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The Design and Synthesis of Fluorinated Dendrimers for Sensitive ^{19}F MRI

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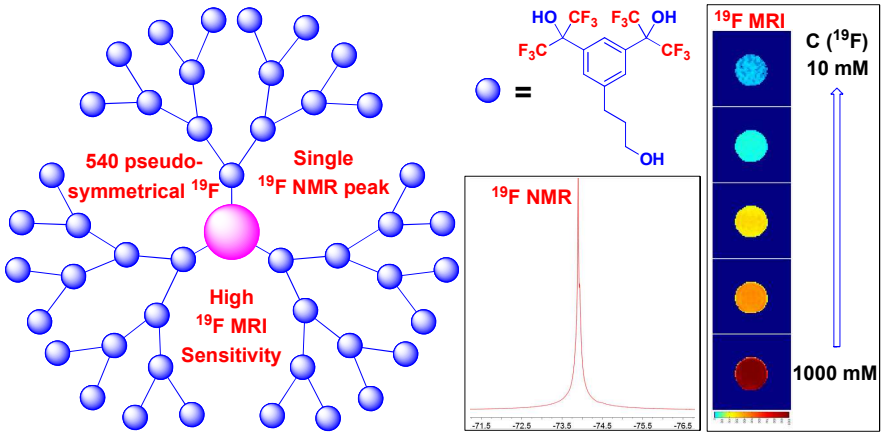
ABSTRACT



To achieve high sensitivity for ^{19}F MRI, a class of novel dendritic molecules with multiple pseudo-symmetrical fluorines were designed and efficiently synthesized. Through iterative bromination and Williamson ether synthesis under mild conditions, a fluorinated dendrimer with 540 pseudo-symmetrical fluorines was conveniently prepared without performing the group protection in a convergent way. The dendrimer is characterized by a strong ^{19}F NMR peak and short relaxation times. Eventually, an appreciably enhanced ^{19}F MRI at an extremely low concentration (18.5 μM) was achieved, which demonstrated the potential utility of such dendritic molecules in highly sensitive ^{19}F MRI.

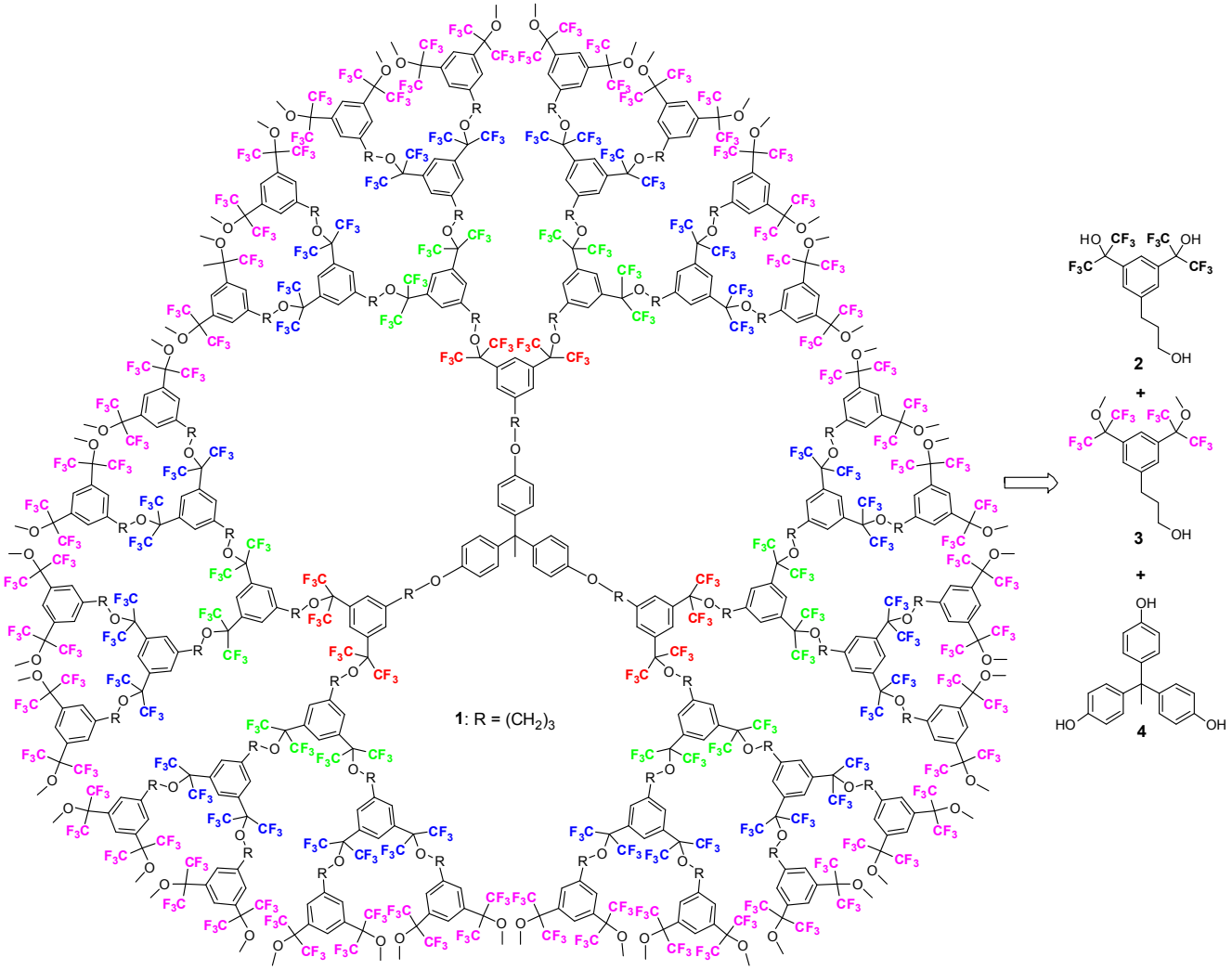
INTRODUCTION

Proton-based magnetic resonance imaging (^{1}H MRI), which provides high-quality three-dimensional images without ionizing radiation, has become an important technique in modern diagnostic medicine. Unfortunately, the intense background signals in ^{1}H MRI causes insufficient discrimination of pathological tissues from normal ones. Compared to ^{1}H MRI, ^{19}F MRI provides high-contrast *in vivo* images without endogenous background signals.[1] Therefore, ^{19}F MRI has attracted considerable attention in recent years. It has been widely used in disease diagnosis,[2] therapy evaluation,[3] tracking targets of interest,[4] monitoring biological reactions[5] and probing local pH or pO_2[6] etc. Our interest lies in ^{19}F MRI-guided drug therapy[7] by taking the advantage of its absence of endogenous signal, 100% natural abundance of ^{19}F, a chemical shift range of over 400 ppm, etc.[1] However, it is a very challenging task to image a drug *in vivo* with ^{19}F MRI because it has such a low sensitivity that a high ^{19}F concentration, a typical concentration of 89 mM for an example,[8] is generally required which is far beyond the *in vivo* concentration of most drugs. In addition, the ^{19}F NMR signal splitting and relatively long relaxation times of perfluorocarbons emulsion-based ^{19}F MRI agents, which are the most used imaging agents for ^{19}F MRI, further deteriorates the sensitivity of ^{19}F MRI.[1, 4] To this end, developing a highly ^{19}F MRI sensitive drug carrier with high fluorine density, single ^{19}F NMR peak and short relaxation times is a strategy of choice to address the sensitivity issues in ^{19}F MRI-guided drug therapy.

Dendrimers have been extensively used in both imaging and drug delivery owing to their attractive properties, such as multi-valence, uniform size, modifiable surface, and available internal cavities.[9] Fluorinated dendrimers, which can incorporate a large number of fluorines into their highly branched scaffolds and therefore achieve high sensitivity for ^{19}F MRI, are promising drug carriers for ^{19}F MRI-guided drug therapy. It is noteworthy that modifying the surface of poly(amidoamine) (PAMAM) dendrimers with linear fluorocarbons has become a general strategy to construct fluorinated dendrimers.[10] However, these fluorinated PAMAM dendrimers are actually unfit for either ^{19}F MRI or

drug delivery because the linear perfluorocarbons on the PAMAM dendrimer surface result in poor aqueous solubility, signal splitting, low signal intensity, etc.[10, 11] Moreover, defected dendrimers, which inevitably formed during the modification of PAMAM dendrimers with perfluorocarbons, increases the uncertainty for their downstream applications.[10, 11] Therefore, it is of great importance to develop novel defect-free fluorinated dendrimers with high ^{19}F MRI sensitivity.

Herein, a novel dendrimer with 540 pseudo-symmetrical fluorines was designed as a potential drug carrier with high ^{19}F MRI sensitivity (Scheme 1, compound **1**). Instead of modifying commercially available dendrimers with perfluorocarbons, dendrimers **1** can be constructed by convergently assembling of fluorinated building blocks **2-3** and 4, 4', 4''-(ethane-1, 1, 1-triyl)triphenol **4**. Ether bonds were chosen for the building blocks conjugation because the acidic bis(trifluoromethyl)carbinols in **2-3** are good nucleophiles for Williamson ether synthesis under basic conditions. Since there are already 12 symmetrical fluorines in building blocks **2-3**, the construction of dendrimer **1** and the introduction of fluorines can be performed simultaneously. Through the assembling of building blocks **2-4**, 540 fluorines are symmetrically distributed on each spherical layer (from core to surface: 36 ^{19}F on 1st layer (red), 72 ^{19}F on 2nd layer (green), 144 ^{19}F on 3rd layer (blue) and 288 ^{19}F on 4th layer (purple)) and pseudo-symmetrically distributed between these layers. As a result, 540 pseudo-symmetrical fluorines are supposed to aggregately emit an apparently single ^{19}F peak with high signal intensity and therefore high ^{19}F MRI sensitivity.

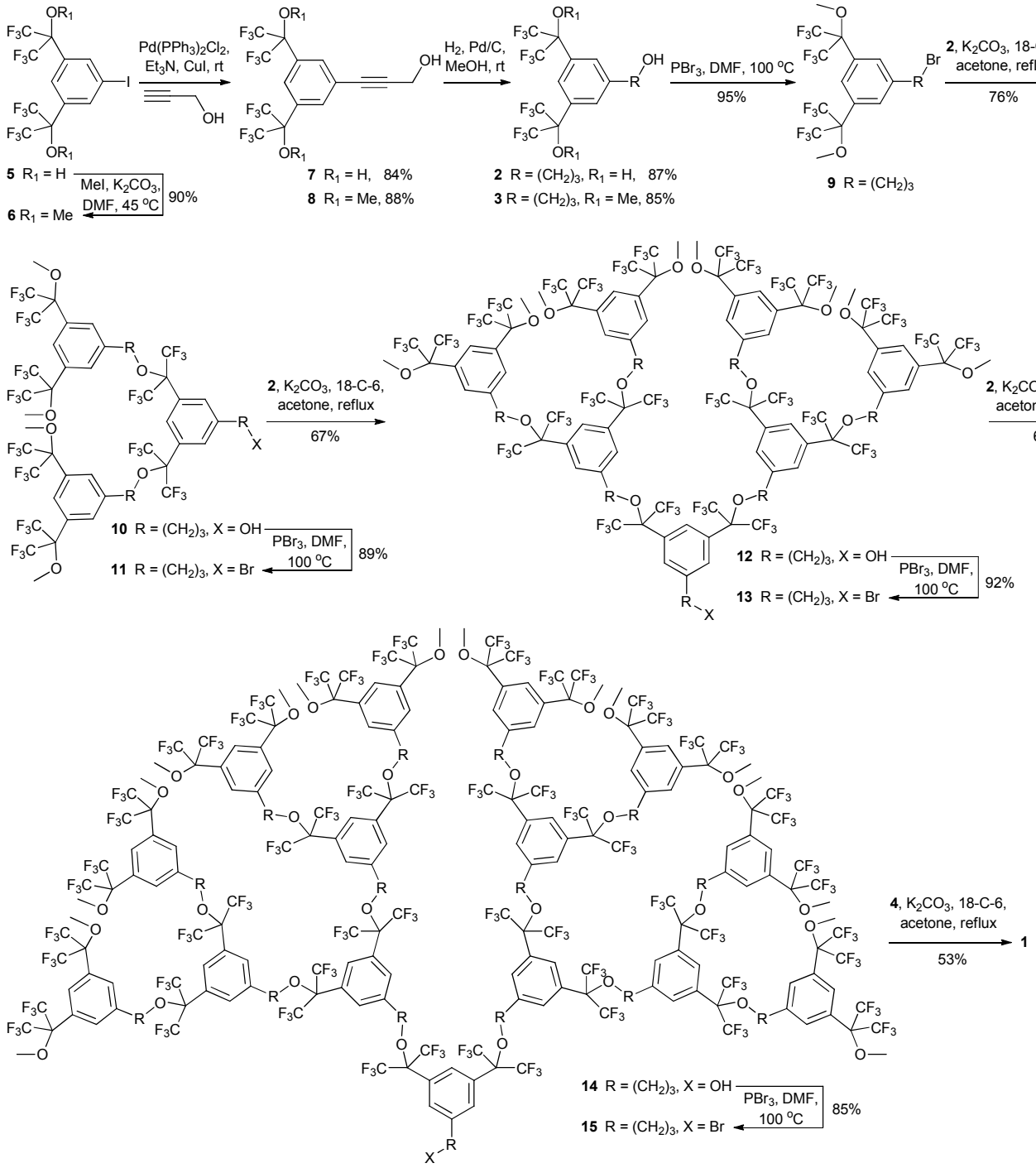


Scheme 1. Target fluorinated dendrimer **1** and its building blocks **2-4**.

RESULTS AND DISCUSSION

With these ideas in mind, a convergent synthesis of dendrimer **1** was then carried out (Scheme 2). The synthesis was started with the construction of building blocks **2-3** from iodobenzene **5** which was prepared through an established method.[12] After unsuccessful attempts on methylation of **5** with dimethyl sulfate, it was then methylated with iodomethane in a sealed vessel to give dimethyl ether **6** in an excellent yield. Iodobenzenes **5-6** were then undergone Sonogashira coupling reaction with propargyl alcohol to give alcohols **7-8** which were hydrogenated to give building blocks **2-3** with good yields in two steps, respectively. With **2-3** in hand, dendrimer **1** was then convergently assembled through ether bonds by taking the advantage of bis(trifluoromethyl)carbinol's good nucleophilicity.

After transforming the hydroxyl group of **3** into a bromine with PBr_3, bromide **9** was then reacted with building block **2** in the presence of K_2CO_3 and 18-crown-6 to form two ether bonds simultaneously without protecting its less acidic hydroxyl group and provided the 1st generation dendron **10** with a 72% yield over two steps. After three cycles of sequential bromination with PBr_3 and Williamson ether synthesis with building block **2**, the third generation dendron **14** was obtained with a high yield. Interestingly, stable phosphite intermediates derived from the alcohols **10** and **12** with PBr_3 were detected during the bromination with PBr_3. It was found that extended reaction time together with excess amount of PBr_3 was necessary to drive the reaction to a completion. It is probably because steric hindrance slowed down further transformation of the phosphite intermediates. Bromination of dendron **14** followed by Williamson ether synthesis with 4, 4', 4''-(ethane-1, 1, 1-triyl)triphenol **4** provided dendrimer **1** on a gram scale. It is noteworthy that high synthetic efficacy was achieved by omission of the protecting group manipulation. Alongside with dendrimer **1**, 4 generations of fluorinated dendrons **3**, **10**, **12**, and **14**, were also obtained during the synthesis.



Scheme 2. Synthesis of fluorinated dendrimer **1**.

The structures of these dendritic molecules were confirmed by ^{1}H, ^{13}C and ^{19}F NMR, MS and element analysis (see Supporting Information). However, for higher generation dendron **15**, no MS data was obtained in spite of repeated tries probably due to their high fluorine content (F% > 40%) and molecular weight.[10c] To illustrate the structure of dendrimer **1**, a newly developed NMR technique called stepwise

filtering of the internal layers of dendrimers was employed (Figure 1).[13] Although ^{19}F NMR has a chemical shift range of over 400 ppm, it can hardly resolute the ^{19}F signals emitted from different layers which is a good indication of the pseudo-symmetry for the 540 fluorines in dendrimer **1**. Interestingly, ^{1}H NMR, which has a much narrower chemical shift range than ^{19}F NMR, can partially resolute the aromatic protons **C-D** signals of different layers. It is probably because the benzene groups near the core and those on the surface have quite different aromatic interactions. As expected, the transverse relaxation time T_2 of protons **a** and **A-B** near the core are much shorter than protons **d** and **C-D** at periphery. During the T_2 filters, internal protons **a** and **A-B** were completely suppressed after a 90 ms and 180 ms filter, respectively. For protons **C-D** and **b-d**, a stepwise selective suppression from the core to the periphery was observed. The periphery methoxyl protons **e** and aromatic protons **C-D** can be observed even after 1,800 ms filter while all the internal protons **b-d** were suppressed. In this way, all the protons in dendrimer **1** were precisely assigned and, together with protons' integration, the structure of dendrimer **1** was clearly solved with NMR in a layer-by-layer fashion.

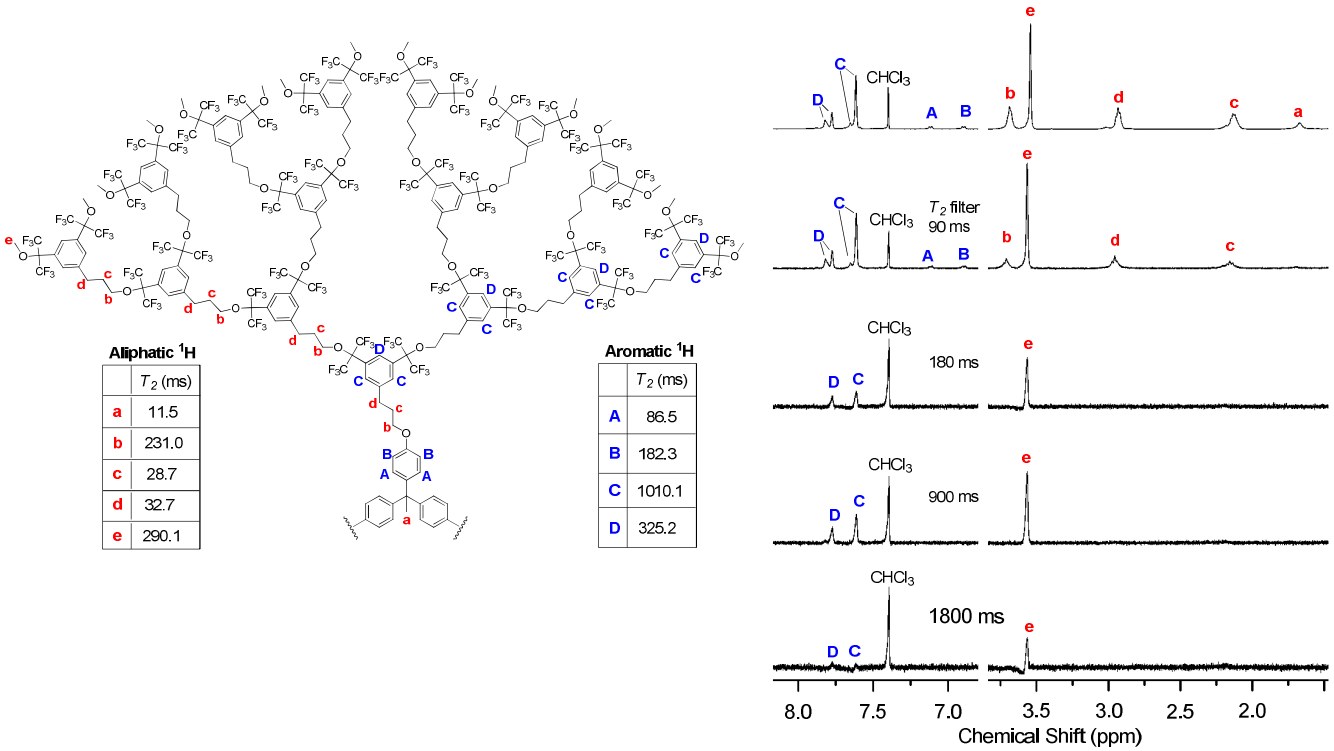


Figure 1. T_2-filtered ^{1}H NMR spectra of dendrimer **1** (^{1}H NMR: 500 MHz, 25 ^{o}C, $CDCl_3$ as

solvent).

Such novel dendritic scaffolds provided a convenient way to assemble a large number of pseudo-symmetrical fluorines for sensitively generating ^{19}F magnetic resonance image or spectroscopy by cumulatively emitting a strong ^{19}F NMR peak. Therefore, ^{19}F NMR spectra of **3**, **10**, **12**, **14**, and **1** were collected and compared side by side (see Supporting Information, Figure S1). As expected, all fluorines on each spherical layer cumulatively emit a ^{19}F signal at the same frequency. While, fluorines on different spherical layers emit ^{19}F signals at very close frequencies and the frequencies differences is less than 38 Hz. Integrations of the splitting-like peaks in **10**, **12** and **14** indicated that they are in proportional to the amount of flurorines on corresponding layers, respectively. Basically, only one apparent ^{19}F peak was detected from **10**, **12**, **14**, and **1**, respectively. It is noteworthy that all 540 fluorines in dendrimer **1** emit one apparent ^{19}F peak with a half peak width of only 26 Hz. Simple ^{19}F NMR peaks from all fluorines in these fluorinated dendrimers can efficiently avoid the imaging artifact and dramatically lower the detectable concentration of imaging agents during downstream ^{19}F MRI applications.

As relaxation times also play important roles in ^{19}F MRI sensitivity, the ^{19}F NMR relaxation behaviors of these dendritic molecules were then investigated (Figure 2). For fluorinated dendrimers, both the longitudinal relaxation time T_1 and the transverse relaxation time T_2 usually decrease dramatically with the increasing of molecular size or molecular weight.[11b] As expected, both T_1 and T_2 decreased dramatically from building block **3** to 1st generation dendron **10**. Although these dendritic molecules have a broad molecular weight range (**3**: 496 Da., **10**: 1,425 Da., **12**: 3,282 Da., **14**: 6,996 Da. and **1**: 21,240 Da.), only slight changes in both T_1 and T_2 among dendrons **10**, **12**, **14** and dendrimer **1** were observed. It is probably because that the highly crowded pseudo-symmetrical environment of fluorines considerablely affects the movement of fluorines in these dendritic molecules. The short T_1 of these dendrons and demdrimer indicated that the mobility of fluorines in dendrimer is very high. It is

noteworthy that these dendritic molecules have significantly shorter relaxation times than those of ^{19}F MRI agents reported so far.[5, 6, 8, 10, 11] As a control, trifluoroethanol (CF_3CH_2OH) under the same conditions gave a considerably longer T_1 of 2379 ms and T_2 of 267 ms. From the sensitivity point of view, short relaxation times dramatically enhance ^{19}F MRI signal by allowing the collection of more transients signals without prolonging data acquisition time.

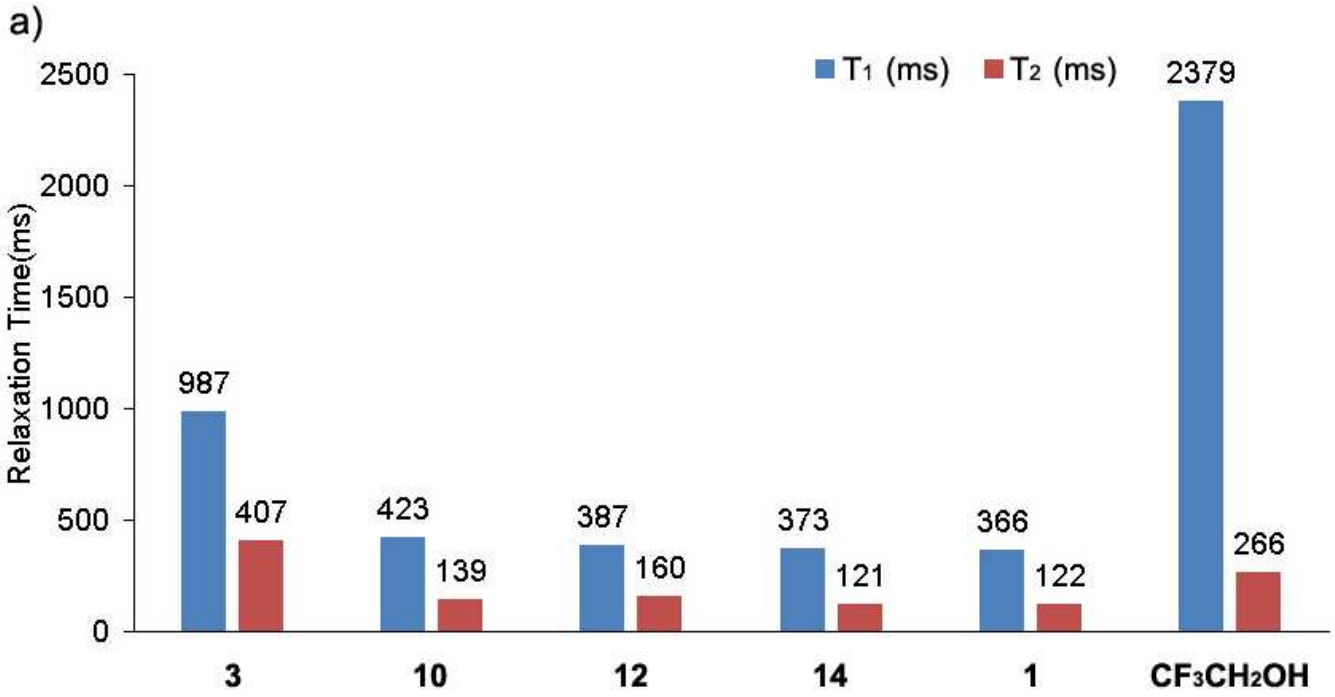


Figure 2. ^{19}F magnetic resonance T_1 and T_2 of dendrons **3**, **10**, **12**, **14**, and dendrimer **1** (^{19}F NMR: 376 MHz, 25 ^{o}C, 0.1 M of ^{19}F in $CDCl_3$).

Based on these observations, such dendritic molecules with a strong ^{19}F NMR peak from a large number of ^{19}F nuclei and short relaxation times are really fit for highly sensitive ^{19}F MRI. Then, ^{19}F MRI phantom experiments of dendrimer **1** with trifluoroethanol as a control was carried out on an array of their solutions in $CDCl_3$ (Figure 3). The ^{19}F MRI phantom images indicated that a solution of dendrimer **1** with a concentration as low as 18.5 μM (or 10 mM in ^{19}F concentration) could be clearly imaged by ^{19}F MRI with a scan time of only 150 seconds. In contrast, trifluoroethanol can be imaged only when the concentration is 16.7 mM and above (or 50 mM in ^{19}F concentration) under the same ^{19}F MRI conditions. In terms of ^{19}F MRI sensitivity, there is an over 900 folds difference between

dendrimer **1** and trifluoroethanol when they were compared in molecular concentration. To our best knowledge, this concentration is the lowest detectable concentration for ^{19}F MRI reported so far. Although a fluorinated polymer modified PAMAM dendrimer with comparable sensitivity was reported by Ito et al,[10c] the dendrimer is actually a complex mixture with a polydispersity index (PDI) of 1.7-1.9. In contrast, dendrimer **1** has a PDI of 1.02 (See Supporting Information). Here, dendrimer **1** has a uniform size which is crucial for quality control and accurate calibration of the imaging agent concentration with its ^{19}F signal intensity in downstream study. As expected, the plot in Figure 3 demonstrated that ^{19}F MRI signal intensity is directly proportional to the ^{19}F concentration. Hence, dendrimer **1** is a promising quantitative drug tracer with high ^{19}F MRI sensitivity because its local concentration may be conveniently calibrated with the ^{19}F signal intensity.

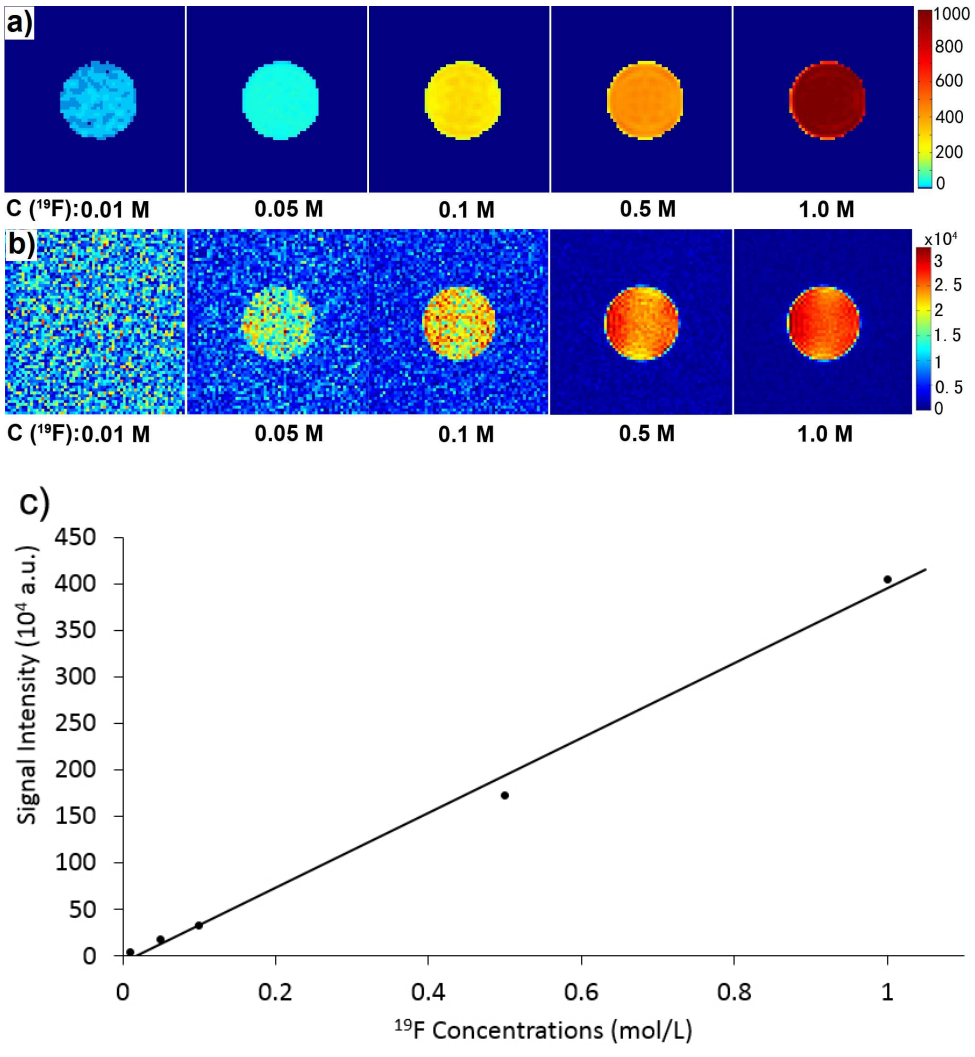


Figure 3. ^{19}F MRI phantom experiments of dendrimer **1** and trifluoroethanol. (Upper (a): Dendrimer **1** in $CDCl_3$. Middle (b): Trifluoroethanol in $CDCl_3$. Lower (c): Plot of ^{19}F signal intensity of dendrimer **1** versus its ^{19}F concentration.)

CONCLUSION AND OUTLOOK

In summary, several novel dendritic molecules with a large number of pseudo-symmetrical fluorines and excellent ^{19}F MRI properties were developed as highly sensitive ^{19}F MRI agents. The target dendrimer (21,240 Da.) was convergently prepared on a gram scale over 11 steps with an overall yield of 8% in the absence of protecting group. These novel dendritic structures exhibited extraordinary features for ^{19}F MRI, including high capability of accumulating pseudo-symmetric fluorines, uniformed ^{19}F NMR signals, short relaxation times, ^{19}F MRI quantifiable concentration, etc. With this fluorinated dendrimer, the detectable concentration of ^{19}F MRI was pushed down to unprecedented 18.5 μM which laid a solid foundation for highly sensitive *in vivo* drugs tracing.

It is noteworthy that the current fluorinated dendrimer, which successfully addressed the long-standing sensitivity problem in ^{19}F MRI, is a proof-of-concept study on developing novel dendritic drug carriers for ^{19}F MRI-guided drug therapy. This work has clearly demonstrated that pseudo-symmetrically assembling a number of fluorines on the internal layers of dendrimer is an efficient way to avoid ^{19}F signal splitting, optimize ^{19}F relaxation time, and therefore achieve high ^{19}F MRI sensitivity and reliable quantification. Modification of the dendrimer with poly(ethylene glycols) into an aqueous soluble unimolecular micelle and delivery of drugs through its hydrophobic cavities without compromising the therapeutic efficacy are currently in progress and will be published in due course.

EXPERIMENTAL SECTION

Dimethyl ether 6. To a stirring mixture of diol **5** (41.0 g, 76.5 mmol) and K_2CO_3 (26.4 g, 191.0 mmol)

in DMF (300 mL) at rt was added MeI (11.9 mL, 27.1 g, 190.8 mmol). The reaction vessel was sealed up and the resulting mixture was then stirred at 45 ^{o}C for 6 h. The reaction was then quenched with water (1500 mL) and extracted with Et_2O (200 mL, 3 times). The combined organic layer was dried over anhydrous $MgSO_4$, filtered, concentrated under vacuum, and purified by flash chromatography on silica gel (EtOAc/Hexanes = 1/20) to give **6** as clear oil (38.8 g, 90% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.51 (s, 6H), 7.82 (s, 1H), 8.05 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 54.6, 81.9-83.0 (m), 94.4, 101.5, 122.2 (q, J = 287.0 Hz), 127.8, 131.1, 139.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ -73.77; MS (EI) *m/z* 495 ($[M\text{-}CF_3]^+$, expected mass for $[C_{13}H_9F_9O_2+2Na]^{2+}$ 495), 564 (M^+, expected mass for $[C_{14}H_9O_2F_{12}I]^+$ 564); HRMS (EI) calcd for $C_{14}H_9O_2F_{12}I$ 563.9456, found 563.9458.

Triol 7. Under an argon atmosphere, to a mixture of diol **5** (30.1 g, 56.2 mmol), $PdCl_2(PPh_3)_2$ (392.8 mg, 0.6 mmol) and CuI (213.2 mg, 1.1 mmol) in Et_3N (200 mL) was added propargyl alcohol (4.7 g, 83.9 mmol) at rt and the resulting mixture was stirred at this temperature overnight. The reaction was quenched with water (800 mL) and the resulting mixture was extracted with EtOAc (200 mL, 3 times). The combined organic layer was dried over anhydrous $MgSO_4$, filtered, concentrated under vacuum and purified by flash chromatography on silica (EtOAc/Hexanes = 1/10) gel to give triol **7** as white powder (21.8 g, 84% yield). ^{1}H NMR (400 MHz, acetone-d_6) δ 4.46 (s, 2H), 7.95 (s, 2H), 8.23 (s, 1H); ^{13}C NMR (100 MHz, acetone-d_6) δ 50.9, 77.3-78.5 (m), 82.9, 92.2, 123.8 (q, J = 286.0 Hz), 125.3, 126.3, 132.3, 133.1; ^{19}F NMR (376 MHz, acetone-d_6) δ -75.85; MS (EI) *m/z* 297 ($[M\text{-}C(CF_3)_2OH]^+$, expected mass for $[C_{12}H_7F_6O_2]^+$ 297), 464 (M^+, expected mass for $[C_{15}H_8O_3F_{12}]^+$ 464); HRMS (EI) calcd for $C_{15}H_8O_3F_{12}$ 464.0282, found 464.0286.

Alcohol 8. Alcohol **8** was prepared by following the same procedure for Sonogashira coupling reaction of diol **5** with propargyl alcohol from iodide **6** as dark oil (26.0 g, 88% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.50 (s, 6H), 4.56 (s, 2H), 7.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 51.5 54.5, 82.4-83.0

(m), 83.8, 89.8, 122.2 (q, J = 288.5 Hz), 124.7, 128.1, 129.6, 133.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ -73.88; MS (ESI) *m/z* 475.1 ($[M\text{-}OH]^+$, expected mass for $[C_{17}H_{11}F_{12}O_2]^+$ 475.1); HRMS (ESI) calcd for $C_{17}H_{13}F_{12}O_3$ 493.0673, found 493.0671.

Building block 2. To a solution of alcohol **7** (16.5 g, 35.6 mmol, in 150 mL methanol) in an autoclave reactor was added palladium on carbon (5.1 g, 10% wt). The reaction mixture was stirred overnight at rt under an atmosphere of 4.0 MPa hydrogen. The catalyst was filtered off and the resulting solution was directly evaporated under vacuum to dryness. The residue was purified by flash chromatography on silica gel (EtOAc/Hexanes = 1/1) to give **2** as clear oil (14.5 g, 87% yield). ^{1}H NMR (400 MHz, Acetone-d_6) δ 1.83-1.90 (m, 2H), 2.88 (t, J = 8.0 Hz, 2H), 3.61 (t, J = 6.0 Hz, 2H), 7.82 (s, 2H), 8.08 (s, 1H); ^{13}C NMR (100 MHz, Acetone-d_6) δ 32.9, 35.4, 61.4, 77.5-78.7 (m), 124.0 (q, J = 284.5 Hz), 124.0, 129.7, 132.3, 144.7; ^{19}F NMR (376 MHz, Acetone-d_6) δ -75.80; MS (ESI) *m/z* 451.1 ($[M\text{-}OH]^+$, expected mass for $C_{15}H_{11}F_{12}O_2$ 451.1), 486.1 ($[M+NH_4]^+$, expected mass for $C_{15}H_{16}F_{12}NO_3$ 486.1), 937.1 ($[2M+H]^+$, expected mass for $C_{30}H_{25}F_{24}O_3$ 937.1), 975.1 ($[2M+K]^+$, expected mass for $C_{30}H_{24}F_{24}O_6K$ 975.1); HRMS (ESI) calcd for $C_{15}H_{13}F_{12}O_3$ 469.0673, found 469.0673.

Building block 3. Building block **3** was prepared by following the same procedure for hydrogenation of triol **2** from alcohol **7** as clear oil (28.5 g, 85% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (s, 1H), 1.88-1.95 (m, 2H), 2.85 (t, J = 8.0 Hz, 2H), 3.49 (s, 6H), 3.72 (t, J = 6.0 Hz, 2H), 7.53 (s, 2H), 7.65 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.3, 34.2, 54.4, 61.8, 82.4-83.6 (m), 122.4 (q, J = 287.0 Hz), 126.0, 129.0, 130.3, 143.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ -74.08; MS (ESI) *m/z* 514.0 ($[M+NH_4]^+$, expected mass for $C_{17}H_{16}F_{12}NO_3$ 514.1), 519.0 ($[M+Na]^+$, expected mass for $C_{17}H_{16}F_{12}O_3Na$ 519.1); HRMS (ESI) calcd for $C_{17}H_{16}F_{12}O_3Na$ 519.0800, found 519.0785.

Bromide 9. General procedure for transforming alcohol into bromides (Using the synthesis of

bromide 9 as an example). To a stirring solution building block **3** (24.4 g, 49.0 mmol) in anhydrous DMF (250 mL) was slowly added PBr_3 (39.3 g, 145.1 mmol) at 0 ^oC and the resulting mixture was stirred at 100 ^oC overnight. The reaction mixture was allowed to cool to rt, quenched with water (1000 mL), extracted with Et_2O (150 mL, 3 times). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and evaporated under vacuum to dryness. The residue was purified by flash chromatography on silica gel (EtOAc/Hexanes = 1/20) to give bromide **9** as clear oil (25.9 g, 95% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 2.15-2.25 (m, 2H), 2.93 (t, J = 8.0 Hz, 2H), 3.41 (t, J = 6.0 Hz, 2H), 3.49 (s, 6H), 7.54 (s, 2H), 7.67 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.3, 33.9, 34.2, 54.4, 82.4-83.6 (m), 122.4 (q, J = 289.0 Hz), 126.4, 129.3, 130.4, 142.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ -74.03; MS (MALDI) *m/z* 558.0 (M^+, expected mass for $C_{17}H_{15}BrF_{12}O_2$ 558.0), 560.0 (M^+, Br isotope peak); HRMS (MALDI) calcd for $C_{17}H_{15}BrF_{12}O_2$ 558.0058, found 558.0060.

First generation dendron (G_1-OH) 10. General procedure for the ether synthesis (Using the synthesis of dendron 10 as an example). Under an argon atmosphere, a mixture of bromide **9** (21.4 g, 38.3 mmol), alcohol **2** (8.2 g, 17.4 mmol), anhydrous K_2CO_3 (6.1 g, 43.6 mmol) and 18-crown-6 (921.3 mg, 3.5 mmol) in dry acetone (200 mL) was refluxed for 48 h. Then, the mixture was allowed to cool to rt. The reaction was quenched with water (400 mL) and the resulting mixture was extracted with EtOAc (150 mL, 3 times). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (EtOAc/Hexanes = 1/10) to give **10** as clear oil (18.9 g, 76% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 1.75 (s, 1H), 1.91-2.05 (m, 2H), 2.07-2.12 (m, 4H), 2.85-2.9 (m, 6H), 3.48 (s, 12H), 3.63-3.73 (m, 6H), 7.53-7.56 (m, 6H), 7.67-7.73 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.4, 31.1, 32.4, 34.2, 54.3, 61.7, 65.7, 82.8-83.3 (m), 122.5 (q, J = 287.5 Hz), 125.6, 126.4, 129.3, 129.5, 130.0, 130.3, 143.0, 144.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ -73.80, -73.78; MS (MALDI) m/z 1447.8 ($[M+Na]^+$, expected mass for $C_{49}H_{40}F_{36}O_7Na$ 1447.8); Anal. Calcd for $C_{49}H_{40}F_{36}O_7$: C, 41.31; H, 2.83; F, 48.00. Found: C, 41.45; H,

2.88; F, 48.89; HRMS (ESI) calcd for $C_{49}H_{41}F_{36}O_7$ 1425.2277, found 1425.2270.

First generation dendron (G_1-Br) 11. Dendron **11** was prepared from alcohol **10** by following the general procedure for transforming alcohol into bromide with extended reaction time (24 h) and excess amount of PBr_3 (5 equivalent) as white powder with an 89% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.95-2.00 (m, 4H), 2.08-2.11 (m, 2H), 2.74-2.86 (m, 6H), 3.29 (t, J = 6.0 Hz, 2H), 3.38 (s, 12H), 3.54 (t, J = 6.0 Hz, 4H), 7.40-7.48 (m, 6H), 7.55-7.65(m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.4, 32.0, 32.2, 33.9, 34.0, 54.4, 65.8, 82.5-83.6 (m), 122.4 (q, J = 287.0 Hz), 126.0, 126.4, 129.3, 29.7, 130.2, 130.3, 142.6, 142.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ -73.89, -73.85; MS (ESI) *m/z* 726.3 ($[M-Br+2Na]^{2+}$, expected mass for $C_{49}H_{39}F_{36}O_6Na_2$ 726.5), 742.2 ($[M-Br+2K]^{2+}$, expected mass for $C_{49}H_{39}F_{36}O_6K_2$ 742.6).

Second generation dendron (G_2-OH) 12. Dendron **12** was prepared from bromide **11** by following the general procedure for the ether synthesis as white powder with a 67% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.88-2.07 (m, 14H), 2.84-2.87 (m, 14H), 3.46-3.48 (m, 24H), 3.61-3.71 (m, 14H), 7.61-7.63 (m, 14H), 7.67-7.71 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31..3, 32.0, 32.3, 34.1, 54.3, 60.2, 61.7, 65.5, 65.7, 82.7-83.3 (m), 122.4 (q, J = 288.0 Hz), 125.9, 126.4, 129.3, 129.4, 129.6, 130.2, 142.9, 143.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ -74.08, -74.05, -73.98; MS (MALDI) m/z 3303.7 ($[M+Na]^+$, expected mass for $C_{113}H_{88}F_{84}NaO_{15}$ 3303.5); Anal. Calcd for $C_{113}H_{88}F_{84}O_{15}$: C, 41.36; H, 2.70; F, 48.63. Found: C, 41.74; H, 2.88; F, 47.21.

Second generation dendron (G_2-Br) 13. Dendron **13** was prepared from alcohol **12** by following the general procedure for transforming alcohol into bromide with extended reaction time (24 h) and excess amount of PBr_3 (5 equivalent) as white powder with a 92% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.90-2.11 (m, 14H), 2.75-2.85 (m, 14H), 3.27-3.30 (m, 2H), 3.37-3.40 (m, 24H), 3.50-3.53 (m, 12H), 7.42-

7.44 (m, 14H), 7.58-7.62 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.4, 32.0, 32.2, 33.9, 34.0, 54.3, 65.7, 82.6-83.3(m), 122.5 (q, *J* = 288.0 Hz), 125.9, 126.4, 129.3, 129.7, 130.3, 142.6, 142.9, 143.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ -74.21, -74.16, -74.09; MS (CI) *m/z* 3360.8 ($[M+NH_4]^+$, expected mass for $C_{113}H_{91}BrF_{84}NO_{14}$ 3360.4), 3363.0 ($[M+NH_4]^+$, Br isotope peak $C_{113}H_{91}BrF_{84}NO_{14}$ 3362.4).

Third generation dendron (G_3-OH) 14. Dendron **14** was prepared from bromide **13** by following the general procedure for the ether synthesis as a white powder with a 66% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.89-2.23 (m, 30H), 2.80-2.94 (m, 30H), 3.46 (s, 48H), 3.58-3.72 (m, 30H), 7.48-7.62 (m, 30H), 7.65-7.76 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.3, 32.0, 34.1, 54.3, 61.7, 65.6, 65.7, 82.6-83.7 (m), 122.5 (q, *J* = 288.0 Hz), 125.9 126.5 129.3 129.7 130.3 143.0,143.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ -73.99, -73.95, -73.91; MS (MALDI) *m/z* 7015.2 ($[M+H+NH_4]^+$, expected mass for $C_{241}H_{189}F_{180}NO_{31}$ 7014.8); Anal. Calcd for $C_{241}H_{184}F_{180}O_{31}$: C, 41.38; H, 2.65; F, 48.88. Found: C, 41.72; H, 2.73 F, 48.56.

Third generation dendron (G_3-Br) 15. Dendron **15** was prepared from alcohol **14** by following the general procedure for transforming alcohol into bromide with extended reaction time (24 h) and excess amount of PBr_3 (5 equivalent) as a white powder with an 85% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.95-2.21 (m, 30H), 2.74-3.0 (m, 30H), 3.38 (t, *J* = 6 Hz, 2H), 3.46 (s, 48H), 3.63 (m, 28H), 7.47-7.61 (m, 30H), 7.65-7.76 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.3, 32.0, 32.1, 33.8, 54.3, 65.6, 65.7, 82.5-83.3 (m), 122.4 (q, *J* = 287.0 Hz), 125.9, 126.4, 129.3, 129.7, 130.2, 142.9, 143.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ -73.92, -73.89.

Dendrimer 1. A mixture of bromide **15** (4.9 g, 0.7 mmol), 1.l.l-tris(4'-hydroxyphenyl)ethane **4** (63.8 mg, 0.2 mmol), anhydrous K_2CO_3 (115.1 mg, 0.8 mmol) and 18-crown-6 (16.5 mg, 0.06 mmol) in dry acetone (100 mL) was refluxed under an atmosphere of argon for 48 h. After the mixture was cooled to

rt, the reaction was quenched with water (300 mL) and extracted with ethyl extracted (100 mL, 3 times). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and evaporated to dryness. The crude product was purified by flash chromatography on silica gel (EtOAc/Hexanes = 1/10) to give **1** as white powder (2.3 g, 54% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.58 (s, 3H), 2.03-2.05 (m, 90H), 2.82-2.93 (m, 90H), 3.44 (s, 144H), 3.59-3.67 (m, 84H), 3.95-4.05 (m, 6H), 6.77-6.79 (m, 6H), 6.99-7.02 (m, 6H), 7.45-7.60 (m, 90H), 7.64-7.77 (m, 45H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.5, 31.4, 32.0, 54.3, 65.8, 82.8-83.4 (m), 113.8, 122.5 (q, J = 288.5 Hz), 124.0, 126.5, 129.4, 129.8, 130.3, 131.3, 143.0, 143.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ -73.94, -73.90; MS (MALDI) *m/z* 21240.4 ($[M+H]^+$, expected mass for $C_{743}H_{565}F_{540}O_{93}$, 21240.5); Anal. Calcd for $C_{743}H_{564}F_{540}O_{93}$: C, 42.02; H, 2.68. Found: C, 42.25; H, 2.76.

ASSOCIATED CONTENT

Supporting Information Available. ^{19}F NMR of dendritic molecules, copies of ^{1}H/^{19}F/^{13}C NMR, MS/HRMS spectra and element analysis of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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