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Accelerated Synthesis of Large Generation Triazine Dendrimers Using Microwave Assisted Reactions: A 24 Hour Challenge

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The expedited synthesis of odd generation triazine dendrimers up to generation 9 can be executed in high yields using microwave irradiation. The efforts commence from commercially-available and inexpensive materials. Execution is facilitated by automated chromatography.

Introduction

Unlike linear polymers that are available in one step through polymerization of monomer(s), the synthesis of dendrimers relies on multiple steps. While burdensome in terms of both scale and time, strategies to reduce these tolls continue to be advanced.[1] In 2010, Hawker and Malkoch reported the synthesis of a generation 6 dendrimer in less than a day exploiting thiol-ene reactivity and click chemistry.[2] Two different, orthogonal monomers were employed. One monomer presented one thiol and two azides. The other presented two alkenes and an alkyne. The iterative synthesis produced highly monodisperse materials at low generations (PDI≤1.03) and the onset of low polydispersity at generations 5 and 6. The only drawback to the strategy rested in the preparation of the monomers which entailed six overnight reactions and four chromatographic purifications. More recently, Malkoch et al. achieved a generation 6 dendrimer derived from bismethylolpropionic acid in less than a day (including the synthesis of starting materials) using the reactivity of carbonyldiimidazole and CsF as a catalyst.[3]

These efforts punctuate a long standing challenge to the community—the rapid and facile synthesis of dendrimers. To this end, many different approaches have been pursued.[4] In most of the cases, hypermonomers are employed that exploit the simplicity of Michael additions,[5] acid-amine conjugations,[6] thiol-ene photoadditions[7] and click chemistry.[8] The "onion peel" dendrimers described by Roy et al. provide a noteworthy example.[9] Our own efforts in accelerating the synthesis of triazine dendrimers using microwave irradiation have inspired us to take on this "24 hour challenge" to synthesis. We have shown that microwave irradiation substantially decrease times of reaction in low generation dendrimers synthesized by convergent route.[10] In light of this success and motivated by the long standing interest of performing an easy and fast synthesis, we decide to extend this chemistry to large generation triazine dendrimers using a divergent approach. We have shown that triazine dendrimers may have potential applications in many areas based on the ability to create versatile structures including areas in gene and drug delivery as well as materials science.[11]

Results and discussion

The synthesis strategy employed here to reach generation 9 dendrimers utilizes a macromonomer, 3, that affords two generations per iterative reaction cycle (Scheme 1).[12] This macromonomer comprises hydrophilic linkers based on 4,7,10-trioxa-1,13-tridecanediamine and BOC-piperazine groups. Previous studies have established that piperazine and other constrained secondary amines provide the necessary reactivity for substitution of a monochlorotriazine.[13] All three building blocks employed; BOC-piperazine, cyanuric chloride, and 4,7,10-trioxa-1,13-tridecanediamine are commercially available and used as received. Cost analysis based on yields and solvent consumption for both synthesis and purification lead to a cost of $280/g of generation 9 dendrimer at the modest scales employed here. Macromonomer 3 is readily prepared in three steps in 50 minutes of total reaction time (Scheme 1). Specifically, cyanuric chloride was disubstituted with BOC-piperazine in tetrahydrofuran (THF) using diisopropylethylamine (DIPEA) as a base with an irradiation time of 10 minutes at 60 °C. The product, 1, is recovered by precipitation. Next, monochlorotriazine 1 is reacted with an excess of 4,7,10-trioxa-1,13-tridecanediamine in dioxane at 95 °C for 30 minutes using cesium carbonate as a base. Following

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chromatography, amine 2, was reacted with cyanuric chloride in THF at 60 °C for 10 minutes with DIPEA as a base to yield 3. Macromonomer 3 was purified by chromatography. The overall yield for this three-step procedure is 55%.

Scheme 1. Synthesis of macromonomer **3** from **1** and **2**. See text for details.

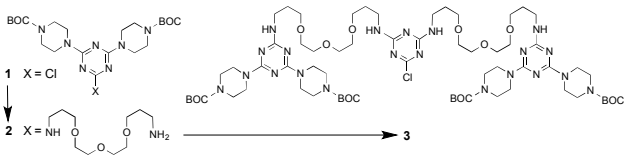

Chart 1 shows the structures of the dendrimers prepared in this study. These materials are named by the generation number "x" as **Gx**. Intermediates carrying BOC protecting groups are identified as **Gx-BOC**. The synthesis is divergent and rests on the availability of large amounts of macromonomer **3.** To prepare the generation one dendrimer, **G1**, macromonomer **3** is reacted with additional **2**. The primary amine of **2** reacts much more sluggishly with monochlorotriazines than piperazine groups. Accordingly, in presence of an excess of **2** in dioxane with cesium carbonate as a base, the reaction requires 95 °C for 2.5 hours. The result, **G1-BOC** is obtained at 60% yield after chromatography.

Deprotection to yield **G1** in dioxane/HCl requires only 6 minutes at 60 ºC in the microwave. The product is obtained quantitatively and used without further purification.

The remaining steps of the synthesis follow this iterative process of addition of **3** and acid-catalyzed deprotection. All addition reactions are executed at 95 °C under microwave irradiation. All deprotection reactions are executed similarly, but at 60 °C. Beyond **G1,** the solvent system used for addition of **3** is dioxane:methanol:water at 2:1:0.1 Deprotections are carried out in 2:1 dioxane:conc. HCl. Chart 2 summarizes the individual yields, cumulative yields, and other attributes of the target molecules. The time for addition of **3** increases as the dendrimer generation increases. However, this increase is offset by the ease of purification: **3** and product dendrimer show markedly different solubility in ether with trace methanol.

Chart 2. Targets, reaction times, yields for individual reactions and the cumulative process (cume) over the entire sequence, isolation procedure (precipitation, chromatography, or extraction), isolation time and theoretical characteristics of the products.

Cmpd	Rxn Time	Yield (%)	Cume (%)	Iso.	Isolation Time	Ends	MW (Da)
1	10 min	82	82	Prec	1 hr	NA	484
2	30 min	70	57	Chrm	2 hr	NA	667
3	10 min	95	55	Chrm	1 hr	NA	1446
G1-BOC	2.5 h	60	33	Chrm	1 hr	6	2077
G1	6 min	Quant.	33	Extr	30 min	6	1477
G3-BOC	4 h	82	27	Chrm.	1 hr	24	9936
G3	6 min	Quant.	27	Extr	30 min	24	7535
G5-BOC	4 h	75	20	Prec	1 hr	96	41K
G5	6 min	Quant.	20	Extr	30 min	96	32K
G7-BOC	6 h	85	17	Prec	1 hr	384	167K
G7	6 min	90	15	Extr	30 min	384	127K
G9-BOC	6 h	80	12	Prec	1 hr	1536	670K

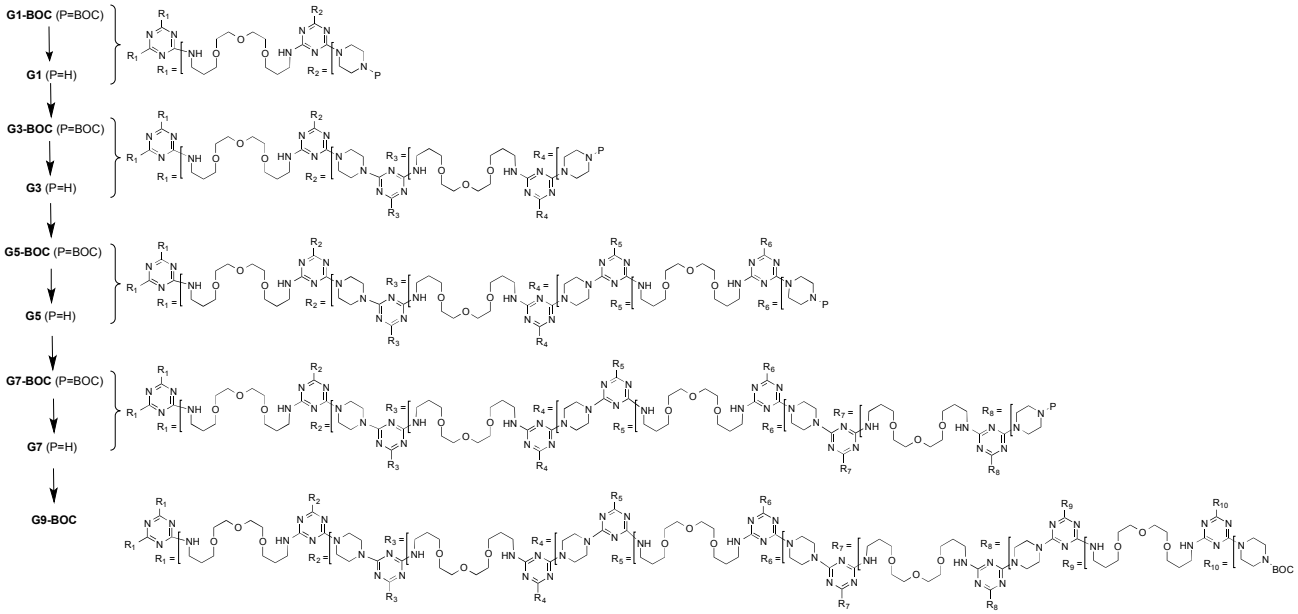

Chart 1. Dendrimers prepared in this study.

Throughout the course of the synthesis, the intermediates and targets can be characterized by ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry. ^{1}H NMR spectra show characteristic loss of BOC groups on deprotection, and appearance of substituted piperazine groups at δ 2.81-2.87. Mass spectrometry shows isotopic resolution and lines for materials up to **G5-BOC**. Defects for **G5** and **G5-BOC** can be seen by ESI-MS. Larger dendrimers show a broad peak that can be attributed to incomplete reaction. Using GPC analysis, PDI values were possible to calculate for G1, G3, G5, and G7 (1.05, 1.09, 1.11 and 1.18). When G5 dendrimer was resubjected to reaction conditions with additional **3**, the PDI value did not decrease, remaining 1.11.

Experimental

Compound 1. 1-Boc-piperazine (11.14 g, 60 mmol) was added to a solution of cyanuric chloride (5.02 g, 27 mmol) in THF (200mL). Afterwards DIPEA (19 mL, 0.109 mol) was added dropwise. The solution was stirred for 2 minutes in order to allow reagents to mix. Then, the solution was separated in multiple vessels and irradiated in the microwave while stirring for 10 minutes at 60ºC using dynamic mode. The crude product was purified by precipitations hexanes/EtOAc to give **1** (10.83 g, 82%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74 (br, 8H, NC**H**$_2$C**H**$_2$NBoc), 3.44 (br, 8H, NCH$_2$C**H**$_2$NBoc), 1.45 (s, 18H, C(C**H**$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 164.4 (**C**$_3$N$_3$), 156.5 (**C**O), 80.1 (**C**(CH$_3$)$_3$), 43.2 (N**C**H$_2$**C**H$_2$N), 28.3 (C(**C**H$_3$)$_3$); MS (ESI-TOF) calcd for $C_{21}H_{34}ClN_7O_4$ 483.2361, found 484.3702 $(M + H)^+$.

Compound 2. A solution of **1** (3g, 6 mmol) with 4,7,10-trioxa-1,13-tridecanediamine (13.65mL, 62 mmol) and Cs_2CO_3 (4g, 12 mmol) in 40 mL of 1,4 dioxane was stirred for 2 minutes. Then, the solution was separated in multiple vessels and irradiated in the microwave while stirring for 30 minutes at 95ºC and then evaporated under vacuum. The residue was dissolved in dichloromethane, washed with brine solution and dried over $MgSO_4$, filtered, and evaporated under vacuum. The solvent system (in column volumes) used was the following: 5CV (100%DCM), 5CV (95:5= DCM: MeOH), 5CV (90:10= DCM: MeOH), 5CV (85:15= DCM: MeOH), 5CV (80:20= DCM: MeOH) to give **2** (3.26 g, 79%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.73 (br, 8H, NC**H**$_2$C**H**$_2$NBoc), 3.67-3.57 (m, 12H, C**H**$_2$OC**H**$_2$C**H**$_2$OC**H**$_2$C**H**$_2$OC**H**$_2$), 3.44 (br, 10H, NHC**H**$_2$CH$_2$CH$_2$O, NCH$_2$C**H**$_2$NBoc), 2.81 (t, 2H, OCH$_2$CH$_2$C**H**$_2$NH$_2$), 1.84 (m, 2H, OCH$_2$C**H**$_2$CH$_2$NH), 1.76 (m, 2H, OCH$_2$C**H**$_2$CH$_2$NH$_2$), 1.47 (s, 18H, C(C**H**$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 165.2 (**C**$_3$N$_3$), 154.8 (**C**O), 79.8 (**C**(CH$_3$)$_3$), 70.5 (O**C**H$_2$**C**H$_2$O), 70.2 (O**C**H$_2$**C**H$_2$O), 70.1 (O**C**H$_2$**C**H$_2$O), 69.5 (two lines, NHCH$_2$CH$_2$**C**H$_2$O, O**C**H$_2$CH$_2$CH$_2$NH$_2$), 43.8 (piperazine), 39.4 (NH**C**H$_2$CH$_2$CH$_2$O), 38.2 (OCH$_2$CH$_2$**C**H$_2$NH$_2$), 32.6 (OCH$_2$**C**H$_2$CH$_2$NH$_2$), 29.6 (NHCH$_2$**C**H$_2$CH$_2$O), 28.6 (C(**C**H$_3$)$_3$); MS (ESI-TOF) calcd for $C_{31}H_{57}N_9O_7$ 667.4381, found 668.5915$(M + H)^+$.

Compound 3 (macromonomer). Compound **2** (3.26 g, 4.8 mmol) was added to a solution of cyanuric chloride (0.411 g, 2.2 mmol) in THF (20mL). Afterwards DIPEA (3.2 mL, 20 mmol) was added dropwise, and the solution was sonicated for 2 minutes in order to allow reagents to mix. Then, the solution was irradiated in the microwave while stirring for 10 minutes at 60ºC using dynamic mode. The solvent system (in column volumes) used was the following: 5 CV (100% DCM), 5 CV (95:5= DCM: MeOH), 5CV (90:10= DCM: MeOH), 5CV (85:15= DCM: MeOH), 5 CV (80:20= DCM: MeOH) to give **3** (3.07g, 95%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.73 (br, 16H, NC**H**$_2$CH$_2$NBoc), 3.69-3.57 (m, 24H, C**H**$_2$OC**H**$_2$C**H**$_2$OC**H**$_2$C**H**$_2$OC**H**$_2$), 3.44 (br, 24H, C$_3$N$_3$-NHC**H**$_2$CH$_2$CH$_2$O, NCH$_2$C**H**$_2$NBoc), 1.86 (m, 8H, OCH$_2$C**H**$_2$CH$_2$NH), 1.48 (s, 36H, C(C**H**$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3 (**C**$_3$N$_3$), 165.7 (**C**$_3$N$_3$), 165.2 (**C**$_3$N$_3$), 154.8 (**C**O), 79.8 (**C**(CH$_3$)$_3$), 70.6 (O**C**H$_2$**C**H$_2$O), 70.3 (O**C**H$_2$**C**H$_2$O), 69.4 (NHCH$_2$CH$_2$**C**H$_2$O), 42.9 (piperazine), 38.9 (NH**C**H$_2$CH$_2$CH$_2$O), 38.3 (NH**C**H$_2$CH$_2$CH$_2$O), 29.6 (NHCH$_2$**C**H$_2$CH$_2$O), 28.8 (NHCH$_2$**C**H$_2$CH$_2$O), 28.4 (C(**C**H$_3$)$_3$); MS (ESI-TOF) calcd for $C_{65}H_{112}ClN_{21}O_{14}$ 1445.8386, found 1447.1735 $(M + H)^+$.

Compound 4 (G1-Boc) A solution of **3** (0.743g, 0.5 mmol) with **2** (1.042g, 2 mmol) and Cs_2CO_3 (1.066g, 3 mmol) in 5mL of 1,4 dioxane and 0.5mL MeOH was stirred for 2 minutes. Then, the solution was irradiated in the microwave while stirring for 2 hours 30 minutes at 95ºC using dynamic mode and then evaporated under vacuum. The residue was dissolved in dichloromethane, washed with brine solution and dried over $MgSO_4$, filtered, and evaporated under vacuum. The crude was purified by automated chromatography. The solvent system (in column volumes) used was the following: 20CV (100% DCM), 5CV (90:10= DCM: MeOH) to give **4** (0.709g, 66%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.71 (br, 24H, NC**H**$_2$CH$_2$NBoc), 3.64-3.52 (m, 36H, C**H**$_2$OC**H**$_2$C**H**$_2$OC**H**$_2$C**H**$_2$OC**H**$_2$) 3.43 (br, 36H, C$_3$N$_3$-NHC**H**$_2$CH$_2$CH$_2$O, BocNC**H**$_2$CH$_2$N), 1.83 (m, 12H, OCH$_2$C**H**$_2$CH$_2$NH), 1.46 (s, 54H, C(C**H**$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 165.26 (**C**$_3$N$_3$), 154.8 (**C**O), 79.8 (**C**(CH$_3$)$_3$), 70.6 (O**C**H$_2$**C**H$_2$O), 70.2 (two lines, O**C**H$_2$**C**H$_2$O), 69.2 (two lines, NHCH$_2$CH$_2$**C**H$_2$O), 42.9 (piperazine), 38.2 (NH**C**H$_2$CH$_2$CH$_2$O), 38.1 (NH**C**H$_2$CH$_2$CH$_2$O), 29.6 (NHCH$_2$**C**H$_2$CH$_2$O), 28.4 (C(**C**H$_3$)$_3$); MS (ESI-TOF) calcd for $C_{96}H_{168}N_{30}O_{21}$ 2077.3000, found 2079.6681 $(M + H)^+$.

Compound 5 (G1 deprotected). A solution of **4** (0.800 g, 0.385 mmol) in concentrated HCl (3 mL) and 1,4 dioxane (6 mL) was stirred for 1 min at room temperature and then was irradiated in the microwave while stirring for two periods of 3 minutes at 60ºC using dynamic mode and then evaporated with air. The residue was dissolved in dichloromethane, washed with 5M NaOH (aq), dried over $MgSO_4$, filtered, and evaporated under vacuum to give **5** (0.571 g, quantitative) as a white solid.^{1}H NMR (400 MHz, $CDCl_3$) δ 3.69 (br, 24H, NC**H**$_2$CH$_2$NH), 3.64-3.51 (m, 36H, C**H**$_2$OC**H**$_2$C**H**$_2$OC**H**$_2$C**H**$_2$OC**H**$_2$) 3.40 (br, 12H, C$_3$N$_3$-NHC**H**$_2$CH$_2$CH$_2$O), 2.83 (br, 24H, HNC**H**$_2$CH$_2$N), 1.82 (m, 12H, OCH$_2$C**H**$_2$CH$_2$NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 165.2 (**C**$_3$N$_3$), 70.6 (O**C**H$_2$**C**H$_2$O), 70.2 (two lines, O**C**H$_2$**C**H$_2$O), 69.3 (NHCH$_2$CH$_2$**C**H$_2$O), 69.2 (NHCH$_2$CH$_2$**C**H$_2$O), 46.0 (NCH$_2$**C**H$_2$NH), 44.2 (N**C**H$_2$CH$_2$NH), 38.2 (NH**C**H$_2$CH$_2$CH$_2$O), 38.1 (NH**C**H$_2$CH$_2$CH$_2$O), 29.6 (NHCH$_2$**C**H$_2$CH$_2$O); MS (ESI-TOF) calcd for $C_{66}H_{120}N_{30}O_9$ 1476.9855, found 1478.2639 $(M + H)^+$.

Compound 6 (G3-Boc). A solution of **3** (2.35g, 1.624 mmol) with **5** (0.200g, 0.135 mmol) and DIPEA (0.42mL, 2.44 mmol) in 4mL of 1,4

dioxane and 0.5mL MeOH was stirred for 2 minutes. Then, the solution was irradiated in the microwave while stirring for 4 hours at 95ºC using dynamic mode and then evaporated under vacuum. The residue was dissolved in dichloromethane, washed with brine solution and dried over $MgSO_4$, filtered, and evaporated under vacuum. The crude was purified by automated chromatography. The solvent system (in column volumes) used was the following: 5CV (99:1= EtoAc:MeOH), 5CV (98:2= EtoAc: MeOH), 5CV (100% DCM) to give **6** (1.1g, 82%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (br, 144H, NC**H**$_2$CH$_2$NBoc, NC**H**$_2$C**H**$_2$N), 3.66-3.53 (m, 180H, C**H**$_2$OC**H**$_2$C**H**$_2$OC**H**$_2$C**H**$_2$OC**H**$_2$), 3.45 (br, 156H, C_3N_3-NHC**H**$_2$CH$_2$CH$_2$O, BocNC**H**$_2$CH$_2$N), 1.86 (m, 60H, OCH$_2$C**H**$_2$CH$_2$NH), 1.47 (s, 216H, C(C**H**$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 165.26 (**C**$_3$N$_3$), 154.8 (**C**O), 79.8 (**C**(CH$_3$)$_3$), 70.6 (OC**H**$_2$C**H**$_2$O), 70.2 (two lines, OC**H**$_2$C**H**$_2$O), 69.3 (two lines, NHCH$_2$CH$_2$C**H**$_2$O), 42.9 (piperazine), 38.2 (NH**C**H$_2$CH$_2$CH$_2$O), 38.1 (NH**C**H$_2$CH$_2$CH$_2$O), 29.6 (NHCH$_2$**C**H$_2$CH$_2$O), 28.4 (C(**C**H$_3$)$_3$); MS (ESI-TOF) calcd for $C_{456}H_{786}N_{156}O_{93}$ 9936.16, found 9944.5803 $(M + H)^+$.

Compound 7 (G3 deprotected). A solution of **6** (0.650 g, 65.4 umol) in concentrated HCl (3 mL) and dioxane (6 mL) was stirred for 1 min at room temperature and then was irradiated in the microwave while stirring for two periods of 3 minutes at 60ºC using dynamic mode and then evaporated with air. The residue was dissolved in dichloromethane, washed with 5 M NaOH (aq), dried over $MgSO_4$, filtered, and evaporated under vacuum to give **7** (0.493 g, quantitative) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (br, 144H, NC**H**$_2$CH$_2$NH, NC**H**$_2$C**H**$_2$N), 3.67-3.53 (m, 180H, C**H**$_2$OC**H**$_2$C**H**$_2$OC**H**$_2$C**H**$_2$OC**H**$_2$), 3.47 (br, 60H, C_3N_3-NHC**H**$_2$CH$_2$CH$_2$O), 2.87 (br, 96H, HNC**H**$_2$CH$_2$N), 1.85 (m, 60H, OCH$_2$C**H**$_2$CH$_2$NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 165.2 (**C**$_3$N$_3$), 70.6 (OC**H**$_2$C**H**$_2$O), 70.2 (OC**H**$_2$C**H**$_2$O), 69.3 (two lines, NHCH$_2$CH$_2$C**H**$_2$O), 46.0 (NCH$_2$C**H**$_2$NH), 44.2 (NC**H**$_2$CH$_2$NH), 43.0 (NC**H**$_2$C**H**$_2$N), 38.1 (NH**C**H$_2$CH$_2$CH$_2$O), 29.6 (NHCH$_2$**C**H$_2$CH$_2$O); MS (ESI-TOF) calcd for $C_{336}H_{594}N_{156}O_{45}$ 7534.90, found 7541.6290 $(M + H)^+$.

Compound 8 (G5-Boc). A solution of **3** (1.84g, 1.274 mmol) with **7** (0.200g, 26.53 µmol) and DIPEA (0.33mL, 1.89 mmol) in 6mL of 1,4 dioxane, 0.5mL MeOH and 0.5mL H_2O was stirred for 2 minutes. Then, the solution was irradiated in the microwave while stirring for 4 hours at 95ºC using dynamic mode and then evaporated under vacuum. The residue was dissolved in dichloromethane, washed with brine solution and dried over $MgSO_4$, filtered, and evaporated under vacuum. The crude was purified by several washes with a solution of 98:2= EtoEt:MeOH to give **8** (0.76g, 75%) as a white solid.^{1}H NMR (400 MHz, $CDCl_3$) δ 3.73 (br, 624H, NC**H**$_2$CH$_2$NBoc, NC**H**$_2$C**H**$_2$N), 3.67-3.53 (m, 756H, C**H**$_2$OC**H**$_2$C**H**$_2$OC**H**$_2$C**H**$_2$OC**H**$_2$), 3.44 (br, 636H, C_3N_3-NHC**H**$_2$CH$_2$CH$_2$O, BocNC**H**$_2$CH$_2$N), 1.85 (m, 252H, OCH$_2$C**H**$_2$CH$_2$NH), 1.48 (s, 864H, C(C**H**$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 165.2, 165.1 (**C**$_3$N$_3$), 154.8 (**C**O), 79.8 (**C**(CH$_3$)$_3$), 70.6 (OC**H**$_2$C**H**$_2$O), 70.2 (two lines, OC**H**$_2$C**H**$_2$O), 69.3 (two lines, NHCH$_2$CH$_2$C**H**$_2$O), 42.9 (piperazine), 38.2 (NH**C**H$_2$CH$_2$CH$_2$O), 38.1 (NH**C**H$_2$CH$_2$CH$_2$O), 29.6 (two lines, NHCH$_2$**C**H$_2$CH$_2$O), 28.4 (C(**C**H$_3$)$_3$); MS (ESI-TOF) calcd for $C_{1896}H_{3258}N_{660}O_{381}$ 41371.59, found 41404.7224 $(M + H)^+$.

Compound 9 (G5 deprotected). A solution of **8** (0.400 g, 9.67umol) in concentrated HCl (2 mL) and dioxane (4 mL) was stirred for 1 min at room temperature and then was irradiated in the microwave while stirring for three periods of 3 minutes at 60ºC using dynamic mode and then evaporated with air. The residue was dissolved in dichloromethane, washed with 5 M NaOH (aq), dried over $MgSO_4$, filtered, and evaporated under vacuum to give **9** (0.307g, quantitative) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.68 (br, 624H, NC**H**$_2$CH$_2$NH, NC**H**$_2$C**H**$_2$N), 3.62-3.49 (br m, 756H, C**H**$_2$OC**H**$_2$C**H**$_2$OC**H**$_2$C**H**$_2$OC**H**$_2$), 3.40 (br, 252H, C_3N_3-NHC**H**$_2$CH$_2$CH$_2$O), 2.81 (br m, 384H, HNC**H**$_2$CH$_2$N), 1.80 (m, 252H, OCH$_2$C**H**$_2$CH$_2$NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 165.2 (**C**$_3$N$_3$), 70.6 (OC**H**$_2$C**H**$_2$O), 70.2 (OC**H**$_2$C**H**$_2$O), 69.3 (NHCH$_2$CH$_2$C**H**$_2$O), 69.2 (NHCH$_2$CH$_2$C**H**$_2$O), 46.0 (NCH$_2$C**H**$_2$NH), 44.2 (NC**H**$_2$CH$_2$NH), 43.0 (NC**H**$_2$C**H**$_2$N), 38.1 (NH**C**H$_2$CH$_2$CH$_2$O), 29.6 (NHCH$_2$**C**H$_2$CH$_2$O); MS (ESI-TOF) calcd for $C_{1416}H_{2490}N_{660}O_{189}$ 31766.55, found 31792.1374 $(M + H)^+$.

Compound 10 (G7-Boc). A solution of **3** (1.75g, 1.2 mmol) with **9** (0.200g, 6.3 µmol) and DIPEA (0.33mL, 1.91 mmol) in 7mL of 1,4 dioxane, 1mL MeOH and 0.5mL H_2O was stirred for 2 minutes. Then, the solution was irradiated in the microwave while stirring for 6 hours at 95ºC using dynamic mode and then evaporated under vacuum. The residue was dissolved in dichloromethane, washed with brine solution and dried over $MgSO_4$, filtered, and evaporated under vacuum. The crude was purified by several washes with a solution of 97:3= EtoEt:MeOH to give **10** (0.850g, 81%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.73 (br, 2544H, NC**H**$_2$CH$_2$NBoc, NC**H**$_2$C**H**$_2$N), 3.65-3.52 (m, 3060H, C**H**$_2$OC**H**$_2$C**H**$_2$OC**H**$_2$C**H**$_2$OC**H**$_2$), 3.43 (br, 2556H, C_3N_3-NHC**H**$_2$CH$_2$CH$_2$O, BocNC**H**$_2$CH$_2$N), 1.84 (m, 1020H, OCH$_2$C**H**$_2$CH$_2$NH), 1.48 (s, 3456H, C(C**H**$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 165.2 (**C**$_3$N$_3$), 154.8 (**C**O), 79.8 (**C**(CH$_3$)$_3$), 70.6 (OC**H**$_2$C**H**$_2$O), 70.2 (two lines, OC**H**$_2$C**H**$_2$O), 69.3 (NHCH$_2$CH$_2$C**H**$_2$O), 69.2 (NHCH$_2$CH$_2$C**H**$_2$O), 42.9 (piperazine), 38.2 (NH**C**H$_2$CH$_2$CH$_2$O), 29.6 (NHCH$_2$**C**H$_2$CH$_2$O), 28.4 (C(**C**H$_3$)$_3$); MS (ESI-TOF) calcd for $C_{7656}H_{13146}N_{2676}O_{1533}$ 167113.30, not found.

Compound 11 (G7 deprotected). A solution of **10** (0.390 g, 2.3 µmol) in concentrated HCl (2.5 mL) and dioxane (5 mL) was stirred for 1 min at room temperature and then was irradiated in the microwave while stirring for three periods of 3 minutes at 60ºC using dynamic mode and then evaporated with air. The residue was dissolved in dichloromethane, washed with 5 M NaOH (aq), dried over $MgSO_4$, filtered, and evaporated under vacuum to give **9** (0.270g, 90%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.71 (br, 2544H, NC**H**$_2$CH$_2$NH, NC**H**$_2$C**H**$_2$N), 3.64-3.51 (br m, 3060H, C**H**$_2$OC**H**$_2$C**H**$_2$OC**H**$_2$C**H**$_2$OC**H**$_2$), 3.44 (br, 1020H, C_3N_3-NHC**H**$_2$CH$_2$CH$_2$O), 2.84 (br, 1536H, HNC**H**$_2$CH$_2$N), 1.83 (m, 1020H, OCH$_2$C**H**$_2$CH$_2$NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 165.2 (**C**$_3$N$_3$), 70.6 (OC**H**$_2$C**H**$_2$O), 70.2 (OC**H**$_2$C**H**$_2$O), 69.3 (NHCH$_2$CH$_2$C**H**$_2$O), 69.2 (NHCH$_2$CH$_2$C**H**$_2$O), 46.0 (NCH$_2$C**H**$_2$NH), 44.2 (NC**H**$_2$CH$_2$NH), 43.0 (NC**H**$_2$C**H**$_2$N), 38.1 (NH**C**H$_2$CH$_2$CH$_2$O), 29.7 (NHCH$_2$**C**H$_2$CH$_2$O); MS (MALDI-TOF) calcd for $C_{5736}H_{10074}N_{2676}O_{765}$ 128693.17, not found.

Compound 12 (G9-Boc). A solution of **3** (0.430g, 0.30 mmol) with **11** (0.050g, 0.39 µmol) and DIPEA (0.08mL, 0.45 mmol) in 3mL of 1,4 dioxane, 1mL MeOH and 0.5mL H_2O was stirred for 2 minutes. Then, the solution was irradiated in the microwave while stirring for

6 hours at 95ºC using dynamic mode and then evaporated under vacuum. The residue was dissolved in dichloromethane, washed with brine solution and dried over $MgSO_4$, filtered, and evaporated under vacuum. The crude was purified by several washes with MeOH to give **10** (0.209g, 80%) as a white wax.^{1}H NMR (400 MHz, $CDCl_3$) δ 3.71 (br, 10224H, NC**H**$_2$CH$_2$NBoc, NC**H**$_2$C**H**$_2$N), 3.63-3.52 (br m, 12276H, C**H**$_2$OC**H**$_2$C**H**$_2$OC**H**$_2$C**H**$_2$OC**H**$_2$), 3.41 (br, 10236H, C_3N_3-NHC**H**$_2$CH$_2$CH$_2$O, BocNC**H**$_2$CH$_2$N), 1.80 (m, 4092H, OCH$_2$C**H**$_2$CH$_2$NH), 1.46 (s, 13824H, C(C**H**$_3$)$_3$);^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 165.2 (**C**$_3$N$_3$), 154.7 (**C**O), 79.8 (**C**(CH$_3$)$_3$), 70.6 (OC**H**$_2$C**H**$_2$O), 70.2 (OC**H**$_2$C**H**$_2$O), 69.3 (NHCH$_2$CH$_2$C**H**$_2$O), 42.9 (piperazine), 38.2 (NH**C**H$_2$CH$_2$CH$_2$O), 29.6 (NHCH$_2$**C**H$_2$CH$_2$O), 28.4 (C(**C**H$_3$)$_3$); MS (MALDI-TOF) calcd for $C_{30696}H_{52698}N_{10740}O_{6141}$ 670080.15, not found.

Conclusions

Advancing dendrimers to applications requires readily available materials. While low generation triazine dendrimers have been readily available for some time,[14] the efficient preparation of moderate and higher generation dendrimers has been elusive until now. Triazines now join the architectures advanced by Hawker, Malkoch, and Roy as rapidly assessable at high generations.

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