JOC The Journal of Organic Chemistry

Article

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

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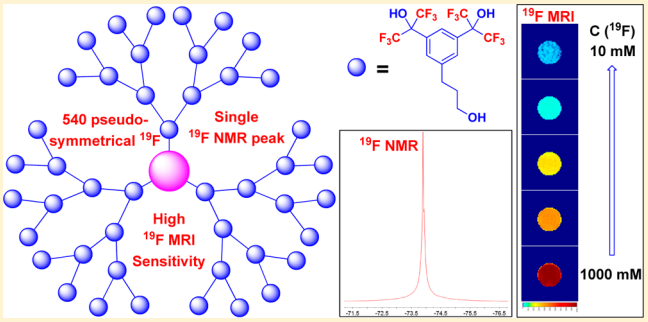
Supporting Information

ABSTRACT: To achieve high sensitivity for ^{19}F MRI, a class of novel dendritic molecules with multiple pseudosymmetrical fluorines was designed and efficiently synthesized. Through iterative bromination and Williamson ether synthesis under mild conditions, a fluorinated dendrimer with 540 pseudosymmetrical 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

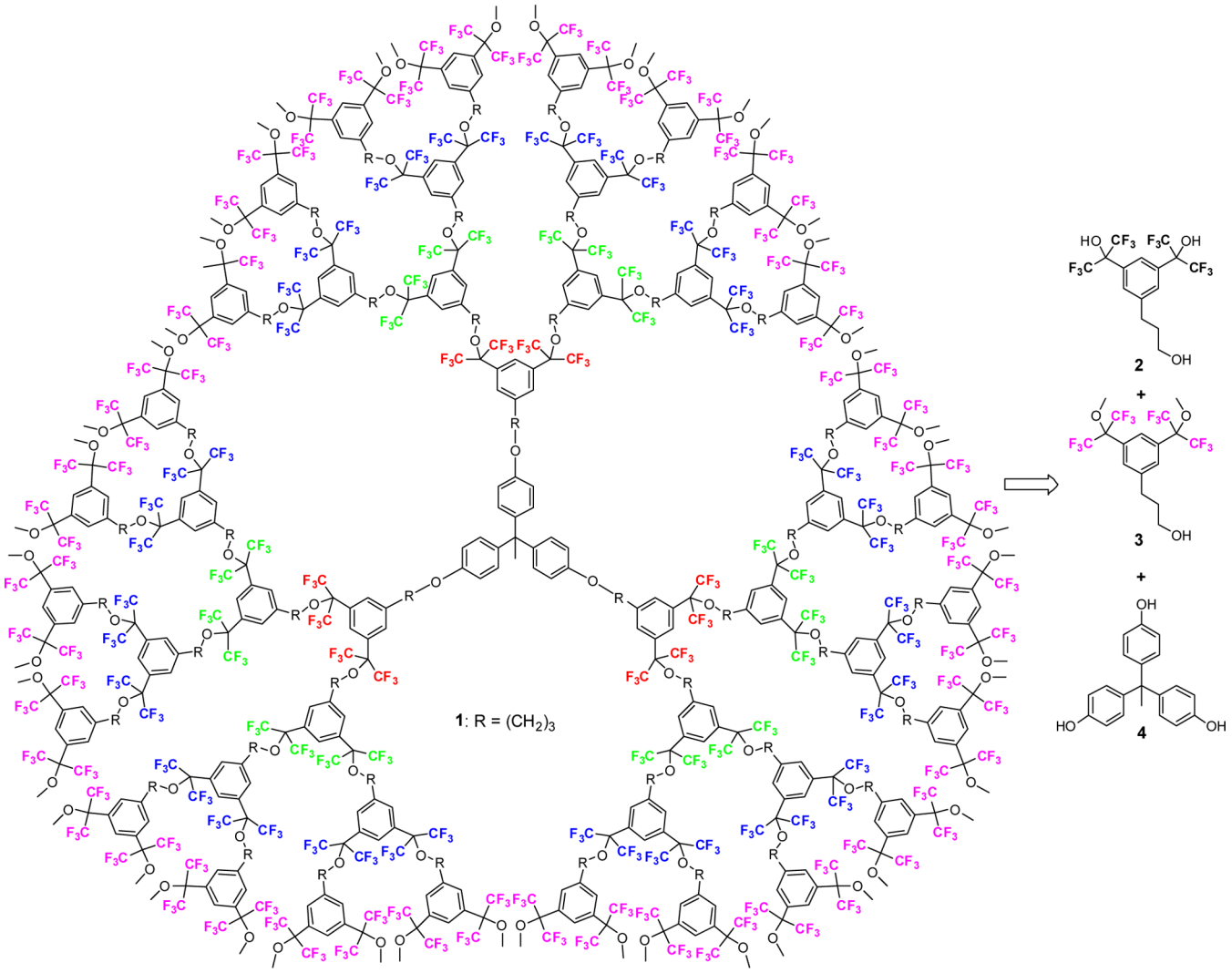
Proton-based magnetic resonance imaging (^{1}H MRI), which provides high-quality three-dimensional images without ionizing radiation, has become an important technique in modern diagnostic medicine. Unfortunately, the intense background signals in ^{1}H MRI causes insufficient discrimination of pathological 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 diagnosing disease,[2] evaluating therapy,[3] tracking targets of interest,[4] monitoring biological reactions,[5] probing local pH or pO_2,[6] and other applications. Our interest lies in ^{19}F MRI-guided drug therapy[7] because of its advantages, including the absence of endogenous signal, the 100% natural abundance of ^{19}F, a chemical shift range of over 400 ppm, and others.[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, for example, using a typical concentration of 89 mM,[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 commonly 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, a single ^{19}F NMR peak, and short relaxation times is a strategy of choice to address the sensitivity issues of ^{19}F MRI-guided drug therapy.

Dendrimers have been extensively used in both imaging and drug delivery owing to their attractive properties, such as multivalence, 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, and so forth.[10,11] Moreover, defect-containing dendrimers, which inevitably form during the modification of PAMAM

Received: February 8, 2015
Published: April 7, 2015

DOI: 10.1021/acs.joc.5b00294
J. Org. Chem. 2015, 80, 4443−4449

Scheme 1. Target Fluorinated Dendrimer 1 and Its Building Blocks, 2−4



dendrimers with perfluorocarbons, increase 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.

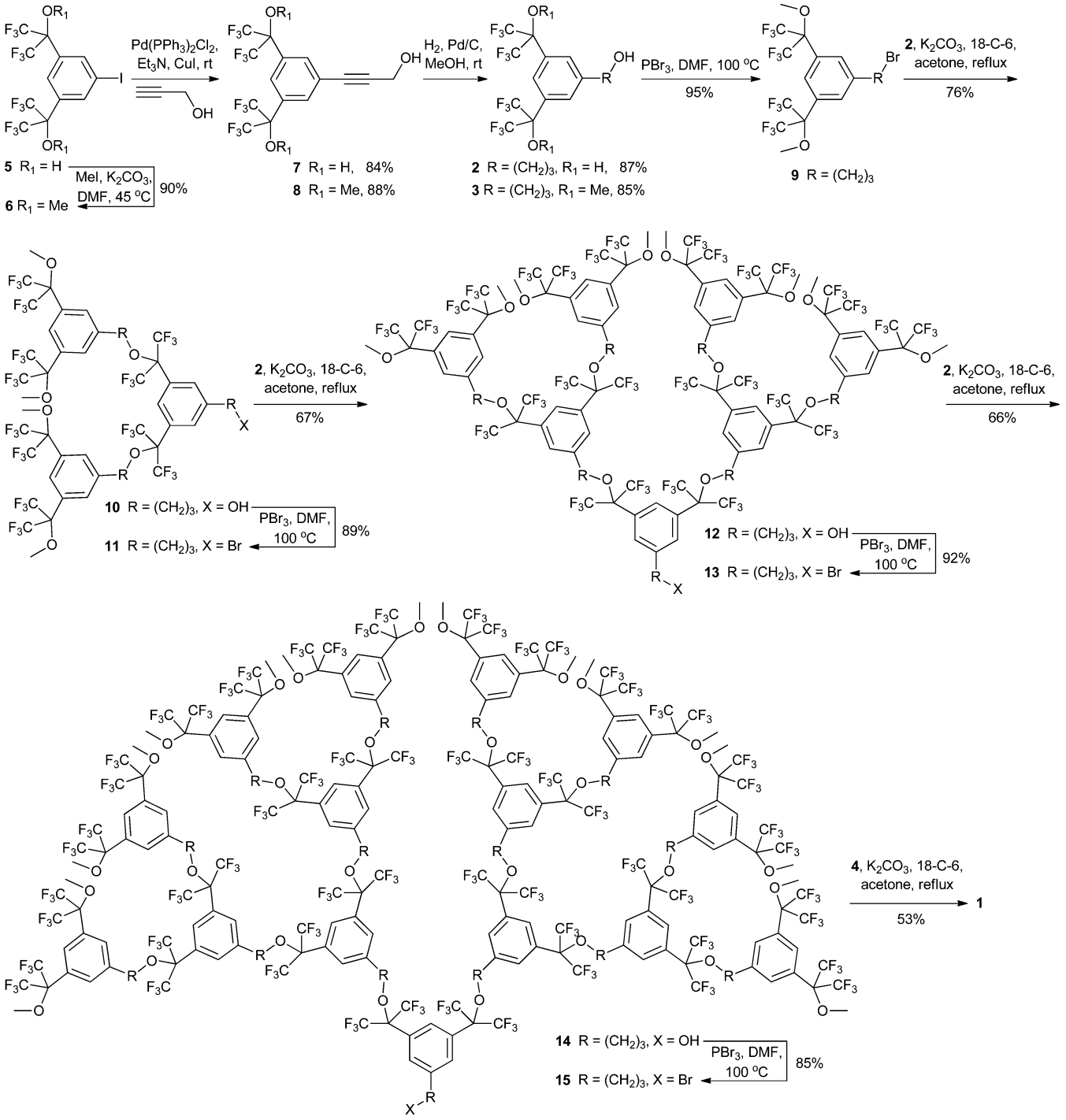
Herein, a novel dendrimer with 540 pseudosymmetrical fluorines was designed as a potential drug carrier with high ^{19}F MRI sensitivity (Scheme 1, compound **1**). Instead of modifying commercially available dendrimers with perfluorocarbons, dendrimers **1** can be constructed by convergently assembling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

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** and **3** from iodobenzene **5**, which was prepared through an established method.[12] After unsuccessful attempts to methylate **5** with dimethyl sulfate, it was then methylated with iodomethane in a sealed vessel to give dimethyl ether **6** in excellent yield. Iodobenzenes **5** and **6** then underwent Sonogashira coupling with propargyl alcohol to give alcohols **7** and **8**, which were hydrogenated to give building blocks **2** and **3** with good yields in two steps, respectively. With **2** and **3** in hand, dendrimer **1** was then convergently assembled through ether bonds by taking 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, providing first-generation dendron **10** in a 72% yield over two steps. After three cycles of sequential bromination with PBr_3 and Williamson ether synthesis with

DOI: 10.1021/acs.joc.5b00294
J. Org. Chem. 2015, 80, 4443−4449

Scheme 2. Synthesis of Fluorinated Dendrimer 1



building block **2**, third-generation dendron **14** was obtained in high yield. Interestingly, stable phosphite intermediates derived from alcohols **10** and **12** with PBr_3 were detected during the bromination with PBr_3. It was found that an extended reaction time together with an excess of PBr_3 was necessary to drive the reaction to completion. This is probably because steric hindrance slowed 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 omitting manipulation of the protecting group. Along with dendrimer **1**, four generations of fluorinated dendrons, **3**, **10**, **12**, and **14**, were also obtained during the synthesis.

The structures of these dendritic molecules were confirmed by ^{1}H, ^{13}C, and ^{19}F NMR, MS, and elemental analysis (see Supporting Information). However, for higher-generation dendron **15**, no MS data was obtained in spite of repeated attempts, probably due to the 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 resolve the ^{19}F signals

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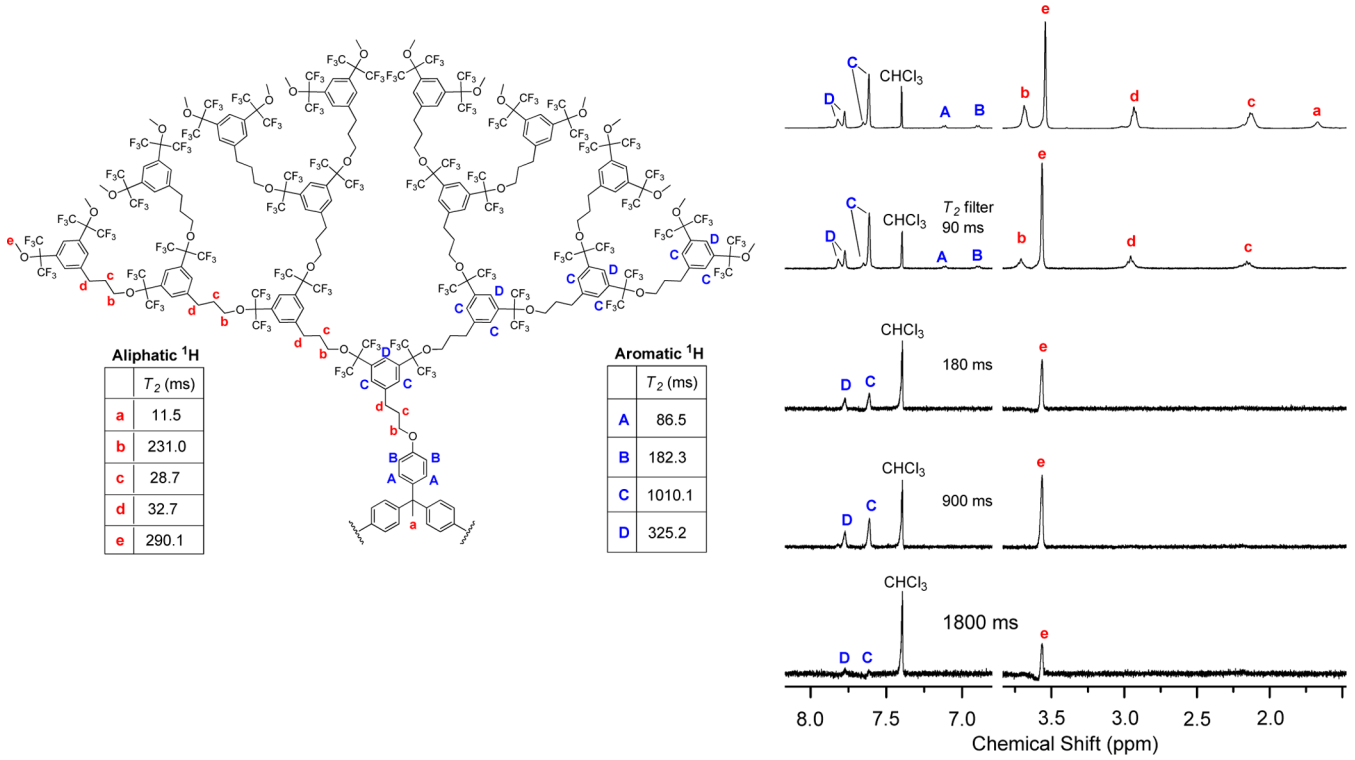

Figure 1. T_2-filtered ^{1}H NMR spectra of dendrimer **1** (^{1}H NMR: 500 MHz, 25 °C, $CDCl_3$ as solvent).

emitted from the different layers, which is a good indication of the pseudosymmetry of the 540 fluorines in dendrimer **1**. Interestingly, ^{1}H NMR, which has a much narrower chemical shift range than that of ^{19}F NMR, can partially resolve the signals of aromatic protons **C** and **D** in the different layers. This 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**, **A**, and **B** near the core are much shorter than that of protons **d**, **C**, and **D** at the periphery. During T_2 filtering, internal protons **a** and **A** and **B** were completely suppressed after applying a 90 or 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** and **D** can be observed even after a 1800 ms filter, whereas all internal protons **b**−**d** were suppressed. In this way, all of 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.

Such novel dendritic scaffolds provide a convenient way to assemble a large number of pseudosymmetrical fluorines for sensitively generating a ^{19}F magnetic resonance image or spectrum 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, whereas 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 proportional to the amount of fluororines in the corresponding layers. Only one apparent ^{19}F peak was detected from **10**, **12**, **14**, and **1**. 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. The simple ^{19}F NMR peaks from all fluorines in these fluorinated dendrimers allow them to efficiently avoid imaging artifacts and dramatically lower the detectable concentration of imaging agents required 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

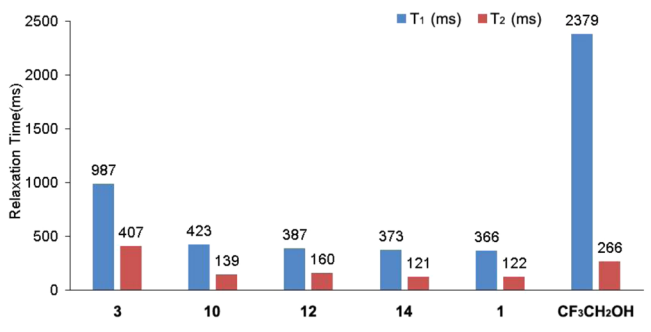

Figure 2. ^{19}F magnetic resonance T_1 and T_2 of dendrons **3**, **10**, **12**, and **14** and dendrimer **1** (^{19}F NMR: 376 MHz, 25 °C, 0.1 M of ^{19}F in $CDCl_3$).

dendrimers, both the longitudinal relaxation time T_1 and the transverse relaxation time T_2 usually decrease dramatically with increasing molecular size or molecular weight.[11b] As expected, both T_1 and T_2 decreased dramatically from building block **3** to first-generation dendron **10**. Although these dendritic molecules have a broad molecular weight range (**3**, 496 Da; **10**, 1425 Da; **12**, 3282 Da; **14**, 6996 Da; and **1**, 21 240 Da), only slight changes in both T_1 and T_2 among dendrons **10**, **12**, and **14** and dendrimer **1** were observed. This is probably because the highly crowded pseudosymmetrical environment of the fluorines

DOI: 10.1021/acs.joc.5b00294
J. Org. Chem. 2015, 80, 4443−4449

considerablely affects their movement in these dendritic molecules. The short T_1 of these dendrons and the dendrimer indicated that the mobility of fluorines in the 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 a sensitivity point of view, shorter relaxation times dramatically enhance the ^{19}F MRI signal by allowing the collection of more transient signals without prolonging the data acquisition time.

On the basis of 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 ideally suited for highly sensitive ^{19}F MRI. Next, ^{19}F MRI phantom experiments of dendrimer **1** with trifluoroethanol as a control were carried out on an array of their solutions in $CDCl_3$ (Figure 3). The ^{19}F MRI phantom

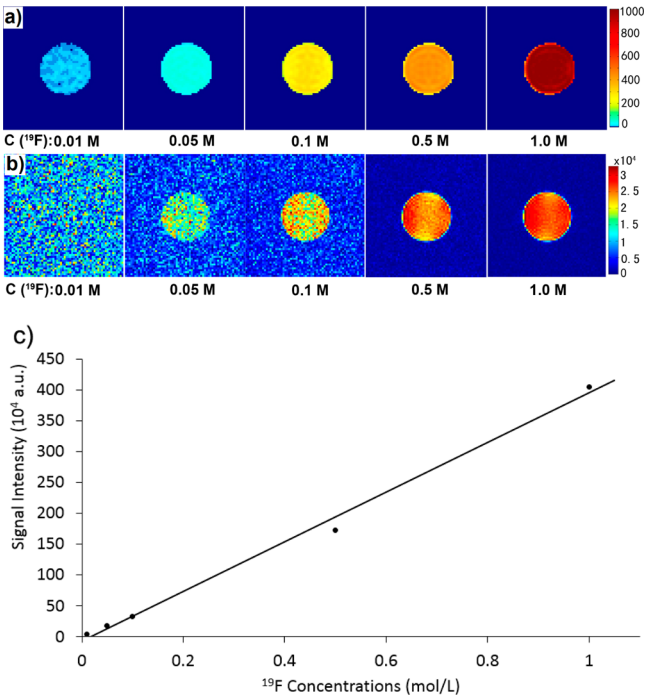

Figure 3. ^{19}F MRI phantom experiments of dendrimer **1** and trifluoroethanol: (a) dendrimer **1** in $CDCl_3$, (b) trifluoroethanol in $CDCl_3$, and (c) plot of ^{19}F signal intensity of dendrimer **1** versus its ^{19}F concentration.

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 s. 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-fold difference between dendrimer **1** and trifluoroethanol when they are compared with regard to molecular concentration. To the best of our 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 for the accurate calibration of the imaging agent's concentration with its ^{19}F signal intensity in downstream studies. As expected, the plot in Figure 3 demonstrated that the ^{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.

CONCLUSIONS AND OUTLOOK

In summary, several novel dendritic molecules with a large number of pseudosymmetrical 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 a high capability to accumulate pseudosymmetric fluorines, uniform ^{19}F NMR signals, short relaxation times, ^{19}F MRI quantifiable concentration, and others. With this fluorinated dendrimer, the detectable concentration for use in ^{19}F MRI was decreased to an unprecedented 18.5 μM, which lays a solid foundation for highly sensitive *in vivo* drug 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 pseudosymmetrically assembling a number of fluorines on the internal layers of a 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 glycol)s into an aqueous soluble unimolecular micelle and delivery of drugs through its hydrophobic cavities without compromising 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, and the resulting mixture was then stirred at 45 °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 layers were 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 a 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 ($[M - CF_3]^+$, 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 layers were 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 a 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,

DOI: 10.1021/acs.joc.5b00294
J. Org. Chem. 2015, 80, 4443−4449

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 − C(CF$_3$)$_2$OH]$^+$, expected mass for [C$_{12}$H$_7$F$_6$O$_2$]$^+$, 297), 464 (M$^+$, expected mass for [C$_{15}$H$_8$O$_3$F$_{12}$]$^+$, 464); HRMS (EI) calcd for C$_{15}$H$_8$O$_3$F$_{12}$, 464.0282; found, 464.0286.

Alcohol 8. Alcohol **8** was prepared by following the same procedure for the Sonogashira coupling of diol **5** with propargyl alcohol from iodide **6**, giving **8** as a 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 − 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 of 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 a 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 − 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$_6$K, 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**, giving **3** as a 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$_3$Na, 519.1); HRMS (ESI) calcd for C$_{17}$H$_{16}$F$_{12}$O$_3$Na, 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 °C, and the resulting mixture was stirred at 100 °C overnight. The reaction mixture was allowed to cool to rt, quenched with water (1000 mL), and extracted with Et$_2$O (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 a clear oil (25.9 g, 95% yield). ^{1}H 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$_2$CO$_3$ (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 a clear oil (18.9 g, 76% yield). ^{1}H 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$_7$Na, 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 an alcohol into a bromide with an extended reaction time (24 h) and an excess of PBr$_3$ (5 equiv), giving a 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$_6$Na$_2$, 726.5), 742.2 ([M − Br + 2K]$^{2+}$, expected mass for C$_{49}$H$_{39}$F$_{36}$O$_6$K$_2$, 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, giving a 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 an alcohol into a bromide with an extended reaction time (24 h) and an excess of PBr$_3$ (5 equiv), giving a 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 ether synthesis, giving 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 an alcohol into a bromide with an extended reaction time (24 h) and an excess of PBr$_3$ (5 equiv), giving 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

DOI: 10.1021/acs.joc.5b00294
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(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), 1,1,1-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 a 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

^{19}F NMR of dendritic molecules, copies of ^{1}H/^{19}F/^{13}C NMR, MS/HRMS spectra, and elemental 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.

■ ACKNOWLEDGMENTS

The authors thank Prof. Yihua Bruce Yu for his help with the preparation of the manuscript. This work was financially supported by the National Natural Science Foundation of China (21372181, 81227902, and 21305156).

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