

Divergent Synthesis of Hydrophilic Dendrons Based on Tri(ethylene glycol) Spacers

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Materials. Phloroglucinol (1,3,5-trihydroxybenzene), tri(ethylene glycol), palladium (10 wt % on activated carbon), and benzyl bromide were purchased from Sigma-Aldrich Chemical Co. All other chemicals were purchased from commercial sources, and used as received without further purification. Potassium carbonate (K_2CO_3) and potassium iodide (KI) were dried at 100 °C for 24 hours before use. Dichloromethane (DCM) and tetrahydrofuran (THF) were refluxed in the presence of calcium hydride (CaH_2) and sodium, respectively, and followed by distillation. *N,N*-Dimethylformamide (DMF) and acetonitrile were dried at least 2 days by static drying mode with 4 Å molecular sieves.

Characterization. 1H - and ^{13}C -NMR spectra were recorded on Varian 200 and Varian 500 instruments, using chloroform-*d* ($CDCl_3$) as the solvent, and tetramethylsilane (TMS) as the internal reference for chemical shifts. Gel permeation chromatography (GPC) determinations were performed on a waters system equipped with a Waters 510 HPLC pump, a Waters M486 tunable absorbance detector, a Waters M410 differential refractive index detector, and three waters styragel HR columns with a continuous porosity of $10^2 - 10^4$ Å. Monodisperse linear polystyrene standards were used for the preparation of the calibration curve. THF (with 2% v/v *N,N*-dimethylacetamide) was used as the eluent, and the rate was 1.0 mL/min at 35 °C. Matrix-assisted laser desorption ionization-time-of-flight mass spectra (MALDI-TOF MS) were performed on a Perceptive Biosystems Voyager-DE STR Biospectrometry, using 2,5-dihydroxy benzoic acid (DHB) as the matrix. The purity of the products was checked by using thin-layer chromatography (TLC; Merck, silica gel 60).

Synthesis. The synthesis is outlined in Schemes S1 and 1.

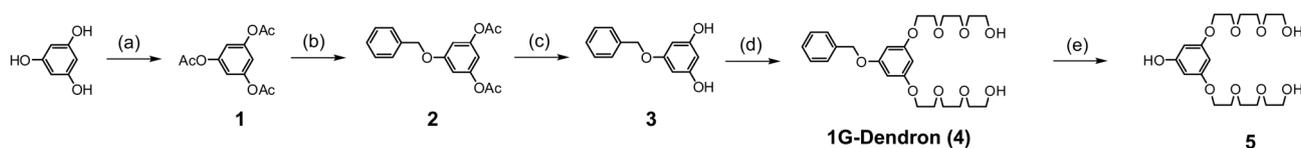
Tri(ethylene glycol) monotosylate. To a solution of tri(ethylene glycol) (70 g, 466.2 mmol), 4-toluenesulfonyl chloride (22.2 g, 116.5 mmol) in anhydrous CH_2Cl_2 (620 mL) under nitrogen was added Et_3N (77.3 mL, 956 mmol) at room temperature. The reaction mixture was stirred at room temperature for 18 hours. The resulting mixture was treated with diluted HCl, and washed with brine. After removing the solvent, the

residue was purified by silica column chromatography (eluent: ethyl acetate) to yield a colorless oil (28.2 g, 80%). 1H -NMR (200 MHz, $CDCl_3$) δ 7.77 (d, $J = 8.4$ Hz, 3H), 7.32 (d, $J = 8.4$ Hz, 2H), 4.14 (m, 2H), 3.67 (m, 4H), 3.56 (m, 6H), 2.42 (s, 3H). ^{13}C -NMR (50 MHz, $CDCl_3$) δ 144.9, 132.9, 129.8, 127.9, 70.7, 69.3, 68.7, 61.7, 21.7. TLC (*n*-hexane:ethyl acetate = 3:7): R_f 0.35.

Phloroglucinol triacetate (1). To a solution of phloroglucinol (30 g, 237.9 mmol), acetic anhydride (97.2 g, 952.1 mmol) in anhydrous THF (360 mL) under nitrogen was added pyridine (77.3 mL, 956 mmol) at room temperature, and the reaction mixture was stirred for 15 hours. After removal of the solvent under reduced pressure, the residue was purified by recrystallization from *n*-hexane to yield a white solid (57.6 g, 97%). 1H -NMR (200 MHz, $CDCl_3$) δ 6.84 (s, 3H), 2.27 (s, 9H). ^{13}C -NMR (50 MHz, $CDCl_3$) δ 168.5, 151.1, 112.8, 21.2. TLC (*n*-hexane: CH_2Cl_2 = 1:4): R_f 0.26.

5-(Benzyloxy)-1,3-phenylene diacetate (2). To a solution of **1** (17.4 g, 69 mmol), sodium hydride with min. 55% (7.2 g, 165.6 mmol) in anhydrous DMF (400 mL) under nitrogen was added benzyl bromide (14.2 g, 82.8 mmol) at room temperature. The mixture was cooled to 0 °C, and H_2O was added dropwise over a period of 3 hours. Then, the reaction mixture was stirred at room temperature for 2 hours, diluted with ethyl acetate (500 mL), washed with brine and water, dried over $MgSO_4$, filtered, concentrated under reduced pressure. The residue was purified by silica column chromatography (*n*-hexane: CH_2Cl_2 = 1:1 to CH_2Cl_2) to yield a white solid (10.5 g, 51%). 1H -NMR (200 MHz, $CDCl_3$) δ 7.40 (m, 5H), 6.63 (d, $J = 1.8$ Hz, 2H), 6.56 (t, $J = 1.8$ Hz, 1H), 5.02 (s, 2H), 2.28 (s, 6H). ^{13}C -NMR (50 MHz, $CDCl_3$) δ 168.9, 159.9, 151.7, 136.2, 128.7, 128.3, 127.7, 108.2, 106.3, 70.6, 21.3. TLC (*n*-hexane: CH_2Cl_2 = 1:4): R_f 0.56.

5-Benzyloxy resorcinol (3). To a solution of **2** (10.5 g, 35 mmol) in methanol (55 mL) was added 5 M KOH aq. solution (70 mL), and the reaction mixture was stirred at 80 °C for 10 hours. The resulting solution was cooled to room temperature, and carefully treated with diluted HCl, and extracted with THF (30 mL)/ CH_2Cl_2 (30 mL). The combined organic layer was washed with brine, and concentrated under reduced pressure.



Scheme S1. Synthetic procedure of **1G-Dendron (4)** and monomeric unit (**5**). Reagents: (a) acetic anhydride, pyridine, THF; (b) NaH, benzyl bromide, DMF, H_2O (dropwise); (c) KOH, MeOH; (d) monotosylated tri(ethylene oxide), K_2CO_3 , KI, CH_3CN ; (e) 10% Pd/C, H_2 , MeOH

The residue was purified by silica column chromatography (CH_2Cl_2 :ethyl acetate = 9:1) to yield a yellowish solid (6.6 g, 87%). $^1\text{H-NMR}$ (200 MHz, CDCl_3) δ 7.34 (m, 5H), 6.07 (d, J = 1.8 Hz, 2H), 5.96 (t, J = 1.8 Hz, 1H), 4.99 (s, 2H), 4.87 (br, 2H). $^{13}\text{C-NMR}$ (50 MHz, CDCl_3) δ 161.0, 157.5, 136.8, 128.7, 128.1, 127.6, 96.1, 95.4, 70.2. TLC (CH_2Cl_2 :AcOEt = 4:1): R_f 0.57.

1G-Dendron (4). To a solution of **3** (4.5 g, 20.8 mmol) and tri(ethylene glycol) monotosylate (22 g, 72.3 mmol) in anhydrous acetonitrile (200 mL) were added K_2CO_3 (8.6 g, 62.2 mmol) and KI (3.45 g, 20.8 mmol), and the reaction mixture was stirred at 95 °C for 23 hours under nitrogen. The resulting solution was cooled to room temperature, and concentrated under reduced pressure. The resulting mixture was dissolved with CH_2Cl_2 , carefully treated with diluted HCl, washed with brine, and concentrated under reduced pressure. The residue was purified by silica column chromatography (ethyl acetate to ethyl acetate: CH_3OH = 47:3) to yield a colorless oil (8.7 g, 87%). $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 7.36 (m, 5H), 6.18 (d, J = 2.5 Hz, 2H), 6.15 (t, J = 2.5 Hz, 1H), 4.99 (s, 2H), 4.07 (m, 4H), 3.82 (m, 4H), 3.71 (m, 8H), 3.68 (m, 4H), 3.60 (m, 4H), 2.69 (br, 2H). $^{13}\text{C-NMR}$ (125 MHz, CDCl_3) δ 160.5, 136.8, 128.5, 127.9, 127.5, 94.6, 72.5, 70.7, 70.3, 70.0, 69.5, 67.3, 61.6. Anal. Calcd for $\text{C}_{25}\text{H}_{36}\text{O}_9$: C, 62.48; H, 7.55, Found: C, 62.41; H, 7.65. TLC (eluent; AcOEt): R_f 0.32.

Compound 5. To a solution of **4** (9.6 g, 20 mmol) in anhydrous CH_3OH (45 mL) was added 10% Pd/C (20% wt, 1.92 g), and the reaction solution was degassed for 5 times with hydrogen. Then, the reaction mixture was stirred at room temperature for 24 hours in the presence of H_2 . Then, Pd catalyst was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by silica column chromatography (ethyl acetate: CH_3OH = 19:1 to 8/1) to yield a colorless oil (6.5 g, 83%). $^1\text{H-NMR}$ (200 MHz, CDCl_3) δ 6.07 (s, 2H), 6.04 (s, 1H), 4.05 (m, 4H), 3.80 (m, 4H), 3.69, (br, 12H), 3.60 (m, 4H), 3.10 (br, 1H), 1.99 (br, 1H). $^{13}\text{C-NMR}$ (50 MHz, CDCl_3) δ 160.5, 158.0, 95.6, 94.3, 72.5, 70.8, 70.4, 69.8, 67.5, 61.8. TLC (ethyl acetate: CH_3OH = 9:1): R_f 0.46.

Compound 6. To a solution of **4** (4.5 g, 9.37 mmol), 4-toluenesulfonyl chloride (9.0 g, 47 mmol) in anhydrous CH_2Cl_2 (60 mL) under nitrogen was added pyridine (3.7 g, 47 mmol) at room temperature, and the reaction mixture was stirred for 3 days. After removal of the solvent under reduced pressure, the resulting mixture was dissolved with CH_2Cl_2 , treated with diluted HCl. Then, the solution was washed with brine, and concentrated under reduced pressure. The residue was purified by silica column chromatography (CH_2Cl_2 :ethyl acetate = 9:1) to yield a brownish oil (5.8 g, 78%). $^1\text{H-NMR}$ (200 MHz, CDCl_3) δ 7.78 (d, J = 8.2 Hz, 4H), 7.32 (m, 5H), 7.31 (d, J = 8.2 Hz, 4H), 6.16 (d, J = 1.6 Hz, 2H), 6.11 (d, J = 1.6 Hz, 1H), 4.99 (s, 2H), 4.15 (m, 4H), 4.05 (m, 4H), 3.78 (m, 4H), 3.69, (m, 12H), 2.42 (s, 6H). $^{13}\text{C-NMR}$ (50 MHz, CDCl_3) δ 160.5, 144.8,

136.8, 133.0, 129.9, 128.6, 128.0, 127.6, 94.6, 94.4, 70.9, 70.1, 69.8, 69.4, 68.8, 67.5, 21.8. TLC (eluent; CH_2Cl_2 :ethyl acetate = 9:1): R_f 0.55.

2G-Dendron (7). To a solution of **6** (2.9 g, 3.67 mmol), **5** (3.2 g, 8.2 mmol) in anhydrous acetonitrile (40 mL) were added K_2CO_3 (1.78 g, 12.8 mmol) and KI (0.61 g, 3.67 mmol), and the reaction mixture was stirred at 95 °C for 30 hours under nitrogen. The resulting solution was cooled to room temperature, and concentrated under reduced pressure. The resulting mixture was dissolved with CH_2Cl_2 , carefully treated with diluted HCl, washed with brine, and concentrated under reduced pressure. The residue was purified by silica column chromatography (ethyl acetate: CH_3OH = 9:1 to 3:2) to yield a yellowish viscous liquid (3.7 g, 82%). $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 7.36 (m, 5H), 6.17 (d, J = 2.0 Hz, 2H), 6.11 (m, 7H), 4.97 (s, 2H), 4.05 (m, 16H), 3.81 (m, 16H), 3.68 (m, 32H), 3.58 (m, 8H), 2.96 (br, 4H). $^{13}\text{C-NMR}$ (125 MHz, CDCl_3) δ 160.4, 136.8, 128.5, 127.9, 127.5, 94.4, 72.5, 70.7, 70.3, 69.9, 69.6, 67.3, 61.6. Anal. Calcd for $\text{C}_{61}\text{H}_{92}\text{O}_{25}$: C, 59.79; H, 7.57, Found: C, 59.73; H, 7.53. TLC (ethyl acetate: CH_3OH = 7:3) R_f 0.43.

Compound 8. To a solution of **7** (3.5 g, 2.86 mmol), 4-toluenesulfonyl chloride (5.5 g, 28.6 mmol) in anhydrous CH_2Cl_2 (50 mL) under nitrogen was added pyridine (2.3 g, 28.6 mmol) at room temperature, and the reaction mixture was stirred for 3 days. The resulting mixture was treated with diluted HCl, washed with brine, and concentrated under reduced pressure. The residue was purified by silica column chromatography (CH_2Cl_2 :ethyl acetate = 9:1) to yield a viscous liquid (3.8 g, 73%). $^1\text{H-NMR}$ (200 MHz, CDCl_3) δ 7.78 (d, J = 8.2 Hz, 8H), 7.32 (m, 5H), 7.31 (d, J = 8.2 Hz, 8H), 6.17 (s, 2H), 6.09 (s, 7H), 4.97 (s, 2H), 4.15 (m, 8H), 4.05 (m, 16H), 3.70, (m, 48H), 2.42 (s, 12H). $^{13}\text{C-NMR}$ (50 MHz, CDCl_3) δ 160.5, 144.8, 136.8, 132.8, 129.8, 129.0, 128.6, 128.2, 127.5, 94.5, 70.8, 70.0, 69.7, 69.3, 68.7, 67.4, 21.7. TLC (CH_2Cl_2 :ethyl acetate = 7:3): R_f 0.51.

3G-Dendron (9). To a solution of **8** (1.43 g, 0.77 mmol), **5** (1.45 g, 3.71 mmol) in anhydrous acetonitrile (24 mL) were added K_2CO_3 (1.03 g, 7.43 mmol) and KI (0.26 g, 1.55 mmol), and the reaction mixture was stirred at 95 °C for 2.5 days under nitrogen. The resulting solution was cooled to room temperature and concentrated under reduced pressure. The resulting mixture was dissolved with CH_2Cl_2 , carefully treated with diluted HCl, washed with brine, and concentrated under reduced pressure. The residue was purified by silica column chromatography (ethyl acetate/ CH_3OH = 4:1 to 1:1) to yield a yellowish viscous liquid (0.57 g, 27%). $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 7.36 (m, 5H), 6.13 (m, 21H), 4.98 (s, 2H), 4.06 (m, 40H), 3.82 (m, 40H), 3.68 (m, 72H), 3.60 (m, 16H), 2.64 (br, 8H). $^{13}\text{C-NMR}$ (125 MHz, CDCl_3) δ 160.4, 136.8, 128.5, 127.9, 127.5, 94.4, 72.5, 70.7, 70.3, 69.9, 69.6, 67.3, 61.6. Anal. Calcd for $\text{C}_{133}\text{H}_{204}\text{O}_{57}$: C, 58.84; H, 7.57, Found: C, 59.01; H, 7.57. TLC (ethyl acetate: CH_3OH = 1:1): R_f 0.47.