New Accelerated Strategy for the Synthesis of Poly(Ether Ketone) Dendrons

Michael A. Abramov,† Ramesh Shukla,†
David B. Amabilino,‡ and Wim Dehaen*,†

Department of Chemistry, University of Leuven, Heverlee (Leuven), B-3001, Belgium, and Institut de Ciènciade Materials de Barcelona (CSIC), 08193 Bellaterra, Spain

wim.dehaen@chem.kuleuven.ac.be

Received May 30, 2001

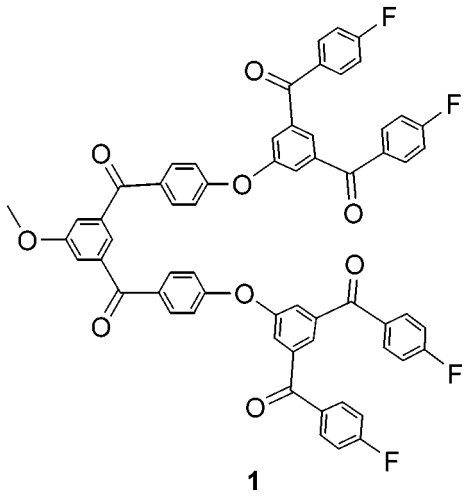
Abstract: A new AB_4-type hypermonomer with four activated aromatic fluorines was prepared and converted to hyperbranched poly(ether ketones) by nucleophilic aromatic substitution of these fluorine atoms with phenolates. The preparation and application of the AB_4 hypermonomer for the accelerated synthesis of a family of poly(ether ketone) dendrons G2−G4 in good yield are described.

The convergent synthesis of dendritic poly(ether ketones), based on AB_2 monomers, has been developed by Morikawa[1] and successfully used by his and other groups to construct monodisperse macromolecules.[2] Also, hyperbranched polymers have been prepared using the same chemistry and building blocks.[3] The drawback of the method, however, is that the buildup of the dendritic wedges is time consuming and the increasing steric hindrance, which occurs at the focal functional group with dendron growth, may inhibit its anchoring to a center core.

Our approach to accelerate the dendrimer growth consists of using an appropriate AB_4 hypermonomer **1** in the assembly of higher-generation poly(ether ketone) dendrons. Such a synthetic strategy was successfully applied in our group for the accelerated synthesis of benzylic polyether dendrons.[4]

Herein, we describe the preparation of a new AB_4-type hypermonomer **1** (Figure 1) and its application for the accelerated synthesis of a family of poly(ether ketone) dendrons (Scheme 1).

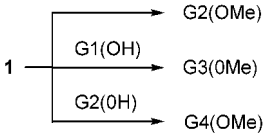
Synthesis. Hypermonomer **1** used for this investigation was obtained in accordance to Scheme 2. We started from 5-methoxyisophthaloyl chloride[5] **2** and prepared **3** by the reported procedure[1a] from **2** and fluorobenzene in the presence of $AlCl_3$. Alternatively, we used monomer **3** obtained from **2** and 4-fluorophenylmagnesium bromide in THF in 60−65% yield. As a side product, 3-(4-fluorobenzoyl)-5-methoxybenzoic acid **3a** was isolated in 30% yield. The separation of **3** and **3a** was straightforward.



1

Figure 1. Hypermonomer **1**.

Scheme 1. Accelerated Strategy for the Synthesis of Poly(Ether Ketone) Dendrons



To deactivate the fluorine atoms of **3** for the controlled synthesis of **1**, we decided to reduce the ketone groups. We tried reduction procedures with hydrazine and sodium cyanoborohydrate, but only hydrogenation on Pd−C was successful; we obtained 3,5-bis(4-fluorobenzyl)anisole **4** as a colorless oil in 96% yield and used it in the next step without purification. Treatment of **4** with 1 N BBr_3 dichloromethane solution gave phenol **5** in 97% yield, 2 equiv of which were condensed with monomer **3** in a DMF−toluene mixture at 150 °C in the presence of potassium carbonate, resulting in anisole **6** in 82% yield.

To reactivate the four fluorine atoms at the aromatic rings, we had to oxidize the methylene groups to ketone functions. Oxidation with pyridinium chlorochromate did not lead to compound **1**, and reaction of **6** with potassium permanganate at room temperature in acetone was very slow and did not reach completion after 30 days. Finally, oxidation of **6** with potassium permanganate in the presence of tetrabutylammonium bromide as a phase transfer catalyst gave **1** in a satisfying yield of 70%.

The AB_4-type hypermonomer **1** was used for the preparation of dendritic poly(ether ketone) by nucleophilic aromatic substitution of the activated fluorine atoms with phenolate generated in the presence of potassium carbonate (Scheme 3). The substitution proceeded at 120−150 °C in a mixture of toluene and DMF.

† University of Leuven.
‡ Institut de Ciènciade Materials de Barcelona (CSIC).

(1) (a) Morikawa, A.; Kakimoto, M.-A.; Imai, Y. *Macromolecules* **1993**, *26*, 6324. (b) Morikawa, A. *Macromolecules* **1998**, *31*, 5999. (c) Morikawa, A.; Ono, K. *Macromolecules* **1999**, *32*, 1062. (d) Miller, T. M.; Neenan, T. H.; Kwock, E. W.; Stein, S. M. *J. Am. Chem. Soc.* **1993**, *115*, 356.

(2) Selected references: (a) Hawker, C. J.; Chu, F. K. *Macromolecules* **1996**, *29*, 4370. (b) Shu, C. F.; Leu, C. M.; Huang, F. Y. *Polymer J.* **1999**, *40*, 6591. (c) Shu, C. F.; Leu, C. M. *Macromolecules* **1999**, *32*, 100. (d) Morikawa, A.; Ono, K. *Polymer J.* **2000**, *32*, 234. (e) Morikawa, A.; Ono, K. *Polymer J.* **2000**, *32*, 255.

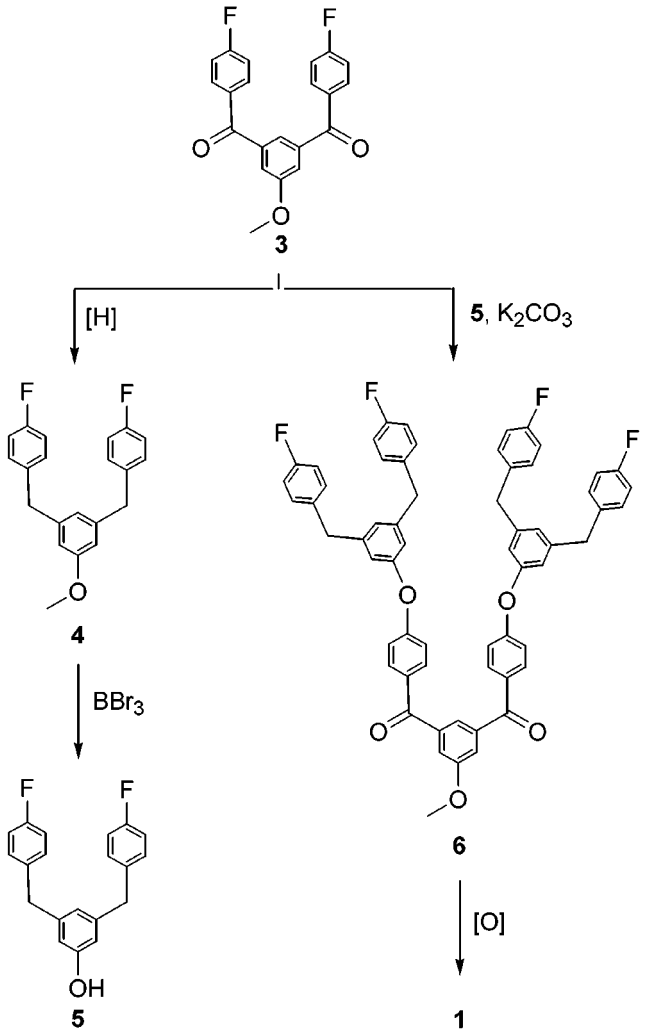
(3) Selected references: (a) Bhatnagar, A.; Mani, R. S.; King, B.; Mohanty, D. K. *Macromol. Chem. and Phys.* **1996**, *197*, 315. (b) Ding, Y.; Hay, A. S. *Macromolecules* **1996**, *29*, 3090. (c) Selampinar, F.; Akbulut, U.; Yildiz, E.; Gungor, A.; Toppare, L. *Synth. Met.* **1997**, *89*, 111. (d) Zhang, S. J.; Zheng, Y. B.; Wu, Z. W.; Tian, M. W.; Yang, D. C.; Yosomiya, R. *Liq. Cryst.* **1998**, *24*, 311. (e) Baxter, I.; Colquhoun, H. M.; Hodge, P.; Kohnke, F. H.; Lewis, D. F.; Williams, D. J.; *J. Mater. Chem.* **2000**, *10*, 309. (f) Fitch, J. W.; Reddy, V. S.; Youngman, P. W.; Wohlfahrt, G. A.; Cassidy, P. E. *Polymer* **2000**, *41*, 2301.

(4) L'abbé, G.; Forier, B.; Dehaen, W. *J. Chem. Soc., Chem. Commun.* **1996**, 2143.

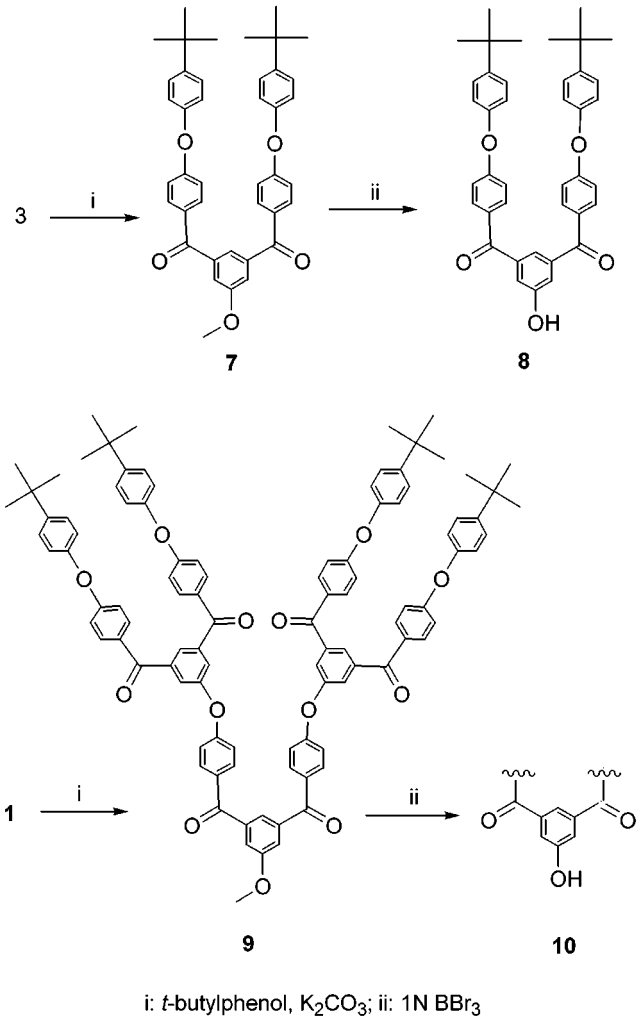
(5) Hwang, Y.-S.; Matsui, M. *Agr. Biol. Chem.* **1971**, *35*, 1812.

10.1021/jo015805j CCC: $22.00 © 2002 American Chemical Society
Published on Web 01/15/2002

Scheme 2. General Synthesis of Hypermonomer 1



Scheme 3. General Synthesis of G-1 and G-2 Phenols 8 and 10



Thus, the G-1 dendron **7** was prepared from monomer **3** and 4-*tert*-butylphenol in 87% yield and converted to the corresponding phenol **8** (92%) with BBr_3 solution. The G-2 dendron **9** was obtained from hypermonomer **1** and 4-*tert*-butylphenol in 88% yield and converted to the G-2 phenol **10** in 83% yield (Scheme 2).

G-3 **11** and G-4 **12** dendritic poly(ether ketones) were prepared in one step in 68 and 54% yields, respectively, from hypermonomer **1** and poly(ether ketone)phenols **8** and **10** (Scheme 4).

In conclusion, we developed a new AB_4 hypermonomer on the basis of (1) a reduction/oxidation strategy for protection/deprotection and (2) the nucleophilic substitution reaction. The latter reaction is then used in an accelerated synthesis of poly(ether ketone) dendrons, starting from the hypermonomer.

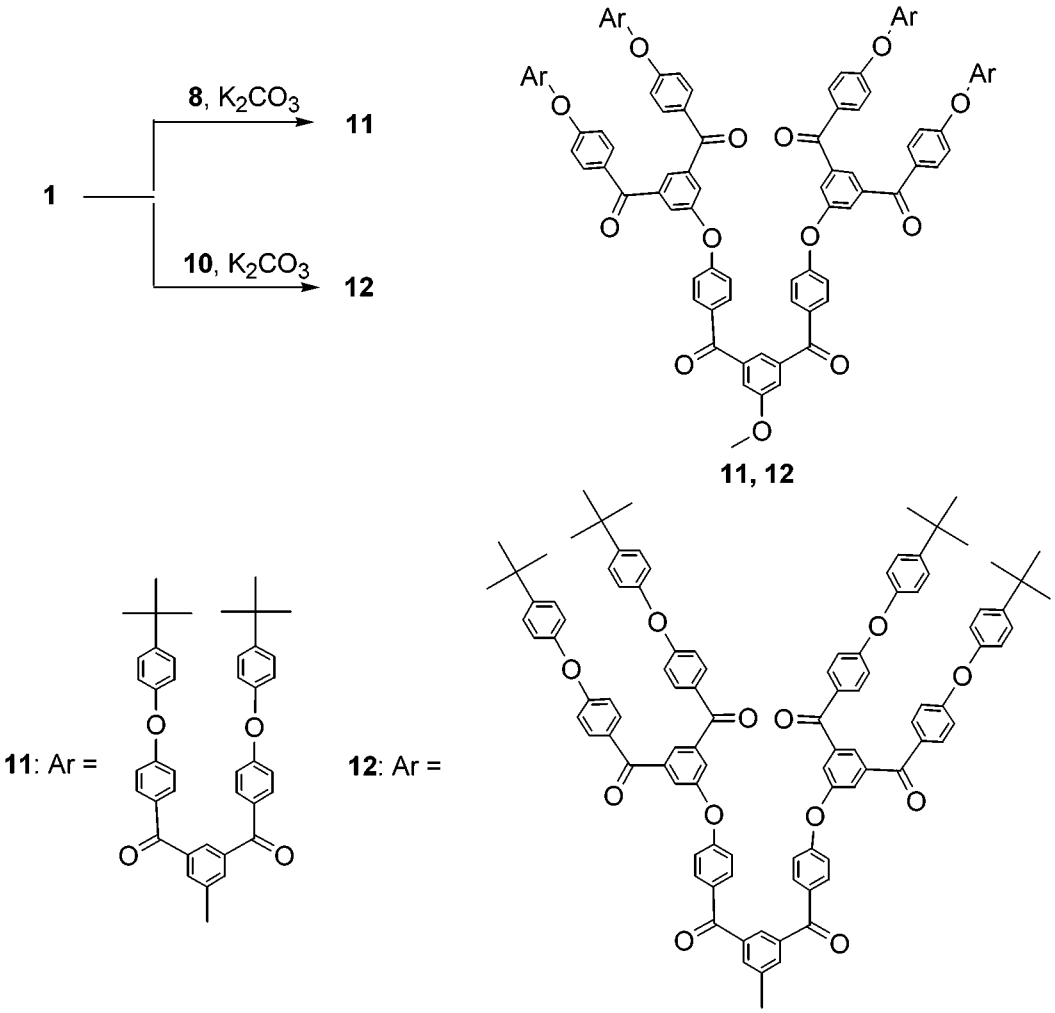
Experimental Section

Materials and Methods. NMR spectra were acquired on commercial instruments (Bruker Avance 300 MHz or Bruker AMX 400 MHz), and chemical shifts are reported in parts per million (δ) referenced to internal residual solvent protons (1H) or the carbon signal of deuterated solvents (13C). Mass spectrometry data were obtained with an HP MS apparatus 5989A (electron impact (EI), 70 eV; chemical ionization (CI), CH4) or a Micromass Quattro II apparatus (electrospray ionization (ESI), solvent mixture: CH_2Cl_2/MeOH + NH_4OAc). MALDI-TOF mass spectra were recorded on a KRATOS ANALYTICAL (Manchester, U.K.) KOMPACT MALDI-2 K-PROBE instrument in positive high (20 kV) mode, which uses a 3 ns pulse from a nitrogen laser (λ = 337 nm) at a target area of 100 μm in diameter and pulse extracts the ions down a linear flight tube (2 m), employing dithranol as a matrix. Melting points were determined using a Reichert Thermovar apparatus. DMF was dried on molecular sieves 4 Å, and THF was freshly distilled from sodium diphenyl ketyl solution. 5-Methoxyisophthaloyl chloride was prepared by the method described.[5]

3,5-Bis{4-[3.5-bis(4-fluorobenzoyl)phenoxy]benzoyl}-anisole 1. To a solution of 3,5-bis[3.5bis(4-fluorobenzyl)phenyloxybenzoyl]anisole **6** (350 mg, 0.38 mmol) and tetrabutylammonium bromide (300 mg) in dichloromethane (10 mL) was added potassium permanganate (1.0 g), and the deeply colored reaction mixture was stirred under reflux for 3 days. The reaction was monitored with TLC. When the starting compound disappeared, the reaction mixture was allowed to cool to room temperature and MeOH was added dropwise. After the solution became colorless, the black precipitate was filtered off and washed with dichloromethane and the solvent was removed under reduced pressure. The product was purified by silica gel column chromatography with dichloromethane/EtOAc (20:1). Yield: 250 mg (67%). ^{1}H NMR ($CDCl_3$, δ, ppm): 3.92 s (3H), 7.12 m (4H), 7.17 m (8H), 7.51 d (2H), 7.69 s (1H), 7.69 d (4H), 7.88 m (14H). ^{13}C NMR ($CDCl_3$, δ, ppm): 55.8, 115, 9 (d, J = 22 Hz), 117.9, 118.5, 123.1, 124.0, 126.4, 132.5, 132.67 (d, J = 7 Hz), 132.73, 132.75, 139.1, 139.8, 156.0, 159.6, 160.4, 165.7 (d, J = 256 Hz), 193.1, 194.0. MS (ESI): m/z 989. Found, %: C, 73.82; H, 3.64. Anal. Calcd for $C_{61}H_{34}F_4O_9$, %: C, 74.09; H, 3.67. M 989.

3.5-Bis(4-fluorobenzoyl)anisole 3. To a solution of 5-methoxyisophthaloyl dichloride **2** (16.3 g, 0.07 mmol) at −78 °C in

Scheme 4. General Synthesis of G-3 11 and G-4 12 Dendritic Poly(Ether Ketones)



THF (150 mL) was added dropwise over a period of about 30 min a solution of the Grignard reagent obtained from Mg (3.9 g, 0.16 mol) and 4-fluorophenyl bromide (28 g, 0.16 mmol) in THF (100 mL). The reaction mixture was allowed to reach room temperature under stirring for 1 h. After addition of water (300 mL), the organic layer was extracted with ether, washed with 1 N NaOH and water, and dried over $MgSO_4$. Evaporation afforded the residue, which after purification by silica gel column chromatography with dichloromethane/ethyl acetate (6:1) gave 14.8 g (60%) of anisole **3**, mp 100−101 °C.[1a]

The next fraction gave 8.2 g (30%) of white solid with an mp = 152−3 °C, which was identified as 3-(4-fluorobenzyl)-5-methoxybenzoic acid **3a**. ^{1}H NMR (DMSO-d_6, δ, ppm): 3.89 s (3H), 7.41 m (2H), 7.47 m (1H), 7.70 m (1H), 7.78 m (1H), 7.86 m (2H), 13.0 v br s (1H). ^{13}C NMR (DMSO-d_6, δ, ppm): 55.7, 115.7 (d, J = 22 Hz), 118.1, 118.7, 122.4, 132.5, 132.5 (d, J = 9 Hz), 138.6, 159.3, 164.5 (d, J = 254 Hz), 166.3, 193.4.

3.5-Bis(4-fluorobenzyl)anisole 4. A slurry of 3.5-bis(4-fluorobenzoyl)anisole **3** (352 mg, 1 mmol), EtOH (20 mL), 36% HCl (0.5 mL), and 5% Pd/C (200 mg) was hydrogenated at room temperature and atmosphere pressure with stirring for 40 h. The catalyst was filtered off and washed with EtOH. The combined ethanolic solutions were boiled with charcoal and filtered, and the filtrate was evaporated under reduced pressure. The viscous residue was dried under vacuum to a constant weight. Yield: 310 mg (96%), colorless oil. ^{1}H NMR ($CDCl_3$, δ, ppm): 3.68 s (3H), 3.84 s (4H), 6.53 s (2H), 6.58 s (1H), 6.93 m (4H), 7.09 m (4H). ^{13}C NMR ($CDCl_3$, δ, ppm): 41.0, 55.0, 112.3, 115.1 (d, J = 22 Hz), 121.9, 130.1 (d, J = 9 Hz), 136.53, 142.56, 160.0, 160.4 (d, J = 254 Hz). MS (EI): m/z 324. Anal. Calcd for $C_{21}H_{18}F_2O$: M 324. The product was used in the next stage without purification.

3.5-Bis(4-fluorobenzyl)phenol 5. To a solution of 3.5-bis-(4-fluorobenzyl)anisole **4** (420 mg, 1.3 mmol) in dichloromethane (2 mL) was added 4 mL of 1 N BBr_3 in dichloromethane under argon at −78 °C, and the mixture was stirred for 1h. The reaction mixture was allowed to warm to room temperature for 2 h, and cold water (20 mL) was added in one portion; the mixture was stirred overnight. The white solid was filtered off, washed with water, dried under reduced pressure, and purified by silica gel column chromatography with dichloromethane. Yield: 390 mg (97%), white solid, mp 104.5−105 °C. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 3.83 s (4H), 4.71 br s (1H), 6.42 s (2H), 6.58 s (1H), 6.93 m (4H), 7.09 m (4H). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 40.8, 113.6, 115.2 (d, J = 22 Hz), 121.9, 130.2 and 130.3 (d, J = 9 Hz), 136.3, 142.9, 155.8, 160.4 (d, J = 254 Hz). MS (EI): m/z M^+ 310. Found, %: C, 77.11; H, 5.16. Anal. Calcd for $C_{20}H_{16}F_2O$, %: C, 77.40; H, 5.20. M 310.

3,5-Bis{4-[3.5-bis(4-fluorobenzyl)phenoxy]benzoyl}-anisole 6. To a solution of 3.5-bis(4-fluorobenzoyl)anisole **3** (176 mg, 0.5 mmol) and 3.5-bis(4-fluorobenzyl)phenol **5** (325 mg, 1.05 mmol) in a mixture of toluene (1 mL) and DMF (2 mL) was added K_2CO_3 (150 mg, 1.09 mmol), and the reaction mixture was stirred under reflux for 3 h in an argon atmosphere. The reaction mixture was diluted with water and extracted with dichloromethane, and the organic layer was washed with water, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography with dichloromethane/ether (20:1). Yield: 410 mg (82%), colorless glass. ^{1}H NMR ($CDCl_3$, δ, ppm): 3.88 s (8H), 3.92 s (3H), 6.72 s (4H), 6.83 s (2H), 6.97 m (12H), 7.11 m (12H), 7.49 s (2H), 7.67 (1H). MS (EI): m/z 933. Found, %: C, 78.36; H, 4.89. Anal. Calcd for $C_{61}H_{44}F_4O_5$, %: C, 78.53; H, 4.75. M 933.

3.5-Bis{4-[4-(*tert*-butyl)phenoxy]benzoyl}anisole 7. A mixture of the monomer **3** (1.06 g, 3 mmol), *tert*-butylphenol (0.95 g, 6.3 mmol), potassium carbonate (0.91 g, 6.6 mmol), DMF (10 mL), and toluene (3 mL) was stirred at 130 °C for 1 h while water was distilled off azeotropically with toluene. The reacton temperature was raised to 150 °C, and the mixture was stirred for 1.5 h. The solvent was removed under reduced pressure, and the residue was washed with water, extracted with methylene chloride, and dried over $MgSO_4$. The product was obtained by evaporation of the solvent and purified by silica gel column chromatography with hexane/EtOAc (6:1). Yield: 1.6 g (87%). ^{1}H NMR ($CDCl_3$, δ, ppm): 1.33 s (18H), 3.90 s (3H), 7.00 m (8H), 7.40 m (4H), 7.50 d (2H), 7.67 t (1H), 7.82 m (4H). ^{13}C NMR ($CDCl_3$, δ, ppm): 31.4, 34.4, 55.8, 116.9, 118.3, 119.7, 123.3, 126.9, 132.4, 139.4, 147.7, 152.8, 159.6, 162.4, 194.3. MS (EI): *m*/*z* 612. Found, %: C, 80.34; H, 6.57. Anal. Calcd for $C_{41}H_{40}O_5$, %: C, 80.36; H, 6.58. M 612.

3.5-Bis{(4-[4-(*tert*-butyl)phenoxy]benzoyl}phenol 8. To a solution of anisole **7** (1.6 g, 2.6 mmol) in dichloromethane (2 mL) was added 4 mL of 1 N BBr_3 in dichloromethane under argon at −78 °C, and the solution was was stirred for 1 h. The reaction mixture was allowed to warm to room temperature for 2 h, and 20 mL of water was added; the mixture was stirred overnight. The organic layer was washed with water and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the product was purified by silica gel column chromatography with dichloromethane/EtOAc (10:1). Yield: 1.43 g (92%). ^{1}H NMR ($CDCl_3$, δ, ppm): 1.33 s (18H), 6.31 br s (1H), 7.00 m (8H), 7.40 m (4H), 7.52 d (2H), 762 t (1H), 7.81 m (4H). ^{13}C NMR ($CDCl_3$, δ, ppm): 31.4, 34.4, 116.9, 119.8, 120.0, 123.4, 126.9, 130.8, 132.6, 139.5, 147.8, 152.8, 156.1, 162.5, 194.6. MS (EI): *m*/*z* 598. Found, %: C, 80.28; H, 6.42. Anal. Calcd for $C_{40}H_{38}O_5$, %: C. 80.24; H. 6.40. M 598.

3,5-Bis[4-(3.5-bis{4-[4-(*tert*-butyl)phenoxy]benzoyl}-phenoxy)benzoyl]anisole 9 was prepared by the same procedure as that for the synthesis of **7** from **1** (300 mg, 0.30 mmol), *tert*-butylphenol (220 mg, 1.50 mmol), potassium carbonate (210 mg, 1.50 mmol), toluene (1 mL), and DMF (2 mL). The product was purified by silica gel column chromatography with dichloromethane/EtOAc (40:1). Yield: 400 mg (88%). ^{1}H NMR ($CDCl_3$, δ, ppm): 1.33 s (36H), 3.91 s (3H), 7.00 m (8H), 7.02 m (8H), 7.10 m (4H), 7.40 m (8H), 7.50 d (2H), 7.67 d (4H), 7.69 t (1H), 7.81 m (8H), 7.87 m (4H), 7.89 t (2H). ^{13}C NMR ($CDCl_3$, δ, ppm): 31.4, 34.4, 55.9, 117.0, 117.9, 118.5, 119.8, 123.1, 123.8, 126.5, 126.9, 130.5, 132.4, 132.5, 132.7, 139.3, 140.3, 147.9, 152.7, 155.8, 160.7, 162.7, 193.4, 194.1. MS (ESI): *m*/*z* 1509. Found, %: C, 80.09; H, 5.73. Anal. Calcd for $C_{101}H_{378}O_{61}$, %: C, 80.35; H, 5.87. M 1509.

3,5-Bis[4-(3.5-bis{4-[4-(*tert*-butyl)phenoxy]benzoyl}-phenoxy)benzoyl]phenol 10 was prepared by the same procedure as that for the synthesis of phenol **8** from anisole **7** (400 mg, 0.26 mmol), dichloromethane (1 mL), and 4 mL of 1 N BBr_3 in dichloromethane. The product was purified by column silica gel chromatography with dichloromethane/EtOAc (25:1). Yield: 330 mg (85%). ^{1}H NMR ($CDCl_3$, δ, ppm): 1.33 s (36H), 6.12 br s (1H), 7.00 m (8H), 7.02 m (8H), 7.10 m (4H), 7.40 m (8H), 7.45 d (2H), 7.66 d (4H), 7.69 t (1H), 7.81 m (8H), 7.86 m (4H), 7.89 t (2H). ^{13}C NMR ($CDCl_3$, δ, ppm): 31.4, 34.4, 117.0, 117.9, 119.8, 120.1, 123.7, 126.5, 126.9, 130.5, 132.3, 132.5, 132.7, 139.5, 140.2, 147.9, 152.7, 155.9, 160.7, 162.7, 193.5, 194.0. MS (ESI): *m*/*z* 1495. Found, %: C, 80.06; H, 5.75. Anal. Calcd for $C_{100}H_{86}O_{13}$, %: C, 80.30; H, 5.80. M 1495.

3,5-Bis(4-{3,5-bis[4-(3.5-bis{4-[4-(*tert*-butyl)phenoxy]-benzoyl}phenoxy)benzoyl]phenoxy}benzoyl)anisole 11 was prepared by the same procedure as that for the synthesis of **9** from **1** (160 mg, 0.16 mmol), phenol **9** (420 mg, 0.70 mmol), potassium carbonate (93 mg, 0.70 mmol), toluene (1 mL), and DMF (2 mL). The product was purified by silica gel column chromatography with dichloromethane/EtOAc (40:1). Yield: 350 mg (68%). ^{1}H NMR ($CDCl_3$, δ, ppm): 1.33 s (72H), 3.90 br s (3H), 7.00 m (16H), 7.02 m (16H), 7.10 m (12H), 7.40 m (16 H), 7.50 d (2H), 7.68 d (12H), 7.70 t (1H), 7.81 m (16H), 7.86 m (12H), 7.90 m (6H). ^{13}C NMR ($CDCl_3$, δ, ppm): 31.4, 34.4, 55.8, 116.9, 117.9, 118.5, 119.8, 123.1, 123.8, 123.9, 126.6, 126.9, 130.4, 131.7, 132.3, 132.4, 132.7, 139.2, 140.0, 140.2, 147.8, 152.6, 155.6, 155.7, 155.8, 160.5, 160.9, 172.1, 162.6, 193.1, 193.3, 194.0. MS (MALDI-TOF): *m*/*z* 3305 [M + H]. Found, %: C, 80.21; H, 5.41. Anal. Calcd for $C_{221}H_{184}O_{29}$, %: C, 80.34; H, 5.61. M 3304.

3.5-Bis{4-[3,5-bis(4-{3,5-bis[4-(3.5-bis{4-[4-(*tert*-butyl)-phenoxy]benzoyl}phenoxy)benzoyl]phenoxy}benzoyl)-phenoxy]benzoyl}anisole 12 was prepared by the same procedure as that for the synthesis of **9** from **1** (31 mg, 0.032 mmol), phenol **10** (190 mg, 0.13 mmol), potassium carbonate (20 mg, 0.14 mmol), toluene (0.5 mL), and DMF (1 mL). The product was purified by silica gel column chromatography with dichloromethane/EtOAc (20:1). Yield: 120 mg (54%). ^{1}H NMR ($CDCl_3$, δ, ppm): 1.33 s (144H), 3.86 m (3H), 6.98 m (32H), 7.00 m (32H), 7.10 m (32H), 7.39 m (32 H), 7.45 m (2H), 7.67 m (24H), 7.70 m (1H), 7.78 m (32H), 7.87 m (28H), 7.91 m (14H). ^{13}C NMR ($CDCl_3$, δ, ppm): 31.4, 34.4, 55.8, 116.9, 117.9, 118.5, 119.8, 123.8, 123.9, 126.4, 126.9, 126.9, 130.4, 131.7, 131.8, 132.4, 132.7, 139.2, 139.9, 140.0, 140.2, 147.8, 152.6, 155.6, 155.7, 155.8, 156.0, 162.1, 162.6, 193.0, 193.3, 194.0. MS (MALDI-TOF): *m*/*z* 6915 [M + Na]. Found, %: C, 79.98; H, 5.50. Anal. Calcd for $C_{461}H_{376}O_{61}$, %: C, 80.34; H, 5.57. M 6892.

Acknowledgment. We thank the University of Leuven, the Ministerie voor Wetenschapsbeleid, and the FWO Vlaanderen for their continuing support. R.S. thanks the University of Leuven for a postdoctoral fellowship. D.B.A. thanks project BQU2000-1157 for financial support and Prof J. Veciana for backing.

JO015805J