Catalytic and β-Stereoselective Mannosylation of Several Glycosyl Acceptors with Mannosyl 6-Nitro-2-benzothiazoate

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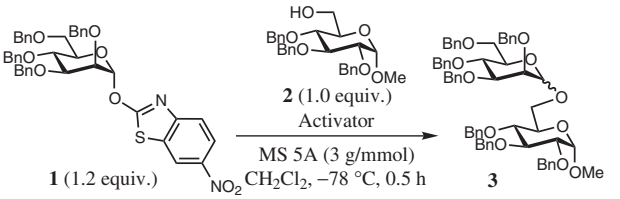
Mannosylation of several glycosyl acceptors with a novel mannosyl donor having the 6-nitro-2-benzothiazoate function at an anomeric position proceeded smoothly in the presence of a catalytic amount of tetrakis(pentafluorophenyl)boric acid [$HB(C_6F_5)_4$] to afford the corresponding disaccharides in high yields with good to high β-stereoselectivities.

β-Mannopyranosyl units are the essential constituents of naturally-occurring biologically active oligosaccharides and glycoconjugates.[1] Generally, formation of β-mannopyranoside is rather difficult by chemical synthesis owing to the following three factors: i) α-mannopyranoside formation is favored by its anomeric effect; ii) steric repulsion of hydroxyl group at *C*-2 position; and iii) opposite participation of neighboring group. Of the methods reported, the catalytic or stoichiometric direct mannosylation[2–9] was shown to be most effective for the convenient construction of β-mannopyranoside, and the reactions using mannosyl compounds such as mannosyl phosphinothioate,[2] phosphate,[3] halides,[4,5] or sulfoxide[5] together with their suitable activators, and a donor having 1,2-stannylene acetal[6] were thus reported. Further, the best results were given when donors having electron-withdrawing protecting group at *O*-2 position[7] or cyclic acetal protecting group at *O*-4,6 position[8] were promoted by activators such as trifluoromethanesulfonates. To develop a convenient method for the stereoselective synthesis of β-mannopyranosides is still one of the most important and challenging topics in carbohydrate chemistry. Highly β-stereoselective glucosylations by using a novel glucosyl donor, α-glucosyl 6-nitro-2-benzothiazoate was recently achieved by our research group.[10] The donor reacted smoothly with glycosyl acceptors in the presence of trifluoromethanesulfonic acid (TfOH) in CH_2Cl_2 to afford the corresponding β-glucosides in high yields. It was noted that β-saccharide was obtained more dominantly by the present method compared with the similar glucosylation reactions which used other α-glucosyl donors such as glucosyl thioform- and trichloroacet-imidates. These results imply that the glycosyl benzothiazoate has a potent and characteristic feature of forming β-saccharide. In this communication, we would like to report on a direct β-stereoselective mannosylation of several glycosyl acceptors using a newly devised donor, α-mannosyl 6-nitro-2-benzothiazoate.

2,3,4,6-Tetra-*O*-benzyl-α-D-mannopyranosyl 6-nitro-2-benzothiazoate (**1**) was prepared easily according to the following procedure. The direct condensation reaction between anomeric hydroxyl group of 2,3,4,6-tetra-*O*-benzyl-α,β-D-mannopyranose and 2-chloro-6-nitrobenzothiazole proceeded smoothly to give α-isomer **1** and β-one in 66% and 24% chemical yields, respectively, in the presence of potassium bis(trimethylsilyl)amide.

Table 1. Mannosylation using various activators



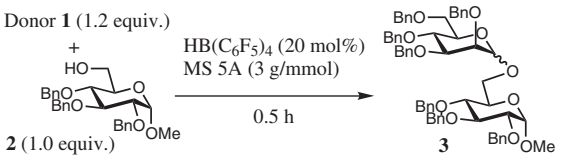
Entry	Activator (mol% based on acceptor)	Yield /% (α/β)[d]
1	$BF_3 \cdot OEt_2$ (120)	70 (78/22)
2	$TrB(C_6F_5)_4$ (120)	97[e] (34/66)
3	TMSOTf (120)	95 (25/75)
4	$HClO_4$ (20)[a]	89 (45/55)
5	TfOH (20)	99 (27/73)
6	$HNTf_2$ (20)[b]	92 (43/57)
7	$HSbF_6$ (20)[b]	90 (44/56)
8	$HB(C_6F_5)_4$ (20)[c]	96 (16/**84**)

[a]Protic acid was genarated from silver salt and ^{t}BuCl in toluene, and the supernatant was used. [b]Protic acid was generated from silver salt and ^{t}BuBr in toluene, and the supernatant was used. [c]Protic acid was generated from silver salt and ^{t}BuBr in toluene - diethyl ether (1:1), and the supernatant was used. [d]The α/β ratios were determined by isolations of both stereoisomers. [e]The reaction was carried out for 1 h.

In the first place, the effect of various activators on the mannosylation of methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**2**) with **1** in CH_2Cl_2 was examined (Table 1). In most cases, the reactions smoothly proceeded at −78 °C to give the corresponding disaccharides **3** in high yields. It was interesting to note that the mannosylation that used activators having triflate or tetrakis(pentafluorophenyl)borate anion gave disaccharides with high β-stereoselectivities (Entries 2, 3, 5, 8). The highest β-stereoselectivity was achieved when tetrakis(pentafluorophenyl)boric acid[11] [$HB(C_6F_5)_4$] was employed (Entry 8, $\alpha/\beta = 14/86$) while $BF_3{\cdot}Et_2O$, a weaker Lewis acid, showed a reversed stereoselectivity (Entry 1, $\alpha/\beta = 78/22$). These results indicate that the present mannosylations were influenced by the kinds of activator acids. Though the reasons why these acids induced the stereoselectivities are not yet clear, significant effects of the acids were certainly shown.

Next, reaction conditions were examined by taking up the reaction of **2** with **1** using 20 mol% catalyst, $HB(C_6F_5)_4$ (Table 2). High β-stereoselectivity was observed when the mannosylation was carried out in CH_2Cl_2, a nonpolar solvent, at −78 °C (Entry 3). On the other hand, the same mannosylation afforded disaccharide with α-stereoselectivity in a nitrile solvent (Entry 1). The nitrile solvent was known to be effective

Table 2. Effects of solvent and reaction temperature

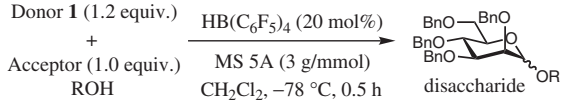


Entry	Solvent	Temp. /°C	Yield /% (α/β)[a]
1	EtCN	–78	49[b] (73/27)
2	Et_2O	–78	89 (38/62)
3	CH_2Cl_2	–78	96 (16/**84**)
4	CH_2Cl_2	–94	92 (28/72)
5	CH_2Cl_2	–60	98 (22/78)
6	CH_2Cl_2	–30	quant. (45/55)
7	CH_2Cl_2	0	quant. (59/41)

[a]The α/β ratios were determined by isolations of both stereoisomers.
[b]The reaction was carried out for 1 h.

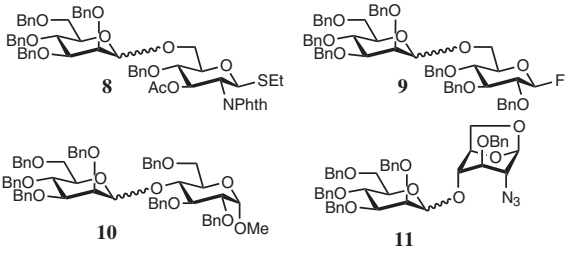
for the construction of α-mannoside.[3,5,12] It was further observed that the present mannosylation using **1** proceeded even at $-94\,^{\circ}C$ (Entry 4) and β-stereoselectivities were shown at the temperatures ranging from $-60\,^{\circ}C$ to $-94\,^{\circ}C$ (Entries 3, 4, 5). However, β-stereoselectivties were not observed when the temperatures were $-30\,^{\circ}C$ to $0\,^{\circ}C$ (Entries 6, 7), and this was probably because S_N1-type process took place competitively and thus α-mannoside was given at those higher temperatures.

Table 3. Mannosylation of several acceptors



Entry	Acceptor (ROH)	Product	Yield /% (α/β)[a]
1	**4**	**8**	83 (10/90)
2	**5**	**9**	82 (11/89)
3	**6**	**10**	77 (25/75)
4	**7**	**11**	89 (30/70)

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



Finally, in order to extend the scope of the present reaction, β-stereoselective mannosylation of several glycosyl acceptors such as thioglycoside **4**, glycosyl fluoride **5**, 4-hydroxyl methyl glycoside **6** and glucosamine derivative **7** with **1** were tried at $-78\,^{\circ}C$ (Table 3). All glycosyl acceptors having primary hydroxyl group reacted smoothly at $-78\,^{\circ}C$ to afford the desired disaccharides in high yields with high β-stereoselectivities (Entries 1, 2).[13] Furthermore, a good β-stereoselectivity was observed in the similar mannosylation using **6** or **7** (Entries 3, 4). To the best of our knowledge, this is the highest yield of β-**11** disaccharide by direct mannosylation between 2,3,4,6-tetra-*O*-benzyl-mannosyl donor and **7**. It was also noted that the chemoselective mannosylations using glycosyl acceptors such as ethyl 3-*O*-acetyl-*O*-4- benzyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (**4**) or 2,3,4-tri-*O*- benzyl-β-D-glucopyranosyl fluoride (**5**) gave good results as well without giving any damage to thio- or fluoro-linkage, respectively (Entries 1, 2).

The donor **1** has a potent and characteristic feature in constructing the β-mannoside and enabled the mannosylation to achieve higher β-stereoselectivity at $-78\,^{\circ}C$ in CH_2Cl_2. Also, it was found that the counter anion of acid catalysts influenced the β-stereoselectivity, and that the highest β-stereoselectivity was observed when $HB(C_6F_5)_4$ was used. Further studies on the effect of hydroxyl protecting group of mannosyl benzothiazoate on stereoselectivity and on mechanism for β-stereoselectivity are now in progress.

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References and Notes

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