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Synthesis of a Spore Surface Pentasaccharide of *Bacillus anthracis*

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An analogue **2** of the pentasaccharide **1** found on the spore surface protein BclA of *Bacillus anthracis* was synthesized by a (3+2) glycosylation approach. A robust building block for 3-linked α-rhamnose is presented. Benzoate groups were used to ensure α-selectivity for the rhamnose units. A radical-initiated reduction with tributyltin hydride was shown to be able to convert the NHTCA group into an acetylated amine as well as an azido group into a free amine on one strike.

Introduction

Recent bioterrorism attacks have emphasized the need for fast and efficient methods to detect and reliably identify biowarfare agents. Anthrax is one of these highly infectious agents and is caused by the Gram-positive spore-forming soil bacterium *Bacillus anthracis*.[1,2] The spores, the durable form of the pathogen, are remarkably resistant to physical stress such as extreme temperatures, radiation, harsh chemicals, desiccation and physical damage. These properties enable the spores to persist in the soil for many years.[3] Inhalation of specially prepared spores will kill most victims if they are not treated within 24–48 h. In autumn 2001 several cases of anthrax infections were the result of the intentional release of spores by placement of contaminated letters in the mail. The death of five people resulted in a widespread panic and brought the US postal system to the brink of collapse. These cases demonstrated the danger of anthrax as a biowarfare agent to terrorize civilian populations. As a result of these attacks a more thorough examination of the mechanisms underlying the pathogenicity, the detection and treatment of organisms such as *B. anthracis* began.

In 2004, a unique tetrasaccharide portion of the major glycoprotein BclA from the surface of *B. anthracis* spores was discovered.[4] The non-reducing end of this carbohydrate is capped with a highly specific monosaccharide that was named anthrose. This monosaccharide moiety has not been found on the spores of other *Bacillus* strains including the closest relatives such as *B. cereus* and *B. thuringiensis*.[4] Therefore, the tetrasaccharide served as an attractive target to create antibodies for the detection of *B. anthracis* spores and to develop a vaccine candidate. We synthesized the tetrasaccharide[5] and used the antigen to create anti-carbohydrate antibodies.[6] These antibodies are able to detect *B. anthracis* endospores in a highly selective manner.[6] Following our initial report, two other groups achieved the synthesis of this tetrasaccharide[7] and corresponding sequences.[8]

Results and Discussion

The tetrasaccharide that has been the focus of several syntheses to date is part of pentasaccharide **1** containing an additional galactosamine residue, presumably by an α-linkage.[4,9] This *N*-acetylated galactosamine serves to connect the oligosaccharide to the surface protein BclA. Here, we describe the first synthesis of the pentasaccharide **2** via a convergent (3+2) approach. The key challenge associated with the synthesis of **2** is the differentiation of the two amino groups in the target molecule. One amine bears an acetyl moiety while the amine on the terminal anthrose is attached to a β-hydroxy carboxylic acid. Trichloroacetyl (TCA) was chosen to mask the amine of galactosamine whereas an azide was taken to mask the amino group on anthrose (Figure 1). This protecting group pattern allows for the assembly of the pentameric structure prior to amine functionalization.

To improve on the previous synthesis,[5] we modified the Fmoc-protected rhamnose building block. The sterically more demanding benzoate (Bz) group replaced the acetate (Ac) as participating group to ensure α-selectivity while at the same time decreases unwanted rearrangements,[10] and thus separation problems. The transformation of known acetal **3**[5] via diol **4** and the corresponding orthoester followed by subsequent ring-opening resulted in the kinetically favored axial benzoate **5**. Placement of the base-labile fluorenylmethoxycarbonyl (Fmoc) group,[11] cleavage of the anomeric *p*-methoxyphenyl (MP) glycoside and reaction of

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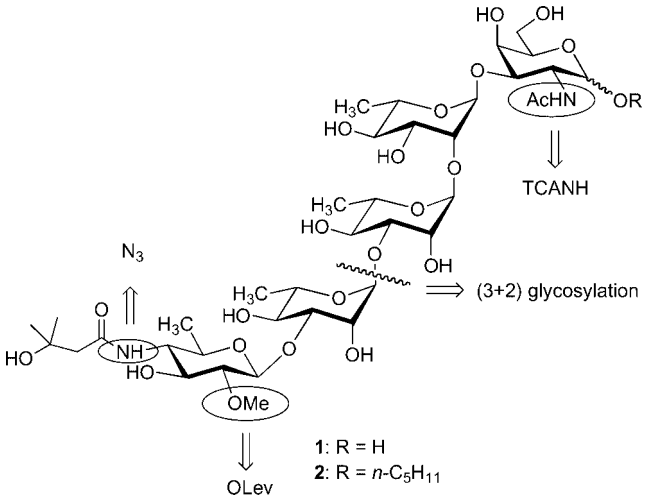
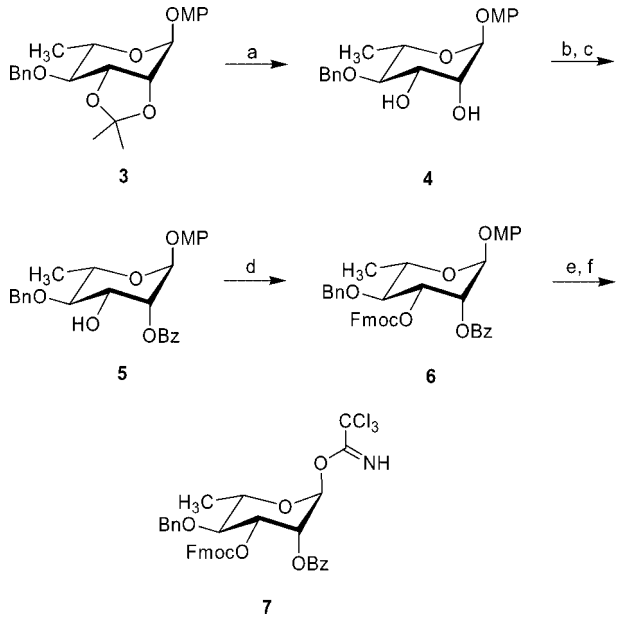


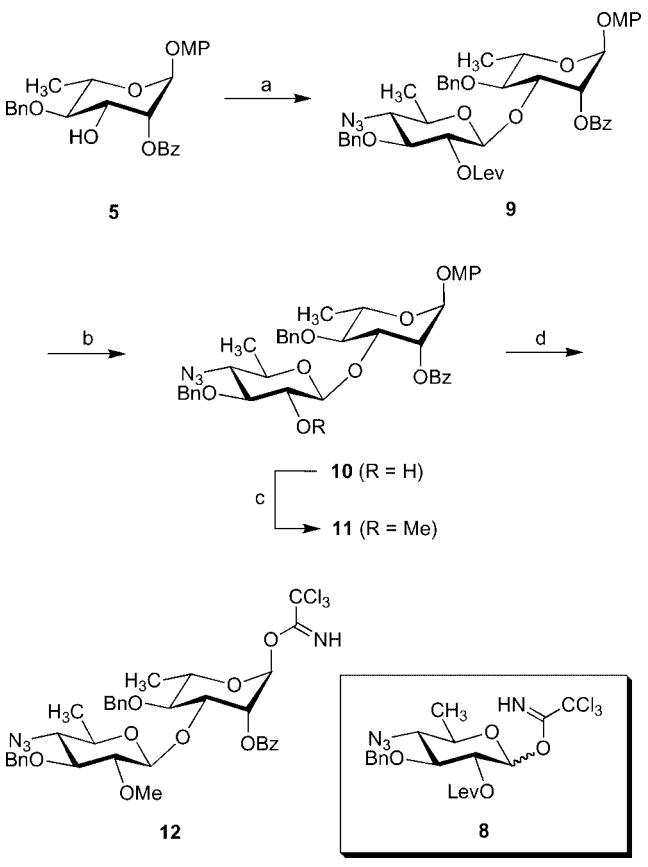
Figure 1. Structure of pentasaccharide **1** attached to the spore surface protein BclA of *B. anthracis* and analogue **2** that was synthesized.

the formed hemiacetal with trichloroacetonitrile in the presence of traces of sodium hydride afforded building block **7** (Scheme 1).[12]



Scheme 1. Synthesis of rhamnose building block **7**. Reagents and conditions: a) HCl (pH 3), MeOH/H_2O (10:1), 45 °C, 89%; b) $PhC(OMe)_3$, CSA (cat.), CH_2Cl_2, 25 °C, 2 h; c) AcOH/H_2O (4:1, v/v), 30 min, 90% (2 steps); d) FmocCl, pyridine, 25 °C, 2 h, 88%; e) CAN, H_2O/CH_3CN (1:1), 25 °C, 2 h, 86%; f) Cl_3CCN, CH_2Cl_2, NaH (cat.), 25 °C, 2 h, 85%.

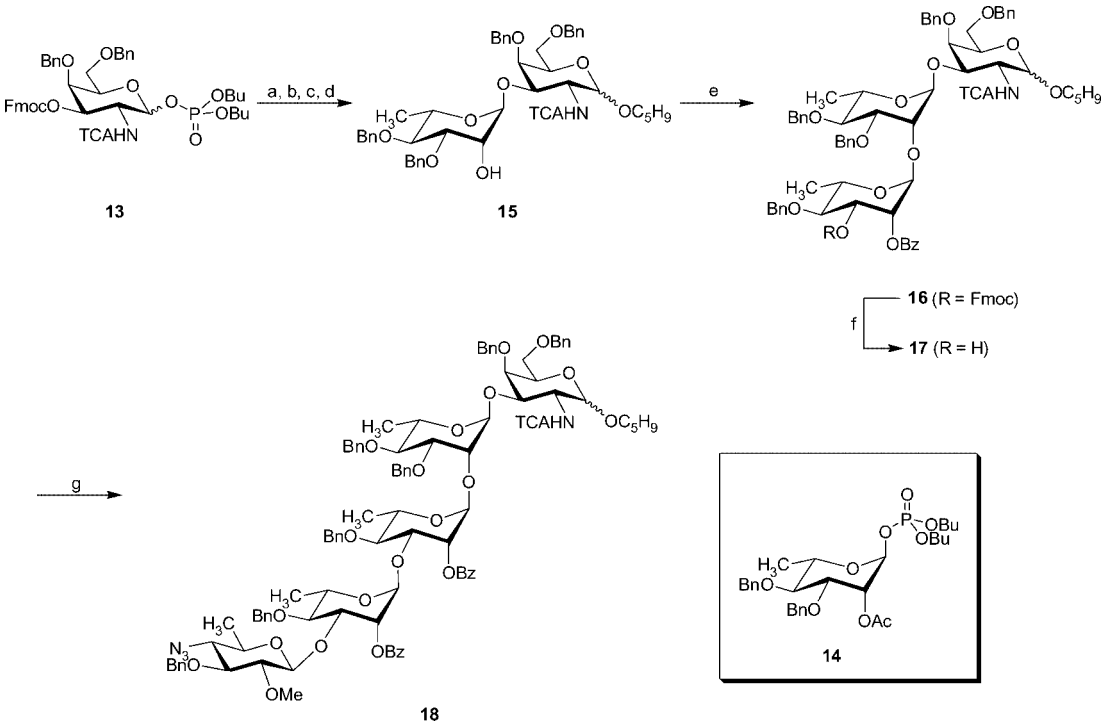
The assembly of the pentasaccharide was performed via a (3+2) approach. The terminal disaccharide unit was assembled by glycosidation of rhamnose **5**, an intermediate in the synthesis of building block **7**, with the known anthrose **8** (Scheme 2). The levulinoyl (Lev) group,[13] which ensured β-selectivity, was replaced by the final methoxy substituent at C2. The commonly used maneuver[12] to convert the methoxyphenyl glycoside into the corresponding trichloroacetimidate yielded disaccharide unit **12**.



Scheme 2. Synthesis of disaccharide building block **12**. Reagents and conditions: a) **8**, TMSOTf, CH_2Cl_2, 0 °C, 1 h, 98%; b) N_2H_4·AcOH, CH_2Cl_2/MeOH (5:1), 25 °C, 12 h, 83%; c) NaH, MeI, DMF, 1 h, 25 °C, 81%; d) 1) CAN, H_3CCN/H_2O (1:1), 25 °C, 85%, 2) Cl_3CCN, CH_2Cl_2, NaH (cat.), 25 °C, 90%.

For the trisaccharide part galactosamine building block **13**[14] was treated with 4-penten-1-ol (Scheme 3). The reaction with the highly reactive pentenol did not proceed with complete β-selectivity as approximately 20% of the corresponding α-anomer was obtained as well. This mixture of anomers was subjected to the subsequent reactions since separation could not easily be achieved at this stage. Removal of Fmoc, glycosidation with rhamnose building block **14**[15] and subsequent removal of acetate by sodium methoxide yielded disaccharide **15**.

Union of **15** and **7** furnished trisaccharide **16**, before Fmoc cleavage exposed the hydroxyl in **17**. Even the use of benzoate groups could not suppress completely the transesterification[10,16] of benzoate to position 3 during Fmoc deprotection. Best conditions for Fmoc removal[17] involved the use of triethylamine in an apolar solvent such as dichloromethane. The commonly used protocol relying on piperidine (20% in DMF) afforded less of the desired trisaccharide **17**. Fully protected pentasaccharide **18** was obtained by coupling trisaccharide **17** and disaccharide **12**.



Scheme 3. Assembly of pentasaccharide **18**. Reagents and conditions: a) 4-penten-1-ol, TMSOTf, CH_2Cl_2, 4-Å mol. sieves, –30 °C, 90 min, 70%; b) 20% piperidine in DMF, 25 °C, 1 h, quant.; c) **14**, TMSOTf, CH_2Cl_2, 0 °C, 90 min, 77%; d) NaOMe, MeOH, 25 °C, 12 h, 91%; e) **7**, TMSOTf, CH_2Cl_2, 0 °C, 90 min, 61%; f) NEt_3, CH_2Cl_2, 25 °C, 4 h, 89%; g) **12**, TMSOTf, CH_2Cl_2, –2 °C, 90 min, 73%.

Prior to the removal of all permanent protecting groups, the *N*-trichloroacetyl group on galactosamine had to be transformed into an *N*-acetyl. The azide on the terminal anthrose unit had to be reduced to a free amine, followed by acylation with 3-hydroxy-3-methylbutanoic acid. Both reductions were achieved in one step (Scheme 4). The radical-initiated reaction of excess tributyltin hydride in toluene at 100 °C converted the NHTCA group of **18** into the desired NHAc group and reduced the azide to a free amine moiety.[18] Potential problems with the β-hydroxy carboxylic acid due to sensitivity to strong bases caused us to remove the benzoate groups in the next step affording **19**. The addition of excess butylamine is required to trap the cleaved benzoate groups that would react otherwise with the free amine on anthrose. Without further purification of **19**, amide bond formation was induced using HATU and Hünig's base to attach the 3-hydroxy-3-methylbutanoic acid to the amine.[19] Purification by reversed-phase HPLC yielded **20**. Even at this stage the separation of the α/β mixture at the anomeric carbon carrying the linker was not possible.[20] Hydrogenolysis of **20** furnished the pentasaccharide target compound **2**.

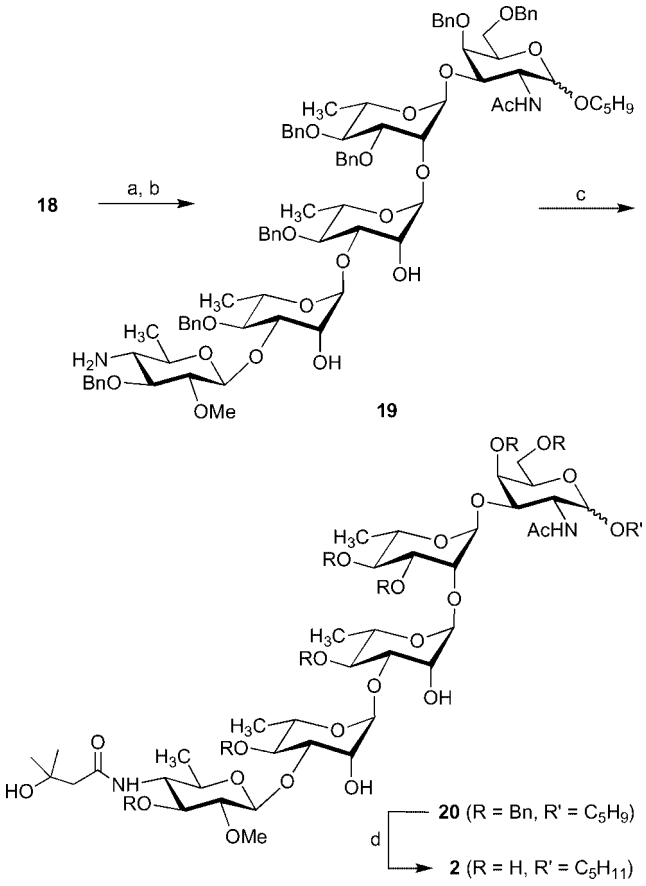
Conclusions

We have reported the first total synthesis of the pentasaccharide attached to BclA spore surface protein of *Bacillus anthracis* by utilizing a convergent (3+2) approach. Key to differentiating the two amino groups is the one-pot conversion of an *N*-trichloroacetyl into an *N*-acetyl group and simultaneous reduction of the azide to a free amine. Excess tributyltin hydride under radical-forming conditions achieved this goal.

Experimental Section

General Methods: All chemicals used were reagent grade and used as supplied except where noted. Dichloromethane (CH_2Cl_2) was purchased from JT Baker and purified by a Cycle-Tainer Solvent Delivery System. Pyridine and acetonitrile were refluxed over calcium hydride and distilled prior to use. Analytical thin-layer chromatography was performed on E. Merck silica gel 60 F_{254} plates (0.25 mm). Compounds were visualized by dipping the plates in a cerium sulfate ammonium molybdate solution or a sulfuric acid/methanol solution (for fully deprotected compounds) followed by heating. Liquid chromatography was performed using forced flow of the indicated solvent on Sigma H-type silica (10–40 mm). HPLC purifications were performed by a Waters system 2420, using a reversed-phase C_{18} column. ^{1}H NMR spectra were obtained on a Varian VXR-300 (300 MHz), Bruker-600 (600 MHz), and are reported in parts per million (δ) relative to $CHCl_3$ (δ = 7.26 ppm) or in the case of CD_3OD as solvent relative to TMS (δ = 0.00 ppm). Coupling constants (J) are reported in Hertz (Hz). ^{13}C NMR spectra were obtained on a Varian VXR-300 (75 MHz), Bruker-600 (150 MHz) and are reported in δ relative to $CDCl_3$ (δ = 77.0 ppm) as an internal reference or to TMS (δ = 0.00 ppm). For α/β mixtures we abstained from measuring $[\alpha]_D$ values.

4-Methoxyphenyl 4-*O*-Benzyl-α-L-rhamnopyranoside (4): Rhamnoside **3** (9.38 g, 23.45 mmol, 1.0 equiv.) was dissolved in MeOH (100 mL) and H_2O (10 mL). A few drops of an aqueous solution of hydrochloric acid (0.1 M) were added until pH 3 is reached. The mixture was heated to 45 °C and stirred for 2 d until TLC indicated



Scheme 4. Completion of the total synthesis of **2**. Reagents and conditions: a) Bu_3SnH (excess), AIBN (cat.), toluene, 100 °C, 2 h, 54%; b) NaOMe, $BuNH_2$ (excess), MeOH, 25 °C, 18 h, 73%; c) 3-hydroxy-3-methylbutanoic acid, HATU, DIPEA, DMF, 25 °C, 4 h, 44% (after HPLC); d) Pd/C, MeOH/THF/H_2O (4:4:1), H_2, 25 °C, 18 h, 63%.

complete conversion. The mixture was extracted with EtOAc (250 mL), washed twice with $NaHCO_3$ solution (100 mL each), dried with Na_2SO_4, and concentrated. The resulting crude product was purified by flash column chromatography on silica gel (hexane/EtOAc, 2:1 → 1:1) to afford 7.52 g (89%) of **4** as a colorless powder: R_f (SiO_2, cyclohexane/EtOAc, 2:1) = 0.11. $[a]_D$ = –109.5 (*c* = 0.86, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.33 (d, *J* = 6.3 Hz, 3 H), 3.10 (br. s, 1 H), 3.44–3.47 (s, 2 H), 3.75 (s, 3 H), 3.88 (m, 1 H), 4.13 (br. s, 2 H), 4.71–4.84 (m, 2 H), 5.39 (d, *J* = 6.6 Hz, 1 H), 6.81 (d, *J* = 9.0 Hz, 2 H), 6.96 (d, *J* = 9.0 Hz, 2 H), 7.28–7.37 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.2, 55.7, 68.0, 71.1, 71.4, 75.1, 81.5, 98.2, 114.6, 117.5, 127.8, 128.5, 138.1, 150.1, 154.7 ppm. MALDI-HRMS: *m*/*z* [M + Na]$^+$ calcd. 383.1465, obsd. 383.1459.

4-Methoxyphenyl 2-*O*-Benzoyl-4-*O*-benzyl-α-L-rhamnopyranoside (5): Rhamnoside **4** (4.51 g, 12.5 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (100 mL). (Trimethoxymethyl)benzene (4.62 g, 25.4 mmol, 2.0 equiv.) was added in one portion and a catalytic amount of CSA was added as well. The reaction mixture was stirred for 2 h at room temperature until the TLC indicated complete conversion [R_f (SiO_2, cyclohexane/EtOAc, 3:1) = 0.64]. The solvent was removed in vacuo and the residue was dissolved in 80% AcOH (150 mL). The reaction mixture was stirred for 30 min at room temperature. The solvent was removed in vacuo and the residue was coevaporated with toluene. Column chromatography on silica gel (hexane/EtOAc, 4:1 → 2:1) yielded 5.25 g (90% over 2 steps) of **5** as a yellow oil; R_f (SiO_2, cyclohexane/EtOAc, 3:1) = 0.30. $[a]_D$ = –85.3 (*c* = 0.48, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.38 (d, *J* = 6.3 Hz, 3 H), 2.18 (m, 1 H), 3.55 (dt, *J* = 2.4, 9.4 Hz, 1 H), 3.77 (s, 3 H), 3.98 (m, 1 H), 4.43 (m, 1 H), 4.78 (d, *J* = 10.8 Hz, 1 H), 4.87 (d, *J* = 10.8 Hz, 1 H), 5.49 (s, 1 H), 5.53 (m, 1 H), 6.82 (d, *J* = 9.0 Hz, 2 H), 6.99 (d, *J* = 9.0 Hz, 2 H), 7.31–7.38 (m, 5 H), 7.46–7.52 (m, 2 H), 7.59–7.64 (m, 2 H), 8.07 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.1, 55.5, 68.1, 70.2, 73.0, 75.1, 81.5, 96.4, 114.5, 117.6, 127.9, 127.9, 128.4, 128.5, 129.5, 129.8, 133.4, 138.0, 150.0, 154.9, 166.1 ppm. MALDI-HRMS: *m*/*z* [M + Na]$^+$ calcd. 487.1727, obsd. 487.1719.

4-Methoxyphenyl 2-*O*-Benzoyl-4-*O*-benzyl-3-*O*-fluorenylmethoxycarbonyl-α-L-rhamnopyranoside (6): Rhamnoside **5** (5.25 g, 11.3 mmol, 1.0 equiv.) was dissolved in pyridine (60 mL). FmocCl (5.87 g, 22.7 mmol, 2.0 equiv.) was added in one portion and the mixture stirred for 2 h at room temperature. Pyridine was removed in vacuo and the residue was adsorbed on silica gel. Column chromatography on silica gel (hexane/EtOAc, 5:1 → 4:1 → 3:1) yielded 6.21 g (88%) of **6** as a colorless solid; R_f (SiO_2, cyclohexane/EtOAc, 3:1) = 0.53. $[a]_D$ = –31.2 (*c* = 0.77, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.40 (d, *J* = 6.3 Hz, 3 H), 3.48 (d, *J* = 4.2 Hz, 1 H), 3.78 (s, 3 H), 3.78 (t, *J* = 9.6 Hz, 1 H), 4.11 (m, 1 H), 4.57 (m, 1 H), 4.72 (d, *J* = 12.0 Hz, 1 H), 4.89 (d, *J* = 11.1 Hz, 1 H), 5.53 (m, 2 H), 5.83 (m, 1 H), 6.84 (d, *J* = 9.0 Hz, 2 H), 7.04 (d, *J* = 9.0 Hz, 2 H), 7.18–7.40 (m, 10 H), 7.50–7.60 (m, 4 H), 7.66 (m, 1 H), 7.75 (d, *J* = 7.5 Hz, 2 H), 8.12 (d, *J* = 7.2 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.2, 46.7, 55.7, 68.3, 70.3, 70.4, 75.3, 76.2, 78.5, 96.4, 114.5, 117.7, 119.9, 119.9, 125.0, 125.3, 127.0, 127.1, 127.7, 127.8, 127.8, 128.3, 128.5, 129.4, 130.0, 133.4, 137.7, 141.1, 141.2, 143.0, 143.5, 149.9, 154.1, 155.0, 165.4 ppm. MALDI-HRMS: *m*/*z* [M + Na]$^+$ calcd. 709.2408, obsd. 709.2436.

2-*O*-Benzoyl-4-*O*-benzyl-3-*O*-fluorenylmethoxycarbonyl-α-L-rhamnopyranosyl Trichloroacetimidate (7): Rhamnoside **6** (1.91 g, 2.8 mmol, 1.0 equiv.) was dissolved in a mixture of acetonitrile (35 mL) and water (35 mL). Cerium ammonium nitrate (4.58 g, 8.3 mmol, 3.0 equiv.) was added and the mixture was vigorously stirred for 2 h at room temperature. After TLC indicated complete removal of the MP group, water (50 mL) and EtOAc (100 mL) were added. The phases were separated, the organic phase was washed twice with water (50 mL each), then with brine (50 mL), and again with water (50 mL). The organic phase was dried with Na_2SO_4, and concentrated. The resulting crude product (deeply yellow) was purified by column chromatography on silica gel (hexane/EtOAc, 3:1 → 2:1) to afford 1.38 g (86%) of the corresponding hemiacetal as an orange foam. This compound (1.34 g, 2.3 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (15 mL) and trichloroacetonitrile (6.70 g, 46.2 mmol, 20.0 equiv.). A catalytic amount of sodium hydride (ca. 10 mg) was added and the mixture was stirred for 2 h at room temperature. The solvent was removed in vacuo and the residue purified by flash column chromatography on silica gel (hexane/EtOAc, 2:1) to afford 1.42 g (85%) of **7** as a slightly yellow oil; R_f (SiO_2, cyclohexane/EtOAc, 3:1) = 0.64. $[a]_D$ = –24.6 (*c* = 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.49 (d, *J* = 6.3 Hz, 3 H), 3.83 (t, *J* = 9.6 Hz, 1 H), 4.20 (m, 1 H), 4.26 (m, 2 H), 4.61 (m, 1 H), 4.74 (d, *J* = 10.8 Hz, 1 H), 4.91 (d, *J* = 11.1 Hz, 1 H), 5.41 (dd, *J* = 3.0, 9.6 Hz, 1 H), 5.91 (m, 1 H), 6.42 (d, *J* = 1.8 Hz, 1 H), 7.16–7.43 (m, 9 H), 7.52–7.60 (m, 4 H), 7.68 (m, 1 H), 7.76 (d, *J* = 7.5 Hz, 2 H), 8.13 (d, *J* = 6.9 Hz, 2 H), 8.77 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 18.3, 29.8, 46.7, 68.9, 70.3, 70.7, 75.5, 76.0, 77.8, 94.9, 119.9, 119.9, 125.0, 125.3, 127.0, 127.1, 127.7, 127.8, 128.0, 128.1, 128.4, 128.5, 129.1, 130.0, 133.6, 137.4, 141.1, 141.2,

142.9, 143.5, 154.0, 160.0, 165.2 ppm. MALDI-HRMS: *m/z* [M + Na]$^+$ calcd. 746.1086, obsd. 746.1073.

4-Methoxyphenyl 4-Azido-3-*O*-benzyl-4,6-dideoxy-2-*O*-levulinoyl-β-D-glucopyranosyl-(1→3)-2-*O*-benzoyl-4-*O*-benzyl-α-L-rhamnopyranoside (9): Rhamnose **5** (360 mg, 0.775 mmol, 1.0 equiv.) and anthrose trichloroacetimidate **8** (485 mg, 0.280 mmol, 1.2 equiv.) were codistilled three times with toluene and dried for 30 min in vacuo. The mixture was dissolved in CH_2Cl_2 (10 mL) and cooled to 0 °C. TMSOTf (26 mg, 21 μL, 0.116 mmol, 0.15 equiv.) was added, the solution stirred for 1 h and quenched by addition of some drops of pyridine. The solvent was removed and the resulting crude product was purified by column chromatography (hexane/EtOAc, 3:1) to afford 630 mg (98%) of **9** as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.21 (d, J = 6.0 Hz, 3 H), 1.29 (d, J = 6.3 Hz, 3 H), 2.00 (s, 3 H), 2.17–2.35 (m, 4 H), 3.12 (t, J = 9.6 Hz, 1 H), 3.27 (m, 1 H), 3.49 (t, J = 9.3 Hz, 1 H), 3.67 (t, J = 9.6 Hz, 1 H), 3.78 (s, 3 H), 3.94 (m, 1 H), 4.37 (dd, J = 3.3, 9.3 Hz, 1 H), 4.64–4.76 (m, 4 H), 4.92 (d, J = 11.7 Hz, 1 H), 5.04 (t, J = 8.4 Hz, 1 H), 5.50 (m, 2 H), 6.83 (d, J = 9.3 Hz, 2 H), 7.01 (d, J = 9.3 Hz, 2 H), 7.25–7.37 (m, 10 H), 7.48 (t, J = 7.5 Hz, 2 H), 7.60 (t, J = 7.5 Hz, 1 H), 8.05 (d, J = 8.7 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 17.8, 18.0, 27.6, 29.5, 37.3, 55.5, 67.3, 68.1, 70.7, 71.9, 73.5, 74.5, 74.8, 78.2, 79.7, 81.1, 96.1, 100.4, 114.5, 117.7, 127.2, 127.5, 127.8, 128.0, 128.3, 129.8, 130.0, 133.0, 137.4, 138.4, 150.0, 155.0, 166.0, 171.2, 206.0 ppm. MALDI-HRMS: *m/z* [M + Na]$^+$ calcd. 846.3209, obsd. 846.3193.

4-Methoxyphenyl 4-Azido-3-*O*-benzyl-4,6-dideoxy-β-D-glucopyranosyl-(1→3)-2-*O*-benzoyl-4-*O*-benzyl-α-L-rhamnopyranoside (10): Compound **9** (630 mg, 0.764 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (25 mL) and hydrazinium acetate (137 mg, 1.492 mmol, 1.95 equiv.) in 5 mL of MeOH was added at room temperature and stirred for 12 h until mass spectrometry indicated complete conversion. The solvent was evaporated and the crude product was purified by column chromatography (3:1 hexane/EtOAc) to afford 501 mg (83%) of **10** as a colorless oil; $[\alpha]_D$ = 13.5 (c = 0.29, $CHCl_3$). IR (thin film, $CHCl_3$): $\tilde{\nu}$ = 3035, 2113, 1718, 1595, 1508, 1451, 1262, 1097, 1036 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.26 (d, J = 5.7 Hz, 3 H), 1.38 (d, J = 6.3 Hz, 3 H), 2.47 (s, 1 H), 3.07 (t, J = 9.6 Hz, 1 H), 3.25 (s, 1 H), 3.37 (t, J = 9.2 Hz, 1 H), 3.50 (m, 1 H), 3.73 (m, 1 H), 3.78 (s, 3 H), 4.00 (m, 1 H), 4.45 (dd, J = 3.3, 9.3 Hz, 1 H), 4.52 (d, J = 7.5 Hz, 1 H), 4.74–4.98 (m, 4 H), 5.50 (m, 1 H), 5.58 (m, 1 H), 6.84 (d, J = 9.3 Hz, 2 H), 7.01 (d, J = 9.3 Hz, 2 H), 7.33–7.46 (m, 10 H), 5.50 (m, 2 H), 7.61 (m, 1 H), 8.09 (d, J = 7.2 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 18.3, 18.4, 55.7, 67.2, 68.4, 70.9, 72.5, 74.9, 75.1, 75.5, 77.8, 80.4, 82.5, 96.3, 103.0, 114.5, 117.7, 127.8, 128.0, 128.0, 128.1, 128.3, 128.3, 128.5, 129.8, 130.0, 133.1, 137.8, 137.9, 149.9, 154.9, 165.7 ppm. MALDI-HRMS: *m/z* [M + Na]$^+$ calcd. 748.2841, obsd. 748.2828.

4-Methoxyphenyl 4-Azido-3-*O*-benzyl-4,6-dideoxy-2-*O*-methyl-β-D-glucopyranosyl-(1→3)-2-*O*-benzoyl-4-*O*-benzyl-α-L-rhamnopyranoside (11): Compound **10** (407 mg, 0.561 mmol, 1.0 equiv.) was dissolved in DMF (5 mL) and cooled to 0 °C. Sodium hydride (29 mg, 0.725 mmol, 1.2 equiv.) was added, then methyl iodide (161 mg, 1.134 mmol, 2.0 equiv.) was added and the mixture was stirred for 1 h. After the TLC indicated complete conversion, the reaction mixture was poured into an acidified aqueous solution (pH 3) and extracted twice with EtOAc. The combined organic phases were washed with brine, dried with Na_2SO_4 and concentrated. Column chromatography on silica gel (hexane/EtOAc, 3:1) was performed to yield 335 mg (81%) of **11** as a colorless oil; $[\alpha]_D$ = 1.8 (c = 0.38, $CHCl_3$). IR (thin film, $CHCl_3$): $\tilde{\nu}$ = 3008, 2110, 1719, 1603, 1505, 1458, 1364 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.29 (d, J = 5.7 Hz, 3 H), 1.40 (d, J = 6.0 Hz, 3 H), 3.05–3.24 (m, 3 H), 3.39 (t, J = 9.3 Hz, 1 H), 3.57 (s, 3 H), 3.76 (m, 3 H), 3.79 (s, 1 H), 4.02 (m, 1 H), 4.51 (dd, J = 3.3, 9.6 Hz, 1 H), 4.68–4.93 (m, 4 H), 5.07 (d, J = 10.5 Hz, 1 H), 5.53 (m, 1 H), 5.59 (m, 1 H), 6.85 (d, J = 9.0 Hz, 2 H), 7.03 (d, J = 9.0 Hz, 2 H), 7.26–7.47 (m, 12 H), 7.62 (m, 1 H), 8.13 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 18.0, 18.2, 55.5, 60.5, 67.4, 68.2, 70.4, 72.9, 75.0, 75.2, 76.2, 80.7, 82.7, 84.3, 96.2, 103.0, 114.5, 117.7, 127.8, 127.9, 128.1, 128.2, 128.3, 128.4, 129.7, 130.1, 133.1, 137.9, 138.0, 150.0, 155.0, 165.7 ppm. MALDI-HRMS: *m/z* [M + Na]$^+$ calcd. 762.2997, obsd. 762.2982.

4-Azido-3-*O*-benzyl-4,6-dideoxy-2-*O*-methyl-β-D-glucopyranosyl-(1→3)-2-*O*-benzoyl-4-*O*-benzyl-α-L-rhamnopyranosyl Trichloroacetimidate (12): Compound **11** (324 mg, 0.438 mmol, 1.0 equiv.) was dissolved in a mixture of acetonitrile and water (14 mL/14 mL), cerium ammonium nitrate (841 mg, 1.534 mmol, 3.5 equiv.) was added in one portion and the mixture was stirred for 2 h until TLC indicated complete conversion into the hemiacetal. The solution was poured into brine and the aqueous phase was extracted twice with EtOAc. The combined organic phases were washed twice with water, dried with Na_2SO_4 and concentrated. The resulting crude product was purified by column chromatography (hexane/EtOAc, 2:1) to yield 235 mg (85%) of the hemiacetal. The hemiacetal was dissolved in CH_2Cl_2 (3 mL) and trichloroacetonitrile (3 mL). A catalytic amount of sodium hydride (8 mg) was added and the mixture was stirred for 60 min. The solvent was removed in vacuo and the residue was purified by column chromatography on silica gel (hexane/EtOAc, 3:1) to afford 259 mg (90%) of **11** as a colorless oil; $[\alpha]_D$ = 30.4 (c = 0.25, $CHCl_3$). IR (thin film, $CHCl_3$): $\tilde{\nu}$ = 3026, 2923, 2103, 1723, 1672, 1600, 1451, 1267, 1092 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.22 (d, J = 5.7 Hz, 3 H), 1.43 (d, J = 6.0 Hz, 3 H), 3.04–3.16 (m, 3 H), 3.37 (t, J = 9.0 Hz, 1 H), 3.52 (s, 3 H), 3.74 (t, J = 9.6 Hz, 1 H), 4.02 (m, 1 H), 4.38 (dd, J = 3.3, 9.6 Hz, 1 H), 4.63 (d, J = 8.1 Hz, 1 H), 4.71 (d, J = 10.2 Hz, 1 H), 4.80 (d, J = 10.5 Hz, 1 H), 4.88 (d, J = 10.8 Hz, 1 H), 5.02 (d, J = 9.9 Hz, 1 H), 5.57 (m, 1 H), 6.35 (m, 1 H), 7.28–7.51 (m, 12 H), 7.62 (m, 1 H), 8.09 (m, 2 H), 8.71 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 17.9, 18.1, 60.4, 67.3, 70.4, 70.6, 71.9, 75.2, 75.3, 75.5, 80.0, 82.5, 84.3, 90.8, 94.7, 103.1, 127.8, 128.1, 128.2, 128.3, 128.4, 128.5, 129.7, 133.2, 137.7, 137.8, 160.0, 165.4 ppm. MALDI-HRMS: *m/z* [M + Na]$^+$ calcd. 799.1675, obsd. 799.1661.

Pent-4-enyl 3,4-Di-*O*-benzyl-α-L-rhamnopyranosyl-(1→3)-4,6-di-*O*-benzyl-2-*N*-trichloroacetyl-α/β-D-galactosaminopyranoside (15): Galactosamine building block **13** (367 mg, 0.399 mmol, 1.0 equiv.) was codistilled three times with toluene and dried in vacuo for 30 min. CH_2Cl_2 (8 mL) was added as well as 4-pentenol (69 mg, 82 μL, 0.798 mmol, 2.0 equiv.) and 4 Å molecular sieves. The suspension was cooled to –30 °C. TMSOTf (86 mg, 72 μL, 0.399 mmol, 1.0 equiv.) was added and the reaction mixture stirred for 90 min. Then, the reaction was quenched by addition of pyridine (0.1 mL). Column chromatography on silica gel (hexane/EtOAc, 3:1) yielded 222 mg (70%, α/β = 1:4) of the pentenyl glycoside as a colorless oil that was subsequently submitted to the next step. The Fmoc-protected pentenyl glycoside (191 mg, 0.240 mmol, 1.0 equiv.) was dissolved in DMF (8 mL) and piperidine (2 mL) was added. The reaction mixture was stirred for 1 h. The volatiles were removed in vacuo, the residue dissolved in CH_2Cl_2 and concentrated. Column chromatography on silica gel (hexane/EtOAc, 5:1 → 2:1) yielded 137 mg (quant.) of the Fmoc-deprotected product as colorless solid. This material (137 mg, 0.239 mmol, 1.0 equiv.) and rhamnosyl phosphate **14** (221 mg, 0.383 mmol, 1.6 equiv.) were codistilled

three times with toluene and dried in vacuo. CH_2Cl_2 (3.5 mL) was added and the solution cooled to 0 °C. TMSOTf (85 mg, 69 μL, 0.383 mmol, 1.6 equiv.) was added and the reaction mixture was stirred for 90 min. TLC analysis indicated one major product. The reaction was quenched by addition of a few drops of pyridine and the solvents were evaporated in vacuo. Column chromatography on silica gel (hexane/EtOAc, 2:1) yielded 172 mg (77%) of the disaccharide as a colorless oil. This oil was subsequently submitted to the next step and was dissolved in MeOH (6 mL) and NaOMe solution (0.5 M in MeOH) was added until pH 12 was reached. The reaction mixture was stirred overnight. The solvents were evaporated and the crude product was purified by column chromatography on silica gel (hexane/EtOAc, 3:1 → 2:1) yielding 149 mg (91%) of **15** as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.33 (d, J = 6.3 Hz, 3 H), 1.68 (m, 2 H), 2.12 (m, 2 H), 3.48 (m, 2 H), 3.53–3.69 (m, 4 H), 3.91 (m, 4 H), 4.05 (m, 2 H), 4.32 (m, 1 H), 4.48 (m, 2 H), 4.63 (m, 4 H), 4.79–5.05 (m, 6 H), 5.79 (m, 1 H), 6.89 (d, J = 7.8 Hz, 1 H), 7.26–7.37 (m, 20 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 18.1, 28.8, 30.1, 56.0, 68.5, 68.7, 69.2, 72.1, 73.5, 73.6, 74.9, 75.1, 75.7, 79.6, 92.6, 99.6, 100.8, 114.9, 127.5, 127.6, 127.7, 127.9, 128.1, 128.2, 128.2, 128.4, 128.4, 137.6, 137.7, 137.8, 138.3, 161.8 ppm. MALDI-HRMS: m/z [M + Na]$^+$ calcd. 920.2705, obsd. 920.2752.

Pent-4-enyl 4-*O*-Benzyl-2-*O*-benzoyl-α-L-rhamnopyranosyl-(1→2)-3,4-di-*O*-benzyl-α-L-rhamnopyranosyl-(1→3)-4,6-di-*O*-benzyl-2-*N*-trichloroacetyl-β-D-galactosaminopyranoside (17): Disaccharide **15** (120 mg, 0.134 mmol, 1.0 equiv.) and rhamnosyl trichloroacetimidate **7** (146 mg, 0.201 mmol, 1.5 equiv.) were codistilled three times with toluene and dried in vacuo. CH_2Cl_2 (2 mL) was added and the solution was cooled to 0 °C. TMSOTf (85 mg, 69 μL, 0.383 mmol, 1.6 equiv.) was added and the reaction mixture was stirred for 90 min. The reaction was quenched by addition of a few drops of pyridine and the solvents were evaporated in vacuo. Column chromatography on silica gel (hexane/EtOAc, 5:1 → 4:1) yielded 119 mg (61%) of trisaccharide **16** as a slightly yellow oil. This oil was subsequently submitted the to next step and dissolved in CH_2Cl_2 (3 mL). NEt_3 (0.2 mL) was added and the solution stirred for 4 h at room temperature. The solvents were removed and the crude product was purified by column chromatography on silica gel (hexane/EtOAc, 3:1 → 2:1) yielding 74 mg (89%) of **17** as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.26–1.45 (m, 6 H), 1.66 (m, 2 H), 2.23 (d, J = 4.2 Hz, 1 H), 3.42–3.54 (m, 3 H), 3.63–3.73 (m, 4 H), 3.83–4.03 (m, 7 H), 4.29 (m, 2 H), 4.39 (m, 2 H), 4.49–5.09 (m, 14 H), 5.50 (s, 1 H), 5.76 (m, 1 H), 7.16 (d, J = 8.1 Hz, 2 H), 7.22–7.38 (m, 25 H), 7.50 (t, J = 7.5 Hz, 2 H), 8.06 (d, J = 7.2 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 18.3, 18.4, 28.8, 30.1, 56.1, 68.2, 68.4, 69.3, 70.4, 72.3, 73.2, 73.4, 73.6, 74.8, 75.0, 75.3, 75.7, 76.3, 79.0, 79.9, 81.8, 92.4, 98.4, 99.2, 100.2, 114.8, 127.5, 127.5, 127.6, 127.7, 127.7, 127.8, 128.0, 128.1, 128.2, 128.2, 128.3, 128.4, 129.6, 129.7, 129.8, 133.2, 137.7, 137.9, 138.1, 138.2, 138.4, 161.8, 166.0 ppm. MALDI-HRMS: m/z [M + Na]$^+$ calcd. 1260.4022, obsd. 1260.4048.

Pent-4-enyl 4-Azido-3-*O*-benzyl-4,6-dideoxy-2-*O*-methyl-β-D-glucopyranosyl-(1→3)-2-*O*-benzoyl-4-*O*-benzyl-α-L-rhamnopyranosyl-(1→3)-2-*O*-benzoyl-4-*O*-benzyl-α-L-rhamnopyranosyl-(1→2)-3,4-*O*-benzyl-α-L-rhamnopyranosyl-(1→3)-4,6-di-*O*-benzyl-2-*N*-trichloroacetyl-α/β-D-galactosaminopyranoside (18): Trisaccharide acceptor **17** (72 mg, 0.058 mmol, 1.0 equiv.) and disaccharide donor **12** (77 mg, 0.099 mmol, 1.7 equiv.) were codistilled three times with toluene and dried for 30 min in vacuo. The mixture was dissolved in CH_2Cl_2 (1.5 mL) and cooled to –2 °C. TMSOTf (3.2 mg, 3 μL, 0.015 mmol, 0.25 equiv.) was added, the solution stirred for 90 min and quenched by addition of some drops of pyridine. The solvent was removed and the resulting crude product was purified by column chromatography (hexane/EtOAc, 5:1 → 4:1 → 3:1) to afford 79 mg (73%) of **18** as a slightly yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.93 (d, J = 5.9 Hz, 3 H), 1.31 (m, 12 H), 1.61 (m, 2 H), 2.04 (m, 2 H), 3.01 (m, 5 H), 3.46 (s, 3 H), 3.82 (m, 12 H), 4.60 (m, 22 H), 5.12 (m, 1 H), 5.27 (m, 1 H), 5.52 (m, 1 H), 5.58 (m, 1 H), 5.76 (m, 1 H), 7.26–7.36 (m, 41 H), 8.08 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 17.9, 18.1, 18.2, 18.3, 18.4, 28.7, 30.1, 56.1, 60.4, 60.5, 67.3, 67.4, 68.3, 68.4, 68.6, 69.3, 70.2, 70.3, 70.8, 72.1, 72.3, 72.5, 73.0, 73.1, 73.2, 73.3, 73.6, 74.2, 74.7, 74.9, 75.0, 75.1, 75.2, 75.3, 75.5, 75.6, 75.7, 75.8, 75.9, 76.0, 76.2, 76.3, 76.6, 76.8, 76.9, 77.0, 77.3, 77.5, 80.0, 80.3, 80.5, 82.4, 84.3, 92.3, 98.1, 98.9, 99.2, 100.1, 102.8, 114.7, 127.0, 127.1, 127.2, 127.3, 127.4, 127.6, 127.7, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4, 128.5, 128.6, 128.7, 128.8, 128.9, 129.6, 129.7, 129.8, 129.9, 130.0, 130.1, 132.9, 133.0, 133.1, 137.5, 137.6, 137.7, 137.8, 137.9, 138.0, 138.1, 138.4, 138.5, 161.7, 165.2, 165.3 ppm. MALDI-HRMS: m/z [M + Na]$^+$ calcd. 1875.6597, obsd. 1875.6556.

Pent-4-enyl 3-*O*-Benzyl-4,6-dideoxy-4-(3-hydroxy-3-methylbutanamido)-2-*O*-methyl-β-D-glucopyranosyl-(1→3)-4-*O*-benzyl-α-L-rhamnopyranosyl-(1→3)-4-*O*-benzyl-α-L-rhamnopyranosyl-(1→2)-3,4-*O*-benzyl-α-L-rhamnopyranosyl-(1→3)-4,6-di-*O*-benzyl-2-*N*-acetyl-α/β-D-galactosaminopyranoside (20): Pentasaccharide **18** (48 mg, 0.026 mmol, 1.0 equiv.), tributyltin hydride (113 mg, 103 μL, 0.388 mmol, 15.0 equiv.) and a catalytic amount of AIBN were dissolved in toluene (2 mL). Argon was bubbled through the solution for 30 min. The reaction mixture was put in a preheated oil bath of 100 °C and stirred for 2 h. Afterwards, the reaction mixture was cooled to room temperature. The solvent was removed and the residue passed through a plug of silica gel (hexane/EtOAc, 1:1 → 0:1). MS (ESI+) shows a strong signal for 1726 [M + H]$^+$ and 1748 [M + Na]$^+$. After removal of the solvent 24 mg (54%) of crude product were obtained. This material (22 mg, 0.013 mmol, 1.0 equiv.) was dissolved in MeOH (4 mL), butylamine (19 mg, 25 μL, 0.255 mmol, 20.0 equiv.) was added, then a solution of NaOMe (0.5 M, 0.4 mL). The reaction mixture was stirred for 18 h. Mass spectrometric (ESI+) analysis indicated the removal of two benzoate groups. The solution was neutralized with Amberlite IR-120 acidic resin, concentrated and passed through a plug of silica gel (CH_2Cl_2/MeOH, 20:1 → 10:1). The product **19** (14 mg, 73%) was not purified further and submitted directly to amide formation. The starting material (14 mg, 0.0092 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (0.5 mL). HATU (5.3 mg, 0.014 mmol, 1.5 equiv.) and ethyldiisopropylamine (2.3 mg, 3 μL, 0.0175 mmol, 1.9 equiv.) were dissolved in a separate flask in CH_2Cl_2 (0.3 mL) and added after 2 min to the solution of the pentasaccharide. The unified solution was stirred for 1 h. Mass spectrometric (ESI+) analysis showed still starting material after 1 h. Therefore, again 3 μL of ethyldiisopropylamine were added and stirred for further 3 h. The solvent was removed in vacuo. HPLC purification by reversed-phase C_{18} column (H_3CCN/H_2O, 6:4 → 0:1, 20% iPrOH, gradient over 30 min) yielded 6.5 mg (44%) of **20** as a colorless foam: ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.23 (m, 3 H), 1.25 (m, 3 H), 1.27 (m, 3 H), 1.28 (m, 3 H), 1.29 (m, 3 H), 1.30 (m, 3 H), 1.31 (m, 2 H), 1.55 (m, 2 H), 1.86 (s, 2 H), 1.92 (s, 3 H), 2.09 (m, 2 H), 2.52 (m, 1 H), 3.16 (m, 3 H), 3.57 (s, 3 H), 3.69 (m, 16 H), 4.05 (m, 3 H), 4.46 (m, 9 H), 4.82 (m, 8 H), 5.17 (d, J = 1.3 Hz, 1 H), 5.29 (d, J = 3.4 Hz, 1 H), 5.54 (m, 1 H), 5.78 (m, 1 H), 7.15–7.32 (m, 35 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.1, 17.8, 17.9, 18.0, 18.2, 18.3, 22.7, 23.1, 23.6, 28.7, 29.3, 29.4, 29.5, 29.6, 29.7, 30.0, 31.9, 33.4, 47.9, 55.4, 55.8, 60.6, 68.0, 68.3, 68.7, 68.9, 69.4, 70.6, 70.8, 70.9, 72.1, 72.2, 72.3, 73.3, 73.4, 73.6, 73.9, 74.8, 74.9, 75.3, 76.2, 76.8, 77.0, 77.2, 78.8, 79.4, 79.8, 80.0, 80.2, 80.9, 84.4, 84.6, 98.9,

99.5, 100.2, 100.9, 103.1, 114.8, 127.4, 127.5, 127.6, 127.7, 127.8, 127.9, 128.9, 128.1, 128.2, 128.3, 128.4, 128.5, 128.6, 138.0, 138.1, 138.2, 138.4, 138.5, 138.6, 170.9, 172.3 ppm. MALDI-HRMS: *m/z* $[M + Na]^+$ calcd. 1639.7861, obsd. 1639.7904.

Pentyl 4,6-Dideoxy-4-(3-hydroxy-3-methylbutanamido)-2-*O*-methyl-β-D-glucopyranosyl-(1→3)-α-L-rhamnopyranosyl-(1→3)-α-L-rhamnopyranosyl-(1→2)-α-L-rhamnopyranosyl-(1→3)-2-*N*-acetyl-α/β-D-galactosaminopyranoside (2): Pentasaccharide **16** (6.5 mg, 0.004 mmol, 1.0 equiv.) was dissolved in MeOH/THF/H_2O (4:4:1, 2 mL). Pd on charcoal (20 mg) was added and the argon atmosphere was substituted by an H_2 atmosphere. The reaction mixture was stirred for 18 h at room temperature. MS (ESI+) experiments showed complete conversion. The mixture was filtered through a pad of celite. The filtrate was concentrated and the residue was purified by a reversed-phase (C_{18}) column chromatography (H_2O/MeOH, 1:0 → 4:1 → 3:1 → 2:1 → 1:1 → 1:2 → 1:3 → 0:1). The product-containing fractions were concentrated and the residue dried by lyophilization. 2.5 mg (63%) of **2** were obtained as a white solid. ^1H NMR (CD_3OD, 600 MHz): δ = 0.91 (t, J = 7.2 Hz, 3 H), 1.20 (m, 3 H), 1.21 (m, 3 H), 1.23 (m, 3 H), 1.24 (m, 3 H), 1.27 (m, 3 H), 1.29 (m, 3 H), 1.41 (m, 4 H), 1.55 (m, 2 H), 1.88 (s, 2 H), 1.99 (s, 3 H), 2.34 (d, J = 13.2 Hz, 1 H), 2.38 (d, J = 13.1 Hz, 1 H), 3.01 (dd, J = 7.8, 9.0 Hz, 1 H), 3.44 (m, 11 H), 3.64 (d, J = 4.4 Hz, 1 H), 3.65 (s, 3 H), 3.73 (d, J = 7.2 Hz, 1 H), 3.76 (d, J = 3.3 Hz, 1 H), 3.85 (m, 5 H), 3.91 (d, J = 2.3 Hz, 1 H), 4.04 (dd, J = 2.0, 3.2 Hz, 1 H), 4.17 (dd, J = 1.7, 3.2 Hz, 1 H), 4.61 (d, J = 7.8 Hz, 1 H), 4.85 (d, J = 7.8 Hz, 1 H), 4.98 (d, J = 2.1 Hz, 1 H), 5.05 (d, J = 1.6 Hz, 1 H) ppm. MALDI-HRMS: *m/z* $[M + Na]^+$ calcd. 1011.4731, obsd. 1011.4712.

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