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The first ring inversion of pyranoses induced by bulky silyl protections at the 2- and 3-positions

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Abstract—The pyranose rings of the 2,3-bis-*O*-*tert*-butyldiphenylsilyl-α- and β-D-glucopyranoses, and of the 2,3-bis-*O*-*tert*-butyldimethylsilyl-β-D-glucopyranose were in the $^1C_4$ form. These findings indicate that the introduction of bulky silyl protecting groups at the 2- and 3-positions can flip a pyranose ring into the axial-rich chair form. Previous such ring inversions have been carried out by the silyl protections at the 3- and 4-positions.

A pair of adjacent bulky silyloxy groups on a pyranose or a pyranoside ring sometimes keeps the ring in the chair form with more axial substituents (the axial-rich chair form). Despite the fact that dozens of such examples have been found so far, previous stable axial-rich conformers always possess the bulky silyloxy groups at least on the C-3 and C-4 positions;[1,2] that is, it has not been observed that a stable axial-rich chair form is induced by the silyloxy groups only on the C-2 and C-3 positions (Fig. 1).[3]

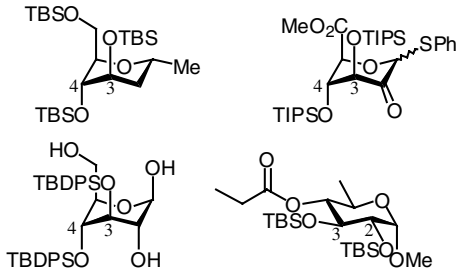
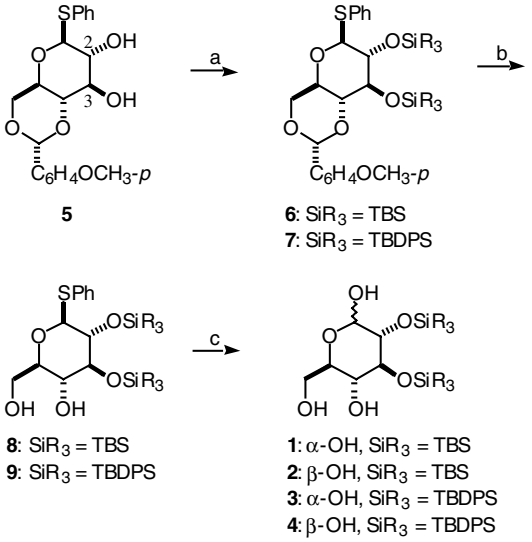


Figure 1. Examples of the stable $^1C_4$ conformers containing silyloxy groups at the 3- and 4-positions,[1a,g,2d] and an example that the 2,3-bis-*O*-silylated compounds retain the $^4C_1$ form.[3]

As a part of our study regarding the ring conformations of six-membered rings possessing bulky silyloxy groups,[1d,g,4,5] we investigated the ring conformation of the silyl-protected D-glucopyranoses **1**–**4** (Scheme 1), which have *tert*-butyldimethylsilyl (TBS) or *tert*-butyldiphenylsilyl (TBDPS) groups on the O-2 and O-3. In this



Scheme 1. Reagents and conditions: (a) TBSOTf or TBDPSOTf, DMF, 2,6-lutidine, 100 °C; (b) *p*-TsOH·H_2O, THF/MeOH (1:1), rt, 70% for **8** (from **5** via **6**), 50% for **9** (from **5** via **7**); (c) NBS, THF/H_2O (1:1), rt, 74% for **1** and **2** (from **8**), 83% for **3** and **4** (from **9**).

Keywords: Ring conformation; $^1C_4$; Pyranose ring; D-Glucose; Bulky silyl protections.
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Table 1. ^{1}H NMR coupling constants and NOESY correlation of **1**–**4**, **10**, and **11**

Compound	Anomer	Protecting group at the 2,3-positions	$^3J_{HH}$ (Hz)[a]				W-coupling (Hz) (position)	NOESY correlation
			H-1–H-2	H-2–H-3	H-3–H-4	H-4–H-5		
1[b]	α	TBS	3.3	8.9	8.5	9.9	—	—
2[b]	β	TBS	1.9	2.1	1.6	2.9	0.8 (H-1–H-3), 0.7 (H-2–H-4)	—
3[b]	α	TBDPS	1.0	2.9	1.5	0.0	1.4 (H-2–H-4)	H-1–H-6
4[b]	β	TBDPS	2.9	2.1	1.0	3.2	0.8 (H-1–H-3), 1.4 (H-2–H-4)	C-1–O*H*–H-6
10[c]	α	—	3.8	9.9	9.6	9.6	—	—
11[c]	β	—	8.0	9.2	9.1	9.8	—	—

[a] At room temperature.
[b] In acetone-d_6.
[c] In D_2O.

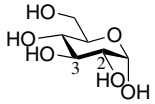
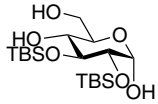
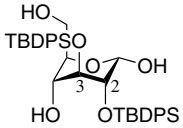
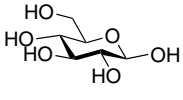
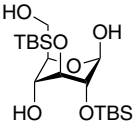
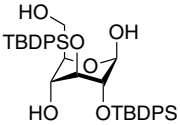
communication, we describe that the introduction of bulky silyl protecting groups to the 2- and 3-positions can flip the ring conformation into the axial-rich chair form.

Compounds **1**–**4** were prepared as follows (Scheme 1). The direct introduction of the two TBS or the two TBDPS groups to the 2- and 3-hydroxy groups of phenyl 4,6-*O*-*p*-methoxybenzylidene-1-thio-β-D-glucopyranoside (**5**)[6] was possible by using the corresponding silyl triflates to provide the bis-silylated **6** and **7**, followed by removal of the *p*-methoxybenzylidene group to afford diols **8** and **9**, respectively.[7,8] The hydrolysis of the phenylthio group of **8** gave anomeric mixtures of the 2,3-bis-*O*-TBS-glucopyranoses **1** and **2** (74:26). Similarly, **9** afforded a mixture of **3** and **4** (63:37). Since these anomeric mixtures cannot be separated, further investigations into the ring conformation were performed using these mixtures.

The anomeric stereochemistries and the ring conformations of **1**–**4** were determined based on the coupling constants in the ^{1}H NMR and NOESY spectra. Table 1 summarizes the vicinal ($^3J_{HH}$) and the w-shaped long-range coupling constants ($^4J_{HH}$), and NOESY correlations. Corresponding data of the α- and β-D-glucopyranoses (**10** and **11**) are also included for comparison.[9] In the anomeric mixture of the bis(TBS)-protected **1** and **2**, the coupling constants of the major isomer were substantially similar to the data of **10**. Therefore, the major isomer was the α-one (**1**) which is in the equatorial-rich chair form, and the minor was the β-isomer (**2**). The large coupling constant between the H-1 and H-2 of the β-glucose **11** was narrowed to 1.9 Hz in **2**, and the other coupling constants were also small. Furthermore, the w-couplings between H-1 and H-3 and between H-2 and H-4 were observed. Therefore, **2** was the β-isomer in the $^1C_4$ conformation (Table 2). In the mixture of the bis(TBDPS)-protected **3** and **4**, both the major and minor isomers showed small vicinal coupling constants and the w-couplings. Therefore, both the α- and β-isomers were in the axial-rich chair form. Thus, the anomeric stereochemistries were determined by NOESY spectra as the major one was the α-isomer (**3**) and the minor was the β-one (**4**), because correlations between H-1 and H-6 and between the hydrogen of the anomeric hydroxy group and H-6 were observed in the major and the minor isomers, respectively. The ring conformations of these α-isomers, therefore, were in the equatorial-rich chair form when the TBS groups were introduced into O-2 and O-3, and in the axial-rich chair form when the TBDPS groups were introduced. Ring conformation of the corresponding β-isomers, **2** and **4**, were both the axial-rich chair forms.[10]

As is the case with the corresponding 3,4-derivatives,[1g] the introduction of the TBDPS groups at the 2- and 3-positions also flipped the pyranose rings into the axial-rich chair form (**3** and **4**). In contrast, the ring conformations of the corresponding bis(TBS)-protected compounds were affected by the anomeric stereochemistry (**1** and **2**). It has been believed that a steric repulsion

Table 2. Ring conformations of the 2,3-bis-*O*-silylated glucopyranoses **1**–**4**, **10**, and **11**

Anomer	Protecting group at the 2- and 3-positions		
	None	TBS	TBDPS
α	 **10**	 **1**	 **3**
β	 **11**	 **2**	 **4**

of adjacent bis-*O*-TBS groups is too small to flip the six-membered rings,[1d,g,2d] and indeed, pyranoses possessing TBS groups at the 3- and 4-positions were in the $^4C_1$ form regardless of their anomeric stereochemistry.[1g] However, the ring of the β-isomer **2** was in the axial-rich chair form. The ring inversion of **2** would be caused by the supports of the anomeric effect and the increased steric hindrance due to the serious equatorial/equatorial interaction not only by the two silyloxy groups but also by each silyloxy group and the adjacent hydroxy group (the C-1 and the C-4 positions) when the ring was the equatorial-rich chair form.[5a] Anyway, it is noteworthy that the introduction of just two TBS groups flipped the pyranose.

In conclusion, we investigated the ring conformations of the four D-glucose derivatives that have bulky silyl protecting groups at the O-2 and O-3. In a previous study for such an axial-rich chair conformation observed in the pyranose and pyranoside rings, the silylation at the O-3 and O-4 was crucial. The stable axial-rich chair conformations described in this communication are the first ring inversion induced by the introduction of just two bulky silyl protecting groups at the 2- and 3-positions. Additionally, ring inversion of a pyranose due to the two TBS groups had not been previously observed, but the ring conformation of **2** indicates that it is possible. Ring inversion due to the protection of the 2- and 3-positions might enable to introduce other protecting groups or substituents than the silyl protecting group into the 1-, 4-, and 6-positions. Since such an axial rich ring conformation has been used for the substrate-controlled stereoselective reactions, these new observations would augment the applicable uses.

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10. The ring conformation of the phenylthio glucosides **8** and **9** were $^4C_1$ and skew boat form, respectively. Details of these conformations will be reported elsewhere.