Facile Synthesis of Fréchet Type Dendritic Benzyl Azides and Dendrimer *via* Cycloaddition Reaction with Tripodal Core

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Fréchet-type dendritic benzyl azides were efficiently synthesized using 5-(azidomethyl)-1,3-dihydroxybenzene as an azide focal point functionalized unit by adding a generation to the existing dendron and applied for the construction of dendrimers containing 1,2,3-triazole rings as connectors *via* click chemistry with a tripodal acetylene core.

Key Words : Azide, Cycloaddition, Dendrimer, 1,2,3-Triazoles

Introduction

Organoazides are versatile intermediates in synthetic organic chemistry, because the azide group can subsequently be converted into several other types of substituent groups.[1] Azides are among the most stable 1,3-dipoles and generally can be stored for indefinite time without significant decomposition. Since the 1,3-dipolar cycloaddition of azides with alkynes was investigated by Huisgen *et al.*[2] it has been attracted much attention because of the synthetic importance of the aromatic and nonaromatic five-membered [1,2,3]-triazole heterocycles.[3] The traditional method for producing the triazole by cycloaddition requires elevated temperature, typically in refluxing conditions and also provides a mixture of 1,4-disubstituted and 1,5-disubstituted triazoles. Over the years, several efforts to control the 1,4- versus 1,5-regioselectivity have been reported.[4] Recently the click chemistry which is the Cu(I)-catalyzed Huisgen [2 + 3] dipolar cycloaddition reaction between an organic azide and a terminal alkyne, has found in many applications in organic chemistry,[5] drug discovery,[6] bioconjugations,[7] material science,[8] and synthesis of polymer[9] and dendrimer.[10] The reaction, characterized by very high yields, mild and simple reaction conditions, oxygen and water tolerance, and simple product isolations, is highly chemoselective affording only the desired 1,2,3-triazole even in the presence of a large variety of other functional groups.

It is interesting to note that Fréchet used a dendritic benzyl azide in an insertion reaction of C_{60}.[11] The dendritic benzyl azide was synthesized by the azidation of the corresponding dendritic benzyl bromide. These poly(benzyl ether) dendrons, now frequently referred to as Fréchet-type dendrons, have been utilized by a number of groups because they are relatively readily accessed and exhibit the chemical stability

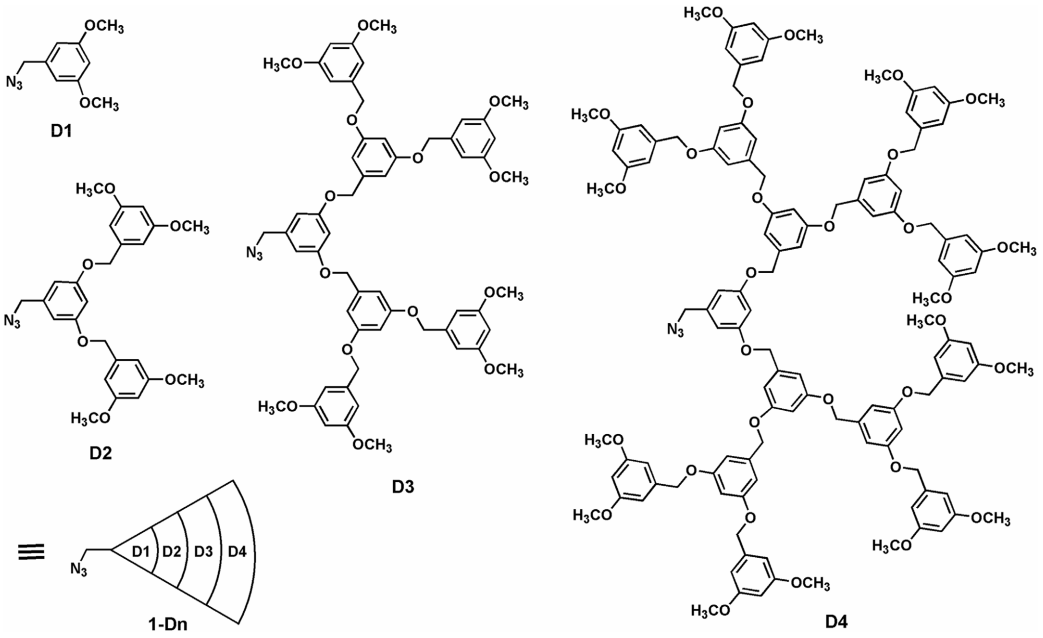


Figure 1. Structures of azide-functionalized Fréchet-type dendrons **1-Dn**.

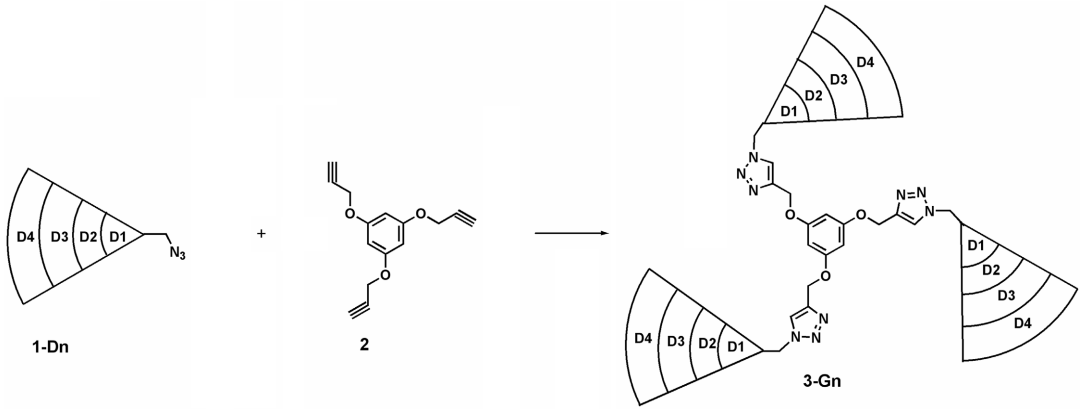


Figure 2. Synthetic strategy of triazole dendrimers **3-Gn** by trimerization

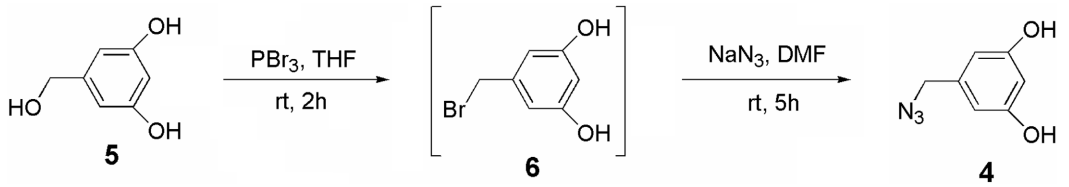
associated with ether linkages.[12] Due to the often tedious purification in intensive iterative dendrimer syntheses, many researchers have sought accelerated approaches that combine the convergent and divergent strategies to reduce the number of linear synthetic steps required to access larger dendritic materials.[12a] Here we present a rapid synthesis of azide-functionalized Fréchet-type dendrons **1-Dn** (Figure 1) by adding a generation to the existing dendron using an azide focal point functionalized unit and their application to the convergent synthesis of dendrimer **3-Gn** using click chemistry with 1,3,5-tris(prop-2-ynyloxy)benzene **2** as a dendrimer core (Figure 2).

Results and Discussion

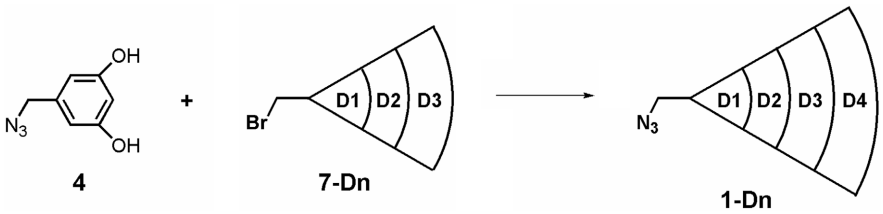
An effective convergent synthesis of dendrons and dendrimers requires a monomer that can undergo the activation and coupling steps in high yield and whose products can be readily isolated from excess starting material and byproducts. In addition, the coupling step must be very efficient to enable complete reaction even when involving sterically demanding high generation dendrons. In response to the tedious purification in intensive iterative dendrimer syntheses, many researchers have combined the convergent and divergent strategies. These procedures generally maintain the versatility and product monodispersity offered by the traditional convergent method, but reduce the number of linear synthetic steps required to access larger dendritic materials. For the effective synthesis of the Fréchet-type dendron azides, we have designed and utilized 5-(azidomethyl)-1,3-dihydroxybenzene **4** as an azide focal point functionalized unit for the efficient synthesis of azide-functionalized Fréchet-type dendrons. The 5-(azidomethyl)-1,3-dihydroxybenzene was obtained by the bromination of 1,3-dihydroxy-5-(hydroxymethyl)benzene **5** with PBr_3 and the azidation of compound **6** using NaN_3 (Scheme 1). Initially we tried to isolate 5-(bromomethyl)-1,3-dihydroxybenzene **6** but it was proven to be unstable.[13] But direct azidation of compound **6** after aqueous workup was successful to isolate 5-(azidomethyl)-1,3-dihydroxybenzene **4** in 75% yield in two steps.

To probe the effectiveness for the synthesis of the azide focal point functionalized Fréchet-type dendrons **1-Dn** (n = 1, 2, 3, and 4: generation of dendron), we have reacted 5-(azidomethyl)-1,3-dihydroxybenzene **4** with the dendritic benzyl bromide **7-Dn** (Scheme 2). The dendritic benzyl bromide **7-Dn** (n = 1, 2, and 3: generation of dendron) was prepared according to the reported procedure.[14] The reaction of compound **4** with first generation dendritic benzyl bromide **7-D1** in acetone in the presence of K_2CO_3 under reflux provided the second generation dendritic benzyl azide **1-D2** in 95% yield. Next, we conducted the reaction for the preparation of higher generation dendrons. The reactions of compound **4** with **7-D2** and **7-D3** in the same condition gave the dendritic benzyl azide **1-D3** and **1-D4** in yields of 92% and 91%, respectively. It was proven that the reaction using an azide focal point functionalized unit added efficiently a generation to the existing dendron. Also the reaction of compound **4** with iodomethane provided the first generation dendritic benzyl azide **1-D1** in 96% yield. All dendrons were compared with the authentic compounds and confirmed by ^1H and ^{13}C NMR spectroscopy and their FAB mass spectra.

For the construction of the triazole dendrimer **3-Gn** *via* the 1,3-dipolar cycloaddition reactions between azido-dendrons



Scheme 1. Synthesis of 5-(azidomethyl)-1,3-dihydroxybenzene **4**.



Scheme 2. Synthesis of azide-functionalized Fréchet-type dendrons **1-Dn**.

1-Dn and the tripodal acetylene **2**, we adapted the click chemistry condition, which is well-documented. The active Cu(I) species, generated in situ by reacting $CuSO_4 \cdot 5H_2O$ with sodium ascorbate as the reducing agent, provide the 1,4-disubstituted 1,2,3-triazole in excellent yield.[15] This convergent method for dendrimer containing triazole units at core can be facilitated by fewer coupling reactions between a dendron-azide and a core-mutiple-alkynes and convenient purifications. Because of the high yields and lack of byproducts provided by the click chemistry for stitching together dendrons and core unit, the various dendrimers having functional building block at core could be obtained easily. The study described herein was started to apply the synthesis of various functional dendrimers convergently with triazole linkages between the core and dendrons.

We carried out the reactions in a 4 : 1 solvent ratio of DMF to H_2O using 5 mol % $CuSO_4 \cdot 5H_2O$ with 10 mol % sodium ascorbate with respect to alkyne at 50-60 °C. The reaction progress could be checked by TLC. The generation and disappearance of the intermediates, which are mono- and/or di-triazole derivatives, were monitored by TLC runs of the reaction mixture. The reaction of 1,3,5-tris(prop-2-ynyloxy)-benzene **2** with **1-D1** in 0.1 *M* solution provided the triazole dendrimer **3-G1** having just 1,4-disubstituted 1,2,3-triazole units in yield of 93% after 6.5 h. Given the success in using click chemistry in the synthesis of first generation dendrimer, we expanded this reaction to get higher generation dendrimers. Reactions of 1,3,5-tris(prop-2-ynyloxy)benzene **2** with **1-D2** and **1-D3** afforded the triazole dendrimers **3-G2** and **3-G3** in yields of 86% and 88%, respectively, after 8h. In case of **1-D4**, the triazole dendrimer **3-G4** was obtained in 87% yield after 11 h. For completion of the reaction between the dendritic azide and the tripodal core, the higher generation dendron takes longer time than the lower generation dendron. This observation led us to imagine that the reaction between the dendritic azide and the tripodal acetylene core was kinetically controlled by the accessibility of azide due to the steric hindrance (bulkiness) of dendron and spatial congestion of tripodal core region. Therefore, the results showed that the formation of triazole between tripodal acetylene and azido-dendrons can be regarded as a new connector to construct various dendrimers and functional materials.

All dendrimers were confirmed by ^1H and ^{13}C NMR spectroscopy. From their ^1H NMR spectra ($CDCl_3$), the peaks of the benzene protons of core and the triazole protons in dendrimers **3-Gn** were found at 6.23 and 7.56 ppm for **3-G1**, 6.23 and 7.52 ppm for **3-G2**, 6.20 and 7.50 ppm for **3-G3**, and 6.15 and 7.44 ppm for **3-G4**, respectively. The peaks of the benzylic protons adjacent to the nitrogen of triazole in dendrimers **3-Gn** were found at 5.44 ppm for **3-G1**, 5.41 ppm for **3-G2**, 5.37 ppm for **3-G3**, and 5.26 ppm for **3-G4**, respectively. As the dendrimer generation increased, the peaks of the benzene protons of core, the triazole protons, and the benzylic protons adjacent to the nitrogen of triazole showed up-field shift. In third and fourth generation dendrimers it is observed that the benzene protons of core, the triazole protons, and the benzylic protons adjacent to the nitrogen of triazole are influenced by the larger dendritic effect changing their microenvironment. Analysis of the dendrimers by 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 3). As expected, the obtained dendrimer possessed a very well-defined molecular structure with very low polydispersity values (PDI = 1.02-1.03).

In summary, we have demonstrated that an efficient route to azide-functionalized Fréchet-type dendrons is now available by adding a generation to the existing dendron using an azide focal point functionalized unit and that the trimerization reactions between tripodal acetylene and azido-dendrons lead to the formation of 1,4-disubstituted triazole dendrimers in high yields. This method may provide an insight into designing various functional symmetrical dendrimers. We are currently working towards the synthesis of fluorophore-encapsulated dendrimers using this strategy for various applications.

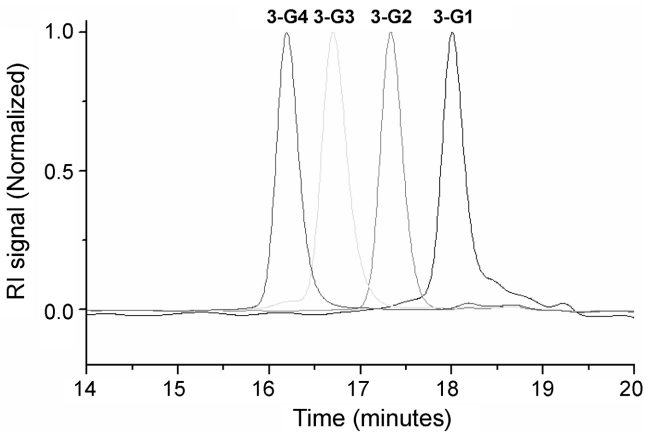


Figure 3. GPC diagram of dendrimer **3-Gn**.

Experimental Section

^{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). When peak multiplicities are given, the following abbreviations are used: s, singlet; d, doublet; t, triplet; 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. EI, FAB, and MALDI mass spectra were obtained from Korea Basic Science Institute 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. All chemicals were obtained from commercial sources and used as received, unless otherwise mentioned.

Synthesis of 5-(azidomethyl)-1,3-dihydroxybenzene (4). Phosphorous tribromide (1.4 g, 5 mmol) was added slowly to a solution of 1,3-dihydroxy-5-(hydroxymethyl)-benzene (0.70 g, 5 mmol) in THF (25 mL) under nitrogen and the resulting mixture was stirred for 2 h at room temperature. The reaction mixture was poured into cold brine (50 mL) and the resulting solution was extracted with EtOAc (50 mL × 3). The combined organic phase was concentrated to provide the crude product. This crude was dissolved with DMF (15 mL) and treated with sodium azide (0.9 g, 15 mmol) and the resulting mixture was stirred for 5 h at room temperature. The reaction mixture was poured into brine (50 mL) and the resulting solution was extracted with EtOAc (50 mL × 3). The combined organic phase was dried with sodium sulfate, concentrated, and purified by column chromatography (EtOAc/Hex, 1 : 1) to afford 5-(azidomethyl)-1,3-dihydroxybenzene **4** (0.62 g, 75%). ^{1}H NMR (500 MHz, DMSO-d6): δ 4.22 (s, 2H), 6.17 (d, J = 1.8 Hz, 1H), 6.19 (d, J = 1.7 Hz, 2H), 9.33 (s, 2H). ^{13}C NMR (125 MHz, DMSO-d6): δ 158.6, 137.3, 106.2, 102.2, 53.7. MS (EI): m/z 165 [M$^+$], 137, 137, 123, 110, 109, 69. HRMS (EI) calcd for $C_7H_7N_3O_2$: 165.0538. found: 165.0538.

General procedure for the preparation of dendritic benzyl azide (1-Dn). A mixture of 5-(azidomethyl)-1,3-dihydroxybenzene **4** (1.0 equiv.) and dendritic benzyl bromide **7-Dn** (2.2 equiv.) in acetone (0.1 *M* solution) in the presence of potassium carbonate (3.0 equiv.) was refluxed for 24-30 h. The resulting mixture was diluted with EtOAc and filtered and the filtrate was concentrated and purified by column chromatography (EtOAc/hexane system or CH_2Cl_2/hexane system) to afford the pure product **1-Dn**. To obtain **1-D1**, iodomethane (3 equiv.) was used instead of dendritic benzyl bromide.

1-D1. 97% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.80 (s, 6H), 4.27 (s, 2H), 6.43 (d, J = 2.1 Hz, 1H), 6.46 (d, J = 2.1 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.1, 137.6, 106.0, 100.1, 55.4, 54.8. MS (EI): m/z 193 [M$^+$], 165, 151, 135. HRMS (EI) calcd for $C_9H_{11}N_3O_2$: 193.0851. found: 193.0851.

1-D2. 95% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.80 (s, 12H), 4.26 (s, 2H), 4.98 (s, 4H), 6.42 (d, J = 2.1 Hz, 2H), 6.55-6.57 (m, 7H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.0, 160.2, 139.0, 137.7, 107.2, 105.2, 101.9, 100.0, 70.1, 55.4, 54.8. MS (EI): m/z 465 [M$^+$], 435, 286, 151. HRMS (EI) calcd for $C_{25}H_{27}N_3O_6$: 465.1900. found: 465.1900.

1-D3. 92% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.79 (s, 24H), 4.26 (s, 2H), 4.97 (s, 12H), 6.41 (m, 4H), 6.53-6.57 (m, 13H), 6.67 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.0, 160.12, 160.08, 159.93, 139.3, 139.1, 139.05, 137.6, 107.2, 106.4, 105.2, 101.8, 101.6, 70.04, 70.0, 55.3, 54.8. MS (FAB): m/z 1008.5 [M$^+$], 981.6, 572.9 460.0, 391.1. HRMS (FAB) calcd for $C_{57}H_{59}N_3O_{14}$: 1009.3997. found: 1010.4075 [M$^+$ + H].

1-D4. 91% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.77 (s, 48H), 4.24 (s, 2H), 4.96 (s, 28H), 6.40 (m, 8H), 6.57 (m, 26H), 6.67 (m, 11H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.0, 160.16, 160.09, 139.2, 139.14, 139.09, 137.7, 107.3, 106.4, 105.2, 101.8, 101.6, 100.0, 70.06, 55.3, 54.8. MS (FAB): calcd for $C_{121}H_{123}N_3O_{30}$: 2097.8191: m/z 2097.9 [M$^+$], 2069.8, 1919.6, 1646.0.

General procedure for the preparation of 1,2,3-triazole dendrimers 3-Gn by reaction between 1,3,5-tris(pro-2-ynyloxy)benzene 2 and azido-dendrons 1-Dn. A solution of 1,3,5-tris(prop-2-ynyloxy)benzene **2** (0.01 mmol) and azido-dendrons **1-Dn** (0.03 mmol) in DMF-H_2O (4 : 1, 1 mL) in the presence of 15 mol % $CuSO_4 \cdot 5H_2O$ with 30 mol % sodium ascorbate was stirred at 50-60 °C for 6.5-11 h. The reaction was monitored by TLC regarding on the disappearance of **1-Dn** and the generation and disappearance of mono- and/or di-triazole derivatives. 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 (EtOAc/hexane system) or recrystallization from EtOAc-hexane to afford the desired product.

3-G1. 93% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.75 (s, 18H), 5.10 (s, 6H), 5.44 (s, 6H), 6.23 (s, 3H), 6.40-6.42 (m, 9H), 7.56 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.3, 160.0, 144.3, 136.5, 122.8, 106.1, 100.5, 95.1, 62.1, 55.4, 54.3. MS (FAB): m/z 819.6 [M$^+$], 662.9, 577.1, 410.1, 391.0. HRMS (FAB) calcd for $C_{42}H_{45}N_9O_9$: 819.3340. found: 820.3418 [M$^+$ + H]. PDI: 1.03.

3-G2. 86% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.77 (s, 36H), 4.91 (s, 12H), 5.08 (s, 6H), 5.41 (s, 6H), 6.24 (s, 3H), 6.40 (m, 6H), 6.47 (m, 6H), 6.52 (m, 12H), 6.55 (m, 3H), 7.52 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.0, 160.3, 160.1, 144.3, 138.8, 136.6, 122.8, 107.2, 105.2, 102.2, 100.0, 95.1, 70.1, 62.0, 55.4, 54.2. MS (FAB): m/z 1635.6 [M$^+$], 1485.6, 1213.9, 1133.0, 663.4. HRMS (FAM) calcd for $C_{90}H_{93}N_9O_{21}$: 1635.6486. found: 1636.6564 [M$^+$ + H]. PDI: 1.02.

3-G3. 88% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.74 (s, 72H), 4.87 (s, 12H), 4.92 (s, 24 H), 5.02 (s, 6H), 5.37 (s, 6H), 6.20 (s, 3H), 6.37 (m, 12H), 6.42 (m, 6H), 6.54 (m, 33H), 6.60 (m, 12H), 7.50 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.0, 160.3, 160.1, 144.2, 139.1, 138.9, 136.7, 122.9, 107.1, 106.4, 105.3, 102.2, 101.7, 100.0, 95.1, 70.0, 61.9, 55.3, 54.1. MS (FAB): calcd for $C_{186}H_{189}N_9O_{45}$: 3268.2778: m/z 3268.6 [M^+], 3119.8, 2848.3, 2222.5. PDI: 1.03.

3-G4. 87% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.71 (s, 144H), 4.81 (s, 12H), 4.87 (s, 72 H), 4.94 (s, 6H), 5.26 (s, 6H), 6.15 (s, 3H), 6.36 (m, 22H), 6.38 (m, 9H), 6.48-6.52 (m, 70H), 6.57 (m, 10H), 6.61 (m, 24H), 7.44 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.0, 160.2, 160.0, 144.1, 139.1, 138.9, 136.8, 123.0, 107.0, 106.4, 106.3, 105.2, 102.0, 101.6, 99.9, 95.0, 70.0, 61.8, 55.3, 53.9. MS (MALDI): calcd for $C_{378}H_{381}N_9O_{93}$: 6533.5361. found: 6572.2007 [M^+ + K]. PDI: 1.02.

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