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Synthesis of Clickable Amphiphilic 1,3-Propanediol Dendrons

A Thesis Presented

by

Xiaoli Liang

to

The Graduate School

in Partial Fulfillment of the

Requirements

for the Degree of

Master of Science

in

Chemistry

Stony Brook University

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Abstract of the Thesis

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Biohybrid materials combine proteins or peptides with synthetic molecules to generate materials with complex functions. Proteins have functions such as enzymatic activity, signal generation/recognition, and materials transfer due to their well-defined structures. Conjugating polymers to proteins has produced nanostructured biohybrid materials. However, only a fraction of the proteins are functional. De novo designed peptides that form the functional part of a protein are interesting alternatives to proteins in biohybrid materials. Nanostructured biohybrid materials are obtained by conjugating liquid crystal mesogens or polymers to peptides. We are interested in making functional biohybrid materials by conjugating amphiphilic dendrons to de novo designed proteins.

Amphiphilic 1,3-propanediol dendrons form lamellar or columnar organization in the crystalline phase. We hypothesize that biohybrid materials obtained by covalently attaching amphiphilic dendrons to the exterior of a de novo designed proteins will have lattice structures

similar to those of the dendrons in the solid-state. To test this hypothesis, we need amphiphilic dendrons to conjugate to the protein. Two new amphiphilic 1,3-propanediol dendrons with azide apex groups have been synthesized. The iterative synthesis of amphiphilic 1,3-propanediol dendrons was improved by adopting the use of 15-crown-5 as a catalyst for the Williamson etherification step. The reactions require shorter time to reach completion, reduce the amount of mono-alkylated intermediates as byproducts, and avoid the use of DMF as a co-solvent. The two new compounds can be attached to de novo designed proteins by the copper-catalyzed azide-alkyne cycloaddition reaction.

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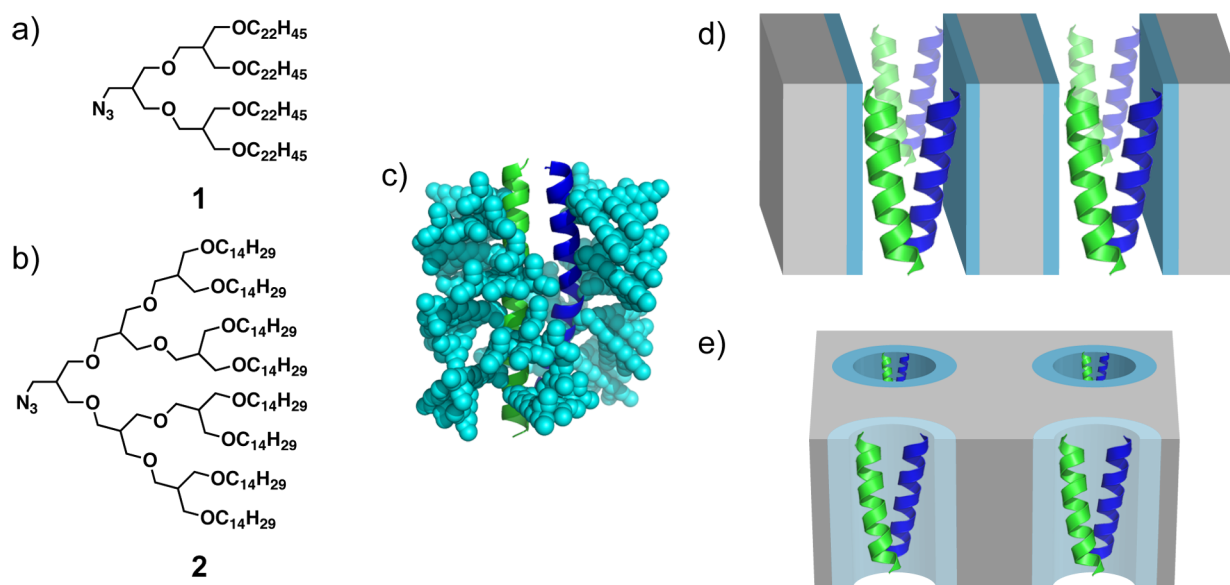
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1. Introduction

An important goal of materials science is to generate synthetic materials with complex functions such as material transfer and signal recognition. One way to achieve this goal is to create biohybrid materials¹⁻³ by combining proteins or peptides and synthetic molecules together. This kind of conjugate is of great interest to scientists because it contains the advantages of both proteins and synthetic polymers. At the same time, these biohybrid materials reduce the disadvantages of both. The purpose of this project is to synthesize amphiphilic 1,3-propanediol dendrons, which can be used to make new biohybrid polymers that self-organize into nanostructured lattices (Scheme 1).



1.1 Biohybrid Materials

Proteins have well-defined structures due to the precise order of different amino acids. Functions such as enzymatic activity, signal generation/recognition, and material transfer are due to proteins forming accurate secondary and tertiary structures. The complex structure of proteins makes them difficult to synthesize. Peptides that form the functional part of a protein cause great interest among scientists.⁴ Peptides are relatively easier to synthesize than proteins, because peptides have shorter sequences of amino acids. Even though both proteins and peptides are used in biohybrid materials, most studies focus on materials containing peptides.¹⁻³ The instability of proteins and peptides makes them difficult to handle and prevents them from generating practical materials. Both natural and synthetic peptides are sensitive to the environmental conditions such as temperature and pH level.¹⁻³ When proteins or peptides are exposed to an improper environment, they denature and lose their function.

Synthetic polymers have large sizes that can be compared to natural proteins. They have high molecular weight, but are not monodisperse. Almost all synthetic polymers lack a certain three-dimensional structure in solution or in bulk. Therefore, they are less sensitive to the external environment than peptides and proteins.

The disadvantages of proteins or peptides and synthetic polymers are reduced by combining the peptides and the synthetic polymers together. Biohybrid materials are a kind of block copolymer, so they can self-organize into different kinds of structured lattices. The polymers can surround the peptides and protect them from the external environment, which can help to increase the stability of the peptide or protein. Thus, the peptides can retain their three-dimensional structure and may retain their function within the biohybrid material.

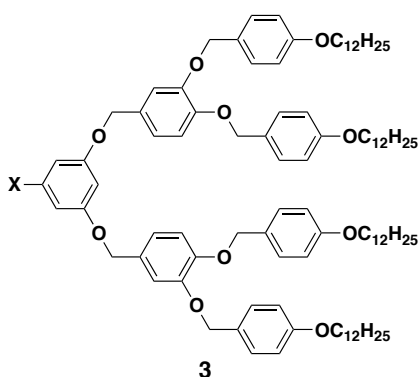
Some challenges remain for biohybrid materials that form structured lattices. First, the peptide or protein may lose its function when self-organized into a lattice. Close packing of the peptides or proteins may make them lose part of the secondary or tertiary structure. Second, the density of functional proteins in the material is limited by the size of the synthetic polymer lattice (10-100 nm). Third, polydispersity of the synthetic polymer makes it difficult to understand how the polymer affects the structure of the protein or peptide.

One way to form organized nanostructures over large areas is to form liquid crystalline mesophases.⁵ Many peptide-polymer conjugates can form block copolymer mesophases, but they require heating up to high temperature or solvent annealing.¹⁻³ These processing conditions limit the applications of biohybrid polymers. Besides, the structures of the peptides may be destroyed by the heat, which results in loss of functional activity. A way to help to solve the above problems is to use amphiphilic dendrons⁶ instead of polymers.

1.2 Self-Organizable Amphiphilic Dendrons

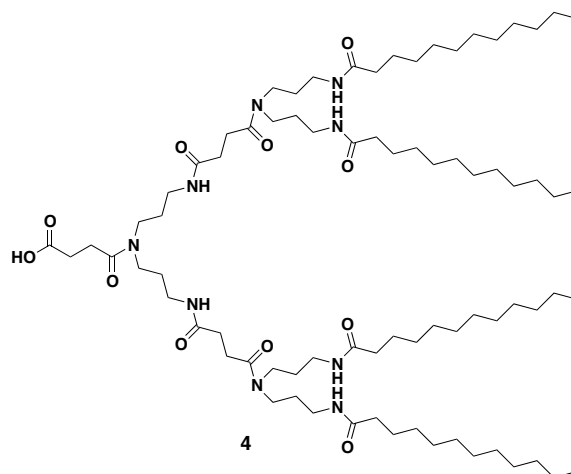
Amphiphilic dendrons are highly branched, monodisperse macromolecules that can self-organize into nanostructured lattices.⁶ Self-organizable amphiphilic dendrons can form thermotropic or lyotropic liquid crystalline mesophases that are similar to block copolymer mesophases.⁶⁻⁷ The type of mesophase that amphiphilic dendrons form is determined by the type of branched unit, sequence of branching patterns, peripheral group, generation of the dendron, and apex group⁶. Amphiphilic dendrons that form mesophases can be considered as candidates for self-organizing biohybrid materials.

Amphiphilic benzyl ether dendrons can form different kinds of thermotropic and lyotropic mesophases. Lamellar, rectangular columnar, hexagonal columnar, $Ia3d$ cubic, $Pm\bar{3}n$ cubic, $Im3m$ cubic, 12-fold liquid quasicrystal and $P4_2/mnm$ tetragonal mesophases have all been reported.⁶ Among these dendrons, the (4-3,4-3,5)12G2-X dendrons⁸⁻¹² (Scheme 2) show strong preference to form thermotropic hexagonal columnar mesophase.⁵ Over 40 kinds of (4-3,4-3,5)12G2-X dendrons that have different cores including ester, carboxylic acid, alcohol and even dipeptides have been synthesized and almost all of them form thermotropic hexagonal columnar mesophase. However, the benzyl groups in the molecules will have influence on the UV and the circular dichroism characterization of the peptides in the peptide-dendron conjugates, which prevent the characterization of the peptides.



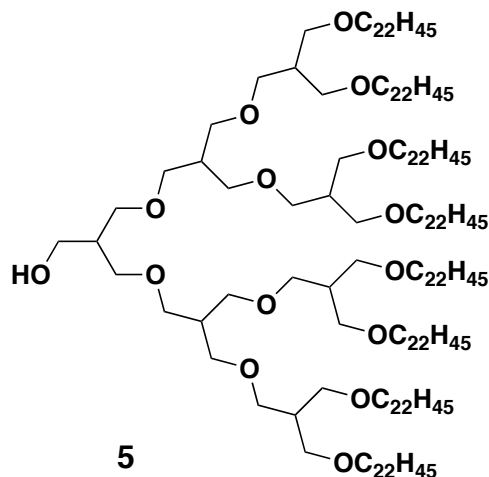
Scheme 2. The chemical structure of (4-3,4-3,5)12G2-X.

Another type of amphiphilic dendron that can be considered is the polyamide dendron shown in Scheme 3.¹³⁻²¹ Amphiphilic polyamide dendrons also form lyotropic and thermotropic liquid crystalline mesophases. The thermotropic columnar phase of **4** was found to be thermodynamically stable. However, hydrophobic and hydrogen bonding interactions between the polyamide dendrons and the coiled-coil dimers may cause loss of secondary structure of the dimers when the polyamide dendrons are attached to the peptides.



Scheme 3. The chemical structure of a second generation amide dendron.

Amphiphilic 1,3-propanediol dendrons such as **5** (Scheme 3)²²⁻²⁴ with long alkyl chain at the end of each branch (Scheme 3) form lamellar or columnar organization in the crystalline phase. They were considered for our project because they contain ether and alkyl chains which have no UV activity and will not interact with the peptides. These amphiphilic 1,3-propanediol dendrons form lamellar or rectangular columnar crystals due to different chain length and different generations. The amphiphilic 1,3-propanediol dendrons do not form liquid crystalline mesophases. However, mesophases were observed for linear-dendritic polymers²⁵⁻²⁶ and Janus-type dendrimers²⁷⁻²⁸ derived from amphiphilic 1,3-propanediol dendrons. We hypothesize that biohybrid materials obtained by covalently attaching amphiphilic 1,3-propanediol dendrons to the exterior of a coiled-coil dimeric protein will have lattice structures similar to those of the dendrons in the solid-state (Scheme 1).



Scheme 4. The chemical structure of a third generation 1,3-propanediol dendron.

1.3 Organization of Peptides and Proteins in Nanostructured Lattices

Many researchers^{29-41, 49-51} have shown that covalently attaching amphiphilic molecules to peptides can form biohybrid materials that have the property of self-organizing into lattices. For example, Klok and co-workers found that polyisoprene-*block*-poly(ϵ -benzyloxycarbonyl-L-lysine) (PI-PZLL) self-organize into hexagonal-in-lamellar structure or hexagonal-in-hexagonal lattices in solid state according to the chain length of the PZLL block.²⁹ Later, the same group generated a series of biohybrid materials by attaching a synthetic polymer to the terminus of de novo designed peptides.³⁰ These materials also self-organized into well-defined lattices. Manners and co-workers showed that covalently attaching amphiphilic benzyl ether dendrons to the end of a stable α -helix poly(γ -benzyl-L-glutamate) formed a material with a well-defined three-dimension shape which can self-assemble in solution to form lyotropic lamellar liquid crystalline phases.³¹

Attaching the polymer to the side of helices that assemble into bundles is less disruptive to the structure of the bundle than attaching the polymer to the end of the helices.³² Attaching polystyrene

to the end of bundle-forming helices leads to a partial loss in peptide secondary structure.³³ Since the polymers were large, they created steric hindrance and destroyed part of the secondary structure of the peptides when they are attached to the end of the peptides. Moreover, the ends and the inner channel of the bundles are easier to access compared to those of the helix bundles with polymers attached to their ends.³² The polymers protect the peptides from the external environment, which stabilizes the structure of the peptides. Xu and co-workers found that by attaching poly(ethylene oxide) to the side of a de novo designed helix bundle, the structure of the bundle is retained in solution and when blended into a block copolymer mesophase.³⁴

Peptides and proteins can retain their structure when organized in liquid crystalline mesophases.^{35-37,39} Three-ring aromatic ester mesogens were attached to the side of the polypeptides by Deming and co-workers.³⁵ The biohybrid material formed a thermotropic liquid crystalline mesophase where both side-chain mesogens and polymer backbones are ordered and coexist in a nematic-hexagonal structure. The peptides in the liquid crystal phase retained their helical conformation. Mann and co-workers showed that electrostatic complexation of cationized ferritin with an ionic polymer surfactant produced a viscous protein liquid that showed thermotropic lamellar liquid crystalline behavior.³⁶ Benzyl ether dendrons were covalently linked to the side of a polypeptide.³⁷ The dendronized polypeptide self-organized into a highly ordered lyotropic liquid crystalline phase. In each of these examples the peptide or protein retains its secondary structure.

Some biohybrid materials show that the proteins in the lattices retain their functionalities.^{34, 38-39} For example, protein-polymer diblock copolymers based on mCherryS131C and poly(*N*-isopropyl acrylamide) self-organize into a nanostructured lamellar phase. The protein retained the β -sheet conformation and one-third of the chromophores remained active.³⁸ Xu and co-workers also reported a biohybrid material based on myoglobin and poly(ethylene oxide).³⁴ The protein-polymer

diblock copolymer was blended with a polystyrene-poly(ethylene oxide) block copolymer that formed a cylindrical mesophase. Myoglobin-containing films oxidized 3,3',5,5'-tetramethylbenzidine in the presence of H₂O₂, which showed that the protein activity was retained. However, in both examples, not all the proteins in the lattice are functional.

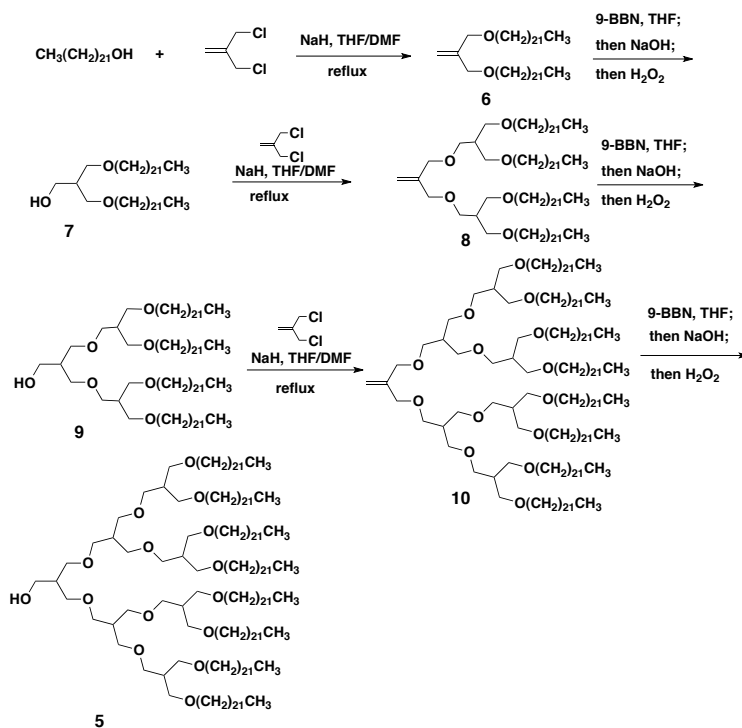
It is important to understand how the function of a protein is affected by attaching synthetic polymer and organization in nanostructured lattices. This information may provide directions to synthesize highly efficient, functional biohybrid materials. Since the research on functional proteins in nanostructured lattices is all using block copolymers, it is difficult to understand these questions. Quantitative analyses are complicated due to the polydispersity of the biohybrid block copolymers. We want to synthesize biohybrid materials which will form mesophases at a relatively low temperature by covalently attaching the amphiphilic 1,3-propanediol dendrons to sides of a coiled-coil dimer protein. In this system, we can understand how the structure of the dimers is affected by the lattices through spectroscopic and thermodynamic analyses.

1.4 Amphiphilic 1,3-Propanediol Dendrons

In our experiments, we adopted the convergent synthesis method.⁴⁰ In the convergent method, reactions go from outside to inside. The synthesis begins from materials that are on the surface of the dendron. The synthesis can be divided into two parts, activation and growth. Each iteration of the activation and the growth steps increases the generation of the dendron. The convergent synthesis method allows the products to be purified more easily than the divergent synthesis method.⁴¹⁻⁴³ Moreover, the convergent method requires much less excess reagents to make the

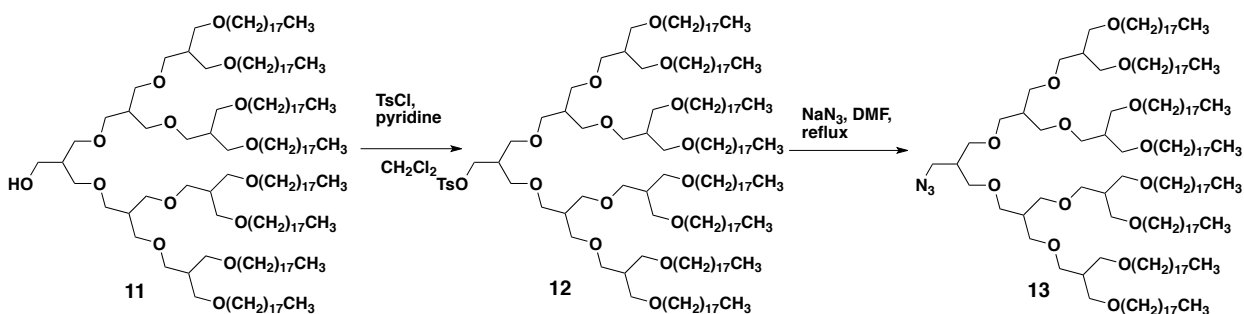
perfect dendrons compared to the divergent synthesis method.⁴¹⁻⁴³ Jayaraman and Fréchet introduced a convergent synthesis of 1,3-propanediol dendrons.²²

First- through fourth-generation amphiphilic 1,3-propanediol dendrons with C₂₂H₂₅ and C₁₄H₂₉ peripheral groups have been synthesized by Cho and co-workers.^{23-24, 44} The methods used by Cho to synthesize the C₂₂ compounds are shown in Scheme 5. An excess of starting alcohol reacts with methallyl dichloride in the presence of NaH to give the first-generation alkene **6** with alkyl chains on the surface. The synthesis of dendron **6** from 1-docosanol (0.92 M) required heating at reflux in a mixture of THF/DMF (7:3 v/v) for 63 h. The yield of the reaction was 60%. In the activation step, the alkenes is treated with 9-borabicyclo[3.3.1]nonane (9-BBN) in THF and then NaOH and H₂O₂ to give the relative alcohol. This step is to activate the focal functional group so that it can be attached to a branch unit. In the growth stage, the alcohols are repeated with methallyl dichloride to give the second-generation alkene. The reactions are repeated to go to even higher generations.



Scheme 5. The synthesis of C₂₂ dendrons of Cho and co-workers.

The dendritic azides we want can be prepared from the dendritic alcohols. Cho and co-workers have synthesized first-, and second-, and third-generation amphiphilic 1,3- propanediol dendrons with azide apex groups (Scheme 6).⁴⁵ The dendrons have C₁₈H₃₇ surface groups. The alcohols were treated with TsCl and pyridine in CH₂Cl₂ to form the tosylate. The dendritic azide was reacted with NaN₃ in refluxing DMF to give the final product. Based on these examples, we planned to synthesize the target dendrons **1** and **2** (Scheme 1).



Scheme 6. The synthesis of **13** of Cho and co-workers.

According to the work of Cho and co-workers,²³⁻²⁴ dendrons with longer chain length or lower generation organize into lamellar structures. The hydrophobic layer of the bilayer becomes thicker when the chain length is longer. Dendrons with shorter chain length or higher generation prefer the columnar structures. The longer the chain length, the more dendrons are required to form the column. As the chain length becomes shorter and the generation becomes higher, the melting point of the dendrons decreases. The first-, second- and third-generation of C22 alcohol self-organize into lamellar structure in bulk while the fourth-generation self-organizes into columnar rectangular structure.²³ The third-generation of C14 alcohol self-organizes into a columnar structure in bulk.²⁴

Many studies have shown that amphiphilic molecules can still self-organize into the same lattices with the insertion of the peptides or proteins. We expect that when we covalently link the

C22-G2 dendrons to the coil-coiled dimers, the conjugates will self-organize into lamellar lattices. The C14-G3 dendron-peptide conjugates will self-organize into columnar lattices.

1.5 Summary

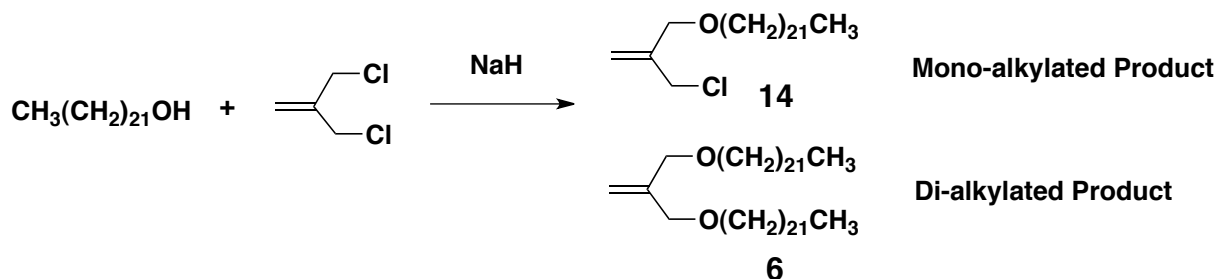
The synthesis of two kinds of amphiphilic 1,3-propanediol dendrons **1** and **2** (Scheme 1) via the convergent method is reported. Dendron **1** is a second-generation dendron with 22 carbons in each surface alkyl chain. Dendron **2** is a third-generation dendrons with 14 carbons in each surface alkyl chain. The C22 second-generation dendrons can form lamellar lattice in solid state while the C14 third-generation form hexagonal lattice. These two kinds of dendrons will be covalently linked to the side of a coiled-coil dimer to form the peptide-polymers conjugates. We expect the conjugates to form a mesophase at low temperature and the dimers can be stable within the lattices. The structure of the lattices we observe should be the same as the structure of the solid-state crystals of C22 second-generation dendrons and C14 third-generation dendrons.

2. Results and Discussion

2.1 Modified Williamson Ether Synthesis for Amphiphilic 1,3-Propanediol Dendrons

In order to make the Williamson ether synthesis reaction faster, safer and more efficient, we make some changes in synthesizing **6** (Scheme 7). Following the method of reported by Cho and co-workers,²³ we found that 1-docosanol had poor solubility in THF, DMF or the mixture of them.

In order to make 0.92 M solution of 1-docosanol, high temperature was required to increase the solubility of 1-docosanol. As the temperature went up to 70 °C, the 1-docosanol began to melt but solubility remained an issue. As the temperature went up above 85 °C, the mixture began to reflux. However, it was difficult to tell if all the 1-docosanol was dissolved or it just mixed with the solvent. After reacting for 63 h, the mixture was worked up and the yield of the **6** was less than 60%.



Scheme 7. The reaction of synthesizing **6**.

One reason for using DMF in this reaction was to increase the boiling point of the solvent so that the reaction mixture could reach a temperature that was high enough to melt 1-docosanol. The other reason for using DMF was that DMF was favorable for this $\text{S}_{\text{N}}2$ reaction since DMF is a polar aprotic solvent. However, the safety of the literature method²³ is a concern. The danger of mixing DMF and hydride reagents was well-known.⁴⁶⁻⁴⁷ DMF will react with the hydride reagents to form a flammable gas, trimethylamine. At such a high temperature, flammability of the organics may cause an explosion. The mixture of DMF and NaH has the same potential problem. Besides, as 1-docosanol was not all dissolved in the solvent, the mixture was not homogenous, which may have influence on the efficiency of the reaction. Thus, we looked for a safer method to synthesize the alkenes (Table 1). THF was considered as the solvent (Table 1, entry 2). The most concentrated solution of 1-docosanol in THF at room temperature we can make is 0.2 M, so the initial concentration of 1-docosanol was 0.2 M. The mixture was heated to reflux. Since the boiling point of THF is much lower than that of DMF, the refluxing temperature (65 °C) is lower than that of

entry 1 in Table 1. The reaction progress was checked by ^1H NMR spectroscopy to see the conversion of the 1-docosanol. The reaction formed two products as shown in Scheme 7, the mono-alkylated product **14** and the di-alkylated product **6**. The mono-alkylated product was difficult to separate from the di-alkylated product. Thus, we wanted to eliminate the amount of the mono-alkylated product. The ratio of the mono-alkylated product to the di-alkylated product (Mono: Di) was also checked by ^1H NMR spectroscopy. The calculation of the conversion of 1-docosanol and the ratio of the mono-alkylated product and the di-alkylated product are discussed in detail in Section 2.2. As for method 2, after 84 h refluxing, the conversion for 1-docosanol was 80%. The ratio of the mono-alkylated product to the di-alkylated product was 1:10. In this method, the conversion of 1-docosanol is not high enough, which affected the yield of the product. Besides, there was almost 10% of the mono-alkylated product in the mixture, which made the purification difficult.

Table 1. Reaction conditions, conversion of methallyl dichloride, and the amounts of **6** and **14** tried to optimize the alkylation reaction

	Solvent	$[\text{C}_{22}\text{H}_{45}\text{OH}]_0$	$[\text{15-crown-5}]_0$	Temperature	t	Conv.	Mono:Di
1	THF/DMF (7:3)	0.92 M	0 M	Reflux	63 h	- ^a	- ^a
2	THF	0.2 M	0 M	Reflux	84 h	80%	1:10
3	THF	0.2 M	0.22 M	25 °C	19.5 h	29%	8:11
4	THF	0.2 M	0.22 M	Reflux	3 h	98%	- ^b

a) Not determined.

b) No mono-alkylated product was observed.

We looked for a more efficient method to synthesize **6**. 15-Crown-5 is a known catalyst in Williamson ether synthesis.⁴⁸ Thus, 15-crown-5 was adopted in our experiment. Since all known experiments using 15-crown-5 as a catalyst in Williamson ether synthesis take place at room temperature for several hours, we ran the experiment at room temperature (Table 1, entry 3). When we checked the reaction by ^1H NMR spectroscopy after reacting at room temperature for 19.5 h,

however, we found that the conversion of the methallyl dichloride was only 29%. The ratio of the mono-alkylated product to the di-alkylated product was 8:11.

We thought this reaction might require heating. Thus, we ran the reaction at the reflux in THF (Table1, entry 4). To our satisfaction, the reaction was complete after 3 h at reflux. The conversion of 1-docosanol was 98%, which meant higher yield of **6**. Moreover, no mono-alkylated peaks were observed by ^1H NMR spectroscopy, which meant the product was much easier to purify. 15-Crown-5 was used in all the subsequent experiments of making the alkenes. The structures of all the compounds were confirmed by ^1H and ^{13}C NMR spectroscopy. The purity was confirmed by TLC and NMR spectroscopy.

2.2 Calculation of Conversion and the Ratio of Mono-Alkylated Product to Di-alkylated Product

The reaction of synthesizing **6** is shown in Scheme 7. The percent conversion is equal to the amount of reacted alcohol (n_{conv}) divided by the total amount of alcohol that should react in the reaction (n_{total}) as shown in equation 1. The reacting alcohol can be converted into either mono-ether **14** or diether **6**. Thus, n_{conv} is equal to the amount of the mono-ether (n_{mono}) plus 2 times the amount of the diether (n_{di}). Equation 2 can be substituted into equation 1 to obtain equation 3.

$$\text{Conv. \%} = [(I_{4.03} + I_{4.08})/4 + I_{3.95}/2] / (0.8I_{0.88}/3) \quad \text{Equation 1}$$

$$\text{Conv. \%} = n_{\text{conv}}/n_{\text{total}} * 100\% \quad [1]$$

$$n_{\text{conv}} = n_{\text{mono}} + 2n_{\text{di}} \quad [2]$$

$$\text{Conv. \%} = (n_{\text{mono}} + 2n_{\text{di}}) / n_{\text{total}} \quad [3]$$

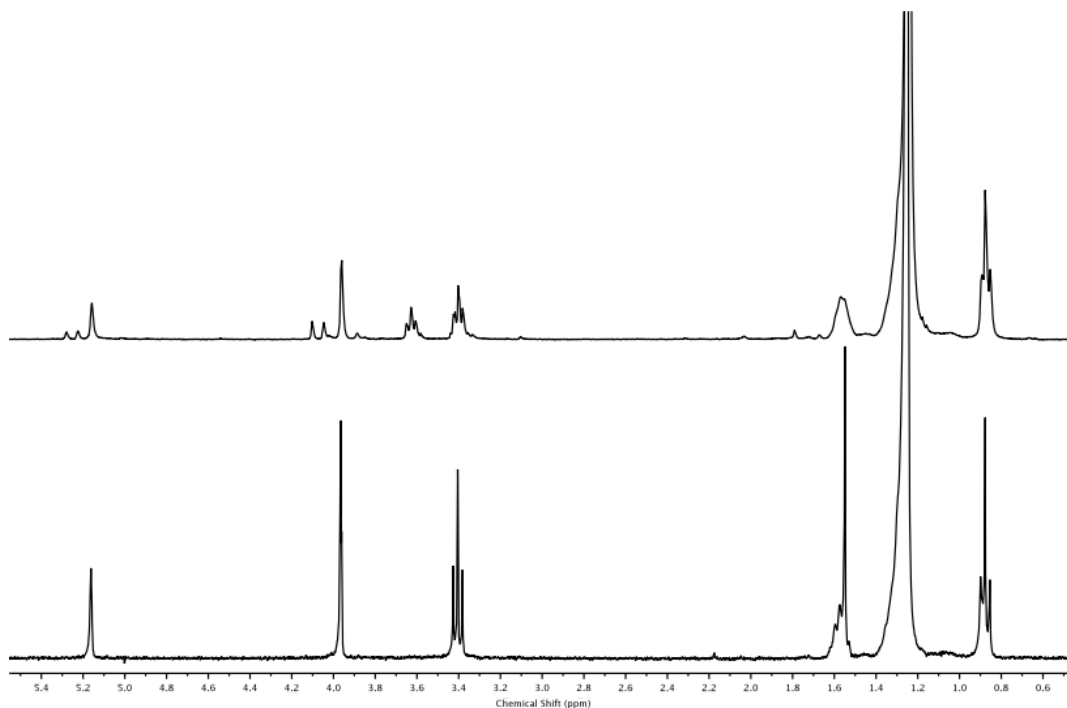


Figure 1. The ^1H NMR spectrum of the incomplete reaction (above) and the complete reaction (below).

The ^1H NMR spectra of the reaction progress and at completion are shown in Figure 1. To determine the percent conversion, we relied on the ratio of the integral of allylic proton resonances from both **14** ($I_{4.03}+I_{4.08}$) and **6** ($I_{3.95}$) and the integral of methyl group resonance from the alkyl chain ($I_{0.88}$). By integrating the peaks around 4.03 and 4.08 ppm, we can determine the amount of **14** in the mixture. The amount of **6** in the reaction mixture can be determined by the integral of the peak at 3.95 ppm. By calculating the amount of **14** and **6**, the conversion of the starting material can be determined. One starting alcohol molecule formed one molecule of **14**. Each molecule **14** has four allylic protons. The integration of the allylic proton resonances ($I_{4.03}+I_{4.08}$) of **14** divided by four is equal to n_{mono} . (Eq. 4)

$$n_{\text{mono}} = (I_{4.03}+I_{4.08})/4 \quad [4]$$

Two starting alcohol molecules form one molecule of **6**. Each molecule **6** has four allylic protons. The integration of the allylic protons resonance ($I_{3.95}$) of **6** divided by four is equal to the amount of **6**. (Eq. 5)

$$n_{di} = I_{3.95}/4 \quad [5]$$

Each alcohol molecule contains one methyl group. The total amount of the methyl groups as well as $[A]_0$ can be determined as 1/3 of the integrated resonances ($I_{0.88}$). Since 2.5 equivalents alcohol were added to 1 equivalent of methallyl dichloride, only 80% ($2/2.5 = 0.8$) of alcohol can take place in the reaction. Thus, the total amount of the reacting alcohol (n_{total}) is equal to $0.8[A]_0$ and can be determined by Eq. 6.

$$n_{total} = 0.8[A]_0 = 0.8I_{0.88}/3 \quad [6]$$

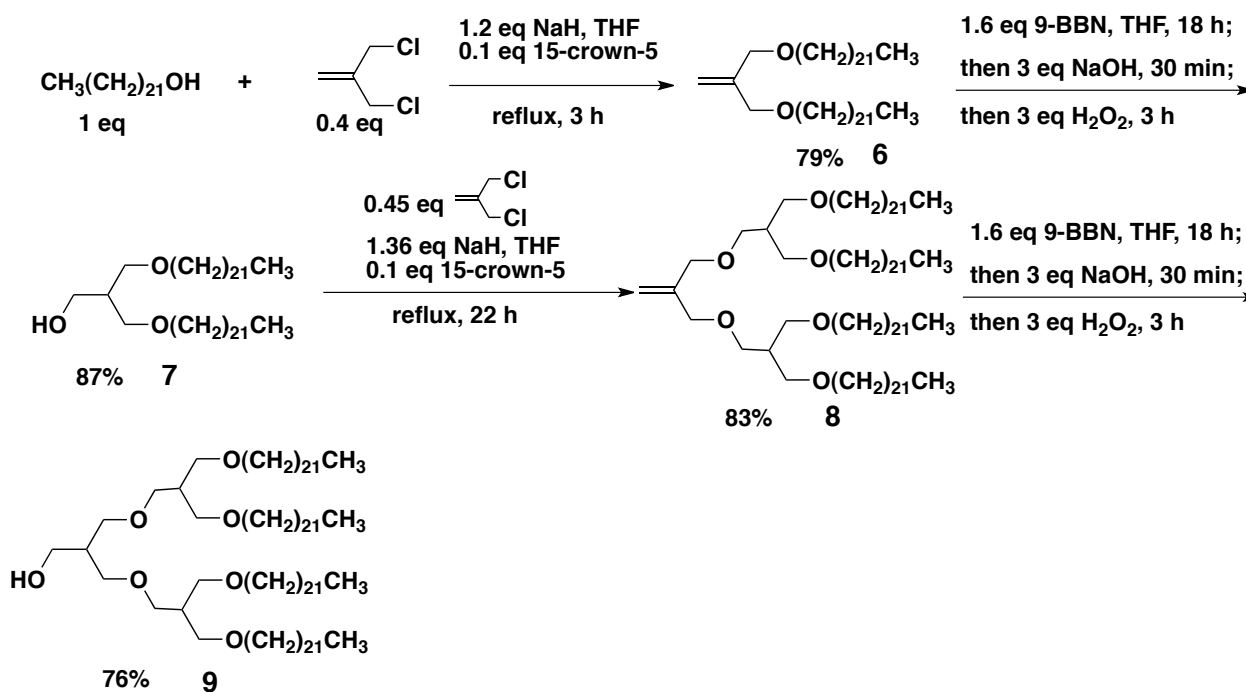
Substitution of (4), (5) and (6) into (3) allows us to calculate Conv. %. (Eq. 7)

$$\text{Conv. \%} = [(I_{4.03} + I_{4.08})/4 + I_{3.95}/2] / (0.8I_{0.88}/3) \quad [7]$$

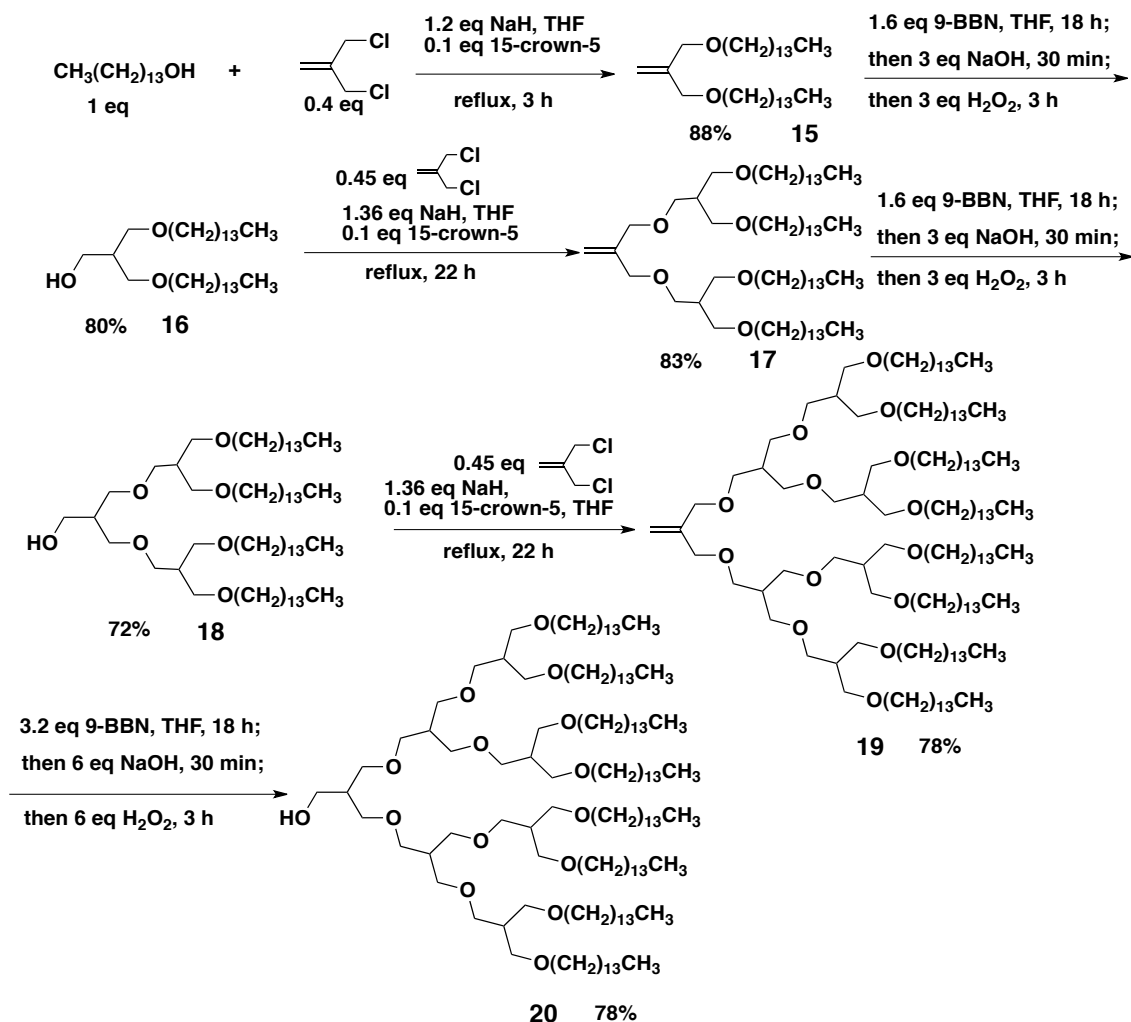
2.3 Synthesis of the Second-Generation Amphiphilic 1,3-Propanediol Dendrons

The methods for making the **9** and **18** are almost the same and are shown in Schemes 8 and 9. The yield of **6** obtained according to method 4 is 79%, much higher than that of method 1. One of the reasons is that the conversion of the starting alcohol 1-docosanol is almost 100%. The other reason is that the purification is easier since there was almost no mono-alkylated product in the mixture. Cho used CHCl_3 as eluent to purify **6** by chromatography. However, the ΔR_f between the mono-alkylated product and the di-alkylated one is less than 0.1 in CHCl_3 according to TLC. This made it very difficult to separate one from the other by flash chromatography. Several times of

recrystallizations were needed. Thus, some product was lost in this way and the yield was 60%. Many different solvents were tried to see if there was a better separation. We found that CHCl_3 was still the best eluent because **6** showed poor solubility in other solvents. However, slowing down the polarity of the eluent and addition of the CHCl_3 gradually helped to separate the mono-alkylated product according to TLC. In 25% CHCl_3 in hexanes, the R_f of **6** was 0.1 and that for the mono-alkylated product was 0.09. In 50% CHCl_3 in hexanes, the R_f of **6** was 0.36 and that for the mono-alkylated product was 0.35. We decided to use a gradient method using from 25% CHCl_3 in hexanes to CHCl_3 as eluent. The result was satisfying. Although some of the **6** was still overlapped with the mono-alkylated product, most of **6** was pure and the recrystallization was not needed. The purity was confirmed by NMR spectroscopy. The yield of **6** was 79%.



Scheme 8. The synthesis of C22 amphiphilic 1,3-propanediol dendrons.



Scheme 9. The synthesis of C14 amphiphilic 1,3-propanediol dendrons.

To reduce the mono-alkylated product and speed up the rate of the reaction, we used 15-crown-5 in synthesizing all the C14 alkenes as well. The method of making **15** is almost the same as that used for making **6** except for the concentration of the starting alcohol 1-tetradecanol. Because 1-tetradecanol had better solubility in THF, the reaction ran in a concentration of 1.83 M of 1-tetradecanol. Since the concentration was higher, only 0.1 equivalents of 15-crown-5 to the 1-tetradecanol was added to the mixture. After 3 h refluxing, the conversion of 1-tetradecanol was almost 100% and no mono-alkylated peaks were observed by NMR spectroscopy. The resulting product was purified by flash chromatography using hexanes to 25% EtOAc in hexanes as eluent.

The yield of **15** was 98%. The purity was confirmed by ^1H NMR spectroscopy.

The methods for making **7** and **16** were almost the same except for the concentration of **6** and **15**. Because **15** had better solubility, the concentration was higher. They were all treated with 0.5 M 9-BBN THF solution and then NaOH and H_2O_2 . ^1H NMR spectroscopy was used to see if all the alkenes were converted into alcohols. They all got 100% conversion after stirring over night with 9-BBN. The yield of **7** was 87% and that of **16** was 80%.

The procedures for making **8** and **17** were almost the same as that for making the first-generation ones except for the concentration of the starting alcohols. Since **7** had better solubility than 1-docosanol, the concentration of **7** in the reaction was 0.24 M. Thus, less 15-crown-5 was added to this reaction. Only 0.1 equivalent 15-crown-5 to **6** was added instead of 1.1 eq of that in making the **6**. The yield of **8** was 87% and that of **17** was 83%. The purity of the compounds was confirmed by NMR. The yield of **8** was higher than that of method used by Cho (66%), probably because the use of 15-crown-5 reduced the amount of the mono-alkylated product. At higher generations, **17** was an oily liquid at room temperature instead of solid as **15** and **16**. The procedures of making **9** and **18** were almost the same except the concentration of **17** was higher than that of **8**. The conversion of the alkenes was checked by ^1H NMR spectroscopy. The yield of **9** was 76% and that of the **18** was 72%. The purity was confirmed by NMR spectroscopy.

2.4 Synthesis of the Third-Generation Amphiphilic 1,3-Propanediol Dendrons

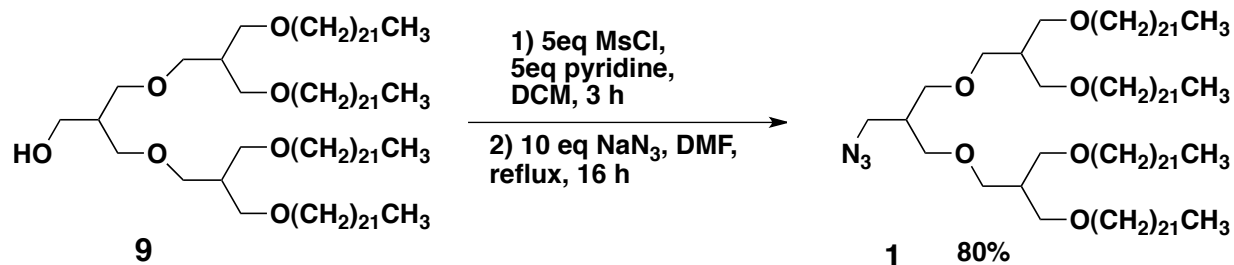
The method of synthesizing **19** was almost the same as that of **17**. The yield of **19** was 78%. However, the procedure for making alcohol **20** was quite different from that of the first two

generations. As seen from Scheme 10, making **20** from **19** required twice the amount of all reagents compared to that of making other alcohols. Besides, the concentration of **19** was lower than that of the other alkenes in the reaction of making their alcohols. Contrary to what one would expect, higher concentrations of **19** actually slowed down the rate of the reaction. At high concentration (0.2 M of **19**), no reaction took place after days according to ^1H NMR spectroscopy and TLC. We first considered that it might be due to the steric bulk of the third-generation dendron. Thus, we doubled the amount of all the reagents and heated the reaction to 40 °C. However, still almost no reaction took place after 5 d according to ^1H NMR spectroscopy and TLC. According to the method used by Cho and co-workers²³, the concentration of the third-generation alkene was 0.036 M, much lower than that of the first and second-generation alkenes. We considered that the third-generation dendrons might form micelles in solution, keeping the functional groups inside and preventing them from reacting with other reagents. Thus, we diluted the concentration of C14 third-generation alkene while keeping the other reaction conditions the same. The reaction worked at a concentration of 0.035 M of **19** with 3.2 equivalents of 9-BBN to the alkene at 40 °C.

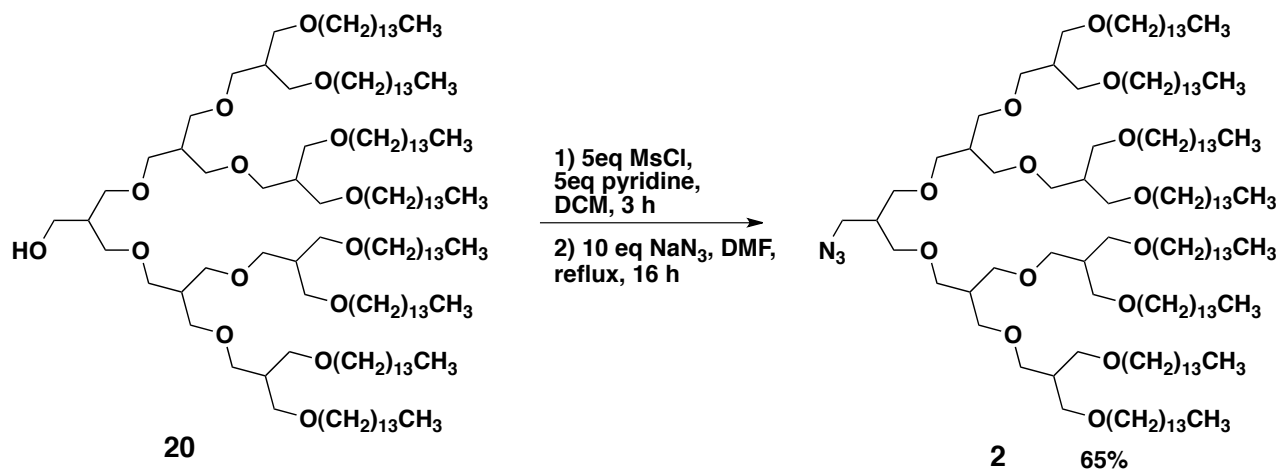
2.5 Synthesis of Amphiphilic 1,3-Propanediol Dendrons Bearing Clickable Azide Groups

We adopted MsCl instead of TsCl used by Cho because we considered that MsCl had a higher reaction activity than that of TsCl. The methods of making **1** and **2** were almost the same and are shown in Schemes 10 and 11. First, the alcohols were treated with 5 equivalents of MsCl and 5 equivalents of pyridine in CH_2Cl_2 to synthesize the intermediate mesylates. The reactions were checked by ^1H NMR spectroscopy. The reactions were done in 3 h. The conversions for both were

almost 100%. According to TLC, the R_f of the mesylate compounds were almost the same as that of the relative alcohols, which was impossible to separate them by flash chromatography. Thus, we had to use this mixture to continue making the azides. The mesylates were treated with 10 equivalents of NaN_3 in DMF. The reaction mixture was heated to reflux and checked by ^1H NMR spectroscopy. The ΔR_f of the azides and the mesylates were about 0.3 for both C22 and C14. The **1** and **2** were purified by flash chromatography. The yield of **1** was 80% and that of the **2** was 65%.



Scheme 10. The synthesis of **1**.



Scheme 11. The synthesis of **2**.

3. Conclusion

Two new amphiphilic 1,3-propanediol dendrons **2** and **1** were synthesized. The iterative synthesis of amphiphilic 1,3-propanediol dendrons was improved by adopting the use of 15-crown-5 as a catalyst for the Williamson ether synthesis. The etherification reactions require shorter time to reach completion, reduce the amount of mono-alkylated intermediates as byproducts, and avoid the use of DMF as a co-solvent.

4. Future Plan

The two new compounds **1** and **2** will be attached to a coiled-coil dimer by the copper-catalyzed azide-alkyne cycloaddition reaction. We expect to find that the third-generation of C14 peptide-dendron conjugates form columnar lattices and the second-generation of C22 peptide-dendrons conjugates form lamellar lattices. X-ray diffraction technique will be used to evaluate the hypothesis.

5. Experimental

5.1 Materials

1-Tetradecanol (99%), 3-chloro-2-chloromethyl-1-propene (99%), sodium hydride (NaH, 95%), 9-borabicyclo[3.3.1]nonane (9-BBN) 0.5 M solution in tetrahydrofuran, and methanesulfonyl chloride (MsCl, 99.7%) were used as received from Aldrich. Anhydrous tetrahydrofuran (THF,

99.9%), dichloromethane (CH_2Cl_2 , A.C.S. reagent), chloroform (CHCl_3 , A.C.S. reagent), and sodium azide (NaN_3 , A.C.S. reagent), were used as received from EMD. Ethyl acetate (EtOAc, A.C.S. reagent), sodium hydroxide (NaOH , A.C.S. reagent), pyridine (A.C.S. reagent), hydrochloric acid (HCl , A.C.S. reagent), sodium bicarbonate (NaHCO_3 , A.C.S. reagent), and anhydrous sodium sulfate (Na_2SO_4 , A.C.S. reagent) were used as received from Fisher. Anhydrous *N,N*-dimethylformamide (DMF, 99.8%), 1-docosanol (98%), chloroform-*d* (CDCl_3 , 99.8+ atom % D), and 15-crown-5 (98%) were used as received from Acros. Sodium chloride (NaCl , A.C.S. reagent), anhydrous magnesium sulfate (MgSO_4 , 99.9%), and potassium carbonate (K_2CO_3 , 1.5-hydrate, A.C.S. reagent) were used as received from J. T. Baker. Hydrogen peroxide (H_2O_2 , 29-32%w/w aq. soln., A.C.S. reagent) and anhydrous dichloromethane (CH_2Cl_2 , 99.7+%) were used as received from Alfa-Aesar. Hexanes (A.C.S. reagent) and tetrahydrofuran (THF, A.C.S. reagent) were used as received from BDH.

5.2 Techniques

Thin layer chromatography (TLC) was performed on 60 Å silica gel plates (Whatman) with fluorescent indicator and the reported eluent. NMR Spectra (^1H , 400 MHz and ^{13}C , 100 MHz) were recorded on multi channel and multi nuclear pulsed field gradient instruments with Varian Unity Inova RF consoles in CDCl_3 at 25 °C unless otherwise noted. Chemical shifts are reported as δ , ppm, using the residual solvent peak (7.26 ppm) as the reference standard. Flash chromatography was performed on a CombiFlash Rf from Teledyne Isco with silica RedisepRf flash column from Teledyne Isco.

5.3 Synthesis

2,2-Bis(docosyloxymethyl)ethane (6). A solution of 11.43 g 1-docosanol (35.0 mmol) in 140 mL anhydrous THF was added dropwise to a suspension of 1.01 g NaH (42.1 mmol) in 20 mL dry THF, 1.62 mL methallyl dichloride (14.0 mmol) and 7.72 mL 15-crown-5 (39.0 mmol) cooled in an ice-water bath under a N₂ atmosphere. The reaction mixture was heated at reflux for 3 h under a N₂ atmosphere while stirring. The reaction mixture was quenched with deionized water. The product was extracted with CHCl₃. The organic washings were combined, washed once with saturated NaCl (aq.) solution and dried over anhydrous Na₂SO₄. The solids were removed by filtration. The CHCl₃ was removed by rotary evaporation. The resulting product was purified by flash chromatography (SiO₂, 25% CHCl₃ in hexanes to CHCl₃) to yield 7.92 g (79.2%) of a colorless solid. TLC (SiO₂, 1:1 hexanes/CHCl₃) *R*_f = 0.36. ¹H NMR (CDCl₃, δ): 5.16 (s, -CCH₂, 2H), 3.96 (s, -CCH₂O, 4H), 3.40 (t, *J* = 6.6 Hz, -OCH₂, 4H), 1.57 (m, -OCH₂CH₂, 4H), 1.20-1.40 (m, -OCH₂CH₂(CH)₁₉CH₃, 44H), 0.88 (t, *J* = 6.6 Hz, -CH₃, 6H). ¹³C NMR (CDCl₃, δ): 143.38 (H₂C=C), 113.25 (H₂C=C), 71.50 (C=CCH₂O), 70.56 (OCH₂), 31.93 (OCH₂CH₂), 29.76 (OCH₂CH₂(CH)₁₉CH₃), 29.71 (OCH₂CH₂(CH)₁₉CH₃), 29.63 (OCH₂CH₂(CH)₁₉CH₃), 29.52 (OCH₂CH₂(CH)₁₉CH₃), 29.37 (OCH₂CH₂(CH)₁₉CH₃), 26.22 (OCH₂CH₂(CH)₁₉CH₃), 22.69 (OCH₂CH₂(CH)₁₉CH₃), 14.09 (CH₃).

2,2-Bis(docosyloxymethyl)ethanol (7). To a solution of 20.66 g **6** (29.30 mmol) in anhydrous 140 mL THF, 92.0 mL 0.5 M 9-BBN in THF solution was added dropwise under a N₂ atmosphere at room temperature. The reaction mixture was stirred under a N₂ atmosphere for 18 h. The reaction was cooled in an ice-water bath; 24.12 mL 3 M NaOH aqueous solution was added and stirred under a N₂ atmosphere at room temperature for 30 min. The reaction mixture was cooled in an ice-water bath while 24.12 mL 30% H₂O₂ aqueous solution was added by dropwise addition to the reaction mixture. After the addition was complete, the reaction mixture was stirred under a N₂

atmosphere at room temperature for 3 h. The THF was removed by rotary evaporation. Anhydrous K_2CO_3 was added to the mixture. The product was extracted with $CHCl_3$. The organic washings were combined, washed once with saturated NaCl (aq.) solution and dried over anhydrous Na_2SO_4 . The Na_2SO_4 was removed by filtration. The $CHCl_3$ was removed by rotary evaporation. The resulting product was purified by repeated recrystallizations from ethyl acetate to yield 17.97 g (87%) of a colorless solid. TLC (SiO_2 , 4:1 hexanes/EtOAc) $R_f = 0.25$. 1H NMR ($CDCl_3$, δ): 3.76 (t, $J = 5.2$ Hz, $-CH_2OH$, 2H), 3.52 (m, $-CHCH_2$, 4H), 3.41 (t, $J = 6.8$ Hz, $-OCH_2$, 4H), 2.93 (t, $J = 5.6$ Hz, $-CH_2OH$, 1H), 2.10 (m, $-CHCH_2$, 1H), 1.56 (m, $-OCH_2CH_2$, 4H), 1.25 (m, $-OCH_2CH_2(CH_2)_{19}CH_3$, 76H), 0.88 (t, $J = 6.8$ Hz, $-CH_3$, 6H). ^{13}C NMR ($CDCl_3$, δ): 71.63 (C(H)CH₂), 71.00 (OCH₂), 64.85 (H₂COH), 41.24 (C(H)CH₂), 31.92 (OCH₂CH₂), 29.70 (OCH₂CH₂(CH)₁₉CH₃), 29.63 (OCH₂CH₂(CH)₁₉CH₃), 29.47 (OCH₂CH₂(CH)₁₉CH₃), 29.36 (OCH₂CH₂(CH)₁₉CH₃), 26.15 (OCH₂CH₂(CH)₁₉CH₃), 22.68 (OCH₂CH₂(CH)₁₉CH₃), 14.09 (CH₃).

2',2'- Bis(2,2-di(docosyloxymethyl)ethoxymethyl)ethane (8). A solution of 17.2 g **7** (23.8 mmol) in anhydrous 100 mL THF was added dropwise to a suspension of 0.83 g NaH (34.6 mmol) in 10 mL dry THF, and 1.25 mL methallyl dichloride (10.8 mmol) and 0.47 mL 15-crown-5 (2.4 mmol) cooled in an ice-water bath under a N_2 atmosphere. The reaction mixture was heated at reflux for 20 h under a N_2 atmosphere while stirring. The reaction mixture was quenched with deionized water. The product was extracted with $CHCl_3$. The organic washings were combined, washed once with saturated NaCl (aq.) solution and dried over anhydrous Na_2SO_4 . The Na_2SO_4 was removed by filtration. The $CHCl_3$ was removed from the filtrate by rotary evaporation. The resulting product was purified by flash chromatography (SiO_2 , hexanes to 10% THF in hexanes), followed by recrystallization from EtOAc to yield 15.0 g (87%) of a colorless solid. TLC (SiO_2 , 9:1 hexanes/THF) $R_f = 0.58$. 1H NMR ($CDCl_3$, δ): 5.13 (s, $-CCH_2$, 2H), 3.94 (s, $-CCH_2O$, 4H), 3.36-

3.46 (m, $-\text{OCH}_2$, 20H), 2.17 (m, $-\text{OCH}$, 2H), 1.54 (m, $-\text{OCH}_2\text{CH}_2$, 8H), 1.00-1.45 (m, $-\text{OCH}_2\text{CH}_2(\text{CH}_2)_{19}\text{CH}_3$, 152H), 0.88 (t, $J = 7.2$ Hz, $-\text{CH}_3$, 12H). ^{13}C NMR (CDCl_3 , δ): 143.19 ($\text{H}_2\text{C}=\text{C}$), 113.14 ($\text{H}_2\text{C}=\text{C}$), 71.79 ($\text{C}=\text{CCH}_2\text{O}$), 71.29 (OCH_2), 69.17 (CHCH_2O), 68.93 (OCH_2CH_2), 40.38 (OCH_2CH_2), 31.93 ($\text{OCH}_2\text{CH}_2\text{CH}_2$), 29.72 ($\text{OCH}_2\text{CH}_2(\text{CH})_{18}\text{CH}_3$), 29.54 ($\text{OCH}_2\text{CH}_2(\text{CH})_{18}\text{CH}_3$), 29.37 ($\text{OCH}_2\text{CH}_2(\text{CH})_{18}\text{CH}_3$), 26.22 ($\text{OCH}_2\text{CH}_2(\text{CH})_{18}\text{CH}_3$), 22.69 ($\text{OCH}_2\text{CH}_2(\text{CH})_{18}\text{CH}_3$), 14.10 (CH_3).

2',2'- Bis(2,2-di(docosyloxymethyl)ethoxymethyl)ethanol (9). To a solution of 7.05 g **8** (4.71 mmol) in anhydrous 40.0 mL THF, 15.1 mL 0.5 M 9-BBN in THF solution was added dropwise under a N_2 atmosphere at room temperature. The reaction mixture was stirred under a N_2 atmosphere for 18 h. The reaction was cooled in an ice-water bath, 4.71 mL 3 M NaOH (aq.) aqueous solution was added and stirred under a N_2 atmosphere at room temperature for 30 min. The reaction mixture was cooled in an ice-water bath while 4.71 mL 30% H_2O_2 (aq.) aqueous solution was added by dropwise addition to the reaction mixture. After the addition was complete, the reaction mixture was stirred under a N_2 atmosphere at room temperature for 3 h. The THF was removed by rotary evaporation. A saturated K_2CO_3 (aq.) aqueous solution was added to the mixture. The product was extracted with CHCl_3 . The organic washings were combined, washed once with saturated NaCl (aq.) solution and dried over anhydrous Na_2SO_4 . The solids were removed by filtration. The CHCl_3 was removed by rotary evaporation. The resulting product was purified by recrystallization from EtOAc to yield 5.45 g (76%) of a colorless solid. TLC (SiO_2 , 9:1 hexanes/THF) $R_f = 0.32$. ^1H NMR (400MHz, CDCl_3 , δ): 3.74 (d, $J = 5.2$, $-\text{CH}_2\text{OH}$, 2H), 3.36-3.52 (m, $-\text{CH}_2\text{O}$, 24H), 2.10-2.20 (m, $-\text{CHCH}_2$, 3H), 1.52-1.56 (m, $-\text{OCH}_2\text{CH}_2$, 8H), 1.25 (m, $-\text{OCH}_2\text{CH}_2(\text{CH}_2)_{19}\text{CH}_3$, 152H), 0.88 (t, $J = 7.2$ Hz, $-\text{CH}_3$, 3H). ^{13}C NMR (CDCl_3 , δ): 71.37 ($\text{C}(\text{H})\text{CH}_2$), 70.11 (OCH_2), 69.21 (H_2COH), 40.29 ($\text{C}(\text{H})\text{CH}_2$), 31.93 (OCH_2CH_2), 29.72

(OCH₂CH₂(CH)₁₉CH₃), 29.68 (OCH₂CH₂(CH)₁₉CH₃), 29.53 (OCH₂CH₂(CH)₁₉CH₃), 29.36 (OCH₂CH₂(CH)₁₉CH₃), 26.20 (OCH₂CH₂(CH)₁₉CH₃), 22.69 (OCH₂CH₂(CH)₁₉CH₃), 14.11 (CH₃).

2',2'- Bis(2,2-di(docosyloxymethyl)ethoxymethyl)ethane azide (1). A solution of 2.0 g **9** (1.32 mmol), 0.51 mL MsCl (6.61 mmol), and 0.53 mL pyridine (6.61 mmol) in 6.6 mL dry CH₂Cl₂ was stirred for 3 h at room temperature under a N₂ atmosphere. The reaction mixture was washed once with 1 M HCl (aq.) solution and three times with saturated NaHCO₃ (aq.) solution. The CH₂Cl₂ layer was washed with saturated NaCl (aq.) solution, and then dried over MgSO₄. After removing CH₂Cl₂ by rotary evaporation, the resulting product was purified by flash chromatography (SiO₂, hexanes to 5% THF in hexanes) to yield 0.6 g (80%) of a colorless solid. TLC (SiO₂, 19:1 hexanes/THF) *R_f* = 0.32. ¹H NMR (CDCl₃, δ): 4.23 (d, *J* = 5.2 Hz, CH₂OMs, 2H), 3.36-3.47 (m, CH₂O, 24H), 2.92 (s, SCH₃, 3H), 2.24 (m, CHCH₂OMs, 1H), 2.12 (m, CHCH₂OCH₂, 2H), 1.54 (m, OCH₂CH₂, 8H), 1.25 (m, OCH₂CH₂(CH₂)₁₉CH₃, 152H), 0.88 (t, *J* = 9.6 Hz, CH₃, 3H). ¹³C NMR (CDCl₃, δ): 71.32 (CH₂O(CH₂)₂₁CH₃), 69.72 (OCH₂CHCH₂O), 69.36 (CH₂CHCH₂N₃), 69.14 (OCH₂(CH₂)₂₁CH₃), 50.39 (CH₂N₃), 40.34 (C(H)CH₂O), 39.99 (C(H)CH₂N₃), 31.93 (OCH₂CH₂), 29.72 (OCH₂CH₂(CH)₁₉CH₃), 29.54 (OCH₂CH₂(CH)₁₉CH₃), 29.37 (OCH₂CH₂(CH)₁₉CH₃), 26.21 (OCH₂CH₂(CH)₁₉CH₃), 22.69 (OCH₂CH₂(CH)₁₉CH₃), 14.11 (CH₃).

2,2- Bis(tetradecyloxymethyl)ethene (15). A solution of 9.36 g 1-tetradecanol (44 mmol) in anhydrous 24 mL THF was added dropwise to a suspension of 1.51 g NaH (62.9 mmol) in 20 mL dry THF, 0.86 mL 15-crown-5 (4.4 mmol) and 2.43 mL methallyl dichloride (21.0 mmol) cooled in an ice-water bath under a N₂ atmosphere. The reaction mixture was heated at reflux for 16 h under a N₂ atmosphere while stirring. The reaction mixture was quenched with deionized water. The product was extracted with EtOAc. The organic washings were combined, washed once with saturated NaCl (aq.) solution and dried over anhydrous MgSO₄. The MgSO₄ was removed by

filtration. The EtOAc was removed by rotary evaporation. The resulting product was purified by flash chromatography (SiO₂, hexanes to 20% EtOAc in hexanes), followed by repeated recrystallizations from acetone to yield 8.84 g (88.4%) of a colorless solid. TLC (SiO₂, 4:1 hexanes/EtOAc) $R_f = 0.81$. ¹H NMR (CDCl₃, δ): 5.16 (s, -CCH₂, 2H), 3.96 (s, -CCH₂O, 4H), 3.40 (t, $J = 6.6$ Hz, -OCH₂, 4H), 1.57 (m, -OCH₂CH₂, 4H), 1.20-1.40 (m, -OCH₂CH₂(CH)₁₁CH₃, 44H), 0.88 (t, $J = 6.6$ Hz, -CH₃, 6H). ¹³C NMR (CDCl₃, δ): 143.36 (H₂C=C), 113.26 (H₂C=C), 71.49 (C=CCH₂O), 70.56 (OCH₂), 31.92 (OCH₂CH₂), 29.75 (OCH₂CH₂(CH)₁₁CH₃), 29.68 (OCH₂CH₂(CH)₁₁CH₃), 29.62 (OCH₂CH₂(CH)₁₁CH₃), 29.51 (OCH₂CH₂(CH)₁₁CH₃), 29.35 (OCH₂CH₂(CH)₁₁CH₃), 26.21 (OCH₂CH₂(CH)₁₁CH₃), 22.68 (OCH₂CH₂(CH)₁₁CH₃), 14.08 (CH₃).

2,2- Bis(tetradecyloxymethyl)ethanol (16). To a solution of 2.00 g **16** (4.17 mmol) in 10.0 mL anhydrous THF, 13.1 mL 0.5 M 9-BBN in THF solution was added dropwise under a N₂ atmosphere at room temperature. The reaction mixture was stirred under a N₂ atmosphere for 18 h. The reaction was cooled in an ice-water bath; 3.43 mL 3 M NaOH (aq.) aqueous solution was added and stirred under a N₂ atmosphere at room temperature for 30 min. The reaction mixture was cooled in an ice-water bath again and 3.43 mL 30% H₂O₂ (aq.) aqueous solution was added dropwise to the reaction mixture. After the addition was complete, the reaction mixture was stirred under a N₂ atmosphere at room temperature for 3 h. The THF was then removed by rotary evaporation. Saturated K₂CO₃ aqueous solution was added to the mixture. The product was extracted with ethyl acetate. The organic washings were combined, washed once with saturated NaCl (aq.) solution and dried over anhydrous MgSO₄. The MgSO₄ was removed by filtration. The EtOAc was removed by rotary evaporation. The resulting product was purified by repeated recrystallizations from acetone to yield 1.60 g (80%) of a colorless solid. TLC (SiO₂, hexanes/EtOAc = 4:1) $R_f = 0.25$. ¹H NMR (CDCl₃, δ): 3.76 (t, $J = 6.0$ Hz, -CH₂OH, 2H), 3.52 (m, -

CHCH₂, 4H), 3.41 (t, *J* = 6.6Hz, -OCH₂, 4H), 2.93 (t, *J* = 5.7Hz, -CH₂OH, 1H), 2.10 (m, -CHCH₂, 1H), 1.57 (m, -OCH₂CH₂, 4H), 1.25 (m, -OCH₂CH₂(CH₂)₁₁CH₃, 44H), 0.88 (t, *J* = 6.3Hz, -CH₃, 6H). ¹³C NMR (CDCl₃, δ): 71.61 (C(H)CH₂), 70.98 (OCH₂), 64.83 (H₂COH), 41.23 (C(H)CH₂), 31.91 (OCH₂CH₂), 29.66 (OCH₂CH₂(CH)₁₁CH₃), 29.62 (OCH₂CH₂(CH)₁₁CH₃), 29.45 (OCH₂CH₂(CH)₁₁CH₃), 29.34 (OCH₂CH₂(CH)₁₁CH₃), 26.13 (OCH₂CH₂(CH)₁₁CH₃), 22.67 (OCH₂CH₂(CH)₁₁CH₃), 14.08 (CH₃).

2,2- Bis(2,2-di(tetradecyloxymethyl)ethoxymethyl)ethene (17). A solution of 19.74 g **16** (39.6 mmol) in 50 mL anhydrous THF was added dropwise to a suspension of 1.30 g NaH (54.1 mmol) in 10 mL dry THF, 2.08 mL methallyl dichloride (18.0 mmol) and 0.78 mL 15-crown-5 (4.0 mmol) cooled in an ice-water bath under a N₂ atmosphere. The reaction mixture was heated at reflux for 22 h under a N₂ atmosphere while stirring. The reaction mixture was quenched with deionized water. The product was extracted with EtOAc. The organic washings were combined, washed once with saturated NaCl (aq.) solution and dried over anhydrous MgSO₄. The MgSO₄ was removed by filtration. The EtOAc was removed by rotary evaporation. The resulting product was purified by flash chromatography (SiO₂, hexanes to 10% EtOAc in hexanes) to yield 15.79 g (83.4%) of a colorless liquid. TLC (SiO₂, 9:1 hexanes/EtOAc) *R*_f = 0.58. ¹H NMR (CDCl₃, δ): 5.14 (s, -CCH₂, 2H), 3.94 (s, -CCH₂O, 4H), 3.46-3.36 (m, -OCH₂, 20H), 2.15 (m, -OCH, 2H), 1.54 (m, -OCH₂CH₂, 8H), 1.20-1.40 (m, -OCH₂CH₂(CH₂)₁₁CH₃, 88H), 0.88 (t, *J* = 6.8 Hz, -CH₃, 12H). ¹³C NMR (CDCl₃, δ): 143.19 (H₂C=C), 113.13 (H₂C=C), 71.79 (C=CCH₂O), 71.29 (OCH₂), 69.17 (CHCH₂O), 68.93 (OCH₂CH₂), 40.39 (OCH₂CH₂), 31.93 (OCH₂CH₂CH₂), 29.71 (OCH₂CH₂(CH)₁₁CH₃), 29.66 (OCH₂CH₂(CH)₁₁CH₃), 29.53 (OCH₂CH₂(CH)₁₁CH₃), 29.37 (OCH₂CH₂(CH)₁₁CH₃), 26.21 (OCH₂CH₂(CH)₁₁CH₃), 22.69 (OCH₂CH₂(CH)₁₁CH₃), 14.09 (CH₃).

2,2 - Bis(2,2-di(tetradecyloxymethyl)ethoxymethyl)ethanol (18). To a solution of 15.8 g **17** (15.1 mmol) in 30.0 mL anhydrous THF, 48.2 mL 0.5 M 9-BBN in THF solution was added dropwise under a N₂ atmosphere at room temperature. The reaction mixture was stirred under a N₂ atmosphere overnight. The reaction was cooled in an ice-water bath, 15.1 mL 3 M NaOH (aq.) aqueous solution was added and stirred under a N₂ atmosphere at room temperature for 30 min. The reaction mixture was cooled in an ice-water bath while 15.1 mL 30% H₂O₂ (aq.) aqueous solution was added dropwise to the reaction mixture. After the addition was complete, the reaction mixture was stirred under a N₂ atmosphere at room temperature for 3 h. The THF was then removed by rotary evaporation. A saturated K₂CO₃ (aq.) solution was added to the mixture. The product was extracted with EtOAc. The organic washings were combined, washed once with saturated NaCl (aq.) solution and dried over anhydrous MgSO₄. The solid were removed by filtration. The EtOAc was removed by rotary evaporation. The resulting product was purified by flash chromatography (SiO₂, hexanes to 10% EtOAc in hexanes) to yield 11.59 g (72%) of a colorless liquid. TLC (SiO₂, 9:1 hexanes/EtOAc) *R*_f = 0.27. ¹H NMR (CDCl₃, δ): 3.73 (t, *J* = 5.6, -CH₂OH, 2H), 3.36-3.60 (m, -CH₂O, 24H), 2.10-2.20 (m, -CHCH₂, 3H), 1.52-1.56 (m, -OCH₂CH₂, 8H), 1.26 (m, -OCH₂CH₂(CH₂)₁₉CH₃, 88H), 0.88 (t, *J* = 6.8Hz, -CH₃, 12H). ¹³C NMR (CDCl₃, δ): 71.34 (C(H)CH₂), 70.09 (OCH₂), 69.20 (H₂COH), 40.27 (C(H)CH₂), 31.91 (OCH₂CH₂), 29.68 (OCH₂CH₂(CH)₁₉CH₃), 29.65 (OCH₂CH₂(CH)₁₉CH₃), 29.50 (OCH₂CH₂(CH)₁₉CH₃), 29.34 (OCH₂CH₂(CH)₁₉CH₃), 26.18 (OCH₂CH₂(CH)₁₉CH₃), 22.67 (OCH₂CH₂(CH)₁₉CH₃), 14.07 (CH₃).

2,2- Bis(2,2-di(2,2-di(tetradecyloxymethyl)ethoxymethyl)ethoxymethyl)ethene (19). A solution of 8 g **18** (7.05 mmol) in 20 mL anhydrous THF was added dropwise to a suspension of 0.25 g NaH (10.2 mmol) in 5 mL dry THF, 0.39 mL methallyl dichloride (3.41 mmol) and 0.37 mL 15-crown-5 (1.88 mmol) cooled in an ice-water bath under a N₂ atmosphere. The reaction mixture was heated at

reflux for 23 h under a N₂ atmosphere while stirring. The reaction mixture was quenched with deionized water. The product was extracted with EtOAc. The organic washings were combined, washed once with saturated NaCl (aq.) solution and dried over anhydrous MgSO₄. The solids were removed by filtration. The EtOAc was removed by rotary evaporation. The resulting product was purified by flash chromatography (SiO₂, hexanes to 10% EtOAc in hexanes) to yield 5.82 g (78%) of a colorless liquid. TLC (SiO₂, 9:1 hexanes/EtOAc) *R*_f = 0.39. ¹H NMR (CDCl₃, δ): 5.13 (s, -CCH₂, 2H), 3.92 (s, -CCH₂O, 4H), 3.30-3.45 (m, -OCH₂, 52H), 2.12 (m, -OCH, 6H), 1.54 (m, -OCH₂CH₂, 16H), 1.20-1.40 (m, -OCH₂CH₂(CH₂)₁₁CH₃, 176H), 0.88 (t, *J*=7.2 Hz, -CH₃, 24H). ¹³C NMR (CDCl₃, δ): 143.10 (H₂C=C), 112.95 (H₂C=C), 71.79 (C=CCH₂O), 71.29 (C=CCH₂OCH₂), 69.68 (C=CCH₂OCH₂CHCH₂O), 69.50 (CH₂CHCH₂OCH₂CH₂), 69.21 (CH₂OCH₂CH₂), 68.93 (OCH₂CH₂), 40.39 (CH₂CHCH₂), 31.93 (OCH₂CH₂), 29.72 (OCH₂CH₂(CH)₁₁CH₃), 29.68 (OCH₂CH₂(CH)₁₁CH₃), 29.56 (OCH₂CH₂(CH)₁₁CH₃), 29.37 (OCH₂CH₂(CH)₁₁CH₃), 26.22 (OCH₂CH₂(CH)₁₁CH₃), 22.68 (OCH₂CH₂(CH)₁₁CH₃), 14.09 (CH₃).

2,2-Bis(2,2-di(2,2-di(tetradecyloxymethyl)ethoxymethyl)ethoxymethyl)ethanol (20). To a solution of 2.0 g **19** (0.92 mmol) in anhydrous THF (20.0 mL), 5.9 mL 0.5 M 9-BBN in THF solution was added dropwise under a N₂ atmosphere in an ice-water bath. The reaction mixture was heated in an oil bath at 40 °C under a N₂ atmosphere for 16h. The reaction was cooled in an ice-water bath, 1.8 mL 3 M NaOH (aq.) solution was added and stirred under a N₂ atmosphere at room temperature for 30 min. The reaction mixture was cooled in an ice-water bath while 1.8 mL 30% H₂O₂ (aq.) solution was added dropwise to the reaction mixture. After the addition was complete, the reaction mixture was stirred under a N₂ atmosphere at room temperature for 3 h. The THF was then removed by rotary evaporation. A saturated K₂CO₃ (aq.) solution was added to the mixture. The product was extracted with EtOAc. The organic washings were combined, washed once with

saturated NaCl (aq.) solution and dried over anhydrous MgSO₄. The solids were removed by filtration. The EtOAc was removed by rotary evaporation. The resulting product was purified by flash chromatography (SiO₂, hexanes to 20% EtOAc in hexanes) to yield 1.6 g (78%) of a colorless liquid. TLC (SiO₂, 4:1 hexanes/EtOAc) *R_f* = 0.30. ¹H NMR (CDCl₃, δ): 3.71 (d, *J* = 7.2 Hz, -CH₂OH, 2H), 3.35-3.60 (m, -CH₂O, 56H), 2.10-2.20 (m, -CHCH₂, 7H), 1.52-1.56 (m, -OCH₂CH₂, 16H), 1.26 (m, -OCH₂CH₂(CH₂)₁₉CH₃, 176H), 0.88 (t, *J* = 8.0 Hz, -CH₃, 24H). ¹³C NMR (CDCl₃, δ): 71.40 (HOCH₂CHCH₂O), 71.18 (HOCH₂CHCH₂OCH₂), 69.94 (HOCH₂CHCH₂OCH₂CHCH₂O), 69.74 (CH₂CHCH₂OCH₂CH₂), 69.50 (CH₂OCH₂CH₂), 69.19 (OCH₂CH₂), 63.90 (HOCH₂), 41.42 (HOCH₂CH), 40.34 (CH₂CHCH₂), 31.93 (OCH₂CH₂), 29.72 (OCH₂CH₂(CH)₁₁CH₃), 29.68 (OCH₂CH₂(CH)₁₁CH₃), 29.56 (OCH₂CH₂(CH)₁₁CH₃), 29.37 (OCH₂CH₂(CH)₁₁CH₃), 26.22 (OCH₂CH₂(CH)₁₁CH₃), 22.68 (OCH₂CH₂(CH)₁₁CH₃), 14.09 (CH₃).

2'',2''- Bis(2',2'-di(2,2-di(tetradecyloxymethyl)ethoxymethyl)ethoxymethyl)ethane azide (2).

A solution of **20** (0.5 g, 0.23 mmol), 0.09 mL methanesulfonyl chloride (1.14 mmol), and 0.09 mL pyridine (1.14 mmol) in 1.6 mL dry CH₂Cl₂ was stirred for 3 h at room temperature under a N₂ atmosphere. The reaction mixture was washed once with 1 M HCl (aq.) solution, and three times with saturated NaHCO₃ (aq.) solution. The CH₂Cl₂ layer was washed with saturated NaCl (aq.) solution, and then dried over MgSO₄. Dichloromethane was removed by rotary evaporation. The resulting liquid was diluted in 1.2 mL dry DMF and 0.14 g NaN₃ was added to the mixture. The mixture was heated at 160 °C in an oil bath under a N₂ atmosphere for 20 h. The mixture was cooled to room temperature. Salts were removed by filtration. The solvent was removed by rotary evaporation. The resulting product was purified by flash chromatography (SiO₂, hexanes to 10% EtOAc in hexanes) to yield 0.32 g (65%) of a colorless liquid. TLC (SiO₂, 9:1 hexanes/EtOAc) *R_f* = 0.32. ¹H NMR (CDCl₃, δ): 3.34-3.45 (m, -CH₂O, N₃CH₂, 58H), 2.10-2.20 (m, -CHCH₂, 7H), 1.52-

1.56 (m, $-\text{OCH}_2\text{CH}_2$, 16H), 1.26 (m, $-\text{OCH}_2\text{CH}_2(\text{CH}_2)_{19}\text{CH}_3$, 176H), 0.88 (t, $J = 6.8$ Hz, $-\text{CH}_3$, 24H).
 ^{13}C NMR (CDCl_3 , δ): 71.30 ($\text{CH}_2\text{O}(\text{CH}_2)_{21}\text{CH}_3$), 69.72 ($\text{OCH}_2\text{CHCH}_2\text{O}$), 69.46 ($\text{CH}_2\text{CHCH}_2\text{N}_3$),
69.20 ($\text{OCH}_2(\text{CH}_2)_{21}\text{CH}_3$), 50.33 (CH_2N_3), 40.36 ($\text{C}(\text{H})\text{CH}_2\text{O}$), 40.04 ($\text{C}(\text{H})\text{CH}_2\text{N}_3$), 31.93
(OCH_2CH_2), 29.72 ($\text{OCH}_2\text{CH}_2(\text{CH})_{19}\text{CH}_3$), 29.68 ($\text{OCH}_2\text{CH}_2(\text{CH})_{19}\text{CH}_3$), 29.37
($\text{OCH}_2\text{CH}_2(\text{CH})_{19}\text{CH}_3$), 26.21 ($\text{OCH}_2\text{CH}_2(\text{CH})_{19}\text{CH}_3$), 22.69 ($\text{OCH}_2\text{CH}_2(\text{CH})_{19}\text{CH}_3$), 14.11 (CH_3).

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