A Simple Method for Controlling Dendritic Architecture and Diversity: A Parallel Monomer Combination Approach

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A novel parallel monomer combination approach to manipulating the architectural disposition of dendritic macromolecules is described. It harnesses the synthetic speed and power of the double-stage convergent growth approach and classical parallel synthesis to prepare diverse series of dendrimers that possess a predetermined number and arrangement of "internal" functional moieties. This methodology is applied for the preparation of a novel family of poly(benzyl ether) dendrimers possessing 1−15 "internal" allyloxy groups, which are displayed in a highly controlled, layer-specific, generational manner.

Introduction

The evolution of dendrimers over the past decade has epitomized macromolecular engineering by permitting unprecedented control of polymer architecture, especially in terms of size and polydispersity, as well as the number and spatial distribution of functional groups within macromolecules.[1] Many of the reports on the derivatization of dendrimers have addressed chemical modification of the core and/or peripheral moieties for a variety of fundamental studies and applications.[2] However, due to the continued expansion of dendrimers into applications that invoke their unique "internal" properties, such as sequestering,[3] drug delivery,[4] and catalysis,[5,6e] there is a growing interest in dendrimers possessing functional moieties that are able to tune the nature of the "internal" functionality and microenvironment. In almost all previous dendrimer families, the interior monomer units have generally been employed as "inert" branched scaffolds to connect the core to the numerous chain ends and their functionalization has received much less attention.[6]

Only a few examples of internally functionalized dendrimers have been reported in the literature. Lochmann et al. described the metalation and post-functionalization of poly(benzyl ether) dendrimers using superbase.[6a] In this way, up to ∼30 potassium ions were introduced into the interiors of [G-4] dendrimers. Subsequent quenching of those carbanionic sites with a variety of electrophiles accessed several novel multifunctional dendrimers that exhibited a range of new properties, such as unusual solubility.

Another dendrimer post-functionalization was reported by Newkome et al.,[6b] who described the generation-specific introduction of boron superclusters into hydrocarbon dendrimers via internal alkyne functionalities for potential use in boron neuron capture therapy cancer treatment and catalysis. The intercalated boron clusters were rendered water-soluble by the surrounding dendrimer.

Majoral and co-workers reported the most systematic approach to the internal functionalization of dendrimers. In several accounts, they have extensively investigated the site-specific grafting of different functional and charged groups,[6c] and even the growth of dendritic wedges within the interior of large phosphorus-containing dendrimers.[6d]

Recently, Piotti and co-workers described the preparation of reversed micellar, internally functionalized dendrimers for the catalysis of simple nucleophilic displacement and elimination reactions.[6e] They prepared poly(benzyl ether) dendrimers of different generations having methyl ester and benzylic alcohol interior moieties. A pronounced microenvironmental effect on catalytic turnover was observed because larger dendrimers, containing a greater number of more polar functional groups, proved

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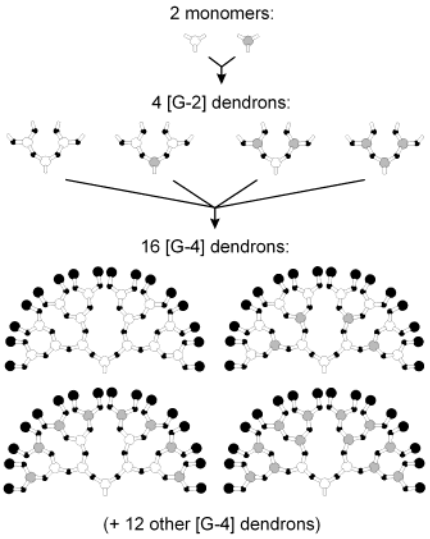

Figure 1. Parallel monomer combination generates 2^G dendrons.

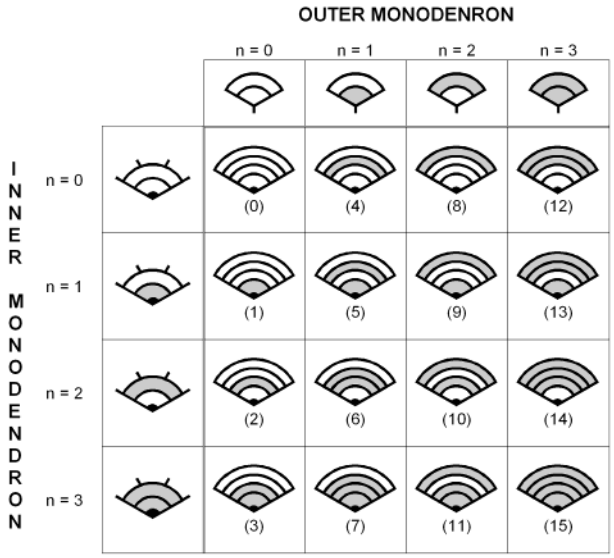

Figure 2. 4 × 4 matrix of allyloxy containing [G-4] monodendrons prepared by synthetically multiplying the arrays of "inner" and "outer" precursors in a parallel manner. The number of "functional" monomers in the dendrons is given in parentheses, and the gray shading indicates their positions within the dendritic "layers".

to be the most effective catalysts for reactions proceeding through polar transition states.

Given these precedents and the growing need for internally functionalized dendrimers, we report the development of a new methodology, the parallel monomer combination approach, for the preparation of a new *series* of internally functionalized dendrimers. It is a powerful synthetic strategy for the systematic preparation of macromolecules with interior functionality introduced via monomer subunits, with utmost control and synthetic efficiency (Figure 1). This approach relies on the premise that any two AB_2 monomers can be combined in parallel to yield four homologous [G-2] monodendrons. These synthons can be further combined in parallel to afford up to 16 different, structurally unique [G-4] dendrons. Parallel combination, in principle, could be reiterated to generate increasing numbers of dendritic fragments in a double exponential manner.[7]

The approach is illustrated with the synthesis of a homologous series of poly(benzyl ether) monodendrons possessing a controlled number and arrangement of allyloxy groups throughout the dendritic backbone. Our methodology, by design, generates these dendrimers with large structural diversity in only a few synthetic steps, by combining the concepts of double-stage convergent growth[8] for speed and modularity, with parallel synthesis for high throughput and control. In practice, the powerful accelerating effect of this synergistic method for the preparation of multiple [G-4] dendrimers was fully exploited, since many of the reactions described below could be conducted simultaneously, typically two to four at a time, without the need for specialized equipment or experimental setup. To our knowledge, this is the first report of the hybridization of classical dendrimer synthesis and a parallel synthetic methodology.

Results and Discussion

We prepared a 4 × 4 matrix of 16 [G-4] dendrons **12a**−**p** possessing 0−15 allylated subunits that are derived from the parallel combination of two four-membered arrays of [G-2] precursors (Figure 2 and Scheme 1). "Inner" and "outer" [G-2] synthons **5a**−**d** and **11a**−**d**, respectively, which possess 0−3 functionalized monomer units in the backbone, are derived from the parallel combination of monomers methyl-3,5-dihydroxybenzoate **2a** and methyl-4-allyloxy-3,5-dihydroxybenzoate **2b**.

Monomer **2b** was selected because it could be prepared easily from methyl gallate **1** and because its structural similarity to **2a** allowed the same efficient activation and coupling chemistries to be used for the dendrimer synthesis. In addition, the allyloxy moiety provides a specific point for subsequent derivatization and post-functionalization when imbedded in the dendrimer framework. Both in principle and in practice, a range of alternative "functional" groups can be incorporated into the dendrimer via derivatization of methyl gallate.[9] The synthesis of **2b** from methyl gallate **1** was previously described by Zhu et al.,[10] in a three-step reaction sequence. Interestingly, we prepared monomer **2b** in a single step by simply stirring methyl gallate in acetone in the presence of a stoichiometric amount of allyl bromide, a catalytic amount of KI, and excess $KHCO_3$, in approximately 70% yield after trituration (Scheme 2).

With monomers **2a** and **2b** in hand, we prepared "inner" tetrasilylated AB_4 hypermonomers **5a**−**d** according to a procedure described by Dehaen and co-workers.[8e] First, the phenolic positions of **2a** and **2b** were protected as their *tert*-butyldiphenylsilyl (TBDPS = P) ethers under standard conditions[11] to afford both first-generation

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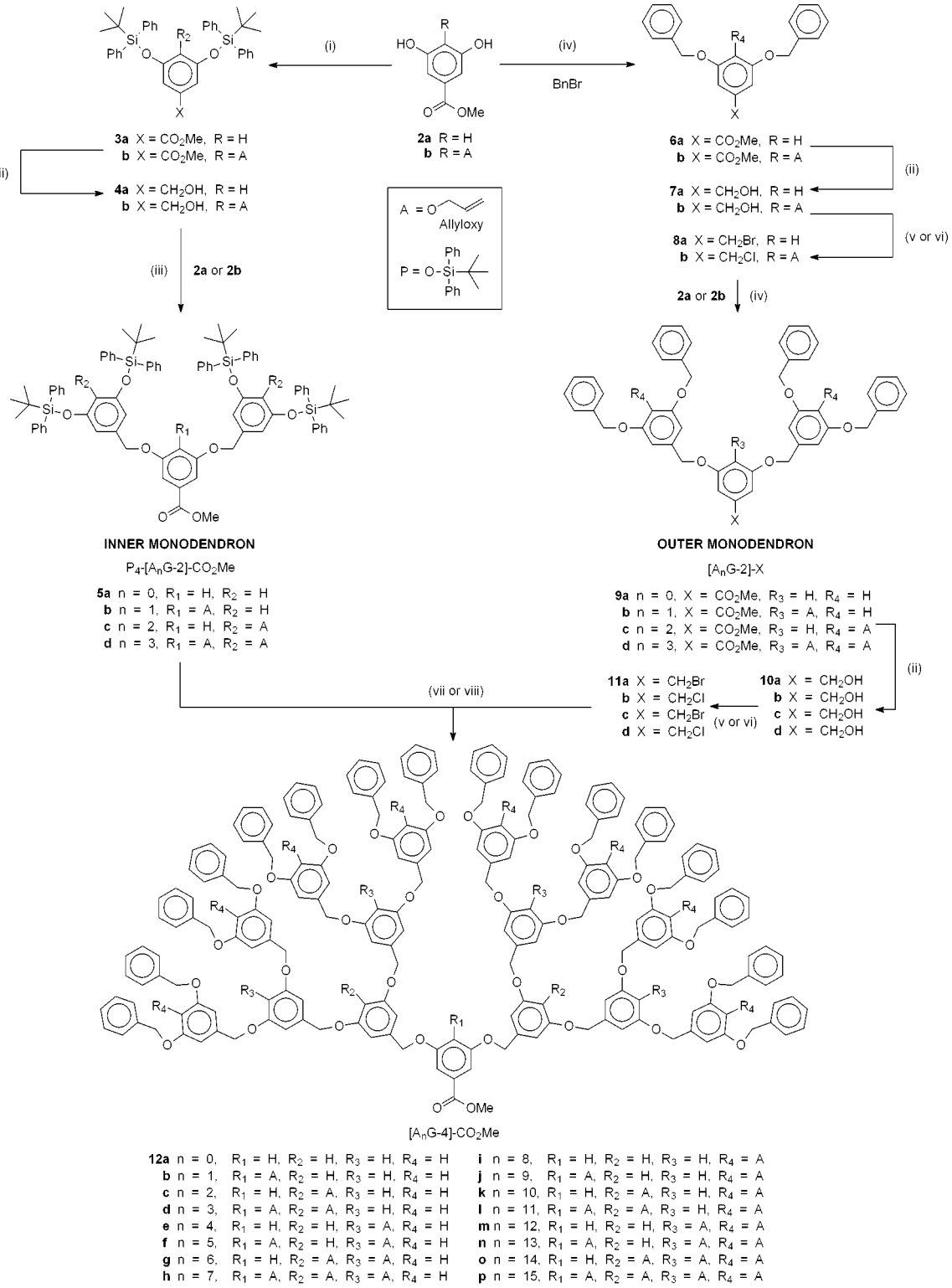
Scheme 1



[a] *reagents and conditions*: (i) TBDPSCl, imidazole, DMF; (ii) $LiAlH_4$, THF, 0 °C; (iii) PPh_3, DEAD, CH_2Cl_2; (iv) K_2CO_3, 18-crown-6, acetone, Δ; (v) PPh_3, CBr_4, THF; (vi) PPh_3, CCl_4, THF, 60 °C; (vii) KF, K_2CO_3, 18-crown-6, acetone, 50 °C; (viii) KF, K_2CO_3, DMF, 60 °C.

dendrons, P_2-[A_nG-1]-CO_2Me (n = 0 and 1, respectively) **3a** and **3b**, in 99% yield. The corresponding alcohols, **4a** and **4b**, were obtained in quantitative yield by reduction of the ester focal point with $LiAlH_4$ followed by the Baeckström workup.[12] Subsequent parallel coupling of the resulting alcohol intermediates with **2a** and **2b** under Mitsunobu conditions yielded the silylated "inner" mono-

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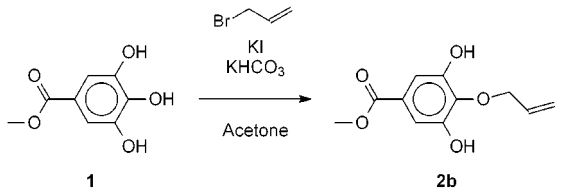
Scheme 2



dendrons **5a**−**d**. Thus, coupling of P_2-[G-1]-CH_2OH **4a** with **2a** and **2b** afforded P_4-[G-2]-CO_2Me **5a**[7e] and P_4-[A_1G-2]-CO_2Me **5b**, in 80 and 76% yield, respectively. Likewise, the homologous synthons **5c** and **5d** (77 and 80% yield, respectively) were obtained by coupling P_2-[A_1G-1]-CH_2OH **4b** with **2a** and **2b**.

The synthesis of "outer" monodendrons **11a**−**d** began by benzylating monomers **2a** and **2b** under standard conditions[13] to give [G-1] dendrons **6a** and **6b** in excellent yield (96 and 98%, respectively). Reduction of the ester moieties with $LiAlH_4$ afforded the corresponding alcohols quantitatively.

Again, the Baeckström's workup[12] procedure facilitated the removal of the Li and Al salts to give the pure products without additional purification. The alcohol intermediates were subsequently activated by conversion to the corresponding halides. Thus, [G-1]-CH_2OH **7a** was brominated using PPh_3/CBr_4 in THF as previously reported.[13] On the other hand, [A_1G-1]-CH_2OH **7b** had to be chlorinated due to the inherent hydrolytic and photoinstability of *p*-alkyloxy-substituted benzylic bromides. Percec and co-workers have reported chlorinations of similar gallate-derived dendrimers using $SOCl_2$ in the presence of scavenger bases.[14] However, to avoid the purchase or preparation of the prohibitively expensive proton sponges, 2,6-di-*tert*-butylpyridine and 4-methyl-2,6-di-*tert*-butylpyridine, we examined other chlorinating agents and found that PPh_3/CCl_4 in refluxing THF cleanly and reproducibly afforded the desired benzyl chlorides in good yields.[15] In this way, [A_1G-1]-CH_2Cl **8b** was prepared from the corresponding alcohol in 75% yield. Parallel combination of these [G-1] halides with **2a** and **2b** under standard Williamson etherification conditions[13] gave [G-2] intermediates **9a**−**d**, [A_nG-2]-CO_2Me (n = 0−3) in excellent yields (>96%) after purification by flash chromatography. Subsequent reduction of esters **9a**−**d** and halogenation (vide supra) gave "outer" bromides [G-2]-CH_2Br **11a** and [A_2G-2]-CH_2Br **11c** and homologous chlorides **11b** and **11d** in good yields (85, 83, 75, and 79%, respectively).

Next, [G-2] "inner" and "outer" precursors **5a**−**d** and **11a**−**d** were systematically combined in a parallel and double-stage convergent manner to give the homologous [G-4] dendrons **12a**−**p**, using modified coupling conditions based on a procedure described by Dehaen and coworkers.[7e] For example, chloride **11b** was coupled with hypermonomer **5a** in the presence of a mixture of KF (5−6 equiv) and K_2CO_3 (2 equiv) in DMF at 60 °C to give [A_4G-4]-CO_2Me **12e** in 75% yield. Similarly, **12f**−**h** and **12m**−**p**, which possess 5−7 and 12−15 allyloxy groups, respectively, were obtained in unoptimized yields of 62−83%. The coupling reactions were conveniently monitored using MALDI-TOF MS to ensure their completeness and the suppression of potentially problematic side products. Surprisingly, these conditions were not suitable for coupling reactions involving bromides **11a** and **11c**. In these cases, MALDI-TOF MS revealed that the [G-2] bromides were quantitatively converted to the corresponding ethers. Presumably, this "degradative" pathway was initiated by the attack of highly soluble K_2CO_3 on the dendritic bromide. Subsequent decomposition of the resulting unstable carbonic ester gives the corresponding, transient benzylic alkoxide that attacks another halide to give the undesired ether. However changing the solvent to acetone, which substantially reduces the amount of K_2CO_3 in solution, adding a catalytic amount of 18-crown-6, and concurrently reducing the reaction temperature to ∼50 °C, permitted the preparation of [G-4] dendrons **12a**−**d** and **12i**−**l** in good yields (61−95%). For example, coupling of "outer" bromide **11a** with silyl dendron **5c** afforded [A_2G-4]-CO_2Me **12c** in excellent yield (95%) after purification. As mentioned above, the mild synthetic requirements enabled us to perform these reactions in parallel, drastically reducing the overall time required to complete the series of monodendrons **12a**−**p**.

Conclusion

In conclusion, we have developed a new approach for the rapid synthesis of poly(benzyl ether) dendrimers that combines the synthetic speed and utility of the double-stage convergent methodology with the throughput and diversity generated by parallel synthesis. The preparation of a new family of [G-4] "allyloxy" containing monodendrons demonstrated that dendritic architecture can be precisely and modularly controlled by applying our method. Although an allyloxy group was selected for synthetic convenience, a wide range of alternative functionality can be introduced via our methodology. Within this new type of radial copolymer,[16] both the exact number and spatial arrangement of the functionalized monomers within the dendrimer backbone can be controlled simply by repetitive, parallel combination of monomers and larger synthons. The [G-4] dendrons **12a**−**p** and similar macromolecules with precisely positioned, derivatizable interior moieties are expected to play a key role in the development of more complex dendritic catalysts[6e] and encapsulating agents. The preparation of small libraries of functionalized dendrimers to be used in the above applications is currently underway.

Experimental Section

Materials and Characterization. All reagents were purchased from Aldrich and used without further purification unless otherwise noted. Potassium carbonate was pulverized and dried at 120 °C overnight prior to use. THF and CH_2Cl_2 were distilled over Na/benzophenone and CaH_2, respectively. Anhydrous *N*,*N*-dimethylformamide (99.8%) was used as received from Aldrich. All reactions were performed under argon. Flash chromatography was performed using Merck Kieselgel 60 (230−

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400 mesh) silica gel. All ^{1}H NMR spectra were acquired at 300 MHz, and ^{13}C NMR spectra were recorded at 125 MHz. Matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) data were acquired using a 337 nm nitrogen laser in positive ion mode. The instrument was calibrated using Bovine Insulin and using α-cyano-4-hydroxycinnamic acid as the matrix system. Analytes (5 mg/mL) were mixed with the matrices (40 mg/mL) in ratios of either 1:4 or 1:2. Electrospray ionization time-of-flight MS (EI-MS) were acquired in positive ion mode with NaI calibration. Samples were prepared as solutions in CH_3CN:H_2O (1:1) and were run at a desolvation temperature of 120 °C. NMR peak assignments are given in the Supporting Information.

Methyl 4-Allyloxy-3,5-dihydroxybenzoate, 2b. A mixture of methyl gallate (20.00 g, 108.62 mmol), allyl bromide (13.13 g, 108.62 mmol), $KHCO_3$ (43.40 g, 434.48 mmol), and KI (0.100 g, 0.60 mmol) were stirred in DMF (100 mL) at 30 °C for 48 h. The mixture was poured into H_2O (1 L), neutralized with concentrated H_2SO_4, and extracted with Et_2O (3 × 150 mL). The combined ethereal extracts were washed with brine (5 × 50 mL), dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (eluting with 70:30 CH_2Cl_2/Et_2O) followed by trituration (2 × 100 mL) with 95:5 hexanes/EtOAc afforded product as a white powder (17.04 g, 70% yield). Spectroscopic and analytical characterization is in accordance with the literature.[10]

General Synthesis of the [G-2] Silyl-Terminated Dendrons 5a−d. To a cooled (0 °C) solution of the ester monomer **2a** or **2b** (0.3 M), [G-1] alcohol (2.1 equiv), and PPh_3 (2.5 equiv) in CH_2Cl_2 was added neat diethylazodicarboxylate (2.5 equiv) dropwise via syringe. The resulting red solution was stirred for 18 h and concentrated to dryness. The product was isolated by flash chromatography.

P_4-[A_1G-2]-CO_2Me, 5b. Prepared from **2b** (0.40 g, 1.78 mmol) and **3a**. The product was isolated by flash chromatography (eluting with 50:50 CH_2Cl_2/hexanes) as an off-white foam (2.40 g, 76% yield): MS (MALDI-TOF MS) *m*/*z* calcd for $[M + Na]^+$ 1445.06, $[M + K]^+$ 1461.17, found 1448.90, 1466.17. Anal. Calcd for $C_{89}H_{96}O_9Si_4$: C, 75.17; H, 6.80. Found: C, 75.42; H, 6.59.

P_4-[A_2G-2]-CO_2Me, 5c. Prepared from **2a** (0.40 g, 2.38 mmol) and **3b**. The product was isolated by flash chromatography (eluting with 50:50 CH_2Cl_2/hexanes) as an off-white foam (3.5 g, 77% yield): MS (MALDI-TOF MS) *m*/*z* calcd for $[M + Na]^+$ 1501.13, $[M + K]^+$ 1517.24, found 1504.12, 1521.14. Anal. Calcd for $C_{92}H_{100}O_{10}Si_4$: C, 74.76; H, 6.82. Found: C, 74.92; H, 6.91.

P_4-[A_3G-2]-CO_2Me, 5d. Prepared from **2b** (0.35 g, 1.56 mmol) and **3b**. The product was isolated by flash chromatography (eluting with 70:30 CH_2Cl_2/hexanes) as an off-white foam (1.91 g, 80% yield): MS (MALDI-TOF MS) *m*/*z* calcd for $[M + Na]^+$ 1557.19, $[M + K]^+$ 1573.30; found 1566.28, 1583.62. Anal. Calcd for $C_{95}H_{104}O_{11}Si_4$: C, 74.37; H, 6.83. Found: C, 74.42; H, 7.05.

General Synthesis of Dendritic Bromides 8a, 11a, 11c. To a THF solution of the dendritic alcohol (1 M) and CBr_4 (1.25 equiv) was added PPh_3 (1.25 equiv) in four equal portions over 10−20 min. Upon complete addition, the mixture turned bright yellow and was subsequently quenched by the addition of saturated NaBr, and extracted with CH_2Cl_2 (3×). The combined organic layers were dried with $MgSO_4$ and concentrated to dryness.

[G-2]-CH_2Br, 11a. Prepared from **10a**. Analytical data and microanalyses were in accordance with literature data.[13]

[A_2G-2]-CH_2Br, 11c. Prepared from **10c** (1.53 g, 1.78 mmol). Flash chromatography (CH_2Cl_2) afforded the product as a white solid (1.23 g, 75% yield): MS (MALDI-TOF MS) calcd for $[M + Na]^+$ 941.27, $[M + K]^+$ 957.27, found 939, 956. Anal. Calcd for $C_{55}H_{51}O_8Br$: C, 71.81; H, 5.59. Found: C, 72.03; H, 5.44.

General Synthesis of Dendritic Chlorides 8b, 11b, 11d. A solution of the dendritic alcohol (1 M), PPh_3 (1.5 equiv), and CCl_4 (4.5 equiv) was stirred in THF at 60 °C for ∼1 h during which time a light yellow-orange precipitate formed. The mixture was diluted with EtOAc, washed with saturated $NaHCO_3$ (2×) and brine, dried over $MgSO_4$, and concentrated to dryness.

[A_1G-2]-CH_2Cl, 11b. Prepared from **10b** (0.53 g, 0.62 mmol). The reaction mixture was precipitated into cold hexanes. Further purification was carried out by flash column chromatography (1:1 CH_2Cl_2/hexanes) (0.42 g, 83% yield): MS (MALDI-TOF MS) *m*/*z* calcd for $[M + Na]^+$ 842.38, $[M + K]^+$ 858.49, found 844.10, 859.95. Anal. Calcd for $C_{52}H_{47}O_7Cl$: C, 76.22; H, 5.78. Found: C, 76.12; H, 6.00.

[A_3G-2]-CH_2Cl, 11d. Prepared from **10d** (1.72 g, 1.90 mmol). The reaction mixture was precipitated into cold hexanes. Further purification was carried out by flash column chromatography (CH_2Cl_2) (1.32 g, 75% yield): MS (MALDI-TOF MS) calcd for $[M]^+$ 931.5, found 934. Anal. Calcd for $C_{58}H_{55}O_9Cl$: C, 74.78; H, 5.95. Found: C, 74.77; H, 5.74.

General Synthesis of [G-4] Dendritic Esters 12a−d and 12i−l. A slurry of the tetrasilylated "inner" dendron (0.05 M), the "outer" bromide **11a** or **11c** (4.5 equiv), KF (6.0 equiv), and K_2CO_3 (2.0 equiv) in acetone was degassed by bubbling argon through the mixture for 5 min. 18-Crown-6 (0.5 equiv) was then added before the reaction mixture was heated to 50 °C for 48 h. The reaction mixture was concentrated to dryness and the residue purified by flash column chromatography.

[A_2G-4]-CO_2Me, 12c. Prepared from **5c** (0.102 g, 0.069 mmol) and **11a**. Flash chromatography (gradient of 80:20 CH_2Cl_2/hexanes to CH_2Cl_2 to 98:2 CH_2Cl_2/Et_2O) afforded the product as a white foam (0.225 g, 95% yield): MS (MALDI-TOF MS) calcd for $[M + K]^+$ 3471, found 3471. Anal. Calcd for $C_{224}H_{196}O_{34}$: C, 78.39; H, 5.76. Found: C, 78.59; H, 5.62.

[A_9G-4]-CO_2Me, 12j. Prepared from **5b** (0.079 g, 0.056 mmol) and **11c**. Flash chromatography (gradient of CH_2Cl_2 to 98:2 CH_2Cl_2/Et_2O) afforded the product as a white foam (0.167 g, 78% yield): MS (MALDI-TOF MS) calcd for $[M + K]^+$ 3863, found 3867. Anal. Calcd for $C_{245}H_{224}O_{41}$: C, 76.94; H, 5.90. Found: C, 77.18; H, 5.81.

General Synthesis of [G-4] Dendritic Esters 12a−d and 12i−l. A slurry of the tetrasilylated "inner" dendron (0.05 M), the "outer" bromide **11a** or **11c** (4.5 equiv), KF (6.0 equiv), and K_2CO_3 (2.0 equiv) in acetone was degassed by bubbling argon through the mixture for 5 min. 18-Crown-6 (0.5 equiv) was then added before the reaction mixture was heated to 50 °C for 48 h. The reaction mixture was concentrated to dryness and the residue purified by flash column chromatography.

[A_5G-4]-CO_2Me, 12f. Prepared from **5b** (0.128 g, 0.087 mmol) and **11b**. The product was isolated as a white foam (0.263 g, 83% yield): MS (MALDI-TOF MS) calcd for [M

+ Na]$^+$ 3623, [M + Ag]$^+$ 3708, found 3626, 3712. Anal. Calcd for $C_{233}H_{208}O_{37}$: C, 77.73; H, 5.82. Found: C, 77.60; H, 6.13.

[A_{15}G-4]-CO_2Me, 12p. Prepared from **5d** (0.091 g, 0.060 mmol) and **11d**. The product was isolated as a white foam (0.154 g, 63% yield): MS (MALDI-TOF MS) calcd for [M + Na]$^+$ 4183, [M + Ag]$^+$ 4268, found 4184, 4267. Anal. Calcd for $C_{263}H_{248}O_{47}$: C, 75.92; H, 6.01. Found: C, 76.16; H, 5.82.

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Supporting Information Available: NMR peaks assignments for all compounds described above as well as spectral and chromatographic information for **3**, **4**, **5a**, **6**−**10**, and **12a**−**e**,**g**−**i**,**k**−**o**. This material is available free of charge via the Internet at http://pubs.acs.org.

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