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# Synthesis of novel polyesteramine dendrimers by divergent and convergent methods

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ABSTRACT

Novel dendrimers having an adamantane structure as a core were synthesized such that even low generation dendrimers had a globular structure. Moreover we tried to give them biodegradable function by using ester bonds. Synthesis of the dendrimers, particularly at higher generations, proved difficult via a stepwise procedure, and thus a convergent route was used in which the adamantane core is coupled to the dendritic segments in the final step. We achieved the synthesis of two separate dendrimers with convergent methods till the third generations. The convergent dendrimers were synthesized in good yields compared with divergent one and both dendrimers were found to have narrow polydispersities by GPC analysis.



## 1. Introduction

Dendrimers are very interesting macromolecules with highly branched structures and globular shapes. Molecular sizes of dendrimers are increased stepwise via repeated reaction sequences. Since the first dendrimers were synthesized by Tomalia et al. [1–3], many kinds of dendrimers have been synthesized [4], used not only for chemical applications but also for biomedical applications [5–11]. For example, commercially available polyamidoamine (PAMAM) and polypropylenimine (PPI) dendrimers are widely used as drugs [6], gene delivery systems [7], and MRI contrast agents [9]. Additionally, these dendrimers provide a high gene transfer efficiency into mammalian cells [12–15]. This transfer efficiency is considered to be a result of the many interior tertiary amines, which exist in the dendrimer, leading to an effect known as a proton sponge [16]. Moreover, these dendrimers have many functional groups such as amino groups and hydroxyl groups on their periphery [12–15,17], and modification of these surface groups with various molecules offers the chance for other potential applications [18–23]. However, for medical applications, dendrimers must be less toxic and more biodegradable than such dendrimers. Recently polyester dendrimers called 'biodendrimers' have been reported [24–26], which have building blocks known to be biocompatible or degradable to natural metabolites in vivo. Other types of polyester dendrimers have been synthesized [27–29] and have shown an antitumor effect [29]. Furthermore, a robust and biodegradable PEGylated dendrimer based on a polyester-polyamide hybrid core has been synthesized and biodistribution and chemotherapy study in tumored mice have been evaluated [30]. However, there are few reports on polyester dendrimers including primary and tertiary amines. To form complexes with plasmid DNA, antisense oligonucleotide or siRNA and other biological molecules, it is necessary for the dendrimers to have primary amines. These amino groups would not only allow complex formation, but would also interact with cellular membranes and enable conjugation with various ligands.

In this study, we designed novel polyester dendrimers **X**–**Z** named 'polyesteramine dendrimers' (Fig. 1).

As the core of the dendrimer, we selected an adamantane structure. Typically, planar or linear molecules, such as ammonia, ethylenediamine, 1,4-diaminobutane, benzene derivatives, lactic acid, succinic acid, adipic acid, and ethylene glycol, have been used for the dendrimer core [4,24–26,28]. These dendrimers maintain a planar structure in lower generations. Adamantane, on the other hand, has a three-dimensional structure, and dendrimers having an adamantane core are expected to have a more globular structure than dendrimers such as PAMAM even in lower generations. In terms of synthesis, PAMAM dendrimers are synthesized by a typical stepwise and iterative two-step reaction sequence [1–3], consisting of amidation of methyl acrylate with ethylenediamine and Michael

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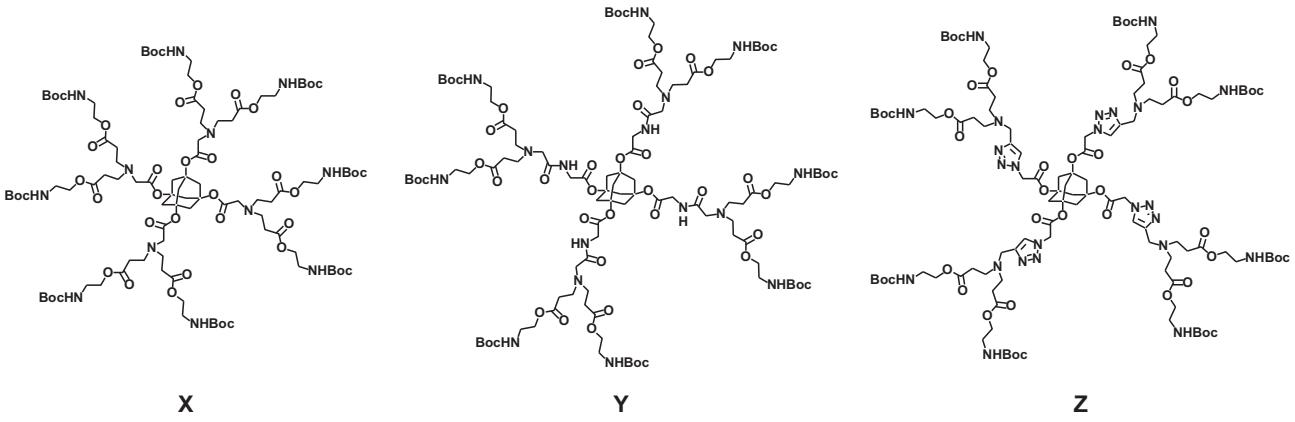



**Fig. 1.** Structures of polyester dendrimers **X**, **Y**, and **Z**.

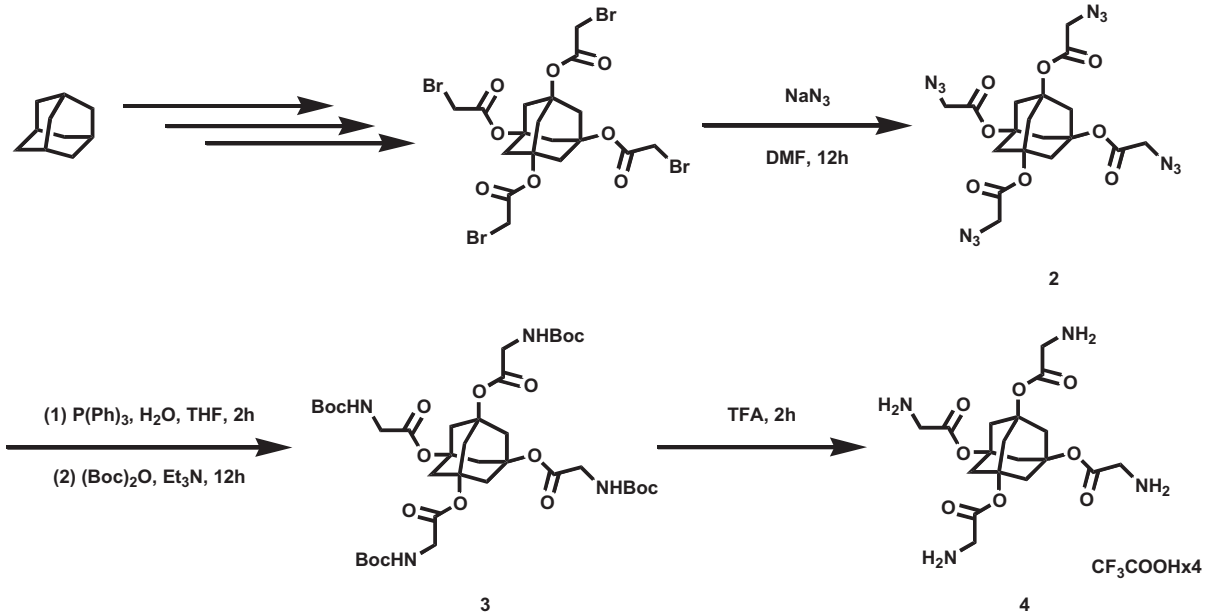
addition of primary amines with methyl acrylate. But it is known that this method sometimes leads to a lot of structural defects and also requires a long reaction time, which is a critical impediment for obtaining dendrimers with a uniform molecular weight, particularly in higher generations [1,2]. Separation of dendrimers having primary amines in the periphery is also a difficult task. In order to resolve these problems, we designed a novel dendrimer having a three-dimensional adamantane core, and synthesized dendrimers via two separate convergent routes employing amidation and Huisgen [3+2] cycloaddition reaction as the key coupling reactions, respectively.

## 2. Results

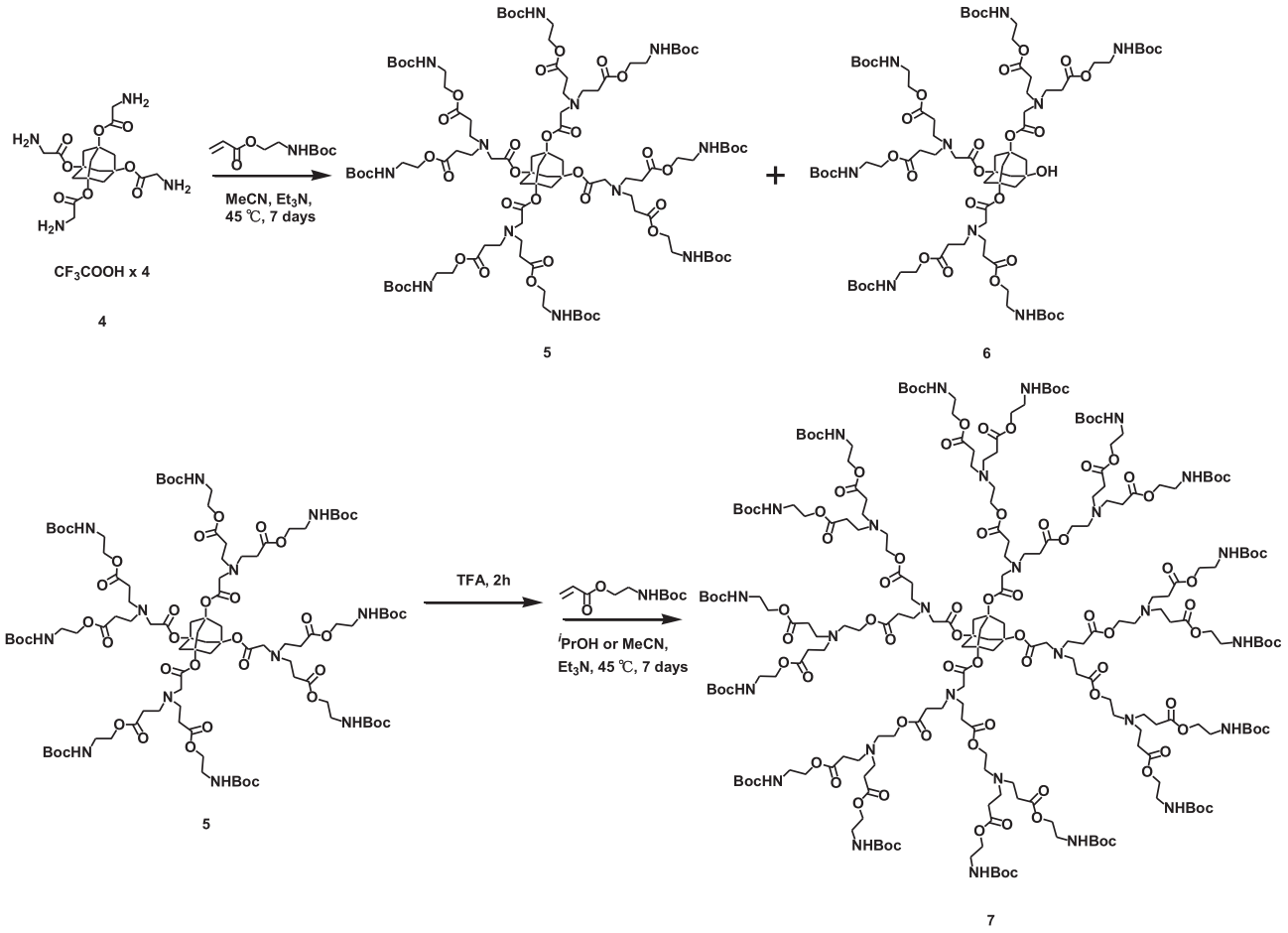
1,3,5,7-Tetrakis(aminoacetoxy)adamantane core **4** was synthesized as shown in Scheme 1. 1,3,5,7-Tetrakis(bromoacetoxy)adamantane, prepared according to a literature procedure, was treated with $NaN_3$ to give azidoacetoxy derivative **2** in 73% yield. Although several attempts to obtain **4** by direct reduction of **2** resulted in a complex mixture, Boc-protected derivative **3** was successfully obtained by reduction of **2** using triphenylphosphine and simultaneous Boc-protection in 76% yield. Deprotection of the Boc group of **3** by treatment with trifluoroacetic acid (TFA) smoothly took place, and the desired glycinoyloxy derivative **4** was isolated as a tetratrifluoroacetate salt in 91% yield.

At first, we examined the usual stepwise elongation method for the synthesis of dendrimer **7** as shown in Scheme 2. Michael reaction of **4** with 2-Boc-aminoethylacrylate **1**, prepared from 2-Boc-aminoethanol and acryloyl chloride, proceeded to give the first generation dendrimer **5** in 32% yield accompanied by the deacylated product **6** in 32% yield. Although we examined the reaction under various conditions, it was not possible to prevent formation of the deacylated product **6**. Next, deprotection of dendrimer **5** by TFA followed by Michael reaction was carried out. However, unfortunately, a complex mixture was given. MALDI-TOF-MS analysis of the crude product showed the existence of a number of incompletely reacted products (Fig. 2). The desired second generation dendrimer **7** was also detected by the spectrum, but could not be isolated from the mixture.

These results indicated that it was going to be difficult to obtain higher generation dendrimers having a uniform molecular weight by the present stepwise method. Therefore, we selected a convergent method for the synthesis of the higher generation dendrimers. We planned for the adamantane core to be coupled with dendritic




**Scheme 1.** Synthesis of two types of adamantane core.




**Scheme 2.** Synthesis of novel dendrimers by divergent method.

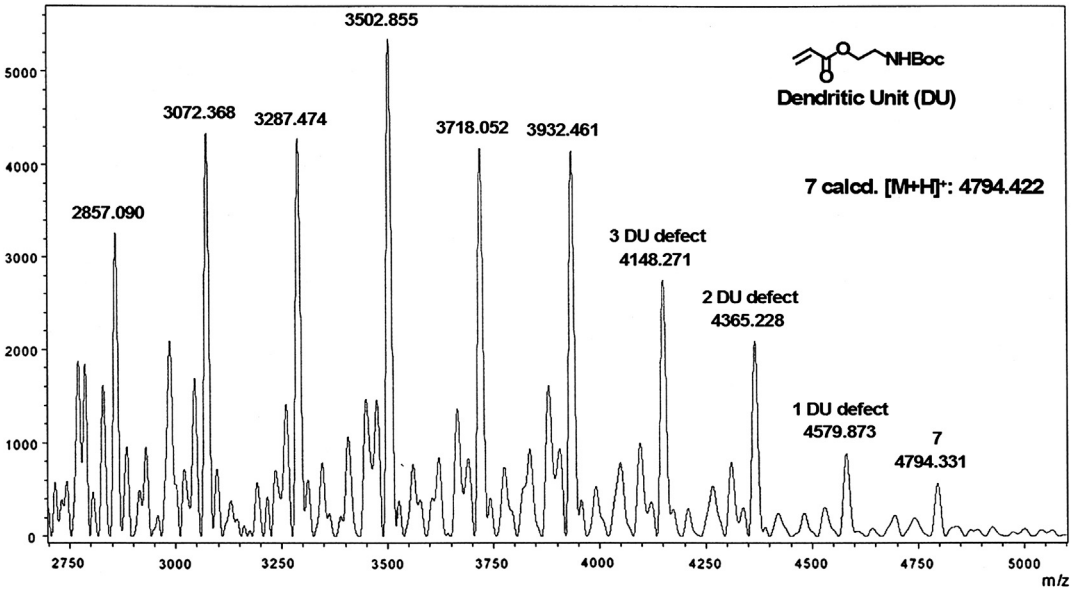
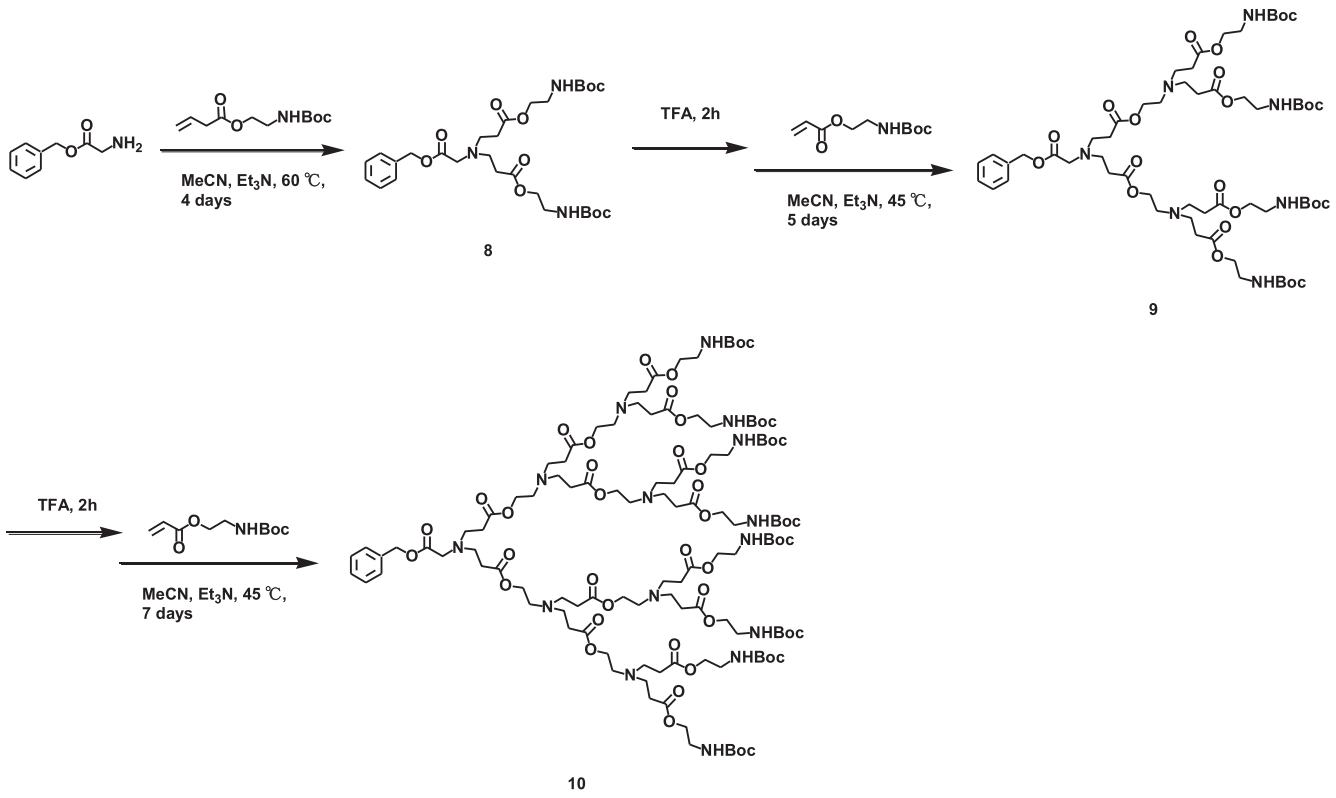



**Fig. 2.** MALDI-TOF-MS spectra of crude Boc-G2 (**7**).

segments by amide formation. The segments were to be synthesized according to a usual procedure (deprotection and Michael reaction) as shown in Scheme 3. Michael reaction of Gly–OBn with acrylate **1** afforded bisadduct **8**, which corresponds to the segment for the first generation, in 93% yield. The segment **9** for the second generation was prepared from **8** by deprotection of the Boc group followed by Michael reaction in 37% yield. Similarly, the segment **10** for the third generation was obtained in 22% yield.




**Scheme 3.** Synthesis of benzyl ester glycine dendrons.

The coupling reaction between the adamantane core **4** with the segment was carried out as shown in Scheme 4. After removal of the benzyl ester of **8** under reductive conditions, the resultant carboxylic acid was coupled with the adamantane core **4** using PyBOP as a condensing agent to give **11** in 87% yield; PyBOP is known to be superior to DCC, TFFH, and a number of other commercially available peptide coupling reagents [31]. The segments for the higher generation dendrimers, **9** and **10**, were also coupled with **4** according to the same procedure to give **12** and **13** in 36% and 22% yields, respectively.

Recently, Huisgen [3+2] dipolar cycloaddition reaction has gained much attention in general synthetic chemistry [32], and has also been applied to the synthesis of dendrimers [33–38]. As it is obvious that azido-intermediate **2** would work as a substrate for the Huisgen reaction with a proper alkyne derivative, we synthesized novel segments having an alkyne structure as shown in Scheme 5. In this case, propargyl amine was employed for the starting material, which reacted quantitatively with acrylate **1** to give **14** as the first generation segment. Segment **15** for the second generation, and segment **16** for the third generation were also obtained in 24% and 14% yields, respectively, via sequential reactions (deprotection by TFA treatment and Michael reaction with acrylate).

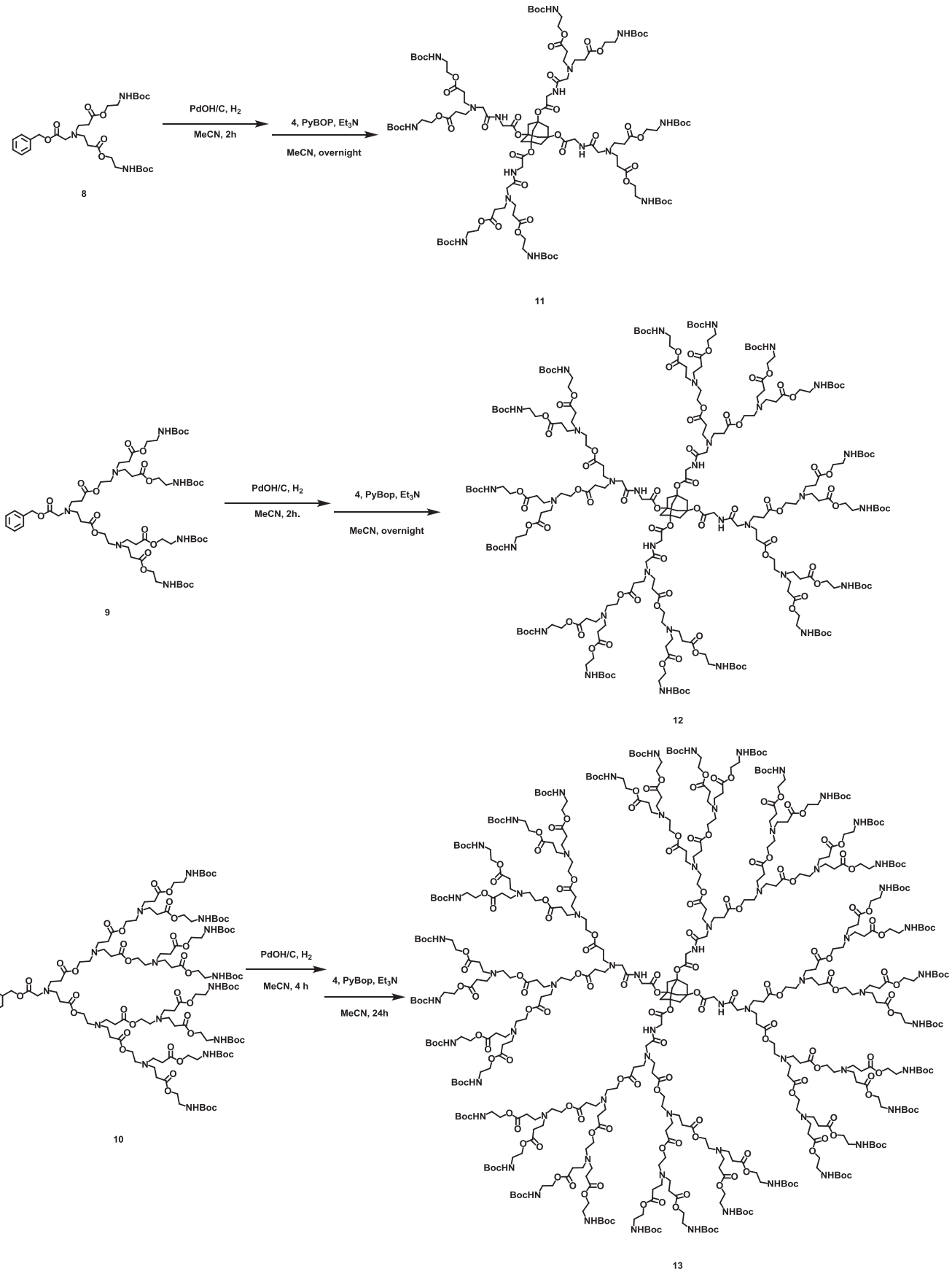
As shown in Scheme 6, dendrimers **17**, **18**, and **19**, were obtained by coupling of azido-derivative **2** with segments **14**, **15**, and **16**, respectively, under the typical conditions of Huisgen reaction. The yield for dendrimers of the higher generation decreased, but was nonetheless satisfactory.

Molecular weight data determined by MALDI-TOF-MASS and gel permeation chromatography (GPC) and polydispersity indices (PDIs) are summarized in Table 1. The mass spectrometry data agrees with the calculated molecular weights. All dendrimers show narrow PDIs, indicating that these compounds were obtained in pure form, thus confirming the effectiveness of a convergent route for the synthesis of dendrimers.

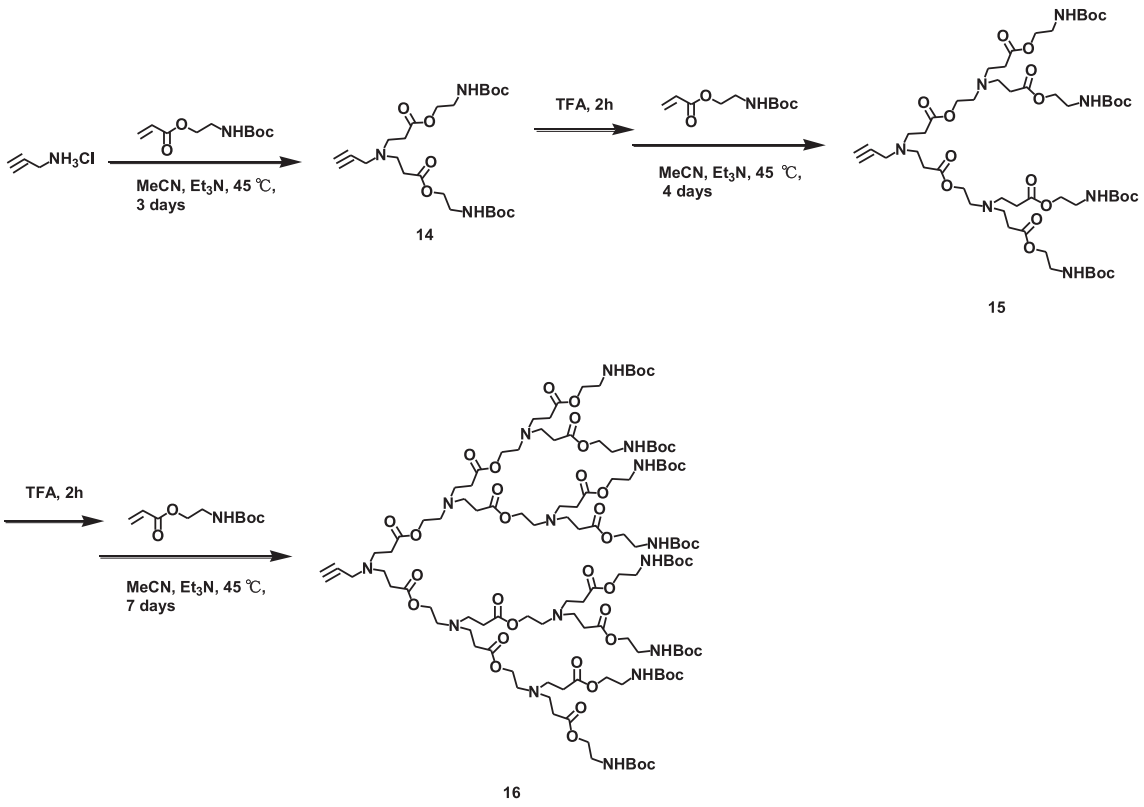
## 3. Discussion

We aimed to synthesize biodegradable polyester dendrimers including primary and tertiary amino groups for biochemical and medical applications. We chose adamantane as a dendrimer core to produce novel dendrimers that were more globular in lower generations than commercially available dendrimers and many other reported dendrimers. The number-average molecular weight ($M_n$) and weight-average molecular weight ($M_w$), which were determined by GPC measurements, deviate from the mass spectrometry data as the generation number increases (Table 1). This result is consistent with the previous data of dendrimers adopting a more globular structure [25,26]. In this study, amide glycine dendrimers **11**–**13** (AG Boc-G1–3) and click chemistry dendrimers **17**–**19** (CC Boc-G1–3) show less $M_w$ than the expected one even at the low generation numbers (G2 and G3). These results suggest that the novel dendrimers possessing an adamantane core have a more globular structure even in lower generations. We constructed molecular models of G1, AG G1, and CC G1, which are compared with PAMAM G1 (Fig. 3). Although PAMAM G1 is planar, the novel G1, AG G1, and CC G1 dendrimers are more steric due to a tetrahedral core. We expect these novel dendrimers to grow up more spherically.

It is known that the transfection activity of PAMAM dendrimers increases with higher generations [12,13]. This enhanced activity is largely considered to be a result of the spherical structure of the dendrimers. That is, the more spherical the dendrimer structures, the better their ability as a gene carrier. However, it is also the case that the higher the dendrimer generation, the greater the toxicity of the dendrimer [8]. If the dendrimers can be degraded and metabolized at physiological conditions after drug delivery, they




**Scheme 4.** Synthesis of amide glycine dendrimers.




**Scheme 5.** Synthesis of click dendrons.

would have greater application as non-viral carriers. Recently, a variety of biodegradable polymers have been used as non-viral carriers for plasmid DNA delivery [39]. Park et al. reported that a poly(amino ester) including primary and tertiary amines and esters exhibited relatively slow biodegradability, as the DNA/polymer complex was maintained for 7 days [40]. By contrast, in synthesis of 1,3,5,7-tetrakis(aminoacetoxy)adamantane bearing free primary amines, generation of primary amino groups led to readily self-degradation. In the synthesis of divergent dendrimer Boc-G1 **5**, the generation of primary amino groups also led to the appearance of incomplete Boc-G1 **6**. Fife et al. reported that the existence of intramolecular neighboring amino groups effectively catalyzed ester hydrolysis [41]. Thus, this phenomenon would be due to high degradability of 1,3,5,7-tetrakis(aminoacetoxy)adamantane bearing neighboring amines. From these results, we considered that the emergence of free primary amino groups is an obstacle to synthesis of polyesteramine dendrimers because of degradation of the adamantane core. Thus, it is very important to limit generation of free primary amines in the synthesis of polyesteramine dendrimers. Using two separate convergent methods, we were able to produce polyesteramine dendrimers until the third generation. The yields of the two kinds of dendrimers synthesized by a convergent approach drop with higher generations, which is consistent with previous observations [31,36]. This could be due to significant retention of the polar dendrimers in the silica column, steric hindrance of the higher generation dendrons, and partial degradability.

## 4. Conclusion

In summary, we have presented divergent and convergent procedures for the synthesis of novel polyesteramine dendrimers. Convergent approaches were more efficient than the divergent method in synthesizing higher generation dendrimers. By monitoring Michael addition reactions in synthesis of the higher generation dendrons and dendrimers with MALDI-TOF-MASS, we found that they were not attained completely in higher generations. Though the low yields must be improved, these methods provide interesting new polyesteramine dendrimers and insight into possible modifications or changes of the periphery and core of such dendrimers. We are currently working toward the characterization of the dendrimers given here and the synthesis of a variety of surface-modified dendrimers. Polyesteramine dendrimers offer many potential platforms in areas such as medicine, catalysis, photonics, and nanotechnology.

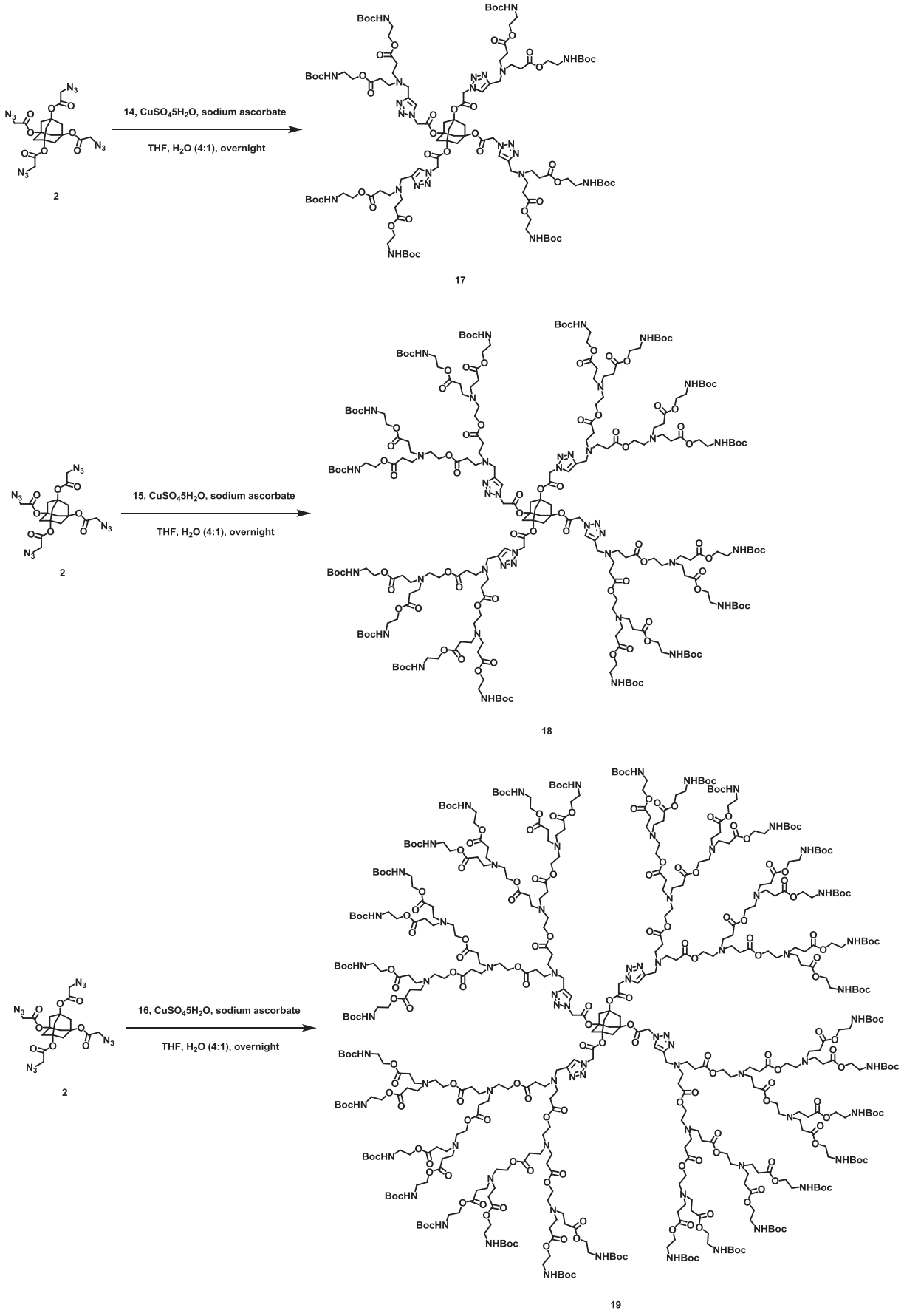
## 5. Experimental

### 5.1. General

All solvents were dried and freshly distilled prior to use. All chemicals were purchased from chemical suppliers. For column chromatography, Fuji Silysia silica gel PSQ-100B (0.100 mm) and FL-100D (0.100 mm) was used. $^{1}$H NMR (270, 300 or 400 MHz) and $^{13}$C NMR (67 or 75 MHz) spectra were recorded on JEOL JNM-EX270, JEOL JNM-AL300, and JEOL JNM-ECS400 spectrometers, respectively. IR spectra were recorded on a JASCO FT/IR-200 and JASCO FT/IR-4200 spectrometer. FAB Mass spectra were measured on a JEOL JMS-600 or JEOL JMS-700 mass spectrometer. MALDI-TOF-Mass spectra were recorded on a Bruker Daltonics Autoflex II TOF/TOF mass spectrometer. Gel permeation chromatography (GPC) was performed using THF as the eluent on a SHIMADZU column and refractive index detector. Polystyrene standards (820, 2460, 4100, 12,400, and 18,100) were used for calibration.

### 5.2. Synthesis of 2-Boc-aminoethylacrylate 1

The dendritic unit **1** was prepared by modification of a published procedure [42]. 2-Aminoethanol (25.4 g, 0.41 mol) was




**Scheme 6.** Synthesis of click chemistry dendrimers.

**Table 1**
MALDI-TOF-MS and GPC data for novel polyesteramine dendrimers

| Dendrimer | GPC | | $M_w/M_n$ | MALDI-TOF-MS | |
|---|---|---|---|---|---|
| | $M_n$ | $M_w$ | | calcd $M_w$ | Found |
| **3** | 1167 | 1178 | 1.01 | 829 | 852 $[M+Na]^+$ |
| **5** | 2623 | 2689 | 1.03 | 2150 | 2151 $[M+H]^+$ |
| **11** | 2625 | 2701 | 1.03 | 2379 | 2379 $[M+H]^+$ |
| **12** | 4536 | 4745 | 1.05 | 5022 | 5022 $[M+H]^+$ |
| **13** | 8550 | 9066 | 1.06 | 10,308 | 10,304 $[M+H]^+$ |
| **17** | 2985 | 3150 | 1.06 | 2475 | 2475 $[M+H]^+$ |
| **18** | 5114 | 5486 | 1.07 | 5118 | 5119 $[M+H]^+$ |
| **19** | 8568 | 8912 | 1.04 | 10,404 | 10,404 $[M+H]^+$ |

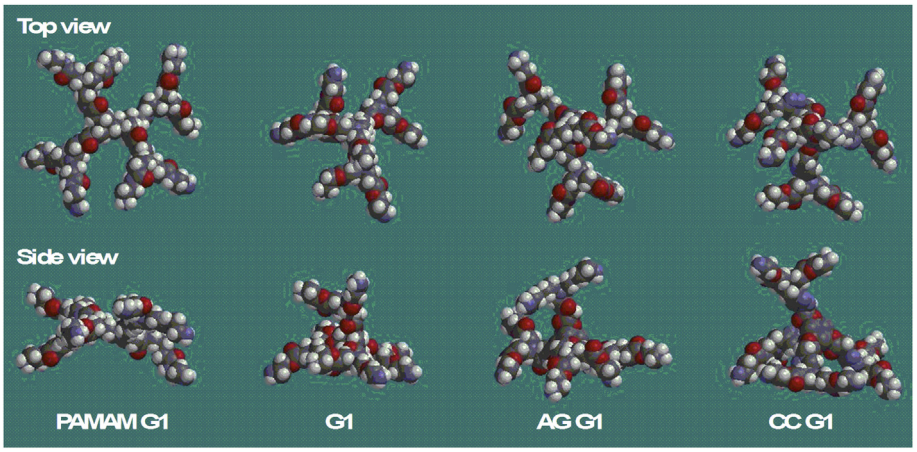



**Fig. 3.** Molecular models of PAMAM G1, G1, AG G1, and CC G1 constructed by Spartan '06.

dissolved in $CHCl_3$ (500 ml) in a flask equipped with a magnetic stirrer, and $(Boc)_2O$ (100.0 g, 0.45 mol) was added. After stirring for 30 min, the concentrated solution was diluted with $CH_2Cl_2$ (500 ml), and triethylamine (113.6 ml, 0.82 mol) and acryloyl chloride (44.5 g, 0.49 mol) were added. After stirring for 1 h under a nitrogen atmosphere, satd $NaHCO_3$ aq solution (200 ml) was added to the reaction mixture. The aqueous layer was extracted with $CH_2Cl_2$ and dried over $Na_2SO_4$. Purification of the concentrated compound was carried out by column chromatography on silica gel using ethyl acetate and hexane as eluent. A pale yellowish oil; 74.9 g, 85%. FTIR: $\nu$ ($cm^{-1}$) 3371, 3095, 3043, 2983, 2938, 1986, 1706. $^1H$ NMR ($CDCl_3$): $\delta$=1.37 (s, 9H), 3.33–3.38 (m, 2H), 4.15 (t, 2H, $J$=5 Hz), 4.98 (br, 1H), 5.78 (dd, 1H, $J$=1, 10 Hz), 6.06 (dd, 1H, $J$=10, 17 Hz), 6.36 (dd, 1H, $J$=1, 17 Hz). $^{13}C$ NMR ($CDCl_3$): $\delta$=28.2, 39.5, 63.6, 79.3, 127.9, 131.1, 155.7, 165.9. MS (FAB): $m/z$ 216 $[M+H]^+$. HRMS (FAB): $m/z$ calcd for $C_{10}H_{17}N_1O_4$ $[M+H]^+$: 216.1158; found: 216.1226. Anal. Calcd for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96; N, 6.51. Found: C, 55.93; H, 7.87; N, 6.47.

## 5.3. Synthesis of adamantane core

*5.3.1. Synthesis of 1,3,5,7-tetrakis(azidoacetoxy)adamantane* ***2***. 1,3,5,7-Tetrakis(bromoacetoxy)adamantane was synthesized from adamantane in three steps according to a literature method [43]. 1,3,5,7-Tetrakis(bromoacetoxy)adamantane (200.0 mg, 0.29 mmol) was dissolved in DMF (2.9 ml) and sodium azide (152.0 mg, 2.34 mmol) was added. After stirring for 2 h under a nitrogen atmosphere, water was added to the reaction mixture together with $CH_2Cl_2$. The aqueous layer was extracted with $CH_2Cl_2$ and dried over $Na_2SO_4$. Purification of the concentrated compound was carried out by column chromatography on silica gel using $CHCl_3$. A white solid; 112.7 mg, 73%. FTIR: $\nu$ ($cm^{-1}$) 2923, 2208, 2108, 1739. $^1H$ NMR ($CDCl_3$) $\delta$=2.62 (s, 12H), 3.80 (s, 8H). $^{13}C$ NMR ($CDCl_3$) $\delta$=43.0, 50.5, 79.1, 167.0. MS (FAB): $m/z$ 555 $[M+Na]^+$. HRMS (FAB): $m/z$ calcd for $C_{18}H_{20}N_{12}O_8$ $[M+Na]^+$: 555.1527; found: 555.1417. Anal. Calcd for $C_{18}H_{20}N_{12}O_8$: C, 40.61; H, 3.79; N, 31.57. Found: C, 40.58; H, 3.78; N, 31.22.

*5.3.2. Synthesis of 1,3,5,7-tetrakis(n-Boc-aminoacetoxy)adamantane* ***3***. The adamantane compound **2** (2.4 g, 4.43 mmol) was dissolved in a 3:1 solvent ratio of THF/$H_2O$ (29.6 ml), and triphenylphosphine (5.1 g, 19.48 mmol) was added. After stirring for 2 h, $(Boc)_2O$ (4.3 g, 19.48 mmol) and triethylamine (3.7 ml, 26.57 mmol) were added to the reaction mixture and stirred overnight. The reaction mixture was extracted with ethyl acetate and dried over $Na_2SO_4$. Purification of the concentrated compound was carried out by column chromatography on silica gel using ethyl acetate and hexane as eluent. A white foam; 2.8 g, 76%. FTIR: $\nu$ ($cm^{-1}$) 3362, 2978, 2934, 1755, 1707. $^1H$ NMR ($CD_3Cl$) $\delta$=1.45 (s, 36H), 2.53 (s, 12H), 3.82 (d, 8H, $J$=6 Hz), 4.93 (t, 4H, $J$=5 Hz). $^{13}C$ NMR ($CDCl_3$) $\delta$=28.3, 42.8, 43.1, 78.6, 80.1, 155.6, 169.0. MS (FAB): $m/z$ 851 $[M+Na]^+$. HRMS (FAB): $m/z$ calcd for $C_{38}H_{60}N_4O_{16}$ $[M+Na]^+$: 851.4004; found: 851.3887. MS (MALDI): $m/z$ calcd for $C_{38}H_{60}N_4O_{16}$ $[M+Na]^+$: 851.400; found: 851.746.

*5.3.3. Synthesis of 1,3,5,7-tetrakis(aminoacetoxy)adamantane tetratrifluoroacetate* ***4***. Compound **3** (2.0 g, 2.38 mmol) was added to TFA (7.5 ml) and stirred for 2 h. The concentrated compound was reprecipitated with ethyl acetate and lyophilized. A white solid; 1.9 g, 91%. FTIR: $\nu$ ($cm^{-1}$) 3362, 2978, 2934, 1755, 1707. $^1H$ NMR ($D_2O$) $\delta$=2.64 (s, 12H), 3.87 (s, 8H). $^{13}C$ NMR ($CD_3OD$) $\delta$=41.5, 43.8, 80.9, 167.2. MS (FAB): $m/z$ 429 $[M+H]^+$. HRMS (FAB): $m/z$ calcd for $C_{18}H_{28}N_4O_8$ $[M+H]^+$: 429.1907; found: 429.1967. Anal. Calcd for $C_{26}H_{32}F_{12}N_4O_{16}\cdot H_2O$: C, 34.60; H, 3.80; N, 6.21. Found: C, 34.44; H, 3.97; N, 5.95.

## 5.4. Synthesis of dendrimers by divergent method

*5.4.1. Synthesis of Boc-G1* ***5***. Compound **4** (519.8 mg, 0.59 mmol) was dissolved in $CH_3CN$ (5.9 ml), and **1** (5.1 g, 23.51 mmol) and triethylamine (650 μl, 4.70 mmol) were added. After stirring for 7 days at 45 °C under a nitrogen atmosphere, the reaction mixture was extracted with ethyl acetate and dried over $Na_2SO_4$. Purification of the concentrated compound was carried out by column chromatography on silica gel using ethyl acetate and hexane as eluent. A pale yellowish foam; 403.8 mg, 32%. FTIR: $\nu$ ($cm^{-1}$) 3380, 2977, 1713. $^1H$ NMR ($CDCl_3$) $\delta$=1.36 (s, 72H), 2.36–2.43 (m, 28H),

2.89 (t, 16H, $J$=6 Hz), 3.26–3.32 (m, 24H), 4.06 (t, 16H, $J$=5 Hz), 5.14 (br, 8H). $^{13}$C NMR ($CDCl_3$) $\delta$=28.3, 33.4, 39.4, 43.3, 49.3, 54.8, 63.5, 78.0, 79.2, 155.6, 169.6, 171.9. MS (FAB): $m/z$ 2150 $[M+H]^+$. MS (MALDI): $m/z$ calcd for $C_{98}H_{164}N_{12}O_{40}$ $[M+H]^+$: 2150.117; found: 2150.650.

*5.4.2. Synthesis of Boc-G2* ***7***. Compound **5** (112 mg, 0.05 mmol) was added to TFA (2.0 ml) and stirred for 2 h. The concentrated compound was reprecipitated with ethyl acetate and lyopholized. The deprotected compound (100 mg, 0.04 mmol) was dissolved in $^{i}$PrOH (0.4 ml), and **1** (1.5 g, 7.07 mmol) and triethylamine (123 μl, 0.88 mmol) were added. After stirring for 7 days at 45 °C under a nitrogen atmosphere, the reaction mixture was extracted with ethyl acetate and dried over $Na_2SO_4$. Purification of the concentrated compound was carried out by column chromatography on silica gel using ethyl acetate and acetone as eluent. A yellowish gum; trace.

## 5.5. Synthesis of benzyl ester glycine dendrons

*5.5.1. Synthesis of BnGD Boc-G1* ***8***. Glycine benzyl ester *p*-toluenesulfonate (2.0 g, 5.92 mmol) was dissolved in $CH_3CN$ (10 ml), and **1** (3.8 g, 17.78 mmol) and triethylamine (1.6 ml, 11.86 mmol) were added. After stirring for 4 days at 60 °C under a nitrogen atmosphere, the reaction mixture was extracted with ethyl acetate and dried over $Na_2SO_4$. Purification of the concentrated compound was carried out by column chromatography on silica gel using ethyl acetate and hexane as eluent. A pale yellowish oil; 3.3 g, 93%. FTIR: $\nu$ ($cm^{-1}$) 3730, 3592, 3368, 3064, 2977, 1958, 1712. $^1$H NMR ($CDCl_3$) $\delta$=1.43 (s, 18H), 2.46 (t, 4H, $J$=7 Hz), 2.98 (t, 4H, $J$=7 Hz), 3.33–3.39 (m, 4H), 3.46 (s, 2H), 4.12 (t, 4H, $J$=5 Hz), 5.13 (m, 4H), 7.34 (s, 5H). $^{13}$C NMR ($CDCl_3$) $\delta$=28.4, 33.4, 39.6, 49.6, 54.5, 63.7, 66.3, 79.4, 128.2, 128.3, 128.5, 135.4, 155.7, 170.8, 172.1. MS (FAB): $m/z$ 596 $[M+H]^+$. HRMS (FAB): $m/z$ calcd for $C_{29}H_{45}N_3O_{10}$ $[M+H]^+$: 596.3105; found: 596.3177.

*5.5.2. Synthesis of BnGD Boc-G2* ***9***. Compound **8** (721 mg, 1.21 mmol) was added to TFA (3 ml) and stirred for 2 h. The concentrated compound was lyopholized. The deprotected compound (916 mg, 1.24 mmol) was dissolved in $CH_3CN$ (14.1 ml), and **1** (6.1 g, 28.31 mmol) and triethylamine (1.2 ml, 8.49 mmol) were added. After stirring for 5 days at 45 °C under a nitrogen atmosphere, the reaction mixture was extracted with ethyl acetate and dried over $Na_2SO_4$. Purification of the concentrated compound was carried out by column chromatography on silica gel using ethyl acetate and hexane as eluent. A yellowish gum; 577 mg, 37%. FTIR: $\nu$ ($cm^{-1}$) 3730, 3372, 2976, 2011, 1957, 1715. $^1$H NMR ($CDCl_3$) $\delta$=1.37 (s, 36H), 2.39 (t, 12H, $J$=7 Hz), 2.64 (t, 4H, $J$=6 Hz), 2.75 (t, 8H, $J$=7 Hz), 2.92 (t, 4H, $J$=7 Hz), 3.27–3.33 (m, 8H), 3.40 (s, 2H), 4.02–4.08 (m, 12H), 5.06 (s, 2H), 5.17 (br, 4H), 7.28 (s, 5H). $^{13}$C NMR ($CDCl_3$) $\delta$=28.3, 32.7, 33.2, 39.4, 49.3, 49.6, 51.8, 54.4, 62.0, 63.5, 66.0, 79.2, 128.0, 128.0, 128.3, 135.3, 155.5, 170.6, 171.8, 171.9. MS (FAB): $m/z$ 1256.6 $[M+H]^+$. HRMS (FAB): $m/z$ calcd for $C_{59}H_{97}N_7O_{22}$ $[M+H]^+$: 1256.6687; found: 1256.6769. MS (MALDI): $m/z$ calcd for $C_{59}H_{97}N_7O_{22}$ $[M+H]^+$: 1256.669; found: 1256.432.

*5.5.3. Synthesis of BnGD Boc-G3* ***10***. Compound **9** (535 mg, 0.43 mmol) was added to TFA (2 ml) and stirred for 2 h. The concentrated compound was lyopholized. The deprotected compound (631 mg, 0.38 mmol) was dissolved in $CH_3CN$ (3.8 ml), and **1** (3.3 g, 15.24 mmol) and triethylamine (740 μl, 5.33 mmol) were added. After stirring for 7 days at 45 °C under a nitrogen atmosphere, the reaction mixture was extracted with ethyl acetate and dried over $Na_2SO_4$. Purification of the concentrated compound was carried out by column chromatography on silica gel using ethyl acetate and acetone as eluent. A brownish gum; 212 mg, 22%. FTIR: $\nu$ ($cm^{-1}$) 3726, 3593, 3371, 2977, 2837, 2013, 1729. $^1$H NMR ($CDCl_3$) $\delta$=1.35 (s, 72H), 2.38 (t, 28H, $J$=6 Hz), 2.63 (t, 12H, $J$=5 Hz), 2.74 (t, 24H, $J$=6 Hz), 2.89 (t, 4H, $J$=7 Hz), 3.27–3.32 (m, 16H), 3.37 (s, 2H), 4.01–4.07 (m, 28H), 5.04 (s, 2H), 5.19 (br, 8H), 7.27 (s, 5H). $^{13}$C NMR ($CDCl_3$) $\delta$=28.3, 32.5, 32.7, 33.2, 39.4, 49.3, 49.4, 49.6, 51.7, 51.8, 54.5, 62.0, 62.1, 63.4, 66.0, 79.1, 127.9, 128.0, 128.3, 135.4, 155.5, 170.6, 171.7, 171.8, 171.8. MS (MALDI): $m/z$ calcd for $C_{119}H_{201}N_{15}O_{46}$ $[M+H]^+$: 2578.943; found: 2576.640.

## 5.6. Synthesis of amide glycine dendrimers

*5.6.1. Synthesis of AG Boc-G1* ***11***. Compound **8** (150 mg, 0.25 mmol) was dissolved in $CH_3CN$ (2.5 ml) and PdOH/C (150 mg) was added. After stirring for 2 h under a hydrogen atmosphere, the reaction mixture was filtered. The concentrated compound was dissolved in $CH_3CN$ (2.5 ml), and **4** (37 mg, 0.042 mmol), PyBOP (109 mg, 0.21 mmol), and triethylamine (47 ul, 0.34 mmol) were added. After stirring for 1 day at room temperature under a nitrogen atmosphere, the reaction mixture was extracted with ethyl acetate and dried over $Na_2SO_4$. Purification of the concentrated compound was carried out by column chromatography on silica gel using ethyl acetate and acetone as eluent. A pale yellowish foam; 87 mg, 87%. FTIR: $\nu$ ($cm^{-1}$) 3331, 2974, 2927, 1712. $^1$H NMR ($CDCl_3$) $\delta$=1.43 (s, 72H), 2.49–2.53 (m, 28H), 2.80 (t, 16H, $J$=6 Hz), 3.13 (s, 8H), 3.33–3.40 (m, 16H), 3.93 (d, 8H, $J$=5 Hz), 4.12 (t, 16H, $J$=5 Hz), 5.28 (br, 8H), 8.04 (t, 4H, $J$=6 Hz). $^{13}$C NMR ($CDCl_3$) $\delta$=28.5, 32.1, 39.5, 41.4, 43.1, 49.6, 58.3, 63.9, 78.5, 79.4, 155.8, 168.2, 171.3, 172.2. MS (MALDI): $m/z$ calcd for $C_{106}H_{176}N_{16}O_{44}$ $[M+H]^+$: 2379.613; found: 2378.987.

*5.6.2. Synthesis of AG Boc-G2* ***12***. Compound **9** (188 mg, 0.15 mmol) was dissolved in $CH_3CN$ (1.5 ml) and PdOH/C (190 mg) was added. After stirring for 2 h under a hydrogen atmosphere, the reaction mixture was filtered. The concentrated compound was dissolved in $CH_3CN$ (1.5 ml), and **4** (22 mg, 0.025 mmol), PyBOP (97 mg, 0.19 mmol), and triethylamine (28 μl, 0.20 mmol) were added. After stirring overnight at room temperature under a nitrogen atmosphere, the reaction mixture was extracted with ethyl acetate and dried over $Na_2SO_4$. Purification of the concentrated compound was carried out by column chromatography on silica gel using ethyl acetate and acetone as eluent. A yellowish gum; 45 mg, 36%. FTIR: $\nu$ ($cm^{-1}$) 3364, 2926, 2854, 1713. $^1$H NMR ($CDCl_3$) $\delta$=1.42 (s, 144H), 2.47–2.51 (m, 60H), 2.74–2.85 (m, 64H), 3.14 (s, 8H), 3.33–3.38 (m, 32H), 3.91 (d, 8H, $J$=4 Hz), 4.12 (t, 48H, $J$=5 Hz), 5.26 (br, 16H), 7.96 (t, 4H, $J$=5 Hz). $^{13}$C NMR ($CDCl_3$) $\delta$=28.4, 31.7, 32.6, 39.5, 49.3, 49.8, 52.0, 57.9, 63.7, 78.5, 79.3, 155.7, 171.3, 172.0. MS (MALDI): $m/z$ calcd for $C_{226}H_{384}N_{32}O_{92}$ $[M+H]^+$: 5022.628; found: 5021.661.

*5.6.3. Synthesis of AG Boc-G3* ***13***. Compound **10** (162 mg, 0.063 mmol) was dissolved in $CH_3CN$ (0.63 ml) and PdOH/C (160 mg) was added. After stirring for 4 h under a hydrogen atmosphere, the reaction mixture was filtered. The concentrated compound was dissolved in $CH_3CN$ (0.63 ml), and **4** (9 mg, 0.010 mmol), PyBOP (41 mg, 0.079 mmol), and triethylamine (12 μl, 0.083 mmol) were added. After stirring for 1 day at room temperature under a nitrogen atmosphere, the reaction mixture was extracted with ethyl acetate and dried over $Na_2SO_4$. Purification of the concentrated compound was carried out by column chromatography on silica gel using ethyl acetate and acetone as eluent. A brownish gum; 24 mg, 22%. FTIR: $\nu$ ($cm^{-1}$) 3364, 2925, 1701. $^1$H NMR ($CDCl_3$) $\delta$=1.43 (s, 288H), 2.46 (t, 124H, $J$=6 Hz), 2.72 (t, 48H, $J$=6 Hz), 2.82 (t, 112H, $J$=6 Hz), 3.15 (s, 8H), 3.33–3.39 (m, 64H), 3.91 (s, 8H), 4.09–4.14 (m, 112H), 5.23 (br, 32H), 7.94 (br, 4H). $^{13}$C NMR ($CDCl_3$) $\delta$=28.4, 32.7, 39.6, 49.7, 52.0, 62.2, 63.6, 79.4, 155.9, 172.3.

MS (MALDI): *m/z* calcd for $C_{466}H_{800}N_{64}O_{188}$ $[M+H]^+$: 10,308.657; found: 10,303.944.

### 5.7. Synthesis of click dendrons

*5.7.1. Synthesis of CD Boc-G1* ***14***. Propargyl amine hydrochloride (915 mg, 10.0 mmol) was dissolved in $CH_3CN$ (10 ml), and **1** (6.5 g, 30.0 mmol) and triethylamine (2.8 ml, 20.00 mmol) were added. After stirring for 3 days at 45 °C under a nitrogen atmosphere, the reaction mixture was extracted with ethyl acetate and dried over $Na_2SO_4$. Purification of the concentrated compound was carried out by column chromatography on silica gel using ethyl acetate and hexane as eluent. A pale yellowish oil; 5.3 g, quant. FTIR: $\nu$ ($cm^{-1}$) 3955, 3728, 3592, 3356, 2976, 2104, 2013, 1706. $^1H$ NMR ($CDCl_3$) $\delta$=1.34 (s, 18H), 2.16 (t, 1H, *J*=2 Hz), 2.38 (t, 4H, *J*=7 Hz), 2.74 (t, 4H, *J*=7 Hz), 3.23–3.30 (m, 4H), 3.35 (d, 2H, *J*=2 Hz), 4.04 (t, 4H, *J*=5 Hz), 5.21 (br, 2H). $^{13}C$ NMR ($CDCl_3$) $\delta$=28.7, 33.2, 39.8, 41.9, 49.2, 63.8, 74.0, 77.9, 79.5, 156.0, 172.2. MS (FAB): *m/z* 486 $[M+H]^+$. HRMS (FAB): *m/z* calcd for $C_{23}H_{39}N_3O_8$ $[M+H]^+$: 486.2737; found: 486.2823.

*5.7.2. Synthesis of CD Boc-G2* ***15***. Compound **14** (1.2 g, 2.54 mmol) was added to TFA (5.0 ml) and stirred for 2 h. The concentrated compound was lyopholized. The deprotected compound (510 mg, 0.81 mmol) was dissolved in $CH_3CN$ (8.1 ml), and **1** (3.5 g, 16.26 mmol) and triethylamine (676 μl, 4.87 mmol) were added. After stirring for 4 days at 45 °C under a nitrogen atmosphere, the reaction mixture was extracted with ethyl acetate and dried over $Na_2SO_4$. Purification of the concentrated compound was carried out by column chromatography on silica gel using ethyl acetate and hexane as eluent. A yellowish gum; 223 mg, 24%. FTIR: $\nu$ ($cm^{-1}$) 3725, 3372, 2976, 2103, 2014, 1711. $^1H$ NMR ($CDCl_3$) $\delta$=1.40 (s, 36H), 2.19 (t, 1H, *J*=2 Hz), 2.43 (t, 12H, *J*=7 Hz), 2.69 (t, 4H, *J*=6 Hz), 2.79 (t, 12H, *J*=7 Hz), 3.31–3.37 (m, 10H), 4.06–4.12 (m, 12H), 5.14 (br, 4H). $^{13}C$ NMR ($CDCl_3$) $\delta$=28.1, 32.6, 32.6, 39.3, 41.5, 48.6, 49.5, 51.7, 61.9, 63.4, 73.2, 77.6, 79.1, 155.4, 171.6, 171.8. MS (FAB): *m/z* 1146.6 $[M+H]^+$. HRMS (FAB): *m/z* calcd for $C_{53}H_{91}N_7O_{20}$ $[M+H]^+$: 1146.6319; found: 1146.6372. MS (MALDI): *m/z* calcd for $C_{53}H_{91}N_7O_{20}$ $[M+H]^+$: 1146.632; found: 1146.663.

*5.7.3. Synthesis of CD Boc-G3* ***16***. Compound **15** (196 mg, 0.17 mmol) was added to TFA (3.0 ml) and stirred for 2 h. The concentrated compound was lyopholized. The deprotected compound was dissolved in $CH_3CN$ (1.6 ml), and **1** (1.4 g, 6.56 mmol) and triethylamine (318 μl, 2.30 mmol) were added. After stirring for 7 days at 45 °C under a nitrogen atmosphere, the reaction mixture was extracted with ethyl acetate and dried over $Na_2SO_4$. Purification of the concentrated compound was carried out by column chromatography on silica gel using ethyl acetate and acetone as eluent. A brownish gum; 55 mg, 14%. FTIR: $\nu$ ($cm^{-1}$) 3727, 3374, 2976, 2838, 2102, 2014, 1731. $^1H$ NMR ($CDCl_3$) $\delta$=1.42 (s, 72H), 2.22 (t, 1H, *J*=2 Hz), 2.45 (t, 28H, *J*=7 Hz), 2.70 (t, 12H, *J*=6 Hz), 2.81 (t, 28H, *J*=7 Hz), 3.33–3.39 (m, 18H), 4.08–4.14 (m, 28H), 5.15 (br, 8H). $^{13}C$ NMR ($CDCl_3$) $\delta$=28.4, 32.7, 32.9, 32.9, 39.6, 41.8, 48.9, 49.6, 49.8, 51.9, 52.0, 62.2, 62.4, 63.7, 73.5, 78.0, 79.4, 155.7, 171.9, 172.0, 172.0. MS (MALDI): *m/z* calcd for $C_{113}H_{195}N_{15}O_{44}$ $[M+H]^+$: 2468.832; found: 2468.015.

### 5.8. Synthesis of click chemistry dendrimers

*5.8.1. Synthesis of CC Boc-G1* ***17***. Compounds **2** (50 mg, 0.090 mmol) and **14** (201 mg, 0.41 mmol) were dissolved in a 4:1 solvent ratio of THF/$H_2O$ (4.1 ml), and $CuSO_4 \cdot 5H_2O$ (21 mg, 0.082 mmol) and sodium ascorbate (33 mg, 0.17 mmol) were added. After stirring overnight, the reaction mixture was extracted with ethyl acetate and dried over $Na_2SO_4$. Purification of the concentrated compound was carried out by column chromatography on silica gel using ethyl acetate and acetone as eluent. A pale yellowish foam; 184 mg, 82%. FTIR: $\nu$ ($cm^{-1}$) 3367, 2928, 1701. $^1H$ NMR ($CDCl_3$) $\delta$=1.34 (s, 72H), 2.41–2.45 (m, 28H), 2.69 (t, 16H, *J*=6 Hz), 3.23–3.29 (m, 16H), 3.75 (s, 8H), 4.03 (t, 16H, *J*=5 Hz), 5.06 (s, 8H), 5.30 (br, 8H), 7.58 (s, 4H). $^{13}C$ NMR ($CDCl_3$) $\delta$=28.3, 32.5, 39.4, 42.6, 47.9, 48.7, 50.9, 53.8, 63.4, 79.1, 124.1, 144.0, 155.6, 164.8, 172.0. MS (MALDI): *m/z* calcd for $C_{110}H_{176}N_{24}O_{40}$ $[M+H]^+$: 2475.712; found: 2474.737.

*5.8.2. Synthesis of CC Boc-G2* ***18***. Compounds **2** (25 mg, 0.046 mmol) and **15** (318 mg, 0.28 mmol) were dissolved in a 4:1 solvent ratio of THF/$H_2O$ (2.8 ml), and $CuSO_4 \cdot 5H_2O$ (14 mg, 0.055 mmol) and sodium ascorbate (22 mg, 0.11 mmol) were added. After stirring overnight, the reaction mixture was extracted with ethyl acetate and dried over $Na_2SO_4$. Purification of the concentrated compound was carried out by column chromatography on silica gel using ethyl acetate and acetone as eluent. A yellowish gum; 85 mg, 36%. FTIR: $\nu$ ($cm^{-1}$) 3371, 2976, 2110, 1731. $^1H$ NMR ($CDCl_3$) $\delta$=1.42 (s, 144H), 2.42–2.53 (m, 60H), 2.70 (t, 16H, *J*=6 Hz), 2.81 (t, 48H, *J*=6 Hz), 3.33–3.39 (m, 32H), 3.82 (s, 8H), 4.08–4.13 (m, 48H), 5.13 (s, 8H), 5.22 (br, 16H), 7.64 (s, 4H). $^{13}C$ NMR ($CDCl_3$) $\delta$=28.4, 32.5, 32.9, 39.6, 42.9, 48.1, 48.7, 49.8, 52.0, 62.2, 63.7, 79.4, 124.1, 155.7, 164.9, 172.1. MS (MALDI): *m/z* calcd for $C_{230}H_{384}N_{40}O_{88}$ $[M+H]^+$: 5118.727; found: 5118.790.

*5.8.3. Synthesis of CC Boc-G3* ***19***. Compounds **2** (8 mg, 0.014 mmol) and **16** (221 mg, 0.089 mmol) were dissolved in a 4:1 solvent ratio of THF/$H_2O$ (890 μl), and $CuSO_4 \cdot 5H_2O$ (4 mg, 0.018 mmol) and sodium ascorbate (7 mg, 0.036 mmol) were added. After stirring overnight, the reaction mixture was extracted with ethyl acetate and dried over $Na_2SO_4$. Purification of the concentrated compound was carried out by column chromatography on silica gel using ethyl acetate and acetone as eluent. A brownish gum; 30 mg, 21%. FTIR: $\nu$ ($cm^{-1}$) 3363, 2925, 1703. $^1H$ NMR ($CDCl_3$) $\delta$=1.43 (s, 288H), 2.42–2.54 (m, 124H), 2.71 (t, 48H, *J*=6 Hz), 2.82 (t, 112H, *J*=7 Hz), 3.34–3.40 (m, 64H), 3.83 (s, 8H), 4.09–4.15 (m, 112H), 5.14 (s, 8H), 5.24 (br, 32H), 7.64 (s, 4H). $^{13}C$ NMR ($CDCl_3$) $\delta$=28.5, 32.7, 32.9, 39.6, 49.6, 49.8, 52.0, 62.2, 63.7, 79.4, 155.7, 172.1, 172.1. MS (MALDI): *m/z* calcd for $C_{470}H_{800}N_{72}O_{184}$ $[M+H]^+$: 10,404.756; found: 10,403.867.

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