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Avoiding Steric Congestion in Dendrimer Growth through Proportionate Branching: A Twist on da Vinci's Rule of Tree Branching

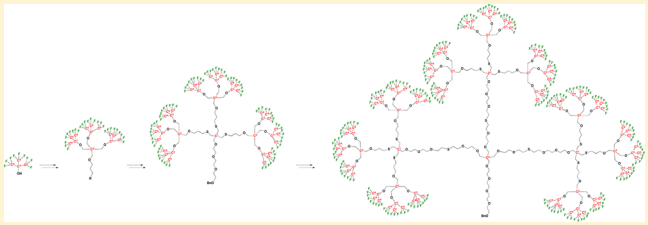
Xuyi Yue,[†] Marc B. Taraban,[‡] Laura L. Hyland,[‡] and Yihua Bruce Yu*[,†,‡]

[†]Department of Pharmaceutical Sciences, University of Maryland, 20 North Pine Street, Baltimore, Maryland 21201, United States

[‡]Fischell Department of Bioengineering, University of Maryland, 2330 Jeong H. Kim Engineering Building #225, College Park, Maryland 20742, United States

Supporting Information

ABSTRACT: Making defect-free macromolecules is a challenging issue in chemical synthesis. This challenge is especially pronounced in dendrimer synthesis where exponential growth quickly leads to steric congestion. To overcome this difficulty, proportionate branching in dendrimer growth is proposed. In proportionate branching, both the number and the length of branches increase exponentially but in opposite directions to mimic tree growth. The effectiveness of this strategy is demonstrated through the synthesis of a fluorocarbon dendron containing 243 chemically identical fluorine atoms with a MW of 9082 Da. Monodispersity is confirmed by nuclear magnetic resonance spectroscopy, mass spectrometry, and small-angle X-ray scattering. Growing different parts proportionately, as nature does, could be a general strategy to achieve defect-free synthesis of macromolecules.



INTRODUCTION

Defect-free synthesis of macromolecules remains a challenge in chemistry, especially for dendrimers, which are finding increased applications in chemistry, materials science, nanotechnology, as well as medicine and pharmacy.[1−7] Dendrimers are tree-like molecules composed of a core ("trunk"), several interior layers ("branches"), and a periphery ("leaves").[8,9] However, conventional dendrimer design grows dendrimers disproportionately: the number of branches grows exponentially, but the length of branches remains unchanged. The length of branches refers to the number of covalent bonds connecting adjacent branching nodes. Such a growth pattern eventually leads to steric congestion and defect dendrimers.[10−14] In this work, we show that steric congestion can be avoided using a bioinspired strategy called proportionate branching. It is based on the observation that, in trees, branches near the trunk are long but few, while branches near the leaves are many but short. Translating this observation into mathematical terms leads to proportionate growth of branch lengths, which parallels da Vinci's rule of proportionate growth of branch diameters.[15] Specifically, the number and the length of branches in a dendrimer both grow exponentially but in *opposite directions*—from the core to the periphery of a dendrimer and from the periphery to the core, respectively, to emulate tree growth.

We illustrate proportionate branching by making four generations of fluorocarbon dendrons. The motivation for making fluorocarbon dendrons is to use them as imaging agents for ^{19}F MRI. Fluorine atoms in a fluorinated dendrimer have identical chemical environments, and their ^{19}F signals coalesce into a single peak for magnetic resonance imaging. Defects in fluorinated dendrimers would lead to split ^{19}F signals, which can create chemical shift image artifacts. Hence, for ^{19}F MRI applications, defect-free synthesis of fluorinated dendrimers is essential.

We have previously made fluorinated asymmetric dendrimers containing 27 fluorine atoms and conducted *in vivo* imaging studies.[16] Each fluorinated asymmetric dendrimer comprises a fluorocarbon dendron where the branching nodes are carbons with 1→3 connectivity and a hydrophilic dendron where the branching nodes are nitrogens with 1→2 connectivity.[17] Using conventional dendrimer design, we were able to grow the hydrophilic dendron for 4 generations without running into steric congestion.[18] However, when we tried to grow the fluorocarbon dendron, we encountered steric congestion and incomplete growth. The fluorocarbon dendron is more prone to steric congestion than the hydrophilic dendron for two reasons: higher branch multiplicity (3 vs 2) and bulkier peripheral group ($-CF_3$ vs $-OH$).[19] This difficulty with growing fluorocarbon dendrons prompted us to examine the issue of dendrimer growth, and we came up with the strategy of proportionate branching.

Using proportionate branching, fluorocarbon dendrons containing 81 and 243 fluorine atoms, which could not be obtained using conventional methods, were successfully

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synthesized. Small-angle X-ray scattering (SAXS) studies reveal that these fluorocarbon dendrons have a dumbbell shape with spherical symmetry, as designed. Our results demonstrate that proportionate branching is an effective strategy to avoid steric congestion in dendrimer synthesis.

RESULTS AND DISCUSSION

Principle of Proportionate Branching. Proportionate branching is characterized by a pair of constants, a and b; a is the branch multiplicity for growing the number of branches, and b is the length multiplier for growing the length of branches. For a G-generation dendrimer, the number of branching nodes in the nth layer is denoted as m_n, and the number of bonds between the nth and the $(n-1)$th layers as l_n, with $1 \le n \le G$. The growth of m_n starts at the core with $m_0 \equiv 1$, and the growth of l_n starts at the periphery with $l_G \equiv 1$. Subsequent growth of m_n and l_n, respectively, follows the recursive formulas $m_n = a \times m_{n-1}$ and $l_{n-1} = b \times l_n$. In other words, m_n and l_n both grow exponentially but in opposite directions, with m_n *growing from the core to the periphery* and l_n *growing from the periphery to the core*.

Branch multiplicity a is determined by the chemistry of the branching atoms: $a = 3$ for 1→3 connectivity and $a = 2$ for 1→2 connectivity. Length multiplier b satisfies $1 \le b \le a$. We define a proportionality constant c as

$$c = \frac{b-1}{a-1} \times 100\% \quad (1)$$

Figure 1 illustrates three levels of proportionate branching, 0, 50, and 100%. When $b = 1$, $c = 0\%$. This is conventional dendrimer growth. When $b = a$, $c = 100\%$. In this case, $m_n \times l_n = a^G$ for $1 \le n \le G$. Hence, at 100% proportionate branching, the product of m_n and l_n is a constant. The essence of da Vinci's rule of tree branching is that $m_n \times d_n^2$ is a constant, where d_n is the diameter of branches in the nth layer.[15] Hence, from the trunk to the leaves, the branches of a dendrimer or a tree get *proportionately* shorter (our rule) or thinner (da Vinci's rule).

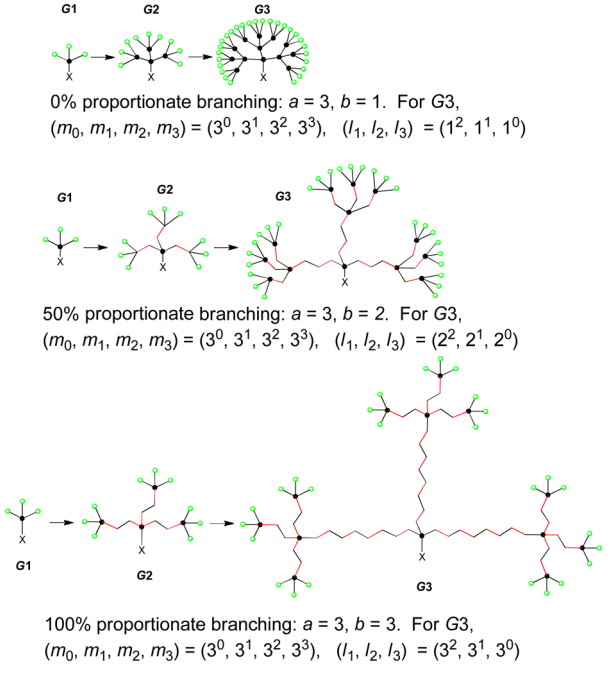
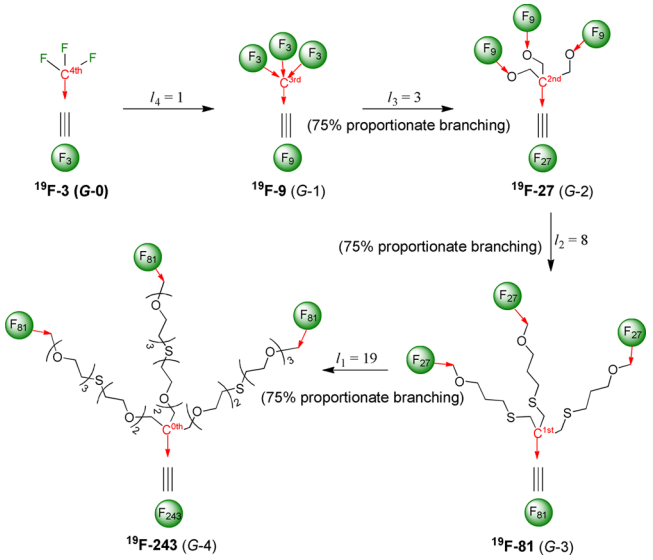


Figure 1. Different levels of proportionate branching for $G = 3$ dendrimers. At 100% proportionate branching, $m_1 \times l_1 = m_2 \times l_2 = m_3 \times l_3 = a^G$; i.e., m_n and l_n are inversely proportional to each other for $1 \le n \le G$, hence the name proportionate branching.

Larger b is beneficial for avoiding steric congestion but elevates synthesis difficulty. To strike a balance, it is sensible to allow b to adopt any appropriate value between 1 and a, including non-integers. The idea is that b should be no larger than absolutely necessary. The optimal value of b depends on branch multiplicity and peripheral group. While b can adopt a non-integer value, l_n, the number of bonds, cannot. The solution is to let l_{n-1} float between $[bl_n - 1, bl_n + 1]$. The exact integer value of l_{n-1} depends on the availability of starting materials and the convenience of synthesis, thereby giving the synthetic chemist some flexibility.

Synthesis of Fluorinated Dendrons. With the proportionate branching strategy in mind, we embarked on a convergent synthesis of four generations of fluorocarbon dendrons as shown in Scheme 1. For detailed structures of the four fluorocarbon dendrons, see Figure S1 in the Supporting Information. Since all branching atoms are tetrahedron carbons, $a = 3$. On the basis of our experience with[16,18,20,21] and reported properties of[22,23] the $-CF_3$ and $-C(CF_3)_3$ groups, we choose $b = 2.5$, hence $c = 75\%$. The l_n values are given in Scheme 1.

Scheme 1. Convergent Synthesis of Fluorocarbon Dendrons at 75% Proportionate Branching ($a = 3$, $b = 2.5$, $c = 75\%$)[a]



[a]For the generation 4 dendron, ^{19}F-243, $(m_0, m_1, m_2, m_3, m_4) = (1, 3, 9, 27, 81)$, $(l_1, l_2, l_3, l_4) = (19, 8, 3, 1)$. The irregularity in l_n values is because b is a non-integer. The calculation of l_n values is given in the synthesis step of that compound.

To implement the convergent synthesis procedure outlined in Scheme 1, we note that the first-generation dendron, perfluoro-*tert*-butanol (^{19}F-9), is commercially available. Hence our synthesis endeavor starts with making the second-generation dendron ^{19}F-27 from ^{19}F-9, as shown in Scheme 2. Pentaerythritol **1**, which is commercially available at a low price, was used as the branching unit to ensure $a = 3$. One of the four hydroxyl groups in **1** was protected with *tert*-butyl acrylate to afford **2** with a moderate yield. This step also contributes three bonds to l_2 (see Scheme 1). Three copies of ^{19}F-9 (**3**) were then grafted onto the remaining three hydroxyl

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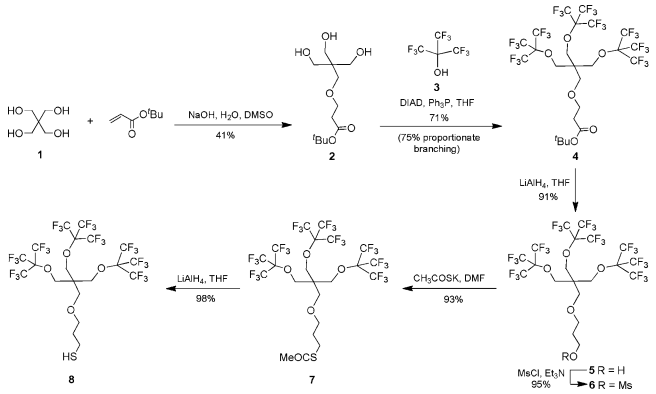
Scheme 2. Synthesis of Two Versions of ^{19}F-27 (5 and 8)[a]



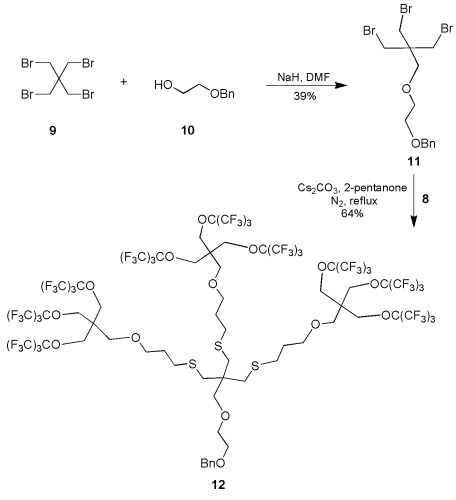
[a]The **3**→**4** step is 75% proportionate branching.

groups in **2** using the classic Mitsunobu reaction to give compound **4**. The combination of pentaerythritol and the Mitsunobu reaction leads to $l_3 = 3$, which lies in the range of $[2.5 \times 1 - 1, 2.5 \times 1 + 1]$. This illustrates the principle that the exact integer value of l_{n-1}, which lies in the range of $[bl_n - 1, bl_n + 1]$, is determined by a combination of starting material and synthesis convenience. From **4**, reduction of the ester group with $LiAlH_4$ gave the hydroxyl version of ^{19}F-27 (compound **5**). Subsequent mesylation of the primary hydroxyl group in **5** afforded mesylate **6**. Nucleophilic substitution of mesylate **6** with potassium thioacetate and then deprotection of the resulting thioester bond in **7** afforded the sulfhydryl version of ^{19}F-27 (compound **8**).

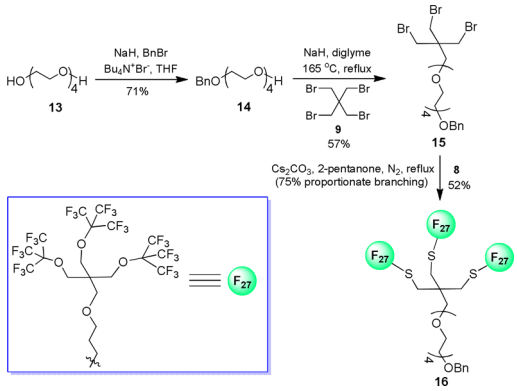
With ^{19}F-27 (**8**) in hand, we turned our attention to the synthesis of ^{19}F-81. Pentaerythritol was used as the branching unit, and grafting ^{19}F-27 onto pentaerythritol utilized the sulfide bond. Model reactions showed that the reaction between **8** and pentaerythritol tribromide proceeded smoothly under a Cs_2CO_3/2-pentanone condition after various trials (Scheme 3; for condition optimization, see Supporting Information).

The target ^{19}F-81 compound **16** can be successfully obtained from tetraethylene glycol **13** (Scheme 4). The l_2 in compound **16**, which lies between $[3 \times 2.5 - 1, 3 \times 2.5 + 1]$, was chosen to be 8. This again is due to a combination of starting material availability and synthesis convenience.

Scheme 3. Model Reaction for Making ^{19}F-81 Compounds



Scheme 4. Synthesis of ^{19}F-81 (Compound 16)[a]



[a]The **8**→**16** step is 75% proportionate branching.

Synthesis of ^{19}F-243 was similar to that of ^{19}F-81 in that pentaerythritol was used as the branching unit and grafting ^{19}F-81 onto pentaerythritol utilized the sulfide bond. To satisfy $l_1 = 19$, the tetraoxyethylene tail in **16** was shortened to the trioxyethylene tail in **20**. However, direct growth from **20** to ^{19}F-243 was hindered by unexpected difficulty in removing the benzyl group in the trioxyethylene tail of ^{19}F-81. To overcome this difficulty, the benzyl group in **18** was replaced by the trityl group in **21**, which was converted to **23**. The trityl group in **23** was easily removed by TFA to expose a free hydroxyl. Subsequent transformation of this hydroxyl group in compound **24** to the sulfhydryl group in compound **27** proceeded smoothly. Three copies of compound **27** were grafted onto the tribromide compound **30** to give ^{19}F-243 (compound **31**) with an 82% yield. In ^{19}F-243, $l_1 = 19$, which is at the lower end of $[2.5 \times 8 - 1, 2.5 \times 8 + 1]$ (Scheme 5).

NMR spectroscopy shows that, as expected, all four fluorinated dendrons emit a single unsplit sharp ^{19}F signal (see Supporting Information), attesting to their potential as imaging agents for ^{19}F MRI.

To illustrate the necessity of 75% proportionate branching, we conducted the following control experiments (Scheme 6). Attempts were made to graft three copies of compound **27** onto compound **15**. If successful, this would have led to a ^{19}F-243 with $l_1 = 13$, which is equivalent to $b = 1.5$ (13 is in the range of $[1.5 \times 8 - 1, 1.5 \times 8 + 1]$), resulting in $c = 25\%$. Such attempts led to no reaction. Replacing bromide in **15** with the more reactive triiodide compound **32** also led to no reaction with **27**. We then extended the three bromide side chains in compound **15** by one oxyethylene unit to give another tribromide compound **35**. Successful grafting of three copies of **27** to **35** would have led to a ^{19}F-243 with $l_1 = 16$, which is equivalent to $b = 2$ (16 is in the range of $[2 \times 8 - 1, 2 \times 8 + 1]$), resulting in $c = 50\%$. However, the reaction was incomplete (see Supporting Information). This demonstrates that 75% proportionate branching is necessary to avoid steric congestion in the synthesis of these fluorocarbon dendrons.

A previously reported strategy, developed by Xu and Moore in 1993, overcomes steric congestion by growing l_n linearly (i.e., $l_{n-1} = b + l_n$), where b is a constant.[24] In contrast, proportionate branching grows l_n exponentially (i.e., $l_{n-1} = b \times l_n$), where b is a constant. Linear growth of l_n is synthetically simpler, but exponential growth of l_n is more likely to avoid steric congestion. Indeed, in the synthesis of the fluorocarbon dendrons from ^{19}F-9 to ^{19}F-243, linear growth of l_n would

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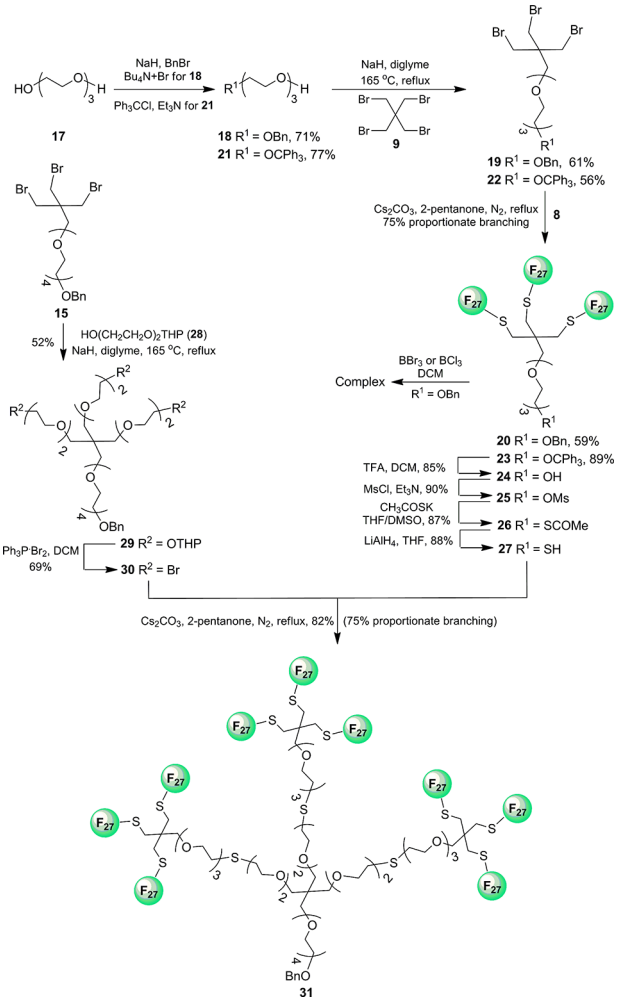
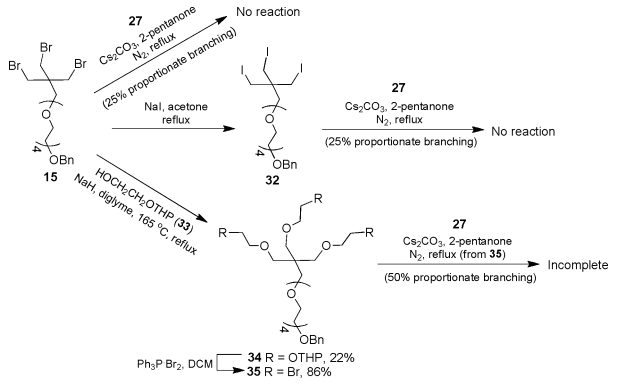
Scheme 5. Synthesis of ^{19}F-243 (Compound 31)[a]



[a]The **8**→**20** (or **23**) and **27**→**31** steps are both 75% proportionate branching.

Scheme 6. Control Experiments for Growing ^{19}F-243 with l_1 = 13 and 16, Which Respectively, Represent 25 and 50% Proportionate Branching for the ^{19}F-81→^{19}F-243 Step



have led to l_3 = 3 (^{19}F-9→^{19}F-27), l_2 = 8 (^{19}F-27→^{19}F-81), and l_1 = 13 (^{19}F-81→^{19}F-243). However, we have shown that for the ^{19}F-81→^{19}F-243 step, l_1 = 13 resulted in no growth at all. Hence, for these fluorocarbon dendrons, linear growth of l_n cannot effectively overcome steric congestion. This is hardly surprising because linear growth of l_n was developed for dendrimers with low branch multiplicity (a = 2) while exponential growth of l_n is developed for dendrimers with high branch multiplicity (a = 3).

Small-Angle X-ray Scattering Characterization. Small-angle X-ray scattering (SAXS) was used to characterize the shape of these fluorocarbon dendrons. To this end, the fluorocarbon dendrons were dissolved in trifluoroethanol (TFE) at a concentration of 276 mM for compound **3** (^{19}F-9), 92.1 mM for compound **5** (^{19}F-27), 30.7 mM for compound **16** (^{19}F-81), and 10.2 mM for compound **31** (^{19}F-243). Note that, in all samples, the molar concentration of fluorine is 2488 mM. All samples are colorless clear solutions.

SAXS profiles of $I(Q)$ versus Q of the four compounds are shown in Figure 2, where $I(Q)$ is the scattering intensity and Q

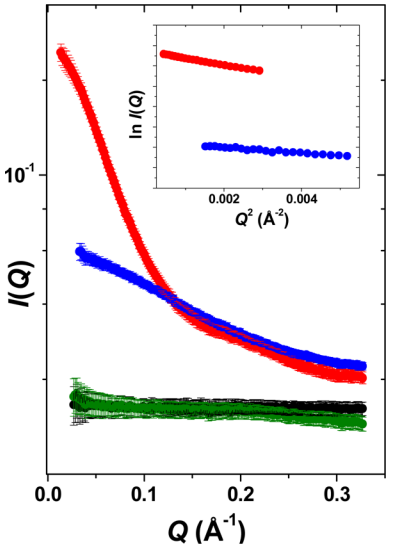


Figure 2. $I(Q)$ vs Q SAXS profiles of ^{19}F-243 (red) and ^{19}F-81 (blue) after solvent subtraction and background correction; the scattering profiles of ^{19}F-27 (green) and ^{19}F-9 (black) are shown for comparison. Inset plot shows the linear region of Guinier plot of ln$I(Q)$ vs Q^2 for globular particles, for the Q range where QR_g < 1.3 (Q range ~ 0.039–0.072 Å^{-1} for ^{19}F-81 and ~0.021–0.054 Å^{-1} for ^{19}F-243). Colors in the inset correspond to the main figure. Statistical error bars correspond to one standard deviation and represent error in scattering intensity estimation.

is the amplitude of the scattering vector and is equal to $(4\pi/\lambda)\sin(\theta/2)$, where θ is the scattering angle and λ is the wavelength of the incident X-ray (0.689 Å). Of these four compounds, only ^{19}F-81 (MW = 2941 Da) and ^{19}F-243 (MW = 9082 Da) are large enough to give sufficient scattering intensity at the aforementioned concentrations. ^{19}F-243 gave much stronger X-ray scattering than ^{19}F-81 in the lower Q region, indicative of much larger scattering particles.

The linearity in the Guinier plot suggests monodispersity for both ^{19}F-81 and ^{19}F-243 in TFE solution. Indeed, indirect Fourier transform of the scattering profiles results in pairwise distance distribution $P(r)$ functions with good quality (fitting quality of the $P(r)$ functions was ~0.7–0.8, which indicates good fit; for an ideal fit, the criterion is 1.0[25]). In the case of ^{19}F-81, the $P(r)$ profile describes an elongated slightly asymmetrical object. In the case of ^{19}F-243, the $P(r)$ profile has two pronounced maxima and is characteristic for distinct dumbbell shaped particles. From the r value at which $P(r)$ = 0, the maximum linear dimension of each particle, d_{max}, could be

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estimated, which is 55 Å for ^{19}F-81 and 85 Å for ^{19}F-243. For each dendron, the maximum distance between the fluorine atoms in the head and the benzyl group in the tail can be estimated by multiplying the number of bonds between them, which is 28 for ^{19}F-81 and 47 for ^{19}F-243, and the average bond length, which is ∼1.7 Å. The resulting values are ∼50 Å for ^{19}F-81 and ∼80 Å for ^{19}F-243, which are in good agreement with d_{max} obtained from SAXS measurement. Such agreement suggests ^{19}F-81 and ^{19}F-243 exist as monomers in TFE, attesting that TFE (F% = 57%), even though relatively polar with a dielectric constant of 28, is a good solvent for ^{19}F-81 (F % = 52%) and ^{19}F-243 (F% = 51%). The values of the radius of gyration, R_g, derived from the above $P(r)$ functions are 17.9 and 24.8 Å for ^{19}F-81 and ^{19}F-243, respectively. For both ^{19}F-81 and ^{19}F-243, R_g is markedly smaller than $d_{max}/2$ (22.5 and 42.5 Å, respectively, for ^{19}F-81 and ^{19}F-243). This indicates that the center of the scattering electron "mass" in both molecules is moved toward the electron-rich fluorocarbon head of each molecule, as one would expect.

To restore low-resolution 3D shapes of ^{19}F-81 and ^{19}F-243, we used the ab initio program DAMMIN.[26] More than 20 possible structures generated by DAMMIN for each ^{19}F-81 and ^{19}F-243 were superimposed using the best-matching alignment program SUPCOMB.[27] The normalized structural discrepancy parameter (NSD), which characterizes structural similarity of DAMMIN results, was ∼0.3 for both substances (NSD = 0 for ideal similarity, and NSD > 1 for systemically different structures). The restored low-resolution 3D shapes of ^{19}F-81 and ^{19}F-243 in TFE solution are both dumbbells (Figure 3C,D), though much less pronounced in the case of ^{19}F-81.

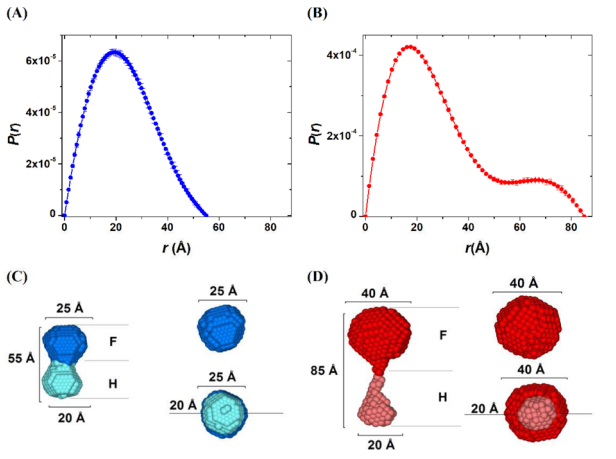

Figure 3. Pairwise distance distribution functions $P(r)$ for ^{19}F-81 (A) and ^{19}F-243 (B) in TFE solution. Side, top, and bottom projections of low-resolution 3D structures of ^{19}F-81 (C) and ^{19}F-243 (D). F and H denote, respectively, the fluorocarbon lobe and the hydrophilic lobe.

Such dumbbell shape is consistent with the chemical structures of ^{19}F-81 and ^{19}F-243, with the larger lobe being the fluorocarbon head and the smaller lobe being the oxyethylene tail. The spherical symmetry of the fluorocarbon head of each molecule is consistent with complete dendrimer growth for both ^{19}F-81 and ^{19}F-243.

From the chemical structures of ^{19}F-81 and ^{19}F-243, one might expect much greater differences between the dimensions of the fluorocarbon head and the oxyethylene tail. However, what SAXS measures is not the geometric volume, but the averaged scattering volume, which is influenced by molecular compactness and flexibility in solution. The apolar fluorocarbon chains are likely to cluster in the relatively polar TFE, leading to smaller than expected scattering volume. The polar oxyethylene tail, $(-OCH_2CH_2-)_4-OBn$, is likely to be flexible in TFE, leading to larger than expected scattering volume.

CONCLUSION

Proportionate branching is proposed to avoid steric congestion in dendrimer growth. The effectiveness of this strategy is demonstrated through the synthesis of four generations of fluorinated dendrons, containing up to 243 chemically identical fluorine atoms per dendron. The SAXS investigation indicates that generations 3 and 4 dendrons both have a dumbbell shape with spherical symmetry for the fluorine part, as designed. Proportionate branching will be particularly useful in making dendrimers with high branch multiplicity and bulky periphery groups. Emulating the structure of living organisms might be a general strategy for making defect-free functional macromolecules. The key is to translate biological observations into principles amenable to chemical synthesis.

EXPERIMENTAL SECTION

General Information. Unless otherwise stated, all chemicals were obtained from commercial sources and used without further purification. Analytical thin layer chromatography (TLC) was performed on precoated silica gel 60 F254 plates with visualization by ultraviolet (UV) irradiation at λ = 254 nm or staining with $KMnO_4$. Purifications were performed by silica gel chromatography. The ^{1}H, ^{19}F, and ^{13}C NMR spectra were carried out on a 500 MHz spectrometer. The ^{1}H, ^{19}F, and ^{13}C NMR spectra were recorded at 500, 470, and 126 MHz, respectively. ^{1}H NMR chemical shifts (δ) are reported in parts per million (ppm) relative to a residual proton peak of the solvent, δ = 7.24 for $CDCl_3$, δ = 2.80 for CD_3COCD_3. Multiplicities are reported as follows: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), or m (multiplet). Broad peaks are indicated by the addition of br. Coupling constants are reported as a J value in hertz (Hz). The number of protons (n) for a given resonance is indicated as nH and is based on spectral integration values. ^{13}C NMR chemical shifts (δ) are reported in ppm relative to $CDCl_3$ (δ = 77.3) or CD_3COCD_3 (δ = 206.8). For ^{19}F NMR, hexafluorobenzene was used as the internal standard at δ −164.9 ppm. Molecular mass was performed on either MALDI-TOF or on an ion trap mass spectrometer using the DirectProbe add-on inserted into the atmospheric pressure chemical ionization (APCI) housing. HRMS data were collected using AccuTOF. For compounds containing 81 and 243 fluorine atoms, HRMS data could not be obtained in spite of repeated tries. However, their LRMS data obtained using a DirectProbe showed the correct mass.

***tert*-Butyl 3-(3-hydroxy-2,2-bis(hydroxymethyl)propoxy)-propanoate (2).** To DMSO (100 mL) was added pentaerythritol **1** (68 g, 0.5 mol); the heterogeneous suspension was heated to 80 °C until the system became clear, then aqueous NaOH (4 g of NaOH in 9 mL of H_2O) was added in one portion, *tert*-butyl acrylate (87 mL, 0.6 mol) was added to the solution dropwise, and vigorous stirring continued overnight at 80 °C. After cooling, the solution was extracted with EtOAc. The combined organic phase was washed with H_2O and brine, concentrated through rotary evaporation, and the residue was subjected to silica gel chromatography using CH_2Cl_2/MeOH as the eluent to give **2** (54.3 g, 0.21 mol, 41% yield) as a clear oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.63 (br, 3H), 3.56 (t, J = 5.5 Hz, 2H), 3.52 (s, 6H), 3.37 (s, 2H), 2.38 (t, J = 5.0 Hz, 2H), 1.37 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.7, 81.2, 72.1, 67.2, 63.6, 45.3, 36.1, 28.1; MS (ESI) m/z 209 $(M - {}^t\text{Bu} + 2H)^+$, 265 $(M + H)^+$, 287 $(M + Na)^+$; HRMS (ESI) calcd for $C_{12}H_{25}O_6$ 265.1651 $(M + H)^+$, 209.1025 $[M - {}^t\text{Bu} + 2H]^+$, found 265.1646, 209.1026, respectively.

***tert*-Butyl 3-(3-((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)-propan-2-yl)oxy)-2,2-bis(((1,1,1,3,3,3-hexa-fluoro-2-**

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(trifluoromethyl)propan-2-yl)oxy)methyl)propoxy)propanoate (4). To a stirred suspension of compound **2** (26.4 g, 100 mmol), triphenylphosphine (118 g, 450 mmol), and 4 Å molecular sieves (15 g) in tetrahydrofuran (700 mL) at 0 °C was added dropwise diisopropylazodicarboxylate (90 mL, 450 mmol). Afterward, the reaction mixture was allowed to warm to room temperature and was stirred for an additional 20 min. Then perfluoro-*tert*-butanol **3** (62.5 mL, 450 mmol) was added in one portion, and the resulting mixture was stirred for 36 h at 45 °C in a sealed vessel. Water (30 mL) was added to the reaction mixture and stirred for an additional 10 min. Then the mixture was transferred to a separatory funnel, and the lower phase was collected. Removal of the perfluoro-*tert*-butanol under vacuum gave the product **4** (65 g, 70.8 mmol, 71% yield) as a clear oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.08 (s, 6H), 3.66 (t, J = 6.0 Hz, 2H), 3.45 (s, 2H), 2.46 (t, J = 6.0 Hz, 2H), 1.45 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.6, 120.4 (q, J = 293.3 Hz), 80.8, 80.4−79.2 (m), 67.4, 66.6, 66.1, 46.4, 36.0, 28.0; ^{19}F NMR (470 MHz, $CDCl_3$) δ −73.50 (s); MS (APCI) m/z 863 (M − ^{t}Bu + 2H)$^+$, 791 (M − ^{t}BuOCOCH$_2$CH$_2$ + 2H)$^+$; HRMS (ESI) calcd for $C_{24}H_{25}F_{27}NO_6$ 936.1251 (M + NH_4)$^+$, 863.0359 [M − ^{t}Bu + 2H]$^+$, found 936.1232, 863.0294, respectively.

3-(3-((1,1,1,3,3,3-Hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)-2,2-bis(((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)-propan-2-yl)oxy)methyl)propoxy)propan-1-ol (5). (−OH version of ^{19}F-27): To a suspension of lithium aluminum hydride (4.1 g, 108 mmol) in THF solution (450 mL) at 0 °C was added dropwise compound **4** (40 g, 43.5 mmol) in THF (100 mL). Afterward, the solution was stirred overnight at room temperature and quenched with dilute HCl carefully, concentrated through rotary evaporation, and subjected to silica gel chromatography using hexane/EtOAc as the eluent to afford alcohol **5** (33.7 g, 39.7 mmol, 91% yield) as a clear oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.02 (s, 6H), 3.69 (t, J = 6.0 Hz, 2H), 3.51 (t, J = 4.5 Hz, 2H), 3.37 (s, 2H), 1.82−1.77 (m, 2H), 1.47 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 120.4 (q, J = 294.7 Hz), 80.1−79.4 (m), 69.3, 66.3, 66.7, 60.4, 46.4, 32.5; ^{19}F NMR (470 MHz, $CDCl_3$) δ −73.40 (s); MS (APCI) m/z 849 (M + H)$^+$; HRMS (ESI) calcd for $C_{20}H_{16}F_{27}O_5$ 849.0567 (M + H)$^+$, 866.0832 [M + NH_4]$^+$, found 849.0577, 866.0811, respectively.

3-(3-((1,1,1,3,3,3-Hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)-2,2-bis(((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)-propan-2-yl)oxy)methyl)propoxy)propyl methanesulfonate (6). Triethylamine (Et_3N, 9.6 mL) and methanesulfonyl chloride (5.4 mL, 68.4 mmol) were added to a solution of compound **5** (20.2 g, 23.8 mmol) dissolved in THF (100 mL) and anhydrous CH_2Cl_2 (200 mL) mixed solvent at 0 °C. The reaction mixture was then stirred at rt overnight. The reaction was quenched with water and extracted with CH_2Cl_2. Evaporation through rotary evaporation followed by flash chromatography on silica gel using hexane/EtOAc as the eluent afforded product mesylate **6** (20.8 g, 22.5 mmol, 95% yield) as a colorless oil: ^{1}H NMR (500 MHz, CD_3COCD_3) δ 4.21 (t, J = 7.5 Hz, 2H), 4.11 (s, 6H), 3.48 (t, J = 5.0 Hz, 2H), 3.42 (s, 2H), 2.94 (s, 3H), 1.94−1.90 (m, 2H); ^{13}C NMR (126 MHz, CD_3COCD_3) δ 122.9 (q, J = 293.0 Hz), 81.2−81.0 (m), 68.6, 68.5, 67.1, 67.0, 47.7, 37.6, 30.7; ^{19}F NMR (470 MHz, CD_3COCD_3) δ −71.19 (s); MS (APCI) m/z 927 (M + H)$^+$, 831 (M − OMs)$^+$; HRMS (ESI) calcd for $C_{21}H_{18}F_{27}O_7S$ 927.0342 (M + H)$^+$, 944.0608 [M + NH_4]$^+$, found 927.0357, 944.0553, respectively.

(*S*)-(3-(3-((1,1,1,3,3,3-Hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)-2,2-bis(((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)-propan-2-yl)oxy)methyl)propoxy)propyl)ethanethioate (7). To a solution of mesylate **6** (10.2 g, 11 mmol) in DMF (100 mL) was added potassium thioacetate (3.8 g, 33 mmol). The reaction mixture was stirred at 50 °C overnight. The mixture was then extracted with DCM, washed successively with water and brine, concentrated through rotary evaporation, and subjected to silica gel chromatography using hexane/EtOAc as the eluent to afford the thioester **7** (9.3 g, 10.3 mmol, 93% yield) as a light yellow liquid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.97 (s, 6H), 3.34 (t, J = 7.0 Hz, 2H), 3.29 (s, 2H), 2.80 (t, J = 6.5 Hz, 2H), 2.21 (s, 3H), 1.73 (t, J = 7.0 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 195.7, 120.4 (q, J = 293.2 Hz), 80.2−79.5 (m), 70.2, 66.2, 65.8, 46.5, 30.5, 29.7, 26.0; ^{19}F NMR (470 MHz, $CDCl_3$) δ −73.25 (s); MS (APCI) m/z 907 (M + H)$^+$; HRMS (ESI) calcd for $C_{22}H_{18}F_{27}O_5S$ 907.0444 (M + H)$^+$, 924.0709 [M + NH_4]$^+$, found 907.0430, 924.0782, respectively.

3-(3-((1,1,1,3,3,3-Hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)-2,2-bis(((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)-propan-2-yl)oxy)methyl)propoxy)propane-1-thiol (8). (−SH version of ^{19}F-27): At 0 °C, to a solution of thioester **7** (8.6 g, 9.5 mmol) in THF (90 mL) was added lithium aluminum hydride (0.90, 23.8 mmol) in one portion under nitrogen. After the starting material was consumed completely as monitored by TLC, the reaction was quenched with dilute HCl carefully under nitrogen, concentrated through rotary evaporation, and subjected to silica gel chromatography using hexane/EtOAc as the eluent to give compound **8** (8.0 g, 9.3 mmol, 98% yield) as a clear oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.02 (s, 6H), 3.46 (t, J = 7.5 Hz, 2H), 3.36 (s, 2H), 2.53 (dd, J = 7.5, 16.0 Hz, 2H), 1.85−1.80 (m, 2H), 1.29 (t, J = 8.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 120.4 (q, J = 293.5 Hz), 79.9−79.4 (m), 69.8, 66.1, 66.6, 46.5, 33.9, 14.0; ^{19}F NMR (470 MHz, $CDCl_3$) δ −73.51 (s); MS (APCI) m/z 865 (M + H)$^+$, 791 (M − HSCH$_2$CH$_2$CH$_2$ + 2H)$^+$; HRMS (ESI) calcd for $C_{20}H_{16}F_{27}O_4S$ 865.0338 (M + H)$^+$, 882.0624 [M + NH_4]$^+$, found 865.0306, 882.0582, respectively.

((2-(3-Bromo-2,2-bis(bromomethyl)propoxy)ethoxy)-methyl)benzene (11). To a suspension of sodium hydride (0.4 g, 10 mmol, 60% dispersion in mineral oil) in 40 mL of DMF at 0 °C was added a solution of monoprotected ethylene glycol **10** (1.0 g, 6.6 mmol) dropwise. The resulting mixture was stirred at 0 °C for 0.5 h and then at rt for another 1 h to give the solution of sodium alcoholate. Pentaerythritol tetrabromide **9** (2.9 g, 7.6 mmol) was added. Afterward, the mixture was heated at 60 °C for 24 h and then cooled to rt. The reaction mixture was quenched with H_2O and extracted with EtOAc, concentrated through rotary evaporation and subjected to silica gel chromatography using hexane/EtOAc as the eluent to give compound **11** (1.18 g, 2.6 mmol, 39% yield) as a light yellow liquid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34−7.33 (m, 4H), 7.29−7.27 (m, 1H), 4.55 (s, 2H), 3.64 (dd, J = 4.5 Hz, 19.0 Hz, 4H), 3.55 (s, 2H), 3.53 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.4, 128.6, 127.88, 127.85, 73.4, 71.3, 70.1, 69.6, 44.0, 35.1; MS (ESI) m/z 458 (M + H)$^+$, 474 (M + NH_4)$^+$; HRMS (ESI) calcd for $C_{14}H_{23}Br_3NO_2$ 475.9258 (M + NH_4)$^+$, found 475.9236.

13-((2-(Benzyloxy)ethoxy)methyl)-1,1,1,25,25,25-hexafluoro-13-(((3-(3-((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)-propan-2-yl)oxy)-2,2-bis(((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)methyl)propoxy)propyl)-thio)methyl)-5,5,21,21-tetrakis(((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)methyl)-2,2,24,24-tetrakis-(trifluoromethyl)-3,7,19,23-tetraoxa-11,15-dithiapentacosane (12). To 45 mL of 2-pentanone solution were added the sulfhydryl compound **8** (570 mg, 0.66 mmol), Cs_2CO_3 (216 mg, 0.66 mmol), and tribromide **11** (75 mg, 0.15 mmol) successively at 0 °C under nitrogen. Then the mixture was brought to reflux at 105 °C overnight until the starting material **11** was completely consumed as monitored by TLC. The reaction mixture was quenched with H_2O, extracted with CH_2Cl_2, concentrated through rotary evaporation, and purified by flash chromatography using hexane/EtOAc as the eluent to afford compound **12** (270 mg, 0.096 mmol, 64% yield) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25−7.23 (m, 4H), 7.18 (br, 1H), 4.46 (s, 2H), 3.97 (s, 18H), 3.53 (s, 4H), 3.36 (s, 2H), 3.34 (s, 6H), 3.27 (s, 6H), 2.59 (s, 6H), 2.45 (t, J = 5.5 Hz, 6H), 1.75−1.69 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.6, 128.5, 127.74, 127.72, 120.4 (q, J = 291.8 Hz), 80.1−79.4 (m), 73.3, 72.7, 70.9, 70.2, 69.6, 66.0, 65.5, 46.4, 44.5, 36.7, 30.4, 29.8; ^{19}F NMR (470 MHz, $CDCl_3$) δ −73.61 (s); MS (MALDI-TOF) m/z 2826 (M + NH_4)$^+$.

1-Phenyl-2,5,8,11-tetraoxatridecan-13-ol (14). To 800 mL of THF were added sodium hydride (16.8 g, 0.42 mol, 60% dispersion in mineral oil) and tetrabutylammonium bromide (11.3 g, 35 mmol) successively at 0 °C. Then tetraethylene glycol (121 mL, 0.7 mol) was added dropwise. Afterward, the solution was stirred at rt for 1 h and then brought to reflux at 80 °C; benzyl bromide (42 mL, 0.35 mol) was added dropwise to the refluxing mixture. The reaction was quenched by H_2O after 20 h and then extracted with ethyl acetate. The

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organic phase was concentrated through rotary evaporation and subject to silica gel chromatography using hexane/EtOAc as the eluent to afford compound **14** (71 g, 0.25 mol, 71% yield) as a clear oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27−7.24 (m, 4H), 7.21−7.19 (m, 1H), 4.49 (s, 2H), 3.63−3.56 (m, 14H), 3.51 (t, J = 5.0 Hz, 2H), 2.94 (t, J = 5.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.2, 128.3, 127.7, 127.5, 73.1, 72.5, 70.58, 70.57, 70.53, 70.3, 69.4, 61.6; MS (ESI) m/z 285 $(M + H)^+$, 307 $(M + Na)^+$, 323 $(M + K)^+$.

17-Bromo-16,16-bis(bromomethyl)-1-phenyl-2,5,8,11,14-pentaoxaheptadecane (15). To a suspension of sodium hydride (1.2 g, 30 mmol, 60% dispersion in mineral oil) in 60 mL of dry diglyme at 0 °C in a 100 mL flask, equipped with magnetic stirrer and a 60 mL addition funnel, was added a solution of monobenzyl protected tetraethylene glycol **14** (7.7 g, 27 mmol) in 15 mL dry diglyme dropwise under nitrogen atmosphere. The resulting mixture was stirred at 0 °C for 1 h and then at rt for another 2 h to give a solution of sodium alcoholate. This alcoholate was added dropwise to the refluxing solution of pentaerythritol tetrabromide **9** (11.6 g, 30 mmol) in 60 mL of diglyme at 165 °C under nitrogen atmosphere. After the addition, the mixture was heated overnight at 165 °C and then cooled to room temperature. The mixture was quenched with H_2O. After solvent evaporation, the residue was extracted with EtOAc and washed with H_2O, concentrated through rotary evaporation, and subjected to silica gel chromatography using hexane/EtOAc as the eluent to afford compound **15** (9.1 g, 15.4 mmol, 57% yield) as a clear oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20−7.17 (m, 4H), 7.13 (br, 1H), 4.42 (s, 2H), 3.52−3.48 (m, 5H), 3.41−3.40 (m, 9H), 3.39 (s, 8H), 3.22 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.2, 128.2, 127.5, 127.4, 73.0, 71.8, 70.8, 70.51, 70.49, 70.46, 70.4, 70.2, 69.6, 69.3, 58.8, 43.6, 34.8; MS (ESI) m/z 606 $(M + NH_4)^+$, 611 $(M + Na)^+$; HRMS (ESI) calcd for $C_{20}H_{32}Br_3O_5$ 590.9779 $(M + H)^+$, 610.9619 $(M + Na)^+$, found 590.9767, 610.9990, respectively.

28,28,28-Trifluoro-16,16-bis(((3-(3-((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)-2,2-bis(((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)methyl)propoxy)-propyl)thio)methyl)-24,24-bis(((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)methyl)-1-phenyl-27,27-bis-(trifluoromethyl)-2,5,8,11,14,22,26-heptaoxa-18-thiaoctacosane (16) (^{19}F-81). To 10 mL of 2-pentanone were added the sulfhydryl compound **8** (691 mg, 0.8 mmol), Cs_2CO_3 (261 mg, 0.8 mmol), and tribromide **15** (105 mg, 0.18 mmol) successively at 0 °C under nitrogen. Then the mixture was brought to overnight reflux at 105 °C. The reaction mixture was quenched with H_2O and extracted with CH_2Cl_2, concentrated through rotary evaporation, and purified by silica gel chromatography using hexane/EtOAc as the eluent to afford compound **16** (270 mg, 0.092 mmol, 52% yield) as a clear oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25−7.23 (m, 4H), 7.19−7.18 (m, 1H), 4.48 (s, 2H), 3.97 (s, 18H), 3.59−3.51 (m, 14H), 3.49 (d, J = 4.5 Hz, 2H), 3.37 (t, J = 7.0 Hz, 6H), 3.31 (s, 2H), 3.29 (s, 6H), 2.58 (s, 6H), 2.46 (t, J = 6.0 Hz, 6H), 1.74 (t, J = 7.0 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.6, 128.5, 127.9, 127.8, 120.4 (q, J = 294.0 Hz), 80.4−79.1 (m), 73.5, 72.7, 70.92, 70.90, 70.88, 70.81, 70.5, 70.2, 69.7, 66.1, 65.7, 46.4, 44.5, 36.7, 30.4, 29.8; ^{19}F NMR (470 MHz, $CDCl_3$) δ −73.38 (s); MS (ESI) m/z 2965 $(M + Na)^+$, 2981 $(M + K)^+$.

2-(2-(2-(Benzyloxy)ethoxy)ethoxy)ethanol (18). The procedure was the same as the synthesis of compound **14**. From 150 g of **17** (1 mol), 16 g of sodium hydride (0.4 mol, 60% dispersion in mineral oil), 62.2 g of benzyl bromide (0.36 mol), 23.4 g of tetrabutylammonium bromide (72.8 mmol) afforded 68 g of **18** (0.28 mol, 78% yield) as a clear oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34−7.28 (m, 4H), 7.27−7.26 (m, 1H), 4.56 (s, 2H), 3.71−3.66 (m, 8H), 3.63−3.60 (m, 2H), 3.59 (s, 2H), 2.76 (t, J = 6.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.3, 128.5, 127.9, 127.8, 73.4, 72.7, 70.8, 70.7, 70.5, 69.5, 61.8; MS (ESI) m/z 241 $(M + H)^+$, 263 $(M + Na)^+$, 279 $(M + K)^+$.

14-Bromo-13,13-bis(bromomethyl)-1-phenyl-2,5,8,11-tetraoxatetradecane (19). The procedure was the same as the synthesis of compound **15**. From 4.4 g of **18** (18.2 mmol), 0.84 g of sodium hydride (21 mmol, 60% dispersion in mineral oil), and 7.74 g of **9** (20 mmol) afforded 6.1 g of **19** (11.2 mmol, 61% yield) as a light yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (br, 4H), 7.26 (br, 1H), 4.55 (s, 2H), 3.67−3.62 (m, 12H), 3.51 (s, 8H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.2, 128.3, 127.6, 127.5, 73.1, 70.9, 70.7, 70.63, 70.58, 70.3, 69.7, 69.4, 43.7, 34.9; MS (ESI) m/z 566 $(M + Na)^+$; HRMS (ESI) calcd for $C_{18}H_{28}Br_3O_4$ 546.9517 $(M + H)^+$, found 546.9536.

25,25,25-Trifluoro-13,13-bis(((3-(3-((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)-2,2-bis(((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)methyl)propoxy)-propyl)thio)-methyl)-21,21-bis(((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)methyl)-1-phenyl-24,24-bis-(trifluoromethyl)-2,5,8,11,19,23-hexaoxa-15-thiapentacosane (20). The procedure was the same as the synthesis of compound **12**. From 548 mg of **19** (1 mmol), 4 g of compound **8** (4.5 mmol), and 1.5 g of Cs_2CO_3 (4.5 mmol) afforded 1.7 g of **20** as a clear oil (0.59 mmol, 59% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34−7.32 (m, 4H), 7.28−7.27 (m, 1H), 4.57 (s, 2H), 4.06 (s, 18H), 3.68−3.62 (m, 10H), 3.59 (d, J = 4.5 Hz, 2H), 3.46 (t, J = 6.5 Hz, 6H), 3.41 (s, 2H), 3.38 (s, 6H), 2.67 (s, 6H), 2.56 (t, J = 7.5 Hz, 6H), 1.87−1.80 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.6, 128.6, 127.9, 127.8, 120.4 (q, J = 293.6 Hz), 80.4−79.2 (m), 73.5, 72.8, 71.0, 70.97, 70.88, 70.63, 70.61, 70.27, 70.23, 69.73, 69.71, 66.1, 65.7, 65.62, 65.60, 65.58, 46.5, 44.5, 36.7, 30.4, 29.9; ^{19}F NMR (470 MHz, $CDCl_3$) δ −73.27 (s); MS (ESI) m/z 2920.8 $(M + Na)^+$.

2-(2-(2-(Trityloxy)ethoxy)ethoxy)ethanol (21). To a CH_2Cl_2 (300 mL) solution of triethylene glycol (21 g, 140 mmol) was added Et_3N (20 mL, 140 mmol); then trityl chloride (19.5 g, 70 mmol) in CH_2Cl_2 (100 mL) was added dropwise at 0 °C. The mixture was stirred overnight and quenched with H_2O. The organic phase was washed with H_2O and brine successively, concentrated through rotary evaporation, and subjected to silica gel chromatography using hexane/EtOAc as the eluent to afford compound **21** (21 g, 53.6 mmol, 77% yield) as a clear liquid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47−7.46 (m, 6H), 7.28 (t, J = 7.0 Hz, 6H), 7.21 (t, J = 7.0 Hz, 3H), 3.68 (s, 8H), 3.60 (br, 2H), 3.25 (br, 2H), 2.57 (br, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.2, 128.8, 127.9, 127.1, 86.8, 72.7, 71.0, 70.8, 70.7, 63.4, 61.9; MS (ESI) m/z 415 $(M + Na)^+$.

14-Bromo-13,13-bis(bromomethyl)-1,1,1-triphenyl-2,5,8,11-tetraoxatetradecane (22). The procedure was the same as synthesis of compound **15**. From 9.3 g (24 mmol) of **9**, 7.84 g (20 mmol) of **21**, and 0.92 g of NaH (60% dispersion in mineral oil, 23 mmol) afforded 7.9 g of **22** (11.3 mmol, 56% yield) as a clear oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47−7.46 (m, 6H), 7.27 (t, J = 8.5 Hz, 6H), 7.20 (t, J = 8.0 Hz, 3H), 3.68−3.63 (m, 10H), 3.51 (s, 2H), 3.49 (s, 6H), 3.24 (t, J = 4.5 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.2, 128.8, 127.8, 127.0, 86.6, 71.09, 70.96, 70.82, 70.80, 70.5, 69.9, 63.5, 43.9, 35.0; MS (ESI) m/z 719 $(M + Na)^+$, 243 $(Ph_3C)^+$; HRMS (ESI) calcd for $C_{30}H_{35}Br_3NaO_4$ 720.9963 $(M + Na)^+$, found 720.9959.

25,25,25-Trifluoro-13,13-bis(((3-(3-((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)-2,2-bis(((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)methyl)propoxy)-propyl)thio)methyl)-21,21-bis(((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)methyl)-1,1,1-triphenyl-24,24-bis(trifluoromethyl)-2,5,8,11,19,23-hexaoxa-15-thiapentacosane (23). The procedure was the same as synthesis of compound **16**. From 14 g (16 mmol) of **8**, 3.1 g (4.4 mmol) of **22**, and 5.8 g of Cs_2CO_3 (17.8 mmol) afforded 12 g of **23** (3.93 mmol, 89% yield) as a clear oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48−7.46 (m, 6H), 7.30−7.25 (m, 6H), 7.23−7.21 (m, 3H), 4.04 (s, 18H), 3.66−3.64 (m, 8H), 3.58 (s, 2H), 3.44 (s, 6H), 3.39 (s, 2H), 3.36 (s, 6H), 3.24 (s, 2H), 2.65 (s, 6H), 2.54−2.53 (m, 6H), 1.82−1.81 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.4, 129.0, 128.0, 127.1, 120.4 (q, J = 293.8 Hz), 86.8, 80.1−79.4 (m), 72.8, 71.1, 70.96, 70.94, 70.85, 70.6, 70.3, 66.1, 65.7, 65.6, 63.6, 46.4, 44.5, 36.7, 30.4, 29.8; ^{19}F NMR (470 MHz, $CDCl_3$) δ −73.61 (s); MS (ESI) m/z 3073 $(M + Na)^+$.

Compound 24. To a solution of **23** (11.6 g, 3.8 mmol) in DCM (400 mL) was added TFA (5.8 mL, 76 mmol) dropwise at 0 °C. After the starting material was consumed completely as monitored by TLC, the solvent was removed through rotary evaporation and the residue was subjected to silica gel chromatography using hexane/EtOAc as the eluent to afford compound **24** (9.1 g, 3.24 mmol, 85% yield) as a viscous liquid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.06 (s, 18H), 3.72 (t, J = 4.0 Hz, 2H), 3.66−3.59 (m, 10H), 3.46 (t, J = 7.5 Hz, 6H), 3.42 (s,

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2H), 3.38 (s, 6H), 2.68 (s, 6H), 2.60 (br, 1H), 2.56 (t, J = 7.5 Hz, 6H), 1.86−1.81 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 120.4 (q, J = 293.6 Hz), 80.4−79.2 (m), 72.9, 72.7, 70.87, 70.84, 70.80, 70.64, 70.3, 66.1, 65.7, 61.9, 46.4, 44.5, 36.7, 30.4, 29.9; ^{19}F NMR (470 MHz, $CDCl_3$) δ −73.34 (s); MS (APCI) m/z 2808 $(M + 2H)^+$, 2658 $(M - HOCH_2CH_2OCH_2CH_2OCH_2CH_2O + H)^+$.

Mesylate 25. Et_3N (0.59 mL, 4.2 mmol) and methanesulfonyl chloride (0.33 mL, 4.2 mmol) were added to a solution of compound **24** (4.75 g, 1.7 mmol) dissolved in THF (40 mL) and anhydrous CH_2Cl_2 (40 mL) mixed solvent at 0 °C. The reaction mixture was then stirred at rt overnight. The reaction was quenched with water and extracted with CH_2Cl_2. Evaporation of the solvent by rotary evaporation followed by flash chromatography on silica gel using hexane/EtOAc as the eluent afforded the product mesylate **25** (3.7 g, 1.28 mmol, 76% yield) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.38 (s, 2H), 4.06 (s, 18H), 3.77 (s, 2H), 3.66−3.58 (m, 8H), 3.47 (s, 6H), 3.41 (s, 2H), 3.38 (s, 6H), 3.08 (s, 3H), 2.67 (s, 6H), 2.56−2.55 (m, 6H), 1.84 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 120.4 (q, J = 294.2 Hz), 80.1−79.4 (m), 72.9, 71.0, 70.9, 70.8, 70.6, 70.2, 69.4, 69.3, 66.1, 65.7, 65.6, 46.4, 44.5, 37.8, 36.7, 30.4, 29.9; ^{19}F NMR (470 MHz, $CDCl_3$) δ −73.45 (s); MS (APCI) m/z 2885 $(M + H)^+$, 2821 $(M - SO_2 + H)^+$, 2657 $(M - MsOCH_2CH_2OCH_2CH_2OCH_2CH_2O)^+$.

Thioacetate 26. To a solution of mesylate **25** (3.6 g, 1.25 mmol) in THF (14 mL) and DMSO (14 mL) mixed solvents was added potassium thioacetate (0.5 g, 4.38 mmol), and the reaction mixture was stirred at 120 °C overnight. The reaction mixture was extracted with DCM, washed with water and brine successively, concentrated through rotary evaporation, and subjected to silica gel chromatography using hexane/EtOAc as the eluent to afford the thioester **26** (3.12 g, 1.09 mmol, 87% yield) as a light yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.06 (s, 18H), 3.63−3.60 (m, 10H), 3.47 (t, J = 6.5 Hz, 6H), 3.42 (s, 2H), 3.39 (s, 6H), 3.11 (t, J = 7.0 Hz, 2H), 2.68 (s, 6H), 2.57 (t, J = 6.5 Hz, 6H), 2.34 (s, 3H), 1.84 (t, J = 7.0 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 120.3 (q, J = 293.8 Hz), 80.1−79.4 (m), 72.7, 71.8, 70.7, 70.60, 70.57, 70.2, 70.0, 66.0, 65.6, 46.4, 44.4, 36.7, 30.6, 30.4, 29.8, 29.0; ^{19}F NMR (470 MHz, $CDCl_3$) δ −73.62 (s); MS (MALDI-TOF) m/z 2881.1 $(M + Na)^+$, 2904.7 $(M + K)^+$.

Free Thiol Compound 27. The procedure was the same as the synthesis of compound **8**. From 3 g (1.05 mmol) of **26** and 0.12 g (3.15 mmol) of $LiAlH_4$ afforded 2.6 g of **27** (0.92 mmol, 88% yield) as a clear oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.06 (s, 18H), 3.63−3.59 (m, 10H), 3.46 (t, J = 6.0 Hz, 6H), 3.41 (s, 2H), 3.36 (s, 6H), 2.71−2.67 (m, 8H), 2.55 (t, J = 6.0 Hz, 6H), 1.83 (t, J = 7.0 Hz, 6H), 1.60 (t, J = 7.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 120.4 (q, J = 297.4 Hz), 80.4−79.2 (m), 73.1, 72.8, 70.9, 70.8, 70.7, 70.6, 70.3, 66.1, 65.7, 46.4, 44.5, 36.7, 30.4, 29.9, 24.5; ^{19}F NMR (470 MHz, $CDCl_3$) δ −73.59 (s); MS (APCI) m/z 2824 $(M + 2H)^+$, 2763 $(M - HSCH_2CH_2 + H)^+$, 2657 $(M - HSCH_2CH_2OCH_2CH_2OCH_2CH_2O)^+$.

2-(2-((Tetrahydro-2*H*-pyran-2-yl)oxy)ethoxy)ethanol (28). To 800 mL of CH_2Cl_2 were added diethylene glycol (57 mL, 0.6 mol) and *p*-toluenesulfonic acid monohydrate (5.7 g, 30 mmol) successively. Then tetrahydropyran (27.4 mL, 0.3 mol) was added dropwise at 0 °C. The reaction mixture was stirred overnight and quenched with H_2O, extracted with CH_2Cl_2, washed with H_2O and brine successively, concentrated through rotary evaporation, and subjected to silica gel chromatography using CH_2Cl_2/MeOH as the eluent to afford compound **28** (32.5 g, 0.17 mol, 57% yield) as a clear oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.59 (t, J = 4.0 Hz, 1H), 3.85−3.80 (m, 2H), 3.68−3.64 (m, 4H), 3.59−3.55 (m, 3H), 3.48−3.44 (m, 1H), 2.98 (br, 1H), 1.81−1.76 (m, 1H), 1.71−1.65 (m, 1H), 1.59−1.46 (m, 4H).

2,2′-((8-(15-Phenyl-2,5,8,11,14-pentaoxapentadecyl)-8-((2-(2-((tetrahydro-2*H*-pyran-2-yl)oxy)ethoxy)-ethoxy)methyl)-3,6,10,13-tetraoxapentadecane-1,15-diyl)bis(oxy))bis-(tetrahydro-2H-pyran) (29). To a suspension of sodium hydride (0.72 g, 18 mmol, 60% dispersion in mineral oil) in 20 mL of dry diglyme at 0 °C in a 100 mL flask, equipped with a magnetic stirrer and an addition funnel, was added a solution of monotetrahydropyranyl protected diethylene glycol **28** (3.42 g, 18 mmol) in 8 mL dry diglyme dropwise under nitrogen atmosphere. The resulting mixture was stirred at 0 °C for 1 h and then at rt for another 2 h to give a solution of sodium alcoholate. This alcoholate was added dropwise to the refluxing solution of compound **15** (2.36 g, 4 mmol) in 10 mL of diglyme under nitrogen atmosphere at 165 °C. Afterward, the mixture was heated at reflux overnight and then cooled to rt. The mixture was quenched with H_2O. After solvent evaporation through rotary evaporation, the mixture was extracted with EtOAc and washed with H_2O and brine, concentrated through rotary evaporation, and subjected to silica gel chromatography using hexane/EtOAc as the eluent to afford compound **29** (1.9 g, 2.07 mmol, 52% yield) as a clear oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36−7.35 (m, 4H), 7.29 (br, 1H), 4.58 (s, 2H), 3.75 (t, J = 6.0 Hz, 6H), 3.68−3.60 (m, 16H), 3.50−3.45 (m, 14H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.4, 128.5, 127.8, 127.7, 98.9, 73.2, 71.05, 70.98, 70.66, 70.63, 70.61, 70.58, 70.56, 70.50, 70.4, 70.3, 70.0, 69.4, 66.7, 62.1, 45.6, 30.6, 25.4, 19.5; MS (ESI) m/z 937 $(M + NH_4)^+$, 942 $(M + Na)^+$, 958 $(M + K)^+$; HRMS (ESI) calcd for $C_{47}H_{86}NO_{17}$ 936.5896 $(M + NH_4)^+$, found 936.5895.

23-Bromo-16,16-bis((2-(2-bromoethoxy)ethoxy)methyl)-1-phenyl-2,5,8,11,14,18,21-heptaoxatricosane (30). To a stirred solution of compound **29** (500 mg, 0.54 mmol) in 10 mL of CH_2Cl_2 was added triphenylphosphine dibromide (1.03 g, 2.45 mmol) at 0 °C. The resulting mixture was stirred at rt overnight. The mixture was diluted with CH_2Cl_2 and washed with water. The CH_2Cl_2 layer was separated, dried over Na_2SO_4, and concentrated through rotary evaporation. The residue was purified by chromatography on silica gel using hexane/EtOAc as the eluent to give tribromide **30** (320 mg, 0.37 mmol, 69% yield) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (s, 4H), 7.26 (s, 1H), 4.54 (s, 2H), 3.79−3.77 (m, 6H), 3.64−3.59 (m, 20H), 3.55 (s, 8H), 3.44 (s, 14H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.2, 128.3, 127.6, 127.5, 73.1, 71.08, 71.02, 70.96, 70.61, 70.58, 70.55, 70.52, 70.32, 70.28, 69.93, 69.87, 69.4, 45.5, 30.6; MS (ESI) m/z 874 $(M + Na)^+$; HRMS (ESI) calcd for $C_{32}H_{59}Br_3NO_{11}$ 872.1618 $(M + NH_4)^+$, found 872.1610.

Compound 31 (^{19}F-243). To 10 mL of 2-pentanone solution were added the sulfhydryl compound **27** (290 mg, 0.1 mmol), Cs_2CO_3 (49 mg, 0.15 mmol), and tribromide **30** (21 mg, 0.025 mmol) successively at 0 °C under nitrogen. Then the mixture was brought to reflux at 105 °C overnight until the starting material **30** was completely consumed as monitored by TLC. The reaction mixture was quenched with H_2O and extracted with CH_2Cl_2, concentrated through rotary evaporation, and purified by flash silica gel chromatography using hexane/EtOAc as the eluent to afford compound **31** (190 mg, 0.021 mmol, 82% yield) as a clear oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (br, 3H), 7.24 (s, 2H), 4.53 (s, 2H), 4.00 (s, 54H), 3.63−3.51 (m, 64H), 3.41 (s, 26H), 3.36−3.33 (m, 24H), 2.71−2.69 (m, 12H), 2.62 (s, 18H), 2.50 (s, 18H), 1.78 (s, 18H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.2, 137.2, 128.6, 127.9, 120.3 (q, J = 294.0 Hz), 72.7, 71.15, 71.12, 70.87, 70.84, 70.80, 70.73, 70.70, 70.59, 70.55, 70.50, 70.34, 70.27, 70.23, 69.65, 66.0, 65.6 46.4, 44.4, 36.7, 32.2, 32.0, 30.4, 29.9, 29.8; ^{19}F NMR (470 MHz, $CDCl_3$) δ −74.16 (s); MS (MALDI-TOF) m/z 9105 $(M + Na)^+$.

17-Iodo-16,16-bis(iodomethyl)-1-phenyl-2,5,8,11,14-pentaoxaheptadecane (32). To an acetone solution (15 mL) of compound **15** (1.18 g, 2 mmol) was added sodium iodide (4.5 g, 30 mmol), then the solution was brought to reflux at 65 °C for 3 days The solvent was removed through rotary evaporation, and the residue was purified by silica gel chromatography using hexane/EtOAc as the eluent to afford compound **32** as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (br, 4H), 7.29 (br, 1H), 4.58 (s, 2H), 3.68−3.65 (m, 16H), 3.52 (s, 2H), 3.37 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.3, 128.4, 127.7, 127.6, 73.2, 71.6, 71.0, 70.70, 70.68, 70.66, 70.4, 69.5, 39.6, 11.8; MS (ESI) m/z 750 $(M + NH_4)^+$, 755 $(M + Na)^+$, 771 $(M + K)^+$; HRMS (ESI) calcd for $C_{20}H_{32}I_3O_5$ 732.9384 $(M + H)^+$, 749.9644 $[M + NH_4]^+$, found 732.9405, 749.9655, respectively.

2-((Tetrahydro-2*H*-pyran-2-yl)oxy)ethanol (33). The procedure was the same as the synthesis of compound **28**. From 62 g of ethylene glycol (1 mol), 9.5 g of *p*-toluenesulfonic acid monohydrate (50 mmol), and 28 g of tetrahydropyran (333 mmol) afforded **33** (30 g, 205 mmol, 62% yield) as a clear oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ

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4.53 (d, J = 3.0 Hz, 1H), 3.87−3.84 (m, 1H), 3.75−3.61 (m, 4H), 3.49−3.47 (m, 1H), 3.15 (br, 1H), 1.82−1.79 (m, 1H), 1.78−1.68 (m, 1H), 1.55−1.46 (m, 4H); MS (ESI) m/z 169 $(M + Na)^+$.

2-((1-Phenyl-16,16-bis((2-((tetrahydro-2*H*-pyran-2-yl)oxy)-ethoxy)methyl)-2,5,8,11,14,18-hexaoxaicosan-20-yl)oxy)-tetrahydro-2*H*-pyran (34). To a suspension of sodium hydride (0.64 g, 16 mmol, 60% dispersion in mineral oil) in 30 mL of dry diglyme at 0 °C in a 100 mL flask, equipped with a magnetic stirrer and an addition funnel, was added a solution of monotetrahydropyranyl protected ethylene glycol **33** (2.34 g, 16 mmol) in 8 mL of dry diglyme dropwise under nitrogen atmosphere. The resulting mixture was stirred at 0 °C for 1 h and then at rt for another 2 h to give a solution of sodium alcoholate. This alcoholate was added dropwise to the 165 °C refluxing solution of pentaerythritol tribromide **15** (2.36 g, 4 mmol) in 15 mL of diglyme under nitrogen atmosphere. Afterward, the mixture was kept refluxing at 165 °C overnight and then cooled to rt. The reaction mixture was quenched with H_2O and, after solvent evaporation, extracted with EtOAc and washed with H_2O, concentrated through rotary evaporation, and subjected to silica gel chromatography using CH_2Cl_2/MeOH as the eluent to afford compound **34** (0.7 g, 0.89 mmol, 22% yield) as a clear oil: ^1H NMR (500 MHz, $CDCl_3$) δ 7.28 (br, 4H), 7.21 (br, 1H), 4.59 (s, 3H), 4.51 (s, 2H), 3.84−3.80 (m, 2H), 3.75−3.73 (m, 2H), 3.61−3.59 (m, 12H), 3.52−3.42 (m, 12H), 3.37−3.35 (m, 14H), 1.79−1.77 (m, 3H), 1.67−1.63 (m, 3H), 1.53−1.46 (m, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.2, 128.2, 127.6, 127.4, 98.5, 73.1, 71.0, 70.8, 70.61, 70.58, 70.57, 70.55, 70.54, 70.3, 70.0, 69.9, 69.4, 66.3, 61.7, 45.6, 30.5, 25.4, 19.3; MS (ESI) m/z 804.5 $(M + NH_4)^+$; HRMS (ESI) calcd for $C_{41}H_{74}NO_{14}$ 804.5109 $(M + NH_4)^+$, found 804.5112.

20-Bromo-16,16-bis((2-bromoethoxy)methyl)-1-phenyl-2,5,8,11,14,18-hexaoxaicosane (35). To a stirred solution of monotetrahydropyranyl protected ethylene glycol **34** (260 mg, 0.33 mmol) in 5 mL of CH_2Cl_2 was added triphenylphosphine dibromide (627 mg, 1.49 mmol) at 0 °C. The resulting mixture was stirred at rt overnight. The mixture was diluted with CH_2Cl_2 and washed with water. The CH_2Cl_2 layer was separated, dried over Na_2SO_4, and concentrated through rotary evaporation. The residue was purified by silica gel chromatography using CH_2Cl_2/MeOH as the eluent to give compound **35** (205 mg, 0.28 mmol, 86% yield) as a yellow oil: ^1H NMR (500 MHz, $CDCl_3$) δ 7.36−7.35 (m, 4H), 7.29 (br, 1H), 4.58 (s, 2H), 3.75 (t, J = 6.0 Hz, 6H), 3.68−3.60 (m, 16H), 3.50−3.45 (m, 14H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.4, 128.5, 127.8, 127.7, 73.3, 71.3, 71.1, 70.81, 70.78, 70.75, 70.69, 70.5, 69.6, 69.5, 69.4, 45.9, 30.9; MS (ESI) m/z 738 $(M + NH_4)^+$, 743 $(M + Na)^+$; HRMS (ESI) calcd for $C_{26}H_{44}Br_3O_8$ 723.0566 $(M + H)^+$, 740.0831 $(M + NH_4)^+$, found 723.0592, 740.0802, respectively.

Reaction between Compounds 35 and 27. To 6 mL of 2-pentanone were added the sulfhydryl compound **27** (160 mg, 0.057 mmol), Cs_2CO_3 (23 mg, 0.07 mmol), and tribromide **35** (10 mg, 0.014 mmol) successively at 0 °C under nitrogen. Then the mixture was brought to overnight reflux at 105 °C until the starting material **35** was completely consumed as monitored by TLC. The reaction mixture was quenched with H_2O, extracted with CH_2Cl_2, concentrated through rotary evaporation, and purified by flash silica gel chromatography using hexane/EtOAc as the eluent to afford a mixture of 59 mg as a clear oil. ^{19}F NMR showed a ratio 2/1 two peaks. ^{19}F NMR (470 MHz, $CDCl_3$) δ −73.72 (s), −74.28 (s).

■ ASSOCIATED CONTENT

Supporting Information

Characterization data of all new compounds and SAXS procedure. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: byu@rx.umaryland.edu.

Notes

The authors declare no competing financial interest.

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