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# Fluorous Mixture Synthesis of Asymmetric Dendrimers

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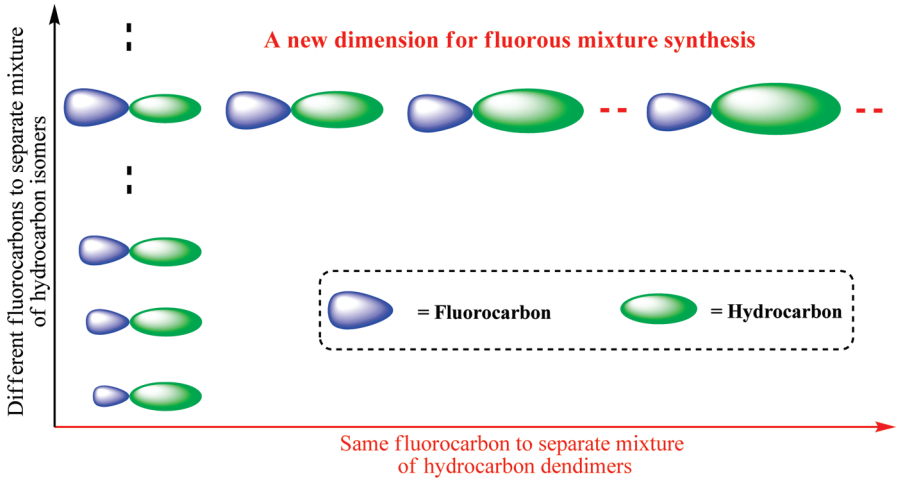
Received January 21, 2010




A divergent fluorous mixture synthesis (FMS) of asymmetric fluorinated dendrimers has been developed. Four generations of fluorinated dendrimers with the same fluorinated moiety were prepared with high efficiency, yield, and purity. Comparison of the physicochemical properties of these dendrimers provided valuable information for their application and future optimization. This strategy has not only provided a practical method for the synthesis and purification of dendrimers, but also established the possibility of utilizing the same fluorinated moiety for FMS.

## Introduction

In recent years, fluorinated dendrimers[1] have attracted considerable attention in the fields of catalysis,[2] materials,[3] and biology.[4] Introduction of fluorocarbons and manipulation of the fluorine content in dendrimers have a great influence on the shape and stability of fluorinated dendrimeric assemblies.[5] Fluorinated dendrimers often exhibit unique physicochemical and biological properties as compared to their nonfluorinated counterparts.[1−5] For example, Percec and co-workers replaced certain hydrogen atoms with fluorine atoms at the tail end of a dendron and found an unexpected change in its structural motif and self-assembling behavior.[1b,5d] However, most, if not all, reported fluorinated dendrimers are water insoluble, an issue that severely limits their bioavailability. Further, efficient synthesis of multigenerational fluorinated dendrimers remains a challenge.[2−5] In this work, we enhance water solubility by synthesizing

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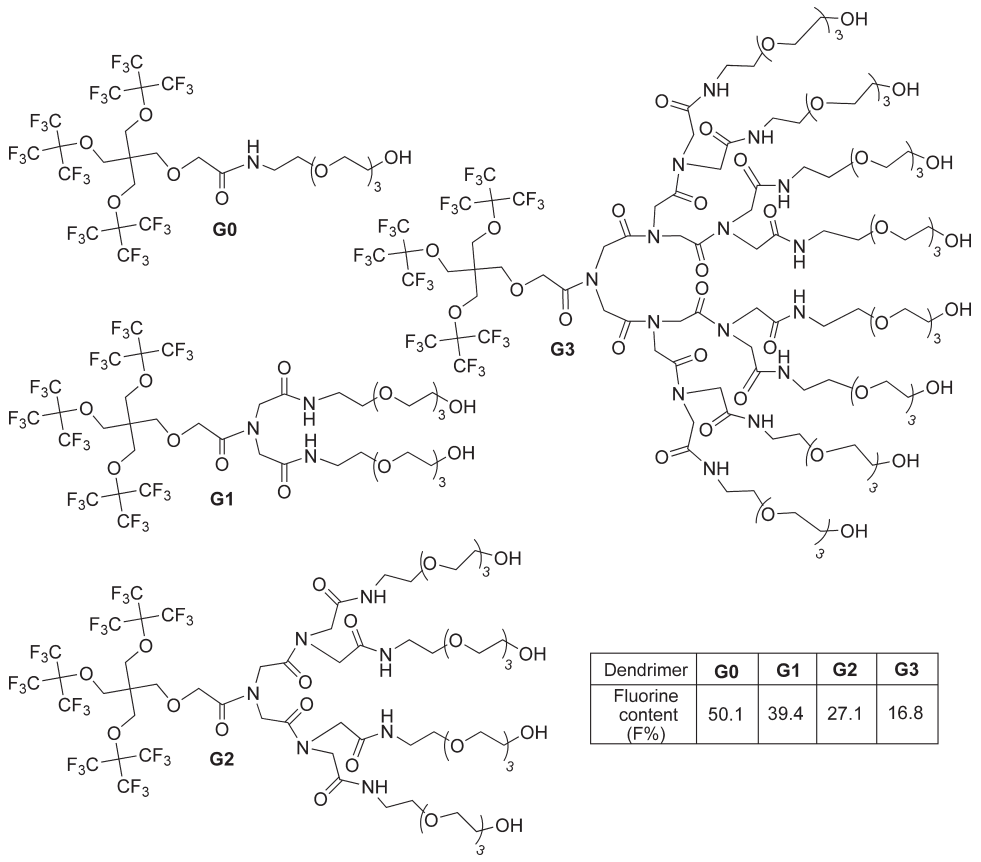
Published on Web 02/19/2010 DOI: 10.1021/jo100102a




| Dendrimer | G0 | G1 | G2 | G3 |
|---|---|---|---|---|
| Fluorine content (F%) | 50.1 | 39.4 | 27.1 | 16.8 |

**FIGURE 1.** Structures and fluorine contents of four fluorinated dendrimers.

hydrophilic asymmetric dendrimers and improve synthesis efficiency by synthesizing several generations of fluorinated dendrimers in one pot using the so-called fluorous mixture synthesis (FMS) method developed for small molecules.[6]

Our interest in fluorinated dendrimers is to employ them as delivery vehicles for $^{19}$F magnetic resonance image (MRI) guided drug therapy. To this end, we have recently developed a dendritic $^{19}$F imaging tracer, $^{19}$FIT (Figure 1, **G2**).[7] $^{19}$FIT is water-soluble and, in animal studies, was rapidly excreted intact. Structurally, $^{19}$FIT is an amphiphilic dendrimer, belonging to the family of asymmetric or Janus dendrimers.[8] In $^{19}$FIT, the two dissimilar dendrons are connected by an amide bond, which is metabolically more stable but synthetically less facile than the disulfide bond used previously for connecting dissimilar dendrons.[8] One way to modulate the physicochemical properties of $^{19}$FIT is to change the number of branches in its hydrophilic dendron, essentially forming dendrimers of different generations.[9] Thus, a method for the simultaneous synthesis of multiple generations of fluorinated dendrimers is of great value. Herein, we report a FMS strategy for the synthesis of four generations of fluorinated dendrimers in one pot.

## Results and Discussion

Conventional FMS is based on conjugating fluorocarbon tags (linear perfluorocarbons of different chain lengths) to nonfluorinated substrates (structural isomers or stereoisomers) for the convenience of purification.[6] The basis for separation is that molecules tagged with different fluorocarbons have different fluorine content (F%) and therefore different retention times in fluorous chromatography. However, for dendrimers, sufficient differences in fluorine content and fluorous chromatography retention time can be produced even with the same fluorocarbon moiety. This

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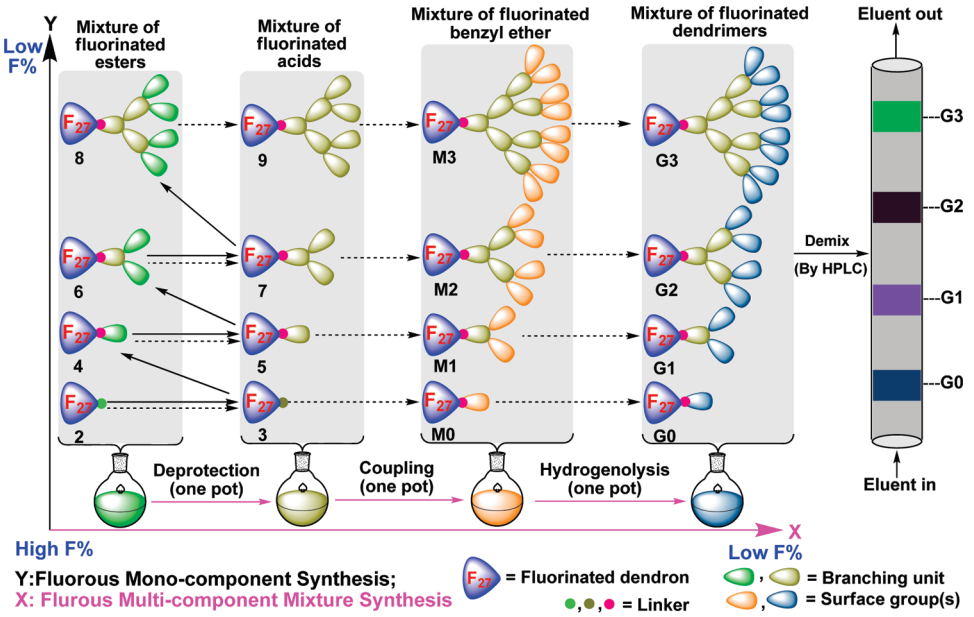
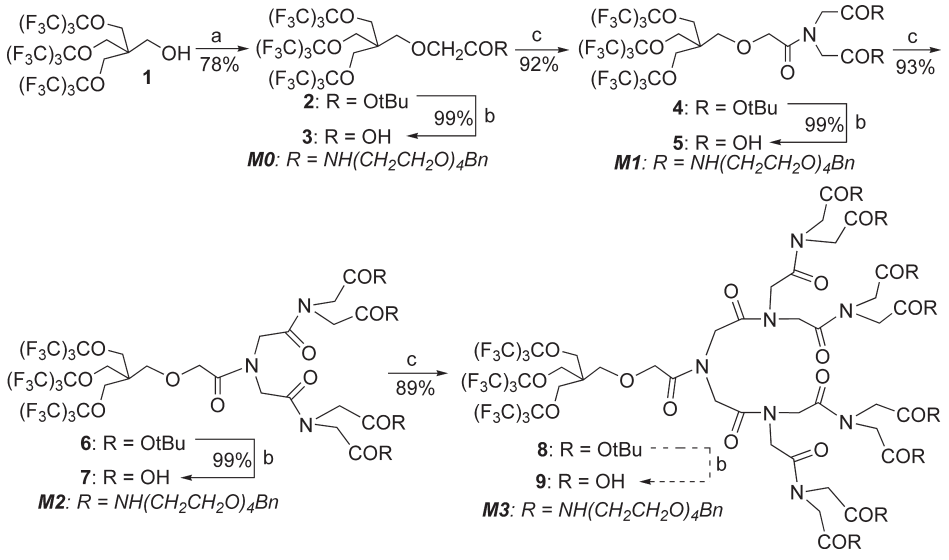
**SCHEME 1. Strategy for the Synthesis of Fluorinated Dendrimers**[a]




[a]**2**, **4**, **6**, and **8** were synthesized individually with use of fluorous monocomponent synthesis (along the *Y*-axis). **2**, **4**, **6**, and **8** were then mixed and underwent fluorous multicomponent synthesis (along the *X*-axis) to give **G0**, **G1**, **G2**, and **G3** as a mixture, which was then separated with preprative HPLC. Each pair of starting material and product is connected by a solid or dashed arrow in mono- and multicomponent synthesis, repsectively.

**SCHEME 2. Fluorous Synthesis of Intermediates 2, 4, 6, and 8**[a,b]




[a]Reagents and conditions: (a) KH, $BrCH_2CO_2$-*t*Bu, THF, rt; (b) TFA, anisole, $CH_2Cl_2$, rt; (c) DIC, HOBt, $HN(CH_2CO_2$-*t*$Bu)_2$, DMF/THF (1/1), rt. [b]Synthesis of **M0**, **M1**, **M2**, and **M3** (in italic) is illustrated in Scheme 3, while the chemical structures of **M0**, **M1**, **M2**, and **M3** are indicated here.

approach, i.e., using the same fluorocarbon moiety for the separation of multigenerational dendrimers, is the strategy we employed in this work (Scheme 1). An FMS of four generations of dendrimers (**G0**−**G3**, Figure 1) has been developed to illustrate this strategy. The difference in the fluorine content between successive generations is over 10%, which would be sufficient for separating the dendrimer mixture with fluorous HPLC.

With these ideas in mind, the intermediates for dendrimers **G0**−**G3** were synthesized sequentially: **1** → **2** → **3** → **4** → **5** → **6** → **7** → **8** (Scheme 2). The treatment of alcohol **1**[7,10] with potassium hydride and *tert*-butyl bromoacetate afforded ester **2**, which then underwent a deprotection−coupling cycle (b−c) three times to give the octaester **8** with a 74% yield over six steps. During the synthesis, intermediates **2**, **4**, and **6** were split into two portions: one for the following step and the other for FMS. All the intermediates (**2**−**8**) were conveniently purified by either fluorous liquid- or solid-phase extractions.

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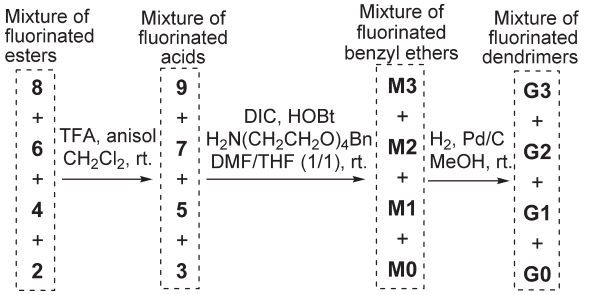
**SCHEME 3. FMS of Fluorinated Dendrimers G0 to G3**




Once all the intermediates were prepared, we commenced FMS of four generations of dendrimers (Scheme 3). The four intermediates **2** (452 mg, 0.5 mmol), **4** (430 mg, 0.4 mmol), **6** (425 mg, 0.3 mmol), and **8** (421 mg, 0.2 mmol) were mixed and the *tert*-butyl group in the resulting mixture was removed with trifluoroacetic acid to yield a mixture of four acids, **3** + **5** + **7** + **9**, which was then coupled with 1-phenyl-2,5,8,11-tetraoxatridecan-13-amine[7,10] to yield a mixture of four benzyl ethers, **M0** + **M1** + **M2** + **M3**. After removal of the benzyl groups through Pd-catalyzed hydrogenolysis, a mixture of four fluorinated dendrimers, **G0** + **G1** + **G2** + **G3**, was obtained. Each of the three steps in Scheme 3 was conducted twice to facilitate complete conversion of the starting materials. After each reaction, excess reagents were removed by solid-phase extraction on fluorous silica gel with the $H_2O$−MeOH−THF eluent system to yield the resulting mixture. Since the synthesis started with the fluorinated core and ended with the surface groups, the result is a divergent FMS of dendrimers.

To finish the FMS, the dendrimer mixture, **G0** + **G1** + **G2** + **G3**, was demixed/purified by HPLC to obtain individual dendrimers. Column selection is crucial for demixing. Unlike conventional FMS where separation is driven solely by the fluorine content, two additional factors, polarity and molecular size, may also influence the separation of **G0**−**G3**. This prompted us to explore separating the mixture by HPLC using three types of columns: FluoroFlash, normal-phase (NP) amide-80, and reversed-phase (RP) C18 columns. The analytical chromatograms showed that all three columns can separate the dendrimer mixture (Figure 2), yet there were some differences in the separation profiles. FluoroFlash and NP-amide-80 columns resulted in the opposite elution order of **G0**−**G3**, but all peaks were sharp. In contrast, the RP-C18 column resulted in the same elution order as FluoroFlash, but the peaks were broad. The fluorinated dendrimer mixture was then separated on a preparative FluoroFlash column to give individual fluorinated dendrimers. Surprisingly, the overall yield was good for all four dendrimers: **G0** (445 mg, 0.435 mmol, 87% yield), **G1** (462 mg, 0.352 mmol, 88%), **G2** (460 mg, 0.243 mmol, 81%), and **G3** (434 mg, 0.142 mmol, 71%).

(11) FluoroFlash column (4.6 × 150 mm, 5 $\mu$m), gradient 60% MeOH−$H_2O$ to 100% MeOH in 15 min and then maintain 100% MeOH, flow rate 1 mL/min; NP-amide-80 column (4.6 × 250 mm, 5 $\mu$m), gradient 100% $CH_3CN$ to 70% $CH_3CN$−$H_2O$ in 30 min, flow rate 1 mL/min; RP-C18 column (4.6 × 250 mm, 5 $\mu$m), gradient 40% $CH_3CN$−$H_2O$ to 70% $CH_3CN$−$H_2O$ in 30 min, flow rate 1 mL/min, rt for all runs. The sample was prepared by dissolving and mixing pure fluorinated dendrimers (5 $\mu$mol each) in methanol (5 mL).

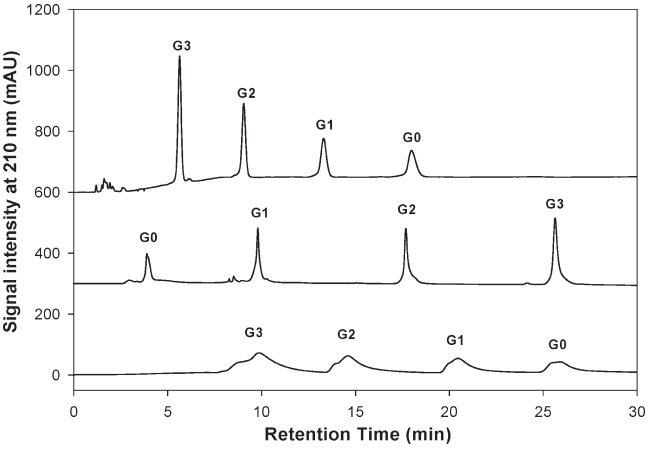



**FIGURE 2.** HPLC separation of fluorinated dendrimer mixture (**G0** + **G2** + **G3** + **G4**).[11] (Signals were vertically displaced for display. Columns: FluoroFlash (top); NP-amide-80 (middle); RP-$C_{18}$ (bottom).)

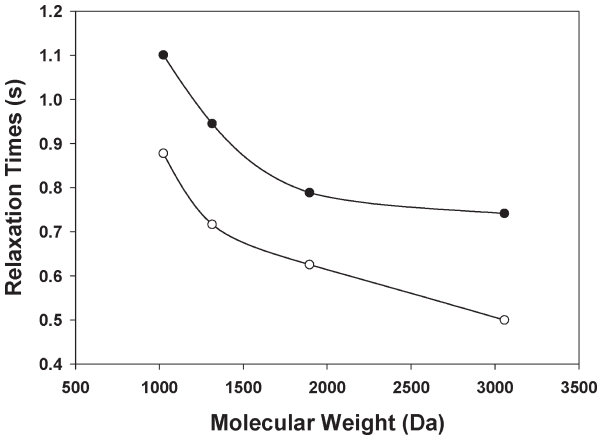



**FIGURE 3.** $^{19}F$ $T_1$ (filled circles) and $T_2$ (hollow circles) of **G0**, **G1**, **G2**, and **G3** (left to right) ($^{19}F$ NMR, 376 MHz, 25 °C, 25 mM in $CD_3OD$).

Each dendrimer emitted a sharp singlet $^{19}F$ NMR signal with a peak width of less than 0.03 ppm (see the Supporting Information). $^{19}F$ NMR relaxation measurements indicated that both the longitudinal relaxation time $T_1$ and the transverse relaxation time $T_2$ decreased from **G0** to **G3** (Figure 3). A similar decrease of $^{19}F$ $T_1$ value with generational number has been previously reported for another class of fluorinated dendrimers.[9b] Such genrational dependency of $^{19}F$ relaxation times might be a reflection of the intrinsic nanoperiodic property pattern of dendrimers.[12] Reduced $T_1$ can increase $^{19}F$ signal intensity in MRI by allowing the collection of more signal transients without prolonging data acquisition time. **G0** and **G1** have very limited water solubility, while **G2** and **G3** have good water solubility (a 150 mM aqueous solution of **G2** has been used in animal studies[7]). By using $^{19}F$ NMR spectroscopy,[13] the critical micelle concentrations of **G2** and **G3** were determined to be 7 and 8 mM, respectively (Figure 4). An ideal $^{19}F$ imaging agent is a compound with a singlet $^{19}F$ signal from multiple fluorine atoms, short $T_1$, and

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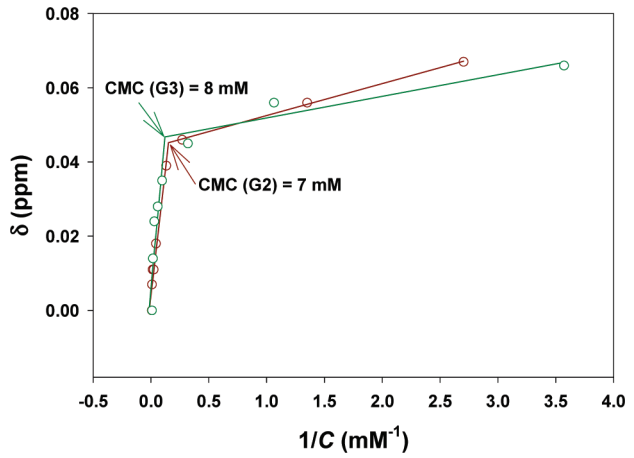


**FIGURE 4.** $^{19}F$ NMR (376 MHz) determination of the critical micelle concentration (CMC) for **G2** (dark red) and **G3** (dark green) in water.

good water solubility. On the basis of the data in hand, **G2** and **G3** have the potential as imaging agents for $^{19}F$ MRI.

## Conclusion

In summary, a fluorous mixture synthesis (FMS) strategy for the rapid preparation of multigenerational fluorinated dendrimers has been developed, which significantly simplifies dendrimer synthesis and purification. If necessary, this method could be adapted for the synthesis of nonfluorinated dendrimers by adopting a removable fluorocarbon moiety.

## Experimental Section

***tert*-Butyl Ester 2 (Step a).** A suspension of potassium hydride (30%, 3.2 g, 24.0 mmol) was added slowly to a stirring solution of alcohol **1** (15.8 g, 20.0 mmol) in tetrahydrofuran (200 mL) at 0 °C. After 10 min, *tert*-butyl bromoacetate (5.9 mL, 7.8 g, 40.0 mmol) was added to the suspension in one portion at rt and the resulting mixture was stirred at rt overnight. After the reaction was quenched with water (20 mL), the mixture was transferred into a separatory funnel and the lower phase was collected as a clear oil. Removal of low boiling point impurities from the oil under vacuum gave the *tert*-butyl ester **2** as a clear oil (14.1 g, 78% yield). $^1H$ NMR (400 MHz, CDCl3) $\delta$ 4.14 (s, 6H), 3.91 (s, 2H), 3.57 (s, 2H), 1.46 (s, 9H).

**General Procedure for the Transformation of *tert*-Butyl Ester into Acid: Preparation of Acid 3 (Step b).** To a stirred solution of *tert*-butyl ester **2** (13.6 g, 15.0 mmol) and anisole (3.0 mL) in dichloromethane (100 mL) at rt was added trifluoroacetic acid (30 mL) and the resulting solution was stirred at rt for 1 h. After evaporation to dryness under vacuum, the residue was dissolved in methanol/toluene (50 mL/30 mL) and evaporated to dryness under vacuum to give the pure acid **3** as a reddish oil (12.6 g, 99% yield), which was used in the next step without further purification. $^1H$ NMR (400 MHz, acetone-$d_6$) $\delta$ 4.29 (s, 6H), 4.14 (s, 2H), 3.73 (s, 2H).

**General Procedure for Coupling Acid and Amine To Yield Amide (Step c). a. Preparation of amide 4:** *N*,*N*-Diisopropylcarbodiimide (6.6 mL, 5.4 g, 42.5 mmol) was added to a stirring solution of *N*-hydroxybenzotriazole (5.7 g, 42.5 mmol) and acid **3** (12.0 g, 14.2 mmol) in dry *N*,*N*-dimethylformamide (200 mL) at rt. After the reaction mixture was stirred for 15 min, di-*tert*-butyl iminodiacetate (10.4 g, 42.5 mmol) was added and the resulting mixture was stirred at rt for 6 h. Water (20 mL) was added to the reaction mixture and the resulting mixture was purified by solid-phase extraction on FlouroFlash silica gel to give the amide **4** as a clear oil (14.1 g, 92% yield), which was used in the next step without further purification. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 4.12 (s, 6H), 4.10 (s, 2H), 4.02 (s, 2H), 3.92 (s, 2H), 3.59 (s, 2H), 1.44 (s, 9H), 1.42 (s, 9H); $^{19}F$ NMR (376 MHz, $CDCl_3$) $\delta$ −73.29 (s).

**b. Diacid 5:** This compound was prepared by employing step b with a 99% yield. $^1H$ NMR (400 MHz, $CD_3OD$) $\delta$ 4.22 (s, 8H), 4.16 (s, 2H), 4.14 (s, 2H), 3.60 (s, 2H).

**c. Tetra-*tert*-butyl ester 6:** This compound was prepared by employing step c with a 93% yield. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 3.80−4.13 (m, 20H), 3.47 (s, 2H), 1.28−1.31 (m, 36H).

**d. Tetraacid 7:** This compound was prepared by employing step b with a 99% yield. $^1H$ NMR (400 MHz, $CD_3OD$) $\delta$ 4.15 (s, 2H), 4.05−4.09 (m, 10H), 3.90−4.01 (m, 6H), 3.53−3.59 (m, 2H), 3.43 (s, 2H).

**e. Octa-*tert*-butyl ester 8:** This compound was prepared by employing step c with an 89% yield. $^1H$ NMR (400 MHz, $CD_3OD$) $\delta$ 4.40 (s, 2H), 4.34 (s, 2H), 4.28 (s, 4H), 4.25 (s, 8H), 4.12−4.17 (m, 12H), 4.03−4.07 (m, 8H), 3.59 (s, 2H), 1.45−1.50 (m, 72H); $^{19}F$ NMR (376 MHz, $CD_3OD$) $\delta$ −71.16 (s); $^{13}C$ NMR (100.7 MHz, $CD_3OD$) $\delta$ 172.0, 171.6, 171.2, 171.1, 171.0, 170.8, 170.6, 169.7, 169.6, 169.55, 169.43, 169.4, 121.6 (q, $J$ = 293.3 Hz), 84.1, 84.0, 83.8, 83.7, 83.1, 83.0, 82.9, 80.3−81.5 (m), 69.5, 68.6, 68.3, 51.6, 51.5, 51.0, 50.8, 50.77, 50.1, 49.9, 49.1, 48.4, 47.2, 28.4, 28.3, 28.29; MS (MALDI-TOF) $m/z$ 2125 ($(M + Na)^+$); HRMS (MALDI-TOF) calcd for $C_{79}H_{110}F_{27}N_7NaO_{27}$ 2124.6916, found 2124.7023.

**Procedure for the Fluorous Mixture Synthesis of Fluorinated Dendrimers G0−G3.** A mixture of monoester **2** (452 mg, 0.5 mmol), diester **4** (430 mg, 0.4 mmol), tetraester **6** (425 mg, 0.3 mmol), and octaester **8** (421 mg, 0.2 mol) was dissolved in dichloromethane (24 mL). This mixture was treated with anisol (1 mL) and trifluoroacetic acid (8 mL) at rt (step b) to give a wax of acids (**3**, **5**, **7**, and **9**). The above procedure was repeated to facilitate the complete conversion of the starting materials. Then the wax was put into the coupling step with 1-phenyl-2,5,8,11-tetraoxatridecan-13-amine (3.5 g, 12.3 mmol) by employing the general coupling procedure (step c) twice to give a mixture of intermediates (**M0**, **M1**, **M2**, and **M3**). The mixture of intermediates was hydrogenolized twice with palladium on carbon (10%, 1.0 g) in methanol over 20 h to give a mixture of fluorinated dendrimers and their side products. After filtration with a pad of Celite, the dendimer mixture was then purified by HPLC on preparative FluoroFlash column (21.1 × 250 mm, flow rate 5 mL/min, gradient from 60% MeOH in water to 100% MeOH in 170 min, then 100% MeOH for 40 min, detection wavelength at 210 nm). After lyophilization, individual fluorinated dendrimers were obtained: **G0** (445 mg, 0.435 mmol, 87% yield), **G1** (462 mg, 0.352 mmol, 88% yield), **G2** (460 mg, 0.243 mmol, 81% yield), and **G3** (349 mg, 0.142 mmol, 71% yield).

**a. Fluorinated dendrimer G0:** $^1H$ NMR (400 MHz, $CD_3OD$) $\delta$ 4.03 (s, 6H), 3.89 (s, 2H), 3.56−3.64 (m, 10H), 3.53−3.55 (m, 6H), 3.44 (s, 2H); $^{19}F$ NMR (376 MHz, $CD_3OD$) $\delta$ −71.11 (s); $^{13}C$ NMR (100.7 MHz, $CDCl_3$) $\delta$ 168.4, 120.0 (q, $J$ = 293.3 Hz), 79.4−79.9 (m), 72.4, 71.0, 70.4, 70.2, 70.1, 70.08, 66.5, 64.9, 61.5, 46.2, 38.7; MS (MALDI-TOF) $m/z$ 1046 ($(M + Na)^+$), 1024 ($(M + H)^+$); HRMS (MALDI-TOF) calcd for $C_{27}H_{28}F_{27}NNaO_9$ 1046.1231, found 1046.1280; $T_1$ ($^{19}F$, 376 MHz, 26 mM in $CD_3OD$) 1.101 s, err = 0.0577; $T_2$ ($^{19}F$, 376 MHz, 25 mM in $CD_3OD$) 0.8779 s, err = 0.0162.

**b. Fluorinated Dendrimer G1:** $^1H$ NMR (400 MHz, $CD_3OD$) $\delta$ 4.23 (s, 6H), 4.21 (s, 2H), 4.05 (s, 2H), 4.04 (s, 2H), 3.60−3.67 (m, 22H), 3.54−3.58 (m, 8H), 3.38−3.43 (m, 4H); $^{19}F$ NMR (376 MHz, $CD_3OD$) $\delta$ −71.08 (s); $^{13}C$ NMR (100.7 MHz, $CD_3OD$) $\delta$ 172.0, 171.4, 170.8, 121.6 (q, $J$ = 292.5 Hz), 80.4−81.4 (m), 73.7, 71.6, 71.4, 71.3, 71.2, 70.4, 70.3, 69.7, 68.7, 68.1, 62.2, 52.4, 47.3,

40.6, 40.4; MS (MALDI-TOF) $m/z$ 1336 ($(M + Na)^+$); HRMS (MALDI-TOF) calcd for $C_{39}H_{50}F_{27}N_3NaO_{15}$ 1336.2708, found 1336.2671; $T_1$ ($^{19}F$, 376 MHz, 25 mM in $CD_3OD$) 0.9453 s, err = 0.0460; $T_2$ ($^{19}F$, 376 MHz, 25 mM in $CD_3OD$) 0.7168 s, err = 0.0251.

**c. Fluorinated Dendrimer G2:** $^1H$ NMR (400 MHz, $CD_3OD$) $\delta$ 4.26 (s, 2H), 4.25 (s, 8H), 4.22 (s, 2H), 4.18 (s, 2H), 4.15 (s, 2H), 4.05 (s, 2H), 4.04 (s, 2H), 3.59−3.67 (m, 42H), 3.53−3.58 (m, 16H), 3.44 (t, $J$ = 4.2 Hz, 4H), 3.38 (t, $J$ = 5.6 Hz, 4H); $T_1$ ($^{19}F$, 376 MHz, 25 mM in $CD_3OD$) 0.7888 s, err = 0.0158; $T_2$ ($^{19}F$, 376 MHz, 25 mM in $CD_3OD$) 0.6255 s, err = 0.00819.

**d. Fluorinated Dendrimer G3:** $^1H$ NMR (400 MHz, $CD_3OD$) $\delta$ 4.39 (s, 2H), 4.35 (s, 2H), 4.21−4.24 (m, 14H), 4.18 (s, 6H), 4.05−4.10 (m, 10H), 3.54−3.67 (m, 116H), 3.42−3.47 (m, 8H), 3.36−3.40 (m, 8H); $^{19}F$ NMR (376 MHz, $CD_3OD$) $\delta$ −71.03 (s); $^{13}C$ NMR (100.7 MHz, $CD_3OD$) $\delta$ 172.1, 171.7, 171.6, 171.59, 171.3, 171.26, 171.1, 171.06, 170.8, 170.7, 170.6, 170.5, 121.5 (q, $J$ = 292.6 Hz), 80.2−81.6 (m), 73.6, 71.5, 71.3, 71.2, 71.17, 71.1, 70.35, 70.3, 70.2, 69.4, 68.6, 68.3, 62.2, 53.3, 53.2, 53.1, 53.08, 52.9, 52.7, 50.5, 50.3, 49.5, 49.3, 48.1, 47.2, 40.5, 40.47, 40.4; MS (MALDI-TOF) $m/z$ 3077 ($(M + Na)^+$); HRMS (MALDI-TOF) calcd for $C_{111}H_{182}F_{27}N_{15}NaO_{51}$ 3078.1602, found 3078.1702; $T_1$ ($^{19}F$, 376 MHz, 25 mM in $CD_3OD$) 0.7415 s, err = 0.00713; $T_2$ ($^{19}F$, 376 MHz, 25 mM in $CD_3OD$) 0.4999 s, err = 0.00365.

**Acknowledgment.** This work was supported by NIH grant EB004416 and the Maryland Nano-Biotechnology Fund to Y.B.Y. We thank Y. Feng, L. Hyland, and K. Joyner for assistance with manuscript preparation.

**Supporting Information Available:** Characterization data of all synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.