ADVANCED CHEMICAL SYNTHESIS OF OLIGOSACCHARIDES

Reported by Jun Li April 21st, 2014

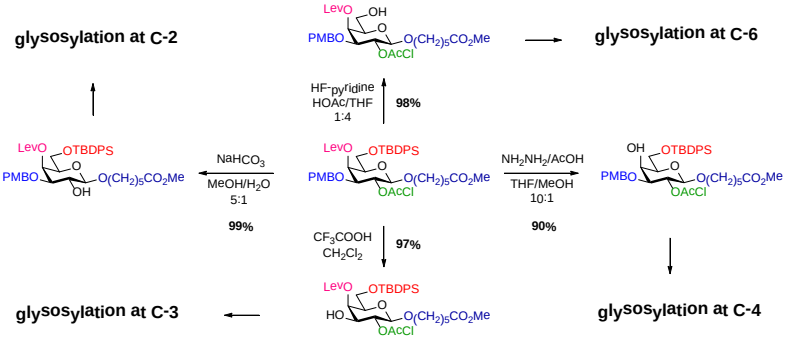
INTRODUCTION

Polysaccharides are a crucial member of the bio-conjugates present in advanced living creatures as polysaccharides were shown to occupy many indispensable functions in various biological processes, e.g. the binding of sperm to egg for fertilization.[1] Compared with its counterparts, nucleic acids and proteins however, polysaccharide roles remained the least understood.[2] One major obstacle towards complete understanding of glycoconjugates is the accessibility to pure polysaccharides.

Extraction from natural sources is unpractical due to low concentration of glycoconjugates naturally presented, as well as their purification; and synthetic approaches to saccharide building blocks are challenging as a consequence of the complexity of their structures. Unlike the linear structures of polypeptides and nucleic acids, polysaccharides can propagate in branching fashions given the number of active hydroxyl groups on the monosaccharide unit. Also, the versatility of glycosylation (i.e. connection of different saccharide building blocks) aggravated the synthetic difficulty.

CLASSIC CHEMICAL SYNTHESIS OF OLIGOSACCHARIDES

Orthogonal protection/deprotection strategy was developed to differentiate hydroxyl groups at different positions on the monosaccharide rings. Regioselective orthogonal protection of thiolgalactopyranoside introduced isopropyl, chloroacetyl, benzyl and acetyl protecting groups at the 2-O, 3-O, 4-O and 6-O positions, respectively.[3] As shown in Scheme 1, these selective functionalization reactions offer practical approaches to oligosaccharides with control of glycosylation position when hydroxyl groups was selectively deprotected. However, tedious and repeated purification is inevitable with these types of approaches.



Scheme 1. Orthogonal deprotection of thiolgalactopyranoside.

AUTOMATED SOLID-PHASE SYNTHESIS OF OLIGOSACCHARIDES

Pioneered by Fréchet in 1971[4], solid-phase assisted strategies have inaugurated a new era in oligosaccharides synthesis, especially when automation of the processes became possible. Seeberger and co-workers first demonstrated automated process for solid-phase oligosaccharides synthesis[5] (SPOS) (Figure 1), where selectively-protected mannoside as a glycosyl donor was anchored on polystyrene

resin via an olefinic linker. Automated cycles of deprotection and glycosylation afforded α–(1→3) octamannoside in 14 h with 34% total yield. Solid-phase substrate facilitates removal of impurities from deprotection and glycosylation by simple rinse and filtration steps. SPOS was used to prepare many oligosaccharides, but is still impeded by several factors, namely limitations of protection-deprotection reactions to accommodate the olefin linker, large excess of saccharide building blocks required and difficulty to delineate molecular diversification.

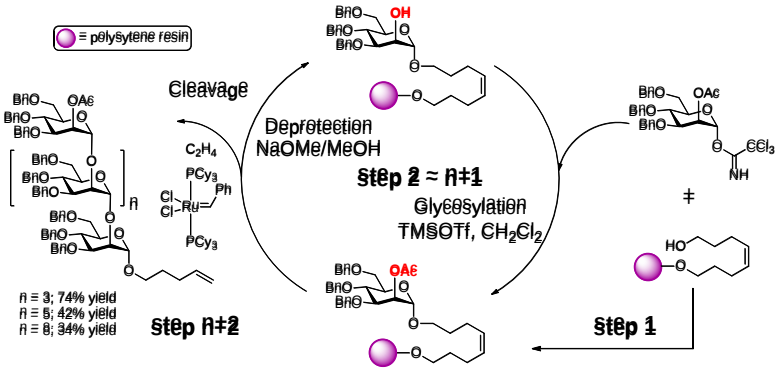


Figure 1. Automated solid-phase assisted synthesis of oligomannoside.

PROGRAMMABLE SOLUTION-PHASE SYNTHESIS OF OLIGOSACCHARIDES

Based on the armed/disarmed concept[6] (i.e. armed saccharide preferentially serves as glycosyl donor while disarmed saccharide serves as glycosyl acceptor), Wong and co-workers established a library pool that calibrates the relative reactivity values (RRVs) of mono/disaccharides normalized to peracetyltolylthiomannoside[7]. The programmable solution-phase synthesis of Globo H[8] is shown in Figure 2, where the desired oligosaccharide structure was input into Optimer software to analyze feasible building blocks based on RRVs. Programmable addition of stoichiometric amount of building blocks afforded stereoselectively the final product in 20 % yield, which was twenty times higher than stepwisely synthesized.[9] Although the synthesis of monosaccharide building blocks is still unavoidable, programmable solution-phase oligosaccharide synthesis circumvented the repeated protection-deprotection procedures of reaction intermediates in glycosylation steps, which considerably reduced the labor and cost.

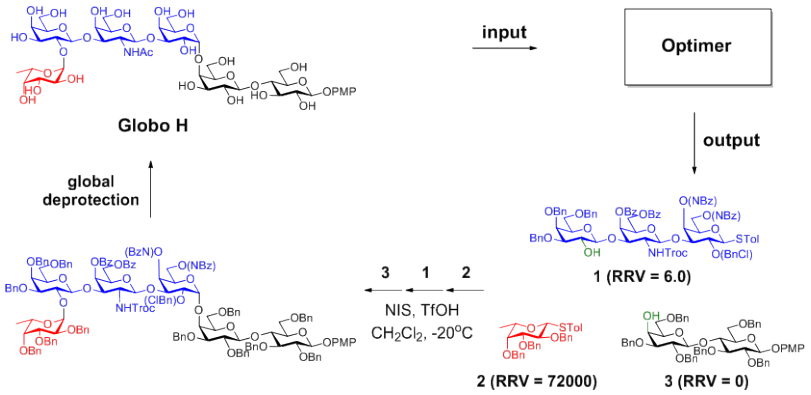


Figure 2. Programmable synthesis of Globo H.

FUTURE PERSPECTIVE

Automated and programmable syntheses of oligosaccharides already provide feasible approaches to challenging glycosylation reactions. The efficient synthesis of building blocks, nevertheless, is still

necessary and would greatly benefit from methodological studies on the generalization of mono/disaccharide functionalization. The combination of chemical and enzymatic synthesis of oligosaccharide will help access structural complexity of glycoconjugates, and therefore further enhancing our understanding of the role of saccharide species in biological systems.

REFERENCES

(1) Pang, P.-C.; Chiu, P.C.N. *et al*. *Science* **2011**, *333,* 1761-1764.
(2) Seeberger, P.H.; Werz, D.B. *Nature* **2007**, *446,* 1046-1051.
(3) Wong, C.-H.; Ye, X.-S. *et al*. *J. Am. Chem. Soc.* **1998**, *120,* 7137-7138.
(4) Fréchet, J.M.; Schuerch, C.J. *J. Am. Chem. Soc*. **1971**, *93*, 492-496.
(5) Plante, O.J.; Palmacci, E.R. *et al*. *Science*, **2001**, *291*, 1523-1527
(6) Mootoo, D.R.; Konradsson, P. *et al*. *J. Am. Chem. Soc*. **1988**, *110,* 5583-5584.
(7) Zhang, Z.Y.; Ollmann, I.R. *et al*. *J. Am. Chem. Soc.* **1999**, *121,* 734-753.
(8) Burkhart, F.; Zhang, Z.Y. *et al*. *Angew. Chem. Int. Ed.* **2001**, *40*, 1274-1277.
(9) Bilodeau, M.T.; Park, T.K. *et al*. *J. Am. Chem. Soc.* **1995**, *117,* 7840-7841.