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

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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 9,082 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 comprised 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 bio-inspired strategy called proportionate branching. It is based on the

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Supporting Information

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

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 ¹⁹F MRI. Fluorine atoms in a fluorinated dendrimer have identical chemical environments and their ¹⁹F signals coalesce into a single peak for magnetic resonance imaging. Defects in fluorinated dendrimers would lead to split ¹⁹F signals, which can create chemical shift image artefacts. Hence for ¹⁹F 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 is comprised of 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 (-CF₃ 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 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 while b is the length multiplier for growing the length of branches. For a G -generation dendrimer, the number of branching nodes in the n -th layer is denoted as m_n , and the number of bonds between the n -th and the $(n-1)$ -th layers as l_n , with $1 \leq n \leq G$. 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 formulae $m_n = a m_{n-1}$ and $l_{n-1} = b l_n$. 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 $1 \leq b \leq a$. 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, $m_n \cdot l_n = a^G$ for $1 \leq n \leq G$. 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 $m_n \cdot d_n^2$ is a constant, where d_n is the diameter of branches in the n -th 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).

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 $[b \cdot l_n - 1, b \cdot l_n + 1]$. 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. Since all branching atoms are tetrahedron carbons, $a = 3$. Based on our experience with ^{16, 18, 20, 21} and reported properties of ^{22, 23} the -CF₃ and -C(CF₃)₃ groups, we choose $b = 2.5$, hence $c = 75\%$. The l_n values are given in Scheme 1.

To implement the convergent synthesis procedure outlined in Scheme 1, we note that the first generation dendron, perfluoro-*tert*-butanol (¹⁹F-9), is commercially available. Hence our synthesis endeavor starts with making the second generation dendron ¹⁹F-27 from ¹⁹F-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 ¹⁹F-9 (**3**) were then grafted onto the remaining three hydroxyl 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 $[b \cdot l_n - 1, b \cdot l_n + 1]$, is determined by a combination of starting material and synthesis convenience. From **4**, reduction of the ester group with LiAlH₄ gave the hydroxyl version of ¹⁹F-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 ¹⁹F-27 (compound **8**).

With ¹⁹F-27 (**8**) in hand, we turned our attention to the synthesis of ¹⁹F-81. Pentaerythritol was used as the branching unit and grafting ¹⁹F-27 onto pentaerythritol utilized the sulfide bond. Model reactions showed that the reaction between **8** and pentaerythritol tribromide proceeded smoothly under a Cs₂CO₃/2-pentanone condition after various trials (Scheme 3; for condition optimisation see SI).

The target ^{19}F -81 compound **16** can be successfully obtained from tetraethylene glycol **13** (Scheme 4). I_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.

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 sulphide bond. To satisfy $I_1 = 19$, the tetraoxyethylene tail in **16** were 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, $I_1 = 19$, 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 SI), 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 $I_1 = 13$, 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 $I_1 = 16$, 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 SI). 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 I_n linearly, i.e., $I_{n-1} = b + I_n$, where b is a constant.²⁴ In contrast proportionate branching grows I_n exponentially, i.e., $I_{n-1} = b \cdot I_n$, where b is a constant. Linear growth of I_n is synthetically simpler but exponential growth of I_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 I_n would have led to $I_3 = 3$ (^{19}F -9 $\rightarrow$ ^{19}F -27), $I_2 = 8$ (^{19}F -27 $\rightarrow$ ^{19}F -81) and $I_1 = 13$ (^{19}F -81 $\rightarrow$ ^{19}F -243). However, we have shown that for the ^{19}F -81 $\rightarrow$ ^{19}F -243 step, $I_1 = 13$ resulted in no growth at all. Hence for these fluorocarbon dendrons, linear growth of I_n cannot effectively overcome steric congestion. This is hardly surprising because linear growth of I_n was developed for dendrimers with low branch multiplicity ($a = 2$) while exponential growth of I_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 2,488 mM. All samples are colorless clear solutions.

SAXS profiles of $I(Q)$ vs. Q of the four compounds are shown in Figure 2, where $I(Q)$ is the scattering intensity and Q 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 = 2,941 Da) and ^{19}F -243 (MW = 9,082 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 pair-wise 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 1.0²⁵). 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 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 Å 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 $d_{\text{max}}/2$ (22.5 Å 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 towards 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 3 C and D), though much less pronounced in the case of ^{19}F -81. 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, $(-\text{OCH}_2\text{CH}_2)_4\text{-OBn}$, 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 $\lambda = 254$ nm or staining with KMnO_4 . Purifications were performed by silica gel chromatography. The ^1H , ^{19}F and ^{13}C NMR spectra were carried out on a 500 MHz spectrometer. The ^1H , ^{19}F and ^{13}C NMR spectra were recorded at 500 MHz, 470 MHz and 126 MHz, respectively. ^1H NMR chemical shifts (δ) are reported in parts per million (ppm) relative to a residual proton peak of the solvent, $\delta = 7.24$ for CDCl_3 , $\delta = 2.80$ 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 $n\text{H}$ and is based on spectral integration values. ^{13}C NMR chemical shifts (δ) are reported in ppm relative to CDCl_3 ($\delta = 77.3$) or CD_3COCD_3 ($\delta = 206.8$). For ^{19}F NMR, hexafluorobenzene was used as the internal standard at $\delta -164.9$ 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 NaOH in 9 mL H_2O) was added in one portion, *tert*-butyl acrylate (87 mL, 0.6 mol) was added to the solution dropwise, 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 $\text{CH}_2\text{Cl}_2/\text{MeOH}$ as the eluent to give **2** (54.3 g, 0.21 mol, 41% yield) as a clear oil. ^1H 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 ($\text{M} - ^t\text{Bu} + 2\text{H}$)⁺, 265 ($\text{M} + \text{H}$)⁺, 287 ($\text{M} + \text{Na}$)⁺; HRMS (ESI): Calcd for $\text{C}_{12}\text{H}_{25}\text{O}_6$ 265.1651 ($\text{M} + \text{H}$)⁺, 209.1025 [$\text{M} - ^t\text{Bu} + 2\text{H}$]⁺, 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-hexafluoro-2-(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). Afterwards, 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. ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (126 MHz, CDCl₃) 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; ¹⁹F NMR (470 MHz, CDCl₃) δ – 73.50 (s); MS (APCI) *m/z* 863 (M – ^tBu + 2H)⁺, 791 (M – ^tBuOCOCH₂CH₂ + 2H)⁺; HRMS (ESI): Calcd for C₂₄H₂₅F₂₇NO₆ 936.1251 (M + NH₄)⁺, 863.0359 [M – ^tBu + 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-(tri-fluoromethyl)propan-2-yl)oxy)methyl)propoxy)propan-1-ol (5)—(–OH version of ¹⁹F-27): To a suspension of lithium aluminium 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). Afterwards, 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. ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (126 MHz, CDCl₃) 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; ¹⁹F NMR (470 MHz, CDCl₃) δ – 73.40 (s); MS (APCI) *m/z* 849 (M + H)⁺; HRMS (ESI): Calcd for C₂₀H₁₆F₂₇O₅ 849.0567 (M + H)⁺, 866.0832 [M + NH₄]⁺, 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-(tri-fluoromethyl)propan-2-yl)oxy)methyl)propoxy)propyl methanesulfonate (6)—Triethylamine (Et₃N, 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 CH₂Cl₂ (200 mL) mixed solvent at 0 °C. The reaction mixture was then stirred at r.t. overnight. The reaction was quenched with water and extracted with CH₂Cl₂. 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. ¹H NMR (500 MHz, CD₃COCD₃) 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); ¹³C NMR (126 MHz, CD₃COCD₃) 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; ¹⁹F NMR (470 MHz, CD₃COCD₃) δ – 71.19 (s); MS (APCI) *m/z* 927 (M + H)⁺, 831 (M – OMs)⁺; HRMS (ESI): Calcd for C₂₁H₁₈F₂₇O₇S 927.0342 (M + H)⁺, 944.0608 [M + NH₄]⁺, 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. ^1H 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 ($\text{M} + \text{H}$) $^+$; HRMS (ESI): Calcd for $\text{C}_{22}\text{H}_{18}\text{F}_{27}\text{O}_5\text{S}$ 907.0444 ($\text{M} + \text{H}$) $^+$, 924.0709 [$\text{M} + \text{NH}_4$] $^+$, found 907.0430, 924.0782 respectively.

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-(tri-fluoromethyl)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 aluminium 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. ^1H 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 ($\text{M} + \text{H}$) $^+$, 791 ($\text{M} - \text{HSCH}_2\text{CH}_2\text{CH}_2 + 2\text{H}$) $^+$; HRMS (ESI): Calcd for $\text{C}_{20}\text{H}_{16}\text{F}_{27}\text{O}_4\text{S}$ 865.0338 ($\text{M} + \text{H}$) $^+$, 882.0624 [$\text{M} + \text{NH}_4$] $^+$, 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 mono-protected 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 r.t. for another 1 h to give the solution of sodium alcoholate. Pentaerythritol tetrabromide **9** (2.9 g, 7.6 mmol) was added. Afterwards, the mixture was heated at 60 °C for 24 h and then cooled to r.t. 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. ^1H 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 ($\text{M} + \text{H}$) $^+$, 474 ($\text{M} + \text{NH}_4$) $^+$; HRMS (ESI): Calcd for $\text{C}_{14}\text{H}_{23}\text{Br}_3\text{NO}_2$ 475.9258 ($\text{M} + \text{NH}_4$) $^+$, found 475.9236.

13-((2-(benzyloxy)ethoxy)methyl)-1,1,1,25,25,25-hexafluoro-13-(((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)propylthio)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 was added the sulfhydryl compound **8** (570 mg, 0.66 mmol), Cs_2CO_3 (216 mg, 0.66 mmol), tribromide **11** (75 mg, 0.15 mmol) successively at 0 °C under nitrogen. Then the mixture was brought to reflux at 105 °C for overnight until the starting material **11** was completely consumed 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. ^1H 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, CDCl₃) 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; ¹⁹F NMR (470 MHz, CDCl₃) δ – 73.61 (s); MS (MALDI-TOF) m/z 2826 (M + NH₄)⁺.

1-phenyl-2,5,8,11-tetraoxatridecan-13-ol (14)—To 800 mL THF was added sodium hydride (16.8 g, 0.42 mol, 60% dispersion in mineral oil), tetrabutylammonium bromide (11.3 g, 35 mmol) successively at 0 °C. Then tetraethylene glycol (121 mL, 0.7 mol) was added dropwise. Afterwards, the solution was stirred at r.t. 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 H₂O after 20 h and then extracted with ethyl acetate. The 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. ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (126 MHz, CDCl₃) 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, a solution of mono-benzyl protected tetraethylene glycol **14** (7.7 g, 27 mmol) in 15 mL dry diglyme was added dropwise under nitrogen atmosphere. The resulting mixture was stirred at 0 °C for 1 h and then at r.t. 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 for overnight at 165 °C and then cooled to room temperature. The mixture was quenched with H₂O. After solvent evaporation, the residue was extracted with EtOAc and washed with H₂O, 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. ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (126 MHz, CDCl₃) 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 + NH₄)⁺, 611 (M + Na)⁺; HRMS (ESI): Calcd for C₂₀H₃₂Br₃O₅ 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(tri-fluoromethyl)-2,5,8,11,14,22,26-hepta-oxa-18-thiaoctacosane (16) (¹⁹F-81)—To 10 mL 2-pentanone was added the sulfhydryl compound **8** (691 mg, 0.8 mmol), Cs₂CO₃ (261 mg, 0.8 mmol), 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 H₂O and extracted with CH₂Cl₂, 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. ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (126 MHz, CDCl₃) 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 ($\text{M} + \text{Na}$) $^+$, 2981 ($\text{M} + \text{K}$) $^+$.

2-(2-(2-(benzyloxy)ethoxy)ethoxy)ethanol (18)—The procedure was the same as the synthesis of compound **14**. From 150 g **17** (1 mol), 16 g sodium hydride (0.4 mol, 60% dispersion in mineral oil), 62.2 g benzyl bromide (0.36 mol), 23.4 g tetrabutylammonium bromide (72.8 mmol) afforded 68 g of **18** (0.28 mol, 78% yield) as a clear oil. ^1H 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 ($\text{M} + \text{H}$) $^+$, 263 ($\text{M} + \text{Na}$) $^+$, 279 ($\text{M} + \text{K}$) $^+$.

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 **18** (18.2 mmol), 0.84 g sodium hydride (21 mmol, 60% dispersion in mineral oil), 7.74 g **9** (20 mmol) afforded 6.1 g **19** (11.2 mmol, 61% yield) as a light yellow oil. ^1H 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 ($\text{M} + \text{Na}$) $^+$; HRMS (ESI): Calcd for $\text{C}_{18}\text{H}_{28}\text{Br}_3\text{O}_4$ 546.9517 ($\text{M} + \text{H}$) $^+$, 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 **19** (1 mmol), 4 g compound **8** (4.5 mmol), 1.5 g Cs_2CO_3 (4.5 mmol) afforded 1.7 g **20** as a clear oil (0.59 mmol, 59% yield). ^1H 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 ($\text{M} + \text{Na}$) $^+$.

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, quenched with H_2O . The organic phase was washed with H_2O and brine successively, concentrated through rotatory 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. ^1H 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 ($\text{M} + \text{Na}$) $^+$.

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) **9**, 7.84 g (20 mmol) **21**, 0.92 g NaH (60% dispersion in mineral oil, 23 mmol) afforded 7.9 g **22** (11.3 mmol, 56% yield) as a clear oil. ^1H 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 ($\text{M} + \text{Na}$) $^+$, 243 (Ph_3C) $^+$; HRMS (ESI): Calcd for $\text{C}_{30}\text{H}_{35}\text{Br}_3\text{NaO}_4$ 720.9963 ($\text{M} + \text{Na}$) $^+$, 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) **8**, 3.1 g (4.4 mmol) **22**, 5.8 g Cs_2CO_3 (17.8 mmol) afforded 12 g **23** (3.93 mmol, 89% yield) as a clear oil. ^1H 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 ($\text{M} + \text{Na}$) $^+$.

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) drop-wise 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. ^1H 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, 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 ($\text{M} + 2\text{H}$) $^+$, 2658 ($\text{M} + \text{H}$) $^+$.

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 r.t. for 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. ^1H 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 ($\text{M} + \text{H}$) $^+$, 2821 ($\text{M} - \text{SO}_2 + \text{H}$) $^+$, 2657 ($\text{M} - \text{MsOCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{O}$) $^+$.

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), the reaction mixture was stirred at 120 °C for 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. ^1H 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 ($\text{M} + \text{Na}$) $^+$, 2904.7 ($\text{M} + \text{K}$) $^+$.

Free thiol compound 27: The procedure was the same as the synthesis of compound **8**. From 3 g (1.05 mmol) **26**, 0.12 g (3.15 mmol) LiAlH_4 afforded 2.6 g **27** (0.92 mmol, 88% yield) as a clear oil. ^1H 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 ($\text{M} + 2\text{H}$) $^+$, 2763 ($\text{M} - \text{HSCH}_2\text{CH}_2 + \text{H}$) $^+$, 2657 ($\text{M} - \text{HSCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{O}$) $^+$.

2-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethoxy)ethanol (28)—To 800 mL CH_2Cl_2 was added diethylene glycol (57 mL, 0.6 mol) and *p*-poluenesulfonic acid monohydrate (5.7 g, 30 mmol) successively. Then tetrahydropyran (27.4 mL, 0.3 mol) was added drop-wise 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 rotatory evaporation and subjected to silica gel chromatography using $\text{CH}_2\text{Cl}_2/\text{MeOH}$ as the eluent to afford compound **28** (32.5 g, 0.17 mol, 57% yield) as a clear oil. ^1H 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-2H-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, a solution of mono-tetrahydropyranyl protected diethylene glycol **28** (3.42 g, 18 mmol) in 8 mL dry diglyme was added dropwise under nitrogen atmosphere. The resulting mixture was stirred at 0 °C for 1 h and then at r.t. 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. Afterwards, the mixture was heated at reflux for overnight and then cooled to r.t. The mixture was quenched with H_2O . After solvent evaporation through rotatory evaporation, the mixture was extracted with EtOAc and washed with H_2O and brine, concentrated through rotatory 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. ^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, 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 ($\text{M} + \text{NH}_4$) $^+$, 942 ($\text{M} + \text{Na}$) $^+$, 958 ($\text{M} + \text{K}$) $^+$; HRMS (ESI): Calcd for $\text{C}_{47}\text{H}_{86}\text{NO}_{17}$ 936.5896 ($\text{M} + \text{NH}_4$) $^+$, 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 r.t. 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 rotatory 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. ^1H 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 ($\text{M} + \text{Na}$) $^+$; HRMS (ESI): Calcd for $\text{C}_{32}\text{H}_{59}\text{Br}_3\text{NO}_{11}$ 872.1618 ($\text{M} + \text{NH}_4$) $^+$, found 872.1610.

Compound 31 (^{19}F -243): To 10 mL 2-pentanone solution was added the sulfhydryl compound **27** (290 mg, 0.1 mmol), Cs_2CO_3 (49 mg, 0.15 mmol), tribromide **30** (21 mg, 0.025 mmol) successively at 0 °C under nitrogen. Then the mixture was brought to reflux at 105 °C for 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. ^1H 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 ($\text{M} + \text{Na}$) $^+$.

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. ^1H 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 ($\text{M} + \text{NH}_4$) $^+$, 755 ($\text{M} + \text{Na}$) $^+$, 771 ($\text{M} + \text{K}$) $^+$; HRMS (ESI): Calcd for $\text{C}_{20}\text{H}_{32}\text{I}_3\text{O}_5$ 732.9384 ($\text{M} + \text{H}$) $^+$, 749.9644 [$\text{M} + \text{NH}_4$] $^+$, found 732.9405, 749.9655.

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

2-((1-phenyl-16,16-bis((2-((tetrahydro-2H-pyran-2-yl)oxy)ethoxy)methyl)-2,5,8,11,14,18-hexaoxaicosan-20-yl)oxy)tetrahydro-2H-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, a solution of mono-tetrahydropyranyl-protected ethylene glycol **33** (2.34 g, 16 mmol) in 8 mL dry diglyme was added dropwise under nitrogen atmosphere. The resulting mixture was stirred at 0 °C for 1 h and then at r.t. 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. Afterwards, the mixture was kept refluxing at 165 °C overnight and then cooled to r.t. The reaction mixture was quenched with H_2O and, after solvent

evaporation, extracted with EtOAc and washed with H₂O, concentrated through rotary evaporation and subjected to silica gel chromatography using CH₂Cl₂/MeOH as the eluent to afford compound **34** (0.7 g, 0.89 mmol, 22% yield) as a clear oil. ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (126 MHz, CDCl₃) 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 + NH₄)⁺; HRMS (ESI): Calcd for C₄₁H₇₄NO₁₄ 804.5109 (M + NH₄)⁺, 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 mono-tetrahydropyranyl protected ethylene glycol **34** (260 mg, 0.33 mmol) in 5 mL of CH₂Cl₂, was added triphenylphosphine dibromide (627 mg, 1.49 mmol) at 0 °C. The resulting mixture was stirred at r.t. overnight. The mixture was diluted with CH₂Cl₂, and washed with water. The CH₂Cl₂ layer was separated, dried over Na₂SO₄ and concentrated through rotary evaporation. The residue was purified by silica gel chromatography using CH₂Cl₂/MeOH as the eluent to give compound **35** (205 mg, 0.28 mmol, 86% yield) as a yellow oil. ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (126 MHz, CDCl₃) 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 + NH₄)⁺, 743 (M + Na)⁺; HRMS (ESI): Calcd for C₂₆H₄₄Br₃O₈ 723.0566 (M + H)⁺, 740.0831 (M + NH₄)⁺, found 723.0592, 740.0802, respectively.

Reaction between compounds **35** and **27**: To 6 mL 2-pentanone was added the sulfhydryl compound **27** (160 mg, 0.057 mmol), Cs₂CO₃ (23 mg, 0.07 mmol), 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 H₂O, extracted with CH₂Cl₂, 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, ¹⁹F NMR showed a ratio 2/1 two peaks. ¹⁹F NMR (470 MHz, CDCl₃) δ –73.72 (s), –74.28 (s).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Knäpen JWJ, van der Made AW, de Wild JC, van Leeuwen PWNM, Wijkens P, Grove DM, van Koten G. *Nature*. 1994; 372:659– 663.
2. Cooper AI, Londono JD, Wignall G, McClain JB, Samulski ET, Lin JS, Dobrynin A, Rubinstein M, Burke ALC, Fréchet JMJ, DeSimone JM. *Nature*. 1997; 389:368– 371.
3. Percec V, Ahn CH, Ungar G, Yeardley DJP, Möller M, Sheiko SS. *Nature*. 1998; 391:161– 164.
4. Percec V, Glodde M, Bera TK, Miura Y, Shiyanovskaya I, Singer KD, Balagurusamy VSK, Heiney PA, Schnell I, Rapp A, Spiess HW, Hudson SD, Duan H. *Nature*. 2002; 419:384– 387. [PubMed: 12352988]

5. Criscione JM, Le BL, Stern E, Brennan M, Rahner C, Papademetris X, Fahmy TM. *Biomaterials*. 2009; 30:3946– 3955. [PubMed: 19443028]
6. Sonke S, Tomalia DA. *Adv Drug Del Rev*. 2005; 57:2106– 2129.
7. Astruc D, Boisselier E, Ornelas C. *Chem Rev*. 2010; 110:1857– 1959. [PubMed: 20356105]
8. Fréchet JMJ. *Science*. 1994; 263:1710– 1715. [PubMed: 8134834]
9. Tomalia DA. *J Nanopart Res*. 2009; 11:1251– 1310. [PubMed: 21170133]
10. Caminade AM, Turrin CO, Sutra P, Majoral JP. *Curr Opin Colloid Interface Sci*. 2003; 8:282– 295.
11. Grayson SM, Fréchet JMJ. *Chem Rev*. 2001; 101:3819– 3868. [PubMed: 11740922]
12. Bryant LH Jr, Brechbiel MW, Wu C, Bulte JWM, Herynek V, Frank JA. *J Magn Reson Imag*. 1999; 9:348– 352.
13. Wooley KL, Hawker CJ, Fréchet JMJ. *J Am Chem Soc*. 1991; 113:4252– 4261.
14. Kawaguchi T, Walker KL, Wilkins CL, Moore JS. *J Am Chem Soc*. 1995; 117:2159– 2165.
15. Eloy C. *Phys Rev Lett*. 2011; 107:258101-1–258101-5. [PubMed: 22243116]
16. Jiang ZX, Liu X, Jeong EK, Yu YB. *Angew Chem Int Ed*. 2009; 48:4755– 4758.
17. Newkome GR, Shreiner C. *Chem Rev*. 2010; 110:6338– 6442. [PubMed: 20666373]
18. Jiang ZX, Yu YB. *J Org Chem*. 2010; 75:2044– 2049. [PubMed: 20170088]
19. Uneyam, K. *Organofluorine Chemistry*. Blackwell; Ames, IA: 2006.
20. Jiang ZX, Yu YB. *J Org Chem*. 2007; 72:1464– 1467. [PubMed: 17243713]
21. Jiang Z-X, Yu YB. *Tetrahedron*. 2007; 63:3982– 3988. [PubMed: 18461118]
22. Szab D, Mohl J, Bálint A-M, Bodor A, Rábai J. *J Fluorine Chem*. 2006; 127:1496– 1504.
23. Nemes A, Tölgyesi L, Bodor A, Rábai J, Szabó D. *J Fluorine Chem*. 2010; 131:1368– 1376.
24. Xu Z, Moore JS. *Angew Chem Int Ed*. 1993; 32:1354– 1357.
25. Svergun DI. *J Appl Cryst*. 1992; 25:495– 503.
26. Svergun DI. *Biophys J*. 1999; 76:2879– 2886. [PubMed: 10354416]
27. Kozin MB, Svergun DI. *J Appl Cryst*. 2001; 34:33– 41.

0% proportionate branching: $a = 3$, $b = 1$. For G_3 ,
 $(m_0, m_1, m_2, m_3) = (3^0, 3^1, 3^2, 3^3)$, $(l_1, l_2, l_3) = (1^2, 1^1, 1^0)$

50% proportionate branching: $a = 3$, $b = 2$. For G_3 ,
 $(m_0, m_1, m_2, m_3) = (3^0, 3^1, 3^2, 3^3)$, $(l_1, l_2, l_3) = (2^2, 2^1, 2^0)$

100% proportionate branching: $a = 3$, $b = 3$. For G_3 ,
 $(m_0, m_1, m_2, m_3) = (3^0, 3^1, 3^2, 3^3)$, $(l_1, l_2, l_3) = (3^2, 3^1, 3^0)$

Figure 1.

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

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 – $0.072 \text{ \AA}^{-1}$ for ^{19}F -81, and ~ 0.021 – $0.054 \text{ \AA}^{-1}$ 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.

Figure 3. Pair-wise 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.

Scheme 1.

Convergent synthesis of fluorocarbendendrons at 75% proportionate branching ($a = 3$, $b = 2.5$, $c = 75\%$). 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.

Scheme 2.

Synthesis of two versions of ^{19}F -27 (5 and 8). The 3 $\rightarrow$ 4 step is 75% proportionate branching.

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Scheme 4.

Synthesis of ^{19}F -81 (compound **16**). The **8**→**16** step is 75% proportionate branching.

Scheme 5.

Synthesis of ¹⁹F-243 (compound **31**). The **8** → **20** (or **23**) and **27** → **31** steps are both 75% proportionate branching.

Scheme 6.

Control experiments for growing ^{19}F -243 with $I_1 = 13$ and 16, which respectively represent 25% and 50% proportionate branching for the ^{19}F -81 $\rightarrow$ ^{19}F -243 step.