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

J. Boilevin<sup>1</sup>, A. Ramirez<sup>2</sup>, T. Darbre<sup>1</sup>, K. Locher<sup>2</sup>, J. L. Reymond<sup>1</sup>\*

<sup>1</sup>Bern University, <sup>2</sup>ETH Zürich

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 (PgIK)<sup>[1]</sup> and oligosaccharyl transferases (OSTs),<sup>[2,3]</sup> 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,<sup>[4]</sup> we designed an accelerated synthesis of novel  $\alpha$ -saturated chiral C<sub>20</sub>- and C<sub>25</sub>-polyprenyl phosphates, essential to obtain LLOs reacting with eurakyotic OSTs, using a stereoselective olefination as the key step.<sup>[5]</sup> Furthermore, we established the synthesis of chitobiose phosphonates from N-acetyl-D-glucosamine involving as key steps C<sub>1</sub>-allylation,  $\beta$ -1,4 glycosylation, condensation with diethyl phosphite and deoxygenation.<sup>[6]</sup> The final products were obtained in 20-50 mg scale in pure form suitable for biochemical and structural studies.

[1] Camilo Perez, Sabina Gerber, Jérémy Boilevin, Monika Bucher, Tamis Darbre, Markus Aebi, Jean-Louis Reymond, Kaspar Locher, *Nature*, **2015**, 524, 433-438.

[2] Christian Lizak, Sabina Gerber, Shin Numao, Markus Aebi, Kaspar Locher, *Nature*, **2011**, 474, 350-355.

[3] Christian Lizak, Sabina Gerber, Gaëlle Michaud, Mario Schubert, Yao-Yun Fan, Monika Bucher, Tamis Darbre, Markus Aebi, Jean-Louis. Reymond, Kaspar Locher, *Nat. Commun.*, **2013**, 4, 2627-2637.

[4] Feng Liu, Balakumar Vijayakrishnan, Amirreza Faridmoayer, Thomas Taylor, Thomas Parsons, Gonçalo Bernardes, Michael Kowarik, Benjamin Davis, *J. Am. Chem. Soc.*, **2014**, 136, 566-570.

[5] Xinggao Fang, Barbara Gibbs, James Coward, *Bioorg. Med. Chem. Lett.*, **1995**, 5, 2701-2706.
[6] Cheng-Kun Lin, Kuo-Ting Chen, Chia-Ming Hu, Wen-Yi Yun, Wei-Chieh Cheng, *Chem. Eur. J.*, **2015**, 21, 1-10.