Synthesis of Lipid Linked Oligosaccharide Substrates and Inhibitors of a eukaryotic Oligosaccharyl transferase

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Here we report the preparation of various synthetic lipid-linked oligosaccharides (LLOs) and their phosphonate analogs. These LLOs act as glycosyl donors in biochemical studies of enzymes involved in protein glycosylation, such as oligosaccharyl flippases (PglK)[1] and oligosaccharyl transferases (OSTs),[2,3] while their phosphonate analogs can be used as inhibitors of the same enzymes. The LLOs were obtained in 16 to 31 steps in a convergent synthesis involving the coupling of a lipid phosphate with a glycosyl phosphate or phosphonate. Inspired by known procedures,[4] we designed an accelerated synthesis of novel α-saturated chiral C_{20}- and C_{25}-polyprenyl phosphates, essential to obtain LLOs reacting with eurakyotic OSTs, using a stereoselective olefination as the key step.[5] Furthermore, we established the synthesis of chitobiose phosphonates from N-acetyl-D-glucosamine involving as key steps C_1-allylation, β-1,4 glycosylation, condensation with diethyl phosphite and deoxygenation.[6] The final products were obtained in 20-50 mg scale in pure form suitable for biochemical and structural studies.

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