Synthesis of Poly(Alkyl Arylether) Dendrimers

Jayaraj Nithyanandhan and Narayanaswamy Jayaraman*  

Department of Organic Chemistry, Indian Institute of Science, Bangalore 560 012, India  

jayaraman@orgchem.iisc.ernet.in  

Manuscript Ref: JO025844a

Supplementary Information

General methods: Chemicals were purchased from commercial sources and were used without further purification. K₂CO₃ (AR grade) was dried at 120°C for 24 h before being used. Solvents were dried and distilled according literature procedures (“Purification of laboratory chemicals”, 3rd Ed., D. D. Perrin, W. L. F. Armarego, Pergamon Press, Oxford, 1988). Analytical TLC was performed on commercial Merck plates coated with silica gel GF₂₅₄ (0.25 mm). Silica gel (100 - 200 mesh) was used for column chromatography. Melting points determined are uncorrected. Gel permeation chromatography (GPC) was carried out on a Phenogel (500 Å) semipreparative column (300 x 7.80 mm) attached to a high-performance liquid chromatography system fitted with a differential refractive index (RI) detector and THF was used as the eluant. Matrix-assisted laser desorption ionization-time-of-flight mass spectra (MALDI-TOF-MS) was performed using either gentisic acid or trans-indole acrylic acid as the matrix. Microanalyses were performed on an automated C, H, N analyzer. ¹H and ¹³C NMR spectral analysis were performed on a 300 MHz and 75 MHz spectrometer, respectively, with residual solvent signal acting as the internal standard. The following abbreviations were used to explain the multiplicities: s, singlet; d, doublet; t, triplet; m, multiplet; band, several overlapping signals; br, broad.
Experimental Section

Tris-5-bromopentyl phloroglucinol (2). To a stirred solution of 1,5- dibromopentane (8.2 g, 35.5 mmol) and K₂CO₃ (4.3 g, 32 mmol) in DMF (20 mL) was added phloroglucinol (1.0 g, 7.9 mmol) in DMF (6 mL) over a period of 20 min. The reaction mixture was stirred for 48 h at room temperature and filtered, and the solvents were removed in vacuo. The resulting residue was dissolved in CH₂Cl₂, washed with water and brine, dried (Na₂SO₄), concentrated, and purified (SiO₂, hexane/EtOAc 9:1) to afford 2 as an oil (2.95 g, 65%). TLC Rf 0.28 (hexane/EtOAc 95:5). ¹H NMR (300 MHz, CDCl₃) δ 1.60 (m, 6 H), 1.78 (m, 6 H), 1.92 (m, 6 H), 3.42 (t, 6 H, J = 6.9 Hz), 3.91 (t, 6 H, J = 6.0 Hz), 6.04 (s, 3 H); ¹³C NMR (75.5 MHz, CDCl₃) δ 24.8, 28.3, 32.3, 33.5, 67.5, 93.8, 160.7; EI MS m/z 572, 574 [M⁺]. Anal. Calcd. for C₂₁H₃₃Br₃O₃: C, 44.02; H, 5.81. Found: C, 43.85; H, 5.84.

Synthesis of 3. A mixture of tris-O-benzyl phloroglucinol (2.0 g, 5.04 mmol), C₆H₁₂ (0.21 g, 2.52 mmol) and Pd-C (10%) in EtOAc / EtOH (3 / 1) (20 mL) was refluxed for 3 h. The reaction mixture was filtered, concentrated and purified (SiO₂, hexane/EtOAc 8:2) to afford 3 as a white solid (1.05 g, 68%).

5-Bromopentyl-3,5-dibenzyl phloroglucinol (4). A mixture of 3 (1.60 g, 5.23 mmol), 1,5 - dibromopentane (3.60 g, 15.7 mmol), K₂CO₃ (2.17 g, 15.7 mmol), and 18-C-6 (cat.) in MeCN (30 mL) was refluxed for 7 h. Solvents were removed in vacuo and the resulting residue was dissolved in CH₂Cl₂, washed with water and brine, dried (Na₂SO₄), concentrated, and purified (SiO₂, hexane/EtOAc 9:1) to afford 4 as white solid (2.29 g, 96%). TLC Rf 0.42 (hexane/EtOAc 95:5). Mp: 44–46 °C. ¹H NMR (300 MHz, CDCl₃) δ 1.60 (m, 2 H), 1.78 (m, 2 H), 1.92 (m, 2 H), 3.42 (t, 2 H, J = 6.6 Hz), 3.91 (t, 2 H, J = 6.3 Hz), 5.0 (s, 4 H), 6.17 (s, 2 H), 6.24 (s, 1 H), 7.40 (m, 10 H); ¹³C NMR (75.5 MHz, CDCl₃) δ 24.8, 28.3, 32.4, 33.5, 67.6, 70.1, 94.6, 127.5,
127.9, 128.5, 136.8, 160.6, 160.8; EI MS m/z 456 and 454 \([M]^+\). Anal. Calcd. for C_{25}H_{27}BrO_3: C, 66.04; H, 5.98. Found: C, 66.31; H, 6.00.

**G1-(OBn)_6 (5).** A mixture of 2 (0.62 g, 1.1 mmol), 3 (1.22 g, 4.0 mmol), K_2CO_3 (0.55 g, 4.0 mmol), 18-C-6 (cat.), and MeCN (20 mL) was refluxed for 15 h and the solvents were then removed in vacuo. The crude residue was dissolved in CH_2Cl_2, washed with water, dried (Na_2SO_4), concentrated, and purified (SiO_2, PhMe/EtOAc 19:1) to afford 5 as a colorless oil (1.28 g, 95%). TLC \(R_f\) 0.66 (hexane/PhMe/EtOAc 9:9:2 ). \(^1\)H NMR (300 MHz, CDCl_3) \(\delta\) 1.59 (m, 6 H), 1.81 (m, 12 H), 3.91 (m, 12 H), 4.98 (s, 12 H), 6.06 (s, 3 H), 6.17 (s, 6 H), 6.23 (s, 3 H), 7.39 (m, 30 H); \(^1^3\)C NMR (75.5 MHz, CDCl_3) \(\delta\) 22.7, 28.9, 67.8, 70.1, 93.8, 94.6, 127.5, 127.9, 128.5, 136.8, 160.6, 160.9; MALDI-TOF MS m/z 1251.3 ([M + H]^+). Anal. Calcd. for C_{81}H_{84}O_{12}: C, 77.86; H, 6.78. Found: C, 77.49; H, 6.83.

**G1-(OH)_6 (6).** A mixture of 5 (1.3 g, 1.0 mmol) and Pd-C (10%, 0.13 g) in EtOAc/MeOH (1:1) (15 mL) was stirred in the presence of H_2 (g) for 7 h. The reaction mixture was filtered and concentrated to afford 6 as white solid (0.61 g, 82%). Mp: 118–120 °C. \(^1\)H NMR (300 MHz, CD_3COCD_3) \(\delta\) 1.61 (m, 6 H), 1.79 (m, 12 H), 3.91 (m, 12 H), 5.94 (s, 9 H), 6.09 (s, 3 H), 8.16 (s, 6 H). \(^1^3\)C NMR (75.5 MHz, CD_3COCD_3) \(\delta\) 23.5, 29.1, 68.2, 68.5, 94.5, 96.3, 160.1, 162.1; MALDI-TOF MS m/z 710.1 ([M + H]^+).

**G2-(OBn)_{12} (7).** A mixture of 6 (0.24 g, 0.33 mmol), 4 (1.20 g, 2.6 mmol), K_2CO_3 (0.37 g, 2.6 mmol), 18-C-6 (cat.), and MeCN (20 mL) was refluxed for 24 h. Solvents were then removed in vacuo and the resulting residue was dissolved in CH_2Cl_2, washed with water, dried (Na_2SO_4), concentrated, and purified (SiO_2, PhMe/EtOAc 8:2) to afford 7 as colorless oil (0.83 g, 85%). TLC \(R_f\) 0.56 (hexane/PhMe/EtOAc 9:9:2). \(^1\)H NMR (300 MHz, CDCl_3) \(\delta\) 1.60 (br, 18 H), 1.80 (br, 36 H), 3.80 (br, 36 H), 4.97 (br, 24 H), 6.05 (br, 12 H), 6.16 (br, 12 H), 6.22 (br, 6 H), 7.38
(br, 60 H); $^{13}$C NMR (75.5 MHz, CDCl$_3$) δ 22.7, 28.9, 67.7, 70.1, 93.8, 94.5, 127.5, 127.9, 128.5, 136.8, 160.6, 160.9; MALDI-TOF m/z 2993.2 ([M + K]$^+$). Anal. Calcd for C$_{189}$H$_{206}$O$_{30}$: C, 76.80; H, 6.96. Found: C, 77.15; H, 7.08.

G2–(OH)$_{12}$ (8). A mixture of 7 (0.40 g, 0.136 mmol), Pd-C (10%, 50 mg), and cyclohexene (1 mL) in THF (20 mL) was refluxed under Ar atmosphere for 24 h. The reaction mixture was then filtered and concentrated to afford 8 as foamy solid (0.20 g, 83%). $^1$H NMR (300 MHz, CD$_3$COCD$_3$) δ 1.63 (br, 18 H), 1.79 (br, 36 H), 3.96 (br, 36 H), 5.94 (br, 18 H), 6.09 (br, 12 H), 8.12 (br, 12 H); $^{13}$C NMR (75.5 MHz, CD$_3$COCD$_3$) δ 23.5, 29.1, 68.2, 68.4, 94.6, 160.1, 162.0. MALDI-TOF m/z 1873.5 ([M + H]$^+$), 1895.5 ([M + Na]$^+$).

G3–(OBn)$_{24}$ (9). A mixture of 8 (0.25 g, 0.133 mmol), 4 (0.95 g, 2.1 mmol), K$_2$CO$_3$ (0.29 g, 2.1 mmol), 18-C-6 (cat.) in MeCN (20 mL) and DMF (2 mL) was refluxed for 30 h. Solvents were then removed in vacuo and the resulting residue was dissolved in CH$_2$Cl$_2$, washed with water, dried (Na$_2$SO$_4$), concentrated, and purified (SiO$_2$, PhMe/EtOAc 8:2) to afford 9 as colorless oil (0.7 g, 82%). TLC $R_f$ 0.47 (hexane/PhMe/EtOAc 9:9:2). $^1$H NMR (300 MHz, CDCl$_3$) δ 1.57 (br, 42 H), 1.79 (br, 84 H), 3.89 (br, 84 H), 4.97(br, 48 H), 6.04 (br, 30 H), 6.16 (br, 24 H), 6.21 (br, 12 H), 7.35 (br, 120 H); $^{13}$C NMR (75.5 MHz, CDCl$_3$) δ 22.7, 28.9, 67.7, 70.0, 93.8, 94.1, 94.5, 127.5, 127.9, 128.5, 136.8, 160.6, 160.8. Anal. Calcd for C$_{403}$H$_{444}$O$_{66}$: C, 76.39; H, 7.03. Found: C, 77.11; H, 7.31.

G3–(OH)$_{24}$ (10). A mixture of 9 (0.14 g, 0.022 mmol), Pd-C (10%, 10 mg), and cyclohexene (1 mL) in THF (20 mL) was refluxed under Ar atmosphere for 24 h. The reaction mixture was then filtered and concentrated to afford 10 as foamy solid (0.080 g, 88%). $^1$H NMR (300 MHz, CD$_3$COCD$_3$) δ 1.60 (br, 42 H), 1.78 (br, 84 H), 3.95 (br, 84 H), 5.95 (br, 36 H), 6.08 (br, 30 H), 8.11 (br, 24 H); $^{13}$C NMR (75.5 MHz, CD$_3$COCD$_3$) δ 23.5, 29.1, 68.5, 94.5, 160.0, 162.0.
G4–(OBn)_{48} (11). A mixture of 10 (0.07 g, 0.016 mmol), 4 (0.26 g, 0.56 mmol), K₂CO₃ (0.079 g, 0.56 mmol), 18-C-6 (cat.), MeCN (20 mL), and DMF (2 mL) was refluxed for 36 h. Solvents were then removed in vacuo and the resulting residue was dissolved in CH₂Cl₂, washed with water, dried over (Na₂SO₄), concentrated, and purified (SiO₂, PhMe/CH₂Cl₂ 8:2) to afford 11 as colorless oil (0.16 mg, 69%). TLC Rₜ 0.48 (hexane/PhMe/EtOAc 9:9:2). ¹H NMR (300 MHz, CDCl₃) δ 1.57 (br, 90 H), 1.78 (br, 180 H), 3.89 (br, 180 H), 4.96 (br, 96 H), 6.04 (br, 66 H), 6.16 (br, 48 H), 6.22 (br, 24 H), 7.39 (br, 240 H); ¹³C NMR (75.5 MHz, CDCl₃) δ 22.7, 29.0, 67.7, 70.0, 93.8, 94.5, 127.5, 127.9, 128.5, 136.9, 160.6, 160.8. Anal. Calcd. for C₈₃₇H₉₂₄O₁₃₈: C, 76.20; H, 7.06. Found: C, 75.03; H, 7.11.
$^1$H NMR spectrum of dendrimer 9 (G3-(OBn)$_{24}$) in DMSO-$d_6$ at 368 K:

GPC profiles of the G-1 (5), G-2 (7), G-3 (9) and G-4 (11) dendrimers in THF: