A Highly Stereoselective Construction of β-Glycosyl Linkages by Reductive Cleavage of Cyclic Sugar Ortho Esters

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Received April 17, 2000

The preparation of β-glycosides by the reductive cleavage of spiro sugar ortho esters is described in this report. This procedure is based on a concept completely different from those of other methods for glycosylation. Twelve sugar ortho esters that commonly possess perhydrospiro[2*H*-pyran-2,2′-pyrano[3,2-*d*][1,3]dioxin] ring systems in their molecules were reduced by $LiAlH_4/AlCl_3$ or $NaCNBH_3/AlCl_3$. Among these ortho esters, those (**9a**−**12a**) prepared from the D-sugar lactones (**1**−**4**) and 2,3-di-*O*-benzyl-α-D-glucopyranoside (**7**) or those (**19a**, **20a**) prepared from the L-sugar lactones (**5**, **6**) and 2,3-di-*O*-benzyl-α-D-galactopyranoside (**8**) were selectively converted into β-(1 → 4)-glycosides (**9b**−**12b** or **19b**, **20b**) in excellent yields by the treatment of $LiAlH_4/AlCl_3$. In contrast, the ortho esters (**13a**−**16a** or **17a**, **18a**) that were prepared from combinations of the D-sugar lactones and **8** or those of the L-sugar lactones and **7** were efficiently reduced with $NaBH_3CN/AlCl_3$ to afford β-(1 → 6)-glycosides (**13b**−**16b** or **17b**, **18b**) selectively. It was remarkable that the resulting disaccharides were obtained with extremely high β-selectivity even in the cases with mannosyl or rhamnosyl glycosides. Moreover, these products would be useful units for the construction of branched saccharides, because the newly formed hydroxy groups could be again glycosylated without further deprotection procedures. The high regio- and stereoselectivity was totally explained by considering the structures and the conformations of these ortho ester molecules and the stereoelectoronic effects of their spiro ring systems. In addition, the preparation of the sugar ortho esters with glucosamine derivatives and the reactivity of these ortho esters are described in this report. *N*-Phthaloyl glucosamine derivatives (**21**, **22**) were efficiently reacted with the benzyl-protected gluconolactone (**1**) in the presence of TMSOMe and TMSOTf to afford ortho esters (**23a**−**c**). After the conversion of the phthalimido functionality to the dibenzyl amino group, glucosylidene-glucosamine (**25**) was reduced with $LiAlH_4/AlCl_3$ to afford β-(1 → 4)-glycoside (**26**) selectively.

Introduction

As the biological significance of oligosaccharides and glyco-conjugates is being revealed, the development of methods for the chemical construction of glycosides is increasingly necessitated.[1] The most important process in saccharide synthesis is the glycosidic bond formation, and various useful methods for glycosylation have been developed in recent years.[2] The known glycosylations are generally based on the activation of glycosyl donors with leaving groups such as fluoride and trichloroacetimidate and phosphorus-centered leaving groups[3] by appropriate promoters. However, we think that other approaches to the construction of glycosyl linkages should also be investigated for the provision of flexible strategy in oligosaccharide synthesis.

We previously reported a new two-step glycosylation procedure, which was a type of method completely different from other ones.[4] As shown in Scheme 1, the first step in our procedure is the formation of ortho esters from two sugar moieties, and the second is the reductive cleavage of a C−O ortho ester bond. With this method, three glycosyl-(1 → 4)-glucosides (**9b**, **10b**, **11b**) were efficiently prepared from the sugar lactones (**1**−**3**) and the 2,3-di-*O*-protected glucopyranoside (**7**) via the ortho esters (**9a**, **10a**, **11a**).[4a,b] It was remarkable that the complete β-selectivity was observed at the anomeric centers of the resulting disaccharides. Moreover, these disaccharides was expected to be useful units for the construction of branched saccharides, because the newly formed alcohol functionality could be again glycosylated.

In this paper, we report the details of the preparation of the glycosides from various combinations of sugar lactones and β-diol type sugars, including the above three cases. All of the glycosides reported here were commonly prepared via 4-*O*,6-*O*-glycosylideneglycosides. We revealed that the regio- and stereoselectivity in the reduction of this type of the sugar ortho esters was explained

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(1) Recent review: Boons, G.-J. *Tetrahedron* **1996**, *52*, 1095.

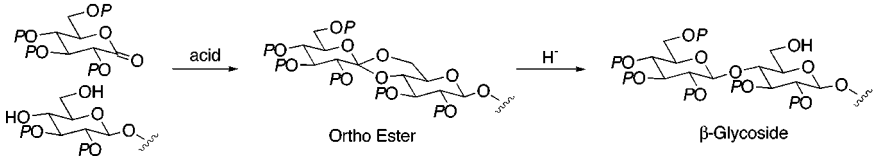
(2) Recent review: (a) Paulsen, H. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 823. (b) Banoub, J.; Boullanger, P.; Lafont, D. *Chem. Rev.* **1992**, *92*, 1167. (c) Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503. (d) Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1380.

(3) (a) Hashimoto, S.; Honda, T.; Ikegami, S. *J. Chem. Soc., Chem. Commun.* **1989**, 685. (b) Hashimoto, S.; Honda, T.; Ikegami, S. *Heterocycles* **1990**, *30*, 775. (c) Hashimoto, S.; Honda, T.; Ikegami, S. *Tetrahedron Lett.* **1990**, *31*, 4769. (d) Hashimoto, S.; Honda, T.; Ikegami, S. *Chem. Pharm. Bull.* **1990**, *38*, 2323. (e) Hashimoto, S.; Yanagiya, Y.; Honda, T.; Harada, H.; Ikegami, S. *Tetrahedron Lett.* **1992**, *33*, 3523. (f) Hashimoto, S.; Umeo, K.; Sano, A.; Watanabe, N.; Nakajima, M.; Ikegami, S. *Tetrahedron Lett.* **1995**, *36*, 2251. (g) Hashimoto, S.; Honda, T.; Yanagiya, Y.; Nakajima, M.; Ikegami, S. *J. Synth. Org. Chem. Jpn.* **1995**, *53*, 620.

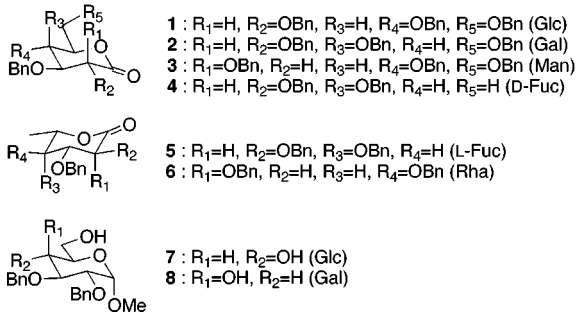
(4) (a) Ohtake, H.; Iimori, T.; Ikegami, S. *Tetrahedron Lett.* **1997**, *38*, 3413. (b) Iimori, T.; Ohtake, H.; Ikegami, S. *Tetrahedron Lett.* **1997**, *38*, 3415. (c) Ohtake, H.; Iimori, T.; Shiro, M.; Ikegami, S. *Heterocycles* **1998**, *47*, 685. (d) Ohtake, H.; Iimori, T.; Ikegami, S. *Synlett* **1998**, 1420.

10.1021/jo0005870 CCC: $19.00
Published on Web 10/31/2000

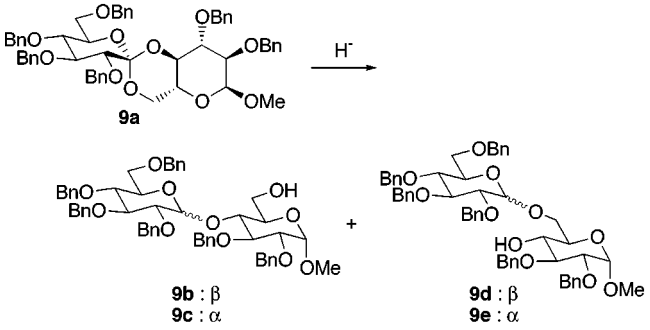
Scheme 1



Scheme 2



Scheme 3

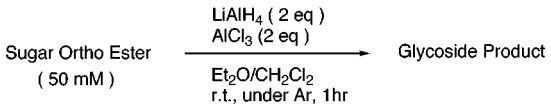


by considering the stereoelectronic effects of the spiro ring systems in ortho ester molecules, which is also reported here in detail. Further, we describe the preparation of the sugar ortho esters with an amino functionality and the reduction of these compounds together in this report.

Preparation of the Sugar Ortho Esters. The first step in our reductive glycosylation method is the formation of the sugar ortho esters. We improved the method for the formation of ortho esters and prepared the 12 sugar ortho esters (**9a**−**20a**) in 80−92% yields. We used the six sugar lactones 2,3,4,6-tetra-*O*-benzyl-D-gluconolactone (**1**),[5] 2,3,4,6-tetra-*O*-benzyl-D-galactonolactone (**2**),[6] 2,3,4,6-tetra-*O*-benzyl-D-mannonolactone (**3**),[6] 2,3,4-tri-*O*-benzyl-D-fuconolactone (**4**),[9] 2,3,4-tri-*O*-benzyl-L-fuconolactone (**5**),[7] and 2,3,4-tri-*O*-benzyl-L-rhamnonolactone (**6**)[9] in this preparation (Scheme 2). The ortho esters **9a**−**14a** were prepared from these sugar lactones and 2,3-di-*O*-benzyl-α-D-glucopyranoside (**7**), and the ortho esters **15a**−**20a** were the products of the reaction of these lactones with 2,3-di-*O*-benzyl-α-D-galactopyranoside (**8**).[8] All of these ortho esters possess perhydrospiro[2*H*-pyran-2,2′-pyrano[3,2-*d*][1,3]dioxin] ring systems commonly in their molecules and were remarkably afforded as single isomers despite the fact that two stereoisomers were possible around the spiro centers. The absolute configurations of the anomeric centers are indicated in Tables 1 and 2. The details of the preparation and the structure determination of these ortho esters have been reported in the preceding paper.[9]

Reduction of the Sugar Ortho Esters with $LiAlH_4$/$AlCl_3$. In the reduction of these sugar ortho esters, there are four possible glycoside products for each ortho ester. For example, the possible products of the glucosylidene-glucoside **9a** are glucosyl-α- or *β*-(1 → 4)-glucoside (**9c** or **9b**) and glucosyl-α- or *β*-(1 → 6)-glucoside (**9e** or **9d**) (Scheme 3). As reported in a previous paper,[4b] we surveyed the reductants to find the efficient conditions for the selective cleavage of the spiro sugar ortho esters

Scheme 4



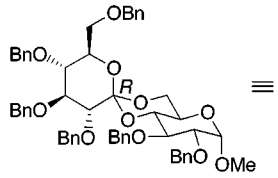
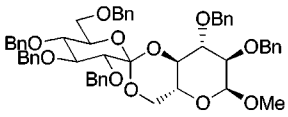
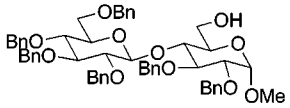
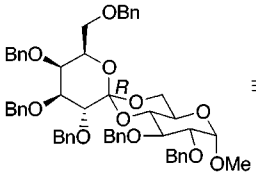
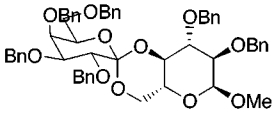
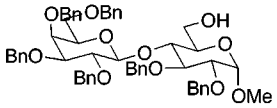
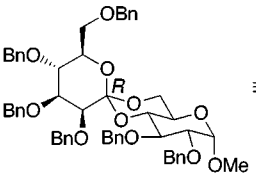
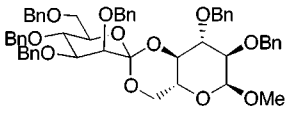
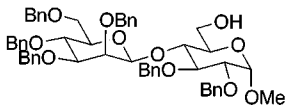
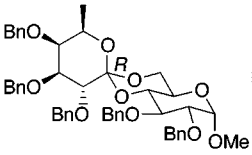
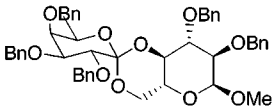
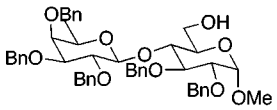
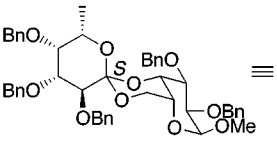
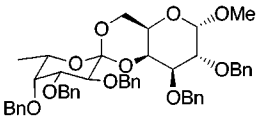
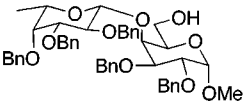
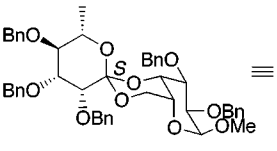
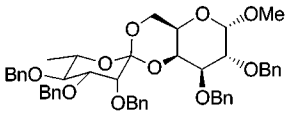
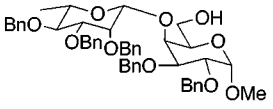
and revealed that the combination of $LiAlH_4$ and $AlCl_3$[10] was an effective reagent for this purpose (Scheme 4).

Table 1 summarizes the results of the reduction of the six sugar ortho esters (**9a**−**12a** or **19a**, **20a**) with $LiAlH_4$/$AlCl_3$, which were prepared from the combinations of D-sugar lactones (**1**−**4**) and **7** or from those of the L-sugar lactones (**5**, **6**) and **8**. As shown in entry 1, the reduction of **9a** smoothly proceeded with 2 equiv of reagents in 2 h at room temperature to afford glucosyl-*β*-(1 → 4)-glucoside **9b** in 92% yield, and other possible isomers, **9c**, **9d** and **9e**, were not detected. Also in the cases with the ortho esters **10a**−**12a** (entry 2−4), glycosyl-*β*-(1 → 4)-glucosides **10b**, **11b**,[11] **12b** were obtained in excellent yields (92−98%) with complete regio- and stereoselectivity. The reduction of the two ortho esters (**19a**, **20a**) containing L-sugar moieties proceeded efficiently under the same reaction conditions, and glycosyl-*β*-(1 → 4)-galactosides were produced selectively again with excellent yields (96−99%; entries 5 and 6). The stereochemistry of the anomeric centers of the resulting disaccharides were determined to be *β* by considering the coupling constant of the signals of the anomeric protons in ^1H NMR or by comparing the spectral data of the products with authentic samples prepared by usual glycosylation methods.

The results in Table 1 were noteworthy first from the point that the sterically congested 4-*O* positions of sugar compounds were efficiently glycosylated by this method. More noticeable was that the resulting disaccharides were afforded with complete *β*-selectivity even in the cases with mannosyl and rhamnosyl donors. While stereoselective *β*-mannosylations or *β*-rhamnosylations based on several new concepts have been reported recently,[12] our procedure is superior in terms of efficiency and selectivity.

(5) (a) Kuzuhara, H.; Fletcher, H. G., Jr. *J. Org. Chem.* **1967**, *32*, 2531. (b) Hanessian, S.; Ugolini, A. *Carbohydr. Res.* **1984**, *130*, 261.
(6) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976.
(7) Cai, S.; Stroud, M. R.; Hakomori, S.; Toyokuni, T. *J. Org. Chem.* **1992**, *57*, 6693.
(8) Kiss, J. v.; Burkhardt, F. *Helv. Chim. Acta* **1970**, *53*, 1000.
(9) Ohtake, H.; Ichiba, N.; Shiro, M.; Ikegami, S. *J. Org. Chem.* **2000**, *65*, 8164.
(10) (a) Bhattacharjee, S. S.; Gorin, P. A. J. *Can. J. Chem.* **1969**, *47*, 1195. (b) Lipták, A.; Jodál, I.; Nánási, P. *Carbohydr. Res.* **1975**, *44*, 1.
(11) Compound **10b** was hydrogenated to be converted into the corresponding debenzylated compound as reported previously: Barresi, F.; Hindsgaul, O. *J. Am. Chem. Soc.* **1991**, *113*, 9376.

Table 1. Reduction of Sugar Ortho Esters with $LiAlH_4/AlCl_3$

Entry	Sugar Ortho Ester		Glycoside Product	Yield[a]
1	 **9a**		 **9b**	92 %
2	 **10a**		 **10b**	98 %
3	 **11a**		 **11b**	98 %
4	 **12a**		 **12b**	92 %
5	 **19a**		 **19b**	96 %
6	 **20a**		 **20b**	99 %

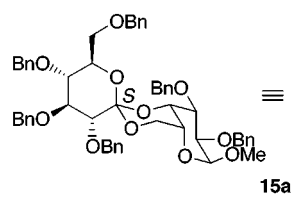
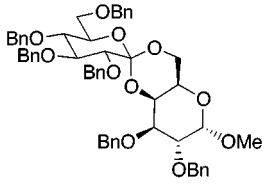
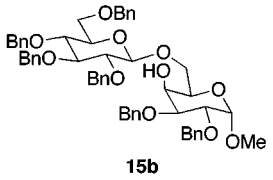
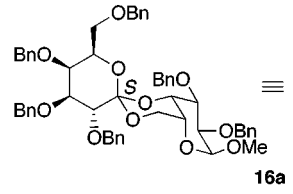
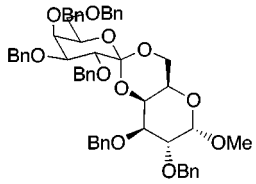
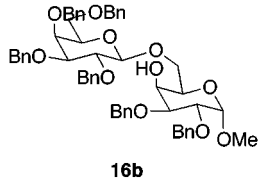
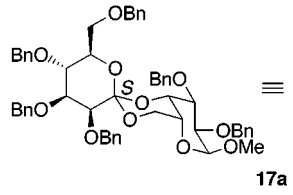
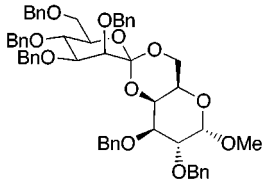
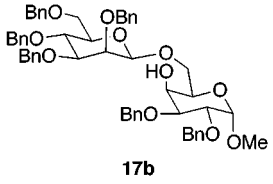
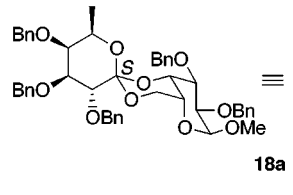
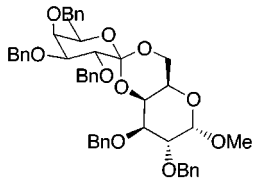
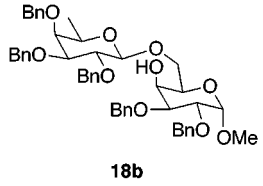
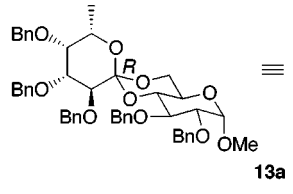
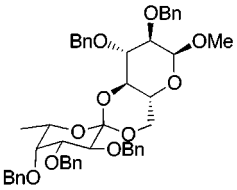
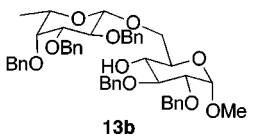
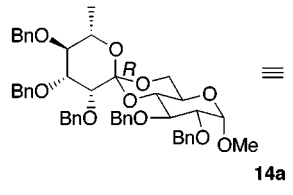
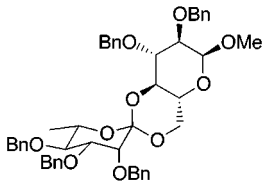
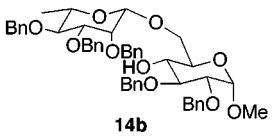
[a] These reactions were carried out for 1 h at rt under Ar in Et_2O/CH_2Cl_2 ([ortho ester] = 50 mM, 2 equiv $LiAlH_4$, 2 equiv $AlCl_3$). Yields are isolated yields.

We also attempted the reduction by $LiAlH_4/AlCl_3$ of the sugar ortho esters prepared from the combinations of the D-sugar lactones and **8** (**15a**−**18a**) and from those of the L-sugar lactones and **7** (**13a**, **14a**). However, these ortho esters were not efficiently reduced or were converted into multiple products by treating with an excess amount of reagents.

Reduction of the Sugar Ortho Esters with $NaBH_3CN/AlCl_3$. To find efficient reagents for the reduction of remainine six sugar ortho esters **13a**−**18a**, we again investigated the reactivity of several reductants.[13−17] As described in the previous paper,[4b] DIBAL[13] and $NaBH_3CN$/acid[14] also had potential as the reagents for the conversion of the sugar ortho esters to glycosides, while BH_3[15] or Et_3SiH/acid[16] or Al(*i*-Bu)$_3$ was not an effective reagent for this purpose. Although the reactivity of DIBAL was similar to that of $LiAlH_4/AlCl_3$, it was revealed that the reduction of these ortho esters with $NaBH_3CN$ proceeded efficiently in the presence of $AlCl_3$.

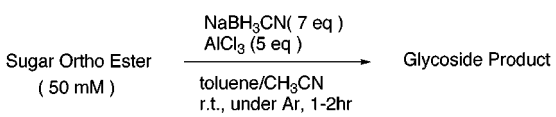
In Table 2, the results of the reduction of six sugar ortho esters **13a**−**18a** with $NaBH_3CN/AlCl_3$ are summarized. As shown in entries 1, 2 and 4, the glucosylidene- (**15a**), galactosylidene- (**16a**) and D-fucosylidene-galactosides (**18a**) were efficiently reduced with these reagents in 1.5−2 h at room temperature using toluene/CH_3CN as solvents to afford glycosyl-β-(1 → 6)-galactosides **15b**, **16b**, and **18b** selectively with 88−97% yields (Scheme 5). Although the reaction did not proceed completely in the case of the mannosylidene ortho ester **17a** (entry 3), mannosyl-β-(1 → 6)-galactoside **17b** was

Table 2. Reduction of Sugar Ortho Esters with $NaBH_3CN/AlCl_3$

Entry	Sugar Ortho Ester	Glycoside Product	Time	Yield[a]
1	 **15a**	  **15b**	2 hr	93 %
2	 **16a**	  **16b**	2 hr	97 %
3	 **17a**	  **17b**	48 hr	42 %[b]
4	 **18a**	  **18b**	2 hr	88 %
5	 **13a**	  **13b**	1 hr	88 %
6	 **14a**	  **14b**	12 hr	78 %[c]

[a] These reactions were carried out at rt under Ar in toluene/CH_3CN ([ortho ester] = 50 mM, 7 equiv $NaBH_3CN$, 5 equiv $AlCl_3$, 100 mg MS3A/2 mL solvents). Yields are isolated yields. [b] Yield 91% based on conversion. [c] α-(1 → 6)-Isomer was detected (6%).

Scheme 5



also afforded as the only resulting glycoside product (91% based on conversion). L-Fucosylideneglucoside **13a** was reduced smoothly to afford L-fucosyl-β-(1 → 6)-glucosides (**13b**) selectively (entry 5). However, the reduction of L-rhamnosylideneglucoside **14a** proceeded slowly, and β-(1 → 6)-isomer **14b** was obtained in a relatively lower yield accompanied by the production of a small amount of the α-1,6-isomer **14c** (α:β = 7:93; entry 6). These results revealed that the reductive glycosylation method was also effective for the preparation of several glycosyl-β-(1 → 6)-glycosides. Unfortunately, the reaction with mannosylidene (**17a**) or rhamnosylidene ortho ester (**14a**) did not proceed efficiently enough; however, the β-selectivities obtained here, especially in the case with the ortho ester **17a**, were excellent. As shown in entries 4 and 5, the yields of the products in the reduction of fucosylidene ortho esters (**13a**, **18a**) were relatively low compared to that of galactosylidene ortho ester (**16a**), which may be caused by the instability of fucosylidene moieties under the reduction conditions.

We first used the ethereal solution of HCl instead of $AlCl_3$ dissolved in CH_3CN because HCl solution was most frequently used for the acceleration of the reactivity of

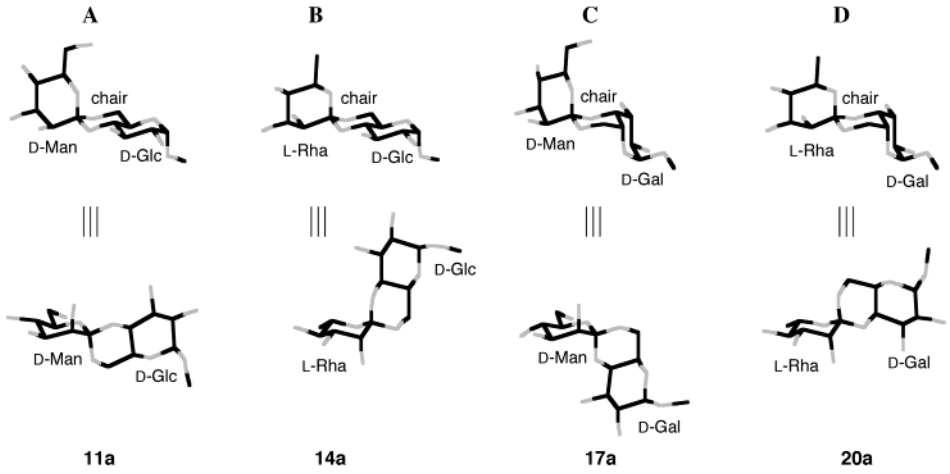


Figure 1. Typical four conformations of sugar ortho ester molecules calculated by LOMD18 using MacroModel ver 6.019. All of the benzyl groups and the hydrogen atoms on the molecules were omitted.

$NaBH_3CN$. However, the sugar ortho esters decomposed to the corresponding lactones and diols by the treatment of etheral HCl. Although it was not clear why these ortho esters were quite stable in ethereal or CH_3CN solution of $AlCl_3$, it would be a plausible explanation that $AlCl_3$ strongly trapped the contaminated anion, such as OH^-, which were necessary for the decomposition of these ortho esters.

The six sugar ortho esters for which $LiAlH_4/AlCl_3$ were effective reagents were tried to be reduced with $NaBH_3CN/AlCl_3$. However, the mismatching between the reagents and ortho esters again occurred. The reactions of these ortho esters did not proceed so efficiently or selectively as those of the ortho esters listed in Table 2.

Consideration of the High Regio- and Stereoselectivity in the Reduction of the Sugar Ortho Esters on the Basis of Their Structures. Above results revealed that the prepared 12 sugar ortho esters were separated into two groups from the point of the reactivity of the reductants and of the regioselectivity in their reductions. According to the X-ray crystallographic analysis and the molecular modeling studies[18,19] reported in the preceding paper,[9] these ortho esters were classified into four groups from the points of the structures of their ring systems. Remarkably, it was revealed that these two classifications were closely related and that the difference or similarity among the reactivity of ortho esters was well explained by considering the structures of the ring systems in their molecules.

As reported in the preceding paper,[9] the structures and conformations of the spiro ring systems of the formed ortho esters depended on whether D- or L-sugar lactones were used as glycosylidene parts and on whether **7** or **8** was used as the diol part. For example, the ring systems of the sugar ortho esters **9a**−**12a** prepared from the D-sugar lactones **1**−**4** and **7** had the same structure. In Figure 1, the typical four structures of the spiro ring systems of ortho esters are shown. The structures A−D in Figure 1 are illustrated on the basis of the calculated conformations[20] of the ortho esters **11a**, **14a**, **17a** and **20a**, respectively. The 5′-oxygen atoms of these ortho esters are commonly in the axial positions of the dioxane rings, which are located at the centers of these molecules (see upper four structures in Figure 1). It is reasonable to think that the stability of these conformations is caused by the anomeric effects derived from the oxygen atoms of dioxane rings.[21] These effects were so significant

(12) (a) Gorin, P. A. J.; Perlin, A. S. *Can. J. Chem.* **1961**, *39*, 2474. (b) Betaneli, V. I.; Ovchinnikov, M. V.; Backinowsky, L. V.; Kochetkov, N. K. *Carbohydr. Res.* **1980**, *84*, 211. (c) Paulsen, H.; Lockhoff, O. *Chem. Ber.* **1981**, *114*, 3102. (d) Srivastava, V. K.; Schuerch, C. *J. Org. Chem.* **1981**, *46*, 1121. (e) Garegg, P. J.; Ossowski, P. *Acta Chem. Scand.* **1983**, *B37*, 249. (f) Rathore, H.; From, A. H. L.; Ahmed, K.; Fullerton. D. S. *J. Med. Chem.* **1986**, *29*, 1945. (g) Crich, D.; Sun, S. *J. Org. Chem.* **1997**, *62*, 1198. β-Mannoside formation via an inversion of configuration at C-2 by a nucleophilic substitution: (h) Kunz, H.; Günther, W. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1086. β-Mannoside formation by radical inversions at anomeric center: (i) Brunckova, J.; Crich, D.; Yao, Q. *Tetrahedron Lett.* **1994**, *35*, 6619. (j) Yamazaki, N.; Eichenberger, E.; Curran, D. P. *Tetrahedron Lett.* **1994**, *35*, 6623. β-Mannoside formation by stereoselective reductions of 2-keto-β-glucoside: (k) Liu, K. K.-C.; Danishefsky, S. J. *J. Org. Chem.* **1994**, *59*, 1892. (l) Lichtenthaler, F. W.; Schneider-Adams, T.; Immel, S. *J. Org. Chem.* **1994**, *59*, 6735. β-Mannoside formation using 1, 2-*O*-*cis*-stannylene acetals: (m) Hodosi, G.; Kovác, P. *J. Am. Chem. Soc.* **1997**, *119*, 2335. β-Mannoside formation by aglycon delivery concept: (n) Barresi, F.; Hindsgaul, O. *Can. J. Chem.* **1994**, *72*, 1447. (o) Dan, A.; Ito, Y.; Ogawa, T. *Tetrahedron Lett.* **1995**, *36*, 7487. (p) Dan, A.; Ito, Y.; Ogawa, T. *J. Org. Chem.* **1995**, *60*, 4680. (q) Stork, G.; La Clair, J. J. *J. Am. Chem. Soc.* **1996**, *118*, 247. β-Mannoside formation via intramolecular nucleophilic substitution: (r) Ivanova, I. A.; Nikolaev, A. V. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3093.

(13) (a) Takasu, M.; Naruse, Y.; Yamamoto, H. *Tetrahedron Lett.* **1988**, *29*, 1947. (b) Mikami, T.; Asano, H.; Mitsunobu, O. *Chem. Lett.* **1987**, 2033.

(14) (a) Garegg, P. J.; Hultberg, H.; Wallin, S. *Carbohydr. Res.* **1982**, *108*, 97. (b) Johansson, R.; Samuelsson, B. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2371.

(15) Stork, G.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1987**, *109*, 1565.

(16) (a) Tsunoda, T.; Suzuki, M., Noyori, R.; *Tetrahedron Lett.* **1979**, 4679. (b) Mori, A.; Ishihara, K.; Yamamoto, H. *Tetrahedron Lett.* **1986**, *27*, 987. (c) DeNinno, M. P.; Etienne, J. B.; Duplantier, K. C. *Tetrahedron Lett.* **1995**, *36*, 669.

(17) Several recent reports for the preparation of partially protected sugar derivatives by reductive methods besides those referred to above: (a) Arasappan, A.; Fuchs, P. L. *J. Am. Chem. Soc.* **1995**, *117*, 177. (b) Okawa, M.; Liu, W. C.; Nakai, Y.; Koshida, S.; Fukase, K.; Kusumoto, S. Synlett. **1996**, 1179. (c) Jiang, L.; Chan, T.-H. *Tetrahedron Lett.* **1998**, *39*, 355.

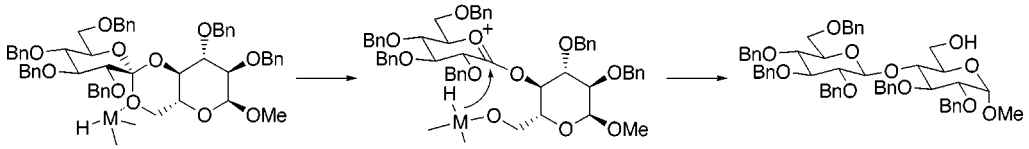
(18) (a) Kolossváry, I.; Guida, W. C. *J. Am. Chem. Soc.* **1996**, *118*, 5011. (b) Cheng, G.; Guida, W. C.; Still, W. C. *J. Am. Chem. Soc.* **1989**, *111*, 4379.

(19) Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendricson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.

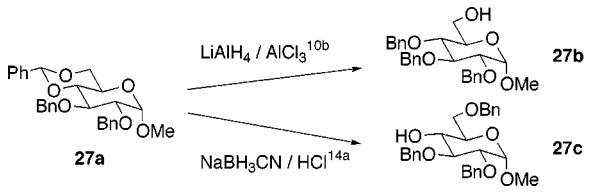
(20) LOMD for ortho ester molecules was continued until around 3000 conformers for each molecule were generated. Even if the steps in LOMD were not enough for the determination of the conformations of the whole molecules including benzyl or phthaloyl protective groups, the conformations of the ring systems in the lower energy conformers were the same in each case.

(21) (a) Lemieux, R. U. In *Molecular Rearrangements*; De Mayo, P., Ed.; Interscience: New York, 1964. (b) Kirby, A. J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*; Springer-Verlag: Berlin, 1983.

Scheme 6



Scheme 7



that all of the ortho esters were afforded as single isomers in the preparation. Considering the structures of the ring systems of the prepared sugar ortho esters, reduction results indicated that the ortho esters (**9a**−**12a**, or **19a**, **20a**) with the A or D type ring system were reduced by $LiAlH_4/AlCl_3$ to afford the corresponding glycosyl-β-(1 → 4)-glycosides in excellent yields but that the reduction with these reagents did not proceed efficiently in the case of the ortho esters (**13a**, **14a**, or **15a**−**18a**) with the B or C type ring system. Further, it was revealed that the ortho esters with the B or C type ring system were efficiently converted into glycosyl-β-(1 → 6)-glycosides by the reduction with $NaBH_3CN/AlCl_3$ but that this combination of the reagents was not effective for the efficient and selective reduction of the other two types (A or D) of ortho esters.

To find the reasons for these features of the reduction results, we tried to reveal the difference or similarity among four structures of the spiro ring systems in Figure 1 and paid attention to the positions of two oxygen atoms of the dioxane ring in each structure with respect to the pyrane ring of glycosylidene moiety. The lower four structures in Figure 1 show the shapes of the spiro ring systems viewed from the axial directions of dioxane rings. It should be noted that the 6-position oxygen atoms were located in the axial positions of pyrane rings in the cases of structures A and D but that 4-position oxygen atoms were in the axial positions in the cases of structure B and C. These considerations revealed the common feature of the above reduction results, that all of the products in Tables 1 and 2 resulted from the selective ring opening at the bonds between the anomeric carbons and the axial oxygen atoms. In the cases of the present reductions, it was appropriate to think that the initial step was the elimination of one of the oxygen atoms in the dioxane ring of each sugar ortho ester and that the second step was the attack of a hydride anion to a resulting oxonium cation (Scheme 6). The higher reactivity of the substituents at the axial positions of the pyran rings in elimination reactions compared to those at the equatorial positions can be rationally explained by the stereoelectronic effects.[22]

The matching or mismatching between the reductants and the substrates in the present reductions was compatible to the well-known selectivity in the reduction of 4-*O*,6-*O*-benzylideneglycosides shown in Scheme 7.[10,14] Although the reasons for the high regioselectivity in the reduction with these reagents have not been clarified even in the cases with simple substrates such as **27a**, 4- and 6-benzyl glycosides (**27b** and **27c**) were afforded selectively from **27a** with $LiAlH_4/AlCl_3$ and $NaBH_3CN$/HCl, respectively.

Finally, the mechanism that accounts for the extremely high β-selectivity should be mentioned. This stereoselectivity would be explained by considering the electronic advantage of the axial anion attack.[23] Moreover, it seemed reasonable to think that a hydride anion on the reducing reagents attacked to the intermediates immediately after the dioxane ring opening or that the reactions shown in Scheme 6 proceeded concertedly. Thus, the attack from an axial direction from which the eliminated oxygen atoms had been bound would be advantageous. As proton atoms attached to the anomeric carbons from the axial direction, β-glycosides were afforded as the resulting products. The high β-selectivity might be the most interesting and important feature of this reductive glycosylation procedure. This superior selectivity was realized by developing a glycosylation method based on the completely different concept.

Preparation and Reduction of the Sugar Ortho Esters Containing Glucosamine Derivatives. The preparation of sugar ortho esters with glucosamine derivatives and the reactivities of these ortho esters were next investigated. We first tried to use *N*-acetylglucosamine derivatives as diol type sugar substrates for the preparation of ortho esters; however, these reactions did not proceed efficiently. As the addition of amide compounds such as DMF inhibited the preparations of the ortho esters from sugar lactones and **7**, the amide part of the substrates might disturb the reactions by a simple interaction with Lewis acid catalyst. Fortunately, it was revealed that the reactions with phthalimide derivatives, which were easily prepared by the established method, proceeded smoothly under the conditions described in the preceding paper.[9] As shown in Scheme 8, *N*-phthaloyl glucosamine **21**[24] was reacted with **1** in the presence of TMSOMe and TMSOTf to afford **23a** in 86% yield. The resulting ortho ester product was afforded as a single isomer, despite the fact that two stereoisomers were possible around the spiro center. It was estimated by molecular modeling studies[18−20,25] that the configuration of the anomeric center of **23a** was *R* and that the conformation of the ring systems of **23a** was shape type A in Figure 1 as in the case of the related ortho ester **9a**.

It was interesting that only two ortho ester products, **23b** and **23c**, were afforded selectively as the products of the reaction of the triol sugar **22**[24] with **1** (Scheme 8). Both of these ortho esters were 4-*O*,6-*O*-glucosylidene-glucosamine, and the configurations of the spiro centers of these ortho esters were the same. 3-Trimethylsilyloxy

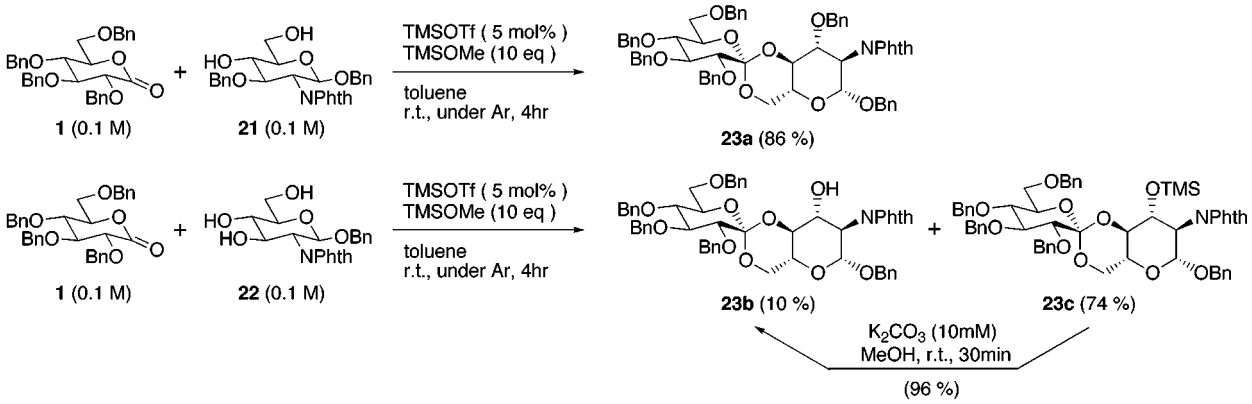
(22) Deslongchamps, P.; Chénevert, R.; Taillefer, R. J.; Moreau, C.; Saunders J. K. *Can. J. Chem.* **1975**, *53*, 1601.

(23) Eliel, E. L.; Nader, F. W. *J. Am. Chem. Soc.* **1970**, *92*, 584.

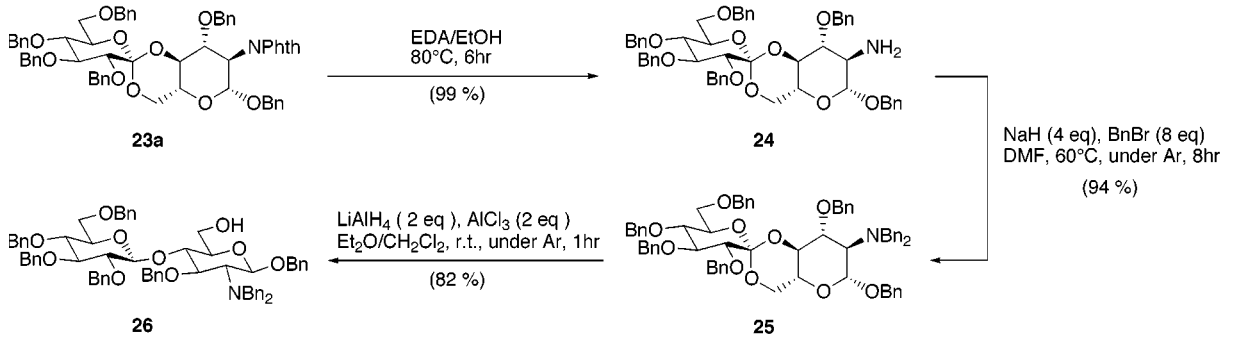
(24) Ogawa, T.; Nakabayashi, S. *Carbohydr. Res.* **1981**, *97*, 81.

(25) LOMD for two possible isomers of ortho ester **23a** were performed, and ΔE values of the most stable comformers of these isomers were compared.[9]

Scheme 8



Scheme 9



product **23c** was easily converted into 3-hydroxy product **23b** by the treatment of methanolic solution of K_2CO_3[26] in 96% yield. Namely, it was possible to prepare a single ortho ester product from trihydroxy sugar **22** and **1** selectively without further protection. The configuration of these ortho esters estimated also to be *R*, because **23a** was obtained from **23b** by benzylation with NaH and benzyl bromide.

As it was estimated that the conformation of the ring systems of **23a** was the A-type shape, this ortho ester was expected to be reduced efficiently by $LiAlH_4/AlCl_3$. However, the *N*-phthalimide functionality was not stable under the reduction conditions with this reagent combination. Thus, **23a** was treated with an excess amount of ethylenediamine in ethanol under reflux conditions according to the reported method for the dephthalation of usual amino sugar glycosides[27] and was converted into **24** quantitatively (Scheme 9). The dibenzylamino compound **25** was also prepared from **24** using NaH and benzyl bromide in 94% yield (Scheme 9). Although **24** resisted the treatment of $LiAlH_4/AlCl_3$, **25** was efficiently reduced with 2 equiv of these reagents to afford β-(1 → 4)-glycoside **26** selectively (Scheme 9), which supported the above estimation for the conformation of the ortho ester ring system.

The present results with glucosamine derivatives may not be so interesting from the point of developing a method for glycosylation; however, they would provide useful information on amino sugar ortho esters. These ortho esters raise interest from the point of designing amino pseudo-saccharide compounds, because the conformations of these molecules are restricted by their unique ortho ester linkages.

Conclusion

Twelve sugar ortho esters (**9a**−**20a**) that possess perhydrospiro[2*H*-pyran-2,2′-pyrano[3,2-*d*][1,3]dioxin] ring systems commonly in their molecules were reduced with $LiAlH_4/AlCl_3$ or $NaBH_3CN/AlCl_3$. The ortho esters (**9a**−**12a**) prepared from the D-sugar lactones (**1**−**4**) and **7** or those (**19a**, **20a**) prepared from the L-sugar lactones (**5**, **6**) and **8** were selectively converted into β-(1 → 4)-glycosides in excellent yields by the treatment of $LiAlH_4/AlCl_3$. In contrast, the other six ortho esters (**15a**−**18a**, or **13a**, **14a**) that were prepared from the combination of the D-sugar lactones and **8** or those of the L-sugar lactones and **7** were efficiently reduced with $NaBH_3CN/AlCl_3$ to afford β-(1 → 6)-glycosides. It was remarkable that extremely high β-selectivity was observed at the anomeric centers of the resulting disaccharides even in the cases with mannosyl or rhamnosyl glycosides. This superior selectivity was realized by developing a glycosylation method based on a completely different concept. Considering the structures of these sugar ortho esters, all of the products were afforded as the result of the cleavage of dioxane rings at the bonds between the anomeric carbons and the oxygen atoms located in the axial positions of pyrane rings of glycosylidene moieties. The higher reactivity at the axial position was rationally explained by considering anomeric effects. It was also revealed that $LiAlH_4/AlCl_3$ and $NaBH_3CN/AlCl_3$ were the appropriate reagents for the reduction at 6-*O* and at 4-*O*, respectively. It should be noted that the resulting disaccharides would be useful units for the synthesis of branched saccharides because they could be used as glycosyl acceptors without further deprotection proce-

(26) Hurst, D. T.; McInnes, A. G. *Can. J. Chem.* **1965**, *43*, 2004.
(27) Kanie, O.; Crawley S. C.; Palcic, M. M.; Hindsgaul, O. *Carbohydr. Res.* **1993**, *243*, 139.

dures. In addition, the method for the preparation of the amino sugar ortho esters was developed, and the features of these ortho esters were revealed. These results would provide useful information for the designing of pseudosaccharide compounds containing an amino functionality.

Experimental Section

General. Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded with a 400 MHz (^{1}H NMR) pulse Fourier transform NMR spectrometer in $CDCl_3$ solution with tetramethylsilane as an internal standard. Thin-layer chromatography (TLC) was performed on precoated plates (Merck TLC aluminum sheets silica 60 F_{254}) with detection by UV light or with phosphomolybdic acid in ethanol/H_2O followed by heating. Column chromatography was performed using SiO_2 (Wakogel C-200, Wako).

Materials. Solvents were freshly distilled prior to use. Reagents for the reduction of sugar ortho esters and the preparation of glucosamine ortho esters were commercial products and were used as received or were purified according to the typical procedures, if necessary. The preparation of the sugar ortho esters except glucosamine derivatives was reported in the preceding paper. Benzyl 3-*O*-benzyl-2-deoxy-2-phthalimido-*β*-D-glucopyranoside (**21**)[24] and benzyl 2-deoxy-2-phthalimido-*β*-D-glucopyranoside (**22**)[24] were prepared according to the established methods.

Calculations. Low-mode search (LOMD)[18] for ortho ester **23a** was performed using MacroModel ver. 6.0[19] with the MM2* derivative of the MM2 force field on a Silicon Graphics IRIS-Indigo workstation until more than 3000 conformers were generated.

Reduction of the Sugar Ortho Esters with $LiAlH_4$/$AlCl_3$. To a solution of ortho ester **9a** (45 mg, 0.05 mmol) in 1:1 Et_2O/CH_2Cl_2 (0.5 mL) was added $LiAlH_4$ (4 mg, 0.1 mmol). The resulting suspension was stirred at room temperature under Ar, and an ethereal solution (0.5 mL) of $AlCl_3$ (13 mg, 0.1 mmol) was slowly added. After 1 h of stirring, the mixture was diluted with Et_2O (4 mL), and a saturated potassium sodium tartrate solution (5 mL) was added cautiously. The mixture was stirred vigorously for 30 min, and then the ether layer was separated. The aqueous layer was extracted twice with Et_2O and then with CH_2Cl_2. The combined extract was washed with brine, dried over Na_2SO_4, filtered, and evaporated to dryness. The product was purified by silica gel column chromatography (Et_2O/hexane 2:1, then Et_2O) to afford **9b** as white solid (42 mg, 92%). The needles of this compound and the glycosides **10b**, **20b** were obtained by recrystallization from Et_2O/hexane.

Methyl 2,3-di-*O*-benzyl-4-*O*-(2,3,4,6-tetra-*O*-benzyl-*β*-D-gluco-pyranosyl)-α-D-glucopyranoside (9b): colorless needle; mp 132.5−134 °C; $[\alpha]^{24}_D$ +19.6° (*c* 1.0, $CHCl_3$); IR (KBr, cm^{-1}) 3474, 2926, 2901, 2870, 1497, 1454, 1402, 1363; MS(FAB) *m/z* 935 (M + K)$^+$, 919 (M + Na)$^+$, 879 (M − OH)$^+$, 828 (M − Bn + Na)$^+$. Anal. Calcd for $C_{55}H_{60}O_{11}$: C, 73.64; H, 6.74. Found: C, 73.58; H, 6.74.

Methyl 2,3-di-*O*-benzyl-4-*O*-(2,3,4,6-tetra-*O*-benzyl-*β*-D-galacto-pyranosyl)-α-D-glucopyranoside (10b): colorless needle; mp 145−146.5 °C; $[\alpha]^{26}_D$ +4.5° (*c* 1.0, $CHCl_3$); IR (KBr, cm^{-1}) 3478, 2891, 2361, 2339, 1497, 1455, 1363; MS(FAB) *m/z* 935 (M + K)$^+$, 919 (M + Na)$^+$, 828 (M − Bn + Na)$^+$. Anal. Calcd for $C_{55}H_{60}O_{11}$: C, 73.64; H, 6.74. Found: C, 73.61; H, 6.77.

Methyl 2,3-di-*O*-benzyl-4-*O*-(2,3,4,6-tetra-*O*-benzyl-*β*-D-manno-pyranosyl)-α-D-glucopyranoside (11b): colorless syrup; $[\alpha]^{24}_D$ −14.3° (*c* 1.1, $CHCl_3$); IR (neat, cm^{-1}) 3464, 3031, 2924, 1605, 1497, 1455, 1364; MS(FAB) *m/z* 935 (M + K)$^+$, 919 (M + Na)$^+$, 828 (M − Bn + Na)$^+$; HRMS(FAB) calcd for $C_{55}H_{58}O_{11}Na$ 919.4034, found 919.4015.

Methyl 2,3-di-*O*-benzyl-4-*O*-(2,3,4-tri-*O*-benzyl-*β*-D-fucopyranosyl)-α-D-glucopyranoside (12b): colorless syrup; $[\alpha]^{22}_D$ +17.6° (*c* 0.7, $CHCl_3$); IR (neat, cm^{-1}) 3380, 2934, 2857, 1724, 1458, 1377; MS(FAB) *m/z* 829 (M + K)$^+$, 813 (M + Na)$^+$, 722 (M − Bn + Na)$^+$; HRMS(FAB) calcd for $C_{48}H_{54}O_{10}Na$ 813.3615, found 813.3615.

Methyl 2,3-di-*O*-benzyl-4-*O*-(2,3,4-tri-*O*-benzyl-*β*-L-fucopyranosyl)-α-D-galactopyranoside (19b): colorless syrup; $[\alpha]^{22}_D$ +31.2° (*c* 1.0, $CHCl_3$); IR (neat, cm^{-1}) 3380, 2926, 1460, 1377; MS(FAB) *m/z* 829 (M + K)$^+$, 813 (M + Na)$^+$, 722 (M − Bn + Na)$^+$; HRMS(FAB) calcd for $C_{48}H_{54}O_{10}Na$ 813.3615, found 813.3616.

Methyl 2,3-di-*O*-benzyl-4-*O*-(2,3,4-tri-*O*-benzyl-*β*-L-rhamnopyranosyl)-α-D-galactopyranoside (20b): colorless needle; mp 78.5−79.5 °C; $[\alpha]^{26}_D$ +64.6° (*c* 0.4, $CHCl_3$); IR (KBr, cm^{-1}) 3348, 2926, 2855, 1462, 1377; MS(FAB) *m/z* 829 (M + K)$^+$, 813 (M + Na)$^+$, 722 (M − Bn + Na)$^+$; HRMS(FAB) calcd for $C_{48}H_{54}O_{10}Na$ 813.3615, found 813.3600, Anal. Calcd for $C_{48}H_{54}O_{10}\cdot{}^1/_2H_2O$: C, 72.07; H, 6.93. Found: C, 72.05; H, 7.01.

Reduction of the Sugar Ortho Esters with $NaBH_3CN$/$AlCl_3$. To a solution of ortho ester **15a** (90 mg, 0.1 mmol) in toluene (1.0 mL) was added $NaBH_3CN$ (42 mg, 0.67 mmol) and molecular sieves 3Å (powder, 100 mg). The resulting suspension was stirred at room temperature under Ar, and a solution of $AlCl_3$ (67 mg, 0.5 mmol) in CH_3CN (1.0 mL) was added slowly. After 2 h of stirring, the mixture was diluted with EtOAc (10 mL), and a saturated potassium sodium tartrate solution (5 mL) was added cautiously. The mixture was stirred vigorously for 1 h, and then the organic layer was separated. The aqueous layer was extracted again with EtOAc, and the combined extract was washed with brine, dried over Na_2SO_4, filtered, and evaporated to dryness. The product was purified by silica gel column chromatography (Et_2O/hexane 1:1, then 2:1) to afford **15b** as a colorless syrup (84 mg, 93%). Two of the following glycosides, **16b** and **18b**, were crystalline compounds, and the needles of them were obtained by recrystallization from Et_2O/hexane.

Methyl 2,3-di-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-*β*-D-gluco-pyranosyl)-α-D-galactopyranoside (15b): colorless syrup; $[\alpha]^{25}_D$ +21.0° (*c* 0.8, $CHCl_3$); IR (neat, cm^{-1}) 3350, 2924, 1462, 1377; MS(FAB) *m/z* 935 (M + K)$^+$, 919 (M + Na)$^+$, 828 (M − Bn + Na)$^+$; HRMS(FAB) calcd for $C_{55}H_{58}O_{11}Na$ 919.4034, found 919.4022.

Methyl 2,3-di-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-*β*-D-galacto-pyranosyl)-α-D-galactopyranoside (16b): colorless needle; mp 99−100 °C; $[\alpha]^{22}_D$ +11.0° (*c* 0.7, $CHCl_3$); IR (neat, cm^{-1}) 3455, 2922, 1711, 1458, 1377; MS(FAB) *m/z* 935 (M + K)$^+$, 919 (M + Na)$^+$, 879 (M − OH)$^+$, 828 (M − Bn + Na)$^+$; HRMS(FAB) calcd for $C_{55}H_{58}O_{11}Na$ 919.4034, found 919.4035. Anal. Calcd for $C_{55}H_{60}O_{11}$: C, 73.64; H, 6.74. Found: C, 73.45; H, 6.97.

Methyl 2,3-di-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-*β*-D-manno-pyranosyl)-α-D-galactopyranoside (17b): colorless syrup; $[\alpha]^{24}_D$ −13.6° (*c* 1.2, $CHCl_3$); IR (neat, cm^{-1}) 3350, 2927, 1460, 1377; MS(FAB) *m/z* 935 (M + K)$^+$, 919 (M + Na)$^+$, 828 (M − Bn + Na)$^+$; HRMS(FAB) calcd for $C_{55}H_{58}O_{11}Na$ 919.4034, found 919.4045.

Methyl 2,3-di-*O*-benzyl-6-*O*-(2,3,4-tri-*O*-benzyl-*β*-D-fucopyranosyl)-α-D-galactopyranoside (18b): colorless needle; mp 85−87 °C; $[\alpha]^{22}_D$ +10.3° (*c* 0.9, $CHCl_3$); IR (neat, cm^{-1}) 3409, 2926, 2855, 1460, 1377; MS(FAB) *m/z* 829 (M + K)$^+$, 813 (M + Na)$^+$, 722 (M − Bn + Na)$^+$; HRMS(FAB) calcd for $C_{48}H_{54}O_{10}Na$ 813.3615, found 813.3597, Anal. Calcd for $C_{48}H_{54}O_{10}$: C, 72.89; H, 6.88. Found: C, 72.82; H, 7.04.

Methyl 2,3-di-*O*-benzyl-6-*O*-(2,3,4-tri-*O*-benzyl-*β*-L-fucopyranosyl)-α-D-glucopyranoside (13b): colorless syrup; $[\alpha]^{22}_D$ +21.2° (*c* 1.5, $CHCl_3$); IR (neat, cm^{-1}) 3347, 2928, 1462, 1377; MS(FAB) *m/z* 829 (M + K)$^+$, 813 (M + Na)$^+$, 722 (M − Bn + Na)$^+$; HRMS(FAB) calcd for $C_{48}H_{54}O_{10}Na$ 813.3615, found 813.3628.

Methyl 2,3-di-*O*-benzyl-6-*O*-(2,3,4-tri-*O*-benzyl-*β*-L-rhamnopyranosyl)-α-D-glucopyranoside (14b): colorless syrup; $[\alpha]^{22}_D$ +53.7° (*c* 1.0, $CHCl_3$); IR (neat, cm^{-1}) 3376, 2926, 1711, 1458, 1377; MS(FAB) *m/z* 829 (M + K)$^+$, 813 (M + Na)$^+$, 722 (M − Bn + Na)$^+$; HRMS(FAB) calcd for $C_{48}H_{54}O_{10}Na$ 813.3615, found 813.3622.

Methyl 2,3-di-*O*-benzyl-6-*O*-(2,3,4-tri-*O*-benzyl-α-L-rhamnopyranosyl)-α-D-glucopyranoside (14c): colorless syrup; $[\alpha]^{25}_D$ −15.0° (*c* 1.1, $CHCl_3$); IR (neat, cm^{-1}) 3474, 3031, 2921,

1497, 1455, 1364; MS(FAB) *m/z* 829 $(M + K)^+$, 813 $(M + Na)^+$, 722 $(M - Bn + Na)^+$; HRMS(FAB) calcd for $C_{48}H_{54}O_{10}Na$ 813.3615, found 813.3618.

Preparation of Glucosamine Ortho Esters. To a suspension of lactone **1** (540 mg, 1.0 mmol) and diol **21** (489 mg, 1.0 mmol) in toluene (10 mL) was added TMSOMe (1.4 mL, 10 mmol) and TMSOTf (9 μL, 5 mol %) at room temperature under Ar. After 1 h of stirring, the solvent was removed under reduced pressure (5 mmHg, 1 h). The reaction vessel was leaked with Ar, and the remainder was again dissolved in toluene. TMSOMe (1.4 mL, 10 mmol) and TMSOTf (9 μL, 5 mol %) were added to the solution, and the mixture was stirred for an additional 30 min. The solvent was removed under reduced pressure again. The remainder was dissolved in CH_2Cl_2 containing 5% of Et_3N and was applied to a silica gel column (Et_2O/hexane 1:2 then 1:1) to afford **23a** as white solid (865 mg, 86%). The ortho esters **23b** and **23c** were also prepared from **1** and triol **22** according to the same procedure in 10% and 74% yields, respectively. The latter ortho ester (**23c**) was converted into the former one (**23b**) in 96% yield by treating a methanol solution of K_2CO_3 (10mM) for 30 min at room temperature.[26] These three ortho esters were all crystalline compounds, and the needles of them were obtained by recrystallization from Et_2O/hexane.

Benzyl 3-*O*-benzyl-2-deoxy-2-phthalimido-4,6-*O*-(2,3,4,6-tetra-*O*-benzyl-D-glucopyranosylidene)-β-D-glucopyranoside (23a): colorless needle; mp 114−115 °C; $[\alpha]^{27}_D$ +34.9° (*c* 1.0, $CHCl_3$); IR (neat, cm^{-1}) 3486, 3031, 2915, 2361, 1781, 1717, 1455, 1389; MS(FAB) *m/z* 1049 $(M + K)^+$, 1033 $(M + Na)^+$, 942 $(M - Bn + Na)^+$. Anal. Calcd for $C_{62}H_{59}NO_{12}$: C, 73.72; H, 5.89; N, 1.39. Found: C, 73.77; H, 5.95; N, 1.53.

Benzyl 2-deoxy-2-phthalimido-4,6-*O*-(2,3,4,6-tetra-*O*-benzyl-D-glucopyranosylidene)-β-D-glucopyranoside (23b): colorless needle; mp 65−66.5 °C; $[\alpha]^{25}_D$ +4.2° (*c* 1.0, $CHCl_3$); IR (neat, cm^{-1}) 3482, 3031, 2923, 2361, 1777, 1717, 1455, 1389; MS(FAB) *m/z* 959 $(M + K)^+$, 943 $(M + Na)^+$, 921 $(M + H)^+$, 852 $(M - Bn + Na)^+$. Anal. Calcd for $C_{55}H_{53}NO_{12}$: C, 71.80; H, 5.81; N, 1.52. Found: C, 71.66; H, 5.92; N, 1.64.

Benzyl 2-deoxy-2-phthalimido-4,6-*O*-(2,3,4,6-tetra-*O*-benzyl-D-glucopyranosylidene)-3-*O*-trimethylsilyl-β-D-glucopyranoside (23c): colorless needle; mp 93.5−94.5 °C; $[\alpha]^{24}_D$ +4.1° (*c* 1.0, $CHCl_3$); IR (neat, cm^{-1}) 3031, 2923, 1777, 1717, 1455, 1389, 1252; MS(FAB) *m/z* 1031 $(M + K)^+$, 1015 $(M + Na)^+$, 993 $(M + H)^+$, 924 $(M - Bn + Na)^+$. Anal. Calcd for $C_{58}H_{61}NO_{12}Si$: C, 70.21; H, 6.20; N, 1.41. Found: C, 70.46; H, 6.32; N, 1.51.

Benzyl 2-Amino-3-*O*-benzyl-2-deoxy-4,6-*O*-(2,3,4,6-tetra-*O*-benzyl-D-glucopyranosylidene)-β-D-glucopyranoside (24). To a solution of **23a** (506 mg 0.50 mmol) in EtOH (20 mL) was added ethylenediamine (5 mL).[27] The mixture was stirred for 6 h at 80 °C under Ar and then evaporated. The residue was directly applied on a silica gel column (AcOEt/hexane 1:1) to afford **24** as colorless needles (434 mg, 99%). The analytical sample was obtained by recrystallization from Et_2O/hexane: mp 109.5−111 °C; $[\alpha]^{25}_D$ +7.7° (*c* 1.1, $CHCl_3$); IR (neat, cm^{-1}) 3031, 2917, 2870, 1455, 1356, 1207; MS(FAB) *m/z* 919 $(M + K)^+$, 903 $(M + Na)^+$, 881 $(M + H)^+$, 812 $(M - Bn + Na)^+$. Anal. Calcd for $C_{54}H_{57}NO_{10}$: C, 73.70; H, 6.53; N, 1.59. Found: C, 73.88; H, 6.57; N, 1.67.

Benzyl 3-*O*-Benzyl-2-deoxy-2-dibenzylamino-4,6-*O*-(2,3,4,6-tetra-*O*-benzyl-D-glucopyranosylidene)-β-D-glucopyranoside (25). A mixture of **24** (87 mg 0.10 mmol), NaH (60% in oil, 17 mg, 0.4 mmol), and benzylbromide (95 μL, 0.8 mmol) in DMF (4 mL) was stirred for 8 h at 60 °C under Ar. The resulting mixture was extracted with AcOEt. The extract was washed twice with water, dried over Na_2SO_4, and evapolated. The residue was purified by silica gel column chromatography (AcOEt/hexane 1:10, then 1:5) to afford **25** as colorless syrup (99 mg, 94%): $[\alpha]^{25}_D$ +0.8° (*c* 1.5, $CHCl_3$); IR (neat, cm^{-1}) 3395, 3063, 3031, 2924, 2867, 2361, 1495, 1455, 1362; MS(FAB) *m/z* 1099 $(M + K)^+$, 1083 $(M + Na)^+$, 1061 $(M + H)^+$, 992 $(M - Bn + Na)^+$; HRMS(FAB) calcd for $C_{68}H_{69}NO_{10}$ 1060.5000, found 1060.4993.

Benzyl 3-*O*-Benzyl-2-deoxy-2-dibenzylamino-4-*O*-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)-β-D-glucopyranoside (26). 25 (53 mg, 0.05 mmol) was reduced with $LiAlH_4$ (4 mg, 0.1 mmol) and $AlCl_3$ (13 mg, 0.1 mmol) according to the procedure describe above to afford **26** as colorless syrup (43 mg, 82%): $[\alpha]^{22}_D$ −16.3° (*c* 0.8, $CHCl_3$); IR (neat, cm^{-1}) 3447, 3063, 3031, 2923, 2867, 1495, 1455, 1360; MS(FAB) *m/z* 1101 $(M + K)^+$, 1085 $(M + Na)^+$, 1063 $(M + H)^+$, 994 $(M - Bn + Na)^+$; HRMS(FAB) calcd for $C_{68}H_{71}NO_{10}$ 1062.5156, found 1062.5145.

Acknowledgment. We are grateful to Misses J. Shimode, J. Nonobe and M. Kitsukawa for spectroscopic measurements. Partial financial support for this research from the Ministry of Education, Science, Sports and Culture of Japan is gratefully acknowledged.

Supporting Information Available: Peak assignments in ^1H NMR and ^{13}C NMR spectra for **9b**−**20b**, **14c**, **23a**, **23b**, **23c**, and **24**−**26**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0005870