Selection of neighboring group participation intermediates of fully acylated donors around the glycosylation sites in oligosaccharide acceptors

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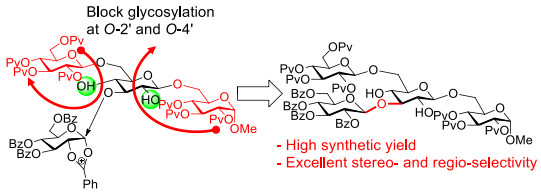
Supporting Information Placeholder



ABSTRACT: Stereo- and regio-selective formation of glycosidic linkages are a challenging topic in oligosaccharide syntheses. The stereoselective construction of 1,2-*trans*-glycosides generally involves neighboring group participation, which is less successful when synthesizing β-1,3-linked oligosaccharides. The combined steric effect of a 2-*O*-substituent and an aglycon moiety in acceptors increases the efficiency of glycosylation *via* neighboring group participation. This steric effect was reduced by using vicinal polyol acceptors and was demonstrated in the synthesis of 1,3-linked branched oligosaccharides.

Stereo- and regio-selective construction of the desired glycosidic linkages is one of the most important tasks in oligosaccharide syntheses.[1] Utilizing the anchimeric assistance (also known as neighboring group participation) of the acyl group at the 2-*O*-position of the glycosyl donors is the best established strategy for preparing 1,2-*trans* glycosides.[2] The carbonyl functionality at the 2-*O*-position of the donor is considered to attack an incipient oxocarbenium ion to give a 1,2-dioxonium ion intermediate, which exclusively leads to the corresponding 1,2-*trans* glycosidic compound. However, the inherent drawbacks of this glycosylation include lack of stereoselectivity and/or extremely low yield of the desired glycoside even when using 2-*O*-acylated donors. As an explanation of this phenomena, Spijker and van Boeckel proposed a double stereodifferentiation concept, in which the unfavorable steric hindrance between the 1,2-dioxonium ion intermediate and the acceptor degraded the stereochemical outcome of the obtained glycoside as shown in Figure 1a.[3] Similar trends were also observed in subsequent studies on glucosylation,[4] mannosylation,[5] and galactosylation.[6] In addition to the 2-*O*-acyl groups, functional groups at remote positions, *e.g.*, 6-*O*-acylated D-glucosyl and 4,6-*O*-acylated D-galactosyl donors, contribute to the formation of 1,2-*cis* glycosides.[7] Although there are controversies around this hypothesis,[8] several research groups have provided evidence supporting the remote participation by performing trapping experiments for dioxonium cation intermediates[9] and by computational calculations.[10]

When investigating the feasibility of using dodecyl thioglycosides as glycosyl donors,[11] we observed complete loss of β-selectivity in the reaction of a fully benzoylated donor and a partially benzoylated gentiopentaoside acceptor to construct a β-1,3-linked oligosaccharides.[12] A similar phenomenon was also observed in the glycosylation with acetylated glucosyl trichloroacetimidates.[13] If these phenomena can be fitted into the category of double stereodifferentiation, why did the relatively small acetyl and benzoyl groups in the acceptors influence the anomeric configuration of the glycosides? Herein, we clarify the influence of the structures of glycosyl acceptors on the glycosylation outcome in the synthesis of branched oligosaccharides.

We first compared the glycosylation of monosaccharide **1** and trisaccharide **2** acceptor with fully benzoylated donor **3** using *N*-iodosuccinimide (NIS)–TfOH[14] as a promoter (Scheme 1). The reaction of **1** with **3** gave β-linked disaccharide **5** in 58%yield, which can be explained by the mechanism involving a "normal" 1,2-dioxonium ion intermediate. On the other hand, acceptor **2** gave an anomeric mixture (α:β = 42:58) of tetrasaccharide **6** in 41% yield. However, we found that the corresponding 6-*O*-benzylated donor **4** afforded a "normal" β-linked tetrasaccharide **7** as the sole product in 40% yield. Since the presence of a non-participating group at the 6-position led to the recovery of stereoselectivity, remote participation of the 6-*O*-benzoyl group in fully benzoylated donor **3** might induce the α-face attack of **2** *via* a 1,6-dioxonium ion intermediate.

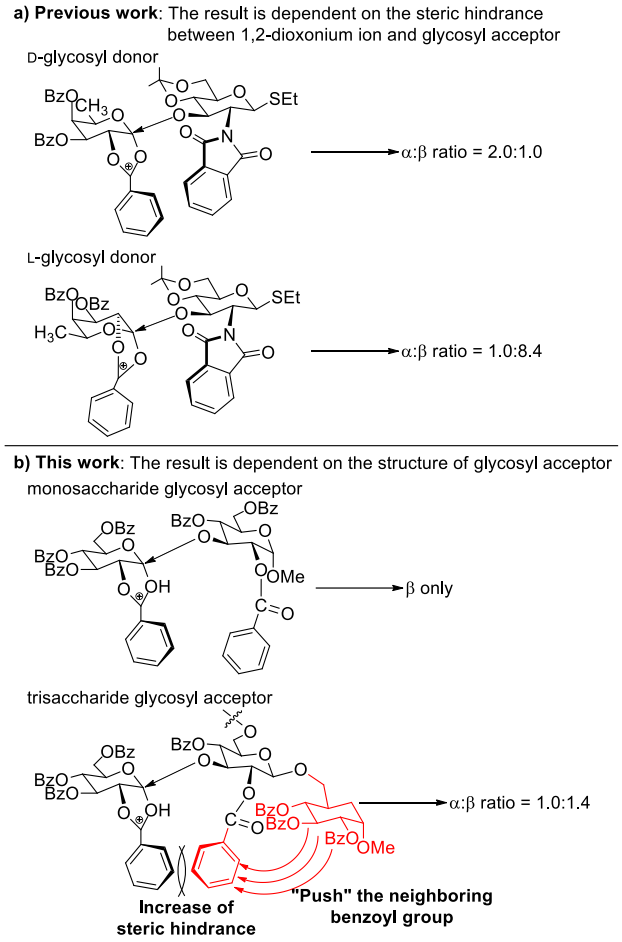
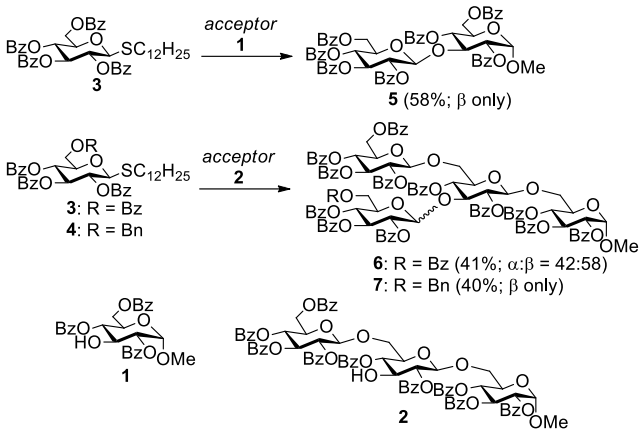


Figure 1. The differences between previous study and current study.

These observations led us to hypothesize that the protected glucose residue at C-1' and the 2'-*O*-benzoyl group (and/or the glucose residue at C-6' and the 4'-*O*-benzoyl group) would act as bulky substituents, obstructing the approach of the 1,2-dioxonium ion intermediate rather than the 1,6-intermediate toward the glycosylation site, i.e., the 3'-hydroxyl group (Figure 1b).

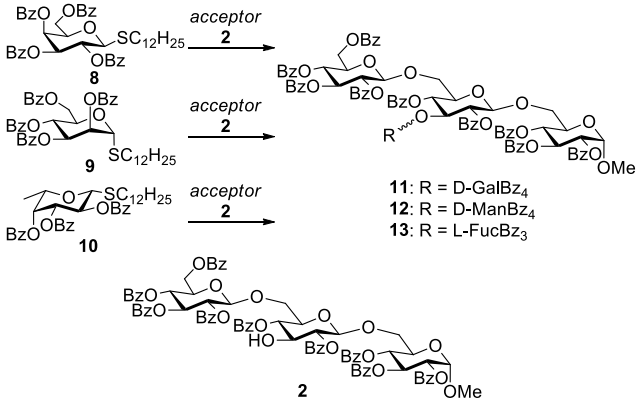
We next examined the behavior of other benzoylated monosaccharide donors (**8**, **9**, or **10**) in the glycosylation with acceptor **2**. As summarized in Table 1, D-mannosyl donor **9** only gave 1,2-*trans* glycoside **12** in 88% yield, while D-galalcosyl donor **8** gave anomeric mixtures of tetrasaccharides **11** in low yield with an α/β ratio of 52.4:47.6. In particular, L-fucosyl donor **10** afforded only α-glycoside product **13**, suggesting a dominant contribution of the transannular participation of the 4-*O*-benzoyl group oriented in the axial direction. These results proposed that steric repulsion between glycosyl donor and acceptor in the transition state is an important factor in determining stereoselectivity. However, it is noted that other factors (e.g., reactivity of the glycosyl donor and acceptor, long-range group participation, or reaction conditions) can affect the stability of the transition state and the outcome of the glycosylation process.

Scheme 1. Glycosylation at 3-position of mono- and trisaccharide acceptor



Reagents and conditions: NIS, TfOH, 4 Å MS, CH_2Cl_2, –20 °C.

Table 1. Results of 1,3-linked glycosylations of trisaccharide acceptor **2**



Entry	Donor	Acceptor	Product	Yield [%] (α/β)[a]
1	D-Glc **3**	**2**	**6**	41 (41.7:58.3)
2	D-Gal **8**	**2**	**11**	48 (52.4:47.6)
3	D-Man **9**	**2**	**12**	88 (α only)
4	L-Fuc **10**	**2**	**13**	62 (α only)

[a]Anomeric ratio determined by integration of the ^{1}H NMR spectrum of the crude reaction mixture.

In this study, we mainly focused on steric hindrance effect that reducing steric hindrance around the glycosylation site would facilitate 1,2-*trans* glycosylation. To this end, we chose a chimera-type trisaccharide acceptor **14** that possesses a 2',3',4'-vicinal triol system, because the absence of protecting groups at the *O*-2' and *O*-4' positions may reduce the steric hindrance around the 3'-OH group, i.e., the glycosylation site (Figure 2). Furthermore, the bulky fully pivaloylated D-glucose residues were expected to inhibit undesired glycosylation at either the 2'- or 4'-position. As expected, the reaction of **14** with donor **3** proceeded smoothly under similar conditions as those with the NIS–TfOH promoter, furnishing pure β-glucoside **15** in an excellent yield of 91% (Scheme 2). The regio-selectivity of the reaction was confirmed after *O*-acetylation. The ^{1}H NMR spectrum of the resulting diacetate **16** showed significant downfield shifts for the H-2' (4.86 ppm) and H-4' (4.77 ppm) signals.

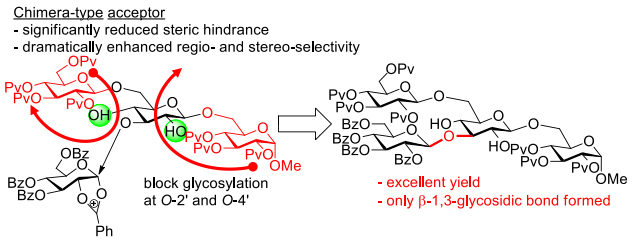
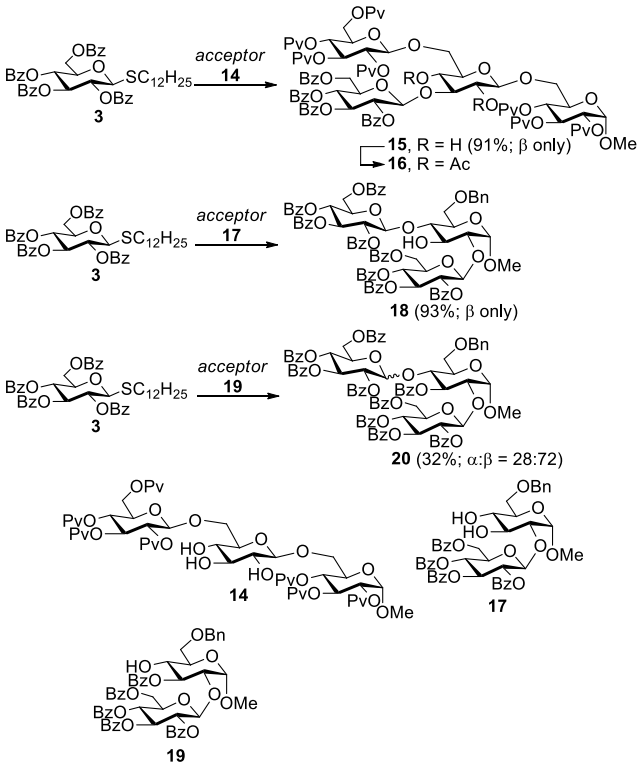


Figure 2. The proposed mechanism for regio- and stereo-selectivity glycosylation.

Furthermore, the newly introduced glycosidic linkage was confirmed to assign a β-anomeric configuration on the basis of the coupling constant ($J_{1''', 2'''}$ = 8.2 Hz) of the anomeric proton at 4.58 ppm (**Figure 3**). The ^{1}H NMR spectrum showed no signal attributable to the α-anomer. Similar phenomena were also observed for the glycosylation at the 4'-position of disaccharide acceptors **17** and **19**. Thus, 3',4'-diol **17** was subjected to glycosylation with **3** under the same reaction conditions, and β-linked trisaccharide **18** was obtained in 93% yield with excellent regio- and stereo-selectivity. In contrast, 3'-*O*-benzoylated acceptor **19** gave the corresponding trisaccharide **20** in poor yield (32%) with an α/β ratio of 28/72. These results clearly indicated the practical utility of vicinal diol or triol acceptors in the synthesis of β-linked branched oligosaccharides.

Encouraged by the excellent results for the preliminary glycosylation of chimera-type acceptors, we attempted to synthesize a well-known branched heptaglucoside **23**. We designed a partially pivaloylated pentaglucoside **22** having two vicinal 2,3,4-triol systems as a glycosyl acceptor.

Scheme 2. Glycosylation of diol acceptor **19** and triol acceptor **14**



Reagents and conditions: NIS, TfOH, 4 Å MS, CH_2Cl_2, –20 °C.

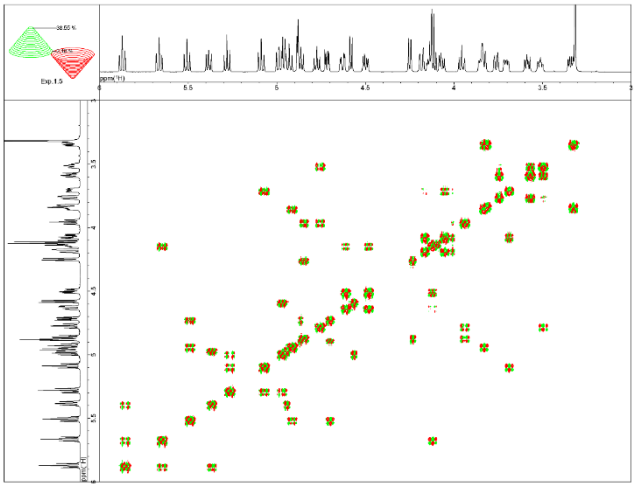
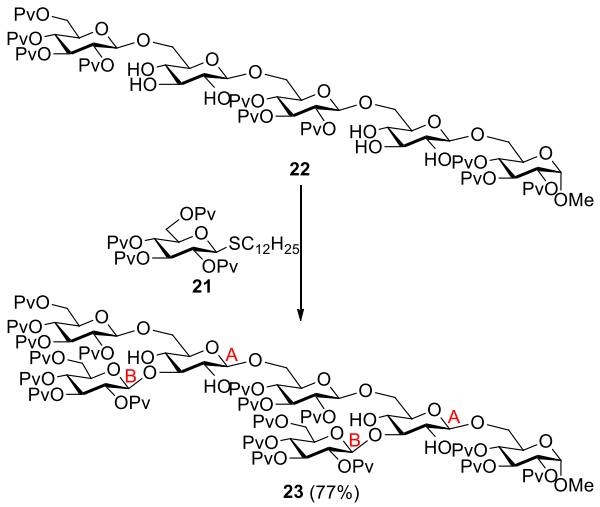


Figure 3. ^{1}H–^{1}H COSY NMR spectrum of compound **16**.

Treatment of a fully pivaloylated thioglucosyl donor **21** with **22** in the presence of NIS–TfOH led to exclusive glycosylation at both the *O*-3 positions of **22**, without any side-reaction at the 2-OH and 4-OH positions. Heptaglucoside **23** was produced in an isolated yield of 77%, and its complete β-selectivity was confirmed by NMR spectroscopy. The ^{1}H NMR spectrum (**Figure 4**) showed two anomeric protons of the two branched D-glucose residues at 5.09 ppm, with a large coupling constant (8.2 Hz). Furthermore, the HMBC NMR spectrum of **23** showed two cross peaks between the anomeric H-1$_B$ of the two branched D-glucose units (5.09 ppm) and C-3 of the two backbone D-glucose units (86.6 ppm), confirming that glycosylation occurred at the two 3-OH groups of **22**.

Scheme 3. Regio- and stereo-specific bis-glycosylarion of a chimera-type acceptor **22**



Reagents and conditions: NIS, TfOH, 4 Å MS, CH_2Cl_2, –40 °C to –20 °C.

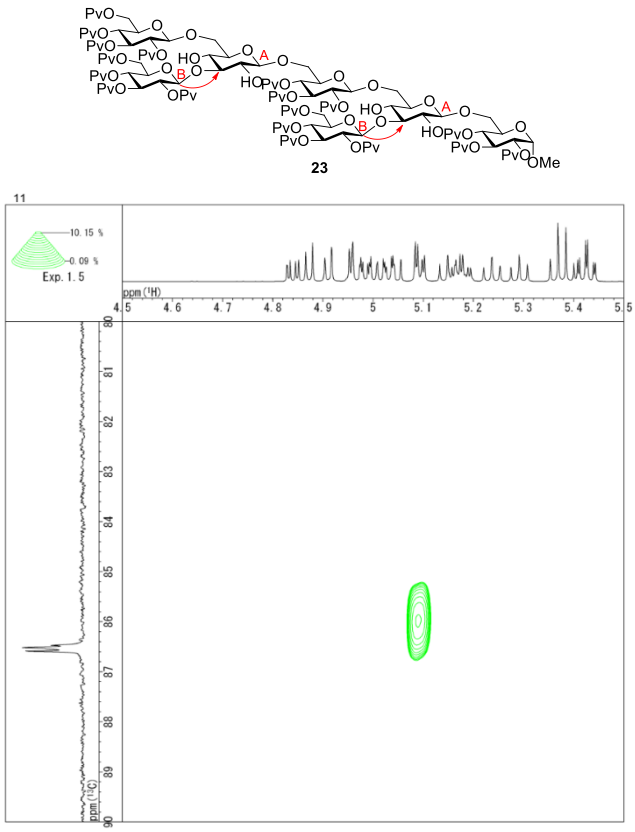


Figure 4. Expansion of ^{1}H-^{13}C HMBC NMR spectra (δ 4.5–5.5 ppm) for compound **23**.

In conclusion, we found that the combined steric effect of a 2-*O*-substituent and an aglycon moiety in the D-glucopyranose residues of glycosyl acceptors played a significant role in yields and stereoselectivity of glycosylation *via* neighboring group participation. The steric hindrance could be reduced by employing vicinal diol or triol acceptors, as was demonstrated in the synthesis of several branched oligosaccharides including the phytoalexin elicitor heptaglucoside, with excellent regio- and stereoselectivity. These findings would provide insights into the regio- and stereo-selective glycosylation of polyol acceptors, which can be extended to the synthesis of various complex oligosaccharides.[15]

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:
Detailed experimental procedures, characterization, and ^{1}H and ^{13}C spectra of new compounds

The Supporting Information is available free of charge on the ACS Publications website.

brief description (file type, i.e., PDF)

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Author Contributions

S.-H. Son and N. Sakairi planned the concept of this project. S.-H. Son and N. Sakairi performed basic synthetic experiments, and S.-H. Son and Y. Byun analyzed and discussed the structures of crucial oligosaccharide products. All authors contributed to editing the final manuscript.

Notes

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