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Investigations into the synthesis of amine-linked neodisaccharides

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Abstract—Six tail-to-tail amine-linked neodisaccharides were synthesised as potential glycomimetics. Primary–primary linked compounds were synthesised using Mitsunobu chemistry with glucose-6-sulfonamides as nucleophiles and primary carbohydrate alcohols as electrophiles. Primary–secondary linked compounds were synthesised by epoxide ring opening with carbohydrate 6-amines. Deprotection of all neodisaccharides was carried out using dissolving metal reduction.

Carbohydrates occurring as polysaccharides and oligosaccharide glycoconjugates take part in biological recognition events with consequences for both usual healthy human function and disease.[1] Glycomimetics are molecules that resemble a carbohydrate but that may be modified in some way.[2] Usefully, a glycomimetic may be mistaken for, or even preferred over, the natural substrate by a carbohydrate binding protein. For example, a disaccharide with a hydrolytically stable inter-glycosidic linkage may be recognised but not cleaved by a glycosidase.[3]

One area of research in our laboratory is the synthesis of disaccharide mimics with unnatural linkages. One particular area of interest is that of non-glycosidically-linked disaccharides, comprising two sugars linked together without using the anomeric centre. We call these structures neodisaccharides and recently reported the synthesis of various thioether-linked examples of this compound class.[4] Conceptually, similar work on ether-linked[5] and *C*-linked[6] tail-to-tail disaccharides has also been published. It is our hypothesis that such neodisaccharides may act as glycomimetics with one sugar binding in its natural orientation to a carbohydrate binding site in an enzyme or lectin, while the other sugar residue assumes an unnatural orientation (Fig. 1). The phenomenon of different monosaccharides adopting different orientations in a given binding site has been observed before. For example, a crystal structure of thiodigalactoside bound into the Galectin-1 binding pocket shows that one galactose residue occupies the same space as the GlcNAc residue in bound LacNAc.[7] Nilsson has shown that some mannosides can mimic galactose in binding to galectins, the proposed binding mode being supported by molecular modelling.[8] Jenkins has reported that N-substituted 3-amino altrose derivatives can act as glucosidase inhibitors, and has proposed that the protonated aminosugar binds to the enzyme in an orientation such that the amine nitrogen lies coincident with the binding position of the exocyclic oxygen in the natural substrate.[9] Adding a second carbohydrate at the aglycon position to such a structure to give an amine neodisaccharide (cf. **II**, Fig. 1) could increase specificity for a given carbohydrate binding protein, and possibly also binding affinity. Thus, methods to synthesise such *N*-linked neodisaccharides are worth investigating.

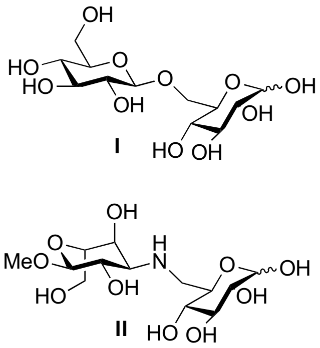

Figure 1. Structures of a β(1→6)-linked disaccharide, gentobiose **I** and its proposed *N*-linked neodisaccharide mimic **II**.

Keywords: Aminosugars; Disaccharides; Carbohydrates; Glycomimetics.

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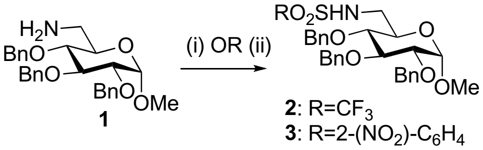
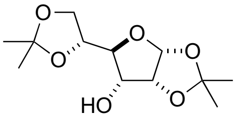
While C_2 symmetric (6–6) *N*-linked neodisaccharides have been fairly widely documented[10] and reports of one *sec–sec* linked compound appeared almost 30 years ago,[11] it was not until earlier this year that the first reports of unsymmetrically substituted amine neodisaccharides appeared: Kroutil used a method based on aziridine opening by amines to give diamino compounds.[12] Thiem generated primary–*sec* linked neodisaccharides by reductive amination.[13] In our own approach, the first results of which are reported in this Letter, we favoured S_N2 type reactions that have the potential to dictate the stereochemical outcome, that is, the C–N bond formation should happen stereospecifically. We focussed on two main approaches: Mitsunobu reactions using sugar sulfonamide nucleophiles; and epoxide opening reactions using sugar amines as nucleophiles.

We first investigated a Mitsunobu approach.[14] Mitsunobu chemistry can be used to form C–N bonds when the NH proton on the nucleophile is sufficiently acidic.[15] Thus, we converted a model amine **1**[16] into its triflyl **2** and nosyl **3** derivatives (Scheme 1). Reaction between equimolar amounts of a C-6 sulfonamide (**2** or **3**) and a primary alcohol (**4**[17] or **5**[18]) under standard Mitsunobu conditions (i.e., DEAD or DIAD, PPh_3 in THF) gave good yields of the corresponding (6–6) *N*-linked C_2-symmetric (**6** and **7**) or unsymmetrical (**8** and **9**) neodisaccharides (Scheme 2). We found that it was necessary to cool the mixture to 0 °C for the addition of the reagents, but that the reaction could then be allowed to warm to rt to complete. Attempting the reaction between **2** and **5** starting at rt failed to give any product–both the starting materials were recovered unreacted.



Scheme 1. Reagents and conditions: (i) Tf_2O (1 equiv), Et_3N (2 equiv), DCM, 0 °C, 64%; (ii) NsCl (1.2 equiv), DMAP (0.1 equiv), Et_3N (1.5 equiv), DCM, rt, 97%.

We then examined the potential formation of a primary–secondary linkage, i.e. by reaction between C-6 triflamide **2** and C-3 alcohol **10**[19] (DIAD (2 + 1 equiv), PPh_3 (2 + 1 equiv), 24 h). However, no reaction was observed by TLC and virtually all the starting triflamide was recovered. This difference in outcome is almost certainly due to the increase in steric bulk in going from a primary to a secondary alcohol. Repeating the reaction in the presence of methanol gave smooth conversion to the N-methylated product **11** (99%), with no neodisaccharide formation.



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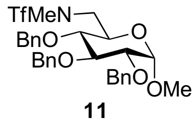

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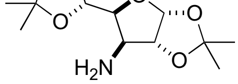

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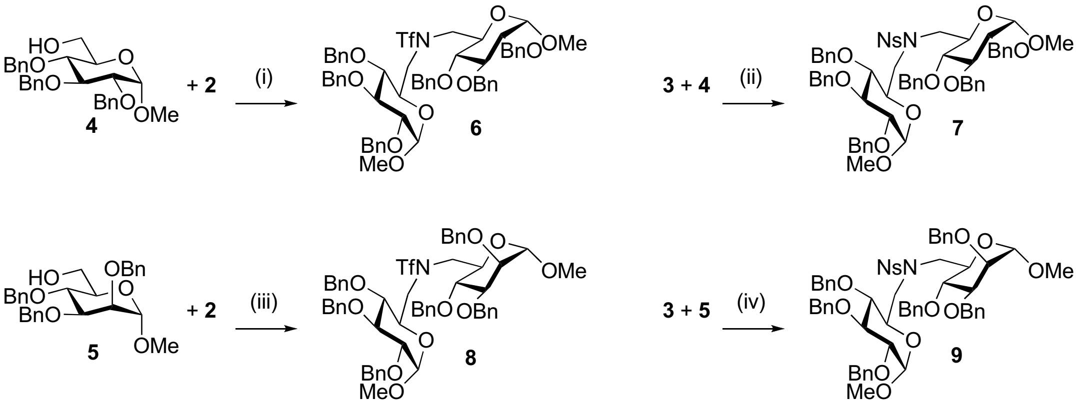
We next turned our attention to an epoxide opening reaction as a stereospecific route to amine-linked neodisaccharides.[20] Thus, C-6 (**1** and **12**[21]) and C-3 (**13**[22]) amines and *allo* **14** and *manno* **15** configured epoxides[23] were synthesised according to the published procedures. Reaction of the *manno* epoxide **15** with C-6 amines **1** and **12** in the presence of $LiClO_4$ (2 equiv) in refluxing acetonitrile gave the *altro* configured neodisaccharides **16** and **17**, respectively, with (3–6) connectivity in excellent regioselectivity, this being dictated by the *trans* diaxial opening[24] of the conformationally locked epoxide. The *allo* epoxide **14** reacted with the C-6 amines **1** and **12** under the same conditions to give the *trans* diaxial (2–6) *N*-linked neodisaccharides **18** and **19**, respectively, once again with excellent regioselectivity (Table 1).

However, trying to open the epoxides **14** and **15** with C-3 amine **13** under these conditions to give a *sec–sec* *N*-linked neodisaccharide failed: only unreacted starting



Scheme 2. Reagents and conditions: (i) DIAD (2 + 2 equiv), Ph_3P (2 + 2 equiv), THF, 0 °C→rt, 7 h, 78%; (ii) DIAD (2 + 0.5 equiv), Ph_3P (2 + 0.5 equiv), THF, 0 °C→rt, 26 h, 78%; (iii) DIAD (3 equiv), Ph_3P (3 equiv), THF, 0 °C→rt, 3 h, 87%; (iv) DEAD (2 + 2 equiv), Ph_3P (2 + 2 equiv), THF, 0 °C→rt, 48 h, 78%.