PERKIN 1 COMMUNICATION

# Assembly of dendritic glycoclusters from monomeric mannose building blocks

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**Mannoside-based dendrimers were prepared by tetrafold glycosidation of selenium-donors with branched alcohol scaffolds. A trisaccharide-based glycocluster could be assembled in one reaction vessel based on reactivity tuning of glycosyl fluorides, orthogonal coupling to a glycosyl selenide and subsequent capture onto the dendritic scaffold.**

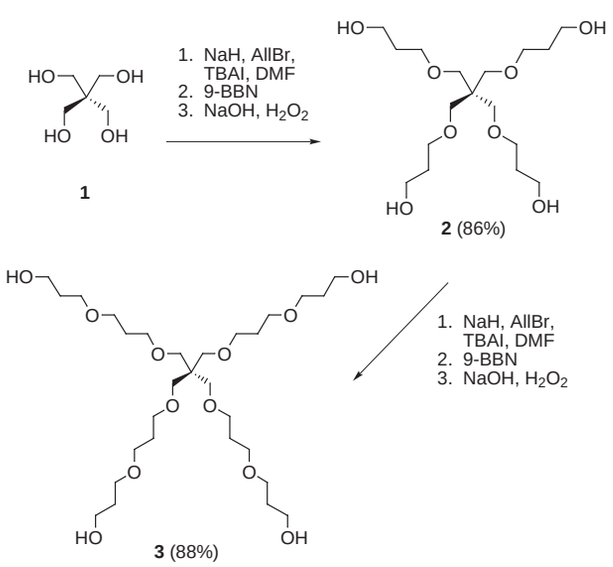


High-mannose oligosaccharides have been shown to have important biological functions.[1] The mannose-binding protein (MBP),[2] an acute phase protein of immune response, recognises a broad array of oligosaccharide moieties on the surface of bacteria, which it is able to distinguish from its own sugar epitopes.[3]

Suitable glycomimetics which are able to compete or even perform better than the naturally occurring carbohydrate ligands are needed for the manipulation of carbohydrate–protein interactions.[4] For this purpose the clustering of glycosides has proved to be advantageous in many instances, as the multipresentation of specific sugar epitopes in one molecule can result in remarkably increased adhesion.[5] Copolymerization[6] and telomerization[7] reactions have been used to incorporate several oligosaccharides. In addition, an increasing number of dendrimers has appeared as core molecules for the synthesis of clustered glycosides.[8]

We have shown previously that the application of the principles of reactivity tuning and orthogonal activation in glycosylation reactions allows rapid access to oligosaccharides utilizing one-pot coupling strategies.[9] As part of our continuing investigations into the utility of one-pot oligosaccharide synthesis, we report the extension of this methodology to illustrate how the final assembled oligosaccharide can be captured onto a dendritic scaffold.

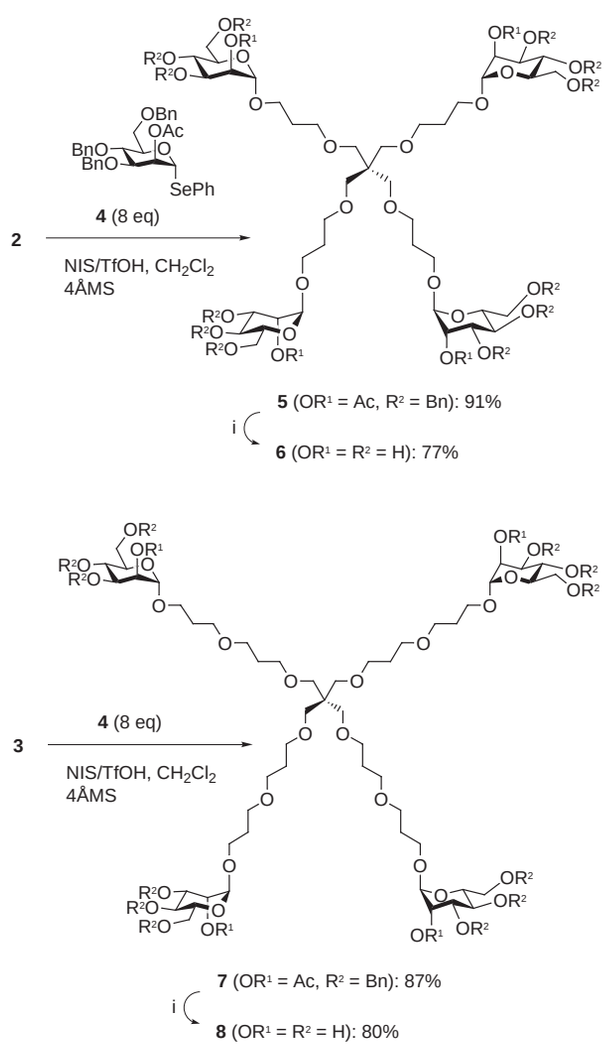
As core scaffolds we have chosen to prepare the tetraalcohols




**Scheme 1**

**2** and **3** which can be readily obtained from pentaerythritol **1**, by employing an iterative allylation–hydroboration strategy, in excellent overall yield (Scheme 1).[10] Further elaboration of the polyether chains to give greater branching or to vary the distances between the carbohydrate units to be attached to the alcohol functions should be straightforward.

In order to test the efficiency of the glycosylation reaction to form tetraantennary glycoclusters, the alcohol **2** was reacted with selenium donor **4**, which was activated by NIS–TfOH,[11] to give the mannoside cluster **5** in high yield (91%) and with complete α-selectivity, as expected (Scheme 2). Deacetylation under

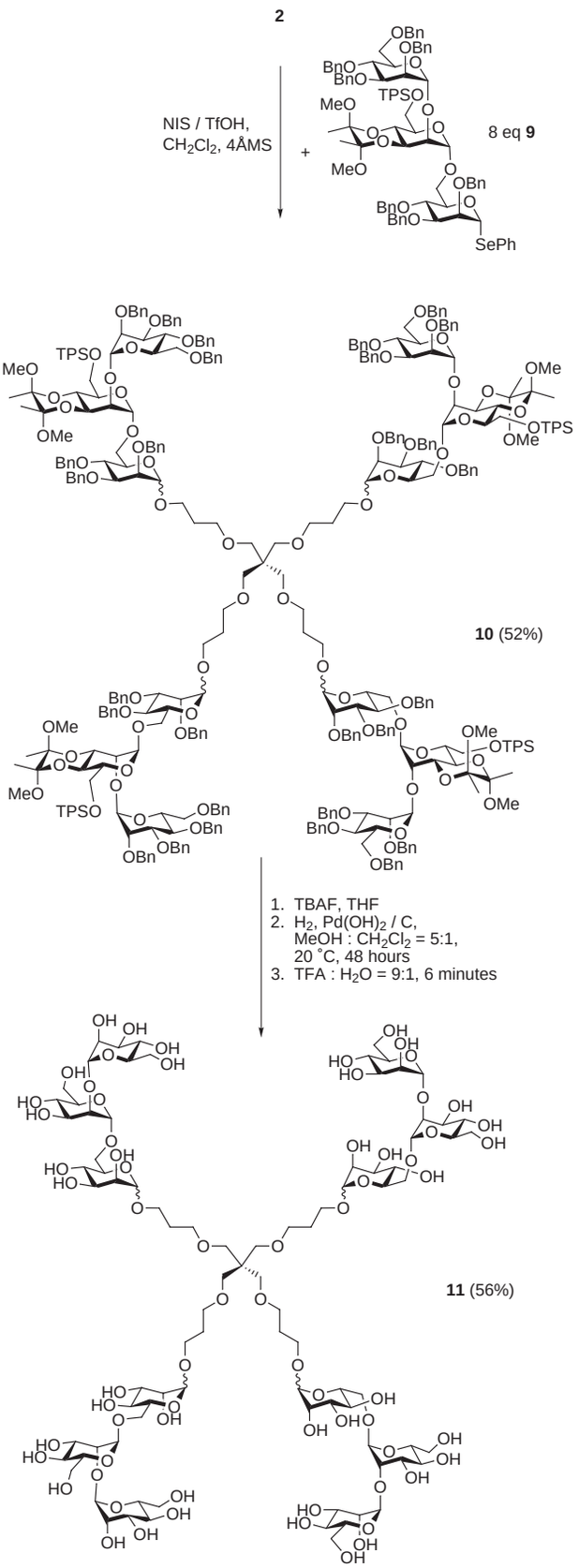



**Scheme 2**

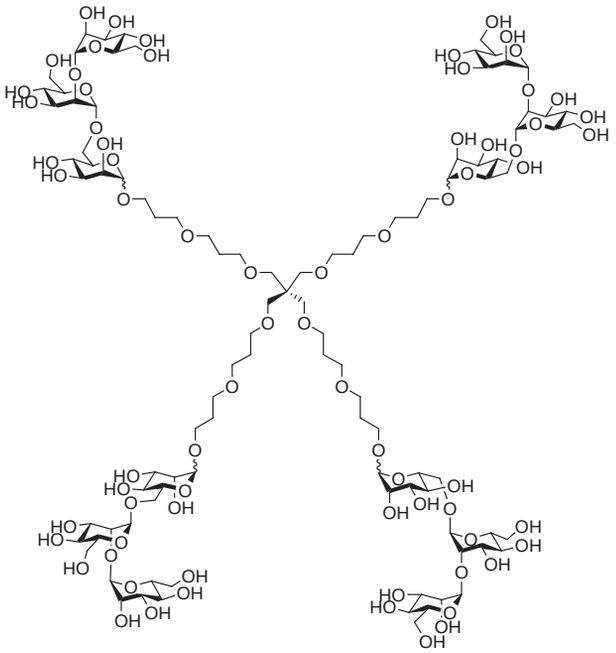
standard conditions and reductive debenzylation employing $Pd(OH)_2/C$ as the catalyst gave the fully deprotected glycocluster **6** in 77% yield. Reaction of the tetraalcohol **3** with selen-

ium donor **4** performed equally well to give the glycocluster **7** (87%). Deprotection of this compound provided tetraantennary mannoside **8** in 80% yield.

Encouraged by these results we next examined the reaction of alcohols **2** and **3** with the selenium trisaccharide donor **9** which we have recently prepared using a one-pot coupling strategy.[9b] Reaction of **9** with tetraol **2** under NIS–TfOH activation conditions gave the tetraantennary glycocluster **10** (Scheme 3) in 52%




**Scheme 3**

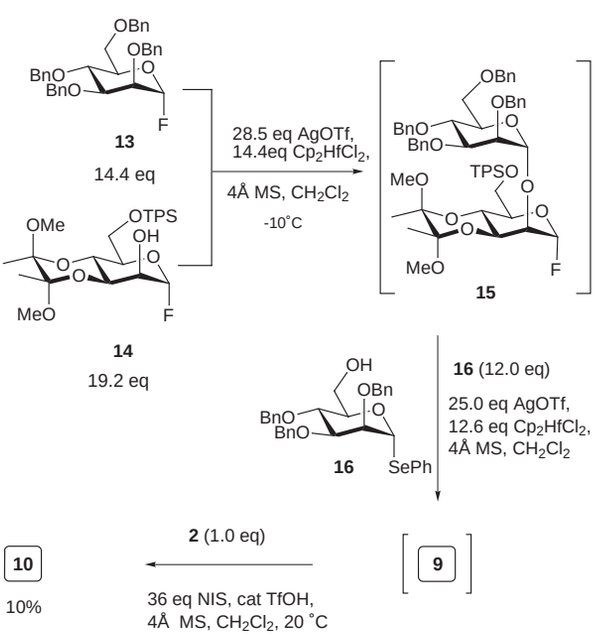


**12**

**Fig. 1**

yield (85% yield per glycosylation step).[12] Deprotection was achieved by desilylation using TBAF, reductive debenzylation using $Pd(OH)_2/C$ as the catalyst and subsequent cleavage of the butane 1,2-diacetal (BDA) protecting groups[13] using a trifluoroacetic acid–water mixture (9:1) to give the deprotected dendrimer **11** in 56% overall yield. Selenide **9** underwent in similar fashion a tetrafold glycosylation with tetraol **3** to give a glycocluster in 50% yield which was subsequently deprotected in 68% overall yield to give the glycocluster **12** (Fig. 1).[12] Structure **12** was confirmed by integration of the respective linker and anomeric signals in the $^1H$ NMR spectra and by MALDI-TOF spectroscopy.[14]

Based on these results the glycocluster **10** was prepared *in one pot* starting with fluoride donor **13** which was coupled onto acceptor **14** to give **15** *in situ* using $HfCp_2Cl_2$–AgOTf as an activation system.[15] Disaccharide **15** was coupled to selenium-acceptor **16** to generate, as an intermediate, trisaccharide **9** which underwent a perglycosylation with tetraalcohol **2** to give glycocluster **10** in 10% overall yield, which represents a 68% yield per glycosylation step (Scheme 4).




**Scheme 4**

We have demonstrated that one-pot reaction technologies are not only efficient in terms of oligosaccharide assembly but are also flexible enough to allow the final products to be further elaborated. We believe that the generation of complex arrays and libraries, with the minimum of protecting group manipulations, can be efficiently realized and our laboratory is continuing to explore the scope of this methodology.

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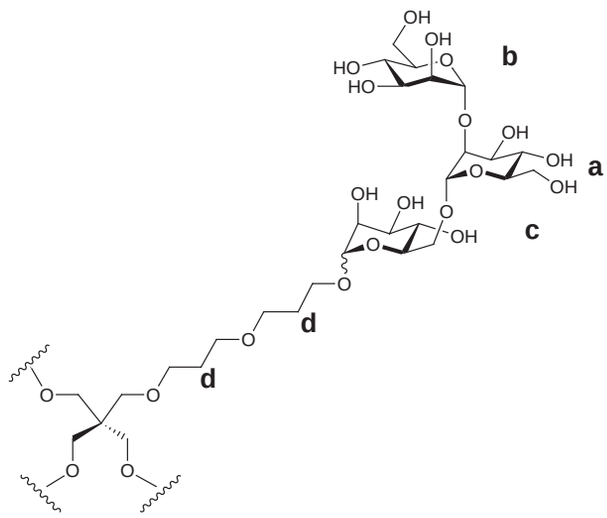


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