Pergamon

Tetrahedron Letters 42 (2001) 4005–4007

TETRAHEDRON LETTERS

# A novel approach to the stereoselective synthesis of β-D-mannopyranosides

Sung-Kee Chung* and Kyu-Hwan Park

*Department of Chemistry, Division of Molecular & Life Sciences, Pohang University of Science & Technology, Pohang 790-784, South Korea*

Received 1 March 2001; revised 10 April 2001; accepted 13 April 2001

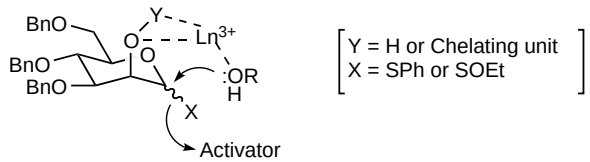
**Abstract**—A non-covalent version of the intramolecular aglycon delivery methodology has been demonstrated for the stereoselective formation of β-D-mannopyranoside in the presence of lanthanide(III) triflate. 

Recently glycobiology has received an increasing amount of attention as understanding of the nature and role of the carbohydrates in biological event increases. The majority of carbohydrates in cells exists as glycoconjugates, e.g. glycoproteins and glycolipids rather than in free forms, and they play critical roles in many important processes such as fertilization, immune response, viral and parasitic infection, cell growth, cell to cell adhesion and inflammation.[1]

Against these backgrounds synthetic carbohydrate chemistry has also made a substantial advances, particularly in the area of glycosylation methods.[2] Glycoproteins invariably contain β-D-mannopyranosyl residues in the glycan core structures. Despite the recent progress in the stereoselective glycosylation methods, 1,2-*cis*-β-D-mannopyranosidic linkage still remains a challenging synthetic problem. A variety of creative methods including intramolecular aglycon delivery (IAD) strategy and others have been reported for the stereoselective construction of β-D-mannopyranosides.[3–7] The IAD strategy involves (1) the covalent attachment of the aglyconic alcohol (glycosyl acceptor) to the 2-OH group of a suitably protected D-mannose derivative (glycosyl donor) via a temporary connector, and (2) an intramolecular glycosyl transfer with concomitant breakage of the connector moiety to give the desired β-D-mannoside product. Various structural units such as dimethyl acetal,[3] dimethyl dialkoxysilane,[4] and *p*-methoxybenzylidene acetal[5] have been successfully employed as the temporary connectors.

We envisaged that the non-covalent version of the IAD strategy might be possible through the agency of lanthanide(III) ion coordination as shown in Scheme 1. Lanthanide ions are considered hard Lewis acids and complex to hard bases such as fluoride ion and oxygen donor ligands.[8] The Lewis acidity and the high coordination numbers of lanthanide(III) salts are expected to be highly favorable for the desired coordination with glycosyl donor as well as glycosyl acceptor. This communication reports experimental results which are interpreted to support for such a non-covalent IAD strategy based on the lanthanide ion coordination.

The required mannosyl donors **1** and **2** were prepared from penta-*O*-acetyl-D-mannopyranoside via 3,4,6-tri-*O*-benzyl-β-D-mannose 1,2-(methyl orthoacetate) essentially according to literature procedures.[9] The glycosyl acceptor **3** was also readily derived from methyl α-D-glucopyranoside.[10] The glycosylation experiments between **1** and **3** were carried out with an equivalent amount of triflic anhydride as the activator in the presence of various lanthanide(III) triflates, and the results are shown in Table 1.[11] Several features of the reaction are to be noted. First and foremost, in the absence of lanthanide ion α-anomer of the disaccharide product **4**[12] is the major product. However, the product



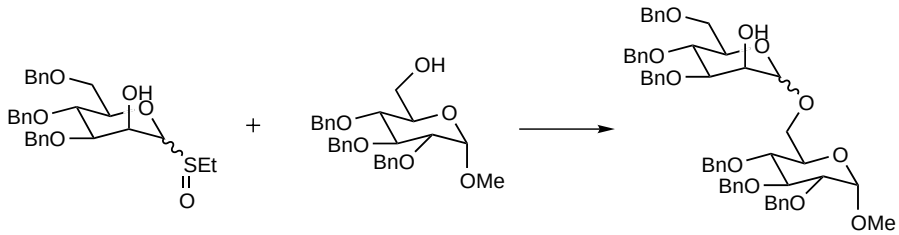

**Scheme 1.**

*Keywords*: glycosylation; intramolecular aglycon delivery; lanthanide ion coordination; β-D-mannopyranoside.

* Corresponding author.

0040-4039/01/$ - see front matter 
PII: S0040-4039(01)00643-8

**Table 1.** Glycosylation between **1** and **3**[17]



**1** **3** **4**

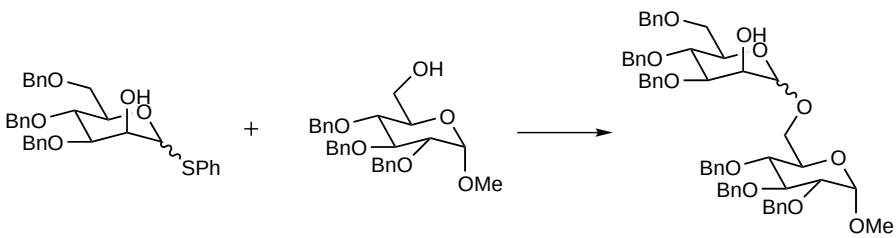
| Run | $Ln(OTf)_3$ (equiv.) | $Tf_2O$ (equiv.) | Solvent | Temp. (°) | Time (h) | Yield (%) | α/β[a] |
|---|---|---|---|---|---|---|---|
| 1 | – | + | $CH_2Cl_2$ | −78→rt | 5 | 43 | 4/1 |
| 2 | Yb (0.3) | + | $CH_2Cl_2$ | −78→rt | 14 | 43 | 1/2 |
| 3 | Yb (1) | + | $CH_2Cl_2$ | −78→rt | 10 | 63 | 1/2 |
| 4 | La (1) | + | $CH_2Cl_2$ | −78→rt | 12 | 51 | 1.7/1 |
| 5 | Eu (1) | + | $CH_2Cl_2$ | −78→rt | 10 | 76 | 1/1.5 |
| 6 | Eu (4) | + | $CH_2Cl_2$ | −78→rt | 9 | 80 | 1/2 |
| 7 | – | + | $CH_3CN$ | −40→rt | 12 | 42 | 5/1 |
| 8 | Eu (1) | + | $CH_3CN$ | −40→rt | 10 | 82 | 1/4.3 |
| 9 | Yb (1) | + | $CH_3CN$ | −40→rt | 12 | 63 | 1/2.8 |
| 10 | Eu (1) | – | $CH_2Cl_2$ | −78→rt | 23 | N.R. | – |

[a] Based on the isolated yields.

stereochemistry is now inverted by the presence of lanthanide ion. Second, a substantial solvent effect was observed; more β-product was obtained in acetonitrile than in dichloromethane (runs 5 and 8). The solvent effect observed was clearly not due to $CH_3CN$ alone (run 7), but might be due to either a better complex formation in acetonitrile or α-nitrilium-nitrile conjugate formation in the course of the reaction.[13] Third, Yb(III) and Eu(III) are found to be much more effective than La(III) in shifting the stereochemistry to the β-side. Perhaps, this may be attributed to the lower solubility of La(III) in dichloromethane.[14] Lastly, it is clear that the glycosylation is not catalyzed by lanthanide ion (run 10), and an excess amount of Ln(III) ion did not significantly affect the stereochemical outcomes (runs 2 and 3, 5 and 6).

Glycosylation experiments between compound **2** and **3** were also performed with several activator systems under varying conditions, and the results are listed in Table 2.[15] With compound **2**, which is expected to be less reactive than compound **1**, better yields were gener-

**Table 2.** Glycosylation between **2** and **3**[17]



**2** **3** **4**

| Run | $Ln(OTf)_3$ (equiv.) | Activator (equiv.) | Solvent | Temp. | Time | Yield (%) | α/β[a] |
|---|---|---|---|---|---|---|---|
| 1 | – | NBS (4) | $CH_2Cl_2$ | rt | 24 h | 24 | 3/1 |
| 2 | – | NIS (4) | $CH_2Cl_2$ | rt | 24 h | 31 | 3.5/1 |
| 3 | – | NIS (4), TfOH (cat.) | $CH_2Cl_2$ | 0°C | 15 min | 56 | 5.3/1 |
| 4 | Eu (1) | – | $CH_2Cl_2$ | rt | 24 h | N.R. | – |
| 5 | Yb (1) | – | $CH_2Cl_2$ | rt | 24 h | N.R. | – |
| 6 | La (1) | – | $CH_2Cl_2$ | rt | 24 h | N.R. | – |
| 7 | Eu (1) | NIS (4) | $CH_2Cl_2$ | rt | 20 min | 48 | 1/2 |
| 8 | Eu (1) | NIS (4), TfOH (cat.) | $CH_2Cl_2$ | 0°C | 20 min | 57 | 1/1.9 |
| 9 | Eu (1) | NIS (4), TfOH (cat.) | $CH_2Cl_2$ | −78°C | 6 h | 64 | 1/3.0 |
| 10 | Yb (1) | NIS (4) | $CH_2Cl_2$ | rt | 20 min | 47 | 1/1.5 |
| 11 | Yb (1) | NIS (4), TfOH (cat.) | $CH_2Cl_2$ | −78°C | 8.5 h | 59 | 1/2.9 |

[a] Based on the isolated yields.

ally obtained with both NIS and triflic acid as the co-activators. A similar lanthanide ion effect on the product stereochemistry is also evident in these experiments, and the best β/α anomeric ratio of ca. 3/1 was obtained with the combination of NIS and TfOH as co-activators, and Eu(III) or Yb(III) at −78°C.

In summary, these results quite clearly demonstrate that indeed the non-covalent version of the IAD strategy is possible through the lanthanide(III) ion coordination between the glycosyl acceptor and the glycosyl donor in which a geometrically well-defined coordination site is present as in compounds **1** and **2**. This coordination effect of lanthanide(III) ion on the glycosylation stereochemistry might be further enhanced by incorporating a better chelating unit on the glycosyl donor as shown in Scheme 1.[16,17]

## Acknowledgements

We gratefully acknowledge the financial support provided by Korea Science and Engineering Foundation and the Ministry of Education/Basic Science Research Institute Fund.

## References

1. (a) Berecibar, A.; Grandjean, C.; Siriwardena, A. *Chem. Rev*. **1999**, *99*, 779–844; (b) Dwek, R. A. *Chem. Rev*. **1996**, *96*, 683–720.
2. (a) Toshima, K.; Tatsuta, K. *Chem. Rev*. **1993**, *93*, 1503–1531; (b) Pausen, H. *Angew. Chem., Int. Ed*. **1982**, *21*, 155–173.
3. (a) Barresi, F.; Hindsgaul, O. *J. Am. Chem. Soc*. **1991**, *113*, 9376–9377; (b) Barresi, F.; Hindsgaul, O. *Synlett* **1992**, 759–761.
4. (a) Stork, G.; Kim, G. *J. Am. Chem. Soc*. **1992**, *114*, 1087–1088; (b) Stork, G.; La Clair, J. J. *J. Am. Chem. Soc*. **1996**, *118*, 247–248.
5. (a) Ito, Y.; Ogawa, T. *Angew. Chem., Int. Ed*. **1994**, *33*, 1765–1767; (b) Ito, Y.; Ohnishi, Y.; Ogawa, T. *Synlett* **1998**, 1102–1104.
6. (a) Valverde, S.; Garcia, M.; Gomez, A. M.; Lopez, J. C. *Chem. Commun*. **2000**, 813–814; (b) Valverde, S.; Garcia, M.; Gomez, A. M.; Lopez, J. C. *Synlett* **2000**, 22–26.
7. Crich, D.; Sun, S. *J. Org. Chem*. **1997**, *62*, 1198–1199.
8. (a) Molander, G. A. *Chem. Rev*. **1992**, *92*, 29–68; (b) Tsuneo, I. *Lanthanides in Organic Synthesis*; Academic Press: London, 1994.
9. (a) Nambiar, S.; Daeuble, J. F.; Doyle, R. J.; Taylor, K. G. *Tetrahedron Lett*. **1989**, *30*, 2179–2182; (b) Franks, N. E.; Montgomery, R. *Carbohydr. Res*. **1968**, *6*, 286–298.
10. (a) Hashimoto, S.; Honda, T.; Ikegami, S. *Chem. Commun*. **1989**, 685–687; (b) Chandhary, S.; Oscar, H. *Tetrahedron Lett*. **1979**, *27*, 579–582.
11. To a stirred solution of **1** (1.0 equiv.), **3** (1.2 equiv.) and $Ln(OTf)_3$ in the indicated solvent over activated molecular sieves (4 Å) under Ar, was added $Tf_2O$. After the indicated time, the reaction was quenched by addition of satd sodium thiosulfate. The products were isolated by filtration and extraction followed by column chromatography on silica gel. The α- and β-anomers showed $R_f$ values on silica gel at 0.15 and 0.29 in EtOAc/hexane (1/2), respectively.
12. Barresi, F.; Hindsgaul, O. *Can. J. Chem*. **1994**, *72*, 1447–1465.
13. Schmidt, R. R.; Behrendt, M.; Toepfer, A. *Synlett* **1990**, 694–696.
14. Bernardo, P. D.; Choppin, G. R.; Portanova, R.; Zanonato, P. L. *Inorg. Chim. Acta* **1991**, *207*, 85–91.
15. Glycosylation experiments were carried out essentially in the same manner as described for **1**.[11]
16. Reactions of the acetoacetylated derivative of **2** with $CH_3OH$ (1 equiv.), NBS (2 equiv.), and $Yb(OTf)_3$ (0–4 equiv.) in $CH_3CN$ at rt for 3–5 h yielded methyl-D-mannoside in ca. 40–60% yields with varying ratios of the α/β anomers; without the added lanthanide salt only the α-anomer was observed, whereas with 4 equiv. of $Yb(OTf)_3$ the β-anomer was obtained exclusively. A more extensive work on the stereoselective mannosylation is currently in progress, and the results will be reported in due course.
17. A referee suggested that the low yields observed in the experiments (Tables 1 and 2) might be due to the glycosylation at the 2-hydroxyl group of the donor themselves (**1** and **2**). However, there usually exists a substantial rate difference between 1° (**3**) and 2° (**1** and **2**) alcoholic acceptors.