H-4 and H-4–H-5. In contrast, the coupling constant between H-6 and H-1 was large indicating that these two hydrogens were in a *trans*-diaxial relationship. The molecular model based on the dihedral angles displayed that **4** was also in the twist form in solution, and the ring conformation resembled that in the solid state.[7]

During the previous conformational changes in the six-membered rings due to the introduction of bulky silyl protecting groups, only the chair forms have been demonstrated.[1–3] For instance, two conformers were observed in solutions of certain *trans*-1,2-bis[(trialkylsilyl)oxy]cyclohexanes. These conformers were estimated as being in the chair form based on the molecular mechanics calculations,[2a] since the direct observation of the conformations is quite difficult in solution. The *myo*-inositol derivatives possessing two bulky silyl protecting groups at the 3,4- or 4,5-positions described in our previous report were also totally in chair form (see Fig. 1).[2b] The unusual conformation of **4** described here is the first observation of the twist form induced by the introduction of bulky silyl protecting groups, and the conformer was stable enough to be isolated. We simply thought that the conformation changes into the axial-rich chair form by crowding as many as possible bulky silyloxy groups into a six-membered ring, but it was not always correct. We shall not forget the possibility of the other ring conformations.

Acknowledgements

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3. The conformation of phenyl 2-*O*-acetyl-1-seleno-3,4,6-tris-*O*-isopropylsilyl-β-D-glucopyranoside might be different from the $^1C_4$ form; Abe, H.; Terauchi, M.; Matsuda, A.; Shuto, S. *J. Org. Chem.* **2003**, *68*, 7439–7447.

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5. X-ray data for **4** was measured on a MacScience dip image plate diffractometer using graphite-monochromated Mo Kα radiation ($l = 0.71073$ Å). All diagrams and calculations were performed using maXus (Bruker Nonius, Delft & MacScience, Japan). The structure was solved by direct method with SIR-97[8] and refined by a full-matrix least-squares method on F2 with SHELXS-97.[9]
Crystallographic data (excluding structure factors) for the structures of **4** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 229721. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ UK (fax: +44-0-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
4: Mp 117.8–120.5 °C, $C_{71}H_{86}O_6Si_4$, $M = 1147.807$, crystal size $0.2\times0.2\times0.1$ mm, monoclinic, space group $P2_1/n$, $a = 13.8460(3)$, $b = 11.7140(4)$, $c = 41.812(2)$ Å, $\alpha = 90.00$, $\beta = 98.1460\ (10)$, $\gamma = 90.00°$, $V = 6713.1\ (4)$ Å^3, $Z = 4$, $D_{calcd} = 1.136$ Mg/m^3, μ(Mo Kα) $= 0.137$ mm^{-1}, measured temperature 298 K, reflections collected 10024, independent reflections 9517, $R = 0.0604$, $wR = 0.1752$.

6. The dihedral angles were calculated from the Karplus equation modified by Haasnoot and Altona: $J = 7.76\cos^2\omega - 1.1\cos\omega + 1.4$, where J is the vicinal coupling constant and ω is the dihedral angle: Haasnoot, C. A. G.; de Leeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783–2792.

7. The crystallographic data of **4** indicated the dihedral angles of the adjacent C–H bonds on the cyclohexane ring as follows: H-1–C-1–C-2–H-2: 32.3°, H-2–C-2–C-3–H-3: 33.1°, H-3–C-3–C-4–H-4: 61.3°, H-4–C-4–C-5–H-5: 101.5°, H-5–C-5–C-6–H-6: 162.3°, and H-6–C-6–C-1–H-1: 170.6°.

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