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Synthesis of Dendrimers from Alkyne-focal Dendrons by Oxidative Homo-coupling of Terminal Acetylene

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General, fast, and efficient fusion methods for the synthesis of dendrimers with 1,3-diynes at a core were developed. The synthetic strategy was employed the oxidative homo-coupling of terminal alkyne. The oxidative homo-coupling reaction of the alkyne-functionalized Fréchet-type dendrons **1-Dm** was allowed to provide first through fourth generation dendrimers **2-Gm** with 1,3-diynes at core. The fusion of the propargyl-functionalized PAMAM dendrons **3-Dm** by homo-coupling of terminal alkyne lead to the formation of symmetric PAMAM dendrimers **4-Gm**. Their structure of dendrimers was confirmed by ^{1}H and ^{13}C NMR spectroscopy, IR spectroscopy, mass spectrometry, and GPC analysis.

Key Words : Alkyne, Click chemistry, Dendrimer, Homo-coupling

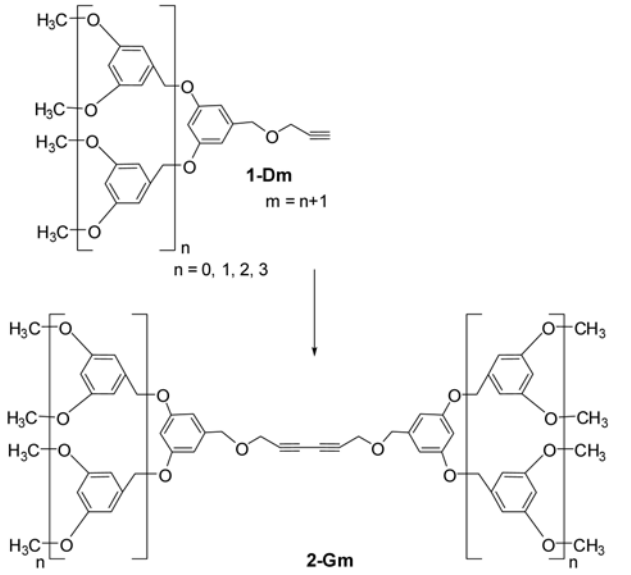
Introduction

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] An effective convergent synthesis of dendrons and dendrimers requires a monomer that can undergo the activation and coupling steps in high yield and whose products can be readily isolated from excess starting material and byproducts.[2] In addition, the coupling step must be very efficient to enable complete reaction even when involving sterically demanding high generation dendrons. 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.[3] We have developed the fusion and stitching methods for the synthesis of dendrimers using click chemistry between an alkyne and an azide.[4] Although many methods for the convergent synthesis of various dendrimers were developed, there is still a demand to develop a simple, convenient, and efficient method for functional dendrimer. In continuation with our research on the synthesis of dendrimers *via* click chemistry using alkyne derivatives, we were fascinated to develop the new click chemistry for the construction of dendrimers using oxidative homo-coupling reaction of the terminal acetylene. Here we report a feasible route to synthesize the symmetric dendrimers from Fréchet type dendrons and poly(amido amine) (PAMAM) dendrons containing alkyne moiety at their focal point by oxidative homo-coupling of terminal alkyne.

Results and Discussion

Terminal alkynes are versatile intermediates in synthetic organic and material chemistry due to their characteristic reactions such as metal-catalyzed coupling reactions including Sonogashira coupling reaction and oxidative homo-coupling, and so on.[5] The palladium-catalyzed coupling of terminal acetylenes to aromatic bromides or iodides in basic amines have been well known since 1975.[6] Taking advantage of this fact, we became interested in the synthesis of self-emissive dendrimer with a fluorescent probe in core region. A relatively few applications using the alkynyl-dendron in dendrimer synthesis have been reported. In the investigation of the reaction between 9,10-dibromoanthracene and alkyne-dendron, we observed that the homo-coupling of alkyne-dendrons was facilitated to provide the dimerized product. Therefore, we turned our attention into the synthesis of dendrimer by oxidative homocoupling of terminal alkyne.

The synthetic strategy for Fréchet-type dendrimers, linked by 1,3-diynes, utilized a convergent method using the alkyne-functionalized Fréchet-type dendrons **1-Dm** (Scheme 1).[7] The alkyne-functionalized Fréchet-type dendrons **1-Dm** was synthesized by the propargylation of the corresponding dendritic benzyl alcohols with propargyl bromide.[4e] From the investigation using compound **1-D1**, we have found that the reaction conducted from THF in the presence of 0.025 equiv of $(PPh_3)_2PdCl_2$/0.015 equiv of CuI with 3 equiv of diisopropyl ethyl amine at 40 °C afforded the desired product. The reaction of alkyne-functionalized dendron **1-D1** for 10 h afforded the dendrimer **2-G1** in yield of 94%, which was purified by column chromatography and the structure of **2-G1** was confirmed by the analyses of ^{1}H and ^{13}C NMR spectra, IR and mass data. Given the first generation dendrimer, we applied repeatedly the homo-coupling of alkyne-dendrons to get higher-generation dendrimers. Reactions of dendron **1-D2** and **1-D3** afforded the dendrimers **2-G2** and **2-G3** in yields of 90 and 88% after 12 and 14 h, respectively. Meanwhile, the dendrimer **2-G4** was obtained from **1-D4** in 85% yield after 17 h. As the gene-



Scheme 1. Synthesis of dendrimers by oxidative homocoupling of alkyne-functionalized Fréchet-type dendrons. *Reagents and conditions:* $(PPh_3)_2PdCl_2$/CuI, diisopropyl ethyl amine, THF, 40 °C.

ration of dendrons increases, the steric hindrance between dendrons will affect the reaction more significantly. Therefore, the higher generation dendron takes longer time than the lower generation dendron.

The ^{1}H NMR signals of the methylene protons of core and the inside benzylic protons in dendrimers **2-Gm** were observed at 4.52 and 4.55 ppm for **2-G1**, 4.24 and 4.54 ppm for **2-G2**, 4.23 and 4.53 ppm for **2-G3**, and 4.19 and 4.49 ppm for **2-G4**, respectively (Figure 1). As the dendrimer generation increased, the peaks of the discussed protons showed up-field shift which may be influenced by the dendritic microenvironment effect.[8] The proton peak in terminal alkyne did not show at 2.47 ppm in the ^{1}H NMR spectrum of dendrimer **2-G1** and the carbon peaks for the ethynylene carbons of dendrimer **2-G1** are at 72.2 and 75.8 ppm which are shielded relative to those for the dendron **1-D1**. IR data also confirmed that neither 3286 cm^{-1} for the H-C≡ bond stretching frequency nor 2115 cm^{-1} for the C≡C bond stretching absorption remain in the final dendrimer (Figure 2). Indeed, the FAB or MALDI mass spectrometry confirm-

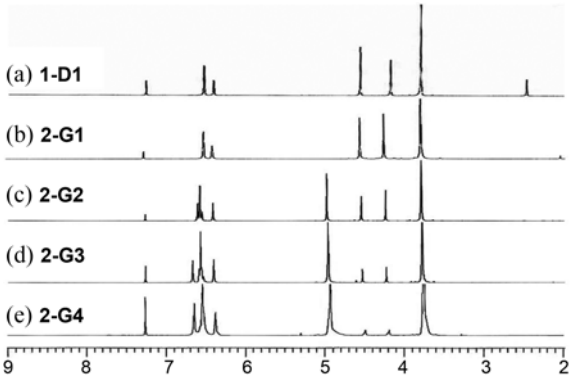


Figure 1. ^{1}H-NMR spectra for (a) **1D-1**, (b) **2-G1**, (c) **2-G2**, (d) **2-G3**, and (e) **2-G4**.

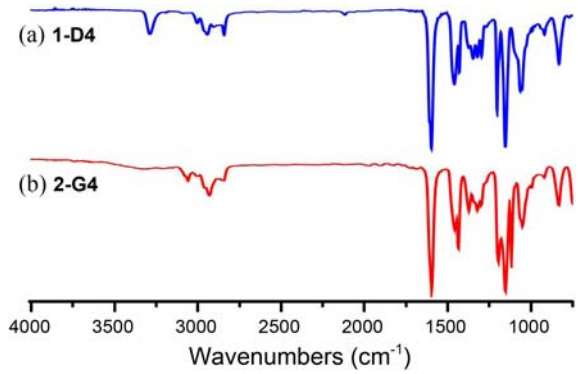


Figure 2. IR spectra for (a) **1-D4** and (b) **2-G4**.

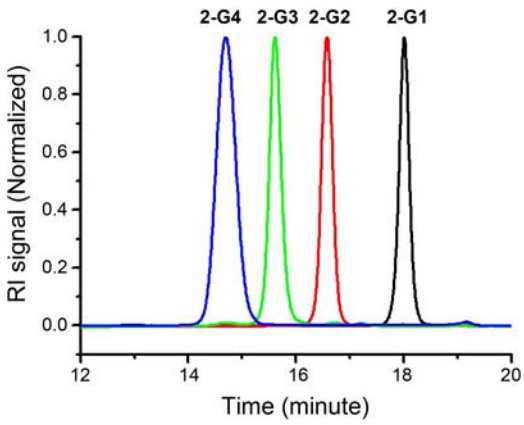
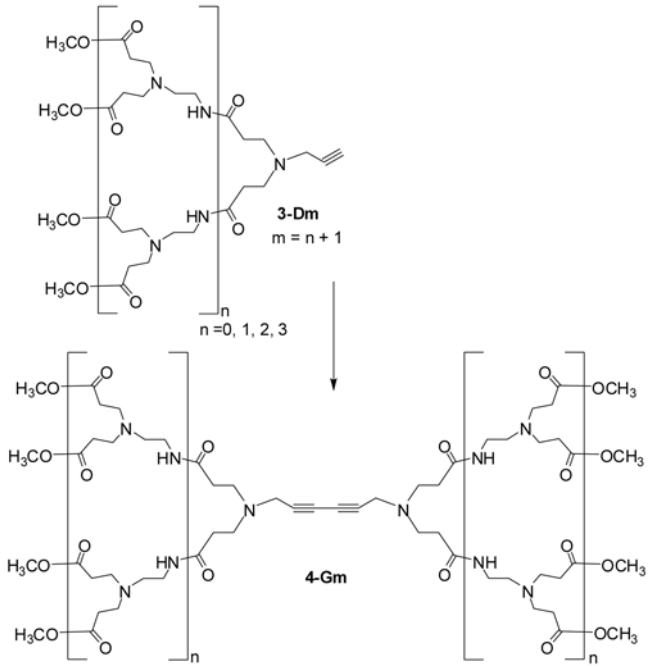


Figure 3. GPC diagrams of dendrimers **2-Gm** obtained from THF eluent.

ed the formation of those dendrimers. From the analysis of gel-permeation chromatography (Figure 3), the dendrimers showed very low polydispersity values (PDI = 1.01-1.02).

Encouraged by this successful proof of concept, we decided to apply toward the homo-coupling of the alkyne-PAMAM dendron which is more hydrophilic than Fréchet type dendrons. The synthetic strategy for PAMAM dendrimers, linked by 1,3-diynes, utilized a convergent method using the alkyne-functionalized PAMAM dendrons **3-Dm** (Scheme 2). The propargyl-functionalized PAMAM dendrons **3-Dm** (m = 1-4: generation of dendron) were synthesized by the divergent approach using propargylamine as an alkyne-focal points.[4f] Based on optimizations for the synthesis of the dendrimers **2-Gm**, we endeavored to find the optimum reaction temperature and time due to the presence of amine unit in PAMAM dendrons. We have found that the reaction conducted from THF in the presence of $(PPh_3)_2PdCl_2$/CuI catalyst system with diisopropyl ethyl amine provided the desired product under short time even room temperature compared to the reaction of Fréchet type dendrons. The reaction of alkyne-functionalized dendron **3-D1** in THF (0.1 M) in the presence of 0.025 equiv of $(PPh_3)_2PdCl_2$/0.015 equiv of CuI and 3 equiv of diisopropyl ethyl amine for 8 h at rt afforded the desired product **4-G1** in yield of 96%. The disappearance of **3-D1** and the appearance of new spot were observed from TLC analysis. The dendrimer **4-G1** was purified by column chromatography



Scheme 2. Synthesis of dendrimers by oxidative homocoupling of propargyl-functionalized PAMAM dendrons. *Reagents and conditions:* $(PPh_3)_2PdCl_2$/CuI, diisopropyl ethyl amine, THF, rt.

and the structure of dendrimer was confirmed by ^1H and ^{13}C NMR spectroscopy, IR spectroscopy, and FAB mass spectra. With this optimistic result, we expanded this reaction to get higher generation dendrimers. Reactions of dendron **3-D2** and **3-D3** afforded the dendrimers **4-G2** and **4-G3** in yields of 95 and 93% after 4.5 and 5.5 h at rt, respectively, which were separated by column chromatography. In case of **3-D4**, the dendrimer **4-G4** was obtained in 89% yield after 7.5 h at rt. It could be assumed that the amino building unit in PAMAM dendron may play a role to accelerate the homo-coupling reaction. This comparative efficiency of the new click methodology is emphasized by the synthesis of the symmetric dendrimers with 1,3-diynes at core. Therefore this approach may provide new methodological insight into introduction of multi-ynes at core of dendrimer and would greatly contribute to researches on the application side.

Structural characterization of the dendrimers **4-Gm** with ^1H NMR, ^{13}C NMR, and IR spectroscopy showed complete fusion of dendrons. From their ^1H NMR spectra ($CDCl_3$), the peaks of the methylene protons of core in dendrimers **4-Gm** were found at 3.48 ppm for **4-G1**, 3.54 for **4-G2**, 3.55 ppm for **4-G3**, and 3.54 ppm for **2-G4**, respectively. As the dendrimer generation increased, the peaks of the discussed protons showed up-field shift which may be influenced by the dendritic microenvironment effect. The proton peak in terminal alkyne did not show at 2.19 ppm in the ^1H NMR spectrum of dendrimer **4-G1** and the carbon peaks for the ethynylene carbons of dendrimer **4-G1** are at 70.0 and 73.6 ppm. The IR spectra show the disappearance of the H-C≡ bond stretching frequencies around 3277 cm^{-1} and the C≡C bond stretching absorptions around 2103 cm^{-1} in the final dendrimer **4-G1** (Figure 4). Analysis of the dendrimers by

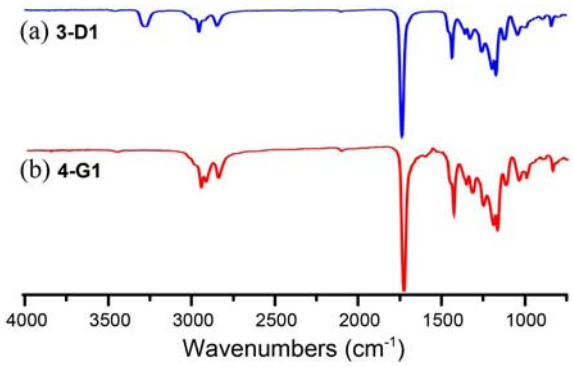


Figure 4. IR spectra for (a) **3-D1** and (b) **4-G1**.

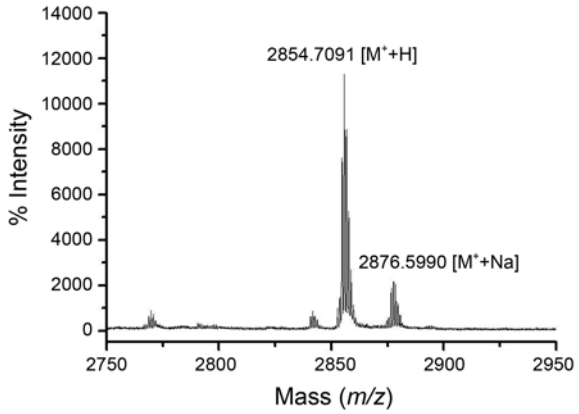


Figure 5. MALDI mass spectrum of dendrimer **4-G3**.

FAB or MALDI mass spectrometry as well as by gel-permeation chromatography (GPC) provides no signs of products with defects that would arise from incomplete coupling (Figure 5). As expected, the obtained dendrimer possessed a very well-defined molecular structure with very low polydispersity values (PDI = 1.01-1.02).

In summary, the convergent synthesis of dendrimers has been described by the oxidative homo-coupling of terminal alkyne. The oxidative homo-coupling reaction of the alkyne-functionalized Fréchet-type dendrons **1-Dm** was allowed to provide first through fourth generation dendrimers **2-Gm** with 1,3-diynes at core. The fusion of the propargyl-functionalized PAMAM dendrons **3-Dm** by homo-coupling of terminal alkyne lead to the formation of symmetric PAMAM dendrimers **4-Gm** in high yields. It has been observed that the amino building unit in PAMAM dendron may play a role to accelerate autocatalytically the homo-coupling reaction. Selection of appropriately functionalized terminal alkynes and dendrons will likely lead to the synthesis of new nanoscopic materials.

Experimental

General. ^1H 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). When peak multiplicities are given, the following abbreviations are used: s,

singlet; d, doublet; t, triplet; q, quartet; quin, quintet; d of d, doublet of a doublet; m, multiplet; br, broad. ^{13}C NMR spectra were proton decoupled and recorded on a 75 or 125 MHz NMR spectrometer using the carbon signal of the deuterated solvent as the internal standard. FAB and MALDI mass spectra were obtained from Korea Basic Science Institute (KBSI) in Daegu or Daejeon and POSTECH. Flash chromatography was performed with 37-75 μm silica gel. Analytical thin layer chromatography was performed on silica plates with F_{254} indicator and the visualization was accomplished by UV lamp or using an iodine chamber. 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.

General Procedure for the Preparation of Dendrimers 2-Gm from Alkyne-dendrons 1-Dm. A solution of alkyne-functionalized dendron **1-Dm** (0.1 mmol), $(PPh_3)_2PdCl_2$ (2.5 mol %), CuI (1.5 mol %), and diisopropyl ethyl amine (3 equiv) in THF (1 mL) was degassed and purged with Ar and stirred at 40 °C for the specified time. The resulting mixture was diluted with EtOAc (30 mL). The organic phase was washed with brine, dried over Na_2SO_4, and filtered and the filtrate was concentrated. The crude product was purified by flash chromatography (EtOAc/hexane system) to afford the dendrimer **2-Gm**.

2-G1: 94% yield. A brownish oil; IR 2936, 2839, 1597, 1458, 1204, 1153, 1053 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.80 (s, 12H), 4.25 (s, 4H), 4.55 (s, 4H), 6.40 (t, *J* = 1.8 Hz, 2H), 6.51 (d, *J* = 1.9 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.7, 58.0, 71.0, 72.2, 75.8, 100.6, 106.2, 139.8, 161.4; MS (FAB): *m/z* 410.90 [M$^+$]; HRMS (FAB) Calcd for $C_{24}H_{26}O_6$: 410.1729. Found: 411.1805 [M$^+$ + H]. PDI: 1.01.

2-G2: 90% yield. A yellowish solid; mp 213-215 °C. IR 2939, 2839, 1597, 1458, 1204, 1153, 1057 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.79 (s, 24H), 4.24 (s, 4H), 4.54 (s, 4H), 4.97 (s, 8H), 6.41 (t, *J* = 2.1 Hz, 4H), 6.55 (t, *J* = 2.1 Hz, 2H), 6.58 (d, *J* = 2.2 Hz, 8H), 6.60 (d, *J* = 2.1 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.8, 58.0, 70.5, 71.1, 72.1, 75.8, 100.4, 102.2, 105.7, 107.4, 139.6, 139.9, 160.4, 161.4; MS (FAB): *m/z* 955.11 [M$^+$ + H]; HRMS (FAB) Calcd for $C_{56}H_{58}O_{14}$: 954.3827. Found: 955.3909 [M$^+$ + H]. PDI: 1.02.

2-G3: 88% yield. A colorless gum; IR 2936, 2839, 1597, 1458, 1204, 1157, 1053 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.78 (s, 48H), 4.23 (s, 4H), 4.53 (s, 4H), 4.97 (s, 24H), 6.41 (t, *J* = 2.1 Hz, 8H), 6.53 (t, *J* = 1.9 Hz, 2H), 6.56-6.57 (m, 20H), 6.59 (d, *J* = 1.5 Hz, 4H), 6.67 (d, *J* = 1.9 Hz, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.8, 58.0, 70.4, 70.5, 71.1, 72.1, 75.9, 100.4, 102.1, 102.2, 105.7, 106.8, 107.3, 139.6, 139.7, 139.9, 160.4, 160.5, 161.4; MS (FAB): *m/z* 2043.6 [M$^+$]; HRMS (FAB) Calcd for $C_{120}H_{122}O_{30}$: 2042.8021. Found: 2042.8022 [M$^+$], 2043.8102 [M$^+$ + H]. PDI: 1.01.

2-G4: 85% yield. A colorless gum; IR 2928, 2839, 1597, 1458, 1435, 1196, 1153, 1119, 1053 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.75 (s, 96H), 4.19 (s, 4H), 4.49 (s, 4H), 4.93 (s, 56H), 6.38 (m, 16H), 6.54-6.57 (m, 50H), 6.65 (m, 24H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.7, 58.0, 70.4, 70.5, 71.1, 72.1, 75.9, 100.4, 102.1, 105.7, 106.8, 107.3, 139.57, 139.65, 139.9, 160.5, 161.4; MS (MALDI): Calcd for $C_{248}H_{250}O_{62}$: 4219.6410. Found: 4220.6485 [M$^+$ + H], 4242.6289 [M$^+$ + Na]. PDI: 1.02.

General Procedure for the Preparation of Dendrimers 4-Gm from Alkyne-dendrons 3-Dm. A solution of alkyne-functionalized dendron **3-Dm** (0.1 mmol), $(PPh_3)_2PdCl_2$ (2.5 mol %), CuI (1.5 mol %), and diisopropyl ethyl amine (3 equiv) in THF (1 mL) was degassed and purged with Ar and stirred at rt for the specified time. The resulting mixture was diluted with EtOAc (30 mL). The organic phase was washed with brine, dried over Na_2SO_4, and filtered and the filtrate was concentrated. The crude product was purified by flash chromatography (EtOAc/hexane system) to afford the dendrimer **4-Gm**.

4-G1: 96% yield. A pale yellowish oil; IR 2954, 5925, 2850, 1737, 1437, 1198, 1175 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.44 (t, *J* = 7.0 Hz, 8H), 2.83 (t, *J* = 7.0 Hz, 8H), 3.48 (s, 4H), 3.66 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 33.4, 43.0, 49.5, 52.0, 70.0, 73.6, 173.0; MS (FAB): *m/z* 453.39 [M$^+$ + H]; HRMS (FAB) Calcd for $C_{22}H_{32}N_2O_8$: 452.2159. Found: 453.2241 [M$^+$ + H]. PDI: 1.01.

4-G2: 95% yield. A pale yellowish oil; IR 2953, 2836, 1737, 1667, 1536, 1438, 1259, 1199, 1178 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.37 (t, *J* = 6.5 Hz, 8H), 2.43 (t, *J* = 6.6 Hz, 16H), 2.54 (t, *J* = 5.9 Hz, 8H), 2.75 (t, *J* = 6.6 Hz, 16H), 2.84 (t, *J* = 6.5 Hz, 8H), 3.28 (q, *J* = 5.7 Hz, 8H), 3.54 (s, 4H), 3.67 (s, 24H), 7.05 (t, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 33.1, 34.3, 37.5, 42.3, 49.7, 49.9, 52.0, 53.4, 70.1, 73.4, 172.2, 173.5; MS (FAB): *m/z* 1253.58 [M$^+$ + H]; HRMS (FAB) Calcd for $C_{58}H_{96}N_{10}O_{20}$: 1252.6802. Found: 1253.6877 [M$^+$ + H]. PDI: 1.01.

4-G3: 93% yield. A pale yellowish oil; IR 2953, 2832, 1737, 1651, 1539, 1437, 1257, 1199, 1177 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.35 (t, *J* = 6.3 Hz, 24H), 2.43 (t, *J* = 6.6 Hz, 32H), 2.53 (t, *J* = 5.8 Hz, 16H), 2.57 (t, *J* = 6.0 Hz, 8H), 2.75 (t, *J* = 6.6 Hz, 32H), 2.79 (t, *J* = 6.6 Hz, 24H), 3.27 (q, *J* = 5.4 Hz, 24H), 3.55 (s, 4H), 3.66 (s, 48H), 7.07 (t, *J* = 5.1 Hz, 8H), 7.69 (t, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 33.1, 34.3, 37.6, 37.9, 42.0, 49.6, 49.9, 50.3, 52.0, 52.9, 53.3, 70.2, 73.4, 172.4, 172.7, 173.4; MS (MALDI): Calcd for $C_{130}H_{224}N_{26}O_{44}$: 2853.6090. Found: 2854.7091 [M$^+$ + H]. PDI: 1.01.

4-G4: 89% yield. A pale yellowish gum; IR 2952, 2830, 1735, 1647, 1541, 1437, 1259, 1199, 1177 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.35 (br, 56H), 2.42 (t, *J* = 6.5 Hz, 64H), 2.53 (t, *J* = 5.6 Hz, 32H), 2.57 (br, 24H), 2.75 (t, *J* = 6.5 Hz, 64H), 2.78-2.79 (m, 56H), 3.26-3.27 (m, 56H), 3.54 (s, 4H), 3.66 (s, 96H), 7.10 (t, 16H), 7.66 (s, 8H), 7.78 (s, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 33.1, 34.2, 37.6, 37.9, 38.0, 42.0, 49.7, 49.9, 50.2, 50.5, 52.0, 52.8, 52.9, 53.3, 70.3, 73.4, 172.6, 172.8, 173.0, 173.5; MS (MALDI): Calcd for $C_{274}H_{480}N_{58}O_{92}$: 6055.4665. Found: 6056.8040 [M$^+$ + H]. PDI: 1.02.

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