Efficient and accelerated growth of multifunctional dendrimers using orthogonal thiol-ene and S_N2 reactions

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General Information:

All chemicals were purchased from commercial sources and were used without further purification. All reactions in organic medium were performed in standard oven dried glassware under an inert atmosphere of nitrogen using fresh dry solvents. Solvents and reagents were deoxygenated for thiol-ene reactions by purging with argon. Silica gel (60 Å, 40-63 μm) was used for column chromatography and TLC analysis was performed on commercial plates coated with silica gel 60 F254. Visualization of the spots on TLC plates was achieved by UV radiation or 5% sulfuric acid in ethanol or mixture molybden-cerium solution (100 ml H2SO4, 900 ml H2O, 25g (NH4)6Mo7O24H2O, 10g Ce(SO4)2) and subsequent development by gentle warming with a heat-gun. 1H NMR and 13C NMR spectra were recorded at 300 or 600 MHz and 75 or 150 MHz, respectively. All NMR spectra were measured at 25°C in the indicated deuterated solvents. Proton and carbon chemical shifts (δ) are reported in ppm and coupling constants (J) are reported in Hertz (Hz). The resonance multiplicity in the 1H NMR spectra are described as “s” (singlet), “d” (doublet), “t” (triplet), and “m” (multiplet) and broad resonances are indicated by “br”. Residual protic solvent of CDCl3 (1H, δ 7.26 ppm; 13C, δ 77.0 ppm), D2O (1H, δ 4.79 ppm and 30.9 ppm for CH3 of Acetone for 13C spectra), DMSO-d6 (1H, δ 2.50 ppm; 13C, δ 39.5 ppm) and MeOD-d4 (1H, δ 3.31 ppm; 13C, δ 49.0 ppm) were used as the internal reference in the 1H- and 13C-NMR spectra. Fourier transform infrared (FTIR) spectra were measured as neat and the absorptions are given in wavenumbers (cm-1). Accurate mass measurements (HRMS) and low-resolution mass spectrometry were performed in positive electrospray mode or MALDI-TOF analysis. Either protonated molecular ions [M+nH]n+, sodium adducts [M+nNa]n+ or ammonium adducts [M+NH4]n+ were used for empirical formula confirmation. Gel Permeation Chromatography (GPC) was performed using THF as the eluent, at 40°C with a 1 mL/min flow rate on a Viscotek VE 2001 GPCmax (SEC System) with Wyatt DSP/Dawn EOS and refractive index RI/LS system as detectors. 2 PLGel mixed B LS (10 μm, 300×7.5 mm) and LS-MALLS detection with performances verified with polystyrene 100 kDa and 2000 kDa were used to determine the number-average molecular weight (Mn) and polydispersity index (Mw/Mn). Calculations were performed with Zimm Plot (model).
Experimental Part:

Scheme 1. Synthesis of bifunctional derivative 3.

4-Chloroacetamidophenol (2): 4-Aminophenol (3.00 g, 27.5 mmol) was added into the suspension of K$_2$CO$_3$ (4.00 g, 30.2 mmol, 1.1 equiv) in acetone/water (40 mL, 3:1). After cooled to -10 °C, chloroacetyl chloride (3.29 mL, 41.25 mmol) was dropwise into the mixture during 30 min. The mixture was stirred at this temperature for 1 hour. Acetone was removed then under reduced pressure and the residue was diluted with EtOAc, washed with H$_2$O, brine, dried over Na$_2$SO$_4$, filtered, and the filtrate was concentrated followed by purification (SiO$_2$, CH$_2$Cl$_2$/MeOH = 98:2) afforded 2 as a brown solid. Yield (3.56 g, 70%). $R_f$ = 0.27 (DCM/MeOH, 96:4); mp = 146°C (non corrected) (Litt. 146°C)$^1$; $^1$H NMR (600 MHz, DMSO-$d_6$): $\delta$ = 10.03 (s, 1H), 9.26 (s, 1H), 7.36 (d, $J$ = 8.8 Hz), 6.71 (d, $J$ = 8.8 Hz), 4.18 (s, 2H); $^13$C NMR (75 MHz, DMSO-$d_6$): $\delta$ = 173.4, 163.3, 139.6, 130.7, 124.7, 53.0. ESI-HRMS Calcd. for C$_8$H$_8$NO$_2$Cl 186.0316 [M+H]$^+$; found 186.0309.

2-Chloro-N-(4-allyloxyphenyl)acetamide (3): Allyl bromide (5.1 mL, 59 mmol) was added slowly to the suspension of 2 (2.20 g, 11.8 mmol) and potassium carbonate (3.25 g, 23.6 mmol) in DMF (20 mL) and stirred the reaction mixture at 50°C for 3 h. The mixture was concentrated to dryness and the residue partitioned between ethyl acetate (100 mL) and water (75 mL). The organic phase collected and washed with NaCl (50 ml) and with the water (50 mL). The organic phase was dried (Na$_2$SO$_4$), filtered and the filtrate was concentrated followed by purification (SiO$_2$, CH$_2$Cl$_2$/MeOH = 98:2) afforded 3, as a solid. Yield: (1.88 g, 71 %); $R_f$ = 0.37 (Hexanes/EtOAc, 3:1); m.p. 138-140°C; IR (neat) $\nu_{max}$ 3267, 3097, 1683, 1611, 1513, 1406, 1289, 1235, 826 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.14 (s, 1H), 7.31 (d, $J$ = 9.0 Hz, 2H), 6.90 (d, $J$ = 9.0 Hz, 2H), 6.11–5.98 (m, 1H), 5.44–5.37 (m, 1H), 5.31–5.27 (m, 1H), 4.53 (dt, $J$ = 5.3, 1.4 Hz, 2H), 4.18 (s, 2H); $^13$C NMR (75 MHz, CDCl$_3$) $\delta$ 163.7, 156.0, 133.0, 129.8, 122.0, 121.9, 117.69, 115.1, 69.0, 42.8. ESI-HRMS Calcd. for C$_{11}$H$_{12}$ClNO$_2$ [M+H]$^+$ 226.0635, found 226.0616.
Scheme 2. S_N2 reactions on 3.

General procedure for selective S_N2 reaction: Thiol (0.6 mmol) was added into the suspension of potassium carbonate (1 mmol) and 3 (0.5 mmol) in DMF (4 mL). The reaction mixture was stirred at rt for 12 h. The mixture was concentrated to dryness and the residue partitioned between ethyl acetate (15 mL) and water (10 mL). The organic phase collected and washed with NaCl (10 mL) and with the water (10 mL). The organic phase was dried (Na_2SO_4), filtered and the filtrate was concentrated followed by purification (SiO_2) afforded the desired compounds.

N-(4-Allyloxyphenyl)-2-(4-bromophenylthio)acetamide (4a): Yield: 93%; \( R_f = 0.41 \) (Hexanes/EtOAc, 3:1); m.p. 135-137°C; IR (neat) \( \nu_{\text{max}} \) 3320, 3254, 1651, 1535, 1512, 1474, 1253, 810 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl_3) \( \delta \) 8.38 (s, 1H), 7.44–7.40 (m, 2H), 7.36–7.33 (m, 2H), 7.22–7.19 (m, 2H), 6.88–6.85 (m, 2H), 6.03–5.97 (m, 1H), 5.42–5.36 (m, 1H), 5.30–5.26 (m, 1H), 4.50 (dt, \( J = 5.2, 1.3 \) Hz, 2H), 3.72 (s, 2H);
\(^{13}\)C NMR (75 MHz, CDCl_3) \( \delta \) 165.4, 155.8, 133.4, 133.1, 132.5, 130.3, 129.8, 121.8, 120.9, 117.7, 115.1, 69.1, 38.1. ESI-HRMS Calcd. for C_{17}H_{16}BrNO_2S [M+H]^+ 380.0143, found 380.0138.

Methyl 3-(2-(4-allyloxyphenylamino)-2-oxoethylthio)propanoate (4b): Yield: 94%; \( R_f = 0.39 \) (EtOAc); m.p. 58-60°C; IR (neat) \( \nu_{\text{max}} \) 3302, 1733, 1655, 1533, 1508, 1412, 1219, 1172, 829 cm\(^{-1}\); \(^1\)H NMR (600 MHz, CDCl_3) \( \delta \) 8.68 (s, 1H), 7.66–7.36 (m, 2H), 7.13–6.73 (m, 2H), 6.07–6.02 (m, 1H), 5.42–5.39 (m, 1H), 5.29–5.27 (m, 1H), 4.52 (dt, \( J = 5.3, 1.5 \) Hz, 2H), 3.70 (s, 3H), 3.37 (s, 2H), 2.89 (t, \( J = 6.8 \) Hz, 2H), 2.67 (t, \( J = 6.8 \) Hz, 2H); \(^{13}\)C NMR (151 MHz, CDCl_3) \( \delta \) 172.1, 166.3, 155.6, 133.2, 130.8, 121.5, 117.7, 115.0, 69.0, 52.0, 36.9, 33.7, 27.9. ESI-HRMS Calcd. for C_{14}H_{19}NO_4S [M+H]^+ 310.1108, found 310.1104.

N-(4-Allyloxyphenyl)-2-(2,3-dihydroxypropythio)acetamide (4c): Yield: 96%; \( R_f = 0.31 \) (Hexanes/EtOAc, 3:2); m.p. 69-71°C; IR (neat) \( \nu_{\text{max}} \) 3296, 3081, 2921, 1651, 1541, 1508, 1413, 1234, 1023, 829 cm\(^{-1}\); \(^1\)H NMR (600 MHz, CD_3OD) \( \delta \) 7.45 (d, \( J = 9.1 \) Hz, 2H), 6.89 (d, \( J = 9.1 \) Hz, 2H), 6.07–6.02 (m, 1H), 5.40–5.37 (m, 1H), 5.23–5.25 (m, 1H), 4.52 (dt, \( J = 5.2, 1.6 \) Hz,
2H), 3.82–3.80 (m, 1H), 3.60–3.54 (m, 2H), 3.40–3.35 (m, 2H), 2.88–2.85 (m, 1H), 2.74–2.70 (m, 1H); $^{13}$C NMR (151 MHz, CD$_3$OD) $\delta$ 170.8, 157.0, 134.9, 132.7, 123.0, 117.4, 115.9, 72.7, 70.0, 65.9, 37.6, 37.1. ESI-HRMS Calcd. for C$_{14}$H$_{19}$NO$_4$S [M+H]$^+$ 298.1113, found 298.1108.

Scheme 3. Thiol-ene reactions on 3.

**General Procedure for selective thiol-ene reaction:** Thiol (1 mmol) was added into a solution of 2,2-dimethoxy-2-phenylacetophenone (DMPA, 0.1 mmol) and 3 (0.5 mmol) in MeOH (or DMF) (1 mL). The reaction mixture was irradiated for 2 h with 365 nm light at room temperature (*classical glassware, UV lamp (365 nm, Model UVGL-58 MINERALIGHT® LAMP) in a cardboard box*). The mixture was concentrated to dryness and the residue was purified (SiO$_2$) to afford the desired compounds.

**Methyl 3-(3-(4-(2-chloroacetamido)phenoxy)propylthio) propanoate (5a):** Yield: 86%; $R_f$ = 0.40 (Hexanes/EtOAc, 3:2); m.p. 58-60°C; IR (neat) $\nu_{max}$ 3274, 3145, 3101, 2957, 1729, 1686, 1660, 1511, 1471, 1438, 1244, 1169, 826 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.44–7.41 (m, 2H), 6.89–6.80 (m, 2H), 4.17 (s, 2H), 4.03 (t, $J$ = 6.0 Hz, 2H), 3.69 (s, 3H), 2.82–2.77 (m, 2H), 2.72 (t, $J$ = 7.0 Hz, 2H), 2.61 (t, $J$ = 7.0 Hz, 2H), 2.10–2.00 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 172.3, 163.6, 163.5, 156.3, 129.8, 129.7, 122.0, 121.9, 114.9, 77.2, 66.4, 51.8, 42.8, 42.8, 34.6, 29.1, 28.6, 27.0. ESI-HRMS Calcd. for C$_{15}$H$_{20}$ClNO$_4$S [M+NH$_4$]$^+$ 363.1140, found 363.1154.

**2-Chloro-N-(4-(3-(2,3-dihydroxypropylthio)-propoxy)-phenyl) acetamide (5b):** Yield: 83%; $R_f$ = 0.43 (EtOAc); m.p. 97-98°C; IR (neat) $\nu_{max}$ 3303, 2923, 2864, 1666, 1534, 1514, 1409, 1240, 1032, 823 cm$^{-1}$; $^1$H NMR (300 MHz, MeOD) $\delta$ 7.47–7.44 (m, 2H), 6.90–6.87 (m, 2H), 4.15 (s, 2H), 4.04 (t, $J$ = 6.1 Hz, 2H), 3.76–3.70 (m, 1H), 3.62–3.50 (m, 2H), 2.75–2.68 (m, 3H), 2.65–2.54 (m, 1H), 2.07–1.98 (m, 2H); $^{13}$C NMR (75 MHz, MeOD) $\delta$ 167.1, 157.5, 132.1, 123.2, 115.7, 72.8, 67.6, 66.0, 44.0, 36.3, 30.5, 30.0. ESI-HRMS Calcd. for C$_{14}$H$_{20}$ClNO$_4$S [M+Na]$^+$ 356.0694, found 356.0709.

2-Azidoethyl 2,3,4,6-tetra-O-allyl-β-D-glucopyranoside (7): Compound 6² (985 mg, 3.95 mmol) in DMF (5 mL) was added to a suspension of NaH (1.264 g, 31.60 mmol, 8.0 equiv., 60 % in mineral oil) in a mixture of hexane/DMF (50 mL, 9:1, v/v). After stirring for 30 min. at room temperature, the reaction mixture was cooled to 0°C, and then allyl bromide (2.73 mL, 31.60 mmol, 8.0 equiv) was added slowly and stirred for 1 h at 0°C and for 3 h at room temperature. The mixture was then cooled with an ice bath; methanol (5 mL) was added slowly into the mixture to quench the excess sodium hydride. After concentration of the mixture to dryness, the residue was mixed with ethyl acetate (200 mL) and washed with brine (saturated NaCl, 50 mL), then washed with water (3x100 mL, with a little amount of hexane), the organic layer was dried over Na₂SO₄, filtered, and concentrated under reduced pressure followed by purification by silica gel column chromatography (Hexane/EtOAc = 85:15) to afford 7, as a colorless oil. Yield: 1.52 g (94%); Rf = 0.39 (hexane/EtOAc 4:1); [α]D -15.2 (c 1, MeOH); IR (neat) νmax 3080, 2867, 2102, 1347, 1305, 1121, 1069, 994, 921 cm⁻¹; ¹H-NMR (300 MHz, CDCl₃) δ 5.93-5.71 (m, 4H), 5.27-5.04 (m, 8H), 4.41-3.91 (m, 10H), 3.68-3.58 (m, 3H), 3.50-3.25 (m, 5H), 3.24-3.13 (m, 1H); ¹³C-NMR (75 MHz, CDCl₃) δ 135.1, 134.9, 134.6, 134.5, 116.8, 116.7, 116.6, 116.3, 103.3, 83.9, 81.3, 77.2, 74.7, 74.2, 73.6, 73.4, 72.2, 68.7, 68.0, 50.8. ESI-HRMS Calcd. for C₂₀H₃₁N₃O₆ [M+NH₄]+ 427.2557, found 427.2544.


2-Chloroacetamido-ethyl 2,3,4,6-tetra-O-allyl-β-D-glucopyranoside (8): PPh₃ (3.55 g, 13.2 mmol) was added to a solution of 7 (1.8 g, 4.4 mmol) in THF:H₂O (3:1 20 mL) and stirred for 12
h at rt. The solvents were concentrated in vacuo and the crude residue was co-evaporated with toluene to remove the residual water. Chloroacetyl chloride (0.42 mL, 5.3 mmol) was added drop-wise to a solution of above crude residue and DIPEA (0.92 mL, 5.3 mmol) in CH$_2$Cl$_2$ (20 mL) and stirred at 0°C for 30 min. and then for 2 hrs at rt. Upon reaction completion, the mixture was concentrated to dryness and residue was purified (SiO$_2$, Hexane/EtOAc = 1:1) to afford 8, as a gum, which was solidified on standing. Yield: 1.29 g (64%); $\delta$ = 0.41 (Hexanes/EtOAc, 1:1); m.p. 54-56°C; $[\alpha]_D^{11.0}$ (c 0.4, MeOH); IR (neat) $\nu$$_{max}$ 3347, 2918, 2872, 1667, 1538, 1071, 996, 928 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.08 (s, 1H), 6.03–5.74 (m, 4H), 5.39–5.05 (m, 8H), 4.34–3.84 (m, 12H), 3.77–3.65 (m, 2H), 3.59–3.47 (m, 3H), 3.35–3.30 (m, 3H), 3.17 (t, $J$ = 8.2 Hz, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 166.0, 135.1, 134.9, 134.7, 134.4, 117.2, 117.0, 116.8, 116.6, 103.4, 84.1, 81.4, 77.4, 74.6, 74.3, 73.7, 73.6, 72.4, 69.0, 68.7, 42.5, 40.0. ESI-HRMS Calcd. for C$_{22}$H$_{34}$ClNO$_7$ [M+Na]$^+$ 482.1916, found 482.1906.

**Compound 9:** AcSH (0.14 mL, 2.0 mmol) was added into the solution of DMPAP (25.6 mg, 0.100 mmol) and 8 (102 mg, 0.22 mmol) in MeOH (2 mL). The reaction mixture was irradiated for 12 h with 365 nm light at room temperature. The mixture was concentrated to dryness and the residue was purified (SiO$_2$, Hexanes:EtOAc = 1:1) to afford 9 as an oil. Yield: 121 mg (72%); $R_f$ = 0.41 (Hexanes/EtOAc, 1:3); $[\alpha]_D^2$ +23.4 (c 1, MeOH); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.08 (s, 1H), 4.20 (d, $J$ = 7.7 Hz, 1H), 4.04 (s, 2H), 3.96–3.37 (m, 15H), 3.31–3.09 (m, 3H), 3.09–3.01 (m, 1H), 2.99–2.84 (m, 7H), 2.31–2.32 (m, 12H), 1.80–1.89 (m, 8H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 195.7, 195.7, 195.6, 195.6, 166.1, 103.4, 84.5, 82.1, 77.9, 77.2, 74.6, 71.8, 71.1, 69.9, 69.7, 68.5, 42.6, 40.0, 30.6, 30.4, 30.2, 29.6, 26.0, 25.9, 25.9. ESI-HRMS Calcd. for C$_{30}$H$_{50}$ClNO$_{11}$S$_4$ [M+Na]$^+$ 786.1853, found: 786.1827.
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Scheme 5. Optimization’s conditions for S₉2 reactions from tetra(thioacetylated) core 10 and chloroacetamide derivative 3.

**General conditions for S₉2 reactions’ optimization:** To a solution of tetra(thioacetylated) core 8 (20.0 mg, 54.3 μmol, 1.0 eq) in dry solvent (MeOH or THF/MeOH (1/1), 2 mL) was added base (MeONa, K₂CO₃, NaOH/NaBH₄ system or KCN, 8.0 eq) under a nitrogen atmosphere and at room temperature. After 5 minutes, 2-chloroacetamide derivative 3 (63.7 mg, 282 μmol, 5.2 eq) was incorporated to the mixture. The resulting yellowish solution was allowed to stir at room temperature for 3 hours under a nitrogen atmosphere. An off-white coloration took place gradually with the formation of insoluble white species. Evaporation to dryness *in vacuo* with rotary evaporator and subsequent purification by column chromatography (SiO₂, CH₂Cl₂/MeOH 99.5:0.5 to 98:2) afforded desired tetraallylated compound S1. *Rf* = 0.18 (CH₂Cl₂/MeOH 97:3); m.p. = 186-188°C; ¹H NMR (600 MHz, DMSO-*d₆*) δ 9.93 (s, 4H), 7.49 (d, *J* = 9.1 Hz, 8H), 6.90 (d, *J* = 9.1 Hz, 8H), 6.08–6.03 (m, 4H), 5.42–5.39 (m, 4H), 5.29–5.27 (m, 4H), 4.53 (m, 8H), 3.38 (s, 8H); ³¹C NMR (151 MHz, DMSO-*d₆*) δ 167.2, 154.2, 133.8, 132.2, 120.8, 117.3, 114.7, 68.3, 43.8, 38.7, 36.9; ESI-HRMS Calcd. for C₄₉H₅₆N₄O₈S₄ [M+H]⁺ 957.3054, found 957.3056.

Cluster 11: NaOMe in MeOH (1M, 0.23 mL) was added to a solution of 10 (14 mg, 0.038 mmol) and chloride 8 (104 mg, 0.23 mmol) in MeOH stirred at rt for 3 h. Upon reaction completion, the solvents were concentrated in vacuo and residue was purified (SiO₂, EtOAc) to afford 11, as a gum. Yield: 64 mg (89%); Rf = 0.64 (CH₂Cl₂/MeOH 9:1).

1H NMR (300 MHz, CDCl₃) δ 7.16 (t, J = 5.6 Hz, 4H), 5.98–5.80 (m, 16H), 5.29–5.12 (m, 32H), 4.34–3.95 (m, 36H), 3.89–3.81 (m, 4H), 3.78–3.67 (m, 8H), 3.60–3.30 (m, 24H), 3.23–3.15 (m, 12H), 2.76 (s, 8H);

13C NMR (75 MHz, CDCl₃) δ 168.8, 135.1, 134.7, 134.4, 117.4, 117.0, 116.8, 116.6, 103.6, 84.1, 81.5, 77.2, 74.5, 74.3, 73.7, 73.6, 72.4, 69.1, 68.9, 44.0, 40.1, 38.7, 36.5. ESI-HRMS Calcd. for C₉₃H₁₄₄N₄O₂₈S₄ [M+H]+ 1896.8972, found 1896.9005.

G(1)-Dendrimer 14: Thioglycerol (0.17 mL, 2 mmol) was added into the solution of DMPAP (10 mg, 0.04 mmol) and 11 (24 mg, 0.012 mmol) in DMF (0.5 mL). The reaction mixture was irradiated for 12 h with 365 nm light at rt. The mixture was concentrated to dryness and the residue was partitioned between ethyl acetate (10 mL) and water (10 mL). The aqueous phase was concentrated and the residue was dialyzed against 1kDa cut-off membrane followed by lyophilization, afforded 14 as viscous oil. Yield: 27 mg (63%); 1H NMR (600 MHz, D₂O) δ 4.31–4.29 (m, 4H), 4.03–4.00 (m, 4H), 3.80–3.19 (m, 120H), 3.03–2.81 (m, 28H), 2.69–2.46 (m, 52H), 1.93–1.76 (m, 32H); 13C NMR (151 MHz, D₂O:CD₃OD) δ 172.5, 103.7, 84.7, 82.6, 78.9, 74.7, 73.2, 72.6, 72.1, 71.8, 70.7, 69.9, 69.2, 67.9, 66.7, 65.9, 65.4, 56.1, 55.3, 40.9, 39.5, 37.3, 35.4, 30.7, 30.3, 29.7, 24.2, 23.4.
Scheme 7. Synthesis of polyol-terminated G(2)-dendrimer 15.

Cluster 12: AcSH (0.43 mL, 0.60 mmol) was added into the solution of DMPAP (24 mg, 0.096 mmol) and 11 (24 mg, 0.012 mmol) in DMF (0.5 mL). The reaction mixture was irradiated for 12 h with 365 nm light at room temperature. The mixture was concentrated to dryness and the
residue was purified (SiO$_2$, EtOAc/MeOH = 19:1) to afford 12 as an oil. Yield: 25 mg (68%); $R_f$ = 0.14 (CH$_2$Cl$_2$/MeOH 24:1); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.16 (s, 4H), 4.20 (d, $J$ = 7.7 Hz, 4H), 3.86–3.49 (m, 60H), 3.27–3.18 (m, 20H), 2.97–2.92 (m, 32H), 2.78 (s, 8H), 2.33 (s, 48H), 1.87–1.78 (m, 32H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 195.8, 195.7, 195.6, 195.5, 168.7, 103.5, 84.5, 82.0, 77.8, 77.2, 74.4, 71.8, 71.1, 69.8, 69.6, 68.8, 44.1, 40.0, 38.7, 36.6, 30.6, 30.6, 30.6, 30.4, 30.2, 29.5, 26.0, 25.9. ESI-HRMS Calcd. for C$_{125}$H$_{208}$N$_4$O$_{44}$S$_{20}$ [M+2H]$^{2+}$ 1556.9372, found 1556.9350.

**Dendrimer 13:** NaOMe in MeOH (1M, 0.21 mL) was added to a solution of 12 (16 mg, 5.14 µmol) and chloride 8 (94 mg, 0.205 mmol) in MeOH stirred at rt for 3 h. Upon reaction completion, the solvents were concentrated in vacuo and residue was purified (SiO$_2$, EtOAc:MeOH 9:1) to afford 11, as a gum. Yield: 34 mg (73%); $R_f$ = 0.55 (CH$_2$Cl$_2$/MeOH 9:1); $^1$H NMR (300 MHz, MeOD) $\delta$ 8.02 (s, 20H), 6.01–5.88 (m, 64H), 5.34–5.12 (m, 128H), 4.37–4.03 (m, 152H), 3.92–3.84 (m, 40H), 3.72–3.61 (m, 80H), 3.45–3.34 (m, 100H), 3.22–3.12 (m, 48H), 2.86 (s, 8H), 2.74–2.68 (m, 32H), 1.92–1.83 (m, 32H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 169.3, 135.2, 135.1, 134.8, 134.5, 117.3, 117.0, 116.8, 116.7, 103.6, 84.1, 81.5, 77.2, 74.6, 74.37, 73.8, 73.6, 72.4, 70.9, 69.8, 69.1, 68.9, 42.7, 40.0, 35.7, 30.0, 29.7, 29.5, 29.1. GPC measurements (THF, 40°C): PDI ($M_w/M_n$) 1.064.

**G(2)-Dendrimer 15:** Thioglycerol (0.082 mL, 0.96 mmol) was added into the solution of DMPAP (26.0 mg, 0.102 mmol) and 13 (30.0 mg, 3.20 µmol) in DMF (0.5 mL). The reaction mixture was irradiated for 12 h with 365 nm light at rt. The mixture was concentrated to dryness and the residue was partitioned between ether (10 mL) and water (10 mL). The aqueous phase was concentrated and the residue was dialyzed against 1kDa cut-off membrane followed by lyophilization, afforded 15 as white solid. Yield: 31 mg (59%). $^1$H NMR (600 MHz, D$_2$O) $\delta$ 4.54 (s, 20H), 4.25–4.22 (br s, 40H), 4.01–3.38 (m, 548H), 3.24–3.04 (m, 160H), 2.95–2.65 (m, 160H), 2.14–1.97 (m, 160 H); $^{13}$C NMR (151 MHz, D$_2$O:Acetone) $\delta$ 172.6, 103.3, 84.3, 82.2, 78.4, 74.4, 72.2, 71.6, 70.8, 70.7, 70.4, 70.3, 70.1, 69.7, 68.9, 67.6, 67.6, 66.4, 65.6, 65.1, 64.9, 55.9, 55.0, 49.2, 49.0, 48.8, 42.0, 41.9, 40.4, 35.8, 35.2, 31.0, 30.4, 30.1, 29.4, 29.0, 23.8, 23.1; MALDI-TOF MS did not show molecular ions. We are investigating other matrices for this new family of dendrimers.
Cluster 17: NaOMe in MeOH (1M, 0.13 mL) was added to a solution of 16 (8.0 mg, 0.013 mmol) and chloride 8 (60 mg, 0.13 mmol) in MeOH (3 mL) and stirred at rt for 3 h. Upon reaction completion, the solvents were concentrated in vacuo and residue was purified (SiO₂, CH₂Cl₂: MeOH 1:19) to afford 17, as a gum. Yield: 34 mg (90%); R_f = 0.18 (CH₂Cl₂/Methanol 24:1); ¹H NMR (600 MHz, CDCl₃) δ 7.19 (t, J = 5.5 Hz, 6H), 5.95–5.83 (m, 24H), 5.25–5.13 (m, 48H), 4.33–4.20 (m, 30H), 4.17–4.12 (m, 18H), 4.08–4.01 (m, 12H), 3.98–3.95 (m, 6H), 3.88–3.84 (m, 6H), 3.81–3.77 (m, 6H), 3.67–3.65 (m, 6H), 3.68–3.65 (m, 6H), 3.58–3.54 (m, 12H), 3.47–3.42 (m, 6H), 3.37–3.3 (m, 30H), 3.19 (t, J = 8.3 Hz, 6H); ¹³C NMR (151 MHz, CDCl₃) δ 169.4, 136.1, 135.1, 135.0, 134.7, 134.3, 117.4, 117.0, 116.7, 116.6, 103.6, 84.0, 81.4, 77.2, 74.4, 73.7, 73.5, 72.3, 69.3, 68.8, 40.1, 36.7, 31.6. ESI-HRMS Calcd. for C₁₄₄H₂₁₆N₆O₄₂S₆ [M+2Na]²⁺ 1469.6530, found 1469.6737.

Galactodendrimer 19: Thiogalactoside 18 (245 mg, 0.829 mmol) was added into the solution of DMPAP (8 mg, 0.08 mmol) and 17 (16 mg, 0.006 mmol) in DMF (0.5 mL). The reaction mixture was irradiated for 12 h with 365 nm light at rt. The mixture was concentrated to dryness and the residue was partitioned between ethyl acetate (10 mL) and water (10 mL). The aqueous phase was concentrated and the residue was dialyzed against 2.5k cut-off membrane followed by lyophilization, afforded 19 as white solid. Yield: 29 mg (52 %); ¹H NMR (300 MHz, D₂O) δ 4.42–4.48 (m, 6H), 4.36–4.33 (24H), 3.95–3.10 (m, 324H), 2.96–2.80 (m, 96H), 2.11–1.95 (m, 48H), 1.80–1.36 (192H); ¹³C NMR (151 MHz, D₂O:Acetone) δ 166.5, 130.1, 104.1, 103.5, 84.3, 82.2, 78.4, 75.7, 74.3, 73.6, 72.4, 71.5, 70.9, 70.3, 69.3, 68.8, 61.6, 57.6, 52.7, 51.4, 49.7, 48.3, 40.6, 31.7, 30.4, 29.3, 29.0, 28.4, 25.4, 23.9, 23.1, 22.7, 21.7; MALDI-TOF-MS Calcd. for C₄₃₂H₇₉₂N₆O₁₈₆S₃₀ [M+Na]⁺ 10028.4, found 10027.9.

Surface plasmon resonance studies: The studies were conducted using a Biacore T200 SPR instrument with a CM5 sensor chip. A continuous flow of HEPES buffer (10 mm HEPES and 150 mm NaCl, pH 7.4) was maintained over the sensor surface at a flow rate of 10 μl/min. The CM5 sensor chip was activated with an injection of a solution containing N-ethyl-N’-(3-diethylaminopropyl) carbodiimide (EDC) (0.2 M) and N-hydroxysuccinimide (NHS) (0.05 M) for 7 minutes. PA-IL lectin (100 μg/mL) in NaOAc buffer (pH 4.2) was injected over the activated flow cell at flow rate of 10 μl/min for 10 minutes to achieve a ~1000 RU
immobilization. The immobilization procedure was completed by an injection of ethanolamine hydrochloride (1 M) (70 μL), followed by a flow of the buffer (100 μL/min.), in order to eliminate physically adsorbed compounds. Ethanol amine alone was used in one of the flow-cell as a reference. Glycodendrimer 19 was dissolved in running HEPES buffer and passed over flow cells of the PA-IL and ethanol amine (Association: 5 min and dissociation: 5 min). The sensor chip was regenerated with 2x5 minutes pulse of methyl-β-D-galactoside (100 mM) followed by an injection of running buffer for 5 minutes. Response units from the surface of PA-IL were subtracted from the surface of ethanol amine to eliminate non-specific interactions, as well as, bulk change in RU due to variation in refractive index of the medium. The primary subtracted sensorgrams were analyzed by 1:1 Langmuir model fitting, using the BIAevaluation software.

![Sensorgrams for the interactions of glycodendrimer 19 (0.038 μM to 20 μM) with the surface bound PA-IL lectin (k_{on}: 6.65e3 M^{-1}s^{-1}; k_{off}: 1.53e-3 s^{-1}. K_D: 230 nM).](image)

**Figure 1.** SPR sensorgrams for the interactions of glycodendrimer 19 (0.038 μM to 20 μM) with the surface bound PA-IL lectin (k_{on}: 6.65e3 M^{-1}s^{-1}; k_{off}: 1.53e-3 s^{-1}. K_D: 230 nM).
References:


Figure 2. $^1$H NMR spectrum of compound 3 (CDCl$_3$, 300 MHz).

Figure 3. $^{13}$C NMR spectrum of compound 3 (CDCl$_3$, 75 MHz).
Figure 4. $^1$H NMR spectrum of compound 4a (CDCl$_3$, 300 MHz).

Figure 5. $^{13}$C NMR spectrum of compound 4a (CDCl$_3$, 75 MHz).
Figure 6. $^1$H NMR spectrum of compound 4b (CDCl$_3$, 600 MHz).

Figure 7. $^{13}$C NMR spectrum of compound 4b (CDCl$_3$, 151 MHz).
**Figure 8.** $^1$H NMR spectrum of compound 4c (CD$_3$OD, 600 MHz).

**Figure 9.** $^{13}$C NMR spectrum of compound 4c (CD$_3$OD, 151 MHz).
Figure 10. $^1$H NMR spectrum of compound 5a (CDCl$_3$, 300 MHz).

Figure 11. $^{13}$C NMR spectrum of compound 5a (CDCl$_3$, 75 MHz).
Figure 12. $^1$H NMR spectrum of compound 5b (CD$_3$OD, 300 MHz).

Figure 13. $^{13}$C NMR spectrum of compound 5b (CD$_3$OD, 75 MHz).
Figure 14. $^1$H NMR spectrum of compound S1 (DMSO-$d_6$, 300 MHz).

Figure 15. $^{13}$C NMR spectrum of compound S1 (DMSO-$d_6$, 151 MHz).
Figure 16. HRMS (ESI⁺) spectra of compound S1.
Figure 17. $^1$H NMR spectrum of compound 7 (CDCl$_3$, 300 MHz).

Figure 18. $^{13}$C NMR spectrum of compound 7 (CDCl$_3$, 75 MHz).
Figure 19. $^1$H NMR spectrum of compound 8 (CDCl$_3$, 300 MHz).

Figure 20. gCOSY spectrum of compound 8 (CDCl$_3$).
Figure 21. $^{13}$C NMR spectrum of compound 8 (CDCl$_3$, 75 MHz).
Figure 22. $^1$H NMR spectrum of compound 9 (CDCl$_3$, 300 MHz).

Figure 23. $^{13}$C NMR spectrum of compound 9 (CDCl$_3$, 75 MHz).
Figure 24. $^1$H NMR spectrum of compound 11 (CDCl$_3$, 300 MHz).

Figure 25. $^{13}$C NMR spectrum of compound 11 (CDCl$_3$, 75 MHz).
Figure 26. Comparison $^1$H NMR spectra for the synthesis of 11 from 8 and 10 showing the appearance of core signals with corresponding integrations.
**Figure 27.** HRMS (ESI$^+$) spectra of compound 11.
Figure 28. $^1$H NMR spectrum of compound 14 (D$_2$O, 600 MHz).

Figure 29. gCOSY spectrum of compound 14 (D$_2$O).
Figure 30. $^{13}$C NMR spectrum of compound 14 (MeOD, 151 MHz).

Figure 31. Sequence of $^1$H NMR spectra for the synthesis of 14 from 10 showing the appearance and disappearance of main signals (chains and functional groups) with corresponding integrations.
Figure 32. $^1$H NMR spectrum of compound 12 (CDCl$_3$, 300 MHz).

Figure 33. $^{13}$C NMR spectrum of compound 12 (CDCl$_3$, 75 MHz).
**Figure 34.** HRMS (ESI⁺) spectra of compound 12.
Figure 35. $^1$H NMR spectrum of compound 13 (Top: CD$_3$OD, 300 MHz; Down: CDCl$_3$, 300 MHz).
Figure 36. gCOSY spectrum of compound 13 (CDCl₃).

Figure 37. $^{13}$C NMR spectrum of compound 13 (CDCl₃, 75 MHz).
Figure 38. GPC traces for compound 13.
Figure 39. $^1$H NMR spectrum of compound 15 (D$_2$O, 600 MHz).

Figure 40. gCOSY trace of compound 15 (D$_2$O, 600 MHz).
Figure 41. $^{13}$C NMR spectrum of compound 15 (D$_2$O, 151 MHz, acetone as reference).

Figure 42. Sequence of $^1$H NMR spectra for the synthesis of 15 from 10 showing the appearance and disappearance of main signals (chains and functional groups) with corresponding integrations.
Figure 43. $^1$H NMR spectrum of compound 17 (CDCl$_3$, 600 MHz).

Figure 44. gCOSY spectrum of compound 17 (CDCl$_3$).
**Figure 45.** $^{13}$C NMR spectrum of compound 17 (CDCl$_3$, 151 MHz).

**Figure 46.** Comparison of $^1$H NMR spectra for the synthesis of 17 from 8 and 10 showing the appearance and disappearance of main signals with corresponding integrations.
Figure 47. HRMS (ESI$^+$) spectra of compound 17.
Figure 48. $^1$H NMR spectrum of compound 19 (D$_2$O, 300 MHz).

Figure 49. $^{13}$C NMR spectrum of compound 19 (D$_2$O, 151 MHz).