Notes

Convergent Synthesis of Symmetrical and Unsymmetrical PAMAM Dendrimers

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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] The two most widely studied dendrimer families are the Fréchet-type polyether and the Tomalia-type PAMAM dendrimers. PAMAM dendrimers are synthesized by the divergent approach. This methodology involves building the dendrimers from the core by an iterative synthetic procedure.[2] The convergent approach to dendrimer synthesis introduced by Fréchet and co-workers revolutionized the synthetic approaches to monodisperse dendrimers.[3] The convergent methodology installs the core in the final step, enabling the incorporation of functionalities. It provides greater structural control than the divergent approach due to its relatively low number of coupling reactions at each growth step. The ability to prepare well-defined (un)symmetrical dendrimers is the most attractive features of the convergent synthesis. Future applications of dendrimers rely on efficient and practical synthetic procedures.

The copper-catalyzed Huisgen [2 + 3] dipolar cycloaddition reaction between an azide and an alkyne leading to 1,2,3-triazole, developed by Sharpless and Tornøe,[4] now appears to offer a simple, reliable, and productive dendrimer synthesis method.[5] The route is clearly a breakthrough in the synthesis of dendrimers and dendritic and polymer materials.[6] Relatively few applications using the alkynyl-dendron in dendrimer synthesis have been reported.[7] 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 and shown the characteristic behaviors. Because of our interest in developing new functinonal dendrimers, we became involved in exploring efficient cycloaddition reaction that provides an easy access to dendrimers. Herein we present the synthesis of propargyl-functionalized PAMAM dendrons **1-D*m*** and their application to the first convergent synthesis of symmetric and unsymmetric PAMAM dendrimers[8] using click chemistry with a bis-azides core.

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Experimental Section

General Procedure for the Preparation of Symmetric PAMAM Dendrimers 3-G*mm* from Propargyl-PAMAM Dendrons 1-D*m* and Bis(azide) Core 2. A mixture of propargyl-dendrons **1-D*m*** (0.13 mmol) and *p*-xylylene diazide **2** (0.06 mmol) in THF−H_2O (4:1, 0.6 mL) in the presence of 10 mol % $CuSO_4 \cdot 5H_2O$ with 20 mol % sodium ascorbate was stirred at room temperature for ∼4 h. The reaction mixture was poured into brine (5 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/methanol system or methanol) to afford the desired product.

3-G11. A ivory solid; mp 114−116 °C; 97% yield. IR: 2952, 2842, 1734, 1437, 1198, 1174, 1047 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.45 (t, J = 6.95 Hz, 8H), 2.76 (t, J = 6.95 Hz, 8H), 3.59 (s, 12H), 3.76 (s, 4H), 5.48 (s, 4H), 7.23 (m, 4H), 7.42 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.11, 145.52, 135.79, 128.94, 123.18, 53.93, 51.95, 49.30, 49.05, 32.85. MS (MALDI): m/z calcd for $C_{30}H_{42}N_8O_8$: 642.3126; found: 643.2782 [M^+ + H], 665.2531 [M^+ + Na]. Anal. Calcd for $C_{30}H_{42}N_8O_8 \cdot H_2O$: C, 54.53; H, 6.71; N, 16.96. Found: C, 54.43; H, 6.63; N, 16.74. PDI: 1.02.

3-G22. A pale yellowish oil; 95% yield. IR: 3311, 2952, 2834, 1735, 1663, 1536, 1437, 1257, 1199, 1177, 1047 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.41 (t, J = 6.64 Hz, 24H), 2.52 (t, J = 5.83 Hz, 8H), 2.74 (t, J = 6.63 Hz, 16H), 2.77 (t, J = 6.60 Hz, 8H), 3.24−3.27 (m, 8H), 3.64 (s, 24H), 3.80 (s, 4H), 5.50 (s, 4H), 7.10 (br s, 4H), 7.25 (m, 4H), 7.52 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.41, 172.45, 145.02, 135.86, 128.92, 123.21, 53.83, 53.31, 52.01, 49.66, 48.19, 37.50, 34.07, 33.08, 30.69. MS (MALDI): m/z calcd for $C_{66}H_{106}N_{16}O_{20}$: 1442.7769; found: 1443.7312 [M^+ + H], 1465.7186 [M^+ + Na]. PDI: 1.04.

3-G33. A pale yellowish gum; 94% yield. IR: 3298, 2951, 2827, 1735, 1651, 1542, 1437, 1257, 1199, 1177, 1047 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.34 (t, J = 6.41 Hz, 16H), 2.41 (t, J = 6.50 Hz, 40H), 2.51−2.56 (m, 24H), 2.73 (t, J = 6.52 Hz, 40H), 2.79 (t, J = 6.30 Hz, 16H), 3.25−3.26 (m, 24H), 3.65 (s, 48H), 3.79 (s, 4H), 5.51 (s, 4H), 7.03 (br s, 8H), 7.25 (m, 4H), 7.59 (s, 2H), 7.70 (br s, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.47, 172.78, 172.67, 144.78, 135.92, 128.96, 123.56, 53.84, 53.34, 52.91, 52.05, 50.30, 49.66, 48.01, 37.86, 37.60, 34.29, 34.03, 33.10, 30.07. MS (MALDI): m/z calcd for $C_{138}H_{234}N_{32}O_{44}$: 3043.7057; found: 3066.5505 [M^+ + Na].

3-G44. A pale yellowish; 86% yield. IR: 3298, 2952, 2923, 2849, 1735, 1649, 1542, 1438, 1257, 1198, 1176, 1046 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.35 (m, 48H), 2.41−2.44 (m, 72H), 2.52−2.56 (m, 56H), 2.73−2.76 (m, 72H), 2.78−2.79 (m, 48H), 3.26−3.27 (m, 56H), 3.66 (s, 96H), 3.80 (s, 4H), 5.52 (s, 4H), 7.11 (br s, 16H), 7.26 (m, 4H), 7.65 (s, 2H), 7.66 (br s, 8H), 7.83 (br s, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.67, 173.08, 172.97, 136.12, 132.92, 131.51, 129.42, 129.17, 123.93, 53.54, 53.12, 53.01, 52.26, 50.68, 50.45, 49.87, 38.12, 37.82, 34.93, 34.44, 33.31, 33.07, 32.51, 30.28, 30.04, 29.95, 29.85. MS (MALDI): calcd for $C_{282}H_{490}N_{64}O_{92}$: 6245.5632; found: 6268.0630 [M^+ + Na].

General Procedure for the Preparation of Unsymmetric PAMAM Dendrimers 5-G*nm* from Azido-PAMAM Dendrons 4-D*n* and Propargyl-PAMAM Dendrons 1-D*m*. A mixture of

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azido-dendrons **4-D*n*** (0.03 mmol) and propargyl-dendrons **1-D*m*** (0.036 mmol) in THF−H_2O (4:1, 0.4 mL) in the presence of 5 mol % $CuSO_4 \cdot 5H_2O$ with 10 mol % sodium ascorbate was stirred at room temperature for ∼4 h. The reaction mixture was poured into brine (5 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/methanol system or methanol) to afford the desired product **5-G*nm***.

5-G31. A pale yellowish oil; 95% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.35 (t, J = 6.4 Hz, 8H), 2.42 (t, J = 6.4 Hz, 20H), 2.47 (t, J = 6.95 Hz, 4H), 2.51−2.56 (m, 12H), 2.74 (t, J = 6.5 Hz, 20H), 2.76−2.79 (m, 12H), 3.26−3.27 (m, 12H), 3.62 (s, 6H), 3.65 (s, 24H), 3.77 (s, 2H), 3.80 (s, 2H), 5.51 (s, 2H), 5.52 (s, 2H), 7.02 (br s, 4H), 7.25 (m, 4H), 7.43 (s, 1H), 7.59 (s, 1H), 7.70 (br s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.46, 173.19, 172.50, 145.67, 135.79, 129.01, 128.93, 123.14, 53.92, 53.29, 52.92, 52.05, 51.93, 50.31, 49.65, 49.34, 49.04, 37.61, 33.89, 33.09, 33.00, 30.03. MS (MALDI): *m*/*z* calcd for $C_{84}H_{138}N_{20}O_{26}$: 1843.0091; found: 1843.9221 [M^+ + H], 1865.9014 [M^+ + Na].

5-G32. A pale yellowish oil; 93% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.34−2.36 (m, 8H), 2.41−2.43 (m, 32H), 2.51−2.57 (m, 16H), 2.73−2.75 (m, 28H), 2.78−2.79 (m, 12H), 3.26−3.27 (m, 16H), 3.65 (s, 12H), 3.66 (s, 24H), 3.81 (s, 4H), 5.51 (s, 2H), 5.52 (s, 2H), 7.04 (br s, 4H), 7.11 (br s, 2H), 7.27 (m, 4H), 7.53 (s, 1H), 7.59 (s, 1H), 7.71 (br s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.44, 172.75, 172.65, 172.49, 144.91, 144.86, 135.94, 135.83, 128.94, 123.52, 123.29, 53.84, 53.31, 52.88, 52.02, 50.27, 49.64, 48.14, 37.83, 37.58, 37.52, 34.25, 34.07, 33.08, 30.05. MS (MALDI): *m*/*z* calcd for $C_{102}H_{170}N_{24}O_{32}$: 2243.2413; found: 2244.1655 [M^+ + H], 2266.1372 [M^+ + Na].

5-G41. A pale yellowish oil; 94% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.35 (t, J = 6.0 Hz, 24H), 2.42 (t, J = 6.5 Hz, 36H), 2.47 (t, J = 6.95 Hz, 4H), 2.52−2.55 (m, 28H), 2.74 (t, J = 6.5 Hz, 36H), 2.77−2.79 (m, 28H), 3.26−3.27 (m, 28H), 3.62 (s, 6H), 3.66 (s, 48H), 3.77 (s, 2H), 3.80 (s, 2H), 5.51 (s, 2H), 5.53 (s, 2H), 7.08 (br s, 8H), 7.26 (m, 4H), 7.46 (s, 1H), 7.64 (br s, 4H), 7.66 (s, 1H), 7.81 (br s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.45, 173.21, 172.86, 172.75, 145.60, 144.79, 136.06, 135.76, 128.94, 123.71, 123.16, 53.92, 53.80, 53.34, 52.92, 52.80, 52.04, 51.93, 51.00, 50.46, 50.23, 49.66, 49.32, 49.00, 37.92, 37.61, 34.24, 33.93, 33.10, 33.00, 32.30, 30.06. MS (MALDI): calcd for $C_{156}H_{266}N_{36}O_{50}$: 3443.9379; found: 3466.8132 [M^+ + Na].

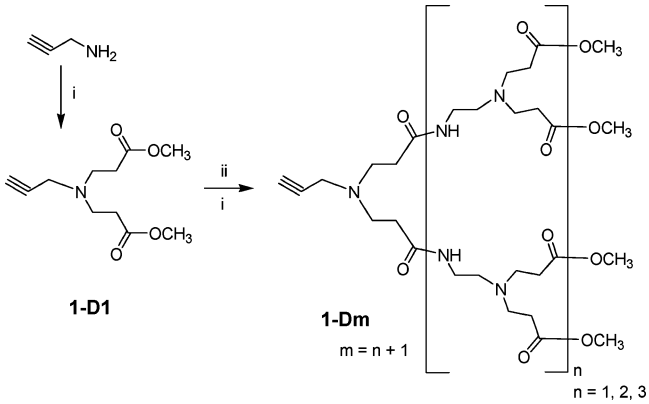
5-G42. A pale yellowish gum; 91% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.33−2.36 (m, 32H), 2.41−2.43 (m, 48H), 2.53−2.56 (m, 32H), 2.73−2.76 (m, 44H), 2.77−2.79 (m, 28H), 3.26−3.27 (m, 32H), 3.64 (s, 12H), 3.66 (s, 48H), 3.80 (s, 4H), 5.51 (s, 2H), 5.53 (s, 2H), 7.07 (br s, 8H), 7.12 (br s, 2H), 7.26 (m, 4H), 7.54 (s, 1H), 7.64 (br s, 4H), 7.65 (s, 1H), 7.82 (br s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.46, 172.90, 172.78, 172.51, 144.71, 136.03, 128.97, 127.27, 123.35, 53.86, 53.33, 52.91, 52.05, 50.47, 50.23, 49.67, 48.07, 37.92, 37.62, 37.54, 34.23, 34.07, 33.10, 32.31, 32.17, 31.97, 30.08. MS (MALDI): calcd for $C_{174}H_{298}N_{40}O_{56}$: 3844.1701; found: 3866.9282 [M^+ + Na].

5-G43. A pale yellowish gum; 85% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.35 (m, 32H), 2.41−2.44 (m, 56H), 2.53−2.56 (m, 40H), 2.74−2.76 (m, 56H), 2.78−2.79 (m, 32H), 3.27 (m, 40H), 3.66 (s, 72H), 3.80 (s, 4H), 5.52 (s, 2H + 2H), 7.07 (br s, 4H + 8H), 7.26 (m, 4H), 7.53 (br s, 1H + 2H), 7.64 (br s, 1H + 4H), 7.82 (br s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.67, 173.07, 172.98, 136.03, 131.51, 129.49, 129.43, 129.20, 124.35, 53.56, 53.14, 52.27, 51.38, 50.63, 50.44, 49.88, 38.14, 37.83, 34.46, 34.18, 33.33, 32.53, 30.30, 29.86. MS (MALDI): calcd for $C_{210}H_{362}N_{48}O_{68}$: 4644.6344; found: 4645.7124 [M^+ + H], 4667.6001 [M^+ + Na], 4668.6089 [M^+ + H + Na].

Results and Discussion

PAMAM dendrons **1-D*m*** (m = 1−4: generation of dendron) are synthesized by the divergent approach using propargylamine as a propargyl focal point shown in Scheme 1. Although we have screened several Lewis acid-catalyzed Michael addition reactions to find the efficient condition in conjugate addition of free amine, we utilized a standard PAMAM synthesis eventually furnishing us with the ester-terminated dendrons. This methodology involves typical stepwise and iterative two-step reaction sequences, consisting of amidation of methyl ester groups with a large excess of ethylenediamine (EDA) and Michael addition of primary amines with methyl acrylate (MA) to produce methyl ester terminal groups. The reaction of propargylamine and 3.5 equiv of MA in methanol gave dendron **D1** in 99% yield. For dendron **D2**, dendron **D1** reacted with 20 equiv of EDA in methanol, and then removal of methanol and excess EDA under vacuum produced the amine-terminated dendron, which was reacted with 7 equiv of MA in methanol to afford dendron **D2** in 99% yield. Dendrons **D3** and **D4** were obtained from **D2** and **D3** by the consecutive amidation and Michael addition reactions, in yields of 90% and 86%, respectively. All dendrons were confirmed by ^{1}H and ^{13}C NMR spectroscopy, IR spectroscopy, and their FAB mass spectra.

Scheme 1[a]

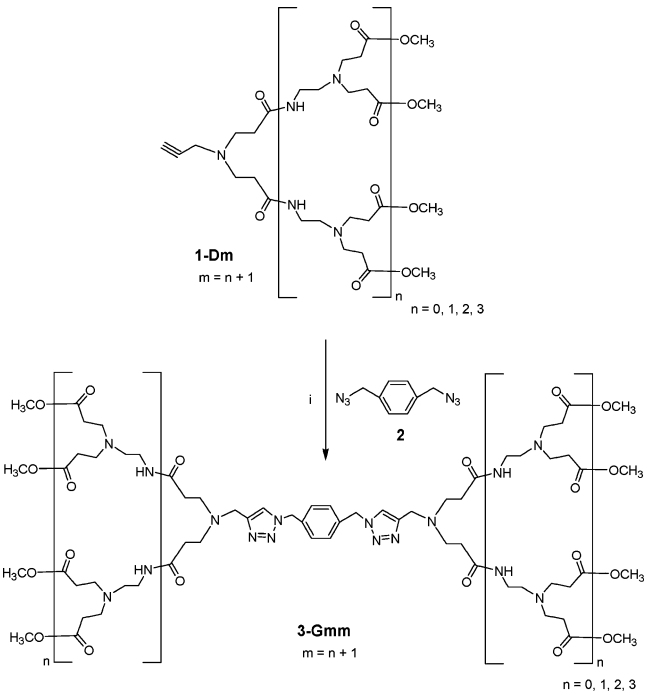


[a] Reagents and conditions: (i) methyl acrylate, MeOH, rt; (ii) ethylenediamine, MeOH, rt.

The inward growth employed by the convergent synthesis is ideally suited for the attachment of diverse core moieties. As a result, building dendrimers via the convergent approach allows for the synthesis of symmetric and unsymmetrical dendrimers and for specific incorporation of function into the dendrimer interior. But, an example in the convergent synthesis of PAMAM dendrimers by the amide coupling between carboxylic acid and amine is reported.[8b] To efficiently connect the propargyl focal point PAMAM dendrons with core unit(s), we intended to use the click condition using Cu(I) species. The Cu(I)-catalyzed Huisgen [2 + 3] dipolar cycloaddition reaction between azides and alkynes is characterized by reliable 1,4-regiospecific 1,2,3-triazole formations, water tolerance, and toleration of a wide range of functionalities.

The bis(azide) core **2**, designed to present two azide functionalities available for dendrimer growth via click reactions with the dendron, was synthesized readily from α,α′-dichloro-*p*-xylene and sodium azide. To test the effectiveness of the dipolar cycloaddition reactions of the bis(azide) core **2** and alkyne-dendrons **1-D*m***, we have screened several conditions using various Cu(I) sources in different solvents. Representatively, the reactions of the bis(azide) core **2** and 2.1 equiv of alkyne-dendrons **1-D1** in the presence of 0.1, 0.2, and 0.5 equiv of CuI in THF at room temperature for 48, 18, and 18 h afforded the desired product **3-G11** in yields of 76%, 90%, and 87%, respectively. The reaction conducted from the condition of 10

Scheme 2[a]



[a] Reagents and conditions: (i) CuI, THF, rt or $CuSO_4 \cdot 5H_2O$/sodium ascorbate, THF/H_2O (4:1), rt.

mol % $CuSO_4 \cdot 5H_2O$ with 20 mol % sodium ascorbate in a 4:1 solvent ratio of THF to H_2O for 1.5 h at room temperature afforded the desired product **3-G11** in yield of 97% (Scheme 2). The generation and disappearance of the mono-triazole derivative were monitored by TLC runs of the reaction mixture. It is unprecedented to find that the desired product obtained from only catalytic amount of CuI without amine additive in THF even at room temperature and the reaction with Cu(I) species in situ generated completed at short reaction time. The accelerated rate of reactions may potentially be explained by anchimeric assistance due to the amino ester part.[9] We are currently investigating the substrate specificity in copper-catalyzed cycloaddition reaction between azide and alkyne.

Given the success in the synthesis of first-generation dendrimer, we expanded this reaction to get higher-generation dendrimers with 5 mol % $CuSO_4 \cdot 5H_2O$ with 10 mol % sodium ascorbate with respect to alkyne in a 4:1 solvent ratio of THF to H_2O shown in Scheme 2. Reaction of the bis(azide) core **2** with 2.1 equiv of **1-D2** and **1-D3** afforded the PAMAM dendrimers **3-G22** and **3-G33** in yields of 95% and 94%, respectively, after 2 and 3 h. In the case of **1-D4**, the PAMAM dendrimer **3-G44** was obtained in 86% yield after 4 h. For completion of the reaction between the dendritic acetylene and the core, the higher-generation dendron takes longer time than the lower-generation dendron which can be differentiated by the accessibility of acetylide due to the steric hindrance (bulkiness) of dendron and spatial congestion of core region. This observation led us to imagine that the reaction between the dendritic acetylene and the core was kinetically controlled. This result showed that the formation of triazole can be regarded as a new connector to construct the symmetric PAMAM dendrimers from dendrons.

All symmetric PAMAM dendrimers were confirmed by ^1H and ^{13}C NMR spectroscopy, IR spectroscopy, and MALDI mass spectra. From their ^1H NMR spectra ($CDCl_3$), the peaks of the benzylic protons adjacent to the nitrogen of triazole and the triazole proton in dendrimers **3-G*mm*** were found at 5.48 and 7.42 ppm for **3-G11**, 5.50 and 7.52 ppm for **3-G22**, 5.51 and 7.59 ppm for **3-G33**, and 5.52 and 7.65 ppm for **3-G44**, respectively. As the dendrimer generation increased, the peaks of the benzylic protons adjacent to the nitrogen of triazole and the triazole proton shifted gradually to downfield which may be influenced by the dendritic effect. IR data also confirmed that neither alkyne (~3277 cm^{-1}) nor azide (2098 cm^{-1}) residues remain in the final dendrimer (Figure 1). Their MALDI mass spectra were exhibited very good correlation with the calculated molecular masses. Analysis of the dendrimers by gel-permeation chromatography (GPC) from THF eluent shows very low polydispersity values, PDI = 1.02 and 1.04 for **3-G11** and **3-G22**, respectively. Unfortunately, GPC analysis for **3-G33** and **3-G44** could not be obtained due to their poor solubility in THF.

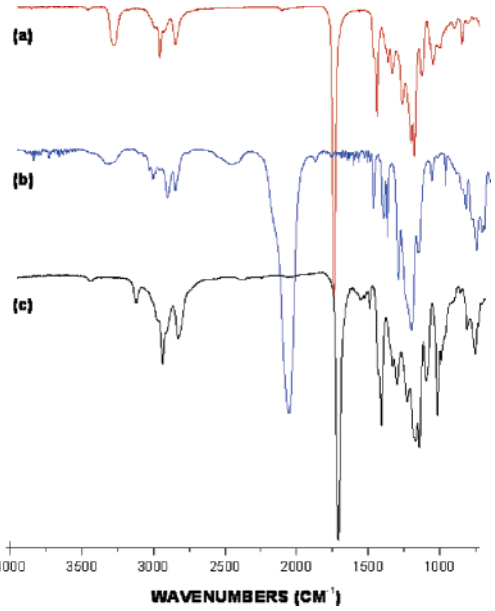
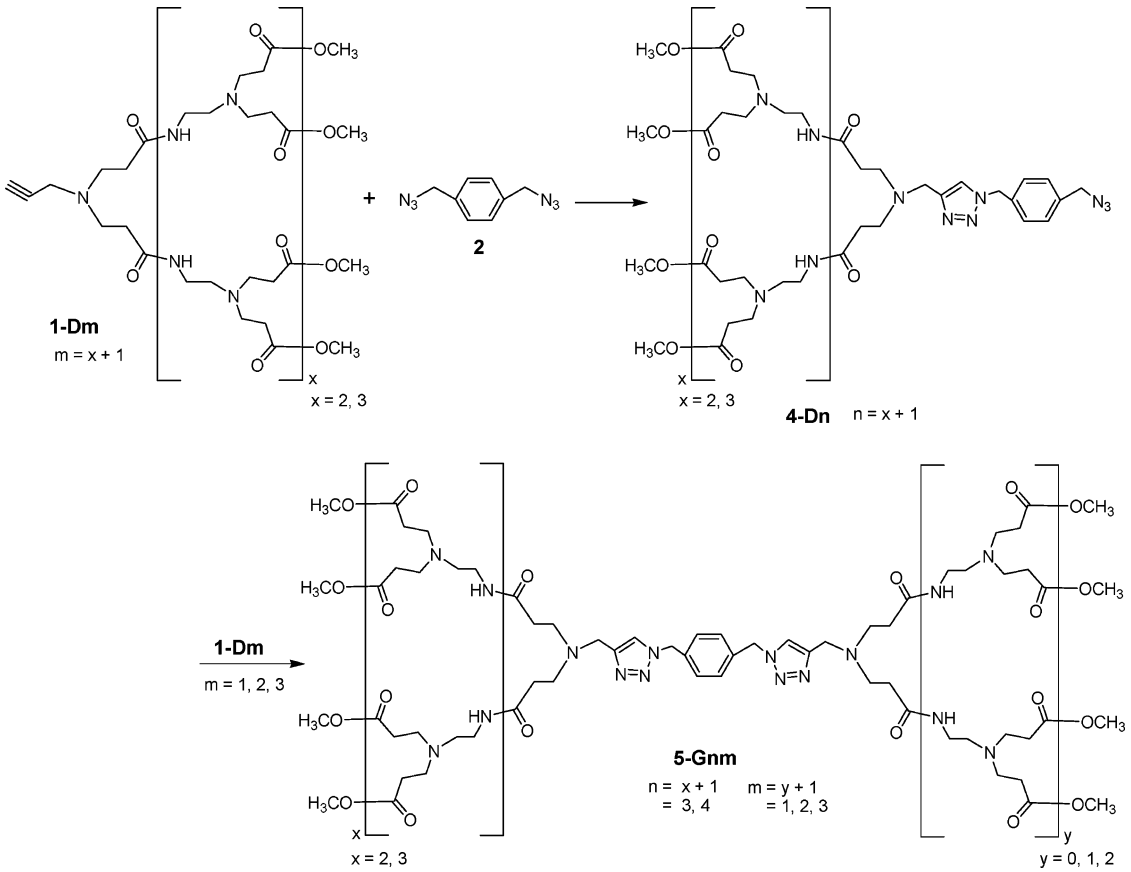


Figure 1. IR spectra for (a) **1-D1**, (b) **2**, and (c) **3-G11**.

To probe the viability of our approach, we next turned our attention toward the construction of unsymmetrical PAMAM dendrimers. Unsymmetric dendrimers were assembled through successive click reactions. In other words, unsymmetric dendrimer growth proceeded via an iterative sequence that involved double click reactions of a bis(azide) core with the alkynyl group of the dendron. We have investigated two synthetic strategies (Scheme 3). The first one is based on the reactions of the third-generation acetylenic-dendron **1-D3** with the lower generation dendrons. The second strategy involves the reactions using the fourth-generation alkyne dendron **1-D4**. The third- and fourth-generation azido-focal dendron **4-D*n*** (n = 3 and 4) were obtained via the copper-catalyzed reaction between the third- and fourth-generation alkyne-focal dendrons **(1-D3** and **1-D4)** and 20 equiv of α,α′-diazido-*p*-xylene in yields of 87% and 90% after 1.5 and 2.5 h, respectively. The reaction of third-generation azido-focal dendron **4-D3** with **1-D1** and **1-D2** in the presence of 5 mol % $CuSO_4 \cdot 5H_2O$ with 10 mol % sodium ascorbate in a 4:1 solvent ratio of THF to H_2O afforded the unsymmetrical PAMAM dendrimers **5-G31** and **3-G32** in yields of 95% and 93%, respectively, after 1.5 and 2.5 h. The reaction of fourth-generation azido-focal dendron **4-D4** with **1-D1**, **1-D2**, and **1-D3** provided the unsymmetrical PAMAM dendrimers **5-G41**, **5-G42**, and **5-G43** in yields of 94%, 91%, and 85%, respectively, after 1.5, 2.5, and 4 h. This result showed that the successive formation of triazole is found to be an efficient

Scheme 3[a]



[a] Reagents and conditions: $CuSO_4 \cdot 5H_2O$/sodium ascorbate, THF/H_2O (4:1), rt.

connector to construct the unsymmetric PAMAM dendrimers from dendrons. We are currently investigated the synthesis of various unsymmetric functional dendrimers using the different kinds of dendrons. All unsymmetric PAMAM dendrimers were also confirmed by ^{1}H and ^{13}C NMR spectroscopy and MALDI mass spectra. From their ^{1}H NMR spectra ($CDCl_3$), we have observed that the chemical shifts of the benzylic protons adjacent to the nitrogen of triazole and the triazole protons in unsymmetric dendrimers **5-G*nm*** were similar to those in the corresponding dendron(s) of symmetric dendrimers **3-G*mm***.

In summary, we have demonstrated for the first time that the propargyl-functionalized PAMAM dendrons are synthesized by the divergent approach using propargylamine as a propargyl focal point and that click reactions between bis(azide) core and the propargyl-functionalized PAMAM dendrons lead to the formation of symmetric PAMAM dendrimers in high yields. Furthermore, such successive reactions between dendrons of different size afford unsymmetrical PAMAM dendrimers. It has been found that the amino-ester building unit may play a role to accelerate autocatalytically the click chemistry reaction. This method can be applied for the fast synthesis of PAMAM dendrimers with different lengths (spacers) at core and may then provide an insight into designing various (un)symmetrical dendrimers such as amphiphilic dendrimers. We are currently working toward synthesis of various functional dendrimers using this strategy for various applications.

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Supporting Information Available: Synthetic experimental details and spectroscopic data of dendrons **1-D*m***, *p*-xylylenediazide **2**, and azido-PAMAM dendrons **4-D*n***; ^{1}H NMR spectra of **1-D*m***; and MALDI mass and ^{1}H NMR spectra of **3-G*mm*** and **5-G*nm***. This material is available free of charge via the Internet at http://pubs.acs.org.

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