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Tetrahedron 61 (2005) 3497–3506

Achievement of ring inversion of *myo*-inositol derivatives due to silyloxy/silyloxy repulsion enhanced by the *trans*-substituents on both sides

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Received 1 December 2004; revised 27 January 2005; accepted 31 January 2005

Abstract—The introduction of quite bulky trialkyl or diarylalkylsilyl groups into vicinal *trans*-hydroxy groups induced a conformational flip of certain multifunctionalized cyclohexane rings from the usual chair form possessing more equatorial substituents (equatorial-rich chair form) into another chair-form that has more axial substituents (axial-rich chair form). This realization was experimentally revealed by the conformational study of the synthetic *myo*-inositol derivatives possessing two *tert*-butyldimethylsilyl (TBS), two triisopropylsilyl (TIPS), or two *tert*-butyldiphenylsilyl (TBDPS) groups on an adjacent *trans*-diol. Among them, the cyclohexane rings of the 4,5-bis-*O*-TIPS-*myo*-inositol, 4,5-bis-*O*-TBDPS-*myo*-inositol, and 1,2,3,6-tetra-*O*-benzyl-4,5-bis-*O*-TBDPS-*myo*-inositol were in the axial-rich chair form. Comparison of the ring conformations also revealed that the order of the repulsion was OTBDPS/OTBDPS > OTIPS/OTIPS > OTBS/OTBS, and the silyloxy/silyloxy repulsion was enhanced when the two silyloxy groups were placed in the center of the contiguous four equatorial substituents.

1. Introduction

The introduction of bulky trialkyl or diarylalkylsilyl groups into a vicinal hydroxy groups induces a conformational bias due to the repulsion between the two bulky silyloxy groups. The first observation of such a conformational distribution control is the *trans*-1,2-anti orientation of *tert*-butyldimethylsilyloxy groups on acyclic compounds reported by Saito and co-workers (Fig. 1).[1] In 1994, Tius' group found that the silyloxy repulsion also changed the conformation of a tetrahydropyrane ring.[2] The introduction of *tert*-butyldimethylsilyl (TBS) groups into the hydroxy groups on the tetrahydropyrane flipped the ring conformation from the usual chair form possessing more equatorial substituents (equatorial-rich chair form) into another chair-form holding more axial substituents (axial-rich chair form). Since then many conformational flips of tetrahydropyrane rings have occurred due to the introduction of bulky silyl groups thus making effective substrate-controlled stereoselective reactions possible.[3,4]

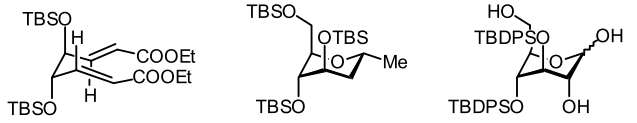

Figure 1. Conformational restrictions of acyclic, tetrahydropyrane, and pyranose derivatives due to the repulsion between adjacent silyloxy groups.[1,2,3f]

Recently, a conformational change in a cyclohexane ring was reported by Marzabadi and co-workers based on the NMR experiments of the *trans*-1,2-bis-silyloxycyclohexanes.[5] They demonstrated that the introduction of triisopropylsilyl (TIPS) and *tert*-butyldiphenylsilyl (TBDPS) groups into *trans*-1,2-cyclohexanediol favored the 1,2-diaxial

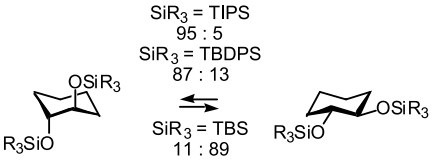

Figure 2. Ring conformation of *trans*-1,2-bis-silyloxycyclohexanes in CD_2Cl_2 at 200 K.[5]

Keywords: Ring conformation; *Myo*-inositol; Axial-rich chair; Silyl protecting groups.
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doi:10.1016/j.tet.2005.01.124

conformation in the solution (Fig. 2). In contrast, the 1,2-diequatorial conformation was favored when TBS, triphenylsilyl, and other smaller silyl protecting groups were introduced. If the silyl groups could flip a cyclohexane ring possessing other functional groups on the same ring, the conformational control would become an essential and effective synthetic means as well as the flipped sugar chemistry.[4,6] Our objective is accomplishing such a conformational control on a multifunctionalized cyclohexane ring, *myo*-inositol, by introduction of two bulky silyl protecting groups.[7]

Myo-inositol has six hydroxy groups on a cyclohexane ring, and five of them occupy the equatorial positions because the compound is generally in the equatorial-rich chair form (Fig. 3). As the previous ring-inversions shows,[2–6] introduction of the bulky silyl groups into a pair of adjacent *trans*-hydroxy groups—generally these are equatorial—has been crucial to flip the ring. Since *myo*-inositol has one axial hydroxy group, there are two different sets of adjacent *trans*-diols, that is, the 3- and 4-positions and the 4- and 5-positions. For the investigation of a conformational change in the multifunctionalized cyclohexane ring due to the repulsion of two bulky silyloxy groups, we designed *myo*-inositol derivatives possessing two TBS, two TIPS, or two TBDPS groups into the adjacent *trans*-diols (3,4- and 4,5-positions). Thus, we synthesized (±)-3,4-bis-*O*-TBS, TIPS, and TBDPS-*myo*-inositols (**1**–**3**) and the corresponding 4,5-analogues **4**–**6** (Fig. 4), and investigated their ring conformations. The conformations of the synthetic intermediate **1p**–**6p** were also studied. The ring conformations were determined based on the coupling constants in the ^{1}H NMR spectra. When the derivatives afforded single crystals, we also carried out X-ray diffraction studies.

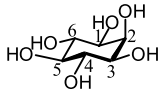


Figure 3. *Myo*-inositol in the equatorial-rich chair form.

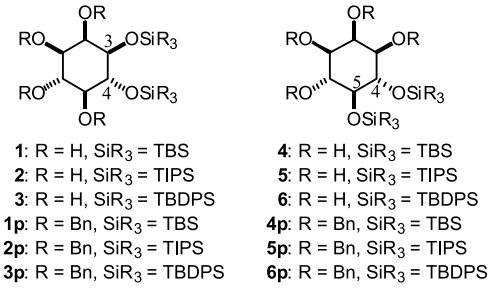
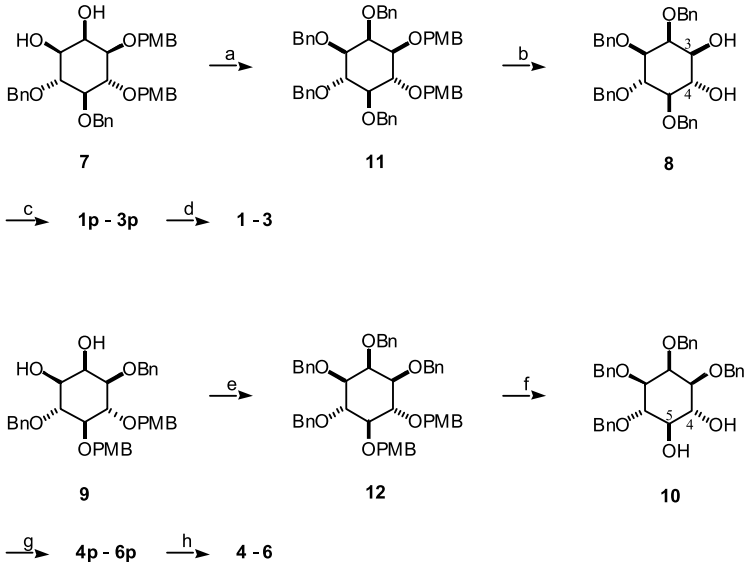


Figure 4. Compounds whose ring conformations were investigated.

2. Results and discussion

2.1. Preparation of the adjacent *trans*-silyloxy derivatives of *myo*-inositol

Scheme 1 shows the syntheses of **1**–**6**. The dibenzylation of (±)-4,5-di-*O*-benzyl-1,6-bis-*O*-(4-methoxybenzyl)-*myo*-inositol (**7**)[8] gave the 1,2,5,6-tetrabenzylated derivative **11**, then removal of the two *p*-methoxybenzyl (PMB) groups with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) produced the 3,4-diol **8**. The protection of the two generated hydroxy groups with TBSOTf, TIPSOTf, and TBDPSOTf[9] gave **1p**, **2p**, and **3p**, respectively, whose benzyl groups were hydrogenated with $Pd(OH)_2$ in THF to give the 3,4-bis-*O*-silylated **1**, **2**, and **3**.[12] The complete removal of the benzyl groups was complicated. These reactions required a long time and sometimes a high hydrogen gas pressure, but the resulting yields of the full debenzylated compounds were not very high. The steric hindrance due to



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, 45 min, 77%, (c) TBSOTf, 2,6-lutidine, DMF, 100 °C, 1 h, 94% to **1p**; TIPSOTf, 2,6-lutidine, DMF, 100 °C, 12 h, 83% to **2p**; TBDPSOTf, 2,6-lutidine, DMF, 100 °C, 7 h, 85% 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, 48% 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, 35% to **5**; H_2 (1 atm), $Pd(OH)_2$, THF, rt, 10 days, 50% to **6**.

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

Compound	$^3J_{HH}$ (Hz) [caluculated dihedral angle (°)]						$^4J_{HH}$ (Hz) (positions)
	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[a]	2.7 [61]	2.9 [59]	9.5 [162]	9.2 [159]	8.8 [155]	9.0 [157]	—
2[a]	2.9 [59]	2.9 [59]	8.1 [149]	8.1 [149]	8.5 [153]	8.5 [153]	—
3[a]	2.8 [60]	2.7 [61]	7.4 [144]	7.2 [143]	7.6 [146]	7.9 [148]	—
1p[b]	2.1 [68]	2.1 [68]	9.3 [160]	9.0 [157]	9.3 [160]	9.6 [164]	—
2p[b]	1.8 [72]	2.4 [64]	9.3 [160]	8.7 [154]	9.0 [157]	9.3 [160]	—
3p[c]	3.0 [58]	1.8 [72]	8.4 [152]	8.1 [149]	8.4 [152]	8.7 [154]	—
8[c]	2.1 [68]	2.4 [64]	9.3 [160]	9.3 [160]	9.3 [160]	9.6 [164]	—
4[a]	3.4 [54]	3.4 [54]	7.2 [143]	7.1 [142]	7.1 [142]	7.4 [144]	—
5[a]	3.4 [54]	3.4 [54]	3.7 [52]	3.9 [50]	3.8 [51]	3.6 [53]	0.8 (H-3–H-5) 1.7 (H-4–H-6) 1.0 (H-5–H-1)
6[a]	3.3 [55]	3.3 [55]	3.6 [53]	3.3 [55]	3.3 [55]	3.6 [53]	0.9 (H-3–H-5) 1.8 (H-4–H-6) 0.9 (H-5–H-1)
4p[b]	2.4 [64]	2.1 [68]	9.6 [164]	8.7 [154]	9.3 [160]	9.6 [164]	—
5p[b]	2.4 [64]	2.4 [64]	8.4 [152]	7.8 [147]	7.8 [147]	9.0 [157]	—
6p[c]	2.7 [61]	3.6 [53]	3.6 [53]	3.3 [55]	3.6 [53]	4.8 [43]	1.2 (H-4–H-6)
10[c]	2.4 [64]	2.4 [64]	9.6 [164]	9.3 [160]	9.3 [160]	9.6 [164]	—

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

the bulky silyl groups supposedly prevents the approach of the benzyl groups to the surface of the catalyst.[3b,10] Starting from (±)-1,4-di-*O*-benzyl-5,6-bis-*O*-(4-methoxybenzyl)-*myo*-inositol (**9**),[11] a similar sequence produced 4,5-bis-*O*-silylated **4p–6p** and **4–6** through the 1,2,3,6-tetrabenzylated derivative **12** and the diol **10**.[12]

2.2. Determination of the ring conformations

Since the original C_s symmetry of the *myo*-inositol was already deformed, the accurate observation of the ^{1}H NMR coupling constants based on both vicinal protons ($^3J_{HH}$) and w-shaped long-range couplings ($^4J_{HH}$) were possible for investigating the ring conformations of **1–6** and **1p–6p**. Table 1 summarizes the coupling constants of **1–6** and **1p–6p** at room temperature and the calculated dihedral angles based on $^3J_{HH}$.[13,14] 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. The calculated values were confirmed for their validity by assembling molecular models. The coupling constants of **8** and **10**, which are the precursor diols for the corresponding silyl-protected compounds, are also listed for 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.

The assembled molecular models based on the dihedral angles indicated that all the 3,4-bis-*O*-silylated *myo*-inositol derivatives **1–3** and **1p–3p** existed in the equatorial-rich chair form (Fig. 5). The coupling constants of the 3,4-bis-*O*-silylated **1–3** and **1p–3p** were substantially similar to those of the 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. Although the coupling constants of the 3,4-bis-*O*-TBDPS-protected **3** were somewhat smaller than the others, the reduced amount did not indicate a drastic change in the ring conformation. Therefore, the introduction of the bulky silyl protecting groups into the 3,4-hydroxy groups of *myo*-inositol did not change the original equatorial-rich chair form.

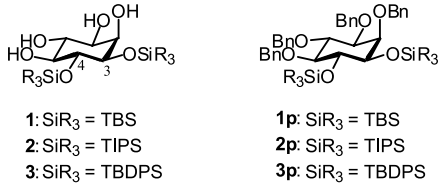


Figure 5. Ring conformation of the 3,4-bis-*O*-silylated *myo*-inositol derivatives.

In contrast, the rings of certain 4,5-bis-*O*-silylated compounds, **5**,**6**, and **6p** existed in the axial-rich chair form (Fig. 6). The coupling constants of these compounds were in the range of 2.7–4.8 Hz (Table 1), and these values indicated that the cyclohexane cores of **5**, **6**, and **6p** were in the axial-rich chair form. The long-range w-couplings due to H-3–H-5, H-4–H-6, and H-5–H-1 supported this conclusion. Furthermore, the X-ray diffraction study elucidated that **6p** existed as the axial-rich chair form in a

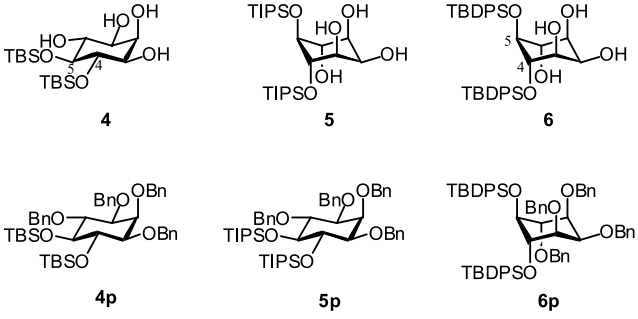


Figure 6. Ring conformation of 4,5-bis-*O*-silylated *myo*-inositol derivatives.

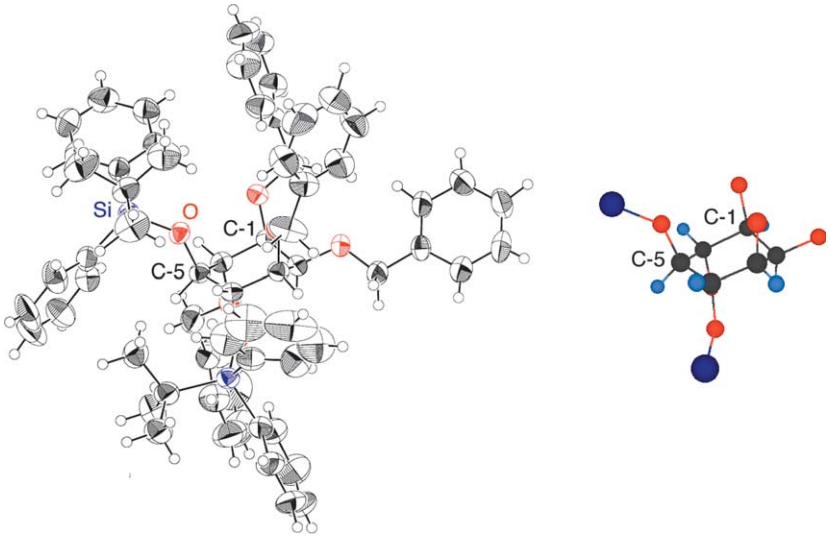


Figure 7. ORTEP drawing and Chem-3D model based on the X-ray diffraction study of **6p**. In the model, the benzyl groups and substituents on the silicon atoms are omitted for clarity.

crystal (Fig. 7). These are the first observations to show that the multifunctionalized cyclohexane rings are able to flip into the axial-rich chair form by the introduction of bulky silyl protections. On the other hand, the tetrabenzylated **4p** and **5p** as well as the tetraol **4** retained the equatorial-rich chair form, 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.

2.3. Considerations of the ring conformations

Marzabadi's report shows that *trans*-1,2-bis(*tert*-butyldimethylsilyloxy)cyclohexane preferred the equatorial-rich chair form (Fig. 2).[5] At first, we postulated that increasing the functional groups surrounding the *trans*-adjacent OTBS groups would reinforce the steric repulsion of the silyloxy groups and flip the multifunctionalized cyclohexane ring into the axial-rich chair form. Contrary to our expectation, however, all the synthesized bis-*O*-TBS-protected compounds, **1**, **1p**, **4**, and **4p** maintained the original equatorial-rich chair form regardless of the introduced places (3,4- or 4,5-positions) and the presence of the benzyl groups. Therefore, the two OTBS groups are not big enough to induce the ring flip of cyclohexane in solution even when they are placed *trans*-adjacent and even in a multifunctionalized cyclohexane.[15]

When the TIPS groups were introduced to the 4,5-positions, the cyclohexane ring of the tetraol **5** was in the axial-rich chair form, but the ring of the corresponding tetra-benzyl-protected **5p** was in the equatorial-rich chair form. Thus the benzyloxy groups prevented the ring flip more than the hydroxy groups. On the basis of this result, we envisaged that the axial-rich conformation of **5** was stabilized by hydrogen bondings.[16] Because the ring flip of **5** occurred in CD_3CN (Table 1), we changed the solvent to CD_3OD. The result listed in Table 2 indicated that the ring conformation of **5** was still the axial-rich chair form even in methanol. The coupling constants were in the range of 3.1–5.6 Hz. The clear long-range w-coupling due to H-4–H-6 (1.2 Hz) was observed along with small (<1 Hz) w-couplings due to H-1–H-3, H-3–H-5, and H-5–H-1. These small couplings were confirmed by the decoupling experiments because the correlated signals became sharper and taller. On the other hand, each NMR spectrum of the benzyl-protected **5p** in $CDCl_3$, acetone-d_6, and CD_3OD indicated that the equatorial-rich chair form was retained in all cases. These observations demonstrated that the influence of both solvent effects and hydrogen bondings were less marked on these ring conformations.

The introduction of TBDPS groups into the 4,5-hydroxy groups of *myo*-inositol, **6** as well as **6p**, induced complete ring flip into the axial-rich chair form. A comparison of the ring conformations of **4**, **5**, **5p**, and **6p** (Fig. 6) demonstrated that the steric repulsion is OTBDPS/OTBDPS $>$OTIPS/OTIPS$>$OTBS/OTBS. Eliel and Satici reported the conformational energy of monosilyloxycyclohexanes.[17] The population of the axial-rich chair form is 9 and 20% in the TIPS derivative and in the TBDPS derivative, respectively

Table 2. ^{1}H NMR coupling constants and calculated dihedral angles of **5** and **5p** in several solvents

Compound	Solvent	$^3J_{HH}$ (Hz) [calculated dihedral angle (°)]					
		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]
5	CD_3CN	3.4 [54]	3.4 [54]	3.7 [52]	3.9 [50]	3.8 [51]	3.6 [53]
5	CD_3OD	3.1 [57]	3.1 [57]	5.1 [40]	4.4 [46]	4.4 [46]	5.6 [40]
5p	$CDCl_3$	2.4 [64]	2.4 [64]	8.4 [152]	7.8 [147]	7.8 [147]	9.0 [157]
5p	CD_3COCD_3	1.7 [74]	2.1 [68]	9.2 [159]	8.2 [150]	8.4 [152]	9.1 [158]
5p	CD_3OD	2.4 [64]	2.2 [66]	9.0 [157]	8.1 [149]	8.3 [151]	9.0 [157]

(Fig. 8). Therefore, the OTBDPS group is easier to axially orient than the OTIPS group when it is the only substituent on the cyclohexane ring. On the contrary, when these silyloxy groups are placed side by side in a *trans*-adjacent manner, the OTIPS/OTIPS repulsion increased more than that of OTBDPS/OTBDPS (Fig. 2).[5] In the multifunctionalized case, the functionalities except for the silyloxy groups are likely to affect the ring conformation.

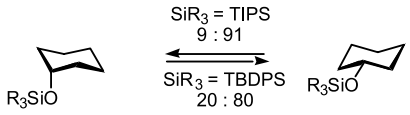


Figure 8. Conformational equilibrium of trialkylsilyloxycyclohexanes in CD_2Cl_2 at 179–188 K.[17]

One of the most important observations is that all the 3,4-bis-*O*-silylated *myo*-inositol derivatives, **1**–**3** and **1p**–**3p** maintained the equatorial-rich chair form in contrast to the ring conformation of the 4,5-bis-*O*-silylated compounds. In *myo*-inositol, both the side-functionalities of the 4- and 5-positions are in the *trans*-relationship. In contrast, one side of the 3,4-bis-*O*-silyloxy derivatives, that is, the 2-position, is in the *cis*-relationship. In these cases, rotation of the C-3–O bond let the bulky silyl group escape into a space in the 2-equatorial direction (Fig. 9) reducing the silyloxy/silyloxy repulsion. In the bis-4,5-*O*-silylated compounds, there is no such space to reduce the repulsion. In the equatorial-rich chair form, the silyloxy/silyloxy repulsion is enhanced when they are located in the center of the contiguous *trans*-hydroxy groups.[15] Because each ring conformation would be the result of a balance between the 1,3-diaxial interactions with the 1,2-diequatorial silyloxy/silyloxy interactions, the bis-4,5-*O*-silylated derivatives, **5**, **6**, and, **6p** are in the axial-rich chair form.

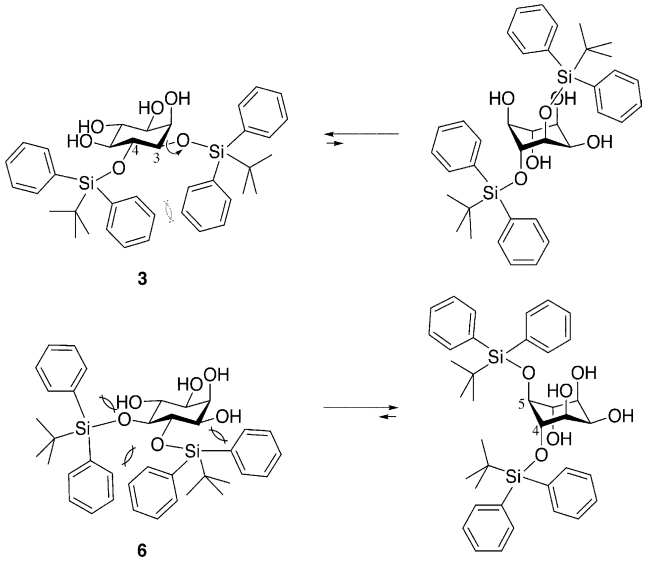


Figure 9.

3. Conclusion

Two adjacent bulky silyloxy groups can flip a cyclohexane-ring into the axial-rich chair form even it is multi-functionalized, as in these reported results. Compounds **5**, **6**, and **6p** are the first axial-rich chair *myo*-inositol derivatives isolated in the pure form, although the ring flip of inositols itself has been previously observed in solution.[18] As well as the famous ring conformation of the *all-trans*-1,2,3,4,5,6-hexaisopropylcyclohexane reported by Biali and co-workers,[19] the flipped compounds are also the counter examples to the general stability of equatorial-rich chair six-membered rings. It is noteworthy that the introduction and removal of the silyl protecting groups switch the ring conformation, that is, the conformation of the multi-functionalized cyclohexane ring has become controllable.

The cyclohexane-ring of *myo*-inositol was flipped into the axial-rich chair form when the TIPS or TBDPS groups were introduced into the 4- and 5-hydroxy groups. In contrast, when the bulky silyl groups were introduced into the 3- and 4-positions, the equatorial-rich chair forms were retained regardless of the variety of the silyloxy groups. This observation displayed an enhanced silyloxy/silyloxy repulsion as expected due to the oxygen functionalities on both sides of the adjacent silyloxy groups. It may be possible to state that the introduction of TBDPS groups will flip the cyclohexane ring when the silylating vicinal hydroxy groups are in the center of the contiguous four equatorial hydroxy groups.

4. Experimental

4.1. General method and materials

All commercially available reagents were used without further purification. All moisture and air sensitive reactions were performed under a positive pressure of argon in a glassware equipped with rubber septa. The glassware was dried under reduced pressure by heating with a heat-gun before use. When necessary, the solvents and reagents were distilled prior to use and were transferred using a syringe or cannula. The reaction mixture was magnetically stirred.

Thin layer chromatography was performed on Merck precoated silica gel 60 F-254 plates or Merck RP-19 F-254 plates. Column chromatography was performed on Merck silica gel 60 (0.063–0.200 mm) or Merck silica gel 60 230–400 mesh for ordinary phase or Nacalai tesque cosmosil 140C18-PREP for reverse phase. Spots were detected by dipping in a solution of 2% anisaldehyde, 5% H_2SO_4 in EtOH or a solution of 10% phosphomolybdic acid in EtOH followed by heating at ca. 200 °C.

The melting points were determined using a Yanagimoto micro-melting point apparatus. The infrared (IR) spectra were recorded on JASCO FT/IR-5300 or 8000 instruments and the major absorbance bands are all reported in wavenumber (cm^{-1}). The nuclear magnetic resonance (NMR) spectra were recorded on α-JEOL 400, Varian UNITY 300 and JEOL JNM-ECA 300 instruments. The spectral settings for the proton (^1H) NMR were as follows: 8.0 kHz spectral width, 32768 data points, 4.10 sec acquisition time, 0.24 Hz digital resolution for the α-JEOL 400; 4.5 kHz spectral width, 64000 data points, 7.11 sec acquisition time, 0.14 Hz digital resolution for the Varian UNITY 300; and 5.6 kHz spectral width, 32768 data points,

5.81 sec acquisition time, 0.17 Hz digital resolution for the JEOL JNM-ECA 300. Chemical shifts of the NMR spectra are reported in δ units downfield from tetramethylsilane. The ^{1}H NMR data are indicated by a chemical shift with the multiplicity, the coupling constants, the integration, and the assignment in parentheses in this order. The multiplicities are abbreviated as s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet, and br: broad. The ^{13}C NMR data are reported as the chemical shift with the hydrogen multiplicity obtained from the DEPT spectra and the number of carbons in parentheses. When the number of carbons could not be analyzed due to heavy overlapping, the number is not indicated. High-resolution mass spectra (HRMS) were obtained on either JEOL JMS-T100LC or a JEOL JMS-700 spectrometer for electrospray ionization (ESI) or fast atom bombardment ionization (FAB) and are reported in units of mass to charge.

4.2. Preparation of the 3,4-bis-*O*-silylated *myo*-inositol derivatives

4.2.1. 1,2,5,6-tetra-*O*-Benzyl-3,4-bis-*O*-(4-methoxybenzyl)-*myo*-inositol (11). NaH (60% in oil, 180 mg, 4.50 mmol) was added to a stirring solution of 5,6-di-*O*-benzyl-3,4-bis-*O*-(4-methoxybenzyl)-*myo*-inositol (**7**)[8] (900 mg, 1.50 mmol) in DMF (5 mL) at room temperature. After stirring for 2 h at room temperature, BnBr (769 mg, 4.50 mmol) was added. After stirring for 10 h at room temperature, the reaction was quenched with saturated NH_4Cl (30 mL). The aqueous mixture was extracted with CH_2Cl_2 (3×10 mL). The combined organic layer was successively washed with water and brine. The combined organic layer was dried over $MgSO_4$, filtered through a cotton-pad, and evaporated. The resulting residue was purified by silica gel chromatography (30 g of SiO_2 eluted with hexane/AcOEt=100/0 to 6/1) to give **11** (791 mg, 68%) as a white powder. mp. 96–98 °C; IR (KBr, disk) ν_{max} (cm^{-1}) 3100, 3080, 3030, 2913, 2838, 1615, 1514, 1454, 1358, 1250, 1096, 1036, 824, 733, 696; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40–7.19 (m, 24H), 6.87–6.78 (m, 4H), 4.90 (d, J=10.8 Hz, 1H), 4.87 (s, 4H), 4.83 (d, J=10.5 Hz, 1H), 4.81 (d, J=10.5 Hz, 1H), 4.74 (d, J=10.2 Hz, 1H), 4.65 (d, J=11.7 Hz, 1H), 4.62 (d, J=6.3 Hz, 1H), 4.56 (d, J=4.8 Hz, 1H), 4.53 (d, J=11.1 Hz, 1H), 4.07 (dd, J=9.6, 9.6 Hz, 1H), 4.05 (dd, J=9.6, 9.6 Hz, 1H), 4.00 (dd, J=2.1, 2.1 Hz, 1H), 3.82 (s, 3H), 3.78 (s, 3H), 3.45 (dd, J=9.3, 9.3 Hz, 1H), 3.34 (dd, J=9.9, 2.1 Hz, 1H), 3.32 (dd, J=9.9, 2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.0 (s, 1C), 138.9 (s, 1C), 138.4 (s, 1C), 131.1 (s, 1C), 130.5 (s, 1C), 129.7 (d), 129.1 (d), 128.3 (d), 128.1 (d), 128.0 (d), 127.7 (d), 127.5 (d), 127.4 (d), 127.3 (d), 113.7 (d, 4C), 83.7 (d, 1C), 81.7 (d, 1C), 81.4 (d, 1C), 80.9 (d, 1C), 80.7 (d, 1C), 75.8 (t, 1C), 75.5 (t, 1C), 74.4 (d, 1C), 74.1 (t, 1C), 72.7 (t, 1C), 72.4 (t, 1C), 55.2 (q, 2C); HRMS-ESI (m/z) $[M+Na]^+$ calcd for $C_{50}H_{52}NaO_8$, 803.3560; found, 830.3563.

4.2.2. 1,2,5,6-tetra-*O*-Benzyl-*myo*-inositol (8). DDQ (1.05 g, 4.66 mmol) was added to a stirring solution of **11** (1.66 g, 2.12 mmol) in CH_2Cl_2/H_2O (17/1, 20 mL) at room temperature. After stirring for 45 min at room temperature, the reaction mixture was filtered through a cotton-Celite pad and evaporated. The resulting residue was purified by silica gel chromatography (75 g of SiO_2 eluted with hexane/AcOEt=2/1 to 1/1) to give **8** (885 mg, 77%) as a white powder. mp. 162–164 °C; IR (KBr, disk) ν_{max} (cm^{-1}) 3387, 3100, 3080, 3040, 2909, 2890, 1453, 1445, 1354, 1132, 1049, 1026, 727, 694; ^{1}H NMR (C_6D_6, 300 MHz) δ 7.40–7.08 (m, 20H), 4.97 (d, J=11.7 Hz, 2H), 4.94 (d, J=11.1 Hz, 1H), 4.85 (d, J=11.7 Hz, 1H), 4.81 (d, J=11.1 Hz, 1H), 4.74 (d, J=11.7 Hz, 1H), 4.42 (d, J=12.3 Hz, 1H), 4.37 (d, J=12.0 Hz, 1H), 4.15 (dd, J=9.6, 9.3 Hz, 1H, H-6), 3.92 (dd, J=9.3, 9.3 Hz, 1H, H-4), 3.84 (dd, J=2.4, 2.1 Hz, 1H, H-2), 3.27 (dd, J=9.3, 9.3 Hz, 1H, H-5), 3.18 (dd, J=9.6, 2.1 Hz, 1H, H-1), 3.15 (dd, J=9.3, 2.4 Hz, 1H, H-3), 2.17 (br, 1H), 2.10 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.6 (s, 3C), 138.1 (s, 1C), 128.5 (d), 128.4 (d), 128.3 (d), 128.1 (d), 128.0 (d), 127.9 (d), 127.7 (d), 127.6 (d), 83.0 (d, 1C), 81.4 (d, 1C), 81.3 (d, 1C), 77.2 (d, 1C), 75.7 (t, 1C), 75.4 (t, 1C), 74.8 (t, 1C), 73.9 (d, 1C), 73.1 (t, 1C), 72.1 (d, 1C); HRMS-FAB (m/z) $[M+H]^+$ calcd for $C_{34}H_{37}O_6$, 541.2590; found, 541.2583.

4.2.3. 1,2,5,6-tetra-*O*-Benzyl-3,4-bis-*O*-*tert*-butyldimethylsilyl-*myo*-inositol (1p). TBSOTf (176 mg, 0.665 mmol) was added to a stirring solution of **8** (90 mg, 0.17 mmol) and 2,6-lutidine (356 mg, 3.33 mmol) in DMF (2 mL). After stirring for 1 h at 100 °C, the reaction mixture was cooled to room temperature and diluted with hexane. The mixture was successively washed with water and brine. The organic layer was dried over $MgSO_4$, filtered through a cotton-pad, and evaporated. The resulting residue was purified by silica gel chromatography (5 g of SiO_2 eluted with hexane/AcOEt=100/0 to 50/1) to give **1p** (120 mg, 94%) as colorless syrup. IR (NaCl, thin film) ν_{max} (cm^{-1}) 3034, 2930, 2859, 1726, 1456, 1360, 1256, 1130, 1069, 839, 777, 735, 696; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45–7.17 (m, 20H), 5.00–4.64 (m, 8H), 4.11 (dd, J=9.3, 9.0 Hz, 1H, H-4), 4.05 (dd, J=9.6, 9.3 Hz, 1H, H-6), 3.85 (dd, J=2.1, 2.1 Hz, 1H, H-2), 3.44 (dd, J=9.6, 2.1 Hz, 1H, H-1), 3.43 (dd, J=9.3, 2.1 Hz, 1H, H-3), 3.25 (dd, J=9.3, 9.0 Hz, 1H, H-5), 0.91 (s, 9H), 0.89 (s, 9H), 0.10–0.00 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 140.0 (s, 1C), 139.4 (s, 1C), 138.9 (s, 1C), 138.5 (s, 1C), 128.4 (d), 128.2 (d), 128.1 (d), 128.0 (d), 127.9 (d), 127.7 (d), 127.3 (d), 127.1 (d), 127.0 (d), 126.7 (d), 84.3 (d, 1C), 82.6 (d, 1C), 80.9 (d, 1C), 80.2 (d, 1C), 75.7 (t, 1C), 75.2 (t, 1C), 74.6 (t, 1C), 74.5 (d, 1C), 73.2 (d, 1C), 72.8 (t, 1C), 26.5 (q, 6C), 18.4 (s, 2C), 18.1 (s, 1C), −2.9 (q, 1C), −3.6 (q, 1C), −3.7 (q, 1C), −4.2 (q, 1C); HRMS-FAB (m/z) $[M+H]^+$ calcd for $C_{46}H_{65}O_6Si_2$, 769.4320; found, 769.4341.

4.2.4. 1,2,5,6-tetra-*O*-Benzyl-3,4-bis-*O*-triisopropylsilyl-*myo*-inositol (2p). TIPSOTf (138 mg, 0.450 mmol) was added to a stirring solution of **8** (50 mg, 0.090 mmol) in 2,6-lutidine (248 mg, 2.32 mmol) at 100 °C. After stirring for 12 h at 100 °C, the reaction mixture was cooled to room temperature, and then diluted with CH_2Cl_2 (10 mL). The mixture was successively washed with water (3 mL) and brine (3 mL). The organic layer was dried over $MgSO_4$, filtered through a cotton-pad, and evaporated. The resulting residue was purified by silica gel chromatography (15 g of SiO_2 eluted with hexane/AcOEt=100/0 to 30/1) to give **2p** (65 mg, 83%) as colorless syrup. IR (KBr, disk) ν_{max} (cm^{-1}) 3090, 3060, 3020, 2946, 2866, 1458, 1130, 1090, 1065, 1026, 883, 735, 685; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40–7.13 (m, 20H), 5.13 (d, J=11.7 Hz, 1H), 5.08 (d,

J=12.0 Hz, 1H), 4.88 (d, J=10.5 Hz, 1H), 4.74 (d, J=12.0 Hz, 1H), 4.73 (d, J=12.0 Hz, 1H), 4.68 (d, J=12.3 Hz, 1H), 4.66 (d, J=12.0 Hz, 1H), 4.61 (d, J=10.5 Hz, 1H), 4.34 (dd, J=9.3, 8.7 Hz, 1H, H-4), 4.06 (dd, J=9.3, 9.0 Hz, 1H, H-6), 3.95 (dd, J=2.4, 1.8 Hz, 1H, H-2), 3.66 (dd, J=9.3, 1.8 Hz, 1H, H-1), 3.48 (dd, J=9.3, 2.4 Hz, 1H, H-3), 3.27 (dd, J=9.0, 8.7 Hz, 1H, H-5), 1.08–0.99 (m, 42H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.6 (s, 1C), 139.5 (s, 1C), 138.7 (s, 1C), 138.4 (s, 1C), 128.4 (d), 128.2 (d), 128.0 (d), 127.9 (d), 127.8 (d), 127.7 (d), 127.4 (d), 127.0 (d), 126.8 (d), 126.7 (d), 126.3 (d), 84.2 (d, 1C), 83.3 (d, 1C), 81.6 (d, 1C), 79.4 (d, 1C), 75.4 (t, 1C), 74.5 (d, 1C), 74.1 (t, 1C), 73.9 (d, 1C), 73.7 (t, 1C), 72.8 (t, 1C), 18.5 (q, 3C), 18.4 (q, 9C), 13.8 (d, 6C); HRMS-FAB (m/z) $[M+H]^+$ calcd for $C_{52}H_{77}O_6Si_2$, 853.5259; found, 853.5245.

4.2.5. 1,2,5,6-tetra-*O*-Benzyl-3,4-bis-*O*-*tert*-butyldiphenylsilyl-*myo*-inositol (3p). TBDPSOTf (144 mg, 0.371 mmol) was added to a stirring solution of **8** (45 mg, 0.083 mmol) in 2,6-lutidine (178 mg, 1.66 mmol) at 100 °C. After stirring for 7 h at 100 °C, the reaction mixture was cooled to room temperature, and then water (5 mL) was added. The aqueous mixture was extracted with hexane (3× 5 mL). The organic layer was successively washed with water (3 mL) and brine (3 mL). The organic layer was dried over $MgSO_4$, filtered through a cotton-pad, and evaporated. The resulting residue was purified by silica gel chromatography (3 g of SiO_2 eluted with hexane/AcOEt=80/1 to 40/1) to give **3p** (72 mg, 85%) as colorless syrup. IR (KBr, disk) ν_{max} (cm^{-1}) 3069, 3050, 3030, 2932, 2859, 1427, 1360, 1113, 824, 737, 696; ^{1}H NMR (C_6D_6, 300 MHz) δ 8.10–6.65 (m, 40H), 5.03 (dd, J=8.4, 8.1 Hz, 1H, H-4), 4.80 (d, J=12.0 Hz, 1H), 4.73 (d, J=12.0 Hz, 1H), 4.71 (d, J=12.0 Hz, 1H), 4.65 (d, J=12.0 Hz, 1H), 4.17 (d, J=11.4 Hz, 1H), 4.14 (dd, J=8.4, 1.8 Hz, 1H, H-3), 4.10 (d, J=12.0 Hz, 1H), 4.06 (d, J=12.0 Hz, 1H), 4.00 (dd, J=8.7, 8.4 Hz, 1H, H-6), 3.96 (d, J=11.7 Hz, 1H), 3.58 (dd, J=3.0, 1.8 Hz, 1H, H-2), 3.46 (dd, J=8.4, 8.1 Hz, 1H, H-5), 3.13 (dd, J=8.7, 3.0 Hz, 1H, H-1), 1.27 (s, 9H), 1.22 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 139.4 (s, 1C), 139.3 (s, 1C), 138.7 (s, 1C), 138.4 (s, 1C), 136.3 (d, 1C), 136.2 (d, 1C), 135.9 (d, 1C), 135.8 (d, 1C), 135.2 (s, 1C), 135.1 (s, 1C), 133.6 (s, 1C), 133.5 (s, 1C), 129.8 (d), 129.6 (d), 129.0 (d), 128.9 (d), 128.1 (d), 128.0 (d), 127.8 (d), 127.6 (d), 127.5 (d), 127.4 (d), 127.3 (d), 127.2 (d), 127.1 (d), 127.0 (d), 126.7 (d), 126.6 (d), 126.2 (d), 83.7 (d, 1C), 82.6 (d, 1C), 81.3 (d, 1C), 75.9 (d, 1C), 74.7 (d, 1C), 74.6 (d, 1C), 74.5 (t, 1C), 72.7 (t, 1C), 72.3 (t, 1C), 71.9 (t, 1C), 27.5 (q, 3C), 27.2 (q, 3C), 19.9 (s, 1C), 19.2 (s, 1C); HRMS-ESI (m/z) $[M+Na]^+$ calcd for $C_{66}H_{73}O_6Si_2$, 1017.4946; found, 1017.4961.

4.2.6. 3,4-bis-*O*-*tert*-Butyldimethylsilyl-*myo*-inositol (1).[12] $Pd(OH)_2$ on C (20 wt %, 329 mg, 0.470 mmol) was added to a stirring solution of **1p** (120 mg, 0.160 mmol) in THF (1 mL). The atmosphere of the flask was replaced with H_2, and the mixture was stirred for 15 days under H_2. The reaction mixture was filtered through a cotton-Celite pad, and the filtrate was evaporated. The resulting residue was purified by silica gel chromatography (3 g of SiO_2 eluted with hexane/AcOEt=1/1) to give **1** (7.9 mg, 12%) as a white powder. mp. 94–97 °C; IR (ZnSe, thin film) ν_{max} (cm^{-1}) 3574, 3214, 2924, 2884, 2855, 2361, 1643, 1472, 1373, 1256, 1132, 1065, 1018, 860, 835, 777, 721, 669; ^{1}H NMR (400 MHz, CD_3CN) δ 3.87 (dd, J=2.9, 2.7 Hz, 1H, H-2), 3.70 (dd, J=9.0, 8.8 Hz, 1H, H-6), 3.51 (dd, J=9.0, 2.7 Hz, 1H, H-1), 3.47 (dd, J=9.5, 9.2 Hz, 1H, H-4), 3.30 (dd, J=9.5, 2.9 Hz, 1H, H-3), 3.05 (dd, J=9.2, 8.8 Hz, 1H, H-5), 0.91 (s, 9H), 0.90 (s, 9H), 0.11 (s, 6H), 0.10 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 76.2 (d, 1C), 75.3 (d, 1C), 75.1 (d, 1C), 74.2 (d, 1C), 74.1 (d, 1C), 72.6 (d, 1C), 26.7 (q, 2C), 26.6 (q, 4C), 19.0 (s, 1C), 18.9 (s, 1C), −2.8 (q, 1C), −3.3 (q, 1C), −3.5 (q, 1C), −4.2 (q, 1C); HRMS-FAB (m/z) $[M+H]^+$ calcd for $C_{18}H_{41}O_6Si_2$, 409.2442; found, 409.2439.

4.2.7. 3,4-bis-*O*-Triisopropylsilyl-*myo*-inositol (2).[12] Same procedure as the debenzylation of **1p** was performed starting from **2p** (147 mg, 0.172 mmol) with $Pd(OH)_2$ on C (20 wt%, 363 mg, 0.517 mmol) in THF (1 mL). The reaction needed 17 days. Purification was performed by silica gel chromatography (3 g of SiO_2 eluted with hexane/AcOEt=3/1 to 1/1) to give **2** (40 mg, 48%) as colorless syrup. IR (ZnSe, thin film) ν_{max} (cm^{-1}) 3385, 2946, 2868, 2361, 2342, 1466, 1385, 1256, 1121, 1059, 1015, 943, 920, 883, 829, 806, 712, 681, 652; ^{1}H NMR (400 MHz, CD_3CN) δ 3.94 (dd, J=8.1, 8.1 Hz, 1H, H-4), 3.93 (dd, J=2.9, 2.9 Hz, 1H, H-2), 3.77 (dd, J=8.1, 2.9 Hz, 1H, H-3), 3.54 (dd, J=8.5, 8.5 Hz, 1H, H-6), 3.36 (dd, J=8.5, 2.9 Hz, 1H, H-1), 3.20 (dd, J=8.5, 8.1 Hz, 1H, H-5), 1.26–1.08 (m, 42H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 75.2 (d, 1C), 75.0 (d, 1C), 73.7 (d, 1C), 73.6 (d, 1C), 73.1(d, 1C), 69.5 (d, 1C), 18.4 (q, 4C), 18.3 (q, 8C), 13.2 (d, 3C), 13.1 (d, 3C); HRMS-FAB (m/z) $[M+H]^+$ calcd for $C_{24}H_{53}O_6Si_2$, 493.3381; found, 493.3383.

4.2.8. 3,4-bis-*O*-*tert*-Butyldiphenylsilyl-*myo*-inositol (3).[12] Same procedure as the debenzylation of **1p** was performed starting from **3p** (347 mg, 0.340 mmol) with $Pd(OH)_2$ on C (20 wt%, 719 mg, 1.00 mmol) in THF (2 mL). The reaction needed 8 days. Purification was performed by silica gel chromatography (20 g of SiO_2 eluted with hexane/AcOEt=4/1 to 2/1) to give **3** (52 mg, 23%) as colorless syrup along with 2-*O*-benzyl-3,4-bis-*O*-TBDPS-*myo*-inositol (54 mg, 24%) as pale yellow syrup. Data for **3**: IR (ZnSe, thin film) ν_{max} (cm^{-1}) 3418, 3073, 3050, 2932, 2892, 2859, 1472, 1427, 1113, 1061, 1006, 939, 826, 741, 704; ^{1}H NMR (400 MHz in CD_3CN) δ 7.75–7.66 (m, 8H), 7.45–7.35 (m, 12H), 4.17 (dd, J=7.4, 7.2 Hz, 1H, H-4), 4.14 (dd, J=7.4, 2.7 Hz, 1H, H-3), 3.66 (dd, J=2.8, 2.7 Hz, 1H, H-2), 3.46 (dd, J=7.9, 7.6 Hz, 1H, H-6), 3.33 (dd, J=7.6, 7.2 Hz, 1H, H-5), 3.28 (dd, J=7.9, 2.8 Hz, 1H, H-1), 1.03 (s, 9H), 0.90 (s, 9H); ^{13}C NMR (100 MHz in $CDCl_3$) δ 136.0 (d, 2C), 135.9 (d, 2C), 135.7 (d, 2C), 135.4 (d, 2C), 133.3 (s, 1C), 132.9 (s, 1C), 138.2 (s, 1C), 132.5 (s, 1C), 130.1 (d, 1C), 130.0 (d, 2C), 129.9 (d, 1C), 127.9 (d, 4C), 127.8 (d, 2C), 127.7 (d, 2C), 75.5 (d, 1C), 75.1 (d, 1C), 73.1 (d, 1C), 73.0 (d, 1C), 72.9 (d, 1C), 67.7 (d, 1C), 27.1 (q, 6C), 19.2 (s, 2C); HRMS-FAB (m/z) $[M+Na]^+$ calcd for $C_{38}H_{48}NaO_6Si_2$, 679.2887; found, 679.2886. Data for 2-*O*-benzyl-3,4-bis-*O*-TBDPS-*myo*-inositol: IR (ZnSe, thin film) ν_{max} (cm^{-1}) 3445, 3073, 3050, 2932, 2894, 2859, 1723, 1472, 1428, 1393, 1271, 1111, 1061, 1007, 824, 758, 704, 611; ^{1}H NMR (400 MHz, CD_3CN) δ 7.72–7.63 (m, 8H), 7.45–7.25 (m, 17H), 4.51 (d, J=12.2 Hz, 1H), 4.38 (d, J=12.2 Hz, 1H), 4.33 (dd, J=6.3, 6.3 Hz, 1H, H-4), 4.21 (dd,

J=6.3, 1.5 Hz, 1H, H-3), 3.62–3.56 (br m, 2H, H-1, H-6), 3.52 (br s, 1H, H-2), 3.45 (br m, 1H, H-5), 1.02 (s, 9H), 0.93 (s, 9H); ^{13}C NMR (100 MHz in $CDCl_3$) δ 137.6 (s, 1C), 136.5 (d), 136.2 (d), 136.0 (d), 135.5 (d), 133.0 (s, 1C), 132.0 (s, 1C), 131.9 (s, 1C), 131.8 (s, 1C), 130.1 (d), 129.8 (d), 129.6 (d), 128.3 (d), 127.9 (d), 127.8 (d), 127.7 (d), 127.5 (d), 127.4 (d), 74.7 (d, 1C), 73.5 (d, 1C), 73.1 (d, 2C), 71.6 (d, 2C), 70.4 (t, 1C), 27.0 (q, 3C), 26.8 (q, 3C), 19.0 (s, 1C), 18.9 (s, 1C); HRMS-ESI (*m/z*) $[M+Na]^+$ calcd for $C_{45}H_{54}NaO_6Si_2$, 769.3357; found 769.3327.

4.3. Preparation of the 4,5-bis-*O*-silylated *myo*-inositol derivatives

4.3.1. 1,2,3,6-tetra-*O*-Benzyl-4,5-bis-*O*-(4-methoxybenzyl)-*myo*-inositol (12).[12] NaH (60% in oil, 190 mg, 4.74 mmol) was added to a stirring solution of 3,6-di-*O*-benzyl-4,5-bis-*O*-(4-methoxybenzyl)-*myo*-inositol (**9**)[11] (950 mg, 1.58 mmol) in DMF (5 mL) at room temperature. After stirring for 2 h at room temperature, BnBr (811 mg, 4.74 mmol) was added. After stirring for 5 h at room temperature, the reaction was quenched with saturated NH_4Cl (30 mL). The aqueous mixture was extracted with CH_2Cl_2 (3×10 mL). The combined organic layer was successively washed with water (5 mL), and brine (5 mL). The combined organic layer was dried over $MgSO_4$, filtered through a cotton-pad, and evaporated. The resulting residue was purified by silica gel chromatography (30 g of SiO_2 eluted with hexane/AcOEt=100/1 to 4/1) to give **12** (1.21 g, 98%) as a white powder. mp. 76–78 °C; IR (KBr, disk) ν_{max} (cm^{-1}) 3100, 3070, 3030, 3005, 2920, 1615, 1514, 1454, 1360, 1252, 1173, 1130, 1092, 1038, 822, 739, 696; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.42–7.25 (m, 26H), 6.84–6.81 (m, 4H), 4.92–4.57 (m, 12H), 4.09–4.01 (m, 3H), 3.79 (s, 3H), 3.78 (s, 3H), 3.44 (dd, J=9.3, 9.3 Hz, 1H), 3.34 (dd, J=9.3, 9.3 Hz, 1H), 3.33 (dd, J=9.9, 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.1 (s, 1C), 139.0 (s, 1C), 138.4 (s, 1C), 131.1 (s, 1C), 129.7 (d), 129.4 (d), 128.4 (d), 128.1 (d), 128.0 (d), 127.8 (d), 127.6 (d), 127.3 (d), 113.8 (d, 8C), 83.5 (d, 1C), 81.8 (d, 1C), 81.5 (d, 1C), 81.0 (d, 2C), 75.8 (t, 1C), 75.6 (t, 1C), 75.5 (t, 1C), 74.4 (d, 1C), 74.1 (t, 1C), 72.8 (t, 2C), 55.3 (q, 2C); HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{50}H_{52}NaO_8$, 803.3560; found, 803.3544.

4.3.2. 1,2,3,6-tetra-*O*-Benzyl-*myo*-inositol (10).[12] DDQ (2.67 g, 11.8 mmol) was added to a stirring solution of **22** (4.18 g, 5.35 mmol) in CH_2Cl_2/H_2O (17/1, 50 mL) at room temperature. After stirring for 6 h at room temperature, the reaction mixture was filtered through a cotton-Celite pad. The mixture was diluted with CH_2Cl_2 (100 mL) and successively washed with saturated $NaHCO_3$ (20 mL) and brine (20 mL). The organic layer was dried over $MgSO_4$, filtered through a cotton-pad, and evaporated. The resulting residue was purified by silica gel chromatography (120 g of SiO_2 eluted with hexane/AcOEt=6/1 to 1/1) to give **10** (2.37 g, 82%) as a white powder. mp. 83–85 °C; IR (KBr, disk) ν_{max} (cm^{-1}) 3549, 3422, 3063, 3030, 2899, 1454, 1364, 1200, 1115, 1063, 1030, 731, 696; ^{1}H NMR (C_6D_6, 300 MHz) δ 7.48–7.08 (m, 20H), 4.93 (d, J=11.4 Hz, 1H), 4.90 (d, J=12.3 Hz, 1H), 4.85 (d, J=11.4 Hz, 1H), 4.83 (d, J=12.3 Hz, 1H), 4.50 (d, J=12.0 Hz, 1H), 4.44 (s, 2H), 4.42 (d, J=12.0 Hz, 1H), 4.21 (dd, J=9.6, 9.3 Hz, 1H, H-4), 4.09 (dd, J=9.6, 9.3 Hz, 1H, H-6), 3.92 (dd, J=2.4, 2.4 Hz, 1H, H-2), 3.46 (dd, J=9.3, 9.3 Hz, 1H, H-5), 3.17 (dd, J=9.6, 2.4 Hz, 1H, H-1), 3.00 (dd, J=9.6, 2.4 Hz, 1H, H-3); ^{13}C NMR (C_6D_6, 100 MHz) δ 140.8 (s, 1C), 139.7 (s, 1C), 139.2 (s, 2C), 128.7 (d), 128.6 (d), 128.5 (d), 128.3 (d), 128.2 (d), 128.1 (d), 128.0 (d), 127.8 (d), 127.6 (d), 127.5 (d), 81.7 (d, 1C), 81.2 (d, 1C), 80.5 (d, 1C), 75.9 (d, 1C), 75.6 (t, 1C), 75.3 (d, 1C), 74.7 (t, 1C), 73.6 (d, 1C), 72.9 (t, 1C), 72.7 (t, 1C); HRMS-FAB (*m/z*) $[M+H]^+$ calcd for $C_{34}H_{37}O_6$, 541.2590; found, 541.2617.

4.3.3. 1,2,3,6-tetra-*O*-Benzyl-4,5-bis-*O*-*tert*-butyldimethylsilyl-*myo*-inositol (4p). TBSOTf (119 mg, 0.448 mmol) was added to a stirring solution of **10** (50 mg, 0.092 mmol) in 2,6-lutidine (248 mg, 2.32 mmol) at 120 °C. After stirring for 10 h at 120 °C, the reaction mixture was cooled to room temperature. Then the mixture was diluted with water (10 mL). The aqueous mixture was extracted with hexane (3×5 mL) and successively washed with water (3 mL) and brine (3 mL). Then it was dried over $MgSO_4$, filtered through a cotton-pad, and evaporated. The resulting residue was purified by silica gel chromatography (6 g of SiO_2 eluted with hexane/AcOEt=100/0 to 30/1) to give **4p** (74 mg, 100%) as colorless syrup. IR (NaCl, thin film) ν_{max} (cm^{-1}) 3090, 3060, 3020, 2930, 2857, 1721, 1456, 1362, 1258, 1128, 1071, 1028, 839, 775, 735, 696; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.41–7.19 (m, 20H), 5.01 (d, J=11.7 Hz, 1H), 4.81 (d, J=11.7 Hz, 1H), 4.76 (d, J=11.7 Hz, 1H), 4.66 (d, J=11.7 Hz, 1H), 4.60 (d, J=12.0 Hz, 1H), 4.52 (d, J=12.0 Hz, 2H), 4.48 (d, J=11.7 Hz, 1H), 4.11 (dd, J=9.6, 8.7 Hz, 1H, H-4), 3.93 (dd, J=2.4, 2.1 Hz, 1H, H-2), 3.78 (dd, J=9.6, 9.3 Hz, 1H, H-6), 3.43 (dd, J=9.3, 8.7 Hz, 1H, H-5), 3.35 (dd, J=9.6, 2.4 Hz, 1H, H-1), 3.11 (dd, J=9.6, 2.1 Hz, 1H, H-3), 0.89 (s, 9H), 0.88 (s, 9H), 0.14 (s, 3H), 0.10 (s, 6H), 0.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 139.6 (s, 1C), 139.4 (s, 1C), 138.3 (s, 1C), 138.2 (s, 1C), 128.2 (d), 128.1 (d), 127.9 (d), 127.7 (d), 127.5 (d), 127.4 (d), 127.3 (d), 127.0 (d), 126.7 (d), 81.7 (t, 1C), 81.5 (t, 1C), 81.3 (t, 1C), 74.8 (t, 1C), 74.3 (t, 1C), 74.1 (d, 1C), 73.1 (d, 1C), 72.7 (t, 1C), 72.4 (t, 1C), 26.7 (q, 6C), 18.3 (s, 1C), 18.2 (s, 1C), −1.9 (q, 1C), −2.1 (q, 1C), −3.0 (q, 1C), −3.1 (q, 1C); HRMS-FAB (*m/z*) $[M+H]^+$ calcd for $C_{46}H_{65}O_6Si_2$, 769.4320; found, 769.4324.

4.3.4. 1,2,3,6-tetra-*O*-Benzyl-4,5-bis-*O*-triisopropylsilyl-*myo*-inositol (5p). TIPSOTf (138 mg, 0.450 mmol) was added to a stirring solution of **10** (50 mg, 0.090 mmol) in 2,6-lutidine (248 mg, 2.32 mmol) at 100 °C. After stirring for 12 h at 100 °C, the reaction mixture was cooled to room temperature, and then diluted with CH_2Cl_2 (10 mL). It was successively washed with water (3 mL), and brine (3 mL). The organic layer was dried over $MgSO_4$, filtered through a cotton-pad, and evaporated. The resulting residue was purified by silica gel chromatography (15 g of SiO_2 eluted with hexane/AcOEt=100/0 to 30/1) to give **5p** (71 mg, 90%) as a white powder. mp. 80–81 °C; IR (KBr, disk) ν_{max} (cm^{-1}) 3030, 3000, 2942, 2865, 1638, 1458, 1355, 1127, 1086, 885, 720, 696, 670; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35–7.22 (m, 20H), 5.15 (d, J=12.3 Hz, 1H), 4.82 (d, J=12.3 Hz, 1H), 4.60 (d, J=12.0 Hz, 3H), 4.56 (d, J=11.4 Hz, 1H), 4.48 (d, J=11.4 Hz, 1H), 4.40 (d, J=11.7 Hz, 1H), 4.23 (dd, J=8.4, 7.8 Hz, 1H, H-4), 4.09 (dd, J=2.4, 2.4 Hz, 1H, H-2), 3.88 (dd, J=9.0, 7.8 Hz, 1H,

H-6), 3.68 (dd, J=7.8, 7.8 Hz, 1H, H-5), 3.51 (dd, J=9.0, 2.4 Hz, 1H, H-1), 3.26 (dd, J=8.4, 2.4 Hz, 1H, H-3), 1.13–1.00 (m, 42H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.8 (s, 1C), 139.3 (s, 1C), 138.3 (s, 1C), 138.2 (s, 1C), 128.3 (d), 128.1 (d), 127.9 (d), 127.7 (d), 127.5 (d), 127.4 (d), 127.3 (d), 127.2 (d), 127.1 (d), 126.7 (d), 126.5 (d), 82.0 (d, 1C), 81.4 (d, 1C), 81.3 (d, 1C), 76.8 (d, 1C), 74.8 (d, 1C), 73.7 (t, 1C), 73.4 (t, 1C), 72.9 (d, 1C), 72.3 (t, 1C), 71.2 (t, 1C), 18.6 (q, 3C), 18.5 (q, 3C), 18.4 (q, 3C), 18.3 (q, 3C), 13.9 (d, 3C), 13.8 (d, 3C); HRMS-FAB (m/z) $[M+H]^+$ calcd for $C_{52}H_{77}O_6Si_2$, 852.5229; found, 853.5247.

4.3.5. 1,2,3,6-tetra-*O*-Benzyl-4,5-bis-*O*-*tert*-butyldiphenylsilyl-*myo*-inositol (6p). TBDPSOTf (86 mg, 0.22 mmol) was added to a stirring solution of **10** (30 mg, 0.055 mmol) and 2,6-lutidine (118 mg, 1.10 mmol) in DMF (0.5 mL) at 100 °C. After stirring for 1.5 h at 100 °C, the reaction mixture was cooled to room temperature. Water (5 mL) was added and the aqueous mixture was extracted with hexane (3×5 mL). The organic layer was successively washed with water (3 mL) and brine (3 mL). Then it was dried over $MgSO_4$, filtered through a cotton-pad, and evaporated. The resulting residue was successively purified by silica gel chromatography (3 g of SiO_2 eluted with hexane/AcOEt=100/0 to 10/1) and by a reverse phase chromatography (6 g of cosmosil 140C18-PREP eluted with MeOH) to give **6p** (70 mg, 100%) as a white powder. The single crystal used for the X-ray diffraction study was obtained by cooling the hot solution of **6p** in EtOH. mp 115.0–117.0 °C; IR (KBr, disk) ν_{max} (cm^{-1}) 3060, 2920, 2857, 1142, 1117, 1057, 815, 790, 737, 698; ^{1}H NMR (C_6D_6, 300 MHz) δ 7.84–7.05 (m, 40H), 4.78 (ddd, J=3.6, 3.3, 1.2 Hz, 1H, H-4), 4.73 (d, J=11.7 Hz, 1H), 4.59 (d, J=12.3 Hz, 1H), 4.58 (d, J=11.7 Hz, 1H), 4.54 (dd, J=3.6, 3.3 Hz, 1H, H-5), 4.53 (d, J=12.3 Hz, 1H), 4.25 (d, J=12.0 Hz, 1H), 4.23 (d, J=12.3 Hz, 1H), 4.23 (dd, J=3.6, 2.7 Hz, 1H, H-2), 4.15 (ddd, J=4.8, 3.6, 1.2 Hz, 1H, H-6), 4.03 (d, J=12.0 Hz, 1H), 4.02 (d, J=12.3 Hz, 1H), 3.98 (dd, J=4.8, 2.7 Hz, 1H, H-1), 3.76 (dd, J=3.6, 3.6 Hz, 1H, H-3), 1.06 (s, 9H), 1.05 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.2 (s, 1C), 139.1 (s, 1C), 134.1 (s, 1C), 134.0 (s, 1C), 129.5 (d), 129.4 (d), 129.3 (d), 129.2 (d), 128.1 (d), 128.0 (d), 127.9 (d), 127.7 (d), 127.5 (d), 127.4 (d), 127.3 (d), 127.1 (d), 127.0 (d), 126.9 (d), 126.6 (d), 81.1 (d, 1C), 79.1 (d, 1C), 78.2 (d, 1C), 74.6 (d, 1C), 74.4 (d, 1C), 73.9 (d, 1C), 72.6 (t, 1C), 71.8 (t, 1C), 71.7 (t, 1C), 71.1 (t, 1C), 26.8 (q, 6C), 19.3 (s, 1C), 19.1 (s, 1C); HRMS-FAB (m/z) $[M+H]^+$ calcd for $C_{66}H_{73}O_6Si_2$, 1017.4946; found, 1017.4959.

4.3.6. 4,5-bis-*O*-*tert*-Butyldimetylsilyl-*myo*-inositol (4). Same procedure as the debenzylation of **1p** was performed starting from **4p** (720 mg, 0.940 mmol) with $Pd(OH)_2$ on C (20 wt%, 1.97 g, 2.80 mmol) in THF (5 mL). The reaction needed 4 days under 100 atm of H_2 at room temperature. Purification was performed by silica gel chromatography (25 g of SiO_2 eluted with hexane/AcOEt=4/1 to 1/1) to give **4** (118 mg, 31%) as a white powder. mp. 121–123 °C; IR (ZnSe, thin film) ν_{max} (cm^{-1}) 3445, 2932, 2859, 1472, 1389, 1254, 1117, 1053, 937, 837, 777, 692; ^{1}H NMR (400 MHz in CD_3CN) δ 3.86 (dd, J=3.4, 3.4 Hz, 1H, H-2), 3.79 (dd, J=7.2, 7.1 Hz, 1H, H-4), 3.63 (dd, J=7.4, 3.4 Hz, 1H, H-1), 3.62 (dd, J=7.2, 3.4 Hz, 1H, H-3), 3.57 (dd, J=7.4, 7.1 Hz, 1H, H-6), 3.49 (dd, J=7.1, 7.1 Hz, 1H, H-5), 0.91 (s, 18H), 0.12–0.11 (m, 12H); ^{13}C NMR (100 MHz in $CDCl_3$) δ 74.3 (d, 1C), 73.8 (d, 1C), 73.7 (d, 1C), 73.6 (d, 1C), 72.3 (d, 1C), 65.6 (d, 1C), 25.7 (q, 6C), 17.9 (s, 1C), 17.8 (s, 1C), −4.8 (q, 1C), −4.9 (q, 2C), −5.0 (q, 1C); HRMS-FAB (m/z) $[M+H]^+$ calcd for $C_{18}H_{41}O_6Si_2$, 409.2442; found, 409.2449.

4.3.7. 4,5-bis-*O*-Triisopropylsilyl-*myo*-inositol (5). Same procedure as the debenzylation of **1p** was performed starting from **5p** (43 mg, 0.050 mmol) with $Pd(OH)_2$ on C (20 wt%, 106 mg, 0.150 mmol) in THF (1 mL). The reaction needed 11 days. Purification was performed by silica gel chromatography (6 g of SiO_2 eluted with hexane/AcOEt=6/1 to 4/1) to give **5** (8.5 mg, 35%) as a white powder. mp. 86–88 °C; IR (ZnSe, thin film) ν_{max} (cm^{-1}) 3420, 2943, 2868, 2361, 2339, 1464, 1385, 1256, 1061, 883, 825, 764, 683; ^{1}H NMR (400 MHz, CD_3CN) δ 4.27 (ddd, J=3.9, 3.7, 1.7 Hz, 1H, H-4), 4.02 (dddd, J=3.9, 3.8, 1.0, 0.9 Hz, 1H, H-5), 3.96 (ddd, J=3.8, 3.6, 1.7 Hz, 1H, H-6), 3.94 (dd, J=3.4, 3.4 Hz, 1H, H-2), 3.83 (ddd, J=3.7, 3.4, 0.7 Hz, 1H, H-3), 3.80 (ddd, J=3.6, 3.4, 1.0 Hz, 1H, H-1), 1.25–1.10 (m, 42H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 74.8 (d, 1C), 74.2 (d, 1C), 74.0 (d, 2C), 72.2 (d, 1C), 64.8 (d, 1C), 18.1 (q, 6C), 18.0 (q, 6C), 12.2 (d, 6C); HRMS-FAB (m/z) $[M+H]^+$ calcd for $C_{24}H_{53}O_6Si_2$, 493.3381; found, 493.3384.

4.3.8. 4,5-bis-*O*-*tert*-Butyldiphenylsilyl-*myo*-inositol (6). Same procedure as the debenzylation of **1p** was performed starting from **6p** (490 mg, 0.480 mmol) with $Pd(OH)_2$ on C (20 wt%, 203 mg, 0.290 mmol) in THF (5 mL). The reaction needed 9.5 days. Purification was performed by silica gel chromatography (15 g of SiO_2 eluted with hexane/AcOEt=4/1 to 3/1) to give **6** (149 mg, 50%) as a white powder. mp. 58–61 °C; IR (NaCl, thin film) ν_{max} (cm^{-1}) 3517, 3073, 2930, 2859, 1472, 1427, 1113, 820, 748, 694; ^{1}H NMR (CD_3CN, 300 MHz) δ 7.62–7.58 (m, 2H), 7.53–7.32 (m, 14H), 7.28–7.22 (m, 4H), 4.18 (ddd, J=3.6, 3.3, 1.8 Hz, 1H, H-4), 4.05 (dddd, J=3.3, 3.3, 0.9, 0.9 Hz, 1H, H-5), 4.00 (dd, J=3.3, 3.3 Hz, 1H, H-2), 3.95 (ddd, J=3.6, 3.3, 1.8 Hz, 1H, H-6), 3.84 (dd, J=3.6, 3.3 Hz, 1H, H-1), 3.59 (dd, J=3.6, 3.3 Hz, 1H, H-3), 0.90 (s, 9H), 0.88 (s, 9H); ^{13}C NMR (CD_3CN, 100 MHz) δ 136.7 (d, 4C), 136.6 (d, 2C), 136.5 (d, 2C), 134.2 (s, 1C), 134.0 (s, 1C), 133.8 (s, 1C), 133.7 (s, 1C), 131.0 (d, 1C), 130.9 (d, 2C), 130.7 (d, 1C), 128.8 (d, 2C), 128.7 (d, 2C), 128.6 (d, 4C), 76.5 (d, 1C), 74.9 (d, 1C), 74.8 (d, 1C), 74.6 (d, 1C), 74.4 (d, 1C), 65.9 (d, 1C), 27.2 (q, 6C), 19.6 (s, 1C), 19.5 (s, 1C); HRMS-FAB (m/z) $[M+H]^+$ calcd for $C_{38}H_{49}O_6Si_2$, 657.3068; found, 657.3039.

4.4. X-ray diffraction study of 6p

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[20] and refined by a full-matrix least-squares method on F2 with SHELXS-97.[21] 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 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk). Data of the analysis are follows: $C_{66}H_{72}O_6Si_2$, $M=1017.46$, crystal size $0.5\times0.3\times0.2$ mm, triclinic, space group $\bar{P}1$, $a=11.75$, $b=13.45$, $c=20.10$ 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, $R=0.082$, $wR=0.224$, GOF$=1.164$.

Acknowledgements

Financial supports by the Naito Foundation (Japan), the Sunbor Grant (Suntory Institute for Bioorganic Research, Japan), and 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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10. Hydrogenation of **3p** afforded 2-*O*-benzyl-3,4-bis-*O*-TBDPS-*myo*-inositol in 24% yield along with the full debenzylated **3**.
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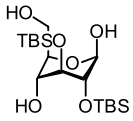

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