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Synthesis of a core trisaccharide building block for the assembly of *N*-glycan neoconjugates

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Dedicated to Professor George Fleet on occasion of his 65th birthday

ABSTRACT

A short and high yielding synthesis of a core trisaccharide **1** as the key building block in the assembly of a library of *N*-glycan neoconjugates is presented. The β-D-Manp-(1→4)-D-GlcpNAc linkage was introduced by inversion of the C-2 position of a β-glucoside. The glucosyl donor was efficiently synthesised following a recently published one-pot strategy. 2-Naphthylmethyl and benzylidene-acetal protection in the terminal mannose permitted selective liberation of main branching sites for subsequent glycosylation. A C5 azido linker attached to the anomeric position, which is stable throughout the synthesis, will allow for the posterior immobilisation of deprotected glycans on a microarray surface.

1. Introduction

Glycosylation is the major and most complex posttranslational modification found in over half of all human proteins and usually occurs at Asn, Ser and Thr residues. It is believed to introduce the level of variability necessary for complex processes in higher organisms. Altered glycosylation is also a common feature of cancer cells resulting in an increase of truncated, incomplete or less often novel glycosylation patterns, some of which are well-known tumour markers.[1] Not surprisingly there is an increasing interest in deciphering the interactions of carbohydrates with specific receptors in molecular recognition processes.

To address the specific functions of glycan structures seems an almost impossible task when confronted with the huge structural diversity of these structures, the usually low affinities of binding to proteins and the problems associated with obtaining sufficiently pure samples from natural sources. Derived from the high-throughput tools of genomics and proteomics, microarray techniques have emerged as the method of choice for the high-throughput detection of binding partners of specific carbohydrate epitopes. Carbohydrate structures are spatially organised and immobilised on a solid support and the interaction with tagged putative receptors measured directly or via tagged non-specific secondary antibodies.[2]

A disadvantage of microarrays is still the supply of sufficient amounts of pure and well-characterised carbohydrate structures. The heterogeneity of protein glycosylation and scarce availability severely hamper the isolation of sufficient amounts of pure material from natural sources for structure activity studies. Chemical synthesis and specifically parallel solid-phase oligosaccharide synthesis, however, hold promise for the rapid generation of large numbers of defined oligosaccharide structures with high purity conveniently modified with a handle for immobilisation. In this regard, the synthesis of *N*-glycan structures has received a great deal of attention in the past and remains a highly active field.[3–32]

We recently started a research programme directed towards the construction of a microarray platform of synthetic *N*-glycans to be able to study the influence of branching type and degree, terminal sugars and core-fucosylation on binding to proteins and other glycans in a high-throughput manner. It was clear from the start that the synthesis of a comprehensive collection of *N*-glycans with the envisioned diversity and equipped with a linker for direct surface immobilisation was a difficult task and should ideally be tackled by an automated parallel solid-phase assembly of optimised building blocks.

Most *N*-glycans share a common pentasaccharidic motif, suggesting that a modular approach based on a key scaffold should be particularly powerful for the synthesis of high-mannose, complex and hybrid type oligosaccharides.[10,33]

Our synthetic strategy for the modular assembly of *N*-glycans from a panel of glycosyl donors based on a trisaccharidic scaffold is illustrated in Scheme 1. Similar approaches have been applied to the solid-phase synthesis of protected *N*-glycan precursors by Schmidt[19,33] and Seeberger.[16] Due to the importance of having easy access to a core trisaccharidic building block (e.g., **1**), a number of approaches have been published to prepare these conveniently protected intermediates.[6,16,21,34] However, access to sufficient amounts of this important type of building block is still hampered by low overall yields and the large number of steps involved. Herein, we report a short, relatively simple and high yielding synthesis of trisaccharide **1**.

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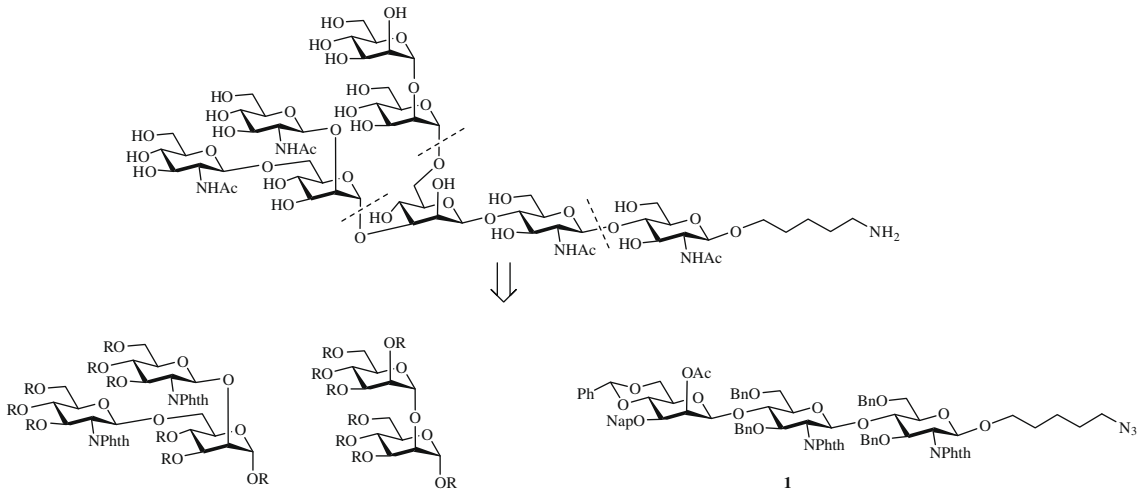
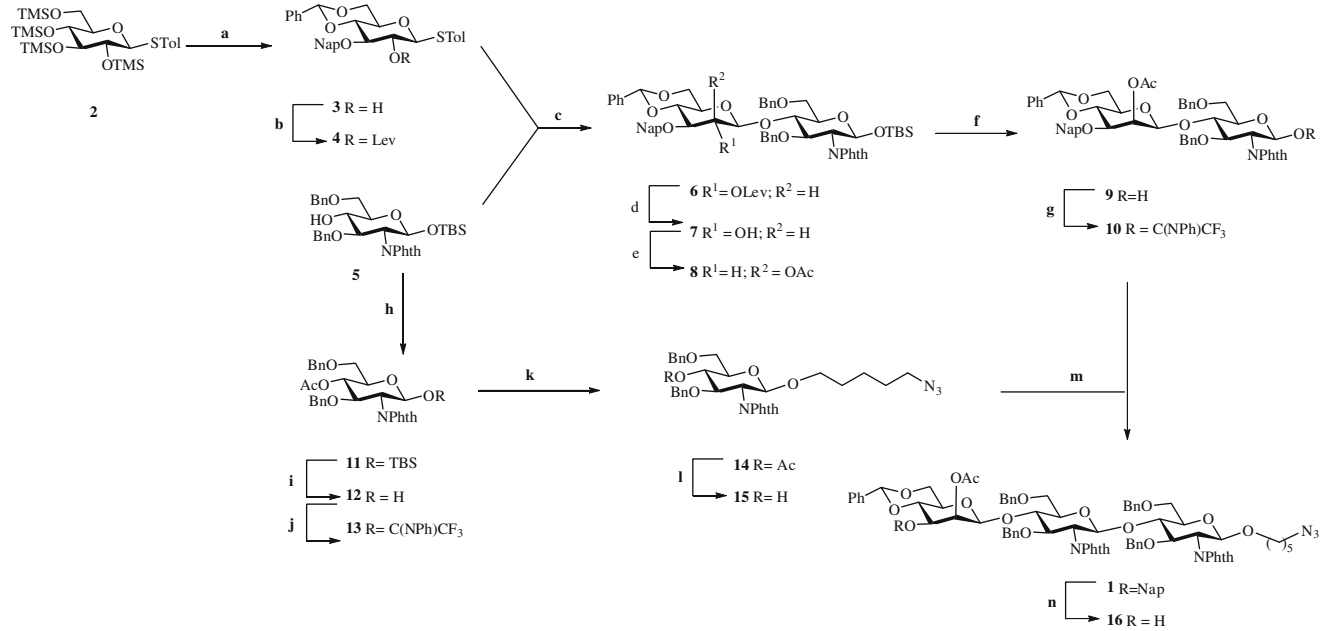


Scheme 1. Retrosynthetic analysis of *N*-glycans.

2. Results and discussion

We envisaged a synthetic approach allowing the selective deprotection of the main substitution sites OH-3, OH-4 and OH-6 of the terminal β-D-mannopyranosyl unit (Scheme 2). Both positions OH-4 and OH-6 were conveniently protected as a benzylidene acetal, whereas OH-3 required an orthogonal group to acetate, benzylidene acetal, azide benzyl and phthalimide functions present in the proposed trisaccharide scaffold. With the 2-naphthyl methyl ether (Nap), which can be easily removed under mild oxidative conditions with DDQ,[35] we found the compatibility and acid stability required for the projected route. Additionally, we required a conveniently protected amino type linker introduced early in the synthesis for posterior conjugation of the deprotected glycans to activated surfaces, nanoparticles or proteins. In this way, we hope to minimise loss of valuable material reported for late stage modifications of *N*-glycans. At the same time, a similar linker will act as a handle for the solid-phase parallel synthesis currently being developed in our laboratory. Working with such an amino type linker over the course of the glycan construction requires orthogonal protection for the amine functionalities of glucosamine, which occur as acetamides in natural glycans, and the linker amino function. We chose phthalimide protection because of its excellent anchimeric assistance in β-selective glycosylations as a glucosamine-protecting group and an azide for masking the terminal amino function of the linker.

For the construction of the β-mannopyranosyl unit we chose an epimerisation route starting from pertrimethylsilylated thioglucoside **2**. Epimerisation of β-glucosides to β-mannosides has been successfully applied in the synthesis of various *N*-glycans and smaller fragments, either via an intramolecular approach[8,11] or by an ultrasound enhanced substitution of a C-2 trifluoromethane-



Scheme 2. Reagents and conditions: (a) (i) TMSOTf, PhCHO, DCM, 0 °C, (ii) 2-NapCHO, Et_3SiH, −86 °C, (iii) TBAF, −86 °C to rt 60%; (b) LevOH, EDC·HCl, DMAP, DCM, 1 h, rt, 98%; (c) NIS, TMSOTf, DCM, −20 °C, 1 h, 85%; (d) N_2H_4·AcOH, MeOH, DCM, 82%; (e) (i) Tf_2O, pyr, DCM, 0 °C ii) Tol, nBu$_4$NOAc, sonication, 18 h, 73%; (f) TBAF, THF, AcOH, rt, 2 h; (g) ClC(NPh)CF_3, K_2CO_3 acetone, rt, 89% over two steps; (h) Ac_2O, pyr, 87%; (i) TBAF, AcOH, 0 °C, 1 h; (j) ClC(NPh)CF_3, K_2CO_3 acetone, rt, 78% over two steps; (k) $HOCH_2(CH_2)_3CH_2N_3$, TMSOTf, mol. sieves, DCM, 3.5 h, 90%; (l) MeONa, MeOH, 1 h, 95%; (m) TMSOTf, DCM, 0 °C to rt, 1 h, 74%; (n) DDQ, DCM, rt 1 h, 70% based on recovered starting material.

sulfonate by an external nucleophile with inversion of configuration.[34,36] With usually good to excellent yields and complete stereoselectivity, epimerisation can be regarded as a reasonably safe method for the preparation of β-mannosides. A drawback of this approach is the usually higher synthetic effort required to produce the β-mannosidic linkage, which is installed via a deprotection, triflation and inversion sequence and the added difficulty of differentiating the OH-2 and OH-3 positions in the glucopyranosyl donor. Making use of a recently published regioselective one-pot protection method for glucose derivatives,[37] we prepared the fully differentiated glucose donor **3** in a one-pot procedure from persilylated thioglycoside **2**. This rapid full differentiation of the glucopyranosyl unit allows the design of a short route for the *N*-glycan core trisaccharide synthesis comparable to the direct β-mannosylation procedure.

Starting from compound **2**, the trimethylsilyl trifluoromethanesulfonate-catalysed acetalisation of OH-4 and OH-6 with benzaldehyde,[13] followed by a highly regioselective reductive arylmethylation at OH-3 with 2-naphthaldehyde in a one-pot reaction at −86 °C, afforded compound **3** in 60% yield. We attribute the lower than reported yield (72%) to the partial cleavage of the silylether groups and loss of selectivity in the one-pot protection. The stepwise introduction of the benzylidene acetal and 2-naphthyl methyl ether from the bis-silylether intermediate afforded higher yields for the single steps but was not economic when compared to the one-pot synthesis. The final protection of position OH-2 as a levulinate afforded the glycosyl donor **4** in a nearly quantitative yield (98%). Glycosylation of the known glucosamine acceptor **5**[38] under NIS/TMSOTf activation proceeded with complete stereoselectivity, owing to the anchimeric assistance of the 2-*O*-levulinate, to give disaccharide **6** in 85% yield. The naturally occurring *manno* configuration was then achieved in a high yielding displacement reaction of a C-2 trifluoromethanesulfonate by an external nucleophile with very good reproducibility and complete stereocontrol. After deprotection of the 2-*O*-levulinate **7** in high yield (82%), the OH-2 position was activated with trifluoromethanesulfonic anhydride and treated with nBu$_4$NOAc under sonication as described by Fuerstner[36] to afford the β-mannopyranosyl derivative **8** in 73% yield over two steps. The newly installed *manno* configuration of acetate **8** was confirmed by determination of a typical H1′ C1′ coupling constant of 160 Hz in a coupled HSQC experiment.

Deprotection of the anomeric TBS-ether in **8** with TBAF/AcOH took place in almost quantitative yield to give hemiacetal **9**, which was activated without further purification as a *N*-phenyltrifluoroacetimidate following standard procedures[39] to afford donor **10** in 89% yield over the two steps. The successful deprotection of the anomeric position of **8** is in sharp contrast with previous results in these series using the more stable thexyldimethylsilylether protection where the reaction was sluggish and low yielding.

Glycosyl acceptor **15** was readily available from the common glucosamine intermediate **5** in 4 steps. After acetylation of the free 4-hydroxyl group **11**, the anomeric silylether **12** was removed and activated as *N*-phenyltrifluoracetimidate **13** in 78% yield over the two steps. Coupling of imidate **13** with 5-azidopentan-1-ol under standard TMSOTf catalysis afforded glycoside **14** in 90% yield, which was deacetylated under Zemplén conditions to yield acceptor **15** equipped with a C5-linker at the anomeric position as a handle for later surface immobilisation. For the final assembly of the trisaccharide scaffold, imidate **10** and acceptor **15** were coupled under TMSOTf catalysis to afford trisaccharide **1** in 74% yield. In this last coupling reaction, the *N*-phenyltrifluoroacetimidates performed better than the analogous trichloroacetimidates, which decomposed more rapidly towards *N*-trichloroacetamides and made a higher excess of donor necessary to achieve comparable yields. The less reactive *N*-phenyltrifluoroacetimidates could in turn be used in nearly equimolar amounts and reacted eventually without producing degradation products which would hamper an efficient purification. Thus, this new route produced the fully differentiated core *N*-glycan trisaccharide **1** in 33% overall yield in just eight steps from the known thioglycoside **3**.[37]

With the trisaccharide **1** in hand, we selectively deprotected the 2-naphthyl methyl ether group in the presence of the benzylidene acetal. In our initial attempts, the oxidative removal of the 2-naphthyl methyl ether was accompanied by partial cleavage of the benzyl groups in the glucosamine residues resulting in low yields of alcohol **16**. Careful monitoring of the reaction progress and quenching after 1 h afforded the desired alcohol **16** in 70% yield based on about 20% yield of recovered starting material. The benzylidene acetal remained untouched under these conditions.

3. Conclusions

In conclusion, we have presented a short and high yielding synthesis to a key trisaccharidic scaffold for the assembly of *N*-glycans as depicted in Scheme 1. Our route improves the published procedures in yield, simplicity and stereochemical outcome and is easily scaled up to provide multigram amounts of the trisaccharide. Protection of the principal branching position in 3-OH, 4-OH and 6-OH as 2-naphthyl methyl ether and benzylidene acetal was shown to be stable under a wide range of reaction conditions and permit selective liberation of 3-OH, 4-OH and 6-OH acceptor functions for subsequent glycosylations. Using this core trisaccharide as a scaffold, we are presently engaged in the assembly of a series of *N*-glycans of the high mannose and the complex type for immobilisation and screening on a microarray platform.

4. Experimental

4.1. General methods

Chemicals were purchased from Sigma–Aldrich or Acros and used without further purification. All reaction solvents were dried over activated 4 Å or 3 Å molecular sieves. Dichloromethane was freshly distilled from CaH_2 previous to use. Thin layer chromatography was carried out using Merck aluminium sheets Silica Gel 60 F_{254} and visualised by UV irradiation (254 nm) or by staining (15 g of vanillin and 2.5 mL of H_2SO_4 concd in 250 mL of EtOH). Purification of compounds was performed on a Biotage SP4 automated flash chromatography system, Biotage AB, Uppsala Sweden or by conventional flash chromatography using Merck 62 Å 230–400 mesh silica gel. All solvents were concentrated using rotary evaporation. All ^{1}H and ^{13}C spectra were acquired on Bruker 500 mg spectrometer and chemical shifts (δ) are given in ppm relative to the residual signal of the solvent used. Splitting patterns are designated as s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Coupling constants (J) are reported in hertz. Optical rotations $[\alpha]_D$ were measured on a Perkin Elmer 341 polarimeter.

The mass spectrometric data were obtained from a Waters LCT Premier XE instrument with a standard ESI source by direct injection. The instrument was operated with a capillary voltage of 1.0 kV and a cone voltage of 200 V. Cone and desolvation gas flow were set to 50 and 500 l/h, respectively; source and desolvation temperatures were 100 °C. The exact mass was determined using glycocholic acid (Sigma) as an internal standard (2 M·Na$^+$, m/z = 953.6058).

4.1.1. *p*-Toluenyl 4,6-*O*-benzylidene-2-*O*-levulinoyl-3-*O*-(2-naphthylmethyl)-L-thio-β-D-glucopyranoside 4

To a stirred solution of compound **3** (300 mg, 0.58 mmol) in CH_2Cl_2 (3.0 mL), levulinic acid (89 μL, 0.87 mmol), 1-(3-dimethyl-

aminopropyl)-3-ethylcarbodiimide hydrochloride (166 mg, 0.87 mmol) and 4-dimethylaminopyridine (50 mg, 0.40 mmol) were added at room temperature. The reaction mixture was stirred until TLC (hexane/EtOAc; 4/1) showed complete conversion of the starting material (2 h). The mixture was diluted with EtOAc (100 mL) and washed with aqueous HCl (0.01 M), water, saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography (hexane/EtOAc, 9/1 to 1/3) to give the title compound as a white solid (350 mg, 98%). R_f 0.39 (hexane/EtOAc, 4/1); $[\alpha]_D^{20} = +7.3$ (*c* 0.76, $CHCl_3$); ^{1}H NMR (500 mg, $CDCl_3$) δ 7.87–7.69 (m, 4H, Ar), 7.56–7.32 (m, 10H, Ar), 7.12 (d, *J* = 8.0, 2H, Ar), 5.59 (s, 1H, OC*H*Ph), 5.05–4.96 (m, 2H, H-2, CH_2Nap), 4.86 (d, *J* = 12.2, 1H, CH_2Nap), 4.62 (d, *J* = 10.1, 1H, H-1), 4.38 (dd, *J* = 5.0, 10.5, 1H, H-6a), 3.85–3.71 (m, 3H, H-3, H-4, H-6b), 3.48 (td, *J* = 5.0, 9.6, 1H, H-5), 2.67 (t, *J* = 6.7, 2H, CH_2Lev), 2.60–2.46 (m, 2H, CH_2Lev), 2.34 (s, 3H, CH_3Tol), 2.13 (s, 3H, CH_3Lev). ^{13}C NMR (126 mg, $CDCl_3$) δ 206.11, 171.20, 138.51, 137.12, 135.55, 133.48, 133.18, 132.96, 129.67, 129.05, 128.28, 128.17, 128.00, 127.90, 127.64, 126.81, 126.12, 126.02, 125.86, 101.28, 87.06, 81.26, 79.59, 74.36, 71.74, 70.48, 68.54, 37.75, 29.79, 28.02, 21.15. HRMS (ESI): *m/z* calcd for $C_{36}H_{36}NaO_7S$: 635.2079 [M+Na]$^+$; found 635.2131.

4.1.2. *tert*-Butyldimethylsilyl 4,6-*O*-benzylidene-2-*O*-levulinoyl-3-*O*-(2-naphthylmethyl)-β-D-glucopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-deoxy-2-phthalamido-β-D-glucopyranoside 6

A mixture of thioglycoside **4** (500 mg, 0.81 mmol), acceptor **5**[38] (328 mg, 0.54 mmol) and 3 Å molecular sieves in dry CH_2Cl_2 (3 mL) was stirred under argon for 45 min at room temperature. The mixture was cooled to −20 °C and *N*-iodosuccinimide (200 mg, 0.81 mmol) was added, followed by trimethylsilyl trifluoromethanesulfonate (15 μL, 0.08 mmol). The reaction mixture was stirred at −20 °C until TLC (hexane/EtOAc; 4/1) showed complete conversion of acceptor (90 min). The reaction was quenched by adding Et_3N (250 μL), filtered through a plug of Celite and the filtrate was concentrated. The crude product was purified by medium pressure flash chromatography (hexane/EtOAc, 95/5 to 60/40) to give the title compound as a white foam (450 mg, 85%). R_f 0.31 (hexane/EtOAc, 4/1); $[\alpha]_D^{20} = +5.7$ (*c* 0.5, $CHCl_3$); ^{1}H NMR (500 mg, $CDCl_3$) δ 7.85–6.91 (m, 26H, Ar), 5.50 (s, 1H, OC*H*Ph), 5.30 (d, *J* = 8.1, 1H, H-1), 5.07–4.95 (m, 2H, H-2′, CH_2Nap), 4.83 (d, *J* = 12.3, 1H, CH_2Nap), 4.75 (m, 2H, CH_2Ph), 4.63 (d, *J* = 8.0, 1H, H-1′), 4.49 (d, *J* = 12.2, 1H, CH_2Ph), 4.44 (d, *J* = 12.4, 1H, CH_2Ph), 4.31–4.19 (m, 2H, H-6a′, H-3), 4.13–3.98 (m, 2H, H-2, H-4), 3.82 (dd, *J* = 3.1, 11.1, 1H, H-6a), 3.73–3.60 (m, 3H, H-6b, H-3′, H-4′), 3.55 (d, *J* = 9.1, 1H, H-5), 3.49 (t, *J* = 10.3, 1H, H-6b′), 3.27 (td, *J* = 4.9, 9.5, 1H, H-5′), 2.75–2.55 (m, 2H, CH_2Lev), 2.52–2.34 (m, 2H, CH_2Lev), 2.12 (s, 3H, CH_3Lev), 0.65 (s, 9H, ^{t}Bu TBS), 0.03 (s, 3H, CH_3TBS), -0.12 (s, 3H, CH_3TBS). ^{13}C NMR (126 mg, $CDCl_3$) δ 206.11, 171.22, 138.70, 138.09, 137.26, 135.80, 133.63, 133.24, 132.94, 131.64, 129.02, 128.43, 128.27, 127.97, 127.90, 127.87, 127.81, 127.75, 127.67, 127.00, 126.53, 126.07, 125.93, 125.86, 123.03, 101.25, 100.67, 93.32, 81.73, 78.56, 78.05, 76.40, 74.89, 74.31, 74.11, 73.72, 73.60, 68.65, 67.91, 65.92, 57.85, 37.68, 29.82, 27.81, 25.33, 17.54, −4.22, −5.50. HRMS (ESI): *m/z* calcd for $C_{63}H_{69}NNaO_{14}Si$: 1114.4385 [M+Na]$^+$; found 1114.4362.

4.1.3. *tert*-Butyldimethylsilyl 4,6-*O*-benzylidene-3-*O*-(2-naphthylmethyl)-β-D-glucopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-deoxy-2-phthalamido-β-D-glucopyranoside 7

To a stirred solution of compound **6** (800 mg, 0.74 mmol) in CH_2Cl_2 (20 mL) was added a solution of hydrazine acetate (102 mg, 1.10 mmol) in MeOH (2.0 mL). The mixture was stirred at room temperature until TLC (hexane/EtOAc; 7/3) showed complete conversion of the starting material (1 h). The mixture was concentrated to dryness and the crude product was purified by medium pressure flash chromatography (hexane/EtOAc, 93/7 to 1/1) to give the title compound as a white solid (600 mg, 82%). R_f 0.41 (hexane/EtOAc, 4/1); $[\alpha]_D^{20} = +22.1$ (*c* 0.95, $CHCl_3$); ^{1}H NMR (500 mg, $CDCl_3$) δ 7.85–6.89 (m, 26H, Ar), 5.52 (s, 1H, OC*H*Ph), 5.33 (d, *J* = 8.1, 1H, H-1), 5.12 (d, *J* = 11.9, 1H, CH_2Nap), 4.98 (d, *J* = 11.9, 1H, CH_2Nap), 4.81 (d, *J* = 12.3, 1H, CH_2Ph), 4.78–4.69 (m, 2H, CH_2Ph, H-1′), 4.62 (d, *J* = 12.2, 1H, CH_2Ph), 4.47 (d, *J* = 12.3, 1H, CH_2Ph), 4.41 (dd, *J* = 8.8, 10.7, 1H, H-3), 4.21–4.10 (m, 3H, H-2, H-4, H-6a′), 4.05 (dd, *J* = 3.1, 11.5, 1H, H-6a), 3.79 (d, *J* = 10.3, 1H, H-6b), 3.70–3.51 (m, 5H, H-5, H-2′, H-3′, H-4′, H-6b′), 3.31–3.19 (m, 2H, H-5′, OH), 0.68 (s, 9H, ^{t}BuTBS), 0.05 (s, 3H, CH_3TBS), −0.10 (s, 3H, CH_3TBS). ^{13}C NMR (126 mg, $CDCl_3$) δ 138.52, 137.72, 137.32, 135.91, 133.71, 133.28, 133.01, 131.61, 128.97, 128.41, 128.24, 128.15, 127.94, 127.79, 127.65, 127.36, 127.10, 126.72, 126.09, 126.01, 125.83, 123.12, 103.63, 101.26, 93.51, 81.27, 80.29, 78.95, 77.93, 75.43, 74.68, 74.56, 74.40, 73.57, 68.67, 68.37, 66.30, 57.98, 25.30, 17.52, −4.25, −5.52. HRMS (ESI): *m/z* calcd for $C_{58}H_{63}NNaO_{12}Si$: 1016.4017 [M+Na]$^+$; found 1016.4034.

4.1.4. *tert*-Butyldimethylsilyl 2-*O*-acetyl-4,6-*O*-benzylidene-3-*O*-(2-naphthylmethyl)-β-D-mannopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-deoxy-2-phthalamido-β-D-glucopyranoside 8

To a cooled (0 °C) solution of compound **7** (1.26 g, 1.27 mmol) in dry CH_2Cl_2 (55 mL), pyridine (4.2 mL, 51.9 mmol) and trifluoromethanesulfonic anhydride (3.5 mL, 20.8 mmol) were added. The reaction mixture was stirred at 0 °C until TLC (hexane/EtOAc; 4/1) showed complete conversion of the starting material (1 h). The mixture was diluted with CH_2Cl_2 and washed with saturated $NaHCO_3$ solution. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated to afford the trifluoromethanesulfonate, which was used in the next step without further purification. The crude product was dissolved in dry toluene (28 mL) and tetrabutylammonium acetate (1.04 g, 3.45 mmol) was added. The resulting suspension was sonicated for 18 h. The reaction mixture was concentrated to dryness and the crude product was purified by flash chromatography (hexane/EtOAc, 4/1) to give the title compound as a white solid (960 mg, 73%, two steps). R_f 0.44 (hexane/EtOAc, 4/1); $[\alpha]_D^{20} = +3.0$ (*c* 0.20, $CHCl_3$); ^{1}H NMR (500 mg, $CDCl_3$) δ 7.84–6.89 (m, 26H, Ar), 5.57 (s, 1H, OC*H*Ph), 5.55 (d, *J* = 2.5, 1H, H-2′), 5.33 (d, *J* = 8.1, 1H, H-1), 4.91–4.79 (m, 2H, CH_2Ar), 4.77–4.68 (m, 3H, CH_2Ar, H-1′), 4.47 (d, *J* = 12.2, 2H, CH_2Ar), 4.32 (t, *J* = 9.7, 1H, H-3), 4.20 (dd, *J* = 4.7, 10.4, 1H, H-6a′), 4.17–4.09 (m, 2H, H-2, H-4), 3.94 (t, *J* = 9.5, 1H, H-4′), 3.83 (dd, *J* = 2.2, 11.0, 1H, H-6a), 3.71 (d, *J* = 11.0, 1H, H-6b), 3.66–3.54 (m, 3H, H-5, H-3′, H-6b′), 3.20 (td, *J* = 4.9, 9.6, 1H, H-5′), 2.22 (s, 3H, CH_3CO), 0.68 (s, 9H, ^{t}BuTBS), 0.05 (s, 3H, CH_3TBS), −0.09 (s, 3H, CH_3TBS). ^{13}C NMR (126 mg, $CDCl_3$) δ 170.30, 168.24, 167.56, 138.64, 137.86, 137.44, 135.26, 133.68, 133.27, 132.95, 131.58, 128.95, 128.43, 128.20, 128.09, 127.91, 127.78, 127.72, 127.60, 127.12, 126.18, 126.14, 125.99, 125.81, 125.36, 123.14, 123.01, 101.55, 99.50 (C-1′, $J_{C1'-H1'}$ = 160.0 Hz), 93.43, 79.24, 77.86, 76.77, 75.72, 74.38, 74.34, 73.42, 71.46, 69.17, 68.56, 68.45, 66.95, 57.83, 25.30, 21.05, 17.52, −4.26, −5.52. HRMS (ESI): *m/z* calcd for $C_{60}H_{65}NNaO_{13}Si$: 1058.4122 [M+Na]$^+$; found 1058.4124.

4.1.5. 2-*O*-Acetyl-4,6-*O*-benzylidene-3-*O*-(2-naphthylmethyl)-β-D-mannopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-deoxy-2-phthalamido-β-D-glucopyranosyl *N*-phenyl trifluoroacetimidate 10

To a cooled (0 °C) stirred solution of compound **8** (200 mg, 0.19 mmol) in THF (1 mL) were added TBAF (1 M in THF, 300 μL, 0.30 mmol) and acetic acid (18 μL, 0.30 mmol). The reaction mixture was stirred at 0 °C until TLC (hexane/EtOAc; 4/1) showed complete conversion of the starting material (2 h). The reaction mixture was diluted with EtOAc (100 mL) and washed with satu-

rated $NaHCO_3$, water and brine. The organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated. The crude product was used in the next step without further purification. To a solution of hemiacetal **9** (170 mg, 0.180 mmol) and ClC(NPh)CF_3[40] (76 mg, 0.36 mmol) in acetone (2 mL), solid potassium carbonate (51 mg, 0.36 mmol) was added at room temperature. The reaction mixture was stirred until TLC (hexane/EtOAc, 3/2) showed complete conversion of the starting material (16 h). The reaction was diluted with acetone, filtered over a plug of Celite and the filtrate was concentrated. The crude product was purified by flash chromatography (hexane/EtOAc/Et_3N, 300/200/1) to give the title compound as a white foam (180 mg, 89%). R_f 0.40 (hexane/EtOAc, 3/2); ^{1}H NMR (500 mg, $CDCl_3$) δ 8.02–6.57 (m, 26H), 6.27 (br s, 1H), 5.56 (s, 1H), 5.47 (d, J = 2.8, 1H), 4.94–4.76 (m, 2H), 4.77–4.67 (m, 2H), 4.63 (s, 1H), 4.49–4.11 (m, 5H), 3.90 (t, J = 9.6, 1H), 3.83–3.54 (m, 4H), 3.49 (dd, J = 3.4, 9.8, 1H), 3.14 (td, J = 4.9, 9.7, 1H), 2.19 (s, 3H). HRMS (ESI): m/z calcd for $C_{62}H_{55}F_3N_2NaO_{13}$: 1115.3554 $[M+Na]^+$; found 1115.3420.

4.1.6. *tert*-Butyldimethylsilyl 4-*O*-acetyl-3,6-di-*O*-benzyl-2-deoxy-2-phthalamido-β-D-glucopyranoside 11

To a cooled (0 °C) solution of **5** (5.0 g, 8.3 mmol) in pyridine (20 mL), Ac_2O (8 mL) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 2 h (until complete conversion). Finally, cold EtOH (100 mL) was slowly added and the mixture was concentrated. The crude product was taken in toluene (3 × 100 mL) and concentrated several times for the azeotropic removal of pyridine. The crude product was purified by flash chromatography (hexane/EtOAc, 2/1) to give the title compound as a clear oil (4.7 g, 87%). $[\alpha]_D^{20} = +47.2$ (c 1.06, $CHCl_3$); ^{1}H NMR (500 mg, $CDCl_3$) δ 7.80–7.70 (m, 4H, Ar); 7.35–6.26 (m, 5H, Ar); 6.04–6.93 (m, 5H, Ar); 5.38 (d, J = 8.0, 1H, H-1); 5.14 (m, 1H, H-4); 4.61 (d, J = 12.0, 1H, CH_aH$_b$Ph); 4.57 (s, 2H, CH_2Ph); 4.48 (dd, J = 9.0, 10.8, 1H, H-3); 4.37 (d, J = 12.0, 1H, CH$_a$$H_b$Ph); 4.22 (dd, J = 8.0, 10.8, 1H, H-2); 3.81–3.77 (m, 1H, H-5); 3.65–3.61 (m, 2H, H-6a, H-6b); 1.96 (s, 3H, CH_3CO); 0.68 (s, 9H, ^{t}BuTBS); 0.07 (s, 3H, CH_3TBS), −0.07 (s, 3H, CH_3TBS); ^{13}C NMR (126 mg, $CDCl_3$) δ 169.72; 138.05, 137.84, 131.59, 127.97, 127.91; 133.87, 128.33, 128.09, 127.80, 127.70, 127.60, 127.41, 123.24, 123.19, 123.15; 93.40; 76.71; 73.60, 73.56; 73.50; 72.63; 69.98; 57.64; 25.30; 20.93; 17.51; −4.20, −5.50; HRMS (ESI): m/z calcd for $C_{36}H_{43}NNaO_8Si$ $[M+Na]^+$ 668.2748, found 668.2662.

4.1.7. 4-*O*-Acetyl-3,6-di-*O*-benzyl-2-deoxy-2-phthalamido-β-D-glucopyranoside *N*-phenyl trifluoroacetimidate 13

A solution of compound **11** (3.45 g, 5.34 mmol) in dry THF (27 mL) was cooled to 0 °C, to which TBAF (1 M in THF, 8.5 mL, 8.55 mmol) and acetic acid (0.47 mL, 8.55 mmol) were added and the resulting mixture was stirred at 0 °C for 2 h. The reaction was quenched with saturated $NaHCO_3$ solution (75 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with saturated NaCl solution, dried over anhydrous $MgSO_4$, filtered and concentrated. The crude hemiacetal **12** was dissolved in acetone (53 mL), ClC(NPh)CF_3 (2.2 g, 10.7 mmol) and K_2CO_3 (1.5 g, 10.7 mmol) were added and the mixture was stirred at room temperature overnight. The reaction was diluted with EtOAc, filtered over a plug of Celite and the solvent evaporated. The crude product was purified by flash chromatography (hexane/EtOAc 2/1) to give the title compound as a clear oil (2.9 g, 78%, two steps). $[\alpha]_D^{20} = +246.0$ (c 2.90, $CHCl_3$); ^{1}H NMR (500 mg, $CDCl_3$ at 50 °C) δ 7.93–7.71 (m, 4H, Ar); 7.37–7.20 (m, 7H, Ar); 7.17–6.95 (m, 5H, Ar); 6.64 (m, 2H, Ar); 6.39 (bs, 1H, H-1); 5.23 (m, 1H, H-3); 4.63 (d, J = 12.0, 1H, CH_aH$_b$Ph); 4.57 (s, 2H, CH_2Ph); 4.50 (m, 2H, H-2, H-5); 4.34 (d, J = 12.0, 1H, CH$_a$$H_b$Ph); 3.73 (m, 1H, H-4); 3.62 (m, 2H, H-6); 1.96 (s, 3H, CH_3CO); ^{13}C NMR (126 mg, $CDCl_3$ at 50 °C) δ 169.72; 167.41; 142.94; 137.83, 137.57, 134.21, 131.52; 133.98, 128.56, 128.37, 128.30, 128.10, 127.98, 127.85, 127.76, 127.67, 127.48, 127.41, 124.37, 123.54, 123.45, 119.30; 93.37; 76.76; 73.97; 71.95, 73.59; 69.17; 54.71; 20.68; HRMS (ESI): m/z calcd for $C_{38}H_{35}FN_2NaO_8$ $[M+Na]^+$ 725.2179, found 725.1815.

4.1.8. 5-Azidopentyl 4-*O*-acetyl-3,6-di-*O*-benzyl-2-deoxy-2-phthalamido-β-D-glucopyranoside 14

A mixture of compound **13** (2.92 g, 4.16 mmol), 5-azidopentan-1-ol (0.64 g, 4.95 mmol) and 3 Å molecular sieves in dry CH_2Cl_2 (38 mL) was stirred under argon for 20 min at room temperature. The mixture was cooled to 0 °C and trimethylsilyltrifluoromethanesulfonate (76 μL, 0.42 mmol) was added. The reaction mixture was warmed to room temperature and stirred overnight. The reaction was quenched by adding Et_3N (100 μL), diluted with CH_2Cl_2, filtered over a plug of Celite and concentrated. The crude product was purified by flash chromatography (hexane/EtOAc 4/1) to give the title compound as a clear oil (2.4 g, 90%). $[\alpha]_D^{20} = +122.6$ (c 2.70, $CHCl_3$); ^{1}H NMR (500 mg, $CDCl_3$) δ 7.72 (m, 5H, Ar); 7.38–7.27(m, 5H, Ar); 7.02–6.90 (m, 4H, Ar); 5.15 (d, J = 8.5, 1H, H-1); 4.61 (d, J = 12.0, 1H, CH_aH$_b$Ph); 4.57 (s, 2H, CH_2Ph); 4.43 (dd, J = 9.0, 10.7, 1H, H-3); 4.33 (d, J = 12.0, 1H, CH$_a$$H_b$Ph); 4.24 (dd, J = 8.5, 10.7, 1H, H-4); 3.82 (m, 2H, H_2, OCHH(CH$_2$)$_4$N$_3$); 3.76 (m, 1H, OCHH(CH$_2$)$_4$N$_3$); 3.63 (m, 1H, H-6); 3.40 (m, 1H, H-5); 2.92 (m, 2H, O(CH$_2$)$_4$CH_2N$_3$); 1.95 (s, 3H, CH_3CO); 1.48-1.31 (m, 4H, 2 × CH$_2$); 1.14 (m, 2H, CH$_2$); ^{13}C NMR (126 mg, $CDCl_3$) δ 169.63, 137.95, 137.71, 133.97, 131.53, 128.36, 128.11, 127.82, 127.69, 127.45, 123.30, 98.23, 76.96, 73.86, 73.60, 73.48, 72.57, 69.71, 69.22, 55.54, 51.09, 28.72, 28.28, 23.03, 21.02, 20.89, 14.21; HRMS (ESI): m/z calcd for $C_{35}H_{38}N_4NaO_8$ $[M+Na]^+$ 665.2680, found 665.2570.

4.1.9. 5-Azidopentyl 3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside 15

To a cooled (0 °C) solution of **14** (4.95 g, 7.93 mmol) in MeOH (35 mL), MeONa (86 mg, 1.59 mmol) in MeOH (3 mL) was added dropwise. The solution was warmed to room temperature and stirred until TLC (hexane/EtOAc, 7/3) showed complete conversion of the starting material (2 h). The reaction mixture was quenched by adding Amberlite IR-120 (H) cationic exchange resin until neutral pH. The resin was filtered, washed with MeOH and the filtrate was concentrated. The crude product was purified by medium pressure flash chromatography (hexane/EtOAc, 91/9 to 45/55) to give the title compound as a transparent oil (4.53 g, 95%). R_f 0.14 (hexane/EtOAc, 3/1); $[\alpha]_D^{20} = +36.0$ (c 0.9, $CHCl_3$); ^{1}H NMR (500 mg, $CDCl_3$) δ 7.82–6.95 (m, 14H, Ar), 5.16 (d, J = 8.3, 1H, H-1), 4.78 (d, J = 12.2, 1H, CH_2Ph), 4.71–4.50 (m, 3H, CH_2Ph), 4.29–4.22 (m, 1H, H-3), 4.20–4.13 (m, 1H, H-2), 3.92–3.74 (m, 4H, H-4, H-5, H-6a, OCHH(CH$_2$)$_4$N$_3$), 3.68–3.65 (m, 1H, H-6b), 3.44–3.33 (m, 1H, OCHH(CH$_2$)$_4$N$_3$), 3.19 (s, 1H, OH), 3.00–2.81 (m, 2H, O(CH$_2$)$_4$CH_2N$_3$), 1.52–1.25 (m, 4H, 2 × CH$_2$), 1.22–1.04 (m, 2H, CH$_2$); ^{13}C NMR (126 mg, $CDCl_3$) δ 138.23, 137.74, 133.92, 131.67, 131.59, 128.52, 128.43, 128.34, 128.28, 128.16, 128.09, 127.91, 127.81, 127.59, 127.42, 123.39, 123.30, 123.2, 98.30, 78.79, 74.34, 74.28, 73.85, 73.76, 70.64, 69.14, 55.46, 51.11, 28.76, 28.30, 23.04; HRMS (ESI): m/z calcd for $C_{35}H_{38}N_4NaO_8$ $[M+Na]^+$ 665.2680, found 665.2570.

4.1.10. 5-Azidopentyl 2-*O*-acetyl-4,6-*O*-benzylidene-3-*O*-(2-naphthylmethyl)-β-D-mannopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-deoxy-2-phthalamido-β-D-glucopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-deoxy-2-phthalamido-β-D-glucopyranoside 1

A mixture of donor **10** (100 mg, 91.0 μmol), acceptor **15** (44 mg, 76.0 μmol) and 3 Å molecular sieves in dry CH_2Cl_2 (0.5 mL) was stirred for 45 min at room temperature. To this mixture, trimethylsilyl trifluoromethanesulfonate (1.6 μL, 9.1 μmol) was added and stirred at room temperature until TLC (hexane/EtOAc, 4/1) showed com-

plete conversion of the starting material (1 h). The reaction was quenched by adding Et_3N (50 μL), filtered through a plug of Celite and the filtrate was concentrated. The crude product was purified by flash chromatography (hexane/EtOAc, 9/1 to 1/4) to give the title compound as a white solid (80 mg, 74%). R_f 0.21 (hexane/EtOAc, 3/2); $[\alpha]_D^{20} = +3.9$ (c 0.15, $CHCl_3$); ^{1}H NMR (500 mg, $CDCl_3$) δ 7.87–6.77 (m, 40H, Ar), 5.54 (s, 1H, OC*H*Ph), 5.52 (d, J = 3.1, 1H, H-2″), 5.27 (d, J = 8.3, 1H, H-1), 4.96–4.92 (m, 1H, H-1′), 4.91–4.80 (m, 3H, CH_2Ar), 4.74–4.67 (m, 2H, CH_2Ar, H-1″), 4.58–4.48 (m, 4H, CH_2Ar), 4.43 (d, J = 12.1, 1H, CH_2Ar), 4.38 (d, J = 12.1, 1H, CH_2Ar), 4.29 (dd, J = 8.7, 10.6, 1H, H-3′), 4.24–4.09 (m, 6H, H-2, H-3, H-4, H-2′, H-4′, H-6a″), 3.91 (t, J = 9.6, 1H, H-4″), 3.74–3.48 (m, 6H, H-6a, H-6b, H-6a′, H-3″, H-6b″, OC*H*H(CH$_2$)$_4$N$_3$), 3.43 (dd, J = 3.7, 11.0, 1H, H-6b′), 3.35–3.20 (m, 3H, H-5, H-5′, OC*H*H(CH$_2$)$_4$N$_3$), 3.13 (td, J = 4.9, 9.7, 1H, H-5″), 2.97–2.80 (m, 2H, O(CH$_2$)$_4$CH_2N$_3$), 2.22 (s, 3H, CH_3CO), 1.45–1.24 (m, 4H, 2 × CH$_2$), 1.13–1.01 (m, 2H, CH$_2$); ^{13}C NMR (126 mg, $CDCl_3$) δ 170.16, 168.42, 167.50, 138.62, 138.31, 137.78, 137.44, 135.25, 133.97, 133.78, 133.57, 133.28, 132.96, 131.64, 131.41, 128.94, 128.44, 128.24, 128.19, 128.09, 128.03, 127.94, 127.77, 127.71, 127.64, 127.60, 127.45, 127.14, 126.82, 126.17, 125.99, 125.82, 125.39, 123.61, 123.09, 101.54, 99.30, 98.06, 97.02, 78.90, 77.82, 76.82, 76.77, 75.86, 75.77, 74.53, 74.35, 74.16, 73.11, 72.73, 71.43, 69.09, 68.81, 68.42, 68.21, 67.80, 66.92, 56.53, 55.68, 51.06, 28.64, 28.24, 22.97, 21.07; HRMS (ESI): m/z calcd for $C_{87}H_{85}N_5NaO_{19}$: 1526.5736 $[M+Na]^+$; found 1526.5637.

4.1.11. 5-Azidopentyl 2-*O*-acetyl-4,6-*O*-benzylidene-β-D-manno-pyranosyl-(1→4)-3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside 16

To a stirred solution of trisaccharide **1** (81 mg, 53.8 μmol) in CH_2Cl_2 (0.5 mL), 2,3-dichloro-5,6-dicyanobenzoquinone (36 mg, 0.160 mmol) was added. The reaction mixture was stirred at room temperature for 60 min. The reaction was quenched by adding saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, filtered and concentrated. The crude product was purified by medium pressure flash chromatography (hexane/EtOAc, 9/1 to 1/4) to give the title compound as a white solid (41 mg, 56%) and 16 mg of unreacted starting material. R_f 0.39 (hexane/EtOAc, 1/1); ^{1}H NMR (500 mg, $CDCl_3$) δ 7.87–6.78 (m, 40H, Ar), 5.48 (s, 1H, OC*H*Ph), 5.33 (d, J = 2.2, 1H, H-2″), 5.28 (d, J = 8.2, 1H, H-1), 4.98–4.93 (m, 1H, H-1′), 4.88 (d, J = 12.5, 2H, CH_2Ph), 4.78 (s, 1H, H-1″), 4.63 (d, J = 12.0, 1H, CH_2Ph), 4.57–4.40 (m, 5H, CH_2Ph), 4.34–4.09 (m, 7H, H-2, H-3, H-4, H-2′, H-3′, H-4′, H-6a″), 3.76–3.61 (m, 6H, H-3″, H-4″, H-6a, H-6b, OCH_2(CH$_2$)$_4$N$_3$), 3.59–3.51 (m, 2H, H-5′, H-6b″), 3.43 (dd, J = 3.8, 11.0, 1H, H-6a′), 3.35–3.12 (m, 5H, H-5, H-6b′, H-5″, OCH_2(CH$_2$)$_4$N$_3$), 2.97–2.80 (m, 2H, O(CH$_2$)$_4$CH_2N$_3$), 2.21 (s, 3H, CH_3CO), 1.53–1.24 (m, 4H, 2 × CH$_2$), 1.19–1.00 (m, 2H, CH$_2$); ^{13}C NMR (126 mg, $CDCl_3$) δ 170.40, 168.37, 167.87, 167.48, 138.58, 138.24, 137.85, 136.99, 133.94, 133.75, 133.56, 131.59, 131.36, 129.19, 128.50, 128.25, 128.20, 127.99, 127.90, 127.76, 127.56, 127.43, 127.12, 126.80, 126.17, 123.57, 123.06, 101.98, 99.17, 98.02, 96.92, 78.99, 78.48, 76.76, 76.72, 75.73, 74.48, 74.29, 74.20, 73.16, 72.71, 71.22, 69.76, 68.77, 68.34, 68.18, 67.63, 66.60, 56.50, 55.64, 51.01, 28.59, 28.19, 22.92, 20.95; HRMS (ESI): m/z calcd for $C_{76}H_{77}N_5NaO_{19}$: 1386.5110 $[M+Na]^+$; found 1386.5156.

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References

1. Varki, A.; Cummings, R.; Esko, J.; Freeze, H.; Hart, G.; Marth, J. *Essentials of Glycobiology*; Cold Spring Harbor: Plainview (NY), 1999.
2. Laurent, N.; Voglmeir, J.; Flitsch, S. L. *Chem. Commun.* **2008**, 4400–4412.
3. Geng, X.; Dudkin, V. Y.; Mandal, M.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 2562–2565.
4. Mandal, M.; Dudkin, V. Y.; Geng, X.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 2557–2561.
5. Miller, J. S.; Dudkin, V. Y.; Lyon, G. J.; Muir, T. W.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 431–434.
6. Dudkin, V. Y.; Miller, J. S.; Danishefsky, S. J. *Tetrahedron Lett.* **2003**, *44*, 1791–1793.
7. Eller, S.; Schuberth, R.; Gundel, G.; Seifert, J.; Unverzagt, C. *Angew. Chem., Int. Ed.* **2007**, *46*, 4173–4175.
8. Unverzagt, C. *Angew. Chem., Int. Ed.* **1994**, *33*, 1102–1104.
9. Unverzagt, C. *Angew. Chem., Int. Ed.* **1996**, *35*, 2350–2353.
10. Unverzagt, C. *Angew. Chem., Int. Ed.* **1997**, *36*, 1989–1992.
11. Unverzagt, C. *Carbohydr. Res.* **1997**, *305*, 423–431.
12. Unverzagt, C. *Chem. Eur. J.* **2003**, *9*, 1369–1376.
13. Unverzagt, C.; Andre, S.; Seifert, J.; Kojima, S.; Fink, C.; Srikrishna, G.; Freeze, H.; Kayser, K.; Gabius, H. J. *J. Med. Chem.* **2002**, *45*, 478–491.
14. Unverzagt, C.; Eller, S.; Mezzato, S.; Schuberth, R. *Chem. Eur. J.* **2007**.
15. Ohnishi, Y.; Ando, H.; Kawai, T.; Nakahara, Y.; Ito, Y. *Carbohydr. Res.* **2000**, *328*, 263–276.
16. Ratner, D. M.; Swanson, E. R.; Seeberger, P. H. *Org. Lett.* **2003**, *5*, 4717–4720.
17. Rising, T.; Claridge, T. D. W.; Davies, N.; Gamblin, D. P.; Moir, J. W. B.; Fairbanks, A. J. *Carbohydr. Res.* **2006**, *341*, 1574–1596.
18. Schuberth, R.; Unverzagt, C. *Tetrahedron Lett.* **2005**, *46*, 4201–4204.
19. Wu, X. Y.; Grathwohl, M.; Schmidt, R. R. *Angew. Chem., Int. Ed.* **2002**, *41*, 4489–4493.
20. Andre, S.; Unverzagt, C.; Kojima, S.; Dong, X.; Fink, C.; Kayser, K.; Gabius, H. J. *Bioconjugate Chem.* **1997**, *8*, 845–855.
21. Dudkin, V. Y.; Crich, D. *Tetrahedron Lett.* **2003**, *44*, 1787–1789.
22. Dudkin, V. Y.; Orlova, M.; Geng, X.; Mandal, M.; Olson, W. C.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 9560–9562.
23. Nakano, J.; Ishiwata, A.; Ohta, H.; Ito, Y. *Carbohydr. Res.* **2007**, *342*, 675–695.
24. Weiss, H.; Unverzagt, C. *Angew. Chem., Int. Ed.* **2003**, *42*, 4261–4263.
25. Li, B.; Zeng, Y.; Hauser, S.; Song, H. J.; Wang, L. X. *J. Am. Chem. Soc.* **2005**, *127*, 9692–9693.
26. Seifert, J.; Lergenmuller, M.; Ito, Y. *Angew. Chem., Int. Ed.* **2000**, *39*, 531.
27. Duffels, A.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1999**, 375–378.
28. Matsuo, I.; Nakahara, Y.; Ito, Y.; Nukada, T.; Nakahara, Y.; Ogawa, T. *Bioorg. Med. Chem.* **1995**, *3*, 1455–1463.
29. Nukada, T.; Kitajima, T.; Nakahara, Y.; Ogawa, T. *Carbohydr. Res.* **1992**, *228*, 157–170.
30. Sadozai, K. K.; Ito, Y.; Nukada, T.; Ogawa, T.; Kobata, A. *Carbohydr. Res.* **1986**, *150*, 91–101.
31. Paulsen, H. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 823–839.
32. Paulsen, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 155–173.
33. Jonke, S.; Liu, K. G.; Schmidt, R. R. *Chem. Eur. J.* **2006**, *12*, 1274–1290.
34. Watt, G. M.; Boons, G.-J. *Carbohydr. Res.* **2004**, *339*, 181–193.
35. Xia, J.; Abbas, S. A.; Locke, R. D.; Piskorz, C. F.; Alderfer, J. L.; Matta, K. L. *Tetrahedron Lett.* **2000**, *41*, 169–173.
36. Furstner, A.; Konetzki, I. *Tetrahedron Lett.* **1998**, *39*, 5721–5724.
37. Wang, C.-C.; Lee, J.-C.; Luo, S.-Y.; Kulkarni, S. S.; Huang, Y.-W.; Lee, C.-C.; Chang, K.-L.; Hung, S.-C. *Nature (London, UK)* **2007**, *446*, 896–899.
38. Chang, R.; Moquist, P.; Finney, N. S. *Carbohydr. Res.* **2004**, *339*, 1531–1536.
39. Yu, B.; Tao, H. C. *Tetrahedron Lett.* **2001**, *42*, 2405–2407.
40. Tamura, K.; Mizukami, H.; Maeda, K.; Watanabe, H.; Uneyama, K. *J. Org. Chem.* **1993**, *58*, 32–35.