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Development of a Scalable Process for α-Amino-ω-methoxyl-dodecaethylene glycol

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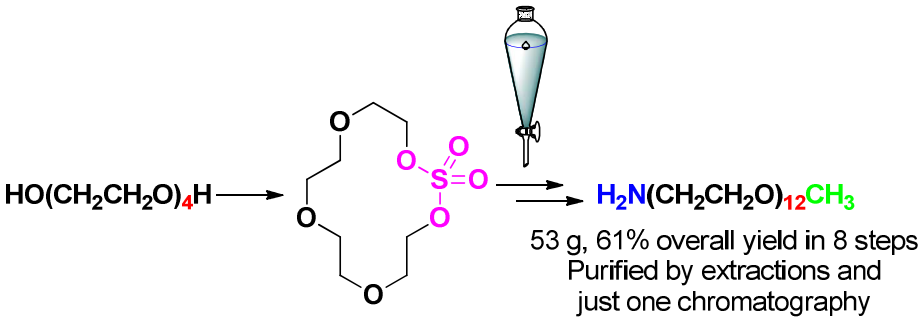


ABSTRACT: We developed a process for the efficient and scalable preparation of heterofunctionalized dodecaethylene glycol from the readily available tetraethylene glycol and its macrocyclic sulfate. By employing the benzyl group as both a protective group and a separative tag, multiple chromatographic separations were avoided. With this method, α-amino-ω-methyl-dodecaethylene glycol was prepared on a 53-g scale with high purity, 61% overall yield in eight steps and one chromatography separation.

Key words: Monodisperse polyethylene glycols, Macrocyclic sulfate, Heterofunctionalized, Separative tag, Scalable preparation

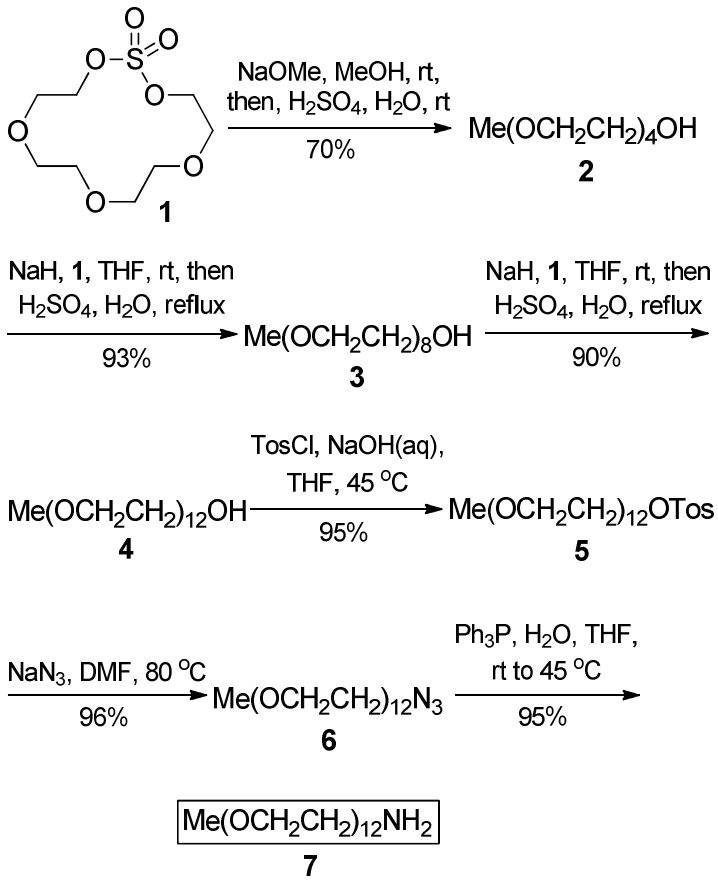
INTRODUCTION

Polyethylene glycols (PEGs) are biocompatible polymers with a broad range of applications. For example, PEGs are the most frequently used polymers in biopharmaceutics to improve solubility and stability, reduce immunogenicity and dosing frequency, and prolong blood circulation.[1-4] However, the heterogeneity of PEGs dramatically complicates their applications.[5-8] To this end, monodisperse PEGs (M-PEGs) are highly valuable because they can avoid the heterogeneity issue associated with regular PEGs.

Even though M-PEGs are structurally simple molecules, preparing M-PEGs on a large scale, especially in heterofunctionalized forms, is far from straightforward. Regular PEGs are very complex mixtures of homologs as a result of polymerization. As such, it is nearly impossible to obtain M-PEGs through accurately monitoring the polymerization process and selectively isolating a specific component from regular PEGs. Unfortunately, the only commercially available starting materials for M-PEGs synthesis are monodisperse building blocks with one to four ethylene glycol units. Because of this, M-PEGs synthesis involves long synthesis and tedious purification. Although many synthetic strategies have been developed for M-PEGs since 1939,[9-19] the application of M-PEGs is severely hampered by challenges in the synthesis of long or heterofunctionalized M-PEGs, convenient purification of the intermediates and products, and, especially, large scale preparation of M-PEGs. Thus, it is of great importance to develop efficient and scalable processes for M-PEGs, especially fully functionalized M-PEGs which can be directly used in biomedical research and development.

Recently, heterofunctionalized monodisperse dodecaethylene glycol **7** was employed as a solubility enhancer and self-assembly modulator in ^{19}F magnetic resonance and fluorescence

dual imaging agents in this group.[20] Through the iteratively nucleophilic ring-opening of macrocyclic sulfate **1**, the amine **7** was efficiently prepared on a 43-g scale with a 51% overall yield in six steps (Scheme 1).[20] The macrocyclic sulfate strategy highlighted the synthesis with high efficacy by avoiding the application of protection and activation groups, as well as high versatility in manipulating the functionalities and length of functionalized M-PEGs.[19,20,21] However, chromatographic purification in each synthetic step severely increased the cost and hampered the large scale preparation of amine **7**. Therefore, a scalable synthesis of **7** without using chromatography is of great importance. It is noteworthy that, besides amine **7**, there are numerous highly valuable functionalized M-PEGs with various lengths and ending groups, such as thiol, alkynyl, carboxylic, etc. Because their synthesis share similar synthetic intermediates and length extension strategies as amine **7**, the synthesis for amine **7** can be easily expanded to them.



Scheme 1. Previous synthesis of heterofunctionalized M-PEGs **7**.

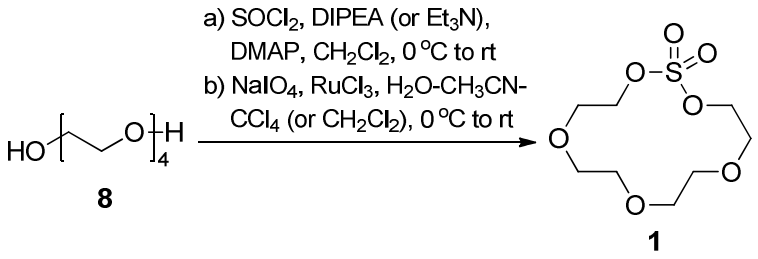
To develop a scalable process for M-PEGs and their derivatives, the purification of intermediates and products is the most challenging issue. PEGs are highly water soluble and high polar oils (for low molecular weight oligoethylene glycols) or waxes (for high molecular weight polyethylene glycols) that can hardly be purified by either crystallization or normal phase silica gel purification. In order to purify M-PEGs and their synthetic intermediates, a few methods have been developed, such as reverse phase chromatography, gel permission chromatography, and precipitation.[9-18] However, both reverse phase chromatography and gel permission chromatography are very expensive and non-scalable. Although precipitation is a straightforward method, it is only fit for high molecular weight M-PEGs. In addition, it can

hardly provide M-PEGs with high purity. In our previous macrocyclic sulfate-based M-PEGs synthesis, a convenient purification process was developed by removing most starting materials and impurities through reverse extraction of the highly water soluble sulfate intermediates.[19-21] But chromatography purification was still required to remove the remaining impurities. Herein, we report an efficient and scalable process for heterofunctionalized M-PEGs through convenient purification of M-PEGs and their synthetic intermediates.

RESULTS AND DISCUSSION

Amine **7** was selected as a representative heterofunctionalized M-PEGs to illustrate the synthetic efficacy with previous synthesis (Scheme 1) as a comparison. The synthesis started with the macrocyclization of tetraethylene glycol **8** on multi-hundred-gram scales. Previously, macrocyclic sulfate **1** was prepared on a 290-g scale in a 55% yield with analytic grade solvents and reagents (Table 1). Without purifying the macrocyclic sulfite intermediate, macrocyclic sulfate **1** was isolated through recrystallization. To develop a cost-effective and green process for **1**, industrial grade solvents and reagents were used directly and environmentally unfriendly carbon tetrachloride was replaced by dichloromethane. Lower yields of **1** were obtained with industrial grade dichloromethane, acetonitrile, and diisopropylethylamine. During the oxidation, higher yields of **1** were obtained with industrial grade dichloromethane as a co-solvent when the reaction was carried out with extended reaction time. Little difference was found when diisopropylethylamine was replaced with much cheaper triethylamine. Dilution of **8** during the macrocyclization could slightly improve the yield of **1**. In terms of cost-effectiveness, the preparation of **1** with industrial grade reagents and solvents at higher concentration (Table 1, entry 4) is highly preferred.

Table 1. Macrocyclization of tetraethylene glycol.



	Solvents and reagents[a]	Conc. of **8** (mol/L)	**1** (g)	Yield (%)
1	Analytic grade	0.06	290	55
2	Industrial grade	0.06	288	37
3	Industrial grade	0.06	190	41
4[b]	Industrial grade	0.06	261	44
5[b]	Industrial grade	0.04	210	46

a. Solvents and reagents are CH_2Cl_2, Et_3N, DIPEA, CH_3CN, and CCl_4.

b. Et_3N and CH_2Cl_2 were used instead of DIPEA and CCl_4.

It is very interesting to point out that a small amount of a side product **9** (1-2% yields) was isolated from the crystallization mother liquid of **1** when tetraethylene glycol **8** was macrocyclized at 0.06 mol/L. Little difference in $^1H/^{13}C$ NMR between **1** and **9** was observed. While, a mass peak, which is twice the molecular weight of **1**, was found in the mass spectrum of **9**. To illustrate the structure of **9**, X-ray crystal structures of **1** and **9** were obtained. Surprisingly, compound **9** is a 28-membered macrocyclic sulfate which is actually a monocyclic dimer of **1** (Figure 1). No catenane-like side product was isolated, which is a common side product in macrocyclization. It is noteworthy that **9** was not observed when **8** was macrocyclized at 0.04 mol/L. Therefore, higher concentration for this macrocyclization actually

promotes the formation of even larger ring-sized dimers instead of intermolecular catenane-like side product.

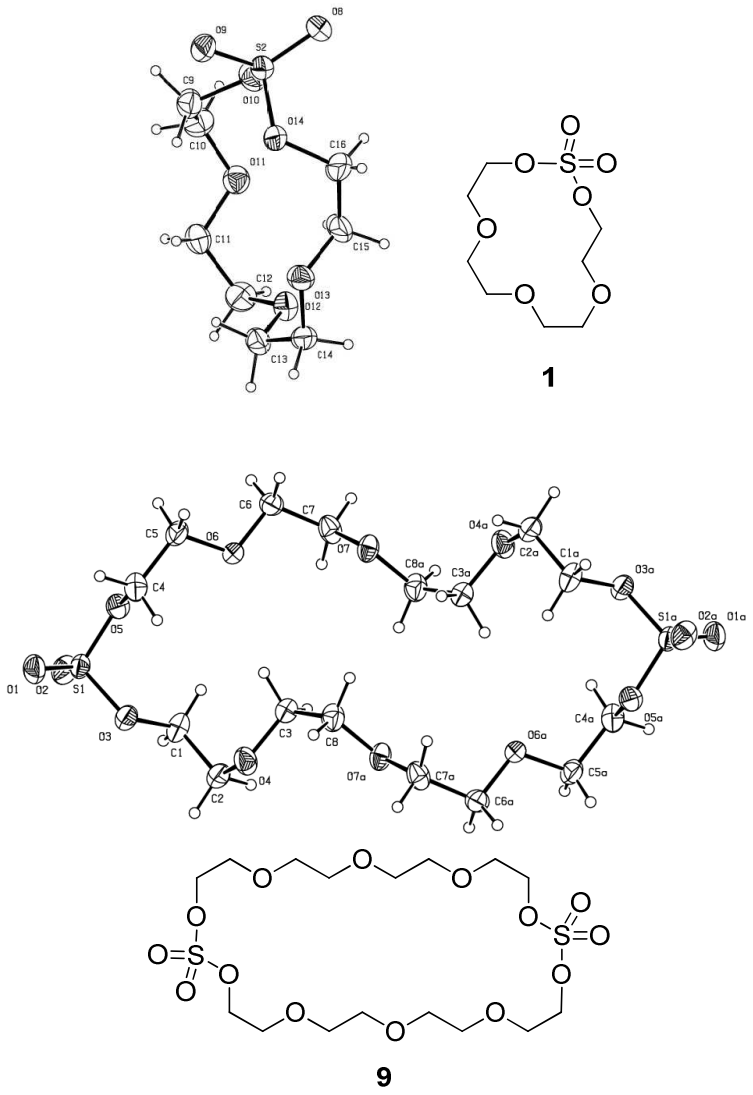
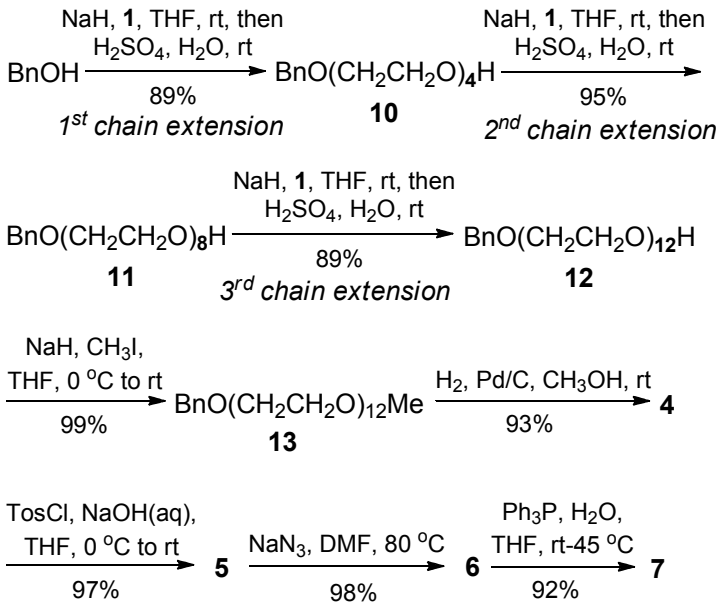


Figure 1. Single-crystal X-ray structures of macrocyclic sulfates **1** and **9**

To avoid column chromatographic purification in the following synthetic steps, the development of straightforward purification methods, like extraction and recrystallization, is of great importance. Since M-PEGs and their synthetic intermediates are usually viscous oils or waxes at room temperature, liquid phase extraction is the method of choice. Although most impurities can be removed by selectively reverse-extraction of the sulfate intermediates, a

column chromatography is used to remove aqueous soluble impurities after hydrolysis of the sulfate intermediates. Another selective extraction of the products into organic phase while leaving impurities in aqueous phase may be an alternative for column chromatography. To improve the efficiency of extraction, some fine tunes on the chemical structures and thus the partition of product and impurities between water and organic solvents are necessary.

With these ideas in mind, benzyl group was then employed as both a separative tag and a protective group. From benzyl alcohol, iterative nucleophilic ring-opening of the macrocyclic sulfate **1** provided monobenzylated dodecaethylene glycol **12**. In these synthetic steps, the monobenzylated M-PEGs **10**-**12** were selectively extracted into diisopropyl ether or dichloromethane while these highly aqueous soluble impurities were left in aqueous phase. As expected, through a selective extraction of the sulfate intermediates into aqueous phase followed by another selective extraction of the hydrolyzed products into organic phase, **10**-**12** were conveniently purified without column chromatography. After methylation of **12** using iodomethane, heterofunctionalized dodecaethylene glycol **13** with low polarity was conveniently purified by flash chromatography on regular silica gel. Hydrogenolysis of the benzyl group afforded monomethylated dodecaethylene glycol **4** without purification. After tosylation of **4**, nucleophilic substitution of tosylate **5** with sodium azide afforded azide **6** with high yields over two steps. Because no side product was observed during these reactions, simple extraction provided **5** and **6** with high purities. Reduction of azide **6** with triphenyl phosphine and water afforded amine **7** which was conveniently purified by selectively extraction **7** into aqueous phase. Finally, amine **7** was prepared from **1** on a 53-g scale with a 61% overall yield in eight steps. $^{1}H/^{13}C$ NMR and mass spectra indicated that high purities of amine **7** and its synthetic intermediates were achieved by convenient extractions and one chromatography.



Scheme 2. Modified synthesis of heterofunctionalized M-PEGs **7**.

This modified synthesis of **7** provided a good example for preparing heterofunctionalized M-PEGs on a large scale with high efficiency. In comparison with previous synthesis, most of the column chromatographic purifications were successfully replaced with extractions, which dramatically simplified the product purification. Although two additional synthetic steps on benzyl group manipulations were introduced, the overall yield was improved from 51% to 61%. Furthermore, the cost-effectiveness was significantly improved by the application of industrial grade solvents and reagents and the replacement of environmentally unfriendly carbon tetrachloride with dichloromethane during the preparation of macrocyclic sulfate.

CONCLUSION

In this work, we successfully demonstrated a scalable and efficient process for heterofunctionalized M-PEGs which was highlighted by low cost, environmental friendliness and convenient purification of the intermediates and product. As a class of highly valuable

compounds with a broad range of applications, M-PEGs suffer from limited availability due to their synthetic difficulties. This process may promote the scalable production of M-PEGs and their derivatives and therefore wide applications of M-PEGs in biomedicine and beyond.

EXPERIMENTAL SECTION

General information. Unless otherwise noted, solvents and reagents were purchased from commercial suppliers and used as received. NMR spectra were recorded on a 400 MHz instrument. Chemical shift values are reported in ppm. ^{1}H NMR spectra were referenced to tetramethylsilane and ^{13}C NMR spectra were referenced to the corresponding deuterated solvent peak. Multiplicities are denoted as follows: s = singlet, t = triplet, m = multiplet. High resolution mass spectra were recorded on a 4.7 Tesla FTMS.

General procedure for the preparation of Macrocyclic sulfate 1. A 50 L jacketed glass reactor was charged with tetraethylene glycol (349.6 g, 1.8 mol), triethylamine (868.6 g, 8.6 mol), DMAP (11.0 g, 0.09 mol) and CH_2Cl_2 (45.0 L). To the stirring solution at 0 ^{o}C was added a solution of $SOCl_2$ (428.3 g, 3.6 mol, in 2.0 L of CH_2Cl_2) over a period of 3 h. After the addition, the reaction was warmed to 25 ^{o}C and monitored by TLC until the complete consumption of tetraethylene glycol. Water (5.0 L) was then added to quench the reaction. The organic lay was collected, washed with water (10.0 L, three times) and concentrated under reduced pressure to provide the macrocyclic sulfite intermediate (243.0 g) as brownish oil. It is noteworthy that, when the reaction mixture volume was far more than 50 L, the macrocyclization reaction was carried out in portions with a 50 L jacketed reactor. Then, to a 50 L jacketed reactor was added the macrocyclic sulfite intermediate (243.0 g, 1.0 mol), CH_2Cl_2 (2.0 L), CH_3CN (2.0 L) and water (3.0 L). After cooled to 0 ^{o}C, $NaIO_4$ (259.6 g, 1.2

mol) and $RuCl_3 \cdot 3H_2O$ (1.3 g, 5.1 mmol) were added. The stirring reaction mixture was gradually warmed to 25 ^oC and monitored by TLC. Upon the completely consumption of the macrocyclic sulfite, the reaction mixture was filtered through a pad of Celite and the solution was washed with water. After removal of the solvent under vacuum, recrystallization of the residue with methanol (0.8 L) at room temperature gave the macrocyclic sulfate **1** (210.0 g, 46%) as a white crystal. Macrocyclic sulfate **1**: ^1H NMR ($CDCl_3$, 400 MHz) δ 3.60-3.68 (m, 4H), 3.68-3.74 (m, 4H), 3.85 (t, J = 6.0 Hz, 4H), 4.48 (t, J = 6.0 Hz, 4H).

Macrocyclic sulfate 9 was obtained as a byproduct with a yield of less than 2% when the reaction was carried out at 0.06 mol/L. ^1H NMR ($CDCl_3$, 400 MHz) δ 3.58-3.75 (m, 16H), 3.78-3.90 (m, 8H), 4.40-4.48 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 68.3, 70.6, 70.3, 72.2; HRMS (ESI) calcd for $C_{16}H_{32}NaO_{14}S_2$ ($[M+Na]^+$) 535.1126, found 535.1136.

General procedure for nucleophilic ring-opening of the macrocyclic sulfate 1. 1-Phenyl-2,5,8,11-tetraoxatridecan-13-ol (10). A suspension of NaH (31.2 g, 60% in mineral oil, 0.8 mol) in anhydrous THF (0.5 L) was cooled to 0 ^oC and a solution of benzyl alcohol (56.2 g, 0.5 mol) in anhydrous THF (1.0 L) was added slowly at 0 ^oC. After 30 min of stirring at 0 ^oC, a solution of macrocyclic sulfate **1** (200.0 g, 0.8 mol) in anhydrous THF (0.5 L) was added slowly. The reaction mixture was stirred until no benzyl alcohol can be detected by TLC and the reaction was quenched with water (0.1 L). After removal of solvent under vacuum, the residue was dissolved in water (2.0 L) and washed with EtOAc (0.5 L, three times). The aqueous layer was concentrated under vacuum. The residue was dissolved in THF (1.5 L) and water (9.2 g, 0.5 mol) which was acidified to pH 3 with concentrated sulfuric acid and stirred overnight at 25 ^oC. The reaction mixture was

neutralized with concentrated NaOH solution and concentrated under vacuum. The residue was diluted with water (1.2 L) and extracted with diisopropyl ether (0.5 L, three times). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under vacuum to yield **10** as clear oil (132.2 g, 89%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.56-3.74 (m, 16H), 4.55-4.58 (m, 2H), 7.24-7.38 (m, 5H).

Monobenzylated octaethylene glycol 11 was prepared from alcohol **10** by following the general procedure for nucleophilic ring-opening of the macrocyclic sulfate **1** as clear oil (101.0 g, 95%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.51-3.75 (m, 32H), 4.50-4.60 (m, 2H), 7.16-7.41 (m, 5H).

Monobenzylated dodecaethylene glycol 12 was prepared from alcohol **11** by following the general procedure for nucleophilic ring-opening of the macrocyclic sulfate **1** as clear oil (124.3 g, 89%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.56-3.76 (m, 48H), 4.47-4.66 (m, 2H), 7.25-7.38 (m, 5H).

α-Benzyl-ω-methyl-dodecaethylene glycol 13. Under an argon atmosphere, to a suspension of NaH (10.8 g, 60% dispersed in mineral oil, 270.9 mmol) in anhydrous THF (1.0 L) at 0 ^{o}C was slowly added a solution of alcohol **12** (115.0 g, 180.6 mmol) in anhydrous THF (0.3 L) and the resulting mixture was stirred for 30 min. Iodomethane (51.3 g, 361.2 mmol) was added and the reaction mixture was stirred overnight at 25 ^{o}C. After quenching the reaction with water (0.1 L), the reaction mixture was concentrated under vacuum and the residue was dissolved in CH_2Cl_2 (0.8 L) and washed with water (0.5 L, three times). The organic layer was concentrated under vacuum and purified by flash chromatography on silica gel (MeOH/CH_2Cl_2 = 1/100) to give ether **13** as clear oil (117.5 g,

99%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.30-3.45 (m, 3H), 3.52-3.58 (m, 2H), 3.60-3.71 (m, 46H), 3.54-3.60 (m, 2H), 7.24-7.39 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 59.0, 69.4, 70.5, 70.56, 70.64, 71.9, 73.2, 127.6, 127.8, 128.4, 138.2; HRMS (ESI) calcd for $C_{32}H_{62}NO_{13}$ ($[M+NH_4]^+$) 668.4216, found 668.4263.

Monomethylated dodecaethylene glycol 4. To a 1 L autoclave was added ether **13** (117.5 g, 180.5 mmol) in MeOH (450 mL) and Pd/C (10% on carbon, 22.5 g) and the mixture was stirred under an atmosphere of hydrogen (3.0 MPa) for 12 h at 25 ^{o}C. After filtration of the mixture through a pad of Celite, the solution was concentrated under vacuum to give alcohol **4** as clear oil (94.1 g, 93%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.38 (s, 3H), 3.52-3.76 (m, 48H).

Tosylate 5. To a solution of alcohol **4** (60.0 g, 107.0 mmol) in THF (300 mL) was added a solution of NaOH (14.9 g, 374.5 mmol) in water (45 mL). After cooled to 0 ^{o}C, a solution of *p*-toluenesulfony chloride (24.5 g, 128.4 mmol) in THF (150 mL) was slowly added and the resulting mixture was stirred overnight at 25 ^{o}C. The reaction mixture was concentrated under vacuum. The residue was dissolved in water (500 mL) and extracted with CH_2Cl_2 (200 mL, three times). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated under vacuum to give tosylate **5** as clear oil (74.4 g, 97%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.32-2.40 (m, 3H), 3.22-3.31 (m, 3H), 3.46-3.61 (m, 46H), 4.02-4.11 (m, 2H), 7.23-7.30 (m, 2H), 7.66-7.73 (m, 2H).

Azide 6. To a solution of tosylate **5** (74.4 g, 104.1 mmol) in DMF (350 mL) was added NaN_3 (13.5 g, 208.1 mmol) and the resulting mixture was stirred at 80 ^{o}C for 4 h. CAUTION: Because remaining NaN_3 can be hazardous, removal of it with the following

method before evaporating the solvent! To this end, the reaction mixture containing the excess NaN_3 was filtered through a pad of Celite, concentrated under vacuum, dissolved in water (500 mL) and extracted with CH_2Cl_2 (300 mL, three times). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under vacuum to give azide **6** as clear oil (59.6 g, 98%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.55 (s, 2H), 3.36-3.44 (m, 5H), 3.52-3.58 (m, 2H), 3.61-3.71 (m, 42H).

Amine 7. To a solution of azide **6** (59.6 g, 101.8 mmol) in THF (500 mL) was added triphenyl phosphine (40.0 g, 152.6 mmol) and the resulting mixture was stirred at room temperature for 30 min. Water (9.2 g, 508.8 mmol) was added and the mixture was stirred overnight at 45 ^{o}C. The reaction mixture was concentrated under vacuum, the residue was dissolved in diethyl ether (500 mL) and washed with water (100 mL, three times). The aqueous layers were combined and concentrated under vacuum to give amine **7** as clear oil (52.6 g, 92%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.86 (t, J = 6.0 Hz, 2H), 3.38 (s, 3H), 3.49-3.57 (m, 4H), 3.61-3.69 (m, 42H).

ASSOCIATE CONTENT

Supporting information with copies of ^{1}H NMR, ^{13}C NMR, and HRMS for **1**, **4-7**, **9-13** and single-crystal X-ray of **1** and **9**.

AUTHOR INFORMATION

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

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