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Authors: Hai Nguyen; Danyang Zhu; Xiaohua Li, PhD; Jianglong Zhu, Ph.D.

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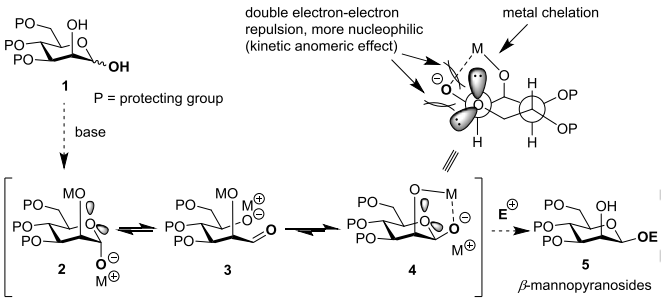
Stereoselective Construction of *β*-Mannopyranosides via Anomeric *O*-Alkylation: Synthesis of the Trisaccharide Core of *N*-linked Glycans

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

Abstract: *A new and efficient approach for direct and stereoselective synthesis of β-mannopyranosides via anomeric O-alkylation has been developed. This anomeric O-alkylation of mannopyranose-derived lactols was believed to occur under synergistic control of kinetic anomeric effect and metal chelation. It was found that the presence of a conformationally flexible C6-oxygen in the sugar-derived lactol donors is required for this anomeric O-alkylation to be efficient, probably due to its chelation with cesium ion. In contrast, the presence of C2-oxygen atom was found to play 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 modification. 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, *e.g.*, 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.

Due to 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 glycoform of biologics by either total chemical synthesis[10] or chemo-enzymatic 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 in order to facilitate the chemical synthesis of *N*-linked glycans for studies of their biological function. Those efforts include: 1) use of non-participating 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 via *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[22] protected *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. In this Communication, we wish to disclose an approach for stereoselective construction of the *β*-mannopyranosidic linkage via anomeric *O*-alkylation.



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

Our laboratory has recently developed a method for stereoselective synthesis of 2-deoxy-*β*-glycosides[24] via anomeric *O*-alkylation[25,26] controlled by kinetic anomeric effect.[25] In addition, we have reported stereoselective synthesis of 2-deoxy-*α*-glycosides via chelation-controlled anomeric *O*-alkylation.[27,28] Based on aforementioned success, we wondered if kinetic anomeric effect in conjunction with chelation control can be applied to the stereoselective synthesis of *β*-mannopyranosides. As shown in Scheme 1, after deprotonation of D-mannose **1** with a suitable base, a mixture of dianion **2** and **4** may be produced and interconvert into each other via open intermediate **3**. Due to the chelation effect (colored in blue), equatorial anomeric alkoxide **4** would be preferentially formed over the axial counterpart **2**. In addition, equatorial anomeric alkoxide **4** should be more nucleophilic than the axial counterpart **2** due to the double electron-electron repulsion (colored in purple, also known as kinetic anomeric effect).[25,29] Subsequent S_N2 reaction of equatorial anomeric alkoxide **4** with suitable electrophiles may afford desired *β*-mannopyranosides (Scheme 1).

Previously, Schmidt reported limited studies on anomeric *O*-alkylation of partially or fully protected D-mannopyranoses with simple primary electrophiles under various conditions.[28c,d] In their experiments either poor to moderate yields[28c] or moderate selectivity[28d] was observed when NaH or KO^{t}Bu was used as base. When 3,4,6-tri-*O*-benzyl-D-mannopyranose (*cf.* **1a**, Table 1) was employed, over-alkylation was found to be a problem.[28c] Some

[*] 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, Michigan 48128 (USA)
E-mail: shannli@umich.edu

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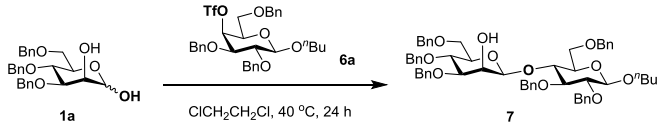
success was also achieved by others[30] when **1a** or other partially protected D-mannopyranoses were converted to their corresponding 1,2-*O*-dibutylstannylene complexes followed by *O*-alkylation with various electrophiles. However, organostannanes are highly toxic and the use of stoichiometric amounts of organostannanes is certainly not desirable.

Table 1. Anomeric *O*-alkylation of 3,4,6-tri-*O*-benzyl-D-mannopyranose **1a** with D-galactose-derived C4-triflate **6a**.[a]

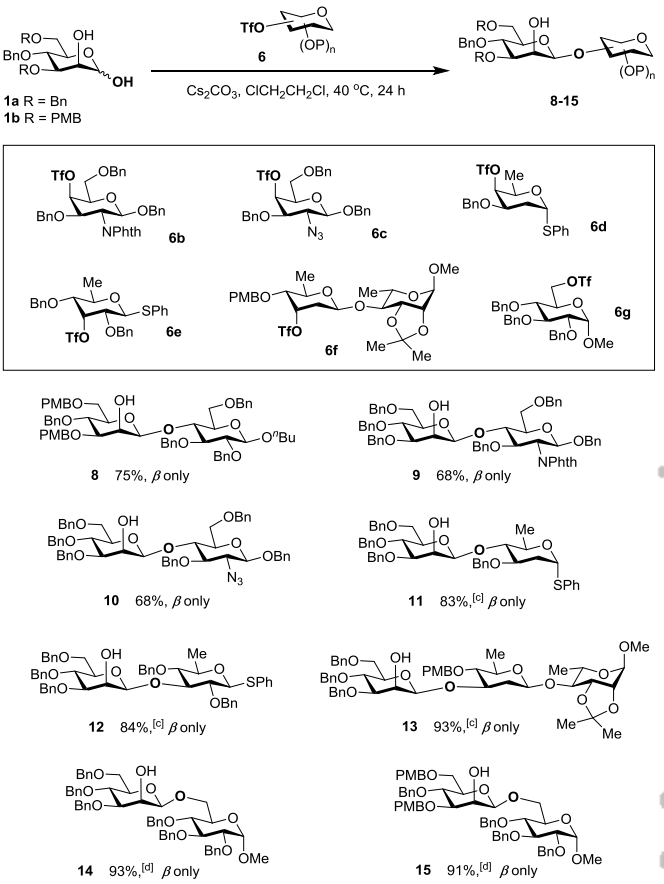


Entry	Reaction condition	Yield,[b] *α*/*β* ratio
1[c]	Cs_2CO_3 (1.5 eq.), triflate **6a** (1.5 eq.)	25%, *β* only
2	Cs_2CO_3 (1.5 eq.), triflate **6a** (1.5 eq.)	48%, *β* only
3	Cs_2CO_3 (2.5 eq.), triflate **6a** (2.0 eq.)	67%, *β* only
4	Cs_3PO_4 (2.5 eq.), triflate **6a** (2.0 eq.)	59%, *β* only
5[d]	Cs_2CO_3 (2.5 eq.), triflate **6a** (2.0 eq.)	64%, *β* only
6	Cs_2CO_3 (3.0 eq.), triflate **6a** (2.5 eq.)	75%, *β* only

[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] Isolated yield (calculated based on the lactol donor **1a**). [c] CH_3CN was used as solvent. [d] This reaction was carried out at 50 °C.

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 3,4,6-tri-*O*-benzyl-D-mannopyranose **1a** and D-galactose-derived C4 secondary triflate **6a** for selective production of the corresponding *β*-mannopyranoside **7** (Table 1). Initially, we applied the optimal conditions that we had discovered previously[24,27] for the synthesis of 2-deoxy glycosides to this type of *β*-mannopyranosylation; however, only trace amount of product was obtained. Changing the solvent to dichloromethane[28c,d] gave similar results. Base-mediated 1,2-elimination of trilate **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 D-mannopyranose **1a** (1 eq.), triflate **6a** (1.5eq.), and Cs_2CO_3 (1.5 eq.) in acetonitrile at 40 °C afforded desired *β*-mannopyranoside **7** in 25% isolated yield (*β* only)[31] (entry 1, Table 1). After screening a range of polar and non-polar solvents as well as co-solvents,[32] we found that 1,2-dichloroethane was the optimal solvent for this reaction which provided desired *β*-mannopyranoside **7** in 48% yield (*β* only) (entry 2). Increasing the amounts of triflate **6a** to 2.0 equivalents and Cs_2CO_3 to 2.5 equivalents increased the isolated yield of *β*-mannopyranoside **7** to 67% (*β* only) (entry 3). Changing the base to Cs_3PO_4 or elevating the reaction temperature afforded inferior isolated yields (entries 4 and 5, respectively). Finally, use of triflate **6a** (2.5 eq.) and Cs_2CO_3 (3.0 eq.) furnished desired *β*-mannopyranoside **7** in 75% yield (*β* only) (entry 6). Attempting to let the reaction proceed longer (40 hours) gave comparable results.[32] No over alkylation at O2 was observed in all these experiments. It should be noted that the use of 2-aminoethyl diphenylborinate (0.1 eq.), a catalyst well-demonstrated by Taylor[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, probably due to 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.

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

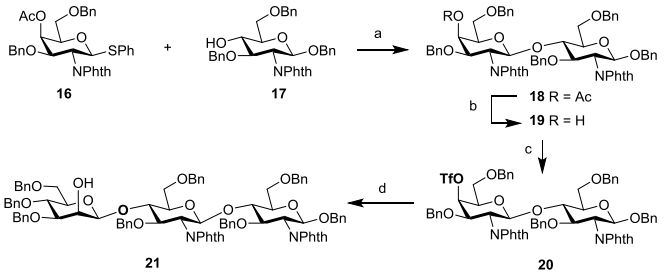


[a] General conditions: lactol **1a** or **1b** (1.0 eq.), triflate **6** (2.5 eq.), Cs_2CO_3 (3.0 eq.), $ClCH_2CH_2Cl$, 40 °C, 24 h. P = Protecting group. [b] Isolated yield (calculated based on the lactol donors **1a** or **1b**). [c] triflate **6** (2.0 eq.) and Cs_2CO_3 (2.5 eq.) were used. [d] triflate **6** (1.5 eq.) and Cs_2CO_3 (1.5 eq.) were used.

With the optimal condition established, we next performed studies on the reaction scope using 3,4,6-tri-*O*-benzyl-D-mannopyranose **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 conditions, *β*-mannopyranosides **8**, **9**, and **10** were produced from **1a/b** and relatively unreactive triflates **6a-c** in synthetically useful to good yields and excellent anomeric selectivity, respectively.[31] In addition, *β*-mannopyranosides **11**, **12**, and **13** were obtained in good to excellent yields and excellent anomeric selectivity[31] from more reactive triflates **6d-f**,[24] even less amount of the triflates (2.0 eq.) were used. Furthermore, if most reactive primary triflate **6g** was employed, only 1.5 eq. of the triflate was needed for the reactions and *β*-mannopyranosides **14** and **15** were gained in excellent yields and anomeric selectivity.[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 glycans **21** (Scheme 2). The synthesis commenced with the traditional glycosylation between known glycosyl donor **16**[35] and acceptor **17**[36] under previously reported condition[37] which afforded desired *β*-linked disaccharide **18** in 97% yield. Deacetylation of **18** afforded desired alcohol **19** which was subsequently subjected to triflation to produce triflate **20**. Finally, cesium carbonate-mediated anomeric *O*-alkylation of 3,4,6-

tri-*O*-benzyl-D-mannopyranose **1a** with triflate acceptor **20** (2.5 eq.) gave the desired trisaccharide core of the *N*-linked glycans **21** in 72% yield (*β* only).

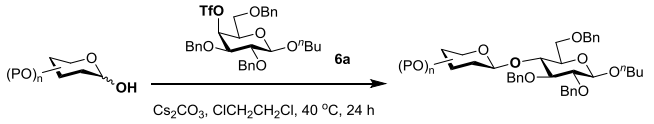


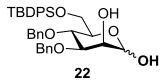
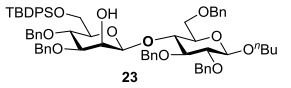
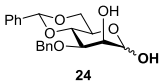
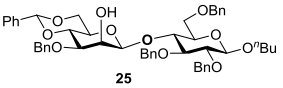
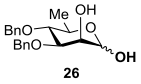
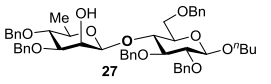
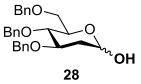
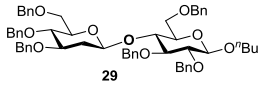
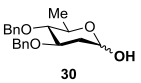
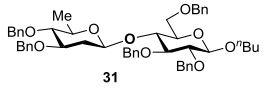
Scheme 2. Synthesis of the trisaccharide core of the *N*-linked glycans via anomeric *O*-alkylation. Reagents and conditions: a) NIS, TfOH, 4Å molecular sieves, CH_2Cl_2, -20 °C, 97%; b) NaOMe, MeOH/THF (1:1), RT, 72% yield; c) Tf_2O, pyridine, CH_2Cl_2, 0 °C, 90% yield; d) **1a** (1.0 eq.), **20** (2.5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

In order 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 of anomeric *O*-alkylation with triflate **6a** (2.0 eq.). As shown in Table 3, while *β*-mannopyranosides **23**[31] was obtained in 40% yield from D-mannopyranose **22** bearing 6-*O*-TBDPS ether (entry 1), surprisingly, we did not observe the production of *β*-mannopyranosides **25** from 4,6-benzylidene protected D-mannopyranose **24** (entry 2). In addition, use of D-rhamnose donor **26** lacking C6-oxygen atom in the reaction afforded only 30% yield of the *β*-linked disaccharide **27**[31] (entry 3). Furthermore, use of 2-deoxy-D-glucose donor **28** (also can be viewed as 2-deoxy-D-mannose) gave the desired *β*-linked disaccharide **29** in 64% yield (entry 4), and this result was comparable to the reaction outcome using 3,4,6-tri-*O*-benzyl-D-mannopyranose **1a** (entry 3, Table 1). However, use of D-olivose **30** (2,6-dideoxy-D-glucose/mannose) only afforded 15% yield of the corresponding 2,6-dideoxy glycoside **31**, albeit excellent anomeric selectivity was achieved. These results suggested that the presence of a conformationally flexible C6-oxygen in the sugar-derived lactol donors is required for this anomeric *O*-alkylation to be efficient, probably due to its chelation with cesium ion. In contrast, the presence of C2-oxygen atom was found to play minor role in this type of reaction.

In conclusion, an efficient approach for stereoselective synthesis of challenging *β*-mannopyranosides has been developed via anomeric *O*-alkylation of mannopyranoside-derived lactols. It was believed that this type of *β*-mannosylation occurs under synergistic control of kinetic anomeric effect and chelation effect. It was found that the presence of a conformationally flexible C6-oxygen in the sugar-derived lactol donors is indispensable for this anomeric *O*-alkylation to be efficient, while the presence of C2-oxygen atom was found to play minor role. This approach has been successfully utilized for the synthesis of the trisaccharide core of the *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.

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



Entry	Donor	Product	Yield, α/β ratio
1	 **22**	 **23**	40%, *β* only
2	 **24**	 **25**	0%
3	 **26**	 **27**	30%, *β* only
4	 **28**	 **29**	64%, *β* only
5	 **30**	 **31**	15%, *β* only

[a] General conditions: lactol donors (1.0 eq.), triflate **6a** (2.0 eq.), Cs_2CO_3 (2.5 eq.), $ClCH_2CH_2Cl$, 40 °C, 24 h. P = Protecting group. [b] Isolated yield (calculated based on the lactol donors).

Acknowledgments

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

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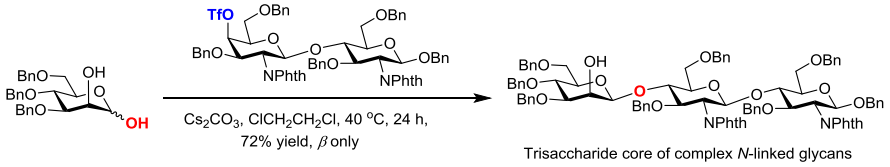
H. Nguyen, D. Zhu, Prof. Dr. X. Li,* Prof. Dr. J. Zhu* _____ **Page – Page**

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



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