Glycosylation

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Stereoselective Construction of β-Mannopyranosides by Anomeric *O*-Alkylation: Synthesis of the Trisaccharide Core of *N*-linked Glycans

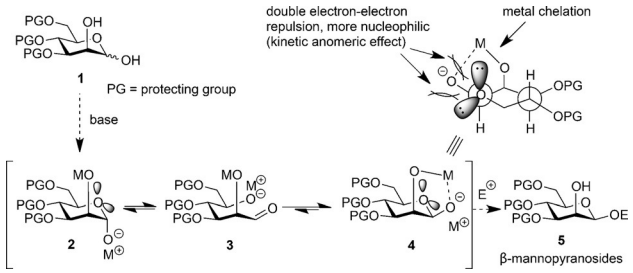
Hai Nguyen, Danyang Zhu, Xiaohua Li, and Jianglong Zhu**

Abstract: *A new and efficient approach for direct and stereoselective synthesis of β-mannopyranosides by anomeric O-alkylation has been developed. This anomeric O-alkylation of mannopyranose-derived lactols is proposed to occur under synergistic control of a kinetic anomeric effect and metal chelation. The presence of a conformationally flexible C6 oxygen atom in the sugar-derived lactol donors is required for this anomeric O-alkylation to be efficient, probably because of its chelation with cesium ion. In contrast, the presence of a C2 oxygen atom plays a minor role. This glycosylation method has been successfully utilized for the synthesis of the trisaccharide core of complex N-linked glycans.*

Protein glycosylation is known as one of the major types of post-translational modifications. In general, there are two types of glycans attached to proteins: 1) *N*-linked glycans attached to asparagine and 2) *O*-linked glycans attached to serine or threonine.[1] Recent biological studies have demonstrated that the glycans of glycoconjugates play essential roles in numerous biological[2] and cellular processes.[3] Cell-surface glycans serve as receptor ligands for proteins, for example, enzymes,[4] antibodies,[5] and lectins.[6] In addition, it was also found that the degree of cell-surface carbohydrate antigen expression is closely associated with tumor progression, and diagnostic results may guide the use of corresponding approach for cancer treatment.[7,8] Furthermore, carbohydrate moieties are known to stabilize protein folding[9] and modify physical, chemical, and biological properties of their carrier molecules.

Because of the heterogeneous glycoforms of glycoproteins, it is difficult to understand the exact function of these complex glycans. To address the challenge, researchers seek to obtain single glycoforms of biologics by either total chemical synthesis[10] or chemoenzymatic synthesis.[11] Although great progress has been achieved,[10,11] the synthesis of complex *N*-linked glycans remains a daunting task. In particular, stereoselective construction of the β-mannopyranoside, one of the key glycosidic linkages existing in structurally complex *N*-linked glycans, is a long-standing challenge in glycosylation chemistry.[12] Over the past several decades, numerous efforts have been dedicated to addressing this difficulty to facilitate the chemical synthesis of *N*-linked glycans for studies of their biological function. Those efforts include: 1) use of a nonparticipating group[13] for protection of O2 and insoluble silver salts for activation of mannopyranosidic halide;[13a–d] 2) inversion of the C2 stereochemistry of β-glucopyranosides[14] or stereoselective reduction[15] of β-2-ulosyl glycosides; 3) de novo synthesis of β-mannopyranosides by α-selective quenching of C1-alkoxy radicals by suitable hydrogen-atom donors;[16] 4) synthesis of β-mannopyranosides involving intramolecular aglycone delivery;[17–20] 5) use of 4,6-*O*-benzylidene-[21] or 4,6-*O*-silylene-protected[22] α-mannopyranosyl triflates; 6) use of hydrogen-bond-mediated aglycone delivery mediated by a remote 3-*O*-picoloyl group.[23] Despite the remarkable success, oftentimes certain amounts of minor α-mannopyranosides were also formed in the reaction and purification of β-mannopyranosides from their corresponding α-anomers could be time-consuming and challenging. Therefore, it would be desirable to develop an approach which ideally only produces β-mannopyranosides. Herein we disclose an approach for stereoselective construction of the β-mannopyranosidic linkage by anomeric *O*-alkylation.

Our group has recently developed a method for stereoselective synthesis of 2-deoxy-β-glycosides[24] by anomeric *O*-alkylation[25,26] controlled by a kinetic anomeric effect.[25] In addition, we have reported stereoselective synthesis of 2-deoxy-α-glycosides by chelation-controlled anomeric *O*-alkylation.[27,28] Based on aforementioned success, we wondered if a kinetic anomeric effect in conjunction with chelation control could be applied to the stereoselective synthesis of β-mannopyranosides. As shown in Scheme 1, after deprotonation of the D-mannose **1** with a suitable base, a mixture of the dianions **2** and **4** may be produced and interconvert via the open intermediate **3**. As a result of the chelation effect, the



Scheme 1. Proposed stereoselective synthesis of β-mannopyranosides by anomeric O alkylation.

[*] H. Nguyen, D. Zhu, Prof. Dr. J. Zhu
Department of Chemistry and Biochemistry and
School of Green Chemistry and Engineering
The University of Toledo
Toledo, OH 43606 (USA)
E-mail: Jianglong.Zhu@Utoledo.edu
Prof. Dr. X. Li
Department of Natural Sciences
University of Michigan-Dearborn, Dearborn, MI 48128 (USA)
E-mail: shannli@umich.edu

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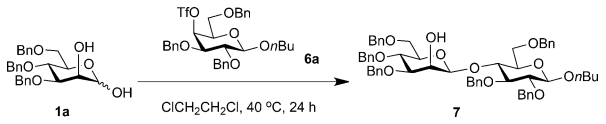
equatorial anomeric alkoxide **4** would be preferentially formed over the axial counterpart **2**. In addition, **4** should be more nucleophilic than **2** because of the double electron–electron repulsion, also known as kinetic anomeric effect.[25,29] Subsequent S_N2 reaction of **4** with suitable electrophiles may afford the desired β-mannopyranosides **5**.

Previously, Schmidt and co-workers reported limited studies on anomeric *O*-alkylation of partially or fully protected D-mannopyranoses with simple primary electrophiles under various reaction conditions.[28c,d] In their experiments either poor to moderate yields[28c] or moderate selectivity[28d] was observed when either NaH or KO^{t}Bu was used as the base. When 3,4,6-tri-*O*-benzyl-D-mannopyranose (see **1a** in Table 1) was employed, over-alkylation was found to be a problem.[28c] Some success was also achieved by others[30] when **1a** or other partially protected D-mannopyranoses were converted into their corresponding 1,2-*O*-dibutylstannylene complexes followed by *O*-alkylation with various electrophiles. However, organostannanes are highly toxic and the use of stoichiometric amounts of organostannanes is certainly not desirable.

In consideration of the natural β-(1→4)-linked mannopyranosidic linkage in complex *N*-linked glycans, we chose to study the anomeric *O*-alkylation reaction between **1a** and the D-galactose-derived C4 secondary triflate **6a** for selective production of the corresponding β-mannopyranoside **7** (Table 1). Initially, we applied the optimal reaction conditions, which we had discovered previously,[24,27] for the

Table 1: Anomeric O alkylation of **1a** with **6a**.[a]



Entry	Reaction conditions	Yield [%][b]
1[c]	Cs_2CO_3 (1.5 equiv), **6a** (1.5 equiv)	25
2	Cs_2CO_3 (1.5 equiv), **6a** (1.5 equiv)	48
3	Cs_2CO_3 (2.5 equiv), **6a** (2.0 equiv)	67
4	Cs_3PO_4 (2.5 equiv), **6a** (2.0 equiv)	59
5[d]	Cs_2CO_3 (2.5 equiv), **6a** (2.0 equiv)	64
6	Cs_2CO_3 (3.0 equiv), **6a** (2.5 equiv)	75

[a] Unless otherwise noted, all reactions were performed using 0.1 mmol of 3,4,6-tri-*O*-benzyl-D-mannopyranose **1a** in 1 mL $ClCH_2CH_2Cl$ at 40 °C for 24 hours. [b] Yield of isolated product (calculated based on **1a**). Only β products are formed. [c] CH_3CN was used as solvent. [d] This reaction was carried out at 50 °C. Tf = trifluoromethanesulfonyl.

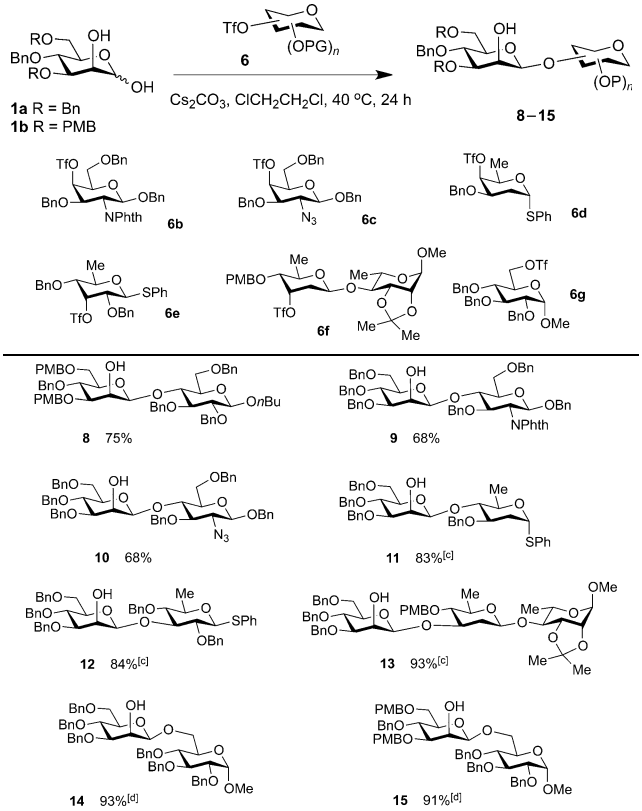
synthesis of 2-deoxy glycosides to this type of β-mannopyranosylation. However, only a trace amount of product was obtained. Changing the solvent to dichloromethane[28c,d] gave similar results. Base-mediated 1,2-elimination of **6a** was found to be the major problem. During the search for bases which could react with **1a** to form more nucleophilic anomeric alkoxides, we were excited to discover that warming a mixture of **1a** (1 equiv), **6a** (1.5 equiv), and Cs_2CO_3 (1.5 equiv) in acetonitrile at 40 °C afforded the desired β-mannopyranoside **7** in 25 % yield upon isolation (β only)[31] (entry 1). After screening a range of polar and nonpolar solvents as well as co-solvents,[32] we found that 1,2-dichloroethane was the optimal solvent for this reaction, which provided **7** in 48 % yield (β only; entry 2). Increasing the amount of **6a** to 2.0 equivalents and Cs_2CO_3 to 2.5 equivalents increased the yield of the isolated **7** to 67 % (β only; entry 3). Changing the base to Cs_3PO_4 or elevating the reaction temperature afforded inferior yields (entries 4 and 5). Finally, use of **6a** (2.5 equiv) and Cs_2CO_3 (3.0 equiv) furnished **7** in 75 % yield (β only; entry 6). Attempting to let the reaction proceed longer (40 hours) gave comparable results.[32] Over alkylation at O2 was not observed in any of these experiments. Notably, the use of 2-aminoethyl diphenylborinate (0.1 equiv.), a catalyst well-demonstrated by Taylor and coworkers[33] for regioselective alkylation of *cis* diols, in this type of β-mannosylation was not effective.[32] These results suggested that the anomeric cesium alkoxide was the key active intermediate for anomeric *O*-alkylation with sugar-derived triflates. The reason why cesium bases turned out to be efficient for this type of β-mannosylation is not entirely clear, but it is probably a result of well-known cesium effect.[34] In addition, in contrast to traditional glycosylations which are usually performed under anhydrous conditions, this anomeric *O*-alkylation with cesium carbonate is not very moisture-sensitive.

With the optimal reaction conditions established, we next performed studies on the reaction scope using **1a** and 4-*O*-benzyl-3,6-di-*O*-(4-methoxybenzyl)-D-mannopyranose (**1b**) with various sugar-derived triflates (**6b–g**). As shown in Table 2, under optimal reaction conditions, the β-mannopyranosides **8**, **9**, and **10** were produced, from **1a/b** and the corresponding relatively unreactive triflates **6a–c**, in synthetically useful to good yields and excellent anomeric selectivity, respectively.[31] In addition, the β-mannopyranosides **11**, **12**, and **13** were obtained in good to excellent yields and excellent anomeric selectivity[31] from the more-reactive triflates **6d–f**,[24] and even less triflate (2.0 equiv) was used. Furthermore, if most reactive primary triflate, **6g**, was employed, only 1.5 equivalents of the triflate was needed for the reaction and the β-mannopyranosides **14** and **15** were obtained in excellent yields and anomeric selectivities.[31]

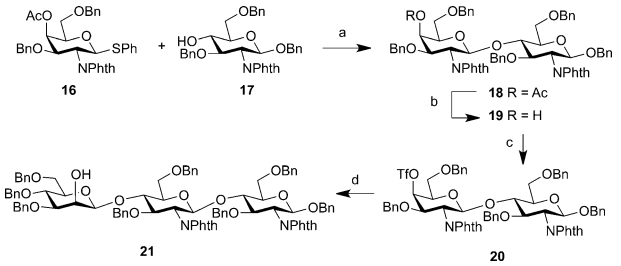
To demonstrate the utilization of this method in complex oligosaccharide synthesis, we next performed the synthesis of the trisaccharide core of the *N*-linked glycan **21** (Scheme 2). The synthesis commenced with the traditional glycosylation between the known glycosyl donor **16**[35] and acceptor **17**[36] under previously reported reaction conditions,[37] which afforded the desired β-linked disaccharide **18** in 97 % yield. Deacetylation of **18** afforded the desired alcohol **19**, which was subsequently subjected to triflation to produce the triflate **20**. Finally, cesium-carbonate-mediated anomeric O alkylation of **1a** with **20** (2.5 equivalents) gave the desired trisaccharide core of the *N*-linked glycan **21** in 72 % yield (β only).

To gain insight into this type of anomeric *O*-alkylation, we studied various D-mannopyranose-type donors, such as 3,4-di-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilyl-D-mannopyranose (**22**), 3-*O*-benzyl-4,6-*O*-benzylidene-D-mannopyranose (**24**), 3,4-di-*O*-benzyl-D-rhamnose (**26**), 3,4,6-tri-*O*-benzyl-2-deoxy-D-glucose (**28**), and 3,4-di-*O*-benzyl-D-olivose (**30**) for this type

Table 2: Cs_2CO_3-mediated β-mannosylation involving various sugar-derived triflates.[a,b]



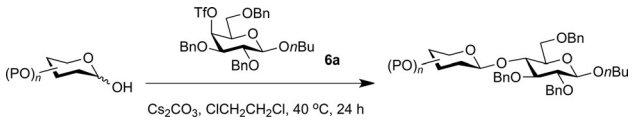
[a] General reaction conditions: either **1a** or **1b** (1.0 equiv), triflate **6** (2.5 equiv), and Cs_2CO_3 (3.0 equiv) in $ClCH_2CH_2Cl$ at 40 °C for 24 h. [b] Yield of the isolated product (calculated based on **1**). Only β products are formed. [c] Use the triflate **6** (2.0 equiv) and Cs_2CO_3 (2.5 equiv). [d] Used the triflate **6** (1.5 equiv) and Cs_2CO_3 (1.5 equiv).

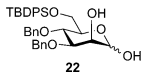
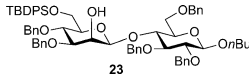
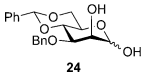
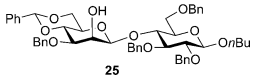
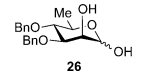
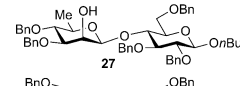
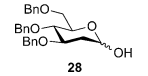
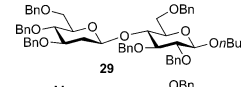
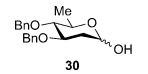
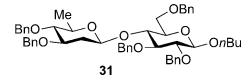


Scheme 2. Synthesis of the trisaccharide core of *N*-linked glycans by anomeric O alkylation. Reagents and conditions: a) NIS, TfOH, 4 Å molecular sieves, CH_2Cl_2, −20 °C, 97%; b) NaOMe, MeOH/THF (1:1), RT, 72% yield; c) Tf_2O, pyridine, CH_2Cl_2, 0 °C, 90% yield; d) **1a** (1.0 equiv), **20** (2.5 equiv), Cs_2CO_3 (3.0 equiv), $ClCH_2CH_2Cl$, 40 °C, 24 h, 72% (yield calculated based on the lactol donor **1a**). NIS = *N*-iodosuccinimide, THF = tetrahydrofuran.

of anomeric *O*-alkylation with **6a** (2.0 equivalents). As shown in Table 3, while the β-mannopyranoside **23**[31] was obtained in 40% yield from **22**, bearing a 6-*O*-TBDPS ether (entry 1), surprisingly, we did not observe the production of the β-mannopyranoside **25** from **24** (entry 2). In addition, use of **26**, lacking a C6 oxygen atom, in the reaction afforded only 30% of the β-linked disaccharide **27**[31] (entry 3). Furthermore, use of **28** (also can be viewed as 2-deoxy-D-mannose) gave the

Table 3: Anomeric O alkylation of various D-mannopyranose-type donors.[a,b]



Entry	Donor	Product	Yield [%]
1	 **22**	 **23**	40
2	 **24**	 **25**	0
3	 **26**	 **27**	30
4	 **28**	 **29**	64
5	 **30**	 **31**	15

[a] General reaction conditions: lactol donors (1.0 equiv), **6a** (2.0 equiv), and Cs_2CO_3 (2.5 equiv) in $ClCH_2CH_2Cl$ at 40 °C for 24 h. [b] Yield of the isolated product (calculated based on the lactol donors). Only β products are formed.

desired β-linked disaccharide **29** in 64% yield (entry 4), and this result was comparable to the reaction outcome **1a** (entry 3, Table 1). However, use of **30** (2,6-dideoxy-D-glucose/mannose) only afforded 15% yield of the corresponding 2,6-dideoxy glycoside **31**, albeit with excellent anomeric selectivity. These results suggested that the presence of a conformationally flexible C6 oxygen atom in the sugar-derived lactol donors is required for this anomeric *O*-alkylation to be efficient, probably because of its chelation with the cesium ion. In contrast, the presence of C2 oxygen atom was found to play a minor role in this type of reaction.

In conclusion, an efficient approach for stereoselective synthesis of challenging β-mannopyranosides has been developed by anomeric *O*-alkylation of mannopyranoside-derived lactols. It was believed that this type of β-mannosylation occurs under synergistic control of the kinetic anomeric effect and chelation effect. It was found that the presence of a conformationally flexible C6 oxygen atom in the sugar-derived lactol donors is indispensable for this anomeric *O*-alkylation to be efficient, while the presence of the C2 oxygen atom was found to play minor role. This approach has been successfully utilized for the synthesis of the trisaccharide core of *N*-linked glycans. Further mechanistic studies of this cesium-carbonate-mediated β-mannosylation and application of this methodology to the synthesis of complex *N*-linked glycans are currently underway.

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Keywords: anomeric *O*-alkylation · glycosylation · *N*-linked glycans · oligosaccharides · β-mannosylation

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