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Highly β-Selective O-Glucosidation Due to the Restricted Twist-Boat Conformation

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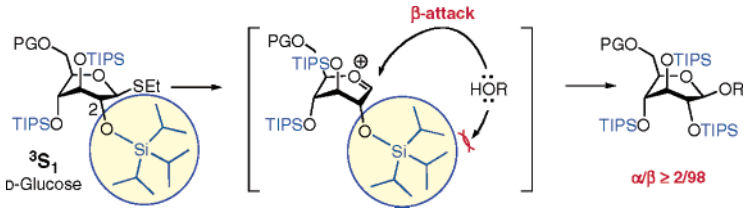
ABSTRACT



Ethyl 1-thio-2,3,4,6-tetrakis-*O*-triisopropylsilyl-β-D-glucopyranoside, ethyl 6-*O*-benzyl-1-thio-2,3,4-tris-*O*-triisopropylsilyl-β-D-glucopyranoside, and ethyl 6-*O*-pivaloyl-1-thio-2,3,4-tris-*O*-triisopropylsilyl-β-D-glucopyranoside induced highly β-selective O-glucosidations. Among them, the 6-O-pivaloylated substrate provided the best selectivity up to α/β = 3:97 with cyclohexylmethanol, and the substrate was used for glucosidations with secondary and tertiary alcohols in a highly β-selective manner. The selectivity would be caused by the twist-boat conformation of the pyranose; this is the first β-selective O-glucosidation based on conformational control of the pyranose ring.

The β-O-glucosidic linkage is an essential structure in numerous natural products containing sugar chains and glycosides of terpenes, steroids, polyphenols, and antibiotics. For the construction of the β-*O*-glucosides, neighboring group participation by a 2-*O*-acyl group has been the most reliable method.[1] When the acyl group cannot be employed due to the synthetic convenience, the benzyl-protected glycosyl donors have often been employed using S_N2-type reactions or the nitrile effect.[2]

However, the latter conditions have occasionally been affected by the steric character of both the glycosyl donors and acceptors; the high β-selectivity has not always appeared.[3] Therefore, the development of stereoselective glycosylations based on a new concept other than the traditional control, such as the participation of neighboring groups, solvent effects, or the properties of leaving groups, would make it flexible to design for the syntheses of the sugar-containing molecules.

A potential for such a new concept is the application of the conformational control of the pyranose rings of glycosyl donors. A six-membered ring has occasionally been in the chair conformation with more axial substituents when bulky trialkylsilyl groups were introduced into a suitable adjacent *trans*-diol.[4] When the six-membered ring is the pyranose of a sugar, such inversion drastically changes its steric and electronic circumstances around the anomeric center, hence it has been used to control the anomeric stereoselectivity during glycosidations.[5] We now report that ethylthioglucosides protected by triisopropylsilyl (TIPS) groups at the 2,3,4-oxygens, that is, ethyl 1-thio-2,3,4,6-tetrakis-*O*-TIPS-β-D-glucopyranoside (**1**), corresponding 6-O-benzylated **2**, and

(1) (a) Stachulski, A. V.; Jenkins, G. N. *Nat. Prod. Rep.* **1998**, *15*, 173−186. (b) Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503−1531.

(2) (a) Schmidt, R. R.; Michel, J. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 731−732. (b) Hashimoto, S.; Hayashi, M.; Noyori, R. *Tetrahedron Lett.* **1984**, *25*, 1379−1382. (c) Ito, Y.; Ogawa, T. *Tetrahedron Lett.* **1987**, *28*, 4701−4704. (d) Schmidt, R. R.; Behrendt, M.; Toepfer, A. *Synlett* **1990**, 694−696. (e) Vankar, Y. D.; Vankar, P. S.; Behrendt, M.; Schmidt, R. R. *Tetrahedron* **1991**, *47*, 9985−9992. (f) Hashihayata, T.; Mandai, H.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 169−178.

(3) (a) Yamada, H.; Nishizawa, M. *Tetrahedron Lett.* **1987**, *28*, 4315−4318. (b) Yu, B.; Tao, H. *Tetrahedron Lett.* **2001**, *42*, 2405−2407.

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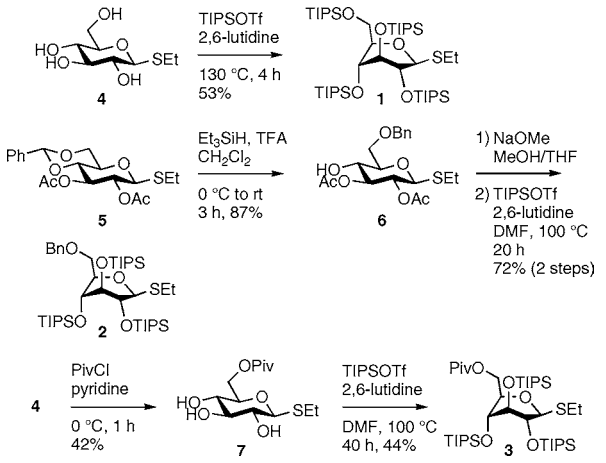
6-O-pivaloylated **3**, showed a highly β-selective O-glucosidation. Among them, **3** provided the best selectivity, which could be used for glucosidations with secondary and tertiary alcohols.

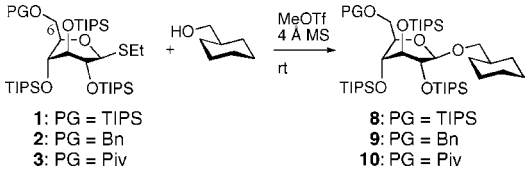
Scheme 1. Preparations of Compounds **1**−**3**



The substrates **1**−**3** were prepared as follows (Scheme 1). Treatment of ethyl 1-thio-β-D-glucopyranoside (**4**)[6] with TIPSOTf afforded **1** in 53% yield. The regioselective reductive cleavage of ethyl 2,3-di-*O*-acetyl-4,6-benzylidene-1-thio-β-D-glucopyranoside (**5**)[7] followed by the deacetylation of **6** and the introduction of the TIPS groups produced **2**. The regioselective pivaloylation of **4**, followed by the TIPS protections of the resulting triol **7**, afforded **3**.

As our preliminary investigations, the glycosidations with cyclohexylmethanol were examined (Table 1). Methyl triflate smoothly activated **1**−**3** to provide the corresponding cyclohexylmethyl glucosides **8**−**10** in a β-selective manner. Small amounts of respective glycals **11** were detected as the byproducts. The stereochemistries of the products were

Table 1. Glucosidation of Ethylthioglucosides Protected by TIPS Groups with Cyclohexylmethanol[a]

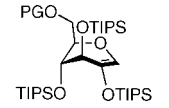


1: PG = TIPS
2: PG = Bn
3: PG = Piv

8: PG = TIPS
9: PG = Bn
10: PG = Piv

entry	glucosyl donor	solvent	time (h)	prod.	yield (%)	α/β ratio[b]
1	**1**	CH_2Cl_2	1.5	**8**	70	14/86
2	**1**	CH_2Cl_2−CH_3CN (3:2)[c]	1.5	**8**	45	11/89
3	**1**	Et_2O	22.0	**8**	77[d]	9/91
4	**1**	*n*-C_6H_{14}	35.5	**8**	73[e]	12/88
5	**1**	$PhCH_3$	7.3	**8**	73	9/91
6	**2**	CH_2Cl_2	1.5	**9**	85	9/91
7	**2**	$PhCH_3$	4.5	**9**	82	6/94
8	**3**	CH_2Cl_2	1.5	**10**	92	5/95
9	**3**	$PhCH_3$	11.0	**10**	84	3/97

[a] A small amount of **11** was detected as the byproduct.



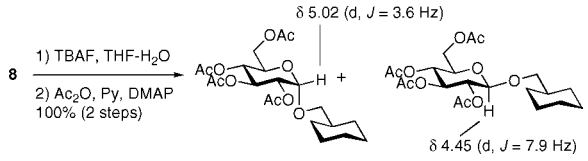
PG = TIPS, Bn, or Piv

11

[b] Determined on the basis of the ^{1}H NMR. [c] CH_3CN itself did not dissolve **1**. [d] Compound **1** remained (4%). [e] Compound **1** remained (5%).

unclear in this stage, but the anomeric ratios could be determined on the basis of the integral of the anomeric peaks in the ^{1}H NMR spectra. The structures of the products were clarified by further transformations, that is, the removal of the TIPS groups to return the ring back to the $^4C_1$ conformers, followed by the acetylation of the resulting hydroxy groups (Scheme 2).

Scheme 2. Clarification of the Structures of **8**[a]



[a] Similar clarifications of **9** and **10** are in the Supporting Information.

First, solvent effects were investigated, but the β-selectivity was unaffected (Table 1, entries 1−5). In CH_2Cl_2 (entry 1), the reaction was complete within 1.5 h and produced a 70% yield of the cyclohexylmethyl glucoside **8**. Although CH_3CN and Et_2O have displayed remarkable stereocontrol effects in previous glycosidations,[2b,c,8] the anomeric selectivity did not drastically change (entries 2 and 3). The use of Et_2O slightly increased the β-selectivity, but the reaction rate decreased. In *n*-hexane, the anomeric selectivity was similar

(4) For the ring inversions of pyranose derivatives: (a) Tius, M. A.; Busch-Peterson, J. *Tetrahedron Lett.* **1994**, *35*, 5181−5184. (b) Walford, C.; Jackson, R. F. W.; Rees, N. H.; Clegg, W.; Heath, S. L. *Chem. Commun.* **1997**, 1855−1856. (c) Yamada, H.; Nakatani, M.; Ikeda, T.; Marumoto, Y. *Tetrahedron Lett.* **1999**, *40*, 5573−5576. (d) Yamada, H.; Tanigakiuchi, K.; Nagao, K.; Okajima, K.; Mukae, T. *Tetrahedron Lett.* **2004**, *45*, 5615−5618. (e) Yamada, H.; Tanigakiuchi, K.; Nagao, K.; Okajima, K.; Mukae, T. *Tetrahedron Lett.* **2004**, *45*, 9207−9209. For the cyclohexane derivatives: (f) Marzabadi, C. H.; Anderson, J. E.; Gonzalez-Outeirino, J.; Gaffney, P. R. J.; White, C. G. H.; Tocher, D. A.; Todaro, L. J. *J. Am. Chem. Soc.* **2003**, *125*, 15163−15173. (g) Okajima, K.; Mukae, T.; Imagawa, H.; Kawamura, Y.; Nishizawa, M.; Yamada, H. *Tetrahedron* **2005**, *61*, 3497−3506.

(5) (a) Hosoya, T.; Ohashi, Y.; Matsumoto, T.; Suzuki, K. *Tetrahedron Lett.* **1996**, *37*, 663−666. (b) Ichikawa, S.; Shuto, S.; Matsuda, A. *J. Am. Chem. Soc.* **1999**, *121*, 10270−10280. (c) Ikeda, T.; Yamada, H. *Carbohydr. Res.* **2000**, *329*, 889−893. (d) Yamada, H.; Ikeda, T. *Chem. Lett.* **2000**, 432−433. (e) Futagami, S.; Ohashi, Y.; Imura, K.; Hosoya, T.; Ohmori, K.; Matsumoto, T.; Suzuki, K. *Tetrahedron Lett.* **2000**, *41*, 1063−1067. (f) Abe, H.; Shuto, S.; Matsuda, A. *J. Am. Chem. Soc.* **2001**, *123*, 11870−11882. (g) Tamura, S.; Abe, H.; Matsuda, A.; Shuto, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1021−1023. (h) Abe, H.; Terauchi, M.; Matsuda, A.; Shuto, S. *J. Org. Chem.* **2003**, *68*, 7439−7447.

(6) Vic, G.; Hastings, J. J.; Howarth, O. W.; Crout, D. H. G. *Tetrahedron: Asymmetry* **1996**, *7*, 709−720.

(7) Lu, S.; O'yang, Q.; Guo, Z.; Yu, B.; Hui, Y. *J. Org. Chem.* **1997**, *62*, 8400−8405.

to those of the others and the reaction rate decreased (entry 4). In toluene and ether, the β-selectivity increased, and the decrease in the reaction rate was lower. The anomeric selectivity was α/β = 14:86 to 9:91 in all cases with **1**; therefore, the anomeric selectivity of this reaction was not solvent-dependent.

The anomeric stereochemistry of the substrate did not affect the β-selectivity. Thus, the α-isomer of **1** similarly demonstrated the β-selectivity in a reaction with cyclohexylmethanol in CH_2Cl_2 at room temperature (72% yield, α/β = 14:86). Therefore, the reaction would proceed via the oxocarbenium ion intermediate.

By replacement of the protecting group at O-6, the β-selectivity increased to α/β = 3:97 (Table 1, entries 6−9). The reaction was faster in CH_2Cl_2, but the β-selectivity was greater in toluene in both cases using **2** and **3**. Considering the substantial yield of the β-glucoside **9** or **10**, the use of **3** in CH_2Cl_2 (entry 8) was fixed as the standard for further applications, although the reaction in toluene (entry 9) provided the best β-selectivity.

The rings of the donors and the products were all in the twist-boat conformation. The observed ring proton vicinal coupling constants in the ^{1}H NMR spectra were linked to ring torsion angles[9] and show that each of **1**−**3** and **8**−**10** is in the $^3S_1$ conformation. Significant long-range ^4J couplings between H-2 and H-4 were detected in all these compounds and support that ring conformation.[4e,10]

Reaction control due to the flipped ring conformation of the glycosyl donors has been previously reported. However, this concept has not been applied to the formation of the β-O-glucosidic bond. In the case of glucose, achievement of the β-selective reaction seems difficult using the $^1C_4$-glucosyl donor (Figure 1). The sole reported attempt of O-glucosidation with a $^1C_4$-glucosyl donor is the reaction of

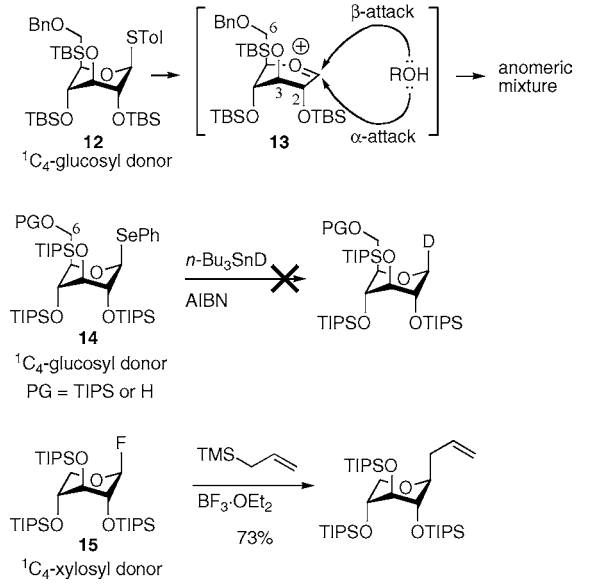


Figure 1. O-Glucosidation using a $^1C_4$-glucosyl donor and examples that show the large steric hindrance of the 6-CH_2 group.

12 with an alcohol, and the α/β ratio of the resulting glucoside was 1:1.[11] Generation of intermediate **13** would be followed by nonselective attack due to the steric hindrance of the β-face by O-3 and C-6 and of the α-face by O-2. Shuto reported that even the radical deuteration cannot proceed using a $^1C_4$ glucose derivative **14**.[5h] In contrast, the β-selective C-allylation using a $^1C_4$ xylose derivative **15** is possible[5g] because xylose lacks the C-6 methylene group. Therefore, to hinder the approach of the glycosyl acceptors, the steric hindrance due to the C-6 methylene group is certainly present in the $^1C_4$-glucosyl donors.

Contrary to this context, thioglucosides **1**−**3** provided the β-selective reaction. The occurrence of the selectivity can be rationalized by assuming an intermediate restricted in the twist-boat conformation as the substrate (Figure 2). In the

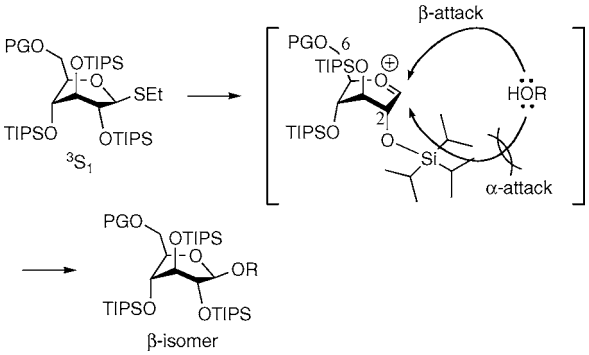


Figure 2. Credible mechanism for our β-selective glucosidation from the $^3S_1$-glucosyl donor. PG = protecting group.

twist conformation adopted, the C-6 hinders the β-face less than in the conventional chair conformation, and the C-2 substituent still hinders the α-face. Therefore, the β-selectivity would be attributed to the restricted twist-boat conformation.

This restricted twist-boat system permitted the highly β-selective glucosidation with more hindered alcohols using **3** (Table 2). The reactions with both (+)- and (−)-menthols afforded similar β-selectivities (entries 2 and 3); consequently, the matching−mismatching effect due to the asymmetry of the glucosyl donor and the acceptors is negligible.[12] The reactions with cholestanol, 1-adamantanol, and methyl

(8) (a) Igarashi, K.; Irisawa, J.; Honma, T. *Carbohydr. Res.* **1975**, *39*, 213−225. (b) Fukase, K.; Hasuoka, A.; Kinoshita, I.; Aoki, Y.; Kusumoto, S. *Tetrahedron* **1995**, *51*, 4923−4932. (c) Schmidt, R. R.; Jung, K. In *Preparative Carbohydrate Chemistry*; Hanessian, S., Eds.; Marcel Dekker: New York, 1997; pp 283−312.

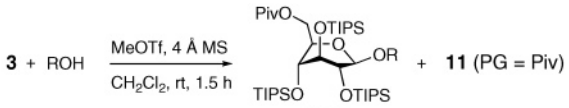
(9) The dihedral angles were calculated from the Karplus equation modified by Haasnoot and Altona: $J = 7.76 \cos^2 w - 1.1 \cos w + 1.4$, where J is the vicinal coupling constant and w is the dihedral angle: Haasnoot, C. A. G.; de Leeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783−2792.

(10) Yamada, H.; Okajima, K.; Imagawa, H.; Nagata, Y.; Nishizawa, M. *Tetrahedron Lett.* **2004**, *45*, 4349−4351.

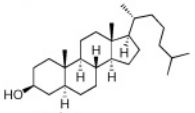
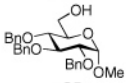
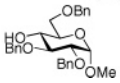
(11) Jensen, H. H.; Bols, M. *Acc. Chem. Res.* **2006**, *39*, 259−265.

(12) (a) Masamune, S.; Choy, W.; Peterson, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1−30. (b) Spijker, N. M.; van Boeckel, C. A. A. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 180−183.

Table 2. Glucosidations of **3** with Various Alcohols



16-22

entry	ROH	prod.	yield of glucoside (%)	α/β ratio	yield of **11** (%)
1		**16**	72	5/95[a]	6
2		**17**	62	2/98[a]	12
3		**18**	58	2/98[a]	29
4		**19**	82	4/96[a]	14
5		**20**	65	5/95[a]	7
6		**21**	69	5/95[b]	17
7		**22**	trace	--	49

[a] Determined on the basis of the ^{1}H NMR. [b] Determined by HPLC.

2,3,4-tri-*O*-benzyl-α-D-glucopyranoside were effective (entries 4−6). In all cases, the byproduct **11** (PG = Piv) was produced. On the other hand, the reaction with methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (entry 7) produced only a trace of the desired glucoside **22**; **11** was the main product in this case. Jensen and Bols reported that axial OR groups increased the reactivity at the anomeric position of sugars using the term "conformationally armed glycosyl donors".[11] Substrate **3** is a typical example of this case, and in reality, the substrate easily generated the oxocarbenium ion intermediate. However, when the next step, which is the formation of the glucosidic C−O bond, is slow as in the reaction with a hindered hydroxy group, a significant amount of **11** would be produced via elimination. The anomeric stereochemistry of each of the products (**16**−**21**) was confirmed as clarification of the structures **8**−**10**.

In conclusion, we have developed a highly β-selective O-glucosidation using thioglucosides whose ring was in the twist-boat conformation. This conformation would be the most significant factor for the selectivity, and the concept was applicable even to a tertiary alcohol. This new method would be an alternative to the traditional β-O-glucosidations.

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Supporting Information Available: Experimental procedures, product characterization, and additional conformational information. This material is available free of charge via the Internet at http://pubs.acs.org.

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