Synthesis of a Series of Focally-Substituted Organothiol Dendrons

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The synthesis of new organothiol-functionalized dendrons of generation 1−4 is described. Several modifications to the original method for preparation of dendrons are detailed that were found to improve the yield and aid in scale-up. A particularly advantageous method for preparation of an aromatic thiol is reported and is employed in this reaction sequence. Several uses of these dendrons are anticipated and briefly described.

I. Introduction

Dendrons are structures that contain multiple branch points as one traverses from the focal point to the peripheral points of the molecular structure.[1−3] Such structures have found great utility in the preparation of new molecular architectures, particularly, in the preparation of dendrimers in which several of the dendrons are covalently linked to a core structure.[3−18] One can envision many other novel architectures that employ dendrons as their building blocks. These might include dendrons attached via their focal points to a surface and the use of dendrons as highly branched ligands surrounding a metallic or semiconducting nanoparticle. To advance the preparation of such new structures, methods for the synthesis of a dendron that contains a specific functional group at its focal point and specific functional groups at its periphery are required. In this paper, we describe the synthesis of dendrons of generations (i.e., degrees of branching) 1−4 that are functionalized with an aromatic thiol group at their focal point (Figure 1). The use of organothiols in the formation of monolayers[19,20] on coinage metals and on gallium arsenide[21,22] and the use of organothiols in the preparation of quantum-size restricted nanoparticles[23−28] suggests several potential uses for these new molecules.

Several challenges were faced when the task of synthesizing thiol-substituted dendrons was approached. The organothiol group is sufficiently reactive that a convenient method for its protection and subsequent deprotection was necessary. Since this group was ultimately to be found at the focal point of the dendron, any convergent synthesis[3,15] (which we deemed to be most expedient to the formation of monodispersed dendrons) would require installation of this function and its deprotection at the end of the synthesis. High yields in these final steps would be the most critical for a high overall yield. Lastly, in preparative materials chemistry, the widespread employment of new molecules often hinges on convenient preparation amenable to scale-up. The synthetic methodology reported herein is convenient, can proceed in a high yield, and is amenable to scale-up to the 10−100 gram scale.

II. Results and Discussion

A. Modified Synthesis of the Fréchet-Type Dendron. The branched structure employed in our synthesis has originally been reported by Fréchet et al.[15] It is based on inexpensive starting materials. With the modifications reported here, it was found that this synthesis could be scaled-up substantially. The sequence for the preparation of such dendrons is illustrated in Schemes 1 and 2. Scheme 1 includes the preparation of the repeat unit

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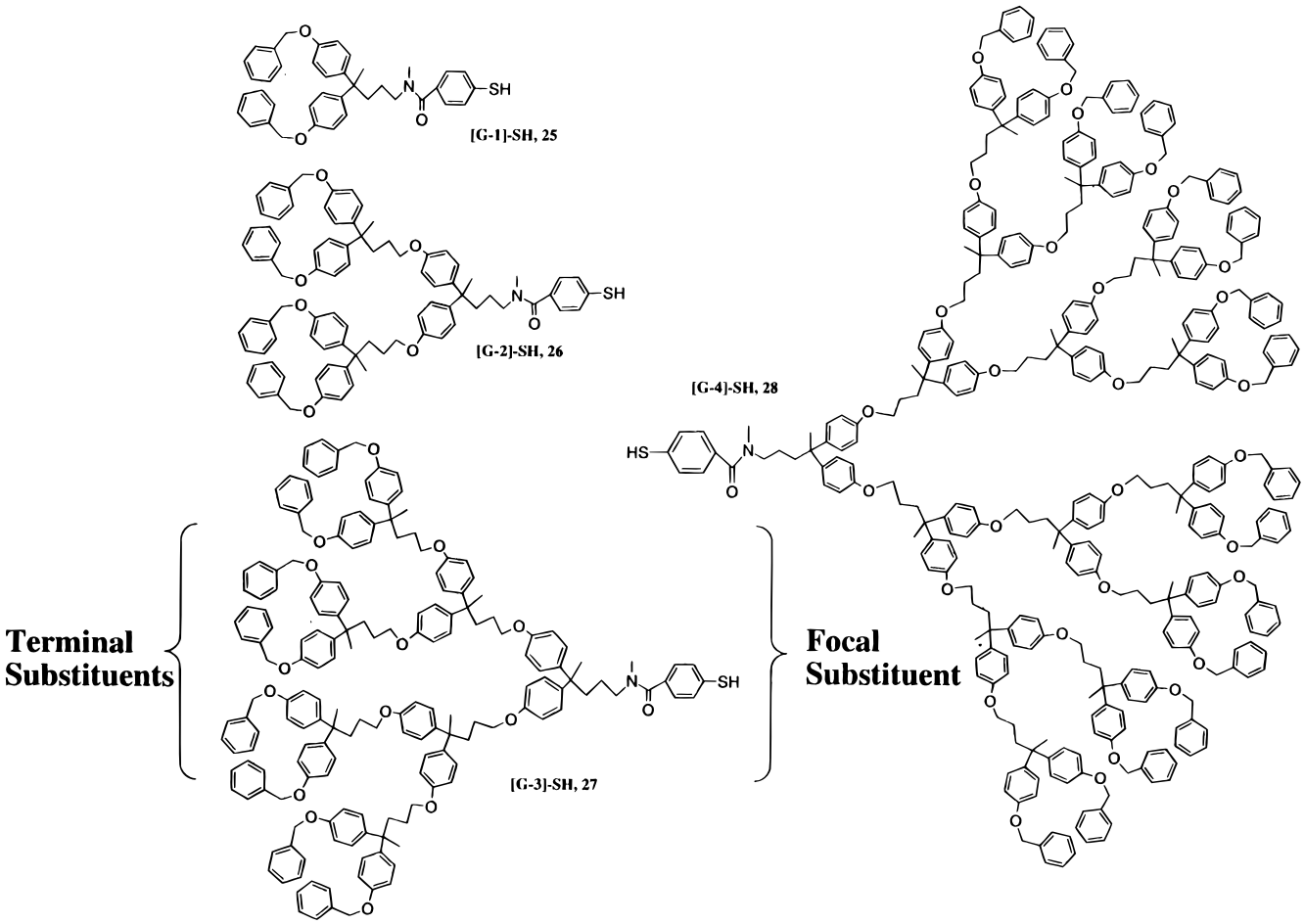
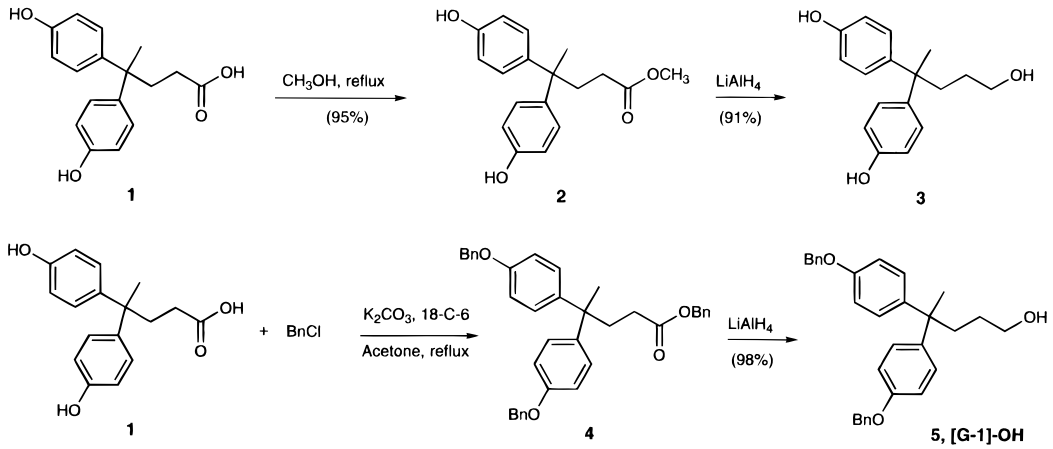


Figure 1. Structures of the first through fourth generation dendrons synthesized.

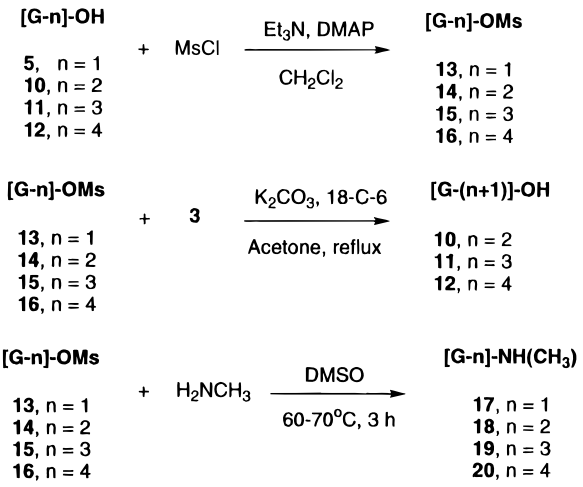
Scheme 1. Synthesis of Repeat Unit 3 and First Generation Alcohol ([G-1]-OH, 5)



(**3**) as well as the first generation focally-substituted with a primary alcohol (**5**). The triol repeat unit **3** can be prepared conveniently and in high yield from the originally reported methyl ester via direct lithium aluminum hydride reduction. Previously, hexamethyl disilazide was employed to protect the phenol alcohols *in situ*.[15] We did not find that the yield of this reaction suffered when this step was omitted. The second step of this sequence was the formation of the terminal unit, **5**. In Fréchet's original report, benzyl bromide was employed in the first step, nominally to cap the phenol alcohols. We note that benzyl bromide also reacts with the carboxylic acid functionality of **1** to form the benzyl ester; thus, 3 equiv (for optimal results, 3.3 equiv of benzyl halide) was required in this transformation. The resulting intermediate, **4**, was not specifically reported in the original paper.[15] We found it convenient to isolate this intermediate (Scheme 1). It was readily and easily purified by crystallization from ethyl acetate after workup. In the presence of potassium carbonate/18-crown-6, we found that benzyl chloride worked equally well in this reaction and was the reagent employed in this synthesis. Both of these modifications permit the synthesis of **3** and **5** in 30−50 g quantities.

The original scheme[15] for the activation of the **[G-*n*]-OH** dendrons (**5, 10**−12) and their coupling with **3** to form the dendron of the next higher generation involved two steps. The first step was conversion of these alcohols

Scheme 2. Conversion of Focally-Substituted Alcohols to the Mesylate, Coupling To Form Higher Generations, and Reaction To Form Focally-Substituted Methylamines



to focally-substituted bromides (e.g., **[G-*n*]-Br**) by treatment with carbon tetrabromide/triphenyl phosphine (eq 1). The second step was a coupling of 2.2 equiv of this

$$\textbf{[G-}n\textbf{]-OH} \xrightarrow{CBr_4/Ph_3P} \textbf{[G-}n\textbf{]-Br} \quad (1)$$

$$2\textbf{[G-}n\textbf{]-Br} + \textbf{3} \xrightarrow[\text{acetone,reflux}]{K_2CO_3,\ 18\text{-C-}6} \textbf{[G-(}n+1\textbf{)]-OH} \quad (2)$$

focally-substituted bromide with the repeat unit **3** to form the focally-substituted alcohol of the next higher generation (eq 2). Neither of these reactions proceeded in high yield, particularly on a >5 g scale. Our best results gave <80% yields for this first step in tetrahydrofuran, methylene chloride, and dimethylformamide. For these reasons, we turned to a mesylate[29] activating/leaving group that, in our experience, is convenient and results in higher yields for both steps (Scheme 2). In this manner, **[G-*n*]-OMs** ($n = 1-4$, compounds **13**−**16**) were prepared in excellent yields (89−96%, 4−16 g scale) and coupled with **3** to form **[G-(*n* + 1)]-OH** ($n = 1-3$, compounds **10**−**12**) also in excellent yields (91−93%, 4−9 g scale).

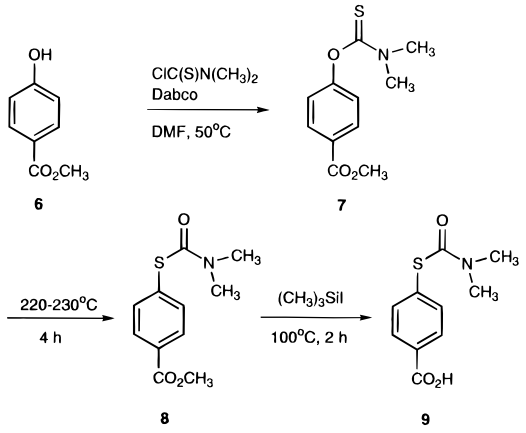
The final step of this sequence was the preparation of a focally-substituted dendron capable of reaction to form a strong bond to a thiol-linking unit. Conversion of **G-*n*-OMs** ($n = 1-4$, compounds **13**−**16**) to **G-*n*-NHMe** ($n = 1-4$, compounds **17**−**20**) was effected by bubbling methylamine through a DMSO solution of the starting material followed by reaction at 60−70 °C in a sealed tube. Yields of these reactions were also high (≥95%), and **G-2-NHMe** (**18**) and **G-4-NHMe** (**19**) were analytically pure after workup. Originally, to avoid the use of methylamine gas, methyltosylamine was employed (eq 3). This reaction gives a high yield of the tosylamine (e.g., **[G-*n*]-NMe(Ts)**) under Mitsonobu conditions (PPh_3/DEAD/TsNHMe, THF, room temperature).[30,31] However, subsequent deprotection (eq 4) failed.[32]

$$\textbf{[G-1]-OH} \xrightarrow[\text{THF, r.t.}]{Ph_3P/\text{DEAD/NHMeTS}} \textbf{[G-1]-NMe(Ts)} \quad (3)$$

$$\textbf{[G-1]-NMe(Ts)} \xrightarrow[\text{THF, } -78 \rightarrow 0]{\text{Na/naphthalene}} \text{dec} \quad (4)$$

B. Synthesis of a Protected Aromatic Thiol Coupling Unit. We sought a convenient route to a protected aromatic thiol that could be used to couple to the dendrons and subsequently deprotect in high yield. It is particularly advantageous to optimize any transformations on the apex of the dendron unit since loss of material at this stage is particularly unfortunate given the lengthy, stepwise method for preparation of the starting materials. Several possibilities were surveyed, and the methodology described below was found to be optimal in this case. Several routes for the protection/deprotection of an aromatic thiol have been described in the literature. These include the formation of thioethers, thioacetals, and thioesters.[33] Some protecting groups (e.g., thioethers) are particularly robust. However, it is not always easy to remove them in high yield.[34] The following procedure can be effected in three steps, none of which require chromatographic purification (Scheme 3).

Scheme 3. Synthesis of a Protected Aromatic Thiol Coupling Unit



Methyl *p*-hydroxybenzoate (**6**) was converted to the thiocarbamate with the addition of dimethylthiocarbamoyl chloride. The product, **7**, can be isolated in the form of large crystals. Rearrangement of **7** to **8** occurs at high temperatures.[35] However, in a sealed tube, little decomposition was observed during this transformation. Furthermore, this reaction could be conducted on a 5 g scale in essentially quantitative yield. The final step in this sequence involved conversion of the ester to the acid with trimethylsilyl iodide.[36] Use of milder Lewis acids (e.g., LiI) has been reported in similar deesterification reactions.[37] However, lower yields were obtained using lithium iodide in this transformation. Satisfactory elemental analysis was obtained on **9** without chromatographic purification.

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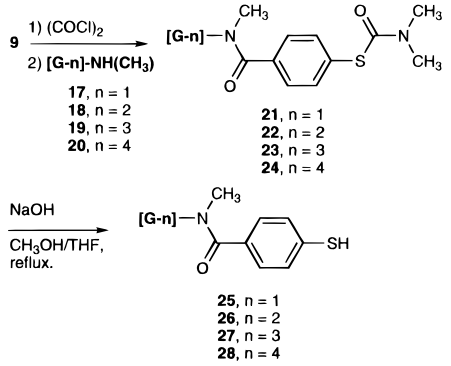
Scheme 4. Coupling/Deprotection of Aromatic Thiol with Dendron



C. Coupling of the Dendron to 9. An amide bond-forming reaction was found to be ideal for the attachment of the protected aromatic thiol to the dendron. This reaction is tolerant of the thiol protecting group and also forms a unit with a ^{1}H NMR signal that is diagnostic for its formation. Generation of the acid chloride of **9** *in situ* followed by coupling to the dendritic methylamine (**17**−**20**) resulted in formation of the amides in acceptable yields (84−96%) (Scheme 4). Deprotection with base to give the final product was straightforward and also proceeded in acceptable yields (73−86%).

III. Summary

Synthesis of organothiol dendrons (**25**−**28**) was accomplished in a straightforward reaction sequence. During the preparation of these compounds several alternatives and improvements were discovered and are described. A route to a protected aromatic thiol apex for the dendron particularly suited to the preparation of such compounds is described as is a facile deprotection route. Several potential uses of these dendrons are envisioned, including their use as encapsulating ligands in the synthesis of hybrid organic−inorganic clusters and as new architectures in the preparation of organic surfaces via their attachment to gold. Experiments of these types will be reported in future publications.

IV. Experimental Section

General Considerations. All starting compounds were purchased from Aldrich Chemical Co. and were used without further purification unless otherwise noted. Acetone was dried from molecular sieves. Methanol was distilled from magnesium methoxide. Chloroform and methylene chloride were distilled from calcium hydride. Tetrahydrofuran was distilled from sodium benzophenone ketyl. All reactions were run under a nitrogen atmosphere. Flash chromatography was run on 230−400 mesh silica gel (Merck). Nuclear magnetic resonance characterization was performed at 300 MHz (^{1}H) or 75 MHz (^{13}C) on a GE-NMR system. Elemental analysis was performed by Atlantic microlaboratories. High-resolution mass spectrometry was performed at the NC State mass spectrometry facility.

Methyl 4,4-Bis(4′-hydroxyphenyl)valerate (2). A solution of 4,4-bis(4′-hydroxyphenylvaleric acid (**1**) (30.0 g, 104.8 mmol) in 200 mL of methanol and 1.5 mL of concentrated H_2SO_4 was heated to reflux under nitrogen overnight. After it was cooled to room temperature, the reaction mixture was quenched with water (100 mL) and extracted with diethyl ether (4 × 150 mL). The organic phase was dried over anhydrous magnesium sulfate and then filtered. The filtrates were evaporated to dryness to give the crude product: yield; 95%; ^{1}H NMR ($CDCl_3$) δ 1.41 (s, 3 H), 2.01 (m, 2 H), 2.25 (m, 2 H), 3.48 (s, 3 H), 4.30−5.10 (br, 2 H), 6.61 (d, 4 H, J = 9 Hz), 6.90 (d, 4 H, J = 9 Hz); ^{13}C NMR ($CDCl_3$) 27.34, 29.86, 36.32, 44.01, 51.31, 114.45, 127.92, 139.88, 154.10, 175.07; IR (cm^{-1}) 3380, 3033, 1716, 1257.

4,4-Bis(4′-hydroxyphenyl)pentanol (3). To a stirred suspension of lithium aluminum hydride (7.529 g , 198 mmol) in dry tetrahydrofuran (200 mL) was added a solution of methyl 4,4-bis(4′-hydroxyphenyl)valerate (**2**) (29.739 g, 98.98 mmol) in dry tetrahydrofuran (300 mL) dropwise at 0 °C under nitrogen. After addition was completed, the reaction mixture was warmed to room temperature and then heated at reflux for 2 h. The reaction mixture was cooled to 0 °C, and 50 mL of saturated ammonium chloride solution was added dropwise. The mixture was filtered, and the filter cake was washed with diethyl ether. The organic layer was washed with saturated sodium chloride solution, dried with anhydrous magnesium sulfate, and then filtered. The filtrates were evaporated to dryness. The crude product was purified by flash chromatography eluting with ethyl acetate to give the product: yield 91%; ^{1}H NMR (CD_3COCD_3) δ 1.30−1.43 (m, 2 H), 1.59 (s, 3 H), 2.05−2.15 (m, 2 H), 2.93 (s, 1 H), 3.58 (t, 2 H, J = 6 Hz), 6,75 (m, 4 H), 7.05 (m, 4 H), 8.14 (s, 2 H); ^{13}C NMR (CD_3COCD_3) 28.18, 28.86, 38.82, 44.89, 62.92, 115.14, 128.77, 141.60, 155.43.

Benzyl 4,4-Bis[4′-(benzyloxy)phenyl]valerate (4). A solution of 4,4-bis(4′-hydroxyphenyl)phenylvaleric acid (**1**) (50 g, 174 mmol), benzyl chloride (88.5 g, 698 mmol), 18-crown-6 (13.8 g, 52.4 mmol), and potassium carbonate (145 g, 1.047 mol) in 350 mL of acetone was heated to reflux under nitrogen for 72 h (overhead stirrer). After it was cooled to room temperature, the reaction mixture was quenched with water (200 mL) and extracted with ethyl acetate (5 × 300 mL). The organic layer was dried over anhydrous magnesium sulfate and filtered. The product was precipitated as a white solid by slowly evaporating the solvent: yield 90%; ^{1}H NMR ($CDCl_3$) δ 1.59 (s, 3 H), 2.18 (m, 2 H), 2.46 (m, 2 H), 5.03 (s, 4 H), 5.08 (s, 2 H), 6.90 (d, 4 H, J = 9 Hz), 7.13 (d, 4 H, J = 9 Hz), 7.30−7.50 (m, 15 H); ^{13}C NMR ($CDCl_3$) 27.72, 30.24, 36.42, 44.43, 66.18, 69.89, 114.19, 127.47, 127.70, 127.86, 128.18, 128.51, 129.41, 129.98, 135.87, 137.04, 141.14, 156.78, 173.71; IR (cm^{-1}) 3064, 3033, 1732, 1509, 1245, 1181, 1025. Anal. Calcd for $C_{38}H_{36}O_4$: C, 81.99; H, 6.52. Found: 81.90; H, 6.55.

Reduction of Benzyl 4,4-Bis[4′-(benzyloxy)phenyl]valerate (5, [G-1]-OH). To a stirred suspension of lithium aluminum hydride (2.74 g, 72 mmol) in dry tetrahydrofuran (100 mL) was added a solution of benzyl 4,4-bis(4′-benzylphenyl ether)valerate (**4**) (20.02 g, 36 mmol) in dry tetrahydrofuran (300 mL) dropwise at 0 °C under nitrogen. This mixture was stirred for 4 h at 0 °C. Then 10 mL of ethyl acetate was added rapidly, the mixture was stirred for 20 min at 0 °C, and then 20 mL of a saturated ammonium chloride solution was added. After this mixture was warmed to room temperature, it was filtered, and the filter cake was washed with diethyl ether. The organic layer was washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and then filtered. The filtrates were evaporated to dryness. The crude product was purified by flash chromatography eluting with 2:3 diethyl ether/petroleum ether to give the [G-1]-alcohol: yield 98%; ^{1}H NMR ($CDCl_3$) δ 1.30−1.40 (m, 2 H), 1.55 (s, 1 H), 1.57 (s, 3 H), 2.05−2.11 (m, 2 H), 3.57 (t, 2 H, J = 6 Hz), 5.01 (s, 4 H), 6.87 (d, 4 H, J = 9 Hz), 7.11 (d, 4 H, J = 9 Hz), 7.26−7.45 (m, 10 H); ^{13}C NMR ($CDCl_3$) 27.85, 28.18, 37.93, 44.66, 63.43, 69.89, 114.06, 127.50, 127.86, 128.22, 128.51, 137.10, 142.08, 156.62; IR (cm^{-1}) 3354, 3063, 3034, 1510, 1244, 1024.

***O*-4-Carbomethoxyphenyl Dimethylthiocarbamate (7).** To a solution of methyl 4-hydroxybenzoate (**6**) (5.20 g, 34.2 mmol) in 60 mL of dimethylformamide were added 1,4-diazabicyclo[2.2.2]octane (Dabco) (5.75 g, 51.3 mmol) and dimethylthiocarbamoyl chloride (5.07 g, 41.0 mmol) in one portion as solids. The mixture was heated at 50 °C for 5 h and then was poured into 100 mL of water. The product was taken into benzene/petroleum ether (4:1), and the organic solution was washed with 1 N HCl (150 mL) and 10% NaOH

(40 mL). Afterthe solution was dried over anhydrous magnesium sulfate, the solvents were removed and the residue was recrystallized from methanol to yield white crystals: yield 90%; ^{1}H NMR ($CDCl_3$) δ 3.33 (d, 3 H, J = 1.5 Hz), 3.43 (d, 3 H, J = 1.5 Hz), 3.89 (s, 3 H), 7.11 (d, 2 H, J = 9 Hz), 8.06 (d, 2 H, J = 9 Hz); ^{13}C NMR ($CDCl_3$) 37.84, 42.27, 51.15, 121.92, 126.73, 129.90, 156.46, 165.34, 185.93; IR (cm^{-1}) 3099, 3065, 1714, 1600, 1538, 1399, 1275, 1208, 1110, 1094.

***S*-4-Carbomethoxyphenyl Dimethylthiocarbamate (8).** *O*-4-carbomethoxyphenyl dimethylthiocarbamate (**7**) (2.04 g, 8.54 mmol) was put into a sealed tube and then heated between 220 and 230 °C for 4 h. TLC and ^{1}H NMR indicated the crude product to be pure enough to be carried on to the next step: crude yield ≥95%; ^{1}H NMR ($CDCl_3$) δ 3.02 (broad s, 3 H), 3.07 (broad s, 3 H), 3.90 (s, 3 H), 7.55 (d, 2 H, J = 9 Hz), 8.01 (d, 2 H, J = 9 Hz); ^{13}C NMR ($CDCl_3$) 36.90, 52.18, 129.77, 130.35, 134.61, 135.07, 165.67, 166.54; IR (cm^{-1}) 3026, 1720, 1654, 1274, 1104.

4-[(Dimethylcarbamoyl)thio]benzoic Acid (9). A mixture of *S*-4-carbomethoxyphenyl dimethylthiocarbamate (**8**) (2.02 g, 8.45 mmol) and iodotrimethylsilane (2.4 mL, 16.9 mmol) was heated to 100 °C under nitrogen for 2 h. After the reaction mixture was cooled to room temperature, it was diluted with diethyl ether (200 mL) and washed with 10% NaOH (3 × 100 mL). The alkaline solution was acidified with 6 N HCl and then extracted with chloroform (3 × 100 mL). The organic layer was dried over anhydrous magnesium sulfate and filtered, and the solvents were evaporated to obtain the product: yield 80−90%; ^{1}H NMR ($CDCl_3$) δ 3.04 (broad s, 3 H), 3.09 (broad s, 3 H), 7.59 (d, 2 H, J = 9 Hz), 8.06 (d, 2 H, J = 9 Hz); ^{13}C NMR ($CDCl_3$) 37.00, 129.67, 130.41, 135.23, 135.52, 165.83, 170.71; IR (cm^{-1}) 3418 (b), 1662, 1292, 1084. Anal. Calcd for $C_{10}H_{11}NO_3S$: C, 53.32; H, 4.92. Found: 53.23; H, 4.87.

General Procedure for Synthesis of Dendritic Mesylates ([G-*n*]-OMs, 13−16). To a solution of the appropriate alcohol **5** or **10**−**12** (1.0 equiv) in methylene chloride (0.5 mmol alcohol/mL CH_2Cl_2) were added methanesulfonyl chloride (2.0 equiv), triethylamine (3.0 equiv), and 4-(dimethylamino)-pyridine (0.02 equiv) with stirring at 0 °C. This mixture was allowed to come to room temperature, and was further stirred at room temperature under nitrogen for 12 h. Water was added to quench the reaction, and the aqueous layer was extracted with methylene chloride (3×). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness. The crude product was purified by flash chromatography, eluting with methylene chloride.

[G-1]-OMs (13): yield 94% (16 g scale); ^{1}H NMR ($CDCl_3$) δ 1.50−1.65 (m, 2 H), 1.59 (s, 3 H), 2.15 (m, 2 H), 2.94 (s, 3 H), 4.15 (t, 2 H, J = 6 Hz), 5.03 (s, 4 H), 6.89 (d, 4 H, J = 9 Hz), 7.10 (d, 4 H, J = 9 Hz), 7.30-7.45 (m, 10 H); ^{13}C NMR ($CDCl_3$) 24.82, 27.79, 37.22, 37.58, 44.56, 69.86, 70.47, 114.16, 127.47, 127.86, 128.12, 128.51, 137.00, 141.40, 156.75; IR (cm^{-1}) 3074, 3034, 1501, 1352, 1241, 1175; HRMS calcd for $C_{32}H_{34}O_5S$; 530.2127, found 530.2129.

[G-2]-OMs (14): yield 92% (8 g scale); ^{1}H NMR ($CDCl_3$) δ 1.45−1.65 (m, 15 H), 2.10 (m, 2 H), 2.17 (m, 4 H), 2.92 (s 3 H), 3.84 (t, 4 H, J = 6 Hz), 4.12 (t, 2 H, J = 6 Hz), 5.01 (s, 8 H), 6.73 (d, 4 H, J = 9 Hz), 6.86 (d, 8 H, J = 9 Hz), 7.03 (d, 4 H, J = 9 Hz), 7.11 (d, 8 H, J = 9 Hz), 7.26−7.44 (m, 20 H); ^{13}C NMR ($CDCl_3$) 24.91, 27.89, 37.29, 37.61, 38.29, 44.53, 44.72, 68.28, 69.92, 70.57, 113.80, 114.10, 127.54, 127.89, 128.09, 128.25, 128.54, 137.10, 141.08, 141.98, 156.68, 156.97; IR (cm^{-1}) 3061, 1508, 1244, 1179; HRMS Calcd for $C_{80}H_{82}O_9S$; 1218.5680, found 1218.5679. Anal. Calcd for $C_{80}H_{82}O_9S$: C, 78.79; H, 6.78. Found: C, 78.71; H, 6.78.

[G-3]-OMs (15): yield 96% (7 g scale); ^{1}H NMR ($CDCl_3$) δ 1.45−1.65 (m, 35 H), 2.05−2.25 (m, 14 H), 2.92 (s, 3 H), 3.84 (t, 12 H, J = 6 Hz), 4.12 (t, 2 H, J = 6 Hz), 5.01 (s, 16 H), 6.73 (d, 12 H, J = 9 Hz), 6.86 (d, 16 H, J = 9 Hz), 7.00−7.16 (m, 28 H), 7.26−7.45 (m, 40 H); ^{13}C NMR ($CDCl_3$) 24.95, 27.92, 37.29, 37.68, 38.29, 44.56, 44.69, 44.75, 68.24, 69.92, 70.54, 113.71, 113.80, 114.09, 127.50, 127.89, 128.09, 128.18, 128.25, 128.51, 137.13, 141.01, 141.63, 142.01, 156.65, 156.81, 156.97; IR (cm^{-1}) 3034, 1607, 1509, 1245, 1180. Anal. Calcd for $C_{176}H_{178}O_{17}S$: C, 81.39; H, 6.91. Found: C, 81.27; H, 6.92.

[G-4]-OMs (16): yield 89% (4 g scale); ^{1}H NMR ($CDCl_3$) δ 1.60−1.85 (m, 75 H), 2.20−2.45 (m, 30 H), 2.99 (s, 3 H), 3.85−4.40 (m, 30 H), 5.13 (s, 32 H), 6.90 (d, 24 H, J = 9 Hz), 7.02 (d, 36 H, J = 9 Hz), 7.18−7.32 (m, 60 H), 7.40−7.60 (m, 80 H); ^{13}C NMR ($CDCl_3$) 20.87, 22.88, 23.62, 24.17, 24.88, 27.85, 28.79, 30.24, 37.09, 37.58, 38.23, 44.46, 44.66, 52.18, 53.35, 64.82, 68.11, 69.79, 70.44, 113.64, 114.06, 127.41, 127.63, 127.80, 128.18, 128.44, 130.80, 137.04, 140.95, 141.53, 141.72, 141.92, 156.59, 156.75, 156.91; IR (cm^{-1}) 3035, 1608, 1510, 1245, 1181. Anal. Calcd for $C_{368}H_{370}O_{33}S$: C, 82.57; H, 6.97. Found: 82.51; H, 6.99.

General Procedure for the Synthesis of Dendritic Alcohols ([G-*n*]-OH, 10−12). A mixture of the dendritic mesylate **13**−**16** (2.1 equiv), 4,4-bis(4′-hydroxyphenyl)pentanol (1.0 equiv), anhydrous potassium carbonate (3.0 equiv), and 18-crown-6 (0.2 equiv) in dry acetone (about 0.1 mmol alcohol/mL acetone) was heated at reflux and stirred vigorously under nitrogen for 60 h. The mixture was cooled, evaporated to dryness under reduced pressure, and partitioned between methylene chloride and water. The aqueous layer was extracted with methylene chloride (3 ×), and the combined organic layers were dried and evaporated to dryness. The crude product was purified by flash chromatography, eluting with methylene chloride increasing to 1:5 ether/methylene chloride to give the dendritic alcohol.

[G-2]-OH (10): yield 91% (9 g scale); ^{1}H NMR ($CDCl_3$) δ 1.20−1.40 (m, 2 H), 1.50−1.62 (m, 13 H), 2.02−2.10 (m, 2 H), 2.14−2.20 (m, 4 H), 3.55 (m, 2 H), 3.83 (t, 4 H, J = 6 Hz), 5.00 (s, 8 H), 6.71 (d, 4 H, J = 9 Hz), 6.85 (d, 8 H, J = 8 Hz), 7.04 (d, 4 H, J = 8 Hz), 7.10 (d, 8 H, J = 9 Hz), 7.28−7.43 (m, 20 H).24.91, 27.89, 28.18, 37.93, 38.29, 44.59, 44.75, 63.43, 68.21, 69.92, 113.67, 114.09, 127.47, 127.86, 128.15, 128.25, 128.51, 137.10, 141.69, 141.98, 156.65, 156.78; IR (cm^{-1}) 3362, 3064, 3031, 1507, 1236, 1183, 1017.

[G-3]-OH (11): yield 92% (8 g scale); ^{1}H NMR ($CDCl_3$) δ 1.25−1.40 (m, 2 H), 1.50−1.70 (m, 33 H), 2.00−2.25 (m, 14 H), 2.62 (s, 1 H), 3.55 (t, 2 H, J = 7 Hz), 3.84 (t, 12 H, J = 6 Hz), 5.01 (s, 16 H), 6.73 (d, 12 H, J = 9 Hz), 6.87 (d, 16 H, J = 9 Hz), 7.02−7.16 (m, 28 H), 7.26−7.45 (m, 40 H); ^{13}C NMR ($CDCl_3$) 24.95, 27.89, 28.24, 37.97, 38.29, 44.59, 44.72, 63.43, 68.21, 69.89, 113.67, 114.10, 114.42, 127.47, 127.73, 127.86, 128.15, 128.25, 128.51, 128.80, 137.10, 141.59, 141.66, 141.98, 156.65, 156.78; IR (cm^{-1}) 3539, 3034, 1511, 1245, 1182, 1025.

[G-4]-OH (12): yield 93% (4 g scale); ^{1}H NMR ($CDCl_3$) δ 1.25−1.70 (m, 75 H), 2.00−2.25 (m, 30 H), 3.54 (t, 2 H, J = 6 Hz), 3.84 (m, 28 H), 5.01 (s, 32 H), 6.73 (d, 28 H, J = 8 Hz), 6.86 (d, 32 H, J = 8 Hz), 7.02−7.16 (m, 60 H), 7.26−7.46 (m, 80 H); ^{13}C NMR ($CDCl_3$) 24.98, 27.92, 38.32, 44.72, 44.79, 63.46, 68.28, 69.96, 113.71, 114.13, 127.50, 127.89, 128.28, 128.54, 137.17, 141.66, 142.01, 156.68, 156.84; IR (cm^{-1}) 3578, 3062, 3035, 1509, 1245, 1181, 1025. Anal. Calcd for $C_{367}H_{368}O_{31}$: C, 83.57; H, 7.03. Found: 83.63; H, 7.07.

General Procedure for the Synthesis of Dendritic Methylamine ([G-*n*]-NHMe, 17−20). Into a sealed tube with a solution of the dendritic mesylate **13**−**16** (1 equiv) in dimethyl sulfoxide (0.5 mmol/mL DMSO) was bubbled methylamine gas for 1 min at room temperature. Then the sealed tube was weighed to make sure at least 10 equiv of methylamine was added. The sealed tube was heated at 60−70 °C for 3 h with stirring. After it was cooled and opened (CAUTION!), water was added, and the mixture was partitioned between methylene chloride and water. The organic layer was dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness. The crude product was pure enough to be carried out to the next step.

[G-1]-NHMe (17): yield ≥95% (2.5 g scale); ^{1}H NMR ($CDCl_3$) δ 1.20−1.35 (m, 2 H), 1.58 (s, 3 H), 2.02−2.08 (m, 2 H), 2.36 (s, 3 H), 2.52 (t, 2 H, J = 7 Hz), 5.01 (s, 4 H), 6.86 (d, 4 H, J = 9 Hz), 7.10 (d, 4 H, J = 9 Hz), 7.26−7.43 (m, 10 H); ^{13}C NMR ($CDCl_3$) 25.24, 27.85, 36.48, 39.58, 44.82, 52.70, 69.92, 114.03, 127.50, 127.89, 128.25, 128.51, 137.13, 142.24, 156.59; IR (cm^{-1}) 3421, 3058, 3034, 1500, 1243, 1181, 1024;

HRMS calcd for $C_{32}H_{35}NO_2$ (M + H) 466.2746, found 466.2748.

[G-2]-NHMe (18): yield ≥95% (>1 g scale); ^{1}H NMR ($CDCl_3$) δ 1.25−1.40 (m, 2 H), 1.55−1.70 (m, 13 H), 2.05−2.15 (m, 2 H), 2.20−2.30 (m, 4 H), 2.41 (s, 3 H), 2.57 (t, 2 H, J = 7 Hz), 3.90 (t, 4 H, J = 6 Hz), 5.06 (s, 8 H), 6.81 (d, 4 H, J = 9 Hz), 6.94 (d, 8 H, J = 9 Hz), 7.14 (d, 4 H, J = 9 Hz), 7.19 (d, 8 H, J = 9 Hz), 7.30−7.50 (m, 20 H); ^{13}C NMR ($CDCl_3$) 24.83, 24.95, 27.76, 36.19, 38.13, 39.39, 40.68, 44.56, 52.41, 68.02, 69.70, 113.48, 113.93, 127.31, 127.70, 127.99, 128.09, 128.34, 136.94, 141.66, 141.82, 156.49, 156.59; IR (cm^{-1}) 3407, 3062, 3034, 1509, 1245, 1181, 1025; HRMS calcd for $C_{80}H_{83}NO_6$; (M + H) 1154.6299, found 1154.6302.

[G-3]-NHMe (19): yield ≥95% (2 g scale); ^{1}H NMR ($CDCl_3$) δ 1.18−1.70 (m, 35 H), 1.95−2.25 (m, 14 H), 2.36 (s, 3 H), 2.37 (s, 1 H), 2.52 (m, 2 H), 3.84 (m, 12 H), 5.01 (s, 16 H), 6.73 (m, 12 H), 6.86 (m, 16 H), 7.00−7.20 (m, 28 H), 7.25−7.45 (m, 40 H); ^{13}C NMR ($CDCl_3$) 24.69, 24.95, 25.14, 27.92, 28.08, 35.90, 38.29, 39.45, 40.94, 44.62, 44.69, 44.75, 52.25, 68.24, 69.92, 113.67, 114.10, 127.50, 127.89, 128.18, 128.25, 128.54, 137.13, 141.63, 142.01, 156.65, 156.81; IR (cm^{-1}) 3418, 3062, 3034, 1510, 1245, 1181, 1025. Anal. Calcd for $C_{176}H_{179}NO_{14}$: C, 83.48; H, 7.12. Found: C, 83.23; H, 7.15.

[G-4]-NHMe (20): yield ≥95% (>1 g scale); ^{1}H NMR ($CDCl_3$) δ 1.20−1.70 (m, 75 H), 2.00−2.40 (m, 36 H), 3.89 (m, 28 H), 5.04 (m, 32 H), 6.80 (d, 28 H, J = 9 Hz), 6.92 (d, 32 H, J = 9 Hz), 7.08−7.22 (m, 60 H), 7.28−7.50 (m, 80 H); ^{13}C NMR ($CDCl_3$) 24.59, 24.65, 24.85, 25.11, 27.40, 27.66, 27.98, 38.19, 40.58, 41.00, 44.59, 44.66, 68.11, 69.25, 69.79, 70.34, 112.77, 113.13, 113.38, 113.74, 114.32, 114.52, 114.87, 114.97, 126.99, 127.81, 127.57, 127.83, 128.22, 128.44, 128.64, 137.04, 141.53, 141.88, 156.55, 156.71; IR (cm^{-1}) 3090, 3035, 1504, 1244, 1181, 1025, 909. Anal. Calcd for $C_{368}H_{371}NO_{30}$: C, 83.59; H, 7.07. Found: C, 83.39; H, 7.02.

General Procedure for Synthesis of Dendritic Amide (21−24). To a solution of the 4-[(dimethylcarbamoyl)thio]-benzoic acid (**9**) (3 equiv) in methylene chloride were added 0.01 equiv of dimethylformamide and oxalyl chloride (15 equiv) via syringe at room temperature. The reaction mixture was stirred for 3 h at room temperature. Then the mixture was evaporated to dryness under reduced pressure and put on a vacuum pump for 20 min. The solid acid chloride was redissolved in methylene chloride and then transferred to a solution of [G-*n*]-NHMe **17**−**20** (1 equiv) and anhydrous triethylamine or pyridine (6 equiv, use of triethylamine resulted in the best yields except for [**G-4**]-**amide** (**24**)) in methylene chloride at 0 °C. The reaction mixture was gradually warmed to room temperature and stirred overnight at room temperature. Water was added to quench the reaction, and the mixture was partitioned between methylene chloride and water. The organic layer was washed with 1 N HCl, 10% NaOH solution, and saturated NaCl solution successively. Then the organic layer was dried over anhydrous magnesium sulfate and filtered, and the solvents were evaporated to dryness. The crude product was purified by flash chromatography eluting with 3% diethyl ether in methylene chloride.

[G-1]-Amide (21): yield 96% (1.7 g scale); ^{1}H NMR ($CDCl_3$) δ 1.25 (m, 2 H), 1.53 (s, 1.5 H), 1.61 (s, 1.5 H), 1.83 (m, 1 H), 2.12 (m, 1 H), 2.75 (1.5 H), 2.92 (1.5 H), 3.06 (m, 6 H), 3.17 (m, 1 H), 3.51 (m, 1 H), 5.03 (s, 4 H), 6.88 (d, 4 H, J = 8 Hz), 7.03 (d, 2 H, J = 8 Hz), 7.12 (d, 2 H), J = 8 Hz), 7.25−7.60 (m, 14 H); ^{13}C NMR ($CDCl_3$) 22.17 (23.65), 27.76, 32.47, 36.80 (37.06), 38.16 (38.65), 44.66, 47.37, 51.44, 69.83, 114.10, 126.92, 127.21, 127.44, 127.82, 128.02 (128.09), 128.44, 130.22, 135.29 (135.00), 137.00 (137.10), 141.50 (141.88), 156.59, 166.06 (166.18), 171.03 (170.48); IR (cm^{-1}) 3062, 3033, 1668, 1633, 1244, 1181, 1089, 1018; HRMS calcd for $C_{42}H_{44}N_2O_4S$ (M + H) 673.3100, found 673.3089.

[G-2]-Amide (22): yield 93% (2.8 g scale); ^{1}H NMR ($CDCl_3$) δ 1.30−1.90 (m, 15 H), 2.00−2.15 (m, 2 H), 2.15−2.30 (m, 4 H), 2.77 (s, 1.5 H), 2.93 (1.5 H), 3.05 (m, 6 H), 3.19 (m, 1 H), 3.51 (m, 1 H), 3.88 (t, 4 H, 6 Hz), 5.03 (s, 8 H), 6.77 (d, 4 H, J = 8 Hz), 6.89 (d, 8 H, J = 9 Hz), 6.98−7.20 (m, 14 H), 7.30−7.60 (m, 22 H); ^{13}C NMR ($CDCl_3$) 24.88, 25.17, 27.82, 28.18, 32.47, 36.84, 37.09, 38.23, 38.68 (38.58), 44.69 (44.62), 47.37, 51.44, 68.18, 69.86, 113.67, 114.03, 126.99, 127.21, 127.44, 127.83, 128.05 (127.99), 128.18, 128.44, 130.19, 135.29, 137.04, 141.14 (141.53), 141.92, 156.59, 156.81, 166.09 (166.21), 171.03 (170.51); IR (cm^{-1}) 3062, 3034, 1668, 1632, 1510, 1245, 1181, 1018; HRMS calcd for $C_{90}H_{92}N_2O_8S$ (M + H) 1360.6574, found 1360.6568.

[G-3]-Amide (23): yield 84% (1.1 g scale); ^{1}H NMR ($CDCl_3$) δ 1.35−1.85 (m, 35 H), 2.05−2.30 (m, 14 H), 2.74 (s, 1.5 H), 2.89 (s, 1.5 H), 3.02 (m, 6 H), 3.15 (m, 1 H), 3.48 (m, 1 H), 3.84 (t, 12 H, J = 6 Hz), 5.01 (s, 16 H), 6.73 (d, 12 H, J = 9 Hz), 6.86 (d, 16 H, J = 9 Hz), 6.90−7.15 (m, 30 H), 7.25−7.55 (m, 42 H); ^{13}C NMR ($CDCl_3$) 24.59, 24.85, 25.20, 27.82, 32.41, 36.71, 36.97, 38.19, 38.61, 44.37, 44.62, 44.91, 60.20, 68.08, 69.76, 113.61, 113.87, 114.00, 126.96, 127.28, 127.34, 127.60, 127.73, 128.15, 128.38, 130.19, 135.23, 137.00, 137.13, 141.08, 141.50, 141.85, 156.55, 156.71, 156.78, 166.02, 170.90 (170.38); IR (cm^{-1}) 3061, 3034, 1666, 1632, 1245, 1181, 1081. Anal. Calcd for $C_{186}H_{188}N_2O_{16}S$: C, 81.55; H, 6.92. Found: 81.55; H, 7.00.

[G-4]-Amide (24): yield 84% (1 g scale); ^{1}H NMR ($CDCl_3$) δ 1.20−1.90 (m, 75 H), 2.10−2.25 (m, 30 H), 2.48 (s, 1.5 H), 2.69 (s, 1.5 H), 3.02 (m, 6 H), 3.25 (m, 1 H), 3.45 (m, 1 H), 3.84 (m, 24 H), 4.20−4.25 (m, 4 H), 5.01 (s, 32 H), 6.74 (d, 28 H, J = 9 Hz), 6.87 (d, 32 H, J = 9 Hz), 7.00−7.20 (m, 62 H), 7.25−7.50 (m, 82 H); ^{13}C NMR ($CDCl_3$) 22.62, 22.91, 23.65, 24.20, 24.91, 27.43, 27.85, 28.82, 29.11, 29.28, 29.60, 30.24, 31.83, 36.80, 38.03, 38.26, 38.61, 44.40, 44.53, 44.69, 64.88, 68.05, 68.18, 69.86, 113.22, 113.64, 114.06, 127.02, 127.25, 127.44, 127.67, 127.83, 128.22, 128.47, 128.70, 130.80, 132.35, 135.19, 135.29, 137.07, 141.08, 141.37, 141.56, 141.75, 141.95, 156.62, 156.78, 157.13, 167.67, 171.03; IR (cm^{-1}) 3070, 3029, 1672, 1607, 1509, 1245, 1811, 1025. Anal. Calcd for $C_{378}H_{380}N_2O_{32}S$: C, 82.62; H, 6.97. Found: C, 82.53; H, 7.02.

General Procedure for Synthesis of Dendritic Thiol ([G-*n*]-SH, 25−28). A flask containing [G-*n*]-amide **21**−**24** (1 equiv) and sodium hydroxide (3 equiv) was flushed with nitrogen, and then a mixture of methanol and tetrahydrofuran (1:1) was added. This heterogeneous mixture was further degassed for 2 h by flushing with nitrogen. The reaction mixture was then refluxed overnight under nitrogen. After it was cooled, the reaction mixture was quenched with 20 mL of 1 N HCl. Then the mixture was partitioned between methylene chloride and water. The organic layer was dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness. The crude product was purified by flash chromatography, eluting with 2% diethyl ether in methylene chloride.

[G-1]-SH (25): yield 78% (2 g scale); ^{1}H NMR ($CDCl_3$) δ 1.25−1.50 (m, 2 H), 1.54 (s, 1.5 H), 1.61 (s, 1.5 H), 1.82 (m, 1 H), 2.10 (m, 1 H), 2.74 (s, 1.5 H), 2.92 (s, 1.5 H), 3.15 (m, 1 H), 3.49 (m, 1 H), 3.52 (s, 1 H), 5.03 (s, 4 H), 6.88 (d, 4 H, J = 9 Hz), 6.95−7.30 (m, 8 H), 7.30−7.50 (m, 10 H); ^{13}C NMR ($CDCl_3$) 23.72 (22.17), 27.72, 32.70 (37.09), 38.29 (38.61), 44.62, 51.60 (47.47), 69.83, 114.09, 127.41, 127.70, 127.83, 128.02, 128.44, 128.60, 132.90 (133.06), 136.97, 141.46 (141.92), 156.62, 171.16 (170.61); IR (cm^{-1}) 3054, 3033, 2563, 1633, 1505, 1244, 1811, 1016; HRMS calcd for $C_{39}H_{39}NO_3S$ (M + H) 602.2729, found 602.2747. Anal. Calcd for $C_{39}H_{39}NO_3S$: C, 77.84; H, 6.53; N, 2.33; S, 5.33. Found: C, 77.56; H, 6.57; N, 2.24; S, 5.14.

[G-2]-SH (26): yield 86% (1 g scale); ^{1}H NMR ($CDCl_3$) δ 1.25−1.90 (m, 15 H), 2.05−2.17 (m, 2 H), 2.17 −2.30 (m, 4 H), 2.77 (m, 1.5 H), 2.94 (m, 1.5 H), 3.16 (m, 1 H), 3.49 (m, 1 H), 3.53 (s, 1 H), 3.89 (t, 4 H, J = 6 Hz), 5.04 (s, 8 H), 6.77 (d, 4 H, J = 8 Hz), 6.90 (d, 8 H, J = 9 Hz), 6.95−7.20 (m, 14 H), 7.25−7.50 (m, 22 H); ^{13}C NMR ($CDCl_3$) 24.17, 24.95, 27.89, 28.24, 37.97, 38.29, 38.68, 44.59, 44.72, 53.38, 68.21, 69.89, 113.67, 114.10, 127.47, 127.73, 127.86, 128.15, 128.25, 128.51, 128.80, 130.90, 137.10, 141.24, 141.66, 141.98, 156.65, 156.78, 171.16; IR (cm^{-1}) 3063, 3034, 2562, 1608, 1510, 1244, 1181, 1016; HRMS calcd for $C_{87}H_{87}NO_7S$ (M + H) 1290.6282, found 1290.6267. Anal. Calcd for $C_{87}H_{87}NO_7S$: C, 80.96; H, 6.79; N, 1.09; S, 2.48. Found: C, 81.01; H, 6.85; N, 1.07; S, 2.36.

[G-3]-SH (27): yield 85% (1.5 g scale); ^{1}H NMR ($CDCl_3$) δ 1.25−1.90 (m, 35 H), 2.10−2.30 (m, 14 H), 2.60−2.90 (m, 3 H), 3.00−3.40 (m, 2 H), 3.50 (s, 1 H), 3.70−3.90 (m, 12 H), 5.02 (s, 16 H), 6.75 (d, 12 H, J = 8 Hz), 6.88 (d, 16 H, J = 8 Hz), 7.00−7.20 (m, 30 H), 7.25−7.50 (m, 42 H); ^{13}C NMR

($CDCl_3$) 24.98, 25.59, 27.92, 38.32, 38.61, 44.59, 44.79, 45.04, 60.36, 67.95, 68.24, 69.92, 113.71, 114.13, 127.50, 127.89, 128.05, 128.18, 128.54, 128.73, 137.13, 141.63, 142.01, 156.68, 156.84, 156.91, 171.13 (170.93); IR (cm^{-1}) 3033, 1607, 1510, 1244, 1180. Anal. Calcd for $C_{183}H_{183}NO_{15}S$: C, 82.37; H, 6.91; N, 0.52; S, 1.20. Found: C, 82.13; H, 6.94; N, 0.50; S, 1.06.

[G-4]-SH (28): yield 73% (0.5 g scale); ^1H NMR ($CDCl_3$) δ 1.30−1.90 (m, 75 H), 1.90−2.30 (m, 30 H), 2.92 (s, 1.5 H), 2.74 (s, 1.5 H), 3.13 (m, 1 H), 3.31 (m, 1 H), 3.88 (m, 28 H), 5.04 (s, 32 H), 6.78 (d, 28 H, $J = 8$ Hz), 6.91 (d, 32 H, $J = 9$ Hz), 7.05−7.25 (m, 62 H), 7.30−7.50 (m, 82 H); ^{13}C NMR ($CDCl_3$) 23.04, 24.91, 25.30, 27.89, 28.40, 29.11, 34.09, 38.26, 38.90, 44.07, 44.53, 44.66, 44.72, 49.79,68.18, 69.51, 69.86, 113.67, 114.06, 114.71, 127.44, 127.83, 128.22, 128.47, 137.07, 141.08, 141.43, 141.59, 141.95, 156.62, 156.78, 156.94, 162.53; IR (cm^{-1}) 3063, 3035, 2540, 1666, 1511, 1244, 1181, 1025. Anal. Calcd for $C_{375}H_{375}NO_{31}S$: C, 83.04; H, 6.97; N, 0.26; S, 0.59. Found: C, 82.81; H, 7.09; N, 0.27; S, 0.56.

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