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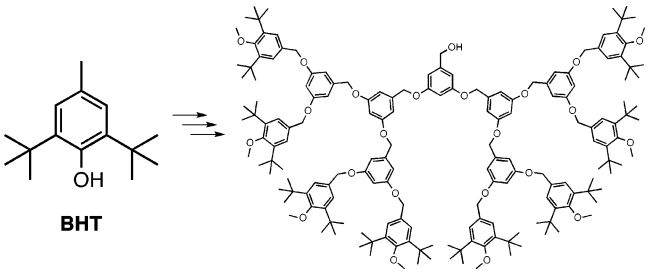
Synthesis and Characterization of BHT-Derived *tert*-Butyl Dendrons

Charles S. Shanahan and Dominic V. McGrath*

Department of Chemistry, University of Arizona, Tucson, Arizona 85721-0041

mcgrath@email.arizona.edu

Received September 19, 2004

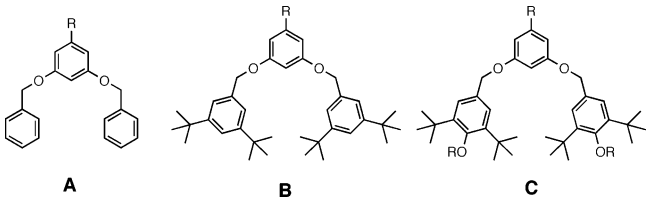


A series of 3,5-poly(aryl ether) dendrons was prepared up to the third generation using inexpensive 3,5-di-*tert*-butyl-4-hydroxytoluene (BHT, **1**) as a starting material.

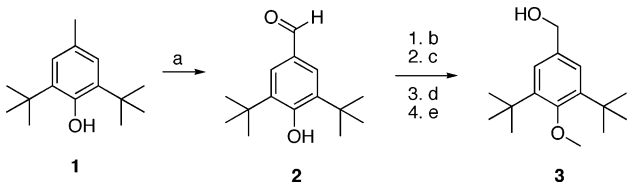
The use of dendritic moieties has proven advantageous in many aspects of materials chemistry.[1] Numerous examples have shown that the addition of dendron moieties to a system can significantly increase solubility, insulate chromophores, and dramatically affect chemical properties.[2] Fréchet-type poly(aryl ether) dendrons[3,4] **A** (Chart 1) are often used for this purpose,[2] but it has been reported that *tert*-butyl groups installed at the periphery of the dendron (**B**) more effectively enhance system solubility and insulation at correspondingly lower generations.[5−7]

Recent efforts in our group to prepare 3,5-di-*tert*-butyl dendrons (**B**) have proven costly not only in price of starting materials but also because of poor yields in the initial steps as reported in the literature.[6e,8] The options for functionalizing the methyl group of 3,5-di-*tert*-butyltoluene in the preparation of dendron **B** include oxidation or radical bromination; these reactions, however, proved problematic. The oxidation route[8] gives low yields, while over-bromination is a problem when NBS bromination conditions are employed.[6e] We sought to overcome these limitations. With a slight structural modification to the target dendrons (**C**), we can now employ 3,5-di-*tert*-butyl-4-hydroxytoluene (BHT, **1**) as the starting material. This results in a much more cost-effective route given that BHT is significantly less expensive than the previously used 3,5-di-*tert*-butyltoluene. Herein, we report the first synthesis and characterization of BHT-derived *tert*-butyl dendrons up to the third generation, demonstrating synthetic as well as fiscal improvements to the previous route to *tert*-butyl dendrons.[6e]

CHART 1



SCHEME 1[a]



[a] Key: (a) NBS/DMSO, 120 °C; (b) $(CH_2OH)_2$, *p*-TsOH, benzene; (c) K_2CO_3, CH_3I, 18-crown-6, acetone/DMF (2:1); (d) HCl (1 M), acetone; (e) KBH_4, THF/MeOH (20:1).

Preparation of the target dendrons began with the synthesis of benzyl alcohol **3**, our critical periphery building block from BHT, using an oxidation/alkylation/reduction sequence. Beginning with an NBS/DMSO oxidation[9] of BHT (Scheme 1), aldehyde **2** was obtained in >90% yields. Direct methylation of **2**, however, gave surprisingly low yields due to the significant formation of a byproduct, possibly the corresponding quinone methide ether. Similar problems were encountered by Tsuri et al.[10] in attempting to alkylate **2** with MOM-Cl under similar conditions. To circumvent the problematic methylation, compound **2** was first protected as the ethylene glycol acetal and the crude product was then subjected to alkylation conditions. The acetal-protecting group served to eliminate the side product of the methylation reaction. However, this was still the most inefficient step in the synthesis, requiring approximately 4 equiv of iodomethane and long reaction times (2−3 days) to drive the reaction to completion. But, again, the product was able to be taken on crude and deprotected under acidic conditions (1 M HCl/acetone). The aldehyde then was reduced with KBH_4 in THF/MeOH to give **3** in 81%

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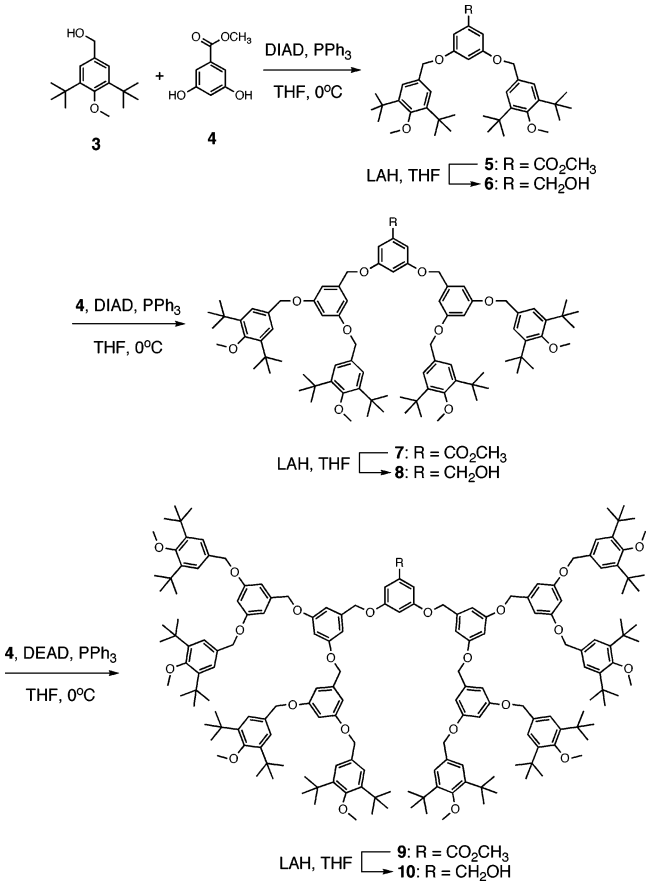
10.1021/jo0483419 CCC: $30.25
Published on Web 01/04/2005

SCHEME 2



yield over four steps. Comparatively, methylation and reduction without protecting the aldehyde gave **3** in only 55−60% yield from **2**.

We emphasize that the preparation of **3** from compound **2** was performed in four steps with only one final recrystallization required for purification. The products of the intermediate steps were difficult to purify by recrystallization due to the unavoidable co-crystallization of impurities, but **3** did not suffer from these limitations. Consequently, having only a single purification step throughout this transformation magnifies the efficiency of our strategy.

With **3** in hand, we prepared the target dendrons in a convergent fashion by coupling of the benzyl alcohols (**3**, **6**, and **8**) with methyl 3,5-dihydroxybenzoate (**4**) under Mitsunobu conditions followed by LAH reduction of the resulting ester (Scheme 2). It is also possible to use less efficient Williamson-ether methodology for the homologation steps by preparing the benzyl bromide or mesylate from the benzyl alcohols (PBr_3 or MsCl, respectively). Each compound (**3**, **5**−**10**) in this synthesis was successfully characterized by ^{1}H and ^{13}C NMR and FAB or MALDI-MS.

It is expected that the BHT dendrons reported here will impart similar properties as the previously reported *tert*-butyl dendrons when applied to a given system. The advantage of the BHT-derived *tert*-butyl dendron series reported here is the efficient, cost-effective route to their preparation.

Experimental Part

General Methods. NMR spectroscopy and mass spectrometry (MS) were obtained using commercially available instrumentation. NMR spectra were recorded in $CDCl_3$ or acetone-d_6 solution with the solvent peaks as internal standards. THF was either distilled from Na or dried over freshly activated 4 Å molecular sieves. Acetone was dried over crushed 3 Å molecular sieves. All other needed reagents were purchased from commercial suppliers and used as received. Flash chromatography was performed by the method of Still et al. (*J. Org. Chem.* **1978**, *43*, 2923−2925) using silica gel (40−63 μm, Merck, Darmstadt, Germany). Thin-layer chromatography (TLC) was performed on precoated plates (silica gel 60 F_{254}, 250 μm, Merck, Darmstadt, Germany). Melting points are uncorrected.

3,5-Di-*tert*-butyl-4-hydroxybenzaldehyde (2). Compound **1** (10 g, 45.4 mmol), NBS (9.7 g, 54.5 mmol), and DMSO (100 mL) were reacted as reported in the literature.[9] After workup, the resulting crude solid was taken up in hexanes (50 mL), and the slurry was allowed to cool in the freezer for approximately 15 min. The solid precipitate was filtered to yield crude yellow crystals. Two additional crops were obtained in a similar fashion. The combined crude filtrants were recrystallized from hexanes/CH_2Cl_2 (5:1) to yield light yellow, flaky crystals (9.89 g, 93%): mp 178−180 °C (lit.[9] mp 179−181 °C); ^{1}H NMR (300 MHz, acetone-d_6) δ 9.87 (s, 1H), 7.76 (s, 2H), 6.93 (s, 1H), 1.47 (s, 18H); ^{13}C NMR (75.4 MHz, acetone-d_6) δ 192.1, 138.3, 130.2, 128.1, 34.5.

3,5-Di-*tert*-butyl-4-methoxybenzyl Alcohol (3). Compound **3**[10] was prepared as follows: A solution of **2** (25.3 g, 107.8 mmol), benzene (200 mL), ethylene glycol (10.0 g, 161.7 mmol, 8.9 mL), and *p*-toluenesulfonic acid (0.21 g, 1.1 mmol) was maintained at reflux equipped with a Dean−Stark trap and reflux condenser. After 48 h, the mixture was allowed to cool to rt. Et_2O (150 mL) was added, and the solution was washed with satd $NaHCO_3$ (100 mL) and water (100 mL × 2). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was precipitated into hexanes to yield the benzylidene acetal as off-white crystals. A mixture of the benzylidene acetal, acetone/DMF (1:1, 100 mL), K_2CO_3 (59.58 g, 431.1 mmol), and 18-crown-6 (cat.) were stirred at reflux for approximately 30 min. Three equivalents of CH_3I (45.89 g, 323.3 mmol, 20.1 mL) was added to the reaction mixture, and the reaction was allowed to proceed for 24 h until an additional 1 equiv of CH_3I (15.3 g, 107.8 mmol, 6.7 mL) was added. The progress of the reaction was monitored by TLC (SiO_2, 4:1 hexanes−EtOAc). After 48 h, the reaction mixture was allowed to cool to rt, taken up in Et_2O (200 mL), and washed with water (100 mL × 2). The resulting organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. The resulting crude methyl ether was taken up in acetone (100 mL) and 1 N HCl (200 mL) and heated to 40 °C. When deprotection was complete (TLC, SiO_2, 4:1 hexanes−EtOAc), Et_2O (150 mL) was added and the reaction mixture was washed with water (100 mL × 3) and satd $NaHCO_3$ (100 mL × 1). The resulting organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. A slurry of the resulting solid aldehyde, THF (200 mL), and KBH_4 (11.64 g, 216 mmol) was heated to 50 °C. MeOH (20 mL) was added slowly to the reaction mixture with stirring, and the mixture was maintained at 50 °C for 24 h. The reaction was quenched by carefully pouring over 1 N HCl (200 mL). Et_2O (200 mL) was added, and the resulting mixture was washed with 1 N HCl (100 mL × 1) and water (100 × 2), dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was precipitated with MeOH/H_2O (10:1) and the precipitate filtered. The crude yellow solid was recrystallized in hexanes to yield **3** as fluffy white crystals (21.9 g, 81% from **2**): mp 99−101 °C (lit.[11] mp 101−102 °C); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.25 (s, 2H), 4.62 (d, J = 5.6 Hz, 2H), 3.69 (s, 3H), 1.62 (t, J = 5.2 Hz, 3H), 1.43 (s, 18H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 159.1, 143.8, 134.7, 125.6, 65.7, 64.2, 35.7, 32.0; MS (FAB$^+$) *m/z* 250.33 ($C_{16}H_{26}O_2$ requires 250.19). Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 76.59; H, 10.08.

Methyl 3,5-Di(3,5-di-*tert*-butyl-4-methoxybenzyloxy)-benzoate ([G-1]-CO_2CH_3, 5). To a cold (0 °C), stirred solution of **3** (3.35 g, 13.4 mmol), **4** (1.07 g, 6.4 mmol), PPh_3 (3.51 g, 13.4 mmol) and dry THF (75 mL) was added DIAD (2.71 g, 13.4 mmol, 2.6 mL) dropwise via syringe. After complete addition, the resulting mixture was stirred for 10 min at 0 °C and was then sonicated[12] for approximately 2 h until the disappearance of **3** was observed by TLC (SiO_2, 4:1 hexanes−EtOAc). The reaction mixture was then concentrated in vacuo, and the resulting solid was recrystallized from MeOH/H_2O (10:1) to yield **5** as a white powder (3.92 g, 97%; purity >95% by NMR): mp 62−64 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (t, J = 1.8 Hz, 2H), 7.31 (s, 4H), 6.85 (t, J = 1.8 Hz, 1H), 4.97 (s, 4H), 3.92 (s, 3H), 3.71 (s, 6H), 1.42 (s, 36H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 166.8, 160.0, 159.5, 143.9, 131.9, 130.2, 126.5, 108.3, 107.3, 70.9, 64.2, 52.2, 35.8, 32.0; MS (FAB$^+$) *m/z* 631.67 (M − H$^+$, $C_{40}H_{56}O_6$ requires 631.40).

3,5-Di(3,5-di-*tert*-butyl-4-methoxybenzyloxy)benzyl Alcohol ([G-1]-CH_2OH, 6). To a stirred slurry of LAH (0.10 g, 2.6 mmol) and dry THF (10 mL) was slowly added **5** (2.5 g, 4.0 mmol). The resulting mixture was allowed to react at rt for approximately 4 h until disappearance of starting material was observed by TLC (SiO_2, 4:1 hexanes−EtOAc). The reaction was quenched sequentially with water (0.1 mL), 4 N NaOH (0.1 mL), and water (0.3 mL) and dried ($MgSO_4$). The resulting mixture was filtered through SiO_2 (about 1.5 in. and washed with Et_2O). The resulting clear filtrate was concentrated in vacuo and the solid recrystallized from MeOH/H_2O (40:1) to yield **6** as a white powder (2.08 g, 87%): mp 148−150 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (s, 3H), 6.67 (d, J = 2.9 Hz, 2H), 6.61 (t, J = 2.7 Hz, 1H), 4.94 (s, 4H), 4.65 (d, J = 3.6 Hz, 2H), 3.70 (s, 6H), 1.76 (t, J = 5.4 Hz, 1H), 1.41 (s, 36H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 160.4, 159.4, 143.8, 143.3, 130.4, 126.5, 105.7, 101.2, 70.7, 65.4, 64.2, 35.8, 32.0; MS (FAB$^+$) *m/z* 605.85 (M + H$^+$, $C_{39}H_{57}O_5$ requires 605.42). Anal. Calcd for $C_{39}H_{57}O_5$: C, 77.44; H, 9.33. Found: C, 77.27; H, 8.93.

Methyl 3,5-Bis(3,5-Di(3,5-di-*tert*-butyl-4-methoxybenzyl-oxy)benzyloxybenzoate ([G-2]-CO_2CH_3, 7). Following the procedure for **5**, **6** (1.4 g, 2.3 mmol), **4** (0.185 g, 1.1 mmol), PPh_3 (0.734 g, 2.8 mmol), DIAD (0.56 g, 2.8 mmol, 0.53 mL), and dry THF (15 mL) yielded **7** as a colorless glass (1.03 g, 70%) after flash chromatography (SiO_2, 5:1 hexanes−EtOAc): mp 90−92 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (s, 8H), 6.83 (t, J = 2.1 Hz, 1H), 6.73 (s, 2H), 6.72 (s, 4H), 6.64 (t, J = 2.4 Hz, 2H), 5.04 (s, 4H), 4.94 (s, 8H), 3.91 (s, 3H), 3.70 (s, 12 H), 1.43 (s, 72H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 167.0, 160.7, 160.0, 159.8, 144.1, 138.9, 132.3, 130.6, 126.8, 108.6, 107.5, 106.7, 101.9, 71.0, 70.5, 64.5, 52.5, 36.0, 32.3; MS (MALDI) *m/z* 1363.93 (M + Na$^+$, $C_{86}H_{116}NaO_{12}$ requires 1363.84), 1379.89 (M + K$^+$, $C_{86}H_{116}KO_{12}$ requires 1379.81). Anal. Calcd for $C_{86}H_{116}O_{12}$: C, 76.98; H, 8.71. Found: C, 76.59; H, 8.75.

3,5-Bis(3,5-Di(3,5-di-*tert*-butyl-4-methoxybenzyloxy)benzyloxybenzyl Alcohol ([G-2]-CH_2OH, 8). Following the procedure for **6**, **7** (0.5 g, 0.37 mmol), LAH (0.02 g, 0.55 mmol), and dry THF (10 mL) yielded **8** as a colorless glass (0.39 g, 80%; purity >95% by NMR) after flash chromatography (SiO_2, CH_2Cl_2): mp 82−84 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (s, 8H), 6.73 (d, J = 1.8 Hz, 4H), 6.64 (m, 4H), 6.57 (t, J = 1.8 Hz, 1H), 5.00 (s, 4H), 4.94 (s, 8H), 4.64 (d, J = 3.9 Hz, 2H), 3.70 (s, 12H), 1.61 (t, J = 6.3 Hz, 1H), 1.43 (s, 72H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 160.4, 160.2, 159.5, 143.8, 143.4, 139.1, 130.4, 126.6, 106.4, 105.7, 101.5, 101.3, 70.8, 70.1, 65.3, 64.2, 35.8, 32.0; MS (MALDI) *m/z* 1335.77 (M + Na$^+$, $C_{85}H_{116}NaO_{11}$ requires 1335.84), 1351.74 (M + K$^+$, $C_{85}H_{116}KO_{11}$ requires 1351.82).

Methyl 3,5-Bis(3,5-bis(3,5-Di(3,5-di-*tert*-butyl-4-methoxy-benzyloxy)benzyloxy)benzyloxybenzoate ([G-3]-CO_2CH_3, 9). Following the procedure for **5**, **8** (0.1 g, 0.086 mmol), **4** (0.0072 g, 0.043 mmol), PPh_3 (0.025 g, 0.095 mmol), DEAD (0.0165 g, 0.095 mmol, 0.015 mL), and dry THF (3 mL) yielded **9** as a colorless glass (0.075 g, 63%) after flash chromatography (SiO_2, 6:1 hexanes−EtOAc): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31 (s, 16H), 6.83 (t, J = 2.4 Hz, 1H), 6.73 (s, 2H), 6.73 (s, 8H), 6.71 (d, J = 1.8 Hz, 4H), 6.64−6.63 (m, 4H), 6.60 (t, J = 2.4 Hz, 2H), 5.01 (s, 4H), 5.00 (s, 8H), 4.938 (s, 16H), 3.89 (s, 3H), 3.69 (s, 24H), 1.43 (s, 144H); ^{13}C NMR (150.8 MHz, $CDCl_3$) δ 166.7, 160.4, 160.2, 159.8, 159.5, 143.8, 139.0, 138.8, 132.1, 130.4, 126.6, 108.4, 107.1, 106.5, 101.7, 101.6, 70.8, 70.23, 70.17, 64.2, 52.2, 35.8, 32.0; MS (MALDI) *m/z* 2782.80 (M + Na$^+$, $C_{178}H_{236}O_{24}Na$ requires 2780.71), 2798.74 (M + K$^+$, $C_{178}H_{236}O_{24}K$ requires 2796.69). Anal. Calcd for $C_{178}H_{236}O_{24}$: C, 77.47; H, 8.62. Found: C, 77.08; H, 8.34.

3,5-Bis(3,5-bis(3,5-di(3,5-di-*tert*-butyl-4-methoxybenzyl-oxy)benzyloxy)benzyloxybenzyl Alcohol ([G-3]-CH_2OH, 10). Following the procedure for **6**, **9** (0.075 g, 0.027 mmol), LAH (0.0022 g, 0.054 mmol)), and dry THF (5 mL) yielded **10** as a colorless glass (0.059 g, 79% yield) after flash chromatography (SiO_2, CH_2Cl_2): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31 (s, 16H), 6.72 (d, J = 2.4 Hz, 8H), 6.70 (d, J = 2.4 Hz, 4H), 6.64 (t, J = 2.4 Hz, 4H), 6.61 (d, J = 1.8 Hz, 2H), 6.60 (t, J = 2.4 Hz, 2H), 6.56 (t, J = 3.0 Hz, 1H), 5.00 (s, 8H), 4.98 (s, 4H), 4.94 (s, 16H), 4.59 (d, J = 6.0 Hz, 2H), 3.69 (s, 24H), 1.67 (t, J = 5.4 Hz, 1H), 1.43 (s, 144H); ^{13}C NMR (150.8 MHz, $CDCl_3$) δ 160.4, 160.2, 160.1, 159.5, 143.8, 143.5, 139.3, 139.0, 130.4, 126.6, 106.44, 106.39, 105.8, 101.6, 101.2, 70.8, 70.1, 70.0, 65.2, 64.2, 35.8, 32.2, 32.0; MS (MALDI) *m/z* 2754.85 (M + Na$^+$, $C_{177}H_{236}O_{23}Na$ requires 2754.73), 2770.83 (M + K$^+$, $C_{177}H_{236}O_{23}K$ requires 2770.70). Anal. Calcd for $C_{177}H_{236}O_{23}$: C, 77.82; H, 8.71. Found: C, 77.45; H, 8.84.

Acknowledgment. This work was funded in part by the National Science Foundation (CHE-0213537). C.S.S. thanks the University of Arizona Undergraduate Biology Research Program (UBRP) funded by the Howard Hughes Medical Institute for a fellowship. D.V.M. is a Dreyfus Teacher−Scholar.

Supporting Information Available: NMR and MS characterization data for compounds **2**, **3**, and **5**−**10**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0483419

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