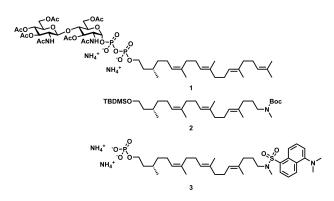
Fluorescent LLOs – Shedding light on OST and ALG enzymes

Mario M. de Capitani, J.-L. Reymond

Departement für Chemie, Biochemie und Pharmazie, Universität Bern, Freiestrasse 3, 3012 Bern mario.decapitani@dcb.unibe.ch

Lipid Linked Oligosaccharides (LLOs) like **1** and their related compounds are important intermediates in the N-Glycosylation pathway in eukaryotes. This pathway is chiefly conducted by ALG and OST enzymes in the endoplasmatic reticulum. In recent years, our laboratory has provided numerous LLOs, inhibitors and related substrates for in-vitro investigations of both classes of enzymes. [1–4]

Extending on this work, we developed a synthetic approach to a fluorescent Dolichol-derived lipid meant to serve in synthetic LLOs. Given the intended role as substrate for in vitro studies, a reliable synthetic approach was required. In anticipation of the usually low yields in the pyrophosphate coupling just prior to final deprotection, the early stages of the synthesis also would need to be performed in multigram to decagram scale. Retrosynthetic analysis revealed lipid **2** as key intermediate, bearing two orthogonally protected end groups. From there, a variety of different N-linked fluorophore and O-linked phosphate-carbohydrate combinations are accessible.



Synthetic access to 2 was envisioned to be possible through either one of two major routes whose main difference lies in the order of lipid elongation and functionalisation. Opting for an early establishment of the N terminus followed by lipid elongation, a synthetic route was devised to give access to **2** in a 13 steps convergent synthesis starting from naturally occurring S-Citronellol and Farnesol. This sequence also featured a heavily modified Wittig-Schlosser reaction [5] and a regioselective oxidation of Farnesol [6] as key steps in establishing functionality and stereochemistry of the final product.

From this intermediate, N-functionalisation using Dansyl chloride and subsequent Ophosphorylation furnished the fluorescent lipid phosphate **3** from which the LLO analogous to **1** could be obtained in two steps to end a 22 step, 15 step longest linear sequence synthesis.

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