Towards the Chemical Synthesis of S-linked Heparan Sulfate Oligosaccharides

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Heparan Sulfate (HS) is a sulfated linear carbohydrate that decorates the cell surface and extracellular matrix and is a key regulator of biological activities.[1] An example of a glycosaminoglycan, HS is composed of L-iduronic acid (IdoA) or its C-5 epimer D-glucuronic acid (GlcA), (β-1→4)-linked to D-glucosamine. Its microstructure is diverse: the amino sugar can be *N*-sulfated (D-GlcNS) or *N*-acetylated (D-GlcNAc), while D-GlcA and L-IdoA are variably substituted with *O*-sulfate groups at the C2. D-GlcN is commonly sulfated at C6 and occasionally at C3 (**Figure 1A**).

Due to HS chemical heterogeneity, structure-to-function correlations with HS binding proteins has largely been impaired. However, the use of native proteins and non-natural oligosaccharides (glycomimetics) have proven successful in probing carbohydrate-protein interactions in the past.[1,2] Such a move towards preparing HS glycomimetics, may enhance our understanding of these interactions. One glycomimetic in particular, *S*-linked glycosides, where the glycosidic linkage oxygen is replaced with sulfur, offers the exciting possibility of studying unique conformational preferences about the thioglycosidic and aglyconic bonds.[3] Subsequent comparison to native sequences will improve our understanding and capability to perturb HS structure-to-function relationships.

Previously, Kovensky and co-workers synthesised *S*-linked disaccharide **1** (**Figure 1B**), a HS mimic of the (β-1→4) linkage, to be incorporated into chemical tools to study HS-protein interactions.[2,3] Our work involves synthesising *S*-linked disaccharide **2** (**Figure 1C**), mimicking the (α-1→4) linkage found in HS, from simple monosaccharide building blocks. Following this, deprotections of **2**, followed by similar SAR studies will be carried to further unmask HS biological function.

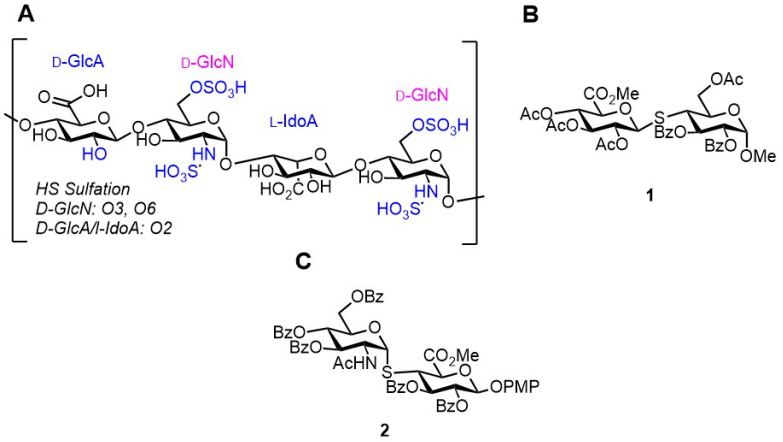

Figure 1: A) HS structure, B) Kovensky's S-disaccharide 1, C) Target Disaccharide 2

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