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An Accelerated, Improved Synthetic Route for the Preparation of Polyether-based Dendritic Fragments

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Abstract: An accelerated, improved synthetic strategy for the rapid construction of two different series of polyether-based dendritic fragments is described. Several modifications to the original method for the preparation of these dendritic fragements are detailed. A new branching agent, 5-(3-hydroxypropyloxy)-1,3-resorcinol **4**, instead of 5-benzyloxy-1,3-resorcinol **2**, is employed in this new synthetic protocol. As a result, the number of synthetic operations in each of the iterative cycle is reduced from three to two, as compared to the original procedure. Each iterative synthetic cycle involves two reactions: a bis-*O*-alkylation reaction of the brancher **4** with a dendritic bromide [Gn]-O(CH_2)$_3$Br to give a dendritic alcohol of the next generation [G(n+1)]-O(CH_2)$_3$OH; followed by a functional group conversion of the dendritic alcohol into the corresponding dendritic bromide [G(n+1)]-O(CH_2)$_3$Br of the same generation. The reaction yields of each iterative cycle are consistently higher than those of the previously reported three step cycle. Using this new protcol, the preparation of a 5th generation dendritic alcohol **15a** could be realized in 10 steps and 23% overall yields from 1,3-dibromopropane.

Keyword: Dendrimers

INTRODUCTION

Dendrimers are macromolecular structures having multiple branching pattern throughout the polymer network.[1] Depending on the nature of their consitutional functionalites, dendritic architectures may possess unique chemical and physical properties which enable them to function as molecular antennae/light harvesting devices,[2] size-selective molecular encapsulators,[3] substrate selective catalysts,[4] components for self-assembled supramolecular systems,[5] molecular magnets,[6] biologically active[7] and electrochemically active materials.[8] In general, these dendritic superstructures are constructed by appending one or several dendrimer fragments to the relevant functional units. To facilitate the preparation of such new architectures, methods for the synthesis of dendritic fragments that contains a specific functional group at its focal point and/or at its periphery are required. Most commonly these dendritic fragments are prepared by either the divergent[9] or convergent[10] iterative synthetic sequence. While the divergent method allows the rapid construction of higher generations in less synthetic steps, the resulting dendrimers are usually produced with structural defects. On the other hand, the convergent method offers the advantage of producing structural perfect dendrimers, although it is more labour intensive.

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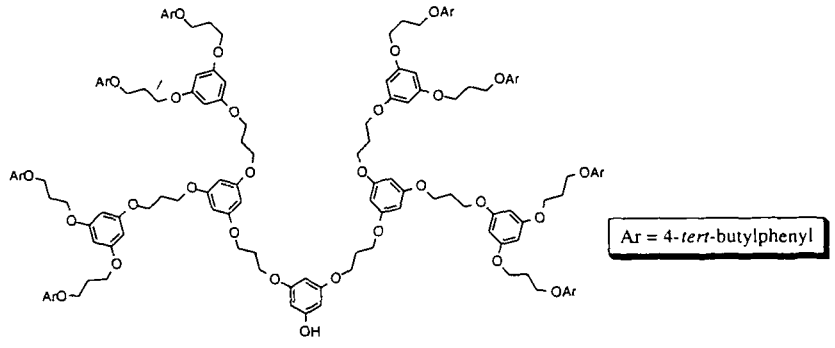

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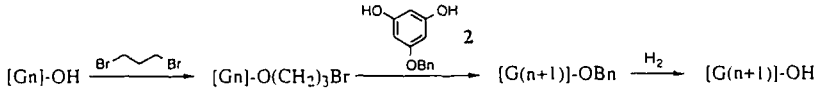
We recently reported a convergent preparation of a series of redox and acid/base stable polyether dendritic fragments **1**[11] having a phenolic functionality at the focal point and showed that they are useful building blocks for redox active metallodendrimers[12] and dendritic catalysts.[13] In this paper we reported an accelerated, improved procedure for the rapid synthesis of these dendrimers in better yields than the original procedure. This new methodology is also amenable to large scale production of dendritic fragments in 10 - 20 g scale.

Results and Discussions

1. Synthetic Strategy

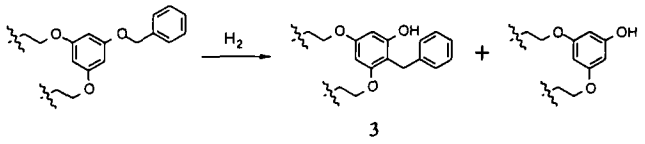
In our previous synthetic strategy, an iterative synthetic cycle involving three separate operations was used (Scheme 1):[11b]

- Mono-*O*-alkylation of a dendritic phenol [Gn]-OH with 1,3-dibromopropane to give a dendritic monobromide [Gn]-O$(CH_2)_3$Br.
- Bis-*O*-alkylation of a branching agent, 5-benzyloxy-1,3-resorcinol **2** with the monobromide [Gn]-O$(CH_2)_3$Br to give a benzyl ether of the next higher generation [G(n+1)]-OBn.
- Dismantling of the benzyl protecting group by catalytic hydrogenolysis to release a dendritic phenol [G(n+1)]-OH.



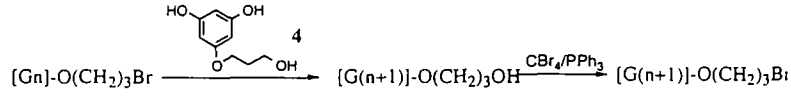
Scheme 1. The original iterative synthetic cycle

Although the original procedure offers a convenient entry to these dendritic polyethers, there are a number of minor problems we later encountered during their large scale preparations. First, the reaction time taken for the catalytic hydrogenolysis becomes increasingly long as one progresses towards the preparation of the higher generation phenols [Gn]-OH. Second, a by-product which has very similar polarity to the dendritic phenol [Gn]-OH, is always produced in minor amount during the hydrogenolysis process. This by-product was later



Scheme 2. Formation of *C*-benzylated phenol during hydrogenolysis

identified as a *C*-benzylated phenol **3** which probably arises from an *O*→*C* migration of the benzyl group (Scheme 2). Third, the formation of bis-*O*-alkylation product [Gn]-O(CH_2)$_3$O-[Gn], which is also one of the minor side products during the coupling between the dendritic phenol [Gn]-OH and 1,3-dibromopropane. Finally, 5-benzyloxy-1,3-resorcinol **2**,[14] the key branching compound used in our synthesis, could only be obtained in our hands in 20% overall yield from phloroglucinol after column chromatographic separation. Although compound **2** is readily prepared in large quantities because it is only one step away from commercially available material, nonetheless, it is highly desirable to devise a new synthetic route which can obviate the necessity of repeated chromatographic separations.

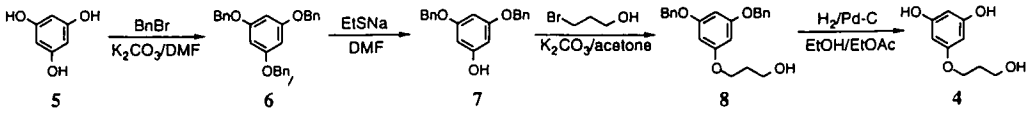


Scheme 3. The new iterative synthetic cycle

In an attempt to eliminate the formation of these by-products and to speed up the synthetic operations, our original route needed to be modified. Instead of performing hydrogenolysis in each reaction cycle, we chose to make use of 5-(3-hydroxypropyloxy)-1,3-resorcinol **4** as an alternative branching agent (Scheme 3). In this new iterative sequence, a dendritic bromide [Gn]-O(CH_2)$_3$Br is reacted with the resorcinol **4** to give a dendritic alcohol of the next generation [G(n+1)]-O(CH_2)$_3$OH. The free hydroxy group is then converted into the corresponding dendritic bromide [G(n+1)]-O(CH_2)$_3$Br by treatment with triphenylphosphine and carbon tetrabromide. It is noteworthy that the troublesome hydrogenolysis reaction is omitted from this new route which essentially eliminates the formation of the *C*-benzylated side-product. Furthermore, the formation of bis-*O*-alkylation side product could also be prevented. The new iterative reaction cycle now consists of two synthetic operations, which should therefore simplify and improve the overall yield of the products, especially for those that require several reaction cycles to prepare.

2. *Preparation of the branching juncture 5-(3-hydroxypropyloxy)-1,3-resorcinol 4*

The new branching agent 5-(3-hydroxypropyloxy)-1,3-resorcinol **4** was prepared according to Scheme 4. Commercially available phloroglucinol **5** was completely *O*-benzylated to give 1,3,5-tribenzyloxybenzene **6**[15] in 59% yield as a solid. One of the benzyl groups in compound **6** was then selectively cleaved by ethane thiolate to give 3,5-dibenzyloxyphenol **7**.[16] Cleavage of the second and the third benzyl groups by the thiolate was retarded by the strong electron density associated with the anion of **7** resulting from mono-debenzylation of **6**. In this

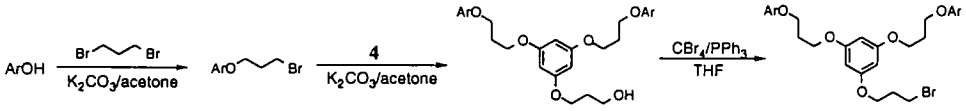


Scheme 4. Synthesis of branching juncture **4**

manner, the phenol **7** could be obtained very cleanly as a solid in 73% yield. The phenolic group was then alkylated with 3-bromopropanol in the presence of potassium carbonate in acetone to give the alcohol **8** in 89% yield. Finally, hydrogenolysis of the two benzyl groups of compound **8** in the presence of hydrogen and 10% palladium on charcoal led to the desired branching agent **4**. Compound **4** was then recrystallized once from EtOAc/hexane to remove other contaminants. The overall yield of compound **4** from phloroglucinol **5** was 29% on a 20 g scale.

3. *Preparation of the surface sectors*

Two dendritic polyether series having different surface features were chosen as our synthetic targets in order to demonstrate the generality of our new synthetic approach. The first series (series a) of dendrimers has a surface sector made up of 4-*tert*-butylphenyl groups which had been prepared earlier using the original three step iterative cycle.[11b] The second series (series b) has a surface sector fabricated with 3,5-dimethylphenyl functionalities. Two key intermediates, 3-bromo-1-(4-*tert*-butylphenoxy)propane **9a**[11b] and 3-bromo-1-(3,5-dimethylphenoxy)propane **9b**, were prepared by reaction of 4-*tert*-butylphenol and 3,5-dimethylphenol, respectively, with excess 1,3-dibromopropane and potassium carbonate (Scheme 5) in refluxing acetone solution. Compounds **9a** and **9b** were thus prepared in 30 g quantity for use as starting materials for subsequent reactions.

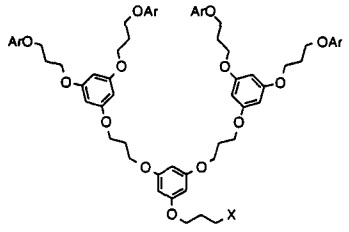


a Ar = 4-*tert*-butylphenyl, b Ar = 3,5-dimethylphenyl

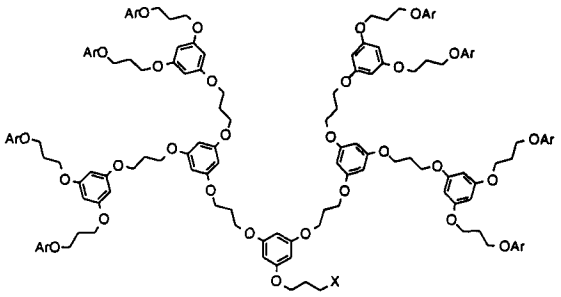
Scheme 5. Synthesis of surface sectors and lower generation dendritic fragments

4. *Synthesis of the dendritic fragments*

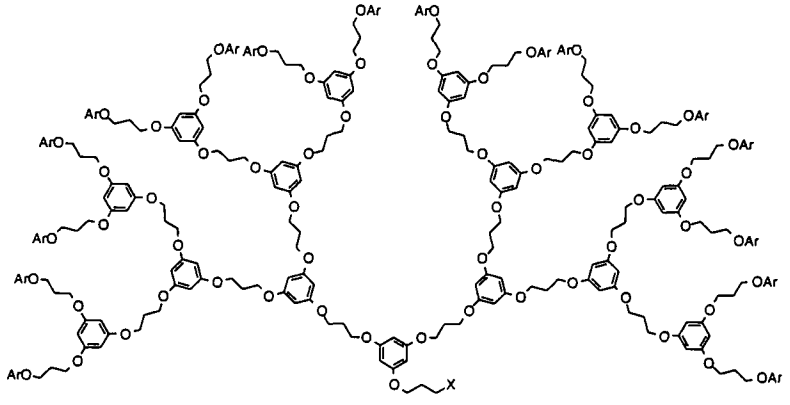
Treatment of the branching agent **4** with 2.2 equiv. of the surface sector [G0]-O(CH_2)$_3$Br (**9a/9b**) in the presence of potassium carbonate and a catalytic amount of 18-crown-6 afforded [G1]-O(CH_2)$_3$OH [**10a** (91%) and **10b** (70%) respectively]. It was found that the alkylation reaction proceeded much more smoothly in THF than in anhydrous acetone solution. In addition, no *C*-alkylation product could be detected from the reaction mixture. The free hydroxy functionality of the brancher **4** remained unreactive under the reaction conditions and was therefore ready for subsequent transformation. Hence, the hydroxy group in [G1]-O(CH_2)$_3$OH could be converted into the corresponding bromide [G1]-O(CH_2)$_3$Br [**11a**[11b] (96%) and **11b** (96%) respectively] by



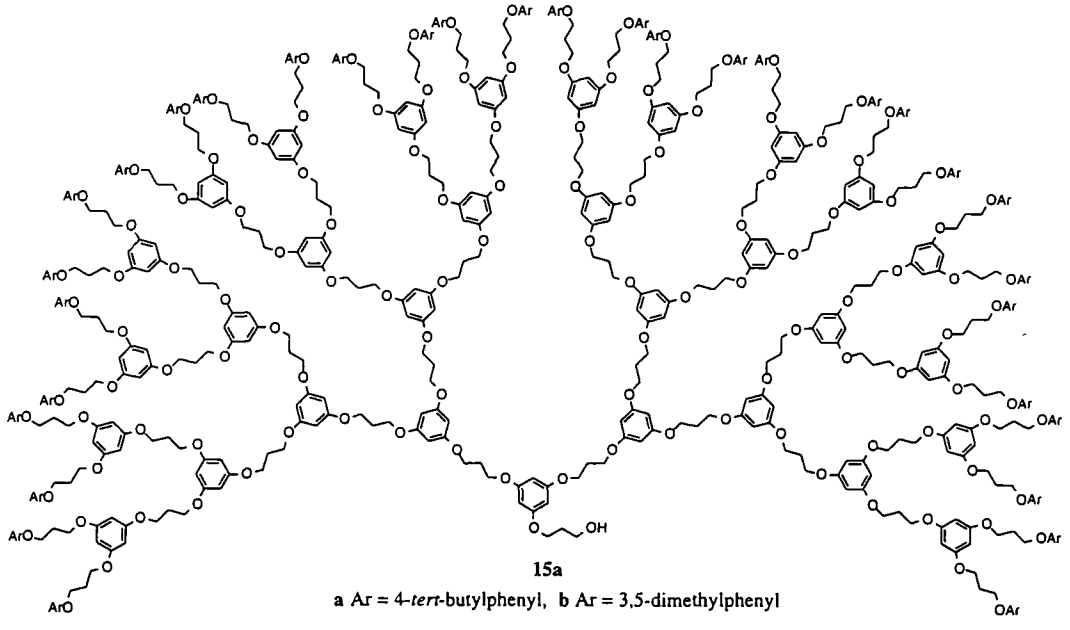
12a/12b (X = OH)
16a/16b (X = Br)



13a/13b (X = OH)
17a (X = Br)



14a (X = OH)
18a (X = Br)



15a

a Ar = 4-*tert*-butylphenyl, **b** Ar = 3,5-dimethylphenyl

reaction with triphenylphosphine and carbon tetrabromide in dry THF. The bromide **11a** obtained from this new synthetic route had spectroscopic properties identical to that prepared from our previous route.[11b] These two synthetic operations then constituted the first iterative preparative cycle.

The new iterative cycle described above was then applied to the synthesis of the higher generation polyether dendritic analogues. Thus, the dendritic alcohols [G(n+1)]-O$(CH_2)_3$OH (n = 1 to 4) **12a-15a** of the 4-*tert*-butylphenyl series could be prepared in good yields by reacting the branching agent **4** with 2.2 equiv. of the dendritic bromides [Gn]-O$(CH_2)_3$Br (n = 1 to 4) **11a**, **16a-18a** respectively. In general, the reaction time required for the bis-*O*-alkyation became longer as the dendrimer generation was higher. The overall yields of the dendritic bromides of various generation prepared by this improved procedure were consistently better than those synthesized using our original method,[11b] demonstrating the superiority of the new route (Table 1). Furthermore, by using this new protocol, the G5 dendritic alcohol **15a**, which was the highest generation dendritic fragment prepared thus far in our laboratory, could be obtained in 71% yields from the G4 dendritic bromide **18a**. Gel permeation chromatography (GPC) analysis of these dendritic fragments yielded a symmetric, mono-modal peak, confirming the homogenity of the reaction product. The structural identities of these dendritic alcohols were consistent with their respective ^{1}H and ^{13}C-NMR spectroscopic data. Hence, for the dendritic alcohols [Gn]-O$(CH_2)_3$OH, the methylene protons adjacent to the hydroxy group appeared as a triplet at around δ 3.8 in their respective ^{1}H-NMR spectra. As expected, this signal intensity became progressively lower towards the higher generation, as compared to that arising from the surface *tert*-butyl groups. In fact, for the case of [G5]-O$(CH_2)_3$OH, both the ^{1}H and ^{13}C-NMR signals of the methylene protons and carbons adjacent to the alcohol functionality were too weak to be observed. GPC analysis of the G4 and G5 dendritic alcohols indicated that the latter had a smaller rentention time than former, a finding which was consistent with their expected molecular size. Mass spectroscopic studies using L-SIMS of the lower generation dendritic alcohols (G ≤ 2) produced molecular ion corresponding to their respective molecular weight . However, the higher generation dendritic alcohols (G ≥ 3) failed to give the molecular ion peak in their respective spectra.

Table 1. Yields (%) of the dendritic fragments (series a)

G (n)	[Gn]-O$(CH_2)_3$Br → [G(n+1)]-O$(CH_2)_3$OH	[G(n+1)]-O$(CH_2)_3$OH → [G(n+1)]-O$(CH_2)_3$Br	[Gn]-O$(CH_2)_3$Br → [G(n+1)]-O$(CH_2)_3$Br
0	91	96	87 (72)*
1	86	99	85 (70)
2	89	94	84 (63)
3	69	81	56
4	71	-	-

* Number in parenthesis denotes corresponding yield prepared by original route.[11b]

The dendritic bromides [Gn]-O$(CH_2)_3$Br (n = 2 to 4) **16a-18a** were readily prepared in good to excellent yields (81 - 99%) by reacting the corresponding dendritic alcohols [Gn]-O$(CH_2)_3$OH (n = 2 to 4) with carbon tetrabromide and triphenylphosphine in either THF or diethyl ether. Upon this functional group transformation, the ^{1}H-NMR signal of the aforementioned methylene protons shifted slightly to δ 3.6, which was consistent with the presence of the bromide functionality. The progress of the reaction could easily be monitored by thin layer chromatographic analysis, as the dendritic bromides had a much higher chromatographic mobility than the

corresponding starting dendritic alcohols. This larger difference of chromatographic mobility also facilitated the purification of these dendritic bromides.

In a similar manner, the 3,5-dimethylphenyl dendritic series (series b, Ar = 3,5-dimethylphenyl) could be prepared using the new iterative route described above. The reaction conditions (*i.e.* solvents, temperature and duration) were used without modification. In general, yields of the bis-*O*-alkylation reaction of the branching juncture **4** were slightly lower than those of the 4-*tert*-butylphenoxy series. Nonetheless, this new synthetic route should be equally applicable to the preparation of other polyether-based dendritic fragments having either electron-donating or electron-withdrawing surface functionalities.

In summary, an accelerated synthetic protocol was developed for the large scale, rapid construction of polyether-based dendritic fragments up to the fifth generation. The use of 5-(3-hydroxypropyloxy)-1,3-resorcinol **4** as the branching agent allows the rapid construction of the desired dendritic fragments in better reaction yields and in less reaction steps.

Experimental Section

The particulars of the analytical instruments employed in the present study were previously described.[11b] Unless otherwise stated, all chemicals were purchased from commercial suppliers and used without further purification. The molecular mass reported in each case is the most abundant molecular isotopic peak for the compound. The surface sector [G0]-O(CH_2)$_3$Br **9a** had been synthesized before.[11b]

1,3,5-Tribenzyloxybenzene 6. Benzyl bromide (230 g, 1.34 mol) was added dropwise to a stirred mixture of phloroglucinol dihydrate (56 g, 0.35 mol) and powdered potassium carbonate (207 g, 1.50 mol) in DMF (600 mL) at 20 °C. The mixture was stirred for 48 h and poured into ice water (1000 mL). The aqueous layer was decanted and the organic oily residue taken up in EtOAc (1000 mL). The organic layer was washed with brine (200 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The desired product was obtained by recrystallization from EtOAc/ethanol and collected by filtration (82 g, 59%), mp 93-94 °C; R_f 0.87 (hexane/EtOAc 4/1); ^{1}H-NMR ($CDCl_3$) 5.00 (s, 6 H), 6.27 (s, 3 H), 7.31-7.42 (m, 15 H); ^{13}C-NMR ($CDCl_3$) 70.1, 94.9, 127.6, 128.0, 128.4, 136.8, 160.6; MS (EI, *m/z*) 396 (M^+, 16%). Anal. Calcd for $C_{27}H_{24}O_3$: C, 81.79; H, 6.10. Found: C, 81.97; H, 6.06.

3,5-Benzyloxyphenol 7. Ethanethiol (15.2 g, 0.24 mol) was added dropwise to a stirred suspension of sodium hydride (60% dispersion in mineral oil, 5.4 g, 0.24 mol) in dry DMF (200 mL) at 0 °C. After 1 h, 1,3,5-tribenzyloxybenzene (56.0 g, 0.13 mol) was added dropwise and the mixture heated to 150 °C for 4 h. The excess solvent was then evaporated under reduced pressure. The residue was taken up in water and extracted with EtOAc (3 × 150 mL). The combined organic layers were washed with saturated brine (50 mL), dried (Na_2SO_4) and chromatographed on silica gel (hexane/EtOAc 4/1) to give the product as an orange oil which was recrystallized from carbon tetrachloride as a light yellow solid (29.0 g, 73%), mp 88-89.5 °C (lit.[16] mp 90-92 °C); R_f 0.54 (hexane/EtOAc 4/1); ^{1}H-NMR ($CDCl_3$) 1.69 (br s, 1 H), 5.00 (s, 4 H), 6.11 (d, J = 2.0, 2 H), 6.25 (t, J = 2.0, 1 H), 7.26-7.36 (m, 10 H); MS (EI, *m/z*) 306 (M^+, 66%). Anal. Calcd for $C_{20}H_{18}O_3$: C, 78.41; H, 5.92. Found: C, 78.38; H, 5.85.

3-(3,5-Dibenzyloxyphenoxy)propanol 8. A mixture of the phenol **7** (18.0 g, 59 mmol), 3-bromopropanol (16.9 g, 121 mmol) and potassium carbonate (13.8 g, 100 mmol) in anhydrous acetone (300 mL) was heated to reflux under nitrogen for 24 h. The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was chromatographed on silica gel (hexane/EtOAc 4/1) to give the alcohol **8** which was recrystallized from carbon tetrachloride as a white solid (16.1 g, 89%), mp 62-63 °C; *Rf* 0.47 (hexane/EtOAc 1/1); ^{1}H-NMR ($CDCl_3$) 1.87 (br s, 1 H), 2.01 (quintet, *J* = 5.9, 2 H), 3.85 (t, *J* = 5.9, 2 H), 4.07 (t, *J* = 5.9, 2 H), 5.01 (s, 4 H), 6.18 (d, *J* = 2.0, 2 H), 6.25 (t, *J* = 2.0, 1 H), 7.25-7.30 (m, 10 H); MS (EI, *m/z*) 364 (M^+, 59%). Anal. Calcd for $C_{23}H_{24}O_4$: C, 75.80; H, 6.64. Found: C, 75.46; H, 6.63.

5-(3-Hydroxypropyloxy)-1,3-resorcinol 4. A suspension of 3-(3,5-dibenzyloxyphenoxy)propanol **8** (20.0 g, 55.0 mmol) and 10% palladium on charcoal (2.0 g) in ethanol/EtOAc (3/1 v/v, 400 mL) was stirred under hydrogen at 20 °C. The reaction progress was monitored by thin layer chromatography until all starting material disappeared. The mixture was filtered through celite and the filtrate concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (hexane/EtOAc 2/1) to afford the product as a white solid (7.7 g, 76%), mp 159-161 °C; *Rf* 0.19 (hexane/EtOAc 1/2); ^{1}H-NMR (d^6-acetone) 1.87 (quintet, *J* = 5.9, 2 H), 3.56-3.60 (br s, 1 H), 3.64 (t, *J* = 6.0, 2 H), 3.92 (t, *J* = 5.9, 2 H), 5.87 (d, *J* = 2.0, 2 H), 5.90 (t, *J* = 2.0, 1 H), 8.08 (br s, 2 H); ^{13}C-NMR (d^6-acetone) 33.6, 59.2, 64.9, 94.3, 96.1, 160.2; MS (EI, *m/z*) 194 (M^+, 100%). Anal. Calcd for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.58; H, 6.68.

General Procedure for Synthesis of Dendritic Alcohols (series a, Ar = 4-*tert*-butylphenyl) [Gn]-O(CH$_2$)$_3$OH (n = 1-5) 10a, 12a-15a. A mixture of the dendritic bromide [G(n-1)]-O(CH$_2$)$_3$Br (2.2 mol eq.), 5-(3-hydroxypropyloxy)-1,3-resorcinol (1.0 mol eq.), 18-crown-6 (0.1 mol eq.) and potassium carbonate (6.0 mol eq.) in dry THF was heated under reflux. The reaction time required was 24 h for n = 1 and 2, 36 h for n = 3, 48 h for n = 4 and 72 h for n = 5, respectively. The reaction mixture was filtered through a pad of silica gel to remove the inorganic materials. The filtrate was concentrated and the crude dendritic alcohol [Gn]-O(CH$_2$)$_3$OH was purified as described in the following text.

[G1]-O(CH$_2$)$_3$OH 10a. This compound was prepared as an oil (91%) from [G0]-O(CH$_2$)$_3$Br and purified by flash chromatography on silica gel (hexane/EtOAc 4/1); R_f 0.31 (hexane/EtOAc 2/1); ^{1}H-NMR ($CDCl_3$) 1.29 (s, 18 H), 1.63 (br s, 1 H), 2.01 (quintet, *J* = 5.9, 2 H), 2.21 (quintet, *J* = 6.0, 4 H), 3.84 (t, *J* = 6.0, 2 H), 4.04-4.16 (m, 10 H), 6.09 (s, 3 H), 6.86 (d, *J* = 8.9, 4 H), 7.28 (d, *J* = 8.9, 4 H); ^{13}C-NMR ($CDCl_3$) 29.7, 31.9, 32.3, 34.5, 61.0, 64.7, 65.0, 66.2, 94.5, 94.6, 114.4, 126.6, 143.8, 157.0, 161.0, 161.2; MS (EI, *m/z*) 564 (M^+, 100%). Anal. Calcd for $C_{35}H_{48}O_6$: C, 74.44; H, 8.57. Found: C, 74.13; H, 8.69. GPC retention time: 34.58 min.

[G2]-O(CH$_2$)$_3$OH 12a. This compound was prepared as an oil (86%) from [G1]-O(CH$_2$)$_3$Br and purified by flash chromatography on silica gel (hexane/EtOAc 4/1); R_f 0.40 (hexane/EtOAc 2/1); ^{1}H-NMR ($CDCl_3$) 1.29 (s, 36 H), 1.74 (t, *J* = 5.4, 1 H), 2.00 (quintet, *J* = 6.0, 2 H), 2.17-2.25 (m, 12 H), 3.82 (q, *J* = 6.0, 2 H), 4.03-4.16 (m, 26 H), 6.09 (s, 9 H), 6.85 (d, *J* = 8.9, 8 H), 7.28 (d, *J* = 9.0, 8 H); ^{13}C-NMR ($CDCl_3$) 29.2, 29.3, 31.5, 31.9, 34.0, 60.5, 64.3, 64.5, 65.7, 94.0, 113.9, 126.2, 143.4, 156.5, 160.7; MS (L-SIMS, *m/z*) 1278 (M^+, 100%). Anal. Calcd for $C_{79}H_{104}O_{14}$: C, 74.26; H, 8.20. Found: C, 74.24; H, 8.05. GPC retention time: 32.44 min.

[G3]-O(CH_2)$_3$OH 13a. This compound was prepared as an oil (89%) from [G2]-O(CH_2)$_3$Br and purified by flash chromatography on silica gel (hexane/EtOAc 4/1); R_f 0.45 (hexane/EtOAc 2/1); ^{1}H-NMR ($CDCl_3$, OH not observed) 1.28 (s, 72 H), 2.01 (quintet, J = 6.0, 2 H), 2.16-2.32 (m, 28 H), 3.80 (t, J = 6.0, 2 H), 4.04-4.16 (m, 58 H), 6.08 (s, 21 H), 6.84 (d, J = 9.0, 16 H), 7.27 (d, J = 9.0, 16 H); ^{13}C-NMR ($CDCl_3$) 29.3, 31.5, 31.9, 34.0, 60.4, 64.3, 64.5, 65.6, 94.1, 113.9, 126.2, 143.4, 156.5, 160.7. Anal. Calcd for $C_{167}H_{216}O_{30}$: C, 74.19; H, 8.05. Found: C, 73.91; H, 8.09. GPC retention time: 30.50 min.

[G4]-O(CH_2)$_3$OH 14a. This compound was prepared as an oil (69%) from [G3]-O(CH_2)$_3$Br and purified by flash chromatography on silica gel (hexane/EtOAc 6/1); R_f 0.54 (hexane/EtOAc 2/1); ^{1}H-NMR ($CDCl_3$, OH not observed) 1.28 (s, 144 H), 2.01 (m, 2 H), 2.16-2.22 (m, 60 H), 3.79 (t, J = 6.0, 2 H), 4.04-4.12 (m, 122 H), 6.09 (s, 45 H), 6.83 (d, J = 9.0, 32 H), 7.27 (d, J = 9.0, 32 H); ^{13}C-NMR ($CDCl_3$) 29.3, 31.5, 34.0, 60.4, 64.3, 64.5, 65.6, 94.1, 113.9, 126.2, 143.3, 156.5, 160.7. Anal. Calcd for $C_{343}H_{440}O_{62}$: C, 74.16; H, 7.98. Found: C, 73.97; H, 7.98. GPC retention time: 28.90 min.

[G5]-O(CH_2)$_3$OH 15a. This compound was prepared as an oil (71%) from [G4]-O(CH_2)$_3$Br and purified by flash chromatography on silica gel (hexane/EtOAc 4/1); R_f 0.62 (hexane/EtOAc 2/1); ^{1}H-NMR ($CDCl_3$) 1.26 (s, 288 H), 2.00-2.20 (m, 126 H), 3.80-4.12 (m, 252 H), 6.09 (s, 93 H), 6.82 (d, J = 9.0, 64 H), 7.26 (d, J = 9.0, 64 H); ^{13}C-NMR ($CDCl_3$) 29.3, 31.5, 34.0, 64.3, 64.5, 94.1, 113.9, 126.2, 143.3, 156.5, 160.7. Anal. Calcd for $C_{695}H_{888}O_{126}$: C, 74.14; H, 7.95. Found: C, 74.22; H, 8.15. GPC retention time: 27.40 min.

General Procedure for Synthesis of Dendritic Bromides (series a, Ar = 4-*tert*-butylphenyl) [Gn]-O(CH_2)$_3$Br (n = 1-4) 11a, 16a-18a. A mixture of the dendritic alcohol [Gn]-O(CH_2)$_3$OH (1.0 mol equiv), carbon tetrabromide (3.0 mol equiv) and triphenylphosphine (3.0 mol equiv) was stirred in dry THF (ether was used as solvent for n = 4) at 20 °C for 9-12 h. The reaction mixture was filtered and the filtered cake washed with dry ether. The combined filtrate was evaporated under reduced pressure to leave a residue which was then purified as described in the following text.

[G1]-O(CH_2)$_3$Br 11a. This compound[11b] was prepared as a white solid (96%) and purified by flash chromatography on silica gel (hexane/EtOAc 10/1), mp 68-70 °C; R_f 0.13 (hexane/ether 10/1); ^{1}H-NMR ($CDCl_3$) 1.29 (s, 18 H), 2.22 (quintet, J = 6.1, 4 H), 2.28 (quintet, J = 6.1, 2 H), 3.58 (t, J = 6.5, 2 H), 4.04 (t, J = 5.8, 2 H), 4.10 (t, J = 6.1, 4 H), 4.12 (t, J = 6.0, 4 H), 6.08 (d, J = 2.0, 2 H), 6.10 (t, J = 2.0, 1 H), 6.85 (d, J = 8.8, 4 H), 7.29 (d, J = 8.8, 4 H).

[G2]-O(CH_2)$_3$Br 16a. This compound[11b] was obtained as a glassy substance (99%) and purified by flash chromatography on silica gel (hexane/EtOAc 9/1); R_f 0.29 (hexane/EtOAc 20/3); ^{1}H-NMR ($CDCl_3$) 1.28 (s, 36 H), 2.19-2.29 (m, 14 H), 3.56 (t, J = 6.4, 2 H), 4.00-4.13 (m, 26 H), 6.09 (s, 9 H), 6.84 (d, J = 8.9, 8 H), 7.29 (d, J = 8.9, 8 H).

[G3]-O(CH_2)$_3$Br 17a. This compound[11b] was prepared as a glassy substance (94%) and purified by flash chromatography on silica gel (hexane/EtOAc 4/1); R_f 0.15 (hexane/EtOAc 5/1); ^{1}H-NMR ($CDCl_3$) 1.28 (s, 72 H), 2.17-2.27 (m, 30 H), 3.54 (t, J = 6.5, 2 H), 3.99-4.12 (m, 58 H), 6.08 (s, 21 H), 6.83 (d, J = 8.8, 16 H), 7.28 (d, J = 8.9, 16 H).

[G4]-O(CH_2)$_3$Br 18a. This compound was prepared as a glassy substance (81%) and purified by flash chromatography on silica gel (hexane/EtOAc 6/1); R_f 0.84 (hexane/EtOAc 2/1); ^{1}H-NMR ($CDCl_3$) 1.27 (s, 144 H), 2.15-2.25 (m, 62 H), 3.53 (t, J = 6.4, 2 H), 4.00-4.11 (m, 122 H), 6.07 (s, 45 H), 6.83 (d, J = 9.0, 32

H), 7.27 (d, J = 9.0, 32 H); ^{13}C-NMR ($CDCl_3$) 29.3, 31.5, 34.0, 64.3, 64.5, 94.1, 113.9, 126.2, 143.3, 156.5, 160.7. Anal. Calcd for $C_{343}H_{439}O_{61}Br$: C, 73.33; H, 7.88. Found: C, 74.01; H, 8.09.

3-Bromo-1-(3,5-dimethylphenoxy)propane 9b. A mixture of 3,5-dimethylphenol (20.0 g, 0.16 mol), 1,3-dibromopropane (65.6 g, 0.33 mol) and potassium carbonate (26.5 g, 0.19 mol) was heated to reflux in acetone (100 mL) for 30 h. The mixture was cooled and filtered. The filtrate was concentrated on a rotary evaporator and the residue purified by flash chromatography on silica gel (hexane/EtOAc 30/1) to give the bromide **9b** (35.0 g, 90%) as a yellow oil. R_f 0.70 (hexane/EtOAc 10/1); ^{1}H-NMR ($CDCl_3$) 2.25 (quintet, J = 6.0, 2 H), 2.27 (s, 6 H), 3.55 (t, J = 6.0, 2 H), 4.02 (t, J = 6.0, 2 H), 6.52 (s, 2 H), 6.58 (s, 1 H); ^{13}C-NMR ($CDCl_3$) 21.4, 30.1, 32.4, 64.9, 112.2, 122.6, 139.2, 158.6; MS (EI, m/z) 244 (M + H$^+$, 25%). Anal. Calcd for $C_{11}H_{15}OBr$: C, 54.34; H, 6.22. Found: C, 54.63; H, 6.29.

General Procedure for the Synthesis of Dendritic Alcohols (series b, Ar = 3,5-dimethylphenyl) [Gn]-O(CH$_2$)$_3$OH (n = 1-3) 10b, 12b, 13b. A mixture of the bromide [G(n-1)]-O(CH$_2$)$_3$Br (2 mol equiv.), 5-(3-hydroxypropyloxy)-1,3-resorcinol (1 mol equiv.), potassium carbonate (3 mol equiv.) and 18-crown-6 (0.1 mol equiv.) was refluxed in THF. The reaction time required was 30, 48 and 72 h for n = 1 to 3 respectively. The reaction mixture was cooled and filtered. After concentration of the filtrate on a rotary evaporator, the crude product was purified as described in the following text.

[G1]-O(CH$_2$)$_3$OH 10b. Flash chromatography of the crude product on silica gel (hexane/EtOAc 5/1) afforded the alcohol (70%) as a pale yellow oil. R_f 0.63 (hexane/EtOAc 1/1); ^{1}H-NMR ($CDCl_3$) 1.73 (br s, 1 H), 2.03 (quintet, J = 6.0, 2 H), 2.21 (quintet, J = 6.0, 4 H), 2.27 (s, 12 H), 3.82 (t, J = 6.0, 2 H), 3.98-4.12 (m, 10 H), 6.09-6.14 (m, 3 H), 6.47 (s, 4 H), 6.59 (s, 2 H); ^{13}C-NMR ($CDCl_3$) 21.4, 22.3, 31.9, 60.5, 64.2, 64.6, 65.8, 94.0, 94.2, 112.2, 122.5, 139.2, 158.9, 160.6. 160.7; MS (EI, m/z) 508 (M^+, 100%). Anal. Calcd for $C_{31}H_{40}O_6$: C, 73.20; H, 7.93. Found: C, 73.50; H, 8.07.

[G2]-O(CH$_2$)$_3$OH 12b. Flash chromatography of the crude product on silica gel (hexane/EtOAc 5/1) afforded the alcohol (50%) as pale yellow glassy substance. R_f 0.69 (hexane/EtOAc 1/1); ^{1}H-NMR ($CDCl_3$) 1.69 (t, J = 6.0, 1 H), 2.02 (quintet, J = 6.0, 2 H), 2.18 (quintet, J = 6.0, 12 H), 2.27 (s, 24 H), 3.83 (q, J = 6.0, 2 H), 4.03-4.11 (m, 26 H), 6.09 (s, 9 H), 6.53 (s, 8 H), 6.58 (s, 4 H); ^{13}C-NMR ($CDCl_3$) 21.4, 29.2, 29.3, 31.9, 60.5, 64.2, 64.5, 65.7, 94.0, 112.2, 122.5, 139.1, 158.9, 160.7; MS (FAB, m/z) 1166 (M + H$^+$, 9%). Anal. Calcd for $C_{71}H_{88}O_{14}$: C, 73.17; H, 7.61. Found: C, 73.42; H, 7.62.

[G3]-O(CH$_2$)$_3$OH 13b. Flash chromatography of the crude product on silica gel (hexane/EtOAc 3/1) afforded the product (45%) as pale yellow glassy substance. R_f 0.78 (hexane/EtOAc 1/1); ^{1}H-NMR ($CDCl_3$) 1.71 (s, 1 H), 2.03 (quintet, J = 6.0, 2 H), 2.21 (m, 28 H), 2.26 (s, 48 H), 3.79–3.81 (m, 2 H), 4.01-4.16 (m, 58 H), 6.08 (s, 21 H), 6.53 (s, 16 H), 6.57 (s, 8 H); ^{13}C-NMR ($CDCl_3$) 21.4, 29.2, 29.3, 31.9, 60.4, 64.2, 64.6, 64.5, 65.7, 94.0, 112.2, 122.5, 139.1, 158.9, 160.7. Anal. Calcd for $C_{151}H_{184}O_{30}$: C, 73.16; H, 7.48. Found: C, 73.22; H, 7.67.

General Procedure for Synthesis of Dendritic Bromides (series b, Ar = 3,5-dimethylphenyl) [Gn]-O(CH$_2$)$_3$Br (n = 1-2) 11b, 16b. A mixture of the alcohol [Gn]-O(CH$_2$)$_3$OH (1 mol equiv.), carbon tetrabromide (2 mol equiv.) and triphenylphosphine (2 mol equiv.) was stirred in THF under 20 °C. The reaction time was 12 and 20 h for the preparation of n = 1 and 2 respectively. The reaction mixture was filtered through

celite and the filtrate concentrated on a rotary evaporator. The crude product was purified as described in the following text.

[G1]-O(CH$_2$)$_3$Br 11b. Flash chromatography of the crude product on silica gel (hexane/EtOAc 30/1) afforded the bromide (96%) as a pale yellow oil. R_f 0.51 (hexane/EtOAc 10/1); ^{1}H-NMR ($CDCl_3$) 2.23 (quintet, J = 6.0, 6 H), 2.29 (s, 12 H), 3.57 (t, J = 6.0, 2 H), 4.03 (t, J = 6.0, 2 H), 4.07-4.12 (m, 8 H), 6.08-6.11 (m, 3 H), 6.54 (s, 4 H), 6.58 (s, 2 H); ^{13}C-NMR ($CDCl_3$) 21.4, 29.3, 29.9, 32.3, 64.1, 64.6, 65.3, 94.1, 94.2, 112.2, 122.5, 139.2, 158.9, 160.5, 160.8; MS (EI, *m/z*) 572 (M + H$^+$, 9%). Anal. Calcd for $C_{31}H_{39}O_{50}Br$: C, 65.15; H, 6.88. Found: C, 65.45; H, 6.89.

[G2]-O(CH$_2$)$_3$Br 16b. Flash chromatography of the crude product on silica gel (hexane/EtOAc 10/1) gave the bromide (96%) as a pale yellow oil. R_f 0.22 (hexane/EtOAc 10/1); ^{1}H-NMR ($CDCl_3$) 2.20 (quintet, J = 6.0, 14 H), 2.31 (s, 24 H), 3.56 (t, J = 6.0, 2 H), 4.03 (t, J = 6.0, 2 H), 4.01-4.13 (m, 24 H), 6.09 (s, 9 H), 6.53 (s, 8 H), 6.58 (s, 4 H); ^{13}C-NMR ($CDCl_3$) 21.4, 29.2, 29.9, 32.3, 64.2, 64.6, 65.3, 94.1, 112.3, 122.5, 139.2, 158.9, 160.7; MS (FAB, *m/z*) 1228 (M^+, 100%). Anal. Calcd for $C_{71}H_{87}O_{13}Br$: C, 69.42; H, 7.14. Found: C, 69.86; H, 7.09.

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