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Modular Synthesis of Core Fucosylated N-Glycans

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Dedicated to Professor Frieder Lichtenthaler on the occasion of his 80th birthday

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A modular synthesis of complex-type N-glycans containing the core fucosyl motif was optimized. The core trisaccharide building block was protected by a methoxyphenyl group for convenient core fucosylation. The trisaccharide was obtained on a large scale from the glycosylation of the corresponding chitobiosyl azide with a glucosyl donor followed by intramolecular inversion. Improved methods were established for the synthesis of the monosaccharide building blocks and for their couplings. The inversion to the β-mannoside was accompanied by previously unnoticed side-reactions resulting in the hydrolytic ring-opening of the iminocarbonate intermediate. The benzylidene-protected core trisaccharide was elongated into a biantennary N-glycan heptasaccharide by two regio- and stereoselective couplings. The final fucosylation also gave some of the β anomer, which could be removed by HPLC to give an α1,6-fucosylated N-glycan octasaccharide.

Introduction

The glycosylation of asparagine residues in proteins (N-glycosylation) is known to modify the biochemical and biophysical properties of the proteins.[1] Recent studies on N-glycoprotein variants have revealed stabilizing effects caused by N-glycan–protein interactions.[2] The diversity of N-glycans in glycoproteins (microheterogeneity) is also gaining attention. In particular cases, the biological activity of single glycoforms can be related to individual oligosaccharide structures.[3] A frequently occurring N-glycan modification contributing to microheterogeneity is core fucosylation,[4] which has been found to be essential for normal growth in animals.[5] Core fucosylation is known to affect the efficiency of serum antibodies,[6] the binding to lectins,[7] and the activity of receptors,[8] and it also serves as a tumor marker.[9] Due to the difficulties in the isolation of sufficient amounts of homogeneous N-glycans of a given structure,[10] the chemical and enzymatic synthesis of N-glycans has become a straightforward alternative.[11] By means of a modular approach, multi-branched N-glycans[12] have become accessible, and the introduction of a core fucosyl moiety is possible concomitantly.[13] The combination of these features with another core modification, the bisecting GlcNAc moiety,[14] allows the generation of virtually all the basic structures of complex-type N-glycans by a common approach. This has been shown for a highly substituted penta-antennary, bisected and core-fucosylated undecasaccharide.[15] In order to be able to introduce the core fucosyl residue at an appropriate stage in the synthesis, we have developed a modified core trisaccharide bearing a *p*-methoxyphenyl group,[16] which can be cleaved selectively.[13] This approach facilitates the introduction of a labile fucosyl moiety in one of the last glycosylations,[14b,17] whereas other strategies rely on an earlier fucosylation[18] or a different disconnection mode.[19] In an alternative approach, α1,6-fucosyltransferases from several organisms have been cloned, and these may be used for enzymatic core fucosylation of complex-type non-galactosylated N-glycans.[20]

Results and Discussion

In order to obtain N-glycans and glycopeptides with a core fucosyl moiety (i.e., **A**; Scheme 1), a route to key building block **B** was developed.[13] Core trisaccharide **B** is functionalized for regio- and stereoselective elongations of the central β-mannoside in a modular fashion, using donors similar to building block **C**. The selective removal of the *p*-methoxyphenyl group permits core fucosylation using donor **D**.

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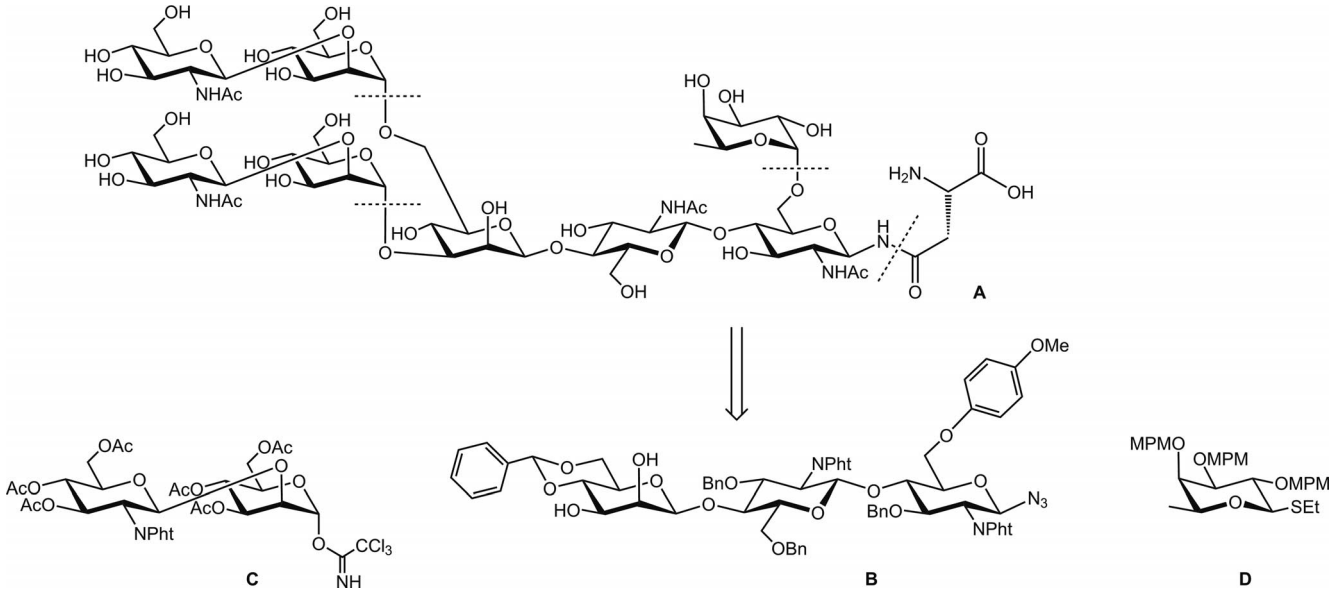
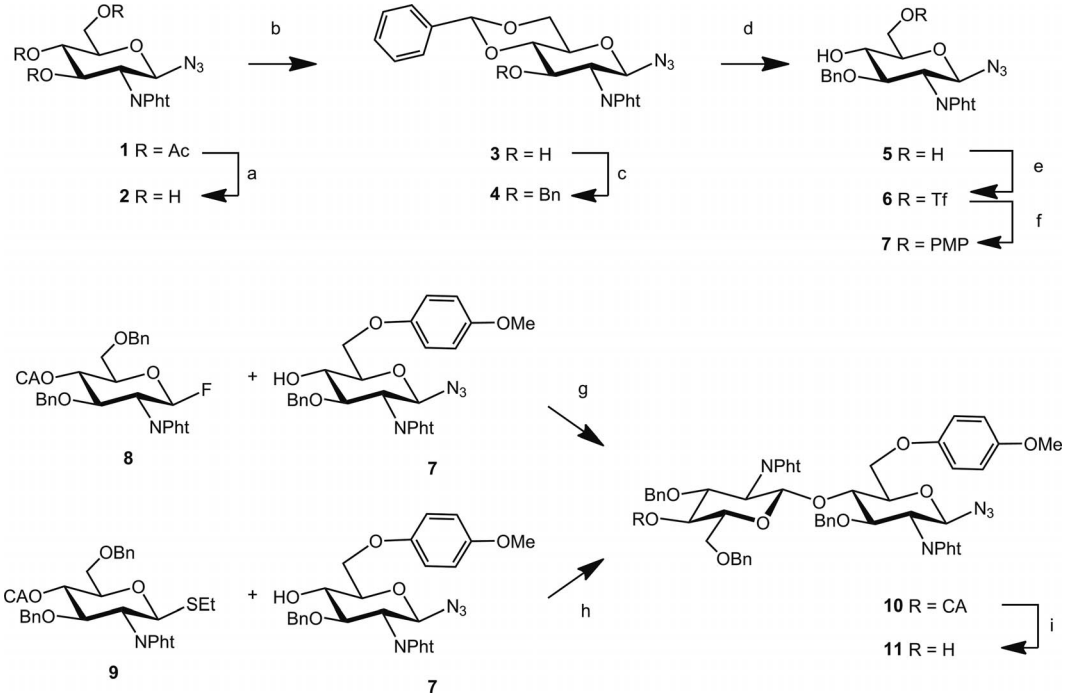


Scheme 1. The chemical synthesis of complex-type N-glycans with a core fucosyl moiety can be accomplished by using modular building blocks **B**–**D**. Core trisaccharide **B** is set up for regio- and stereoselective elongations of the β-mannoside using donor **C** and for core fucosylation (donor **D**) after removal of the *p*-methoxyphenyl group; MPM = *p*-methoxybenzyl.

As the core trisaccharide building block **B** could also be used for the synthesis of core-fucosylated N-glycans bearing an additional bisecting GlcNAc moiety,[14b,15] a more efficient route to **B** was needed. While investigating a large-scale synthesis of **B**, we successfully shortened several key steps of the initial approach,[13] providing improved access to **B** and its derivatives.

The *p*-methoxyphenyl group of the core trisaccharide **B** is selectively cleavable by oxidation, and this allows convenient core fucosylation even at a late stage of the N-glycan synthesis. The presence of an azido group at the reducing end simplifies the attachment of the N-glycan to amino acids or spacers by an amide bond.[21] The highly functionalized GlcNAc building block **7** was envisioned for the re-



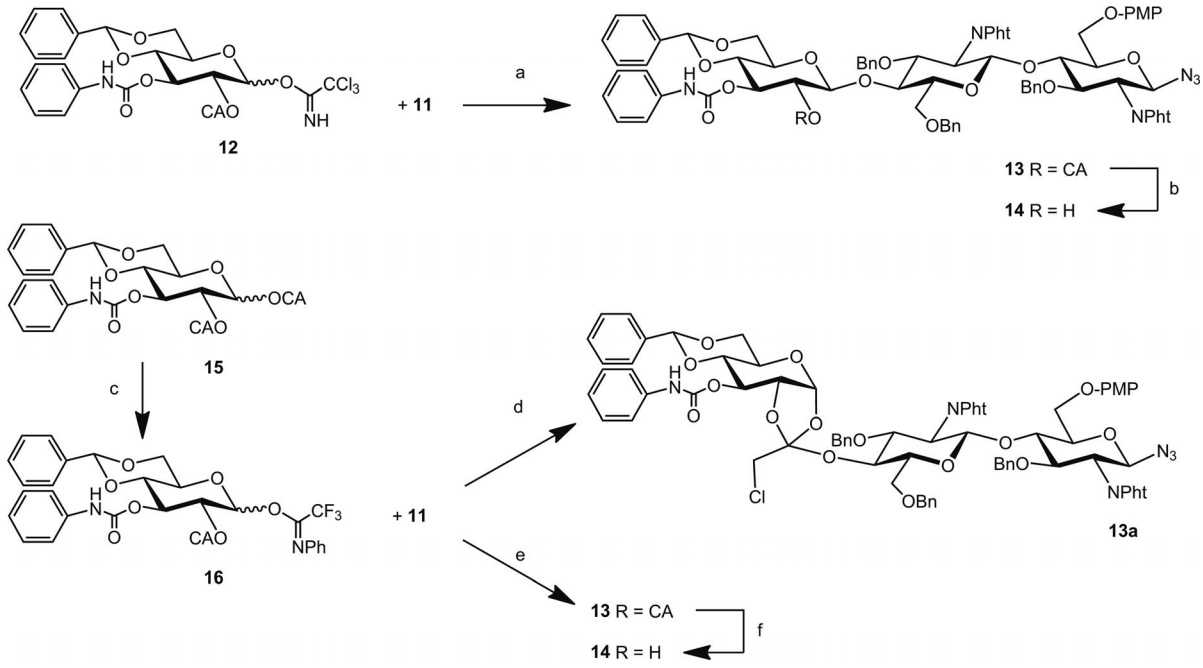
Scheme 2. (a) NaOMe, MeOH, 98%; (b) benzaldehyde dimethyl acetal, *p*TsOH/H_2O, CH_3CN, 78%; (c) BnBr, NaH, DMF, 67%; (d) *p*TsOH/H_2O, CH_2Cl_2, MeOH, H_2O, 85%; (e) Tf_2O, 2,6-lutidine, CH_2Cl_2, –80 °C; (f) *p*-methoxyphenol, 2 N NaOH, aliquat 336; (e)–(f) 89%; (g) $BF_3{\cdot}OEt_2$, CH_2Cl_2; (h) NIS, TfOH, CH_2Cl_2; (i) K_2CO_3, CH_2Cl_2, MeOH; (g) + (i) 87%; (h) + (i) 70%; CA = chloroacetyl.

ducing end (Scheme 2), but initially, it was only accessible by a tedious multistep procedure.[13] In this first-generation approach, a 3-*O*-benzylated glycosyl fluoride intermediate was synthesized, and the *p*-methoxyphenyl group (PMP) was introduced by a Mitsunobu reaction[22] prior to the conversion of the fluoride to the desired azide (i.e., **7**). Carrying out the required conversions in a different order led to a shorter sequence but also to undesired by-products. In particular, the partial halogenation of the *p*-methoxyphenyl group during the transformation of the thioglycoside into a glycosyl fluoride by using the *N*-bromosuccinimide-HF/pyridine method was troublesome.[23] It was found that a halogenated *p*-methoxyphenyl group could still be cleaved by oxidation, but the additional heterogeneity complicated NMR spectroscopy and MS analysis throughout the entire synthesis.

We were thus seeking an improved synthesis of acceptor **7** in which the different protecting groups could be installed in a more direct manner. A short approach was found by starting from readily available azide **1**,[24] requiring only a few protecting-group manipulations. In order to selectively introduce the 3-*O*-benzyl group, the acetates of **1** were removed, followed by 4,6-*O*-benzylidenation. The purified benzylidene acetal (i.e., **3**) was benzylated to give **4**, which could be isolated conveniently on a larger scale by crystallization. After acidic hydrolysis of the benzylidene acetal, the diol (i.e., **5**) was first tosylated at O-6, but nucleophilic substitution of the tosylate with *p*-methoxyphenolate was unsuccessful. Thus, the more reactive 6-triflate was generated at low temperature by using triflic anhydride in the presence of the sterically hindered base 2,6-dimethylpyridine.[25] On warming up, triflate **6** reacted smoothly with aqueous sodium *p*-methoxyphenolate under phase-transfer conditions to give the desired PMP ether **7** in 89% yield in a one-pot reaction. This fast and easily scaleable approach considerably improved the availability of acceptor **7**.

Subsequently, the synthesis of chitobioside **10** was investigated. Use of fluoride **8**[26] and boron trifluoride–diethyl ether as an activator gave a high conversion to disaccharide **10**, but purification at this stage was not practical, since acceptor **7** could not be separated from the product by flash chromatography. After subjecting the crude glycosylation mixture to a mild dechloroacetylation, the separation improved and yielded disaccharide **11** in 87% over two steps. A shorter route to **11** was tried by glycosylation of **7** with thioglycoside **9**.[26] Compound **9** serves as a direct precursor for fluoride **8**, which is difficult to purify on larger scales due to a strong tendency of **8** to crystallize during flash chromatography. Despite the presence of the readily halogenated PMP group in **7**, the mild activation of thioglycoside **9** provided disaccharide **11** in 70% yield overall without by-products. This was accomplished by using only a small excess of NIS in combination with a quenching workup at low temperatures.

The installation of β-mannosides remains a difficult task,[27] and we carried it out by glycosylation with glucosyl donor **12**,[26] followed by an intramolecular inversion according to the methodology developed by Kunz.[28] When promoting the coupling of donor **12** and chitobiosyl acceptor **11** with TMSOTf, trisaccharide **13** appeared to form



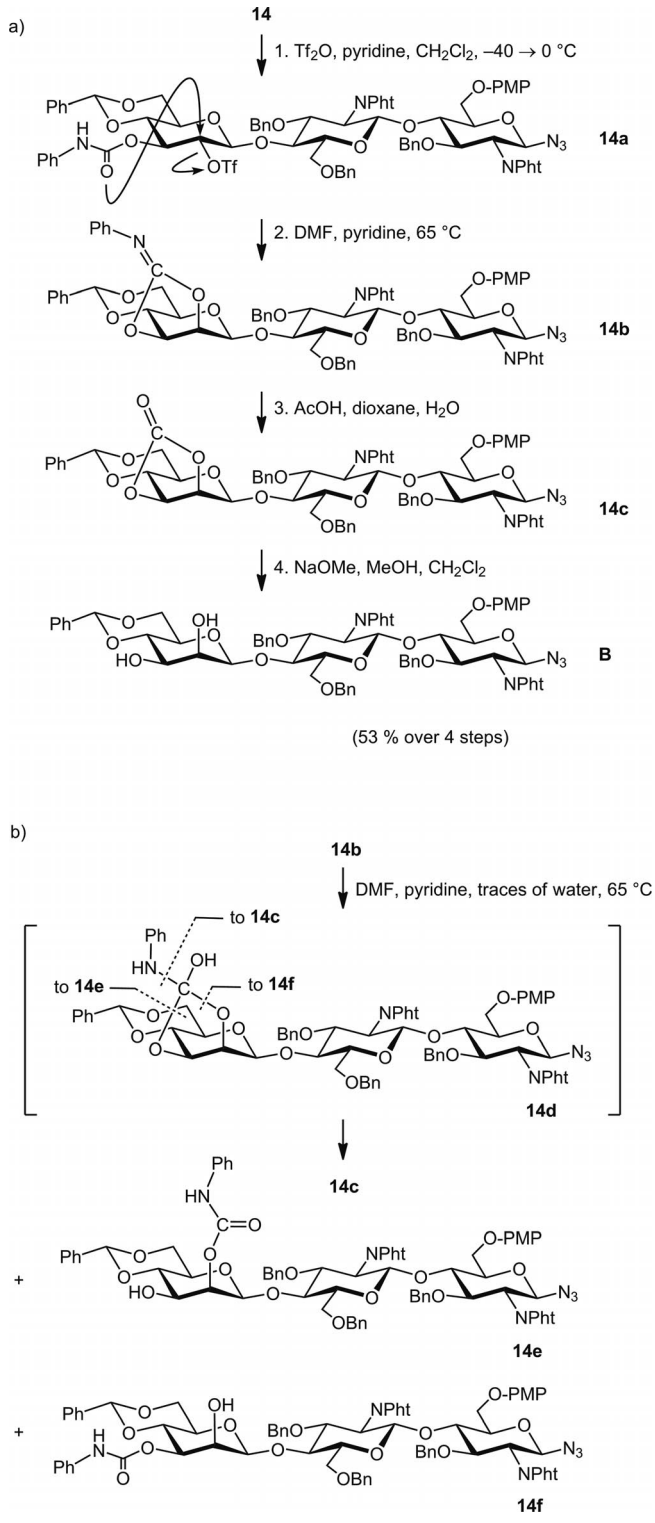
Scheme 3. (a) TMSOTf (0.6 equiv.), CH_2Cl_2, 0 °C, 30 min; 23 °C, 4 h; (b) K_2CO_3, CH_2Cl_2, MeOH; (a)–b) 50%; (c) (1) hydrazine acetate, DMF, 0 °C, 71%, (2) CF_3(C=NPh)Cl, DBU, CH_2Cl_2, 0 °C, 92%; (d) TMSOTf (0.05 equiv.), CH_2Cl_2, 0 °C, 75%; (e) (1) TMSOTf (0.05 equiv.), CH_2Cl_2, 0 °C, 40 min, (2) TfOH, CH_2Cl_2, 0 °C, 40 min, 89%; (f) K_2CO_3, CH_2Cl_2, MeOH; (e)–(f) 89%; PMP = *p*-methoxyphenyl.

readily (Scheme 3). The isolation of the trisaccharide required a dechloroacetylation step to give **14**, which improved the separation from unreacted acceptor **11**. However, the final yields of **14** were variable and rarely exceeded 50%. This led us to the assumption that the reaction might proceed through a stable orthoester intermediate, since it appeared to be essential to stir the glycosylation reaction mixture at room temperature for some time if reasonable yields were to be achieved. The formation of orthoesters by using 3-*O*-phenylcarbamoylated glucosyl donors was described by Kunz[28a] and has similarly been observed for a 2,3-di-*O*-chloroacetylated thioglucoside donor,[29] which also served as a precursor for a β-mannoside. As an alternative glucosyl donor, we synthesized *N*-phenylimidate **16**[30] from precursor **15**.[26] Donor **16** showed a rapid reaction with **11** to give an orthoester intermediate, which slowly reacted to form the desired trisaccharide (i.e., **13**). In this case, the conversion could be monitored by TLC and HPLC-MS. When the reaction temperature was kept below 0 °C and only a minimal amount of TMSOTf (0.05 equiv.) was used, the reaction yielded mainly orthoester **13a**.

Orthoester **13a** could be purified by flash chromatography, and data from its ^{1}H and ^{13}C NMR spectra, i.e., $J_{1,2}$ = 5.5, $J_{C\text{-}1,H\text{-}1}$ = 192 Hz and a downfield ^{13}C shift of the glucose C-2 to δ = 78.2 ppm, were consistent with the glucose orthoester structure. After confirming the presence of an orthoester in **13a**, we attempted to improve its conversion to β-glucosyl trisaccharide **13** by directly isomerizing the orthoester in situ. This required several rounds of optimization, which were followed by HPLC-MS. Acceptor **11** was quickly converted into orthoester **13a** when using 0.05 equiv. of TMSOTf at 0 °C. The most effective in situ rearrangement conditions for orthoester **13a** were found to be the subsequent addition of triflic acid (0.4 equiv.) to the reaction mixture. The overall glycosylation sequence was prone to side-reactions, which only occurred when leaving the temperature window of 0–5 °C, when adding too much TfOH for the rearrangement, or when using TfOH for both the activation and the isomerization steps. When the glycosylation was promoted by TMSOTf alone, a significant amount of silylated acceptor formed, which reduced the total yield. By using the optimized conditions for the β-glucosylation of chitobiosyl acceptor **11**, the isolated yield of trisaccharide **14** reproducibly increased from 50 to 89%.

We next investigated the conversion of β-glucoside **14** to β-mannoside **B**. The multistep inversion procedure gave variable yields in our hands. As depicted (Scheme 4a), the intramolecular inversion from the *gluco* to the *manno* configuration is initiated by formation of a secondary triflate using triflic anhydride/pyridine.

According to the published procedure,[28a] the triflate **14a** was heated in DMF/pyridine leading to an intramolecular attack by the carbonyl oxygen atom of the carbamate. The resulting cyclic iminocarbonate (i.e., **14b**) was usually accompanied by some hydrolysis product **14c**. Mild acidic hydrolysis of iminocarbonate **14b** completed the conversion to carbonate **14c** without affecting the benzylidene acetal. The cyclic carbonate was removed by methanolysis under weakly basic conditions to give the desired β-mannosyl trisaccharide (i.e., **B**) in 53% yield. The β-*manno* configuration of core trisaccharide **B** was confirmed by a C-1,H-1 coupling constant of 163 Hz, which is typical for this link-



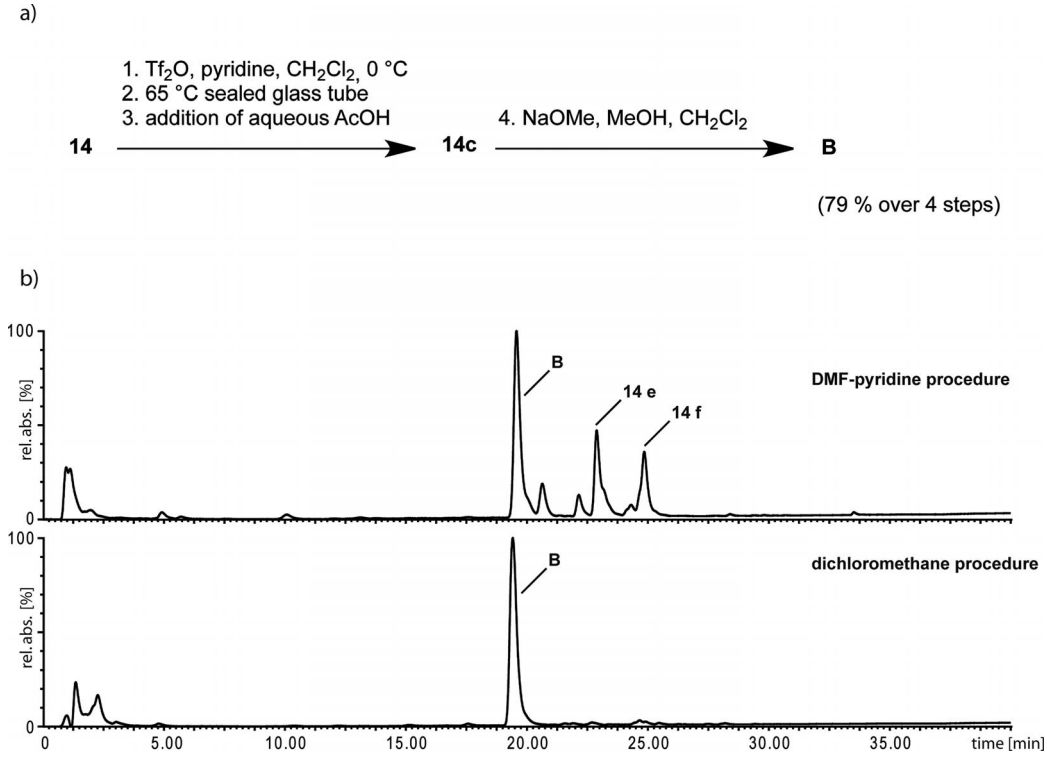
Scheme 4. (a) Four-step inversion sequence of *gluco*-configured trisaccharide **14** to β-mannoside **B**. (b) Traces of water can lead to undesired ring-opening of cyclic iminocarbonate **14b** in DMF/pyridine.

age.[31] The reported yield for the corresponding inversion sequence on a disaccharide was much higher.[28a] Since the four reactions can be performed in a one-pot manner, a significant loss of product could be due to side-reactions. We noticed the occurrence of by-products with an R_f value close to that of the starting material (i.e., **14**). After methanolysis, these by-products could be isolated by flash chromatography; their ^{1}H NMR spectrum revealed a complex mixture with no starting material **14** present. This indicated that hydrolysis of the triflate in **14a** to give **14** had not taken place under the reaction conditions, and that the by-products should thus derive from triflate **14a** or the ensuing intermediates.

According to HPLC-MS, the two major by-products had the same mass as trisaccharide **14**. After purification of these by-products by HPLC, they were structurally characterized by a series of 2D-NMR experiments.[32] The complete NMR assignments indicated that two isomeric β-*manno*-configured carbamates **14e** and **14f** had formed in a 1:1 ratio (Scheme 4b). These by-products may arise through base-catalyzed ring opening of the cyclic iminocarbonate in **14b**.[33] In the presence of trace amounts of water, labile tetrahedral intermediate **14d** can form, and this can lead either to hydrolysis of the imine (forming **14c**) or to ring-opening. The latter process can generate the two regioisomeric phenylcarbamates (i.e., **14e**,**f**) of the *manno*-configured core trisaccharide.

The pH-dependent ring-opening of cyclic *N*-phenyliminocarbonate model compounds has been studied in detail.[33] It was found that hydrolysis of the imine bond occurred only at pH < 6, whereas more basic conditions gave increasing amounts of carbamates. The reaction conditions during the inversion of **14a** in DMF/pyridine can be considered to be weakly basic, which mainly resulted in hydrolysis to **14c**, but also led to a pH-dependent fraction of carbamates **14e**,**f**.

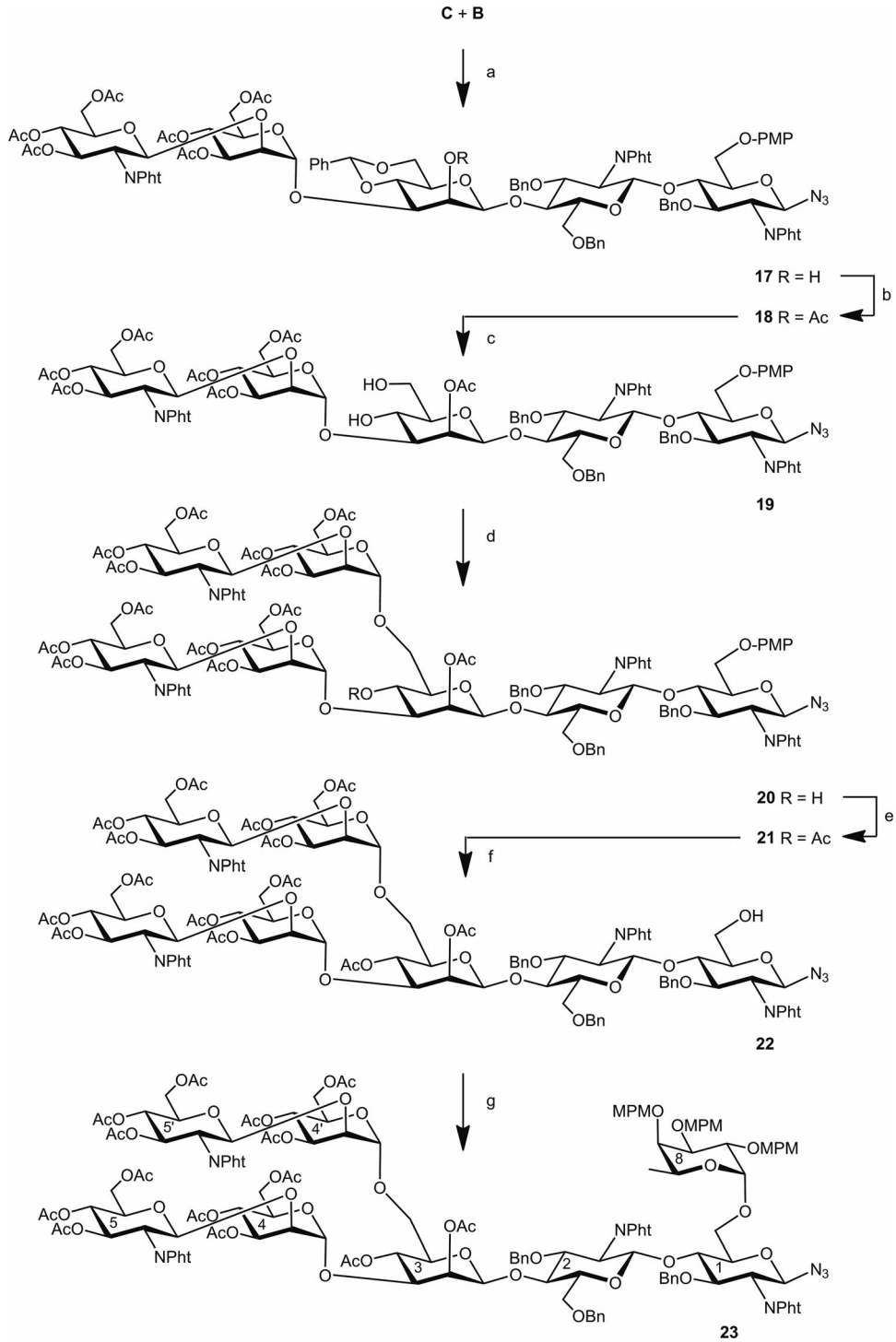
We then searched for an inversion protocol that would minimize these side-reactions by screening alternative solvents (dichloromethane, acetonitrile, THF). Evaluation by HPLC-MS suggested dichloromethane to be a promising solvent; however, the reaction rate of the inversion was low, even under refluxing conditions. When utilizing a pressure-stable glass vial, the sample could be heated to 65 °C, and the reaction proceeded to completion within 21 h. According to HPLC-MS, the inversion of crude **14a** in dichloromethane gave almost exclusively the desired iminocarbonate (i.e., **14b**), which hydrolyzed to the desired carbonate (i.e., **14c**) under TLC or LC-MS conditions. The formation of very small quantities of by-products can be attributed to the anhydrous conditions of the inversion step and the sufficiently acidic conditions during controlled hydrolysis at room temperature. We also tried to avoid the pressure-stable vial by using the higher boiling solvents chloroform or 1,2-dichloroethane for triflate formation, followed by heating to 65 °C using a reflux condenser plugged by a balloon for pressure equilibration. Disappointingly, by-products **14e** and **14f** were formed in amounts similar to those of the DMF/pyridine procedure. This outcome may be attributed to traces of water, which were not rigorously excluded in this unsealed approach.



Scheme 5. (a) Optimized conditions for the inversion of **14**. (b) HPLC comparison of crude **B** obtained after standard inversion in DMF/pyridine or optimized inversion conditions in CH_2Cl_2.

The one-pot protocol was thus simplified by generating the triflate **14a** in dichloromethane, followed by an in situ inversion in the same solvent at elevated temperature (Scheme 5a). An increased amount of sodium methoxide during removal of the cyclic carbonate prevented the formation of methyl carbonate intermediates. Under these conditions, the optimized four-step inversion protocol gave only trace amounts of by-products, which is clear when comparing the HPLC profiles of the different inversion procedures (Scheme 5b). The decrease in the amount of by-products raised the final yield of **B** from 53 to 79%.

With sufficient quantities of core trisaccharide **B** prepared, the attachment of the two antennae was investigated. Elongation with trichloroacetimidate donor **C**[34] proceeded



Scheme 6. (a) $BF_3{\cdot}OEt_2$, CH_2Cl_2, 79%; (b) Ac_2O, pyridine; (c) *p*TsOH/H_2O, CH_3CN; (b)–(c) 80%; (d) **C**, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 73%; (e) Ac_2O, pyridine; (f) CAN, toluene, CH_3CN, water; (e)–(f) 90%; (g) **D**, $CuBr_2$, Bu_4NBr, DMF, CH_2Cl_2, 85% after flash chromatography, 77% after HPLC.

in a regio- and steroselective manner to give the desired α1,3-linked pentasaccharide **17** with a $J_{C\text{-}1,H\text{-}1}$ value of 173.8 Hz for the newly established α-mannosidic linkage (Scheme 6). Activation of trichloroacetimidate[35] **C** by using boron trifluoride–diethyl ether is fully compatible with the presence of the PMP group in the acceptor and did not lead to glycosylation at multiple sites. After acetylation of OH-2[3], intermediate pentasaccharide **18** was debenzylidenated directly. The resulting diol (i.e., **19**) was treated with donor **C** in a second regio- and stereoselective reaction to give biantennary heptasaccharide **20**, as indicated by a $J_{C\text{-}1,H\text{-}1}$ value of 173.5 Hz for the 1,6-linked α-mannoside. The remaining 4-hydroxy group of the β-mannoside was acetylated in order to prevent fucosylation at this position. Oxidative removal of the PMP group[36] was carried out by using cerium(IV) ammonium nitrate (CAN) under biphasic conditions.[37] Heptasaccharide acceptor **22** was then fucosylated with *p*-methoxybenzyl-protected thiofucoside **D**[38] by using $CuBr_2$ in combination with tetrabutylammonium bromide in DMF/CH_2Cl_2.[39] Careful HPLC-MS analysis showed that the desired α-fucosylated octasaccharide was accompanied by some β-anomer (α/β ratio 7:1). The formation of β-fucosides has also been noted by others when primary alcohols were used as acceptors.[17b,18] Despite intensive attempts to separate the anomers by flash chromatography, an HPLC purification was required at this stage by using either a C8 reverse-phase column and an acetonitrile/water gradient or a diol column with ethyl acetate/hexane as the eluent. The final yields of pure α-anomer **23** were 68 and 77%, respectively, by these two purification methods. After deprotection, the core-fucosylated octasaccharide was coupled to a spacer and elongated enzymatically.[21] These conjugates were incorporated into neoglycoproteins, which were used for biological studies focusing on the role of core fucosylation.[7]

Conclusions

We have optimized the synthesis of a biantennary core-fucosylated N-glycan of the complex type. The key building block is a selectively functionalized core trisaccharide, which allows high-yielding glycosylations of the β-mannoside in a modular way, and permits fucosylation at any desired stage of the synthesis. The optimizations were guided by mechanistic analysis, and resulted in robust protocols suitable for large-scale synthesis of this versatile core trisaccharide.

Experimental Section

General Methods: Solvents were dried according to standard methods. Molecular sieves were activated prior to use by heating under high vacuum. Optical rotations were measured with a Perkin–Elmer 241 polarimeter at 589 nm. NMR spectra were recorded with Bruker AC 250, Avance 360, AMX 500 and DMX 500 instruments or a Jeol JNM-EX-270 spectrometer. Coupling constants are reported in Hz. The compounds were clearly characterized by full assignment of the ^1H and ^{13}C resonances from a set of 1D and 2D NMR experiments.[32] For mass spectra, a Varian CH5 instrument was used in the fast atom bombardment mode (FAB) with an *m*-nitrobenzyl alcohol matrix (NBA). ESI-TOF mass spectra were recorded with a Micromass LCT instrument coupled to an Agilent 1100 HPLC apparatus. Flash chromatography was performed on silica gel 60, (230–400 mesh, Merck Darmstadt). The reactions were monitored by thin layer chromatography on coated aluminum plates (silica gel 60 GF_{254}, Merck Darmstadt). Spots were detected by UV light or by charring with a 1:1 mixture of 2 N H_2SO_4/0.2% resorcinol monomethyl ether in ethanol.

2-Deoxy-2-phthalimido-β-D-glucopyranosyl Azide (2): A solution of sodium (0.72 g, 31.3 mmol) dissolved in absolute methanol (68 mL) was added to a suspension of azide **1** (78.2 g, 169.9 mmol) in absolute methanol (670 mL). The mixture was stirred at room temperature under argon for 25 min. After complete reaction (TLC: cyclohexane/acetone, 1:1), the pH was adjusted to 6–7 by adding Amberlyst® 15. The mixture was filtered, the solvent was removed in vacuo, and the residue was dried under high vacuum to give crude **2** (55.9 g, 98.4%). R_f = 0.29 (cyclohexane/acetone, 1:1). $[\alpha]_D^{23}$ = –31.5 (*c* = 1.0, CH_3OH). ^1H NMR (270 MHz, [D$_6$]DMSO): δ = 7.94–7.87 (m, 4 H, Pht), 5.54 (d, $J_{OH,3}$ = 4.9 Hz, 1 H, 3-OH), 5.33 (d, $J_{1,2}$ = 9.5 Hz, 1 H, 1-H), 5.30 (d, $J_{OH,4}$ = 7.3 Hz, 1 H, 4-OH), 4.73 (dd, $J_{OH,6}$ = 5.7 Hz, 1 H, 6-OH), 4.08 (m, 1 H, 3-H), 3.79–3.68 (m, 2 H, 6a-H, 2-H), 3.54 (m, 1 H, 6b-H), 3.43 (m, 1 H, 5-H), 3.27 (m, 1 H, 4-H) ppm. ^{13}C NMR (68 MHz, [D$_6$]DMSO): δ = 168.4 (C=O), 168.1 (C=O), 135.4 (Pht), 135.3 (Pht), 131.8 (Pht-C_q), 131.5 (Pht-C_q), 124.0 (Pht), 123.8 (Pht), 85.8 (C-1), 80.2 (C-5), 70.9 (C-3), 70.6 (C-4), 61.1 (C-6), 57.2 (C-2) ppm. ESI-MS: *m*/*z* = 357.23 [M + Na]$^+$.

4,6-*O*-Benzylidene-2-deoxy-2-phthalimido-β-D-glucopyranosyl Azide (3): Benzaldehyde dimethyl acetal (83.5 mL, 559.6 mmol) and *p*-toluenesulfonic acid monohydrate (0.72 g, 3.79 mmol) were added to a suspension of crude triol **2** (53.6 g, 160.3 mmol) in anhydrous acetonitrile (560 mL) under argon. Undissolved starting material was solubilized by sonicating the reaction mixture in an ultrasonic bath. After stirring at room temperature for 15 min, *p*-toluenesulfonic acid monohydrate (3.20 g, 16.8 mmol) was added, and the reaction mixture was stirred for 90 min. After complete reaction (TLC: cyclohexane/acetone, 2:1), the pH was adjusted to a value of 9 by adding triethylamine (4.0 mL, 28.9 mmol). After removing the solvent in vacuo, the residue was diluted with CH_2Cl_2 (1.5 L). The organic phase was washed with water (1 L), dried with $MgSO_4$ and concentrated. The residue was purified by flash chromatography (cyclohexane/acetone, 9:1→5:1→2:1) to give **3** (52.8 g, 78.0%). R_f = 0.36 (cyclohexane/acetone, 2:1). $[\alpha]_D^{24}$ = –43.9 (*c* = 1.0, $CHCl_3$). ^1H NMR (270 MHz, [D$_6$]DMSO): δ = 7.97–7.88 (m, 4 H, Pht), 7.48–7.37 (m, 5 H, Ar), 5.84 (d, $J_{3,OH}$ = 5.2 Hz, 1 H, 3-OH), 5.68 (s, 1 H, PhC*H*=), 5.54 (d, $J_{1,2}$ = 9.6 Hz, 1 H, 1-H), 4.42–4.28 (m, 2 H, 3-H, 6a-H) 3.91–3.63 (m, 4 H, 2-H, 6b-H, 5-H, 4-H) ppm. ^{13}C NMR (68 MHz, [D$_6$]DMSO): δ = 167.7, 167.3 (C=O), 137.4 (C_q), 134.9 (Pht), 131.2, 130.8 (C_q), 129.0, 128.1, 126.3 (Ar), 123.5, 123.3 (Pht), 100.8 (Ph*C*H=), 85.7 (C-1), 80.6 (C-4), 68.4 (C-5), 67.4 (C-6), 67.1 (C-3), 56.9 (C-2) ppm. ESI-MS: *m*/*z* = 439.37 [M + NH_4]$^+$, 444.32 [M + Na]$^+$.

4,6-*O*-Benzylidene-3-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl Azide (4): Benzyl bromide (30.1 mL, 248.3 mmol) was added to a solution of benzylidene acetal **3** (50.0 g, 118.4 mmol) in anhydrous *N*,*N*-dimethylformamide (106 mL) under argon. The reaction mixture was cooled to 0 °C, and sodium hydride (60% dispersion in mineral oil, 8.05 g, 201.3 mmol) was added in portions. The mixture was stirred at 0 °C for 1.5 h, followed by stirring at room temperature for 2 h. After complete reaction (TLC: cyclohexane/ace-

tone, 1.5:1), the pH was adjusted to 7–8 by adding acetic anhydride (46.8 mL, 499.7 mmol), and the mixture was then stirred at room temperature for 1 h. The solvents were removed in vacuo, and the residue was dissolved in CH_2Cl_2 (1 L), washed with water (1 L), dried with $MgSO_4$, and concentrated in vacuo. Recrystallization from diethyl ether gave crystalline **4** (34.07 g). The mother liquor was concentrated and purified by flash chromatography (CH_2Cl_2/acetone, 100:1) to give additional **4** (6.66 g). The total yield of **4** was 40.73 g (67.1%). R_f = 0.56 (cyclohexane/acetone, 1.5:1); R_f = 0.62 (CH_2Cl_2/acetone, 100:1). M.p. 133–136 °C. $[\alpha]_D^{24}$ = +39.7 (c = 1.0, $CHCl_3$). ^{1}H NMR (270 MHz, [D$_6$]DMSO): δ = 7.89–7.80 (m, 4 H, Pht), 7.51–7.38 (m, 5 H, Ar), 7.00–6.86 (m, 5 H, Ar), 5.79 (s, 1 H, =CHPh), 5.57 (d, $J_{1,2}$ = 9.4 Hz, 1 H, 1-H), 4.71 (d, J_{gem} = 12.2 Hz, 1 H, CH_2O), 4.41 (d, J_{gem} = 12.2 Hz, 1 H, CH_2O), 4.36–4.32 (m, 2 H, 3-H, 6a-H), 4.01–3.86 (m, 3 H, 2-H, 4-H, 6b-H), 3.77 (m, 1 H, 5-H) ppm. ^{13}C NMR (68 MHz, [D$_6$]DMSO): δ = 167.1 (C=O), 137.6 (C_q), 137.3 (C_q), 134.9 (Pht), 130.6, (C_q), 128.9, 128.2, 127.9, 127.5, 127.4, 126.0 (Ar), 123.5 (Pht), 100.2 (=CHPh), 85.6 (C-1), 81.3 (C-4), 74.3 (C-3), 73.3 (CH_2O), 67.8 (C-5), 67.4 (C-6), 54.6 (C-2) ppm. ESI-MS: m/z = 535.27 [M + Na]$^+$, 551.25 [M + K]$^+$, 1047.55 [2 M + Na]$^+$.

3-*O*-Benzyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl Azide (5): *p*-Toluenesulfonic acid monohydrate (38.0 g, 200 mmol) was added to a solution of **4** (22.33 g, 43.6 mmol) in a mixture of absolute CH_2Cl_2 and absolute methanol (1:1, 700 mL). After stirring at room temperature for 15 min, water (2 mL) and *p*-toluenesulfonic acid monohydrate (23.9 g, 126 mmol) were added. The mixture was stirred for 1.5 h, and then more water (9 mL) was added. After 1.5 h (TLC: cyclohexane/ethyl acetate, 1.5:1), the pH was adjusted to 7 by adding triethylamine (17.8 mL). The solvent was removed in vacuo, and the residue was dried under high vacuum. The crude product was purified by flash chromatography (cyclohexane/ethyl acetate, 3:1→1:1→1:3→100% ethyl acetate) to give **5** (15.80 g, 85.4%). R_f = 0.34 (cyclohexane/ethyl acetate, 1:1.5). $[\alpha]_D^{24}$ = +22.3 (c = 1.0, $CHCl_3$). ^{1}H NMR (270 MHz, [D$_6$]DMSO): δ = 7.87–7.76 (m, 4 H, Pht), 6.96–6.84 (m, 5 H, Ar), 5.64 (d, $J_{OH,4}$ = 6.2 Hz, 1 H, 4-OH), 5.38 (d, $J_{1,2}$ = 9.4 Hz, 1 H, 1-H), 4.79 (dd, $J_{OH,6a,b}$ = 5.6 Hz, 1 H, 6-OH), 4.76 (d, J_{gem} = 12.2 Hz, 1 H, CH_2O), 4.42 (d, J_{gem} = 12.2 Hz, 1 H, CH_2O), 4.11 (dd, $J_{2,3}$ = 10.4, $J_{3,4}$ = 7.6 Hz, 1 H, 3-H), 3.84–3.75 (m, 2 H, 2-H, 6a-H), 3.64–3.46 (m, 3 H, 6b-H, 4-H, 5-H) ppm. ^{13}C NMR (68 MHz, [D$_6$]DMSO): δ = 167.4 (C=O), 167.1 (C=O), 138.2 (C_q), 134.8 (Pht), 130.6, (C_q), 127.8, 127.3, 127.1 (Ar), 123.4 (Pht), 85.1 (C-1), 79.4 (C-5), 78.3 (C-3), 73.5 (CH_2O), 70.9 (C-4), 60.2 (C-6), 54.7 (C-2) ppm. ESI-MS: m/z = 442.28 [M + NH$_4$]$^+$, 447.21 [M + Na]$^+$, 866.40 [2 M + NH$_4$]$^+$, 871.36 [2 M + Na]$^+$.

3-*O*-Benzyl-2-deoxy-6-*O*-(*p*-methoxyphenyl)-2-phthalimido-β-D-glucopyranosyl Azide (7): A solution of diol **5** (6.3 g, 14.8 mmol) and 2,6-lutidine (14.0 mL, 118.2 mmol) in absolute CH_2Cl_2 (350 mL) was cooled to –80 °C under argon. Trifluoromethanesulfonic anhydride (4.13 mL, 24.7 mmol) was added dropwise, and after 20 min, the starting material had been completely converted into the triflate **6** (TLC: hexane/acetone, 1.2:1). Subsequently, dilute NaOH (2 N, 105 mL), *p*-methoxyphenol (12.8 g, 103.0 mmol) and phase-transfer catalyst aliquat 336 (3.5 mL) were added separately, and the reaction mixture was allowed to gradually warm up to room temperature whilst being stirred. After 5 h of vigorous stirring, more *p*-methoxyphenol (1.0 g, 8.1 mmol) was added, and after a further 30 min, complete consumption of **6** was observed (TLC: hexane/acetone, 1.5:1). The reaction mixture was washed with dilute HCl and dilute $KHCO_3$ solution. The organic phase was dried with $MgSO_4$, concentrated, and purified by flash chromatography (hexane/ethyl acetate, 4:1→3:1→1:1→1:2) to give **7** (7.0 g, 88.9%). R_f = 0.49 (hexane/acetone, 1.5:1). $[\alpha]_D^{21}$ = +14.0 (c = 0.2, CH_2Cl_2). ^{1}H NMR (270 MHz, [D$_6$]DMSO): δ = 7.90–7.70 (m, 4 H, Pht), 7.00–6.85 (m, 9 H, PMP, Ph), 5.90 (d, $J_{4,OH}$ = 7.1 Hz, 1 H, 4-OH), 5.48 (d, $J_{1,2}$ = 9.4 Hz, 1 H, 1-H), 4.80 (d, J_{gem} = 12.0 Hz, 1 H, OCH_2), 4.44 (d, J_{gem} = 12.0 Hz, 1 H, OCH_2), 4.30–4.10 (m, 3 H, 6a-H, 3-H, 6b-H), 3.92–3.82 (m, 2 H, 2-H, 5-H), 3.75–3.62 (m, 4 H, OCH_3, 4-H) ppm. ^{13}C NMR (68 MHz, [D$_6$]DMSO): δ = 167.40 (C=O), 153.55, 152.54 (C-*i* PMP, C-4 PMP), 138.15 (C-*i* Ph), 134.79 (C-4/5 Pht), 130.66 (C-1/2 Pht), 127.79, 127.36 (C-2/6 Ph, C-3/5 Ph), 127.18 (C-4 Ph), 123.42 (C-3/6 Pht), 115.63, 114.69 (C-2/6 PMP, C-3/5 PMP), 85.10 (C-1), 78.25 (C-3), 76.94 (C-5), 73.67 (OCH_2), 70.98 (C-4), 67.56 (C-6), 55.30 (OCH_3), 54.60 (C-2) ppm. ESI-MS: m/z = 548.64 [M + NH$_4$]$^+$, 553.63 [M + Na]$^+$.

3,6-Di-*O*-benzyl-4-(chloroacetyl)-2-deoxy-2-phthalimido-β-D-glucopyranosyl-(1→4)-3-*O*-benzyl-2-deoxy-6-*O*-(*p*-methoxyphenyl)-2-phthalimido-β-D-glucopyranosyl Azide (10) and 3,6-Di-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl-(1→4)-3-*O*-benzyl-2-deoxy-6-*O*-(*p*-methoxyphenyl)-2-phthalimido-β-D-glucopyranosyl Azide (11)

Method A (via Fluoride 8): A suspension of azide **7** (3.23 g, 6.1 mmol), fluoride **8** (4.5 g, 7.9 mmol), and freshly activated ground molecular sieves (4 Å) (5.4 g) in absolute CH_2Cl_2 (80 mL) was stirred for 60 min. Subsequently, boron trifluoride–diethyl ether (0.37 mL, 2.9 mmol) was added. After 90 min (TLC: hexane/acetone, 2:1), the suspension was diluted with CH_2Cl_2, filtered through Celite and washed with dilute $KHCO_3$ solution. The organic phase was dried with $MgSO_4$ and concentrated. The crude mixture was subjected to dechloroacetylation since the acceptor could not be removed efficiently at this stage. R_f(**10**) = 0.24 (hexane/acetone, 2:1).

The crude mixture containing **10** was dissolved in absolute CH_2Cl_2 (160 mL) and absolute methanol (80 mL). Ground K_2CO_3 (1.6 g) was added, and the suspension was stirred for 10 min (TLC: CH_2Cl_2/methanol, 80:1). The solids were filtered off, and the filtrate was adjusted to a pH of 5–6 with acetic acid (0.6 mL) and then concentrated in vacuo. The residue was purified by flash chromatography (hexane/acetone, 2.5:1) to give **11** (5.32 g, 87.3% over two steps). R_f = 0.20 (hexane/acetone, 2:1). $[\alpha]_D^{22}$ = +28.6 (c = 1, CH_2Cl_2).

Method B (via Thioglycoside 9): A suspension of azide **7** (1.83 g, 3.45 mmol), thioglycoside **9** (2.74 g, 4.5 mmol), and freshly activated ground molecular sieves (4 Å) (4.76 g) in absolute CH_2Cl_2 (59 mL) was cooled to –30 °C. *N*-Iodosuccinimide (0.97 g, 4.3 mmol) was added, and the mixture was stirred for 30 min. Trifluoromethanesulfonic acid (55 μL, 0.6 mmol) was added, and stirring was continued for 30 min at –35 to –30 °C (TLC: toluene/acetone, 8:1). The reaction was stopped by filtering the suspension through Celite into a stirred solution of sodium thiosulfate (10%, cooled to 0 °C). The aqueous phase was extracted with CH_2Cl_2, and the combined organic extracts were washed with dilute $KHCO_3$ solution and dried with $MgSO_4$. The solvent was removed, and the residue was dried under high vacuum to give 4.43 g of residue, which was used in the following reaction without further purification. R_f(**10**) = 0.52, (toluene/acetone, 8:1). ESI-MS: m/z = 1095.57 [M + NH$_4$]$^+$, 1100.53 [M + Na]$^+$, 1116.56 [M + K]$^+$.

The residue (4.43 g) was dissolved in absolute CH_2Cl_2 (93 mL) and absolute methanol (48 mL) under argon. Ground K_2CO_3 (0.95 g), which had been activated prior to use by heating under high vacuum, was added. The mixture was stirred for 30 min (TLC: toluene/acetone, 8:1), and then the K_2CO_3 was removed by filtration through Celite. The pH of the filtrate was adjusted to 6–7 by adding acetic acid (0.12 mL). After concentration in vacuo, the residue was

purified by flash chromatography (cyclohexane/acetone, 5:1→3:1) to give **11** (2.42 g, 70.1% over two steps). R_f = 0.40 (toluene/acetone, 8:1), R_f = 0.50 (hexane/acetone, 1.5:1). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 7.85–7.70 (m, 8 H, Pht), 7.33–7.24 (m, 7 H, Ar), 6.99–6.71 (m, 12 H, Ar), 5.63 (d, $J_{4,OH}$ = 7.2 Hz, 1 H, 4^2-OH), 5.34 (d, $J_{1,2}$ = 9.5 Hz, 1 H, 1^1-H), 5.22 (d, $J_{1,2}$ = 8.2 Hz, 1 H, 1^2-H), 4.84 (d, J_{gem} = 12.3 Hz, 1 H, OCH$_2$), 4.74 (d, J_{gem} = 12.1 Hz, 1 H, OCH$_2$), 4.63 (d, J_{gem} = 12.3 Hz, 1 H, OCH$_2$), 4.52 (d, 1 H, OCH$_2$), 4.38 (d, 1 H, OCH$_2$), 4.36 (d, 1 H, OCH$_2$), 4.22–4.14 (m, 2 H, 4^1-H, 3^1-H), 4.03 (dd, $J_{2,3}$ = 9.5, $J_{3,4}$ = 8.2 Hz, 1 H, 3^2-H), 3.98–3.95 (m, 2 H, 2^2-H, 6a^1-H), 3.88–3.78 (m, 4 H, 6a^2-H, 2^1-H, 6b^1-H, 5^1-H), 3.72 (s, 3 H, OCH$_3$), 3.58 (dd, $J_{5,6b}$ = 5.5, J_{gem} = 11.0 Hz, 1 H, 6b^2-H), 3.49–3.41 (m, 2 H, 4^2-H, 5^2-H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 167.9, 167.5, 167.1 (C=O), 153.7, 151.8 (C-*i* PMP, C-4 PMP), 138.2, 138.0, 137.3 (C-*i* Ph), 134.9 134.7 (C-4/5 Pht), 130.7, 130.6 (C-1/2 Pht), 128.2, 127.9, 127.8, 127.4, 127.2 (C-2/6 Ph, C-3/5 Ph, C-4 Ph), 123.5, 123.3 (C-3/6 Pht), 115.5, 114.6 (C-2/6 PMP, C-3/5 PMP), 96.3 (C-1^2), 84.8 (C-1^1), 78.5 (C-3^2), 76.2 (C-3^1, C-5^2), 75.0 (C-5^1), 74.6 (C-4^1), 73.5 (OCH$_2$), 72.3 (OCH$_2$), 71.6 (C-4^2), 69.0 (C-6^2), 66.3 (C-6^1), 55.9 (C-2^2), 55.3 (OCH$_3$), 54.5 (C-2^1) ppm. ESI-MS: *m*/*z* = 1024.43 [M + Na]$^+$. $C_{56}H_{51}N_5O_{13}$ (1002.0): calcd. C 67.12, H 5.13, N 6.99; found C 67.34, H 5.24, N 6.59.

4,6-*O*-Benzylidene-2-*O*-(chloroacetyl)-3-(phenylcarbamoyl)-β-D-glucopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl-(1→4)-3-*O*-benzyl-2-deoxy-6-*O*-(*p*-methoxyphenyl)-2-phthalimido-β-D-glucopyranosyl Azide (13) and 4,6-*O*-Benzylidene-3-(phenylcarbamoyl)-β-D-glucopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl-(1→4)-3-*O*-benzyl-2-deoxy-6-*O*-(*p*-methoxyphenyl)-2-phthalimido-β-D-glucopyranosyl Azide (14)

Method A (via Donor 12): A suspension of disaccharide azide **11** (4.36 g, 4.4 mmol), imidate **12** (5.76 g, 9.5 mmol), and freshly activated ground molecular sieves (4 Å) (5.0 g) in absolute CH_2Cl_2 (180 mL) was stirred at 0 °C for 30 min. Subsequently, TMSOTf (470 μL, 2.6 mmol) was added. The reaction mixture was allowed to warm to ambient temperature, and then stirred for an additional 4 h (TLC: cyclohexane/acetone, 1.5:1), diluted with CH_2Cl_2, and filtered through Celite. After washing with dilute $KHCO_3$ solution, the organic phase was dried with $MgSO_4$ and concentrated in vacuo. The crude mixture was directly subjected to dechloroacetylation since the product could not be purified efficiently at this stage. R_f(**13**) = 0.45 (cyclohexane/acetone, 1.5:1).

The crude mixture containing **13** was dissolved in absolute CH_2Cl_2 (90 mL) and absolute methanol (40 mL). Ground K_2CO_3 (2.0 g) was added, and the suspension was stirred for 30 min (TLC: cyclohexane /acetone, 2:1). The solids were then filtered off, and the filtrate was adjusted to a pH of 5–6 with acetic acid (0.15 mL) and then concentrated in vacuo. The residue was purified by flash chromatography (cyclohexane/acetone, 4:1) to give **14** (2.99 g, 50.1% over two steps). R_f = 0.10 (cyclohexane/acetone, 2:1). $[\alpha]_D^{22}$ = +11.3 (*c* = 1, CH_2Cl_2).

Method B (via Donor 16): Disaccharide **11** (3.0 g, 3 mmol), donor **16** (2.85 g, 4.5 mmol), and ground molecular sieves (4 Å) (6.0 g) in absolute CH_2Cl_2 (126 mL) were stirred at room temperature under argon for 30 min. The mixture was cooled in an ice bath for 10 min, and then dilute TMSOTf (150 μmol, 540 μL of TMSOTf/CH_2Cl_2, 1:19) was added over 5 min. After 40 min (TLC: toluene/acetone, 8:1), TfOH (109 μL, 1.23 mmol) was added, and stirring was continued for a further 40 min. The reaction was stopped by filtration through Celite into a stirred dilute $KHCO_3$ solution. The organic phase was washed with dilute $KHCO_3$ solution, dried with $MgSO_4$, and concentrated to give crude **13** (5.67 g). R_f(**11**) = 0.27, R_f(**13a**) = 0.33, R_f(**13**) = 0.40 (toluene/acetone, 8:1).

The crude trisaccharide **13** (5.67 g) was dissolved in absolute CH_2Cl_2 (60 mL) and absolute methanol (30 mL) under argon. Ground K_2CO_3 (1.38 g), which had been activated prior to use by heating under high vacuum, was added. The mixture was stirred for 1 h (TLC: toluene/acetone, 8:1), and then the K_2CO_3 was removed by filtration through Celite. The pH of the filtrate was adjusted to 5–6 by adding acetic acid (0.4 mL). After concentration in vacuo, the residue was purified by flash chromatography (cyclohexane/acetone, 3.5:1) to give **14** (3.64 g, 88.8% over two steps). R_f = 0.24 (toluene/acetone, 8:1). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 9.66 (s, 1 H, NH), 7.83–7.60 (m, 8 H, Pht), 7.43–7.24 (m, 15 H, Ph), 6.99–6.70 (m, 14 H, PMP, Ph), 5.88 (d, $J_{2,OH}$ = 5.4 Hz, 1 H, 2^3-OH), 5.53 (s, 1 H, PhCH=), 5.31 (d, $J_{1,2}$ = 9.5 Hz, 1 H, 1^1-H), 5.20 (d, $J_{1,2}$ = 8.4 Hz, 1 H, 1^2-H), 4.97 (dd, $J_{2,3}$ = $J_{3,4}$ = 9.5 Hz, 1 H, 3^3-H), 4.83 (d, J_{gem} = 12.5 Hz, 1 H, OCH$_2$), 4.74 (d, J_{gem} = 11.8 Hz, 1 H, OCH$_2$), 4.63 (d, J_{gem} = 12.0 Hz, 1 H, OCH$_2$), 4.62 (d, $J_{1,2}$ = 7.5 Hz, 1 H, 1^3-H), 4.55 (d, 1 H, OCH$_2$), 4.36 (d, 1 H, OCH$_2$), 4.26 (d, 1 H, OCH$_2$), 4.18 (dd, $J_{3,4}$ = 9.9, $J_{4,5}$ = 8.8 Hz, 1 H, 4^1-H), 4.16–4.11 (m, 2 H, 3^2-H, 3^1-H), 4.07 (m, 1 H, 6a^3-H), 4.00–3.88 (m, 5 H, 6a^2-H, 2^2-H, 4^2-H, 6a^1-H, 6b^2-H), 3.81 (dd, $J_{2,3}$ = 10.2 Hz, 1 H, 2^1-H), 3.79–3.76 (m, 2 H, 6b^1-H, 5^1-H), 3.71 (s, 3 H, OCH$_3$), 3.61 (dd, $J_{3,4}$ = $J_{4,5}$ = 9.5 Hz, 1 H, 4^3-H), 3.58 (m, 1 H, 6b^3-H), 3.55 (m, 1 H, 5^2-H), 3.41 (m, 1 H, 2^3-H), 3.32 (m, 1 H, 5^3-H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 168.0, 167.3, 167.1 (C=O), 153.6, 151.8 (C-*i*, C-4 PMP), 152.9 (C=O Phcm), 139.1, 138.6, 138.1, 137.9, 137.3 (C-*i* Ph, C-4 PhCH=), 135.3, 134.1 (C-4/5 Pht), 130.5 (C-1/2 Pht), 129.3, 128.9, 128.7, 128.4, 128.0, 127.8, 127.6, 127.4, 127.2, 126.7, 125.4 (C-2/6 Ph, C-3/5 Ph, C-4 Ph, C-3/5 Phcm), 124.1 (C-3/6 Pht), 122.8 (C-4 Phcm), 118.8, 117.5 (C-2/6 Phcm), 115.1, 114.8 (C-2/6 Mp), 103.1 (C-1^3), 100.3 (PhCH=), 96.4 (C-1^2), 84.7 (C-1^1), 78.1 (C-4^3), 78.0 (C-4^2), 76.4 (C-3^2), 76.3 (C-3^1), 74.9 (C-4^1, C-5^1), 74.8 (C-5^2), 74.0 (C-3^3), 73.7 (OCH$_2$), 72.5 (C-2^3), 72.1 (OCH$_2$), 67.7 (C-6^2), 67.6 (C-6^3), 66.3 (C-6^1), 65.6 (C-5^3), 55.9 (C-2^2), 55.3 (OCH$_3$), 54.9 (C-2^1) ppm. ESI-MS: *m*/*z* = 1393.42 [M + Na]$^+$.

4,6-*O*-Benzylidene-2-*O*-chloroacetyl-3-*O*-(*N*-phenylcarbamoyl)-α,β-D-glucopyranosyl-(*N*-phenyl)trifluoroacetimidate (16): Compound **15** (17.05 g, 31.6 mmol) was dissolved in DMF (25.6 mL) at room temperature under an argon atmosphere. The solution was stirred in an ice bath for 30 min, and then hydrazine acetate (1.45 g, 15.7 mmol) was added. After 5 min, more hydrazine acetate (1.45 g, 15.7 mmol) was added. After 1 h (TLC: hexane/acetone, 2:1), acetone (34 mL) was added, and the reaction mixture was stirred at 0 °C for 15 min. The DMF was removed by coevaporation with toluene under high vacuum. The residue was dissolved in CH_2Cl_2, washed with water (2×), brine (2×), and dilute $KHCO_3$ solution. The organic phase was dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography (cyclohexane/acetone, 4:1) to give the intermediate hemiacetal (10.4 g, 70.9%). R_f = 0.25 (hexane/acetone, 2:1).

The hemiacetal (13.0 g, 28.0 mmol) was dissolved in CH_2Cl_2 (700 mL) under argon. *N*-Phenyltrifluoroacetimidoyl chloride (9.1 mL, 56.1 mmol) and DBU (4.17 mL, 28.0 mmol) were sequentially added at 0 °C, and the reaction mixture was stirred for 40 min (TLC: hexane/acetone, 2:1). The solvent was removed in vacuo, and the residue was purified by flash chromatography (cyclohexane/acetone, 5:1→4:1→2:1) to give **16** (anomeric mixture α/β = 1:3, 16.34 g, 91.8%) R_f = 0.41 (hexane/acetone, 2:1). $[\alpha]_D^{25}$ of α-anomer = +37.5 (*c* = 0.15, CH_2Cl_2); $[\alpha]_D^{22}$ of β-anomer = +38.6 (*c* = 0.5, CH_2Cl_2).

α-Anomer: ^{1}H NMR (360 MHz, $CDCl_3$, 50 °C): δ = 7.49–7.30 (m, 11 H, Ar), 7.15–7.07 (m, 2 H, Ar), 6.83–6.81 (m, 2 H, Ar), 6.57 (s, 1 H, NH), 6.55 (br. s, 1 H, 1-H), 5.64 (dd, $J_{2,3}$ = $J_{3,4}$ = 9.8 Hz, 1 H, 3-H), 5.56 (s, 1 H, PhCH=), 5.27 (dd, $J_{1,2}$ = 3.7, $J_{2,3}$ = 9.8 Hz, 1 H, 2-H), 4.37 (dd, $J_{5,6}$ = 4.9, J_{gem} = 10.4 Hz, 1 H, 6a-H), 4.14 (m, 1 H, 5-H), 4.06 (s, 2 H, CH_2Cl), 3.85–3.77 (m, 2 H, 4-H, 6b-H) ppm. ^{13}C NMR (90 MHz, $CDCl_3$, 50 °C): δ = 167.0 (C=O), 152.2 (C=O), 143.2, 137.6, 136.9 (C-*i* Ar), 129.4, 129.3, 129.1, 128.5, 126.5, 125.1, 124.2, 119.6, 119.4 (C-Ar), 102.2 (PhCH=), 92.9 (C-1), 78.9 (C-4), 72.1 (C-2), 70.5 (C-3), 68.7 (C-6), 65.5 (C-5), 40.4 (CH_2Cl) ppm.

β-Anomer: ^{1}H NMR (360 MHz, $CDCl_3$, 50 °C): δ = 7.45–7.06 (m, 14 H, Ar), 6.86 (m, 1 H, Ar), 6.61 (s, 1 H, NH), 5.93 (br. s, 1 H, 1-H), 5.53 (s, 1 H, PhCH=), 5.37–5.29 (m, 2 H, 3-H, 2-H), 4.39 (dd, $J_{5,6}$ = 4.9, J_{gem} = 10.5 Hz, 1 H, 6a-H), 4.05 (s, 2 H, CH_2Cl), 3.86–3.78 (m, 2 H, 4-H, 6b-H), 3.58 (m, 1 H, 5-H) ppm. ^{13}C NMR (90 MHz, $CDCl_3$, 50 °C): δ = 166.4 (C=O), 152.3 (C=O), 143.1, 137.5, 136.8 (C-*i* Ar), 129.4, 129.3, 129.1, 128.5, 126.4, 125.1, 124.3, 119.5 (C-Ar), 102.1 (PhCH=), 95.0 (C-1), 78.3 (C-4), 73.4 (C-3), 73.0 (C-2), 68.6 (C-6), 67.4 (C-5), 40.4 (CH_2Cl) ppm. ESI-MS: *m*/*z* = 657.96 $[M + Na]^+$, 673.98 $[M + K]^+$.

Orthoester 13a: A suspension of disaccharide azide **11** (200 mg, 0.2 mmol), imidate **16** (192 mg, 0.3 mmol), and freshly activated ground molecular sieves (4 Å) (0.4 g) in absolute CH_2Cl_2 (8.4 mL) was stirred at ambient temperature under argon for 30 min. The mixture was cooled in an ice bath for 10 min, and dilute TMSOTf (10 μmol, 36 μL of TMSOTf/CH_2Cl_2, 1:19) was added over 5 min. After 30 min (TLC: toluene/acetone, = 8:1), the reaction was stopped by filtration through Celite into a stirred dilute $KHCO_3$ solution. The mixture was extracted, and the organic phase was dried with $MgSO_4$. After removal of the solvent in vacuo, the residue was dried under high vacuum to give crude orthoester **13a**. The crude product was dissolved in absolute CH_2Cl_2 (4.2 mL) and absolute methanol (2.1 mL). Ground K_2CO_3 (92 mg), which had been activated prior to use by heating under high vacuum, was added. The reaction mixture was stirred for 1 h (TLC: toluene/acetone, 8:1), and then the solids were removed by filtration through Celite. The pH of the filtrate was adjusted to 5–6 by adding acetic acid (16 μL). After concentration in vacuo, the residue was purified by flash chromatography (cyclohexane/acetone, 4:1) to give **13a** (212 mg, 75.0%). R_f = 0.33 (toluene/acetone, 8:1). $[\alpha]_D^{25}$ = +27.4 (*c* = 0.5, CH_2Cl_2). ^{1}H NMR (360 MHz, $[D_6]$DMSO): δ = 9.90 (s, 1 H, NH), 7.84–7.50 (m, 8 H, Pht), 7.40–7.16 (m, 14 H, Ar), 6.98–6.60 (m, 15 H, Ar), 6.20 (d, $J_{1,2}$ = 5.5 Hz, 1 H, 1^3-H), 5.70 (s, 1 H, PhCH=), 5.32 (d, $J_{1,2}$ = 9.6 Hz, 1 H, 1^1-H), 5.22 (dd, $J_{2,3}$ = 3.4, $J_{3,4}$ = 9.1 Hz, 1 H, 3^3-H), 5.17 (d, $J_{1,2}$ = 7.5 Hz, 1 H, 1^2-H), 4.90 (d, J_{gem} = 12.0 Hz, 1 H, OCH_2), 4.87–4.83 (m, 2 H, OCH_2, 2^3-H), 4.65 (d, J_{gem} = 12.3 Hz, 1 H, OCH_2), 4.48 (d, J_{gem} = 12.3 Hz, 1 H, OCH_2), 4.41–4.34 (m, 2 H, OCH_2, $6a^3$-H), 4.17–3.72 (m, 19 H, 3^2-H, 3^1-H, 4^1-H, OCH_2, 2^2-H, CH_2Cl, 5^3-H, $6a^2$-H, $6a^1$-H, 4^3-H, 4^2-H, 2^1-H, $6b^1$-H, $6b^3$-H, 5^1-H, OCH_3), 3.57 (m, 1 H, $6b^2$-H), 3.45 (m, 1 H, 5^2-H) ppm. ^{13}C NMR (90 MHz, $[D_6]$DMSO): δ = 168.0, 167.3, 167.1 (C=O), 153.6, 152.3, 151.7, 138.7, 138.6, 138.0, 137.1 (C-q Ar, C=O Phcm), 134.8, 134.5, 134.4 (C-4/5 Pht), 130.7, 130.6, 130.4 (C-q Ar), 129.0, 128.7, 128.1, 127.7, 127.6, 127.5, 127.2, 127.1, 126.8, 126.1, 123.4, 123.3, 122.7 (Ar), 119.1 (C-q orthoester), 118.4, 115.4, 114.5 (Ar), 100.4 (PhCH=), 98.9 (C-1^3), 96.4 (C-1^2), 84.8 (C-1^1), 78.5 (C-3^2), 78.2 (C-2^3), 76.1 (C-3^1, C-4^3), 75.2 (OCH_2), 75.1 (C-4^1), 74.9 (C-5^1), 74.8 (C-5^2), 73.7 (OCH_2), 73.4 (C-3^3), 73.1 (C-4^2), 72.3 (OCH_2), 68.5 (C-6^2), 67.5 (C-6^3), 66.3 (C-6^1), 62.6 (C-5^3), 55.8 (C-2^2), 55.3 (OCH_3), 54.5 (C-2^1), 46.8 (CH_2Cl) ppm. ESI-MS: *m*/*z* = 1464.04 $[M + NH_4]^+$, 1468.92 $[M + Na]^+$, 1484.90 $[M + K]^+$.

4,6-*O*-Benzylidene-β-D-mannopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl-(1→4)-3-*O*-benzyl-2-deoxy-6-*O*-(*p*-methoxyphenyl)-2-phthalimido-β-D-glucopyranosyl Azide (B)

Method A (by Inversion in DMF): A solution of trisaccharide **14** (12.73 g, 9.3 mmol) in absolute CH_2Cl_2 (450 mL) and absolute pyridine (6 mL) was cooled to –40 °C. Subsequently, trifluoromethanesulfonic anhydride (3.22 mL, 19.6 mmol) was added dropwise. The mixture was allowed to warm up to 0 °C over 10 min, and it was stirred for 2 h until the starting material disappeared (TLC: hexane/acetone, 1.2:1). The mixture was concentrated in a rotary evaporator by maintaining a bath temperature of 5 °C, and then dried under high vacuum for 20 min.

The residue, which contained triflate **14a**, was dissolved in dry DMF (60 mL) and dry pyridine (6 mL) and stirred at 65 °C for 3 h (TLC: CH_2Cl_2/methanol, 50:1). The solvents were evaporated under high vacuum at 45 °C. The residue was dried under high vacuum, dissolved in CH_2Cl_2 (500 mL), washed with $KHCO_3$ solution, dried with $MgSO_4$, and concentrated.

The residue, which contained the imino carbonate **14b**, was dissolved in dioxane (60 mL), and a mixture of acetic acid (18 mL) and water (12 mL) was added. The mixture was kept at 4 °C for 10 h, followed by room temperature for 3 h (TLC: hexane/acetone, 2:1). After concentration, the remaining volatiles were coevaporated with toluene (2 × 20 mL). The residue was dissolved in CH_2Cl_2 (600 mL). The solution was washed with dilute HCl (2×) and dilute $KHCO_3$ solution, dried with $MgSO_4$, and concentrated in vacuo. The residue, which contained the cyclic carbonate **14c**, was dried under high vacuum and subsequently dissolved in absolute CH_2Cl_2 (400 mL). A solution of methanolic sodium methoxide (20 mL, 0.1%) was added. The mixture was stirred for 50 min (TLC: hexane/acetone, 1.5:1) and then neutralized with acetic acid. After evaporation of the solvents, the residue was coevaporated with toluene (20 mL) and then dissolved in CH_2Cl_2 (600 mL). The solution was washed with dilute $KHCO_3$ solution, dried with $MgSO_4$, and concentrated in vacuo. The final product was purified by flash chromatography (cyclohexane/acetone, 3:1 → 2:1) to give **B** (6.12 g, 52.6% over four steps). R_f(**14a**) = 0.42 (hexane/acetone, 1.2:1); R_f(**14b**) = 0.58 (CH_2Cl_2/methanol, 50:1); R_f(**14c**) = 0.33 (hexane/acetone, 1.5:1); R_f(**14e**,**f**) = 0.52 (cyclohexane/ethyl acetate, 1:1); R_f(**B**) = 0.15 (cyclohexane/ethyl acetate, 1:1); R_f(**B**) = 0.24 (hexane/acetone, 2:1). $[\alpha]_D^{22}$ = +24.5 (*c* = 1.0, CH_2Cl_2).

Method B (by Inversion in CH_2Cl_2): A solution of trisaccharide **14** (1 g, 729 μmol) in absolute CH_2Cl_2 (18 mL) and absolute pyridine (470 μL, 5.8 mmol) was stirred in a pressure-stable glass vial at 0 °C for 15 min. Trifluoromethanesulfonic anhydride (250 μL, 1.5 mmol) was added dropwise, and the mixture was stirred at 0 °C for 45 min until the starting material disappeared (TLC: cyclohexane/acetone, 2:1). The solution was heated in the pressure-stable glass vial (***CAUTION!***) for 22 h with a bath temperature of 65 °C until the reaction was complete (TLC: CH_2Cl_2/methanol, 40:1). Subsequently, the mixture was acidified with acetic acid (1.25 mL, 21.8 μmol). Water (836 μL) was added, and the biphasic mixture was vigorously stirred at ambient temperature for 6 h. After complete reaction (TLC: CH_2Cl_2/methanol, 40:1), the solvents were evaporated. The crude carbonate was dissolved in CH_2Cl_2, washed with 1 M HCl and 2 M $KHCO_3$ solution, dried with $MgSO_4$, and concentrated.

Subsequently, the residue was dissolved in absolute CH_2Cl_2 (18 mL), and a solution of sodium methoxide in absolute methanol (3.6 mL, 109 mM) was added. The solution was stirred at ambient temperature for 3 h. Further sodium methoxide in absolute meth-

anol (3.6 mL, 109 mM) was added, and stirring was continued for a further 2 h until the reaction was complete (TLC: cyclohexane/ethyl acetate, 1:1). The solution was neutralized with acetic acid (1 mL). After removal of the solvents, the residue was purified by flash chromatography (cyclohexane/ethyl acetate, 1.5:1 → 1:1 → 1:2) to give **B** (722 mg, 79.1%). R_f(**14a**) = 0.33 (cyclohexane/acetone, 2:1); R_f(**14b**) = 0.38 (CH_2Cl_2/methanol, 40:1); R_f(**14c**) = 0.43 (CH_2Cl_2/methanol, 40:1); R_f(**B**) = 0.11 (cyclohexane/ethyl acetate, 1:1). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 7.85–7.61 (m, 8 H, Pht), 7.41–7.25 (m, 10 H, Ar), 6.94–6.73 (m, 14 H, Ar), 5.51 (s, 1 H, PhCH=), 5.34 (d, $J_{1,2}$ = 9.5 Hz, 1 H, 1^2-H), 5.21 (d, $J_{1,2}$ = 8.4 Hz, 1 H, 1^1-H), 4.92 (d, $J_{2,OH}$ = 4.4 Hz, 1 H, 2^3-OH), 4.90 (d, $J_{3,OH}$ = 6.9 Hz, 1 H, 3^3-OH), 4.83 (d, 1 H, OCH$_2$), 4.81 (d, 1 H, OCH$_2$), 4.62 (d, $J_{1,2}$ < 1.0 Hz, 1 H, 1^3-H), 4.62–4.55 (2 d, J_{gem} = 12.1 Hz, 2 H, OCH$_2$), 4.36 (d, J_{gem} = 12.5 Hz, 1 H, OCH$_2$), 4.33 (d, J_{gem} = 11.9 Hz, 1 H, OCH$_2$), 4.20 (dd, $J_{3,4}$ = $J_{4,5}$ = 8.9 Hz, 1 H, 4^2-H), 4.18–4.10 (m, 2 H, 3^2-H, 3^1-H), 4.02 (dd, J_{gem} = 10.1, $J_{5,6a}$ = 4.7 Hz, 1 H, 6a^3-H), 3.98–3.94 (m, 3 H, 2^1-H, 4^1-H, 6a^2-H), 3.86–3.78 (m, 5 H, 6a^1-H, 6b^2-H, 2^2-H, 5^2-H, 2^3-H), 3.72 (s, 3 H, OCH$_3$), 3.72–3.68 (m, 2 H, 6b^1-H, 4^3-H), 3.56 (dd, J_{gem} < 1 Hz, 1 H, 6b^3-H), 3.52 (m, 1 H, 3^3-H), 3.44 (m, 1 H, 5-H), 3.09 (m, 1 H, 5^3-H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 167.9, 167.1 (C=O), 153.6, 151.7 (C-*i* PMP, C-4 PMP), 138.3, 138.2, 137.9, 137.8 (C-*i* Ar), 134.8, 134.6 (C-4/5 Pht, C-4 PhCH=), 130.5 (C-1/2 Pht), 128.7, 128.2, 127.9, 127.7, 127.6, 127.3, 127.1, 127.0, 126.3 (C-2/6 Ph, C-3/5 Ph), 123.4 (C-3/6 Pht), 115.4, 114.5 (C-2/6 PMP, C-3/5 PMP), 100.9 (PhCH=), 100.4 ($J_{C\text{-}1,H\text{-}1}$ = 162.8 Hz from a coupled HMQC-spectrum, C-1^{3}β), 96.5 (C-1^2), 84.8 (C-1^1), 78.3 (C-4^3), 77.4 (C-4^1), 76.3 (C-3^2), 76.1 (C-3^1), 74.9 (C-4^2, C-5^2), 74.6 (C-5^1), 73.6 (OCH$_2$), 72.1 (OCH$_2$), 70.8 (C-2^2), 69.9 (C-3^3), 68.0 (C-6^1), 67.8 (C-6^3), 66.8 (C-5^3), 66.4 (C-6^2), 55.9 (C-2^2), 55.3 (OCH$_3$), 54.5 (C-2^1) ppm. ESI-MS: *m*/*z* = 1274.0 [M + Na]$^+$. $C_{69}H_{65}N_5O_{18}$ (1252.31): calcd. C 66.18, H 5.23, N 5.59; found C 66.39, H 5.25, N 5.36.

4,6-*O*-Benzylidene-2-(phenylcarbamoyl)-β-D-mannopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl-(1→4)-3-*O*-benzyl-2-deoxy-6-*O*-(*p*-methoxyphenyl)-2-phthalimido-β-D-glucopyranosyl Azide (14e) and 4,6-*O*-Benzylidene-3-(phenylcarbamoyl)-β-D-mannopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl-(1→4)-3-*O*-benzyl-2-deoxy-6-*O*-(*p*-methoxyphenyl)-2-phthalimido-β-D-glucopyranosyl Azide (14f): A fraction containing a mixture of **14e** and **14f** was obtained after flash chromatography of the product mixture of the inversion reaction of **14** in DMF. This mixture was separated by HPLC: Supelco Ascentis C18, 5 µm (10 × 250 mm), 4 mL/min, 80–85% water/acetonitrile + 0.1%TFA.

Data for 14e: R_f = 0.26 (CH_2Cl_2/methanol, 30:1). $[\alpha]_D^{22}$ = –0.3 (*c* = 0.7, CH_2Cl_2). ^{1}H NMR (360 MHz, [D$_6$]DMSO): δ = 9.63 (s, 1 H, NH), 7.88–7.64 (m, 8 H, Pht), 7.54–7.21 (m, 14 H, Ar), 6.98 (dd, *J* = 7.2, *J* = 7.3 Hz, 1 H, Ar), 6.89–6.62 (m, 14 H, Ar), 5.55–5.47 (m, 2 H, 3^3-OH, =CH-Ph), 5.31 (d, $J_{1,2}$ = 9.6 Hz, 1 H, 1^1-H), 5.28 (dd, $J_{1,2}$ < 1, $J_{2,3}$ = 3.0 Hz, 1 H, 2^3-H), 5.20 (d, $J_{1,2}$ = 8.0 Hz, 1 H, 1^2-H), 4.91 (d, $J_{1,2}$ < 1 Hz, 1 H, 1^3-H), 4.82 (d, J_{gem} = 12.5 Hz, 1 H, OCH$_2$), 4.72 (d, J_{gem} = 12.4 Hz, 1 H, OCH$_2$), 4.63 (d, J_{gem} = 12.1 Hz, 1 H, OCH$_2$), 4.56 (d, J_{gem} = 12.1 Hz, 1 H, OCH$_2$), 4.33 (d, J_{gem} = 12.4 Hz, 1 H, OCH$_2$), 4.29 (d, J_{gem} = 12.5 Hz, 1 H, OCH$_2$), 4.19–4.07 (m, 2 H, 3^1-H, 4^1-H), 4.06–3.91 (m, 4 H, 6a^3-H, 3^2-H, 4^2-H, 2^2-H), 3.90–3.70 (m, 8 H, 6a^1-H, 6a^2-H, 3^3-H, 2^1-H, 6b^2-H, 6b^1-H, 5^1-H, 4^3-H), 3.68 (s, 3 H, OCH$_3$), 3.63–3.54 (m, 1 H, 6b^3-H), 3.51–3.43 (m, 1 H, 5^2-H), 3.26–3.17 (m, 1 H, 5^3-H) ppm. ^{13}C NMR (90 MHz, [D$_6$]DMSO): δ = 167.1 (C=O Pht), 153.6, 153.2, 151.7 (C-4 PMP, C-*i* PMP, C=O Phcm), 139.3, 138.4, 138.0, 137.6 (C-*i* Ar), 134.8, 134.5 (C-4/5 Pht), 130.5 (C-1/2 Pht), 128.9, 128.6, 128.2, 128.0, 127.9, 127.7, 127.6, 127.3, 127.2, 127.1, 126.9, 126.3 (C Ar), 123.4, 123.3 (C-3/6 Pht), 122.2, 118.2 (C Ar), 115.4, 114.4 (C-2/6, C-3/5 PMP), 101.1(=CH-Ph), 99.4 (C-1^3), 96.4 (C-1^2), 84.7 (C-1^1), 78.5 (C-3^3), 78.5 (C-4^3), 78.3 (C-4^2), 76.5 (C-3^1), 76.2 (C-3^2), 75.3 (C-4^1), 75.0 (C-5^1), 74.1 (C-5^2), 73.6 (OCH$_2$), 73.6 (OCH$_2$), 72.5 (C-2^3), 72.1 (OCH$_2$), 67.8 (C-6^2), 67.8 (C-6^3), 66.6 (C-5^3), 66.6 (C-6^1), 55.9 (C-2^2), 55.3 (OCH$_3$), 54.4 (C-2^1) ppm. ESI-MS: *m*/*z* = 1393.39 [M + Na]$^+$.

Data for 14f: R_f = 0.35 (CH_2Cl_2/methanol, 30:1). $[\alpha]_D^{22}$ = +6.4 (*c* = 0.7, CH_2Cl_2). ^{1}H NMR (360 MHz, [D$_6$]DMSO): δ = 9.85 (s, 1 H, NH), 7.90–7.73 (m, 7 H, Pht), 7.64–7.57 (m, 1 H, Pht), 7.51–7.21 (m, 14 H, Ar), 6.97 (dd, *J* = 7.5, *J* = 7.4 Hz, 1 H, Ar), 6.94–6.70 (m, 14 H, Ar), 5.56 (s, 1 H, =CH-Ph), 5.41 (d, 1 H, $J_{OH,2}$ = 5.1 Hz, 2^3-OH), 5.35 (d, $J_{1,2}$ = 9.5 Hz, 1 H, 1^1-H), 5.20 (d, $J_{1,2}$ = 8.4 Hz, 1 H, 1^2-H), 4.89–4.77 (m, 4 H, 3^3-H, OCH$_2$, OCH$_2$, 1^3-H), 4.65 (d, J_{gem} = 12.2 Hz, 1 H, OCH$_2$), 4.59 (d, J_{gem} = 12.2 Hz, 1 H, OCH$_2$), 4.38 (d, J_{gem} = 12.5 Hz, 1 H, OCH$_2$), 4.33 (d, J_{gem} = 12.2 Hz, 1 H, OCH$_2$), 4.24–4.10 (m, 4 H, 3^1-H, 4^1-H, 2^3-H, 3^2-H), 4.09–3.91 (m, 5 H, 6a^3-H, 4^3-H, 2^2-H, 4^2-H, 6a^1-H), 3.90–3.77 (m, 4 H, 6a^2-H, 2^1-H, 6b^1-H, 5^1-H), 3.76–3.68 (m, 4 H, 6b^2-H, OCH$_3$), 3.67–3.58 (m, 1 H, 6b^3-H), 3.50–3.43 (m, 1 H, 5^2-H), 3.37–3.27 (m, 1 H, 5^3-H) ppm. ^{13}C NMR (90 MHz, [D$_6$]DMSO): δ = 167.1 (C=O Pht), 153.6, 152.8, 151.7 (C-4 PMP, C-*i* PMP, C=O Phcm), 139.0, 138.2, 137.9, 137.5 (C-*i* Ar), 134.8, 134.7 (C-4/5 Pht), 130.6 (C-1/2 Pht), 128.9, 128.7, 128.3, 128.0, 127.8, 127.7, 127.6, 127.4, 127.1, 127.0, 126.1 (C Ar), 123.4 (C-3/6 Pht), 122.4, 118.1 (C Ar), 115.4, 114.5 (C-2/6, C-3/5 PMP), 100.8 (=CH-Ph), 100.2 (C-1^3), 96.5 (C-1^2), 84.8 (C-1^1), 78.1 (C-4^2), 76.3 (C-4^1), 76.2 (C-3^2), 75.1 (C-4^3), 74.9 (C-3^1), 74.8 (C-5^1), 74.6 (C-5^2), 73.7 (OCH$_2$), 73.7 (OCH$_2$), 72.7 (C-3^3), 72.3 (OCH$_2$), 68.6 (C-2^3), 68.3 (C-6^2), 67.7 (C-6^3), 66.5 (C-5^3), 66.4 (C-6^1), 55.9 (C-2^2), 55.3 (OCH$_3$), 54.5 (C-2^1) ppm. ESI-MS: *m*/*z* = 1388.43 [M + NH$_4$]$^+$.

3,4,6-Tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl-(1→2)-3,4,6-tri-*O*-acetyl-α-D-mannopyranosyl-(1→3)-4,6-*O*-benzylidene-β-D-mannopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl-(1→4)-3-*O*-benzyl-2-deoxy-6-*O*-(*p*-methoxyphenyl)-2-phthalimido-β-D-glucopyranosyl Azide (17): A suspension of trisaccharide **B** (2.62 g, 2.09 mmol), imidate **C** (3.42 g, 3.94 mmol), and freshly activated ground molecular sieves (4 Å) (3.0 g) in absolute CH_2Cl_2 (60 mL) was stirred at –25 °C for 30 min. Subsequently, boron trifluoride–diethyl ether (0.13 mL, 1.04 mmol) was added, and the mixture was allowed to warm up to –15 °C over 2 h, and then stirred at room temperature for 1 h (TLC: cyclohexane/acetone, 1.5:1). The suspension was diluted with CH_2Cl_2, filtered through Celite and washed with a dilute $KHCO_3$ solution. The organic phase was dried with $MgSO_4$ and concentrated. The residue was purified by flash chromatography (cyclohexane/acetone, 3:1 → 2:1) to give **17** (3.23 g, 79%). R_f = 0.46 (hexane/acetone, 1:1). $[\alpha]_D^{23}$ = –5.3 (*c* = 0.4, CH_2Cl_2). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 7.91–6.69 (m, 36 H, Pht, Ar), 5.61 (s, 1 H, PhCH=), 5.51 (dd, $J_{2,3}$ = $J_{3,4}$ = 10.0 Hz, 1 H, 3^5-H), 5.34 (d, $J_{1,2}$ = 9.5 Hz, 1 H, 1^1-H), 5.20–5.17 (m, 2 H, $J_{1,2}$ = 9.5 Hz, 1^2-H, 2^3-OH), 5.01 (dd, $J_{2,3}$ = 2.8, $J_{3,4}$ = 10.2 Hz, 1 H, 3^4-H), 4.94 (d, $J_{1,2}$ = 8.5 Hz, 1 H, 1^5-H), 4.89–4.74 (m, 5 H, 4^5-H, 4^4-H, 1^4-H, OCH$_2$), 4.56 (2 d, J_{gem} = 12.2 Hz, 2 H, OCH$_2$), 4.52 (d, $J_{1,2}$ < 1.0 Hz, 1 H, 1^3-H), 4.38–4.31 (2 d, 2 H, OCH$_2$), 4.21–4.13 (m, 2 H, 4^1-H, 3^1-H), 4.09–3.90 (m, 9 H, 3^2-H, 2^5-H, 6a^3-H, 6a^5-H, 6a^1-H, 2^2-H, 2^4-H, 5^4-H, 4^2-H), 3.89–3.68 (m, 10 H, 4^3-H, 6a^2-H, 6b^1-H, 2^1-H, 5^1-H, 2^3-H, 6b^5-H, OCH$_3$), 3.65 (m, 1 H, 6b^2-H), 3.59–3.52 (m, 4 H, 6a^4-H, 6b^4-H, 6b^3-H, 3^3-H), 3.40 (m, 1 H, 5^2-H), 3.11 (m, 1 H, 5^3-H), 2.66 (m, 1 H, 5^5-H), 2.03, 1.97, 1.95, 1.90 (4 s, 12 H, OAc), 1.80 (s, 6 H, OAc) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 169.88, 169.76, 169.63, 169.19, 167.13 (C=O), 153.62,

151.77 (C-4 PMP, C-*i* PMP), 138.33, 138.19, 137.98, 137.79 (C-*i* Ar), 134.88 (C-4/5 Pht, C-4 PhCH=), 130.60 (C-1/2 Pht), 128.34, 128.13, 127.82, 127.71, 127.64, 127.40, 127.09, 126.56 (C-2/6 Ph, C-3/5 Ph, C-4 Ph), 123.46 (C-3/6 Pht), 115.42, 114.53 (C-2/6, C-3/5 PMP), 101.08 (PhCH=), 99.70 ($J_{C\text{-}1,H\text{-}1}$ = 162.3 Hz from a coupled HMQC spectrum, C-1^{3}β), 97.56 ($J_{C\text{-}1,H\text{-}1}$ = 173.8 Hz from a coupled HMQC spectrum, C-1^{4}α), 96.5 (C-1^2), 95.42 (C-1^5), 84.82 (C-1^1), 77.90 (C-3^3), 77.28 (C-4^3), 77.04 (C-4^2), 76.34 (C-3^1), 76.00 (C-3^2), 75.00 (C-4^1), 74.90 (C-5^1), 74.66 (C-5^2), 73.71, 73.61 (OCH_2), 73.01 (C-5^4), 72.34 (OCH_2), 70.85 (C-5^5), 69.84 (C-2^3), 69.54 (C-3^5), 69.05 (C-4^4), 68.33 (C-4^5), 68.02 (C-6^2), 67.66 (C-6^3), 67.60 (C-2^4), 66.43 (C-6^1), 66.18 (C-5^3), 65.13 (C-3^4), 62.03 (C-6^4), 61.23 (C-6^5), 55.83 (C-2^2), 55.37 (OCH_3), 54.56 (C-2^1), 53.69 (C-2^5), 20.39, 20.13 (OAc) ppm. ESI-MS: *m/z* = 1979.77 $[M + Na]^+$.

3,4,6-Tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl-(1→2)-3,4,6-tri-*O*-acetyl-α-D-mannopyranosyl-(1→3)-2-*O*-acetyl-4,6-*O*-benzylidene-β-D-mannopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl-(1→4)-3-*O*-benzyl-2-deoxy-6-*O*-(*p*-methoxyphenyl)-2-phthalimido-β-D-glucopyranosyl Azide (18): Pentasaccharide **17** (550 mg, 280.9 μmol) was dissolved in pyridine/acetic anhydride (5 mL, 2:1) and stirred for 1 d. The mixture was concentrated in vacuo, coevaporated with toluene (5 mL, 3×) and dried under high vacuum. The residue was dissolved in CH_2Cl_2, and the solution was washed with 1 M HCl and dilute $KHCO_3$ solution, dried with $MgSO_4$, and concentrated. The crude pentasaccharide **18** (562 mg, quant.) was used directly in a subsequent debenzylidenation reaction. R_f = 0.26 (hexane/acetone, 1.2:1). $[\alpha]_D^{23}$ = +1.3 (*c* = 1, CH_2Cl_2). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 7.90–6.68 (m, 36 H, Pht, Ar), 5.72 (s, 1 H, PhCH=), 5.52 (dd, $J_{2,3}$ = $J_{3,4}$ = 10.0 Hz, 1 H, 3^5-H), 5.33 (d, $J_{1,2}$ = 8.5 Hz, 1 H, 1^1-H), 5.31 (m, 1 H, 2^3-H), 5.21 (d, $J_{1,2}$ = 8.5 Hz, 1 H, 1^2-H), 4.90–4.78 (m, 8 H, 1^5-H, 1^4-H, 4^4-H, 4^5-H, 1^3-H, OCH_2, 3^4-H), 4.60–4.54 (2 d, J_{gem} = 12.0 Hz, 2 H, OCH_2), 4.35 (d, J_{gem} = 12.4 Hz, 1 H, OCH_2), 4.19 (d, J_{gem} = 11.5 Hz, 1 H, OCH_2), 4.14 (m, 2 H, 3^1-H, 4^1-H), 4.08–3.94 (m, 9 H, 3^2-H, 6a^3-H, 2^5-H, 3^3-H, 4^2-H, 2^2-H, 6a^5-H, 6a^1-H, 2^4-H), 3.87–3.68 (m, 11 H, 6a^2-H, 6b^1-H, 2^1-H, 4^3-H, 5^1-H, 5^4-H, 6b^5-H, OCH_3, 6b^2-H), 3.64–3.52 (m, 3 H, 6b^3-H, 6a^4-H, 6b^4-H), 3.43 (m, 1 H, 5^2-H), 3.23 (m, 1 H, 5^3-H), 2.51 (m, 1 H, 5^5-H), 2.03, 1.99, 1.98, 1.95, 1.90, 1.79, 1.78 (7 s, 21 H, OAc). ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 169.82, 169.73, 169.16, 169.08, 167.09 (C=O), 153.59, 151.77 (C-4 PMP, C-*i* PMP), 138.30, 138.02, 137.93, 137.38 (C-*i* Ar), 134.93, 134.79 (C-4/5 Pht, C-4 PhCH=), 130.55 (C-1/2 Pht), 128.29, 128.17, 127.84, 127.74, 127.47, 127.32, 127.21, 127.08, 126.47 (C-2/6 Ph, C-3/5 Ph, C-4 Ph), 123.41 (C-3/6 Pht), 115.41, 114.48 (C-2/6, C-3/5 PMP), 100.96 (PhCH=), 97.52 ($J_{C\text{-}1,H\text{-}1}$ = 166.4 Hz from a coupled HMQC spectrum, C-1^{3}β), 96.78 ($J_{C\text{-}1,H\text{-}1}$ = 176.1 Hz from a coupled HMQC spectrum, C-1^{4}α), 96.47 (C-1^2), 95.14 (C-1^5), 84.76 (C-1^1), 78.39 (C-4^3), 76.90 (C-4^2), 76.38 (C-3^1, C-3^2), 75.19 (C-4^1), 74.91 (C-5)^1, 74.23 (C-5^2), 73.93, 73.68 (OCH_2), 73.46 (C-3^3), 72.73 (C-2^4), 72.14 (OCH_2), 70.81 (C-5^5), 70.33 (C-2^3), 69.51 (C-3^5), 68.53 (C-3^4), 68.23 (C-5^4), 68.09 (C-4^5), 67.88 (C-6^2), 67.54 (C-6^3), 66.45 (C-6^1), 65.55 (C-5^3), 64.52 (C-4^4), 61.77 (C-6^4), 60.96 (C-6^5), 55.89 (C-2^2), 55.33 (OCH_3), 54.50 (C-2^1), 53.54 (C-2^5), 20.44, 20.31, 20.04 (OAc) ppm. ESI-MS: *m/z* = 1000.6 $[M + 2 H]^{2+}$.

3,4,6-Tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl-(1→2)-3,4,6-tri-*O*-acetyl-α-D-mannopyranosyl-(1→3)-2-*O*-acetyl-β-D-mannopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl-(1→4)-3-*O*-benzyl-2-deoxy-6-*O*-(*p*-methoxyphenyl)-2-phthalimido-β-D-glucopyranosyl Azide (19): *p*-Toluenesulfonic acid monohydrate (560 mg, 2.9 mmol) was added to a solution of pentasaccharide **18** (560 mg, 280 μmol) in absolute acetonitrile (5.6 mL). After stirring for 45 min (TLC: hexane/acetone, 1.2:1), the reaction was stopped by adding pyridine (259 μL, 3.21 mmol), and then the solvents were evaporated in vacuo. The residue was dissolved in CH_2Cl_2, and the solution was washed with dilute $KHCO_3$ solution, dried with $MgSO_4$, and concentrated. The residue was purified by flash chromatography (hexane/acetone, 1:1) to give **19** (428.3 mg, 80.0%). R_f = 0.1 (hexane/acetone, 1.2:1). $[\alpha]_D^{23}$ = +6.5 (*c* = 1, CH_2Cl_2). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 7.87–6.68 (m, 31 H, Pht, Ar), 5.63 (dd, $J_{2,3}$ = $J_{3,4}$ = 9.9 Hz, 1 H, 3^5-H), 5.43 (d, $J_{4,OH}$ = 4.7 Hz, 1 H, 4^3-OH), 5.29 (d, $J_{1,2}$ = 8.5 Hz, 1 H, 1^5-H), 5.27 (d, $J_{1,2}$ = 9.5 Hz, 1 H, 1^1-H), 5.13 (d, $J_{1,2}$ = 8.0 Hz, 1 H, 1^2-H), 5.07 (dd, $J_{2,3}$ = 3.0, $J_{1,2}$ < 1.0 Hz, 1 H, 2^3-H), 4.97 (dd, $J_{3,4}$ = $J_{4,5}$ = 9.4 Hz, 1 H, 4^5-H), 4.92 (dd, $J_{3,4}$ = $J_{4,5}$ = 10.1 Hz, 1 H, 4^4-H), 4.87 (d, $J_{1,2}$ < 1.0 Hz, 1 H, 1^4-H), 4.81 (d, J_{gem} = 12.0 Hz, 1 H, OCH_2), 4.75 (d, J_{gem} = 12.4 Hz, 1 H, OCH_2), 4.71 (dd, $J_{2,3}$ = 3.0, $J_{3,4}$ = 10.4 Hz, 1 H, 3^4-H), 4.61 (d, $J_{1,2}$ < 1.0 Hz, 1 H, 1^3-H), 4.46 (2 d, J_{gem} = 12.3 Hz, 2 H, OCH_2), 4.42 (dd, $J_{6,OH}$ = 5.4 Hz, 1 H, 6^3-OH), 4.29 (d, J_{gem} = 12.4 Hz, 1 H, OCH_2), 4.22–4.15 (m, 3 H, 6a^5-H, OCH_2, 2^4-H), 4.12–4.09 (m, 3 H, 4^1-H, 2^5-H, 3^1-H), 4.01–3.88 (m, 6 H, 3^2-H, 6b^5-H, 4^2-H, 2^2-H, 6a^1-H, 5^5-H), 3.82–3.56 (m, 12 H, 2^1-H, 6b^1-H, 5^4-H, 6a^2-H, 5^1-H, OCH_3, 6a^3-H, 6a^4-H, 6b^4-H, 6b^2-H), 3.52–3.42 (m, 3 H, 4^3-H, 6b^3-H, 3^3-H), 3.32 (m, 1 H, 5^2-H), 3.03 (m, 1 H, 5^3-H), 1.99, 1.95, 1.94, 1.90, 1.89, 1.84, 1.75 (7 s, 21 H, OAc) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 170.07, 169.86, 169.68, 169.68, 169.22, 167.07 (C=O), 153.57, 151.74 (C-4 PMP, C-*i* PMP), 138.30, 138.13, 137.92 (C-*i* Ar), 134.83 (C-4/5 Pht), 130.55 (C-1/2 Pht), 128.19, 127.73, 127.68, 127.55, 127.34, 127.04 (C-2/6 Ph, C-3/5 Ph, C-4 Ph), 123.42 (C-3/6 Pht), 115.39, 114.47 (C-2/6, C-3/5 PMP), 97.47 ($J_{C\text{-}1,H\text{-}1}$ = 177.5 Hz from a coupled HMQC spectrum, C-1^{4}α), 97.12 ($J_{C\text{-}1,H\text{-}1}$ = 163.7 Hz from a coupled HMQC spectrum, C-1^{3}β), 96.49 (C-1^2), 95.99 (C-1^5), 84.75 (C-1^1), 76.70 (C-3^2), 76.60 (C-4^2), 76.47 (C-5^3), 76.34 (C-3^1), 75.74 (C-3^3), 75.11 (C-4^1), 74.90 (C-5^1), 74.45 (C-5^2), 73.83, 73.67 (OCH_2), 73.43 (C-2^4), 72.19 (OCH_2), 71.01 (C-5^5), 70.53 (C-2^3), 69.67 (C-3^5), 69.07 (C-3^4), 68.62 (C-4^5), 68.10 (C-5^4), 68.00 (C-6^2), 66.76 (C-4^3), 66.42 (C-6^1), 64.47 (C-4^4), 61.86 (C-6)^4, 61.65 (C-6^5), 60.36 (C-6^3), 55.89 (C-2^2), 55.32 (OCH_3), 54.85 (C-2^1), 53.64 (C-2^5), 20.51, 20.36, 20.07 (OAc) ppm. ESI-MS: *m/z* = 977.4 $[M + 2 Na]^{2+}$.

3,4,6-Tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl-(1→2)-3,4,6-tri-*O*-acetyl-α-D-mannopyranosyl-(1→3)-[3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl-(1→2)-3,4,6-tri-*O*-acetyl-α-D-mannopyranosyl-(1→6)]-2-*O*-acetyl-β-D-mannopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl-(1→4)-3-*O*-benzyl-2-deoxy-6-*O*-(*p*-methoxyphenyl)-2-phthalimido-β-D-glucopyranosyl azide (20): A suspension of pentasaccharide **19** (414 mg, 217 μmol), imidate **C** (280 mg, 323 μmol), and freshly activated ground molecular sieves (4 Å) (1.0 g) in absolute CH_2Cl_2 (50 mL) was stirred at –40 °C for 45 min. Subsequently, boron trifluoride–diethyl ether (10 μL, 81 μmol) was added over 5 min. The mixture was warmed to –10 °C over 2 h, and then stirred at room temperature for 3 h (TLC: hexane/acetone, 1.2:1). The suspension was diluted with CH_2Cl_2, filtered through Celite and washed with dilute $KHCO_3$ solution. The organic phase was dried with $MgSO_4$ and concentrated. The residue was purified by flash chromatography (hexane/acetone, 1:1) to give **20** (414 mg, 73.0%). R_f = 0.10 (hexane/acetone, 1.2:1). $[\alpha]_D^{22}$ = +6.9 (*c* = 1, CH_2Cl_2). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 7.83–7.70 (m, 16 H, Pht), 7.55–7.11 (m, 5 H, Ar), 6.82–6.60 (m, 14 H, Ar), 5.65 (dd, $J_{2,3}$ = $J_{3,4}$ = 9.8 Hz, 1 H, 3^5-H), 5.52 (dd, $J_{2,3}$ = $J_{3,4}$ = 9.8 Hz, 1 H, 3$^{5'}$-H), 5.51 (d, $J_{4,OH}$ = 4.7 Hz, 1 H, 4^3-OH), 5.31 (d, $J_{1,2}$ = 8.5 Hz, 1 H, 1^5-H), 5.27 (d, $J_{1,2}$ = 9.5 Hz, 1 H, 1^1-H), 5.17 (d, $J_{1,2}$ = 8.5 Hz, 1 H, 1$^{5'}$-H), 5.10 (d, $J_{1,2}$ = 8.2 Hz, 1 H, 1^2-H), 5.08 (dd, $J_{1,2}$ < 1.0, $J_{2,3}$ = 2.7 Hz, 1 H, 2^3-H), 5.00 (dd, $J_{3,4}$ = $J_{4,5}$ = 9.8 Hz, 1 H, 4^5-

H), 4.99–4.87 (m, 4 H, 4^4-H, $4^{4'}$-H, $4^{5'}$-H, $3^{4'}$-H), 4.83–4.75 (m, 2 H, 1^3-H, OCH_2), 4.71 (dd, $J_{2,3}$ = 2.7, $J_{3,4}$ = 10.2 Hz, 1 H, 3^4-H), 4.66–4.57 (m, 2 H, 1^4-H, OCH_2), 4.51–4.42 (2 d, J_{gem} = 12.2 Hz, 2 H, OCH_2), 4.35–4.26 (m, 3 H, $1^{4'}$-H, OCH_2), 4.22–3.88 (m, 13 H, $6a^5$-H, 2^4-H, 2^5-H, 3^1-H, $2^{5'}$-H, $6a^{5'}$-H, $2^{4'}$-H, 4^1-H, 3^2-H, 2^2-H, 4^2-H, 5^5-H, $6b^5$-H), 3.83–3.54 (m, 15 H, $6a^1$-H, 2^1-H, 5^4-H, $6a^2$-H, $6b^{5'}$-H, $6b^1$-H, OCH_3, $6a^4$-H, $6b^4$-H, 5^1-H, $5^{4'}$-H, $6a^{4'}$-H, $6b^2$-H), 3.47–3.19 (m, 8 H, $6a^3$-H, $6b^3$-H, 4^3-H, 3^3-H, $5^{5'}$-H, $6b^{4'}$-H, 5^2-H, 5^3-H), 2.01, 1.97, 1.96, 1.95, 1.93, 1.90, 1.87, 1.79, 1.77, 1.76 (13 s, 39 H, OAc) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 170.15, 170.09, 169.91, 169.84, 169.67, 169.63, 169.55, 169.24, 169.16, 167.70, 167.25 (C=O), 153.53, 151.78 (C-4 PMP, C-*i* PMP), 138.29, 138.17 (C-*i* Ar), 134.83, 134.71, 134.60 (C-4/5 Pht), 130.78, 130.56 (C-1/2 Pht), 128.29, 127.78, 127.68, 127.44, 127.38, 127.19, 126.91 (C-2/6 Ph, C-3/5 Ph, C-4 Ph), 123.37 (C-3/6 Pht), 115.33, 114.42 (C-2/6, C-3/5 PMP), 97.88 ($J_{C\text{-}1,H\text{-}1}$ = 172.8 Hz from a coupled HMQC spectrum, C-$1^4\alpha$), 97.16 ($J_{C\text{-}1,H\text{-}1}$ = 173.5 Hz from a coupled HMQC spectrum, C-$1^{4'}\alpha$), 96.89 ($J_{C\text{-}1,H\text{-}1}$ = 162.9 Hz from a coupled HMQC spectrum, C-$1^3\beta$), 96.64 (C-1^2), 96.23 (C-$1^{5'}$), 96.11 (C-1^5), 84.80 (C-1^1), 76.97 (C-4^2), 76.81 (C-3^1), 76.00 (C-3^2), 75.73 (C-3^3), 75.41 (C-4^1), 75.10 (C-5^1), 74.47 (C-5^2), 74.14 (C-5^3), 73.92 (C-$2^{4'}$), 73.88 (OCH_2), 73.54 (C-2^4), 73.53, 72.36 (OCH_2), 71.07 (C-5^5), 70.80 (C-$5^{5'}$), 70.46 (C-2^3), 69.76 (C-$3^{5'}$), 69.74 (C-3^5), 69.68 (C-$3^{4'}$), 69.08 (C-3^4), 68.63 (C-4^5), 68.37 (C-$4^{5'}$), 68.15 (C-5^4), 67.80 (C-6^2), 67.57 (C-$5^{4'}$), 67.11 (C-6^3), 66.91 (C-4^3), 66.42 (C-6^1), 64.70 (C-4^4), 64.43 (C-$4^{4'}$), 61.81 (C-6^4), 61.80 (C-6^5), 61.64 (C-$6^{4'}$), 61.37 (C-$6^{5'}$), 55.77 (C-2^2), 55.27 (OCH_3), 54.54 (C-2^1), 53.87 (C-$2^{5'}$), 53.78 (C-2^5), 20.63, 20.51, 20.38, 20.36, 20.25, 20.07 (OAc) ppm. ESI-MS: *m*/*z* = 1331.0 $[M + 2\ Na]^{2+}$.

3,4,6-Tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl-(1→2)-3,4,6-tri-*O*-acetyl-α-D-mannopyranosyl-(1→3)-[3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl-(1→2)-3,4,6-tri-*O*-acetyl-α-D-mannopyranosyl-(1→6)]-2,4-di-*O*-acetyl-β-D-mannopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl-(1→4)-3-*O*-benzyl-2-deoxy-6-*O*-(*p*-methoxyphenyl)-2-phthalimido-β-D-glucopyranosyl Azide (21) and 3,4,6-Tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl-(1→2)-3,4,6-tri-*O*-acetyl-α-D-mannopyranosyl-(1→3)-[3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl-(1→2)-3,4,6-tri-*O*-acetyl-α-D-mannopyranosyl-(1→6)]-2,4-di-*O*-acetyl-β-D-mannopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl-(1→4)-3-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl Azide (22)

Step 1 (Acetylation): Heptasaccharide **20** (390 mg, 149 μmol) was dissolved in pyridine/acetic anhydride (5 mL, 2:1) and stirred for 1 d. The mixture was concentrated in vacuo, coevaporated with toluene (5 mL, 3×) and dried under high vacuum. The residue was dissolved in CH_2Cl_2, and the solution was washed with 1 M HCl and dilute $KHCO_3$ solution, dried with $MgSO_4$, and concentrated. The crude product **21** (396 mg, quant.) was not purified, but was used directly in the following step. R_f = 0.26 (hexane/acetone, 1.2:1).

Step 2 (Removal of the PMP Group): Water (2.45 mL) and CAN (165 mg, 301 μmol) were added to a solution of crude heptasaccharide **21** (80 mg, 30 μmol) in toluene (2.45 mL) and acetonitrile (2.82 mL), and the solution was stirred for 15 h. The mixture was diluted with ethyl acetate (10 mL) and washed with saturated $KHCO_3$ solution and brine. After drying with $MgSO_4$, the organic phase was concentrated. The residue was purified by flash chromatography (hexane/acetone, 1:1) to give **22** (69 mg, 90%). R_f = 0.16 (hexane/acetone, 1.2:1). $[\alpha]_D^{22}$ = –12.0 (*c* = 1, CH_2Cl_2). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 7.93–7.63 (m, 16 H, Pht), 7.34–7.12 (m, 5 H, Ar), 6.93–6.74 (m, 10 H, Ar), 5.63 (dd, $J_{2,3}$ = $J_{3,4}$ = 9.8 Hz, 1 H, 3^5-H), 5.58 (dd, $J_{2,3}$ = $J_{3,4}$ = 9.8 Hz, 1 H, $3^{5'}$-H), 5.29 (d, $J_{1,2}$ = 8.5 Hz, 1 H, 1^5-H), 5.26 (dd, $J_{1,2}$ < 1.0, $J_{2,3}$ = 2.7 Hz, 1 H, 2^3-H), 5.23 (d, $J_{1,2}$ = 9.5 Hz, 1 H, 1^1-H), 5.21 (d, $J_{1,2}$ = 8.5 Hz, 1 H, $1^{5'}$-H), 5.20 (d, $J_{1,2}$ = 8.2 Hz, 1 H, 1^2-H), 5.06–4.84 (m, 6 H, 4^5-H, 4^4-H, $4^{5'}$-H, $4^{4'}$-H, $3^{4'}$-H, 4^3-H), 4.82 (d, J_{gem} = 12.2 Hz, 1 H, OCH_2), 4.76 (dd, $J_{6,OH}$ = 5.4 Hz, 1 H, 6^1-OH), 4.75 (d, $J_{1,2}$ < 1.0 Hz, 1 H, 1^3-H), 4.72 (dd, $J_{2,3}$ = 3.1, $J_{3,4}$ = 10.5 Hz, 1 H, 3^4-H), 4.67 (d, J_{gem} = 11.9 Hz, 1 H, OCH_2), 4.56–4.51 (m, 3 H, 1^4-H, OCH_2), 4.35 (2 d, J_{gem} = 12.3 Hz, 2 H, OCH_2), 4.30 (m, 1 H, $1^{4'}$-H), 4.24 (dd, $J_{5,6}$ = 4.8, J_{gem} = 12.8 Hz, 1 H, $6a^5$-H), 4.18–3.90 (m, 13 H, 2^5-H, 3^2-H, 2^4-H, $6a^{5'}$-H, $2^{5'}$-H, 3^1-H, $2^{4'}$-H, 4^1-H, $6b^5$-H, 5^5-H, 2^2-H, 4^2-H, 3^3-H), 3.82–3.64 (m, 7 H, 5^4-H, 2^1-H, $6a^4$-H, $6b^{5'}$-H, $6a^{4'}$-H, $6b^4$-H), 3.55–3.36 (m, 8 H, $5^{4'}$-H, $5^{5'}$-H, $6b^{4'}$-H, $6b^4$-H, $6a^3$-H, 5^2-H, $6a^1$-H, 5^3-H), 3.31 (m, 1 H, 5^1-H), 3.18–3.16 (m, 2 H, $6b^3$-H, $6b^1$-H), 2.26, 2.03, 2.00, 1.99, 1.98, 1.96, 1.94, 1.93, 1.90, 1.84, 1.81, 1.80, 1.79, 1.75 (14 s, 42 H, OAc). ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 170.13, 170.10, 169.96, 169.89, 169.80, 169.67, 169.60, 169.55, 169.27, 169.24, 169.16, 167.70, 167.25 (C=O), 138.35, 138.12 (C-*i* Ar), 135.06, 134.89, 134.77, 134.60 (C-4/5 Pht), 130.75, 130.60 (C-1/2 Pht), 128.21, 127.75, 127.70, 127.53, 127.35, 127.24, 127.01 (C-2/6 Ph, C-3/5 Ph, C-4 Ph), 123.40 (C-3/6 Pht), 97.76 ($J_{C\text{-}1,H\text{-}1}$ = 173.5 Hz from a coupled HMQC spectrum, C-$1^4\alpha$), 96.95 ($J_{C\text{-}1,H\text{-}1}$ = 173.5 Hz from a coupled HMQC spectrum, C-$1^{4'}\alpha$), 96.87 ($J_{C\text{-}1,H\text{-}1}$ = 163.7 Hz from a coupled HMQC spectrum, C-$1^3\beta$), 96.80 (C-1^2), 96.08 (C-1^5), 96.05 (C-$1^{5'}$), 84.85 (C-1^1), 77.33 (C-4^2), 77.05 (C-5^1), 76.71 (C-3^1), 75.99 (C-3^2), 74.91 (C-4^1), 74.31 (C-5^2), 73.72, 73.65 (OCH_2), 73.45 (C-$2^{4'}$), 73.41 (C-2^4), 73.08 (C-3^3), 72.25 (OCH_2), 71.26 (C-5^3), 71.05 (C-5^5), 70.93 (C-$5^{5'}$), 70.13 (C-2^3), 69.78 (C-3^5), 69.68 (C-$3^{5'}$), 69.53 (C-$3^{4'}$), 69.30 (C-4^3), 68.79 (C-3^4), 68.54 (C-4^5), 68.59 (C-5^4), 68.48 (C-$4^{5'}$), 67.99 (C-6^4), 67.74 (C-$5^{4'}$), 67.06 (C-6^3), 64.45 (C-4^4), 64.43 (C-$4^{4'}$), 61.74 (C-$6^{4'}$), C-6^5, 61.62 (C-$6^{5'}$), 58.81 (C-6^1), 55.74 (C-2^2), 54.61 (C-2^1), 53.85 (C-2^5), 53.80 (C-$2^{5'}$), 20.93, 20.52, 20.48, 20.36, 20.25, 20.07 (OAc) ppm. ESI-MS: *m*/*z* = 1299.0 $[M + 2\ Na]^{2+}$.

3,4,6-Tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl-(1→2)-3,4,6-tri-*O*-acetyl-α-D-mannopyranosyl-(1→3)-[3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl-(1→2)-3,4,6-tri-*O*-acetyl-α-D-mannopyranosyl-(1→6)]-2,4-di-*O*-acetyl-β-D-mannopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl-(1→4)-[2,3,4-tri-*O*-(*p*-methoxybenzyl)-α-L-fucopyranosyl-(1→6)]-3-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl Azide (23): A suspension of heptasaccharide **22** (116 mg, 45.6 μmol), ethyl thiofucoside **D** (49 mg, 86.1 μmol), and freshly activated ground molecular sieves (4 Å) (30 mg) in absolute CH_2Cl_2 (410 μL) and DMF (330 μL) was stirred at ambient temperature for 10 min. After addition of tetrabutylammonium bromide (21 mg, 64.5 μmol) and copper(II) bromide (15 mg, 65 μmol), the suspension was stirred for 2 d. The suspension was then diluted with CH_2Cl_2, and triethylamine (13.8 μL, 100 μmol) and ethanethiol (7.6 μL, 100 μmol) were added. The mixture was then filtered through Celite. The filtrate was concentrated, and the residue was purified by flash chromatography (hexane/acetone, 1:1) to give **23** as a mixture of anomers (119 mg, 85.3%). Further purification was achieved by HPLC using the following conditions: Eclipse XDB-C8, 5 μm, 4.6×150 mm, 75–95% (water/acetonitrile + 0.1% HCOOH) or Diol-60 5 μm, 6.0×300 mm, 60–70% (hexane/ethyl acetate). R_f = 0.16 (hexane/acetone, 1.2:1). $[\alpha]_D^{22}$ = –13.9 (*c* = 0.43, CH_2Cl_2). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 7.94–7.70 (m, 16 H, Pht), 7.38–6.74 (m, 27 H, Ar), 5.64 (dd, $J_{2,3}$ = $J_{3,4}$ = 10.2 Hz, 1 H, 3^5-H), 5.57 (dd, $J_{2,3}$ = $J_{3,4}$ = 10.2 Hz, 1 H, $3^{5'}$-H), 5.42 (d, $J_{1,2}$ = 8.5 Hz, 1 H, 1^2-H), 5.28 (d, $J_{1,2}$ = 8.5 Hz, 1 H, 1^5-H), 5.25 (dd, $J_{1,2}$ < 1.0, $J_{2,3}$ = 2.4 Hz, 1 H, 2^3-H), 5.18 (d, $J_{1,2}$ = 9.8 Hz, 1 H, 1^1-H), 5.16 (d,

$J_{1,2}$ = 8.5 Hz, 1 H, $1^{5'}$-H), 5.03 (dd, $J_{3,4}$ = $J_{4,5}$ = 9.3 Hz, 1 H, 4^5-H), 4.98 (dd, $J_{3,4}$ = $J_{4,5}$ = 10.2 Hz, 1 H, 4^4-H), 4.92 (dd, $J_{3,4}$ = $J_{4,5}$ = 9.8 Hz, 1 H, $4^{5'}$-H), 4.89–4.86 (m, 4 H, $4^{4'}$-H, $3^{4'}$-H, 4^3-H, CH_2O), 4.79 (d, $J_{1,2}$ < 1.0 Hz, 1 H, 1^3-H), 4.72–4.63 (m, 6 H, 3^4-H, CH_2O), 4.58 (d, $J_{1,2}$ = 3.0 Hz, 1 H, $1^8\alpha$-H), 4.56 (d, $J_{1,2}$ < 1.0 Hz, 1 H, 1^4-H), 4.54–4.46 (m, 3 H, CH_2O), 4.38–4.32 (m, 3 H, CH_2O), 4.28 (d, $J_{1,2}$ < 1.0 Hz, 1 H, $1^{4'}$-H), 4.26–4.21 (m, 2 H, 3^2-H, $6a^5$-H), 4.17–4.04 (m, 6 H, 2^5-H, 4^1-H, $6a^{5'}$-H, $2^{5'}$-H, 2^4-H, 3^1-H), 4.02–3.91 (m, 6 H, $2^{4'}$-H, 2^2-H, $6b^5$-H, 4^2-H, 3^3-H, 5^5-H), 3.86–3.78 (m, 6 H, 2^1-H, 5^2-H, 5^8-H, 5^4-H, $6a^2$-H, $6b^{5'}$-H), 3.74, 3.73 (2 s, 6 H, CH_3O), 3.71 (m, 2 H, 2^8-H, $6a^4$-H), 3.69 (s, 3 H, CH_3O), 3.65–3.56 (m, 4 H, 3^8-H, $6b^4$-H, $6b^2$-H, 4^8-H), 3.54–3.37 (m, 8 H, 5^1-H, $6a^{4'}$-H, $6a^1$-H, $5^{4'}$-H, $5^{5'}$-H, $6b^{4'}$-H, 5^3-H, $6a^3$-H), 3.29 (m, 1 H, $6b^1$-H), 3.17 (m, 1 H, $6b^3$-H), 2.25, 2.07, 2.03, 1.99, 1.98, 1.97, 1.94, 1.93, 1.92, 1.83, 1.80, 1.79, 1.78, 1.75 (14 s, 42 H, OAc), 0.92 (d, $J_{5,6}$ = 6.4 Hz, 3 H, H-6^8) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 170.02–169.10, 167.99–167.06 (C=O), 158.62, 158.60, 158.46 (C-4 MPM), 138.30, 138.09, 137.93 (C-*i* Ar), 134.93, 134.82, 134.54 (C-4/5 Pht, C-1 MPM), 130.89, 130.74, 130.61, 130.51 (C-1/2 Pht), 129.35–127.06 (C-Ar), 123.37 (C-3/6 Pht), 113.54, 113.44, 113.35 (C-3/5 MPM), 97.67 ($J_{C\text{-}1,H\text{-}1}$ = 174.3 Hz from a coupled HMQC spectrum, C-$1^4\alpha$), 97.30 ($J_{C\text{-}1,H\text{-}1}$ = 165.1 Hz from a coupled HMQC spectrum, C-$1^3\beta$), 96.96 ($J_{C\text{-}1,H\text{-}1}$ = 173.6 Hz from a coupled HMQC spectrum, C-$1^{4'}\alpha$), 96.54 (C-1^8), 96.26 (C-1^2), 96.03 (C-$1^{5'}$), 96.01 (C-1^5), 84.26 (C-1^1), 78.16 (C-2^8), 78.15 (C-4^2), 77.04 (C-4^8), 76.23 (C-3^2), 75.85 (C-3^1), 75.24 (C-5^1), 74.60 (C-4^1), 74.02 (C-5^2), 73.80, 73.67, 73.63 (OCH_2), 73.39 (C-3^8), 73.32 (C-$2^{4'}$), 73.26 (C-2^4), 73.19 (C-3^3), 72.25, 71.48 (OCH_2), 71.03 (C-5^3), 70.98 (C-5^5, OCH_2), 70.83 (C-$5^{5'}$), 69.85 (C-2^3), 69.65 (C-3^5), 69.53 (C-$3^{5'}$), 69.32 (C-$3^{4'}$, C-4^2), 69.28 (C-4^3), 68.64 (C-3^4), 68.47 (C-5^4), 68.45 (C-5^5), 68.38 (C-$4^{5'}$), 67.63 (C-$5^{4'}$), 67.50 (C-6^2), 67.09 (C-6^3), 65.58 (C-5^8), 64.32 (C-4^4), 64.31 (C-$4^{4'}$), 63.55 (C-6^1), 61.60 (C-6^5), 61.59 (C-$6^{4'}$), 61.50 (C-6^4), 61.46 (C-$6^{5'}$), 55.56 (C-2^2), 54.96, 54.88, 54.81 (OCH_3), 54.65 (C-2^1), 53.69 (C-2^5), 53.63 (C-$2^{5'}$), 20.85, 20.37, 20.29, 20.11, 20.02, 19.90, 19.75 (OAc), 16.06 (C-6^8) ppm. FAB-MS: *m*/*z* = 3081 $[M + Na]^+$.

Supporting Information (see footnote on the first page of this article): HPLC traces, ^{1}H and ^{13}C NMR spectra of key compounds.

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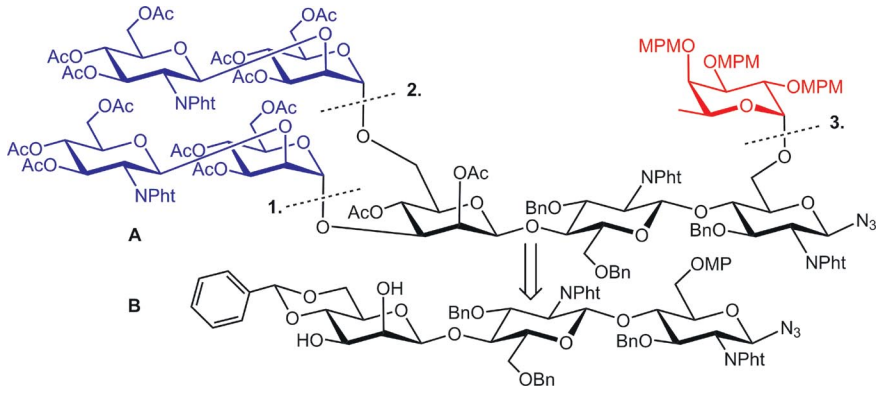
Oligosaccharide Synthesis



A modular synthesis of core-fucosylated N-glycans was optimized, leading to the bi-antennary octasaccharide N-glycan **A**. Several obstacles to the synthesis of functionalized core trisaccharide building block **B** were overcome, leading to an improved and efficient protocol for β-mannosylation by intramolecular inversion.

Keywords: Carbohydrates / Glycosylation / Oligosaccharides / Glycoproteins / Stereoselectivity

