# A Study on the Effect of Lanthanide Ion Coordination on the Stereoselective Synthesis of β-Mannopyranosides

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A great deal of attention has been given to the development of glycosylation methodologies in connection with increasing importance of glycoconjugates, *e.g.* glycoproteins and glycolipids, in biological events such as fertilization, immune response, viral and parasitic infection, cell growth, cell to cell adhesion and inflammation.[1] Stereoselective formation of the β-*O*-mannopyranoside bond, one of the major linkages in common core structure of glycoconjugates, has proven to be the most challenging type among the synthetic glycosidic linkages. A number of creative methods have been devised for the stereoselective formation of β-mannopyarnoside.[2-7] One of the most notable methods involves intramolecular aglycone delivery (IAD), developed by Hindsgaul,[2] Stork,[3] and Ogawa.[4] This methodology works through the pre-attachment of the glycosyl acceptor by means of a suitable tether covalently to the *O*-2 position of mannopyranosyl donor, and a subsequent intramolecular aglycon transfer with removal of the temporary tether. Various types of structural moieties such as dimethyl acetal, dimethyl dialkoxysilane, and *p*-methoxybenzylidene acetal have been used as tethers. Another successful protocol involves a direct coupling of aglycons to mannosyl sulfoxide donor to give a high β-selectivity *via* α-mannosyl triflate as a reactive intermediate.[5] Stepwise preparative methods to generate α-mannosyl triflate intermediates have also been reported.[5e,6]

We previously reported that a non-covalent version of the IAD strategy might also be possible utilizing the multiply coordinating ability of lanthanide (III) ions.[8] Because of their Lewis acidity and the high coordination numbers, lanthanide (III) ions are expected to be highly conducive to the coordination between mannosyl donor and glycosyl acceptor and thus, a directing effect was anticipated. Furthermore, it was envisaged that the β-directing effect might be further enhanced by attaching a better chelating moiety to the mannosyl donor molecules. In the initial attempts to test this idea, the chelating moieties such as 2-acetoxyacetyl and 2-(2-methoxyethoxy)-acetyl groups were examined, and it was found that generally poor yields were obtained presumably because of complications arising from the neighboring group participation. Thus, a non-participating moiety, 2-methoxyethoxymethyl, has been studied as a potential chelator of lanthanide (III) triflate.

In order to investigate the effect of lanthanide ion on the non-covalent IAD strategy, a series of experiments between mannosyl donor **1** and MeOH were carried out with 3 equivalents of *N*-iodosuccinimide (NIS) as activator in the presence of ytterbium (III) triflate, and the results are shown in Table 1. First, the α-anomer was found to be the major product in the absence of lanthanide ion (run 4). However, the ratio of α/β was shifted toward the β-anomer in the presence of ytterbium (III) triflate (runs 5 and 6). The lanthanide ion effects could also be seen in the decrease of reaction time and the improved yields. It appears that the equi-molar equivalents of mannosyl donor, lanthanides ion, and glycosyl acceptor are involved in determining the anomeric ratio (runs 1, 2, and 3), and this may be taken as an evidence for the intramolecular delivery through the lanthanide metal coordination.

We next turned to the glycosylation experiments with mannosyl donor **1** and another 1° alcohol acceptor **2**, which were also carried out with NIS as activator, and the results are summarized in Table 2. In this series of experiments, the effect of ytterbium (III) triflate on the β-selectivity can also be seen with about 7-fold increase of the β/α anomeric ratio (runs 1 and 4). It is clear that the glycosylation was not catalyzed by the lanthanide ion (run 7), and a varying amount of ytterbium (III) triflate did affect the anomeric ratio (runs 2 through 4). The use of TMSOTf, a known co-

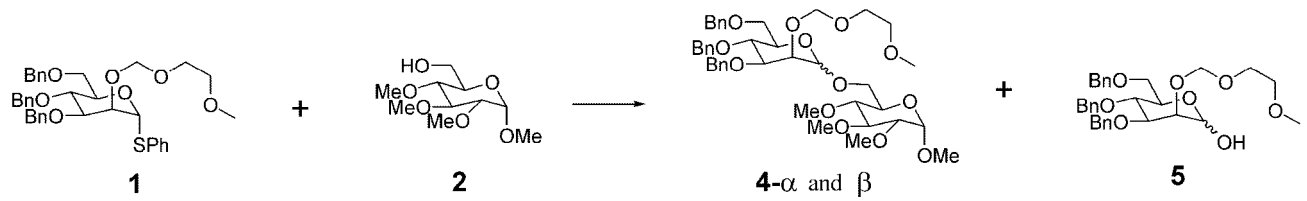
**Table 1.** Glycosylation between 1 and MeOH


**1** **3**-α and β

| Run | MeOH (eq.) | NIS (3 eq.) | $Yb(OTf)_3$ (eq.) | MS (3A, mg) | Time (h) | Yield (%) | $\alpha/\beta^a$ |
|---|---|---|---|---|---|---|---|
| 1 | 50 | + | 2 | – | 3 | 83.4 | 2.40/1 |
| 2 | 2 | + | 2 | – | 3 | 54.5 | 1/1.91 |
| 3 | 1.1 | + | 2 | – | 3 | 52.9 | 1/2.48 |
| 4 | 1.1 | + | – | 100 | 20 | 31.5 | 2.25/1 |
| 5 | 1.1 | + | 2 | 100 | 3 | 58.7 | 1/5.29 |
| 6 | 1.1 | + | 5 | 100 | 3 | 50.5 | 1/3.06 |

[a]based on the isolated yields.

**Table 2**. Glycosylation between **1** and **2**




**1** **2** **4**-α and β **5**

| Run | NIS (1.5 eq.) | Co-activator (eq.) | Solvent | Temp. (°C) | Time (h) | Yield **4** (%) | $\alpha/\beta^a$ | Yield **5** (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | + | – | $CH_3CN$ | -20 → r.t. | 18 | 26.9 | 1.30/1 | 45.5 |
| 2 | + | $Yb(OTf)_3$(0.2) | $CH_3CN$ | -20 → r.t. | 8.5 | 76.9 | 1/1.41 | 12.7 |
| 3 | + | $Yb(OTf)_3$(2) | $CH_3CN$ | -20 → r.t. | 2 | 78.1 | 1/3.39 | 12.3 |
| 4 | + | $Yb(OTf)_3$(5) | $CH_3CN$ | -20 | 1 | 67.5 | 1/5.44 | 18.2 |
| 5 | + | TMSOTf(0.2) | $CH_3CN$ | -20 → r.t. | 3 | 60.3 | 1/1.31 | 21.0 |
| 6 | + | TMSOTf(5) | $CH_3CN$ | -20 | 0.4 | 25.0 | 1/1.04 | – |
| 7 | – | $Yb(OTf)_3$(2) | $CH_3CN$ | -20 → r.t. | 24 | N.R. | – | – |

[a]based on the isolated yields.

activator, also had a small effect on the anomeric ratio of the product, perhaps through the leaving group modification (run 5 and 6).[5]

In summary, although the precise mechanistic definition to demonstrate the coordination of lanthanide is not yet possible, the experimental data suggest that the non-covalent IAD strategy could be achieved through the lanthanide ion coordination. However, the effect of 2-methoxyethoxymethyl group as a chelating appendage for lanthanide ion was not as successful as anticipated when compared to the previous results without it.[8] Thus, efforts to devise a more convenient and better chelating unit on the glycosyl donor in order to achieve much improved β-selectivities in the mannosylation are still on-going.

## Experimental Section

**General procedures**. All reactions were carried out under Ar atmosphere. All solvents were dried and freshly distilled by standard techniques prior to use. $^1$H-NMR spectra were recorded at 300 MHz and $^{13}$C-NMR at 75.5 MHz. Chemical Shifts are reported in $\delta$ ppm downfield from the signal of tetramethylsilane. Stereochemistry of the glycosylated products was determined on the basis of the value of specific rotation by the Hudson's classical isorotational rule, wherein a particular β-mannoside has less positive/more negative specific rotation than the corresponding α-anomer,[9] and further confirmed by the magnitude of the $^1J_{CH}$ coupling between H-1 and C-1, wherein a value of around 160 Hz signifies the β-configuration and 170 Hz the α-anomer.[10] The $^1J_{CH}$ coupling constant of the disaccharide was determined by $^{13}$C-coupled NMR spectrum.

**Phenyl 2-*O*-(2-methoxyethoxymethyl)-3,4,6-tri-*O*-benzyl-1-thio-α-D-mannopyranoside (1)**. To a solution of phenyl 3,4,5-tri-O-benzyl-1-thio-α-D-mannopyranoside, prepared from penta-*O*-acetyl D-mannopyranoside according to literature procedures,[11] in freshly distilled THF was added NaH (133 mg, 5.28 mmol) at 0 °C, and the mixture was stirred for 15 min, treated with MEMCl (0.60 mL, 5.28 mmol), and warmed up to rt. After stirring for 1.5 h, the reaction mixture was quenched with 1 N HCl, extracted with ethyl acetate, and the extract was washed with aq. $NaHCO_3$ and brine, and purified by column chromatography to give **1** as an oil: $[\alpha]_D$ = +119.14 (c 1.16 $CHCl_3$); $^1$H-NMR ($CDCl_3$) $\delta$ 7.47-7.44 (m, 2H), 7.36-7.21 (m, 18H), 5.66 (d, 1H, $J$ = 1.5), 4.91, 4.54 (d, each 1H, $J$ = 10.8), 4.85 (d, 2H, $J$ = 7.6), 4.76-4.71 (m, 2H), 4.62, 4.47 (d, each 1H, $J$ = 12.00), 4.33-4.27 (m, 2H), 4.00 (t, 1H, $J$ = 9.5), 3.88 (dd, 1H, $J$ = 3.0, 9.3), 3.84-3.79 (m, 1H), 3.78-3.68 (m, 3H), 3.43-3.37 (m, 2H), 3.27 (s, 3H); $^{13}$C-NMR ($CDCl_3$) $\delta$ 138.84, 138.79, 138.45, 134.89, 132.04, 129.38-127.76, 95.77, 87.31, 80.33, 76.74, 75.65, 75.46, 73.69, 73.07, 72.72, 71.99, 69.57, 67.59, 59.34

**Methyl 2,3,4-tri-*O*-methyl-α-D-glucopyranoside (2)**.[12] To a solution of methyl α-D-glucopyranoside in freshly distilled pyridine was added trityl chloride (1.2 eq) at rt. After stirring for 20 hrs, the reaction mixture was diluted with ethyl acetate, washed with iced 1 N HCl, aq. $NaHCO_3$ and brine, dried over $MgSO_4$, concentrated, and recrystallized to give white solid, methyl 6-*O*-trityl-α-D-glucoside (78.9%). The solid was dissolved in DMSO, and treated with NaH, and iodomethane (each 6.2 eq). After stirring for 5 hrs at rt, the reaction mixture was diluted with ethyl acetate, washed with 1 N HCl, aq. $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated to give oil. This crude product was stirred in MeOH with pTsOH (1.0 eq) at rt for 1 hr, the solvent was evaporated, and diluted with ethyl acetate, washed with aq. $NaHCO_3$ and brine, dried, concentrated to give a solid, which was purified on column chromatography (52.8% over two steps). $[\alpha]_D$ = +147.2 (c 0.63 $CHCl_3$); $^1$H-NMR ($CDCl_3$) $\delta$ 4.81 (d, 1H, $J$ = 3.4), 3.84-3.81 (m, 1H), 3.77-3.69 (m, 1H), 3.63 (s, 3H), 3.57 (s, 4H), 3.52 (s, 4H), 3.41 (s, 3H), 3.20-3.13 (m, 2H), 2.22 (t, 1H, $J$ = 5.8); $^{13}$C-NMR ($CDCl_3$) $\delta$ 97.86, 83.76, 82.20, 79.94, 71.02, 62.17, 61.20, 60.89, 59.37, 55.50

**General procedure of the glycosylation**. A solution of **1** (1.0 equiv.), acceptor, and $Yb(OTf)_3$ in acetonitrile over

activated molecular sieves (4 Å) under Ar was stirred for 30 min. at rt. and cooled to -20 °C, and treated with NIS solution in acetonitrile. After the indicated reaction time. the reaction was quenched with sat. sodium thiosulfate. The products were extracted with ethyl acetate. and the extract was washed with aq. $NaHCO_3$ and brine, and dried over $MgSO_4$. and concentrated under vacuum. and the product was purified by preparative thin layer chromatography on silica gel.

**Methyl 3,4,6-*O*-benzyl-2-*O*-(2-methoxyethoxymethyl)-α-D-mannopyranoside (3-a).**[11b] $[\alpha]_D$ = +45.86 (c 0.87 $CHCl_3$): $^1J_{CH}$ = 169.1 Hz; $^1$H-NMR ($CDCl_3$) $\delta$ 7.36-7.15 (m. 15H). 4.87 (d. 3H. $J$ = 11.0), 4.82 (d. 1H, $J$ = 1.7), 4.73-4.63 (m. 3H), 4.54 (d. 1H, $J$ = 12.2). 4.50 (d. 1H, $J$ = 10.8). 4.03 (m. 1H), 3.89-3.87 (m, 2H), 3.84-3.65 (m. 5H). 3.47 (t, 1H, $J$ = 4.5). 3.36 (s, 3H), 3.35 (s. 3H); $^{13}$C-NMR ($CDCl_3$) $\delta$ 138.82. 128.76-128.08, 100.20, 96.22, 80.14, 76.28, 75.48. 75.39, 74.18. 73.78, 72.62, 72.06. 69.77, 67.50, 59.33. 55.20.

**Methyl 3,4,6-*O*-benzyl-2-*O*-(2-methoxyethoxymethyl)-β-D-mannopyranoside (3-b).**[2a] $[\alpha]_D$ = +17.56 (c 1.31 $CHCl_3$): $^1J_{CH}$ = 155.4 Hz; $^1$H-NMR ($CDCl_3$) $\delta$ 7.38-7.17 (m. 15H). 4.99-4.89 (m. 2H), 4.86-4.79 (m, 2H). 4.61 (s, 1H). 4.59-4.57 (m. 2H). 4.50 (t, 2H, $J$ = 10.7). 4.24 (dd, 1H, $J$ = 7.32, 2.7). 4.06-4.00 (m, 1H). 3.85-3.75 (m. 3H). 3.72-3.61 (m. 2H). 3.60-3.50 (m. 3H). 3.44 (s, 3H), 3.36 (s. 3H); $^{13}$C-NMR ($CDCl_3$) $\delta$ 138.87, 138.78. 138.48, 128.77-127.87. 101.29. 97.58. 82.48. 76.28, 75.47, 75.28, 73.89. 72.22. 72.10, 71.85, 70.20, 69.05, 59.38, 56.14.

**Methyl 2,3,4-tri-*O*-methyl-6-*O*-[3,4,6-*O*-benzyl-2-*O*-(2-methoxyethoxymethyl)-α-D-mannopyranosyl]-(1→6)-α-D-glucopyranoside (4-α).** $[\alpha]_D$ = +67.00 (c 1.11 $CHCl_3$): $^1J_{CH}$ = 170.4 Hz; $^1$H-NMR ($CDCl_3$) $\delta$ 7.36-7.15 (m, 15H). 4.99 (d, 1H, $J$ = 1.56), 4.88 (d, 1H. $J$ = 11.1), 4.85 (bs. 2H). 4.74 (d, 1H. $J$ = 3.7), 4.67 (dd. 2H. $J$ = 11.8. 7.6), 4.62 (s. 1H), 4.52 (dd. 2H. $J$ = 6.8, 12.2). 4.05 (bs, 1H), 3.91-3.89 (m. 2H). 3.86-3.78 (m, 3H). 3.76-3.72 (m, 3H). 3.69-3.65 (m. 1H). 3.62 (s, 3H), 3.60-3.55 (m, 1H). 3.52 (s. 3H). 3.49 (s. 3H). 3.46 (t. 3H. $J$ = 4.5). 3.36 (s. 3H), 3.33 (s. 3H). 3.16 (dd. 1H. $J$ = 3.6. 9.6). 3.03 (dd. 1H. $J$ = 9.0. 9.7); $^{13}$C-NMR ($CDCl_3$) $\delta$ 139.04. 138.87. 138.68. 128.76-126.30. 99.34. 97.65. 96.05. 84.11. 82.31. 80.06. 79.67. 75.40. 74.09. 73.70. 72.50. 72.04. 70.18. 69.73. 67.47. 66.52. 61.16. 60.84. 59.30. 55.37.

**Methyl 2,3,4-tri-*O*-methyl-6-*O*-[3,4,6-*O*-benzyl-2-*O*-(2-methoxyethoxymethyl)-β-D-mannopyranosyl]-(1→6)-α-D-glucopyranoside (4-b).** $[\alpha]_D$ = +14.00 (c 0.98 $CHCl_3$): $^1J_{CH}$= 152.9 Hz; $^1$H-NMR ($CDCl_3$) $\delta$ 7.36-7.16 (m. 15H), 5.04 (dd, 2H, $J$ = 6.7. 19.2). 4.88 (dd. 2H, $J$ = 8.2, 10.7), 4.77 (d. 1H. $J$ = 3.5). 4.60 (d, 2H, $J$ = 12.6). 4.51 (dd, 3H, $J$ = 10.9. 21.5). 4.29 (d, 1H. $J$ = 2.7), 4.04-3.99 (m. 2H). 3.84-3.79 (m, 2H). 3.76-3.66 (m. 3H), 3.65-3.63 (m, 1H), 3.62 (s, 3H). 3.59-3.53 (m, 5H). 3.51 (s. 3H). 3.50 (s. 3H) 3.36 (s, 3H). 3.31 (s, 3H). 3.20 (dd, 1H. $J$ = 3.6. 9.7), 3.13 (d, 1H. $J$ = 9.8); $^{13}$C-NMR ($CDCl_3$) $\delta$ 138.77, 138.64, 129.23-127.98. 101.39, 97.83, 97.14, 84.04. 82.23. 80.12. 76.22, 75.44, 75.27, 73.88, 72.20. 71.70. 70.53, 70.09. 69.01. 67.51, 61.13, 60.76. 59.33. 55.38.

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