Progress from the Past Decade Toward Key Challenges in Chemical *O*-Glycosylation

Reported by N. Ian Rinehart 2/19/2019

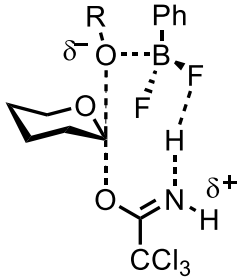
Background & Significance

The glycosciences have expanded our understanding of the role complex oligo- and polysaccharides (or more generally, glycans) play in biological systems. Historically, carbohydrates—the largest class of biomolecules—were only implicated in structural systems, energy storage, and as primary metabolites. The past few decades of research have elucidated the role of carbohydrates and glycoconjugates in core homeostatic systems from cell-cell recognition, cell growth, signal transduction, fertilization, immune system response, and cancer metastasis. The challenges of glycan synthesis and the intractability of natural isolation hamper research into their role in these key biological systems. In contrast to the study of nucleic acids or peptides—where methods for amplification or over-expression enable the isolation of material for study—the study of glycans still rely on synthetic chemistry and chemical glycosylation to provide pure research samples. The past decade has advanced the state-of-the-art in the chemical synthesis of glycans significantly by addressing key frontiers in the synthesis of glycans: (1) the synthesis of 1,2-*cis* glycosides in high anomeric purity, (2) high-yielding reactions, (3) The development of branching methods (4) catalytic activation of glycosyl donors, (5) avoiding protection and deprotection steps, (6) improved atom economy and reagent stoichiometry, and (7) automation of glycan synthesis to enable non-specialists to obtain authentic samples.

Preorganization of Donor and Acceptors to Promote Stereospecificity

The past decade of research has yielded methods that provide pre-organization of both donor and acceptor, enabling stereospecific glycosylations. Methods for the generation of 1,2-*cis* glycosides are known, but limited in scope. A general methodology is still needed. The most important advances towards this goal will be discussed, including the use of pendant groups that pre-organize reactive partners to one face of the glycosyl donor and catalysts that pre-organize the reactive partners via a hydrogen bonding network.

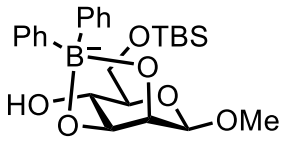
Stereospecific Glycosylation by Preorganization



Temporary Masking of Acceptor

The use of temporary hydroxyl masking groups on a glycosyl acceptor to promote the formation of partially unprotected glycan products ready for subsequent glycosylation will be discussed. The development of this strategy throughout the past decade and its culmination in two complementary strategies to provide 1,2-*cis* or 1,2-*trans* glycosides will be discussed.

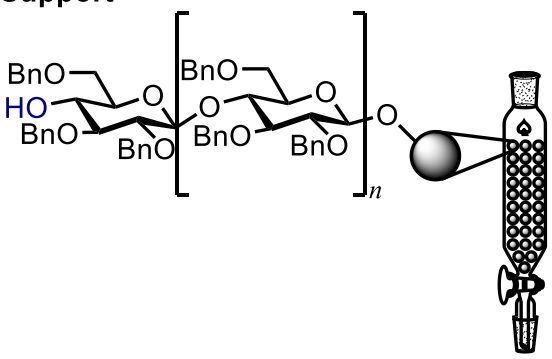
Masking/Activation of Unprotected Acceptors



Automation and Solid-Phase Synthesis

The automation of polypeptide and polynucleicacid synthesis has revolutionized medicine. In the last decade, major synthetic endeavors and the development of standardized quality control measures have made automated glycan assembly a tenable long-term solution by exploiting inherently selective 1,2-*trans* glycosylations using anchimeric assistance of acyl C-2 *O*-Acyl protecting groups. The strategies of automated glycan synthesis will be covered as well as the synthesis of 1,2-*cis* glycosides. The use of a modified HPLC instrument as an automated glycan synthesizer, permitting non-specialists to create glycans without purchasing a dedicated synthesizer, will be covered.

Automated Glycan Synthesis on Solid Support



Key References:

1. Yu, Biao and coworkers. *J. Am. Chem. Soc.,* **2013**, 135, 18396−18405.
2. Schmidt R., and coworkers. *J. Am. Chem. Soc.* **2015**, 137, 12653−12659.
3. Jacobsen and coworkers. *Science,* **2017**, *355*, 6321, 162-166.
4. Toshima, K., Takahashi, D., and coworkers. *J. Am. Chem. Soc.*, **2018**, *140*, 3644–3651
5. Seeberger and coworkers. *Nat. Comm.* **2016**, 7, 12482.