

Dendrimer Disassembly by Benzyl Ether Depolymerization

Sheng Li, Michael L. Szalai, Robert M. Kevwitch, and Dominic V. McGrath*

Department of Chemistry, University of Arizona, Tucson, AZ 85721

Phone: 520-626-4690; Fax: 520-621-8407; E-mail: mcgrath@u.arizona.edu

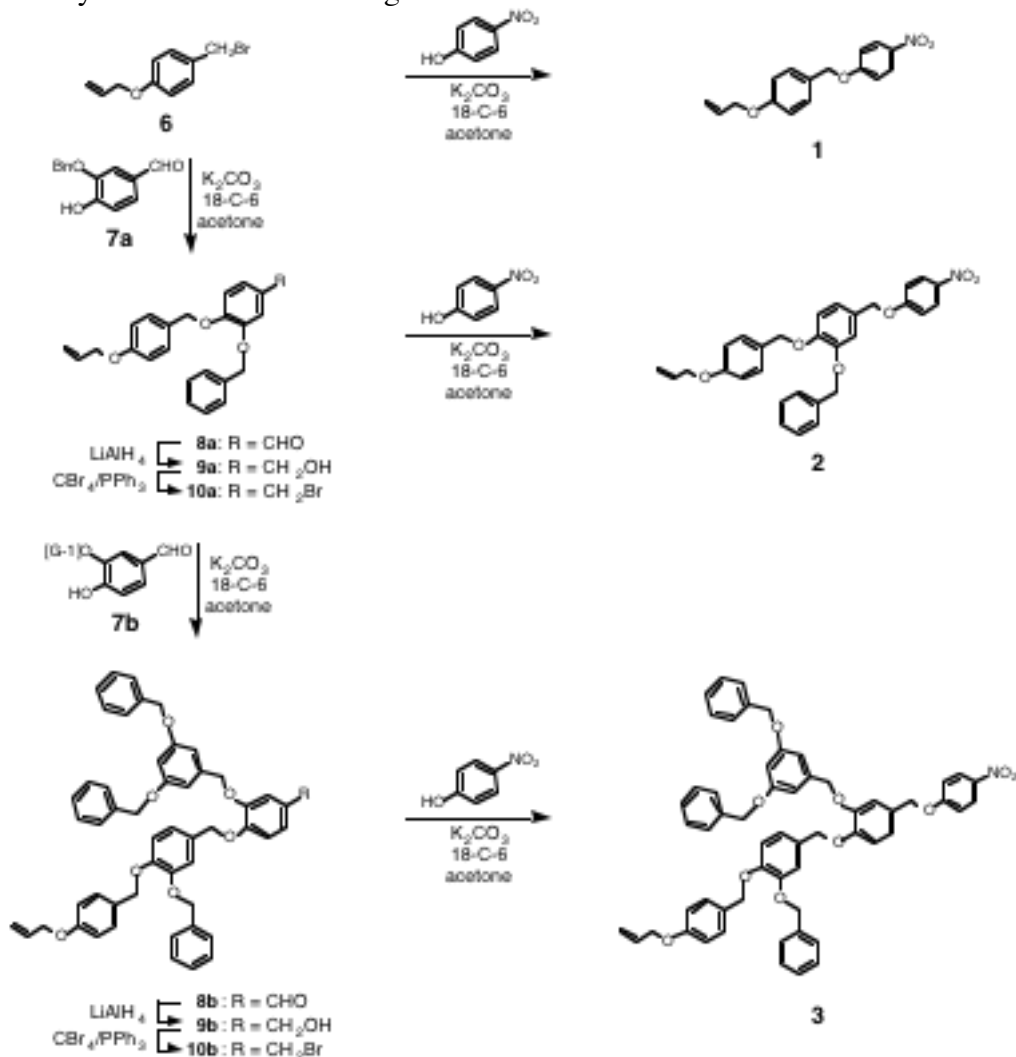
Supporting Information

Synthesis of Dendrons 1–3:

Experimental Part

Materials and Methods. NMR spectroscopy and mass spectrometry (MS) were obtained using commercially available instrumentation. Tetrahydrofuran (THF) was distilled under N₂ from sodium-benzophenone ketyl. Acetone was dried over crushed 3Å molecular sieves. Potassium carbonate (granular, J.T. Baker) was dried at 100 °C at reduced pressure and stored in a vacuum oven. Fréchet-type dendritic bromide¹ [G-1]Br and compound **6**² were prepared according to literature methods. All other compounds were prepared according to Schemes S1 and S2 as detailed in the following procedures. All needed reagents were purchased from commercial suppliers and used as received. Flash chromatography was performed by the method of Still et al.³ using silica gel (32-63µ, Scientific Adsorbants, Inc., Atlanta GA). Thin-layer chromatography (TLC) was performed on precoated plates (Silica Gel HLO, F-254, Scientific Adsorbants, Inc.).

Scheme S1: Synthesis of Zeroth through Second Generation Dendrons **1–3**.



4-Allyloxybenzyl alcohol, 4-nitrophenyl ether (1). A mixture of 4-allyloxy benzyl bromide (**6**) (0.10 g, 0.44 mmol), K₂CO₃ (0.14 g, 1.0 mmol), 18-crown-6 (13 mg, 0.05 mmol), and *p*-nitrophenol (61 mg, 0.44 mmol) in 10 mL dry acetone was heated to reflux for 16h with stirring. The reaction mixture was cooled to RT, evaporated to dryness, and the residue was partitioned between CH₂Cl₂ (10 mL) and water (20 mL). The aqueous phase was separated and extracted with CH₂Cl₂ (2x10 mL). The combined organic phase was washed with brine (2x20 mL), dried, and concentrated. Purification by flash chromatograph (SiO₂, 10:30:60 ether-dichloromethane-hexane) yielded **1** (94 mg, 75%) as a colorless solid: ¹H NMR (500 MHz, CDCl₃) δ 8.18, 7.10 (AA'BB',

4H), 7.32, 6.88 (AA'BB', 4H), 6.03 (m, 1H), 5.41 (dd, $J = 1.5, 17.5$ Hz, 1H), 5.28 (dd, $J = 1.5, 10.0$ Hz, 1H), 4.53 (dt, $J = 5.0, 1.5$ Hz, 2H). ^{13}C NMR (62.9 MHz, CDCl_3) δ 133.0, 129.3, 127.6, 125.9, 117.8, 117.6, 115.0, 114.8, 114.6, 71.5, 70.5, 68.8.

4-(4-Allyloxybenzyloxy)-3-benzyloxybenzyl alcohol, 4-nitrophenyl ether (2). A mixture of **10a** (0.15 g, 0.34 mmol), K_2CO_3 (0.14 g, 1.0 mmol), 18-crown-6 (5 mg, 0.02 mmol), and *p*-nitrophenol (48 mg, 0.34 mmol) in 10 mL dry acetone was heated to reflux for 16h with stirring. The reaction mixture was cooled to RT, evaporated to dryness, and the residue was partitioned between CH_2Cl_2 (10 mL) and water (20 mL). The aqueous phase was separated and extracted with CH_2Cl_2 (2x10 mL). The combined organic phase was washed with brine (2x20 mL), dried, and concentrated. Purification by flash chromatograph (SiO_2 , 10:35:55 ether-dichloromethane-hexane) yielded **2** (0.12 g, 71%) as a colorless solid: ^1H NMR (500 MHz, CDCl_3) δ 8.16 (d, $J = 9.0$ Hz, 2H), 7.40-7.28 (m, 6H), 6.97-6.89 (m, 8H), 6.03 (m, 1H), 5.39 (dd, $J = 1.5, 17.5$ Hz, 1H), 5.27 (dd, $J = 1.5, 10.0$ Hz, 1H), 5.14 (s, 2H), 5.08 (s, 2H), 5.01 (s, 2H), 4.52 (dt, $J = 5.0, 1.5$ Hz, 2H). ^{13}C NMR (62.9 MHz, CDCl_3) δ 163.6, 159.1, 158.4, 149.3, 141.5, 141.0, 137.0, 133.2, 129.3, 128.9, 128.5, 127.8, 127.3, 125.9, 121.0, 117.7, 115.2, 114.8, 114.7, 71.3, 71.1, 70.6, 68.8; MS (FAB) m/z 497.3 (M^+ , 0.7%, $\text{C}_{30}\text{H}_{27}\text{NO}_6$ requires 497.2).

4-[4-(4-Allyloxybenzyloxy)-3-benzyloxybenzyloxy]-3-(3,5-bisbenzyloxybenzyloxy)benzyl alcohol, 4-nitrophenyl ether (3). A mixture of bromide **10b** (0.46 g, 0.53 mmol), K_2CO_3 (0.14 g, 1.0 mmol), 18-crown-6 (8 mg, 0.03 mmol), and *p*-nitrophenol (74 mg, 0.53 mmol) in 20 mL dry acetone was heated to reflux for 16h with stirring. The reaction mixture was cooled to RT, evaporated to dryness, and the residue was partitioned between CH_2Cl_2 (10 mL) and water (20 mL). The aqueous phase was separated and extracted with CH_2Cl_2 (2x10 mL). The combined organic phase was washed with brine (2x20 mL), dried, and concentrated. Purification by flash chromatograph (SiO_2 , 10:35:55 ether-dichloromethane-hexane) yielded **3** (0.39 g, 79%) as a colorless solid: ^1H NMR (500 MHz, CDCl_3) δ 8.14 (d, $J = 9.0$ Hz, 2H), 7.36-7.27 (m, 19H), 7.05-6.85 (m, 8H), 6.68 (d, $J = 2.0$ Hz, 2H), 6.52 (t, $J = 2.0$ Hz, 1H), 6.04 (m, 1H), 5.40 (dd, $J = 1.5, 17.0$ Hz, 1H), 5.27 (dd, $J = 1.0, 10.0$ Hz, 1H), 5.08 (s, 2H), 5.04 (s, 2H), 5.03 (s, 2H), 5.00 (s, 2H),

4.97 (s, 2H), 4.94 (s, 4H), 4.51 (dt, $J = 5.0, 1.5$ Hz, 2H). ^{13}C NMR (62.9 MHz, CDCl_3) δ 163.6, 160.1, 158.5, 158.2, 149.0, 148.9, 142.0, 139.5, 137.2, 136.7, 133.2, 128.9, 128.5, 128.4, 128.0, 127.7, 127.5, 127.4, 125.8, 121.0, 120.6, 117.6, 115.0, 114.8, 114.6, 114.5, 114.4, 106.6, 101.8, 71.2, 71.1, 70.5, 70.0, 68.8; MS (FAB) m/z 922.5 ($\text{M}+\text{H}$, 0.8%, $\text{C}_{58}\text{H}_{52}\text{NO}_{10}$ requires 922.4).

3-Benzyloxy-4-hydroxybenzaldehyde (7a).⁴ A literature procedure was used with some modification.⁴ A solution of 3, 4-dihydroxy benzaldehyde (11.0 g, 80 mmol) in dry DMF (30 ml) was slowly added to a suspension of NaH (3.84 g, 160 mmol) in dry DMF (30 mL) at RT. After 30 min under stirring, benzyl chloride (9.2 g, 73 mmol) was slowly dropped in at 0 °C. The resulting mixture was kept at 0 °C for 16 h. After removal of DMF in vacuo, the residue was acidified with HCl, extracted with ethyl acetate (50 mL), washed with brine (4x50 mL) and dried (Na_2SO_4). After removal of the solvent, the residue was recrystallized twice in ether/hexane to give the product **7a** (8.95 g, 54%) as a colorless solid: ^1H NMR (500 MHz, CDCl_3) δ 9.80 (s, 1H), 7.49 (d, $J = 1.5$ Hz, 2H), 7.44-7.40 (m, 5H), 7.05 (d, $J = 8.0$ Hz, 1H), 6.18 (s, 1H), 5.16 (s, 2H).

3-(3,5-Bisbenzyloxybenzyloxy)-4-hydroxybenzaldehyde (7b). A literature procedure was used with some modification.⁴ A solution of 3, 4-dihydroxy benzaldehyde (2.07 g, 15.0 mmol) in dry DMF (30 ml) was slowly added to a suspension of NaH (0.72 g, 30 mmol) in dry DMF (30 mL) at RT. After 30 min under stirring, [G-1]Br (3.0 g, 7.82 mmol) was slowly added in at 0 °C. The resulting mixture was kept at 0 °C for 16 h. After removal of DMF in vacuo, the residue was acidified with HCl, extracted with ethyl acetate (50 mL), washed with brine (4x50 mL) and dried (Na_2SO_4). Purification by flash chromatograph (SiO_2 , 35:65 ethyl acetate-hexane) yielded **7b** (2.72 g, 79%) as a colorless solid: ^1H NMR (500 MHz, CDCl_3) δ 9.76 (s, 1H), 7.45-7.31 (m, 12H), 7.05 (d, $J = 9.0$ Hz, 1H), 6.64 (d, $J = 2.0$ Hz, 2H), 6.61 (t, $J = 2.0$ Hz, 1H), 5.05 (s, 2H), 5.02 (s, 4H). ^{13}C NMR (62.9 MHz, CDCl_3) δ 190.8, 160.1, 151.8, 146.2, 137.7, 136.5, 129.6, 128.5, 128.0, 127.4, 114.7, 110.3, 106.8, 101.9, 70.9, 70.0.

4-(4-Allyloxybenzyloxy)-3-benzyloxybenzaldehyde (8a). A mixture of 4-allyloxy benzyl bromide (**6**) (3.0 g, 13.2 mmol), K_2CO_3 (2.76 g, 20.0 mmol), and 3-benzyloxy-4-hydroxy benzaldehyde (**7a**) (3.0 g, 13.2 mmol) in 30 mL dry DMF was heated to 80 °C for 24h with

stirring. After removal of DMF in vacuo, the residue was partitioned between CH₂Cl₂ (20 mL) and water (20 mL). The aqueous phase was separated and extracted with CH₂Cl₂ (2x10 mL). The combined organic phase was washed with brine (3x30 mL), dried, and concentrated. Purification by flash chromatograph (SiO₂, 10:35:55 ether-dichloromethane-hexane) yielded **8a** (2.55 g, 51%) as a colorless solid: ¹H NMR (500 MHz, CDCl₃) δ 9.79 (s, 1H), 7.46-7.29 (m, 9H), 7.02 (d, *J* = 8.5 Hz, 1H), 6.90 (dt, *J* = 9.0, 3.0 Hz, 2H), 6.03 (m, 1H), 5.40 (dd, *J* = 1.5, 17.0 Hz, 1H), 5.28 (dd, *J* = 1.5, 10.0 Hz, 1H), 5.18 (s, 2H), 5.16 (s, 2H), 4.52 (dt, *J* = 5.0, 1.5 Hz, 2H). ¹³C NMR (62.9 MHz, CDCl₃) δ 190.8, 158.5, 154.3, 149.2, 136.5, 133.1, 130.2, 129.8, 128.8, 128.5, 128.4, 128.0, 127.3, 126.7, 117.8, 114.8, 113.2, 112.4, 70.9, 70.7, 68.8.

4-[4-(4-Allyloxybenzyloxy)-3-benzyloxybenzyloxy]-3-(3,5-

bisbenzyloxybenzyloxy)benzaldehyde (8b). A mixture of benzyl bromide **10a** (3.25 g, 7.40 mmol), K₂CO₃ (1.38 g, 10.0 mmol), 18-crown-6 (0.11 g, 0.40 mmol), and **7b** (3.26 g, 7.40 mmol) in 30 mL dry acetone was heated to reflux for 16h with stirring. The reaction mixture was cooled to RT, evaporated to dryness, and the residue was partitioned between CH₂Cl₂ (20 mL) and water (20 mL). The aqueous phase was separated and extracted with CH₂Cl₂ (2x20 mL). The combined organic phase was washed with brine (2x30 mL), dried, and concentrated. Purification by flash chromatograph (SiO₂, 10:40:50 ether-dichloromethane-hexane) yielded **8b** (5.15 g, 87%) as a colorless solid: ¹H NMR (500 MHz, CDCl₃) δ 9.79 (s, 1H), 7.43-7.26 (m, 19H), 7.03 (d, *J* = 2.0 Hz, 1H), 6.97-6.94 (m, 2H), 6.88-6.84 (m, 3H), 6.71 (d, *J* = 2.5 Hz, 2H), 6.52 (t, *J* = 2.0 Hz, 1H), 6.04 (m, 1H), 5.40 (ddd, *J* = 1.5, 1.5, 17.5 Hz, 1H), 5.28 (dd, *J* = 1.5, 10.0 Hz, 1H), 5.12 (s, 2H), 5.10 (s, 2H), 5.07 (s, 2H), 4.96 (s, 4H), 4.94 (s, 2H), 4.51 (dt, *J* = 5.0, 1.5 Hz, 2H). ¹³C NMR (62.9 MHz, CDCl₃) δ 190.7, 160.1, 158.3, 154.1, 149.1, 149.0, 148.9, 139.0, 137.1, 136.7, 133.2, 130.2, 129.4, 129.3, 128.9, 128.5, 128.4, 127.9, 127.7, 127.5, 127.3, 126.6, 120.4, 117.6, 115.0, 114.6, 114.2, 113.1, 112.3, 106.0, 101.6, 71.1, 71.0, 70.7, 70.0, 68.8; MS (FAB) *m/z* 798.3 (M⁺, 0.35%, C₅₂H₄₆O₈ requires 798.3).

4-(4-Allyloxybenzyloxy)-3-benzyloxybenzyl alcohol (9a). To a suspension of LiAlH₄ (0.57 g, 15.0 mmol) in anhydrous ether (50 mL) at 0 °C was added with stirring aldehyde **8a** (3.05 g, 8.14

mmol). The reaction was allowed to warm to RT under N₂ while stirring (1h) and then quenched by slow addition of water (10 mL), followed by 5% H₂SO₄ (20 mL). After the mixture was allowed to stir at ambient temperature (1h), the organic layer was separated, the aqueous phase was further extracted with ether (2x20 mL), and the combined organic phase was washed with brine and dried (Na₂SO₄). Concentration in vacuo yielded **9a** as a colorless solid (2.83 g, 92%) which was used without further purification: ¹H NMR (500 MHz, CDCl₃) δ 7.44-7.28 (m, 7H), 6.98-6.83 (m, 5H), 6.04 (m, 1H), 5.40 (dd, *J* = 1.5, 17.5 Hz, 1H), 5.28 (dd, *J* = 1.0, 10.0 Hz, 1H), 5.13 (s, 2H), 5.06 (s, 2H), 4.54 (s, 2H), 4.52 (dt, *J* = 5.0, 1.5 Hz, 2H). ¹³C NMR (62.9 MHz, CDCl₃) δ 158.3, 149.2, 148.4, 137.2, 134.4, 133.2, 129.5, 129.0, 128.4, 127.7, 127.3, 120.1, 117.6, 115.4, 114.6, 114.0, 71.2, 71.1, 68.8, 65.1; MS (FAB) *m/z* 376.2 (M⁺, 5%, C₂₄H₂₄O₄ requires 376.2).

4-[4-(4-Allyloxybenzyloxy)-3-benzyloxybenzyloxy]-3-(3,5-bisbenzyloxybenzyloxy)benzyl alcohol (9b). To a suspension of LiAlH₄ (0.57 g, 15.0 mmol) in anhydrous ether (50 mL) at 0 °C was added with stirring a solution of **8b** (5.01 g, 6.26 mmol) in THF. The reaction was allowed to warm to RT under N₂ while stirring (1h) and then quenched by slow addition of water (10 mL), followed by 5% H₂SO₄ (30 mL). After the mixture was allowed to stir at ambient temperature (1h), the organic layer was separated, the aqueous phase was further extracted with ether (2x20 mL), and the combined organic phase was washed with brine and dried (Na₂SO₄). Concentration in vacuo yielded **9b** as a colorless solid (4.62 g, 92%) which was used without further purification: ¹H NMR (500 MHz, CDCl₃) δ 7.44-7.26 (m, 15H), 7.11-6.83 (m, 10H), 6.71 (d, *J* = 1.5 Hz, 2H), 6.52 (t, *J* = 1.5 Hz, 1H), 6.03 (m, 1H), 5.41 (dd, *J* = 1.5, 17.5 Hz, 1H), 5.28 (dd, *J* = 1.5, 10.0 Hz, 1H), 5.07 (s, 2H), 5.04 (s, 2H), 5.02 (s, 2H), 4.96 (s, 6H), 4.53 (s, 2H), 4.51 (dt, *J* = 5.0, 1.5 Hz, 2H). ¹³C NMR (62.9 MHz, CDCl₃) δ 160.0, 158.3, 154.1, 149.1, 149.0, 148.9, 139.0, 137.0, 136.9, 133.2, 130.2, 129.4, 129.3, 128.9, 128.5, 128.2, 127.9, 127.7, 127.6, 127.3, 126.5, 120.4, 117.6, 115.0, 114.6, 114.2, 113.0, 112.3, 106.0, 101.6, 71.1, 71.0, 70.0, 68.8, 65.3; MS (FAB) *m/z* 800.5 (M⁺, 0.6%, C₅₂H₄₈O₈ requires 800.3).

4-(4-Allyloxybenzyloxy)-3-benzyloxybenzyl bromide (10a). To a solution of alcohol **9a** (1.50 g, 3.98 mmol) and CBr₄ (1.99 g, 6.0 mmol) in THF (5 mL) at 0 °C was added portionwise

PPh₃ (1.57 g, 6.0 mmol). The reaction mixture was allowed to stir at RT and was monitored by TLC (SiO₂, 25:75 ethyl acetate-hexane). After the reaction was completed, water (5 mL) and CH₂Cl₂ (20 mL) were added, the organic layer was separated, and the aqueous layer was further extracted with CH₂Cl₂ (2x10 mL). The combined organic layer was washed with brine, dried (Na₂SO₄) and concentrated. Purification by flash chromatograph (SiO₂, 25:75 ethyl acetate-hexane) yielded **10a** (1.41 g, 81%) as a colorless oil: ¹H NMR (500 MHz, CDCl₃) δ 7.43-7.28 (m, 7H), 6.98-6.85 (m, 5H), 6.04 (m, 1H), 5.40 (ddd, *J* = 1.5, 2.0, 17.5 Hz, 1H), 5.27 (ddd, *J* = 1.0, 1.5, 10.0 Hz, 1H), 5.13 (s, 2H), 5.05 (s, 2H), 4.52 (dt, *J* = 5.5, 1.5 Hz, 2H), 4.42 (s, 2H). ¹³C NMR (62.9 MHz, CDCl₃) δ 158.5, 149.7, 148.4, 137.2, 134.3, 133.2, 129.1, 129.0, 128.4, 128.0, 127.7, 127.3, 120.1, 117.6, 115.4, 114.6, 114.0, 71.1, 70.6, 68.8, 35.4.

4-[4-(4-Allyloxybenzyloxy)-3-benzyloxybenzyloxy]-3-(3,5-bisbenzyloxybenzyloxy)benzyl bromide (10b). To a solution of **9b** (2.50 g, 3.12 mmol) and CBr₄ (1.33 g, 4.00 mmol) in THF (5 mL) at 0 °C was added portionwise PPh₃ (1.05 g, 4.00 mmol). The reaction mixture was allowed to stir at RT and was monitored by TLC (SiO₂, 30:70 ethyl acetate-hexane). After the reaction was completed, water (5 mL) and CH₂Cl₂ (20 mL) were added, the organic layer was separated, and the aqueous layer was further extracted with CH₂Cl₂ (2x20 mL). The combined organic layer was washed with brine, dried (Na₂SO₄) and concentrated. Purification by flash chromatograph (SiO₂, 10:40:50 ether-dichloromethane-hexane) yielded **10b** (2.23 g, 83%) as a colorless solid: ¹H NMR (500 MHz, CDCl₃) δ 7.42-7.28 (m, 15H), 7.10-6.83 (m, 10H), 6.70 (d, *J* = 2.0 Hz, 2H), 6.52 (t, *J* = 2.0 Hz, 5.06 (s, 2H), 5.04 (s, 2H), 5.02 (s, 2H), 4.97 (s, 6H), 4.51 (dt, *J* = 5.0, 1.5 Hz, 2H), 4.40 (s, 2H). ¹³C NMR (62.9 MHz, CDCl₃) δ 146.2, 145.8, 145.6, 143.8, 137.0, 133.5, 133.0, 130.4, 130.1, 129.6, 128.8, 128.5, 128.0, 127.5, 127.2, 122.7, 117.8, 117.4, 115.0, 114.7, 112.9, 71.2, 70.2, 68.8, 34.5.

General disassembly reaction procedures for 1–3 in DMF solution are as follows. A quartz cuvette is charged with 2.00 mL of a solution of NaBH_4 in DMF (1.0 mg/1.0 mL). To this is added 20 μL of a 3 mM solution of substrate in DMF followed by 20 μL of a solution of $\text{Pd}(\text{PPh}_3)_4$ in DMSO (1.0 mg/1.0 mL). Monitoring of the reaction begins exactly 75 seconds following the final addition.

UV-Vis Characterization of the Disassembly Process in DMF:

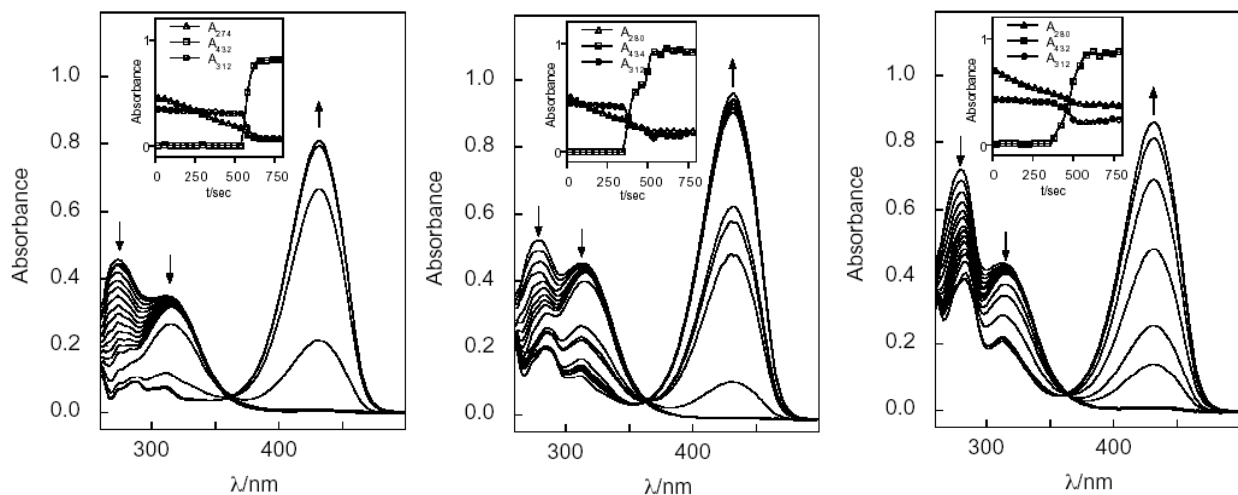


Figure S1. (a) UV spectra recorded during the disassembly reaction of **1** in DMF (40 s intervals). Inset: UV absorbance of the main absorption bands as a function of time. (b) UV spectra recorded during the disassembly reaction of **2** in DMF (40 s intervals). Inset: UV absorbance of the main absorption bands as a function of time. (c) UV spectra recorded during the disassembly reaction of **3** in DMF (40 s intervals). Inset: UV absorbance of the main absorption bands as a function of time.

General disassembly reaction procedures for 1–3 in THF solution are as follows. To a solution of dendron (0.03 mmol) in dry THF (2.0 mL) under N_2 was added $Pd(PPh_3)_4$ (2 mg) and $NaBH_4$ (2 mg). The reaction mixture was maintained at RT. At precise time intervals a 20 μ L aliquot of the reaction mixture was extracted by syringe and diluted into a 20 mL volume of THF-aqueous Na_2CO_3 (10%) (9:1). A UV-Vis absorption spectrum of the resulting solution was recorded immediately.

UV-Vis Characterization of the Disassembly Process in THF:

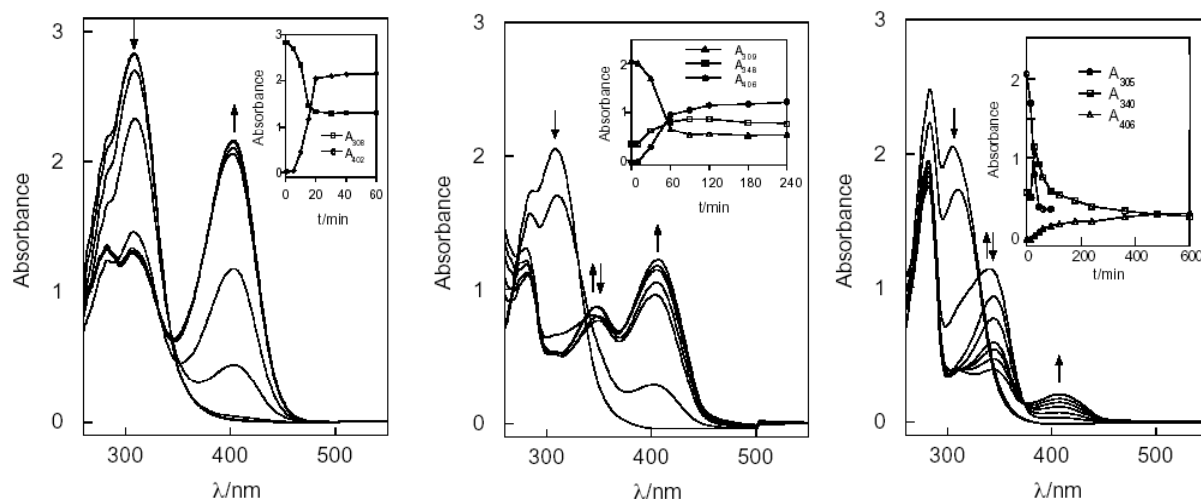


Figure S2. (a) UV spectra recorded during the disassembly reaction of **1** in THF. Inset: UV absorbance of the main absorption bands as a function of time. (b) UV spectra recorded during the disassembly reaction of **2** in THF. Inset: UV absorbance of the main absorption bands as a function of time. (c) UV spectra recorded during the disassembly reaction of **3** in THF. Inset: UV absorbance of the main absorption bands as a function of time.

References and Notes

- (1) Hawker, C.J.; Fréchet, J.M.J. *J. Am. Chem. Soc.* **1990**, *112*, 7638-7647.
- (2) Nakayama, T.; Nomura, M.; Haga, K.; Ueda, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2979-2984.
- (3) Still, W.C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923-2925.
- (4) Santangelo, F. *Synthetic Communications* **1996**, *26*, 2863.