An Efficient Synthesis of Poly(aryl ether) Monodendrons and Dendrimers Based on 3,5-Bis(Hydroxymethyl)phenol

Tammy L. Tyler and James E. Hanson*

Department of Chemistry, Seton Hall University, South Orange, New Jersey 07079-2694

Received January 12, 1999. Revised Manuscript Received October 4, 1999

A convergent method for synthesis of poly(aryl ether) dendrimers based on 3,5-bis(hydroxymethyl)phenol has been developed. An activated and protected A_2B monomer (3,5-bis(bromomethyl)phenyl hexadecanesulfonate **1**) was prepared in five steps from dimethyl 5-hydroxyisophthalate, and then used in a repetitive two-step sequence for synthesis of monodendrons. In the first step of the sequence, 2 equiv of a phenol-terminated monodendron (G*n*-OH) react under mildly basic conditions (K_2CO_3) with protected monomer **1** to give an alkanesulfonate-terminated monodendron (G(*n*+1)-hds), one generation larger than the phenolic starting material. In the second step, the alkanesulfonate-protected monodendron is deprotected in strong base (NaOH) to give a new phenol-terminated monodendron (G(*n*+1)-OH), which is then ready for further coupling to protected monomer **1**. Iteration of the coupling and deprotection reactions results in the formation of increasingly large monodendrons. The hexadecanesulfonate group serves a dual purpose: as a protecting group for the phenol during coupling and to increase the difference in polarity between protected and deprotected materials. Monodendrons up to six generations (MW > 13 000) have been synthesized and characterized by techniques including NMR, IR, and SEC/LS. A trifunctional core was generated by reaction of 1,3,5-trihydroxybenzene with 1,8-dibromooctane. This electrophilic core was then coupled with the nucleophilic phenol focused monodendrons up to the fourth generation to give dendrimers, which were then characterized by SEC/LS. Polydispersities were found to be less than 1.02 for all materials, both monodendrons and dendrimers. This synthetic method allows rapid and efficient synthesis of poly(aryl ether) monodendrons and dendrimers. The monodendrons have a nucleophilic phenol focal group, which is useful for further chemistry. The deprotected poly(aryl ether) monodendrons approximate constitutional isomers of those synthesized by Frechet, allowing the first direct comparison of such isomeric dendrimers.

The development of efficient synthetic methods for dendrimers and other highly branched polymers have enhanced the recent interest in these materials.[1−7] Synthetic techniques currently exist for dendrimers based on many different functional groups, including polyamides,[8] polyamines,[9] polyesters,[10,11] polyethers,[12−14] and pure hydrocarbon polymers.[15,16] These syntheses generally follow either a divergent[17] or convergent[12,15] method, although there have been some other approaches.[18−21] Although many methods are established for dendrimer synthesis, further developments and improvements remain significant.[22−29]

(1) Tomalia, D. A.; Naylor, A. M.; Goddard, W. A., III. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 138.
(2) Kim, Y. H. *Adv. Mater.* **1992**, *4*, 764.
(3) Tomalia, D. A.; Durst, H. D. *Topics Curr. Chem.* **1993**, *165*, 193.
(4) *Advances in Dendritic Macromolecules*; Newkome, G., Ed.; JAI Press: Greenwich, CT, 1994.
(5) Frechet, J. M. J. *Science* **1994**, *263*, 1710.
(6) Voit, B. I. *Acta Polym.* **1995**, *46*, 87.
(7) Hawker, C. J.; Devonport, W. *Step-Growth Polymers for High Performance Materials*; Hedrick, J. L., Labadie, J. W., Eds.; ACS Symposium Series 624; American Chemical Society: Washington, DC, 1996; p 186.
(8) Tomalia, D. A.; Baker, H.; Dewald, J.; Hall, M.; Kallos, G.; Martin, S.; Roeck, J.; Ryder, J.; Smith, P. *Macromolecules* **1986**, *19*, 2466.
(9) de Brabander-van den Berg, E. M. M.; Meijer, E. W. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1308.
(10) Hawker, C. J.; Lee, R.; Frechet, J. M. J. *J. Am. Chem. Soc.* **1991**, *113*, 4583.
(11) Hawker, C. J.; Frechet, J. M. J. *J. Am. Chem. Soc.* **1992**, *114*, 8405.
(12) Hawker, C. J.; Frechet, J. M. J. *J. Chem. Soc., Chem. Commun.* **1990**, 1010.
(13) Hawker, C. J.; Frechet, J. M. J. *J. Am. Chem. Soc.* **1990**, *112*, 7638.
(14) Wooley, K. L.; Hawker, C. J.; Frechet, J. M. J. *J. Am. Chem. Soc.* **1993**, *115*, 11496.
(15) Miller, T. M.; Neenan, T. X. *Chem. Mater.* **1990**, *2*, 346.
(16) Xu, Z. F.; Kahr, M.; Walker, K. L.; Wilkins, C. L.; Moore, J. S. *J. Am. Chem. Soc.* **1994**, *116*, 4537.
(17) Newkome, G. R.; Yao, Z.; Baker, G. R.; Gupta, V. K. *J. Org. Chem.* **1985**, *50*, 2003.
(18) Uhrich, K. E.; Hawker, C. J.; Frechet, J. M. J.; Turner, S. R. *Macromolecules* **1992**, *25*, 4583.
(19) Miller, T. M.; Neenan, T. X.; Kwock, E. W.; Stein, S. M. *J. Am. Chem. Soc.* **1993**, *115*, 356.
(20) Xu, Z.; Kahr, M.; Walker, K. L.; Wilkins, C. L.; Moore, J. S. *J. Am. Chem. Soc.* **1994**, *116*, 4537.
(21) Kawaguchi, T.; Walker, K. L.; Wilkins, C. L.; Moore, J. S. *J. Am. Chem. Soc.* **1995**, *117*, 2159.
(22) Stewart, G. M.; Fox, M. A. *Chem. Mater.* **1998**, *10*, 860.
(23) McElhanon, J. R.; Wu, M.-J.; Escobar, M.; McGrath, D. V. *Macromolecules* **1996**, *29*, 8979.
(24) Hawker, C. J.; Mecerreyes, D.; Elce, E.; Dao, J.; Hedrick, J. L.; Barakat, I.; Dubois, P.; Jerome, R.; Wolksen, W. *Macromol. Chem. Phys.* **1997**, *198*, 155.
(25) Lach, C.; Muller, P.; Frey, H.; Mulhaupt, R. *Macromol. Rapid Comm.* **1997**, *18*, 253.
(26) Krska, S. W.; Seyferth, D. *J. Am. Chem. Soc.* **1998**, *120*, 3604.
(27) Morgenroth, F.; Mullen, K. *Tetrahedron* **1997**, *53*, 15349.

10.1021/cm990023g CCC: $18.00 © 1999 American Chemical Society
Published on Web 11/24/1999

Convergent syntheses of dendrimers offer certain advantages in reducing or eliminating defects and providing greater control of the molecular architecture. Convergent dendrimer syntheses require an activated and protected A_2B monomer: activated at the A sites and protected at the B site. A two-step sequence is typically used: first, *coupling* of this A_2B monomer with two dendritic branches or monodendrons with activated B sites to form a new, larger monodendron; and second, *deprotection* (or *activation*) of the B site on this resulting larger monodendron, preparing it for use in the next coupling step. A number of syntheses following this general pattern have been published, each giving a different molecular architecture.[4] We report the development of a synthetic method for a new type of poly(aryl ether) dendrimer based on 3,5-bis(hydroxymethyl)phenol. This method uses very simple chemistry for the coupling and deprotection steps, and allows for the relatively rapid synthesis of large monodendrons. An unusual protecting group strategy has been employed, where the protecting group also serves to dramatically alter the polarity of the compound and therefore improve the purification. These newly synthesized dendrimers are effectively constitutional isomers of dendrimers from a popular published synthesis.[12] The two isomeric types of poly(aryl ether) dendrimers differ in the chemical nature of their focal groups (the B sites): one is nucleophilic and the other is electrophilic, providing complementary chemistry. With both types of poly(aryl ether) dendrimers available, we have also begun the first direct comparison of such isomeric dendrimers.[30]

Experimental Section

All reagents and solvents were purchased from commercial vendors and used as received, except for tetrahydrofuran (THF) when used as a reaction solvent, which was distilled from sodium and benzophenone. Merck Kieselgel 60 F254 silica gel plates with a thickness of 0.25 mm were used for analytical thin-layer chromatography (TLC). All flash chromatography was performed using 200−400 mesh, 60 Å silica gel from Aldrich Chemical. Melting points were observed on a Meltemp apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectra were acquired on a General Electric QE−300 FT-NMR and are reported in δ units relative to tetramethylsilane, along with the peak splitting (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet) and integration. Infrared (IR) spectra were acquired on a MIDAC PRS FT-IR at 4 cm^{-1} resolution on NaCl disks. Chemical analyses were performed by Schwartzkopf Microanalytical Laboratories, Inc. in Woodside, NY.

Size-Exclusion Chromatography. Size-exclusion chromatography (SEC) was performed on a system incorporating a Waters 510 pump with a Waters in-line solvent degasser, a Rheodyne injector, a Waters 410 refractive index detector, and a Precision Detectors PD2000 multiangle light-scattering detector. The SEC column was a Jordi-Gel 500 Å mixed-bed column with a length of 500 mm and an inner diameter of 10 mm. HPLC-grade THF was used as the solvent, with a flow rate of 1.5 mL/min. All SEC data was analyzed using Precision Acquire software from Precision Detectors. Narrow molecular weight polystyrene standards from the Toyo Soda Company were used for calibration. All injections were made using a 50-μL injector loop, with sample concentrations from 1.00 to 15.00 mg/mL. Values for $\delta n/\delta c$ were calculated from literature values on a weight percentage basis. The $\delta n/\delta c$ value for poly(aryl ether) dendritic structures in THF is 0.206,[13,14] while the $\delta n/\delta c$ value for long alkane chains in THF was calculated to be 0.0272 on the basis of studies of fatty acids.[31]

Dimethyl 5-[(Hexadecanesulfonyl)oxy]isophthalate (3). A solution of 6.2 g (29 mmol) dimethyl 5-hydroxyisophthalate (**2**) in 100 mL of dry toluene was treated with 8.2 mL of triethylamine (5.9 g, 58 mmol, 2 equiv) and stirred under argon for 30 min. A total of 10.0 g (30 mmol, 1.05 equiv) of hexadecanesulfonyl chloride was added, and the solution stirred at room temperature for 48 h. An equal volume of dilute HCl was then added, and the resulting mixture was extracted with diethyl ether (3 × 50 mL). The ether layers were combined and washed with saturated NaCl, then dried over $MgSO_4$. The solution was filtered, and removal of the solvent in vacuo gave 7.4 g (14.8 mmol, 99%) of **3** as white crystals: mp 72−74 °C. The product was used without further purification. IR: 2958, 2923, 2852, 1732, 1600, 1463, 1435, 1362, 1326, 1243, 1160, 1105, 997, 929, 917, 813, 762, 681, cm^{-1}. NMR: (dioxane-d_8) δ 8.55 (s, 1H), 8.10 (s, 2H), 3.97 (s, 6H), 3.40 (m, 2H), 1.91 (m, 2H), 1.26 (m, 26H), 0.90 (t, 3H).

3,5-Bis(hydroxymethyl)phenyl Hexadecanesulfonate (4). A solution of 7.5 g (15 mmol) of **3** in 100 mL of dry THF was stirred under argon. Potassium borohydride (4.05 g, 75 mmol, 5 equiv) and lithium chloride (3.18 g, 75 mmol, 5 equiv) were added slowly, and the solution was stirred and gently refluxed for 24 h. The reaction was then quenched with water, and the resulting mixture was extracted with diethyl ether (3 × 50 mL). The combined ether layers were washed with saturated NaCl and dried over $MgSO_4$. The solution was filtered, and the solvent removed in vacuo. Recrystallization from dichloromethane gave 6.0 g of **4** as white crystals (14 mmol, 93% yield). IR: 2952, 2919, 2849, 1594, 1470, 1448, 1362, 1351, 1278, 1214, 1175, 1166, 1150, 1126, 1052, 1041, 1022, 970 cm^{-1}. NMR: (acetone-d_6) δ 7.30 (s, 1H), 7.20 (s, 2H), 4.65 (s, 4H), 3.40 (t, 2H), 1.95 (m, 2H), 1.50 (m, 2H), 1.40 (m, 24H), 0.88 (t, 3H). Analysis: Calculated for $C_{24}H_{42}O_5S$ C, 65.12; H, 9.56; S, 7.24. Found C, 65.84; H, 9.59; S, 7.26.

3,5-Bis(chloromethyl)phenyl Hexadecanesulfonate (5). Diol **4** (6.0 g, 14 mmol) was dissolved in sufficient thionyl chloride to allow stirring in a 100-mL round-bottom flask. The flask was fitted with a drying tube containing $CaSO_4$ and stirred with gentle heating for 36 h. The excess thionyl chloride was then quenched by slow addition of a concentrated solution of $NaHCO_3$. The resulting aqueous solution was extracted with diethyl ether (3 × 50 mL). The combined ether portions were washed with saturated NaCl and dried over $MgSO_4$. Concentration of the filtered solution in vacuo gave 6.2 g (13 mmol, 96%) of **5** as white crystals: mp 70−72 °C. The product was used with no further purification. IR: 2922, 2851, 1725, 1651, 1644, 1471, 1338, 1164, 1127, 984, 824, 757, 717, cm^{-1}. NMR: (acetone-d_6) δ 7.30 (s, 1H), 7.20 (s, 2H), 4.80 (s, 4H), 3.40 (t, 2H), 1.95 (m, 2H), 1.50 (m, 2H), 1.40 (m, 24H), 0.88 (t, 3H).

3,5-Bis(bromomethyl)phenyl Hexadecanesulfonate (1). Dichloride **5** (6.2 g, 13 mmol) was dissolved in a solution of 26 mL of dibromomethane (2 mL per mmol) and 13 mL of *N*,*N*-dimethylformamide (1 mL per mmol). Sodium bromide (2.7 g, 39 mmol, 3 equiv) was added, and the mixture was heated to 100 °C with stirring. After 12 h, the mixture was allowed to cool and then poured into 50 mL of diethyl ether. An equal volume of 15% aqueous NaCl was then added, and the organic layer was allowed to separate. The aqueous layer was extracted twice more with 50 mL of diethyl ether, and the ether portions were combined, washed three times with 15% aqueous NaCl, and dried over $MgSO_4$. After filtration, the solvent was

(28) Zeng, F.; Zimmerman, S. C. *J. Am. Chem. Soc.* **1996**, *118*, 5326.
(29) Jayaraman, M.; Frechet, J. M. J. *J. Am. Chem. Soc.* **1998**, *120*, 12996.
(30) To our knowledge there have been no direct comparisons of such isomeric dendrimers. Dendrimers have been compared to linear analogues (Hawker, C. J.; Malmstrom, E. E.; Frank, C. W.; Kampf, J. P. *J. Am. Chem. Soc.* **1997**, *119*, 9903), and there have been comparisons of different dendrimer architectures (Zimmerman, S. C.; Wang, Y.; Bharathi, P.; Moore, J. S. *J. Am. Chem. Soc.* **1998**, *120*, 2172).
(31) *CRC Handbook of Chemistry and Physics*, 63rd ed.; Weast, R. C., Astle, M. J., Eds.; CRC Press: Boca Raton, FL, 1982.

removed in vacuo to provide the crude product. This product was generally found to contain ~67% bromide and 33% chloride, and was subjected to the reaction conditions again to effect more complete bromination. Following this second bromination, the product was more than 95% brominated. This product was recrystallized twice, first from acetonitrile and then from hexanes to give 6.1 g (11 mmol, 82%) of **1** as white crystals: mp 65−67 °C. IR: 2953, 2921, 2850, 1645, 1614, 1590, 1471, 1449, 1337, 1327, 1287, 1216, 1164, 1125, 975, 895, 825, 697 cm^{-1}. NMR: (acetone-d_6) δ 7.30 (s, 1H), 7.20 (s, 1H), 4.70 (s, 4H), 3.40 (t, 2H), 1.95 (m, 2H), 1.50 (m, 2H), 1.40 (m, 24H), 0.88 (t, 3H). Analysis: Calculated for $C_{24}H_{40}O_3SBr_2$ C, 50.71; H, 7.09. Found C, 50.60; H, 6.98.

General Procedures for the Synthesis of Poly(aryl ether monodendrons). *Coupling.* One equivalent of monomer **1**, 2.1 equiv of the appropriate phenol, and 10 equiv of potassium carbonate were dissolved in a minimal amount of anhydrous acetone and stirred under argon for 12−36 h at room temperature. The progress of the reaction was monitored by TLC. Once reaction was complete by disappearance of **1**, water was added, and the solution was extracted with an appropriate organic solvent: diethyl ether for G1-hds (**6**) and G2-hds (**8**) and chloroform for all higher generations. The combined organic layers were washed with saturated NaCl and dried over $MgSO_4$. Different purification procedures were followed for each generation as detailed below.

Deprotection. The protected monodendron was dissolved in dry THF, and 95% ethanol was added until the mixture became turbid. Sodium hydroxide was then added and the reaction mixture stirred under argon at room temperature for 12−48 h. The progress of the reaction was monitored by TLC. When complete, water was added and the mixture extracted three times with dichloromethane. The organic layers were combined and dried over Na_2SO_4. The crude product was typically quite pure, but the exact purification procedures followed for different generations are detailed below.

3,5-Bis(phenoxymethyl)phenyl Hexadecanesulfonate (G1-hds) (6). Monomer **1** (3.0 g, 5.3 mmol), phenol (1.49 g, 15.8 mmol, 3 equiv), and K_2CO_3 (7.3 g, 53 mmol, 10 equiv) were dissolved in a minimum amount of anhydrous acetone and stirred with reflux for 48 h under argon. The reaction was worked up as described in the general procedure. The crude oily product was purified by flash chromatography (35% chloroform in hexanes, gradually adding up to 5% diethyl ether) to give 1.26 g of **6** (2.1 mmol, 40%) as a clear oil. IR: 2924, 2853, 1599, 1588, 1496, 1455, 1376, 1288, 1239, 1173, 1153, 1125, 1079, 1056, 1028, 973, 951, 865, 821, 753, 721, 690 cm^{-1}. NMR: (acetone-d_6) δ 7.60 (s, 1H), 7.45 (s, 2H), 7.30 (t, 4H), 7.05 (d, 4H), 7.00 (t, 2H), 5.20 (s, 4H), 3.42 (t, 2H), 1.95 (m, 2H), 1.50 (m, 2H), 1.38 (m, 24H), 0.88 (t, 3H). Analysis: Calculated for $C_{36}H_{50}O_5S$ C, 72.69, H, 8.47; S, 5.39. Found C, 72.04; H, 8.24; S, 5.45.

3,5-Bis(phenoxymethyl)phenol (G1-OH) (7). G1-hds (**6**) (1.26 g, 2.1 mmol) was deprotected using the general procedure above to give **7**. Purification by flash chromatography (10% ethyl acetate in hexanes) gave 0.60 g of **7** (1.95 mmol, 93%) as a yellow oil. IR: 3426, 2921, 2852, 1652, 1599, 1558, 1495, 1455, 1384, 1300, 1234, 1154, 818, 753, 690 cm^{-1}. NMR: (acetone-d_6) δ 7.48 (t, 4H), 7.09 (s, 1H), 6.99 (d, 6H), 6.90 (s, 2H), 5.08 (s, 4H). Analysis: Calculated for $C_{20}H_{18}O_3$ C, 78.41; H, 5.92. Found C, 78.46; H, 6.45.

3,5-Bis[3′,5′-bis(phenoxymethyl)phenoxymethyl]-phenyl Hexadecanesulfonate (G2-hds) (8). G1-OH (7) (0.60 g, 1.95 mmol) was reacted with monomer 1 using the general procedure above. The crude product was purified with flash chromatography using 10% chloroform in hexanes with the gradual addition of diethyl ether to the eluent to give 0.75 g of 8 (0.74 mmol, 76% yield) as a clear viscous oil. IR: 2926, 2855, 1599, 1496, 1455, 1376, 1300, 1240, 1172, 1127, 1078, 1032, 980, 879, 818, 754, 691 cm^{-1}. NMR: (acetone-d_6) δ 7.61 (s, 1H), 7.42 (s, 2H), 7.28 (t, 8H), 7.20 (m, 2H), 7.12 (m, 4H), 7.00 (d, 8H), 6.95 (t, 4H), 5.23 (s, 4H). 5.08 (s 8H) 3.42 (t, 2H), 1.95 (m, 2H), 1.50 (m, 2H), 1.38 (m, 24H), 0.88 (t, 3H).

3,5-Bis[3′,5′-bis(phenoxymethyl)phenoxymethyl]-phenol (G2-OH) (9). G2-hds (**8**) (0.75 g, 0.74 mmol) was deprotected using the general procedure above. The crude product was purified by flash chromatography using 50−55% chloroform in hexanes to give 0.48 g of **9** (0.66 mmol, 89% yield) as a slightly yellow oil. IR: 2935, 2880, 1598, 1495, 1455, 1374, 1295, 1237, 1170, 1153, 1077, 1031, 881, 851, 753, 689 cm^{-1}. NMR: (acetone-d_6) δ 7.28 (t, 8H), 7.20 (s, 2H), 7.09 (s, 4H), 7.00 (m, 8H), 6.95 (m, 7H), 5.05 (m, 12H). Analysis: Calculated for $C_{48}H_{42}O_7$ C, 78.88; H, 5.79. Found C, 78.96; H, 5.90.

3,5-Bis[3′,5′-bis[3″,5″-bis(phenoxymethyl)phenoxymethyl]phenoxymethyl]phenyl Hexadecanesulfonate (G3-hds) (10). G2-OH (**9**) (0.48 g, 0.66 mmol) was reacted with monomer **1** using the general coupling conditions. Purification by chromatography with 0.5% diethyl ether in chloroform gave 0.37 g of **10** (0.20 mmol, 60% yield) as a clear tacky gum. NMR: (acetone-d_6) δ 7.50 (s, 1H), 7.38 (s, 2H), 7.25 (t, 16H), 7.16 (s, 6H), 7.08 (s, 12H), 6.98 (d, 16H), 6.88 (t, 8H), 5.03 (m, 28H), 3.42 (t, 2H), 1.95 (m, 2H), 1.50 (m, 2H), 1.38 (m, 24H), 0.88 (t, 3H).

3,5-Bis[3′5′-bis[3″,5″-bis(phenoxymethyl)phenoxymethyl]phenoxymethyl]phenol (G3-OH) (11). G3-hds (**10**) (0.37 g, 0.20 mmol) was deprotected using the general conditions. Column chromatography with 50−55% chloroform in hexanes gave 0.30 g of **11** (0.19 mmol, 94% yield) as a slightly yellow glass. IR: 3405, 1685, 1620, 1520, 1495, 1455, 1374, 1295, 1170, 1077, 881, 851, 689 cm^{-1}. NMR: (acetone-d_6) δ 7.25 (t, 16H), 7.16 (s, 6H), 7.08 (s, 12H), 6.98 (d, 16H), 6.88 (m, 11H), 5.03 (m, 28H). Analysis: Calculated for $C_{104}H_{90}O_{15}$ C, 79.07; H, 5.74. Found C, 79.13; H, 5.66.

3,5-Bis[3′,5′-bis[3″,5″-bis[3‴,5‴-bis(phenoxymethyl)-phenoxymethyl]phenoxymethyl]phenoxymethyl]-phenyl Hexadecanesulfonate (G4-hds) (12). G3-OH (**11**) (0.30 g, 0.19 mmol) was reacted with monomer **1** using the general coupling conditions. Purification by flash chromatography using carbon tetrachloride with up to 5% ethyl acetate gave 0.20 g of **12** as a clear glass (0.056 mmol, 59% yield). IR: 2926, 1599, 1496, 1455, 1376, 1300, 1240, 1078, 1032, 818, 754, 691 cm^{-1}. NMR: (acetone-d_6) δ 7.58 (s, 1H), 7.49 (s, 2H), 7.37 (t, 32H), 7.23 (s, 14H), 7.18 (s, 28H), 7.08 (d, 32H), 7.00 (t, 16H), 5.12 (m, 60H), 3.42 (t, 2H), 1.95 (m, 2H), 1.50 (m, 2H), 1.38 (m, 24H), 0.88 (t, 3H).

3,5-Bis[3′,5′-bis[3″,5″-bis[3‴,5‴-bis(phenoxymethyl)-phenoxymethyl]phenoxmethyl]phenoxymethyl]-phenol (G4-OH) (13). G4-hds (**12**) (0.20 g, 0.056 mmol) was deprotected using the general conditions. Purification by flash chromatography with 40% chloroform in hexanes gave 0.18 g of **13** as a clear yellow glass (0.054 mmol, 97% yield). NMR: (acetone-d_6) δ 7.20 (t, 32H), 7.09 (s, 14H), 7.01 (s, 28H), 6.93 (m, 51H), 4.95 (m, 60H).

3,5-Bis[3′,5′-bis[3″,5″-bis[3‴,5‴-bis[3⁗,5⁗-bis(phenoxymethyl)phenoxmethyl]phenoxymethyl]phenoxymethyl]-phenyl Hexadecanesulfonate (G5-hds) (14). G4-OH (**13**) (0.18 g, 0.054 mmol) was reacted with monomer **1** using the general coupling conditions. Purification by flash chromatography with up to 4% ethyl acetate in carbon tetrachloride gave 0.17 g of **14** as a clear glass (0.025 mmol, 93% yield). IR: 2921, 2852, 1598, 1494, 1456, 1376, 1299, 1239, 1154, 1035, 754, 688, 668 cm^{-1}. NMR: (DMSO-d_6) δ 7.32 (m, 67H), 7.10 (m, 189H), 5.09 (m, 124H), 3.45 (m, 2H), 1.95 (m, 2H), 1.50 (m, 2H), 1.30 (m, 24H), 0.95 (m, 3H).

3,5-Bis[3′,5′-bis[3″,5″-bis[3‴,5‴-bis[3⁗,5⁗-bis(phenoxymethyl)phenoxymethyl]phenoxymethyl]phenoxymethyl]-phenol (G5-OH) (15). G5-hds (**14**) (0.17 g, 0.025 mmol) was dissolved in THF and treated with a 5-fold excess of potassium *tert*-butoxide (0.014 g, 0.125 mmol). The mixture was stirred for 3 days, then poured into water, and extracted with dichloromethane (3 × 10 mL). The organic solution was dried over Na_2SO_4, filtered, and concentrated. Purification by preparative TLC using 10% ethyl acetate in carbon tetrachloride as the eluent gave 0.10 g of **15** as a clear glass (0.015 mmol, 60% yield). NMR analysis gave broad resonances in the chemical shift ranges expected for **15**. The SEC-LS data for this compound are consistent with the expected molecular weight (Table 1).

3,5-Bis[3′,5′-bis[3″,5″-bis[3‴,5‴-bis[3⁗,5⁗-bis[3⁗⁗,5⁗⁗-bis(phenoxymethyl)phenoxymethyl]phenoxymethyl]-

Table 1. SEC/LS Data for Monodendrons[a]

compound	nominal MW (Daltons)	LS MW[b] (Daltons)	polydispersity[c]	ret. vol. (mL)
Hexadecanesulfonate (hds)-Focused Monodendrons				
6 G1-hds	595	601	1.02	21.4
8 G2-hds	1019	1015	1.01	20.4
10 G3-hds	1868	1819	1.01	19.1
12 G4-hds	3566	3546	1.01	17.9
14 G5-hds	6963	6512	1.01	16.9
16 G6-hds	13754	13529	1.01	15.9
Phenol (OH)-Focused Monodendrons				
7 G1-OH	306	397	1.01	23.7
9 G2-OH	731	713	1.01	21.3
11 G3-OH	1580	1494	1.01	19.5
13 G4-OH	3278	3303	1.01	18.1
15 G5-OH	6674	6581	1.02	16.9

[a] Waters 410 refractive index (RI) detector, Precision Detectors PD2000 light scattering (LS) detector, and 500-mm Jordi-Gel 500 Å mixed-bed column with THF as eluent. [b] LS molecular weights (M_w) calculated using specific refractive index increments $\delta n/\delta c$ based on weight percents: 0.206 for monodendrons[13,14] and 0.0272 for hexadecanesulfonate protecting groups (projected from the fatty acid derivatives).[31] [c] Polydispersity index M_w/M_n calculated from LS and RI signals.

phenoxymethyl]phenoxymethyl]phenoxymethyl]-phenyl Hexadecanesulfonate (G6-hds) (16). G5-OH (**15**) (0.10 g, 0.015 mmol) was reacted with monomer **1** using the general coupling conditions. Purification by preparative TLC using 10% ethyl acetate in carbon tetrachloride gave 0.04 g of **16** as a clear glass (0.003 mmol, 44% yield). NMR analysis gave broad resonances in the chemical shift ranges expected for **16**. The SEC-LS data for this compound are consistent with the expected molecular weight (Table 1).

1,3,5-Tris(8′-bromooctyloxy)benzene (C8) (17). Phloroglucinol dihydrate (0.5 g, 3.1 mmol), 1,8-dibromooctane (25 g, 92 mmol, 30 equiv), potassium carbonate (2.6 g, 19 mmol, 6 equiv), and 18-crown-6 (0.16 g, 0.6 mmol, 0.2 equiv) were dissolved in 25 mL of anhydrous acetone and refluxed 12 h under argon. The solution was concentrated in vacuo, then added to 50 mL of water. This was extracted with diethyl ether (3 × 30 mL), and the combined organic fractions were washed with saturated NaCl and dried over anhydrous $MgSO_4$. The resulting orange oil was dissolved in hexane and "oiled out" by addition of methanol to remove the excess 1,8-dibromooctane. The hexane/methanol solution was decanted from the oily crude product, which was then purified by flash chromatography using 5% diethyl ether in hexanes to give 0.97 g of **17** as a clear oil (1.4 mmol, 45% yield). IR: 2930, 2855, 1598, 1462, 1385, 1276, 1247, 1160, 1061, 817, 723, 680 cm^{-1}. NMR: (acetone-d_6) δ 6.06 (s, 3H), 3.95 (t, 6H), 3.50 (t, 6H), 1.82 (m, 12H), 1.49 (m, 24H). Analysis: Calculated for $C_{30}H_{51}Br_3O_3$ C, 51.52; H, 7.35. Found C, 51.57; H, 7.50.

General Procedure for Dendrimer Synthesis. One equivalent of tribrominated core molecule (C8) and 3.1 equiv of the appropriate phenol (GnOH) were dissolved in anhydrous acetone and treated with 3.1 equiv of anhydrous potassium carbonate and 0.2 equiv of 18-crown-6. The mixture was refluxed for up to 72 h under argon, and then poured into an equal volume of water. The mixture was then extracted with diethyl ether, and the ether extracts were dried over $MgSO_4$. The solution was then concentrated in vacuo and purified as described below for each individual dendrimer.

1,3,5-Tris(8′-phenoxyoctyloxy)benzene (C8G0) (18). Core C8 (**17**) (80 mg, 0.11 mmol) and phenol (50 mg, 0.37 mmol) were reacted using the general procedure. The ether layer was washed once with 10% sodium hydroxide to remove excess phenol before concentrating. The crude material was purified by flash chromatography using 10% ethyl acetate in hexanes to give 40 mg of **18** (0.05 mmol, 48% yield). IR: 3056, 2934, 2857, 1600, 1497, 1464, 1387, 1301, 1291, 1265, 1245, 1162, 1061, 882, 817, 753, 740, 704, 692 cm^{-1}. NMR: (acetone-d_6) δ 7.30 (t, 6H), 6.95 (m, 9H), 6.23 (s, 3H), 3.92 (m, 12H), 1.82 (m, 12H), 1.49 (m, 24H).

Table 2. SEC/LS Data for Dendrimers[a]

compound	nominal MW (Daltons)	LS MW[b] (Daltons)	polydispersity[c]
18 C8G0	738	825	1.00
19 C8G1	1374	1387	1.00
20 C8G2	2646	2412	1.01
21 C8G3	5190	5183	1.00
22 C8G4	10278	10369	1.00

[a] Waters 410 refractive index (RI) detector, Precision Detectors PD2000 light scattering (LS) detector, and 500-mm Jordi-Gel 500 Å mixed-bed column with THF as eluent. [b] LS molecular weights (M_w) calculated using specific refractive index increments $\delta n/\delta c$ based on weight percents: 0.206 for monodendrons and phloroglucinol[13,14] and 0.0272 for alkane spacers (projected from the fatty acid derivatives).[31] [c] Polydispersity index M_w/M_n calculated from LS and RI signals.

1,3,5-Tris[8′-[3″,5″-bis(phenoxymethyl)phenoxy]octyloxy]benzene (C8G1) (19). Core C8 (**17**) (50 mg, 0.07 mmol) and G1OH (**7**) (70 mg, 0.23 mmol) were reacted using the general procedure. The crude material was purified by flash chromatography using 10% ethyl acetate in hexanes to give 40 mg of **19** (0.03 mmol, 43% yield). IR: 3038, 2930, 2855, 1599, 1495, 1459, 1380, 1328, 1298, 1239, 1162, 1057, 1032, 1013, 881, 818, 753, 690 cm^{-1}. NMR: (acetone-d_6) δ 7.30 (t, 12H), 7.15 (s, 3H), 6.99 (s, 6H), 6.97 (d, 12H), 6.92 (t, 6H), 6.09 (s, 3H), 5.09 (s, 12H), 3.97 (m, 12H), 1.75 (m, 12H), 1.46 (m, 24H).

1,3,5-Tris[8′-[3″,5″-bis[3‴,5‴-bis(phenoxymethyl)phenoxymethyl]phenoxy]octyloxy]benzene (C8G2) (20). Core C8 (**17**) (22 mg, 0.032 mmol) and G2OH (**9**) (72 mg, 0.10 mmol) were reacted using the general procedure. The crude material was purified by preparative TLC using 10% ethyl acetate in hexanes to give 30 mg of **20** (0.01 mmol, 31% yield). Analysis by SEC-LS gave the expected molecular weight (Table 2).

1,3,5-Tris[8′-[3″,5″-bis[3‴,5‴-bis[3⁗,5⁗-bis(phenoxymethyl)phenoxymethyl]phenoxymethyl]phenoxy]octyloxy]-benzene (C8G3) (21). Core C8 (**17**) (4 mg, 0.006 mmol) and G3OH (**11**) (29 mg, 0.02 mmol) were reacted using the general procedure. The crude material was purified by preparative TLC using 15% ethyl acetate in hexanes to give **21**. Analysis by SEC-LS gave the expected molecular weight (Table 2).

1,3,5-Tris[8′-[3″,5″-bis[3‴,5‴-bis[3⁗,5⁗-bis(3⁗′,5⁗′-bis-(phenoxymethyl)phenoxymethyl]phenoxymethyl]-phenoxymethyl]phenoxy]octyloxy]benzene (C8G4) (22). Core C8 (**17**) (2 mg, 0.003 mmol) and G4OH (**13**) (30 mg, 0.009 mmol) were reacted using the general procedure. The crude material was purified by preparative TLC using 15% ethyl acetate in hexanes to give **22**. Analysis by SEC-LS gave the expected molecular weight (Table 2).

Results

The dendritic polymers reported here are formally condensation polymers of the A_2B monomer 3,5-bis(hydroxymethyl)phenol. The activated and protected A_2B monomer used in the synthesis is 3,5-bis(bromomethyl)phenyl hexadecanesulfonate (**1**). This compound has the two hydroxymethyl groups activated as benzyl bromides and the phenol protected as an alkanesulfonate ester. Initial studies had demonstrated that sulfonate esters were useful protecting groups for the phenol, but the more common methanesulfonate and *p*-toluenesulfonate esters were not easily separated from the unprotected phenols due to their similar polarities. The long alkyl chain of the hexadecanesulfonate ester provides sufficient nonpolar character to the protected materials to effect separation by standard chromatographic techniques.

Monomer **1** was synthesized in five steps from dimethyl 5-hydroxyisophthalate (**2**) using literature meth-

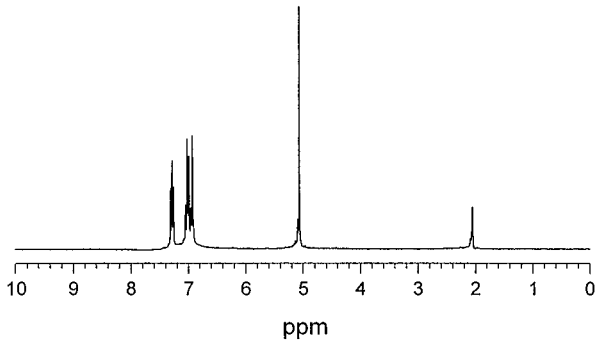


Figure 1. ^{1}H nuclear magnetic resonance spectrum of G1-OH **7** in acetone-d_6. The peak at 2.05 ppm is due to acetone-d_6.

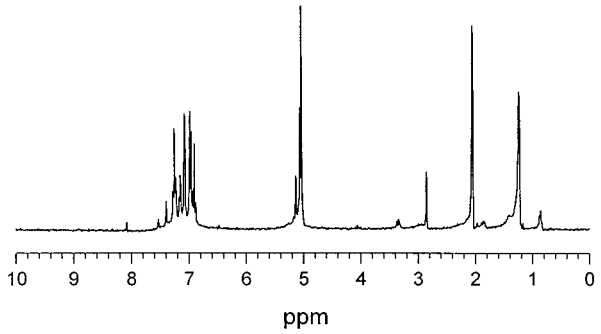
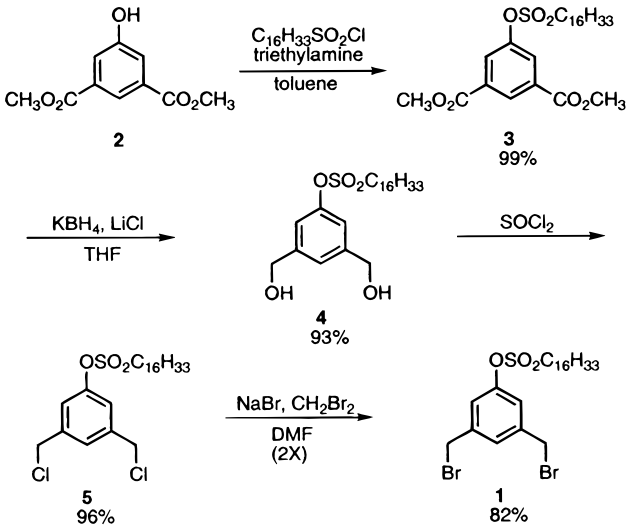


Figure 2. ^{1}H nuclear magnetic resonance spectrum of G3-hds **10** in acetone-d_6. The peak at 2.05 ppm is due to acetone-d_6 and the peak at 2.85 ppm is due to water.

ods as shown in Scheme 1.[32−35] Several transformations in this sequence are noteworthy. Lithium aluminum hydride was found to reduce both the carboxylate and sulfonate esters, contrary to literature reports.[36] Lithium borohydride (prepared in situ from potassium borohydride and lithium chloride) was therefore employed for the reduction of the carboxylate esters.[33] Direct conversion of diol **4** to dibromide **1** gave poor results in our hands, although both relatively gentle conditions (Ph_3P/CBr_4) and harsher conditions (HBr or $SOBr_2$) were attempted. Better results were obtained by conversion of diol **4** to dichloride **5** with thionyl chloride followed by conversion of dichloride **5** to dibromide **1**. The conversion of dichloride **5** to the more reactive dibromide **1** by halogen−halogen exchange is an equilibrium process and was performed twice to more efficiently provide complete bromination.[35] The overall yield for synthesis of **1** starting from **2** was 70%.

Using monomer **1**, synthesis of poly(aryl ether) monodendrons is straightforward as shown in Scheme 2. Coupling of phenol to **1** under standard conditions for phenyl ether synthesis[34] gives first-generation hexadecanesulfonate-terminated monodendron G1-hds **6** in 82% yield. No phase-transfer catalyst is required for this reaction or any other coupling reaction in the mono-

Scheme 1. Synthesis of Protected Monomer 1



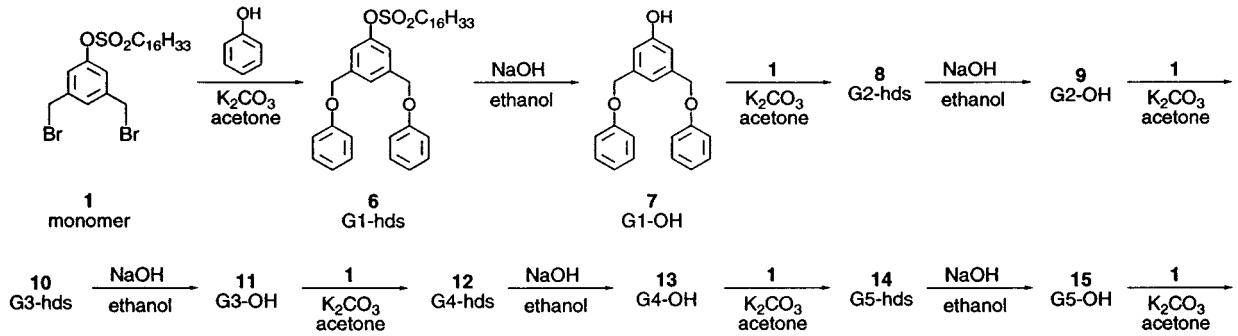
dendron synthesis. Strictly anhydrous conditions during coupling are necessary for optimal yield of pure product, as the presence of water can lead to premature cleavage of the sulfonate ester. When sulfonate cleavage is desired to activate the phenol for further coupling, strongly basic conditions readily give the first-generation phenol G1-OH **7** in 93% yield.[37] This sequence of coupling and deprotection steps is repeated to give higher generation monodendrons. To date we have made and characterized hexadecanesulfonate-terminated materials up to sixth generation (G6-hds **16**, nominal MW = 13 754), and phenol terminated materials up to fifth generation (G5-OH **15**, nominal MW = 6674). The monodendrons were purified by flash chromatography, typically using chloroform in hexanes as the eluent.

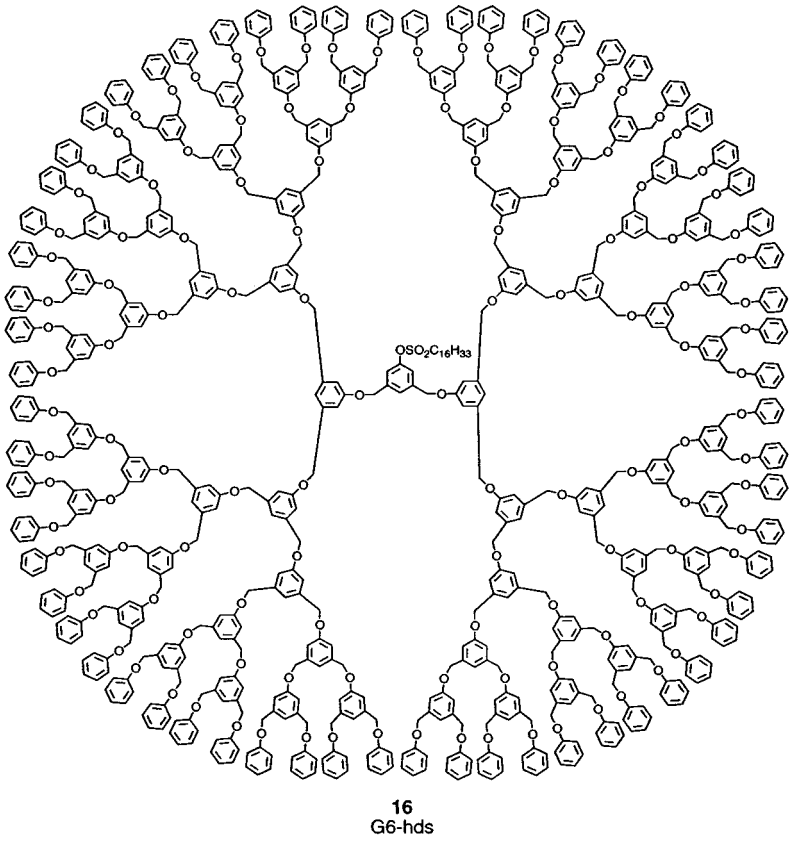
Nuclear magnetic resonance (NMR) and size-exclusion chromatography with light scattering detection (SEC/LS) were found to be the most useful characterization techniques for analysis of the structure and purity of these materials. Monodendrons up through the fourth generation could be readily characterized by NMR spectroscopy. The fifth- and sixth-generation monodendrons did not give high-resolution spectra, as the resonances were broadened, apparently due to slow tumbling. This is not unexpected for such large molecules, particularly in a relatively viscous solvent such as DMSO-d_6. Representative NMR spectra for G1-OH **7** and G3-hds **10** are shown in Figures 1 and 2. The spectra are relatively simple, as is expected for such repetitive and symmetrical structures. The aromatic hydrogens of the monodendrons gave resonances between 7.6 and 6.9 ppm, the benzyl ether hydrogens gave resonances between 5.3 and 4.9 ppm, and the hexadecanesulfonate protecting group hydrogens gave resonances between 3.5 and 0.8 ppm. All generations also gave IR spectra consistent with the proposed structures. Elemental analysis gave good data for the lower generation compounds, but the tendency of the higher molecular weight materials to occlude solvent made consistent results difficult to achieve.

SEC/LS is a powerful technique for analysis of dendrimers.[13,14] SEC/LS data for both phenolic and hexa-

(32) Hanson, J. E.; Reichmanis, E.; Houlihan, F. M.; Neenan, T. X. *Chem. Mater.* **1992**, *4*, 837.
(33) Brown, H. C.; Narasimhan, S.; Choi, Y. M. *J. Org. Chem.* **1982**, *47*, 4702.
(34) Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. *Vogel's Textbook of Practical Organic Chemistry*, 5th ed.; Longman Scientific and Technical Publishers: New York, 1989; p 558.
(35) Babler, J. H.; Spina, K. P. *Synth. Commun.* **1984**, *14*, 1313.
(36) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; John Wiley and Sons: New York, 1991.
(37) Lantos, I.; Loev, B. *Tetrahedron Lett.* **1975**, 2011.

Scheme 2. Synthesis of Hexadecanesulfonate (hds)- and Hydroxyl (OH)-Terminated Monodendrons





16
G6-hds

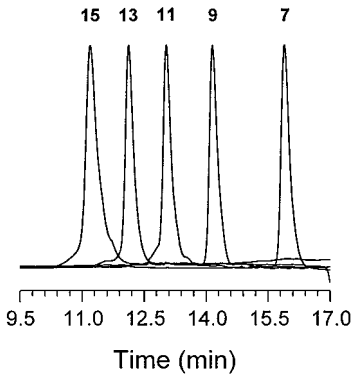
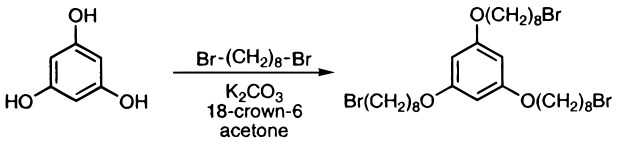


Figure 3. SEC chromatograms showing the refractive index signal from G1-OH (**7**), G2-OH (**9**), G3-OH (**11**), G4-OH (**13**), and G5-OH (**15**).

Scheme 3. Synthesis of Polyfunctional Core C8 17

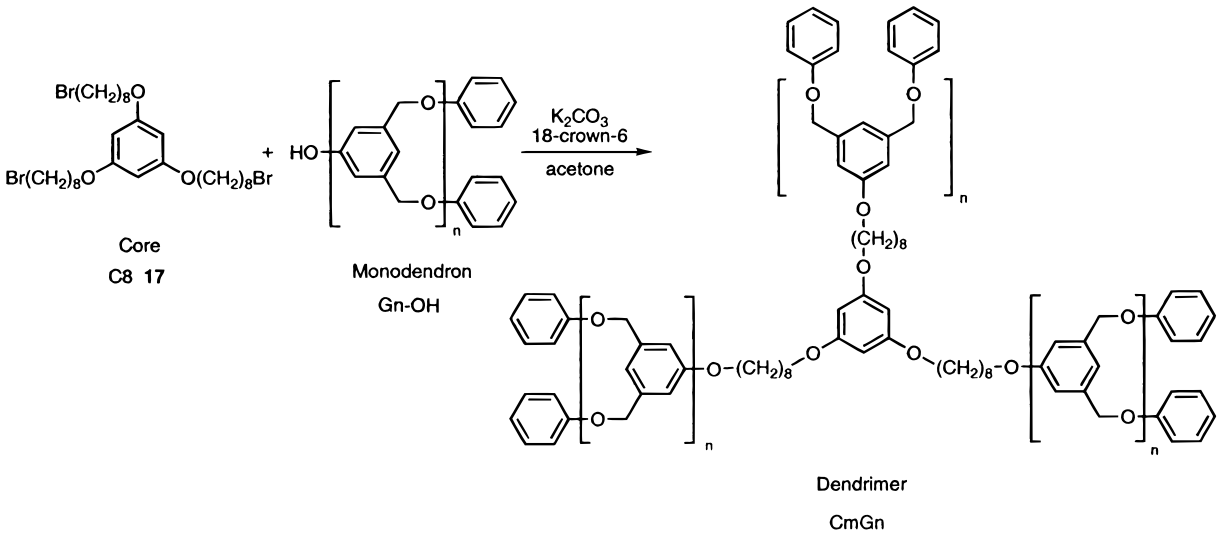


C8 **17**

decanesulfonate monodendrons were consistent with essentially monodisperse ($M_w/M_n \leq 1.02$) materials of the appropriate size. The data are summarized in Table 1, and chromatograms for the phenolic monodendrons (G1-OH **7** to G5-OH **15**) are shown in Figure 3. The difference in retention volume between the protected and deprotected monodendrons decreased with increasing size. This is expected, as the hexadecanesulfonate protecting group makes a smaller relative contribution for higher generations.

Dendrimers can be constructed by attachment of two or more of the monodendrons to a polyfunctional core. A selection of such dendrimers have been synthesized to demonstrate the utility of this method in the preparation of polydendrons or dendrimers. A polyfunctional core was prepared that contained three symmetrically disposed electrophilic sites for reaction of the nucleophilic phenol focal groups. This core was synthesized

Scheme 4. Synthesis of Dendrimers



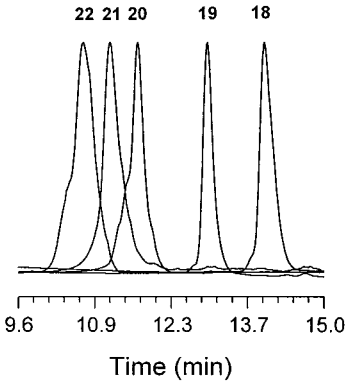


Figure 4. SEC chromatograms showing the refractive index signal from C8G0 (**18**), C8G1 (**19**), C8G2 (**20**), and C8G3 (**21**), and C8G4 (**22**).

by reaction of phloroglucinol (1,3,5-trihydroxybenzene) with the α,ω-dibromide 1,8-dibromooctane as shown in Scheme 3. The polyfunctional core C8 **17** was then coupled with phenol-focused monodendrons up through the fourth generation, as shown in Scheme 4. The resulting C8G*n* dendrimers were purified by flash chromatography or preparative TLC, and characterized by SEC-LS. NMR was not found to be very useful for characterization of the dendrimers, as the only change upon reaction is the transformation of the alkyl bromide groups at the end of the octyl chains to alkyl phenyl ethers. This produces only a minimal change in the NMR spectrum, particularly for the higher generations. SEC-LS results for the dendrimers are summarized in Table 2 and chromatograms are shown in Figure 4.

Discussion

The synthetic method reported here is an efficient approach to the synthesis of poly(aryl ether) monodendrons and dendrimers. Following preparation of monomer **1**, the coupling and deprotection reactions are quite rapid and purification is relatively easy. This allows the rapid synthesis of large monodendrons. The phenol-focused monodendrons can be readily attached to polyfunctional electrophilic cores to provide polydendrons or dendrimers. Characterization of the monodendrons by NMR and SEC/LS and dendrimers by SEC/LS is also quite straightforward and demonstrates that the materials can be made with minimal defects.

The hexadecanesulfonate protecting group is essential to this method. Methanesulfonate and *p*-toluenesulfonate groups are also effective protecting groups for the phenol, but separation of the sulfonates and free phenols is found to be difficult following deprotection. The hexadecanesulfonate group provides sufficient nonpolar character to allow efficient separation and is also relatively inexpensive. Sulfonate protecting groups for the phenol may be adaptable to a solid-phase method as has been employed by Moore.[38,39] The sulfonate protecting group does show some sensitivity to water during the coupling reaction, requiring strictly anhydrous conditions during the coupling to prevent premature deprotection and the formation of defect structures.

The poly(aryl ether) dendrimer synthesis of Frechet is based on 3,5-dihydroxybenzyl alcohol,[12−14] and the resulting materials are essentially isomers of those reported here. The forms of the two polymers with a hydroxyl group at the focus differ by a single methylene group, a difference which becomes negligible at higher molecular weights. For example, the third-generation phenol-focused monodendron described here has a nominal molecular weight of 1580, while the third-generation benzyl alcohol-focused monodendron from Frechet's synthesis has a nominal molecular weight of 1594. This is a difference of less than 1%, and the difference decreases to less than 0.1% for the sixth-generation compounds. The hydroxyl focal groups are quite different chemically: one is phenolic and one is aliphatic. Linear condensation polymers can often be made from either AB monomers or AA and BB monomers to give structures that are similar, such as Nylon 6 vs Nylon 6,6.[40] These two types of poly(aryl ether) dendrimers are similarly constructed from A_2B monomers vs AB_2 monomers, but there is an added element of directionality due to the uniform branching. While the chain ends of a linear polymer are essentially equivalent, the ends of

(38) Bharathi, P.; Patel, U.; Kawaguchi, T.; Pesak, D. J.; Moore, J. S. *Macromolecules* **1995**, *28*, 5955.
(39) Bharathi, P.; Moore, J. S. *J. Am. Chem. Soc.* **1997**, *119*, 3391.
(40) *Polymer Handbook*, 2nd ed.; Brandrup, J., Immergut, E. H., Eds.; John Wiley and Sons: New York, 1975.

growing dendrimer chains are quite different: one end is the focal group, the other ends are the terminal groups. Like the trees for which they are named, dendrimers have two well-defined directions: down to the root and up to the branches. The different substitution patterns of the aromatic rings in these isomeric polymers might cause measurable differences in conformational structure due to the different rotational potentials for ether oxygens and methylene groups. However, comparison of SEC retention volumes of the isomeric poly(aryl ether) monodendrons revealed no detectable differences, and co-injection of third-generation monodendrons from both syntheses gave simultaneous elution. This suggests that the sizes and conformations of the two types of monodendrons are indistinguishable in THF solution. Studies in other solvents and the solid state are in progress to determine if any conformational differences can be detected.

These two poly(aryl ether) dendrimer syntheses are complementary, since one provides a nucleophilic group at the focal point while the other provides an electrophilic group. The current synthesis requires a more complex multistep sequence to generate the activated and protected A_2B monomer. The iterative chemistry, however, is simpler and (in our hands) more rapid and robust. The coupling steps do not generally require a phase-transfer agent, since the phenoxide is the focal group of the monodendron. In effect, the monodendron *is* the phase-transfer agent, improving the solubility of the ionic phenoxide nucleophile. Furthermore, the bromination chemistry (which in our hands has always produced the greatest difficulties in the Frechet synthesis[12−14]) is performed only on the monomer, not on the growing monodendrons which are the product of many synthetic steps. These differences may make this new synthesis appealing in many instances.[41]

We are currently extending our studies of these dendritic polymers by further characterizing their physical properties. If the two isomeric poly(aryl ether) dendrimer structures can be shown to have nearly identical properties, it will be possible to use them interchangeably in construction of dendrimer materials. The synthetic flexibility provided by the availability of both nucleophilic and electrophilic focal groups on such very similar materials should make poly(aryl ether) dendrimer structures even more attractive in dendrimer research.

Acknowledgment. This research was supported by the National Science Foundation under grant DMR-9412292.

CM990023G

(41) Gilat, S. L.; Adronov, A.; Frechet, J. M. J. *Polym. Mater. Sci. Eng.* **1997**, *77*, 91.