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Tetrahedron Letters
Tetrahedron Letters 45 (2004) 5615–5618

# Ring conformations of D-glucose derivatives possessing two bulky silyl protecting groups at the 3,4-positions; the first observation of a stable full-axial chair conformer without bridge structures

Hidetoshi Yamada,* Koki Tanigakiuchi, Kohei Nagao, Kotaro Okajima and Tatsuya Mukae

*School of Science and Technology, Kwansei Gakuin University, 2-1 Gakuen, Sanda 669-1337, Japan*

Received 20 April 2004; revised 21 May 2004; accepted 26 May 2004
Available online 15 June 2004

**Abstract**—The ring conformations of 3,4-bis-*O*-*tert*-butyldimethylsilyl- and 3,4-bis-*O*-*tert*-butyldiphenylsilyl-D-glucopyranoses as well as the corresponding phenyl 1-thio-D-glucopyranosides were investigated. Observations showed that the introduction of the two *tert*-butyldiphenylsilyl groups can flip the pyranose-ring into the $^1C_4$ conformation possessing more axial substituents. All the substituents of the 3,4-bis-*O*-*tert*-butyldiphenylsilyl-β-D-glucopyranose were axially oriented.


The introduction of bulky trialkylsilyl or alkyldiarylsilyl protecting groups into adjacent diols on a tetrahydropyran ring sometimes flips the ring from a chair form with more equatorial substituents (equatorial-rich chair form) into another chair form that has more axial substituents (axial-rich chair form) (Fig. 1).[1,2] Although such conformational inversions have been used for substrate-controlled stereoselective synthetic reactions,[2,3] the relative thermodynamical stability in such ring-flips has not been rationalized. This communication reports the ring conformation of D-glucose derivatives bearing two *tert*-butyldimethylsilyl (TBS) or two *tert*-butyldiphenylsilyl (TBDPS) groups at the 3,4-positions. The first D-glucose derivative whose substituents are all oriented axially is also disclosed.

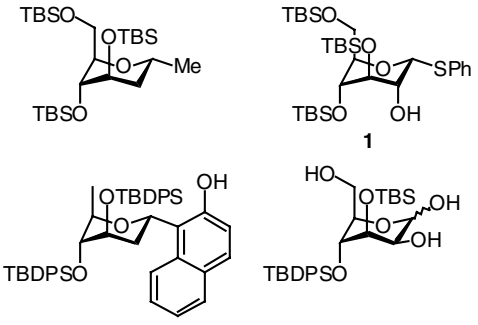


**Figure 1.** Examples of the stable conformers of tetrahydropyrane rings existing in the axial-rich chair form induced by two or more bulky trialkylsilyloxy groups.[1a,b,d,2]

We prepared the 3,4-bis-*O*-*tert*-butyldimethylsilyl- and 3,4-bis-*O*-*tert*-butyldiphenylsilyl-D-glucopyranoses **2**–**5** (Scheme 1) to investigate the ring conformations. We studied the ring conformation of the corresponding phenylthioglucosides **6**–**9** as well, which were the synthetic intermediates of **2**–**5**, because these compounds were comparable to the phenylthioglucoside **1** (Fig. 1) reported by Walford and co-workers, whose stable axial-rich chair conformation has already been established by X-ray crystallography.[1b]

Compounds **2**–**5** were synthesized as follows (Scheme 1). Discrimination of the 3,4-positions was achieved by applying van Boeckel's method using the 1,1,2,2-tetraisopropyldisiloxanyl (TIPDS) group.[4] Thus, the respective treatment of the phenyl 1-thio-D-glucopyranosides **10**[5] and **11**[6] with $TIPDSCl_2$ followed by migration of the generated 4,6-TIPDS protection into the 3,4-positions under acidic conditions provided **12** and **13**. Each

*Keywords*: Ring conformation; $^1C_4$; Pyranose ring; D-Glucose; Bulky silyl protecting groups.
* Corresponding author. Tel.: +81-79-565-8342; fax: +81-79-565-9077; e-mail: hidetosh@kwansei.ac.jp

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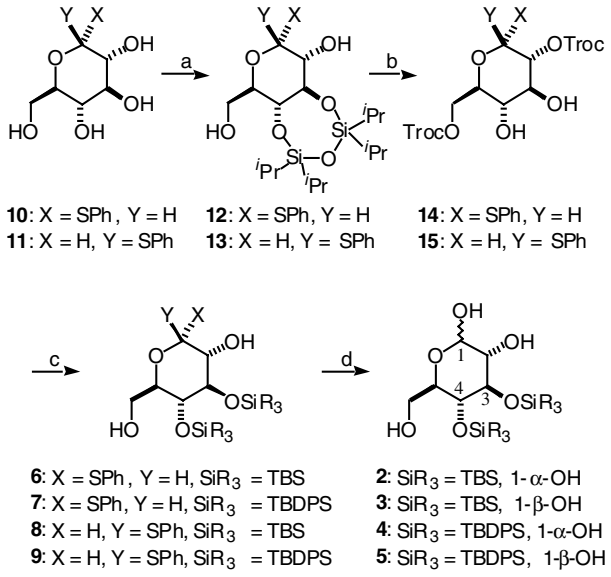
doi:10.1016/j.tetlet.2004.05.126




**10**: X = SPh, Y = H **12**: X = SPh, Y = H **14**: X = SPh, Y = H
**11**: X = H, Y = SPh **13**: X = H, Y = SPh **15**: X = H, Y = SPh

**6**: X = SPh, Y = H, $SiR_3$ = TBS **2**: $SiR_3$ = TBS, 1-α-OH
**7**: X = SPh, Y = H, $SiR_3$ = TBDPS **3**: $SiR_3$ = TBS, 1-β-OH
**8**: X = H, Y = SPh, $SiR_3$ = TBS **4**: $SiR_3$ = TBDPS, 1-α-OH
**9**: X = H, Y = SPh, $SiR_3$ = TBDPS **5**: $SiR_3$ = TBDPS, 1-β-OH

**Scheme 1.** Reagents and conditions: (a) $TIPDSCl_2$, pyridine, rt, then cat. *p*-TsOH, DMF, rt, 49% for **12** (from **10**) or 66% for **13** (from **11**); (b) TrocCl, TMEDA, $CH_2Cl_2$, rt then TBAF, AcOH, THF, rt, 58% for **14** (from **12**) or 96% for **15** (from **13**); (c) TBSOTf or TBDPSOTf, 2,6-lutidine, DMF, 60–100 °C, then Zn dust, AcOH, $Et_2O$, rt, 51% for **6** (from **14**), 27% for **7** (from **14**), 31% for **8** (from **15**), or 52% for **9** (from **15**); (d) NBS, THF/$H_2O$ (1:1), rt, 68% for **2** and **3** (from **8**) or 56% for **4** and **5** (from **9**).

compound was independently introduced the 1,1,1-trichloroethoxycarbonyl (Troc) groups[7] at the 2- and 6-positions followed by removal of the TIPDS group to give 3,4-diols **14** and **15**, respectively. The introduction of the TBS and TBDPS groups into the 3,4-diol of **14** followed by cleavage of the Troc groups provided **6** and **7**. Similar treatment of **15** afforded **8** and **9**. Hydrolysis of the phenylthio group of **8** and **9** produced anomeric mixtures of the desired 3,4-bis-*O*-TBS-glucopyranoses **2** and **3** (α:β = 60:40), and the corresponding bis(TBDPS)-protected **4** and **5** (α:β = 89:11), respectively.

The ring conformations of **2**–**9** were determined by $^1H$ NMR analyses. Table 1 summarizes the coupling constants due to the vicinal protons on each pyranose- or pyranoside ring.[8] The coupling constants of **1** (Fig. 1) and the nonsilylated **10** and **11** (Scheme 1) are also listed for comparison.[9] The coupling constants of **10** and **11** were observed in $CD_3OD$. Other compounds were recorded in acetone-$d_6$ because of the good separation of each signal.

The pyranoses protected by the two TBS groups, **2** and **3**, were in the $^4C_1$ form (Fig. 2). Although the coupling constants of **2** were smaller than those of the nonsilylated **10** (Table 1), the molecular model assembled based on the dihedral angles calculated by the Karplus equations indicated that the ring conformation of **2** was still in the range of the equatorial-rich chair ($^4C_1$) form, even though the ring was slightly flattened like a reclining chair.[10,11] The coupling constants of the β-isomer **3** were similar to those of **11**. Therefore, both pyranoses possessing TBS groups at the 3,4-positions, **2** and **3**, maintained the equatorial-rich chair form.

On the other hand, the pyranoses protected by the two TBDPS groups, **4** and **5**, existed in the $^1C_4$ conformation (Fig. 2), because the $^1H$ NMR spectra of **4** and **5** did not show large coupling constants due to the 1,2-diaxial protons (Table 1). The range of the coupling constants was substantially similar to those of **1** in which the $^1C_4$ conformation is confirmed by an X-ray study.[1b] The long range w-couplings between H-2 and H-4 and between H-3 and H-5 also supported the conformation in solution. It is noteworthy that all substituents on the pyranose ring of the β-isomer **5** were axially oriented, and this is the first observation of a stable 'full-axial' chair conformer of the D-glucose derivative without a bridge structure.[12]

Whereas the ring conformation of the pyranoses **2**–**5** differed in the use of the TBS or TBDPS groups, the ring conformations of the corresponding thioglucosides were

**Table 1.** Coupling constants in the $^1H$ NMR spectra of **1**–**11**

| Compound | Substituent at the anomeric position | Protecting groups at the 3,4-positions | $^3J_{HH}$ (Hz) | | | | W-coupling (Hz) (position) |
|---|---|---|---|---|---|---|---|
| | | | H-1–H-2 | H-2–H-3 | H-3–H-4 | H-4–H-5 | |
| **1**[a] | α-SPh | TBS[c] | 2.9 | 5.5 | 4.5 | 3.1 | 1.0 (H-2–H-4) |
| **2**[a] | α-OH | TBS | 3.1 | 7.0 | 6.3 | 6.3 | — |
| **3**[a] | β-OH | TBS | 7.0 | 8.4 | 7.6 | 8.6 | — |
| **4**[a] | α-OH | TBDPS | 2.2 | 5.2 | 2.7 | 1.5 | 1.5 (H-2–H-4), 0.8 (H-3–H-5) |
| **5**[a] | β-OH | TBDPS | 4.8 | 2.4 | 2.9 | 1.9 | 1.1 (H-2–H-4), 1.0 (H-3–H-5) |
| **6**[a] | α-SPh | TBS | 2.9 | 5.7 | 4.7 | 4.0 | 1.3 (H-2–H-4) |
| **7**[a] | α-SPh | TBDPS | 2.0 | 3.0 | 3.0 | 1.5 | 1.5 (H-2–H-4), 1.9 (H-3–H-5) |
| **8**[a] | β-SPh | TBS | 9.3 | 7.2 | 7.2 | 8.0 | — |
| **9**[a] | β-SPh | TBDPS | 7.8 | 1.2 | 3.3 | 1.2 | 1.2 (H-2–H-4), 1.2 (H-3–H-5) |
| **10**[b] | α-SPh | — | 5.2 | 10.0 | 8.8 | 10.0 | — |
| **11**[b] | β-SPh | — | 9.6 | 8.8 | 7.6 | 9.2 | — |

[a] In acetone-$d_6$.
[b] In $CD_3OD$.
[c] The compound possesses one more TBS group at O-6.

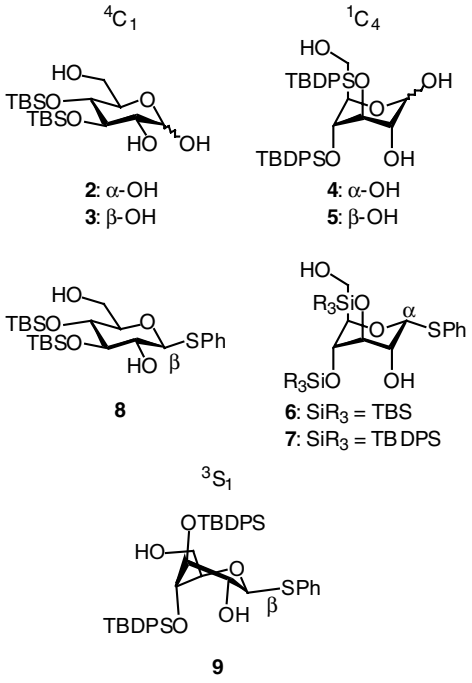



**Figure 2.** Ring conformation of 3,4-*O*-silylated D-glucose derivatives.

affected more by the configuration of the anomeric position than by the variation in the silyl groups. Thus, the coupling constants of the α-thioglucosides **6** and **7** (Table 1) were fundamentally similar to those of **1**, therefore, these rings were both in the $^1C_4$ conformation (Fig. 2). On the other hand, the ring of the β-isomers **8** and **9** were not in the axial-rich chair form. The coupling constants of **8** were similar to the data of the nonsilylated **11** indicating that the ring was in the range of $^4C_1$. In contrast, the coupling constants of **9** due to H-2–H-3, H-3–H-4, and H-4–H-5 were small, and two w-couplings due to H-2–H-4 and H-3–H-5 were observed. The coupling constant between H-1 and H-2, however, indicated that these protons were *trans*-diaxial. Based on this information, the ring of **9** would be in the skew form ($^3S_1$).[13,14] Therefore, the α-thioglucosides **6** and **7** were in the $^1C_4$ form with the equatorial phenylthio group. Similarly, the β-phenylthio groups of both **8** and **9** were equatorially oriented, and, for this reason, these rings were not in the $^1C_4$ form.

Jackson's group mentioned the reasons of the ring flip on the tris(TBS)-protected **1** (see Fig. 1) in their report, that is the *A*-value of the phenylthio group is not sufficiently large to force the other substituents axial,[15] and the adjacent TBS groups at C-3 and C-4 are more sterically encumbered when they are diequatorial than when they are diaxial.[1b] In our observations, the rings of the bis(TBS)-protected **2** and **3** were not in the $^1C_4$ (Fig. 2). In contrast, the corresponding bis(TBS)-protected α-phenylthioglucoside **6** was in the $^1C_4$ form. Thus, the steric repulsion of the adjacent *O*-TBS groups at the C-3 and C-4 itself is too short to flip the ring;[1d,2d,16] thus support of the phenylthio group achieved it.

In conclusion, the introduction of the two TBDPS groups at the 3,4-positions of the D-glucopyranose fundamentally flipped the ring into the axial-rich chair form, but use of the two TBS groups itself was too short to flip. Among the compounds prepared for this study, **5** showed that a glucose derivative can stably exist in the full-axial chair conformation without a bridge structure. The axial-rich chair form of **6** is seemingly the ring-flip induced by just two TBS groups, however, the cause of this stability is the support of the phenylthio group at the anomeric position.

## Acknowledgements

Financial support by the Naito Foundation (Japan), the Sunbor Grant (Suntory Institute for Bioorganic Research, Japan), and the Cosmetology Research Foundation (Japan) is gratefully acknowledged.

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