Available online at www.sciencedirect.com
SCIENCE DIRECT®
Carbohydrate Research 339 (2004) 2069–2075
Carbohydrate RESEARCH

Synthesis of lactoside glycodendrons using photoaddition and reductive amination methodologies

Alshakim Nelson and J. Fraser Stoddart*

Department of Chemistry and Biochemistry, California NanoSystems Institute, University of California, Los Angeles, 405 Hilgard Avenue, Los Angeles, CA 90095 USA

Received 25 March 2004; received in revised form 10 May 2004; accepted 16 June 2004

Abstract—Carbohydrate-based divalent and tetravalent lactoside glycodendrons were constructed in a convergent manner. The dendrons were synthesized beginning with the photoaddition of hepta-*O*-acetyl-1-thio-β-lactose, in an anti-Markovnikov manner, to a bis-allyl AB_2 trisaccharide to form a divalent dendron. Following two nearly quantitative deprotection steps, the divalent lactoside was coupled to another AB_2 trisaccharide by reductive amination to afford a tetravalent dendron. These paucivalent compounds were characterized by NMR spectroscopy and mass spectrometry.

Keywords: Glycodendrimers; Multivalency; Photoaddition; Reductive amination

1. Introduction

Nature uses complex polysaccharides—where the carbohydrate residues act as both the recognition units and multivalent scaffolds—to regulate biological phenomena.[1] With multivalency[2] playing such a crucial role in physiological and pathological processes, there is increasing interest[3] in the synthesis of glycodendrimers[4] and glycopolymers[5] as structural mimetics of naturally-occurring glycoproteins and glycolipids. In our own research efforts,[6] we have focused on carbohydrate-based architectures,[7] where the constitutional, configurational, and conformational diversity of carbohydrates is used to control the presentation of saccharide ligands. While nature has a myriad of enzymes to catalyze the synthesis of its polysaccharides efficiently, chemists have to rely upon mild and selective chemical approaches to construct multivalent carbohydrate-based architectures. While glycosylation[6b,8] and amide-bond formation[6b,9] are common strategies for synthesizing carbohydrate-based dendrimers, we have sought to explore other chemical approaches for coupling carbohydrate monomers together to form glycodendrimers. Photoaddition reactions[10] between thiols and allyl ethers have been incorporated previously[11] in the synthesis of glycoconjugates. Reductive aminations between an aldehyde and an amino functionality also constitute mild conditions by which multivalent dendrons and dendrimers can be synthesized.[6b,c,12] These reactions have proven to be highly efficient and chemoselective, a consideration, which is particularly important in dendrimer syntheses[3b] where many reactions are necessary for increasing generations. Here, we discuss the utility of combining the photoaddition and reductive amination methodologies in the synthesis of carbohydrate-based dendrons using a convergent approach.

2. Results and discussion

AB_2 trisaccharides **3** and **6** were chosen as the monomer units for the formation of dendrons. This choice permits the formation of large, water-soluble molecules with adequate spacing between the arms of the growing

* Corresponding author. Tel.: +1-310-206-7078; fax: +1-310-206-1843; e-mail: stoddart@chem.ucla.edu

0008-6215/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.carres.2004.06.011

dendrons and dendrimers. The reducing end (A) of the trisaccharides contain an isopropylidene-protected aldehyde group, capable of reacting with amino groups under reductive alkylation conditions. Depending on the type of reaction to be used, the remaining two monosaccharides (B_2) possess, at the 6-position of the pyranose ring, either allyl functionalities for photoaddition, or methylamino ones for reductive amination.

The trisaccharide **1** was synthesized as described previously.[13] The silyl protecting groups were removed efficiently using IBr[14] to expose the two primary hydroxyl groups in the trisaccharide **2**. Because attempted allylation of this trisaccharide **2** under basic conditions using NaH and allyl bromide resulted in a mixture of products, the two primary hydroxyl groups were allylated under acidic conditions using allyltrichloroacetimidate and triflic acid to afford the trisaccharide **3** (Scheme 1). The allylation proceeded best when a 3:7 mixture of dichloromethane and cyclohexane was used as the solvent to minimize the thermal rearrangement[15] of the imidate to the amide.

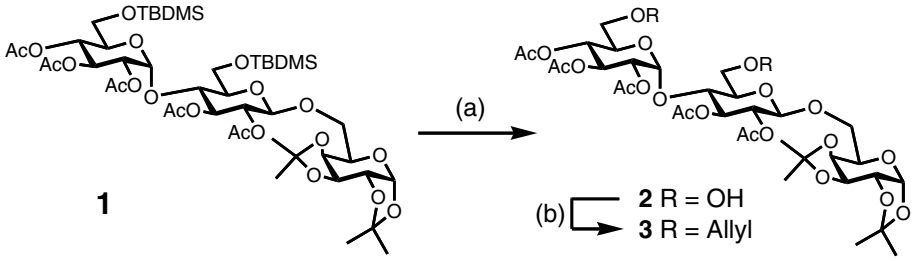
We chose the photoaddition of thiolactosides to allyl ethers as a versatile method to incorporate glycosides onto the periphery of the dendrons. Hepta-*O*-acetyl-1-thio-β-lactose[11b] and the trisaccharide **3** were stirred under a mercury lamp for 3 h in methanol to afford (Scheme 2) the dendron **4**. The reaction was remarkably efficient, with the anti-Markovnikov addition proceeding in 75% yield. The divalent dendron **4** was then fully deprotected using sodium methoxide in methanol, followed by cleavage of the acetal protecting groups using 90% aqueous trifluoroacetic acid to yield the dendron **5**. While the photoaddition proceeds with retention of the stereochemistry at the anomeric center of hepta-*O*-acetyl-1-thio-β-lactose moieties, a small amount (<1%) of the α-anomer was observed in the ^{1}H NMR spectrum of the dendron.

Reductive amination was employed to form the next generation dendron. The reducing end of dendron **5** and the amino functionalities of the bis-methylamino trisaccharide[13] **6** were coupled together (Scheme 3) using sodium cyanoborohydride in a 1:1 mixture of methanol and water as the solvent. The lower yield (48%), relative to that for the formation of the first generation dendron by reductive amination[6b] can be attributed to the steric bulk of the growing dendron. Nonetheless, the second generation dendron **7** was isolated and characterized by NMR spectroscopy and mass spectrometry. HMQC experiments (Fig. 1) were particularly useful in verifying that the appropriate number of anomeric signals were present. Crosspeaks were present for each of the seven chemically distinct anomeric signals in the dendron **7**.

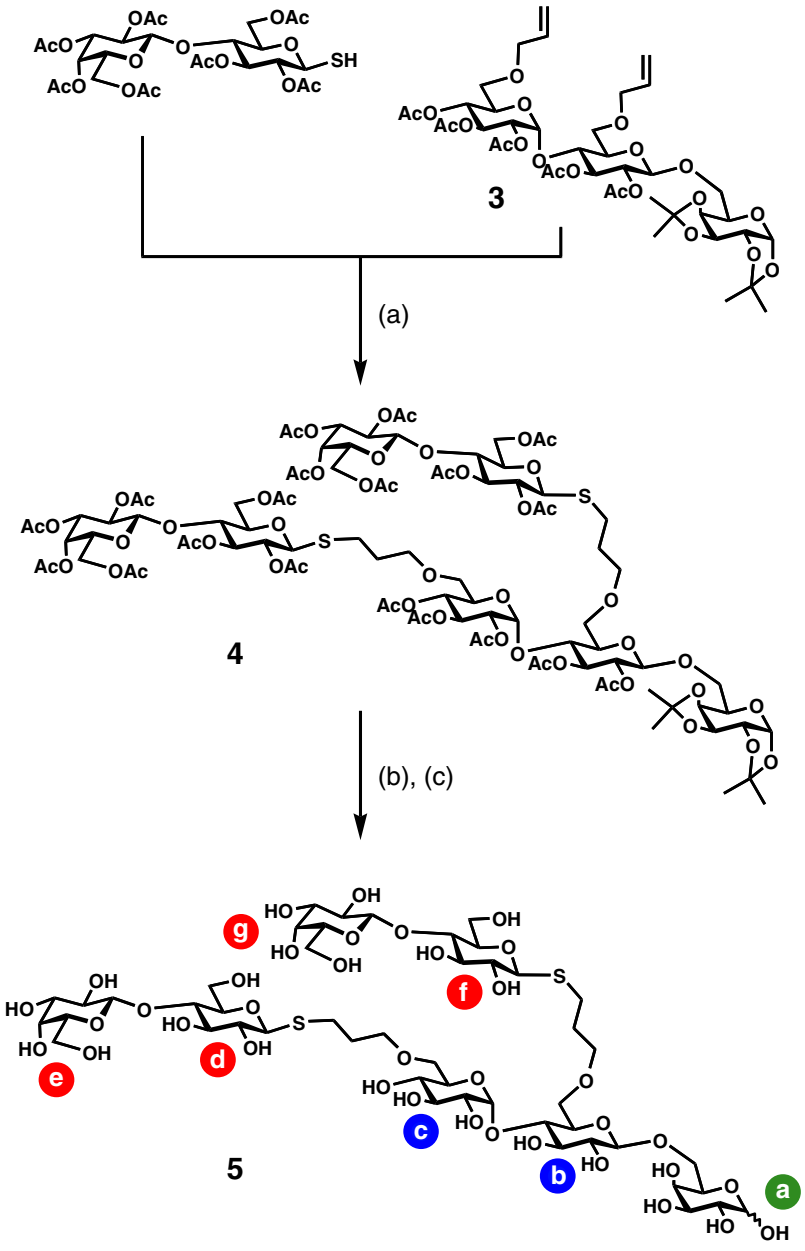
In conclusion, AB_2 trisaccharide monomers were used in the synthesis of di- and tetravalent lactoside dendrons in a convergent manner using photoaddition and reductive amination during the coupling steps. These reactions are not only mild and chemoselective, but they also have the added benefit of working well in polar solvents such as methanol and water. While the β-thiolactoside was coupled to the periphery of the dendrons, the procedure is versatile, and should be capable of extension to the attachment of other thioglycosides or thiol-containing ligands.

3. Experimental

Trisaccharide[13] **1** and hepta-*O*-acetyl-1-thio-β-lactose[11b] were prepared as described in the literature. Allyltrichloroacetimidate was purchased from Senn Chemicals. All other chemicals were purchased from Aldrich and used as received. Solvents were used as purchased, except for CH_2Cl_2 (distilled from CaH_2) and CH_3OH (distilled from Mg turnings). All photoadditions were performed in borosilicate glass vials. Analytical TLC was performed on silica gel 60-F_{254} (Merck) with detection by fluorescence and/or by charring following immersion in a 5% H_2SO_4/EtOH. Flash chromatography was performed with silica gel 60 (Silicycle). Preparative gel permeation chromatography was performed using (1) a 25×900 mm column of Sephadex LH20 resin (Sigma), eluting with CH_3OH or (2) a 5×100 cm column of Sephadex G-25 resin (Amersham Pharmacia Biotech), eluting with 5% *n*-BuOH in water. Reversed-phase HPLC was conducted by using a Hypersil 5 μm BDS C-18 silica column (ThermoQuest;



Scheme 1. Reagents and conditions: (a) IBr, CH_3OH, 84%. (b) Allyltrichloroacetimidate, triflic acid, 3:12 CH_2Cl_2–C_6H_{12}, 0 °C, 54%.

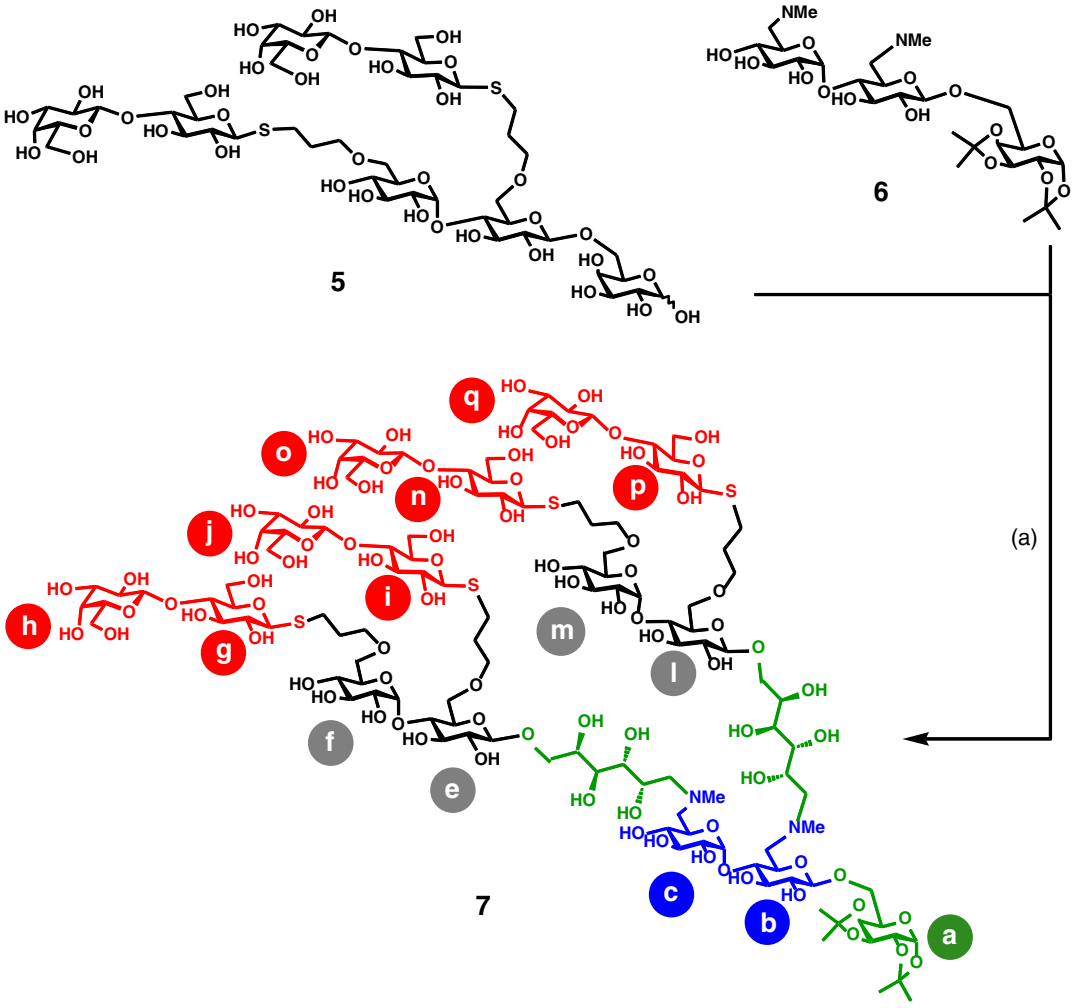


Scheme 2. Reagents and conditions: (a) hν, CH_3OH, 75%. (b) $NaOCH_3$, CH_3OH, 97%. (c) 90% aq TFA, quant. yield.

4.6×150 mm). ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 500 spectrometer (at 500 and 125 MHz, respectively) at ambient temperature. ^1H and ^{13}C NMR spectra were referenced using their residual solvent signals. The following abbreviations were used to explain the signal multiplicities or characteristics: s, singlet; d, doublet; dd, doublet of doublet; pd, pseudo-doublet; pt, pseudo-triplet; m, multiplet; b, broad. Electrospray mass spectrometry (ESI) was performed using a Sciex API IIIR triple quadrupole electrospray mass spectrometer using H_2O/MeCN/HCOOH, 50:50:0.1 as the mobile phase. High resolution matrix-assisted laser-desorption ionization (HR-MALDI) spectra were recorded using dihydroxybenzoic acid as the matrix on an IonSpec Ultima 7.4 Tesla FTMS instrument.

3.1. 2,3,4-Tri-*O*-acetyl-α-D-glucopyranosyl-(1→4)-2,3-di-*O*-acetyl-β-D-glucopyranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (2)

Trisaccharide[13] **1** (2.5 g, 2.44 mmol) was dissolved in CH_3OH (1 mL). IBr (7.3 mL, 7.3 mmol) was added to the solution with stirring and the brown reaction mixture was stirred at ambient temperature for 3 h. The solution was quenched by the addition of aqueous



Scheme 3. Reagents and conditions: (a) $NaCNBH_3$, AcOH, H_2O, CH_3OH, 48%.

$Na_2S_2O_3$, before being washed with aqueous $NaHCO_3$ solution (2×100 mL) and brine (2×100 mL). The organic layer was dried (Na_2SO_4) and concentrated. Column chromatography using CH_2Cl_2–EtOAc (7:3) as the elution solvent afforded **2** as a white foam (1.6 g, 84%). ^{1}H NMR ($CDCl_3$): δ 1.29 (s, 3H, C(C*H*$_3$)$_2$), 1.31 (s, 3H, C(C*H*$_3$)$_2$), 1.42 (s, 3H, C(C*H*$_3$)$_2$), 1.48 (s, 3H, C(C*H*$_3$)$_2$), 1.97–2.02 (m, 15H, 5×COC*H*$_3$), 2.75 (br s, 2H, O*H*), 3.47–3.52 (m, 1H), 3.61–3.69 (m, 2H), 3.80–3.99 (m, 4H), 4.14–4.21 (m, 2H, H-4a, H-4b), 4.27 (dd, 1H, $J_{1,2}$ = 5.0, $J_{2,3}$ = 7.9 Hz, H-2a), 4.56 (dd, 1H, $J_{2,3}$ = 7.9, $J_{3,4}$ = 2.4 Hz, H-3a), 4.61 (d, 1H, $J_{1,2}$ = 7.9 Hz, H-1b), 4.80–4.88 (m, 2H, H-2b, H-2c), 4.91 (dd, 1H, $J_{3,4}$ = 10.1, $J_{4,5}$ = 10.1 Hz, H-4c), 5.28 (dd, 1H, $J_{2,3}$ = 3.5, $J_{3,4}$ = 3.5 Hz, H-3b), 5.38 (dd, 1H, $J_{2,3}$ = 10.1, $J_{3,4}$ = 10.1 Hz, H-3c), 5.42 (d, 1H, $J_{1,2}$ = 4.2 Hz, H-1c), 5.42 (d, 1H, $J_{1,2}$ = 5.0 Hz, H-1a); ^{13}C NMR ($CDCl_3$): δ 20.7, 20.8, 21.1, 24.4, 25.1, 26.0, 26.1, 60.7, 61.2, 67.4, 69.1, 69.5, 70.4, 70.6, 70.7, 71.1, 72.2, 74.5, 75.6, 76.8, 77.2, 77.4, 77.5, 95.4, 96.3, 101.1, 108.7, 109.5, 169.9, 170.1, 170.2, 170.5, 170.7; HR-MALDI-TOF found m/z 817.2741 $[M + Na]^+$. Calcd for $C_{34}H_{50}O_{21}Na$ 817.2742.

3.2. 2,3,4-Tri-*O*-acetyl-6-*O*-allyl-α-D-glucopyranosyl-(1→4)-2,3-di-*O*-acetyl-6-*O*-allyl-β-D-glucopyranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (3)

Diol **2** (2.1 g, 2.6 mmol) and allyl trichloroacetimidate (1.3 mL, 9.5 mmol) were combined under argon flow and dissolved in a 3:7 CH_2Cl_2–C_6H_{12} mixture (10 mL). Triflic acid (63 μL) was added slowly and the solution was stirred at ambient temperature for 4 h, after which time another portion of the allyl trichloroacetimidate (1.3 mL, 9.5 mmol) and triflic acid (63 μL) were added. The reaction mixture was allowed to stir for another 16 h before the solution was quenched by the addition of pyridine. The solvent was removed in vacuo to provide an oil that was purified by column chromatography (1:1,

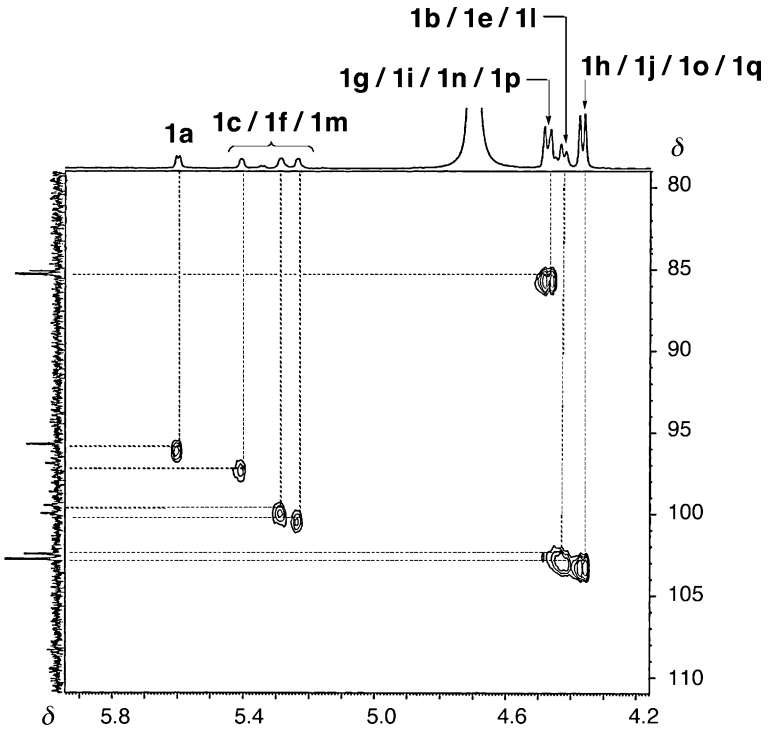


Figure 1. HMQC NMR (500 MHz, D_2O) of tetralactoside dendron **9**.

hexanes–EtOAc) affording **3** (1.2 g, 54%) as a white foam. ^{1}H NMR ($CDCl_3$): δ 1.29 (s, 3H, C(CH_3)$_2$), 1.31 (s, 3H, C(CH_3)$_2$), 1.43 (s, 3H, C(CH_3)$_2$), 1.48 (s, 3H, C(CH_3)$_2$), 1.96–2.05 (m, 15H, 5×COCH_3), 3.42 (dd, 1H, $J_{5,6}$ = 3.6, $J_{6,6'}$ = 10.8 Hz, H-6c), 3.50–3.56 (m, 2H, H-5b, H-6′c), 3.67 (dd, 1H, H-6′a, $J_{5,6'}$ = 7.3, $J_{6,6'}$ 11.1 Hz), 3.71 (dd, 1H, $J_{5,6}$ = 2.0, $J_{6,6'}$ = 11.6 Hz, H-6b), 3.80 (dd, 1H, $J_{5,6}$ = 3.7, $J_{6,6'}$ = 11.6 Hz, H-6′b), 3.88–4.11 (m, 8H), 4.18 (dd, 1H, $J_{4,5}$ = 1.8, $J_{3,4}$ = 7.9 Hz, H-4a), 4.28 (dd, 1H, $J_{1,2}$ = 2.4, $J_{2,3}$ = 5.0 Hz, H-2a), 4.53–4.59 (m, 2H, H-1b, H-3a), 4.78–4.86 (m, 2H, H-2b, H-2c), 5.12 (dd, 1H, $J_{3,4}$ = 10.0, $J_{4,5}$ = 10.0 Hz, H-4c), 5.15–5.31 (m, 5H, H-3b, OCH$_2$CHCH_2), 5.35 (dd, 1H, $J_{2,3}$ = 9.6, $J_{3,4}$ = 10.0 Hz, H-3c), 5.41 (d, 1H, $J_{1,2}$ = 3.9 Hz, H-1c), 5.49 (d, 1H, $J_{1,2}$ = 5.0 Hz, H-1a), 5.79–5.94 (m, 2H, OCH_2CHCH$_2$); ^{13}C NMR ($CDCl_3$): δ 20.6, 20.6, 20.7, 20.7, 20.9, 24.4, 25.0, 25.9, 26.0, 67.5, 67.9, 68.4, 68.9, 69.0, 69.1, 69.7, 70.3, 70.4, 70.6, 71.1, 71.4, 72.0, 72.6, 72.7, 74.4, 75.4, 94.9, 96.2, 101.1, 108.6, 109.3, 117.1, 117.5, 134.3, 134.6, 169.4, 169.8, 170.1, 170.3, 170.5; HR ESI found m/z 897.3362 $[M + Na]^+$. Calcd for $C_{40}H_{58}O_{21}Na$ 897.3368.

3.3. Dendron 4

Hepta-*O*-acetyl-1-thio-β-lactose[11b] (195 mg, 0.3 mmol) and the bisallyl derivative **3** (40 mg, 0.05 mmol) were dissolved in dry CH_3OH (5 mL) in a 3 dram vial. The solution was bubbled with argon for 20 min before exposing the mixture to an Hg lamp for 5 h. The solvent was then evaporated in vacuo to give an off-white solid, which was purified by flash chromatography (3:7, hexanes–EtOAc) yielding **4** (58 mg, 75%) as a white solid. ^{1}H NMR ($CDCl_3$): δ = 1.21 (s, 6H, 2×C(CH_3)$_2$), 1.32 (s, 3H, C(CH_3)$_2$), 1.39 (s, 3H, C(CH_3)$_2$), 1.69–1.78 (m, 4H, SCH$_2$CH_2), 1.85 (s, 6H, 2×COCH_3), 1.88–1.97 (m, 36H, 14×COCH_3), 2.00 (s, 3H, COCH_3), 2.02 (s, 3H, COCH_3), 2.03 (s, 3H, COCH_3), 2.53–2.69 (m, 4H, SCH_2CH$_2$), 3.27–3.35 (m, 2H), 3.37–3.60 (m, 8H), 3.66–3.73 (m, 2H), 3.77–3.90 (m, 6H), 3.97–4.03 (m, 8H), 4.08 (dd, 1H), 4.18 (dd, 1H), 4.34–4.49 (m, 8H), 4.65–4.72 (m, 2H), 4.79–4.87 (m, 4H), 4.94–5.12 (m, 3H), 5.07–5.17 (m, 3H), 5.19–5.25 (m, 3H), 5.28 (d, 1H, $J_{1,2}$ = 3.8 Hz, H-1c), 5.37 (d, 1H, $J_{1,2}$ = 4.9 Hz, H-1a); ^{13}C NMR ($CDCl_3$): δ 13.48, 18.89, 20.26, 20.39, 20.48, 20.50, 20.55, 20.62, 20.65, 20.66, 20.75, 20.79, 24.17, 24.81, 25.76, 25.82, 27.09, 27.26, 29.75, 29.94, 30.41, 60.63, 62.07, 64.06, 66.47, 67.39, 68.41, 68.78, 68.90, 69.08, 69.24, 69.43, 69.76, 70.07, 70.18, 70.23, 70.44, 70.79, 70.99, 71.69, 72.05, 73.62, 73.62, 74.16, 74.83, 76.11, 76.35, 76.38, 83.50, 83.60, 94.88, 95.98, 100.86, 100.89, 100.95, 108.37, 109.10, 168.80, 169.07, 169.32, 169.42, 169.58, 169.76, 169.85, 169.89, 170.00, 170.05, 170.26, 170.92.

3.4. Dendron 5

Sodium methoxide (0.8 mL) was added to a solution of the dendron **3** (730 mg, 0.33 mmol) in CH_3OH (50 mL). After stirring for 3.5 h, the solution was neutralized

using Amberlite IR-120 H^+ resin, filtered, and then concentrated to provide the **5** as a white solid (452 mg, 97%); ^{1}H NMR (CD_3OD): δ 1.31 (s, 3H, $C(CH_3)_2$), 1.34 (s, 3H, $C(CH_3)_2$), 1.39 (s, 3H, $C(CH_3)_2$), 1.52 (s, 3H, $C(CH_3)_2$), 1.84–1.95 (m, 4H, SCH_2CH_2), 2.71–2.87 (m, 4H, SCH_2CH_2), 3.22–3.33 (m, 4H), 3.40–3.84 (m, 35H), 3.85–3.93 (m, 2H), 3.97–4.60 (m, 2H), 4.24–4.45 (m, 6H), 4.59–4.65 (m, 2H), 5.07–5.16 (m, 1H, H-1c), 5.50 (d, 1H, $J_{1,2} = 4.9$ Hz, H-1a); ^{13}C NMR (CD_3OD): δ 23.22, 24.10, 24.95, 26.27, 29.75, 60.72, 61.02, 61.16, 67.57, 68.77, 69.11, 69.46, 69.50, 69.97, 70.40, 70.39, 71.00, 72.28, 72.48, 72.61, 72.95, 73.25, 73.63, 74.05, 75.50, 75.88, 75.90, 76.35, 78.90, 79.22, 80.61, 85.44, 85.56, 96.17, 101.73, 103.26, 103.52, 108.60, 108.97; HR-MALDI-TOF found m/z 1403.4700 $[M + Na]^+$. Calcd for $C_{54}H_{92}O_{36}S_2Na$ 1403.4707. The deacetylated product (508 mg, 0.36 mmol) was then stirred in a 90% aqueous TFA solution for 15 min. The solvent was reduced in vacuo to afford the fully deprotected dendron **5** as an off-white solid. The compound was redissolved in H_2O and lyophilized to afford a fluffy white solid (474 mg, quant. yield). ^{1}H NMR (D_2O): δ 1.79 (m, 4H, SCH_2CH_2), 2.61–2.69 (m, 4H, SCH_2), 3.15–3.93 (m, 46H), 4.09–4.15 (m, 0.4H, 2aα), 4.31 (d, 2H, H-1d, H-1f), 4.33–4.41 (m, 3.6H, H-1aβ, H-1b, H-1e, H-1g), 5.11 (d, 0.4H, H-1aα), 5.19 (d, 1H, H-1c); ^{13}C NMR (D_2O): δ 26.56, 29.08, 60.06, 60.87, 68.40, 68.67, 68.80, 68.91, 69.28, 69.30, 69.59, 69.66, 70.79, 70.98, 71.10, 71.60, 71.87, 72.36, 72.47, 72.60, 72.68, 73.01, 73.64, 75.19, 75.62, 75.90, 78.05, 78.50, 85.23, 96.28, 102.73; HR-MALDI-TOF found m/z 1323.4111 $[M + Na]^+$. Calcd for $C_{48}H_{84}O_{36}S_2Na$ 1323.4081.

3.5. Dendron 7

Acetic acid (1.4 mL, 60 mmol) was added to a solution of **5** (78 mg, 60 mmol), **6** (14 mg, 23 mmol), and $NaCNBH_3$ (131 mg, 2.1 mmol) in a 1:1 solution of CH_3OH (1 mL) and H_2O (1 mL). The reaction mixture was stirred and heated under reflux for 20 h. The mixture was allowed to cool to room temperature, before being concentrated and redissolved in H_2O (0.5 mL) and purified by preparative reverse-phase HPLC (C-18 reversed-phase: CH_3OH–H_2O, 0:100 to 100:0, retention time = 6.0 min) to afford the pure lactoside glycodendron **7** (35 mg, 48%); ^{1}H NMR (D_2O): δ 1.26, 1.27, 1.36, 1.47 (12H, 4s, $2\times C(CH_3)_2$), 1.79–1.88 (m, 8H, SCH_2CH_2), 2.29, 2.33 (2s, 6H, $2\times NCH_3$), 2.6–2.8 (m, 8H, SCH_2), 3.1–4.1 (m, 112H), 4.36–4.45 (m, 9H, H-1b, H-1f, H-1g, H-1i, H-1m, H-1n, H-1p), 4.29–4.35 (m, 4H, H-1h, H-1j, H-1o, H-1q), 5.19, 5.24 (2d, 2H, $^3J_{1,2} = 3.7$, 2.8 Hz, H-1e, H-1l), 5.36 (d, 1H, $^3J_{1,2} = 3.5$ Hz, H-1c), 5.56 (d, 1H, $^3J_{1,2} = 4.8$ Hz, H-1a); Selected ^{13}C NMR (D_2O): δ 23.2, 23.9, 24.8, 24.9 ($2\times C(CH_3)_2$), 26.6 (SCH_2), 29.7, (SCH_2CH_2), 44.9, 45.0 ($2\times NCH_3$), 85.1, 85.2 (C-1g, C-1i, C-1n, C-1p), 95.7 (C-1a), 96.7 (C-1c), 102.5, 102.8 (C-1f, C-1m), 109.9, 110.0 (C-1e, C-1l); ESI m/z found 1591.3 $[M + 2H]^{2+}$. Calcd for $C_{122}H_{214}N_2O_{84}S_4$ 3179.1418.

References

1. *Essentials of Glycobiology*; Varki, A., Cummings, R., Esko, J., Freeze, H., Hart, G., Marth, J., Eds.; Cold Spring Harbor: New York, 1999.
2. (a) Mammen, M.; Choi, S.-K.; Whitesides, G. M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2754–2794; (b) Lee, R. T.; Lee, Y. C. *Glycoconj. J.* **2000**, *17*, 543–551; (c) Lundquist, J. J.; Toone, E. *J. Chem. Rev.* **2002**, *102*, 555–578; (d) Kitov, P. I.; Bundle, D. R. *J. Am. Chem. Soc.* **2003**, *125*, 16271–16284.
3. (a) Rockendorf, N.; Lindhorst, T. *Top. Curr. Chem.* **2001**, *217*, 201–238; (b) Turnbull, W. B.; Stoddart, J. F. *Rev. Mol. Biotechnol.* **2002**, *90*, 231–255; (c) Cloninger, M. *J. Curr. Opin. Chem. Biol.* **2002**, *6*, 742–748.
4. (a) Roy, R. *Polym. News* **1996**, *21*, 226–232; (b) Roy, R.; Baek, M.-G.; Rittenouse-Olson, K. *J. Am. Chem. Soc.* **2001**, *123*, 1809–1816; (c) Woller, E. K.; Walter, E. D.; Morgon, J. R.; Singel, D. J.; Cloninger, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 8820–8826; (d) Autar, R.; Khan, A. S.; Schad, M.; Hacker, J.; Liskamp, R. M. J.; Pieters, R. *J. Chem. Bio. Chem.* **2003**, *4*, 1317–1325.
5. (a) Spaltenstein, A.; Whitesides, G. M. *J. Am. Chem. Soc.* **1991**, *113*, 686–687; (b) Choi, S. K.; Mammen, M.; Whitesides, G. M. *J. Am. Chem. Soc.* **1997**, *119*, 4103–4111; (c) Bovin, N. V. *Glycoconjugate J.* **1998**, *15*, 431–446; (d) Mortell, K. H.; Weatherman, R. V.; Kiessling, L. L. *J. Am. Chem. Soc.* **1996**, *118*, 2297–2298; (e) Cairo, C. W.; Gestwicki, J. E.; Kanai, M.; Kiessling, L. L. *J. Am. Chem. Soc.* **2002**, *124*, 1615–1619; (f) Arranz-Plaza, E.; Tracy, A. S.; Siriwardena, A.; Pierce, J. M.; Boons, G.-J. *J. Am. Chem. Soc.* **2002**, *124*, 13035–13046; (g) Thobhani, S.; Ember, B.; Siriwardena, A.; Boons, G.-J. *J. Am. Chem. Soc.* **2003**, *125*, 7154–7155.
6. (a) Colonna, B.; Harding, V. D.; Nepogodiev, S. A.; Raymo, F. M.; Spencer, N.; Stoddart, J. F. *Chem. Eur. J.* **1998**, *4*, 1244–1254; (b) Turnbull, W. B.; Pease, A. R.; Stoddart, J. F. *ChemBioChem* **2000**, *1*, 70–74; (c) Turnbull, W. B.; Kalovidouris, S. A.; Stoddart, J. F. *Chem. Eur. J.* **2002**, *8*, 2988–3000; (d) Kalovidouris, S. A.; Blixt, O.; Nelson, A.; Vidal, S.; Turnbull, W. B.; Paulson, J. C.; Stoddart, J. F. *J. Org. Chem.* **2003**, *68*, 8485–8493.
7. Lee, Y. C.; Townsend, R. R.; Hardy, M. R.; Lonngren, J.; Arnarp, J.; Haraldsson, M.; Lönn, H. *J. Biol. Chem.* **1983**, *258*, 199–202; André, S.; Kaltner, H.; Furuike, T.; Nishimura, S.-I.; Gabius, H.-J. *Bioconjugate Chem.* **2004**, *15*, 87–98.
8. (a) Dubber, M.; Linhorst, T. K. *J. Org. Chem.* **2000**, *65*, 5275–5281; (b) Backinowsky, L. V.; Abronina, P. I.; Shashkov, A. S.; Grachev, A. A.; Kochetkov, N. K.; Nepogodiev, S. A.; Stoddart, J. F. *Chem. Eur. J.* **2002**, *8*, 4412–4423.
9. (a) Sadalapure, K.; Lindhorst, T. K. *Angew. Chem., Int. Ed.* **2000**, *39*, 2010–2013; (b) Ghorai, S.; Bhattacharjya, A.; Basak, A.; Mitra, A.; Williamson, R. T. *J. Org. Chem.* **2003**, *68*, 617–620.
10. Griesbaum, K. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 273–287.

11. (a) Kieburg, C.; Dubber, M.; Lindhorst, T. K. *Synlett* **1997**, 1447–1449; (b) Fulton, D. A.; Stoddart, J. F. *Org. Lett.* **2000**, *2*, 1113–1116; (c) Fulton, D. A.; Stoddart, J. F. *J. Org. Chem.* **2001**, *66*, 8309–8319.
12. Dubber, M.; Lindhorst, T. K. *Synthesis* **2001**, 327–330.
13. Turnbull, W. B.; Pease, A. R.; Stoddart, J. F. *ChemBioChem* **2000**, *1*, 70–74.
14. Kartha, K. P. R.; Field, R. A. *Synlett* **1999**, *3*, 311–312.
15. Wessel, H. P.; Iverson, T.; Bundle, D. R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2247–2250.