Peptide templated synthesis of oligosaccharides

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Introduction

Recent advances in analytical techniques have made it possible to look at very small quantities of carbohydrates, allowing us to get a better understanding of their role in biological processes. It is known that cell surface carbohydrates take part in many biological processes such as viral and bacterial recognition and also inflammatory responses. It is therefore very important for us to be able to produce specific carbohydrates to study both their function, and find ways of blocking their function, ie. stopping the recognition process between the cell surface carbohydrate and the target site.

Resin bound peptide templates

Standard methods for oligosaccharide preparation are time consuming, as each step requires separation and purification before the addition of the next unit. Efficient automated methods for saccharide synthesis are hence urgently required.

We have developed an exciting new method for the preparation of saccharides which is amenable to automation. The strategy employs a peptide template, bound to a polystyrene resin, to control the synthesis of the saccharide. The peptide consists of a repeating Gly-Pro- backbone as shown below. The sugar units that will form the oligosaccharide are first attached to the proline via a carbonate linker. Peptide synthesis yields a pentasaccharide decorated with the monosaccharide building blocks. The glycosylation reaction is performed with the peptide still attached to the resin. The glycosidation reaction 'zips-up' the saccharides on the peptide, with coupling occurring only at the glycosyl donor and acceptor sites. This facilitates the recovery of a very clean sample at the end of the synthesis as the resin may be washed at every stage.

The backbone ensures the sequence is correct, leaving only the α and β linkages between the units to control. The final step is to remove to the resulting oligosaccharide from the peptide backbone.

Disaccharide formation

Upon glycosylation, the desired (1$\rightarrow$4) disaccharide is recovered with an α/β anomeric ratio of 8:1. When the addition sequence of the sugars is reversed, ie the glycosyl acceptor is added to the peptide first and glycosyl donor second, the ratio changes to a 1:1 mixture. These results show that the peptide template can influence the stereoselectivity of the glycosidation process.

Sugar Building Block

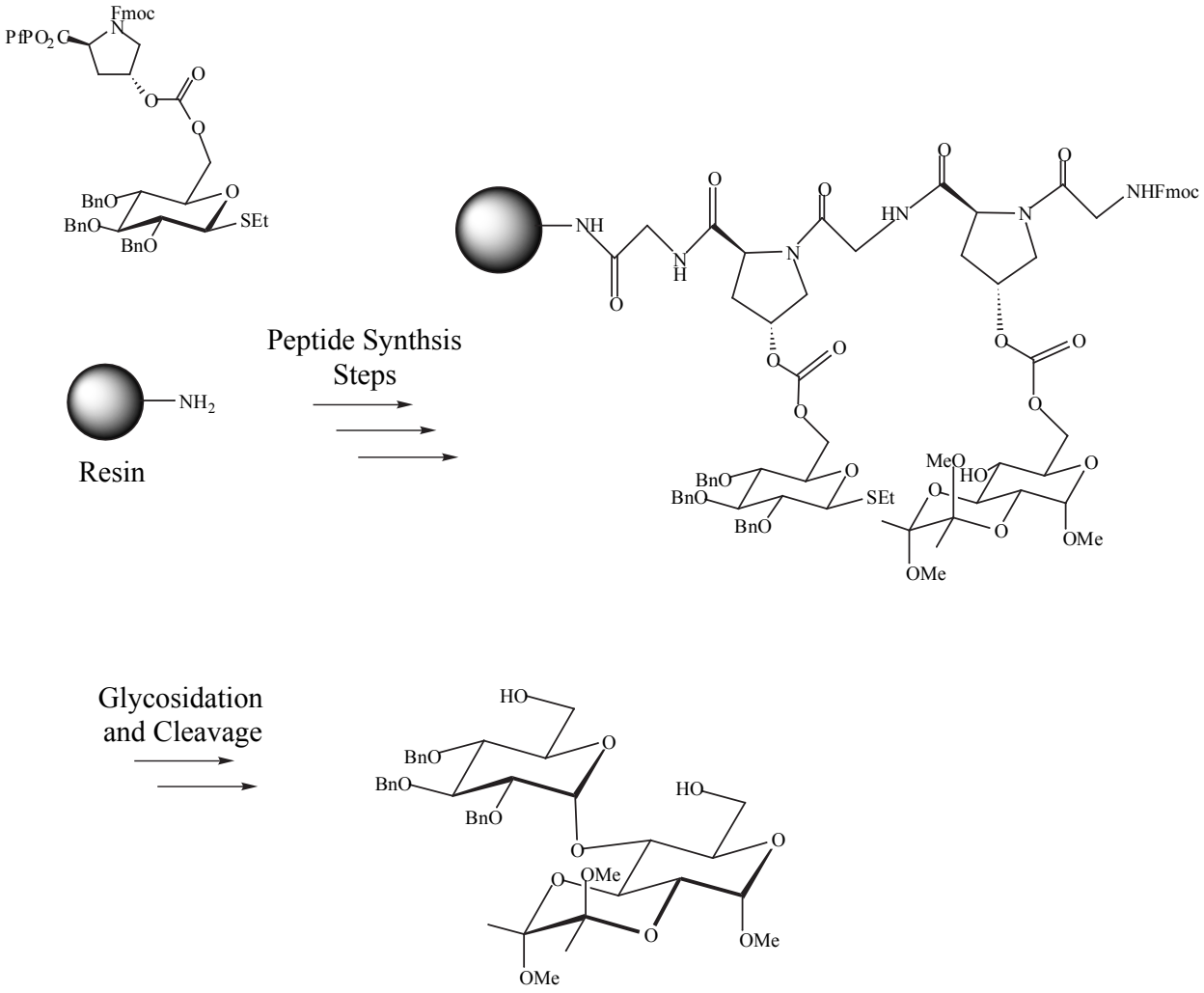

Figure 1. Scheme showing the formation of peptide template on solid polymer resin, glycosidation of the sugars, and cleavage of the disaccharide from the resin.

The same system for disaccharide synthesis may also be applied to the synthesis of the Glc-Man and Glc-Gal disaccharides.

Trisaccharides and beyond

Our attention is currently focussed on the synthesis of larger sugars using this methodology and on understanding how the peptide controls the selectivity of the glycosidation process.

Funding

We acknowledge the support of the EPSRC