Introduction

Carbohydrates constitute one of the most important classes of biomolecules in nature, where they have manifold functions. They serve as a source of energy and as structural material in plants, and they also play a key role in cell–cell recognition and communication,[1] cellular differentiation,[2] and immune response,[3] both in healthy and disease states of living organisms.

Carbohydrates, which serve functions in cell–cell interactions, are typically covalently bound to biomolecules such as proteins, peptides and lipids to form various glycoconjugates. Glycopeptides, in particular, are well known for their biological functions including antibacterial and antibiotic activity.[4] They are formed by the anomeric conjugation of carbohydrates with the side chains of specific amino acids. For the investigation of their multi-faceted biological functions, synthetic access to glycopeptides and mimetics thereof is desired. Thus, suitable conjugation methods have been widely explored in recent years,[5] including biorthogonal reactions such as native chemical ligation,[6] Staudinger ligation,[7] Diels–Alder ligation,[8] tetrazine ligation,[9] as well as different “click chemistry” approaches.[10]

We have demonstrated earlier that the Amadori rearrangement can also be considered as a versatile synthetic method for the preparation of glycoconjugates. This reaction allows the conjugation of aldoses 1 to amino components achieving C-glycosyl-type neoglycoconjugates such as 2 (Scheme 1).[11]

Scheme 1. Amadori rearrangement furnishes C-glycosyl-type neoglycoconjugates (1-amino-1-deoxy ketoses 2) from aldoses 1.

The conjugation through a C-glycosidic linkage is of particular interest for biological investigations, because this type of linkage is not sensitive towards enzymatic hydrolysis, in contrast to the more common O- and N-glycosidic bonds. In spite of this, the Amadori rearrangement has not been extensively employed in the past because of several challenges accompanying this reaction. For example, the reversibility of several steps including the introduction of the amine and the subsequent isomerization to the aminodeoxy ketose product often leads to low yields. Furthermore, the rearrangement product can enter the Maillard reaction cascade,[12] leading to a range of side and degradation products. In addition, the formation of anomeric mixtures of both furanoside and pyranoside Amadori products causes difficulties during the isolation of one desired isomer. Nevertheless, we have earlier shown the versatility of the Amadori rearrangement in various applications,[11b,11c,13] therefore we commenced a program to further investigate the scope and limitations of this rearrangement as a new glycoconjugation method. Herein, we focus on the use of (i) diamines, (ii) more complex amino-functionalized glycosides, and...
(iii) amino acids, as amino components for the Amadori rearrangement to achieve more complex C-glycosyl-type glycoconjugates.

Results and Discussion

Amadori Rearrangement with Diamines

To optimize the reaction conditions for a double Amadori rearrangement, which has not been investigated as yet, commercially available D-glycero-D-gulo aldoheptose (3) and 1,6-diaminohexane were employed (Scheme 2). The Amadori rearrangement of 3 was performed with 0.5 equiv. of the diamine and 1 equiv. of acetic acid in ethanol with 1,4-dioxane as co-solvent. This led to a double Amadori rearrangement at both amino groups to give N,N′-bis-(1-deoxy-α-D-glucohept-2-ulopyranosyl)-1,6-diaminohexane (4) with a high yield of 82 % after purification. However, chromatographic purification required a two-step protocol employing ion exchange chromatography on CG-120-II (Na+) Amberlite® resin using a water/NH4OH gradient and subsequent conventional silica gel chromatography.

During our investigation applying various amines in the Amadori rearrangement, we observed an H/D exchange in the NMR spectra at position C-1. This isotopic exchange was previously detected by Heyns and co-workers[14] who noted that signals of protons at the position C-1 in Amadori rearrangement compounds decreased on prolonged storage of solutions in D2O because of H/D exchange, which significantly accelerated with increasing pH values[13] (see the Supporting Information).

Inspired by the success of the double Amadori rearrangement with p-xylylenediamine, we next investigated the use of 4-aminobenzylamine (15) as a bidirectional linker. Here, we aimed at a regioselective single Amadori rearrangement involving the benzyl aminogroup, whereas the arylamino group was intended to remain available for subsequent modifications. Indeed, the reaction of both aldoheptoses 3 and 9 with diamine 15 gave exclusively the singly modified rearrangement products 16 and 17 in 73 % in both cases (Scheme 3).

To investigate the scope of the reaction with respect to the sugar moieties, D-glycero-D-galacto aldoheptose (9), synthesized in six steps from D-mannose,[13c] was used as an alternative heptose to 3, giving access to D-manno-configured Amadori rearrangement products (Scheme 2). In previous studies, such D-manno-configured neoglycoconjugates were tested as inhibitors of bacterial adhesion.[13c] Treatment of aldoheptose 9 with 1,6-diaminohexane, under the same reaction conditions exceptified with aldoheptose 3, gave, after 2 d at 70 °C, the disubstituted product 10 in 60 % yield.

When p-xylylenediamine was employed as the amino component under the same reaction conditions, heptose 3 gave N,N′-bis-(1-deoxy-α-D-glucohept-2-ulopyranosyl)-p-xylylenediamine (5) in 76 % yield. With substrate 9, the corresponding rearrangement product 11 was isolated in 61 % yield.

The analogous reaction with 2,2′-(ethylenedioxy)bis(ethylamine) gave rearrangement product 7 in only 23 % yield and the corresponding monosubstituted Amadori rearrangement product 6, which was concomitantly obtained in 56 % yield. In this case, the low yield of 7 might be explained by the limited availability of the second amino group, which remains free after the first Amadori rearrangement, leading to 6. Likewise, when sugar substrate 9 was employed with 2,2′-(ethylenedioxy)bis(ethylamine) under the same reaction conditions, only 29 % of the bis-compound 13 was isolated, whereas the corresponding mono-compound 12 was isolated in a yield of 55 %.

On the other hand, when 4,7,10-trioxa-1,13-tridecanediamine was employed as the amino component and an excess of aldoheptose 3 (3 equiv.) was used, the Amadori rearrangement gave exclusively the disubstituted product 8 in a yield of 58 %. Aldoheptose 9 gave, under the same reaction conditions, exclusively product 14 in a yield of 54 %. Hence, the amount of monosubstitution vs. disubstitution of diamines can be controlled by selecting the amount of aldose in a quantifiable manner. Additionally, the availability of the second amino group increases with the chain length of the spacer of the respective diamines.

During our investigation applying various amines in the Amadori rearrangement, we observed an H/D exchange in the NMR spectra at position C-1. This isotopic exchange was previously detected by Heyns and co-workers[14] who noted that signals of protons at the position C-1 in Amadori rearrangement compounds decreased on prolonged storage of solutions in D2O because of H/D exchange, which significantly accelerated with increasing pH values[13] (see the Supporting Information).

Inspired by the success of the double Amadori rearrangement with p-xylylenediamine, we next investigated the use of 4-aminobenzylamine (15) as a bidirectional linker. Here, we aimed at a regioselective single Amadori rearrangement involving the benzyl aminogroup, whereas the arylamino group was intended to remain available for subsequent modifications. Indeed, the reaction of both aldoheptoses 3 and 9 with diamine 15 gave exclusively the singly modified rearrangement products 16 and 17 in 73 % in both cases (Scheme 3).

The regioselective ligation reaction with 15 can be rationalized on the basis of the pKa values of the amino group. Given

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Scheme 2. Double Amadori rearrangement with different diamines employing heptoses 3 and 9 of the D-gluco and D-manno series, respectively. OEG = oligo(ethylene glycol).

Scheme 3. Diamine 15, having two differing pKa values, allows for regioselective Amadori rearrangement.
that basicity is a crucial parameter for the nucleophilicity of amines, which is required for the success of the Amadori rearrangement, (4-aminobenzyl)amine (15), with $pK_a$ values of 9.3 for the benzylic amine and 4.6 for the aniline amino group, reacts selectively at the benzylic position. Products 16 and 17, respectively, can be further ligated in amide coupling reactions, thiourea bridging or other ligation reactions involving amines. In addition, the amino group can be converted into an azido function, which is amenable for click chemistry.

**Amadori Rearrangement with Amino-Functionalized Carbohydrates**

To utilize the Amadori rearrangement for the synthesis of more complex glycoconjugates, amino-functionalized glycosides were used as amino components. To this end, 3-O-(amino-propyl)-functionalized mannosides 20 and 23 were synthesized by applying a procedure for tin-mediated regioselective etherification of glycosides, which we have disclosed earlier (Scheme 4). Thus, mannosides 18 and 21, respectively, were treated with dibutyltin oxide to achieve the corresponding stannylidene acetal intermediates. These were treated with $N$-(3-bromopropyl)phthalimide in the same reaction vessel after the solvent was exchanged from MeOH to $N,N$-dimethylformamide (DMF) to deliver the respective 3-O-functionalized mannosides 19 and 22 after regioselective opening of the tin acetal ring. Although the yields were moderate in this step, this is an advantageous direct approach to selectively 3-O-functionalize mannosides without the need for protecting-group chemistry. The free amines 20 and 23 were obtained after hydrazinolysis of 19 and 22 in 80 and 89 % yields, respectively.

In the next step, amino-functionalized mannosides 20 and 23 as well as known 2-aminooethyl $\alpha$-D-mannopyranoside (24) were employed in the Amadori rearrangement with $\alpha$-glycero-$\alpha$-gulo aldoheptose (3) as well as $\alpha$-glycero-$\alpha$-galacto aldoheptose (9) (Scheme 5). First, 2-aminooethyl $\alpha$-D-mannopyranoside (24) was treated with 3 and 9 to obtain the rearrangement products 25 in a yield of 45 % and 26 in 65 % yield, respectively. Next, in the $\alpha$-manno series employing substrate 9, 2-(benzyloxyacarbonylamino)ethyl 3-O-(3-aminopropyl) $\alpha$-D-mannopyranoside (20) gave Amadori rearrangement compound 27 in 39 % yield. Propynyl-3-O-(3-aminopropyl) $\alpha$-D-mannopyranoside (23) gave compound 28 in 25 % yield. In these cases, the reactions had to be stopped after 5 d at 70 °C to avoid side-product formation and degradation, and, consequently, the obtained yields were rather moderate. Neverthe-

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**Scheme 4.** Regioselective synthesis of the amino-functionalized mannosides 20 and 23.

**Scheme 5.** Synthesis of complex glycoconjugates employing Amadori rearrangement of heptoses 3 or 9 with amino-functionalized mannosides 20, 23, and 24 as amino components.
less, both compounds are valuable intermediates, because they offer orthogonal groups at the anomeric position for further modification: compound 27, bearing a masked amino function, and compound 28, a versatile propargyl group.

Synthesis of Amino Acid Glycoconjugates by Amadori Rearrangement

We then investigated the use of the Amadori rearrangement as a conjugation method for the synthesis of C-glycosyl-type amino acid glycoconjugates. Thus, we employed partly protected lysine derivatives 29, 31, and 33 as well as dipeptide 35 and tripeptide 38 as amino components (Scheme 6).

When d-glycero-d-galacto aldoheptose (9) was treated with Nα-(tert-butoxycarbonyl)-L-lysine (29) under acidic conditions, the corresponding Amadori rearrangement product 30 was obtained in a yield of 63 %. Using Nα-(benzyloxycarbonyl)-L-lysine (31) as amino component, the d-glucos-configured product was obtained in 73 %, and the d-mannos-configured product 32 was isolated in 65 % yield. Likewise, methyl Nα-(tert-butoxycarbonyl)-L-lysinate (33) was treated with aldoheptose 9 to obtain the desired rearrangement product 34 in 68 % yield.

We wanted to employ dipeptides as well as tripeptides as amino components for the Amadori rearrangement (Scheme 6). Therefore, the L-lysine-containing di- and tripeptides 35 and 38, respectively, were synthesized by applying standard peptide coupling procedures. Dipeptide 35 employed in the Amadori rearrangement of d-glycero-d-gulo aldoheptose (3) and d-glycero-d-galacto aldoheptose (9) gave compounds 36 (81 %) and 37 (62 %), respectively. Likewise, tripeptide 38 furnished glycopeptide mimetics 39 (39 %) and 40 (49 %) from the aldoheptoses 3 and 9, respectively.

Conclusions

We demonstrated that the Amadori rearrangement is an attractive conjugation method for the synthesis of C-glycosyl-type glycoconjugate mimetics without the need for protecting-group manipulations.

Symmetrical diamino components gave the respective di-substituted Amadori rearrangement products in acceptable yields. Interestingly, the ratio of mono-sugar conjugation vs. bis-sugar Amadori products can be controlled in a preparatively useful manner by controlling the amount of sugar substrate employed. The regioselectivity of the Amadori rearrangement employing unsymmetrical diamines can be controlled by taking the pK_a value as a parameter for the nucleophilicity of the respective amino components into account. Amines with a pK_a range between 8 and 12 are more efficient nucleophiles for this reaction than less basic amines. Amino-functionalized glycosides can also be employed as amino components in the Amadori reaction. By the choice of the aglycon, such as a masked amino function or a versatile propargyl group, different applications for the obtained building blocks can be envisaged. Lysine derivatives as well as lysine-containing di- and tripeptides in the Amadori rearrangement lead to C-glycosyl-type glycopeptide mimetics, which can be used as building blocks for glycopeptide and glycoprotein synthesis. In all cases the α-anomeric configuration of the respective Amadori products was obtained exclusively, as has been shown earlier in the d-glucos as well as d-mannos series. In the context of configuration of the sugar substrate, no significant differentiation in the obtained yields was observed.

Despite the fact that yields for this conjugation method may occasionally be found in a preparatively moderate range and product purification may be extensive in a few cases, conjugation through a C-glycosidic linkage leads to versatile building...
blocks for different applications, in particular for biological investigations, because this type of conjugation is not sensitive towards enzymatic or chemical hydrolysis in a physiological environment.

Experimental Section

Materials and General Methods: All chemicals were purchased from Sigma Aldrich and used without further purification. Moisture-sensitive reactions were carried out under nitrogen in dry glassware. NMR spectra were recorded with Bruker Ultrashield spectrometers at 300.36 (1H) and 75.33 (13C) MHz, respectively. Higher resolution NMR spectra were recorded with VARIAN INOVA 500 MHz at 500.619 (1H) and 125.894 (13C) MHz, respectively. Chemical shifts are reported relative to internal tetramethylsilane (δ = 0.00 ppm), D2O (δ = 4.79 ppm), [D6]DMSO (δ = 2.50 ppm) or [D6]MeOH (δ = 4.78, 3.31 ppm). Full assignment of the peaks was achieved with the aid of 2D NMR techniques (1H-1H COSY and 1H-13C HSQC). Optical rotations were measured with a Perkin–Elmer 341 polarimeter (so- dual D-line: 589 nm, length of cell: 1 dm, temp.: 20 °C) in the medium D-line: 589 nm, length of cell: 1 dm, temp.: 20 °C) in the medium D-line: 589 nm, length of cell: 1 dm, temp.: 20 °C) in the medium.

General Method A (Diamines): To a solution of the respective aldoheptose (2 equiv.) in a mixture of EtOH and 1,4-dioxane, the amino compound (1 equiv.) and acetic acid (1 equiv.) were added, and the reaction mixture was stirred at 70 °C until TLC showed satisfactory consumption of the starting material. The reaction mixture was concentrated under reduced pressure, and the crude product was purified by ion exchange chromatography as well as with silica gel chromatography with the solvent system indicated.

General Method B (Amines): To a solution of the respective aldolheptose (1 equiv.) in a mixture of EtOH and 1,4-dioxane, the amino compound and acetic acid (1 equiv.) were added, and the reaction mixture was stirred at 70 °C until TLC showed satisfactory consumption of the starting material. The reaction mixture was concentrated under reduced pressure, and the crude product was purified by silica gel column chromatography with the solvent system indicated.

N,N′-Bis(1-deoxy-α-D-glucopyranose)-2,2′-ethylenedioxibis(ethylamine) (7): By applying general method A, d-glycero-D-gulo-heptopyranose (3; 300 mg, 1.43 mmol, 2 equiv.) was treated with 2,2′-ethylenedioxybis(ethylamine) (139 μL, 0.952 mmol, 1 equiv.) in EtOH (6 mL) and 1,4-dioxane as co-solvent in the presence of acetic acid (109 μL, 1.90 mmol, 2 equiv.) at 70 °C for 2 d. The solvents were removed under reduced pressure, and the crude product was passed through an ion exchange CG-120-II (Na+) Amberlite® resin column (H2O; H2O containing 1 % of conc. NH4OH) followed by purification by silica gel column chromatography (CH2Cl2/MeOH, 1:1, v/v containing 25 % of conc. NH4OH) to give disubstituted product 5 (281 mg, 0.540 mmol, 76 %). 1H NMR (300 MHz, D2O): δ = 7.43–7.36 (br. s, 4 H, Ph), 3.92 (br. s, 4 H, 4, 8-H), 3.84–3.61 (m, 8 H, 7-H, 7'-H, 6-H, 4-H), 3.40 (d, δJ,6,9 = 9.3 H z, 2 H, 5-H), 2.97 (d, δJ,9,1 = 12.5 H z, 2 H, 1-H), 2.89 (d, δJ,9,1 = 11.8 H z, 2 H, 1'-H) ppm. 13C NMR (125 MHz, D2O/D2O, 9:1 v/v): δ = 136.0, 129.3 (6 C, phenyl), 96.5 (C-2), 73.6, 72.4, 72.3 (C 3, C-6, C-4, C-3), 69.5 (C-9), 60.7 (C-7), 53.0 (C-1), 52.1 (C-8) ppm. HRMS (MALDI): m/z calcd. for C22H36N2O12 [M + Na]+ at 543.2173; found 543.2173.

N,N′-Bis(1-deoxy-α-D-glucopyranose)-2,2′-ethylenedioxibis(ethylamine) (7): By applying general method A, d-glycero-D-gulo-heptopyranose (3; 300 mg, 1.43 mmol, 2 equiv.) was treated with 2,2′-ethylenedioxybis(ethylamine) (139 μL, 0.952 mmol, 1 equiv.) in EtOH (6 mL) and 1,4-dioxane as co-solvent in the presence of acetic acid (109 μL, 1.90 mmol, 2 equiv.) at 70 °C for 2 d. The solvents were removed under reduced pressure, and the crude product was passed through an ion exchange CG-120-II (Na+) Amberlite® resin column (H2O; H2O containing 1 % of conc. NH4OH) to give disubstituted product 5 (281 mg, 0.540 mmol, 76 %). 1H NMR (300 MHz, D2O): δ = 7.43–7.36 (br. s, 4 H, Ph), 3.92 (br. s, 4 H, 4, 8-H), 3.84–3.61 (m, 8 H, 7-H, 7'-H, 6-H, 4-H), 3.40 (d, δJ,6,9 = 9.3 H z, 2 H, 5-H), 2.97 (d, δJ,9,1 = 12.5 H z, 2 H, 1-H), 2.89 (d, δJ,9,1 = 11.8 H z, 2 H, 1'-H) ppm. 13C NMR (125 MHz, D2O/D2O, 9:1 v/v): δ = 136.0, 129.3 (6 C, phenyl), 96.5 (C-2), 73.6, 72.4, 72.3 (C 3, C-6, C-4, C-3), 69.5 (C-9), 60.7 (C-7), 53.0 (C-1), 52.1 (C-8) ppm. HRMS (MALDI): m/z calcd. for C22H36N2O12 [M + Na]+ at 543.2173; found 543.2173.

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containing 1% of conc. NH₄OH) followed by purification by silica gel column chromatography (CHCl₃/MeOH, 1:1; v/v containing 25% of conc. NH₂OH) to give disubstituted product 8 (168 mg, 0.278 mmol, 58%). [α]D20 = +31.7 (c = 2.83, H₂O). ¹H NMR (300 MHz, D₂O): δ = 3.85–3.62 (m, 16 H, 12-H, 11-H, 7-H, 7′-H, 6-H, 4-H), 3.59 (t, 4 H, 10-H), 3.42 (dd, J₂₂,₂₃ = 9.4 Hz, 2 H, 5-H), 2.98 (d, J₁₁,₁₂ = 12.6 Hz, 2 H, 1-H), 2.87 (d, 2 H, 1′-H), 2.81 (t, 4 H, 8-H), 1.82 (t, 4 H, 9-H) ppm. ¹³C NMR (125 MHz, D₂O): δ = 95.4 (C-2), 73.4, 72.6, 72.5 (3 C, C-6, C-4, C-3), 69.5, 69.4, 69.3 (3 C, C-12, C-11, C-10), 68.4 (C-5), 60.6 (C-7), 53.3 (C-1), 46.8 (C-6), 25.9 (C-9) ppm. HRMS (MALDI): m/z calcd. for C₂₂H₃₆N₂O₁₂ [M + H]+* 605.2333; found 605.2334.

**Compound 12:** ¹H NMR (300 MHz, D₂O): δ = 3.99–3.56 (m, 14 H, 1, 11-H, 10-H, 9-H, 7-H, 7′-H, 6-H, 5-H, 4-H, 3-H), 3.46 (d, J₁₁,₁₂ = 13.0 Hz, 1 H, 1-H), 3.27 (d, 1 H, 1′-H), 3.18–3.15 (4 H, 4-H, 3-H), 3.08 (d, J₁₁,₁₂ = 12.5 Hz, 2 H, 1-H), 2.78 (t, 4 H, 8-H), 1.90 (m, 4 H, 9-H) ppm. ¹³C NMR (125 MHz, D₂O/H₂O, 9:1 v/v): δ = 96.5 (C-2), 73.1 (C-6), 71.8, 70.9 (2 C, C-4, C-3), 69.5, 69.3, 68.8 (3 C, C-12, C-11, C-10), 66.5 (C-5), 61.1 (C-7), 53.9 (C-1), 46.5 (C-8), 26.9 (C-9) ppm. HRMS (MALDI): m/z calcd. for C₂₄H₂₄N₂O₁₄ [M + H]+* 605.3133; found 605.3135.

**N,N′-Bis(1-deoxy-α-α-manno-hept-2-ulopyranosyl)-1,6-hexane- diamine (10):** By applying general method A, d-glycero-d-galacto-heptopyranosyl (9; 204 mg, 0.971 mmol, 2 equiv.) was treated with 1,6-diaminohexane (56 mg, 0.485 mmol, 1 equiv.) in EtOH (4 mL) and 1,4-dioxane as co-solvent in the presence of acetic acid (56 μL, 1.90 mmol, 2 equiv.) at 70 °C for 2 d. The solvents were removed under reduced pressure, and subsequent column chromatography (CHCl₃/MeOH, 1:1, v/v containing 25% of conc. NH₂OH) gave disubstituted product 10 (146 mg, 0.292 mmol, 60%). [α]D20 = +11.0 (c = 1.62, H₂O). ¹H NMR (300 MHz, D₂O): δ = 3.98–3.86 (m, 10 H, 7-H, 7′-H, 6-H, 4-H, 3-H), 3.66 (dd, J₂₂,₂₃ = 9.3, J₃₃,₃₄ = 9.5 Hz, 2 H, 5-H), 3.42 (d, J₁₁,₁₂ = 12.9 Hz, 2 H, 1-H), 2.87 (d, 2 H, 1′-H), 2.81 (t, 4 H, 8-H), 1.82 (t, 4 H, 9-H) ppm. ¹³C NMR (125 MHz, D₂O): δ = 95.1 (C-2), 73.5, 72.1 (3 C, C-6, C-4, C-3), 69.5, 69.4, 69.3 (3 C, C-12, C-11, C-10), 68.4 (C-5), 60.6 (C-7), 53.3 (C-1), 46.8 (C-6), 25.9 (C-9) ppm. HRMS (MALDI): m/z calcd. for C₂₂H₂₂N₂O₁₂ [M + H]+* 521.1660; found 521.1662.

**N,N′-Bis(1-deoxy-α-α-manno-hept-2-ulopyranosyl)-p-xylene- diamine (11):** By applying general method A, d-glycero-d-galacto-heptopyranosyl (9; 300 mg, 1.43 mmol, 2 equiv.) was treated with p-xylenediamine (97 mg, 0.714 mmol, 1 equiv.) in EtOH (5 mL) and 1,4-dioxane as co-solvent in the presence of acetic acid (82 μL, 1.43 mmol, 2 equiv.) at 70 °C for 2 d. The solvents were removed under reduced pressure, and the crude product was passed through an ion exchange CG-120-II (Na+) Amberlite® resin column (H₂O; H₂O containing 1% of conc. NH₂OH) followed by purification by silica gel column chromatography (CHCl₃/MeOH, 1:1; v/v containing 25% of conc. NH₂OH) to give disubstituted product 11 (226 mg, 0.434 mmol, 61%). [α]D20 = +14.1 (c = 3.4, H₂O). ¹H NMR (300 MHz, D₂O): δ = 7.46–7.39 (br. s, 4 H, phenyl), 4.00 (br. s, 4 H, 8-H, 8′-H), 3.93–3.80 (m, 6 H, 7-H, 7′-H, 6-H, 4-H, 3-H), 3.79–3.66 (m, 4 H, 7′-H, 6-H, 5-H), 3.59 (dd, J₂₂,₂₃ = 9.5, J₃₃,₃₄ = 9.6 Hz, 2 H, 5-H), 3.01 (d, J₁₁,₁₂ = 13.4 Hz, 2 H, 1-H), 2.97 (d, 2 H, 1′-H) ppm. ¹³C NMR (125 MHz, D₂O/H₂O, 9:1 v/v): δ = 135.8, 129.3 (6 C, phenyl), 96.7 (C-2), 73.1 (C-6), 71.6, 70.9 (2 C, C-4, C-3), 66.6 (C-5), 61.1 (C-7), 53.1 (C-1), 51.9 (C-8) ppm. HRMS (MALDI): m/z calcd. for C₂₄H₂₄N₂O₁₂ [M + H]+* 521.2347; found 521.2346.

**N,N′-Bis(1-deoxy-α-α-manno-hept-2-ulopyranosyl)-2,2′-ethyl-enedioxybis(ethyleneamidine) (13):** By applying general method A, d-glycero-d-galacto-heptopyranosyl (9; 400 mg, 1.90 mmol, 2 equiv.) was treated with 2,2′-ethenedioxybis(ethyleneamidine) (139 mg, 0.952 mmol, 1 equiv.) in EtOH (6 mL) and 1,4-dioxane as co-solvent in the presence of acetic acid (109 mg, 1.90 mmol, 2 equiv.) at 70 °C for 4 d. The solvents were removed under reduced pressure, and the crude product was passed through an ion exchange CG-120-II (Na+) Amberlite® resin column (H₂O; H₂O containing 1% of conc. NH₂OH) followed by purification by silica gel column chromatography (CHCl₃/MeOH, 3:1; v/v containing 1% of conc. NH₂OH) to give disubstituted product 13 (148 mg, 0.278 mmol, 29%) and monosubstituted product 12 (178 mg, 0.523 mmol, 55%).
1-(2-[α-Mannopyranosyl]ethylamino)-1-deoxy-α-gluco-hept-2-ulose (21): By applying general method B, d-glycero-d-gulo-heptopyranose (3; 105 mg, 0.500 mmol, 1.1 equiv.) was treated with 2-aminoethyl α-α-mannopyranoside (20; 100 mg, 0.448 mmol, 1 equiv.) in EtoH (4 mL) and 1,4-dioxane as co-solvent in the presence of acetic acid (26 μL, 0.448 mmol, 1 equiv.) at 70 °C for 4 d. The solvents were removed under reduced pressure, and subsequent column chromatography (CHCl3/MeOH, 1:1 v/v containing 1 % of conc. NH4OH) gave product 21 (84 mg, 0.202 mmol, 56 %). [α]20D = +64.8 ° (c = 1.15, H2O). 1H NMR (300 MHz, D2O); δ = 4.90 (d, 1 H, 1-H, 2-H), 4.32 (dd, Jα,β = 2.2 Hz, H-3), 4.24 (dd, Jα,β = 1.9 Hz, 1-H, 2-H, 3-H), 3.87–3.75 (m, 9 H, OCH2CH2NH2, H2NH), 3.67–3.55 (m, 8 H, OCH2CH2NH2), 3.27–3.13 (m, 11 H, 4-H, 5-H, 6-H, 7-H), 2.40–2.24 (m, 3 H, 2-H, 3-H, 4-H) ppm. HRMS (MALDI): m/z calcd. for C21H32N2O8 [M + H]+ 416.1768; found 416.1768.

N-[(α-Mannopyranosyl)ethylamino]-1-deoxy-α-gluco-hept-2-ulose (26): By applying general method B, d-glycero-d-galacto-heptopyranose (9; 94 mg, 0.448 mmol, 1 equiv.) was treated with 2-aminoethyl α-α-mannopyranoside (20; 100 mg, 0.448 mmol, 1 equiv.) in EtoH (4 mL) and 1,4-dioxane as co-solvent in the presence of acetic acid (26 μL, 0.448 mmol, 1 equiv.) at 70 °C for 4 d. The solvents were removed under reduced pressure, and subsequent column chromatography (CHCl3/MeOH, 1:1 v/v containing 1 % of conc. NH4OH) gave product 26 (64 mg, 0.155 mmol, 35 %). [α]20D = +11.2 ° (c = 1.15, H2O). 1H NMR (300 MHz, D2O); δ = 4.90 (s, 1 H, 1-H), 4.24 (dd, Jα,β = 2.2 Hz, H-3), 4.24 (dd, Jα,β = 1.9 Hz, 1-H, 2-H, 3-H), 3.87–3.75 (m, 9 H, OCH2CH2NH2, H2NH), 3.67–3.55 (m, 8 H, OCH2CH2NH2), 3.27–3.13 (m, 11 H, 4-H, 5-H, 6-H, 7-H), 2.40–2.24 (m, 3 H, 2-H, 3-H, 4-H) ppm. HRMS (MALDI): m/z calcd. for C21H32N2O8 [M + H]+ 416.1768; found 416.1768.

Propargyl 3-O-(3-phthalamido)α-α-mannopyranoside (22): To a solution of mannose 21 (327 mg, 1.50 mmol) in anhydrous methanol (13 mL), dibutyltin oxide (392 mg, 1.57 mmol) was added, and the solution was heated to reflux for 4 h. The solvent was then evaporated, and the crude product was desolvised in anhydrous N,N-dimethylformamide (13 mL). N-(3-Propargylphthalimide) (1.49 g, 5.55 mmol) and cesium fluoride (229 mg, 1.49 g, 5.55 mmol) was added, and the reaction mixture was stirred at room temperature for 2 d. The solvent was then evaporated, and purification of the crude product by column chromatography (di-chloromethane/ethyl acetate, 1:1 → 1:3 → ethyl acetate/methanol, 10:1) gave pure 22 (182 mg, 0.450 mmol, 30 %) as a colorless foam at 70 °C.

2-(Benzyloxy carbonylamino) ethyl 3-O-(3-phthalimidopropyl)-α-α-mannopyranoside (19): To a solution of the benzylxycarbonyl-protected mannoside 18 (3.29 g, 9.19 mmol) in anhydrous methanol (90 mL), dibutyltin oxide (2.40 g, 9.65 mmol) was added, and the solution was heated to reflux for 2 h. The solvent was evaporated, and the crude product was dissolved in anhydrous N,N-dimethylformamide (90 mL). N-(3-Bromopropyl)phthalimide (9.12 g, 34.00 mmol) and cesium fluoride (1.90 g, 9.19 mmol) were added, and the reaction mixture was stirred at room temperature for 3 d. The solvent was then evaporated, and purification of the crude product by column chromatography (CHCl3/EtOAc/MeOH, 10:5:1 → 5:5:1) gave pure 19 (1.87 g, 3.44 mmol, 37 %) as colorless foam. [α]20D = +32.7 (c = 0.4 CHCl3). 1H NMR (500 MHz, D2O); δ = 7.87–7.82 (m, 4 H, Ar-H), 7.37–7.29 (m, 6 H, NH, Ar-H), 5.02 (s, 2 H, PhCH2O), 4.65 (s, 1 d, 1 H, 1-H), 3.82–3.80 (m, 1 H, 2-H), 3.72–3.62 (m, 3 H, PhNCH2), 3.61–3.56 (m, 2 H, 2H, CH2NH), 3.51–3.48 (m, 1 H, 4-H), 3.37–3.40 (m, 3 H, OCH2CH2CH3, 6′-H), 3.38–3.35 (m, 1 H, 5-H), 3.27 (dd, Jα,β = 3.0 Hz, Jα,γ = 9.2 Hz, 1 H, 3-H), 3.24–3.14 (m, 2 H, CH2NH), 1.85 (p, Jα = 6.7, Jβ = 6.7 Hz, 2 H, 2H, CH2CH2NH) ppm. 13C NMR (126 MHz, D2O); δ = 168.0 (C=O), 134.9, 133.6, 133.0 (C-1), 128.3 (C-2), 127.8 (C-3), 127.7 (C-4), 127.5 (C-5), 127.0 (C-6), 78.6 (C-7), 78.4 (C-8), 71.9 (C-9), 79.6 (C-10), 66.8 (C-11), 64.4 (C-12), 61.8 (C-13), 60.9 (C-14), 54.9 (C-15), 51.5 (C-16), 40.1 (C-17), 37.5 (C-18), 36.5 (C-19), 32.7 (C-20), 29.2 (C-21), 24.3 (C-22), 18.3 (C-23), 18.0 (C-24), 17.0 (C-25), 16.7 (C-26), 13.7 (C-27), 13.7 (C-28), 12.9 (C-29), 12.8 (C-30).
and 1,4-dioxane as co-solvent in the presence of acetic acid (55 μL, 0.952 mmol, 1 equiv.) at 70 °C for 4 d. The solvents were removed under reduced pressure, and subsequent column chromatography (CHCl3/MeOH, 6:1, v/v containing 1 % of conc. NH4OH) gave product 30 (263 mg, 0.600 mmol, 63 %). [α]D20 = +21.8 (c = 2.87, MeOH).

1H NMR (300 MHz, [D2]MeOH): δ = 3.87 (t, 1 H, 12-H), 3.82–3.73 (m, 3 H, 7-H, 6-H, 3-H), 3.72–3.59 (m, 2 H, 7'-H, 4',H), 3.57 (dd, J1,12 = 8.5, J4,5 = 9.5 Hz, 1 H, 12-H), 3.25 (d, J1,12 = 12.7 Hz, 1 H, 1'-H), 2.93 (t, 2 H, 8-H), 1.79–1.51 (m, 4 H, 9-H, 11-H), 1.41–1.27 (br. s, 11 H, 10-H, Boc) ppm. 13C NMR (75 MHz, [D2]MeOH): δ = 179.5 (C-13), 157.6 (C-14), 96.1 (C-12), 80.1 (C-15), 75.1 (C-4), 74.6 (C-3), 72.5 (C-6), 67.8 (C-5), 62.5 (C-7), 56.7 (C-12), 54.9 (C-1), 49.2 (C-8), 33.6 (C-11), 28.8 (Boc), 26.3 (C-9), 23.6 (C-10) ppm. HRMS (MALDI): m/z calcd. for C51H35N2S2O14 [M + H]+ 843.2292; found 843.2293.

1-[[(5S)-5-(Benzoxycarbonylamino)-5-(methoxycarbonyl)-pentoxy]l]amino)-1-deoxy-α-D-manno-hept-2-ulos (32): By applying general method B, o-glycero-D-galacto-heptopyranos (9; 200 mg, 0.952 mmol, 1 equiv.) was treated with N6-(benzoxycarbonyl)-L-lysine (31; 267 mg, 0.952 mmol, 1 equiv.) in EtOH (4 mL) and 1,4-dioxane as co-solvent in the presence of acetic acid (55 μL, 0.952 mmol, 1 equiv.) at 70 °C for 4 d. The solvents were removed under reduced pressure, and subsequent column chromatography (CHCl3/MeOH, 6:1, v/v containing 1 % of conc. NH4OH) gave product 32 (292 mg, 0.618 mmol, 65 %). [α]D20 = +122.2 (c = 0.545, MeOH).

1H NMR (300 MHz, [D2]MeOH): δ = 7.38–7.23 (m, 5 H, Ph), 5.05 (br. s, 2 H, 15-H), 4.07–3.96 (m, 1 H, 12-H), 3.86 (dd, J4,5 = 3.2 Hz, 1 H, 3-H), 3.86–3.73 (m, 3 H, 7'-H, 6-H, 7-H), 3.72–3.66 (m, 1 H, 4-H), 3.65 (dd, J4,5 = 8.5, J9,6 = 9.4 Hz, 1 H, 12-H), 3.29 (d, 1 H, 1-H), 3.09 (d, J1,12 = 12.2 Hz, 1 H, 1'-H), 2.97 (t, 2 H, 8-H), 1.91–1.59 (m, 4 H, 9-H, 11-H), 1.42 (q, 2 H, 10-H) ppm. 13C NMR (75 MHz, [D2]MeOH): δ = 179.1 (C-13), 158.1 (C-14), 138.4, 129.3, 128.9, 128.8 (6 C, Ph), 96.1 (C-2), 75.1 (C-4), 74.8 (C-3), 72.6 (C-5), 67.8 (C-5), 67.4 (C-15), 62.5 (C-7), 57.2 (C-12), 55.1 (C-8), 49.2 (C-9), 33.5 (C-11), 26.4 (C-9), 23.5 (C-10) ppm. HRMS (MALDI): m/z calcd. for C41H35N2O22 [M + H]+ 743.2135; found 743.2137.

1-[[(5S)-5-(tert-Butoxycarbonylamino)-5-(methoxycarbonyl)-pentoxy]l]amino)-1-deoxy-α-D-manno-hept-2-ulos (34): By applying general method B, o-glycero-D-galacto-heptopyranos (9; 300 mg, 1.43 mmol, 1 equiv.) was treated with methyl N6-(tert-butoxycarbonyl)-L-lysinate (33; 370 mg, 1.42 mmol, 1 equiv.) in EtOH (5 mL) and 1,4-dioxane as co-solvent in the presence of acetic acid (82 μL, 1.43 mmol, 1 equiv.) at 70 °C for 3 d. The solvents were removed under reduced pressure, and subsequent column chromatography (CHCl3/MeOH, 6:1, v/v containing 1 % of conc. NH4OH) gave product 34 (438 mg, 0.968 mmol, 68 %). [α]D20 = +0.63 (c = 2.06, MeOH).

1H NMR (300 MHz, [D2]MeOH): δ = 4.15–4.05 (m, 1 H, 12-H), 3.89 (dd, J4,5 = 3.3 Hz, 1 H, 3-H), 3.87–3.77 (m, 3 H, 7-H, 7',H, 6-H), 3.76–3.67 (m, 2 H, 4-H, OCH3), 3.66 (dd, J4,5 = 9.0, J9,6 = 9.3 Hz, 1 H, 12-H), 3.37 (d, J1,12 = 12.3 Hz, 1 H, 1'-H), 3.15 (d, 1 H, 1'-H), 3.06 (t, 2 H, 8-H), 1.91–1.59 (m, 4 H, 9-H, 11-H), 1.53–1.33 (br. s, 11 H, 10-H, Boc) ppm. 13C NMR (75 MHz, [D2]MeOH): δ = 174.7 (C-13), 158.1 (C-14), 95.9 (C-2), 80.7 (C-15), 75.1 (C-4), 74.8 (C-3), 72.4 (C-6), 67.6 (C-5), 62.3 (C-7), 55.1 (C-1), 54.8 (C-12), 52.7 (OCH3), 49.2 (C-8), 32.0 (C-11), 28.7 (Boc), 26.2 (C-9), 23.9 (C-10) ppm. HRMS (MALDI): m/z calcd. for C47H39N2O23 [M + H]+ 703.2583.
removed under reduced pressure, and subsequent column chromatography (CHCl₃/MeOH, 3:1, v/v containing 1 % of conc. NH₄OH) gave product 36 (119 mg, 0.227 mmol, 81 %). ¹H NMR (300 MHz, [D₂]MeOH): δ = 4.29 (q, 1 H, 1-H), 3.93 (t, 1 H, 12-H), 3.68–3.44 (m, 7 H, 7-H, 7′-H, 6-H, 4-H, OCH₃), 3.15–3.06 (dd, 2 H, 5-H, 3-H), 3.12 (d, J₁₇₂₀ = 12.7 Hz, 1 H, 1-H), 3.05 (d, J₁₉₁₈ = 12.5 Hz, 1 H, 1′-H), 2.87–2.75 (m, 2 H, 8-B, 9-H), 1.63–1.48 (m, 3 H, 9-H, 11-H), 1.49 (t, 1 H, 11-H, 9-H), 1.33 (t, 1 H, 11-H, 9-H), 1.21 (br s, 1 H, 10-H, Boc), 1.19 (dd, 3 H, 18-H, ppm). ¹³C NMR (75 MHz, [D₂]MeOH): δ = 174.7, 174.5 (2 C, C-17, C-13), 157.7 (C-14), 96.2 (C-2), 80.6 (C-15), 75.1, 74.6, 74.5 (3 C, C-6, C-4, C-3), 71.4 (C-5), 62.5 (C-7), 55.3 (C-1), 54.4 (C-12), 52.8 (OCH₃), 49.9 (C-8), 49.4 (C-16), 32.8 (C-11), 28.7 (Boc), 26.5 (C-9), 23.8 (C-10), 17.4 (C-18) ppm. Methyl N⁵-( tert-Butyloxy carbonyl)-L-lysyl-N⁸-(1-deoxy-α-L-d-manno-hept-2-ulose)-L-lysyl-L-ala nitine [37] by applying general method B, 1,1-dioxane as co-solvent in the presence of acetic acid (41 µL, 0.714 mmol, 1 equiv.) at 70 °C for 3 d. The solvents were removed under reduced pressure, and subsequent column chromatography (CHCl₃/MeOH, 6:1, v/v containing 1 % of conc. NH₄OH) gave product 37 (23 mg, 0.441 mmol, 62 %). ([α]₂⁰ = −123 (c = 0.86, MeOH). ¹H NMR (300 MHz, [D₂]MeOH): δ = 4.42 (q, 1 H, 16-H), 4.10–4.00 (m, 1 H, 12-H), 3.87–3.80 (m, 3 H, 7-H, 6-H, 3-H), 3.79–3.68 (m, 5 H, 7’-H, 4-H, OCH₃), 3.64 (dd, J₁₉₂₃ = 8.9, J₃₄ = 9.5 Hz, 1 H, 5-H), 3.20 (d, J₁ₜ₉ = 12.5 Hz, 1 H, 1-H), 3.02 (d, 1 H, 1′-H), 2.92 (t, 2 H, 8-H), 1.84–1.56 (m, 4 H, 9-H, 11-H), 1.52–1.35 (m, 14 H, 18-H, 10-H, Boc) ppm. ¹³C NMR (75 MHz, [D₂]MeOH): δ = 174.4, 174.6 (2 C, C-17, C-13), 157.8 (C-14), 96.3 (C-2), 80.7 (C-15), 75.1, 74.9, 74.5 (2 C, C-4, C-3), 72.7 (C-6), 67.9 (C-5), 62.6 (C-2), 55.8 (C-1), 55.4 (C-12), 52.8 (OCH₃), 49.9 (C-8), 49.2 (C-16), 32.9 (C-11), 28.7 (Boc), 27.5 (C-9), 23.9 (C-10), 17.4 (C-18) ppm. HRMS (MALDI): m/z calcd. for C₂₉H₄₈N₆O₁₂ [M + H]⁺ 621.3347; found 621.3349.

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