DOI: 10.1002/ejoc.200900437

Utilizing Staudinger Ligation for the Synthesis of Glycoamino Acid Building Blocks and Other Glycomimetics

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Keywords: Ligation / Amino acids / Glycomimetics / Glycoconjugates / Azides

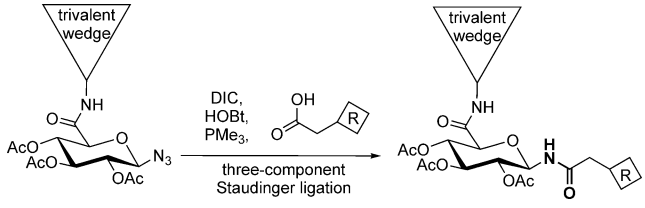
The synthesis of amide-linked glycomimetics is of interest in the glycosciences as they represent a typical linkage in biologically important glycoconjugates. We have addressed the synthesis of three types of *N*-glycosyl amide architectures, which were targeted using Staudinger ligation. This facile method has allowed us to synthesize a collection of *N*-glycosyloctanamides, *N*-glycosyloxyethyl amino acids and multivalent glycoclusters. The last two classes represent molecules that can be used as building blocks in solid-phase peptide synthesis for the preparation of multivalent glycoconjugates.

Introduction

The glycocalyx of eukaryotic cells is of high molecular complexity[1] and of central biological importance in cell communication processes.[2] Among other glycoconjugates, *O*- and *N*-linked glycoproteins are constituents of this complex glyco environment and key to many of the unsolved problems relating to glycocalyx function.[3]

The isolation of *N*-glycoproteins and -peptides from physiological sources is problematic[4] and their chemical synthesis difficult.[5] Therefore, the modification of natural, highly branched glycoconjugates into various glycomimetics, such as glycodendrimers and -clusters, has become an important strategy in glycoscience.[6] In *N*-linked glycopeptides the saccharide portion is attached through a glycosyl amide bond to an asparagine side-chain of the peptide backbone. This type of linkage has been utilized for the synthesis of a variety of branched glycomimetics[7] and recently we found that Staudinger ligation is a versatile method for accessing amide-linked glycomimetics such as the wedged glycosyl amide glycocluster shown in Scheme 1.[8]

Although the Staudinger reaction was developed by Staudinger and Meyer in 1919 for the conversion of azides into the corresponding amines,[9] it was not until 65 years later that Garcia et al. first reported on Staudinger ligation,



Scheme 1. Three-component Staudinger ligation allows the conversion of dendron-functionalized glycosyl azides into wedged glycoamides.[8]

which involves the formation of an amide bond from the reaction between an azide and a carboxylic acid in the presence of trialkyl- or triarylphosphanes.[10] A simple and efficient method for utilizing this ligation method for the synthesis of *N*-linked glycoamino acids was developed by Inazu and Kobayashi in 1993.[11] Since then a number of modifications to this approach have been established in which activated carboxylic acids were employed for the synthesis of glycosyl amides,[8,12] including Bertozzi and co-workers' "traceless" Staudinger ligation in which the aza-ylide intermediate is trapped by a methoxycarbonyl group.[13]

Based on our good experiences with the Staudinger ligation method,[8] which proceeds under mild reaction conditions and tolerates both protected as well as unprotected substrates, it became our goal to utilize three-component Staudinger ligation to access amide-linked glycomimetics of three types: (i) *N*-glycosyloctanamides, (ii) *N*-mannosyloxyethyl amino acids and (iii) trivalent glycocluster amino acids (Figure 1). These glycomimetics are needed for functional studies with multivalent carbohydrate assemblies.

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.200900437.

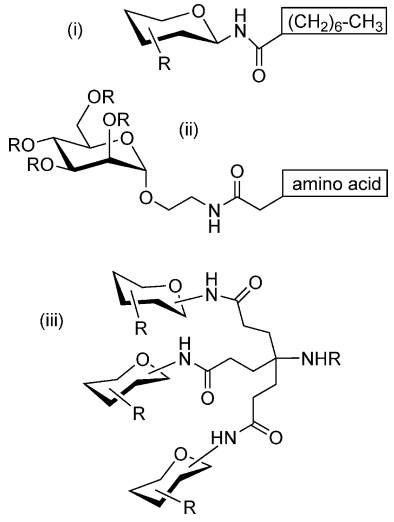


Figure 1. Three types of target molecules approached by the Staudinger ligation: (i) *N*-glycosyloctanamides, (ii) *N*-mannosyloxyethyl amino acids and (iii) glycocluster amides.

Results and Discussion

N-Glycosyloctanamides

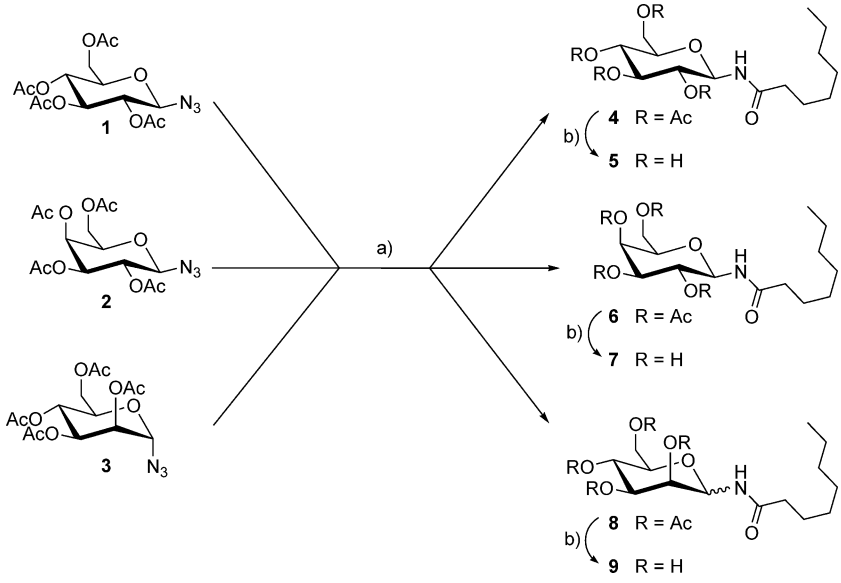
To study the supramolecular behaviour of amphiphilic glycoconjugates with varied sugar configurations we aimed to synthesize the three different *N*-glycosyl amides **4**, **6** and **8** (Scheme 2). These types of molecules are typically synthesized by the reaction of glycosylamines with activated carboxylic acid derivatives.[14] However, glycosylamines are relatively unstable and thus this method has often been shown to be rather unsatisfactory. Staudinger ligation provides a facile alternative in this case. Boullanger et al. utilized octanoyl chloride under Staudinger conditions[12a,15] to access the amphiphilic target glycosyl amides. We employed octanoic acid in combination with tri-*n*-butylphosphane, DIC (diisopropylcarbodiimide) and HOBt (1-hydroxybenzotriazole), thus saving one step and allowing milder reaction conditions. It is important to conduct the reaction at a low temperature because when the reaction was carried out at room temp., for example, no ligation product was observed.[8]

Accordingly, the well-known β-glycosyl azides **1** and **2** and the α-mannosyl azide **3**[16] led to the corresponding amides **4**, **6** and **8**, which could be deprotected according to Zemplén and Pacsu[17] to furnish the corresponding amphiphiles **5**, **7** and **9** in high yields. Yields were in the same range regardless of the sugar series employed. However, in the case of the α-mannosyl azide **3**, anomerization occurred at the anomeric centre, leading to an α,β mixture of products in the ratio of 3:1. Anomerization is a frequently reported problem in this reaction and proceeds via the glycosyl iminophosphorane intermediate (Scheme 3).[18] In the case of the β-glycosyl amides **7** and **8** the stereochemistry at the anomeric position was retained.

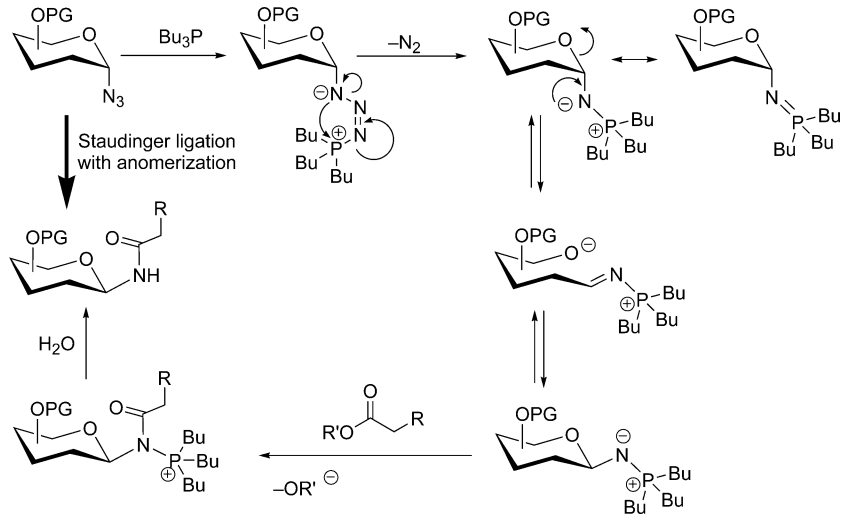
Anomeric mixtures could be separated by HPLC, however, to circumvent the problem of the anomerization of glycosyl azides we aimed to use azidoalkyl glycosides as alternative substrates in the Staudinger ligation.

N-Mannosyloxyethyl Amino Acids

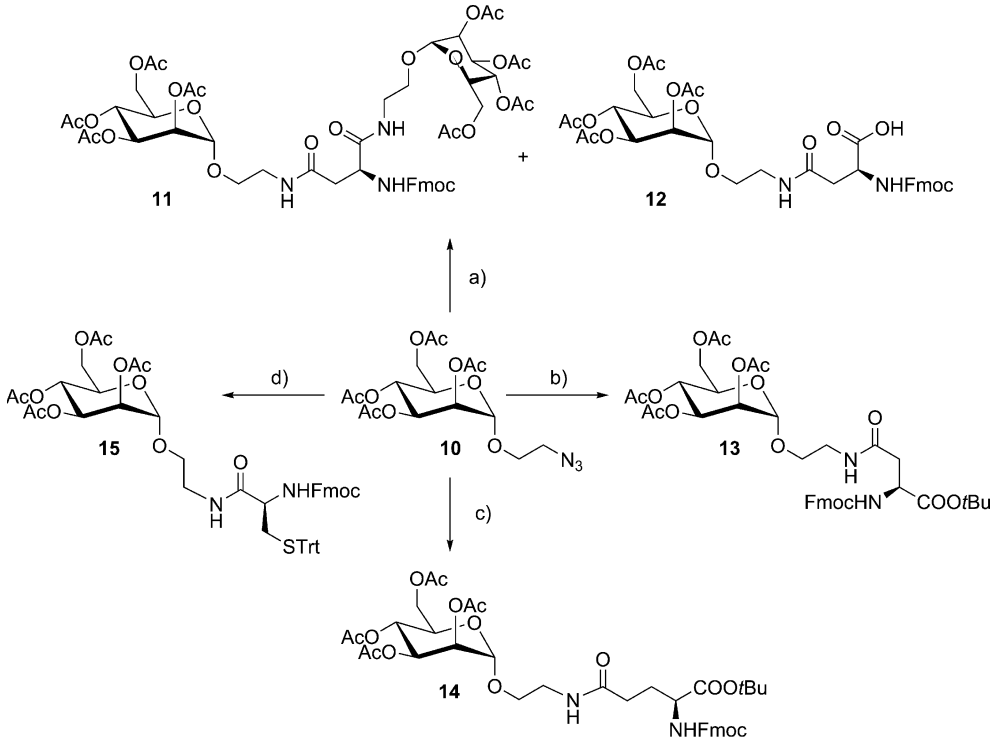
For our studies on mannose-specific bacterial adhesion,[19] we require a variety of glycoamino acid mimetics. We employed 2-azidoethyl mannoside **10** (Scheme 4) as the starting material in the Staudinger-type ligation reactions to obtain mannose-modified amino acids and to exclude the problem of anomerization at the anomeric centre.



Scheme 2. Synthesis of *N*-glycosyloctanamides using the Staudinger ligation strategy. Reagents and conditions: a) Octanoic acid, DIC, HOBt, $(n\text{Bu})_3\text{P}$, THF, 0 °C→r.t., overnight; 81% for **4**, 71% for **6**, 67% for **8** (α/β = 3:1); b) NaOMe, dry MeOH, 24 h, r.t.; 99% for **5**, 84% for **7**, 95% for **9**.



Scheme 3. Anomerization during Staudinger ligation can occur via the intermediate glycosyl iminophosphorane.



Scheme 4. Synthesis of *N*-mannosyloxyethyl amino acids. Reagents and conditions: General procedure: amino acid derivative, **10**, DIC, HOBt, $(n\text{Bu})_3\text{P}$, THF, 0 °C→r.t. a) Fmoc-Asp-OH, 32%; b) Fmoc-Asp(OH)-O*t*Bu, 72%; c) Ph_3P instead of $(n\text{Bu})_3\text{P}$, Fmoc-Glu-(OH)-O*t*Bu, 64%, d) Fmoc-Cys(Trt)-OH, 61%.

Thus, mannoside **10**, which was easily obtained from mannose in three steps,[20] was treated with the corresponding Fmoc-protected amino acid building blocks derived from aspartic acid, glutamic acid or cysteine, respectively, and treated with DIC and HOBt to activate the acid and tributylphosphane, activating the azido-modified mannoside (Scheme 4). Two different aspartic acid derivatives were employed, Fmoc-protected aspartic acid (Fmoc-Asp-OH) and the corresponding *tert*-butyl ester Fmoc-Asp(OH)-O*t*Bu. In the latter case the monoligated product **13** was targeted and obtained in high yield. With the free acid Fmoc-Asp-OH, ligation of both carboxy groups was intended. Indeed, Staudinger ligation led to the dimeric amide **11** as the main coupling product (32%) together with the glycoamino acid **12** (28%). Overall, this result is satisfactory as both ligation products could be easily separated from one another and **12** could be converted into **11** after an additional ligation step. Even though **12** is an undesired product of this reaction, it is an appealing building block en route to mixed glycoclusters or for capping the *N*-terminus of various glycopeptide derivatives.

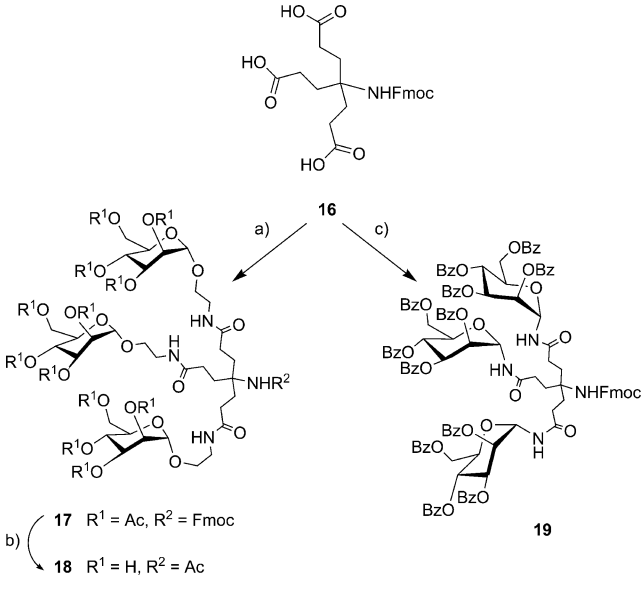
In analogy to the Staudinger ligation of **10** with Fmoc-Asp(OH)-O*t*Bu, reaction with the glutamic acid derivative Fmoc-Glu(OH)-O*t*Bu proceeded equally well, delivering the glycoamino acid derivative **14**. The protected cysteine building block Fmoc-Cys(Trt)-OH led to the ligation product **15** under the same conditions. The mannosidic cysteine **15** has the potential to dimerize as it can form the corresponding disulfide after deprotection of the thio function.

The glycoamino acid derivatives thus obtained in Scheme 4 will be employed in the solid-phase synthesis of glycopeptides, for which it is advantageous to use *O*-protected building blocks because they are more stable than the OH-unprotected analogues, are more easily cleaved from the resin and purification of the cleaved products is facilitated in comparison with unprotected glycopeptides. Staudinger ligation has proved its worth in achieving the required *O*-acylated glycoamino acid building blocks for SPPS. Otherwise, synthesis of the products in Scheme 4 by standard peptide-coupling utilizing the acetyl-protected mannoside requires additional protection and deprotection steps to avoid undesired *O*→*N* acetyl group migration.

Glycocluster Amides

Encouraged by these results, we set out to employ Staudinger ligation in the synthesis of glycoclusters based on Newkome and co-workers' branched triacid **16**.[21] Peptide-coupling of unprotected 2-aminoethyl α-D-mannoside with the trivalent wedge **16** has been reported previously,[22] and led to the OH-unprotected product, which was extremely difficult to purify. The *O*-acetylated 2-aminoethyl α-D-mannoside, on the other hand, cannot be employed in standard peptide-coupling due to the risk of *O*→*N* acetyl group migration. Staudinger ligation allows the protected azidoethyl mannoside **10** to be utilized in peptide-coupling with the triacid **16** (Scheme 5). To activate the acid, again a combination of DIC and HOBt was used, but trimethylphosphane was employed instead of the more hindered tri-*n*-butylphosphane. At 0 °C no product formation was observed, whereas at –70 °C the amide-linked glycocluster **17** was obtained in over 50% yield. In addition to the desired product, the formation of a defect derivative carrying only two mannoside moieties was observed. When the Fmoc-protected cluster **17** was submitted to a deprotection/acetylation/de-*O*-acetylation sequence, the OH-free cluster glycoside **18** was obtained, which is of interest as an inhibitor of type 1 fimbriae-mediated bacterial adhesion.[23]

Reaction of the triacid **16** with 2,3,4,6-tetra-*O*-benzoyl-α-D-mannosyl azide[24] under analogous conditions led to the trivalent glycocluster **19** in somewhat moderate yield after size-exclusion chromatography. Surprisingly, no anomerization occurs in this case, according to careful NMR analysis.



Scheme 5. Synthesis of amide-linked glycoclusters. Reagents and conditions: a) **10**, DIC, HOBt, $P(CH_3)_3$, –70 °C→r.t., overnight, 52%; b) CH_2Cl_2, morpholine, 4 h, room temp., then Ac_2O, pyridine, room temp., overnight, 68%; NaOMe, MeOH, 4 h, room temp., quant.; c) 2,3,4,6-tetra-*O*-benzoyl-α-D-mannosyl azide,[24] DIC, HOBt, $P(CH_3)_3$, –70 °C→r.t., overnight, 34%.

Conclusions

Protected glycoamino acids are convenient building blocks in carbohydrate chemistry and for SPPS (solid-phase peptide synthesis). However, their synthesis by the standard peptide-coupling of an amine and an activated carboxylic acid utilizing *O*-acetyl-protected glycoside intermediates is afflicted by undesired *O*→*N* acetyl group migration. This problem can be solved by Staudinger ligation, which allows the formation of amide-linked glycomimetics from carbohydrate azides and carboxylic acid derivatives, such as amino acids, mediated by a combination of DIC, HOBt and a suitable phosphane. This allowed us to prepare a collection of new mannosidic amino acids **11**–**15** by employing the acetylated azidoethyl mannoside **10**. A slightly modified ligation protocol also allowed us to prepare glycocluster amides **17**–**19**, which are quite sophisticated building blocks for the construction of multivalent glycoconjugates. Indeed it can be concluded that Staudinger ligation allows a direct and fast access to versatile amide-linked glycoconjugates in a one-pot process, including amphiphilic glycosyl amides **5**, **7** and **9**.

Experimental Section

General Methods: Thin-layer chromatography was performed on silica gel plates (GF 254, Merck). Detection was effected by UV irradiation and subsequent charring with 10% sulfuric acid in EtOH followed by heat treatment. Flash chromatography was performed on silica gel 60 (230–400 mesh, particle size 0.040–0.063 mm, Merck) using distilled solvents. Optical rotations were measured with a Perkin–Elmer 241 polarimeter (sodium D-line: 589 nm, length of cell: 1 dm). ^1H and ^{13}C NMR spectra were recorded with Bruker DRX-500 and AV-600 spectrometers. Chemical shifts are reported relative to internal tetramethylsilane (δ = 0.00 ppm) or D_2O (δ = 4.76 ppm). Air- and/or moisture-sensitive

reactions were carried out under nitrogen. Commercial reagents were used without purication unless otherwise noted.

General Procedure for the Staudinger Ligation: The corresponding azide-functionalized carbohydrate (1 equiv.) and the carboxylic acid (1.8 equiv.) were combined with HOBt (1.8 equiv.) in a Schlenk flask and dried for more than 1 h in vacuo. This mixture was dissolved in dry THF under nitrogen and cooled to 0 °C. Then DIC (1.8 equiv.) was added and the solution was stirred for 10 min, followed by the addition of tri-*n*-butylphosphane (1–1.8 equiv.) and stirring for 1 h at 0 °C. Then the reaction mixture was stirred overnight at room temp., diluted with water (50 mL) and extracted twice with ethyl acetate (30 mL). The combined organic phases were washed with brine, dried with $MgSO_4$ and the mixture was filtered and concentrated under reduced pressure. The crude product was purified by silica gel chromatography.

General Procedure for *O*-Acetyl Deprotection According to Zemplén and Pacsu:[17] The protected *N*-glycosyl amide was dissolved in dry MeOH (5 mL) and sodium methoxide (1 M solution in MeOH, 100 μL) was added. The mixture was stirred for 4 h, neutralized with Amberlite IR120 (H), filtered and the solvents evaporated to dryness. The substrate was dissolved in water and subjected to lyophilization.

***N*-Octanoyl-β-D-glucopyranosyl Amide (5):** According to the general procedure for Staudinger ligation, glucosyl azide **1** (318 mg, 853 μmol), octanoic acid (221 mg, 1.53 mmol, 1.8 equiv.), HOBt (233 mg, 1.75 mmol, 2.1 equiv.), DIC (255 μL, 1.64 mmol, 1.9 equiv.) and tri-*n*-butylphosphane (212 μL) were allowed to react in THF (40 mL). Silica gel column chromatography (cyclohexane/EtOAc, 1:1) gave compound **4** (326 mg, 688 μmol, 81%) as an amorphous colourless solid. The deprotected title compound was prepared from **4** (84.0 mg, 178 μmol) according to Zemplén and Pacsu and obtained as an amorphous colourless solid (54.0 mg, 177 μmol, 99%). The analytical data were identical to those reported in the literature.[15]

***N*-Octanoyl-β-D-galactopyranosyl Amide (7):** According to the general procedure for Staudinger ligation, glycosyl azide **2** (305 mg, 820 μmol, 1 equiv.), octanoic acid (207 mg, 1.44 mmol, 1.8 equiv.), HOBt (217 mg, 1.61 mmol, 1.9 equiv.), DIC (240 μL, 1.56 mmol, 1.9 equiv.) and tri-*n*-butylphosphane (200 μL) were allowed to react in THF (40 mL). After purification by silica gel column chromatography (cyclohexane/EtOAc, 1:1) the protected ligation product **6** was obtained as a colourless oil (274 mg, 579 μmol, 71%). Deprotection of **6** (278 mg, 610 μmol) was achieved according to Zemplén and Pacsu, yielding the title compound **7** as an amorphous colourless solid (151 mg, 494 μmol, 84%). The analytical data were identical to those reported in the literature.[15]

***N*-Octanoyl-α,β-D-mannopyranosyl Amide (9):** According to the general procedure for Staudinger ligation, mannosyl azide **3** (303 mg, 812 μmol, 1 equiv.), octanoic acid (207 mg, 1.56 mmol, 1.8 equiv.), HOBt (213 mg, 1.56 mmol, 1.9 equiv.), DIC (240 μL, 1.56 mmol, 1.9 equiv.) and tri-*n*-butylphosphane (200 μL) were allowed to react in THF (40 mL) and the product was purified by chromatography on silica gel (cyclohexane/EtOAc, 1:1) to yield protected **8** (259 mg, 547 μmol, 67%) as a colourless oil. The deprotected title compound **9** was prepared from **8** (203 mg, 429 μmol) according to Zemplén and Pacsu and obtained as anomeric mixture in the form of an amorphous colourless solid (124 mg, 406 μmol, 95%); anomeric ratio according to ^{1}H NMR, α:β = 3:1. The analytical data were identical to those reported in the literature.[15]

***N*-[2-(2′,3′,4′,6′-Tetra-*O*-acetyl-α-D-mannopyranosyloxy)ethyl]-N^{α}-(fluoren-9-ylmethoxycarbonyl)-N^{δ}-[2-(2′,3′,4′,6′-tetra-*O*-acetyl-α-D-mannopyranosyloxy)ethyl]-L-asparagine Amide (11):** According to a slightly altered protocol for the Staudinger ligation, mannosyl azide **10** (1.9 g, 4.5 mmol, 2.3 equiv.), Fmoc-Asp-OH (674 mg, 1.9 mmol, 1.0 equiv.), HOBt (662 mg, 4.9 mmol, 2.6 equiv.), DIC (758 μL, 4.9 mmol, 2.6 equiv.) and tri-*n*-butylphosphane (1.2 mL, 4.9 mmol, 2.6 equiv.) were allowed to react in a Schlenk flask under N_2. The crude product was purified by silica gel chromatography (EtOAc/MeOH, 9:1) to yield **11** (669 mg, 0.61 mmol, 32%) as a colourless foam and the byproduct N^{α}-(fluoren-9-ylmethoxycarbonyl)-N^{δ}-[2-(2′,3′,4′,6′-tetra-*O*-acetyl-α-D-mannopyranosyloxy)ethyl]-L-asparagine (**12**; 393 mg, 0.54 mmol, 28%) as a white foam.

Data for 11: $[\alpha]_D^{20}$ = +30.4 (*c* = 1.3, MeOH). ^{1}H NMR (600 MHz, CD_3OD, TMS): δ = 7.83 (d, ^3J = 7.5 Hz, 2 H, Ar-H), 7.69 (d, ^3J = 7.3 Hz, 2 H, Ar-H), 7.43 (t, ^3J = 7.7 Hz, 2 H, Ar-H), 7.35 (t, ^3J = 7.4 Hz, 2 H, Ar-H), 5.33 (dd, $^3J_{2',3'}$ = 3.4, $^3J_{3',4'}$ = 10.0 Hz, 2 H, 2×3′-H), 5.31 (dd, $^3J_{1',2'}$ = 1.7, $^3J_{2',3'}$ = 3.4 Hz, 2 H, 2×2′-H), 5.33 (dd ≈ t, $^3J_{4',5'}$ = 9.9 Hz, 2 H, 2×4′-H), 4.89 (d, $^3J_{1',2'}$ = 1.7 Hz, 2 H, 2×1′-H), 4.54 (t, $^3J_{H\text{-}\alpha,H\text{-}\beta}$ = 6.3 Hz, 1 H, α-H), 4.44 (dd, $^3J_{CH\text{-Fmoc},CH\text{-Fmoc}}$ = 7.2, $^2J_{CHH\text{-Fmoc},CH\text{-Fmoc}}$ = 10.6 Hz, 1 H C*H*H-Fmoc), 4.40–4.34 (m, 1 H, CH*H*-Fmoc), 4.26 (dd, $^3J_{5',6'}$ = 5.2, $^2J_{6',6''}$ = 12.2 Hz, 2 H, 2×6a′-H), 4.30–4.24 (m, 1 H, C*H*-Fmoc), 4.14 (dd, $^3J_{5',6'}$ = 7.1, $^2J_{6',6''}$ = 14.2 Hz, 2 H, 2×6b′-H), 4.10–4.04 (m, 2 H, 2×5′-H), 3.85–3.77 (m, 2 H, 2×OC*H*HCH$_2$), 3.64–3.67 (m, 2 H, 2×OCH*H*CH$_2$), 3.51–3.46 (m, 2 H, 2×OCH$_2$C*H*H), 3.44–3.38 (m, 2 H, 2×OCH$_2$CH*H*), 2.76 (dd, $^3J_{H\text{-}\alpha,H\text{-}\beta}$ = 5.7, $^2J_{H\text{-}\beta,H\text{-}\beta'}$ = 14.4 Hz, 1 H, β-Ha), 2.68 (dd, $^3J_{H\text{-}\alpha,H\text{-}\beta'}$ = 7.7, $^2J_{H\text{-}\beta,H\text{-}\beta'}$ = 14.5 Hz, 1 H, β-Hb), 2.16, 2.07, 2.05, 1.98 (each s, each 6 H, 8×CO$_2$C*H*$_3$) ppm. ^{13}C NMR (150 MHz, CD_3OD, TMS): δ = 173.7 (NH-*C*O-CH$_2$), 172.9, 172.4, 171.6, 171.5 (8×*C*O$_2$CH$_3$), 158.0 (*C*O$_2$-Fmoc), 145.2 (Ar-C), 142.6 (Ar-C), 128.8 (Ar-C), 128.2 (Ar-C), 126.2 (Ar-C), 120.9 (Ar-C), 98.9 (C-1′), 70.8 (C-2′), 70.7 (C-3′), 70.7 (C-5′), 68.1 (*C*H$_2$-Fmoc), 67.8 (O*C*H$_2$CH$_2$), 67.3 (C-4′), 63.6 (C-6′), 53.4 (*C*-α), 48.4 (*C*H-Fmoc), 40.3 (OCH$_2$*C*H$_2$), 38.9 (C-β), 20.8, 20.6, 20.6, 20.5 (8×CO$_2$*C*H$_3$) ppm. MS (MALDI-TOF): calcd. for $[C_{51}H_{63}N_3O_{24} + Na]^+$ 1124.36; found 1124.59; calcd. for $[C_{51}H_{63}N_3O_{24} + K]^+$ 1140.34; found 1140.57.

***N*$^{\alpha}$-(Fluoren-9-ylmethoxycarbonyl)-N^{δ}-[2-(2′,3′,4′,6′-tetra-*O*-acetyl-α-D-mannopyranosyloxy)ethyl]-L-asparagine *tert*-Butyl Ester (13):** According to the general procedure for Staudinger ligation, mannosyl azide **10** (150 mg, 0.36 mmol, 1 equiv.), Fmoc-Asp(OH)-O*t*Bu (324 mg, 0.78 mmol, 1.8 equiv.), HOBt (105 mg, 0.78 mmol, 1.8 equiv.), DIC (121 μL, 0.78 mmol, 1.8 equiv.) and tri-*n*-butylphosphane (100 μL, 0.40 mmol, 1.1 equiv.) were allowed to react in a Schlenk flask under N_2. The crude product was purified by silica gel chromatography (cyclohexane/EtOAc, 1:1), followed by a second chromatography (cyclohexane/EtOAc/MeOH, 5:4:1) to give **13** (207 mg, 0.26 mmol, 72%) as a colourless foam. $[\alpha]_D^{20}$ = +28.6 (*c* = 1.4, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.76 (d, ^3J = 7.5 Hz, 2 H, Ar-H), 7.60 (d, ^3J = 7.2 Hz, 2 H, Ar-H), 7.39 (t, ^3J = 7.4 Hz, 2 H, Ar-H), 7.30 (t, ^3J = 7.4 Hz, 2 H, Ar-H), 6.18 (br. s, 1 H, CH$_2$N*H*CO), 6.05 (d, $^3J_{NH,H\text{-}\alpha}$ = 8.2 Hz, 1 H, N*H*-Fmoc), 5.33 (dd, $^3J_{2',3'}$ = 3.2, $^3J_{3',4'}$ = 9.9 Hz, 1 H, 3′-H), 5.29–5.24 (m, 2 H, 2′-H, 4′-H), 4.82 (d, $^3J_{1',2'}$ = 1.6 Hz, 1 H, 1′-H), 4.51 (br. s, 1 H, α-H), 4.41–4.37 (m, 1 H, C*H*H-Fmoc), 4.33–4.29 (m, 1 H, CH*H*-Fmoc), 4.27 (dd, $^3J_{5',6'}$ = 5.5, $^2J_{6',6''}$ = 12.2 Hz, 1 H, 6a′-H), 4.23 (m, 1 H, C*H*-Fmoc), 4.12 (dd, $^3J_{5,6''}$ = 2.5, $^2J_{6',6''}$ = 12.2 Hz, 1 H, 6b′-H), 3.98 (ddd, $^3J_{4',5'}$ = 9.9, $^3J_{5',6'}$ = 5.5, $^3J_{5',6''}$ = 2.5 Hz, 1 H, 5′-H), 3.78–3.72 (m, 1 H, OC*H*HCH$_2$), 3.60–3.51 (m, 2 H, OC*H*HCH$_2$, OCH$_2$C*H*H), 3.46–3.37 (m, 1 H, OCH$_2$CH*H*), 2.91 (dd, $^3J_{H\text{-}\alpha,H\text{-}\beta'}$ = 5.6, $^2J_{H\text{-}\beta a,H\text{-}\beta b}$ = 15.1 Hz, 1 H, β-Ha), 2.90 (dd, $^3J_{H\text{-}\alpha,H\text{-}\beta b}$ = 5.9, $^2J_{H\text{-}\beta a,H\text{-}\beta b}$ = 15.1 Hz, 1 H, β-Hb), 2.14, 2.09, 2.04, 1.98 (each s, each 3 H, 4×CO$_2$C*H*$_3$), 1.47 (s, 9 H, CC*H*$_3$) ppm. ^{13}C

NMR (150 MHz, $CDCl_3$, TMS): δ = 170.6 (NH*C*OC-β), 170.1 (*C*O_2-*t*Bu), 170.0, 169.9, 169.9, 169.6 (4 × *C*O_2CH_3), 156.2 (*C*O_2-Fmoc), 143.9 (Ar-C), 141.2 (Ar-C), 127.6 (Ar-C), 127.0 (Ar-C), 125.2 (Ar-C), 119.9 (Ar-C), 97.7 (C-1′), 82.3 (*C*CH_3), 69.3 (C-2′), 68.9 (C-3′), 68.7 (C-5′), 67.4 (O*C*H_2CH_2), 67.1 (*C*H_2-Fmoc), 66.2 (C-4′), 62.5 (C-6′), 51.4 (*C*-α), 47.1 (*C*H-Fmoc), 39.1 (OCH_2*C*H_2), 38.1 (*C*-β), 27.9 [C(*C*H_3)$_3$], 20.8, 20.7, 20.6, 20.6 (4 × CO_2*C*H_3) ppm. HRMS (ESI): calcd. for [$C_{39}H_{48}N_2O_{15}$ + Na]$^+$ 807.2952; found 807.2964.

N^{α}-(Fluoren-9-ylmethoxycarbonyl)-N^{δ}-[2-(2′,3′,4′,6′-tetra-*O*-acetyl-α-D-mannopyranosyloxy)ethyl]-L-glutamine *tert*-Butyl Ester (14): According to a slightly altered protocol for the Staudinger ligation, mannosyl azide **10** (150 mg, 0.36 mmol, 1 equiv.), Fmoc-Glu(OH)-O*t*Bu (266 mg, 0.64 mmol, 1.8 equiv.), HOBt (105 mg, 0.78 mmol, 1.8 equiv.), DIC (121 μL, 0.78 mmol, 1.8 equiv.) and triphenylphosphane (170 mg, 0.64 mmol, 1.8 equiv.) were allowed to react in a Schlenk flask under N_2. The crude product was purified by silica gel chromatography (cyclohexane → cyclohexane/EtOAc, 1:1 → EtOAc) to give **14** (186 mg, 0.23 mmol, 64%) as a colourless foam. $[\alpha]_D^{20}$ = +16.4 (*c* = 0.8, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.75 (d, ^3J = 7.4 Hz, 2 H, Ar-H), 7.61 (d, ^3J = 7.4 Hz, 2 H, Ar-H), 7.38 (m_c, 2 H, Ar-H), 7.30 (m_c, Ar-H), 6.47 (br., 1 H, CH_2N*H*CO), 5.67 (d, $^3J_{NH,H-\alpha}$ = 7.9 Hz, 1 H, N*H*-Fmoc), 5.35 (dd, $^3J_{2',3'}$ = 3.5, $^3J_{3',4'}$ = 10.0 Hz, 1 H, 3′-H), 5.27 (dd, $^3J_{1',2'}$ = 1.6, $^3J_{2',3'}$ = 3.4 Hz, 1 H, 2′-H), 5.26–5.24 (m, 1 H, 4′-H), 4.82 (d, $^3J_{1',2'}$ = 1.6 Hz, 1 H, 1′-H), 4.42–4.37 (m, 2 H, C*H*$_2$-Fmoc), 4.25 (dd, $^3J_{5',6'}$ = 5.5, $^2J_{6',6''}$ = 12.2 Hz, 1 H, 6a′-H), 4.25–4.19 (m, 2 H, C*H*-Fmoc, α-H), 4.05–4.01 (m, 1 H, 6b′-H), 3.99 (m_c, 1 H, 5′-H), 3.80–3.75 (m, 1 H, OC*H*HCH$_2$), 3.58–3.50 (m, 2 H, OCH*H*CH$_2$, OCH$_2$C*H*H), 3.45–3.41 (m, 1 H, OCH$_2$CH*H*), 3.16–3.03 (m, 1 H, γ-Ha), 2.98–2.78 (m, 1 H, γ-Hb), 2.31–2.25 (m, 2 H, β-H), 2.12, 2.11, 2.07, 1.96 (each s, each 3 H, 4 × CO_2C*H*$_3$), 1.47 (s, 9 H, CC*H*$_3$) ppm. ^{13}C NMR (150 MHz, $CDCl_3$, TMS): δ = 171.1 (*C*OC-γ), 170.6 (*C*OO-*t*Bu), 169.9, 169.9, 169.6, 169.5 (4 × *C*O_2CH_3), 157.1 (*C*O_2-Fmoc), 143.9 (Ar-C), 141.3 (Ar-C), 127.7 (Ar-C), 127.0 (Ar-C), 125.2 (Ar-C), 119.9 (Ar-C), 97.8 (C-1′), 82.4 (*C*CH_3), 69.3 (C-2′), 69.0 (C-3′), 68.9 (C-5′), 67.3 (O*C*H_2CH_2), 67.0 (*C*H_2-Fmoc), 66.1 (C-4′), 62.4 (C-6′), 53.8 (*C*-α), 49.0 (*C*H-Fmoc), 39.0 (OCH_2*C*H_2), 32.4 (*C*-γ), 29.1 (*C*-β), 27.9 [C(*C*H_3)$_3$], 20.8, 20.6, 20.6, 20.5 (4 × CO_2*C*H_3) ppm. HRMS (ESI): calcd. for [$C_{40}H_{50}N_2O_{15}$ + Na]$^+$ 821.3109; found 821.3118.

***N*-[2-(2′,3′,4′,6′-Tetra-*O*-acetyl-α-D-mannopyranosyloxy)ethyl]-N^{α}-(fluoren-9-ylmethoxycarbonyl)-*S*-(triphenymethyl)-L-cysteine Amide (15):** According to the general procedure for Staudinger ligation, mannosyl azide **10** (2.20 g, 6.9 mmol, 1 equiv.), Fmoc-Cys(Trt)-OH (5.67 g, 12.4 mmol, 1.8 equiv.), HOBt (1.54 g, 12.4 mmol, 1.8 equiv.), DIC (1.77 mL, 12.4 mmol, 1.8 equiv.) and tri-*n*-butylphosphane (1.7 mL, 6.9 mmol, 1 equiv.) were allowed to react in a Schlenk flask under N_2. The crude product was purified by silica gel chromatography (EtOAc/toluene, 1:1) to give **15** (3.93 g, 4.21 mmol, 61%) as a colourless foam. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ = 7.76–7.70 (m, 2 H, Ar-H), 7.60–7.55 (m, 2 H, Ar-H), 7.43–7.34 (m, 8 H, Ar-H), 7.29–7.13 (m, 11 H, Ar-H), 5.33 (dd, $^3J_{2,3}$ = 3.6, $^3J_{3,4}$ = 10.1 Hz, 1 H, 3′-H), 5.27–5.22 (m, 2 H, 2′-H, 4′-H), 4.76 (br. s, 1 H, 1′-H), 4.45–4.33 (m, 2 H, C*H*$_2$-Fmoc), 4.23 (dd, $^3J_{5',6'}$ = 5.6, $^2J_{6',6''}$ = 12.2 Hz, 1 H, 6a′-H), 4.19 (t, $^3J_{CH2\text{-}Fmoc,CH\text{-}Fmoc}$ = 6.5 Hz, 1 H, C*H*-Fmoc), 4.07 (dd, $^3J_{5',6''}$ = 2.4, $^2J_{6',6''}$ = 12.2 Hz, 1 H, 6b′-H), 3.97–3.92 (m, 1 H, 5′-H), 3.75 (m_c, 1 H, α-H), 3.72–3.68 (m, 1 H, OC*H*HCH$_2$), 3.54–3.47 (m, 1 H, OCH*H*CH$_2$), 3.45–3.29 (m, 2 H, C*H*$_2$N), 2.74 (dd, $^3J_{H-\alpha,H-\beta}$ = 7.4, $^2J_{H-\beta,H-\beta'}$ = 12.9 Hz, 1 H, β-Ha), 2.74 (dd, $^3J_{H-\alpha,H-\beta'}$ = 7.6, $^2J_{H-\beta,H-\beta'}$ = 12.9 Hz, 1 H, β-Hb), 2.12, 2.04, 1.99, 1.97 (each s, each 3 H, 4 × CO_2C*H*$_3$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ = 170.6 (*C*O-C-α), 169.9, 169.8, 169.7, 169.7 (4 × *C*O_2CH_3), 155.9 (Ar-C), 144.4 (Ar-C), 143.8 (Ar-C), 143.7 (Ar-C), 143.7 (Ar-C), 129.6 (Ar-C), 129.6 (Ar-C), 129.0 (Ar-C), 128.2 (Ar-C), 128.1 (Ar-C), 127.7 (Ar-C), 120.0 (Ar-C), 97.7 (C-1′), 69.4 (C-3′), 69.0 (C-2′), 68.7 (C-5′), 67.05 (O*C*H_2CH_2), 66.2 (*C*H_2-Fmoc), 66.2 (C-4′), 62.5 (C-6′), 53.99 (C-α), 47.2 (*C*H-Fmoc), 39.1 (*C*H_2N), 33.1 (C-β), 20.8 (CO*C*H_3), 20.7 (CO*C*H_3), 20.7 (CO*C*H_3), 20.7 (CO*C*H_3) ppm. HRMS (ESI): calcd. for [$C_{53}H_{54}N_2O_{13}S$ + Na]$^+$ 981.3244; found 981.3223.

3-Cascade:*N*-fluorenylmethoxycarbonyl-aminomethane[3]:1-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyloxy)-3-aza-4-oxo-hexane (17): Fmoc-protected triacid **16** (110 mg, 0.234 mmol), mannosyl azide **10** (584 mg, 1.40 mmol) and HOBt (104 mg, 772 mmol) were dried in a Schlenk flask under vacuum for 1 h. This mixture was dissolved in dry THF (20 mL) under an inert atmosphere, DIC (81 μL, 772 mmol) was added and the solution stirred for 10 min. Then trimethylphosphane (1 M solution in THF, 2.41 mL, 2.1 mmol) was added at –70 °C and it was stirred for 12 h at room temp. The reaction was quenched by the addition of water, the aqueous phase was washed with CH_2Cl_2 (3 × 15 mL) and the combined organic phases dried with $MgSO_4$. The mixture was filtered, evaporated and purification by silica gel column chromatography (cyclohexane/EtOAc, 1:1.5) led to the pure product **17** (194 mg, 0.122 mmol, 52%) in the form of a white foam. $[\alpha]_D^{20}$ = +2.9 (*c* = 0.8, CH_2Cl_2). ^{1}H NMR (600 MHz, $CDCl_3$, TMS): δ = 7.75 (d, *J* = 7.15 Hz, 2 H, Ar-H), 7.62–7.61 (m, 2 H, Ar-H), 7.39 (m_c, 2 H, Ar-H), 7.30 (m_c, 2 H, Ar-H), 5.29 (dd, $^3J_{2,3}$ = 3.3, $^3J_{3,4}$ = 10.0 Hz, 3 H, 3 × 3-H), 5.26 (d, $^3J_{3,4}$ = 9.7 Hz, 3 H, 3 × 4-H), 5.24 (dd, $^3J_{1,2}$ = 1.7, $^3J_{2,3}$ = 3.2 Hz, 3 H, 3 × 2-H), 4.83 (d, $^3J_{1,2}$ = 1.5 Hz, 3 H, 3 × 1-H), 4.38 (br. s, 2 H, 2 × C*H*$_2$Fmoc), 4.23 (dd, $^3J_{5,6}$ = 5.6, $^2J_{6,6'}$ = 12.2 Hz, 3 H, 3 × 6-Ha), 4.18 (t, ^3J = 6.6 Hz, 1 H, C*H*Fmoc), 4.13 (dd, $^3J_{5,6'}$ = 2.6, $^2J_{6,6'}$ = 12.3 Hz, 3 H, 3 × 6-Hb), 3.98 (ddd, $^3J_{4,5}$ = 9.5, $^3J_{5,6}$ = 5.4, $^3J_{5,6'}$ = 2.5 Hz, 3 H, 3 × 5-H), 3.76 (m_c, 3 H, 3 × man-OCH*H*CH$_2$), 3.57–3.50 (m, 6 H, 3 × man-OC*H*HCH$_2$, 3 × man-OCH$_2$C*H*H), 3.41–3.36 (m, 3 H, 3 × man-OCH$_2$CH*H*), 2.21 [m_c, 6 H, 3 × C(O)C*H*$_2$CH$_2$], 2.14, 2.09, 2.03, 1.96 (each s, each 9 H, 12 × CO_2C*H*$_3$), 1.98 [m_c, 6 H, 3 × C(O)CH$_2$C*H*$_2$] ppm. ^{13}C NMR (150 MHz, $CDCl_3$, TMS): δ = 173.3 (HN*C*OCH$_2$CH$_2$), 170.7, 170.1, 169.7 (4 *C*O_2CH_3), 154.8 (NH*C*O_2), 144.1, 144.4, 127.6, 127.0, 125.1, 120.0 (Ar-C), 97.4 (C-1), 69.5 (C-2), 69.2 (C-3), 68.8 (C-5), 67.0 (man-O*C*H_2CH_2), 66.2 (C-4), 65.8 (NHCO$_2$*C*H_2), 62.6 (C-6), 57.2 (*C*NHFmoc), 47.5 (*C*H-fluorene), 39.0 (man-OCH$_2$*C*H_2), 31.2 [C(O)*C*H$_2$CH$_2$], 30.7 [C(O)CH$_2$*C*H$_2$], 21.0, 20.8, 20.7, 20.7 (CO$_2$*C*H$_3$) ppm. HRMS (ESI): calcd. for [$C_{73}H_{96}N_4O_{35}$ + Na]$^+$ 1611.5753; found 1611.5917.

3-Cascade:*N*-acetyl-aminomethane[3]:1-(α-D-mannopyranosyloxy)-3-aza-4-oxo-hexane (18): Glycocluster **17** (80 mg, 5.03 mmol) was dissolved in dry CH_2Cl_2 (5 mL) and morpholine (500 μL) under an inert atmosphere. The reaction mixture was stirred for 4 h at room temp. and then evaporated in vacuo. The residue was dried under high vacuum overnight, dissolved in acetic anhydride (1 mL) and pyridine (3 mL) and stirred at room temp. for 16 h. The solvent was evaporated and the crude product was subjected to silica gel column chromatography (EtOAc/MeOH, 1:1.5) to give the peracetylated product as a slightly coloured syrup (47 mg, 0.034 mmol, 68% over two steps). This completely acetylated glycocluster was dissolved in dry methanol (5 mL) and sodium methoxide (1 M solution in MeOH, 100 μL) was added. The reaction mixture was stirred for 4 h at room temp., neutralized by the addition of Amberlite IR120 (H), filtered and the solvents evaporated. The purity of the compound was confirmed by RP HPLC on a LiChrosorb RP-8 column at a flow rate of 10 mL/min using a linear acetonitrile/water gradient of 10% to 100% acetonitrile over 80 min to

yield the title compound **18** as a white lyophilisate (19 mg, 0.021 mmol, quant.). $[\alpha]_D^{20}$ = +1.5 (*c* = 1.0, MeOH). ^{1}H NMR (600 MHz, CD_3OD, TMS): δ = 4.81 (d, $^3J_{1,2}$ = 1.6 Hz, 3 H, 3×1-H), 3.88 (dd, $^3J_{5,6}$ = 2.2, $^2J_{6,6'}$ = 11.7 Hz, 3 H, 3×6-Ha), 3.86 (dd, $^3J_{1,2}$ = 1.7, $^3J_{2,3}$ = 3.3 Hz, 3 H, 3×2-H), 3.81 (m, 3 H, 3×OC*H*HCH$_2$), 3.75 (dd, $^3J_{5,6}$ = 6.6, $^2J_{6,6'}$ = 11.6 Hz, 3 H, 3×6-Hb) 3.74 (dd, $^3J_{2,3}$ = 3.5, $^3J_{3,4}$ = 9.7 Hz, 3 H, 3×3-H), 3.64 (dd ≈ t, ^3J = 9.7 Hz, 3 H, 3×4-H), 3.61–3.57 (m, 6 H, 3×5-H, 3×OCH*H*CH$_2$), 3.49–3.46 (m, 3 H, 3×OCH$_2$C*H*H), 3.43–3.40 (m, 3 H, 3×OCH$_2$CH*H*), 2.24 [m$_c$, 6 H, 3×C(O)C*H*$_2$CH$_2$], 2.03 [m$_c$, 6 H, 3×C(O)CH$_2$C*H*$_2$], 2.01 [s, 3 H, NHC(O)C*H*$_3$] ppm. ^{13}C NMR (150 MHz, CD_3OD, TMS): δ = 176.1 [NH*C*(O), HN*C*OCH$_2$CH$_2$], 101.7 (C-1), 74.8 (C-5), 72.6 (C-3), 72.1 (C-2), 68.9 (C-4), 67.2 (man-O*C*H$_2$CH$_2$), 63.0 (C-6), 59.3 (*C*NHAc), 40.5 (man-OCH$_2$*C*H$_2$), 31.8 [C(O)*C*H$_2$CH$_2$], 31.2 [C(O)CH$_2$*C*H$_2$], 23.5 [NHC(O)*C*H$_3$] ppm. HRMS (ESI): calcd. for [$C_{36}H_{64}N_4O_{22}$ + Na]$^+$ 927.3910. Found, 927.3995.

3-Cascade:*N*-Fluorenylmethoxycarbonylaminomethane[3]:1-(2,3,4,6-Tetra-*O*-benzoyl-α-D-mannopyranosyl)-1-aza-2-oxobutane (19): Fmoc-protected triacid **16** (59 mg, 0.12 mmol), 2,3,4,6-tetra-*O*-benzoyl-α-D-mannosyl azide[24] (336 mmol, 0.540 mmol) and HOBt (49 mg, 0.36 mmol) were dried under vacuum in a Schlenk flask for about 1 h. Then this mixture was dissolved in dry THF (20 mL) under an inert atmosphere, DIC (55 μL, 0.36 mmol) was added and the solution stirred for 10 min. Then trimethylphosphane solution (1 M in THF, 540 μL, 540 mmol) was added at –70 °C and the reaction mixture stirred overnight. The reaction was quenched by the addition of water, the aqueous phase was extracted with CH_2Cl_2 (3×15 mL) and the combined organic phases dried with $MgSO_4$. The mixture was filtered, the solvent was removed in vacuo and the residue purified by silica gel column chromatography (cyclohexane/EtOAc, 1:1) followed by GPC on LH-20 (CH_2Cl_2/CH_3OH, 1:1) to yield pure **19** (89 mg, 0.040 mmol, 34%) as a white amorphous solid. $[\alpha]_D^{20}$ = +0.6 (*c* = 0.9, CH_2Cl_2). ^{1}H NMR (600 MHz, $CDCl_3$, TMS): δ = 8.04 (m$_c$, 6 H, Ar-H), 7.96 (m$_c$, 5 H, Ar-H), 7.90 (m$_c$, 6 H, Ar-H), 7.74 (m$_c$, 5 H, Ar-H), 7.60 (m$_c$, 2 H, Ar-H), 7.53–7.47 (m, 10 H, Ar-H), 7.40–7.30 (m, 20 H, Ar-H), 7.26 (m$_c$, 6 H, Ar-H), 7.20 (m$_c$, 8 H, Ar-H), 6.85 (br. s, 3 H, N*H*COCH$_2$), 6.02 (dd ≈ t, ^3J = 10.03 Hz, 3 H, 3×4-H), 5.81 (dd, $^3J_{1,2}$ = 1.1, $^3J_{2,3}$ = 4.0 Hz, 3 H, 3×2-H), 5.74 (d, ^3J = 9.53 Hz, 3 H, 3×1-H), 5.68 (dd, $^3J_{2,3}$ = 3.1, $^3J_{3,4}$ = 10.1 Hz, 3 H, 3×3-H), 5.02 (m$_c$, 1 H, CH$_2$C*H*), 4.64 (dd, $^3J_{5,6}$ = 2.5, $^2J_{6,6'}$ = 12.4 Hz, 3 H, 3×6-Ha), 4.35 (dd, $^3J_{5,6}$ = 3.7, $^2J_{6,6'}$ = 12.2 Hz, 3 H, 3×6-Hb), 4.18 (m$_c$, 3 H, 3×5-H), 3.82 (m$_c$, 2 H, C*H*$_2$CH), 1.82 [m$_c$, 6 H, 3×C(O)C*H*$_2$CH$_2$], 1.75 [m$_c$, 6 H, 3×C(O)CH$_2$C*H*$_2$] ppm. ^{13}C NMR (150 MHz, $CDCl_3$, TMS): δ = 172.6–165.3 (3×NH*C*O, 12×Ph*C*O), 157.0 (NH*C*O$_2$), 143.9–119.8 (Ar-C), 76.6 (C-1), 74.1 (C-5), 72.6 (C-3), 70.9 (C-2), 66.3 (C-4), 65.7 (NHCO$_2$*C*H$_2$), 62.4 (C-6), 57.1 (*C*NHFmoc), 47.2 (*C*H-fluorene), 31.3 [C(O)*C*H$_2$CH$_2$], 30.5 [C(O)CH$_2$*C*H$_2$] ppm. HRMS (ESI): calcd. for [$C_{127}H_{108}N_4O_{32}$ + Na]$^+$ 2223.6844; found 2224.8521.

Supporting Information (see footnote on the first page of this article): ^{13}C NMR spectra of **4**–**9**, **11**, **13**–**15**, **17**–**19** and mass spectra of **11**, **13**–**15**, **17**–**19**.

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Received: April 20, 2009
Published Online: June 22, 2009

