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Convergent Synthesis and Characterization of Dumbbell Type Dendritic Materials by Click Chemistry

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General, fast, and efficient stitching methods for the synthesis of dendrimers with linear PEG units at a core, as dendritic-linear-dendritic materials, were developed. The synthetic strategy involved the click reaction between an alkyne and an azide. The linear core building blocks, three dialkyne-PEG units, were chosen to serve as the alkyne functionalities for dendrimer growth *via* click reactions with the azide-dendrons. These three building blocks were employed together with the azide-functionalized Fréchet-type dendrons in a convergent strategy to synthesize the Fréchet-type dendrimers with different linear core units. Their structure of dendrimers was confirmed by ^{1}H and ^{13}C NMR spectroscopy, IR spectroscopy, mass spectrometry, and GPC analysis.

Key Words : Alkyne, Azide, Click reaction, Dendritic-linear-dendritic materials, Dendrimer

Introduction

Dendrons and dendrimers are the most intensely investigated subset of dendritic polymers. Dendrimers, which are prepared by repetition of a given set of reactions using either divergent or convergent strategies, are highly branched and regular macromolecules with well-defined structures and have served as functional objects in nanotechnology and nanoscience.[1] The amphiphilic dendrimer polymers consisting of both hydrophobic and hydrophilic regions in the same molecule appear as an important issue throughout the physical and life sciences and can be considered unimolecular micelles. Amphiphilic dendrimer polymers can be classified into dendritic-linear polymers possessing a hydrophilic dendritic component and a hydrophobic linear polymer (or vice versa).[2] Dendritic-linear diblock copolymers have been synthesized by the stepwise preparation methods, which proceed in either a convergent or divergent strategy.[3-10]

The building blocks of the linear-dendritic copolymers are only two, but they could be positioned in several distinct configurations due to the presence of multiple anchoring points in both of them. The size (length and generation) and the polarity of the blocks would determine the relative hydrophobic/hydrophilic balance. The characteristic feature of the linear-dendritic triblock copolymers is the attachment of two monodendrons to the extremities of a single linear chain. The variation of chain length and dendrimer size in this group also offers interesting macromolecular geometries.[11] The reaction, which leads to quantitative formation of linear-dendritic structures, is absolutely necessary for their synthesis. The coupling chemistry has a similar effect on the outcome of the synthesis. Recent solid chemistry is the click chemistry which is the copper-catalyzed 1,3-dipolar cycloaddition reaction between alkyne and azide developed by Sharpless and Tornøe.[12] This reaction is characterized by mild and simple reaction conditions, reliable 1,4-regiospecific 1,2,3-triazole formations, and tolerance towards water as well as a wide range of functionalities, and is clearly a breakthrough in the synthesis of dendrimers[13,14] and dendritic and polymer materials.[15-17] We have developed the fusion and stitching methods for the synthesis of dendrimers using click chemistry between an alkyne and an azide.[14] We are intrigued to apply this methodology for the synthesis of dendritic-linear- dendritic materials. Taking advantage of this fact, herein we report the synthesis of Fréchet-type dendrimers with PEG core moieties by the stitching method of dendrons (Figure 1). Because of the high yields and lack of byproducts provided by the click chemistry for stitching together dendrons and core unit, the various dendritic-linear-dendritic materials could be obtained easily and shown the characteristic behaviors.

Results and Discussion

The convergent approach to dendrimer synthesis introduced by Fréchet and co-workers revolutionized the synthetic approaches to monodisperse dendrimers.[18,19] The convergent methodology installs the core in the final step, enabling the incorporation of functionalities. The ability to prepare well-defined symmetrical dendrimers is the most attractive features of the convergent synthesis. The convergent approach allows for a large degree of chemical diversity such that functional groups can be incorporated at nearly central position in the dendritic architecture. The inward growth employed by the convergent synthesis is ideally suited for the synthesis of dendritic-linear-dendritic polymers.

The synthetic strategy for Fréchet-type dendrimers with PEG uints at core, linked by the triazole units, utilized a convergent method using the azide-functionalized Fréchet-type dendrons and the dialkyne-PEG units (Figure 1). To

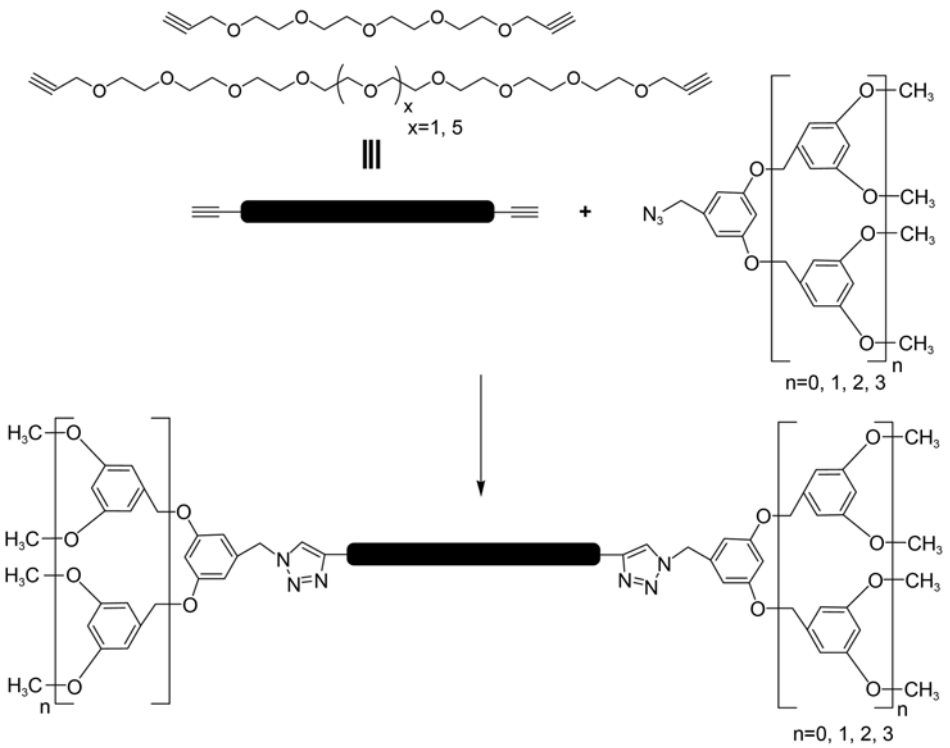
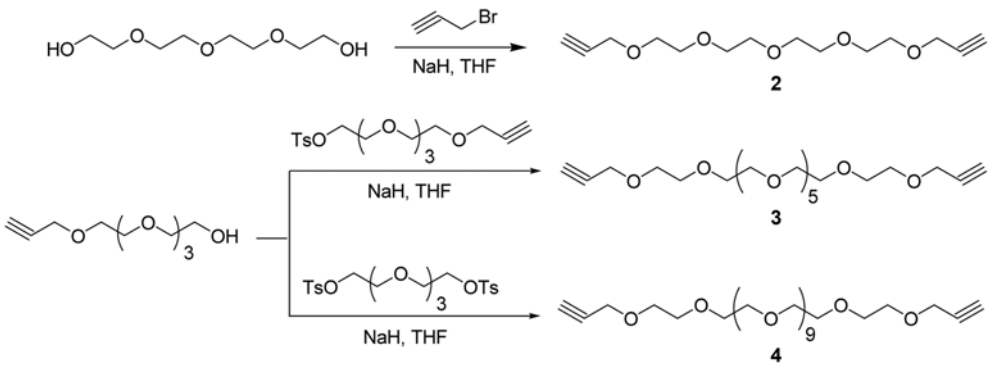


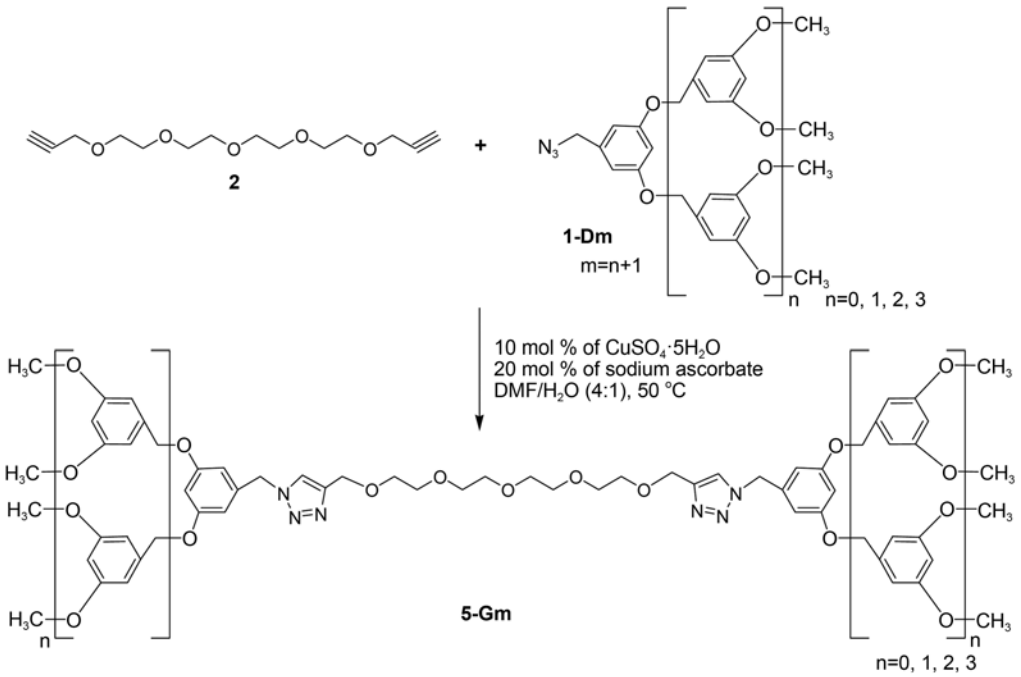
Figure 1. Structures of dendrons and synthetic strategy of dumbbell type dendritic materials.

efficiently connect the azide focal point Fréchet-type dendrons with the dialkyne-PEG units, the synthetic approach selected is based on the click chemistry between an alkyne and an azide in the presence of Cu (I) species.[20] The azide focal point Fréchet-type dendrons **1-Dm** (*m* = 1-4: generation of dendron) are synthesized by according to the reported procedure respectively.[14c,14e,21] **T**he dialkyne-PEG compound **2**, **3**, and **4** were prepared from the bis-propargylation of tetraethylene glycol, the O-alkylation reaction of monoalkyne-tetraethylene glycol with the tosylated monoalkyne-tetraethylene glycol, and the O-alkylation reaction of monoalkyne-tetraethylene glycol with tetraethylene glycol ditosylate, respectively (Scheme 1).

First of all, the efficiency of the click reaction between the azide-dendron and dialkyne-PEG units was evaluated by performing the model coupling reactions between azide-dendron **1-D1** and tetra(ethyleneglycol)-di(alkynes) **2** (Scheme 2). The reaction conducted from the condition of 5 mol % of $CuSO_4 \cdot 5H_2O$ with 10 mol % of sodium ascorbate with respect to the alkyne in a 4:1 solvent ratio of DMF to H_2O for 1 h 10 min at 50 afforded the desired product **5-G1** in yield of 99%. The disappearance of di(alkynes) **2** as well as generation and disappearance of the mono-triazole derivative were monitored by TLC runs of the reaction mixture. The dendrimer **5-G1** was purified by column chromatography and the structure of dendrimer was confirmed by ^{1}H and ^{13}C NMR spectroscopy, IR spectroscopy, and FAB mass spectra. Given the success in the synthesis of first generation dendrimer, we expanded this reaction to get higher generation dendrimers. Reactions of the di(alkynes) **2** with 2.2 equiv of **1-D2** and **1-D3** afforded the dendrimers **5-G2** and **5-G3** in yields of 98 and 97%, respectively, after 30 and 15 min, which were separated by column chromatography. In case of **1-D4**, the dendritic-linear-dendritic



Scheme 1. Synthesis of dialkynes-PEG compounds **2**, **3**, and **4**.



Scheme 2. Synthesis of dendrimers **5-Gm** by click reaction between dialkynes-PEG derivative **2** and azide-functionalized dendrons **1-Dm**.

material **5-G4** was obtained in 95% yield after 45 min. This comparative efficiency of the click methodology is emphasized by the synthesis of the dendritic-linear-dendritic materials with the tailored core unit.

The structures of the dendrimers **5-Gm** were confirmed by ^{1}H NMR, ^{13}C NMR, and IR spectroscopy. From the ^{1}H NMR spectra ($CDCl_3$), the peaks of the methylene protons adjacent to the nitrogen of triazole, the triazole proton, and the methylene protons adjacent to the carbon of triazole in dendrimers **5-Gm** were found at 5.42, 7.54, and 4.64 ppm for **5-G1**, 5.40, 7.51, and 4.64 ppm for **5-G2**, 5.39, 7.51, and 4.63 ppm for **5-G3**, and 5.35, 7.48, and 4.61 ppm for **5-G4**, respectively (Figure 2). As the dendrimer generation increased, the peaks of all discussed protons shifted slightly to down-field which may be influenced by the dendritic microenvironment effect.[22] Analysis of the dendrimers by mass spectrometry as well as by gel-permeation chromatography (GPC) provides no signs of products with defects that would arise from incomplete coupling. As expected, the obtained dendrimer possessed a very well-defined molecular structure with very low polydispersity values (PDI = 1.01). The IR spectra shows the disappearance of the acetylene peak at ~3302 cm^{-1} and the azide peak at ~2100 cm^{-1} in the final dendrimer while the ^{1}H NMR revealed no alkyne peak at around δ 2.43 ppm (Figure 2).

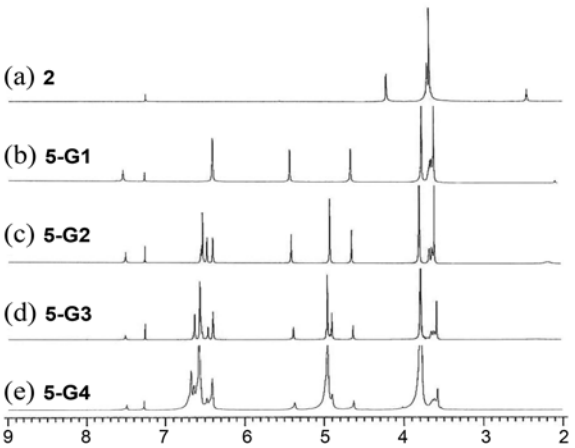
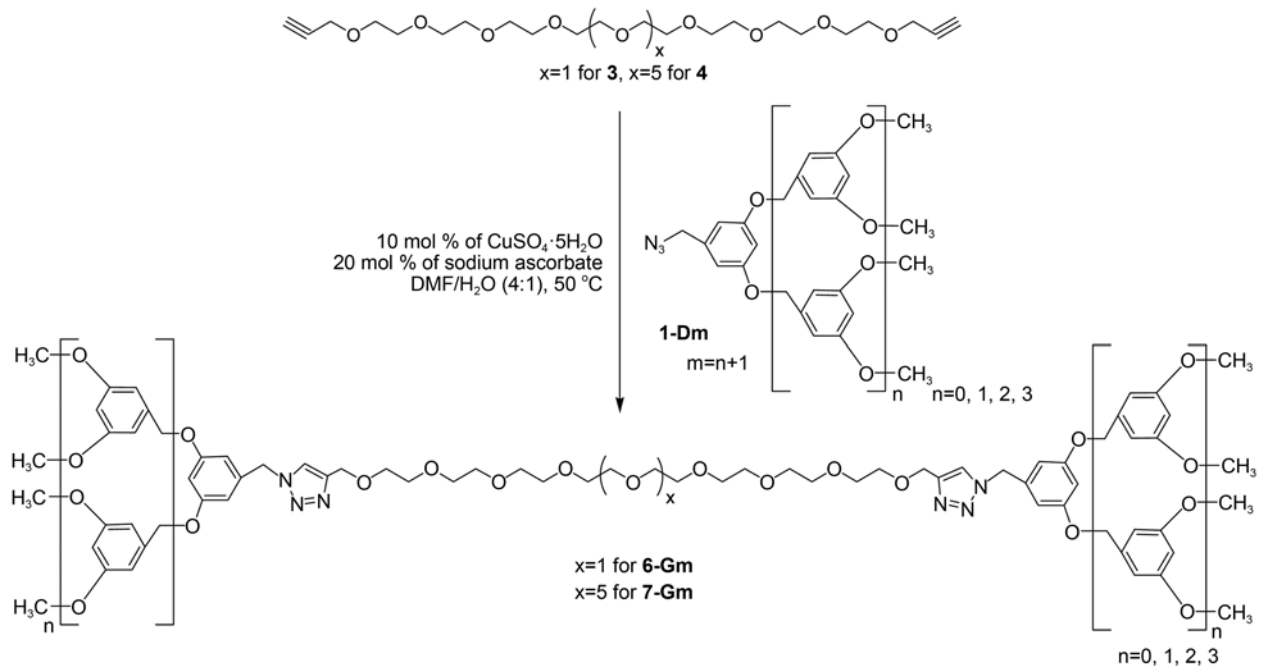


Figure 2. ^{1}H-NMR spectra for (a) **2**, (b) **5-G1**, (c) **5-G2**, (d) **5-G3**, and (e) **5-G4**.

To realize this strategy in the synthesis of the dendritic-linear-dendritic materials, we next turned our attention toward the click reaction between the azide-dendron **1-D1** and octa(ethyleneglycol)-di(alkynes) **3** (Scheme 3). Based on optimizations for the synthesis of the dendrimers **5-Gm**, click reactions for the construction of linear-dendritic copolymers **6-Gm** were carried out in a 4:1 solvent ratio of DMF to H_2O using 5 mol % $CuSO_4·5H_2O$ with 10 mol % sodium ascorbate with respect to alkyne. Reaction of the octa(ethyleneglycol)-di(alkynes) **3** and 2.2 equiv of azide-dendron **1-D1**, conducted for 1.5 h at 50 °C, afforded the desired product **6-G1** in yield of 99%. The disappearance of di(alkynes) **3** as well as generation and disappearance of the mono-triazole derivative were also monitored by TLC runs of the reaction mixture. The linear-dendritic copolymer **6-G1** was purified by column chromatography and the structure of **6-G1** was confirmed by ^{1}H and ^{13}C NMR spectroscopy, IR spectroscopy, and FAB mass spectra. Reactions of the octa(ethyleneglycol)-di(alkynes) **3** with 2.2 equiv of **2-D2** and **2-D3** afforded the desired product **6-G2** and **6-G3** in yields of 98 and 98%, respectively, after 1.4 and 1 h, which were separated by column chromatography. In case of **2-D4**, the dendritic-linear-dendritic material **6-G4** was obtained in 97% yield after 15 min. This result showed that



Scheme 3. Synthesis of dendrimers **6-Gm** and **7-Gm** by click reaction between dialkynes-PEG derivatives **3** and **4** and azide-functionalized dendrons **1-Dm**.

the click reaction can be regarded as a very efficient one for convergent synthesis of the dendritic-linear-dendritic materials with the tailor-made core unit.

From the ^{1}H NMR spectra ($CDCl_3$), the peaks of the methylene protons adjacent to the nitrogen of triazole, the triazole proton, and the methylene protons adjacent to the carbon of triazole in dendrimers **6-Gm** were found at 5.41, 7.50, and 4.64 ppm for **6-G1**, 5.40, 7.49, and 4.65 ppm for **6-G2**, 5.40, 7.50, and 4.64 ppm for **6-G3**, and 5.38, 7.49, and 4.63 ppm for **6-G4**, respectively. Analysis of the dendrimers by mass spectrometry as well as by gel-permeation chromatography (GPC) provides no signs of products with defects that would arise from incomplete coupling. As expected, the obtained dendrimer possessed a very well-defined molecular structure with very low polydispersity values (PDI = 1.01). The IR spectra shows the disappearance of the acetylene peak at ~3248 cm^{-1} and the azide peak at ~2100 cm^{-1} in the final dendrimer (Figure 3) while the ^{1}H NMR revealed no alkyne peak at around δ2.40 ppm.

Encouraged by this successful proof of concept, we decided to apply this methodology into the synthesis of another dendritic-linear-dendritic materials so that we next turned our attention toward the click reaction between the azide-dendron **1-D1** and dodeca(ethyleneglycol)-di(alkynes) **4** (Scheme 3). Based on optimizations for the synthesis of the dendrimers **5-Gm** and **6-Gm**, click reactions for the construction of linear-dendritic copolymers **7-Gm** were carried out in a 4:1 solvent ratio of DMF to H_2O using 5 mol % $CuSO_4$·$5H_2O$ with 10 mol % sodium ascorbate with respect to alkyne. Reaction of the dodeca(ethyleneglycol)-di(alkynes) **4** and 2.2 equiv of azide-dendron **1-D1**, conducted for 1.5 h at 50 °C, afforded the desired product **7-G1** in yield of 98%.

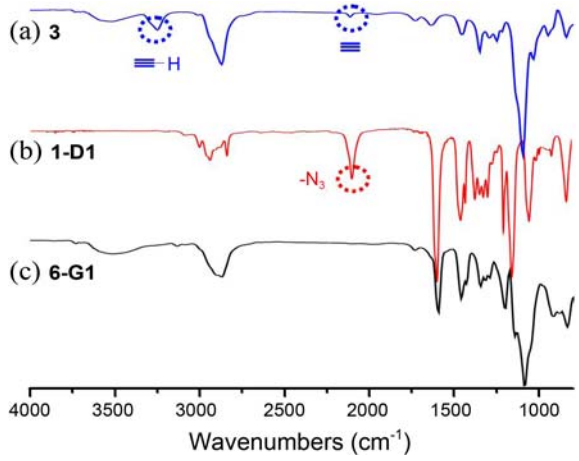


Figure 3. IR spectra for (a) **3**, (b) **1-D1**, and (c) **6-G1**.

The disappearance of di(alkynes) **4** as well as generation and disappearance of the mono-triazole derivative were also monitored by TLC runs of the reaction mixture. The linear-dendritic copolymer **7-G1** was purified by column chromatography and the structure of **7-G1** was confirmed by ^{1}H and ^{13}C NMR spectroscopy, IR spectroscopy, and FAB mass spectra. Given the success in the synthesis of first generation dendrimer, we expanded this reaction to get higher generation dendrimers. Reactions of the dodeca(ethyleneglycol)-di(alkynes) **4** with 2.2 equiv of **2-D2**, **2-D3**, and **2-D3** afforded the desired product **7-G2**, **7-G3**, and **7-G3** in yields of 97, 95, and 96%, respectively, after 2 h, which were separated by column chromatography. Therefore, the formation of regiospecific 1,4-disubstituted triazoles *via* copper(I)-catalyzed [2+3]-dipolar cycloaddition reaction between an

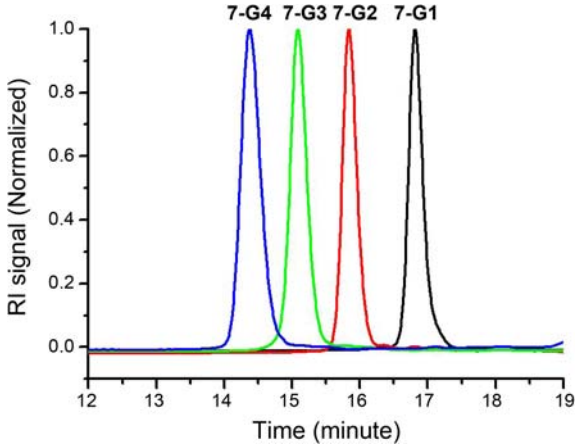


Figure 4. GPC diagrams of dendrimers **7-Gm** obtained from THF eluent.

alkyne and an azide can be regarded as a new and efficient methodology to construct the dendritic-linear-dendritic materials with the tailored core unit.

Structural characterization of the dendrimers **7-Gm** with ^{1}H NMR, ^{13}C NMR, and IR spectroscopy showed no defects due to incomplete reaction. From the ^{1}H NMR spectra ($CDCl_3$), the peaks of the methylene protons adjacent to the nitrogen of triazole, the triazole proton, and the methylene protons adjacent to the carbon of triazole in dendrimers **7-Gm** were found at 5.40, 7.50, and 4.63 ppm for **7-G1**, 5.40, 7.49, and 4.65 ppm for **7-G2**, 5.41, 7.50, and 4.65 ppm for **7-G3**, and 5.38, 7.49, and 4.63 ppm for **7-G4**, respectively. The ^{1}H NMR revealed no alkyne peak at around δ 2.41 ppm in the final dendrimer. IR data also confirmed that neither alkyne (~3248 cm^{-1}) nor azide (~2100 cm^{-1}) residues remain in the final dendrimer. Analysis of the dendrimers by mass spectrometry as well as by gel-permeation chromatography (GPC) provides no signs of products with defects that would arise from incomplete coupling (Figure 4). As expected, the obtained dendrimer possessed a very well-defined molecular structure with very low polydispersity values (PDI = 1.01-1.02).

In summary, we have demonstrated general, fast, and efficient stitching methods for the synthesis of dendritic-linear-dendritic materials with linear PEG units and Fréchet-type dendrons. The stitching method was based on the click chemistry protocol between an alkyne and an azide. The linear building blocks, three dialkyne-PEG compound **2**, **3**, and **4**, were chosen to serve as the core in dendrimer, were stitched together with the azide-functionalized Fréchet-type dendrons in a convergent strategy to lead to the formation of three kinds of dendritic-linear-dendritic materials with different linear core units, respectively, in high yields. Therefore, the click reaction can be regarded as a very efficient one for convergent synthesis of the dendritic-linear-dendritic materials with the tailor-made core unit. This approach may provide new methodological insight into introduction of various linear functional cores and would greatly contribute to researches on the application side.

Experimental

General. ^{1}H NMR spectra were recorded on a 300 or 500 MHz NMR spectrometer using the residual proton resonance of the solvent as the internal standard. Chemical shifts are reported in parts per million (ppm). FAB and MALDI mass spectra were obtained from Korea Basic Science Institute (KBSI) in Daegu and POSTECH. Polydispersity (PDI) of dendrimers was determined by gel permeation chromatography (GPC) analysis relative to polystyrene calibration (Agilent 1100 series GPC, Plgel 5 μm MIXED-C, refractive index detector) in THF solution.

Synthesis of Monoproparyl-tetraethylene Glycol. NaH (55%, 0.65 g, 15 mmol) was treated to a solution of tetraethylene glycol (5.83 g, 30 mmol) in THF (20 mL) and stirred for 1 h, followed by adding of propargyl chloride (0.75 g, 10 mmol) under ice bath. The resulting mixture was stirred at rt for 20 h and treated with saturated ammonium chloride aqueous solution (40 mL). The resulting solution was extracted with methylene chloride (40 mL × 3). The organic phase was dried with magnesium sulfate and concentrated. The residue was purified by column chromatography from EtOAc to afford the desired product (1.88 g, 81%). A yellowish oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.43 (t, J = 2.4 Hz, 1H), 2.63 (s, 1H), 3.63-3.74 (m, 16H), 4.20 (d, J = 2.4 Hz, 2H).

Synthesis of Tetra(ethyleneglycol)-di(alkynes) 2. NaH (55%, 0.56 g, 12.87 mmol) was treated to a solution of tetraethylene glycol (1 g, 5.15 mmol) in THF (51 mL) and stirred for 1 h, followed by adding of propargyl bromide (1.44 mL, 12.87 mmol) under ice bath. The resulting mixture was stirred at rt for 24 h and treated with saturated ammonium chloride aqueous solution (100 mL). The resulting solution was extracted with methylene chloride (50 mL × 4). The organic phase was dried with magnesium sulfate and concentrated. The residue was purified by column chromatography from EtOAc/*n*-Hexane = 1:2 to afford the desired product **2** (1.36 g, 98%). A colorless oil; IR 3302, 3017, 2878, 2122, 1720, 1219, 1096 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.43 (t, J = 2.3 Hz, 2H), 3.63 (s, 8H), 3.66-3.69 (m, 8H), 4.20 (d, J = 2.4 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 58.0, 68.7, 70.0, 70.2, 74.4, 79.3; MS (FAB): *m/z* 270.97 [M^+ + H]; HRMS (FAB) Calcd for $C_{14}H_{22}O_5$: 270.1467. Found: 271.1544 [M^+ + H].

Synthesis of Octa(ethyleneglycol)-di(alkynes) 3. NaH (55%, 68 mg, 1.55 mmol) was treated to a solution of monoproparyl-tetraethylene glycol (270 mg, 1.16 mmol) in THF (6 mL) and stirred for 1 h, followed by adding a solution of monopropargyl(tetraethylene glycol) tosylate (300 mg, 0.78 mmol) in THF (2 mL). The resulting mixture was stirred at rt for 24 h and treated with saturated ammonium chloride aqueous solution (20 mL). The resulting solution was extracted with methylene chloride (20 mL × 4). The organic phase was dried with magnesium sulfate and concentrated. The residue was purified by column chromatography from EtOAc/MeOH = 10:1 to afford the desired product **3** (180 mg, 52%). A colorless oil; IR 3248, 2870, 2114, 1458, 1350,

1096 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.40 (t, J = 2.3 Hz, 2H), 3.58 (s, 16H), 3.59 (s, 8H), 3.61-3.63 (m, 8H), 4.13 (d, J = 2.3 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 58.7, 69.4, 70.7, 70.9, 75.0, 80.0; MS (FAB): *m/z* 447.18 [M^+ + H]; HRMS (FAB) Calcd for $C_{22}H_{38}O_9$: 446.2516. Found: 447.2593 [M^+ + H].

Synthesis of Dodeca(ethyleneglycol)-di(alkynes) 4. NaH (55%, 69 mg, 1.60 mmol) was treated to a solution of monoproparyl-tetraethylene glycol (370 mg, 1.60 mmol) in THF (15 mL) and stirred for 1 h, followed by adding a solution of (tetraethylene glycol) ditosylate (200 mg, 0.40 mmol) in THF (3 mL). The resulting mixture was stirred at rt for 30 h and treated with saturated ammonium chloride aqueous solution (30 mL). The resulting solution was extracted with methylene chloride (30 mL × 4). The organic phase was dried with magnesium sulfate and concentrated. The residue was purified by column chromatography from EtOAc/MeOH = 10:1 to afford the desired product **3** (131 mg, 53%). A colorless oil; IR 3248, 2870, 2114, 1458, 1350, 1096 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.41 (t, J = 2.2 Hz, 2H), 3.61 (s, 24H), 3.62 (s, 16H), 3.65-3.66 (m, 8H), 4.17 (d, J = 2.1 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 58.3, 69.0, 70.3, 70.5, 74.5, 79.6; MS (FAB): *m/z* 623.59 [M^+ + H]; HRMS (FAB) Calcd for $C_{30}H_{54}O_{13}$: 622.3564. Found: 623.3640 [M^+ + H].

General Procedure for the Preparation of Dendrimers 5-Gm from Azide-Dendrons 1-Dm and Tetra(ethyleneglycol)-di(alkynes) 2. A mixture of azido-dendrons **1-Dm** (0.22 mmol) and tetra(ethyleneglycol)-di(alkynes) **2** (0.1 mmol) in DMF-H_2O (4:1, 2 mL) in the presence of 10 mol % $CuSO_4 \cdot 5H_2O$ with 20 mol % sodium ascorbate was stirred at 50 °C for ~1 h. The reaction mixture was poured into brine (20 mL) and the resulting solution was extracted with EtOAc (20 mL × 3). The combined organic phase was dried with sodium sulfate, concentrated, and purified by column chromatography to afford the desired product **5-Gm**.

5-G1. R_f 0.2 (EtOAc:MeOH = 10:1); A yellowish oil; 99% yield; IR 2916, 2878, 1597, 1466, 1350, 1204, 1150, 1088 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.59 (s, 8H), 3.61-3.64 (m, 8H), 3.74 (s, 12H), 4.64 (s, 4H), 5.42 (s, 4H), 6.39 (s, 6H), 7.54 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 54.1, 55.3, 64.50, 64.54, 69.7, 70.39, 70.44, 100.3, 106.1, 122.6, 136.6, 145.4, 161.2; MS (FAB): *m/z* 657.0 [M^+ + H]; HRMS (FAB) Calcd for $C_{32}H_{44}N_6O_9$: 656.3170. Found: 657.3246 [M^+ + H]. PDI: 1.01.

5-G2. R_f 0.35 (EtOAc:MeOH = 10:1); A yellowish oil; 98% yield; IR 2947, 2878, 1597, 1458, 1350, 1204, 1150, 1057 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.59 (s, 8H), 3.61-3.66 (m, 8H), 3.78 (s, 24H), 4.64 (s, 4H), 4.92 (s, 8H), 5.40 (s, 4H), 6.40 (t, J = 2.1 Hz, 4H), 6.47 (d, J = 1.9 Hz, 4H), 6.53 (d, J = 2.1 Hz, 8H), 6.55 (t, J = 2.0 Hz, 2H), 7.51 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 54.6, 55.8, 65.0, 70.2, 70.5, 70.86, 70.92, 100.4, 102.5, 105.6, 107.7, 123.1, 137.1, 139.2, 145.6, 160.7, 161.4; MS (FAB): *m/z* 1201.3 [M^+ + H], 1223.2 [M^+ + H]; HRMS (FAB) Calcd for $C_{64}H_{76}N_6O_{17}$: 1200.5267. Found: 1201.5350 [M^+ + H]. PDI: 1.01.

5-G3. R_f 0.3 (EtOAc); A yellowish oil; 97% yield; IR 2932, 2870, 1597, 1458, 1373, 1204, 1157, 1057 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.57 (s, 8H), 3.59-3.64 (m, 8H), 3.77 (s, 48H), 4.63 (s, 4H), 4.90 (s, 8H), 4.95 (s, 16H), 5.39 (s, 4H), 6.40 (t, J = 2.1 Hz, 8H), 6.46 (m, 4H), 6.53 (t, J = 2.0 Hz, 2H), 6.55 (m, 4H), 6.56 (d, J = 2.0 Hz, 16H), 6.63 (d, J = 1.8 Hz, 8H), 7.51 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 54.5, 55.8, 65.0, 70.2, 70.5, 70.86, 70.92, 100.4, 102.1, 102.5, 105.7, 106.8, 107.6, 123.2, 137.2, 139.3, 139.5, 145.9, 160.5, 160.7, 161.4; MS (MALDI): Calcd for $C_{128}H_{140}N_6O_{33}$: 2288.9461. Found: 2312.3873 [M^+ + Na]. PDI: 1.01.

5-G4. R_f 0.3 (EtOAc:*n*-Hexnae = 2:1); A yellowish oil; 95% yield; IR 2940, 2878, 1597, 1458, 1373, 1204, 1153, 1053 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.56 (s, 8H), 3.60-3.62 (m, 8H), 3.76 (s, 96H), 4.61 (s, 4H), 4.89 (s, 8H), 4.94 (s, 48H), 5.35 (s, 4H), 6.40 (m, 16H), 6.46 (m, 8H), 6.56 (m, 42H), 6.63 (m, 8H), 6.66 (m, 16H), 7.48 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 53.9, 55.2, 64.5, 69.6, 69.9, 70.3, 70.4, 99.8, 101.5, 101.8, 105.1, 106.3, 107.1, 122.6, 136.9, 138.8, 139.0, 139.1, 145.4, 159.9, 160.2, 160.9; MS (MALDI): Calcd for $C_{256}H_{268}N_6O_{65}$: 4465.7850. Found: 4505.7410 [M^+ + K]. PDI: 1.01.

General Procedure for the Preparation of Dendrimers 6-Gm from Azide-Dendrons 1-Dm and Octa(ethyleneglycol)-di(alkynes) 3. A mixture of azido-dendrons **1-Dm** (0.22 mmol) and octa(ethyleneglycol)-di(alkynes) **3** (0.1 mmol) in DMF-H_2O (4:1, 2 mL) in the presence of 10 mol % $CuSO_4 \cdot 5H_2O$ with 20 mol % sodium ascorbate was stirred at 50 °C for ~1.5 h. The reaction mixture was poured into brine (20 mL) and the resulting solution was extracted with EtOAc (20 mL × 3). The combined organic phase was dried with sodium sulfate, concentrated, and purified by column chromatography to afford the desired product **6-Gm**.

6-G1. R_f 0.2 (EtOAc:MeOH = 5:1); A yellowish oil; 99% yield; IR 2870, 1597, 1466, 1350, 1204, 1150, 1096 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.61 (s, 24H), 3.62-3.66 (m, 8H), 3.74 (s, 12H), 4.64 (s, 4H), 5.41 (s, 4H), 6.39 (s, 4H), 6.40 (t, J = 1.8 Hz, 2H), 7.50 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 54.5, 55.8, 65.1, 70.1, 70.85, 70.91, 100.8, 106.5, 123.0, 137.1, 146.0, 161.7; MS (FAB): *m/z* 833.6 [M^+ + H]; HRMS (FAB) Calcd for $C_{40}H_{60}N_6O_{13}$: 832.4218. Found: 833.4291 [M^+ + H]. PDI: 1.01.

6-G2. R_f 0.2 (EtOAc:MeOH = 10:1); A yellowish oil; 98% yield; IR 2878, 1597, 1458, 1350, 1204, 1150, 1096, 1057 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.60 (s, 24H), 3.62-3.67 (m, 8H), 3.78 (s, 24H), 4.65 (s, 4H), 4.91 (s, 8H), 5.40 (s, 4H), 6.40 (t, J = 1.8 Hz, 4H), 6.47 (d, J = 1.8 Hz, 4H), 6.53 (d, J = 1.9 Hz, 8H), 6.55 (s, 2H), 7.49 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 54.5, 55.8, 65.1, 70.2, 70.5, 70.87, 70.93, 100.4, 102.5, 105.6, 107.7, 123.0, 137.2, 139.2, 146.0, 160.7, 161.4; MS (FAB): *m/z* 1377.6 [M^+ + H]; HRMS (FAB) Calcd for $C_{72}H_{92}N_6O_{21}$: 1376.6316. Found: 1377.6388 [M^+ + H]. PDI: 1.01.

6-G3. R_f 0.3 (EtOAc:MeOH = 10:1); A yellowish oil; 98% yield; IR 2932, 2878, 1597, 1458, 1327, 1204, 1150, 1096, 1049 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.60 (s, 24H), 3.61-3.66 (m, 8H), 3.78 (s, 48H), 4.64 (s, 4H), 4.91 (s, 8H), 4.96 (s, 16H), 5.40 (s, 4H), 6.40 (m, 8H), 6.46 (m, 4H),

6.56 (m, 22H), 6.63 (d, J = 1.4 Hz, 8H), 7.50 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 54.0, 55.3, 64.6, 69.7, 70.1, 70.5, 99.9, 101.7, 102.0, 105.2, 106.4, 107.2, 122.6, 136.8, 138.9, 139.1, 146.4, 160.1, 160.3, 161.0; MS (MALDI): Calcd for $C_{136}H_{156}N_6O_{37}$: 2465.0510. Found: 2488.8962 [M^+ + Na]. PDI: 1.01.

6-G4. R_f 0.4 (EtOAc); A yellowish oil; 97% yield; IR 2940, 2878, 1597, 1450, 1319, 1204, 1150, 1049 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.59 (s, 24H), 3.61-3.65 (m, 8H), 3.76 (s, 96H), 4.63 (s, 4H), 4.90 (s, 8H), 4.95 (s, 48H), 5.38 (s, 4H), 6.39 (m, 16H), 6.47 (m, 4H), 6.52 (m, 2H), 6.56 (m, 44H), 6.63 (m, 8H), 6.66 (d, J = 1.3 Hz, 8H), 7.49 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 53.9, 55.2, 64.6, 69.7, 70.0, 70.37, 70.44, 99.9, 101.6, 101.9, 105.2, 106.4, 107.2, 122.6, 136.9, 138.8, 139.09, 139.14, 145.6, 160.0, 160.3, 160.9; MS (MALDI): Calcd for $C_{264}H_{284}N_6O_{69}$: 4641.8899. Found: 4664.6483 [M^+ + Na]. PDI: 1.01.

General Procedure for the Preparation of Dendrimers 7-Gm from Azide-Dendrons 1-Dm and Dodeca(ethyleneglycol)-di(alkynes) 4. A mixture of azido-dendrons **1-Dm** (0.22 mmol) and dodeca(ethyleneglycol)-di(alkynes) **4** (0.1 mmol) in DMF-H_2O (4:1, 2 mL) in the presence of 10 mol % $CuSO_4 \cdot 5H_2O$ with 20 mol % sodium ascorbate was stirred at 50 °C for ~2 h. The reaction mixture was poured into brine (20 mL) and the resulting solution was extracted with EtOAc (20 mL × 3). The combined organic phase was dried with sodium sulfate, concentrated, and purified by column chromatography to afford the desired product **7-Gm**.

7-G1. R_f 0.15 (EtOAc:MeOH = 5:1); A yellowish oil; 98% yield; IR 2870, 1597, 1458, 1350, 1204, 1153, 1099, 1053 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.60 (s, 40H), 3.61-3.65 (m, 8H), 3.73 (s, 12H), 4.63 (s, 4H), 5.40 (s, 4H), 6.38-6.39 (m, 6H), 7.50 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 54.1, 55.3, 64.6, 69.6, 70.39, 70.45, 100.3, 106.0, 122.5, 136.6, 145.5, 161.2; MS (FAB): *m/z* 1009.19 [M^+ + H]; HRMS (FAB) Calcd for $C_{48}H_{76}N_6O_{17}$: 1008.5267. Found: 1009.5347 [M^+ + H]. PDI: 1.01

7-G2. R_f 0.25 (EtOAc:MeOH = 5:1); A yellowish oil; 97% yield; IR 2870, 1597, 1458, 1350, 1204, 1153, 1103, 1053 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.61 (s, 40H), 3.62-3.66 (m, 8H), 3.78 (s, 24H), 4.65 (s, 4H), 4.91 (s, 8H), 5.40 (s, 4H), 6.39 (m, 4H), 6.47 (m, 4H), 6.52 (m, 8H), 6.55 (m, 2H), 7.49 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 54.0, 55.3, 64.6, 69.7, 70.0, 70.4, 70.5, 99.9, 102.0, 105.1, 107.2, 122.5, 136.7, 138.7, 145.5, 160.3, 160.9; MS (FAB): *m/z* 1554.3 [M^+ + H]; HRMS (FAB) Calcd for $C_{80}H_{108}N_6O_{25}$: 1552.7364. Found: 1553.7435 [M^+ + H]. PDI: 1.01

7-G3. R_f 0.3 (EtOAc:MeOH = 10:1); A yellowish oil; 95% yield; IR 2936, 2874, 1597, 1458, 1346, 1204, 1153, 1103, 1053 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.62 (s, 40H), 3.62-3.65 (m, 8H), 3.78 (s, 48H), 4.65 (s, 4H), 4.92 (s, 8H), 4.97 (s, 16H), 5.41 (s, 4H), 6.40 (t, J = 2.0 Hz, 8H), 6.46 (d, J = 1.8 Hz, 4H), 6.56-5.67 (m, 22H), 6.63 (d, J = 1.9 Hz, 8H), 7.50 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 54.0, 55.3, 64.6, 69.7, 70.0, 70.5, 99.9, 101.6, 101.9, 105.2, 106.3, 107.1, 122.6, 136.8, 138.8, 139.0, 145.5, 160.0, 160.2, 160.9; MS (MALDI): Calcd for $C_{144}H_{172}N_6O_{41}$: 2641.1559. Found: 2664.2074 [M^+ + Na]. PDI: 1.01

7-G4. R_f 0.4 (EtOAc); A yellowish oil; 96% yield; IR 2936, 2878, 1597, 1458, 1346, 1204, 1153, 1053 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.60-3.64 (m, 48H), 3.76 (s, 96H), 4.63 (s, 4H), 4.91 (s, 8H), 4.95 (s, 48H), 5.38 (s, 4H), 6.39 (m, 16H), 6.47 (m, 4H), 6.55-6.56 (m, 46H), 6.63 (d, J = 1.4 Hz, 8H), 6.66 (d, J = 1.6 Hz, 16H), 7.49 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 53.8, 55.1, 64.4, 69.5, 69.8, 70.3, 99.7, 101.4, 101,7, 105.0, 106.2, 107.0, 122.6, 136.8, 138.7, 138.96, 139.02, 145.3, 159.9, 160.1, 160.8; MS (MALDI): Calcd for $C_{272}H_{300}N_6O_{73}$: 4817.9947. Found: 4840.9252 [M^+ + Na]. PDI: 1.02.

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