Solid-Phase Synthesis of Cyclic *C*-Glycoside/Amino Acid Hybrids by Carbamate Coupling Chemistry and On-Support Cyclization

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A solid-supported synthesis of cyclic *C*-glycoside/amino acid conjugates is described. For this purpose, *N*-(*tert*-butoxycarbonyl)-[6-*O*-(*p*-nitrophenoxycarbonyl)-2,3,4-tri-*O*-(*p*-toluoyl)-β-D-glycopyranosyl]methylamines derived from galactose and glucose were prepared and used as activated monomers together with appropriately protected amino acids. The solid phase assembly of the linear precursor was conducted by alternating peptide and carbamate coupling, using glutamate immobilized through its γ-carboxy function to a SCAL linker as a handle. On-support cyclization followed by cleavage from the support gave the desired conjugates. Removal of the *p*-toluoyl protections was carried out in solution phase by methoxide ion-catalyzed transesterification in methanol.

Introduction

Interactions of carbohydrates with proteins play a key role in intercellular trafficking, receptor binding and signaling.[1–6] To elucidate the underlying features of these interactions, numerous carbohydrate-based mimics and molecular scaffolds, such as multiantennary glycoclusters,[7] glycodendrimers,[8] glycopeptides,[9] cyclodextrin-based glycoclusters and dendrimers,[10] and glycopolymers,[11] have been synthesized. In most of these conjugates, nature-like synthetic monomers are coupled to a polyfunctional scaffold.

In recent years, attention has increasingly been paid to the synthesis of mixed conjugates that consist of structural units of more than one type of biopolymers, usually sugars and amino acids. Sugar amino acids,[12] in which the sugar pyranose or furanose ring bears a carboxylate and an amino function, have received particular interest. Such monomers have been used to prepare linear and cyclic homooligomers[12b,13] and sugar amino acid/amino acid oligomers,[12b,14] which are expected to find applications as conformationally constrained scaffolds and building blocks in synthesis of multifunctional mimics of carbohydrates or glycopeptides. These syntheses have been successfully accomplished both in solution and on solid-phase applying traditional peptide chemistry. The cyclizations have usually been performed in solution[13b–13c,13e,14b–14g] or achieved upon release from the solid support.[14a]

We now report on a novel protocol for preparation of cyclic carbohydrate/amino acid hybrids on a solid support. Fully protected β-D-galacto- (**1**) and β-D-glucopyranosylmethylamine (**2**) 6-*O*-(*p*-nitrophenyl)carbonates (Figure 1) have been prepared and used for solid-supported construction of cyclic tetrameric conjugates **20**–**22** consisting of alternating sugar and amino acid constituents. Carbamate and peptide couplings followed by PyBOP activated on-support cyclization gave the desired conjugates in more than 20% overall yield.

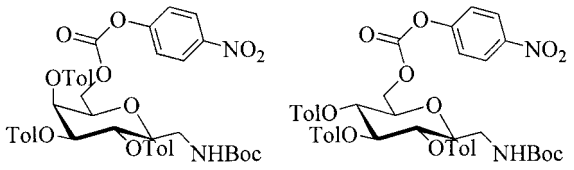

Figure 1. The Glycosylmethylamine carbonates **1** and **2** used as building blocks.

Results

Synthesis of the *C*-Glycoside Building Blocks 1 and 2: The *N*-Boc-protected 2,3,4-tri-*O*-toluoyl-β-D-glycopyranosylmethylamine 6-*O*-(*p*-nitrophenyl) carbonates (**1**, **2**) were synthesized by combining several previously published methods, as outlined in Scheme 1. Commercially available peracetylated β-D-galactopyranose **3** was first converted to its 1-deoxy-1-cyano analog **5** by trimethylsilyl cyanide (TMSCN) treatment in nitromethane in the presence of boron trifluoride–diethyl ether ($BF_3{\cdot}Et_2O$).[15] An analogous reaction with peracetylated β-D-glucopyranose, however, failed, as also reported previously in literature.[16] Only a trace amount of the desired product was obtained and its isolation was complicated by the formation of a cyanoethyl-

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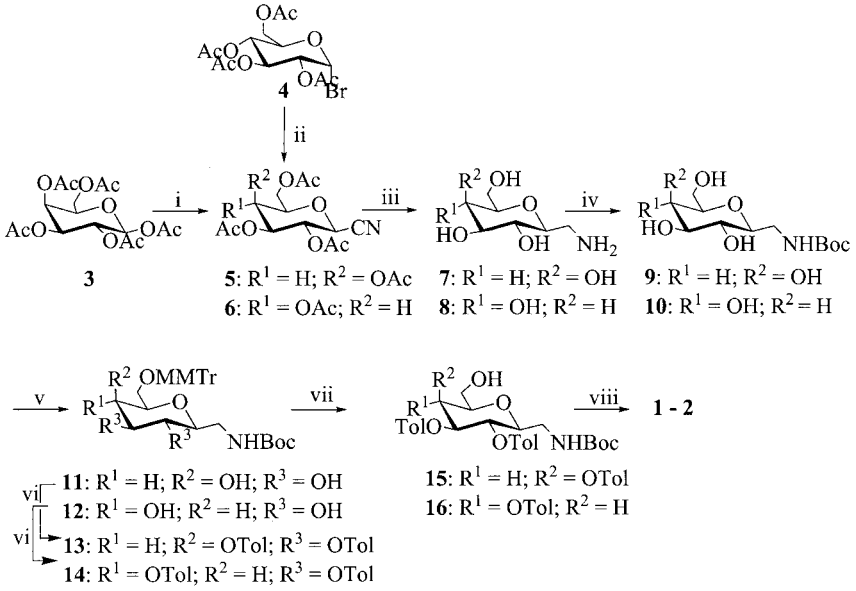
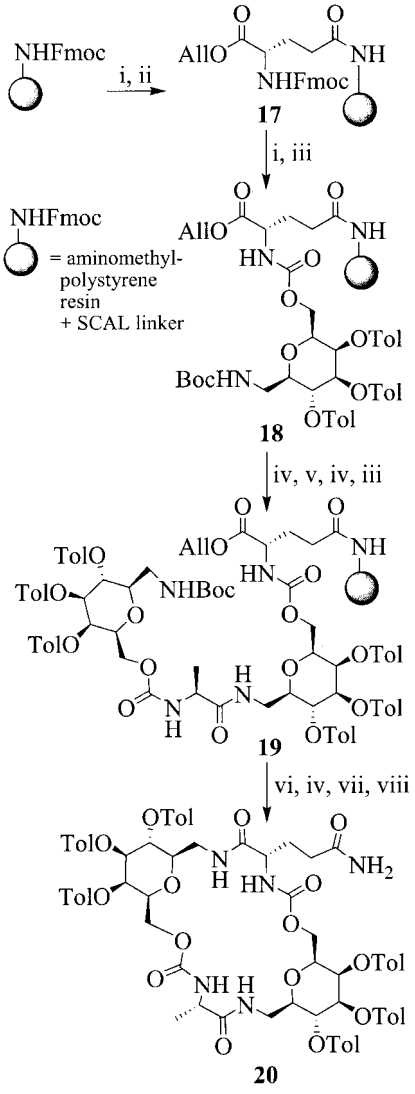


Scheme 1. Conditions: (i) TMSCN, $BF_3{\cdot}Et_2O$, $MeNO_2$, 74%; (ii) $Hg(CN)_2$, melt, 85 °C, 41%; (iii) $LiAlH_4$, THF, (iv) Boc_2O, 2 mol L^{-1} NaOH, MeCN, H_2O, **9**: 53% (from **5**), **10**: 14% (from **6**), (v) MMTrCl, NEt_3, DMAP, DMF, **11**: 69%,**12**: 77%; (vi) *p*-MeBzCl, pyridine, **13**: 79%, **14**: 52%;(vii) I2, MeOH, CH_2Cl_2, **15**: 98%, **16**: 97%; (viii) *p*-nitrophenyl chloroformate, DMAP, pyridine, **1**: 52%, **2**: 66%.

idine derivative as a major product. Hence, an alternative reaction of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**4**) with $Hg(CN)_2$ in melt[17] was applied to obtain the desired cyanide **6**. Reduction of the cyano group with $LiAlH_4$ in THF[18] afforded the free amines in a fully deacetylated form (**7**, **8**). No chromatographic purification was conducted after the $LiAlH_4$ reduction, but the crude products were subjected to selective protection of the amino function with a Boc group, which gave **9** and **10** in an overall yield of 53% and 14% from **5** and **6**, respectively. A 4-methoxtrityl protection was then introduced at the primary hydroxy function[14c] (**11**, **12**), and the secondary hydroxy functions were subsequently esterified with *p*-toluoyl chloride (**13**, **14**). The toluoyl protective groups were chosen instead of the more common acetates, since upon the solid-phase synthesis they serve as chromophores allowing more efficient detection of the synthesized conjugates and quantification of each coupling step. The trityl protection was removed with iodine in MeOH[19] (**15**, **16**) and the exposed hydroxy function was esterified with *p*-nitrophenyl chloroformate in pyridine to obtain *p*-nitrophenyl carbonates **1** and **2**.

Synthesis of Cyclic *C*-Glycoside/Amino Acid Hybrids: Carbamate coupling chemistry has previously been applied to the solid-supported synthesis of oligourea- and oligocarbamate-based analogs of peptides and carbohydrates. Such oligomers are aimed at being resistant towards proteases and glycosidases. In addition, their hydrogen bonding properties and, hence, folding patterns differs from those of native peptides and oligosaccharides. Several oligourea-[20] and oligocarbamate-based[21] peptidomimics have been prepared by solid phase synthesis using isocyanates,[20a] *p*-nitrophenyl carbamates[20b–20e] and *p*-nitrophenyl carbonates[21] as activated monomeric building blocks. Carbohydrate mimics have, in turn, been obtained by coupling of azasugar building blocks activated in situ with bis(4-nitrophenyl) carbonate.[22] In the present study, solid-supported carbamate coupling and normal peptide coupling were utilized in an alternating manner to obtain cyclic tetrameric *C*-glycoside/amino acid-conjugates consisting of two sugar and two amino acid units. The strategy employed is depicted in Scheme 2.

The synthesis of cyclic *C*-glycoside/amino acid conjugate **20** was started by immobilization of a safety catch acid-labile linker (SCAL, Figure 2)[23] to an aminomethyl-polystyrene support by 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo-[4,5-*b*]pyridinium hexafluorophosphate 3-oxide (HATU)-promoted coupling.[24] The linker withstands a wide variety of conditions (including both Boc and Fmoc chemisty), but it may be converted cleavable by reduction of the sulfoxide bonds. According to quantification of benzofulvene released from the support-bound Fmoc-protected linker, the loading was 160 μmol g^{-1}. After standard Fmoc removal by 20% piperidine in DMF, a N^{α}-Fmoc-protected allyl glutamate (Fmoc-Glu-OAll) was anchored through its γ-carboxy function to the exposed amino group of the linker to obtain **17**. The reaction was carried out in DMF using 7-(azabenzotriazol-1-yl)-*N*-oxy-tris(pyrrolidino)phosphonium hexafluorophosphate (PyAOP)[25] as an activator. The Fmoc-protection was again removed and the first Boc-protected galactosyl 6-*O*-carbonate **1** was attached to obtain **18**. *N*-Methylpyrrolidone (NMP) was used as a solvent in this carbamate coupling, 1-hydroxybenzotriazole (HOBt) as an auxiliary nucleophile and *N*,*N*-diisopropylethylamine (DIEA) as the base. For the next coupling, the conventional Boc chemistry was applied. Accordingly, the Boc protection was removed acidolytically (25% TFA in dichloromethane), and Boc-Ala-OH was coupled by the PyAOP activation described above. The subsequent Boc de-



Scheme 2. Conditions: (i) Piperidine, DMF, (ii) Fmoc-Glu-OAll, PyAOP, DIEA, DMF; (iii) **1**, DIEA, HOBt, NMP; (iv) TFA, CH_2Cl_2; (v) Boc-Ala-OH, PyAOP, DIEA, DMF; (vi) $Pd(OAc)_2$, Bu_3SnH, PPh_3, AcOH, CH_2Cl_2; (vii) PyBOP, DIEA, DMF; (viii) 0.1% HBr in AcOH, TFA, CH_2Cl_2.

protection was followed by coupling of the second galactosyl carbonate **1** to give the linear resin-bound precursor **19**. According to HPLC analysis of small aliquots released from the support, both of the carbamate couplings were virtually quantitative, consistent with the reports in literature.[21,22] Deprotection of the *C*-terminal allyl ester by a palladium-catalyzed cleavage reaction[26] and subsequent Boc removal from the *N*-terminus then allowed cyclization on a solid support. (Benzotriazol-1-yl)-*N*-oxy-tris(pyrrolidino)phosphonium hexafluorophosphate (PyBOP)[27] as a coupling reagent at fivefold excess in the presence of DIEA (10 equiv.) gave an almost quantitative cyclization, as shown by the RP HPLC analysis of the crude product (Figure 3). No marked difference was observed when PyAOP was employed as a coupling reagent, while HATU as the activator increased the amount of side products. Cleavage from the support by consecutive treatments with 0.1% HBr in AcOH (2 h at room temperature) and 50% TFA in dichloromethane (2 h at room temperature), followed by semipreparative HPLC purification, gave the desired amino acid/carbohydrate conjugate **20** in a protected form. After HPLC purification, conjugate **20** was characterized by HRMS (Table 1; entry 1).

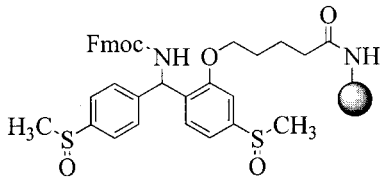


Figure 2. An aminomethyl-polystyrene support derivatized with a SCAL linker.

The applicability of the protocol to the construction of cyclic *C*-glycoside/amino acid conjugates was further verified by preparation of two additional cyclic conjugates **21** and **22** in a larger scale. The composition of the desired fully protected conjugates was verified by HRMS from analytical HPLC samples (Table 1, entries 2–3). Semipreparative HPLC-purification of the crude products then gave **21** and **22** in overall 20 and 24% isolated yields, respectively (based on the initial loading of the resin). In the case of conjugate **22**, the Fmoc protection of the lysine side chain was, however, removed by piperidine treatment prior to the cleavage from the support to facilitate the subsequent RP HPLC purification. Finally, the purified conjugates were further characterized by ^1H NMR spectroscopy.

Conversion of the synthesized *C*-glycoside/amino acid conjugates into a globally deprotected form was demonstrated by using conjugate **21** as a model compound. Among the alternative methods tested, the conventional base-catalyzed transesterification in 50 mmol·L^{-1} methanolic sodium methoxide (24-h treatment at room temperature)[7i] proved to be the method of choice. The deprotected conjugate was isolated by analytical RP HPLC in a 71% yield, and the composition of the purified product **23** was verified by HRMS (see Supporting Information; for details see also the footnote on the first page of this article). The reaction conditions, however, required special attention, since cleavage of the ester bonds was unexpectedly readily accompanied by hydrolysis of the carbamate bonds under aqueous conditions. While under strictly anhydrous conditions the toluoyl esters were cleanly removed without any sign of hydrolysis side products, treatment with sodium methoxide in aqueous methanol or with 33% aq. ammonia resulted in complete hydrolysis of the carbamate bonds. In dry methanolic ammonia no carbamate bond cleavage took place, but the ammonolysis of the ester bonds was sluggish. After treatment for 24 h, the deprotection was still incomplete. Similar results were obtained when a lower concentration of sodium methoxide (20 mmol·L^{-1}) was used.

An analogous Fmoc-protected galactosyl 6-*O*-carbonate building block was also prepared and used in the solid-supported synthesis similarly to **1**. The coupling of the carbonate was successful, but introduction of the next building

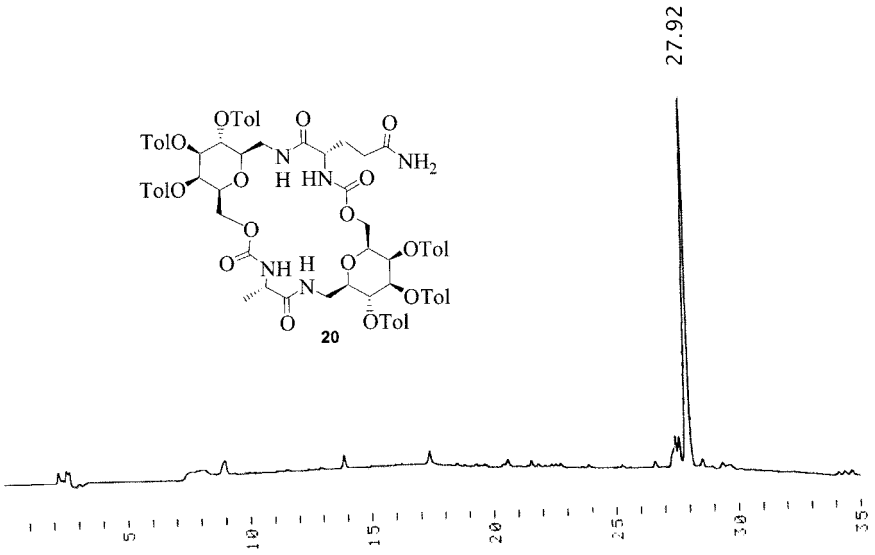
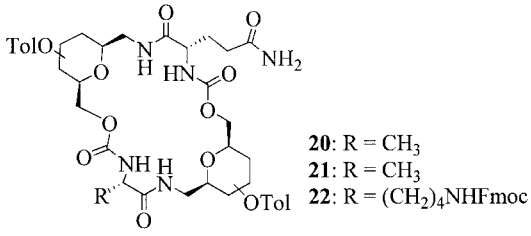


Figure 3. RP HPLC profile of crude **20**. Hypersil Hypurity C18 (150×4.6 mm, 5 μm), gradient from aqueous 0.1% TFA to acetonitrile in 30 min, flow 1.0 mL min^{-1}, detection at 215 nm.

Table 1. The synthesized *C*-glycoside/amino acid conjugates **20**–**22** and their calculated ($M_{calcd.}$) and found (M_{found}) LC/ESI-HRMS molecular masses.



20-22

Entry	Conjugate	Sequence	$[(M + 2H^+)/2]_{found}$	$[(M + 2H^+)/2]_{calcd.}$
1	**20**	Cyclo[Glu-Gal(Tol)$_3$-Ala-Gal(Tol)$_3$]	673.7588	673.7550
2	**21**	Cyclo[Glu-Glc(Tol)$_3$-Ala-Gal(Tol)$_3$]	673.7578	673.6550
3	**22**	Cyclo[Glu-Glc(Tol)$_3$-Lys(Fmoc)-Glc(Tol)$_3$]	813.3210	813.3180

block, whether it was another sugar carbonate or an ordinary amino acid, proved to be unsuccessful. Kaiser ninhydrin test[28] indicated that no free amino groups were present, which, according to our opinion, probably results from the *O*→*N* acyl migration upon the basic Fmoc removal.

In summary, a novel solid-phase protocol for preparation of cyclic *C*-glycoside/amino acid hybrids has been developed. The key building blocks are *N*-Boc-protected glycosylmethylamines bearing a 4-nitrophenoxycarbonyl group on the primary sugar hydroxy function. While the active carbonate ester readily reacts with a solid-supported amino group by formation of a stable urethane linkage, the methylamino group allows chain elongation with commercially available *N*-Boc-protected amino acids. Accordingly, a linear precursor consisting of alternating sugar and amino acid units may be conveniently assembled on a γ-carboxy-immobilized glutamic acid handle and cyclized on-support in high yield. To the best of our knowledge, this is first entirely on-resin techniques introduced for the preparation cyclic carbohydrate/amino acid hybrids. Exploitation of urethane coupling for introduction of the *C*-glycoside units appears advantageous for two reasons. Firstly, the alternating urethane/amide backbone is in all likelihood less susceptible to enzymatic degradation than a peptide backbone. Secondly, preparation of *C*-glycoside building blocks as active carbonates is more straightforward than their conversion to carboxylic acids, and the risk of elimination to a 4,5-ene upon removal of the toluoyl protections by base-catalyzed transesterification is diminished compared to sugar ligands bearing a carbonyl group at C5. Insertion of an amino acid between the two sugar units also plays a dual role. The use of commercially available amino acids increases the chemical diversity, but more importantly, their side chain functionalities allow post-synthetic conjugation of the cyclic constructs. Two or more tetrameric macrocycles may be linked to a chain-like structure with the aid appropriate bifunctional tethers or they may be attached to a multipodal scaffold to benefit from a cluster effect. Alter-

natively, the side-chain functionalities may be used for conjugation to peptides or oligonucleotides.

Experimental Section

General: See electronic supporting information for detailed information. The NMR spectra were recorded with Bruker 400, 500 0r 600 MHz in deuteriochloroform, unless otherwise stated. The chemical shifts are given in ppm from internal TMS, and the coupling constants are reported in Hertz. The mass spectra were recorded with Applied Biosystems Mariner System 5272 mass spectrometer using ESI ionization method. Analytical and semipreparative RP HPLC analyses were performed with a Hypersil Hypurity™ Elite C18 columns (150 × 4.6 mm, 5 μm or 250 × 10 mm, 5 μm, respectively), applying a gradient elution from 0.1% aq. TFA to acetonitrile in 30 min (flow rates 1.0 mL min^{-1} or 3.0 mL min^{-1}, respectively). Eluent detection was monitored by UV absorbance at 215 nm.

2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl Cyanide (5): Compound **5** was prepared according to the procedure reported previously.[15] The product was obtained as a white crystalline solid in a 75% yield. The ^1H and ^{13}C NMR spectra were in accordance with published data.[16]

(β-D-Galactopyranosyl)methylamine (7): Compound **7** was prepared according to a previously published procedure starting from compound **5** (3.30 g, 9.24 mmol).[18] The yield of a white solid powder was 61% (1.10 g). The ^{13}C NMR spectrum was identical with the data published by Bhat and Gervay–Hague.[16]

***N*-(*tert*-Butoxycarbonyl)-(β-D-galactopyranosyl)methylamine (9):** Compound **7** (1.10 g, 5.69 mmol) was dissolved in a mixture of acetonitrile (20 mL) and water (5 mL), and aq. NaOH (2 mol·L^{-1}, 4.3 mL, 8.54 mmol) and Boc_2O (1.24 g, 5.69 mmol) were added. The mixture was left to stand overnight at ambient temperature. The solvents were removed in vacuo, the solid residue was extracted several times with boiling methanol and the hot extracts were filtered through Celite. The combined extracts were evaporated to dryness and the residue was purified by silica gel chromatography (10% to 20% MeOH in CH_2Cl_2) to yield **9** as a white solid in a 86% yield (1.47 g). ^1H NMR (D_2O, 500 MHz): δ = 3.84 (br. s, 1 H, 5-H), 3.37–3.64 (complex, 6 H, H-1,2,3,6,6′,7), 3.21 (m, 1 H, H-4), 3.10 (m, 1 H, H-7′), 1.33 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (D_2O, 100 MHz): δ = 158.3 (C=O, Boc), 81.1 (C_q, Boc), 80.1, 78.5 (C-1,5), 73.8, 69.1, 68.5 (C-2,3,4), 61.5 (C-6), 41.3 (C-7), 27.6 (Boc CH_3) ppm. HRMS (ESI) $[M + H]^+$ calcd. 294.1547, obsd. 294.1558.

***N*-(*tert*-Butoxycarbonyl)-[6-*O*-(4-methoxytrityl)-β-D-galactopyranosyl]methylamine (11):** Compound **11** was prepared according to a previously published prodecure using compound **9** (1.80 g, 6.14 mmol) as a starting material.[14c] The yield of the white solid foam after isolation by silica gel column chromatography (2 to 10% MeOH in CH_2Cl_2) was 69% (2.40 g). ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.46 (d, 3 H, H-MMTr), 7.17–7.35 (m, 9 H, H-MMTr), 6.84 (d, 2 H, H-MMTr), 5.53 (br. s, 1 H, NH), 5.05, 4.40, 4.16 (each m, each 1 H, OH-2,3,4), 3.80 (s, 3 H, $MMTrOCH_3$), 3.63, 3.58, 3.35, 3.26 (each m, each 2 H, H-1,3,4,5,6,6′,7,7′), 3.05 (m, 1 H, H-2), 1.45 (s, 9 H, *t*Bu) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 158.6 (MMTrC), 157.9 (C=O, Boc) 144.3, 135.4, 130.4, 128.4, 127.9, 127.0, 113.1 (MMTrC), 86.57 (C_q, MMTr), 80.4 (C_q, Boc), 79.3 (C-5), 74.16, 68.9, 67.3 (C-1,2,3,4), 62.4 (C-6), 55.2 ($MMTrOCH_3$), 41.2 (C-7), 28.3 (Boc CH_3) ppm. HRMS (ESI) $[M + Na]^+$ calcd. 588.2568, obsd. 588.2561.

***N*-(*tert*-Butoxycarbonyl-[6-*O*-(4-methoxytrityl)-2,3,4-tri-*O*-(*p*-toluoyl)-β-D-galactopyranosyl]methylamine (13):** Compound **11** (700 mg, 1.24 mmol) was coevaporated twice with dry pyridine, and dissolved in dry pyridine (20 mL). *p*-Toluoyl chloride (737 μL, 5.57 mmol) was added, and the reaction mixture was shaken overnight at 50 °C. The mixture was poured into ice-cold water, extracted with dichloromethane, washed with saturated $NaHCO_3$, and dried with Na_2SO_4. The solution was concentrated in vacuo and coevaporated to dryness with toluene. The oily residue was purified by silica gel chromatography (CH_2Cl_2) to give **13** as a white amorphous solid in a 79% yield (870 mg). ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.96 (t, 2 H, H-Tol), 7.68 (t, 2 H, H-Tol), 7.11–7.31 (m, 18 H, H-Tol, H-MMTr), 7.04 (d, 2 H, H-Tol), 6.67 (d, 2 H, H-MMTr), 6.06 (br. s, 1 H, NH), 5.60–5.64 (m, 2 H, H-3,4), 5.54 (t, J = 9.8 Hz, 1 H, H-2), 4.03 (m, 1 H, H-6), 3.67–3.72 (m, 4 H, $MMTrOCH_3$, H-5), 3.76, 3.57, 3.43, 3.22 (each m, each 1 H, H-1,6′,7,7′), 2.29, 2.35 and 2.46 (each s, each 3 H, $TolCH_3$), 1.44 (s, 9 H, *t*Bu) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 165.8, 165.2 (C=O, Tol), 158.5 (C=O, Boc), 144.2, 143.7, 134.9, 130.3, 130.1, 129.9, 129.4, 129.1, 128.9, 128.3, 128.1, 127.8, 127.7 (MMTrC, TolC), 113.2 (MMTrC), 86.6 (C_q, MMTr), 79.4 (C_q, Boc), 75.9 (C-5), 72.6, 69.4, 68.5, 68.2 (C-1,2,3,4), 60.8 (C-6), 55.0 ($MMTrOCH_3$), 41.8 (C-7), 28.4 (Boc CH_3), 21.7, 21.6 (Tol CH_3) ppm. HRMS (ESI) $[M + Na]^+$ calcd. 942.3779, obsd. 942.3824.

***N*-(*tert*-Butoxycarbonyl-[2,3,4-tri-*O*-(*p*-toluoyl)-β-D-galactopyranosyl]methylamine (15):** Compound **13** (870 mg, 0.95 mmol) was dissolved in a mixture of methanolic iodine (5 mL, 1% iodine in MeOH) and dichloromethane (1 mL). After stirring the mixture overnight at room temperature, excess of dichloromethane was added and the solution was extracted twice with neutral aq. Na_2SO_3 (10%, m/v). The organic phase was dried with Na_2SO_4 and the solvents evaporated to dryness. The product was separated by silica gel chromatography (0% to 5% MeOH in CH_2Cl_2) to yield 566 mg (98%) **15** as a clear oil. ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.01 (d, 2 H, H-Tol), 7.79 (d, 2 H, H-Tol), 7.69 (d, 2 H, H-Tol), 7.44 (d, 2 H, H-Tol), 7.04 (d, 2 H, H-Tol), 6.85 (d, 2 H, H-Tol), 5.81 (d, J = 2.9 Hz, 1 H, H-4), 5.73 (t, J = 9.8 Hz, 1 H, H-2), 5.63 (dd, J = 3.2 and 10.0 Hz Hz, 1 H, H-3), 5.30 (br. s, 1 H, NH), 4.02 (m, 1 H, H-6), 3.76–3.81 (m, 3 H, H-1,5,6′), 3.70 (br. s, 1 H, OH-6), 3.58, 3.21 (each m, each 1 H, H-7, H,7′), 2.29, 2.37 and 2.47 (each s, each 3 H, $TolCH_3$), 1.45 (s, 9 H, *t*Bu) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 167.1, 166.0, 165.6 (C=O, Tol and Boc), 144.6, 144.3, 144.0, 130.1, 129.9, 129.8, 129.4, 129.2, 129.0 (C-Tol), 79.4 (C_q, Boc), 77.6 (C-5), 72.5, 69.5, 68.0, 67.5, 60.9, 52.0 (C-1,2,3,4,6), 41.5 (C-7), 28.4 (Boc CH_3), 21.7 (Tol CH_3) ppm. HRMS (ESI) $[M + H]^+$ calcd. 648.2770, obsd. 648.2803.

***N*-(*tert*-Butoxycarbonyl-[6-*O*-(*p*-nitrophenoxycarbonyl)-2,3,4-tri-*O*-(*p*-toluoyl)-β-D-galactopyranosyl]methylamine (1):** Compound **15** (400 mg, 0.62 mmol) was dried by repeated coevaporations with dry pyridine and dissolved in dry pyridine (10 mL). *p*-Nitrophenyl chloroformate (149 mg, 0.74 mmol) and a catalytic amount of DMAP were added. The mixture was left to stand overnight at ambient temperature. The solution was poured into ice-cold 1 mol·L^{-1} aq. HCl, extracted with ethyl acetate, washed with water, and dried with Na_2SO_4. The residue was applied onto a short dried silica gel column and the pure compound was isolated by eluting with a gradient of ethyl acetate (10% to 30%) in hexane. Carbonate **1** was obtained as a white amorphous solid in a 52% yield (260 mg). ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.27 (d, 2 H, H-$PhNO_2$), 7.95 (d, 2 H, H-Tol), 7.82 (d, 2 H, H-Tol), 7.65 (d, 2 H, H-Tol), 7.38 (d, 2 H, H-$PhNO_2$), 7.29 (d, 2 H, H-Tol), 7.15 (d, 2 H, H-Tol), 7.03 (d, 2 H, H-Tol), 5.94 (d, J = 2.6 Hz, 1 H, H-4), 5.71 (t, J = 10.0 Hz, 1 H, H-2), 5.60 (dd, J = 3.1 and 10.2 Hz, 1

H, H-3), 5.15 (br. s, 1 H, NH), 4.40–4.49 (m, 2 H, H-5,6), 4.28, 3.89, 3.73, 3.29 (each m, each 1 H, H-1,6′,7,7′), 2.30, 2.35 and 2.46 (each s, each 3 H, Tol CH_3), 1.46 (s, 9 H, *t*Bu) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 166.2, 166.0 (C=O, Tol), 162.0, 156.0 (C=O, Boc and $PhNO_2$), 155.5, 152.0 (C-$PhNO_2$), 144.7, 144.2, 144.0, 129.9, 129.8, 129.1, 126.2, 125.9, 125.4 (C-Tol), 121.76, 115.6 (C-$PhNO_2$), 80.0 (C_q, Boc), 72.5 (C-5), 68.0, 67.5, 66.0 (C-1,2,3,4,6), 41.5 (C-7), 28.4 (Boc CH_3), 21.6 (Tol CH_3) ppm. HRMS (ESI) $[M + H]^+$ calcd. 813.2865, obsd. 813.2873.

2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl Cyanide (6): Compound **6** was prepared from 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide reacting with $Hg(CN)_2$ in melt at 80 °C under argon, applying the method reported previously.[17] The ^1H and ^{13}C NMR spectra were in accordance with published data.[16]

(β-D-Glucopyranosyl)methylamine (8): Compound **8** was obtained from **6** (6.00 g, 16.8 mmol) by a previously published procedure.[18] The yield of the white solid product was 79% (2.55 g). The ^{13}C NMR spectrum was identical with the data published by Gervay–Hague et al.[16]

***N*-(*tert*-Butoxycarbonyl)-(β-D-glucopyranosyl)methylamine (10):** Compound **10** was prepared as described for **9**, using compound **8** (2.55 g, 13.2 mmol) as the starting material. The yield of the white solid was 18% (700 mg). The ^1H and ^{13}C NMR spectra were in accordance with published data.[14c]

***N*-(*tert*-Butoxycarbonyl-[6-*O*-(4-methoxytrityl)-β-D-glucopyranosyl]-methylamine (12):** Compound **12** was obtained from **10** (700 mg, 2.39 mmol) by a previously published procedure.[14c] The yield of the white solid foam after isolation by silica gel column chromatography (2 to 10% MeOH in DCM) was 77% (1.00 g). The ^1H and ^{13}C NMR spectra were in accordance with published data.[14c]

***N*-(*tert*-Butoxycarbonyl-[6-*O*-(4-methoxytrityl)-2,3,4-tri-*O*-(*p*-toluoyl)-β-D-glucopyranosyl]methylamine (14):** Compound **14** was synthesized as described for **13**, using compound **12** (1.00 g, 1.77 mmol) as the starting material. The product was obtained as a clear oil in a 52% yield (830 mg). ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.84 (t, 2 H, H-Tol), 7.74 (d, 2 H, H-Tol), 7.26–7.35 (m, 11 H, H-Tol, H-MMTr), 7.18 (m, 7 H, H-Tol, H-MMTr), 7.07 (d, 2 H, H-Tol), 6.84 (d, 2 H, H-MMTr), 5.93 (t, *J* = 9.6 Hz, H-3), 5.40 (m, 2 H, H-2,4), 5.19 (br. s, 1 H, NH), 3.81–3.87 (m, 5 H, $MMTrOCH_3$, H-6,6′), 3.66–3.75 (m, 3 H, H-1,5,7), 3.20 (m, 1 H, H-7′), 2.37, 2.36 and 2,29 (each s, each 3 H, Tol CH_3), 1.44 (s, 9 H, *t*Bu) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 166.4, 166.0, 165.9 (C=O, Tol), 158.7 (C=O, Boc), 147.1, 144.6, 143.9, 139.3, 130.0, 129.9, 129.7, 129.2, 129.1, 129.0, 127.9, 127.2, 126.3, 125.8 (MMTrC, TolC), 113.2 (MMTrC), 81.7 (C_q, MMTr), 79.5 (C_q, Boc), 78.6 (C-5), 73.7, 70.2, 69.5, 61.4 (C-1,2,3,4,6), 55.3 ($MMTrOCH_3$), 41.3 (C-7), 28.4 (Boc CH_3), 21.7 (Tol CH_3) ppm. HRMS (ESI) $[M + Na]^+$ calcd. 942.3824, obsd. 942.3858.

***N*-(*tert*-Butoxycarbonyl)-[2,3,4-tri-*O*-(*p*-toluoyl)-β-D-glucopyranosyl]-methylamine (16):** Compound **16** was synthesized as described for **15** using compound **14** (830 mg, 0.90 mmol) as the starting material. The product was obtained as a clear oil in a 97% yield (566 mg). ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.83 (t, 4 H, H-Tol), 7.71 (d, 2 H, H-Tol), 7.18 (t, 4 H, H-Tol), 7.06 (d, 2 H, H-Tol), 5.93 (t, *J* = 11.1 Hz, 1 H, H-3), 5.40 (q, *J* = 9.7 Hz, 2 H, H-2,4), 5.20 (br. s, 1 H, NH), 3.84 (m, 2 H, H-6,6′), 3.66–3.75 (m, 3 H, H-1,5,7), 3.20 (m, 1 H, H-7′), 2.36 (s, 6 H, Tol CH_3), 2.29 (s, 3 H, Tol CH_3), 1.43 (s, 9 H, *t*Bu) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 166.4, 165.9, 165.7 (C=O, Tol), 155.9 (C=O, Boc), 144.6, 144.2, 143.9, 130.0, 129.9, 129.7, 129.2, 129.1, 128.9 (C-Tol), 79.6 (C_q, Boc), 78.6 (C-5), 73.6, 70.2, 69.5, 61.4 (C-1,2,3,4,6), 41.3 (C-7), 28.4 (Boc CH_3), 21.7, 21.6 (Tol CH_3) ppm. HRMS (ESI) $[M + H]^+$ calcd. 648.2803, obsd. 648.2776.

***N*-(*tert*-Butoxycarbonyl)-[6-*O*-(*p*-nitrophenoxycarbonyl)-2,3,4-tri-*O*-(*p*-toluoyl)-β-D-glucopyranosyl]methylamine (2):** Compound **2** was synthesized as described for **1** using compound **16** (566 mg, 0.87 mmol) as a starting material. The carbonate **2** was obtained as a clear oil in a 66% yield (470 mg). ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.28 (d, 2 H, H-$PhNO_2$), 7.81 (d, 4 H, H-Tol), 7.69 (d, 2 H, H-Tol), 7.41 (d, 2 H, H-$PhNO_2$), 7.16 (t, 4 H, H-Tol) 7.06 (d, 2 H, H-Tol), 5.92 (t, *J* = 9.5 Hz, H-3), 5.58 (t, *J* = 9.3 Hz, 1 H, H-4), 5.42 (t, *J* = 9.8 Hz, 1 H, H-2), 5.09 (br. s, 1 H, NH), 4.44–4.54 (m, 2 H, H-6,6′), 4.05, 3.88, 3.68, 3.27 (each m, each 1 H, C-1,5,7,7′), 2.36 (s, 6 H, Tol CH_3), 2.28 (s, 3 H, Tol CH_3), 1.44 (s, 9 H, *t*Bu) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 166.0, 165.7, 156.0 (C=O, Tol, Boc, $PhNO_2$), 155.5, 152.3 (C-$PhNO_2$), 145.4, 144.3, 144.1, 129.9, 129.1, 126.1, 125.3 (C-Tol), 121.8, 115.4 (C-$PhNO_2$), 80.0 (C_q, Boc), 75.5 (C-5), 73.6, 69.8, 68.9, 60.5 (C-1,2,3,4,6), 41.5 (C-7), 28.3 (Boc CH_3), 21.7 (Tol CH_3) ppm. HRMS (ESI) $[M + Na]^+$ calcd. 835.2685, obsd. 835.2705.

Loading of the Resin with SCAL Linker: Aminomethyl-polystyrene employed as a solid support was first acylated with a Fmoc-protected SCAL linker by treating the resin (300 mg) with Fmoc-SCAL (3 equiv.), HATU (3 equiv.) and DIEA (6 equiv.) in DMF (2 mL) for 5 h at room temperature. According to UV spectroscopic quantification of benzofulvene released from the linker, a loading of 160 μmol g^{-1} was obtained. The support was filtered, washed with DMF, dichloromethane and MeOH, and dried under reduced pressure. The unreacted amino groups were capped with Ac_2O in THF containing *N*-methylimidazole and lutidine.

Synthesis of *C*-Glycoside/Amino Acid Conjugates 20–22: The Fmoc group was first removed from the linker with piperidine in DMF (1:4, v/v, 10 min at room temperature). The exposed amino function was then coupled with the side chain carboxyl group of Fmoc-Glu-OAll by adding 10 equiv. of Fmoc-Glu-OAll, 10 equiv. PyAOP and 20 equiv. of DIEA to a suspension of the solid support (50 to 150 mg) in DMF (1 mL). The mixture was shaken for 3 h at ambient temperature. The solid support was filtered, washed with DMF, dichloromethane and MeOH, and dried in vacuo. The Fmoc group was again removed as described above, and then the first Boc-protected glycosyl 6′-*O*-*p*-nitrophenyl carbonate (**1** or **2**; 5 equiv.) and DIEA (5 equiv.) were added to a suspension of the solid support in 100 μmol·L^{-1} solution of HOBt in NMP (1 mL). After shaking the mixture for 5 h at room temperature, the resin was filtered off, washed with NMP, dichloromethane and MeOH, and dried in vacuo. The Boc group was removed with 25% TFA in dichloromethane (1 mL, 1 h at room temperature) and the filtered support was washed with 10% pyridine in dichloromethane, and consecutively with DMF, dichloromethane and MeOH, and dried under reduced pressure. A coupling solution containing the appropriate amino acid (10 equiv., Boc-Ala-OH or Boc-Lys(Fmoc)-OH), PyAOP (10 equiv.) and DIEA (20 equiv.) in DMF (1 mL) was then added, and the mixture was shaken for 5 h at ambient temperature. The resin was filtered, washed with DMF, dichloromethane, and MeOH, and dried under reduced pressure. The Boc deprotection and subsequent coupling of the second Boc-protected glycosyl *p*-nitrophenyl carbonate were then carried out as described above to furnish the support-bound linear precursor. The completeness of all couplings of the Boc-protected building blocks was checked by releasing the product from an aliquot of the resin and analyzing the samples by HPLC. Next, the allyl protection from the *C*-terminus was removed by palladium-catalyzed hydrostannolysis by Bu_3SnH.[26] Accordingly, a mixture of $Pd(OAc)_2$ (2 equiv.) and

PPh_3 (12 equiv.) in dichloromethane (1 mL) and AcOH (12 equiv.) was added onto the resin, and then Bu_3SnH (12 equiv.) was added. The mixture was left to stand at room temperature for 20 min. The resin was filtered, washed/neutralized with 10% pyridine in dichloromethane, and consecutively washed several times with DMF, dichloromethane and MeOH, and dried in vacuo. After standard Boc removal from the *N*-terminus, PyBOP (5 equiv.) and DIEA (10 equiv.) were added onto the resin swelled in DMF (1 mL), and the cyclization was allowed to proceed overnight at room temperature. The support was filtered, washed with DMF, dichloromethane and MeOH, and dried under reduced pressure. At this stage, a small aliquot of the solid support was withdrawn from the synthesis column, and the authenticity of **20**–**22** was verified by HRMS (Table 1) of the analytical HPLC samples. An additional piperidine treatment was conducted at the end of the synthesis of conjugate **22** to remove the Fmoc protection from the side chain amino function of the lysine residue prior the cleavage from the support. The cyclic conjugates were then cleaved from the solid support. The resin was first swollen with a small amount of dichloromethane and 1 mL of 0.1% HBr in AcOH was added. The mixture was shaken for 2 h at room temperature. The support was filtered, washed with dichloromethane and MeOH, and dried in vacuo. The resin was suspended in a mixture of TFA in dichloromethane (1 mL, 1:1, v/v). After shaking for 2 h at room temperature, the solution was collected by filtration and the solvents evaporated to dryness, affording **20**–**22** as crude reaction products. The residues were diluted with a mixture of 0.1% aq. TFA and EtOH and purified by HPLC. The conjugates **21** and **22**, which were prepared in a larger quantity, were further characterized by ^{1}H NMR spectroscopy. PDQF and HMBC spectra were also utilized.

Cyclo[Glu-Glc(Tol)$_3$-Ala-Gal(Tol)$_3$] (21): The overall isolated yield: 20%: ^{1}H NMR ([D$_6$]DMSO, 600 MHz): δ = 7.89 (dd, 2 H, H-Tol), 7.73–7.81 (m, 7 H, H-Tol), 7.65 (br. s, 1 H, NH), 7.60 (m, 2 H, H-Tol), 7.52 (m, 2 H, H-Tol), 7.40, 7.26–7.31 (m, 7 H, H-Tol), 7.19 (m, 2 H, H-Tol), 7.14 (d, 2 H, H-Tol), 6.78 (m, 1 H, NH), 6.69 (m, 1 H, NH), 5.88 (m, J = 9.5 Hz, GlcH-3), 5.76 (m, 2 H, NH, GalH-3), 5.53 (t, J = 9.3 Hz, 1 H, GlcH-4), 5.42 (m, 2 H, GalH-2,4), 5.14 (t, J = 9.5 Hz, GlcH-2), 4.23 (m, 1 H, GlcH-5), 3.99–4.09 (m, 6 H, GalH-1,5,6, GlcH-1,6, AlaH-α), 3.82 (m, 2 H, GalH-6′, GluH-α), 3.75 (m, 1 H, GalH-7), 3.50 (br. s, H_2O residual peak), 3.33 (m, 1 H, GlcH-6′), 3.28 (m, 1 H, GlcH-7), 3.10 (m, 1 H, GlcH-7′), 2.97 (m, 1 H, GalH-7′), 2.42 (s, 3 H, Tol CH_3), 2.33 (m, 9 H, Tol CH_3), 2.26 (m, 6 H, Tol CH_3), 1.98 (m, 2 H, GluH-γ), 1.75 (m, 1 H, GluH-β), 1.65 (m, 1 H, GluH-β′), 1.15 and 0.98 (two d, 3 H, AlaH-β) ppm. The ^{1}H NMR spectrum also exhibited smaller peaks at 5.99, 5.91, 5.24 and 1.50 as well as smaller overlapping peaks at 4.35 and 1.78 ppm, presumably due to slow conformational exchange at ambient temperature.

Cyclo[Glu-Glc(Tol)$_3$-Lys-Glc(Tol)$_3$] (22): The overall isolated yield: 24%: ^{1}H NMR ([D$_6$]DMSO, 600 MHz): δ = 7.75 (m, 8 H, H-Tol), 7.68 (m, 2 H, NH), 7.59 (m, 4 H, NH), 7.53 (t, 2 H, NH), 7.28 (m, 10 H, H-Tol), 7.20 (m, 6 H, H-Tol), 5.92 (m, J = 8.2 and 9.5 Hz Hz, 2 H, GlcH-3), 5.60 (q, J = 8.2 and 9.5 Hz Hz, 2 H, GlcH-4), 5.15 (t, J = 9.5 Hz, 2 H, GlcH-2), 4.18 (t, J = 10.1 Hz, 2 H, GlcH-5), 4.03–4.13 (m, 4 H, GlcH-1,7), 3.78–3.84 (m, 4 H, LysH-α, GluH-α), 3.66 (br. s, H_2O residual peak), 3.26–3.42 (m, 4 H, GlcH-6,7′), 3.17–3.24 (m, 2 H, GlcH-6′), 2.73 (m, 2 H, LysH-ε), 2.33 (br. s, 12 H, Tol CH_3), 2.28 (br. s, 6 H, Tol CH_3), 1.91–2.10 (m, 2 H, GluH-γ), 1.83 (m, 1 H, GluH-β), 1.72 (m, 1 H, GluH-β′), 1.63 (m, 1 H, LysH-β), 1.48 (m, 3 H, LysH-β′,δ), 1.23 (br. s, 2 H, LysH-γ) ppm.

Deprotection of 21: Compound **21** (1.8 mg, 1.34 μmol) was dissolved in dry 50 mmol·L^{-1} sodium methoxide in methanol (400 μL), and the reaction was allowed to proceed at room temperature for 24 h. Sodium methoxide was neutralized with DOWEX 50WXB-200 (H+). After filtration of the resin, methanol was removed under reduced pressure, and the dried residue was dissolved in water, extracted with diethyl ether and evaporated under reduced pressure. The crude product was diluted with 0.1% aq. TFA and purified by RP HPLC (for the chromatographic conditions, see Supporting Information) to afford **23** in a 71% yield (0.6 mg). HRMS (ESI) $[M + Na]^+$ calcd. 660.2335, obsd. 660.2358.

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