ORGANIC LETTERS

2007
Vol. 9, No. 15
2755−2758

Highly β-Selective and Direct Formation of 2-*O*-Glycosylated Glucosides by Ring Restriction into Twist-Boat

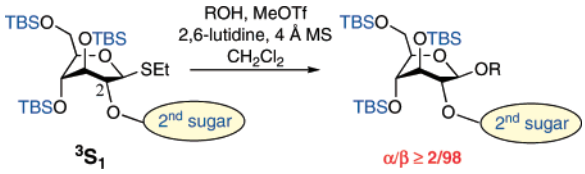
Yasunori Okada, Osamu Nagata, Miyoko Taira, and Hidetoshi Yamada*

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

hidetosh@kwansei.ac.jp

Received March 24, 2007 *(Revised Manuscript Received June 12, 2007)*

ABSTRACT



Three disaccharide donors, ethyl 2-*O*-(2,3,4-tris-*O*-*tert*-butyldimethylsilyl-β-D-xylopyranosyl)-3,4,6-tris-*O*-*tert*-butyldimethylsilyl-1-thio-β-D-glucopyranoside, ethyl 2-*O*-(2,3,4-tris-*O*-*tert*-butyldimethylsilyl-α-L-rhamnopyranosyl)-3,4,6-tris-*O*-*tert*-butyldimethylsilyl-1-thio-β-D-glucopyranoside, and ethyl 2-*O*-(2,3,4,6-tetrakis-*O*-*tert*-butyldimethylsilyl-β-D-glucopyranosyl)-3,4,6-tris-*O*-*tert*-butyldimethylsilyl-1-thio-β-D-glucopyranoside, produced a highly β-selective glycosidation up to α/β = 2/98 using MeOTf as the activator and 2,6-lutidine as an additive. The ring conformations of the glucose part in these disaccharide donors were all restricted to $^3S_1$, and the conformation would lead to the stereoselectivity.

The 2-*O*-glycosylated β-*O*-glucosidic structure (Figure 1, **A**) is ubiquitously found as a component in natural glycosides of aliphatic alcohols,[1] coumarins,[2] flavonoids,[3] terpenoids,[4] and steroids.[5] These glycosides often show biological activities and sometimes are sweet.[6] Previous stereoselective synthetic approaches to the 2-*O*-glycosylated β-*O*-glucosides have necessitated a linear route [Figure 1, (1)];[7] that is, the β-selective introduction of the first glucosyl moiety to an alcohol of the aglycon by way of support of the 2-*O*-acyl

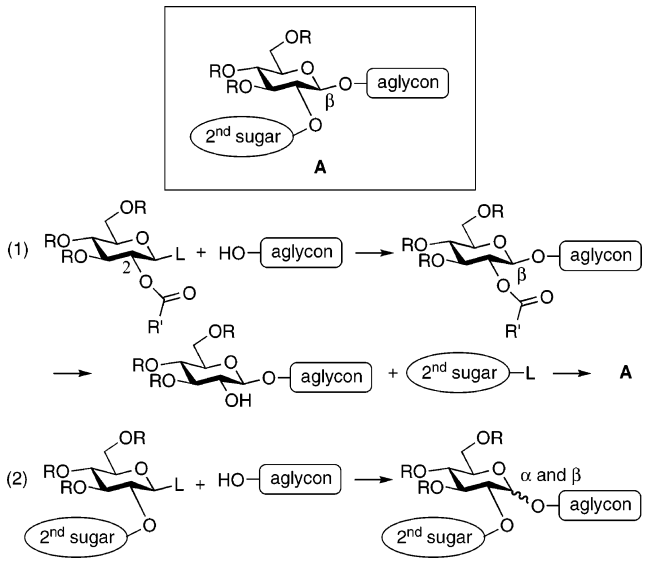


Figure 1. Conceptual structure of the 2-*O*-glycosylated β-*O*-glucoside (**A**) and its previous synthetic routes. L = leaving group.

(1) Recently reported glycosides of aliphatic alcohol containing **A**: (a) Jassbi, A. R.; Zamanizadehnajari, S.; Kessier, D.; Baldwin, I. T. *Z. Naturforsch., B: Chem. Sci.* **2006**, *61*, 1138−1142. (b) Setzer, W. N.; Vogler, B.; Schmidt, J. M.; Petty, J. L.; Haver, W. A. *Planta Med.* **2005**, *71*, 686−688. (c) MacMillan, J. B.; Linigton, R. G.; Andersen, R. J.; Molinski, T. F. *Angew. Chem., Int. Ed.* **2004**, *43*, 5946−5951. (d) Rencurosi, A.; Michell, E. P.; Cioci, G.; Perez, S.; Pereda-Maranda, R.; Imberty, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5918−5922.

(2) Recently reported glycosides of coumarins containing **A**: (a) Xiao, W.; Li, S.; Shen, Y.; Li, X.; Sun, H. *Heterocycles* **2005**, *65*, 1189−1196. (b) Mohamed, M. A.; Marzouk, M. S. A.; Moharram, F. A.; El-Sayed, M. M.; Baiuomy, A. R. *Phytochemistry* **2005**, *66*, 2780−2786.

(3) Recently reported glycosides of flavonoids containing **A**: (a) Prieto, J. M.; Sicilano, T.; Braca, A. *Fitoterapia* **2006**, *77*, 203−207. (b) Saleem, M.; Kim. H. J.; Han, C. K.; Jin, C.; Lee, Y. S. *Phytochemistry* **2006**, *67*, 1390−1394. (c) Xie, W.; Li, P.; Jia, Z. *Pharmazie* **2005**, *60*, 233−236. (d) Toki, K.; Saito, N.; Morita, Y.; Hoshino, A.; Iida, S.; Shigihara, A.; Honda, T. *Heterocycles* **2004**, *63*, 1449−1453.

10.1021/ol070720b CCC: $37.00
Published on Web 06/28/2007

group, cleavage of the acyl-protecting group of the resulting monoglucoside, and introduction of the second sugar. On the other hand, the direct introduction of the 2-*O*-glycosylated glucosyl donors can change the synthetic route to a convergent one. However, this method has often provided a mixture of anomeric isomers [Figure 1, (2)][8] because there is no positive factor enhancing the β-selectivity such as neighboring group participation. Therefore, the development of a method for the highly β-selective and direct introduction of a 2-*O*-glycosylated glucosyl moiety would facilitate the synthesis of the 2-*O*-glycosylated β-*O*-glucosides.

We recently reported that the restricted twist-boat conformation of a glucosyl donor could provide a highly β-selective glucosidation without the need for traditional control methods such as through the participation of neighboring groups, solvent effects, or properties of the leaving groups that produce S_N2-like displacements [Figure 2, (3)].[9]

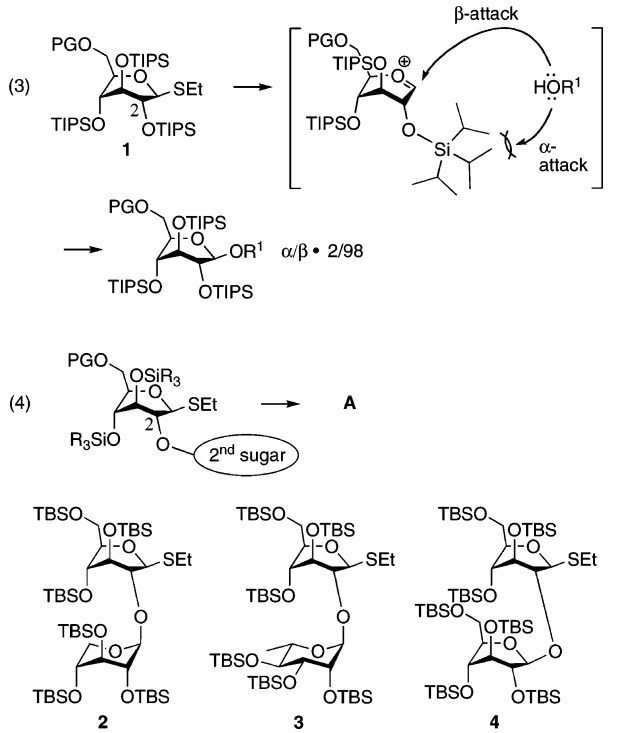


Figure 2. Reported β-glucosidation based on the restricted twist-boat conformation (3), the concept of this paper (4), and disaccharide donors that displayed the β-selective direct glycosidations. PG = protecting group.

The introduction of bulky trialkylsilyl protecting groups restricts the conformation of the pyranose ring as illustrated by **1**, and the 2-*O*-triisopropylsilyl (TIPS) group hinders the approach of a glucosyl acceptor from the α-face to afford the corresponding β-*O*-glucoside. Such ring restrictions have also resulted from the introduction of bulky trialkylsilyl groups into the 3-*O* and 4-*O* positions.[10] In light of these combined observations, it occurred to us that the silyl group on the 2-*O* position could potentially be replaced by sugars [Figure 2, (4)]. We herein report that disaccharide donors, that is, ethyl 2-*O*-(2,3,4-tris-*O*-*tert*-butyldimethylsilyl-β-D-xylopyranosyl)-3,4,6-tris-*O*-*tert*-butyldimethylsilyl-1-thio-β-D-glucopyranoside (**2**), ethyl 2-*O*-(2,3,4-tris-*O*-*tert*-butyldimethylsilyl-α-L-rhamnopyranosyl)-3,4,6-tris-*O*-*tert*-butyldimethylsilyl-1-thio-β-D-glucopyranoside (**3**), and ethyl 2-*O*-(2,3,4,6-tetrakis-*O*-*tert*-butyldimethylsilyl-β-D-glucopyranosyl)-3,4,6-tris-*O*-*tert*-butyldimethylsilyl-1-thio-β-D-glucopyranoside (**4**), displayed a preference for highly β-selective glycosidation. This is a new method for the highly β-selective and direct formation of 2-*O*-glycosylated glucosides that is based upon conferment of a twist boat conformation in the sugar acceptor undergoing glycosylation.

The disaccharides **2**−**4** were stereoselectively synthesized by the respective glycosylation of a thioglucoside **5**[11] with trichloroacetimidates **6**−**8**, followed by deprotection and introduction of TBS groups (Scheme 1). Thus, $BF_3{\cdot}Et_2O$-catalyzed xylosylation of **5** with **6**[12] in CH_2Cl_2 afforded disaccharide **9** β-selectively. The acetyl groups in **9** were first removed to provide the hexaol **10**, to which the TBS groups were introduced by heating the mixture of **10**,

(4) Recently reported glycosides of terpenoids containing **A**: (a) Dou, D.; Li, W.; Guo, N.; Fu, R.; Pei, Y.; Koike, K.; Nikaido, T. *Chem. Pharm. Bull.* **2006**, *54*, 751−753. (b) Cheng, G.; Zhang, Y.; Zhang, X.; Tang, H.; Cao, W.; Gao, D.; Wang, X. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4575−4580. (c) Min, B.; Oh, S.; Ahn, K.; Kim. J.; Lee. J.; Kim, D.; Kim, E.; Lee, H. *Planta Med.* **2004**, *70*, 1210−1215. (d) Haddad, M.; Miyamoto, T.; Lacaille-Dubois, M. *Helv. Chim. Acta* **2004**, *87*, 1228−1238. (e) Suksamrarn, S.; Wongkrajang, K.; Kirtikara, K.; Suksamrarn, A. *Planta Med.* **2003**, *69*, 877−879.

(5) Recently reported glycosides of steroids containing **A**: (a) Hayes, P. Y.; Hasylla Jahidin, A.; Lehmann, R.; Penman, K.; Kitching, W.; De Voss, J. J. *Tetrahedron Lett.* **2006**, *47*, 6965−6969. (b) Ono, M.; Nishimura, K.; Suzuki, K.; Fukushima, T.; Igoshi, K.; Yoshimitsu, H.; Ikeda, T.; Nohara, T. *Chem. Pharm. Bull.* **2006**, *54*, 230−233. (c) Zhou, X.; He, X.; Wang, G.; Gao, H.; Zhou, G.; Ye, W.; Yao, X. *J. Nat. Prod.* **2006**, *69*, 1158−1163. (d) Fujiwara, Y.; Takaki, A.; Uehara, Y.; Ikeda, T.; Okawa, M.; Yamaguchi, K.; Ono, M.; Yoshimitsu, H.; Nohara, T. *Tetrahedron* **2004**, *60*, 4915−4920.

(6) Kinghorn, A. D.; Kim, N.-C. *Discovering new natural sweeteners, Optimising Sweet Taste in Foods*; Woodhead and CRC: Cambridge and Boca Raton, 2006; pp 292−306.

(7) Stepwise constructions of glycosides containing **A**: (a) Hou, S.; Zou, C.; Zhou, L.; Lei, P.; Yu, D. *Chem. Lett.* **2005**, *34*, 1220−1221. (b) Sun, J.; Han, X.; Yu, B. *Synlett* **2005**, 437−440. (c) Brito-Arias, M.; Pereda-Miranda, R.; Heathcock, C. H. *J. Org. Chem.* **2004**, *69*, 4567−4570. (d) Du, Y.; Wei, G.; Linhardt, R. J. *J. Org. Chem.* **2004**, *69*, 2206−2209. (e) Suhr, R.; Pfefferkorn, P.; Weingarten, S.; Thiem. J. *Org. Biomol. Chem.* **2003**, *1*, 4373−4379. (f) Nicolaou, K. C.; Michell, H. J.; Jain, N. F.; Winssinger, N.; Hughes, R.; Bando, T. *Angew. Chem., Int. Ed.* **1999**, *38*, 240−244.

(8) Recently reported direct introduction of di- and greater saccharides: (a) Kim, Y.-J.; Wang, P.; Navarro-Villalobos, M.; Rohde, B. D.; Derryberry, J.; Gin, D. Y. *J. Am. Chem. Soc.* **2006**, *128*, 11906−11915. (b) Hou, S.; Xu, P.; Zhou, L.; Yu, D.; Lei, P. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2454−2458. (c) Peng, W.; Li, Y.; Zhu, C.; Han, X.; Yu, B. *Carbohydr. Res.* **2005**, *340*, 1682−1688. (d) Zou, C.; Hou, S.; Shi, Y.; Lei, P.; Liang, X. *Carbohydr. Res.* **2003**, *338*, 721−727. (e) Cheng, M. S.; Wang, Q. L.; Tian, Q.; Song, H. Y.; Liu, Y. X.; Li, Q.; Xu, X.; Miao, H. D.; Yao, X. S.; Yang, Z. *J. Org. Chem.* **2003**, *68*, 3658−3662. (f) Ikeda, T.; Miyashita, H.; Kajimoto, T.; Nohara, T. *Tetrahedron Lett.* **2001**, *42*, 2353−2356. (g) Ikeda, T.; Kajimoto, T.; Kinjo, J.; Nakayama, K.; Nohara, T. *Tetrahedron Lett.* **1998**, *39*, 3513−3516.

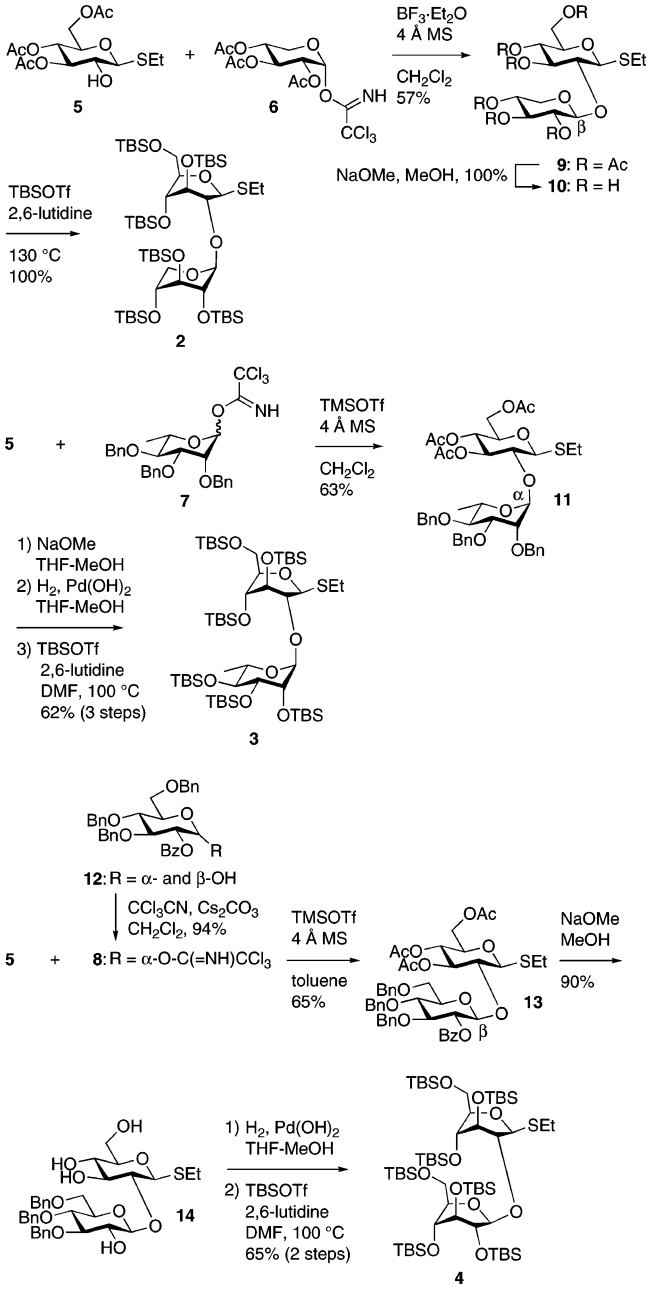
(9) Okada, Y.; Mukae, T.; Okajima, K.; Taira, M.; Fujita, M.; Yamada, H. *Org. Lett.* **2007**, in press.

(10) (a) Yamada, H.; Tanigakiuchi, K.; Nagao, K.; Okajima, K.; Mukae, T. *Tetrahedron Lett.* **2004**, *45*, 5615−5618. (b) Yamada, H.; Nakatani, M.; Ikeda, T.; Marumoto, Y. *Tetrahedron Lett.* **1999**, *40*, 5573−5576.

(11) Liu, M.-Z.; Fan, H.-N.; Guo, Z.-W.; Hui, Y.-Z. *J. Carbohydr. Chem.* **1996**, *15*, 1139−1145.

(12) Mori, M.; Ito, Y.; Ogawa, T. *Carbohydr. Res.* **1990**, *195*, 199−204.

Scheme 1. Preparation of the Disaccharide Donors **2**−**4**

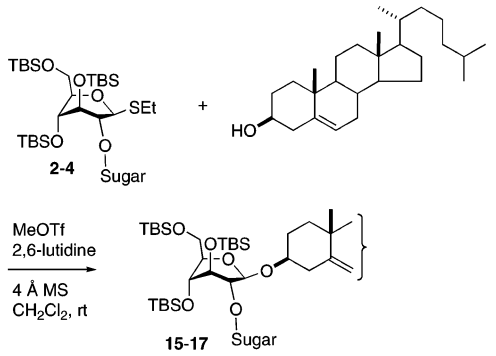


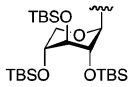
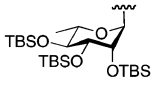
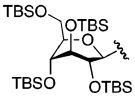
TBSOTf, and 2,6-lutidine at 130 °C to give **2**. The introduction of six TIPS groups to **10** was not complete, even using TIPSOTf. The rhamnosylation of **5** with **7**[13] (α/β = 77/23) provided α-rhamnoside **11**. The acetyl and benzyl groups in **11** were successively removed by methanolysis and hydrogenolysis. Despite the presence of an ethylthio group in the molecule, the hydrogenolysis successfully proceeded. Finally, six TBS groups were introduced to afford **3**. The glucosylation of **5** with a glucosyl trichloroacetimidate **8**, which was prepared from **12**[14] by treatment with trichloroacetonitrile and Cs_2CO_3,[15] afforded the disaccharide **13** with good β-selectively in toluene. The acetyl and benzoyl groups in **13** were first removed to give **14**, in which three benzyl groups were cleaved by hydrogenolysis to provide the corresponding heptaol. Seven TBS groups were then introduced to give **4**.

The ring conformation of each of the glucose components in **2**−**4** was in the $^3S_1$ conformation; the xylose in **2** flipped to $^1C_4$, and the rhamnose part in **3** stayed in the $^1C_4$ form that is the general conformation of the sugar. The observed ring-proton vicinal coupling constants in the ^{1}H NMR spectra were linked to ring torsion angles.[16] The molecular models assembled on the basis of these dihedral angles displayed the aforementioned conformations.[17] Significant long-range ^4J couplings were detected in all these compounds and supported the proposed ring conformations.[10,18]

The glycosidation reactions of **2**, **3**, and **4** with cholesterol proceeded in a highly β-selective manner to give **15**, **16**, and **17**, respectively (Table 1). These disaccharide donors

Table 1. Glycosidations of the Disaccharide Donors **2**−**4** with Cholesterol



entry	glycosyl donor	sugar	time (h)	yield (%)	α/β ratio	prod
1	**2**		2.0	56	3/97	**15**
2	**3**		1.0	43	4/96	**16**
3	**4**		1.5	45	4/96	**17**

were activated by MeOTf (4 equiv) in CH_2Cl_2 in the presence of molecular sieves (4 Å) and 2,6-lutidine (2 equiv). The α/β ratio was determined on the basis of the integral ratio of the anomeric protons in the ^{1}H NMR spectra. The reaction conditions were similar to our previous report using **1** except for the use of 2,6-lutidine. In this case, migration of the TIPS

(13) Rathore, H.; From, A. H. L.; Ahmed, K.; Fullerton, D. S. *J. Med. Chem.* **1986**, *29*, 1945−1952.
(14) Mach, M.; Schlueter, U.; Mathew, F.; Fraser-Reid, B.; Hazen, K. C. *Tetrahedron* **2002**, *58*, 7345−7354.
(15) Egusa, K.; Kusumoto. S.; Fukase, K. *Eur. J. Org. Chem.* **2003**, 3435−3445.
(16) Haasnoot, C. A. G.; de Leeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783−2792.

group was not observed unless 2,6-lutidine was used. However, during the glycosidation of the TBS-protected **2** with cholesterol, migration of a TBS group occurred without 2,6-lutidine to provide the TBS-protected cholesterol as the major product. An *O*-TBS bond is generally more sensitive under acidic conditions than an *O*-TIPS bond.[19] Additionally, the relatively strong steric repulsion due to the adjacent TBS groups facilitated the cleavage of one of the *O*-TBS bonds with trifluoromethanesulfonic acid, which was generated during the reaction. The cleavage provided TBSOTf which would react with cholesterol. The addition of 2,6-lutidine was therefore fundamental in these cases as an acid scavenger.

The structures of the cholesteryl disaccharides **15**−**17** were clarified by further transformations (Figure 3), namely the

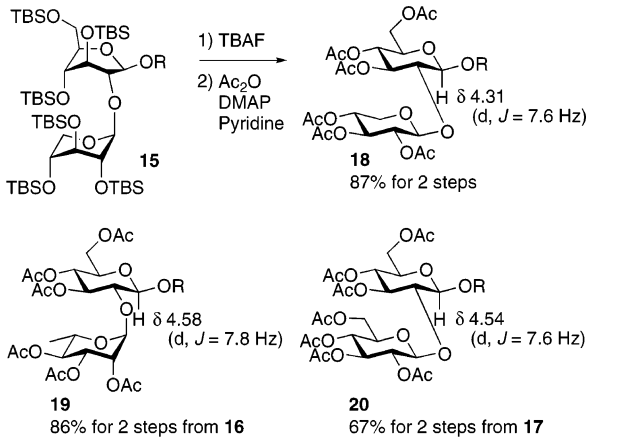


Figure 3. Clarifications of the anomeric stereochemistry. R = cholesteryl.

removal of the TBS groups to return the conformation of the sugars back to their generally stable forms and by acetylation of the resulting hydroxy groups. Thus, the 3/97 anomeric mixture of **15** was treated with TBAF to remove all of the TBS groups, and then the resulting six hydroxy groups were acetylated to give an anomeric mixture (α/β = 1/99) of the corresponding hexaacetate **18** in 87% yield. In the ^{1}H NMR of β-**18**, the coupling constant between the H-1 and H-2 of the glucose part was 7.6 Hz, and the other coupling constants due to the adjacent hydrogens on the pyranose ring were around 10 Hz. Compounds **16** and **17** were similarly treated as above to give **19** and **20**, respectively, structures of which were confirmed as well as **18**.

The direct β-glycosidation of the disaccharides was useful for glycosylation of steroidal and carbocyclic alcohol aglycons, but was difficult to achieve with carbohydrate acceptors. The reaction of **2** with a tertiary alcohol, 1-adamantanol, provided the corresponding glycoside β-selectively (α/β = 2/98) in 65% yield. On the other hand, with methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside and methyl 2,4,6-tri-*O*-benzyl-α-D-glucopyranoside, only a trace of the corresponding trisaccharide was detected in each case.

In conclusion, we have introduced 2-*O*-glycosyl-D-glucosyl units β-selectively. The stereoselectivity was controlled by the restricted twist-boat conformation of the glucose part in the disaccharide donors. Despite the use of cholesterol or 1-adamantanol as the aglycon in this study, multistep preparations of the aglycon parts have often occurred in the syntheses of glycosides. For the aglycons, straightforward constructions with repeated monoglycosidation tend to be adopted in the completion steps for the target glycosides. The results disclosed here demonstrate that the convergent synthesis of the 2-*O*-glycosylated β-*O*-glucosides became possible.

Acknowledgment. This work was partly supported by a Grant-in-Aid for Scientific Research (16510170) from JSPS and a Grant-in-Aid for Scientific Research on Priority Areas (17035086) from MEXT.

Supporting Information Available: Experimental procedures and product characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Spartan ('04 Windows) constructed the molecular models of **2**−**4**. Each model was optimized by a simple MMFF calculation after constraint of the dihedral angles (H-1−C-1−C-2−H-2, H-2−C-2−C-3−H-3, H-3−C-3−C-4−H-4, and H-4−C-4−C-5−H-5) to the calculated dihedral angles based on the observed coupling constants ($^3J_{H-H}$) in each ^{1}H NMR spectrum.

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