DEVELOPMENT OF A NOVEL LIGATION STRATEGY FOR SYNTHESIS OF THERAPEUTIC GLYCOPEPTIDES

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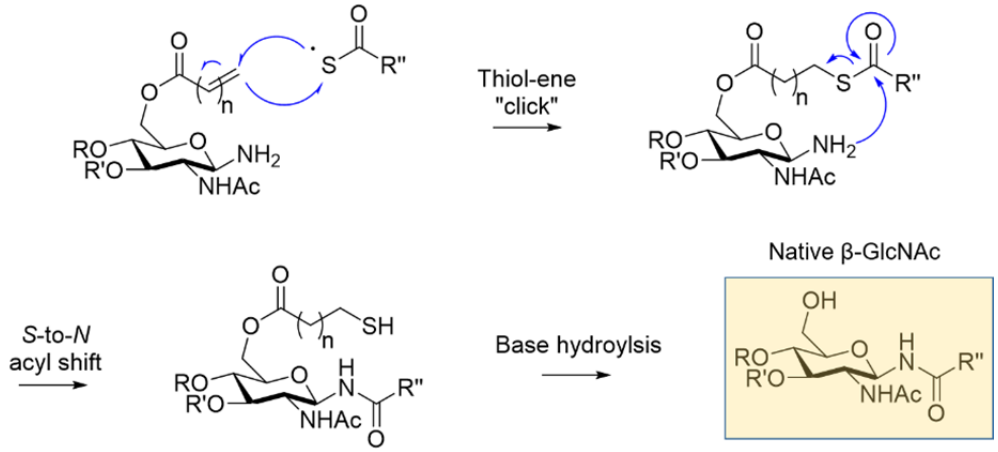
Glycosylation is an important post-translational modification which influences the stability, structural dynamics and pharmacokinetics of proteins. While it is one of the most abundant protein modifications, heterogeneity within biological glycans makes the study of single glycoforms extremely difficult. Access to homogenous glycosylated proteins is hampered by a number of factors - the lack of appropriate cell glycosylation machinery in recombinant approaches prevents isolation from bacterial/fungal and insect models, and synthetic approaches rely on forcing conditions and large excesses of reagents.

While many methods to access *N*-glycopeptides exist, the significant drawbacks associated with each technique warrant the design of new methodologies. An approach tolerated under physiological conditions and with a facile radical initiation was envisioned. This work examines radical ligation onto modified *N*-acetylglucosamine residues, and a spontaneous *S*-to-*N* acyl shift over varying transition state (TS) sizes to furnish *N*-linked glycopeptides with native amide bonds.



Scheme 1. General outline.

[1] D. M. Lynch, H. M. Burke, E. M. Scanlan, 2019, *manuscript in preparation*