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ARTICLE TYPE

Regio- and stereoselective β-mannosylation using a boronic acid catalyst and its application to the synthesis of a tetrasaccharide repeating unit of lipopolysaccharide derived from *E. coli* O75

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Regio- and stereoselective β-mannosylations using 1,2-anhydromannose and diol sugar acceptors in the presence of a boronic acid catalyst proceeded smoothly to give the corresponding β-mannosides with high regio- and β–stereoselectivities in high yields without further additives under mild conditions. In addition, this glycosylation method was applied successfully to the synthesis of a tetrasaccharide repeating unit of lipopolysaccharide (LPS) derived from *E. coli* O75.

One of the most challenging aspects of oligosaccharide synthesis is establishing the regio- and α/β-stereoselectivity of the glycosidic linkages. For α/β-stereoselectivity, a method based on neighboring-group participation from a 2-*O*-acyl functionality in the glycosyl donor is most promising for providing 1,2-*trans*-glycosides. However, the stereoselective synthesis of 1,2-*cis*-glycosides, especially β-mannosides, remains difficult due to the non-availability of neighboring-group participation and both anomeric and steric effects of the axial substituent at the C2 position.[1] To overcome these obstacles, efforts have been made to develop efficient methods, including direct β-mannosylation using silver salts with mannosyl halides as glycosyl donors,[2] inversion of the C2 configuration of β-glucosides,[3] intramolecular aglycon delivery (IAD),[4] anomeric *O*-alkylations,[5] use of 4,6-*O*-benzylidene-,[6] 4,6-*O*-arylboronate-[7] or 4,6-*O*-silylene-[8] protected mannosyl donors, hydrogen-mediated aglycon delivery (HAD) with 3- and/or 6-*O*-picoloyl mannosyl donors,[9] use of a glycosyl-acceptor-derived borinic ester catalyst with 1,2-anhydromannose donor,[10] and use of 2,6-[11] or 3,6-lactone mannosyl donors.[12] For regioselectivity, efficient approaches using organotin[13] or organoboron reagents[14-16] have been developed; however, most of the glycosylations were regio- and 1,2-*trans*-selective, and few were regio- and 1,2-*cis*-selective.

In this context, regio- and 1,2-*cis*-α-stereoselective glycosylations using 1,2-anhydroglucose donor **1** and diol

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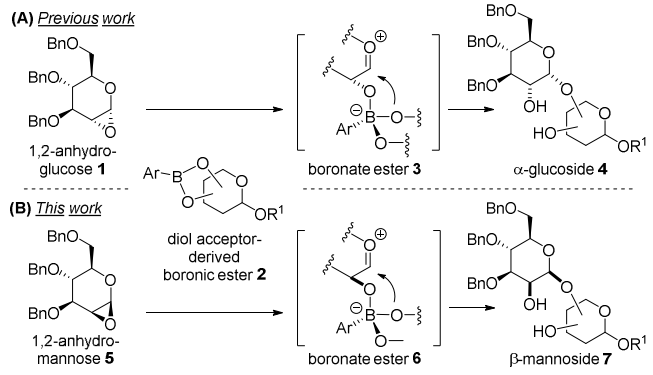

Scheme 1 Regio- and stereoselective (A) α-glucosylation and (B) β-mannosylation using a glycosyl-acceptor-derived boronic ester.

glycosyl acceptors in the presence of the corresponding glycosyl-acceptor-derived boronic ester catalyst **2** have been recently reported.[17]

In the present study, the reactions proceeded smoothly to provide the corresponding α-glucoside **4** with high regio- and stereoselectivities in high yield under mild conditions (Scheme 1A). Based on previous work, the boronic ester **2** was expected to act as an activator of 1,2-anhydromannose **5**[18] to generate β-mannoside **7** with high regio- and stereoselectivities (Scheme 1B). This report describes a novel regio- and stereoselective β-mannosylation of **5** and a diol glycosyl acceptor utilizing a boronic acid catalyst and its application to the synthesis of a tetrasaccharide repeating unit of LPS derived from *E. coli* O75.

Initial investigation led to the selection of 1,2-anhydromannose **5** and 4-methoxyphenylboronic acid (**8a**), phenylboronic acid (**8b**), 4-fluorophenylboronic acid (**8c**), and 4-nitrophenylboronic acid (**8d**) as the glycosyl donor and arylboronic acids, respectively. First, glycosylation of **5** and the 1,3-diol sugar acceptor, glucoside **9**, was attempted using catalytic amounts of the glycosyl-acceptor-derived boronic esters **10a–d,** which were prepared by mixing **9** and catalytic amounts of **8a–d** in refluxing toluene, followed by concentration in vacuo**,** respectively, under different reaction conditions. The results indicated that glycosylation of **5** and **9** using **8a**, which possesses an electron-donating methoxy group, in MeCN at 25 °C for 6 h proceeded to give (1,6) mannoside **11** in 43% yield with a 51:49 β/α ratio as a single regioisomer (Table 1, entry 1).[19] To improve the β-

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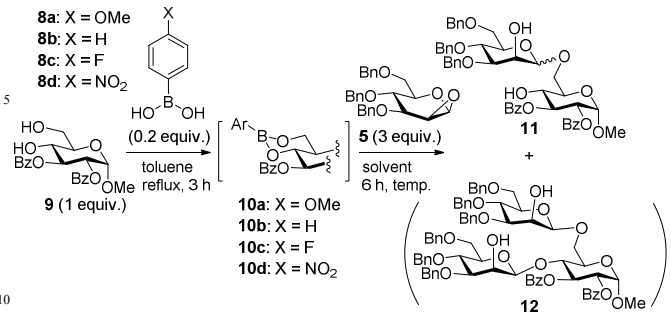
Table 1 Glycosylations of **5** and **9** using glycosyl-acceptor-derived boronic ester catalysts **10a**–**d** under different reaction conditions.



entry	boronic acid	temp (°C)	solvent	yield of **11** (%)	β/α ratio of **11**	yield of **12** (%)
1	**8a**	25	MeCN	43	51/49	0
2	**8b**	25	MeCN	69	83/17	0
3	**8c**	25	MeCN	72	92/8	0
4	**8d**	25	MeCN	79	β only	10
5	**8d**	0	MeCN	87	β only	trace
6	**8d**	−20	MeCN	90	β only	0
7	**8d**	−20	THF	81	94/6	0
8	**8d**	−20	CH_2Cl_2	46	43/57	0
9	**8d**	−20	toluene	56	52/48	0

stereoselectivity, the electrostatic effect of substituents on the benzene ring in the boronic acids was investigated using **8b-d**. When **8b** with no substituent or **8c** with an electron-withdrawing fluorine group was used, both the chemical yield and β-stereoselectivity of **11** increased significantly (Table 1, entries 2 and 3). Furthermore, when **8d** with a strong electron-withdrawing nitro group was used, β(1,6) mannoside **11β** was obtained as a single isomer in 79% yield, along with trisaccharide **12** in 10% yield as an overreaction byproduct[20] (Table 1, entry 4). The anomeric configurations of **11α** and **11β** were determined from their $^1J_{CH}$ coupling constants, 168 and 158 Hz, respectively.[21] The results suggest that the electron-donating group in **10a** reduces the Lewis acidity of the boron atom, causing weak activation of **5** by **10a**, and intermolecular S_N2 type substitution of **9** from the α-face of **5**. However, the electron-withdrawing group in **10d** increases the Lewis acidity of the boron atom, which causes activation of **5** by **10d**, formation of the oxonium cation, and S_N1 type intramolecular nucleophilic attack of the boron-bound oxygen atom in the boronate ester from the same β-face of the oxonium cation (Fig. 1). The high regioselectivity observed can be explained through the following proposed transition state models. During glycosylation of **5** and **9** using **10d**, compound **5** approaches from the equatorial face of the boron atom in **10d** to minimize steric hindrance, and generates the oxonium cation involving the boronate ester. At this stage, since significant steric hindrance between the anomeric proton of the oxonium cation and the benzene ring of the boronate ester destabilizes the TS-1 transition state, glycosylation by the oxygen atom at the 6-position occurs through the favored TS-2 to give **11β** (Fig. 2A).

Next, the reaction temperature and solvent were optimized for glycosylation of **5** and **9**. When the glycosylations were conducted at 0 °C and −20 °C, the chemical yields of **11β** increased to 87% and 90%, respectively, because of the decreased

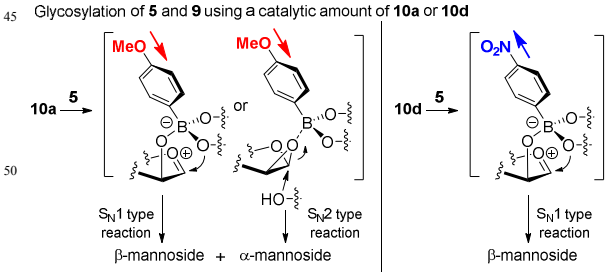
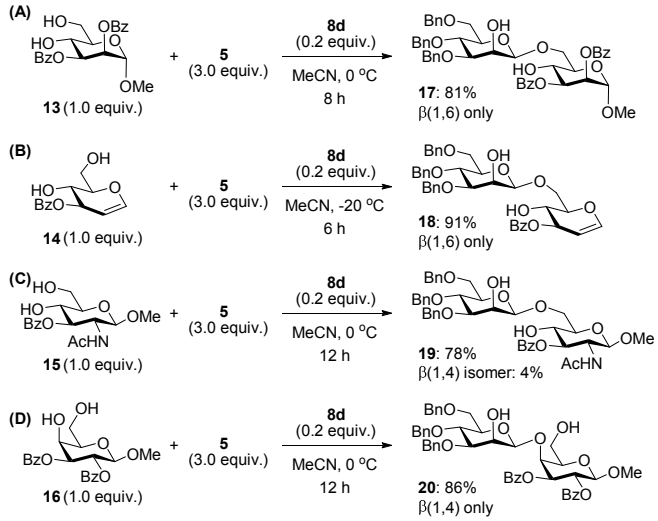


Fig. 1 Electrostatic effect of the substituents on the benzene ring in **10a** and **10d** during glycosylation of **5** and **9**.

yield of **12** (Table 1, entries 5 and 6). The solvent effect was also examined using THF, CH_2Cl_2, and toluene. The results indicated that only MeCN gave complete β-stereoselectivity for the glycosylation reaction (Table 1, entries 6–9). Thus, glycosylaton of **5** and **9** using **10d** in MeCN at −20 °C for 6 h provided the best outcome, producing **11β** in 90% yield as a single isomer (Table 1, entry 6). In addition, when the glycosylation of **5** and **9** using **8d** without pre-formation of **10d** was examined, almost the same result was obtained (85% yield as a single isomer). This result indicated that pre-formation of **10d** was not necessary for this glycosylation reaction.

Next, the regioselectivity and applicability of this glycosylation method was examined using several 1,3-diol sugar acceptors (**13**-**16**; Scheme 2). The use of mannoside **13** and glucal **14** as glycosyl acceptors in the presence of **8d** provided excellent regio- and β-stereoselectivities, and produced only the corresponding β(1,6) mannosides **17** and **18** as single isomers in 81% and 91% yields, respectively (Schemes 2A and 2B).[19] In addition, when glucosaminide **15** was employed for glycosylation using **8d**, the corresponding regioisomer β(1,4) mannoside was obtained in 4% yield, but high regioselectivity and excellent β-stereoselectivity were observed, and the β(1,6) mannoside **19** was obtained in high yield (Scheme 2C).[19] Interestingly, when galactoside **16** was employed under the same reaction conditions, excellent regio- and β-stereoselectivities were observed, and only glycosylation at the axial 4-OH proceeded to give the β(1,4) mannoside **20** as a single isomer in high yield (Scheme 2D).[19] The high regioselectivity observed may be due to the proposed



Scheme 2 Glycosylation of **5** and the 1,3-diol sugar acceptors **13**-**16** using **8d**.

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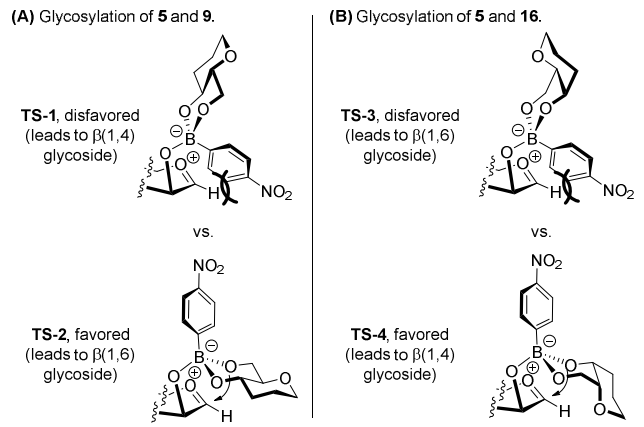
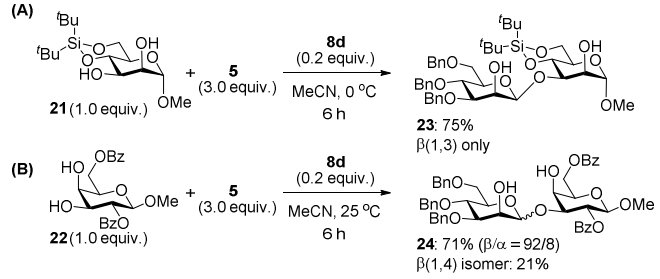


Fig. 2 Proposed rationale for the regioselectivity in the glycosylation of (A) **5** and **9**, and (B) **5** and **16**.

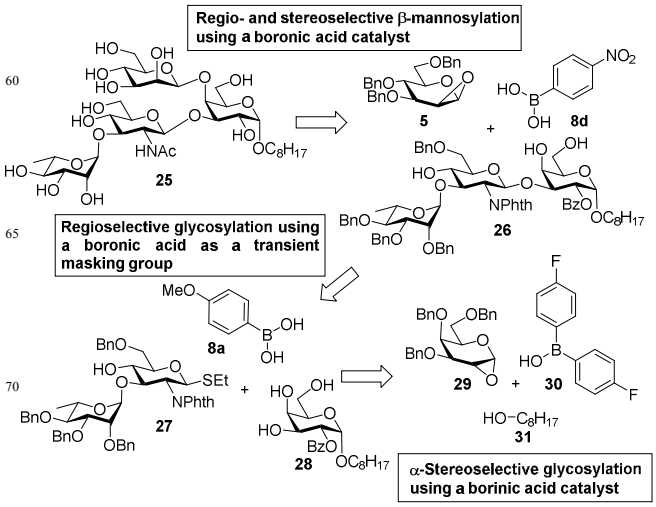
transition state models TS-3 and TS-4 shown in Fig. 2B. Thus, in the glycosylation of **5** and **16** using **8d**, steric hindrance between the anomeric proton of the oxonium cation and the benzene ring of the boronate ester destabilized TS-3. Therefore, **20** was regioselectively obtained through the favored TS-4. In addition, these results interestingly indicate that the observed regioselectivities in the glycosylations were completely opposite to those in the previously reported glycosylations using 1,2-anhydroglucose donor.[17]

To investigate further the generality of this present method, we next examined the glycosylations of **5** with *cis*-1,2-diol sugar acceptors, that is the mannoside **21** and galactoside **22**. When the glycosylation of **5** and **21** using **8d** was conducted, the β(1,3) glycoside **23** was obtained in 75% yield as a single isomer with excellent β-stereoselectivity (Scheme 3A).[19] When the glycosylation of **5** and **22** in the presence of **8d** was conducted, it was found that the glycosylation also proceeded smoothly to give **24** in 71% yield with high β-stereoselectivity (β/α = 92/8) along with minor β(1,4) isomer in 21% yield (Scheme 3B).[19] These results indicate that although the regioselectivity in the glycosylation of **5** and **22** was moderate, *cis*-1,2-diol acceptors also can be applied for the present glycosylation method.



Scheme 3 Glycosylation of **5** and the *cis*-1,2-diol sugar acceptors **21** and **22** using **8d**.

Finally, the present glycosylation method was applied to the synthesis of the octyl tetrasaccharide glycoside **25**. The tetrasaccharide structure in **25** was reported by Erbing and co-workers[22] as a repeating unit of O-specific side-chains of LPS derived from *E. coli* O75. Structurally, the main difficulty in the synthesis of the tetrasaccharide is direct and stereoselective construction of β(1,4) mannosidic linkage. In 2012, although



Scheme 4 Retrosynthetic analysis of the tetrasaccharide **25**.

Misra *et al*. reported the synthesis of the tetrasaccharide structure as its 4-methoxyphenyl (PMP) glycoside, they used the inversion method of the C2 configuration of the β-glucoside.[23] The retrosynthetic analysis of **25** is shown in Scheme 4. Compound **25** could be synthesized by the present regio- and stereoselective β-mannosylation of **5** and trisaccharide **26** using **8d** as a catalyst, followed by deprotection reactions. The trisaccharide **26** could be prepared by regioselective glycosylation of **27** and **28** using **8a** as a transient masking group[16] of the 1,3-diol in **28**. α-Galactoside **28** would be prepared by 1,2-*cis*-α-stereoselective glycosylation[24] of **29** and octanol (**31**) using a bis(4-fluorophenyl)borinic acid (**30**).

The synthetic scheme for **25** is summarized in Scheme 5. First, the α-galactoside **32** was synthesized through α-stereoselective glycosylation of 1,2-anhydrogalactose **29** and octanol (**31**) using a catalytic amount of **30** in THF at 0 °C for 24 h, producing the desired α-galactoside **32** in 74% yield with excellent α-stereoselectivity. The anomeric configuration of **32** was determined by a coupling constant, $J_{1,2}$ = 4.0 Hz. Compound **32** was converted into the triol acceptor **28** by benzoylation and debenzylation. Next, glycosylation of **27** and **28** was examined using a stochiometric amount of **8a** as a transient masking group of the 1,3-diol. After mixing **28** and **8a** in acetone at reflux for 2 h, followed by concentration *in vacuo* to form boronic ester **33**, glycosylation of **27** (synthetic scheme is shown in the ESI) in the presence of MS 4 Å in DCE/toluene at −30 °C for 3 h was conducted. The glycosylation proceeded smoothly to give β(1,3) glycoside **26** ($J_{1,2}$ = 8.5 Hz) in 96% yield with complete regioselectivity.[19] Next, glycosylation of **26** and **5** was conducted using a catalytic amount of **8d** in MeCN at 0 °C for 24 h, which resulted in 91% yield of the desired β(1,4) mannoside **34** ($^1J_{CH}$ = 161 Hz)[21] with complete regio- and β-stereoselectivity.[19] These results demonstrate the high efficiency and generality of the present glycosylation method. In addition, removal of benzoyl and phthaloyl groups, followed by acetylation gave **35**. Finally, deprotection of the benzyl and acetyl groups in **35** furnished the desired tetrasaccharide **25**.

In conclusion, the first regio- and stereoselective β-mannosylation were developed utilizing a boronic acid catalyst without any further additives under mild reaction conditions. The

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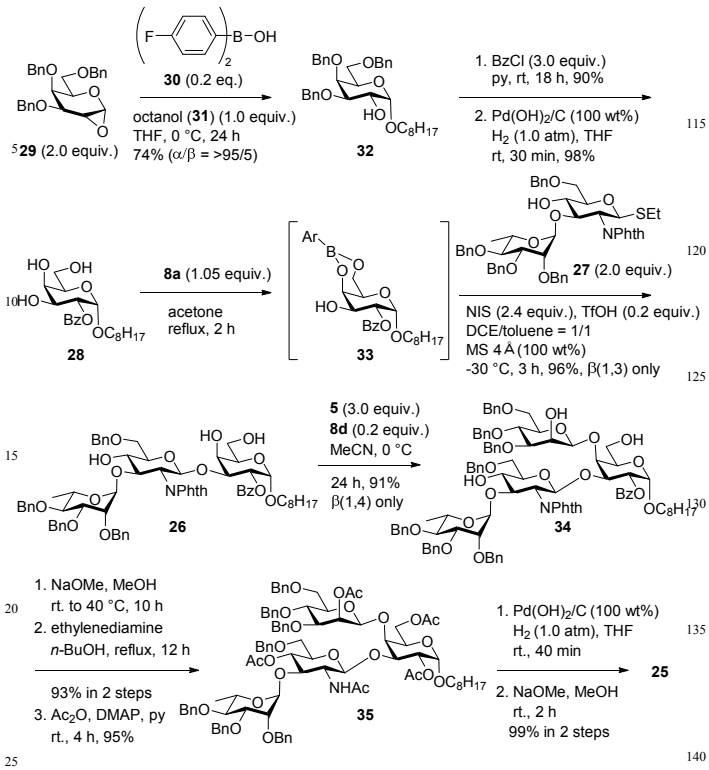

Scheme 5 Synthetic scheme for tetrasaccharide **25**.[25]

use of 1,2-anhydromannose donor **5** and 4-nitrophenylboronic acid (**8d**) in MeCN was effective for the glycosylations with several diol acceptors. Furthermore, this glycosylation method was applied successfully to the synthesis of the tetrasaccharide repeating unit of LPS derived from *E. coli* O75. Therefore, we anticipate that this method will be widely applicable to the other types of donors, such as the 1,2-anhydromannose donors protected with ester protecting groups, and the acceptors for the synthesis of the other compounds. These applications and detailed mechanistic studies of this method are now underway.

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19 The glycosidic linkage of the obtained glycoside was confirmed by acetylation or benzoylation, and subsequent ^{1}H NMR analysis of the corresponding acetylated or benzoylated glycoside, respectively. see the ESI.

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