Highly α-Stereoselective One-pot Sequential Glycosylation Using Glucosyl Thioformimidate Derivatives

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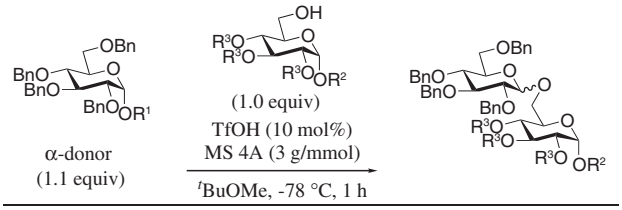
Several trisaccharides were prepared by efficient highly α-stereoselective one-pot sequential glycosylation using glucosyl *p*-trifluoromethylbenzylthio-*p*-trifluoromethylphenyl formimidates (abbreviated to: glucosyl thioformimidates) in the presence of a catalytic amount of TfOH. Factors that controlled the high α-stereoselectivity were determined by characteristic properties of thioformimidate groups contained both in glucosyl donor and acceptor.

Development of new strategies for oligosaccharide synthesis[1] is of growing importance and many examples of preparing various saccharides have been reported: namely, glycosylations based on strategies such as armed-disarmed,[2] latent-active,[3] one-pot,[4] orthogonal,[5] solid-phase,[6] two-stage activation[7] and so on were carried out. A one-pot sequential glycosylation method is among the most promising strategies because of its efficiency in preparing saccharide-building blocks with alleviated laborious purification processes. Therefore, chemical methods for one-pot syntheses of oligosaccharides have currently been shown by many research groups.[8]

Several one-pot sequential glycosylation reactions for the synthesis of liner trisaccharide by utilizing armed-disarmed or orthogonal strategies were reported from our laboratory.[9] Further, total synthesis of branched hepta-β-saccharide having phytoalexin-elicitor activity was then achieved by using a combination of glucosyl fluorides and thioglycosides.[10] All the β-linkages of the saccharide were controlled by the assistance of neighboring effect of 2-*O*-benzoyl protecting group. On the other hand, catalytic and highly α-stereoselective one-pot sequential glycosylation that satisfies requirements for the efficient synthesis of complex oligosaccharide has not yet been reported. In this communication, we would like to report on an efficient catalytic and extremely high α-stereoselective one-pot sequential glycosylation by using glucosyl thioformimidates.[11,12]

It was shown in our previous report[12] that the catalytic and highly 1,2-*cis* or 1,2-*trans* stereoselective and chemoselective glycosylation between armed and disarmed glucosyl thioformimidates was effectively achieved at −78 °C in *t*-BuOMe or EtCN by using a catalytic amount of TfOH and MS 4A. It is interesting to note that the glycoside was formed in good yield with extremely high 1,2-*cis* stereoselectivity when *t*-BuOMe was used as a solvent under kinetic conditions at −78 °C. Then, stereoselective glycosylations were tried under the same condition by using glucosyl trichloroacetimidate,[13] a donor, with several acceptors (Table 1). In every case, high 1,2-*cis* stereoselectivity was achieved when glucosyl thioformimidate was used as a donor (entries 1 vs 2, 3 vs 4, 5 vs 6). In addition, it was also shown that the stereoselectivity of glycosylation was dependent on the nature of an acceptor, that is, its substituents at anomeric position and its

Table 1. Highly α-stereoselective glycosylation using both 'armed' and 'disarmed' glycosyl thioformimidates



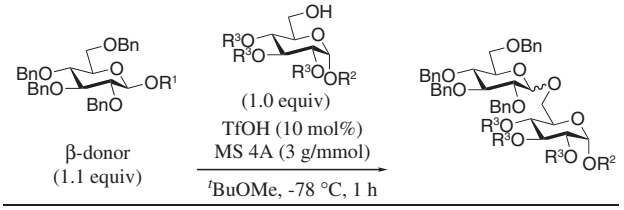
Entry	R^1	R^2	R^3	Yield / % (α / β)[a]
1[12]	N-*p*-CF_3Ph, S-*p*-CF_3Bn	N-*p*-CF_3Ph, S-*p*-CF_3Bn	Bz	93 (95 / 5)
2	NH, CCl_3	N-*p*-CF_3Ph, S-*p*-CF_3Bn	Bz	70 (89 / 11)
3	N-*p*-CF_3Ph, S-*p*-CF_3Bn	Me	Bz	98 (89 / 11)
4	NH, CCl_3	Me	Bz	89 (75 / 25)
5	N-*p*-CF_3Ph, S-*p*-CF_3Bn	Me	Bn	97 (55 / 45)
6	NH, CCl_3	Me	Bn	99 (25 / 75)

[a]The α / β ratios were determined by HPLC analysis.

protecting groups at C-2, 3, 4 positions (entries 1 vs 3 vs 5, 2 vs 4 vs 6). A similar tendency was also observed when β-isomer[14] was used as a donor (Table 2). It was considered that this high 1,2-*cis* stereoselectivity using glucosyl thioformimidate as a donor turned up by the effect of in situ anomerization,[15] that is, the rate of anomerization of glucosyl thioformimidate from α-isomer to β-one seemed to be faster compared with that of conventional glucosyl trichloroacetimidate. Thus, the reaction seemed to have proceeded by its β-isomer which existed in rapid equilibrium with more stable α-isomer. Further, highly α-stereoselective glycosylation was also observed when disarmed glucosyl thioformimidate was used as an acceptor, which was probably because the above bulky leaving group prevented the acceptor to approach the donor from β-side.

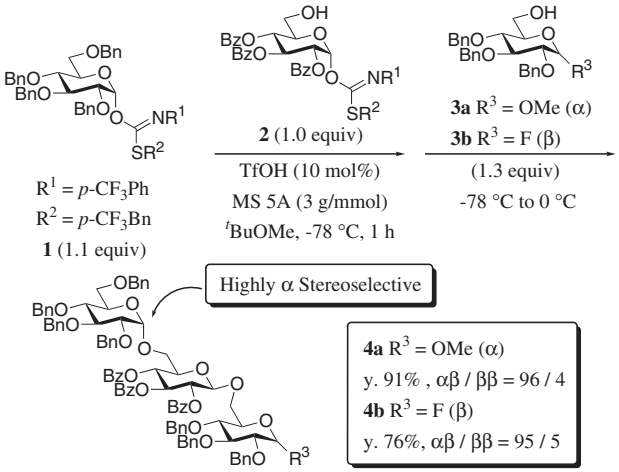
Next, one-pot sequential glycosylation was tried (Scheme 1). In the first step, the armed-disarmed chemoselective glycosylation between **1** and **2** was performed in the presence of 10 mol% of TfOH and MS 5A in *t*-BuOMe at −78 °C. After **1** was completely consumed, which was monitored by TLC, the second glycosylation was carried out to yield the trisaccharide **4a**[16] in high yield by successive addition of glucosyl acceptor **3a** at −78 °C and a gradual raise in its temperature up to 0 °C. Formation of β-linkage in the second glycosylation was controlled by the assistance of neighboring effect of 2-*O*-benzoyl protecting group of the disaccharide donor. When glucosyl fluoride **3b** was used as an acceptor, the desired trisaccharide **4b** was also obtained in good yield without giving any damage to a reducing end of the

Table 2. Highly α-stereoselective glycosylation using both 'armed' and 'disarmed' glycosyl thioformimidates



Entry	R^1	R^2	R^3	Yield / % (α / β)[a]
1	N-*p*-CF_3Ph, S-*p*-CF_3Bn	N-*p*-CF_3Ph, S-*p*-CF_3Bn	Bz	74 (92 / 8)
2	NH, CCl_3	N-*p*-CF_3Ph, S-*p*-CF_3Bn	Bz	65 (88 / 12)
3	N-*p*-CF_3Ph, S-*p*-CF_3Bn	Me	Bz	95 (90 / 10)
4	NH, CCl_3	Me	Bz	97 (78 / 22)
5	N-*p*-CF_3Ph, S-*p*-CF_3Bn	Me	Bn	98 (86 / 14)
6	NH, CCl_3	Me	Bn	99 (60 / 40)

[a]The α / β ratios were determined by HPLC analysis.

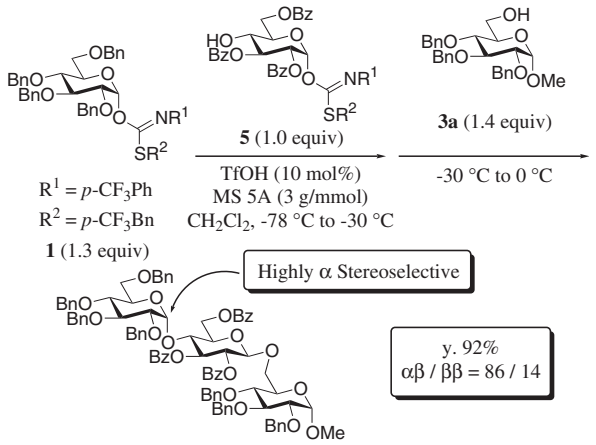


Scheme 1. Catalytic one-pot trisaccharide (Glcα1-6Glcβ1-6Glc) synthesis using both 'armed' and 'disarmed' glycosyl thioformimidates.

acceptor. In the case of using glucosyl acceptor **5**[17] having secondary alcohol at C-4 position, one-pot sequential glycosylation also proceeded by a similar procedure in CH_2Cl_2 to afford the trisaccharide in good yield with high α-stereoselectivity (Scheme 2).

Thus, simple and efficient highly α-stereoselective one-pot sequential glycosylations were achieved by using glucosyl thioformimidates in the presence of a catalytic amount of TfOH. The factors controlling high α-stereoselectivity were determined by the characteristic properties of thioformimidate groups contained both in glucosyl donor and acceptor. Therefore, it is noted that the glucosyl thioformimidates are useful both as a donor and an acceptor for the synthesis of α-linked oligosaccharide.

The typical experimental procedure of one-pot sequential glycosylation is as follows: to a stirred suspension of MS 5A (88 mg), **1** (29.1 mg, 0.032 mmol) and **2** (25.0 mg, 0.029 mmol) in *t*-BuOMe (2.0 mL) was added a toluene solution (ca. 0.1 mL) of



Scheme 2. Catalytic one-pot trisaccharide (Glcα1-4Glcβ1-6Glc) synthesis using both 'armed' and 'disarmed' glycosyl thioformimidates.

TfOH (0.48 mg, 3.2 μmmol) at −78 °C. After the reaction mixture was stirred for 1 h, **3a** (17.7 mg, 0.038 mmol) was successively added at −78 °C and the temperature was gradually raised up to 0 °C. Then, reaction mixture was quenched by adding saturated aqueous $NaHCO_3$ at 0 °C. The mixture was filtered through the pad of celite, and aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine, and dried over Na_2SO_4. After filtration and evaporation, the resulted residue was purified by preparative TLC (hexane/EtOAc 3:1) to give the desired trisaccharide **4a** (39.0 mg, 91%, $\alpha\beta/\beta\beta = 96{:}4$).

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14 NMR data of glucosyl thioformimidate (β-isomer): ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.08 (d, 1H, J = 7.4 Hz, H-1), ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 96.9 (C-1), (α-isomer): ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.71 (brs, 1H, H-1), ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 93.7 (C-1).
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16 The structures of trisaccharides are determined by ^{1}H and ^{13}C NMR. Selected NMR data of **4a** (major isomer: Glcα1-6Glcβ1-6Glc): ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.45 (d, 1H, J = 3.7 Hz, H-1), 4.72 (d, 1H, J = 3.4 Hz, H-1″), 4.76 (d, 1H, J = 7.9 Hz, H-1′), ^{13}C NMR (125 MHz, $CDCl_3$) δ 97.3 (C-1″), 97.9 (C-1), 100.8 (C-1′).
17 Glucosyl acceptor **5** was prepared in 91% yield by migration of 4-benzoyl group of glucosyl acceptor **2**[12] using TBAF (1.1 equiv) in THF at 0 °C.