Polyethylene glycols (PEGs) are the most used polymers in biomedicine, while the introduction of PEGs to targets (PEGylation) has become one of the most successful drug development strategies in the pharmaceutical industry. Until 2017, 17 PEGylated drugs had been approved by the U.S. FDA (data from www.fda.gov). In biomedicine, PEGs above 4000 Da are mainly used as PEGylation agents for biomacromolecules, while PEGs below 4000 Da, more appropriately named as oligoethylene glycols (OEGs), are extensively used as PEGylation agents, formulation additives, water-soluble and biocompatible linkers and scaffolds in nanomedicine, drug conjugates, probes, etc. The biomedical impact of PEGylation lies in the so-called “stealth” effects of PEGs, which has been regarded as the “gold-standard” for biopolymers. With the “stealth” effects, the PEGylated targets usually exhibit increased solubility and stability, reduced immunogenicity and dosing frequency, and optimized pharmacokinetics.

Although the first PEGylated drug was approved in 1990, two major issues still compromise PEGs’ biomedical application. First, as complex mixtures of homologues, the heterogeneity issue of polydisperse PEGs leads to many difficulties in PEGylation, purification, characterization, clinical application, and drug regulatory approval. Although many synthetic strategies to monodisperse PEGs (M-PEGs) have recently been developed and many benefits of M-PEGs have been clearly demonstrated, polydisperse PEGs are still overwhelmingly used in biomedicine. Second, as linear polymers with only two functional terminals, the synthesis of multifunctionalized PEGs and multiam PEGs requires long synthesis and tedious purification, which results in their low synthetic efficacy and high prices. Multifunctionalized PEGs are highly valuable linkers and scaffolds in biomedicine, while multiam PEGs have multivalence effects and superior “stealth” effects than their linear counterparts. Therefore, the development of effective and scalable synthetic strategies for monodisperse, multifunctionalized, and multiam PEGs will not only address many long-lasting issues in PEGs but also greatly promote their biomedical applications.

As the amide bond is widely used in bioconjugation due to its easy formation, biodegradability, and biocompatibility, modification of PEGs into amines or acids has become a routine strategy to functionalize PEGs. A macrocyclic sulfate (MCS) strategy for convenient mono- and dual-functionalization of M-PEGs with an amino or azide group was developed in this group, which led to many multifunctional M-PEGs. Recently, an unexpected side product was isolated when we hydrogenated octaethylene glycol monoazide into the corresponding amine, in which the azide was reduced and dimerized into a secondary amine, aza-M-PEG, with three functional groups (Scheme 1). Although reductive dimerization reactions of azides were reported by Ahn and Undheim, it has not been fully investigated on OEGs azides. Herein, we explored the reductive dimerization reaction on M-PEG monoazides and employed it as a convenient and scalable strategy to azam-M-PEGs, multifunctionalized, and multiam M-PEGs (Scheme 1). Nucleophilic ring-opening of M-OEG MCS would conveniently afford the starting materials, M-OEG monoazides, from which...
multifunctionalized aza-M-OEGs and derivatives could be prepared in one step. Further, the aza-M-OEGs could be conveniently transformed into multiarm M-OEGs in one step, of which fluorinated dendrimers, hexa-arm M-OEGs with 54 symmetrical fluorines, were designed as F-19 magnetic resonance imaging (19F MRI)-traceable biomaterials.

With the ideas in mind, the M-OEG monoazides were first prepared on multigram scales (Scheme 2). Through the nucleophilic ring-opening of tetraethylene glycol MCS 1, a series of monofunctionalized M-OEGs 2−4 were obtained, including M-OEGs monoazides 2−4, which were further transformed into methylated M-OEGs monoazides 7−11 with high efficacy.

Then, octaethylene glycol monoazide 4 was employed as the model substrate to optimize the reductive dimerization conditions. First, with methanol as a solvent and 1 atm of hydrogen gas as an H-source, easily available palladium on carbon (Pd/C) was identified from a panel of palladium catalysts as the most effective catalyst for the reaction, including PdCl2(PPh3)2, PdCl2, Pd(dbu)2, Pd[PPh3]4, Pd-(AcO)2, Pd(OH)2/C, and Pd/C (Table 1, entries 1−7).

Under the conditions, aza-M-OEGs 12 was obtained with a high 1H NMR yield of 95%. Second, no aza-M-OEGs 12 was detected when other hydrogen sources were used, including N2H4·H2O, Hantzsch ester (HEH), and HCOOH (Table 1, entries 8−10). Third, alcohols, especially methanol, were identified as the solvent of choice for the reaction (Table 1, entries 11−17). No aza-M-OEGs 12 was detected when the reaction was carried out in THF, CH3CN, DCM, acetone, or HCO2H. Finally, many fine-tunings of the reaction conditions, such as adjusting the substrate concentration, reaction temperature, and time, to further improve the yield of aza-M-OEGs 12 turned out to be unsuccessful (Table 1, entries 18−23).

Under the optimized reaction conditions, the substrate scope of this reaction was explored (Scheme 3). The functional groups (OH, OMe, and OC(CF3)3) on the other terminal of M-OEG monoazides 2−4 and 7−11 showed little influence on the yields. It is probably because they were too far away from carbon (Pd/C) was identified from a panel of palladium catalysts as the most effective catalyst for the reaction, including PdCl2(PPh3)2, PdCl2, Pd(dbu)2, Pd[PPh3]4, Pd-(AcO)2, Pd(OH)2/C, and Pd/C (Table 1, entries 1−7).

Table 1. Reaction Conditions Optimization

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<tr>
<th>entry</th>
<th>catalyst</th>
<th>H-source</th>
<th>solvent</th>
<th>yield %</th>
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<tr>
<td>1</td>
<td>PdCl2(PPh3)2</td>
<td>H2</td>
<td>MeOH</td>
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</tr>
<tr>
<td>2</td>
<td>PdCl2</td>
<td>H2</td>
<td>MeOH</td>
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<tr>
<td>3</td>
<td>Pd(dbu)2</td>
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<td>MeOH</td>
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<td>4</td>
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<td>H2</td>
<td>MeOH</td>
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<tr>
<td>5</td>
<td>Pd(AcO)2</td>
<td>H2</td>
<td>MeOH</td>
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<tr>
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*Unless otherwise noted, the reactions were carried out with 4 (0.05 mmol) and a catalyst (0.01 mmol) in 1.0 mL of solvent at rt for 12 h under a H2 atmosphere. * Determined by 1H NMR analysis using 1,3,5-trimethoxybenzene as the internal standard. * The yield of the corresponding primary amine of compound 12. * Reaction proceeded in 0.02 M. * Reaction proceeded in 0.01 M. * Reaction performed at 0 °C. * Reaction performed at 45 °C. * Reaction performed for 1 h. * Reaction proceeded for 6 h.

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Note

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the azide reaction center to exert their electronic and steric effects during this reaction. Due to the same reason, the size of M-OEGs (n = 4, 6, and 8) had little impact on the yield. On 0.5 mmol scales, aza-M-OEGs 12−19 with a variety of M-OEG sizes (n = 4, 6, 8) and terminal groups (X = OH, OMe, and OC(CF$_3$)$_3$) were prepared from a panel of M-OEG monoazides with good isolate yields.

With the reductive dimerization strategy, a variety of functionalized aza-M-OEGs were conveniently prepared (Scheme 4). First, the aza-M-OEGs 12−17 are valuable branched M-PEGylation agents for carboxylic group-containing targets, which could simultaneously introduce two M-OEG chains into targets through a biocompatible and biodegradable amide bond. To carry the chemistry one step further, easily available M-OEG monoazides 7−9 were employed to M-PEGylate an acyl chloride, BzCl, through in situ reductive dimerization−amidation, which provided M-OEG amides 20−22 in one step with good yields. Second, through in situ reductive dimerization−amidation, aza-M-OEGs-containing acids 23−25 were conveniently prepared as branched M-PEGylation agents for amines and alcohols. Third, the newly formed secondary amines in the reductive dimerization were in situ protected with CbzCl to give amides 26−31, which facilitated the further transformation of amides 26−31 into multifunctionalized M-OEGs. Finally, hexa-arm M-OEGs 32 and 33 were conveniently prepared as M-OEG "stars" through the in situ reductive dimerization−amidation.

As a promising imaging technology in biomedicine, 19F MRI provides in vivo images without background signals, tissue depth limit, and ionizing radiation. By taking advantage of M-OEGs' high biocompatibility and solubility, many fluorinated M-OEG dendrimers have been developed as novel biomaterials for 19F MRI-guided drug therapy in this group. With the reductive dimerization strategy, many valuable building blocks for the rapid construction of 19F MRI-traceable biomaterials were conveniently prepared, including amines 18 and 19, acids 34, 35, and amides 36−39 (Scheme 5). Recent perfluoro-tert-butylated amphiphilic M-PEG dendrimers were found to self-assemble onto nanoparticles and transform them into 19F MRI-traceable theranostics. Therefore, hexa-arm M-PEGs 40 and 41 with 6 perfluoro-tert-butyl groups were conveniently prepared as self-assemble and 19F MRI-traceable amphiphilic M-OEG dendrimers in one step with a high yield, respectively.

Finally, the physicochemical and biologic potential of M-OEG dendrimers 40 and 41 as 19F MRI-traceable biomaterials were investigated. First, the lipophilicity of dendrimers 40 and 41 was evaluated by n-octanol/water partition coefficients, logP, and measurements (Figure 1a). Dendrimer 41 with octaethylene glycol moieties showed dramatically higher
hydrophilicity than dendrimer 40 with tetraethylene glycol moieties (logP: 0.784 versus 1.939). Accordingly, dendrimer 41 was soluble in water, while dendrimer 40 was hardly soluble in water. Second, the self-assembly behavior of dendrimers 40 and 41 was investigated with the solvent-dependent 19F NMR (Figure 1b, from 100% methanol to 100% D2O), in which the chemical shift changes and peak broadening indicated their self-assembly in D2O. Further, dynamic light scattering (DLS) of dendrimer 41 solution indicated that dendrimer 41 self-assembled into highly homogenized nanoparticles with a diameter of 116 nm and a super low polydispersity (PDI) of 0.019 (Figure 1c). The particle size and PDI are in the optimal range of nanomedicines. Third, 19F MRI sensitivity of dendrimers 40 and 41 was evaluated by in vitro 19F MRI experiments (Figure 1d). With 54 symmetric dendrimers (Figure 1b, from 100% methanol to 100% D2O), in which the united 19F NMR signal, dendrimers 40 and 41 exhibited high 19F MRI sensitivity, which were detected at a low concentration of 0.23 mM with a short scan time of 160 s. Fourth, the biocompatibility of dendrimers 40 and 41 was evaluated by the cell viability assay (Figure 1e,f). To provide in vitro data for the future in vivo 19F MRI study in a HepG2 human liver cancer xenograft mouse model, HepG2 cells and mouse fibroblast L929 cells were chosen for the cell viability assay. High biocompatibility of dendrimers 40 and 41 was observed, while 41 exhibited even higher biocompatibility than 40 due to its higher M-OEG content. Therefore, hexa-arm M-OEG 41 was identified as a promising 19F MRI-(traceable) biomaterial with high solubility, self-assembly ability, 19F MRI sensitivity, and biocompatibility.

In conclusion, we have explored the reductive dimerization of M-OEG monoazides and developed a convenient and practical strategy to a series of valuable aza-M-OEGs in biomedicine, including M-PEGylation agents, multifunctionalized, and highly branched M-OEGs. The mild reaction conditions and convenient in situ processes facilitated the convenient preparation of a broad range of valuable aza-M-OEG derivatives. Based on the chemistry, a water-soluble, self-assemble, 19F MRI sensitive, and bio compatible hexa-arm M-OEG dendrimer was conveniently prepared in two steps as a high-performance 19F MRI-traceable biomaterial. In an era of accurate medicine, although the drawbacks of polydisperse PEGs are obvious, M-PEGs have not received a broad application in biomedicine due to their synthetic difficulty and limited availability. Our M-OEG monoazides reductive dimerization—aldimination strategy and M-OEG macrocyclic sulfates ring-opening strategy significantly simplified the multifunctionalized and multiant M-OEGs synthesis, which would greatly promote the application of M-PEGs in biomedicine and transform PEGylation into a reliable and quantitative science. The application of the hexa-arm M-OEG dendrimer as 19F MRI-traceable drug delivery vehicles is currently in progress and will be published in due course.

**EXPERIMENTAL SECTION**

Preparation of Monofunctionalized M-OEG 2–6. 2-(2-(2-(2-Azidoethoxy)ethoxy)ethoxy)ethan-1-ol (3).

To a solution of cyclic sulfate 1 (prepared according to the procedure,7a 20.0 g, 78.0 mmol) in DMF (200 mL) was added NaN3 (6.6 g, 101.5 mmol), and the resulting mixture was stirred at 80 °C overnight. After the mixture was cooled to room temperature, excess NaN3 was filtered by a pad of Celite. DMF was removed under a vacuum, and the resulting residue was dissolved in THF (150 mL). Then, water (2.8 mL) was added, and H2SO4 was added to adjust the pH to 3.0. The mixture was stirred until hydrolysis was completed. The reaction mixture was neutralized with saturated NaHCO3 solution, concentrated under a vacuum, and purified by flash chromatography on silica gel with ethyl acetate/petroleum ether (1:1) as eluents to obtain compound 2 as a clear oil (13.5 g, 79% yield). 1H NMR (400 MHz, CDCl3): δ 3.74–3.71 (m, 2H), 3.69–3.67 (m, 10H, 3.63–3.60 (m, 2H), 3.41 (t, J = 5.0 Hz, 2H).

17-Azido-3,6,9,12,15-pentaoxahexadecan-1-ol (3).10 Compound 3 was obtained from compound 1 as a light yellow oil in 83% yield by employing the same synthetic procedures as compound 2. (Compound 3 was purified by silica gel column chromatography (ethyl acetate/petroleum ether = 1:1) as a light yellow oil in 83% yield (12.0 g) by employing the same synthetic procedures as compound 2.) 1H NMR (400 MHz, CDCl3): δ 3.66–3.59 (m, 20H), 3.54–3.52 (m, 2H), 3.32 (t, J = 5.0 Hz, 2H).

23-Azido-3,6,9,12,15,18,21-heptaoxatricosan-1-ol (4).11a Compound 4 was obtained from compound 1 as a light yellow oil in 85% yield by employing the same synthetic procedures as compound 2. (Compound 4 was purified by silica gel column chromatography (MeOH/DCM = 1:60) as a light yellow oil in 85% yield (5.48 g) by employing the same synthetic procedures as compound 2.) 1H NMR (400 MHz, CDCl3): δ 3.74–3.71 (m, 2H), 3.69–3.66 (m, 26H), 3.62–3.60 (m, 2H), 3.41–3.38 (m, 2H).

14,14,14-Trifluoro-13,13-bis(trifluoromethyl)-3,6,9, 12-tetraoxide-decan-1-ol (5).10 Compound 5 was obtained from compound 1 as a light yellow oil in 89% yield by employing the same synthetic procedures as compound 2. (Compound 5 was purified by silica gel column chromatography (ethyl acetate/petroleum ether = 1:2) as a light yellow oil in 89% yield (5.60 g) by employing the same synthetic procedures as compound 2.) 1H NMR (500 MHz, CDCl3): δ 3.70–3.65 (m, 8H), 3.62–3.60 (m, 2H).

26,26,26-Trifluoro-25,25-bis(trifluoromethyl)-3,6,9, 12,15,18,21,24-octaoxahexacosan-1-ol (6). Compound 6 was obtained from compound 1 as a light yellow oil in 80% yield by employing the same synthetic procedures as compound 2. (Compound 6 was purified by silica gel column chromatography (ethyl acetate/petroleum ether = 1:1) as a light yellow oil in 80% yield (6.32 g) by employing the same synthetic procedures as compound 2.) 1H NMR (400 MHz, CDCl3): δ 4.16 (t, J = 4.9 Hz, 2H), 3.75–3.71 (m, 4H), 3.69–3.60 (m, 26H).

13C NMR (126 MHz, CDCl3): δ 116.8, 108.0, 104.7, 72.0, 71.8, 71.5, 71.2, 71.0, 70.8, 70.6, 70.4, 70.2, 69.8, 69.6, 69.4, 69.2, 68.9.
**Preparation of M-OEG Monoazides 10 and 11.**

Compound 8 was obtained from compound 3 as a light yellow oil in 87% yield by employing the same synthetic procedures as compound 7. (Compounds 8 was purified by silica gel column chromatography (ethyl acetate/petroleum ether = 1:2) as a light yellow oil in 87% yield (1.36 g) by employing the same synthetic procedures as compound 7.) 1H NMR (400 MHz, CDCl3): δ 3.69 – 3.64 (m, 28H), 3.66 – 3.57 (m, 20H), 3.55 (m, 40H), 3.49 (m, 4H). 13C{1H} NMR (101 MHz, CDCl3): δ 72.8, 72.7, 70.45, 70.35, 70.03, 70.01, 69.8, 61.3, 48.4. HRMS (ESI) m/z: [M + Na]+ calculated for C92H184NaO35, 1638.1442; found, 1638.1448.

**Preparation of M-OEG Monoazides 10 and 11.**

Di(2,5,8,11-tetraoxatridecan-13-yl)amine (15). Compound 15 was obtained from compound 17 as a light yellow oil in 73% yield by employing the same synthetic procedures as compound 12. (Compound 15 was purified by silica gel column chromatography (MeOH/DCM = 1:10) as a light yellow oil in 73% yield (124 mg) by employing the same synthetic procedures as compound 12.) 1H NMR (400 MHz, CDCl3): δ 3.59 – 3.57 (m, 4H), 3.49 (m, 4H), 3.31 (s, 6H), 2.84 (t, J = 5.3 Hz, 4H). 13C{1H} NMR (101 MHz, CDCl3): δ 71.9, 70.70, 70.56, 70.53, 70.51, 70.47, 70.40, 70.42, 70.3, 70.2, 68.6, 61.5, 48.4. HRMS (ESI) m/z: [M + Na]+ calculated for C26H55NNaO12, 568.3304; found, 568.3304.

**Di(2,5,8,11-tetraoxatridecan-13-yl)amine (15).** Compound 15 was obtained from compound 17 as a light yellow oil in 73% yield by employing the same synthetic procedures as compound 12. (Compound 15 was purified by silica gel column chromatography (MeOH/DCM = 1:10) as a light yellow oil in 73% yield (124 mg) by employing the same synthetic procedures as compound 12.) 1H NMR (400 MHz, CDCl3): δ 3.59 – 3.57 (m, 4H), 3.49 – 3.47 (m, 4H), 3.31 (s, 6H), 2.84 (t, J = 5.3 Hz, 4H). 13C{1H} NMR (101 MHz, CDCl3): δ 71.9, 70.70, 70.56, 70.53, 70.51, 70.47, 70.40, 70.42, 70.3, 70.2, 68.6, 61.5, 48.4. HRMS (ESI) m/z: [M + Na]+ calculated for C26H55NNaO12, 568.3304; found, 568.3304.

**Di(2,5,8,11-tetraoxatridecan-13-yl)amine (15).** Compound 15 was obtained from compound 17 as a light yellow oil in 73% yield by employing the same synthetic procedures as compound 12. (Compound 15 was purified by silica gel column chromatography (MeOH/DCM = 1:10) as a light yellow oil in 73% yield (124 mg) by employing the same synthetic procedures as compound 12.) 1H NMR (400 MHz, CDCl3): δ 3.59 – 3.57 (m, 4H), 3.49 – 3.47 (m, 4H), 3.31 (s, 6H), 2.84 (t, J = 5.3 Hz, 4H). 13C{1H} NMR (101 MHz, CDCl3): δ 71.9, 70.70, 70.56, 70.53, 70.51, 70.47, 70.40, 70.42, 70.3, 70.2, 68.6, 61.5, 48.4. HRMS (ESI) m/z: [M + Na]+ calculated for C26H55NNaO12, 568.3304; found, 568.3304.
light yellow oil in 71% yield (130 mg) by employing the same synthetic procedures as compound 12. 

19 H NMR (400 MHz, CDCl3): δ 4.16 (t, J = 4.9 Hz, 4H), 3.73 (t, J = 4.8 Hz, 4H), 3.69–3.61 (m, 20H), 2.86 (t, J = 5.3 Hz, 4H), 3.15

19C{1H} NMR (101 MHz, CDCl3): δ 120.4 (q, J = 293.1 Hz), 79.8 (dd, J = 59.6, 29.8 Hz), 71.1, 70.6, 70.4, 70.3, 69.4, 69.3, 49.1. 

19F NMR (376 MHz, CDCl3): δ −73.57. HRMS (ESI) m/z: [M + Na]+ calcd for C26H63F18NNaO16: 73.57. HRMS (ESI) m/z: [M + Na]+ calcd for C24H33F18NNaO8: 73.19; found, 73.57. HRMS (ESI)

19F NMR (376 MHz, CDCl3): δ −73.55. HRMS (ESI) m/z: [M + Na]+ calcd for C41H75NNaO17: 73.57; found, 73.55.

19F NMR (376 MHz, CDCl3): δ −73.55. HRMS (ESI) m/z: [M + Na]+ calcd for C22H43NNaO11: 72.15; found, 72.14.

19F NMR (376 MHz, CDCl3): δ −73.55. HRMS (ESI) m/z: [M + Na]+ calcd for C22H43NNaO11: 72.15; found, 72.14.

19F NMR (376 MHz, CDCl3): δ −73.55. HRMS (ESI) m/z: [M + Na]+ calcd for C22H43NNaO11: 72.15; found, 72.14.

19F NMR (376 MHz, CDCl3): δ −73.55. HRMS (ESI) m/z: [M + Na]+ calcd for C22H43NNaO11: 72.15; found, 72.14.

19F NMR (376 MHz, CDCl3): δ −73.55. HRMS (ESI) m/z: [M + Na]+ calcd for C22H43NNaO11: 72.15; found, 72.14.

19F NMR (376 MHz, CDCl3): δ −73.55. HRMS (ESI) m/z: [M + Na]+ calcd for C22H43NNaO11: 72.15; found, 72.14.

19F NMR (376 MHz, CDCl3): δ −73.55. HRMS (ESI) m/z: [M + Na]+ calcd for C22H43NNaO11: 72.15; found, 72.14.

19F NMR (376 MHz, CDCl3): δ −73.55. HRMS (ESI) m/z: [M + Na]+ calcd for C22H43NNaO11: 72.15; found, 72.14.

19F NMR (376 MHz, CDCl3): δ −73.55. HRMS (ESI) m/z: [M + Na]+ calcd for C22H43NNaO11: 72.15; found, 72.14.

19F NMR (376 MHz, CDCl3): δ −73.55. HRMS (ESI) m/z: [M + Na]+ calcd for C22H43NNaO11: 72.15; found, 72.14.

19F NMR (376 MHz, CDCl3): δ −73.55. HRMS (ESI) m/z: [M + Na]+ calcd for C22H43NNaO11: 72.15; found, 72.14.
HRMS (ESI) m/z: [M + Na]+ calcld for C_{26}H_{45}NNaO_{10}, 526.2623; found, 526.2618.

**Benzyl Bis(17-hydroxy-3,6,9,12,15-pentaazahepta decyl)-carbamate (27)**. Compound 27 was obtained from compound 3 as a light yellow oil in 56% yield by employing the same synthetic procedures as compound 26. (Compound 27 was purified by silica gel column chromatography (MeOH/DCM = 1:30) as a light yellow oil in 56% yield (123 mg) by employing the same synthetic procedures as compound 26.) \(^1\)H NMR (400 MHz, CDCl₃): δ 7.38–7.31 (m, 5H), 5.12 (s, 2H), 3.72 (t, J = 4.5 Hz, 4H), 3.66–3.51 (m, 44H). \(^{13}\)C{\(^1\)H} NMR (101 MHz, CDCl₃): δ 156.2, 136.8, 128.5, 128.0, 127.9, 72.7, 70.6, 70.50, 70.48, 70.45, 70.38, 70.3, 70.2, 69.7, 69.4, 67.1, 61.6, 48.1, 47.6. HRMS (ESI) m/z: [M + Na]+ calcld for C_{26}H_{45}NNaO_{10}⁺, 702.5671; found, 702.5686.

**Benzyl Bis(23-hydroxy-3,6,9,12,15,18,21-heptaoxa tricosyl)-carbamate (28)**. Compound 28 was obtained from compound 4 as a light yellow oil in 52% yield by employing the same synthetic procedures as compound 26. (Compound 28 was purified by silica gel column chromatography (MeOH/DCM = 1:30) as a light yellow oil in 52% yield (112 mg) by employing the same synthetic procedures as compound 26.) \(^1\)H NMR (400 MHz, CDCl₃): δ 7.38–7.29 (m, 5H), 5.12 (s, 2H), 3.72 (t, J = 4.5 Hz, 4H), 3.66–3.51 (m, 60H). \(^{13}\)C{\(^1\)H} NMR (101 MHz, CDCl₃): δ 156.0, 136.6, 128.4, 127.8, 127.7, 72.6, 70.39, 70.36, 70.32, 70.29, 70.2, 70.0, 69.5, 69.2, 66.9, 61.1, 48.0, 47.5. HRMS (ESI) m/z: [M + Na]+ calcld for C_{26}H_{45}NNaO_{10}⁺, 702.5671; found, 702.5686.

\(N, N'-\text{Bis}(2,5,8,11,13,16-pentaoxaoctadecan-18-yl)oxy)-N, N'-\text{N-tetra}(2,5,8,11,14,17-hexaoxanadecan-19-yl)benzene-1,3,5-tricarboxamide (33)**. Compound 33 was obtained from compound 8 as a light yellow oil in 90% yield by employing the same synthetic procedures as compound 23. (Compound 33 was purified by silica gel column chromatography (MeOH/DCM = 1:20) as a light yellow oil in 90% yield (221 mg) by employing the same synthetic procedures as compound 23.) \(^1\)H NMR (400 MHz, CDCl₃): δ 7.41 (s, 3H), 3.69–3.64 (m, 12H), 3.59–3.55 (m, 98H), 3.52–3.47 (m, 19H), 3.45–3.44 (m, 15H), 3.31 (s, 18H). \(^{13}\)C{\(^1\)H} NMR (100 MHz, CDCl₃): δ 7.41 (s, 3H), 3.69–3.64 (m, 12H), 3.59–3.55 (m, 98H), 3.52–3.47 (m, 19H), 3.45–3.44 (m, 15H), 3.31 (s, 18H). \(^{19}\)F NMR (376 MHz, CDCl₃): δ 166.99, 136.53, 125.77, 71.29, 71.26, 69.99, 69.85, 69.61, 68.52, 58.34, 58.30, 49.11, 46.64. HRMS (ESI) m/z: [M + Na]+ calcld for C_{44}H_{69}F_{18}NNaO_{19}, 1899.0912; found, 1899.0909.

**Preparation of \(^{19}\)F MRI-Traceable Biomaterials and Their Building Blocks 34–42**. \(^1\)J, \(^1\)J-Trifluoro-16-exo-15:14-trifluoro-13,13-bis(trifluoromethyl)-3,6,9,12-tetraoxatetradecyl-2,2-bis(trifluoromethyl)-3,6,9,12-tetraoxadecyl-15-azanoadecan-19-ic Acid (34)**. Compound 34 was obtained from compound 12 as a light yellow oil in 58% yield by employing the same synthetic procedures as compound 23. (Compound 34 was purified by silica gel column chromatography (MeOH/DCM = 1:40) as a light yellow oil in 58% yield (120 mg) by employing the same synthetic procedures as compound 23.) \(^1\)H NMR (400 MHz, CDCl₃): δ 4.16 (t, J = 4.8 Hz, 4H), 3.73 (t, J = 4.8 Hz, 4H), 3.68–3.56 (m, 24H), 2.79 (t, J = 6.6 Hz, 2H), 2.56 (t, J = 6.6 Hz, 2H), 1.31 (CH₃) NMR (101 MHz, CDCl₃): δ 176.1 (C=O), 173.1, 120.4 (q, J = 293.7, 292.8 Hz), 72.98 (dd, J = 60.6, 30.3 Hz), 71.71, 71.15, 70.91, 70.66, 70.64, 70.59, 70.46, 69.48, 69.46, 69.43, 69.37, 69.60, 49.11, 46.64, 30.28. \(^{19}\)F NMR (376 MHz, CDCl₃): δ −73.54. HRMS (ESI) m/z: [M + Na]+ calcld for C_{37}H_{31}F_{18}NNaO₄⁺, 1702.3512; found, 1702.3517.

\[^{19}\]F-NMR (376 MHz, CDCl₃): δ −73.55. HRMS (ESI) m/z: [M + Na]+ calcld for C_{37}H_{31}F_{18}NNaO₄⁺, 1702.3512; found, 1702.3517.

\[^{19}\]F-NMR (376 MHz, CDCl₃): δ −73.55. HRMS (ESI) m/z: [M + Na]+ calcld for C_{37}H_{31}F_{18}NNaO₄⁺, 1702.3512; found, 1702.3517.

\[^{19}\]F-NMR (376 MHz, CDCl₃): δ −73.55. HRMS (ESI) m/z: [M + Na]+ calcld for C_{37}H_{31}F_{18}NNaO₄⁺, 1702.3512; found, 1702.3517.

\[^{19}\]F-NMR (376 MHz, CDCl₃): δ −73.55. HRMS (ESI) m/z: [M + Na]+ calcld for C_{37}H_{31}F_{18}NNaO₄⁺, 1702.3512; found, 1702.3517.

\[^{19}\]F-NMR (376 MHz, CDCl₃): δ −73.55. HRMS (ESI) m/z: [M + Na]+ calcld for C_{37}H_{31}F_{18}NNaO₄⁺, 1702.3512; found, 1702.3517.
employing the same synthetic procedures as compound (MeOH/DCM = 1:60) as a light yellow oil in 63% yield (130 mg) by employing the same synthetic procedures as compound 20. (Compound 37 was purified by silica gel column chromatography (MeOH/DCM = 1:60) as a light yellow oil in 63% yield (130 mg) by employing the same synthetic procedures as compound 20.) 1H NMR (400 MHz, CDCl3): δ 7.42–7.37 (m, 3H), 4.15 (t, J = 4.9 Hz, 4H), 3.76–3.72 (m, 10H), 3.69–3.58 (m, 45H), 3.55–3.50 (m, 3H). 261H] NMR (101 MHz, CDCl3): δ 156.0, 136.7, 128.1, 127.9, 120.2 (q, J = 292.9 Hz), 79.7 (dd, J = 60.6, 30.3 Hz), 71.0, 70.54, 70.51, 70.47, 70.2, 69.6, 69.3, 69.2, 66.9, 48.0, 47.6. 19F NMR (376 MHz, CDCl3): δ = –73.53. HRMS (ESI) m/z: [M + Na]+ calcd for C49H61F18NNaO17, 962.2179; found, 962.2176.

Benzyl Bis[14,14,14-trifluoro-13,13,13-trifluoro methyl]-12-tetraoxatetradecyl]carbamate (38). Compound 38 was obtained from compound 12 as a light yellow oil in 62% yield by employing the same synthetic procedures as compound 26. (Compound 38 was purified by silica gel column chromatography (MeOH/DCM = 1:60) as a light yellow oil in 62% yield (133 mg) by employing the same synthetic procedures as compound 26.) 1H NMR (400 MHz, CDCl3): δ 7.35–7.30 (m, 3H), 5.13 (s, 2H), 4.15 (t, J = 4.9 Hz, 4H), 3.72 (t, J = 4.9 Hz, 4H), 3.67–3.52 (m, 24H). 261C] NMR (101 MHz, CDCl3): δ 156.2, 136.9, 128.5, 128.0, 127.9, 120.4 (q, J = 292.9 Hz), 79.8 (dd, J = 59.3, 30.3 Hz), 71.1, 70.7, 70.5, 70.4, 69.8, 69.5, 69.3, 67.1, 48.2, 47.7. 19F NMR (376 MHz, CDCl3): δ = –73.57. HRMS (ESI) m/z: [M + Na]+ calcd for C49H71F18NNaO18, 1284.4170; found, 1284.4169.

Benzyl Bis[26,26,26-trifluoro-25,25,25-bis(trifluoro methyl)-12-tetraoxatetradecyl]carbamate (39). Compound 39 was obtained from compound 13 as a light yellow oil in 67% yield by employing the same synthetic procedures as compound 26. (Compound 39 was purified by silica gel column chromatography (MeOH/DCM = 1:60) as a light yellow oil in 67% yield (140 mg) by employing the same synthetic procedures as compound 26.) 1H NMR (400 MHz, CDCl3): δ 7.38–7.30 (m, 3H), 5.12 (s, 2H), 4.15 (t, J = 4.9 Hz, 4H), 3.73 (t, J = 4.9 Hz, 4H), 3.69–3.61 (m, 46H), 3.58–3.51 (m, 16H). 261C] NMR (101 MHz, CDCl3): δ 172.2, 136.8, 129.1, 128.3, 126.8, 120.3 (q, J = 291.9 Hz), 79.7 (dd, J = 59.3, 28.3 Hz), 71.02, 70.97, 70.6, 70.51, 70.48, 69.3, 69.2, 69.0, 45.2. 19F NMR (376 MHz, CDCl3): δ = –73.55. HRMS (ESI) m/z: [M + Na]+ calcd for C49H84F22NNaO18+, 1314.4276; found, 1314.4274.

Compound 40 was obtained from compound 18 as a light yellow oil in 93% yield by employing the same synthetic procedures as compound 32. (Compound 40 was purified by silica gel column chromatography (MeOH/DCM = 1:30) as a light yellow oil in 93% yield (148 mg) by employing the same synthetic procedures as compound 32.) 1H NMR (400 MHz, CDCl3): δ 7.50 (s, 3H), 4.15 (t, J = 4.8 Hz, 12H), 3.76–3.58 (m, 66H), 3.52–3.51 (m, 16H). 261C] NMR (101 MHz, CDCl3): δ 170.7, 137.2, 126.4, 120.4 (q, J = 291.3 Hz), 79.8 (dd, J = 59.2, 29.5 Hz), 71.1, 70.6, 70.5, 70.4, 69.4, 69.3, 69.1, 69.0, 45.3. 19F NMR (376 MHz, CDCl3): δ = –73.54. HRMS (ESI/MSI) m/z: [M + Na]+ calcd for C50H92F20NNaO18+, 2594.5496; found, 2593.5537.

Scaled Synthesis of 40. To a solution of compound 11 (400 mg, 0.35 mmol) in dry DCM (15 mL) at 0 °C were added 1,3,5-benzenetricarbonyl trichloride (22.9 mg, 0.09 mmol) and Et3N (0.04 mmol, 0.26 mmol), and the reaction was stirred for 3 h under an Ar atmosphere. The reaction mixture was poured into water and extracted with DCM. The organic layers were washed with saturated NH4Cl, dried over Na2SO4, and concentrated in a vacuum. The product was isolated by column chromatography on silica gel to give 41 as a light yellow oil (259 mg, 83% yield) with MeOH/DCM (1:30) as eluents.

ASSOCIATED CONTENT
Supporting Information
The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c00331.

Experimental procedures, compounds characterizations, copies of 1H/19F/13C NMR spectra, and mass spectra (PDF)

AUTHOR INFORMATION
Corresponding Authors
Zhigang Yang — Hubei Province Engineering and Technology Research Center for Fluorinated Pharmaceuticals and School of Pharmaceutical Sciences, Wuhan University, Wuhan 430071, China; orcid.org/0000-0002-4857-4850; Email: zgyang@whu.edu.cn
Zhong-Xing Jiang — Hubei Province Engineering and Technology Research Center for Fluorinated Pharmaceuticals and School of Pharmaceutical Sciences, Wuhan University, Wuhan 430071, China; orcid.org/0000-0003-2601-4366; Email: zxjiang@whu.edu.cn

Authors
Jing Zhang — Hubei Province Engineering and Technology Research Center for Fluorinated Pharmaceuticals and School of Pharmaceutical Sciences, Wuhan University, Wuhan 430071, China
Yuan Yuan — Hubei Province Engineering and Technology Research Center for Fluorinated Pharmaceuticals and School of Pharmaceutical Sciences, Wuhan University, Wuhan 430071, China
Yu Li — State Key Laboratory of Magnetic Resonance and Atomic and Molecular Physics, National Center for Magnetic Resonance in Wuhan, Wuhan Institute of Physics and Mathematics, Innovative Academy of Precision Measurement Science and Technology, Chinese Academy of Sciences, Wuhan 430071, China
Hao Yang — Hubei Province Engineering and Technology Research Center for Fluorinated Pharmaceuticals and School of Pharmaceutical Sciences, Wuhan University, Wuhan 430071, China
Huaibin Zhang — Hubei Province Engineering and Technology Research Center for Fluorinated Pharmaceuticals and School of Pharmaceutical Sciences, Wuhan University, Wuhan 430071, China
Shizhen Chen — State Key Laboratory of Magnetic Resonance and Atomic and Molecular Physics, National Center for Magnetic Resonance in Wuhan, Wuhan Institute of Physics and Mathematics, Innovative Academy of Precision Measurement Science and Technology, Chinese Academy of Sciences, Wuhan 430071, China
The authors declare no competing financial interest.

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# REFERENCES


