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Synthetic Carbohydrate Dendrimers, Part 8[+]

Toward the Synthesis of Large Oligosaccharide-Based Dendrimers

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KEYWORDS:

carbohydrates · chemoselective ligation · dendrimers · oligosaccharides · reductive amination

It is now generally acknowledged that cell surface protein – carbohydrate interactions play a crucial role in a wide range of biological processes[1] necessary for both normal physiological function and the onset of disease. Although protein – carbohydrate interactions typically display high dissociation constants with K_d values in the mM to μM range,[2] Nature can still attain physiologically useful avidities through the cooperative binding[3] of multiple copies of the ligands and receptors—the so-called multivalent effect.[4]

Synthetic chemists have successfully exploited this trick from Nature's toolbox in the synthesis of neoglycoconjugates ranging from small cluster glycosides[5] through neoglycoproteins[6] to polymers bearing many pendant saccharide residues.[7] These synthetic tools have not only provided inhibitors with greatly enhanced affinities over monovalent ligands, but they have also led to considerable advances in our understanding[4, 8] of the nature of multivalent interactions. Glycodendrimers[9] are a special class of neoglycoconjugates that combines the well-defined structural homogeneity of small clusters with the nanoscale dimensions of glycopolymers. Most of the glycodendrimer research reported to date has involved the construction of dendrimers bearing saccharide residues only on their peripheries through the use of either i) a convergent strategy[10] or by ii) the divergent modification of preexisting dendrimers.[11] However, monosaccharides are multifunctional building blocks and, as such, they are often found in Nature in branched oligomers and polymers.[1b] Indeed, the use of carbohydrates as building blocks for dendrimer construction confers a number of desirable properties on the dendrimer. In addition to water solubility and biocompatibility, it should be possible to exploit the known conformational preferences[12] of oligosaccharide monomers in order to mold the dendrimer's size and shape in a predetermined manner.

We recently described[13] the synthesis of oligosaccharide dendrimers based on β-D-glucopyranosyl repeating units. This synthesis, however, fell foul of the dogma of chemical carbohydrate synthesis—protecting group chemistry. In addition to the extensive chemical manipulations required to effect both regio- and stereoselectivity, the bulky appendages associated with the saccharide unit introduce considerable steric crowding which restricts the growth of highly branched molecules. Here, we report a very different strategy for the synthesis of oligosaccharide-based glycodendrons using reductive amination[14] as a chemoselective coupling reaction which allows the synthesis to be undertaken using a minimal number of i) protecting groups and ii) protecting-group manipulations.

Since one of our aims is to address the synthesis of large glycodendrimers, it seemed appropriate to base our synthetic strategy on an *oligosaccharide*—rather than on a monosaccharide[13]—*monomer*. We chose a linear trisaccharide, in the first instance, as it leads to the construction of glycodendrons and glycodendrimers with open and extended branches, while allowing the key reactions to be performed at the primary centers on hexopyranose units. In particular, we wanted to locate amino functions at the C-6 positions of the two non-reducing saccharide units: These two B groups find a complementary A function in the masked formyl group associated with the reducing sugar. Convergent dendron synthesis results[15] typically in a higher homogeneity of structure as a consequence of only a few reactions at a time being performed on each molecule. To achieve such a synthesis, we require an orthogonal protecting-group strategy—albeit with a minimal number of protecting groups present overall. UV-active *N*-benzoyl groups were chosen i) to allow easy detection following HPLC, as well as ii) to provide the necessary orthogonal protection of the primary amino functions with respect to the reducing terminal isopropylidene acetals, which can be hydrolyzed selectively in the presence of acid catalysts. We chose a maltosylgalactose derivative as the first AB_2 *trisaccharide monomer* to investigate because of i) the ease of its synthesis and ii) its relatively simple ^{1}H NMR spectrum that results from having distinctive and well resolved "signature" resonances associated with the α- and β-anomeric protons. The result of a molecular modeling study[16] of a first-generation dendrimer, comprising three first-generation 9-mer wedges attached to a trivalent benzeneoid core, is shown in Figure 1. While the "diameter" of this first-generation dendrimer is of the order of 8 nm, the second one has a "diameter" in the region of 11 – 12 nm. The modeling studies also indicate that such dendrimers have extended open structures which, although flexible about their galactityl linkers, still retain the conformational preferences of the maltosyl branching units.

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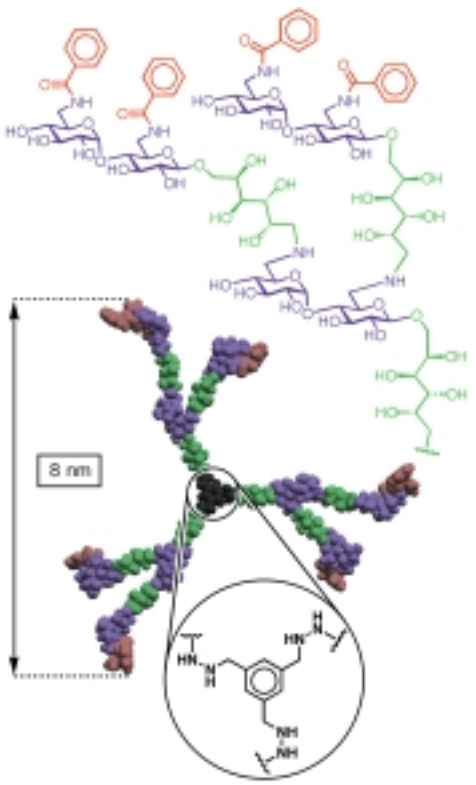
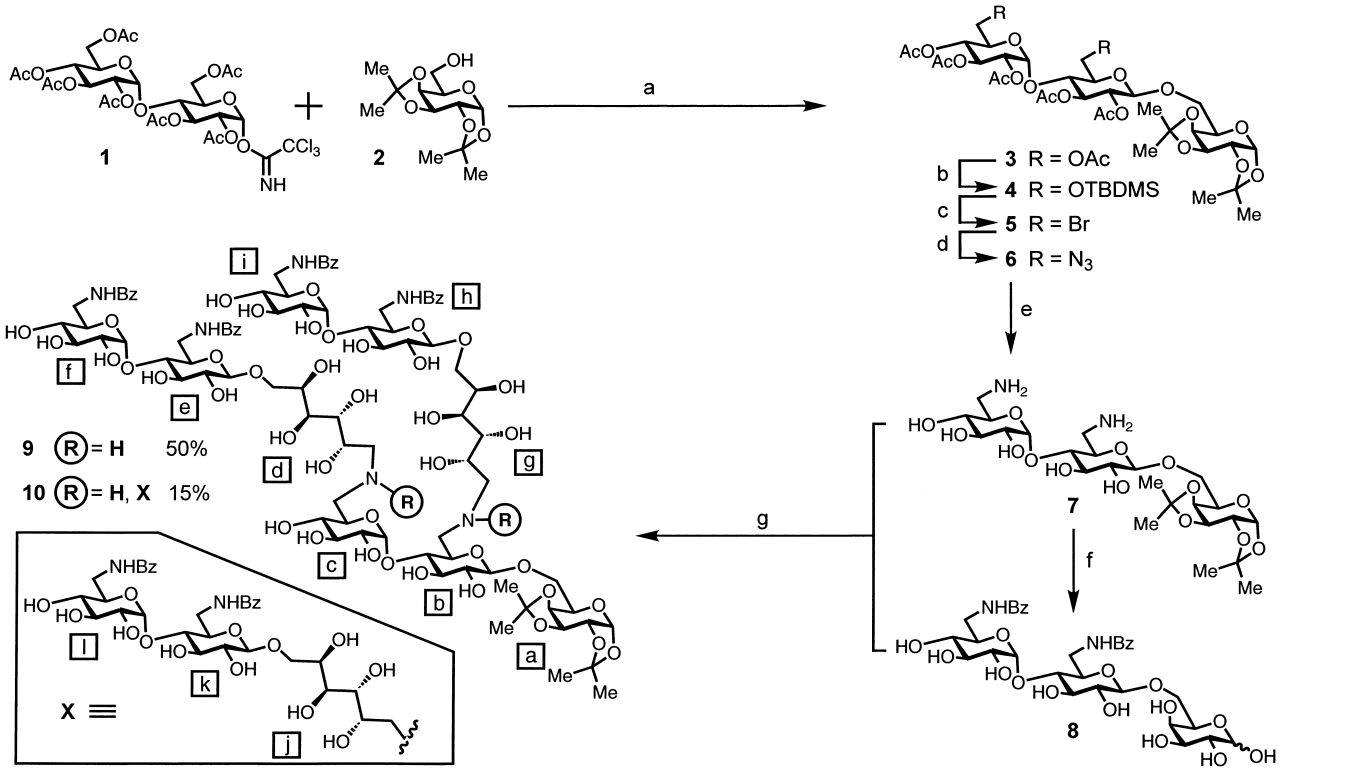


Figure 1. *Molecular model[16] of a first-generation dendrimer based on a trivalent benzeneoid core depicted in black. Maltosyl units are shown in blue, galactityl units in green and* N*-benzoyl protecting groups in red.*

Scheme 1 outlines the initial synthesis of a first-generation dendron **9**, starting from the known[17] peracetylated α-maltosyl trichloroacetimidate **1** and 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**2**). Glycosylation of acceptor **2** with glycosyl donor **1** using TMSOTf as the promoter gave the protected trisaccharide derivative **3**. To introduce amino functions at the primary positions on the two glucosyl residues, the trisaccharide was deacetylated and then the primary hydroxy groups were protected as TBDMS ethers before reacetylating the secondary ones to give compound **4**. Treatment with triphenylphosphine and bromine allowed **4** to be converted,[18] in one step, to the dibromide **5**, which reacted readily with sodium azide to provide the diazide **6** in excellent yield. Acetyl transfer from *O*-4c to *N*-6c was avoided by deacetylating **6** prior to reduction of the azide functions by hydrogenation to give the first of the desired AB_2 monomers **7**.[19] The aldehyde-protected version of the AB_2 monomer was transformed into its *N*-protected counterpart **8** by *N*-acylation with benzoyl chloride followed by acid-catalyzed hydrolysis of the isopropylidene groups to give the second of the desired AB_2 monomers as the reducing sugar. Although the reductive amination of **8** by **7** can be performed in aqueous solution, it occurs much more quickly in methanolic solution, affording the bis-secondary amine **9** as the major product. HPLC analysis indicated[20] the presence of a minor component (Figure 2a), which was subsequently characterized as a 1:1 mixture of overalkylated products **10** having a tertiary amine group in either of the D-glucosyl units. Partial ^{1}H NMR spectra for compounds **9** and **10** are shown in Figure 3a, b. Further



Scheme 1. *Synthesis of the first-generation dendron* ***9****. a) TMSOTf/CH_2Cl_2/4 Å MS, 81%; b) 1. NaOMe/MeOH, 2. TBDMSCl/C_5H_5N, 3. Ac_2O/C_5H_5N, 73% (over three steps); c) $Br_2/PPh_3/CH_2Cl_2$, 95%; d) NaN_3/DMF, 95%; e) 1. NaOMe/MeOH, 2. $H_2/Pd(OH)_2$ on C/MeOH, 91% (over two steps); f) 1. BzCl/Na_2CO_3/H_2O, 2. NaOMe/MeOH, 3. TFA/H_2O (9:1), 63% (over three steps); g) $NaCNBH_3$/AcOH/MeOH. Monosaccharide residue labels for compounds* ***9*** *and* ***10*** *relate to ^{1}H NMR spectra assignments given in Figure 3. Bz = benzoyl; TBDMS =* tert*-butyldimethylsilyl; TMSOTf = trimethylsilyl trifluoromethanesulfonate.*

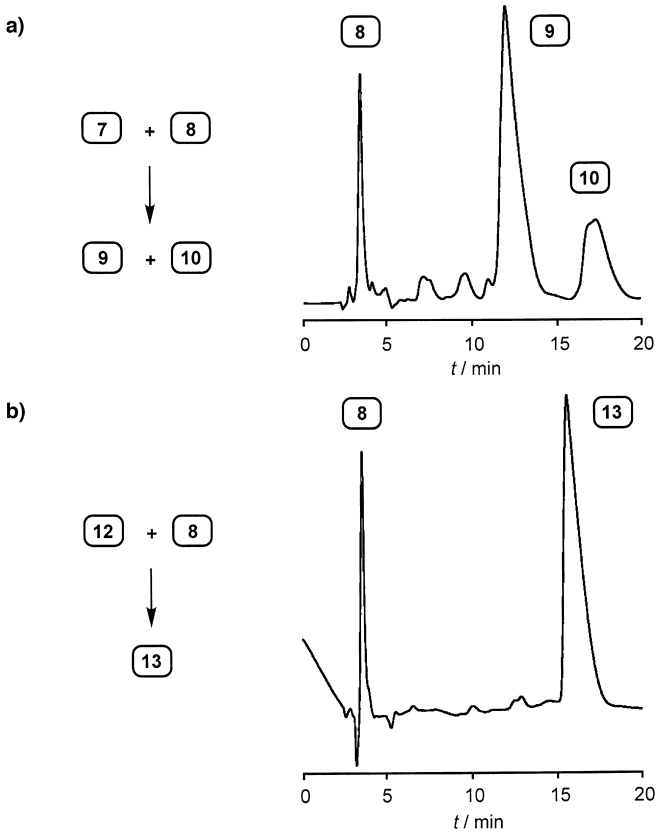


Figure 2. HPLC profiles of the products of the reductive amination, as outlined in a) Scheme 1 and b) Scheme 2.

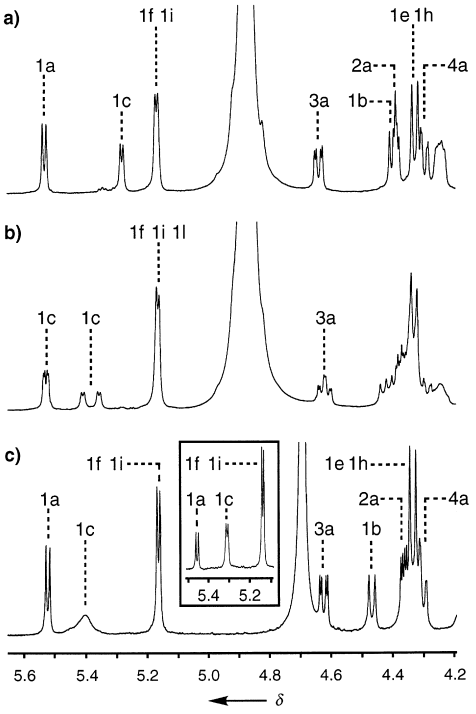
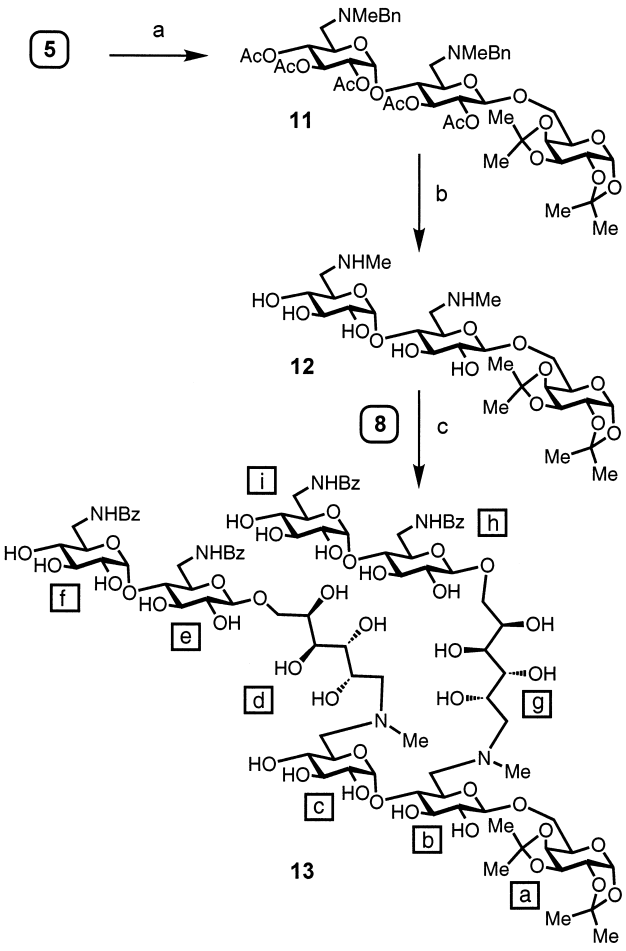


*Figure 3. Partial ^{1}H NMR (400 MHz, CD_3OD) spectra showing the anomeric proton signals for a) compound **9** (300 K), b) the isomeric mixture **10** (300 K), and c) compound **13** (320 K). The α-anomeric proton signals observed for **13** in CD_3SOCD_3 (400 MHz) at 400 K are inset in the box. Monosaccharide residue labels "a" to "l" are as given in Schemes 1 and 2.*

alkylation to give a bis-tertiary amine proved difficult, presumably as a consequence of increased steric interactions in **10** compared with those present in compound **9**. The fact that the reductive amination turns out to be an efficient method for preparing branched oligosaccharides assumes greater significance when one considers that it can be achieved with minimal protection from easily prepared trisaccharides. Although the yield of the pure nonasaccharide was limited by the reactivity of the secondary amino functions in **9**, we found that it was possible to prevent overalkylation by using unhindered secondary amine functions in the AB_2 monomer (Scheme 2). Heating



*Scheme 2. Synthesis of the bis-tertiary amine **13**. a) 1. MeNHBn/Δ, 2. Ac_2O/C_5H_5N, 58% (over two steps); b) 1. NaOMe/MeOH, 2. H_2/$Pd(OH)_2$ on C/MeOH, 50% (over two steps); c) $NaCNBH_3$/AcOH/MeOH, 78%. Monosaccharide residue labels for compound **13** relate to ^{1}H NMR spectra assignments given in Figure 3. Bn = benzyl.*

the acetylated dibromide **5** in benzylmethylamine afforded,[21] after reacetylation to aid its purification by chromatography and subsequent characterization, the fully protected compound **11**. To obtain the bis(methylamino) AB_2 monomer **12**,[19] the acetyl protecting groups in **11** were removed completely prior to hydrogenolysis. The AB_2 monomer underwent reductive alkylation under similar conditions to those used to obtain the mixture of **9** and **10** (Figure 2a) in Scheme 1. On this occasion, however,

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as evidenced by the HPLC trace (Figure 2b), we obtained the bis-tertiary amine **13** as its bis-TFA salt in 78% yield. The ^{1}H NMR spectrum for this compound (Figure 3c) displays similar signals to that of compound **9** (Figure 3a), albeit with considerable broadening of the anomeric 1c proton signal, which only sharpens to give the expected doublet at high temperature (inset in Figure 3c).

We are actively pursuing the extension of this methodology for the synthesis of higher order glycodendrons and their attachment onto both trivalent benzenoid cores (Figure 1) and carbohydrate-based cores including cyclodextrin derivatives.[22] Also, we are investigating methods by which we will be able to attach large bioactive oligosaccharides[23] and proteins[24] in a well-defined manner to the peripheral positions of such glycodendrimers.

Experimental Section

8: Benzoyl chloride (164 μL, 1.42 mmol) was added dropwise to a solution of diamine **7**[19] (350 mg, 0.60 mmol) and K_2CO_3 (210 mg, 1.50 mmol) in dioxane (2.3 mL) and H_2O (3.5 mL) at 0 °C. After warming to RT overnight, the solution was concentrated and the residue was treated with NaOMe/MeOH (60 μmol/6 mL) to remove the benzoate esters. Following neutralization (Amberlite IR-120 H^+), the solution was filtered and concentrated. Column chromatography (SiO_2, CH_2Cl_2/MeOH, 9:1 to 85:15) gave 6,6′-bisbenzamido-6,6′-dideoxy-β-D-maltosyl-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose as an amorphous solid (335 mg, 71%). This product was treated with 90% aqueous TFA (5 mL) at RT for 15 min before concentration to give **8** as an amorphous solid after freeze drying from H_2O (237 mg, 88%). MS (FAB): *m/z*: 711.3 $[M+H]^+$, 733.1 $[M+Na]^+$. Although the mixture of anomers of **8** gives rise to very complex ^{1}H and ^{13}C NMR spectra, on treating the reducing sugar with $NaBH_4$ in MeOH, a single alditol was obtained. MS (ES): *m/z*: 713.3 $[M+H]^+$, 735.2 $[M+Na]^+$; ^{1}H NMR (400 MHz, CD_3OD): $\delta = 3.18-3.35$ (m, 4H), 3.48–3.56 (m, 2H), 3.60–3.72 (m, 8H), 3.87 (dd, $J = 2.6$, 14.0 Hz, 1H), 3.90 (td, $J = 1.3$, 6.3 Hz, 1H), 3.98 (dd, $J = 4.9$, 9.8 Hz, 1H), 4.06–4.13 (m, 3H), 4.30 (d, $J = 7.8$ Hz, 1H), 5.15 (d, $J = 3.7$ Hz, 1H), 7.25 (t, $J = 7.6$ Hz, 2H), 7.37 (m, 1H), 7.44 (t, $J = 7.4$ Hz, 2H), 7.52 (m, 1H), 7.74 (d, $J = 7.5$ Hz, 4H); ^{13}C-NMR (125 MHz, CD_3OD): $\delta = 42.4$, 42.7, 65.0, 70.2, 71.2, 71.3, 71.7, 73.1, 73.2, 73.6, 74.3, 74.5, 74.6, 75.1, 77.5, 84.6, 103.5, 104.5, 128.3, 128.5, 129.4, 129.5, 132.5, 132.7, 135.5 (2C), 170.3, 170.9.

13: A solution of **8** (37 mg, 52 μmol), **12**·2TFA[19] (16.5 mg, 20 μmol), acetic acid (1.1 μL, 20 μmol), and sodium cyanoborohydride (8.3 mg, 130 μmol) in MeOH (750 μL) was heated under reflux for 2 h, at which time HPLC analysis indicated[20] the reaction to be complete. The reaction mixture was cooled to RT and diluted with H_2O (15 mL), before being subjected to medium-pressure column chromatography (15 g C-18 reversed phase,[20] MeOH/H_2O/TFA, 0:100:0.0001 to 100:0:0.0001) to afford pure **13**·2TFA (34 mg, 78%). MS (ES): *m/z*: 1001.1 $[M+2H-2TFA]^{2+}$, 2001.2 $[M+H-2TFA]^+$; ^{1}H NMR (400 MHz, CD_3OD): $\delta = 1.30$, 1.34, 1.38, 1.50 (4×s, 12H), 3.00–3.10 (br. m, 6H), 3.22 (d, $J = 9.4$ Hz, 2H), 3.28–3.37 (m, 11H), 3.48–3.73 (m, 23H), 3.87 (dd, $J = 2.8$, 14.1 Hz, 1H), 3.97 (dd, $J = 5.2$, 10.1 Hz, 1H), 4.02–4.20 (m, 11H), 4.30–4.38 (m, 6H), 4.47 (d, $J = 7.8$ Hz, 1H), 4.63 (dd, $J = 2.4$, 7.9 Hz, 1H), 5.16 (d, $J = 3.8$ Hz, 1H), 5.40 (br. s, 1H), 5.52 (d, $J = 5.0$ Hz, 1H), 7.26 (t, $J = 7.8$ Hz, 1H), 7.36 (m, 2H), 7.43 (m, 4H), 7.52 (m, 2H), 7.73 (m, 8H).

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[16] The molecular model of a first-generation dendrimer is the result of a molecular dynamics (MD) simulation. Each individual component—the core, branching units, terminal units—was constructed within the input submode of MacroModel 5.0, and the conformation was optimized by using the Polak–Ribiere (PRCG) algorithm (E. Polak, G. Ribière, *Rev. Fr. Inf. Rech. Oper.* **1969**, *16*, 35–48), considering aqueous solvation via the generalized Born surface area (GB/SA) model for water (W. C. Still, A. Tempczyk, R. C. Hanley, T. Hendrickson, *J. Am. Chem. Soc.* **1990**, *112*, 6127–6129), and the Amber* force field (S. J. Weiner, P. A. Kollman, D. T. Nguyen, D. A. Case, *J. Comput. Chem*. **1986**, *7*, 230–252). Each structure was then subjected to 10 ps of MD at 300 K (1.5 fs timestep), followed by subsequent minimization to a final energy gradient < 0.05 kJ Å^{-1}. The components were then linked within the INPUT submode to form the first-generation dendrimer. Minimization, followed by 10 ps of MD and further minimization, provided the structure as shown in Figure 1.

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[19] HR-MS and NMR data (^{1}H NMR: 400 MHz, ^{13}C NMR: 100 MHz; CD_3OD) for compounds **7** and **12**: **7**: HR-MS (FAB): calcd for $C_{24}H_{42}N_2O_{14}$ 583.2714 $[M+H]^+$, observed *m/z*: 583.2737; ^{1}H NMR: $\delta = 1.34$, 1.35, 1.40, 1.53 (4 × s, 12H), 2.75 – 2.83 (m, 2H), 3.03 (dd, $J = 2.7$, 13.4 Hz, 1H), 3.10 – 3.20 (m, 2H), 3.27 (dd, $J = 7.9$, 9.3 Hz, 1H), 3.39 (m, 2H), 3.45 (dd, $J = 3.6$, 13.4 Hz, 1H), 3.58 – 3.72 (m, 4H), 4.03 – 4.09 (m, 2H), 4.32 (br. d, $J = 9.5$ Hz, 1H), 4.32 (d, $J = 7.9$ Hz, 1H), 4.38 (dd, $J = 2.4$, 5.0 Hz, 1H), 4.64 (dd, $J = 2.4$, 7.9 Hz, 1H), 5.19 (d, $J = 3.6$ Hz, 1H), 5.52 (d, $J = 5.0$ Hz, 1H); ^{13}C NMR: $\delta = 24.6$, 25.1, 26.3 (2C), 43.6, 43.7, 68.8, 69.8, 71.9, 72.0, 72.4, 73.0, 74.0, 74.2, 74.6, 74.7, 76.0, 77.5, 82.9, 97.7, 102.8, 104.6, 110.0, 110.4. **12**: HR-MS (FAB): calcd for $C_{26}H_{46}N_2O_{14}$ 611.3027 $[M+H]^+$, observed: *m/z*: 611.3032; ^{1}H NMR: $\delta = 1.32$, 1.34, 1.39, 1.51 (4 × s, 12H), 2.76 (br. s, 6H), 3.10 – 4.08 (br. m, 14H), 4.13 (dd, $J = 3.6$, 10.5 Hz, 1H), 4.30 (dd, $J = 1.5$, 7.9 Hz, 1H), 4.38 – 4.43 (m, 2H), 4.65 (dd, $J = 2.3$, 7.9 Hz, 1H), 5.33 (br. s, 1H), 5.53 (d, $J = 5.0$ Hz, 1H); ^{13}C NMR: $\delta = 24.5$, 25.1, 26.2, 26.3, 34.1, 34.6, 51.3, 52.1, 68.9, 70.0, 70.2, 70.8, 71.8, 71.9, 72.5, 73.2, 73.3, 74.2, 74.7, 76.1, 81.1, 97.8, 100.2, 104.2, 110.1, 110.5.

[20] Reversed-phase HPLC was conducted by using a Hypersil 5 μm BDS C-18 silica column (ThermoQuest; 4.6 × 250 mm) under isocratic elution ($MeOH/H_2O$/TFA, 65:35:0.0001) with UV detection using a Dynamax PDA-2 diode array detector. Medium-pressure preparative reversed-phase chromatography was performed on fully endcapped C-18 silica gel 100 (230 – 400 mesh, Fluka), eluting with the gradient of solvents indicated in 10% steps.

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