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Synthesis of Branched Monodisperse Oligoethylene Glycols and ^{19}F MRI-Traceable Biomaterials through Reductive Dimerization of Azides

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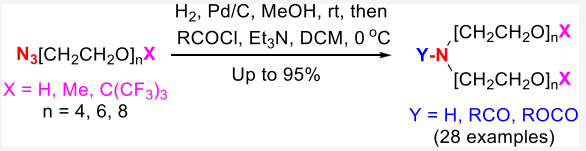
ABSTRACT: Multifunctionalized and branched M-OEGs represent valuable PEGylation agents, linkers, and scaffolds in biomedicine. However, the tedious synthesis limited their availability and application. We herein present an azide reductive dimerization method for the convenient synthesis of aza-M-OEGs and derivatives, which provides easy access to a variety of multifunctionalized and branched M-OEGs in one step. With this method, hexa-arm M-OEGs with 54 symmetrical fluorines were synthesized in two steps as a water-soluble, self-assemble, ^{19}F MRI sensitive, and biocompatible dendritic biomaterial.



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.[1] 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.[2]

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.[3] Although many synthetic strategies to monodisperse PEGs (M-PEGs) have recently been developed[4] and many benefits of M-PEGs have been clearly demonstrated,[5] polydisperse PEGs are still overwhelmingly used in biomedicine. Second, as linear polymers with only two functional terminals, the synthesis of multifunctionalized PEGs and multiarm 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 multiarm PEGs have multivalence effects and superior "stealth" effects than their linear counterparts.[6] Therefore, the development of effective and scalable synthetic strategies for monodisperse, multifunctionalized, and multiarm 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 routing strategy to functionalize PEGs. A macrocyclic sulfate (MCS) strategy for convenient mono- and dual-functionalization of M-OEGs with an amino or azide group was developed in this group,[7] which led to many multifunctional "smart" biomaterials.[8] 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-OEG, with three functional groups (Scheme 1). Although reductive dimerization reactions of azides were reported by Ahn and Undheim, respectively,[9] it has not been fully investigated on OEGs azides.[10] Herein, we explored the reductive dimerization reaction on M-OEG monoazides and employed it as a convenient and scalable strategy to aza-M-OEGs, multifunctionalized, and multiarm M-OEGs (Scheme 1). Nucleophilic ring-opening of M-OEG MCS would conveniently afford the starting materials, M-OEG monoazides, from which

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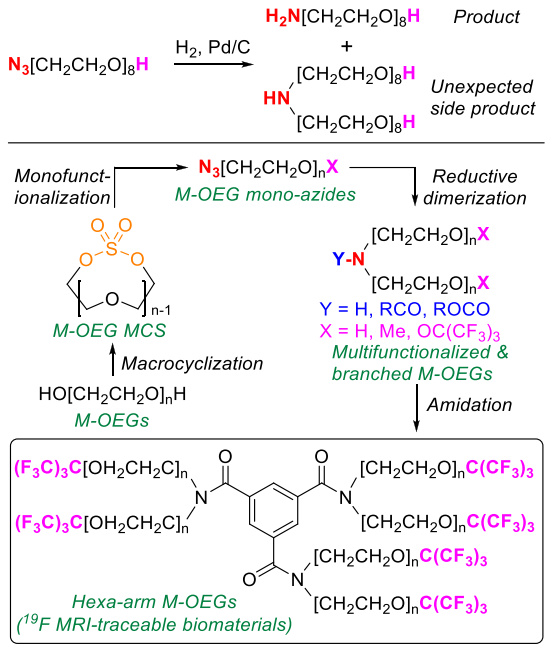
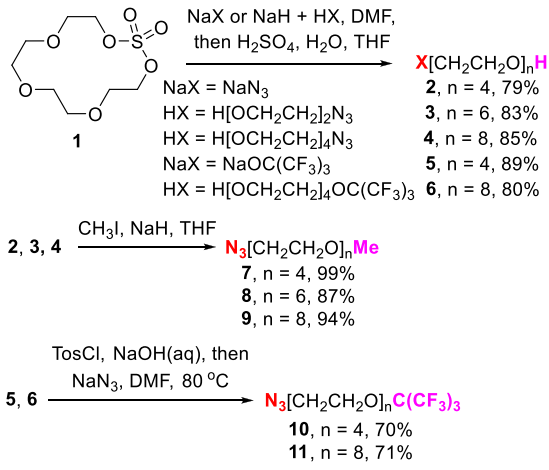
Scheme 1. Synthesis of Multifunctionalized and Multiarm M-OEGs through Reductive Dimerization



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 (^{19}F MRI)-traceable biomaterials.

With the ideas in mind, the M-OEG monoazides were first prepared on multigram scales (Scheme 2). Through the

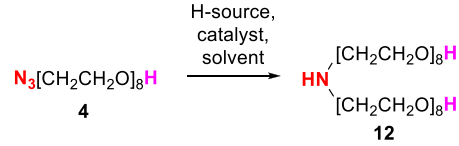
Scheme 2. Synthesis of M-OEG Monoazides 2−4 and 7−11



nucleophilic ring-opening of tetraethylene glycol MCS **1**, a series of monofunctionalized M-OEGs **2**−**6** were obtained, including M-OEGs monoazides **2**−**4**, which were further transformed into methylated M-OEGs monoazides **7**−**9** and perfluoro-*tert*-butylated M-OEGs monoazides **10** and **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 $PdCl_2(PPh_3)_2$, $PdCl_2$, $Pd(dba)_2$, $Pd(PPh_3)_4$, $Pd(AcO)_2$, $Pd(OH)_2/C$, and Pd/C (Table 1, entries 1−7).

Table 1. Reaction Conditions Optimization[a]



entry	catalyst	H-source	solvent	yield %[b] (yield %[c])
1	$PdCl_2(PPh_3)_2$	H_2	MeOH	
2	$PdCl_2$	H_2	MeOH	28 (56)
3	$Pd(dba)_2$	H_2	MeOH	37 (81)
4	$Pd(PPh_3)_4$	H_2	MeOH	22 (64)
5	$Pd(AcO)_2$	H_2	MeOH	15 (32)
6	$Pd(OH)_2/C$	H_2	MeOH	18 (72)
7	Pd/C	H_2	MeOH	95
8	Pd/C	$N_2H_4{\cdot}H_2O$	MeOH	
9	Pd/C	HCOOH	MeOH	
10	Pd/C	HEH	MeOH	
11	Pd/C	H_2	EtOH	55 (14)
12	Pd/C	H_2	*i*PrOH	63 (30)
13	Pd/C	H_2	THF	
14	Pd/C	H_2	CH_3CN	
15	Pd/C	H_2	DCM	
16	Pd/C	H_2	acetone	
17	Pd/C	H_2	HCO_2H	
18[d]	Pd/C	H_2	MeOH	82
19[e]	Pd/C	H_2	MeOH	65
20[f]	Pd/C	H_2	MeOH	88 (17)
21[g]	Pd/C	H_2	MeOH	32 (48)
22[h]	Pd/C	H_2	MeOH	23 (16)
23[i]	Pd/C	H_2	MeOH	71 (14)

[a]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 H_2 atmosphere. [b]Determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as the internal standard. [c]The yield of the corresponding primary amine of compound **12**. [d]Reaction proceeded in 0.02 M. [e]Reaction proceeded in 0.01 M. [f]Reaction performed at 45 °C. [g]Reaction performed at 0 °C. [h]Reaction proceeded for 1 h. [i]Reaction proceeded for 6 h.

Under the conditions, aza-M-OEGs **12** was obtained with a high ^{1}H NMR yield of 95%. Second, no aza-M-OEGs **12** was detected when other hydrogen sources were used, including $N_2H_4{\cdot}H_2O$, 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, CH_3CN, DCM, acetone, or HCO_2H. 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 $OC(CF_3)_3$) 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

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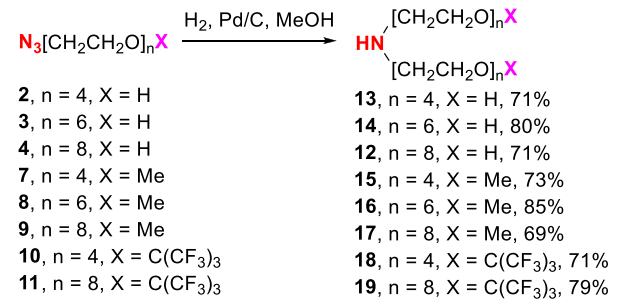
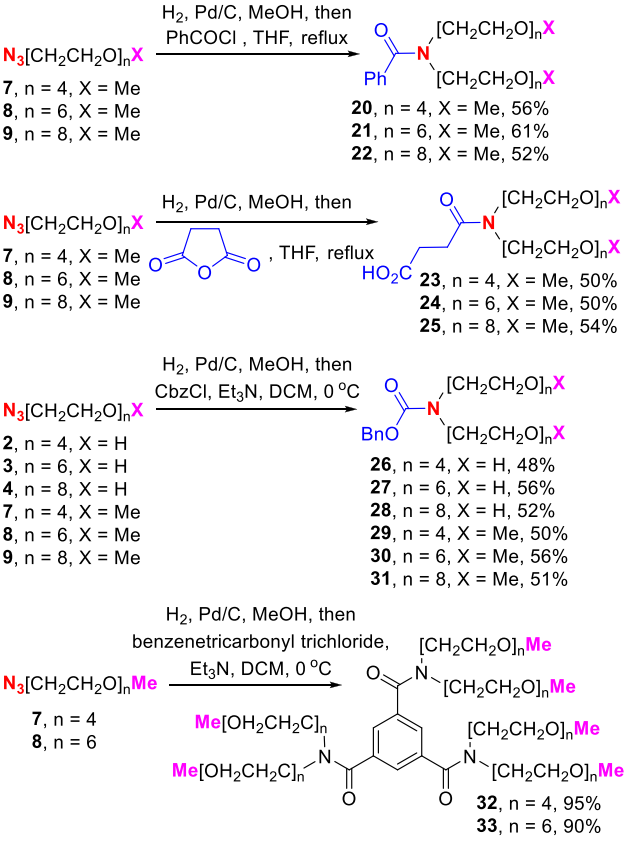
Scheme 3. Reductive Dimerization of M-OEG Monoazides to aza-M-OEGs



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-

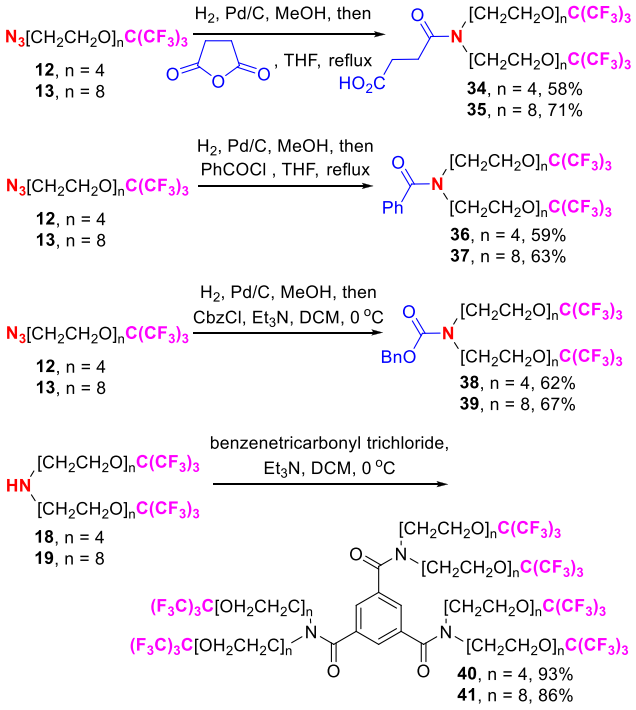
Scheme 4. Synthesis of Functionalized and Multiarm M-OEGs through Reductive Dimerization–Amidation of M-OEG Monoazides



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, ^{19}F 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 ^{19}F MRI-guided drug therapy in this group.[8] With the reductive dimerization strategy, many valuable building blocks for the rapid construction of ^{19}F MRI-traceable biomaterials were conveniently prepared, including amines **18** and **19**, acids **34**, **35**, and amides **36**–**39** (Scheme 5). Recently, perfluoro-

Scheme 5. Synthesis of ^{19}F MRI-Traceable Biomaterials and Their Building Blocks



tert-butylated amphiphilic M-PEG dendrimers were found to self-assemble onto nanoparticles and transform them into ^{19}F MRI-traceable theranostics.[8b−d] Therefore, hexa-arm M-PEGs **40** and **41** with 6 perfluoro-*tert*-butyl groups were conveniently prepared as self-assemble and ^{19}F 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 ^{19}F 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

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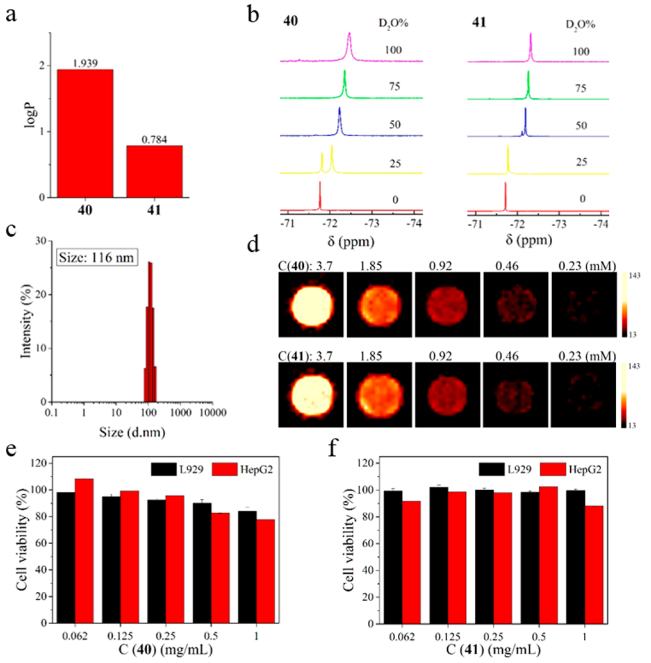

Figure 1. (a) *n*-Octanol/water partition coefficients logP, (b) solvent-dependent ^{19}F NMR, (c) DLS, (d) *in vitro* ^{19}F MRI, (e, f) and cell viability assay of M-OEG dendrimers **40** and **41**.

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 ^{19}F NMR (Figure 1b, from 100% methanol to 100% D_2O), in which the chemical shift changes and peak broadening indicated their self-assembly in D_2O. 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, ^{19}F MRI sensitivity of dendrimers **40** and **41** was evaluated by *in vitro* ^{19}F MRI experiments (Figure 1d). With 54 symmetric fluorines and a united ^{19}F NMR signal, dendrimers **40** and **41** exhibited high ^{19}F 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* ^{19}F 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 ^{19}F MRI-traceable biomaterial with high solubility, self-assembly ability, ^{19}F 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* process facilitated the convenient preparation of a broad range of valuable aza-M-OEG derivatives. Based on the chemistry, a water-soluble, self-assemble, ^{19}F MRI sensitive, and biocompatible hexa-arm M-OEG dendrimer was conveniently prepared in two steps as a high-performance ^{19}F 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−amidation strategy and M-OEG macrocyclic sulfates ring-opening strategy significantly simplified the multifunctionalized and multiarm 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 ^{19}F 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 (**2**).*[7a,11a] To a solution of cyclic sulfate **1** (prepared according to the procedures,[7a] 20.0 g, 78.0 mmol) in DMF (200 mL) was added NaN_3 (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 NaN_3 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 H_2SO_4 was added to adjust the pH to 3.0. The mixture was stirred until hydrolysis was completed. The reaction mixture was neutralized with saturated $NaHCO_3$ 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). ^{1}H NMR (400 MHz, $CDCl_3$): 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-pentaoxaheptadecan-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**.) ^{1}H NMR (400 MHz, $CDCl_3$): 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**.) ^{1}H NMR (400 MHz, $CDCl_3$): 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-tetraoxatetradecan-1-ol (**5**).*[7a] 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**.) ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.16 (t, J = 4.8 Hz, 2H), 3.75−3.72 (m, 4H), 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**.) ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.16 (t, J = 4.9 Hz, 2H), 3.75−3.71 (m, 4H), 3.69−3.60 (m, 26H). ^{13}C NMR (126 MHz,

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$CDCl_3$): δ 120.3 (q, J = 293.6 Hz), 79.7 (dd, J = 60.5, 30.2 Hz), 72.5, 71.7, 71.0, 70.57, 70.55, 70.53, 70.51, 70.50, 70.49, 70.47, 70.3, 69.3, 69.2, 67.0, 61.6. HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{20}H_{33}F_9NaO_9^+$: 611.1873; found, 611.1864.

Preparation of M-OEG Monoazides 7−9. *13-Azido-2,5,8,11-tetraoxatridecane (**7**).*[11b] A solution of compound **2** (5.00 g, 22.81 mmol) in anhydrous THF (10 mL) was added to a suspension of NaH (60% in mineral oil, 1.09 g, 27.37 mmol), and the resulting suspension was stirred for 1 h. Iodomethane (2.84 mL, 45.61 mmol) was added dropwise to the reaction mixture, which was stirred for an additional 45 min. After cooling to 0 °C in an ice bath, the reaction mixture was quenched slowly with H_2O and extracted with DCM. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under a vacuum to give a yellow oil, which was purified by column chromatography on silica gel with ethyl acetate/petroleum ether (1:3) as eluents to provide compound **7** as a light yellow oil (5.28 g, 99% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 3.69−3.64 (m, 12H), 3.57−3.55 (m, 2H), 3.40 (t, J = 5.2 Hz, 2H), 3.38 (s, 3H).

*19-Azido-2,5,8,11,14,17-hexaoxanonadecane (**8**).*[11b] Compound **8** was obtained from compound **3** as a light yellow oil in 87% yield by employing the same synthetic procedures as compound **7**. (Compound **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, $CDCl_3$): δ 3.69−3.63 (m, 20H), 3.56−3.54 (m, 2H), 3.40 (t, J = 5.1 Hz, 2H), 3.38 (s, 3H).

*25-Azido-2,5,8,11,14,17,20,23-octaoxapentacosane (**9**).*[11c] Compound **9** was obtained from compound **4** as a light yellow oil in 94% yield by employing the same synthetic procedures as compound **7**. (Compound **9** was purified by silica gel column chromatography (ethyl acetate/petroleum ether = 1:2) as a light yellow oil in 94% yield (1.93 g) by employing the same synthetic procedures as compound **7**.) ^1H NMR (400 MHz, $CDCl_3$): δ 3.69−3.63 (m, 28H), 3.56−3.54 (m, 2H), 3.40 (t, J = 5.1 Hz, 2H), 3.38 (s, 3H).

Preparation of M-OEG Monoazides 10 and 11. *14-Azido-1,1,1-trifluoro-2,2-bis(trifluoromethyl)-3,6,9,12-tetraoxatetradecane (**10**).*[11d] To a solution of alcohol **5** (5.0 g, 12.1 mmol) in THF (25 mL) was added a solution of NaOH (1.70 g, 42.5 mmol) in water (6.8 mL). After the solution was cooled to 0 °C, a solution of *p*-toluenesulfonyl chloride (2.77 g, 14.6 mmol) in THF (15 mL) was slowly added, and the resulting mixture was stirred overnight at rt. The reaction mixture was concentrated under a vacuum. The residue was dissolved in water (30 mL) and extracted with DCM. The organic layers were concentrated under a vacuum to obtain crude sulfonate as a light yellow oil. To a solution of crude sulfonate in DMF (27 mL) was added NaN_3 (1.18 g, 18.2 mmol), and the resulting mixture was stirred at 80 °C for 4 h. Then, the reaction mixture containing excess NaN_3 was filtered through a pad of Celite, concentrated under a vacuum, dissolved in water (50 mL), and extracted with DCM. The combined organic layers were dried over anhydrous Na_2SO_4, concentrated under a vacuum, and purified by flash chromatography on silica gel with ethyl acetate/petroleum ether (1:9) as eluents to obtain azide **10** as a light yellow oil (4.2 g, 70% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 4.16 (t, J = 4.9 Hz, 2H), 3.74 (t, J = 4.8 Hz, 2H), 3.70−3.65 (m, 10H), 3.39 (t, J = 5.0 Hz, 2H). ^{19}F NMR (376 MHz, $CDCl_3$): δ −73.55.

*26-Azido-1,1,1-trifluoro-2,2-bis(trifluoromethyl)-3,6,9,12,15,18,-21,24-octaoxahexacosane (**11**).*[11e] Compound **11** was obtained from compound **6** as a light yellow oil in 71% yield by employing the same synthetic procedures as compound **10**. (Compound **11** was purified by silica gel column chromatography (ethyl acetate/petroleum ether = 1:2) as a light yellow oil in 71% yield (3.70 g) by employing the same synthetic procedures as compound **10**.) ^1H NMR (400 MHz, $CDCl_3$): δ 4.15 (t, J = 4.9 Hz, 2H), 3.73 (t, J = 4.9 Hz, 2H), 3.69−3.63 (m, 26H), 3.39 (t, J = 5.1 Hz, 2H). ^{19}F NMR (376 MHz, $CDCl_3$): δ −73.57.

Synthesis of aza-M-OEGs 12−19. *3,6,9,12,15,18,21,27,30,33,-36,39,42,45-Tetradecaoxa-24-azaheptatetracontane-1,47-diol (**12**).* Under an atmosphere of H_2, a mixture of compound **4** (200.0 mg, 0.51 mmol) and Pd/C (10% on carbon, 107.6 mg, 0.10 mmol) in dry MeOH (10 mL) was stirred at rt overnight. The mixture was filtrated through a pad of Celite, and the filtrate was concentrated. The crude product was purified by column chromatography on silica gel to give **12** as a light yellow oil (130 mg, 71% yield) with MeOH/DCM (1:10) as eluents. ^1H NMR (400 MHz, $CDCl_3$): δ 3.74−3.71 (m, 4H), 3.67−3.60 (m, 56H), 2.89 (t, J = 5.3 Hz, 4H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 72.8, 72.7, 70.61, 70.56, 70.53, 70.50, 70.47, 70.4, 70.33, 70.26, 70.2, 68.0, 61.5, 48.3. HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{32}H_{67}NNaO_{16}^+$, 744.4352; found, 744.4346.

*3,6,9,15,18,21-Hexaoxa-12-azatricosane-1,23-diol (**13**).* Compound **13** was obtained from compound **2** as a light yellow oil in 71% yield by employing the same synthetic procedures as compound **12**. (Compound **13** was purified by silica gel column chromatography (MeOH/DCM = 1:10) as a light yellow oil in 71% yield (120 mg) by employing the same synthetic procedures as compound **12**.) ^1H NMR (400 MHz, $CDCl_3$): δ 3.73−3.71 (m, 4H), 3.67−3.59 (m, 24H), 2.84 (t, J = 5.1 Hz, 4H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 72.8, 72.7, 70.45, 70.35, 70.03, 70.01, 69.8, 61.3, 48.8. HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{16}H_{35}NNaO_8^+$, 392.2255; found, 392.2252.

*3,6,9,12,15,21,24,27,30,33-Decaoxa-18-azapentatriac ontane-1,35-diol (**14**).* Compound **14** was obtained from compound **3** as a light yellow oil in 80% yield by employing the same synthetic procedures as compound **12**. (Compound **14** was purified by silica gel column chromatography (MeOH/DCM = 1:10) as a light yellow oil in 80% yield (142 mg) by employing the same synthetic procedures as compound **12**.) ^1H NMR (400 MHz, $CDCl_3$): δ 3.66−3.64 (m, 5H), 3.62−3.57 (m, 31H), 3.51 (dt, J = 17.6, 5.1 Hz, 8H), 2.82 (t, J = 5.1 Hz, 4H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 72.7, 70.60, 70.56, 70.53, 70.51, 70.47, 70.44, 70.42, 70.3, 70.2, 68.6, 61.5, 48.4. HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{24}H_{51}NNaO_{12}^+$, 568.3303; found, 568.3304.

*Di(2,5,8,11-tetraoxatridecan-13-yl)amine (**15**).* Compound **15** was obtained from compound **7** 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 = 1:30) as a light yellow oil in 73% yield (124 mg) by employing the same synthetic procedures as compound **12**.) ^1H NMR (400 MHz, $CDCl_3$): δ 3.66−3.59 (m, 24H), 3.56 (dd, J = 5.8, 3.5 Hz, 4H), 3.38 (s, 6H), 2.84 (t, J = 5.3 Hz, 4H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 71.9, 70.53, 70.51, 70.47, 70.4, 70.32, 70.27, 59.0, 49.1. HRMS (ESI) *m/z*, $[M + Na]^+$ calcd for $C_{18}H_{39}NNaO_8^+$: 420.2568; found, 420.2563.

*Di(2,5,8,11,14,17-hexaoxanonadecan-19-yl)amine (**16**).* Compound **16** was obtained from compound **8** as a light yellow oil in 85% yield by employing the same synthetic procedures as compound **12**. (Compound **16** was purified by silica gel column chromatography (MeOH/DCM = 1:30) as a light yellow oil in 85% yield (152 mg) by employing the same synthetic procedures as compound **12**.) ^1H NMR (400 MHz, $CDCl_3$): δ 3.59−3.57 (m, 40H), 3.49−3.47 (m, 4H), 3.31 (s, 6H), 2.84 (t, J = 5.2 Hz, 4H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 71.9, 70.6, 70.52, 70.50, 70.48, 70.45, 70.41, 70.2, 69.7, 59.0, 48.8. HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{26}H_{55}NNaO_{12}^+$, 596.3616; found, 596.3615.

*Di(2,5,8,11,14,17,20,23-octaoxapentacosan-25-yl)amine (**17**).* Compound **17** was obtained from compound **9** as a light yellow oil in 69% yield by employing the same synthetic procedures as compound **12**. (Compound **17** was purified by silica gel column chromatography (MeOH/DCM = 1:20) as a light yellow oil in 69% yield (126 mg) by employing the same synthetic procedures as compound **12**.) ^1H NMR (400 MHz, $CDCl_3$): δ 3.59−3.53 (m, 56H), 3.51−3.48 (m, 4H), 3.31 (d, J = 5.3 Hz, 6H), 2.79 (t, J = 5.2 Hz, 4H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 71.7, 70.4, 70.3, 70.11, 70.07, 58.8, 48.9. HRMS (ESI) *m/z*, $[M + Na]^+$ calcd for $C_{34}H_{71}NNaO_{16}^+$: 772.4665; found, 772.4661.

*Bis(14,14,14-trifluoro-13,13-bis(trifluoromethyl)-3,6,9,12-tetraoxatetradecyl)amine (**18**).* Compound **18** was obtained from compound **10** as a light yellow oil in 71% yield by employing the same synthetic procedures as compound **12**. (Compound **18** was purified by silica gel column chromatography (MeOH/DCM = 1:40) as a

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light yellow oil in 71% yield (130 mg) by employing the same synthetic procedures as compound **12**.) ^{1}H NMR (400 MHz, $CDCl_3$): 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). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): 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. ^{19}F NMR (376 MHz, $CDCl_3$): δ −73.57. HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{24}H_{33}F_{18}NNaO_8^+$, 828.1811; found, 828.1812.

For the scaled synthesis of **18**, under an atmosphere of H_2, a mixture of compound **10** (1.0 g, 2.3 mmol) and Pd/C (10% on carbon, 487 mg, 0.46 mmol) in dry MeOH (46 mL) was stirred at rt overnight. The mixture was filtrated through a pad of Celite, and the filtrate was concentrated. The crude product was purified by column chromatography on silica gel to give **12** as a light yellow oil (570 mg, 62% yield) with MeOH/DCM (1:40) as eluents.

*Bis(26,26,26-trifluoro-25,25-bis(trifluoromethyl)-3,6,9,12,-15,18,21,24-octaoxahexacosyl)amine (**19**).* Compound **19** was obtained from compound **11** as a light yellow oil in 79% yield by employing the same synthetic procedures as compound **12**. (Compound **19** was purified by silica gel column chromatography (MeOH/DCM = 1:30) as a light yellow oil in 79% yield (149 mg) by employing the same synthetic procedures as compound **12**.) ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.16 (t, J = 4.9 Hz, 4H), 3.74 (t, J = 4.8 Hz, 4H), 3.68−3.59 (m, 52H), 2.84 (t, J = 5.3 Hz, 4H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 120.3 (q, J = 293.3 Hz), 79.7 (dd, J = 59.6, 29.6 Hz), 71.0, 70.61, 70.57, 70.53, 70.49, 70.4, 70.3, 69.4, 69.3, 49.1. ^{19}F NMR (376 MHz, $CDCl_3$): δ −73.55. HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{40}H_{65}F_{18}NNaO_{16}^+$, 1180.3908; found, 1180.3909.

*Scaled Synthesis of **19**.* Under an atmosphere of H_2, a mixture of compound **11** (1.6 g, 2.6 mmol) and Pd/C (10% on carbon, 555 mg, 0.52 mmol) in dry MeOH (52 mL) was stirred at rt overnight. The mixture was filtrated through a pad of Celite, and the filtrate was concentrated. The crude product was purified by column chromatography on silica gel to give **12** as a light yellow oil (985 mg, 66% yield) with MeOH/DCM (1:30) as eluents.

Preparation of Functionalized and Multiarm M-OEGs 20−33. *N,N-Di(2,5,8,11-tetraoxatridecan-13-yl)benzamide (**20**).* Under an atmosphere of H_2, a mixture of compound 7 (200.0 mg, 0.86 mmol) and Pd/C (10% on carbon, 182.5 mg, 0.17 mmol) in dry MeOH (17 mL) was stirred at rt overnight. The mixture was filtrated through a pad of Celite, and the filtrate was concentrated. Under argon atmosphere, the crude product was stirred in dry DCM. After the mixture was cooled to 0 °C in an ice bath, Et_3N (0.25 mL, 1.81 mmol) and benzoyl chloride (0.12 mL, 1.03 mmol) were added, and the mixture was stirred for 1 h at 0 °C and another 2 h at rt. The reaction mixture was poured into water and extracted with DCM. The combined organic layers were washed with saturated NH_4Cl, dried over anhydrous Na_2SO_4, and then filtered and concentrated in a vacuum. The crude product was purified by column chromatography on silica gel to give **20** a light yellow oil (120 mg, 56% yield) with MeOH/DCM (1:40) as eluents. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43−7.36 (m, 5H), 3.76 (s, 4H), 3.66−3.58 (m, 20H), 3.55−3.50 (m, 8H), 3.37 (s, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 172.3, 136.8, 129.2, 128.3, 126.9, 71.9, 70.59, 70.55, 70.5, 69.1, 59.0, 49.6, 45.3. HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{25}H_{43}NNaO_9^+$, 524.2830; found, 524.2828.

*N,N-Di(2,5,8,11,14,17-hexaoxanonadecan-19-yl) benzamide (**21**).* Compound **21** was obtained from compound **8** as a light yellow oil in 61% yield by employing the same synthetic procedures as compound **20**. (Compound **21** was purified by silica gel column chromatography (MeOH/DCM = 1:40) as a light yellow oil in 61% yield (128 mg) by employing the same synthetic procedures as compound **20**.) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35−7.29 (m, 5H), 3.69 (s, 3H), 3.60−3.53 (m, 35H), 3.48−3.45 (m, 10H), 3.30 (s, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 172.2, 136.7, 129.1, 128.2, 126.8, 71.8, 70.5, 70.45, 70.38, 69.0, 58.9, 49.5, 45.2. HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{33}H_{59}NNaO_{13}^+$, 700.3879; found, 700.3872.

*N,N-Di(2,5,8,11,14,17,20,23-octaoxapentacosan-25-yl)-benzamide (**22**).* Compound **22** was obtained from compound **9** as a light yellow oil in 52% yield by employing the same synthetic procedures as compound **20**. (Compound **22** was purified by silica gel column chromatography (MeOH/DCM = 1:40) as a light yellow oil in 52% yield (108 mg) by employing the same synthetic procedures as compound **20**.) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42−7.37 (m, 5H), 3.76 (s, 4H), 3.66−3.59 (m, 50H), 3.56−3.52 (m, 10H), 3.38 (s, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 172.3, 136.7, 129.2, 128.3, 126.8, 71.8, 70.5, 70.4, 69.0, 59.0, 49.6, 45.2. HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{41}H_{75}NNaO_{17}^+$, 876.4927; found, 876.4919.

*15-Oxo-14-(2,5,8,11-tetraoxatridecan-13-yl)-2,5,8,11-tetraoxa-14-azaoctadecan-18-oic Acid (**23**).* Under an atmosphere of H_2, a mixture of compound 7 (200.0 mg, 0.86 mmol) and Pd/C (10% on carbon, 182.5 mg, 0.17 mmol) in dry MeOH (17 mL) was stirred at rt overnight. The mixture was filtrated through a pad of Celite, and the filtrate was concentrated. Under an argon atmosphere, a solution of the crude product and phthalic anhydride (85.8 mg, 0.86 mmol) in 10 mL of dry THF was refluxed in an oil bath for 3 h. The solvent was evaporated under reduced pressure, and the residue was dissolved in DCM. The solution was washed with saturated NH_4Cl, dried over anhydrous Na_2SO_4, and then filtered and concentrated in a vacuum. After removal of the solvent, the crude product was purified by column chromatography on silica gel to give **23** a light yellow oil (106 mg, 50% yield) with MeOH/DCM (1:20) as eluents. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.65−3.54 (m, 32H), 3.38 (s, 6H), 2.77 (t, J = 6.5 Hz, 2H), 2.65 (t, J = 6.5 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 175.6, 173.0, 71.9, 70.8, 70.6, 70.54, 70.47, 70.42, 70.37, 70.3, 69.4, 67.0, 59.0, 58.9 49.0, 46.4, 29.9, 28.1. HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{22}H_{43}NNaO_{11}^+$, 520.2728; found, 520.2728.

*20-(2,5,8,11,14,17-Hexaoxanonadecan-19-yl)-21-oxo-2,5,8,11,14,17-hexaoxa-20-azatetracosan-24-oic Acid (**24**).* Compound **24** was obtained from compound **8** as a light yellow oil in 50% yield by employing the same synthetic procedures as compound **23**. (Compound **24** was purified by silica gel column chromatography (MeOH/DCM = 1:30) as a light yellow oil in 50% yield (105 mg) by employing the same synthetic procedures as compound **23**.) ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.59−3.53 (m, 42H), 3.51−3.48 (m, 6H), 3.31 (s, 6H), 2.69 (t, J = 6.6 Hz, 2H), 2.58 (t, J = 6.6 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 175.3, 172.8, 71.8, 70.7, 70.5, 70.44, 70.41, 70.38, 70.32, 70.28, 70.2, 69.3, 68.9, 58.9, 48.9, 46.3, 29.8, 28.1. HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{30}H_{59}NNaO_{15}^+$, 696.3777; found, 696.3773.

*27-Oxo-26-(2,5,8,11,14,17,20,23-octaoxapentacosan-25-yl)-2,5,8,11,14,17,20,23-octaoxa-26-azatriacontan-30-oic Acid (**25**).* Compound **25** was obtained from compound **9** as a light yellow oil in 54% yield by employing the same synthetic procedures as compound **23**. (Compound **25** was purified by silica gel column chromatography (MeOH/DCM = 1:20) as a light yellow oil in 54% yield (112 mg) by employing the same synthetic procedures as compound **23**.) ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.68−3.58 (m, 58H), 3.57−3.54 (m, 6H), 3.38 (s, 6H), 2.78 (t, J = 6.6 Hz, 2H), 2.65 (t, J = 6.6 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 174.9, 173.3, 72.0, 70.9, 70.7, 70.63, 70.60, 70.57, 70.5, 70.4, 69.4, 69.0, 59.1, 49.1, 46.5, 30.2, 28.3. HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{38}H_{75}NNaO_{19}^+$, 872.4825; found, 872.4824.

*Benzyl Bis(2-(2-(2-(2-hydroxyethoxy)ethoxy) ethoxy)ethyl)-carbamate (**26**).* Under an atmosphere of H_2, the mixture of compound **2** (200.0 mg, 0.86 mmol) and Pd/C (10% on carbon, 182.5 mg, 0.17 mmol) in dry MeOH (17 mL) was stirred at rt overnight. The mixture was filtrated through a pad of Celite, and the filtrate was concentrated. Under an argon atmosphere, the crude product was stirred in dry DCM, and Et_3N (0.15 mL, 1.03 mmol) and CbzCl (0.12 mL, 0.86 mmol) were added in the mixture at 0 °C; the mixture was stirred for 3 h. The reaction mixture was poured into water and extracted with DCM. The combined organic layers were dried over anhydrous Na_2SO_4 and then filtered and concentrated in a vacuum. The crude product was purified by column chromatography on silica gel to give **26** as a clear oil (111 mg, 48% yield) with MeOH/DCM (1:30) as eluents. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36−7.31 (m, 5H), 5.12 (s, 2H), 3.72 (t, J = 4.5 Hz, 4H), 3.65−3.53 (m, 28H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 156.2, 136.8, 128.6, 128.04, 127.95, 72.7, 70.7, 70.6, 70.5, 70.4, 69.8, 69.5, 67.2, 61.7, 48.3, 47.7.

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HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{24}H_{41}NNaO_{10}^+$, 526.2623; found, 526.2618.

*Benzyl Bis(17-hydroxy-3,6,9,12,15-pentaoxahepta 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, $CDCl_3$): 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). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): 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: $[M + Na]^+$ calcd for $C_{32}H_{57}NNaO_{14}^+$, 702.3671; found, 702.3668.

*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, $CDCl_3$): 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). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): 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, 61.4, 48.0, 47.5. HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{40}H_{73}NNaO_{18}^+$, 878.4720; found, 878.4713.

*Benzyl Di(2,5,8,11-tetraoxatridecan-13-yl) carbamate (**29**).* Compound **29** was obtained from compound **7** as a light yellow oil in 50% yield by employing the same synthetic procedures as compound **26**. (Compound **29** was purified by silica gel column chromatography (MeOH/DCM = 1:40) as a light yellow oil in 50% yield (109 mg) by employing the same synthetic procedures as compound **26**.) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35−7.30 (m, 5H), 5.12 (s, 2H), 3.65−3.51 (m, 32H), 3.37 (s, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 156.2, 136.8, 128.5, 128.0, 127.9, 72.0, 70.65, 70.60, 70.56, 70.5, 70.4, 69.7, 69.5, 67.1, 59.1, 48.2, 47.7. HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{26}H_{45}NNaO_{10}^+$, 554.2936; found, 554.2938.

*Benzyl Di(2,5,8,11,14,17-hexaoxanonadecan-19-yl)carbamate (**30**).* Compound **30** was obtained from compound **8** as a light yellow oil in 56% yield by employing the same synthetic procedures as compound **26**. (Compound **30** was purified by silica gel column chromatography (MeOH/DCM = 1:40) as a light yellow oil in 56% yield (124 mg) by employing the same synthetic procedures as compound **26**.) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38−7.31 (m, 5H), 5.12 (s, 2H), 3.67−3.63 (m, 36H), 3.58−3.52 (m, 12H), 3.38 (s, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 156.4, 136.7, 128.6, 128.1, 127.9, 72.0, 70.63, 70.59, 70.57, 70.5, 70.4, 69.8, 69.6, 67.3, 59.1, 48.2, 47.6. HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{34}H_{61}NNaO_{14}^+$, 730.3984; found, 730.3981.

*Benzyl Di(2,5,8,11,14,17,20,23-octaoxapentacosan-25-yl)-carbamate (**31**).* Compound **31** was obtained from compound **9** as a light yellow oil in 51% yield by employing the same synthetic procedures as compound **26**. (Compound **31** was purified by silica gel column chromatography (MeOH/DCM = 1:30) as a light yellow oil in 51% yield (110 mg) by employing the same synthetic procedures as compound **26**.) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38−7.30 (m, 5H), 5.12 (s, 2H), 3.68−3.51 (m, 64H), 3.38 (s, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 156.1, 136.7, 128.4, 127.9, 127.8, 71.8, 70.5, 70.45, 70.39, 70.2, 69.6, 69.3, 67.0, 58.9, 48.0, 47.5. HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{42}H_{77}NNaO_{18}^+$, 906.5033; found, 906.5031.

*N^1,N^1-Bis(2-(4-(2-methoxyethoxy)butoxy)ethoxy)-N^3,N^3,N^5,N^5-tetra(2,5,8,11-tetraoxatridecan-13-yl) benzene-1,3,5-tricarboxamide (**32**).* To a solution of compound **7** (167 mg, 0.50 mmol) in dry DCM (15 mL) at 0 °C were added 1,3,5-benzenetricarbonyl trichloride (33.4 mg, 0.13 mmol) and Et_3N (0.05 mL, 0.38 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 NH_4Cl, dried over Na_2SO_4, and concentrated in a vacuum. The product was isolated by column chromatography on silica gel to give **32** as a light yellow oil (127 mg, 95% yield) with MeOH/DCM (1:20) as eluents. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (s, 3H), 3.69−3.67 (m, 12H), 3.59−3.44 (m, 84H), 3.31 (s, 18H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 170.4, 137.0, 126.2, 71.7, 70.39, 70.36, 70.3, 70.1, 68.9, 68.8, 58.8, 49.6, 45.1. HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{63}H_{117}N_3NaO_{27}^+$, 1370.7767; found, 1370.7767

*N^1,N^1-Bis((2,5,8,13,16-pentaoxaoctadecan-18-yl)oxy)-N^3,N^3,N^5,N^5-tetra(2,5,8,11,14,17-hexaoxanonadecan-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 **32**. (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 **32**.) ^{1}H NMR (400 MHz, $CDCl_3$): 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). $^{13}C\{^1H\}$ ^{1}H NMR (400 MHz, $CDCl_3$): 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 NMR (101 MHz, $CDCl_3$): δ 169.9, 136.5, 125.7, 71.29, 71.26, 69.9, 69.85, 69.81, 68.5, 68.2, 58.34, 58.30, 49.1, 44.6. HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{87}H_{165}N_3NaO_{39}^+$, 1899.0912; found, 1899.0909.

Preparation of ^{19}F MRI-Traceable Biomaterials and Their Building Blocks 34−41. *1,1,1-Trifluoro-16-oxo-15-(14,14,14-trifluoro-13,13-bis (trifluoromethyl)-3,6,9,12-tetraoxatetradecyl)-2,2-bis (trifluoromethyl)-3,6,9,12-tetraoxa-15-azanonadecan-19-oic 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, $CDCl_3$): 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), 2.65 (t, J = 6.6 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 176.3, 173.1, 120.4 (q, J = 293.7, 292.8 Hz), 79.8 (dd, J = 60.6, 30.3 Hz), 71.17, 71.15, 70.9, 70.71, 70.66, 70.64, 70.59, 70.4, 69.48, 69.46, 69.43, 69.37, 69.0, 49.1, 46.6, 30.0, 28.2. ^{19}F NMR (376 MHz, $CDCl_3$): δ −73.54. HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{28}H_{37}F_{18}NNaO_{11}^+$, 928.1971; found, 928.1970.

*1,1,1-Trifluoro-28-oxo-27-(26,26,26-trifluoro-25,25-bis-(trifluoromethyl)-3,6,9,12,15,18,21,24-octaoxahexa cosyl)-2,2-bis-(trifluoromethyl)-3,6,9,12,15,18,21,24-octaoxa-27-azahentriacontan-31-oic Acid (**35**).* Compound **35** was obtained from compound **13** as a light yellow oil in 71% yield by employing the same synthetic procedures as compound **23**. (Compound **35** was purified by silica gel column chromatography (MeOH/DCM = 1:30) as a light yellow oil in 71% yield (145 mg) by employing the same synthetic procedures as compound **23**.) ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.16 (t, J = 4.9 Hz, 4H), 3.73 (t, J = 4.9 Hz, 4H), 3.69−3.57 (m, 56H), 2.79 (t, J = 6.5 Hz, 2H), 2.65 (t, J = 6.5 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 175.2, 173.1, 120.3 (q, J = 293.0 Hz), 79.8 (dd, J = 62.1, 30.3 Hz), 71.1, 70.8, 70.62, 70.58, 70.54, 70.51, 70.49, 70.4, 69.4, 69.3, 69.0, 49.0, 46.5, 30.0, 28.2. ^{19}F NMR (376 MHz, $CDCl_3$): δ −73.55. HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{44}H_{69}F_{18}NNaO_{19}^+$, 1280.4069; found, 1280.4066.

*N,N-Bis(14,14,14-trifluoro-13,13-bis(trifluoromethyl)-3,6,9,12-tetraoxatetradecyl)benzamide (**36**).* Compound **36** was obtained from compound **12** as a light yellow oil in 59% yield by employing the same synthetic procedures as compound **20**. (Compound **36** was purified by silica gel column chromatography (MeOH/DCM = 1:60) as a light yellow oil in 59% yield (126 mg) by employing the same synthetic procedures as compound **20**.) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42−7.36 (m, 5H), 4.15 (t, J = 4.8 Hz, 4H), 3.77−3.50 (m, 28H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 172.4, 136.9, 129.3, 128.4, 126.9, 120.4 (q, J = 293.8 Hz), 79.9 (dd, J = 60.6, 30.3 Hz), 71.2, 70.70, 70.68, 70.5, 69.5, 69.4, 69.2, 49.7, 45.4. ^{19}F NMR (376 MHz, $CDCl_3$): δ −73.47. HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{31}H_{37}F_{18}NNaO_9^+$, 932.2073; found, 932.2073.

*N,N-Bis(26,26,26-trifluoro-25,25-bis(trifluoro methyl)-3,6,9,12,15,18,21,24-octaoxahexacosyl) benzamide (**37**).* Compound **37** was obtained from compound **13** as a light yellow oil in

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63% yield 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**.) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42−7.37 (m, 5H), 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, 5H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 156.0, 136.7, 128.4, 127.9, 127.8, 120.2 (q, J = 292.9 Hz), 79.7 (dd, J = 60.6, 30.3 Hz), 71.0, 70.54, 70.51, 70.47, 70.4, 70.2, 69.6, 69.3, 69.2, 66.9, 48.0, 47.6.; ^{19}F NMR (376 MHz, $CDCl_3$): δ −73.53. HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{47}H_{69}F_{18}NNaO_{17}^+$, 1284.4170; found, 1284.4169.

*Benzyl Bis(14,14,14-trifluoro-13,13-bis(trifluoro methyl)-3,6,9,12-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**.) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35−7.30 (m, 5H), 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). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 156.2, 136.9, 128.5, 128.0, 127.9, 120.4 (q, J = 292.9 Hz), 79.8 (dd, J = 59.6, 30.3 Hz), 71.1, 70.7, 70.5, 70.4, 69.8, 69.5, 69.3, 67.1, 48.2, 47.7. ^{19}F NMR (376 MHz, $CDCl_3$): δ −73.57. HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{32}H_{39}F_{18}NNaO_{10}^+$, 962.2179; found, 962.2176.

*Benzyl Bis(26,26,26-trifluoro-25,25-bis(trifluoro methyl)-3,6,9,12,15,18,21,24-octaoxahexacosyl)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**.) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38−7.30 (m, 5H), 5.12 (s, 2H), 4.15 (t, J = 4.9 Hz, 4H), 3.73 (t, J = 4.9 Hz, 5H), 3.69−3.61 (m, 46H), 3.58−3.51 (m, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): 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, 49.6, 45.2. ^{19}F NMR (376 MHz, $CDCl_3$): δ −73.55. HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{48}H_{71}F_{18}NNaO_{18}^+$, 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**.) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (s, 3H), 4.15 (t, J = 4.8 Hz, 12H), 3.76−3.58 (m, 68H), 3.52−3.51 (m, 16H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 170.7, 137.2, 126.4, 120.4 (q, J = 293.1 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, 49.8, 45.3. ^{19}F NMR (376 MHz, $CDCl_3$): δ −73.54. HRMS (MAIDI) m/z: $[M + Na]^+$ calcd for $C_{81}H_{99}F_{54}N_3NaO_{27}^+$, 2594.5496; found, 2593.5537.

*Scaled Synthesis of **40**.* To a solution of compound **11** (400 mg, 0.50 mmol) in dry DCM (15 mL) at 0 °C were added 1,3,5-benzenetricarbonyl trichloride (33.0 mg, 0.12 mmol) and Et_3N (0.05 mL, 0.37 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 NH_4Cl, dried over Na_2SO_4, and concentrated in a vacuum. The product was isolated by column chromatography on silica gel to give **41** as a light yellow oil (292 mg, 92% yield) with MeOH/DCM (1:30) as eluents.

Compound **41** was obtained from compound **19** as a light yellow oil in 86% yield by employing the same synthetic procedures as compound **32**. (Compound **41** was purified by silica gel column chromatography (MeOH/DCM = 1:30) as a light yellow oil in 86% yield (135 mg) by employing the same synthetic procedures as compound **32**.) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (s, 3H), 4.08 (t, J = 4.9 Hz, 12H), 3.68−3.65 (m, 20H), 3.62−3.51 (m, 145H), 3.45−3.43 (m, 15H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 170.5, 137.2, 126.3, 120.3 (m, J = 293.9 Hz), 79.7 (dd, J = 59.4, 30.0 Hz), 71.0, 70.59, 70.55, 70.5, 69.3, 69.2, 69.0, 49.7, 45.3. ^{19}F NMR (376 MHz, $CDCl_3$): δ −73.47. HRMS (MAIDI) m/z: $[M + Na]^+$ calcd for $C_{129}H_{195}F_{54}N_3NaO_{51}^+$, 3651.1787; found, 3651.0635.

*Scaled Synthesis of **41**.* 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 Et_3N (0.04 mL, 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 NH_4Cl, dried over Na_2SO_4, 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 ^{1}H/^{19}F/^{13}C NMR spectra, and mass spectra (PDF)

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Notes

The authors declare no competing financial interest.

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