Intramolecular Pre-Organization of Oligosaccharides: The Synthesis of Cyclic Inhibitors Towards Monoclonal Antibody SYA/J6

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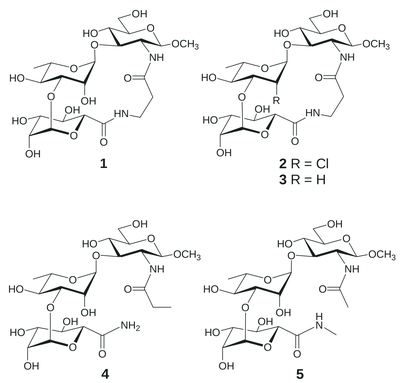
Introduction

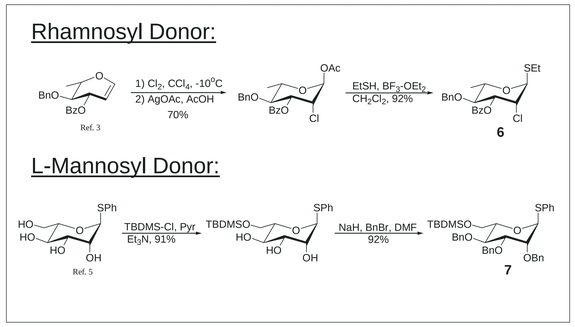
Functional group replacement and pre-organization of ligands in their bound conformation are two approaches for the rational design of high affinity carbohydrate inhibitors of protein-saccharide interactions. To date, neither has shown great promise. Here we attempt to combine both modification types to create high affinity oligosaccharides.

Recently, we showed that pre-organization of the *Shigella flexneri* variant Y trisaccharide antigen (α-L-Rha-(1-3)-α-L-Rha-(1-3)-β-D-GlcNAc-OMe) to give the tethered trisaccharide **1** resulted in 1.9 kcal mol^{-1} higher binding energy with monoclonal antibody (mAb) SYA/J6. However, the affinity gain was of enthalpic (1.5 kcal mol^{-1}) rather than entropic origin.[1] Other modifications to the central rhamnose ring (2´-deoxy- and 2´-chloro-2´-deoxy) of the trisaccharide have produced inhibitors with high binding affinity.[2,3,4]

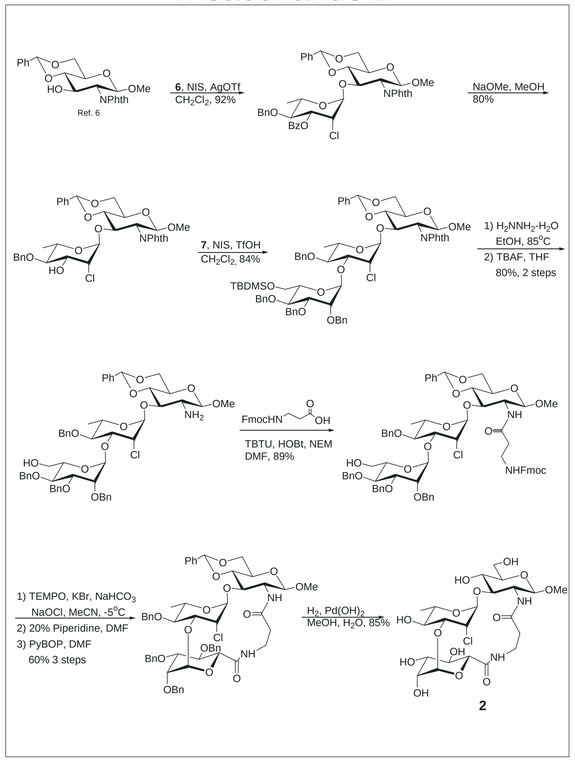
Here we combine molecular pre-organization of the native trisaccharide as exemplified by **1** with 2´-deoxy- and 2´-chloro-2´-deoxy modifications to give ligands **2** and **3**. Reference compounds **4** and **5** (non-tethered variants of **1**) were synthesized to verify that the tether was uniquely responsible for the increased affinity of **1**. Preliminary binding data are also reported.



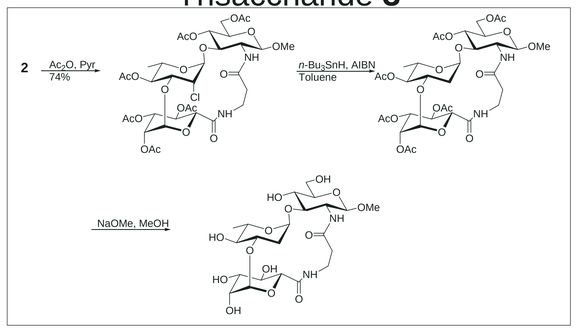
Scheme 1: Monosaccharide Donors



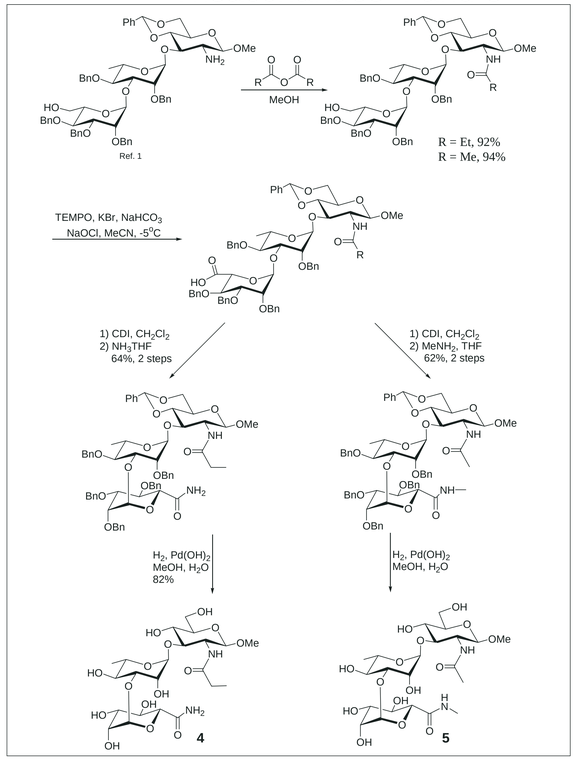
Scheme 2: Assembly of Tethered Trisaccharide **2**



Scheme 3: Synthesis of Tethered Trisaccharide **3**



Scheme 4: Assembly of Tethered Trisaccharides **4** and **5**



Summary and Conclusions

An efficient synthetic route to tethered cyclic oligosaccharide inhibitors and acyclic reference compounds is described.

Initial ELISA data show that the free energy gains from paired modifications result in higher affinity ligands but the free energy gains of single site variants are not additive. This suggests that the mode of binding for each ligand modified at single sites differs so that it is impossible to productively pair tethering and functional group replacement.

Acknowledgements

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