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An efficient method for preparing fully *O*-silylated pyranoses conformationally restricted in the unusual $^1C_4$-form

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Abstract—An efficient method for preparing fully *O*-silylated pyranoses, which are conformationally restricted in the unusual $^1C_4$-form, was developed. Thus, successive treatment of pyranosides, such as xylose and glucose derivatives, with NaH and TIPSOTf or TBSOTf in THF at room temperature gave the corresponding fully *O*-silylated products.

Effective protection of the hydroxyls of compounds is often essential for their efficient chemical transformations. Trialkylsilyl groups, such as triethylsilyl (TES), *tert*-butyldimethylsilyl (TBS) or triisopropylsilyl (TIPS) groups, are widely used for protecting hydroxyls owing to their ease of selective introduction and removal under mild reaction conditions.[1]

It has been recognized that introducing bulky silyl protecting groups at the 3,4-*trans*-hydroxy groups of pyranoses causes a flip of their conformation leading to an unusual $^1C_4$-form, in which the bulky substituents are in axial positions due to mutual steric repulsion.[2–5] Suzuki and co-workers first reported this conformational feature of 3,4-bis-*O*-silylated pyranosides and efficiently synthesized aryl α-*C*-glycosides using a conformation-flipped donor.[2] Later, we successfully constructed the tricyclic sugar moiety of the nucleoside antibiotic herbicidin B, via a facially selective hydrogenation of the enone system of a substrate, the conformation of which was effectively restricted by steric repulsion between the bulky silyl groups on the pyranose ring.[4] We also found that α-*C*-glucosides are stereoselectively prepared via intramolecular radical cyclization reactions when the conformation of the substrates is fixed in a $^1C_4$-form by introducing bulky silyl groups at the 3,4-*trans*-hydroxyls.[5] These results suggest that the conformationally flipped silylated sugars are highly useful intermediates for synthesizing various carbohydrates and related compounds. A drawback of this strategy is the rather lengthy process for producing the silylated sugars. These sugars are generally prepared via silylation of the glycals followed by further transformation of the 1,2-unsaturated moiety,[2,4,5] since direct silylation of the 3,4-*trans*-hydroxyls of pyranoses under usual silylation conditions have been unsuccessful, presumably because of the bulkiness of the silyl group.

In our continuous study on *C*-glycosidation reactions, we needed various conformationally flipped pyranoses, therefore, we planned to develop a straightforward method for preparing these useful *O*-silylated pyranoses having the unusual $^1C_4$-conformation.

We first investigated the direct introduction of TIPS groups at all three hydroxyls on phenyl 1-β-D-selenoxyloside (**1**), since 1-phenylseleno sugars are useful as donors in various glycosidation reactions. After examination of various reaction conditions,[6–8] we found that the successive treatment of **1** with NaH and TIPSOTf effectively gave the desired **3**.[9] Thus, after stirring **1** with NaH (10 equiv.) in THF for 10 min, the resulting mixture was subsequently treated with TIPSOTf (4.0 equiv.) at room temperature to give the fully-silylated product **3** in 78% yield, as shown in Scheme 1(a). In this reaction, the use of silyl triflates may be essential for completing the silylation; the reaction with TIPSCl, instead of the triflate, gave none of the fully silylated **3**. Phenyl 1-β-D-thioxyloside (**2**) was next used as a substrate. Treatment of 1-β-thioxyloside **2** under the same reaction conditions with NaH and TIPSOTf also afforded the desired 2,3,4-tris-*O*-TIPS-xyloside **4** in 85% yield (Scheme 1(a)).

Keywords: conformation; protecting groups; glycosides; silicon compounds.

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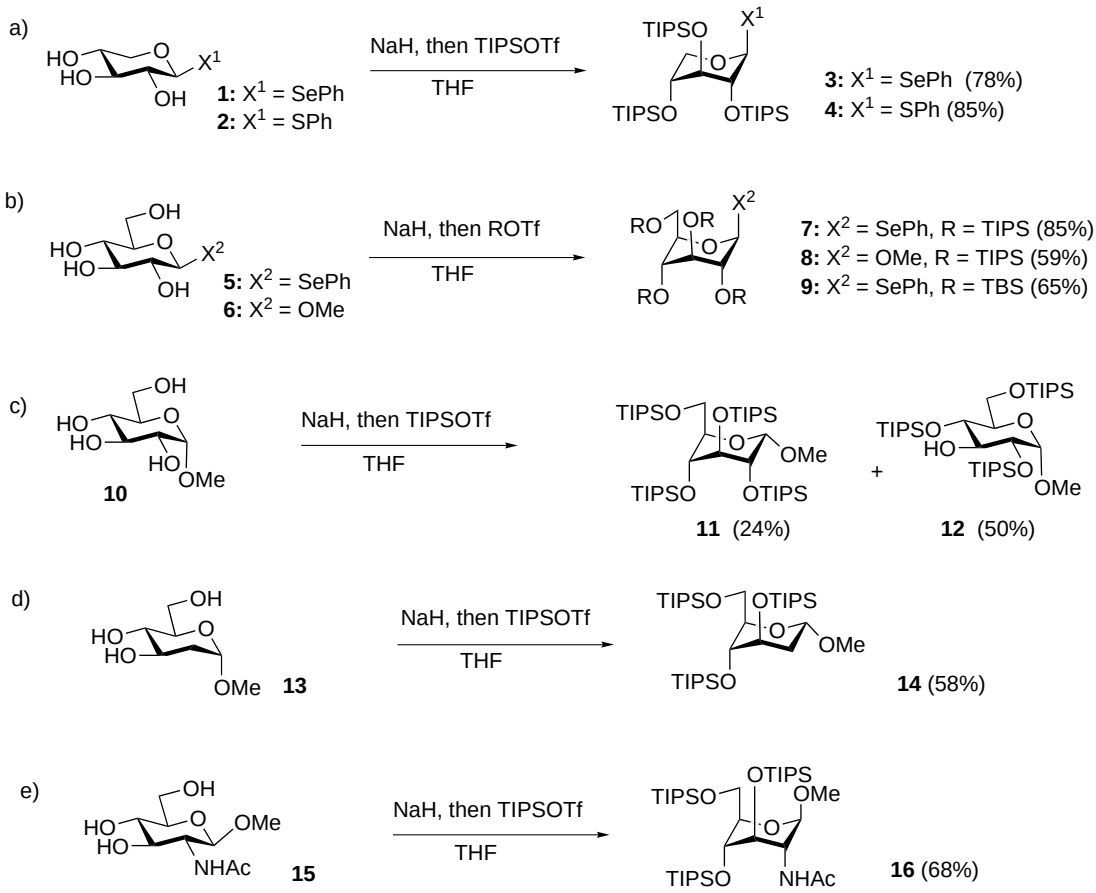

Scheme 1.

D-Glucopyranosides were next examined as the substrates in this reaction, as shown in Scheme 1(b) and (c). Phenyl 1-β-selenoglucoside (**5**) was treated by the above method with NaH (10 equiv.) and TIPSOTf (5.0 equiv.) to give the corresponding tetrakis-*O*-silylated products **7**[9] in 85% yield. The same treatment of methyl β-glucoside **6** also gave the tetrakis-*O*-silylated product **8** (59%). TBS groups were similarly introduced at all four hydroxyls of phenyl selenoglucoside **5** to produce **9** in 65% yield, when TBSOTf, instead of TIPSOTf, was used in this reaction system. On the other hand, similar treatment of methyl α-D-glucoside (**10**) with NaH and TIPSOTf also gave the fully silylated product **11** in 24% yield, where the 2,4,6-tris-*O*-silylated α-glucoside **12** was obtained as the major product in 50% yield.

The silylation reactions with other hexopyranoses having 3,4-*trans*-hydroxyl groups as a substrate were further investigated. When methyl α-D-2-deoxylglucoside (**13**) was treated under the silylation conditions, it gave the corresponding tris-*O*-TIPS product **14** in 58% yield. 1-*O*-Methyl-3,4,6-tris-*O*-TIPS-*N*-acetyl-D-glucosamine (**16**)[9] was successfully obtained in 68% yield by the same treatment of 1-β-*O*-methyl-*N*-acetyl-D-glucosamine (**15**). These results suggest that the pyranoses having an all-*trans*-substituted structure may be suitable to be fully silylated by this method.[10] Thus, we have confirmed that bulky silyl groups can be introduced at all of the free hydroxyls of pyranosides, such as xylose and glucose derivatives, on treatment with NaH followed by TBS- or TIPSOTf in THF at room temperature to give the corresponding fully *O*-silylated products. In carbohydrate chemistry, especially on pyranoses, silyl ethers have not been used so much for protecting the hydroxyls as esters, acetals, and ethers.[11] The likely reason is that, at least to some extent, simultaneous silylation of the hydroxyls on pyranoses has not been so easy. Therefore, these *O*-silylated sugars produced by the present method could be used effectively in carbohydrate chemistry.

Typical procedure: After a mixture of **5** (958 mg, 3.0 mmol) and NaH (60% in oil, 1.21 g, 30 mmol) in THF (20 mL) was stirred at room temperature for 10 min under argon, TIPSOTf (4.02 mL, 15.0 mmol) was slowly added over 20 min, and the resulting mixture was further stirred at the same temperature for 2 h. The usual work-up and purification by silica gel column chromatography (hexane/benzene) gave **7** (2.51 g, 85%) as an oil.

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6. When **1** was treated with TIPSOTf/2,6-lutidine in CH_2Cl_2, well known efficient conditions for the introduction of a bulky silyl group at sterically hindered hydroxyls (Corey, E. J.; Cho, H.; Rucker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455–3458) the corresponding 2,4-bis-*O*-TIPS product was obtained in 89% yield.
7. Treatment of **1** with KH and TIPSCl in the presence of 18-crown-6 in THF, which was reported to be effective in silylating extremely hindered alcohols (Braish, T. F.; Fuchs, P. L. *Synth. Commun.* **1986**, *16*, 111–115) resulted in many spots on TLC.
8. Successive treatment of **1** with BuLi (3.5 equiv.) and TIPSOTf (4.0 equiv.) in THF produced the desired fully silylated **3** in only 10% yield.
9. Physical data of the typical products are as follows. **3** (oil): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.58–7.24 (m, 5H, Ar), 5.66 (s, 1H, H-1), 4.58 (d, 1H, H-5a, $J=12.3$ Hz), 4.20 (s, 1H, H-3), 3.99 (s, 1H, H-2), 3.75 (s, 1H, H-4), 3.19 (d, 1H, H-5b, $J=12.3$ Hz), 1.08 (m, 63H, TIPS×3); HRMS (ESI) calcd for $C_{38}H_{74}O_4SeSi_3Na$ 781.3957 (MNa^+), found 781.3984. Anal. calcd for $C_{38}H_{74}O_4SeSi_3$: C, 60.20; H, 9.84. Found: C, 59.92; H, 9.59. **7** (oil): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.62–7.21 (m, 5H, Ar), 5.47 (d, 1H, H-1, $J=2.9$ Hz), 4.31 (br s, 1H, H-2), 4.25 (dd, 1H, H-6a, $J=6.0$, 9.9 Hz), 4.14 (br s, 1H, H-3), 4.04 (br s, 1H, H-4), 4.02 (m, 2H, H-5, H-6b). 1.06 (m, 84H, TIPS×4); HRMS (ESI) calcd for $C_{48}H_{96}O_5SeSi_4Na$ 967.5397 (MNa^+), found 967.5389. Anal. Calcd for $C_{48}H_{96}O_5SeSi_4{\cdot}H_2O$: C, 59.89; H, 10.26. Found: C, 59.57; H, 10.20. **16** (oil): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.56 (d, 1H, NH, $J=9.9$ Hz), 4.84 (d, 1H, H-1, $J=1.8$ Hz), 4.28 (ddd, 1H, H-2, $J=1.8$, 3.0, 9.9 Hz), 4.14 (m, 2H, H-6×2), 4.08 (dd, 1H, H-3, $J=2.0$, 3.0 Hz), 3.94 (dd, 1H, H-5, $J=8.5$, 11.4 Hz), 3.81 (d, 1H, H-4, $J=2.0$ Hz), 3.49 (s, 3H, OMe), 1.96 (s, 3H, OAc), 1.09–1.05 (m, 63H, TIPS×3); MS (ESI) m/z 727 (MNa^+). Anal. calcd for $C_{36}H_{77}NO_6Si_3$: C, 61.40; H, 11.02; N, 1.99. Found C, 61.33; H, 11.04; N, 1.80. The small $J_{2,3}$ and $J_{3,4}$ values of these silylated pyranosides in their ^{1}H NMR spectra showed that their conformations were restricted to the unusual $^1C_4$-form.
10. When methyl α-D-mannoside was used as a substrate in this reaction, none of the desired fully silylated product was obtained, where methyl 2,4,6-tris-*O*-TIPS-α-D-mannoside was obtained in 68% yield.
11. For example see: *Preparative Carbohydrate Chemistry*; Hanessian, S., Eds.; Marcel Dekker: New York, 1997.