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One-Pot Synthesis of Glucosamine Oligosaccharides

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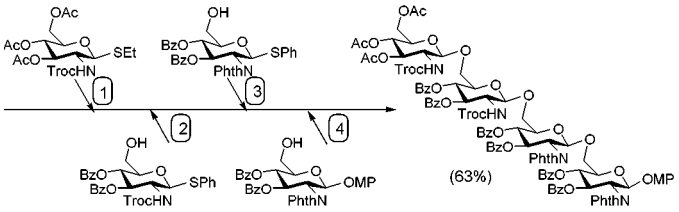
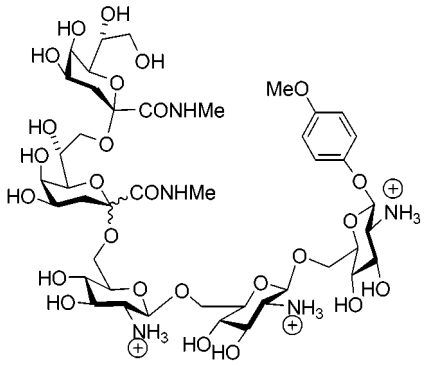
ABSTRACT



Tuning the reactivity of glycosyl donors derived from 2-amino-2-deoxy glucose by selective introduction of different N-protecting (NPhth and NHTroc) and anomeric leaving groups (ethylthio and phenylthio) enabled highly efficient oligosaccharide synthesis in a one-pot manner. One-pot sequential glycosylation of three and four units of 2-amino-2-deoxy glucose gave trisaccharides and tetrasaccharide in 50−81% yields.

Although the abundance of carbohydrates in nature and their diverse role in biological systems make them attractive for various chemical and biological research efforts, no systematic study on their potency as possible specific catalysts has yet been performed. We assumed that in the framework of systematic research it would be possible to rationally design and synthesize oligosaccharide structures capable of catalyzing certain chemical transformations. As a first example of such structure, we recently reported[1] a synthesis of pentasaccharide **1** that shows marked rate enhancement and specificity for the hydrolysis of GTP to GDP and orthophosphate. However, since the synthesis of **1** required the total of 32 chemical steps with an overall yield of 2.2%, the observed low availability of the product has made the extensive mechanistic and kinetic studies of this reaction difficult. This fact prompted us to elaborate more efficient and rapid methodology for the construction of **1** and related structures. As part of this effort, we show that the triglucosamine part of **1**, as well as its structural analogues and tetraglucosamine, can be efficiently constructed in a one-pot manner.



1

Since the reactivity of a glycosyl donor can be influenced by different factors such as the choice of protecting group,[2] the choice of leaving group,[3] the configuration of the glycoside,[4] and the choice of promoter, various approaches to accomplishing one-pot synthesis of oligosaccharides have recently been reported.[5,6] While the majority of one-pot

(1) Solomon, D.; Fridman, M.; Zhang, J.; Baasov, T. *Org. Lett.* **2001**, in press.

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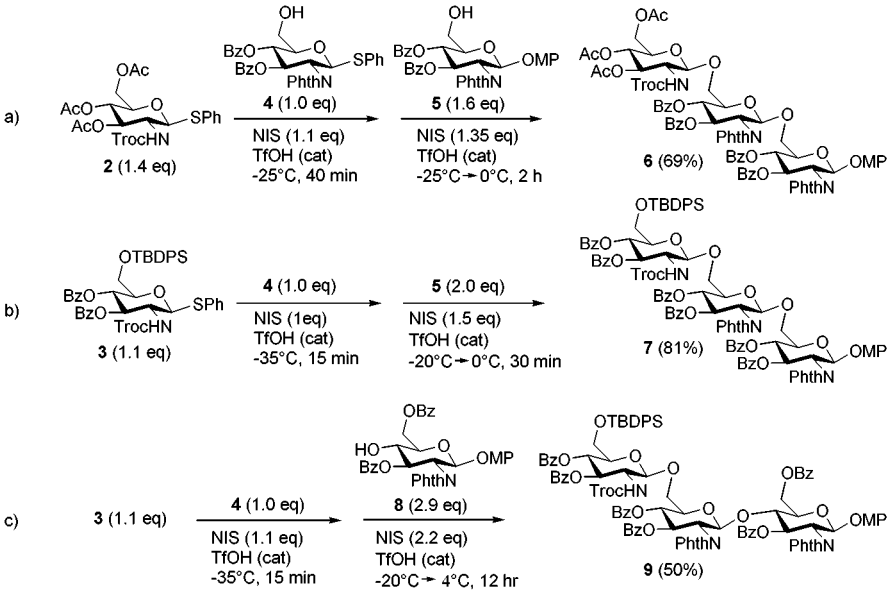
Scheme 1



Bz: benzoyl; *Troc*: trichloroethoxycarbonyl; *Phth*: phthaloyl; *TBDPS*: *tert*-butyldiphenylsilyl; *MP*: *p*-methoxyphenyl

synthetic techniques to date have been largely qualitative, the strategies developed by the Ley[6a] and Wong[6b] groups are of note for their quantitative nature. The latter group has demonstrated that the reactivity of 2-amino sugar donors can be sufficiently tuned by the protecting group at the nitrogen. For example, it has been shown that N-Troc-protected glucosamine is 33.7-fold more reactive than the corresponding N-Phth-protected glucosamine. We reasoned that this reactivity difference should be large enough to benefit one-pot oligoglucosamine synthesis. Using this strategy, a number of triglucosamines were prepared as model studies (Scheme 1).

All donors used in this study were thioglycosides[7] because they are stable under most reaction conditions frequently used for the construction of building blocks. The desired glucosamine building blocks **2**−**5** were designed to allow, through neighboring group participation, selective β-(1 → 6)-glycoside bond formation.[8] The protecting groups used served admirably in terms of ease of attachment and removal and survivability under the reaction conditions. Thus, using N-Troc-protected thiophenyl glucosides **2** and **3** as most reactive donors, the N-Phth-protected thiophenyl glucoside **4** as less reactive donor acceptor, and the *p*-methoxyphenyl glucoside **5** as the reducing end acceptor, the trisaccharides **6** and **7** were synthesized in 69% and 81% isolated yields, respectively (Scheme 1a,b). To further prove the feasibility of the strategy for the preparation of β-(1 → 4)-glycoside bond formation, compound **8** was used as the reducing end acceptor and the trisaccharide **9** was prepared in the isolated yield of 50% (Scheme 1c).

By introducing an additional level of reactivity difference, we attempted to extend the above methodology and perform a four-component synthesis to produce a tetraglucosamine oligosaccharide in a one-pot sequential glycosidation. While this may be done in different strategies, we specifically limited ourselves in using thioglucosides as versatile glycosyl donors and ester groups as the only type of protection, because of the ease of attachment and removal. As a consequence of these limitations we wished to control the reactivity of glucosamine by using different thiol aglycons. Indeed, perbenzoylated ethylthio galactoside has been shown to be more reactive than the identically protected phenylthio galactoside.[9a] However, this reactivity difference failed to be sufficient enough when other sugar cores were used as coupling pairs.[9b,10] This issue has recently been solved by using solvent reactivity effect introduced by Oscarson and

(3) (a) Raghavan, S.; Kahne, D. *J. Am. Chem. Soc.* **1993**, *115*, 1580. (b) Kanie, O.; Ito, Y.; Ogawa, T. *J. Am. Chem. Soc.* **1994**, *116*, 12073. (c) Yamada, H.; Harada, T.; Miyazaki, H.; Takahashi, T. *Tetrahedron Lett.* **1994**, *35*, 3979. (d) Grice, P.; Ley, S. V.; Pietruszka, J.; Priepke, H. W. M.; Walther, E. P. E. *Synlett* **1995**, 781.

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(5) (a) Geurtsen, R.; Holmes, D. S.; Boons, G.-J. *J. Org. Chem.* **1997**, *62*, 8145. (b) Grice, P.; Ley, S. V.; Pietruszka, J.; Osborn, M. I.; Henning, W. M.; Priepke, H. W. M.; Warriner, S. L. *Chem. Eur. J.* **1997**, 431. (c) Green, L.; Hinzen, B.; Ince, S. J.; Langer, P.; Ley, S. V.; Warriner, S. L. *Synlett* **1998**, *4*, 440.

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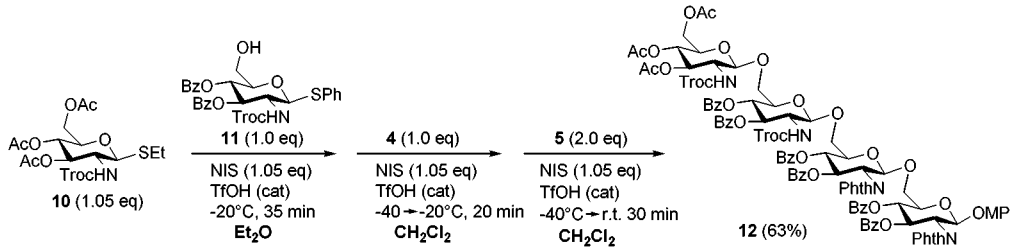
(7) Veeneman, G. H.; van Leuwen, S. H.; van Boom, J. H. *Tetrahedron Lett.* **1990**, *31*, 1331.

(8) The monosaccharides used in this study were prepared by standard methods. All new compounds exhibited satisfactory spectral and analytical data. Yields refer to spectroscopic and chromatographic homogeneous materials.

(9) (a) Choudhury, A. K.; Mukherjee, L.; Mukhopadhyay, B.; Roy, N. *J. Carbohydr. Chem.* **1999**, *18*, 361. (b) Lahmann, M.; Oscarson, S. *Org. Lett.* **2000**, *2*, 3881.

Scheme 2



co-workers.[9b] This group demonstrated that ethylthio glycosides can be selectively activated by using Et_2O as a solvent, whereas the activation of phenylthio glycoside was only possible by addition of CH_2Cl_2. We wished to extend this chemistry by investigating the possibility of combining the solvent reactivity effect with different N-protected groups for the assembly of glucosamine oligosaccharides. This is successfully accomplished in a one-pot synthesis of tetrasaccharide **12** from the monosaccharide building blocks (Scheme 2).

When the ethylthio glucoside **10** (1.05 equiv) and the phenylthio glucoside **11** (1.0 equiv) were dissolved in Et_2O and the promoter NIS/TfOH was added (−20 °C, 35 min), only **10** was activated to give the corresponding phenylthio disaccharide in almost quantitative yield according to TLC. Subsequent addition of **4** (1.0 equiv) and an additional amount of promoter dissolved in CH_2Cl_2 (at this stage the ratio Et_2O/CH_2Cl_2 is ∼5:7) yielded the corresponding trisaccharide within 20 min. Finally, addition of acceptor **5** (2.0 equiv) to the above mixture followed by 1.05 equiv of NIS and TfOH (cat.) gave the desired tetraglucosamine **12** in 63% isolated yield.

(10) When the coupling reaction between **10** (1.05 equiv) and **11** (1.0 equiv) was carried out in CH_2Cl_2 in the presence of 1.0 equiv of NIS and catalytic amount of TfOH, a complex product mixture was obtained according to TLC.

In conclusion, efficient one-pot syntheses of various triglucosamine oligosaccharides have been accomplished by selective introduction of the Troc and Phth protecting groups at the amine function. By using the combination of this concept with the solvent reactivity effect of ethylthio and phenylthio leaving groups, highly effective one-pot four-component synthesis of a tetraglucosamine oligosaccharide was performed. It is anticipated that the methods outlined here will have broad utility in the synthesis of many diverse glycoconjugates containing 2-amino-2-deoxy sugar residues, as well as for the assembly of highly functionalized complex oligosaccharides. One-pot synthesis of the target pentasaccharide **1**, as well as the synthesis of its structural analogues, are in progress and will be reported in due course.

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Supporting Information Available: Selected procedures and data for compounds **6**, **7**, **9**, and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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