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Tetrahedron Letters
Tetrahedron Letters 45 (2004) 3157–3160

Stable axial-rich chair conformer of *myo*-inositol derivatives due to introduction of two adjacent bulky silyl protections

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Received 15 January 2004; revised 16 February 2004; accepted 16 February 2004

Abstract—The ring-conformational change of *myo*-inositol derivatives by introducing two *tert*-butyldimethylsilyl, triisopropylsilyl, or *tert*-butyldiphenylsilyl groups into the 1,2-*trans* hydroxy groups—3,4- and 4,5-positions—were investigated. The cyclohexane cores of the 4,5-bis-*O*-silylated derivatives with *tert*-butyldiphenylsilyl or triisopropylsilyl groups were present in the axial-rich chair form.

Introduction of trialkylsilyl or alkyldiarylsilyl groups into vicinal diols sometimes induces significant changes in conformation. Such conformational changes have been observed in the acyclic 1,2-disilyloxy compounds and the tetrahydropyrane rings bearing two or more silyloxy groups (Fig. 1).[1–3] Recently, conformational flips of cyclohexane rings have been carried out by introducing bulky silyl groups into *trans*-1,2-cyclohexanediol.[4] Control of the ring conformation is important to develop substrate-controlled stereoselective reactions, because such conformational changes have been effectively used in stereoselective reactions.[1,3,5] We have aimed at accomplishing such conformational flip on a multifunctionalized cyclohexane ring, and here we report that certain *myo*-inositol derivatives possessing two adjacent silyl protections were stably present in the chair conformation with more axial substituents (the axial-rich chair form).

We introduced two *tert*-butyldimethylsilyl (TBS), two isopropylsilyl (TIPS), or two *tert*-butyldiphenylsilyl (TBDPS) groups into adjacent *trans*-diols (3,4- and 4,5-positions) of *myo*-inositol, because the flips of cyclohexane rings were achieved by the introduction of the bulky silyl groups into *trans*-1,2-cyclohexanediol.[4] Thus, (±)-3,4-bis-*O*-TBS-*myo*-inositol (**1**), (±)-3,4-bis-*O*-TIPS-*myo*-inositol (**2**), and (±)-3,4-bis-*O*-TBDPS-*myo*-inositol (**3**), and the corresponding 4,5-analogues **4**–**6** (Fig. 2) were prepared and investigated the conformations. We also studied the ring conformations of tetrabenzylated **1p**–**6p**, which were the synthetic intermediates of **1**–**6**.

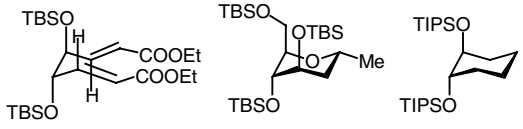
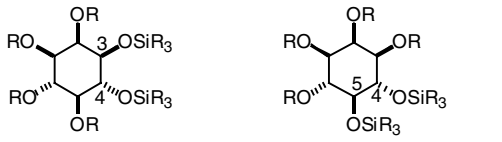


Figure 1. Conformational changes of acyclic, tetrahydropyrane, and cyclohexane derivatives due to the adjacent trialkylsilyloxy groups.[1,2a,4]



1: R = H, SiR_3 = TBS
2: R = H, SiR_3 = TIPS
3: R = H, SiR_3 = TBDPS
1p: R = Bn, SiR_3 = TBS
2p: R = Bn, SiR_3 = TIPS
3p: R = Bn, SiR_3 = TBDPS

4: R = H, SiR_3 = TBS
5: R = H, SiR_3 = TIPS
6: R = H, SiR_3 = TBDPS
4p: R = Bn, SiR_3 = TBS
5p: R = Bn, SiR_3 = TIPS
6p: R = Bn, SiR_3 = TBDPS

Figure 2. Compounds whose ring conformations were investigated.

Keywords: Ring conformation; *myo*-Inositol; Axial-rich chair; Silyl protecting groups.
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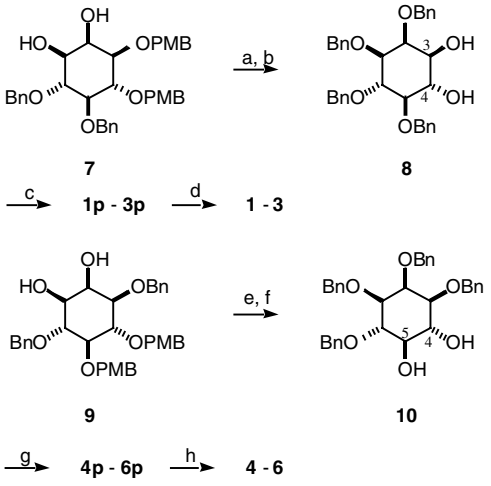
doi:10.1016/j.tetlet.2004.02.080

Compounds **1**–**6** were synthesized as follows (Scheme 1). Dibenzylation of the known *myo*-inositol derivative **7**[6] followed by removal of the two *p*-methoxybenzyl (PMB) groups provided the 3,4-diol **8**. Protection with TBSOTf, TIPSOTf, and TBDPSOTf[7] gave **1p**, **2p**, and **3p**, respectively, which were hydrogenated to give 3,4-bis-*O*-silylated **1**, **2**, and **3**. Starting from the known **9**,[8] a similar sequence obtained 4,5-bis-*O*-silylated **4p**–**6p** and **4**–**6**.



Scheme 1. Reagents and conditions: (a) NaH, DMF, rt, 2 h, then BnBr, rt, 10 h, 68%; (b) DDQ, 17:1 CH_2Cl_2–H_2O, rt, 1 h, 79%; (c) TBSOTf, 2,6-lutidine, DMF, 100 °C, 1 h, 93% to **1p**. TIPSOTf, 2,6-lutidine, DMF, 100 °C, 12 h, 83% to **2p**. TBDPSOTf, 2,6-lutidine, DMF, 100 °C, 20 h, 81% to **3p**; (d) H_2 (1 atm), $Pd(OH)_2$, THF, rt, 15 days, 12% to **1**. H_2 (1 atm), $Pd(OH)_2$, THF, rt, 17 days, 47% to **2**. H_2 (100 atm), $Pd(OH)_2$, THF, rt, 8 days, 23% to **3**; (e) NaH, DMF, rt, 2 h, then BnBr, rt, 5 h, 98%, (f) DDQ, 17:1 CH_2Cl_2–H_2O, rt, 6 h, 82%; (g) TBSOTf, 2,6-lutidine, DMF, 120 °C, 10 h, 100% to **4p**. TIPSOTf, 2,6-lutidine, DMF, 100 °C, 12 h, 90% to **5p**. TBDPSOTf, 2,6-lutidine, DMF, 100 °C, 1.5 h, 100% to **6p**; (h) H_2 (100 atm), $Pd(OH)_2$, THF, rt, 5 days, 31% to **4**. H_2 (1 atm), $Pd(OH)_2$, THF, rt, 11 days, 34% to **5**. H_2 (1 atm), $Pd(OH)_2$, THF, rt, 10 days, 50% to **6**.

The respective ring conformations of **1**–**6** and **1p**–**6p** were determined based on the coupling constants due to the vicinal protons on the cyclohexane rings ($^3J_{HH}$) in ^{1}H NMR spectra. The accurate coupling constants based on both vicinal protons and w-shaped long range couplings were observed,[9] since the original *Cs* symmetry of the *myo*-inositol was already deformed. Table 1 summarizes the coupling constants of **1**–**6** and **1p**–**6p** at room temperature. Coupling constants of **8** and **10**, which are the precursor diols for the corresponding silyl-protected compounds, are also listed for a comparison. The coupling constants of the tetraols **1**–**6** were measured in CD_3CN and those of the tetrabenzyl derivatives **1p**–**6p** were the data in $CDCl_3$. When the signals heavily overlapped, C_6D_6 was employed.

Molecular models assembled based on dihedral angles calculated by the Karplus equation indicated that all the 3,4-bis-*O*-silylated *myo*-inositol derivatives **1**–**3** and **1p**–**3p** existed in the chair conformation with more equatorial substituents (equatorial-rich chair form) (Fig. 3).[10] The coupling constants of the 3,4-bis-*O*-silylated **1**–**3** and **1p**–**3p** were substantially similar to those of non-silylated diol **8** indicating the large values due to the protons in the 1,2-diaxial relationship at H-3–H-4, H-4–H-5, H-5–H-6, and H-6–H-1. Therefore, introduction of the bulky silyl protecting groups at the 3,4-hydroxy groups of *myo*-inositol did not change the original equatorial-rich chair form.

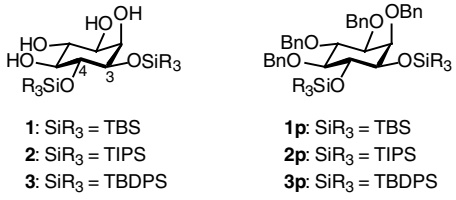


Figure 3. Ring conformation of 3,4-bis-*O*-silylated *myo*-inositol derivatives.

Table 1. ^{1}H NMR coupling constants of **1**–**6**, **1p**–**6p**, **8**, and **10**

Compound	Protecting group						$^3J_{HH}$ (Hz)					
	O-1	O-2	O-3	O-4	O-5	O-6	H-1–H-2	H-2–H-3	H-3–H-4	H-4–H-5	H-5–H-6	H-6–H-1
1[c]	—	—	TBS	TBS	—	—	2.8	2.9	9.2	9.0	8.7	8.6
2[c]	—	—	TIPS	TIPS	—	—	3.0	2.9	7.6	7.6	7.9	8.3
3[c]	—	—	TBDPS	TBDPS	—	—	2.8	2.7	7.4	7.2	7.6	7.9
1p[b]	Bn	Bn	TBS	TBS	Bn	Bn	2.1	2.1	9.3	9.0	9.0	9.6
2p[b]	Bn	Bn	TIPS	TIPS	Bn	Bn	1.8	2.4	9.3	8.7	9.0	9.3
3p[a]	Bn	Bn	TBDPS	TBDPS	Bn	Bn	1.8	2.1	8.7	8.4	8.1	8.4
8[a]	Bn	Bn	—	—	Bn	Bn	2.1	2.4	9.3	9.3	9.3	9.6
4[c]	—	—	—	TBS	TBS	—	3.4	3.4	7.2	7.1	7.1	7.4
5[c]	—	—	—	TIPS	TIPS	—	3.4	3.4	3.7	3.9	3.8	3.6
6[c]	—	—	—	TBDPS	TBDPS	—	3.3	3.3	3.6	3.3	3.3	3.6
4p[b]	Bn	Bn	Bn	TBS	TBS	Bn	2.1	2.4	9.6	8.7	9.6	9.6
5p[b]	Bn	Bn	Bn	TIPS	TIPS	Bn	2.4	2.4	8.4	7.8	7.8	9.0
6p[a]	Bn	Bn	Bn	TBDPS	TBDPS	Bn	2.7	3.6	3.6	3.3	3.6	4.8
10[a]	Bn	Bn	Bn	—	—	Bn	2.4	2.4	9.6	9.3	9.3	9.3

[a] In C_6D_6.
[b] In $CDCl_3$.
[c] In CD_3CN.

On the other hand, a part of the compounds silylated at the 4,5-positions, **5**, **6**, and **6p**, existed in the axial-rich chair form (Fig. 4). The coupling constants of these compounds were in the range of 2.7–4.8 Hz (Table 1), and these values suggested that **5**, **6**, and **6p** took the axial-rich chair conformation. Long range w-couplings due to H-3–H-5, H-4–H-6, and H-5–H-1 supported this conclusion.[11] Furthermore, the X-ray diffraction study showed that **6p** existed as the axial-rich chair form in the solid state (Fig. 5).[12] These are the first observations to show that the multifunctionalized cyclohexane rings are able to flip into the axial-rich chair conformation by introduction of vicinal bulky silyloxy groups.

In contrast, the tetrabenzylated **4p** and **5p** as well as the tetraol **4** retained the equatorial-rich chair form (Fig. 4), although the silyl protections were introduced at the 4,5-positions. The coupling constants of these compounds were generally similar to those of the nonsilylated diol **10** indicating the large values due to the 1,2-diaxial H-3–H-4, H-4–H-5, H-5–H-6, and H-6–H-1.

Although the *trans*-1,2-bis[(trialkylsilyl)oxy]cyclohexanes tend to take the 1,2-diaxial chair conformation, the cyclohexane rings of the 3,4-bis-*O*-silylated **1**–**3** and **1p**–**3p** as well as the 4,5-bis-*O*-silylated **4**, **4p**, and **5p** retained the equatorial-rich chair form. In contrast, the

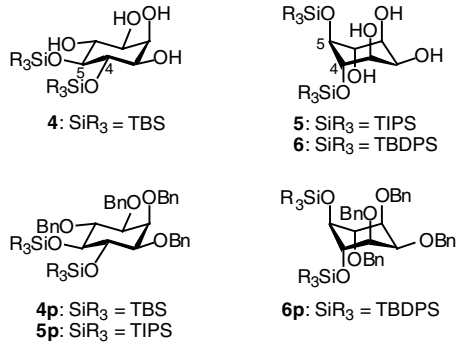


Figure 4. Ring conformation of 4,5-bis-*O*-silylated *myo*-inositol derivatives.

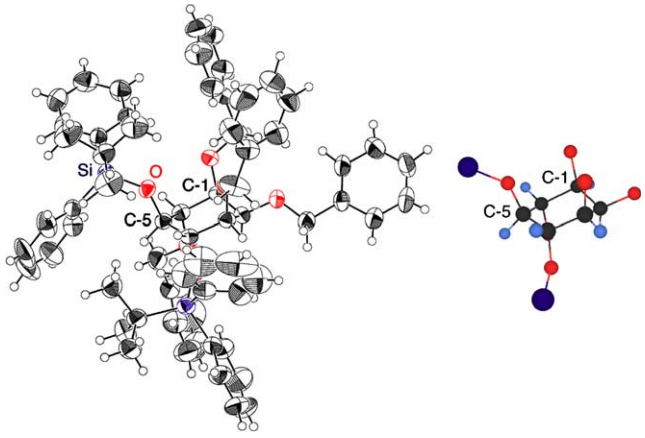


Figure 5. ORTEP drawing and Chem-3D model based on the X-ray diffraction study of **6p**. In the model, the benzyl groups and substituents on the silicon atoms are omitted for clarity.

4,5-bis-*O*-silylated **5**, **6**, and **6p** existed in the axial-rich chair form. Therefore, the two TBS groups are not big enough to induce the ring flip.[4] Introduction of TBDPS groups into the 4,5-hydroxy groups of *myo*-inositol, **6** as well as **6p**, induced complete flipping into the axial-rich chair conformation probably due to the serious equatorial/equatorial interaction with the hydroxy or benzyloxy groups at the C-3 and C-6 positions. The TIPS- and benzyl-protected **5p** took the equatorial-rich chair conformation, in contrast, tetraol **5** existed in the axial-rich chair form due to the balance of the increased 1,3-diaxial interactions with the 1,2-diequatorial silyloxy/silyloxy interactions. Because we anticipated that the delicate balance could be upset by a decrease in strength of intramolecular hydrogen bondings, we changed the solvent used for NMR experiments.[13] The ring of **5**, however, existed in the axial-rich chair form even in methanol-d_4. Thus, the influence of the hydrogen bondings would be small. NMR spectra of benzyl-protected **5p** in the different solvents indicated that variation of the solvents did not affect the ring conformation, because the equatorial-rich chair form was retained in all cases.[12] Therefore, the steric repulsion of the silyl protecting groups would be the main cause of these conformational changes, and comparison of the ring conformations of **4**, **5**, **5p**, and **6p** indicates that the steric repulsion is in the order of TBDPS, TIPS, and then TBS.

In conclusion, the cyclohexane ring of *myo*-inositol was flipped into the axial-rich chair form when TIPS or TBDPS groups were introduced into the 4- and 5-hydroxy groups. Although the ring flip of inositols itself has been previously observed,[14] we have first isolated the pure *myo*-inositol derivatives as in the axial-rich chair form. These results indicate that two adjacent bulky silyloxy groups can flip the multifunctionalized cyclohexane ring, and showed that the axial-rich and equatorial-rich chair conformations are in delicate balance. Finally we would like to state that the ring of the *all-trans*-1,2,3,4,5,6-hexaisopropylcyclohexane, reported by Biali and co-workers, is the most famous stable axial-rich chair conformer.[15]

Acknowledgements

Financial supports by the Naito Foundation (Japan), the Sunbor Grant (Suntory Institute for Bioorganic Research, Japan), the Cosmetology Research Foundation (Japan) are gratefully acknowledged. Thanks are also due to Professor Yutaka Watanabe (Ehime University, Japan) for his helpful discussions.

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9. Proton NMR Spectra were recorded on α-JEOL 400 or Varian UNITY 300 or JEOL ECA 300 spectrometers. The spectral settings were as follows: 8.0 kHz spectral width, 32,768 data points, 4.10 s acquisition time, 0.24 Hz digital resolution for α-JEOL 400; 4.5 kHz spectral width, 64,000 data points, 7.11 s acquisition time, 0.14 Hz digital resolution for Varian UNITY 300; 5.6 kHz spectral width, 32,768 data points, 5.81 s acquisition time, 0.17 Hz digital resolution for Varian UNITY 300.
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11. The observed coupling constants due to H-3–H-5, H-4–H-6, and H-5–H-1 were 0.8, 1.7, and 1.0 Hz for **5**, and 0.9, 1.8, and 0.9 Hz for **6**, respectively. The w-coupling due to H-4 and H-6 (1.2 Hz) was observed for **6p**.
12. X-ray data for **6p** 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[16] and refined by a full-matrix least-squares method on F2 with SHELXS-97.[17] Crystallographic data (excluding structure factors) for the structure of **6p** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 227525. 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). **6p**: mp 115.0–117.0 °C, $C_{66}H_{72}O_6Si_2$, $M = 1017.46$, crystal size $0.5 \times 0.3 \times 0.2$ mm, triclinic, space group $P\bar{1}$, $a = 11.75$, $b = 13.45$, $c = 20.10$ Å, $\alpha = 87.80$, $\beta = 78.71$, $\gamma = 66.80$ Å, $V = 2862.55$ Å^3, $Z = 2$, D calcd $= 1.180$ Mg m^{-3}, μ(Mo Kα) $= 0.113$ mm^{-1}, measured temp 298 K, reflections collected 9656, independent reflections 9085, $R = 0.082$, $wR = 0.24$, GOF $= 1.164$.
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