***SUPPORTING INFORMATION***

# Facile Access to Internally Functionalized Dendrimers through Efficient and Orthogonal Click Reactions

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**General Methods and Materials**

Unless otherwise noted, ACS reagent grade chemicals and solvents were purchased from Aldrich and used without further purification. Analytical thin layer chromatography (TLC) was performed on commercial Merck plates coated with silica gel GF254 (0.24 mm thick). Flash column chromatography was carried out by using silica gel (Merck Kieselgel 60 (230-400 mesh, ASTM)). $^{1}$H NMR (500MHz and 200 MHz) and $^{13}$C NMR (162 MHz and 60MHz) analysis was done on Bruker AC 500 and 200 spectrometers, respectively, with the chemical shift reported in ppm and referenced to signals from residual protons of the solvents. Size Exclusion Chromatography (SEC) was carried out at room temperature on a Waters chromatograph connected to a Waters 410 differential refractometer and Waters Styragel® columns (HR-0.5, HR-2, HR-4, HR-5) using *LiBr-free N,N'*-dimethylformamide (DMF) as eluent (flow rate: 1 mL/min). All Gn($OH_x$)-$Ene_z$ samples were passed through basic $Al_2O_3$ plug before injection into SEC instrument. A Waters 410 differential refractometer and a 996 photodiode array detector were employed. The molecular weights of the polymers were calculated relative to linear polystyrene standards. Infrared spectroscopic experiments were completed on a Perkin-Elmer Spectrum 100 Fourier transform infrared spectrometer (FTIR). Typically, 4 scans at a resolution of 4 $cm^{-1}$ were recorded on each sample by using an attenuated total reflection (ATR) apparatus. Mass spectral data were collected on a Bruker UltraFlex MALDI-TOF MS with SCOUT-MTP Ion Source (Bruker Daltonics, Bremen) equipped with a $N_2$-laser (337nm), a gridless ion source and reflector design. All spectra were acquired using a reflector-positive method with an acceleration voltage of 25kV and a reflector voltage of 26,3kV. The detector mass range was set to 500-10000Da in order to exclude high intensity peaks from the lower mass range. The laser intensity was set to the lowest value possible to acquire high resolution spectra. The obtained spectra were analyzed with FlexAnalysis Bruker Daltonics, Bremen, version 2.2. Matrix

preparation for MALDI-TOF experiment: A solution 0.1M of HABA (or DHB) in THF was prepared and trifluoro acetic acid (TFA) sodium salt (one tip of a knife) was added. Sample preparation: 5 mg of sample were dissolved in THF. 5 ml of this solution was added to 20 ml of the matrix solution. 0.05 ml of the sample-matrix solution was added to the MALDI target plate. Ultra-violet/visible light absorption and fluorescence spectra were recorded in DMF using quartz cuvettes of 1 cm path length on a Cary 50 spectrophotometer and a Cary Eclipse Fluorescence spectrophotometer, respectively. For fluorescence measurements, the samples were not degassed and were excited at $\lambda_{exc}$ = 280 nm, slit widths were set to 5 nm bandpass for excitation and 5 nm bandpass for emission.

**General procedure for 'amine-epoxy' reaction.** The reaction between $Gn(OH_x)$-$Amine_y$ and allyl glycidyl ether (4.0 eq. to each amine moiety) was carried out overnight at room temperature using methanol as a solvent. Methanol and unreacted allyl glycidyl ether were then removed under reduced pressure and the crude product was precipitated into hexanes or diethyl ether and dried (yield 97-98%).

**General procedure for 'thiol-ene' reaction.** The **'**thiol-ene' reaction between $Gn(OH_x)$-$Ene_z$ and cysteamine hydrochloride (3.0 eq to each 'ene' moiety) was carried out using 2,2-dimethoxy-2-phenylacetophenone (0.05 eq. to each 'ene' moiety) as photo-initiator in methanol. The reaction mixture was sparged with dry nitrogen for about 20 mins and then exposed to the hand-held UV-lamp ($\lambda_{exc}$ = 365nm) for 60 minutes. Triethylamine and water were then added to the reaction mixture until the pH of the solution became 10 (to neutralize the hydrochloride salt and obtain free amines). Methanol and excess triethylamine were then removed under reduced pressure. The aqueous layer was extracted with chloroform three times followed by two washes with aq. brine solution. The organic fraction was dried over anhydrous $MgSO_4$, filtered, and concentrated. The concentrated reaction mixture was precipitated twice into diethyl ether. Diethyl

ether was then decanted off, leaving behind viscous dendrimer that was dissolved in a minimum amount of chloroform and transferred to a small container, then dried under high vacuum (yield 85-95%).

**Synthesis of G1(OH$_4$)-Ene$_4$, 3.** Allyl glycidyl ether (16.8 g, 147 mmol, 8.0 equiv) and p-xylylenediamine (2.5 g, 18.36 mmol, 1.0 equiv) were dissolved in 10 mL of methanol and the reaction mixture was stirred overnight at room temperature. Methanol and excess allyl glycidyl ether were removed and 5 mL of tetrahydrofuran (THF) was added. The crude product in THF was then precipitated into 1L of n-hexane resulting in the formation of a suspension. This suspension was allowed to stir for 8 hours after which a viscous liquid appeared at the bottom of the flask. Stirring was then stopped and the solution was allowed to stay still for 3 hours. After this time the n-hexane solution became clear and was decanted carefully, leaving behind the viscous yellow oil. This process was repeated twice and the product, **3**, was obtained as viscous yellow oil in 98% (10.7 g) yield. The product was dried under low pressure and was used in the next step without further purification; $^1$H NMR (500MHz, d$_6$-DMSO): δ 7.25 (s, 4 H, Ar-*H*), 5.86 (m, 4 H, -C*H*=CH$_2$), 5.23 (m, 4 H, -CH=C*H*$_2$), 5.13 (m, 4 H, -CH=C*H*$_2$), 4.57 (dd, *J* = 4, 19.5 Hz, 4 H), 3.91 (m, 8 H), 3.73 (m, 4 H), 3.643 (m, 4 H), 3.36 (m, 4 H), 3.25 (m, 4 H), 2.52 (m, 4 H), 2.42 (m, 4 H); $^{13}$C NMR (500 MHz, d$_6$-DMSO): δ 137.8, 137.6, 135.34, 128.50, 116.13, 72.97, 71.21, 67.79, 67.46, 59.27, 58.06, 57.64; IR (neat): 3420, 2853, 1646, 1511, 1452, 1420, 1349, 1263, 1076, 997, 922, 871, 804, 770 cm$^{-1}$; GPC (LiBr-free DMF): $M_n$ = 4400, $M_w$ = 4500, PDI: 1.01; MALDI Calcd: [M]$^+$ ($C_{32}H_{52}N_2O_8$) m/z = 592.76. Found: MALDI-TOF MS: [M+K]$^+$ *m/z* = 630.07.

**Synthesis of G1($OH_4$)-$Amine_4$, 5.** G1($OH_4$)-$Ene_4$ (2.0 g, 3.37 mmol, 1.0 equiv), cysteamine hydrochloride (4.60 g, 40.5 mmol, 12 equiv), and 2,2-dimethoxy-2-phenylacetophenone (173 mg, 0.675 mmol, 0.2 equiv) were added in a 25 mL round bottomed flask. Methanol (5 mL) was added as a solvent and the mixture was sparged with dried nitrogen for 20 minutes at room temperature and then exposed to the 365 nm UV-lamp for 60 minutes. A triethylamine and water mixture (9:1) was added into the resulting reaction mixture until the pH of the solution became 10. Methanol and excess triethylamine were evaporated and the aqueous, cloudy mixture was extracted with chloroform (x3), followed by two washes with aq. brine solution. The organic fraction was dried over anhydrous $MgSO_4$, filtered, and most of chloroform was evaporated. The concentrated solution was precipitated twice into 500 mL of diethyl ether and the resulting suspension was stirred for 12 hours, after which a viscous precipitate appeared at the side walls of the flask. Diethyl ether was then decanted off and the pale yellow liquid was collected and dissolved in a minimum amount of chloroform, transferred to a small container, and dried under low pressure. (2.7 g, 88%); $^1$H NMR (500MHz, $d_6$-DMSO): δ 7.25 (s, 4 H, Ar-*H*), 3.70 (m, 4 H), 3.64 (m, 4 H), 3.41 (m, 8 H), 3.33 (m, 4 H), 3.23 (m, 4 H), 2.67 (t, *J* = 7 Hz, 8 H), 2.50 (m, 4 H), 2.38 (m, 4 H), 1.71 (m, 8 H); $^{13}$C NMR (500 MHz, $d_6$-DMSO): δ 138.31, 138.16, 129.00, 128.95, 79.65, 73.98, 73.93, 69.50, 68.24, 67.98, 59.76, 58.55, 58.15, 42.06, 35.83, 30.09, 28.18; IR (neat): 3351, 3290, 2916, 2856, 1593, 1454, 1364, 1267, 1109, 1018, 878, 751 $cm^{-1}$; GPC (DMF): $M_n$ = 7500, $M_w$ = 7600, PDI = 1.01

**Synthesis of G2($OH_{12}$)-$Ene_8$, 6.** G1($OH_4$)-$Amine_4$ (2.0 g, 2.22 mmol, 1.0 equiv) and allyl glycidyl ether (4.05 g, 35.5 mmol, 16 equiv) was dissolved in methanol (10 mL) and the reaction mixture was stirred overnight at room temperature. Methanol and unreacted allyl glycidyl ether

were removed. The crude reaction mixture was diluted with 3 mL of tetrahydrofuran (THF) and precipitated twice into 500 mL of diethyl ether. The resulting suspension was stirred for 24 hours, after which a viscous precipitate appeared at the side walls of the flask. Diethyl ether was then decanted off and the pale yellow neat liquid was collected and dried under low pressure. (3.9 g, 97%); $^{1}$H NMR (500 MHz, $d_6$-DMSO): δ 7.24 (s, 4 H, Ar-*H*), 5.87 (m, 8 H, -C*H*=$CH_2$), 5.25 (m, 8 H, -CH=C*H*$_2$), 5.13 (m, 8 H, -CH=C*H*$_2$), 4.52 (d, *J* = 9.8 Hz, 12 H), 3.94 (m, 16 H), 3.70 (m, 4 H), 3.65 (m, 12 H), 3.38 (m, 24 H), 3.33 (m, 4 H), 3.23 (m, 4 H), 2.68 (m, 8 H), 2.54 (m, 16 H), 2.51 (m, 12 H), 2.40 (m, 12 H), 1.70 (m, 8 H); $^{13}$C NMR (500 MHz, $d_6$-DMSO): δ 137.58, 135.34, 128.44, 116.12, 79.12, 73.44, 73.38, 72.68, 71.25, 69.03, 68.02, 67.76, 67.42, 59.22, 58.18, 57.99, 57.86, 57.57, 55.20, 55.17, 29.50, 28.83, 28.78, 27.98, 27.95; IR (neat): 3390, 2857, 1646, 1421, 1265, 1106, 997, 924, 753 cm$^{-1}$; GPC (LiBr-free DMF): $M_n$ = 10400, $M_w$ = 10900, PDI: 1.04; MALDI Calcd: $[M]^+$ ($C_{88}H_{160}N_6O_{24}S_4$) m/z = 1814.5. Found: MALDI-TOF MS: $[M+Na]^+$ *m/z* = 1836.69. $[M+K]^+$ *m/z* = 1852.70.

**Synthesis of G2(OH$_{12}$)-Amine$_8$** G1(OH$_{12}$)-Ene$_8$ (3.36 g, 1.853 mmol, 1.0 equiv), cysteamine hydrochloride (5.05 g, 44.5 mmol, 24 equiv), and 2,2-dimethoxy-2-phenylacetophenone (0.19 g, 0.741 mmol, 0.4 equiv) were added into a 25 mL round bottomed flask. Methanol (5 mL) was added and the solution was sparged with dried nitrogen for 20 minutes then exposed to the 365 nm UV-lamp for 60 minutes. A triethylamine and water mixture was added to the reaction mixture until the pH of the solution became 10 and methanol and excess triethylamine were removed. The reaction mixture was extracted with chloroform (x3), followed by two washes with aq. brine solution. The organic fraction was dried over anhydrous $MgSO_4$, filtered, and concentrated. The concentrated solution was precipitated twice into 500 mL of diethyl ether and

the suspension was stirred for 8 hours, after which a viscous precipitate appeared at the side walls of the flask. Diethyl ether was then decanted off and the pale yellow liquid was collected and dried (3.98 g, 88%).; $^{1}$H NMR (500MHz, $d_6$-DMSO): δ 7.24 (s, 4 H, Ar-*H*), 3.71 (m, 4 H), 3.64 (m, 12 H), 3.45 (m, 24 H), 3.40 (m, 12 H), 3.34 (m, 12 H), 3.29 (m, 16 H), 3.23 (m, 16 H), 3.16 (m, 16 H), 2.67 (m, 24 H), 2.52 (m, 16 H), 2.51 (m, 12 H), 2.39 (m, 12 H), 1.74 (m, 24 H); $^{13}$C NMR (500 MHz, $d_6$-DMSO): δ 128.51, 73.48, 73.18, 69.21, 69.04, 68.62, 67.97, 67.75, 67.43, 64.88, 58.15, 57.86, 55.17, 34.88, 29.57, 29.51, 28.86, 27.98, 27.68; IR (neat): 3346, 3282, 2914, 2859, 1591, 1438, 1268, 1110, 1031, 886, 762 $cm^{-1}$.

**Synthesis of G3($OH_{28}$)-$Ene_{16}$, 7.** G2($OH_{12}$)-$Amine_8$ (3.5 g, 1.44 mmol, 1.0 equiv) and allyl glycidyl ether (5.26 g, 46.1 mmol, 32 equiv) were dissolved in methanol (10 mL) and the reaction mixture was stirred overnight at room temperature. Methanol and unreacted allyl glycidyl ether were removed and 3 mL of tetrahydrofuran (THF) was added into the reaction mixture. The diluted reaction mixture was precipitated into 1 L of diethyl ether twice and the suspension was stirred for 8 hours, after which a viscous precipitate appeared at the side walls of the flask. Diethyl ether was then decanted off and the yellow liquid was collected and dried under low pressure. (5.99 g, 98 %); $^{1}$H NMR (500MHz, $d_6$-DMSO): δ 7.24 (s, 4 H, Ar-*H*), 5.87 (m, 16 H, -C*H*=$CH_2$), 5.25 (m, 16 H, -CH=C*H*$_2$), 5.13 (m, 16 H, -CH=C*H*$_2$), 4.52 (m, 28 H), 3.95 (m, 32 H), 3.71 (m, 4 H), 3.65 (m, 28 H), 3.38 (m, 56 H), 3.23 (m, 24 H), 2.68 (m, 24 H), 2.54 (m, 48 H), 2.51 (m, 28 H), 2.40(m, 28 H), 1.73 (m, 24 H); $^{13}$C NMR (500 MHz, $d_6$-DMSO): δ 135.85, 128.95, 116.61, 79.64, 73.69, 73.47, 73.2 0, 71.76, 69.58, 68.53, 68.48, 68.27, 68.23, 58.69, 58.38, 55.69, 30.02, 29.34, 29.29, 28.48; IR (neat): 3407, 2857, 1646, 1421, 1333, 1267, 1106, 997, 924, 733, 700 $cm^{-1}$; GPC (LiBr-free DMF): $M_n$ = 17900, $M_w$ = 19200, PDI: 1.07; MALDI

Calcd: $[M]^+$ ($C_{200}H_{376}N_{14}O_{56}S_{12}$) m/z = 4257.97. Found: MALDI-TOF MS: $[M+K]^+$ *m/z* = 4301.14.

**Synthesis of G3(Naphthalene$_{28}$)-Ene$_{16}$** Thionyl chloride (0.90 mL, 12.2 mmol) was added to a solution of Naphthalene-1-acetic acid (2.45 g, 13.1 mmol) in *N*-methyl-2-pyrrolidone (NMP, 15 mL) at room temperature under nitrogen. The solution was stirred for 30 min and then dried under reduced pressure for 30 minutes. G3(OH$_{28}$)-Ene$_{16}$ (1.00 g, 0.235 mmol) and 4-Dimethylaminopyridine (DMAP, 130 mg) in NMP (8 mL) were added and stirring was continued for 64 h at 60 $^oC$. The reaction mixture was cooled to room temperature, extracted with DCM and iced aqueous $NaHCO_3$ solution. The organic layer was dried over $Na_2SO_4$ and the solvent was removed by rotary evaporation. The product was isolated by column chromatography (silica gel, hexane/ ethyl acetate) to give G3(Naphtha$_{28}$)-Ene$_{16}$ (1.0 g, 48%). $^1H$ NMR ($CDCl_3$, 500MHz, ppm): δ 8.05 (28 H, s, Ar-*H*), 7.90-7.70 (56 H, m, Ar-*H*), 7.57-7.32 (112 H, m, Ar-*H*), 7.07 (4 H, s, Ar-*H*), 5.79 (16 H, m, -C*H*=$CH_2$), 5.25-5.09 (32 H, m, -CH=C$H_2$), 5.05 (20 H, s, -C$H_2$-), 4.07 (60 H, m, -C$H_2$-), 3.83 (32 H, s, -C$H_2$-), 3.59-3.10 (88 H, m, -C$H_2$-), 2.75-2.29 (120 H, m, -C$H_2$-), 1.65 (32 H, m, -C$H_2$-); IR (neat): 3047, 2859, 1728, 1598, 1511, 1420, 1399, 1247, 1168, 1132, 1047, 1018, 927, 779, 732 $cm^{-1}$. GPC (DMF without LiBr): $M_n$ = 17000, $M_w$ = 18400, PDI: 1.08

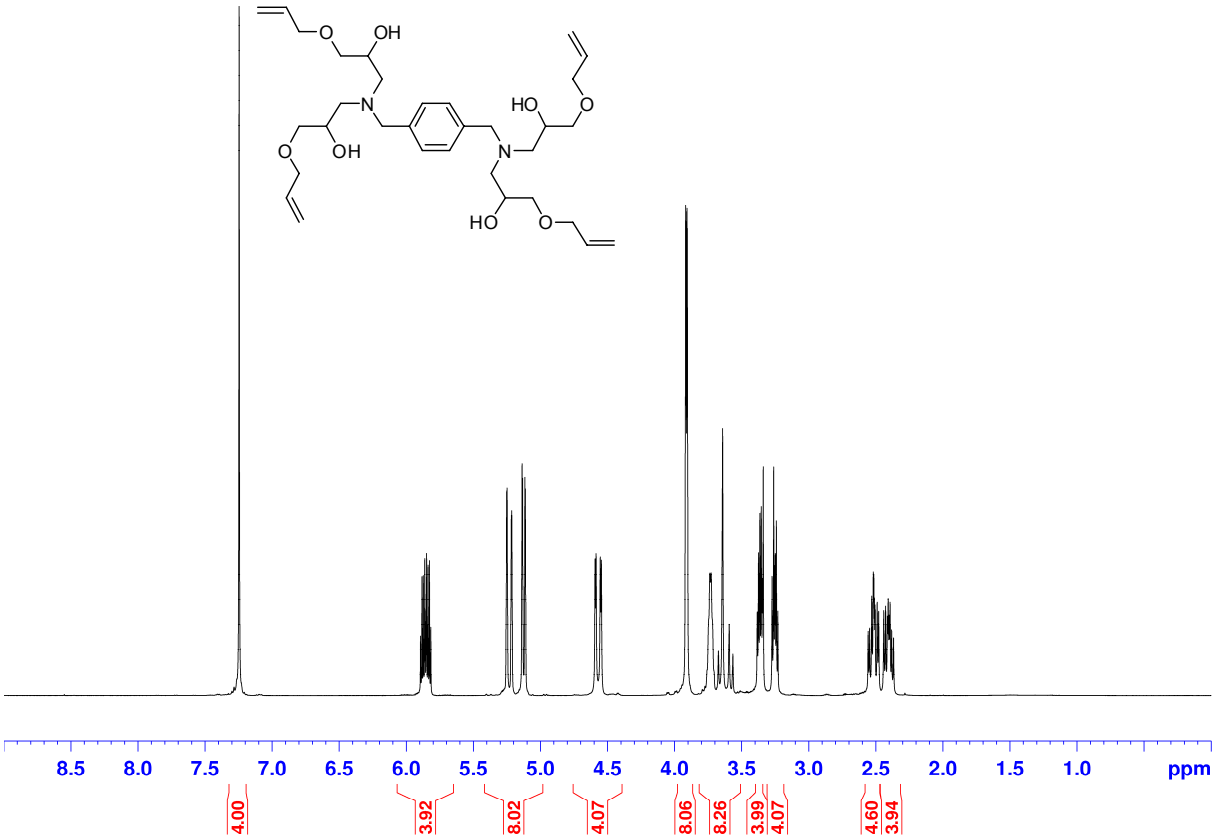
**Synthesis of G3(Naphthalene$_{28}$)-TEG$_{16}$, 9.** G3(Naphthalene$_{28}$)-Ene$_{16}$ (500 mg, 0.056 mmol, 1.0 equiv), 2-(2-(2-methoxyethoxy)ethoxy)ethyl 2-mercaptoacetate (638 mg, 2.68 mmol, 48 equiv), and 2,2-dimethoxy-2-phenylacetophenone (11.4 mg, 0.045 mmol, 0.8 equiv) were added in a 25 mL round bottomed flask. Dichloromethane (5 mL) was added to the reaction mixture and the reaction mixture was sparged with nitrogen for 20 minutes and then exposed to a 365 nm UV-

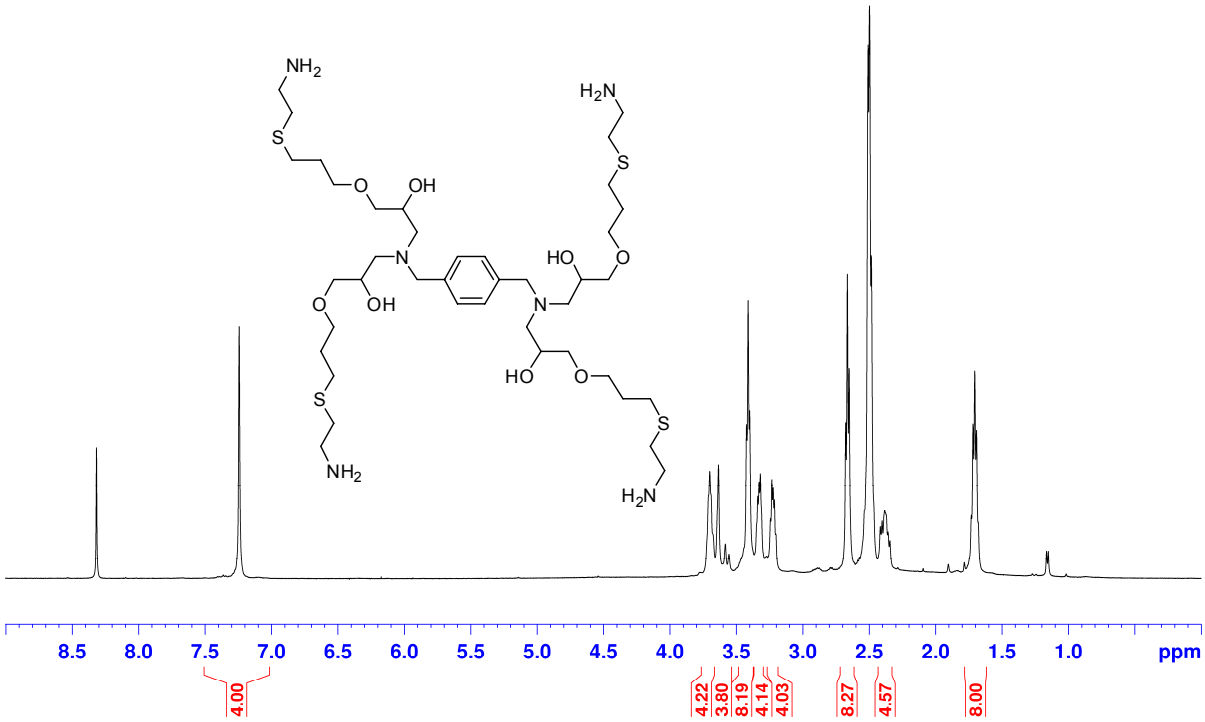
lamp for 60 minutes. Dichloromethane was evaporated and the concentrated solution was precipitated twice into 250 mL of diethyl ether and the suspension was stirred for 8 hours, after which a viscous precipitate appeared at the side walls of the flask. Dichloromethane was then decanted off and the yellow viscous liquid was collected and dried under low pressure. (690 mg, 97%); $^{1}$H NMR (500MHz, $d_6$-DMSO): δ 7.98-7.68 (84 H, m, Ar-*H*), 7.58-7.25 (112 H, m, Ar-*H*), 7.03 (4 H, s, Ar-*H*), 5.05-4.83 (28 H, m, -OC*H*($CH_2$)), 4.22-3.91 (96 H, m, -C$H_2$-), 3.65-3.01 (384 H, m, -C$H_2$-), 2.68-2.20 (104 H, m, -C$H_2$-), 1.75-1.41 (76 H, m, -C$H_2$-); $^{13}$C NMR (500MHz, $CDCl_3$): δ 170.1, 170.4, 133.8, 132.1, 130.6, 128.7, 128.0, 126.3, 125.8, 125.5, 123.9, 71.9, 70.6, 70.2, 70.1, 69.8, 69.5, 68.9, 64.3, 59.0, 54.9, 54.8, 54.7, 54.6, 39.3, 33.4, 29.7, 29.2, 28.9, 28.8; IR (neat): 2869, 1728, 1599, 1511, 1451, 1398, 1353, 1265, 1108, 1040, 960, 852, 781, 734 $cm^{-1}$; UV-vis (DMF) $\lambda_{max}$ = 282 nm; $\Phi_{fluorescence}$ (DMF) = 8.7% (using naphthalene as a reference); GPC (LiBr-free DMF): $M_n$ = 21700, $M_w$ = 25000, PDI: 1.15

**Synthesis of 2-(2-(2-methoxyethoxy)ethoxy)ethyl 2-mercaptoacetate (TEG)** 8.2 g of triethylene glycol monomethyl ether (50 mmol) was mixed with 4.6 g of thioglycolic acid (50 mmol) and 2.15 g of *p*-toluenesulfonic acid (12.5 mmol) in 300 mL of anhydrous toluene. 5 g anhydrous magnesium sulfate was then added and the reaction mixture was refluxed for 12 hours. After which the reaction mixture was washed with water, aq. brine solution, and saturated aq. $NaHCO_3$ and purified by column chromatography using a mixture of ethyl acetate and hexanes (70% yield); $^{1}$H NMR (500MHz, $CDCl_3$): δ = 4.115 (m, 2H), 3.55 (m, 2H), 3.48 (m, 6H), 3.37 (m, 2H), 3.21 (m, 3H), 3.13 (m, 2H), 1.92 (m, 1H, -S*H*). $^{13}$C NMR (500 MHz, $CDCl_3$): δ = 170.63 (*C*=O), 71.75, 70.35, 68.68, 64.47, 58.76, 26.19 ppm. IR (neat): 2876, 2560, 1733, 1453,

1416, 1352, 1279, 1100, 1038, 961, 850, 700 $cm^{-1}$. Calcd: $[M]^+$ ($C_9H_{18}O_5S$) *m/z* = 238.09; found ESI-MS: $[M+Na^+]$ *m/z* = 261.07, $[2M+Na^+]$ *m/z* = 499.16

**$^1$H-NMR of the dendrimers:**

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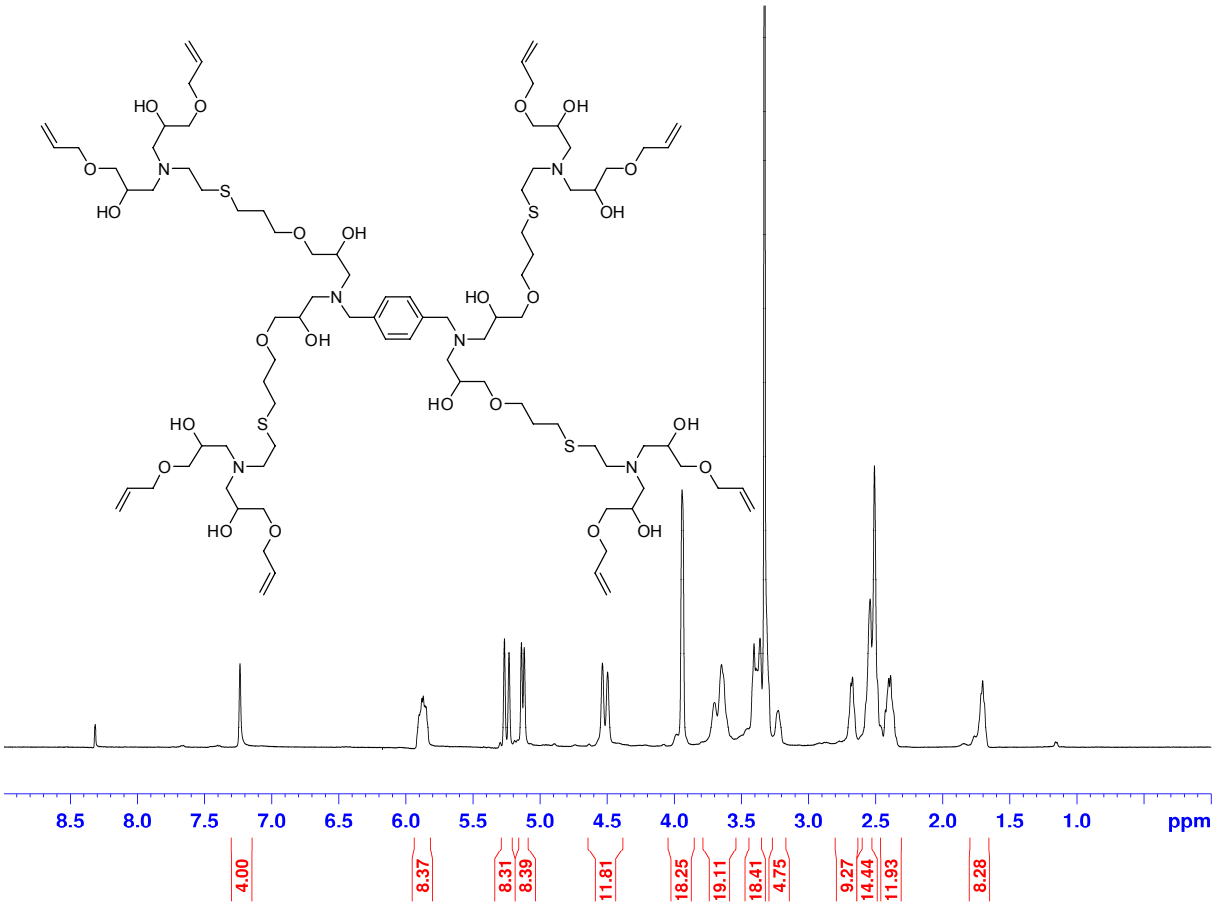
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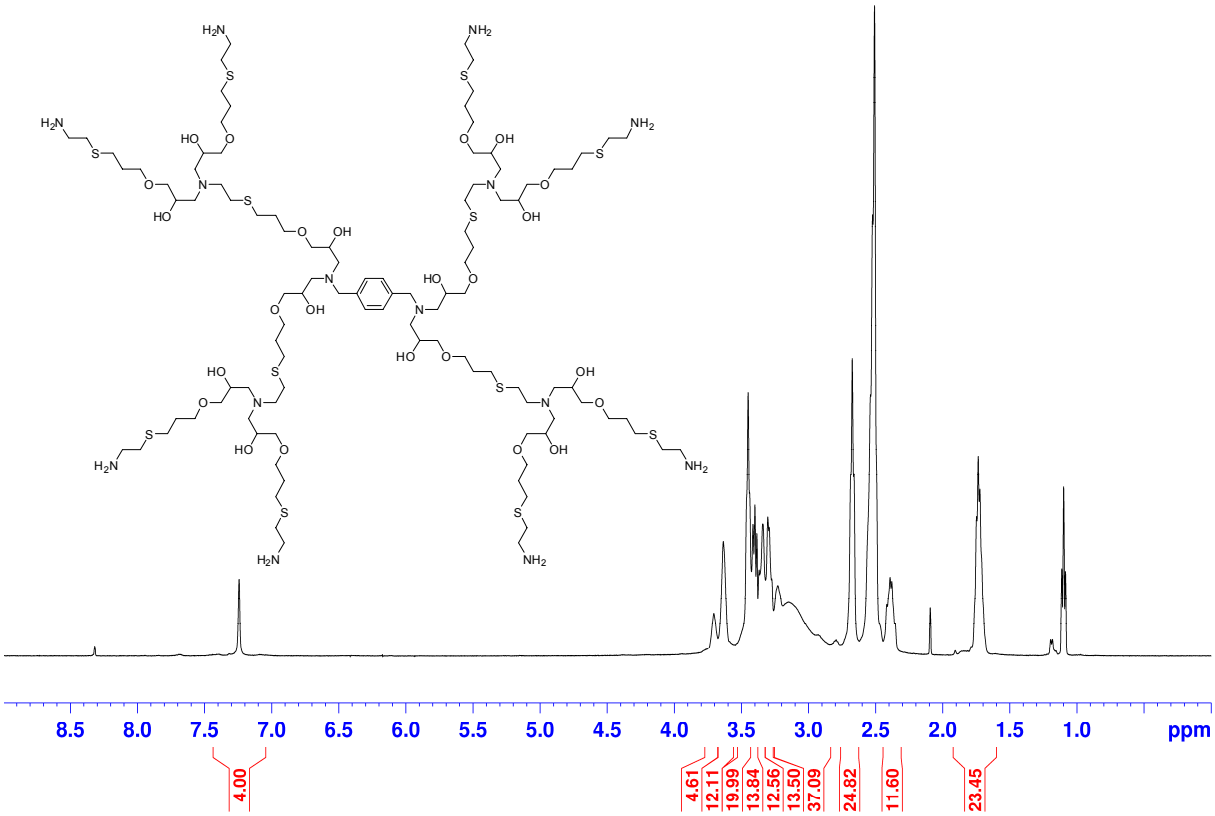
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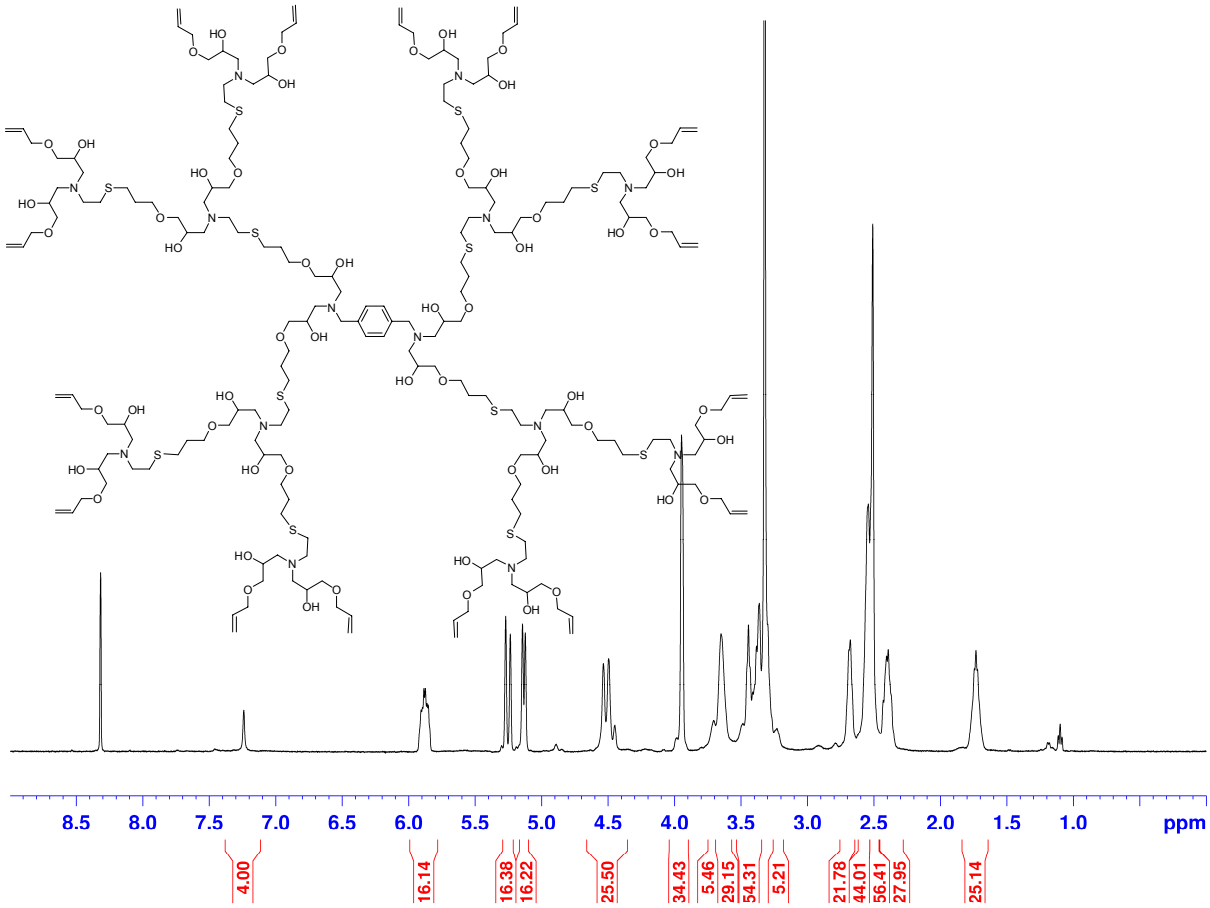
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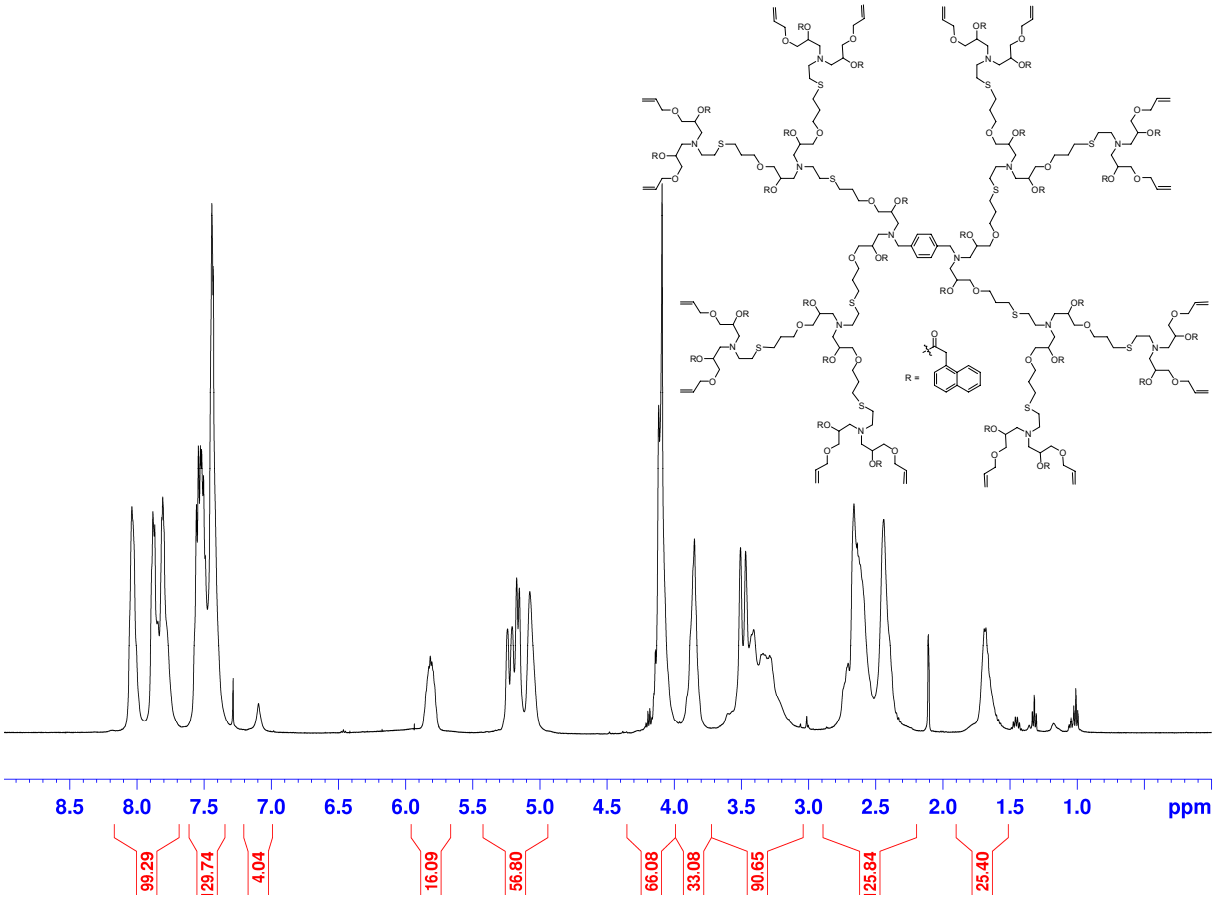
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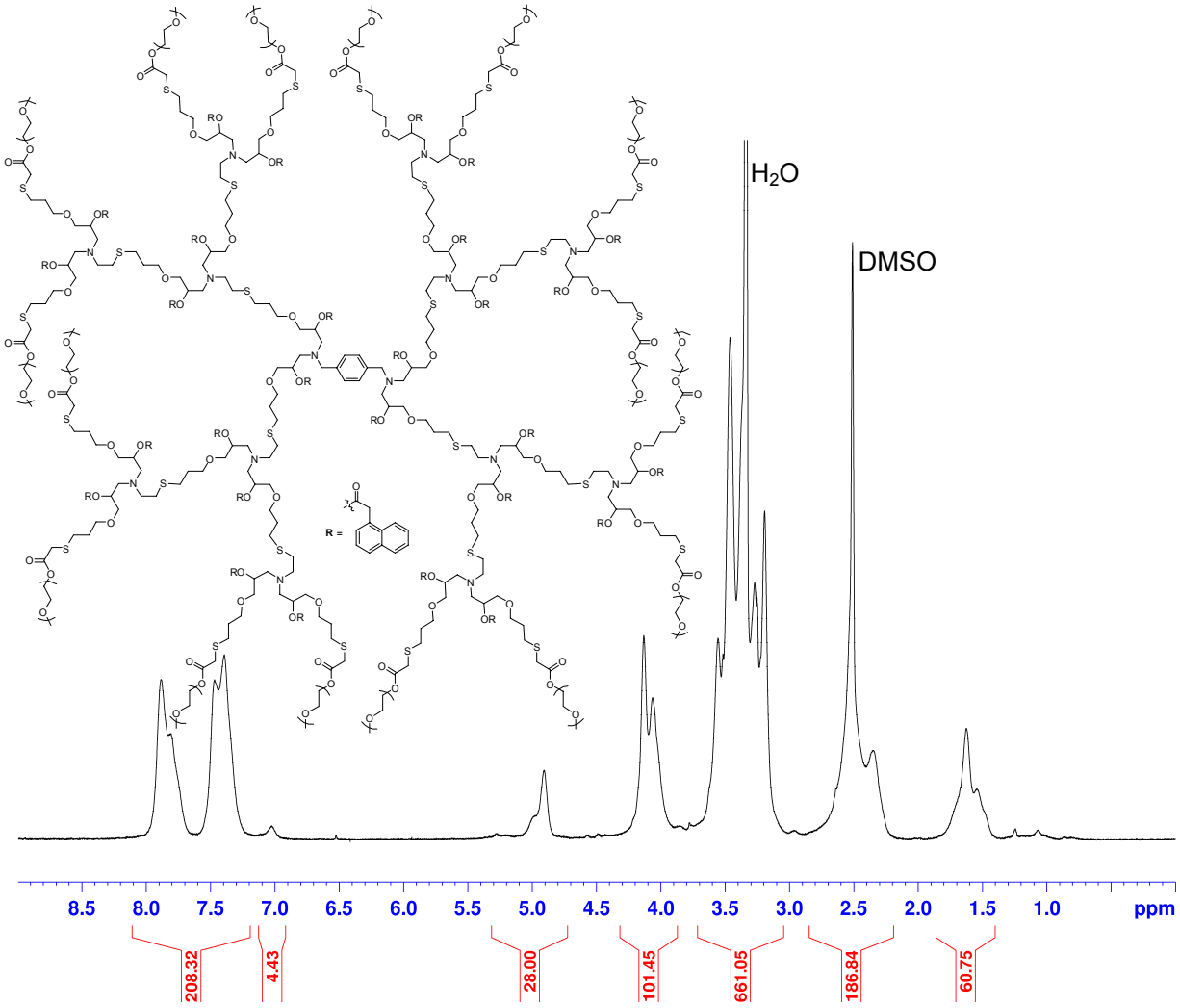
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