EFFECTIVE INDUCTION OF $\beta$-SELECTIVITY USING $\alpha$- OR $\beta$-MANNOSYL 6-NITRO-2-BENZOTHIAZOATE IN MANNOSYLATION

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Abstract – Highly $\beta$-selective mannosylations of glycosyl acceptors with an $\alpha$-mannosyl 6-nitro-2-benzothioate donor (1$\alpha$) were carried out smoothly in the presence of a catalytic amount of tetrakis(pentafluorophenyl)boric acid [HB(C$_6$F$_5$)$_4$] to afford the corresponding disaccharides in good to high yields: it was proved that high $\beta$-selectivity was entirely dependent on the characteristic properties of a donor (1$\alpha$) and a catalyst, HB(C$_6$F$_5$)$_4$. Interestingly, it was observed that in situ anomerization from 1$\beta$ to 1$\alpha$ took place rapidly when $\beta$-mannosyl donor (1$\beta$) was treated with a catalytic amount of HB(C$_6$F$_5$)$_4$ in CH$_2$Cl$_2$.

$\beta$-Mannopyranosyl units are the essential constituents of naturally-occurring biologically-active oligosaccharides and glycoconjugates.\textsuperscript{1} However, formation of $\beta$-mannopyranoside is considered somewhat difficult in chemical synthesis because of the following three reasons: i) $\alpha$-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 $\beta$-mannopyranoside, catalytic or stoichiometric direct mannosylation\textsuperscript{2-9} turned out to be one of the most effective methods. Reactions using mannosyl donors such as mannosyl phosphinothioate,\textsuperscript{2} phosphate,\textsuperscript{3} halide,\textsuperscript{4,5} or sulfoxide\textsuperscript{5} in combination with suitable activators, and a donor having 1,2-stannylene acetal\textsuperscript{6} were then reported. Best results were obtained when donors having an electron-withdrawing protecting group at O-2 position\textsuperscript{7} or a cyclic acetal protecting group at O-4,6 position\textsuperscript{8} were activated by trimethylsilyl triflate, benzenesulfonyl 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,\textsuperscript{10,11} it was reported that highly β-selective mannosylations of glycosyl acceptors with an α-mannosyl 6-nitro-2-benzothiazolate donor (1α) were carried out smoothly in the presence of a catalytic amount of tetrakis(pentafluorophenyl)boric acid\textsuperscript{12} [HB(C\textsubscript{6}F\textsubscript{5})\textsubscript{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.

\begin{table}[h]
\centering
\begin{tabular}{cccc}
\hline
Entry & Acceptor (ROH) & Product & Yield /% (α/β)\textsuperscript{a} \\
\hline
1 & 2 & 5 & 96 (16/84) \\
2 & 3 & 6 & 83 (10/90) \\
3 & 4 & 7 & 89 (30/70) \\
\hline
\end{tabular}
\end{table}

\textsuperscript{a}The α/β ratios were determined by isolations of both stereoisomers.

2,3,4,6-Tetra-O-benzyl-D-mannopyranosyl 6-nitro-2-benzothiazolate (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\textsuperscript{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 \((\mathbf{2})\) with \(1\alpha\) or the corresponding α-mannosyl trichloroacetimidate donor \((\mathbf{10})\)\(^{13}\) was tried in the presence of \(\mathbf{11}\) 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 \((\mathbf{11})\) in \(\text{CH}_2\text{Cl}_2\), a nonpolar solvent. It was noted that mannosylation using \(\text{HB(C}_6\text{F}_5)_4\) was carried out with moderate β-selectivity by using \(\mathbf{10}\). Thus, high β-selectivity proved to be entirely dependent on the characteristic property of a combination of a donor \((1\alpha)\) and a catalyst \(\text{HB(C}_6\text{F}_5)_4\).

![Scheme 1. Preparation of Mannosyl 6-Nitro-2-benzothiazoate](image)

**Table 2. Effects of 6-Nitro-2-benzothiazolinone \((\mathbf{11})\) and Donor**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Donor</th>
<th>Additive (\mathbf{11}) /mol. amt.</th>
<th>Yield /% ((\alpha/\beta))(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(1\alpha)</td>
<td>0</td>
<td>96 (16/84)</td>
</tr>
<tr>
<td>2</td>
<td>(1\alpha)</td>
<td>2.4</td>
<td>85 (19/81)</td>
</tr>
<tr>
<td>3</td>
<td>(\mathbf{10})</td>
<td>0</td>
<td>67 (36/64)</td>
</tr>
<tr>
<td>4</td>
<td>(\mathbf{10})</td>
<td>1.2</td>
<td>71 (35/65)</td>
</tr>
</tbody>
</table>

\(^a\)The \(\alpha/\beta\) ratios were determined by isolations of both stereoisomers.

Next, mannosylation of \(\mathbf{2}\) with a β-isomer of donor \((1\beta)\) 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 \((1\alpha)\). In order to study its mechanism, a reaction using \(1\beta\)
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-\textit{t}-butylpyridine. It was interesting to note that the \textit{\alpha}-isomer (1\textit{\alpha}) was obtained in 47\% yield while \textit{\beta}-isomer (1\textit{\beta}) was not detected at all. This result possibly indicates the \textit{in situ} anomeration to take place rapidly. To the best of our knowledge, this is the first report on \textit{in situ} anomeration in which the imidate-type glycosyl donor was treated with acids.

As shown in Table 2, mannosyl 6-nitro-2-benzothiazolate donor enabled the mannosylation to achieve higher \textit{\beta}-selectivity than mannosyl trichloroacetimidate. It may be considered that the mannosylation reaction using \textit{\beta}-donor (1\textit{\beta}) proceeded \textit{via} rapid \textit{in situ} anomeration to 1\textit{\alpha} before forming disaccharide with glycosyl acceptor (2) and that the mannosylation consequently took place more dominantly \textit{via} \textit{S}_{\text{N}}2-like concerted process between an \textit{\alpha}-isomer (1\textit{\alpha}) and a glycosyl acceptor (Scheme 3).

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

The mannosyl 6-nitro-2-benzothiazolate was found to behave as an efficient donor and to have a potent feature for the construction of stereoselective \textit{\beta}-mannoside linkage. Further study on applying a glycosyl benzothiazolate for an oligosaccharide synthesis is now in progress.
Scheme 3. Postulated Mechanism of β-Selective Mannosylation

Scheme 4. Mannosylation Using HB(C₆F₅)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 CH₂Cl₂ (1.25 mL) was successively added HB(C₆F₅)₄ (0.050 M toluene-Et₂O (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. NaHCO₃. Then, the mixture was filtered through Celite and the aqueous layer was extracted with CH₂Cl₂. The combined organic layer was washed with brine and dried over Na₂SO₄. 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(C₆F₅)₄ as Catalyst: To a stirred suspension of MS 5A (113 mg)
and 1β (0.045 mmol) in CH₂Cl₂ (0.94 mL) was successively added HB(C₆F₅)₄ (0.050 M toluene-Et₂O (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. NaHCO₃, filtered through Celite and the aqueous layer was extracted with CH₂Cl₂. The combined organic layer was washed with brine and dried over Na₂SO₄. After filtration and evaporation, the resulting residue was purified by preparative TLC (silica gel, hexane/EtOAc/Et₃N = 3/1/0.04) to afford 1α (15.3 mg, 47%) as a single isomer.

ACKNOWLEDGEMENT
This study was supported in part by the Grant of the 21st Century COE Program from the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan.

REFERENCES AND NOTES
§ Dedicated to the celebration of the 30th anniversary of Heterocycles.
