Synergistic Glycosylation as Key to the Chemical Synthesis of an Outer Core Octasaccharide of *Helicobacter pylori*

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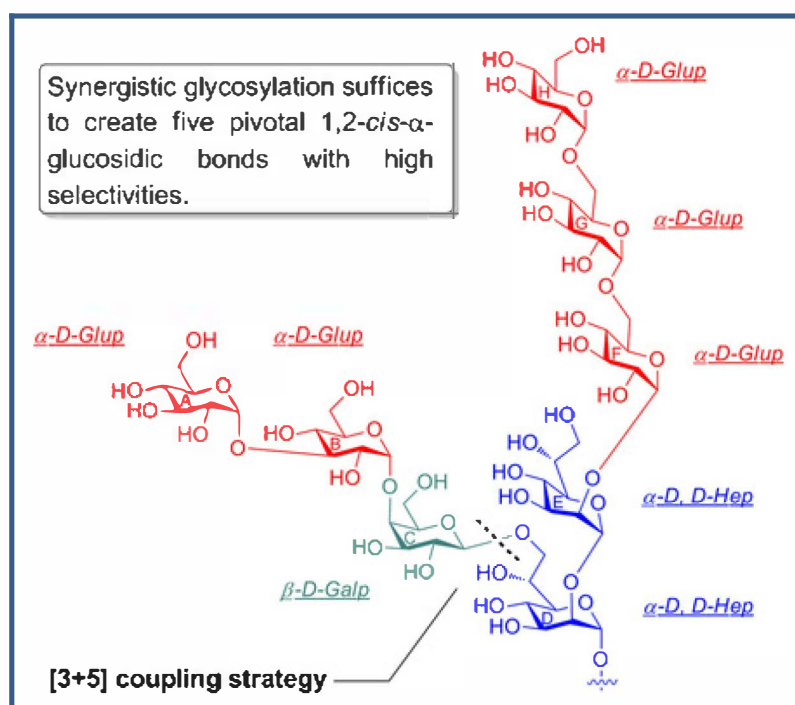
Constructing glycans of the stomach: *H. pylori* is a bacterial pathogen that infects more than half of the world's population. A synergistic glycosylation strategy was developed to construct the lipopolysaccharide of the pathogen as a first step towards developing a glycoconjugate vaccine.

Synergistic Glycosylation as Key to the Chemical Synthesis of an Outer Core Octasaccharide of *Helicobacter pylori*

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Dedicated to the memory of Prof. Dr. Werner G. G. Reutter

Abstract: *Helicobacter pylori*, a widespread gastric bacterial pathogen that infects 90% of the population in developing countries, causes chronic gastritis, peptic ulcers and gastric cancer. Battling *H. pylori* infection is a serious challenge due to the increased resistance to antibiotics and the lack of vaccines. The lipopolysaccharide covering the *H. pylori* cell-surface outer membrane is an attractive target for the development of a glycoconjugate vaccine. Here, we report a [3+5] convergent synthesis of an outer core octasaccharide of *H. pylori* employing just three orthogonally protected building blocks. A synergistic glycosylation strategy enables the creation of five pivotal 1,2-*cis*-α-glucosidic bonds consist of four types of linkages using just three monomers. This strategy can be expanded to many 1,2-*cis*-α-gluoside-containing oligosaccharides both in solution and on solid phase.

The bacterial pathogen *Helicobacter pylori* has coevolved with humans, and colonizes over half of the world´s population.[1] In contrast to other Gram-negative bacterial pathogens, *H. pylori* is able to sustain the acidic environment of the stomach and establish chronic infections.[2] *H. pylori* infections are a major global health problem, since the pathogen causes not only chronic gastritis of asymptomatic carriers, but also leads to gastric and duodenal ulcers, and gastric malignancies. *H. pylori* is estimated to be responsible for 5% of all cancer cases and more than 60% of gastric cancer cases.[3] In 1994, *H. pylori* was recognized as a category I human carcinogen by the World Health Organization.[4] To date, the treatment of *H. pylori* infections relies on various combinations of antibiotics that gradually lose effectiveness due to increased clinical resistance.[5] No *H. pylori* vaccines exist even though various bacterial antigens, including urease, vacuolating cytotoxin A, cytotoxin-associated antigen, neutrophil-activating protein have been tested.[5a,6]

Protein-saccharide conjugates induce the T-cell mediated production of antibodies to the corresponding pathogen and thereby convey immunological memory.[7] Glycoconjugates, derived by coupling carbohydrate antigens to immunogenic protein carriers, are safe and efficacious human vaccines.[8]

Lipopolysaccharide (LPS) is a main *H. pylori* cell wall component and LPS-associated serotypes have been discovered.[9] Recently, *Monteiro et al.* demonstrated the potential of a LPS-based vaccine against *H. pylori*, where the conserved core undecasaccharide[9b,10] **1** (Figure 1) was identified as a promising antigen for the development of a glycoconjugate vaccine targeting all strains.[11] Since extraction and purification does not provide enough pure carbohydrate antigens, synthetic carbohydrate fragments of *H. pylori* LPS will enable immunological investigations.[11d,12]
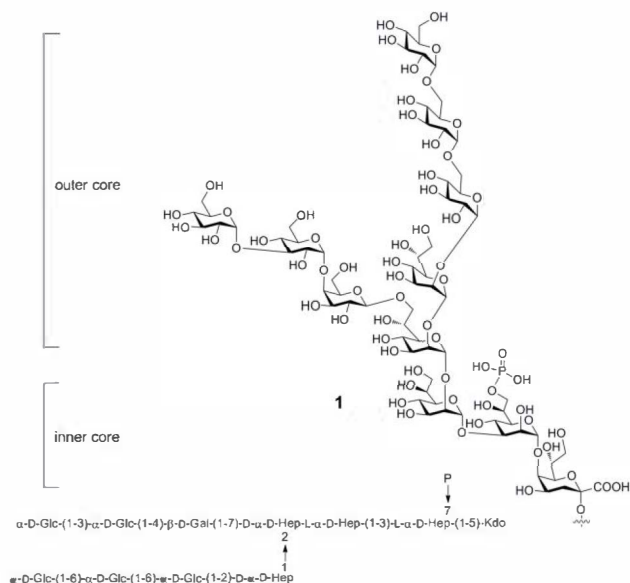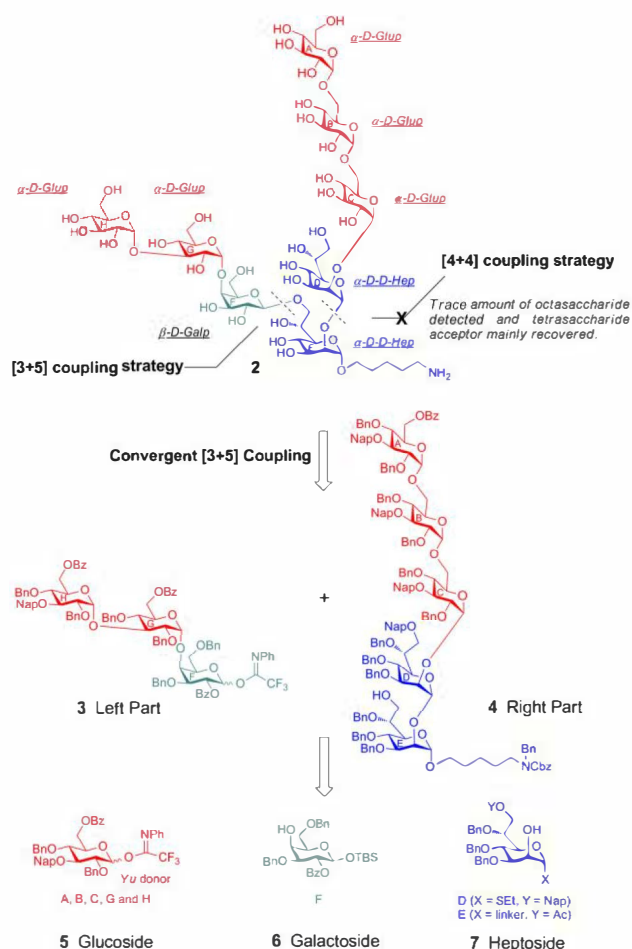

Figure 1. Structure of core undecasaccharide **1** of *Helicobacter pylori*.

The outer core octasaccharide portion of core undecasaccharide **1** is the key synthetic target. The retrosynthetic analysis of the outer core octasaccharide **2** bearing an amyl amine linker (Scheme 1) reveals that reliable α-selective glycosylations are essential to install five pivotal 1,2-*cis*-α-glucosidic bonds.[13] Convergent strategies can focus either on a [4+4] or a [3+5] key coupling. Therefore, three primary building blocks, glucoside **5** (Scheme 1, A, B, C, G and H), galactoside **6** (Scheme 1, F) and heptoside **7** (Scheme 1, D and E) are required in multigram quantities. The selective formation of five 1,2-*cis*-α-glucosidic bonds (α-D-Glu) is the most challenging aspect of the assembly of octasaccharide **2**. Many oligo- and polysaccharides that contain 1,2-*cis*-O-glycosidic linkages are biologically important.[14] Numerous successful methods[15] for the installation of 1,2-*cis*-α-glycosides have been developed but a general method is still elusive.[16]

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     Supporting information for this article is given via a link at the end of the document.

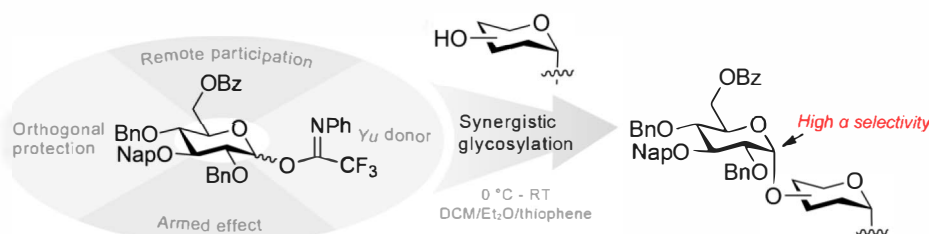**Scheme 1.** Retrosynthetic analysis of octasaccharide **2**.

leaving groups had only little effect on the diastereoselectivity of the glycosylation. Glycosyl trichloroacetimidates (*Schmidt* donor)[19] and thioglycosides,[20] are the most popular glycosylating agents. Recently, the *Yu* donor has evolved as an effective and alternative glycosylating agent;[21] (3) Reaction temperature: is an important factor to select a proper glycosyl donor. While *Schmidt* glycosylation proceeds at low temperature, *Yu* donors are generally activated under mild condition,[21] which well meets the required reaction temperature for Bz-capped C6 hydroxyl group to drive the remote anchimeric assistance;[17,22] (4) Solvents system: diethyl ether (Et$_2$O) ensures better α selectivity as does the additive thiophene.[15c,16] A combination of solvents and additive (DCM/Et$_2$O/thiophene) was considered to improve the selectivity. Taking the four aspects, leaving group, protecting group at 6-position, as well reaction temperature and solvents laid out in detail above into account, the building blocks for the synergistic glycosylation strategy were designed (Figure 2). Next, this strategy was tested using the designated *Yu* donor **5** for the assembly of oligosaccharides.

Orthogonally protected *Yu* donor **5**, together with four glycosyl acceptors **7D**, **8**, **9** and **10** (synthesis details see Supporting Information) were utilized to test the formation of four different types of 1,2-*cis*-α-glucosidic bonds (Scheme 2) present in octasaccharide **2** (Scheme 1, **8** for 1→6 bond between A and B; **9** for 1→3 bond between G and H; **10** for 1→4 bond between F and G; **7D** for 1→2 bond between C and D). After careful optimization of the glycosylations, the assembly of all disaccharides (Figure 5) involving donor **5** (1.0 equiv.) and acceptors **7D**, **8**, **9** and **10** (1.2–1.5 equiv.) were successfully promoted by using catalytic TMSOTf (0.15 equiv.) in the presence of a solvent mixture (DCM/Et$_2$O=1/2) at 0 °C - RT. The addition of ten equivalents thiophene enhanced the α

Figure 2. Synergistic glycosylation by using a versatile *Yu* donor for high α selectivity in the presence of DCM/Et$_2$O/thiophene at 0 °C - RT.

Here, we report a synergistic glycosylation strategy (Figure 2), which relies on an integrated design centered on an orthogonally protected glycosyl trifluroacetimidate (*Yu* donor) **5**. Several aspects of glycoside formation were taken into consideration: (1) Protecting groups: remote participation by placement of benzoate esters (Bz) on the C3 and/or C6 hydroxyl groups results in higher selectivities during the construction of 1,2-*cis*-α-glucosidic bonds.[17] The C2-hydroxyl is protected with a benzyl ether (Bn) as a non-participating group. In anticipation of chain elongation, naphthalene ether (Nap) was placed for orthogonal protection of the C3-hydroxyl; (2) Leaving group: aside from occasional S$_N$-2 like inversion transformations, most glycosylation reactions proceeded *via* an S$_N$-1 displacement mechanism.[16,18] Accordingly, the orientation of the anomeric

selectivity.[16,23] Three disaccharides **11** ($^3J_{H1/H2}$ = 3.5 Hz), **12** ($^3J_{H1/H2}$ = 3.6 Hz) and **14** ($^3J_{H1/H2}$ = 3.6 Hz) were synthesized in good yields (53-75%) as exclusively 1,2-*cis*-α-glucosidic disaccharides were obtained. The union of donor **5** and acceptor **10** (synthesis details see Supporting Information) yielded only 28% of target disaccharide **13** ($^3J_{H1/H2}$ = 3.5 Hz) due to the intermolecular migration of the ethylthio functional group from acceptor to donor.[24] To avoid this undesired migration, 1-*O*-TBS glycoside **6** (synthesis details see Supporting Information) was employed for the synthesis, and exclusively α-linked disaccharide **15** ($^3J_{H1/H2}$ = 3.8 Hz) was obtained in 72% yield. According to these disaccharides models, the synergistic glycosylation strategy enabled the selective formation of four types of 1,2-*cis*-α-glucosidic bonds present in octasaccharide **2**.
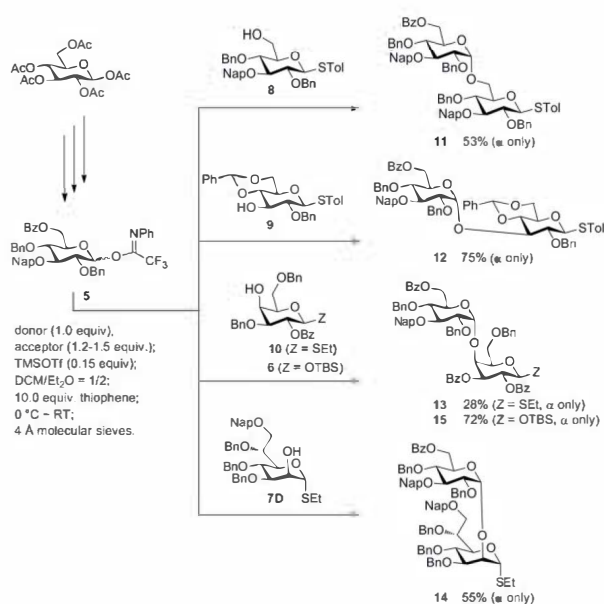
Scheme 2. Model synthesis of 1,2-*cis*-α-glucosidic disaccharides **11-15** through synergistic glycosylation strategy.

The remaining primary glycosylating building block **7E** (synthesis details see Supporting Information) was synthesized by glycosylation of an amyl amine linker with **7D**. With all required glycosides **5**, **6** and **7** in hand, the assembly of octasaccharide **2** commenced (Scheme 1). Initially, a [4+4] convergent entry where the final coupling was tried between two heptosides **7D** and **7E** was evaluated. However, only traces of octasaccharide were detected while tetrasaccharide acceptor was mainly recovered (Scheme 1) because steric hindrance in **7E** impeded the completion of the planned coupling. Therefore, the union of **3** and **4** following a [3+5] entry (Scheme 1) was selected for octasaccharide assembly because the free C7-hydroxyl group in **7E** is better accessible than the free hydroxyl group at the C2-postion of **7E**.
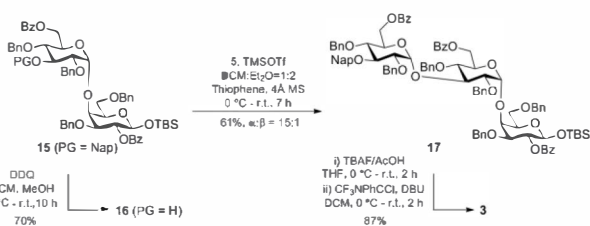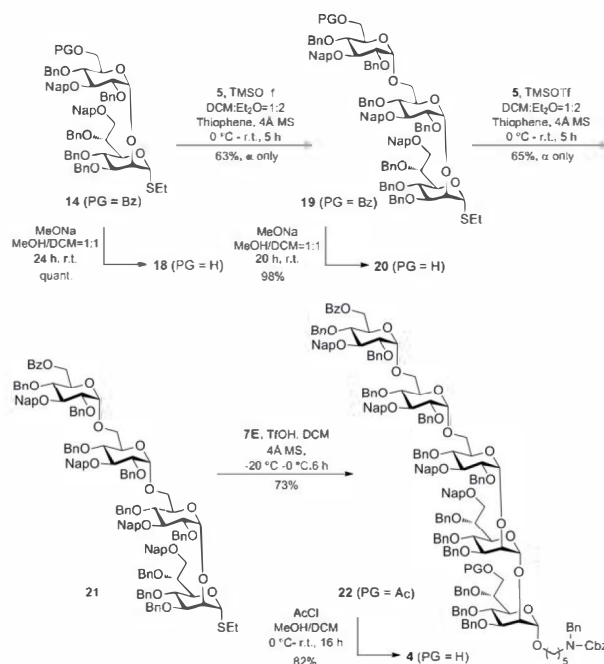

Scheme 3. Synthesis of trisaccharide fragment **3** containing two 1,2-*cis*-α-glucosidic linkages (1→3 and 1→4 bonds).

Trisaccharide **3**, containing two 1,2-*cis*-α-glucosidic linkages, was synthesized stepwise from the reducing to the non-reducing end (Scheme 3). The orthogonally protected *Yu* donor **5**, activated by using catalytic TMSOTf, reacted with galactosyl acceptor **6** to access disaccharide **15** in 72% yield (α exclusively) (Scheme 2). The Nap protecting group was removed smoothly with the help of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[25] to give disaccharide acceptor **16**. The second glycosylation using **5** afforded trisaccharide **17** ($^3J_{H1/H2}$ = 3.5 Hz,

$δ_{H-1}$ = 5.68 ppm) in 61% yield (α/β = 15/1). Subsequent transformations completed the synthesis of trisaccharide trifluroacetimidate **3** in high yield (Scheme 3).

The synthesis of pentasaccharide fragment **4** commenced by coupling *Yu* donor **5** with heptosyl acceptor **7D**, to form exclusively the α-linked disaccharide **14** (Scheme 2). Subsequent removal of the temporary benzoyl protecting group was realized by sodium methoxide to afford **18** (Scheme 4). The second and third couplings were achieved employing the synergistic glycosylation strategy, to afford trisaccharide **19** ($^3J_{H1/H2}$ = 3.6 Hz, $δ_{H-1}$ = 5.00 ppm) and tetrasaccharide **21** ($^3J_{H1/H2}$ = 3.6 Hz, $δ_{H-1}$ = 5.13 ppm) in good yields. Finally, heptosyl acceptor **7E** was added to the solution of tetrasaccharide promoted by triflic acid[26] to give pentasaccharide **22** in 73% yield. The selective deprotection of acetyl (Ac) protecting group of **22** using 10% acetyl chloride,[27] prevented the cleavage of benzoyl protecting groups, to yield pentasaccharide acceptor **4** (Scheme 4). The two saccharide fragments **3** and **4** containing five 1,2-*cis*-α-glucosidic linkages were efficiently prepared through a synergistic glycosylation strategy in good yields with very high α selectivities (only α in four cases and α/β = 15/1 in one case). Union of saccharides **3** and **4** to furnish target octasaccharide **2** was investigated next.

Scheme 4. Synthesis of pentasaccharide fragment **4** containing three 1,2-*cis*-α-glucosidic linkages (one 1→2 and two 1→6 bonds).

A convergent [3+5] synthesis strategy (Scheme 5) was used for the final coupling of trisaccharide *Yu* donor **3** with pentasaccharide acceptor **4** catalyzed by TMSOTf to afford the fully protected octasaccharide **23** in good yield. Subsequent removal of all acyl protecting groups and global deprotection furnished the target octasaccharide **2** in 63% yields over two steps after final purification (Scheme 5).
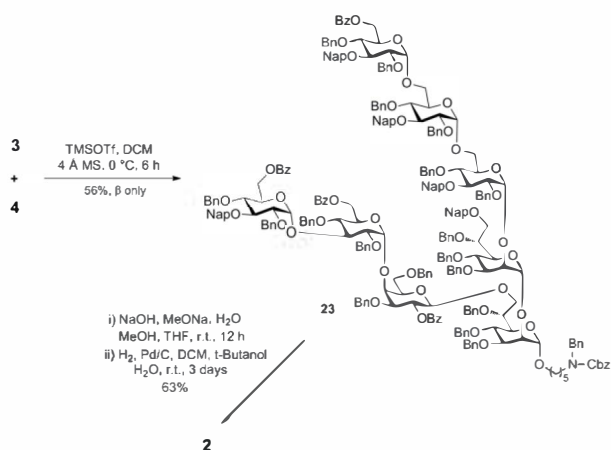
Scheme 5. Coupling of **3** and **4** to afford the target octasaccharide **2**.

In conclusion, the first chemical synthesis of the outer core octasaccharide of *H. pylori* is described. A synergistic glycosylation strategy based on orthogonally protected *Yu* donors enabled the selective formation of five 1,2-*cis*-α-glucosidic linkages present in octasaccharide **2** in good yields and with very high α selectivities. The synthetic octasaccharide **2** can be covalently bound to carrier protein via the reducing end amyl amine linker for further antigenic and immunogenic investigations, en route to the development of a glycoconjugate *H. pylori* vaccine.[11d,28] The scope of this strategy can be expanded to synthesize 1,2-*cis*-α-gluoside-containing oligosaccharides both in solution and on solid phase.

Acknowledgements

Conflict of interest

The authors declare no conflict of interest.

Keywords: *helicobacter pylori*•synergistic glycosylation•1,2-*cis*-α-glucosides•oligosaccharides•glycosylation

[1] a) J. Parsonnet, G. D. Friedman, D. P. Vandersteen, Y. Chang, J. H. Vogelman, N. Orentreich, R. K. Sibley, *N. Engl. J. Med.* **1991**, *325*, 1132-1136; b) J. Parsonnet, G. D. Friedman, D. P. Vandersteen, Y. Chang, J. H. Vogelman, N. Orentreich, R. K. Sibley, R. M. Peek, M. J. Blaser, *Nat. Rev. Cancer* **2002**, *2*, 28-37; c) J. C. Atherton, *Annu. Rev. Pathol. Mech. Dis.* **2006**, *1*, 63-96.

[2] a) B. Marshall, J. R. Warren, *Lancet* **1984**, *323*, 1311-1315; b) D. R. Scott, E. A. Marcus, D. L. Weeks, G. Sachs, *Gastroenterology* **2002**, *123*, 187-195.

[3] a) A. Axon, *Scand. J. Gastroenterol.* **1996**, *31*, 47-53; b) B. J. Marshall, H. M. Windsor, *Med. Clin. N. Am.* **2005**, *89*, 313-344; c) P. Correa, M. B. Piazuelo, *US gastroenterol. Hepatol. Rev.* **2011**, *7*, 59.

[4] IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Schistosomes, liver flukes and Helicobacter pylori. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Lyon, 7-14 June 1994. *IARC Monogr. Eval. Carcinog. Risks Hum.* **1994**, *61*, 1-241.

[5] a) D. Y. Graham, *Gastroenterology* **1998**, *115*, 1272-1277; b) M. M. Gerrits, A. H. van Vliet, E. J. Kuipers, J. G. Kusters, *Lancet Infect. Dis.* **2006**, *6*, 699-709; c) G. Del Giudice, P. Malfertheiner, R. Rappuoli, *Expert Rev. Vaccines* **2009**, *8*, 1037-1049.

[6] a) B. Corthésy, S. Boris, P. Isler, C. Grangette, A. Mercenier, *J. Infect. Dis.* **2005**, *192*,1441-1449; b) P. Malfertheiner, V. Schultze, B. Rosenkranz, S. H. Kaufmann, T. Ulrichs, D. Novicki, F. Norelli, M. Contorni, S. Peppoloni, D. Berti, *Gastroenterology* **2008**, *135*, 787-795; c) N. R. Salama, M. L. Hartung, A. Müller, *Nat. Rev. Microbiol.* **2013**, *11*, 385-399; d) M. Zeng, X.-H. Mao, J.-X. Li, W.-D. Tong, B. Wang, Y.-J. Zhang, G. Guo, Z.-J. Zhao, L. Li, D.-L. Wu, *Lancet* **2015**, *386*, 1457-1464.

[7] a) W. F. Goebel, O. T. Avery, *J. Exp. Med.* **1931**, *54*, 431-436; b) R. Schneerson, O. Barrera, A. Sutton, J. B. Robbins, *J. Exp. Med.* **1980**, *152*, 361-376; c) V. Pozsgay, *Curr. Top. Med. Chem.* **2008**, *8*, 126-140; d) F. Berti, R. Adamo, *ACS Chem. Boil.* **2013**, *8*, 1653-1663.

[8] a) C. Jones, *An. Acad. Bras. Cienc.* **2005**, *77*, 293-324; b) C. Anish, B. Schumann, C. L. Pereira, P. H. Seeberger, *Chem. Biol.* **2014**, *21*, 38-50; c) R. Adamo, *Acc. Chem. Res.* **2017**, *50*, 1270-1279.

[9] a) I. M. Simoons-Smit, B. J. Appelmelk, T. Verboom, R. Negrini, J. L. Penner, G. O. Aspinall, A. P. Moran, S. F. Fei, B. Shi, W. Rudnica, *J. Clin. Microbial.* **1996**, *34*, 2196-2200; b) M. A. Monteiro in *Advances in Carbohydrate Chemistry and Biochemistry*, Vol 57 (Ed: D. Horton), Elsevier, Oxford, **2001**, pp. 99-158.

[10] a) G. O. Aspinall, M. A. Monteiro, H. Pang, E. J. Walsh, A. P. Moran, *Biochemistry* **1996**, *35*, 2489-2497; b) S. Britton, E. Papp-Szabo, J. Simala-Grant, L. Morrison, D. E. Taylor, M. A. Monteiro, *Carbohydr. Res.* **2005**, *340*, 1605-1611.

[11] a) C. R. Raetz, C. Whitfield, *Annu. Rev. Biochem.* **2002**, *71*, 635-700; b) A. Hoare, M. Bittner, J. Carter, S. Alvarez, M. Zaldivar, D. Bravo, M. A. Valvano, I. Contreras, *Infect. Immun.* **2006**, *74*, 1555-1564; c) M. A. Monteiro, S. Britton, L. A. Applebee, S. Baqar, *Vaccine* **2011**, *29*, 3098-3102; d) J.A. Ferreira, L.Silva, M. A. Monteiro, M. A. Coimbra in *Carbohydrate Chemistry: Chemical and Biological Approaches, Vol 37* (Ed: A. P. Rauter and T . K. Lindhorst), The Royal Society of Chemistry, Cambridge, **2012**, pp. 160-193.

[12] K.-C. Chu, C.-Y. Wu, *Future Med. Chem.* **2012**, *4*, 1767-1770.

[13] P.-C. Gao, S.-Y. Zhu, H. Gao, J.-S. Yang, *J. Am. Chem. Soc.* **2016**, *138*, 1684-1688.

[14] a) J. B. Robbins, C.-J. Lee, S. C. Rastogi, G. Schiffman, J. Henrichsen, *Infect. Immun.* **1979**, *26*, 1116-1122; b) S. Slovin et al, *Proc. Natl. Acad. Sci.* **1999**, *96*, 5710-5715; c) C. Zhao, M. Li, Y. Luo, W. Wu, *Carbohydr. Res.* **2006**, *341*, 485-491; d) M. T. Walvoort, H. van den Elst, O. J. Plante, L. Kröck, P. H. Seeberger, H. S. Overkleeft, G. A. van der Marel, J. D. Codée, *Angew. Chem. Int. Ed.* **2012**, *51*, 4393-4396; *Angew. Chem.* **2012**, *124*, 4469 –4472.

[15] a) F. J. Kronzer, C. Schuerch, *Carbohydr. Res.*, **1974**, *34*, 71-78. b) R. U. Lemieux, K. B. Hendriks, R. V. Stick, K. James, *J. Am. Chem. Soc.*, **1975**, *97*, 4056-4062; c) A. Ishiwata, Y. Munemura, Y. Ito, *Tetrahedron* **2008**, *64*, 92-102; d) A. Ishiwata, Y. J. Lee, Y. Ito, *Org. Biomol. Chem.* **2010**, *8*, 3596-3608; e) T. J. Boltje, J.-H. Kim, J. Park, G.-J. Boons, *Nat. Chem.* **2010**, *2*, 552-557; f) S. R. Lu, Y. H. Lai, J. H. Chen, C. Y. Liu, K. K. T. Mong, *Angew. Chem. Int. Ed.* **2011**, *50*, 7315-7320; *Angew. Chem.* **2011**, *123*, 7453 –7458; g) H. S. Hahm, M. Hurevich, P. H. Seeberger, *Nat. Commun.* **2016**, *7*, 12482.

[16] S. S. Nigudkar, A. V.Demchenko, *Chem. Sci.* **2015**, *6*, 2687-2704.

[17] a) C. A. A. van Boeckel, T. Beetz, *Recl. Trav. Chim. Pays-Bas,* **1985**, *104*, 171-173; b) J. Kalikanda, Z. Li, *J. Org. Chem.* **2011**, *76*, 5207-5218; c) J. Kalikanda, Z. Li, *J. Org. Chem.* **2011**, *76*, 5207-5218; d) B. S. Komarova, Y. E. Tsvetkov, N. E. Nifantiev, *Chem. Rec.* **2016**, *16*, 488- 506.

[18] a) A. F. Bochkov, G. E. Zaikov, *Chemistry of the O-Glycosidic Bond: Formation and Cleavage*, Pergamon Press: New York, **1979**, pp.5-79; b) A. V. Demchenko, *Synlett.* **2003**, *2003*, 1225-1240; b) T. Fang, Y. Gu, W. Huang, G.-J. Boons, *J. Am. Chem. Soc.* **2016**, *138*, 3002-3011.

[19] a) R. R. Schmidt, J. Michel, *Angew. Chem. Int. Ed.* **1980**, *19*, 731-732; *Angew. Chem.* **1980**, *92*, 763-744; b) P. Peng, R. R. Schmidt, *Accounts Chem. Res.* **2017**, *50*, 1171-1183.

[20] a) R. M. Williams, A. O. Stewart, *Tetrahedron Lett.* **1983**, *24*, 2715-2718; b) G. Lian, X. Zhang, B. Yu, *Carbohydr. Res.* **2015**, *403*, 13-22.

[21] a) B. Yu, H. Tao, *Tetrahedron Lett.* **2001**, *42*, 2405-2407; b) B. Yu, J. Sun, X. Yang, *Accounts Chem. Res.* **2012**, *45*, 1227-1236.

[22] Y. P. Cheng, H. T. Chen, C. C. Lin, *Tetrahedron Lett.* **2002**, *43*, 7721-7723.

[23] a) J. Park, S. Kawatkar, J. H. Kim, G. J. Boons, *Org. Lett.* **2007**, *9*,1959-1962; b) Y. H. Tsai, S. Götze, I. Vilotijevic, M. Grube, D. V. Silva, P. H. Seeberger, *Chem. Sci.* **2013**, *4*, 468-481.

[24] a) F. Belot, J. C. Jacquinet, *Carbohydr.Res.* **1996**, *290*, 79-86; b) A-R. de Jong, B. Hagen, V. van der Ark, H. S. Overkleeft, J. D. Codée, G. A. Van der Marel, *J. Org. Chem.* **2011**, *77*, 108-125.

[25] a) Y. Oikawa, T. Yoshioka, O. Yonemitsu, *Tetrahedron Letters* **1982**, *23*, 885-888; b)R. Pragani, P. H. Seeberger, *J. Am. Chem. Soc.* **2010**, *133*, 102-107.

[26] a) G. H. Vwneman, S. H. van Leeuwen; J. H. van Boom, *Tetrahedron Lett.* **1990**, *31*,1331–1334; b) E. Danieli, L. Lay, D. Proietti, F. Berti, P. Costantino, R. Adamo, *Org. Lett.* **2010**, *13*, 378-381; c) B. Schumann, S. G. Parameswarappa, M. P. Lisboa, N. Kottari, F. Guidetti, C. L. Pereira, P. H. Seeberger, *Angew. Chem. Int. Ed.* **2016**, *55*, 14431-14434. *Angew. Chem.* **2016**, *128*, 14644-14648.

[27] a) N. E. Byramova, M. V. Ovchinnikov, L. V. Backinowsky, K. Kochetkov, *Carbohydr. Res.* **1983**, *124*, C8; b) Y. Yang, C. E. Martin, P. H.Seeberger, *Chem. Sci.* **2012**, *3*, 896-899.

[28] a) R. Adamo, A. Nilo, B. Castagner, O. Boutureira, F. Berti, G. J. Bernardes, *Chem. Sci.* **2013**, *4*, 2995-3008; b) L. Kong, B. Vijayakrishnan, M. Kowarik, J. Park, A. N. Zakharova, L. Neiwert, A. Faridmoayer, B. G. Davis, *Nat. Chem.* **2016**, *8*, 242-249.