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1,2-*cis*-α-Stereoselective Glycosylation Utilizing a Glycosyl-Acceptor-Derived Borinic Ester and Its Application to the Total Synthesis of Natural Glycosphingolipids

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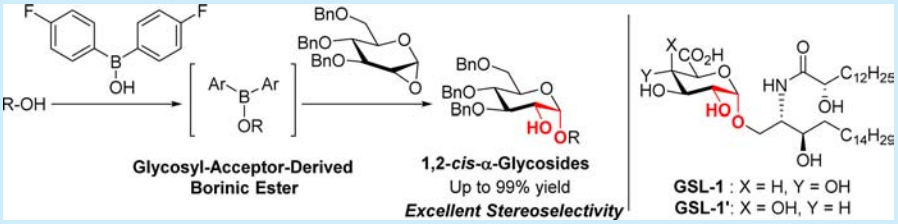
Supporting Information

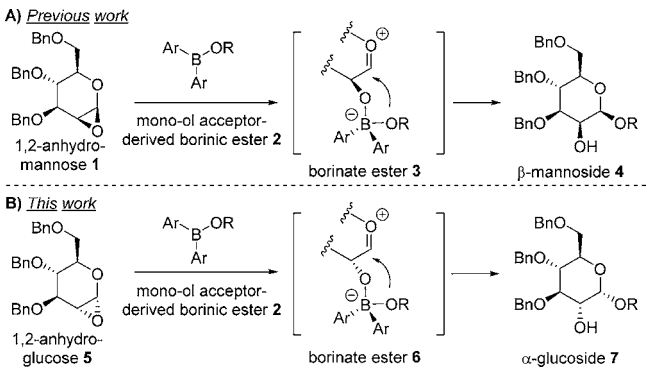


ABSTRACT: 1,2-*cis*-α-Stereoselective glycosylations were conducted using a 1,2-anhydroglucose donor and mono-ol acceptors in the presence of a glycosyl-acceptor-derived borinic ester. Reactions proceeded smoothly under mild conditions to provide the corresponding α-glycosides with high stereoselectivity in moderate to high yields. In addition, the present method was applied successfully to the direct glycosylation of a protected ceramide acceptor and the total synthesis of natural glycosphingolipids (GSLs).

1,2-*cis*-α-Glycosidic linkages are prevalent in many biologically active natural products and glycoconjugates, such as glycolipids. To understand the precise biological roles and structure−activity relationships of these carbohydrates, the syntheses of homogeneous and structurally well-defined carbohydrates have attracted attention in many research fields.[1] However, the stereoselective synthesis of 1,2-*cis*-α-glycosides is a challenge due to the lack of neighboring group participation from a 2-*O*-acyl functional group of a glycosyl donor. To overcome this challenge, efficient indirect[2] and direct[3] methods have been developed. For an example of the indirect method, Hindsgaul et al.[4] reported intramolecular aglycon delivery (IAD), which was extended by Stork et al.,[5] Bols,[6] and Ogawa and Ito.[7] For examples of the direct method, Liu and Danishefsky[8] reported 1,2-*cis*-α-stereoselective glycosylation of a 1,2-anhydroglucose donor and stannylated glycosyl acceptors. Boons et al.,[9] Turnbull et al.,[10] and Fairbanks et al.[11] have reported approaches based on six-membered ring neighboring group participation. Recently, Demchenko et al.[12] reported 1,2-*cis*-α-stereoselective glucosylations involving hydrogen bond-mediated aglycon delivery (HAD) with a 4-*O*-picoloyl thioglucosyl donor.

Another study reported[13] the regio- and 1,2-*cis*-α-stereoselective glycosylation of a 1,2-anhydro donor and a diol acceptor-derived boronic ester catalyst. However, this method could be applied only to 1,2- or 1,3-diol acceptors. More recently, a study[14] on the 1,2-*cis*-β-stereoselective glycosylation of 3,4,6-tri-*O*-benzyl (Bn)-1,2-anhydromannose (**1**) and a mono-ol acceptor-derived borinic ester **2** was reported. In that study, the reaction proceeded smoothly to provide the corresponding β-mannoside **4** with high stereoselectivity in high yield, without any additives under mild conditions (Scheme 1A). Based on these previous studies, the mono-ol acceptor-derived borinic ester **2** was expected to act as an activator of 1,2-anhydroglucose **5**[15] to generate the α-glucoside **7** with high stereoselectivity (Scheme 1B). The present report describes a novel direct and 1,2-*cis*-α-stereoselective glycosylation of **5** and mono-ol acceptors utilizing a glycosyl-

Scheme 1. (A) β-Stereoselective Mannosylation Using a Glycosyl-Acceptor-Derived Borinic Ester; (B) α-Stereoselective Glucosylation using a Glycosyl-Acceptor-Derived Borinic Ester



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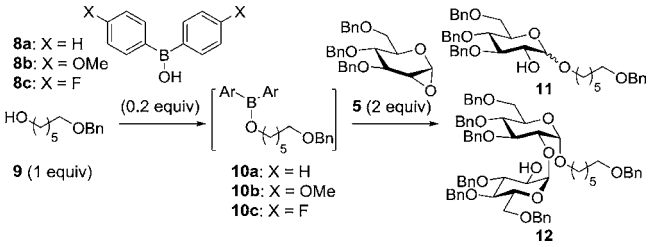
acceptor-derived borinic ester **2** and its application to the total synthesis of natural GSLs.

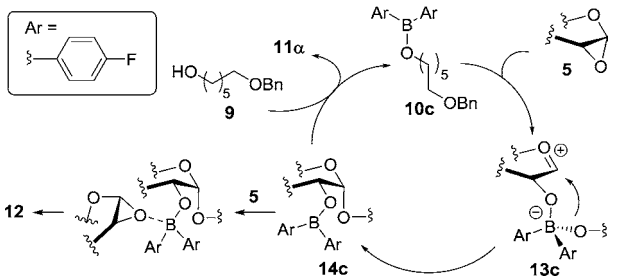
Initial investigations led to the selection of 1,2-anhydroglucose **5** and diphenylborinic acid (**8a**),[16] di(4-methoxy)-phenylborinic acid (**8b**),[17] and di(4-fluoro)phenylborinic acid (**8c**)[17] as the glycosyl donor and arylborinic acids, respectively. First, glycosylation of **5** and 6-*O*-benzyl-1-hexanol (**9**)[18] was attempted using catalytic amounts of **8a**–**c** under different reaction conditions. The results indicated that the glycosylation of **5** and **9** using **8a** in MeCN at −40 °C for 3 h proceeded to give glycoside **11** in 60% yield with a 53:47 α/β ratio (Table 1, entry 1). To improve the α-stereoselectivity, the electrostatic effect of substituents on the benzene ring in the borinic esters was investigated using **8b** and **8c**. When **8b**, which possesses an electron-donating methoxy group, was used, complete β-stereoselectivity was obtained (Table 1, entry 2). In sharp contrast, when **8c**, which possesses an electron-withdrawing fluorine group, was used, glycoside **11** was obtained in 56% yield with high α-stereoselectivity along with disaccharide **12** in 17% yield as a byproduct (Table 1, entry 3). The configurations of both glycosidic bonds in **12** were confirmed to be α by ^{1}H NMR analysis. This result suggests that the borinic ester **10c** induced sequential α-stereoselective glycosylation to provide **12** (Scheme 2). In addition, the results of the electrostatic effect studies suggested that the electron-donating group in **10b** reduced the Lewis acidity of the boron atom, resulting not in oxonium cation formation but S_N2 intermolecular nucleophilic attack of **9** from the β-face of **5**. In contrast, the electron-withdrawing group in **10c** increased the Lewis acidity of the boron atom, resulting in oxonium cation formation, which led to S_N1 type intramolecular nucleophilic attack of the boron-bound oxygen atom in **13c** from the same α-face of **5**. Furthermore, according to the chemical features of the borinic esters, it is reasonable to assume that the electron-donating group in **10b** reduces the activation rate, but increases the glycosylation rate, whereas the electron-withdrawing group in **10c** increases the activation rate, but reduces the glycosylation rate.

Table 1. Glycosylations of 5 and 9 Using Borinic Acids 8a–c under Several Reaction Conditions



entry	borinic acid	solvent	temp (°C)	time (h)	yield (%) 11 (α:β)	yield (%) 12
1	**8a**	MeCN	−40	3	60 (53:47)	0
2	**8b**	MeCN	−40	3	33 (β only)	0
3	**8c**	MeCN	−40	3	56 (96:4)	17
4	**8c**	toluene	−40	3	76 (26:74)	0
5	**8c**	CH_2Cl_2	−40	3	52 (23:77)	0
6	**8c**	Et_2O	−40	3	8 (25:75)	0
7	**8c**	THF	−40	3	61 (95:5)	0
8	**8c**	THF	−40	6	82 (95:5)	6
9	**8c**	THF	−60	6	85 (α only)	0

Scheme 2. Proposed Catalytic Cycle for Glycosylation of 5 and 9 Using 8c and Proposed Mechanism for the Generation of 12



Taken together, the experimental results and these features of the borinic esters suggest that the rate-determining step of this reaction is the activation step, not the intramolecular glycosylation step, which was the rate-determining step in our previously reported boronic ester catalyzed 1,2-*cis*-α-glycosylation.[13]

Next, the effect of the reaction solvent on the glycosylation of **5** and **9** was investigated using **8c** in toluene, CH_2Cl_2, Et_2O, and THF. The results showed that the use of toluene and CH_2Cl_2 led to β-stereoselectivity (Table 1, entries 4 and 5). When Et_2O was used, the chemical yield of **11** was much lower than that using MeCN as the solvent (Table 1, entry 6). In contrast, when THF was used, the reaction proceeded smoothly to provide **11** in 61% yield with high α-stereoselectivity without any accompanying **12** (Table 1, entry 7). Thus, THF was the best solvent for this reaction. These results on the effect of the reaction solvent may suggest that strong coordinating solvents such as THF and MeCN attack from the β-face of **5** to facilitate the oxonium cation formation.

Next, the reaction time and temperature were optimized. When glycosylation was conducted at −40 °C for 6 h, the chemical yield of **11** increased by up to 82% yield but was accompanied by **12** in 6% yield (Table 1, entry 8). To suppress overreaction, glycosylation was examined at −60 °C for 6 h, which resulted in the production of **11** in the best yield (85%) with complete α-stereoselectivity (Table 1, entry 9).

The scope and limitations of the glycosylation method were also investigated using several alcohols. The results indicated that the use of primary alcohols **15**–**19** and secondary alcohols **20**–**22** allowed glycosylation to proceed smoothly under mild conditions to provide the corresponding α-glucosides **25**–**32** in high yields with excellent α-stereoselectivity (Table 2, entries 1–8). However, when secondary alcohols **23** and **24** were used, the chemical yields of the corresponding α-glucosides **33** and **34** were much lower than those of **25**–**32**, probably due to the low binding affinities of the relatively hindered **23** and **24** toward **8c**. Thus, glycosylation of **5** and **23** or **24** in the presence of 2 equiv of **8c** in THF was examined. The glycosylation proceeded to give **33** and **34** in 59% and 38% yields, respectively, with complete α-stereoselectivity (Table 2, entries 9 and 10). These results suggested that the chemical yield depended on the chemical structure of the glycosyl acceptor, because the reactivity of the glycosylation step and the activation step of **5** by the glycosyl-acceptor-derived borinic ester were strongly influenced by steric effects of the glycosyl acceptor.

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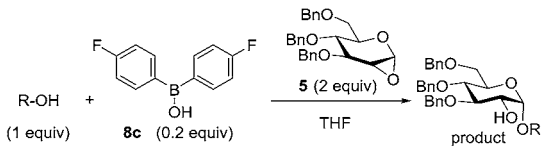
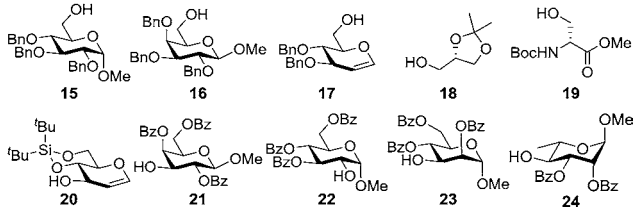
Table 2. Glycosylations of 5 and Alcohols Using a Catalytic Amount of 8c



acceptors:



entry	acceptor	temp (°C)	time (h)	product	yield (%)	α/β ratio
1	**15**	−80	6	**25**	99	α only
2	**16**	−60	6	**26**	85	α only
3	**17**	−80	3	**27**	99	α only
4	**18**	−80	3	**28**	89	α only
5	**19**	−40	6	**29**	99	α only
6	**20**	−40	6	**30**	75	α only
7[a]	**21**	−40	6	**31**	82	α only
8	**22**	−40	24	**32**	80	α only
9[b]	**23**	−80	6	**33**	59	α only
10[a,b]	**24**	−40	24	**34**	38	α only

[a]MeCN was employed as a solvent. [b]2 equiv of **8c** were used.

In addition, the present glycosylation method was applied to the total synthesis of biologically active natural GSLs, GSL-1, and GSL-1′ (Figure 1A). GSL-1 was isolated from *F. devorans*

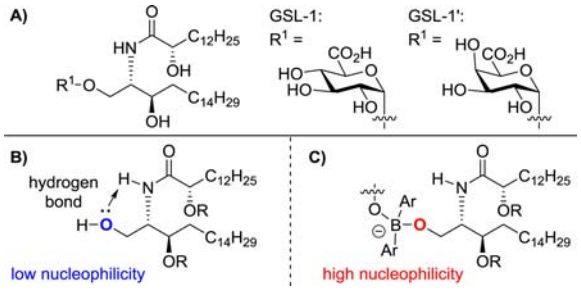
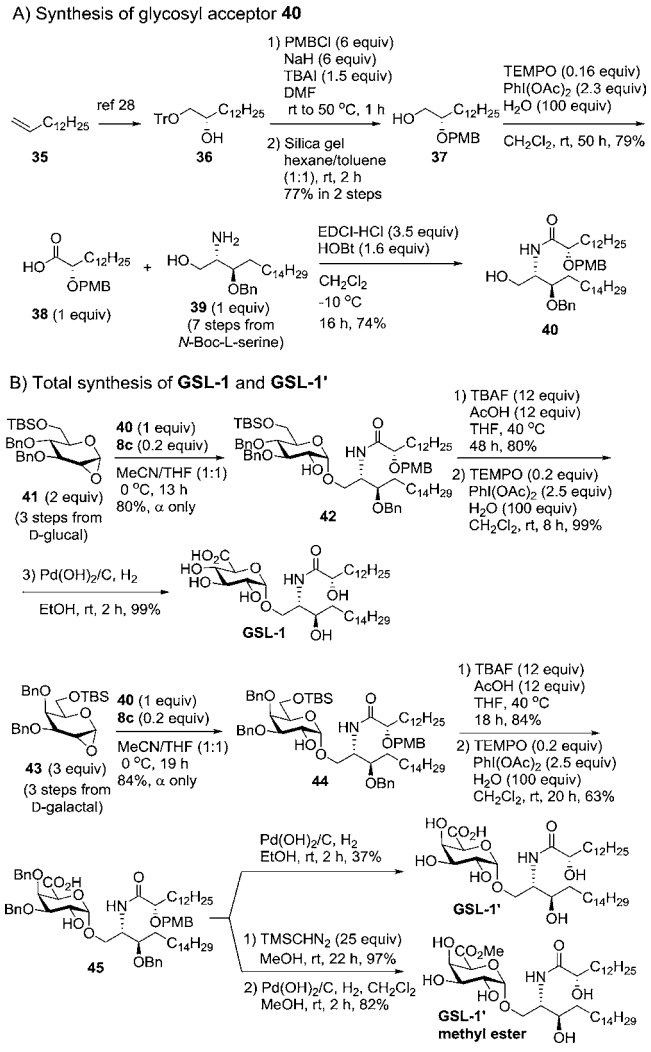


Figure 1. Nucleophilicity of the C-1 OH group in the ceramide acceptor.

ATCC 10829[19] and *S. paucimobilis*,[20] and GSL-1′ was isolated from *S. wittichii*[21] and *S. yanoikuyae*.[22] Structurally, these compounds contain the hydrophobic moiety ceramide, and the hydrophilic monosaccharide group 1,2-*cis*-α-glucuronic or galacturonic acid. These GSLs are recognized by human natural killer T (NKT) cells after binding to CD1d and induce a significant immune response.[23] From a synthetic standpoint, two problems need to be overcome in the direct glycosylation of a glycosyl donor and ceramide acceptor: 1,2-*cis*-α-stereoselectivity and low nucleophilicity of the C1 hydroxyl group in the ceramide acceptor due to hydrogen bond formation between the electron pair on the C1 oxygen and amide hydrogen (Figure 1B).[24] To manage the low nucleophilicity, sphingosine-derived acceptors, such as an azido-sphingosine,[25] have been widely used in the synthesis of various GSLs. Savage et al.[26] and Wong et al.[27] reported the total synthesis of GSL-1 and GSL-1′ using azido-sphingosine and *N*-Boc-sphingosine, respectively. In contrast, although Seeberger et al.[28] reported the total synthesis of GSL-1′ using a protected ceramide acceptor, the α-stereoselectivity probably could be improved. The present method was designed to overcome both of these obstacles since the protected ceramide-derived borinate ester could increase the nucleophilicity of the boron bound oxygen atom and lead to 1,2-*cis*-α-stereoselective glycosylation (Figure 1C). The synthetic schemes of GSL-1 and GSL-1′ are summarized in Scheme 3.

Scheme 3. Total Synthesis of GSL-1 and GSL-1′



Initially, alcohol **36**[28] was prepared from 1-tetradecene (**35**). Protection of a hydroxyl group in **36** as a *p*-methoxybenzyl (PMB) ether, followed by deprotection of a Tr group, provided **37** in 77% overall yield. Oxidation of the resulting primary hydroxyl group in **37**, followed by amidation with **39**,[29] afforded the ceramide acceptor **40** in good yield. Next, glycosylation of **40** and **41** (Scheme S1 in the Supporting Information (SI)) was performed using a catalytic amount of **8c**. The result showed that the desired α-glucoside **42** was obtained in 80% yield with excellent α-stereoselectivity. Deprotection of the TBS group in **42** and oxidation of the resulting primary hydroxyl group, followed by removal of the benzyl and PMB groups, furnished the desired GSL-1. The ^{1}H

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NMR, ^{13}C NMR, and HRMS data for a sample of synthetic GSL-1 were identical to those reported.[26]

Next, glycosylation of **40** and **43** (Scheme S2 in SI) was examined using a catalytic amount of **8c**. This reaction also proceeded smoothly to provide the desired α-galactoside **44** in 84% yield with excellent α-stereoselectivity. Deprotection of the TBS group in **44**, followed by oxidation of the resulting primary hydroxyl group, gave partly protected GSL-1′ **45**. Removal of the Bn and PMB groups in **45** furnished GSL-1′. Finally, methyl esterification of **45**, followed by removal of the Bn and PMB groups, furnished the GSL-1′ methyl ester, confirmed by comparing the ^{1}H NMR data to those reported.[22]

In conclusion, direct and highly α-stereoselective glycosylation of 1,2-anhydroglucose **5** and mono-ol acceptors has been developed utilizing a glycosyl-acceptor-derived borinic ester under mild conditions. The use of di(4-fluoro)phenylborinic acid (**8c**) in THF or MeCN was effective for glycosylation with several mono-ol acceptors. This method was applied successfully to the direct glycosylation of a protected ceramide acceptor and the total synthesis of GSL-1 and GSL-1′. Detailed mechanistic studies of this method, its application to other types of acceptors, and the synthetic studies of other biologically active compounds using this method are underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02488.

Experimental methods and synthetic details; ^{1}H and ^{13}C NMR data (PDF)

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Notes

The authors declare no competing financial interest.

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