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EFFECTIVE INDUCTION OF β-SELECTIVITY USING α- OR β-MANNOSYL 6-NITRO-2-BENZOTHIAZOATE IN MANNOSYLATION

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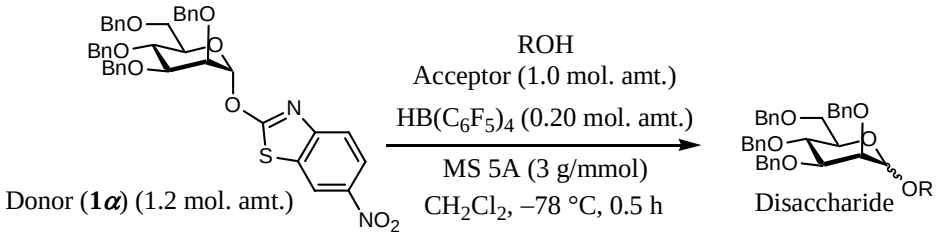
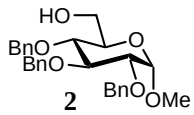
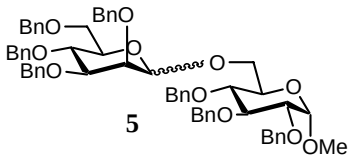
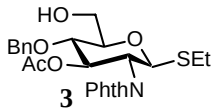
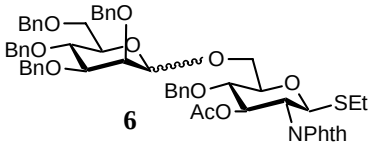
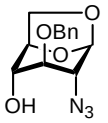
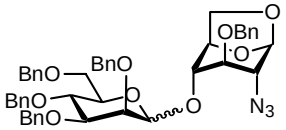
Abstract – Highly β-selective mannosylations of glycosyl acceptors with an α-mannosyl 6-nitro-2-benzothiazoate donor (**1α**) were carried out smoothly in the presence of a catalytic amount of tetrakis(pentafluorophenyl)boric acid [$HB(C_6F_5)_4$] to afford the corresponding disaccharides in good to high yields: it was proved that high β-selectivity was entirely dependent on the characteristic properties of a donor (**1α**) and a catalyst, $HB(C_6F_5)_4$. Interestingly, it was observed that *in situ* anomerization from **1β** to **1α** took place rapidly when β-mannosyl donor (**1β**) was treated with a catalytic amount of $HB(C_6F_5)_4$ in CH_2Cl_2.

β-Mannopyranosyl units are the essential constituents of naturally-occurring biologically-active oligosaccharides and glycoconjugates.[1] However, formation of β-mannopyranoside is considered somewhat difficult in chemical synthesis because of the following three reasons: i) α-mannopyranoside formation is favored by its anomeric effect; ii) steric repulsion of hydroxy group at *C*-2 position; and iii) opposite participation of its neighboring group. For the convenient construction of β-mannopyranoside, catalytic or stoichiometric direct mannosylation[2-9] turned out to be one of the most effective methods. Reactions using mannosyl donors such as mannosyl phosphinothioate,[2] phosphate,[3] halide,[4,5] or sulfoxide[5] in combination with suitable activators, and a donor having 1,2-stannylene acetal[6] were then reported. Best results were obtained when donors having an electron-withdrawing protecting group at *O*-2 position[7] or a cyclic acetal protecting group at *O*-4,6 position[8] were activated by trimethylsilyl triflate, benzenesulfenyl triflate / 2,6-di-*t*-butyl-4-methylpyridine (DTBMP), or trifluoromethanesulfonic

anhydride / DTBMP. Though the above methods were known well-effective, further development of a new and convenient method for the stereoselective synthesis of β-mannopyranosides is still important and challenging in carbohydrate chemistry. In the previous papers,[10,11] it was reported that highly β-selective mannosylations of glycosyl acceptors with an α-mannosyl 6-nitro-2-benzothiazoate donor (**1**α) were carried out smoothly in the presence of a catalytic amount of tetrakis(pentafluorophenyl)boric acid[12] [$HB(C_6F_5)_4$] to afford the corresponding disaccharides in good to high yields (Table 1). To the best of our knowledge, these are the highest yields of β-disaccharides (**5** and **7**) by direct mannosylations between 2,3,4,6-tetra-*O*-benzyl-mannosyl donor and acceptors (**2** and **4**). In this communication, we would like to report on a mechanistic study for the induction of β-selectivity in mannosylation using **1**.

Table 1. β-Selective Mannosylation with α-Mannosyl 6-Nitro-2-benzothiazoate[11]



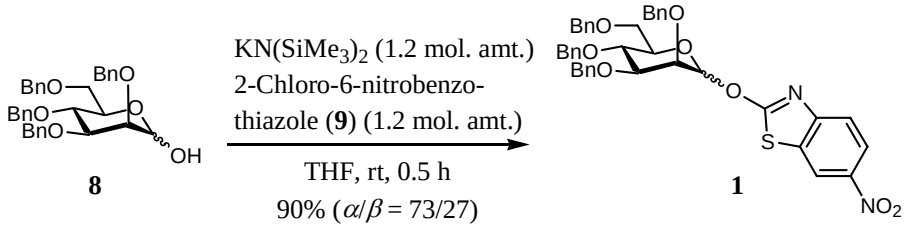
Entry	Acceptor (ROH)	Product	Yield /% (α/β)[a]
1	 **2**	 **5**	96 (16/84)
2	 **3**	 **6**	83 (10/90)
3	 **4**	 **7**	89 (30/70)

[a]The α/β ratios were determined by isolations of both stereoisomers.

2,3,4,6-Tetra-*O*-benzyl-D-mannopyranosyl 6-nitro-2-benzothiazoate (**1**) was prepared easily by the following procedure. That is, direct condensation between anomeric hydroxy group of 2,3,4,6-tetra-*O*-benzyl-D-mannopyranose (**8**) and 2-chloro-6-nitrobenzothiazole[10] (**9**) proceeded smoothly and gave α-isomer (**1**) and β-one in 66% and 24% chemical yields, respectively, in the presence of potassium bis(trimethylsilyl)amide (Scheme 1).

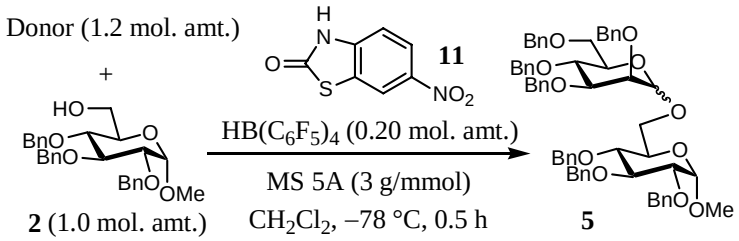
Since 6-nitro-2-benzothiazolinone (**11**) formed together with the desired mannoside, the influence of **11**

on β-selectivity and yield was considered. In order to study the induction of β-selectivity, mannosylation of methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**2**) with **1**α or the corresponding α-mannosyl trichloroacetimidate donor (**10**)[13] was tried in the presence of **11** by which neither β-selectivity nor yield were influenced (Table 2). This may be due to the extreme insolubility of the 6-nitro-2-benzothiazolinone (**11**) in CH_2Cl_2, a nonpolar solvent. It was noted that mannosylation using $HB(C_6F_5)_4$ was carried out with moderate β-selectivity by using **10**. Thus, high β-selectivity proved to be entirely dependent on the characteristic property of a combination of a donor (**1**α) and a catalyst $HB(C_6F_5)_4$.



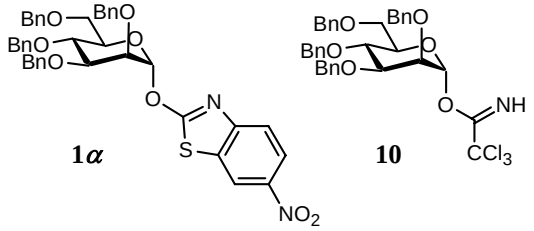
Scheme 1. Preparation of Mannosyl 6-Nitro-2-benzothiazoate

Table 2. Effects of 6-Nitro-2-benzothiazolinone (**11**) and Donor



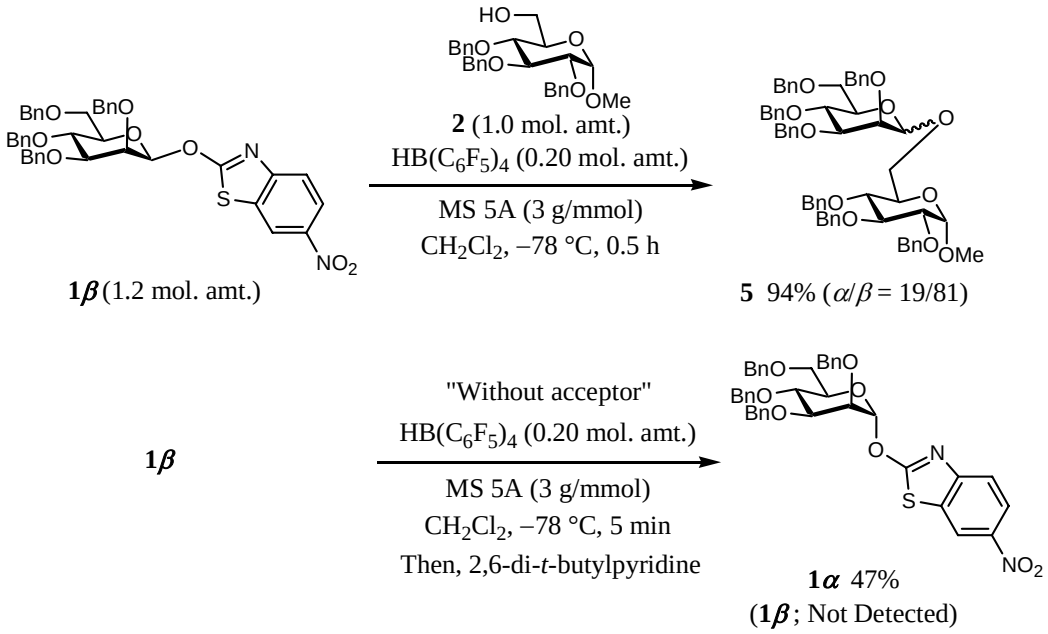
Entry	Donor	Additive **11** /mol. amt.	Yield /% (α/β)[a]
1	**1**α	0	96 (16/84)
2	**1**α	2.4	85 (19/81)
3	**10**	0	67 (36/64)
4	**10**	1.2	71 (35/65)

[a]The α /β ratios were determined by isolations of both stereoisomers.



Next, mannosylation of **2** with a β-isomer of donor (**1**β) was tried under the above-mentioned conditions (Scheme 2). Interestingly, β-selective mannosylation also proceeded smoothly to give disaccharide in high yield similar to the case using α-donor (**1**α). In order to study its mechanism, a reaction using **1**β

was tried in the absence of glycosyl acceptor (**2**) under the same conditions. After stirring for only 5 min, the reaction mixture was swiftly quenched with a proton scavenger, 2,6-di-*t*-butylpyridine. It was interesting to note that the α-isomer (**1**α) was obtained in 47% yield while β-isomer (**1**β) was not detected at all. This result possibly indicates the *in situ* anomerization to take place rapidly. To the best of our knowledge, this is the first report on *in situ* anomerization in which the imidate-type glycosyl donor was treated with acids.

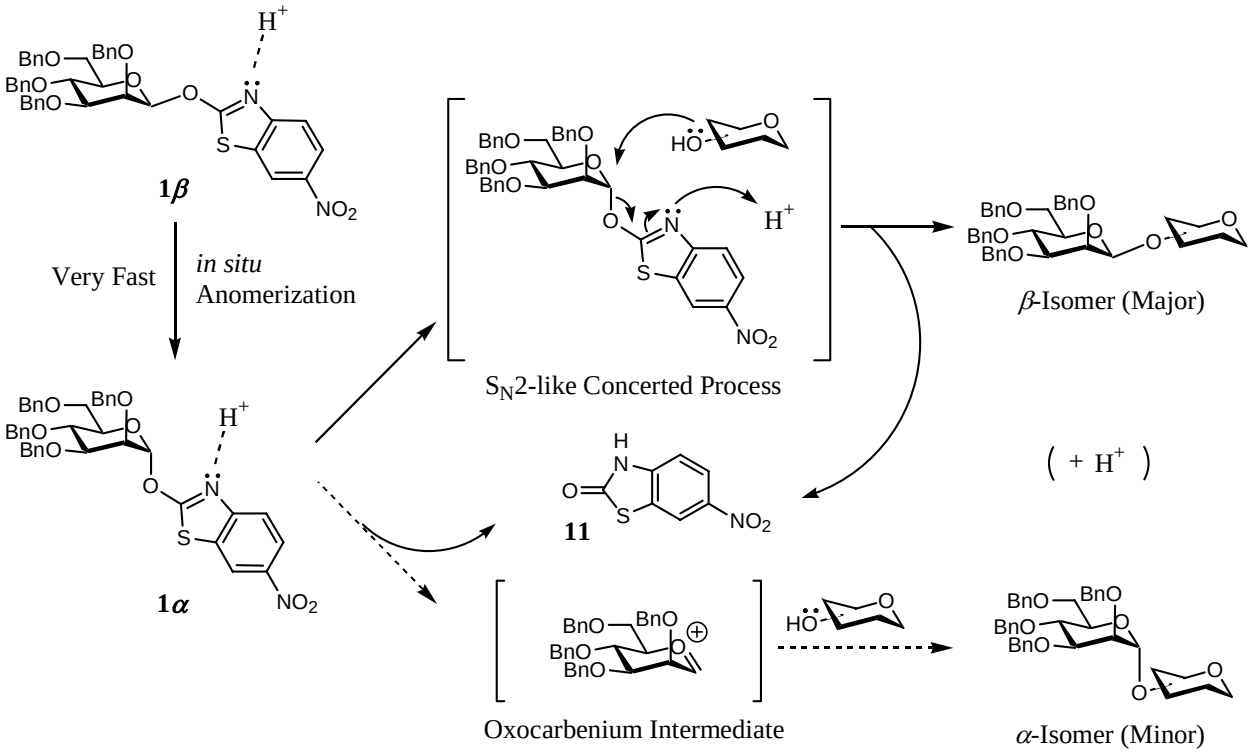


Scheme 2.

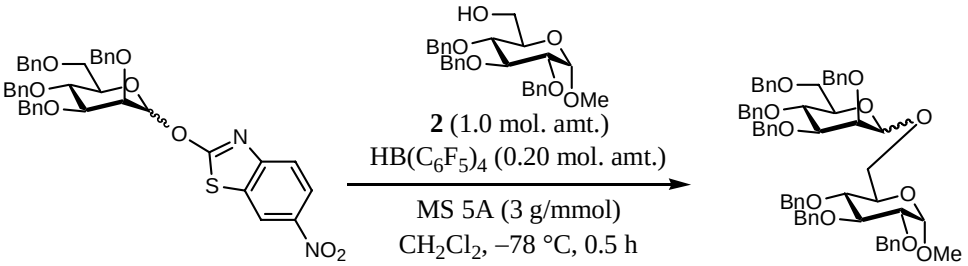
As shown in Table 2, mannosyl 6-nitro-2-benzothiazoate donor enabled the mannosylation to achieve higher β-selectivity than mannosyl trichloroacetimidate. It may be considered that the mannosylation reaction using β-donor (**1**β) proceeded *via* rapid *in situ* anomerization to **1**α before forming disaccharide with glycosyl acceptor (**2**) and that the mannosylation consequently took place more dominantly *via* S_N2-like concerted process between an α-isomer (**1**α) and a glycosyl acceptor (Scheme 3).

Additionally, it was found that the β-selective mannosylation could be performed by using a mixture of α- and β-donors (**1**) (α/β = 73/27: obtained by the condensation reaction) as shown in Scheme 4. This result may extend the utility of mannosyl 6-nitro-2-benzothiazoate donor because there was no need for a separation procedure of the two isomers (**1**α) and (**1**β).

The mannosyl 6-nitro-2-benzothiazoate was found to behave as an efficient donor and to have a potent feature for the construction of stereoselective β-mannoside linkage. Further study on applying a glycosyl benzothiazoate for an oligosaccharide synthesis is now in progress.



Scheme 3. Postulated Mechanism of β-Selective Mannosylation



Scheme 4.

Mannosylation Using HB(C_6F_5)$_4$ as Catalyst: To a stirred suspension of MS 5A (150 mg), mannosyl donor (**1**) or (**10**) (0.06 mmol), and glycosyl acceptor (**2**) (0.050 mmol) in CH_2Cl_2 (1.25 mL) was successively added HB(C_6F_5)$_4$ (0.050 M toluene-Et_2O (1:1), 0.20 mL, 0.01 mmol) at –78 °C. After the completion of the mannosylation reaction by monitoring TLC, the reaction was quenched by adding of sat. aq. $NaHCO_3$. Then, the mixture was filtered through Celite and the 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 resulting residue was purified by preparative TLC (silica gel, hexane/EtOAc/acetone = 10/10/1) and afforded the corresponding disaccharide (**5**). The ratio was determined by isolating of both isomers.

in situ Anomerization Reaction Using HB(C_6F_5)$_4$ as Catalyst: To a stirred suspension of MS 5A (113 mg)

and **1β** (0.045 mmol) in CH_2Cl_2 (0.94 mL) was successively added $HB(C_6F_5)_4$ (0.050 M toluene-Et_2O (1:1), 0.15 mL, 7.50 μmol) at −78 °C. After stirring for 5 min, the reaction was quenched by adding of 2,6-di-*t*-butylpyridine (20.2 μL, 0.090 mmol). Then, the mixture was added sat. aq. $NaHCO_3$, filtered through Celite and the 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 resulting residue was purified by preparative TLC (silica gel, hexane/EtOAc/Et_3N = 3/1/0.04) to afford **1α** (15.3 mg, 47%) as a single isomer.

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REFERENCES AND NOTES

§ Dedicated to the celebration of the 30th anniversary of *Heterocycles*.

1. Reviews: K. Toshima and K. Tatsuta, *Chem. Rev*.,1993, **93**, 1503; B. Ernst, G. W. Hart, and P. Sinaÿ, "*Carbohydrate in Chemistry and Biology*," Part 1, WILEY-VCH, Weinheim etc., 2000; J. J. Gridley and H. M. I. Osborn, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1471.
2. T. Yamanoi, K. Nakamura, H. Takeyama, K. Yanagihara, and T. Inazu, *Bull. Chem. Soc. Jpn*., 1994, **67**, 1359.
3. O. J. Plante, R. B. Andrade, and P. H. Seeberger, *Org. Lett*., 1999, **1**, 211; O. J. Plante, E. R. Palmacci, and P. H. Seeberger, *Org. Lett*., 2000, **2**, 3841.
4. H. Paulsen and O. Lockhoff, *Chem. Ber*., 1981, **114**, 3102; P. Garegg and P. Ossowski, *Acta Chem. Scand*., 1983, **B37**, 249; C. A. A. van Boeckel and T. Beetz, *Recl. Trav. Chim. Pays-Bas*., 1987, **106**, 596.
5. K. Toshima, K. Katsumi, and S. Matsumura, *Synlett*, 1998, 643; H. Nagai, K. Kawahara, S. Matsumura, and K. Toshima, *Tetrahedron Lett*., 2001, **42**, 4159.
6. G. Hodosi and P. Kovác, *J. Am. Chem. Soc*., 1997, **119**, 2335.
7. V. K. Srivastava and C. Schuerch, *Carbohydr. Res*., 1980, **79**, C13; A. -H. Adel, Abdel-Rahman, J. Simon, E. S. El Ashry, and R. R. Schmidt, *Angew. Chem., Int. Ed*., 2002, **41**, 2972.
8. D. Crich and S. Sun, *J. Org. Chem*., 1996, **61**, 4506; D. Crich and M. Smith, *J. Am. Chem. Soc*., 2002, **124**, 8867.
9. K. Tatsuta and S. Yasuda, *Tetrahedron Lett*., 1996, **37**, 2453; W. -S. Kim, H. Sasai, and M. Shibasaki, *Tetrahedron Lett*., 1996, **37**, 7797.
10. T. Mukaiyama, T. Hashihayata, and H. Mandai, *Chem. Lett*., 2003, **32**, 340.

11. T. Hashihayata, H. Mandai, and T. Mukaiyama, *Chem. Lett*., 2003, **32**, 442.
12. $HB(C_6F_5)_4$ was generated according to literal procedure. H. Jona, H. Mandai, W. Chavasiri, K. Takeuchi, and T. Mukaiyama, *Bull. Chem. Soc. Jpn*., 2002, **75**, 291.
13. Review on glycosyl trichloroacetimidate: R. R. Schmidt and W. Kinzy, Adv. *Carbohydr. Chem. Biochem*., 1994, **50**, 21.