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Rapid, Semi-automated Convergent Synthesis of Low Generation Triazine Dendrimers using Microwave Assisted Reactions

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Microwave assisted synthesis allows for the rapid access of low generation triazine dendrimers in high yields. Products include a macromonomer and alkyne functionalized dendrimers from generation one to three. Using a microwave-assisted, convergent synthetic approach, two nucleophilic aromatic substitution reactions are executed on cyanuric chloride in 10 min at 60 °C using primary amines. Substitution of the resulting monochlorotriazine with a diamine requires 95 °C for 30 min. Purifications are accomplished using an automated chromatography system such that the generation three dendrimer can be prepared from the starting materials in less than one day.

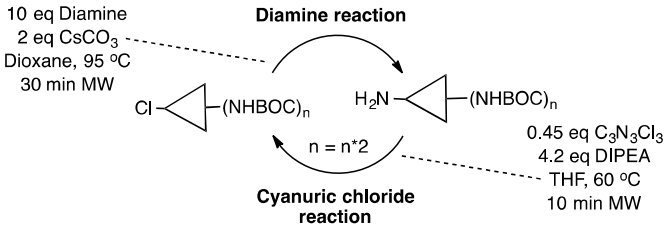
Introduction

The synthesis of dendrimers is iterative in nature. Multiple synthetic steps are required regardless of whether a convergent or divergent strategy is adopted. While synthetic strategies have been advanced to reduce burden,[1] dendrimer synthesis is rarely executed rapidly.[2] One method for increasing reaction rates and accelerating synthesis is to employ microwave irradiation instead of conventional thermal heating baths.[3] Microwave assisted reactions have been employed with triazines in the past,[4] but the benefits that these accelerations could have in multistep dendrimer synthesis remain largely unexplored. Others have employed microwave assisted reactions to small generation dendrons[5] or the functionalization of dendrimers with ligands using click chemistry.[6] Here, we explore the use of microwave assisted reactions in the convergent synthesis of triazine dendrons and dendrimers up to generation 3.

The iterative nature of the synthesis is shown in Scheme 1. In brief, a monochlorotriazine dendron (left) is reacted with excess diamine to yield the amine dendron (right). Upon purification, the amine dendron is dimerized to yield the next generation target. The choice of diamine is an important design criterion for many reasons including reactivity and solubility.

Reactivity. The reactivity of amines with substituted triazines has been studied with competition reactions.[7] Cyanuric chloride undergoes substitution with diamines twice

Scheme 1. Iterative cycle for convergent dendrimer synthesis



at moderate temperatures. The third substitution requires significantly more time and energy. This reactivity difference can be exploited to provide the desired products in high yields. In comparison, constrained secondary amines including alkyl-linked bispiperidines are much more reactive and can lead to undesired trisubstituted triazines.

Solubility. A range of diamines can be used for the synthesis of small generation triazine dendrimers including piperazine, aminomethylpiperidine, aliphatic diamines, and *p*-aminobenzylamine.[8] We recently reported the synthesis of the largest dendrimer prepared to date, a generation 13 architecture with a theoretical molecular weight of 8.4 MDa. Success derived from overcoming solubility challenges.[9] The hydrophilic diamine utilized conveyed solubility in organic solvents for protected intermediates and solubility in water when deprotected. Previous efforts that utilized both this diamine and piperazine were limited to generation 9 materials.[10]

Hydrophobic diamines commonly limited triazine dendrimer synthesis to generation 5 materials.[11]

Other Design Criteria. Our interest in the use of triazine dendrimers in aqueous environments is consistent with our pursuit of biomedical applications including drug delivery.[12] While both therapeutic and diagnostic parameters are emerging, the role of dendrimers with combined—so-called theranostic—activities is now inherent in all structures that we prepare.[12] To accommodate the dual roles, we have begun to incorporate alkynes at the focus of these dendrimers.[13] With click chemistry, these groups could ultimately host fluorescent dyes or imaging agents. Here, click chemistry is probed using a Bolton-Hunter like agent that can facilitate studies through either traditional scintillation or PET-imaging strategies using isotopes of iodine.

Results and discussion

The synthesis of generation 0-3 dendrons is shown in Scheme 2. Dendron **1** results from disubstitution of cyanuric chloride with a mono-BOC protected diamine. The reaction requires 10 minutes at 60 °C in THF using diisopropylethylamine (DIPEA) as a base and a slight excess of the nucleophilic amine. The reaction is readily monitored by thin layer chromatography.

The use of slightly less than 0.5 equivalents of cyanuric chloride in this step ensures complete conversion due to an excess of diamine:monosubstitution products are not observed upon completion of the reaction. Substitution of **1** with excess diamine to yield **2** requires harsher conditions. The use of a large excess of diamine reduces the formation of the undesired dimer. Compound **2** results when 10 equivalents of diamine are reacted at 95 °C in dioxane using cesium carbonate as a base for a period of 30 minutes. Selective disubstitution of cyanuric chloride with **2** yields **3** as the iterative process is repeated. Compound **3** is of significant interest to us. It is the macromonomer that is employed in the divergent synthesis of large generation dendrimers.[9] All the compounds provide satisfactory ^{1}H and ^{13}C NMR and mass spectra.

Using a benchtop microwave (CEM Discover SP microwave in dynamic mode) and automated chromatography (Teledyne Isco CombiFlash® Rf 200) saves time and solvent. The entire synthesis of macromonomer **3** can be executed in 5h on a gram scale at ~81% overall yield.

The choice of solvents for these reactions was based on the temperatures required for reaction, the ability of these solvents to absorb microwave radiation, and inertness. While not the best microwave absorbers, dioxane and tetrahydrofuran were chosen over dimethylformamide, dimethylacetamide, and diglyme for boiling point. In addition, dioxane promotes the solubility of cesium carbonate over hydrocarbon alternatives.

The success seen with **3** led us to examine whether this convergent approach could be extended to larger generation dendrimers. Table 1 compiles all of the results of these efforts including data from mass spectrometry.

Scheme 2. Synthesis. Diamine addition (10 equiv) reactions occur at 95 °C in dioxane for 30 min. using 2 eq of $CsCO_3$. Cyanuric chloride additions (0.45 equiv) occur at 60 °C in THF for 10 min. using 4.2 equiv. of DIPEA.

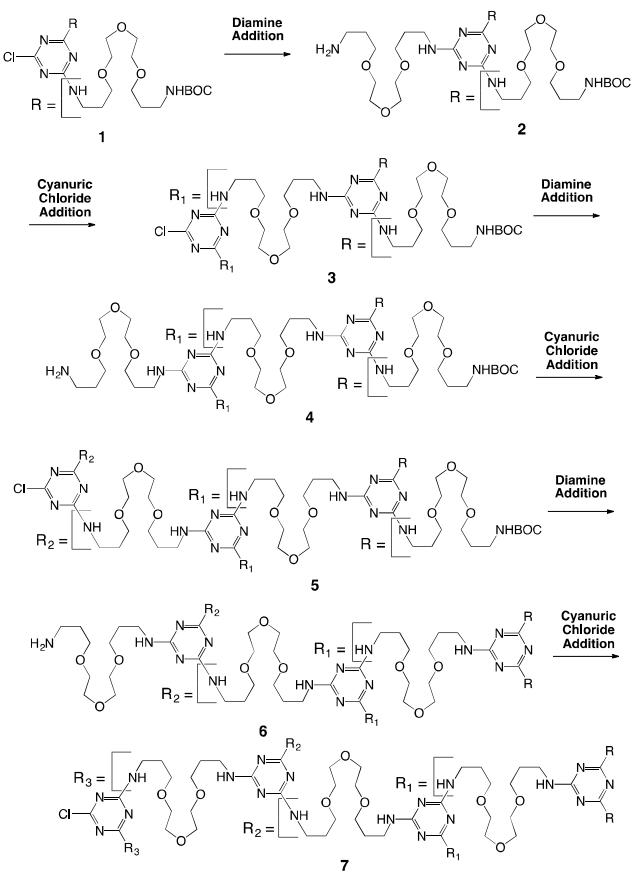


Table 1. Summary of yield and data from mass spectrometry. "Ends" refers to the number of peripheral groups the dendron presents.

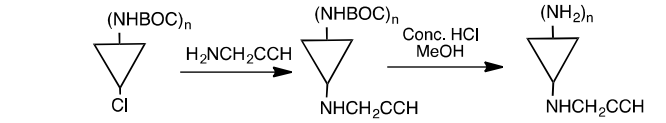
Cmpd	Focus	Yield	Ends	Calcd	Obsd
1	Cl	95%	2	751.42	752.44
2	NH_2	87%	2	935.63	938.63
3	Cl	98%	4	1982.22	1984.47
4	NH_2	85%	4	2166.42	2168.49
5	Cl	91%	8	4443.80	4447.67
6	NH_2	82%	8	4628.00	4532.20
7	Cl	70%	16	9366.96	9374.72

For the first three generations of dendrons, yields for the dimerization of amine with cyanuric chloride to yield the monochlorotriazine (with a Cl atom at the focus) proceed in yields ranging from 91-98%. This yield drops precipitously to 70% for the generation 3 dendron. Nucleophilic aromatic substitution of the monochlorotriazine with diamine proceeds in yields ranging from 82-87%. The ^{1}H and ^{13}C NMR spectra are

consistent with expectation. While ^{1}H NMR signals are broad, the integration is consistent with successful iteration. Signals from the ^{13}C are more telling, as the triazine lines at 167 and 169 for trisubstituted and disubstituted triazines reveal iterative nature of the synthesis until the single chlorine substituted carbon of **7** cannot be discerned above the other 44 substituted triazine carbons atoms. Mass spectrometry shows a single species for these compounds represented by either a singly charged adduct or with the presence of lines corresponding to multiply charged adducts. While these materials appear to be single chemical entities, gel permeation chromatography yielded a broad peak for each protected dendrimer. Measured polydispersities for **3**, **5**, and **7** were 1.14, 1.36, and 1.48, respectively.

With monochlorotriazines **3**, **5**, and **7** in hand, reaction with propargyl amine was pursued (Scheme 2). The microwave conditions adopted utilized 3 eq. of Cs_2CO_3 dissolved in dioxane at 95º C. The sluggish reaction with propargyl amine was combatted with consecutive irradiation (three times) each of 30 minute duration using a 30 fold excess of propargyl amine. Consistent with earlier substitution reactions, compounds **8**-**10** were obtained in 93%, 93% and 68% isolated yields, respectively. Deprotection of BOC groups on these materials proceeded using a 2:1 mixture of methanol and concentrated HCl with microwave irradiation for two periods of 3 minutes at 60ºC. The yields of **11-13** were assigned as quantitative. The alkyne at the focus of the G1 dendrimer, **3**, is amenable to click functionalization with 4-(2-azidoethyl)phenol. The reaction proceeds in 4h at 81% yield.

Scheme 3. Elaboration to alkyne core and deprotection



n			
4	**3**	**8** 93%	**11** *quant.*
8	**5**	**9** 93%	**12** *quant.*
16	**7**	**10** 68%	**13** *quant.*

Experimental

Compound 1. *N*-BOC-4,7,10-trioxa-1,13-tridecanediamine (4.03 g, 12.6 mmol) was added to a solution of cyanuric chloride (1.06 g, 5.72 mmol) in THF (50 mL). Afterwards DIPEA (4.38 mL, 13.2 mmol) was added dropwise. The solution was stirred for 2 minutes in order to allow reagents to mix. Then, the solution was irradiated in the microwave while stirring for 10 minutes at 60 ºC using dynamic mode. The crude product was purified using an automatic chromatographer. The solvent system (in column volumes) used was the following: 4 CV (100% Hexanes to 100% EtOAc), 20CV(100% EtOAc) to give **1** (4.08 g, 95%) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.67-3.45 (m, 28H, C**H$_2$**OC**H$_2$**C**H$_2$**OC**H$_2$**C**H$_2$**OC**H$_2$**, C_3N_3-NHC**H$_2$**CH$_2$CH$_2$O), 3.24 (br m, 4H, BocNHC**H$_2$**), 1.88-1.75 (m, 8H, OCH$_2$C**H$_2$**CH$_2$), 1.44 (s, 18H, C(C**H$_3$**)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 168.0, 165.9 (**C**$_3$N$_3$), 156.1 (**C**O), 78.8 (**C**(CH$_3$)$_3$), 70.5 (O**C**H$_2$CH$_2$O), 70.2 (two lines, O**C**H$_2$**C**H$_2$O), 69.5 (CH$_2$CH$_2$**C**H$_2$O), 69.3 (CH$_2$CH$_2$**C**H$_2$O), 38.4 (**C**H$_2$CH$_2$CH$_2$O), 29.5 (**C**H$_2$CH$_2$CH$_2$O), 28.6 (NHCH$_2$**C**H$_2$CH$_2$O), 28.4 (C(**C**H$_3$)$_3$); MS (ESI-TOF) calcd for $C_{33}H_{62}ClN_7O_{10}$ 751.4247, found 752.4382 (M + H)$^+$.

Compound 2. A solution of **1** (6.66g, 8.85 mmol) with 4,7,10-trioxa-1,13-tridecanediamine (7.8 g, 35.4 mmol) and Cs_2CO_3 (5.77g, 17.7 mmol) in 40 mL of 1,4 dioxane was stirred for 2 minutes. Then, the solution was 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 separation was performed using a solid loading method in a 25 g preloaded cartridge. The solvent system (in column volumes) used was the following: 30CV (90:10 DCM:MeOH), 20CV (85:15 DCM: MeOH), 15CV (5:1:1% DCM:MeOH:NH4OH) to give 5 (7.2 g, 87%) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.63-3.34 (m, 42H, C**H$_2$**OC**H$_2$**C**H$_2$**OC**H$_2$**C**H$_2$**OC**H$_2$**, C_3N_3-NHC**H$_2$**CH$_2$CH$_2$O), 3.20 (m, 4H, BocNHC**H$_2$**), 2.79 (t, *J* = 6.6, 2H, OCH$_2$CH$_2$C**H$_2$**NH$_2$), 1.82-1.73 (m, 12H, OCH$_2$C**H$_2$**CH$_2$), 1.40 (s, 18H, C(C**H$_3$**)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0 (**C**$_3$N$_3$), 156.2 (**C**O), 78.8 (**C**(CH$_3$)$_3$), 70.6 (O**C**H$_2$CH$_2$O), 70.3 (O**C**H$_2$CH$_2$O), 70.2 (two lines, O**C**H$_2$**C**H$_2$O), 69.5 (CH$_2$CH$_2$**C**H$_2$O), 69.3 (CH$_2$CH$_2$**C**H$_2$O), 39.5 (**C**H$_2$CH$_2$CH$_2$O), 38.5 (**C**H$_2$CH$_2$CH$_2$O), 38.1 (**C**H$_2$CH$_2$CH$_2$O), 32.7 (OCH$_2$**C**H$_2$CH$_2$NH$_2$), 29.7 (NHCH$_2$**C**H$_2$CH$_2$O), 28.5 (C(**C**H$_3$)$_3$); MS (ESI-TOF) calcd for $C_{43}H_{85}N_9O_{13}$ 935.6267, found 936.6724(M + H)$^+$.

Compound 3 (macromonomer). Compound **2** (4.08 g, 4.36 mmol) was added to a solution of cyanuric chloride (0.366 g, 1.98 mmol) in THF (20 mL). Afterwards DIPEA (3.2 mL, 9.32 mmol) was added dropwise, and the solution was stirred 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: 1 CV (100% DCM to 95:5 DCM:MeOH), 15CV (95:5 DCM:MeOH), 10CV (90:10 DCM:MeOH), 20CV (85:15 DCM: MeOH) to give **1** (3.85g, 98%) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.65-3.43 (m, 88H, C**H$_2$**OC**H$_2$**C**H$_2$**OC**H$_2$**C**H$_2$**OC**H$_2$**, C_3N_3-NHC**H$_2$**CH$_2$CH$_2$O), 3.21 (br m, 8H, BocNHC**H$_2$**), 1.83-1.70 (m, 24H, OCH$_2$C**H$_2$**CH$_2$), 1.44 (s, 36H, C(C**H$_3$**)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9 (**C**$_3$N$_3$), 165.6 (**C**$_3$N$_3$), 156.1 (**C**O), 78.8 (**C**(CH$_3$)$_3$), 70.5 (O**C**H$_2$CH$_2$O), 70.2 (two lines, O**C**H$_2$**C**H$_2$O), 69.5 (CH$_2$CH$_2$**C**H$_2$O), 69.3 (CH$_2$CH$_2$**C**H$_2$O), 38.4 (**C**H$_2$CH$_2$CH$_2$O), 38.1 (**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 $C_{89}H_{168}ClN_{21}O_{26}$ 1982.2158, found 1984.4671 (M + H)$^+$.

Compound 4. A solution of **1** (2.043g, 1.03 mmol) with 4,7,10-trioxa-1,13-tridecanediamine (2.27g, 10.3 mmol) and Cs_2CO_3 (0.67g, 2.06 mmol) in 10 mL of 1,4 dioxane was stirred for 2 minutes. Then, the solution was irradiated in the microwave while stirring for 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: 1 column volume (CV) (100% DCM), 3CV (100% DCM to 90:1 DCM:MeOH), 10CV (90:10 DCM:MeOH), 2CV (90:10 DCM:MeOH to 85:15= DCM:MeOH), 2CV (85:15 DCM:MeOH to 80:20 DCM:MeOH), 5CV (80:20 DCM:MeOH), 10CV (5:1:1% DCM:MeOH:NH_4OH) to give **4** (1.89g, 85%) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.64-3.46

(m, 102H, C**H**$_2$OC**H**$_2$C**H**$_2$OC**H**$_2$C**H**$_2$OC**H**$_2$, C_3N_3-NHC**H**$_2$CH$_2$CH$_2$O), 3.21 (br m, 8H, BocNHC**H**$_2$), 2.0 (m, 2H, NH$_2$C**H**$_2$CH$_2$CH$_2$O) 1.84-1.73 (m, 28H, OCH$_2$C**H**$_2$CH$_2$), 1.43 (s, 36H, C(C**H**$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.11 (**C**$_3$N$_3$), 157.06 (**C**O), 79.28 (**C**(CH$_3$)$_3$), 71.01 (O**C**H$_2$CH$_2$O), 70.7 (two lines, O**C**H$_2$**C**H$_2$O), 69.97 (CH$_2$CH$_2$**C**H$_2$O), 69.67 (CH$_2$CH$_2$**C**H$_2$O), 39.77 (NH$_2$**C**H$_2$CH$_2$CH$_2$O), 38.75 (**C**H$_2$CH$_2$CH$_2$O), 38.34 (**C**H$_2$CH$_2$CH$_2$O), 32.73 (NH$_2$CH$_2$**C**H$_2$CH$_2$O), 29.87 (NHCH$_2$**C**H$_2$CH$_2$O), 28.64 (C(**C**H$_3$)$_3$); MS (ESI-TOF) calcd for $C_{99}H_{191}N_{23}O_{29}$ 2166.4178, found 2168.4939 $(M + H)^+$.

Compound 5 (G2-C l) Compound **4** (2.95 g, 1.36 mmol) was added to a solution of cyanuric chloride (0.114 g, 0.62 mmol) in THF (6 mL). Afterwards DIPEA (0.46 mL, 2.6 mmol) was added dropwise. The solution was stirred 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 crude product was purified automated chromatography. The solvent system (in column volumes) used was the following: 1 CV (100% DCM to 95:5 DCM:MeOH), 15CV (95:5 DCM:MeOH), 10CV (90:10 DCM: MeOH), 5CV (85:15 DCM:MeOH), 5CV (80:20 DCM:MeOH) to give **5** (2.5g, 91%) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.65-3.44 (m, 208H, C**H**$_2$OC**H**$_2$C**H**$_2$OC**H**$_2$C**H**$_2$OC**H**$_2$, C_3N_3-NHC**H**$_2$CH$_2$CH$_2$O), 3.21 (br m, 16H, BocNHC**H**$_2$), 1.83-1.74 (m, 56H, OCH$_2$C**H**$_2$CH$_2$), 1.44 (s, 72H, C(C**H**$_3$)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6 (**C**$_3$N$_3$), 157.02 (**C**O), 79.29 (**C**(CH$_3$)$_3$), 70.97 (O**C**H$_2$**C**H$_2$O), 70.64 (two lines, O**C**H$_2$**C**H$_2$O), 69.94 (CH$_2$CH$_2$**C**H$_2$O), 69.64 (CH$_2$CH$_2$**C**H$_2$O), 38.73 (**C**H$_2$CH$_2$CH$_2$O), 38.38(**C**H$_2$CH$_2$CH$_2$O), 29.73 (NHCH$_2$**C**H$_2$CH$_2$O), 28.6 (C(**C**H$_3$)$_3$); MS (ESI-TOF) calcd for $C_{201}H_{380}ClN_{49}O_{58}$ 4443.7980, found 4447.6713 $(M + H)^+$.

Compound 6. A solution of **5** (1.59 g, 0.36 mmol) with 4,7,10-trioxa-1,13-tridecanediamine (0.79g, 3.6 mmol) and Cs_2CO_3 (0.23g, 0.72 mmol) in 3.6 mL of 1,4 dioxane was stirred for 2 minutes. Then, the solution was irradiated in the microwave while stirring for 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 twice by automated chromatography. The solvent system (in column volumes) used was the following: 1CV (100% DCM to 95:5 DCM:MeOH), 14CV (95:5 DCM:MeOH), 10CV (90:10 DCM:MeOH), 10CV (85:15 DCM:MeOH), 5CV (80:20 DCM: MeOH), 10CV (5:1:1% DCM:MeOH:NH_4OH) to give **6** (1.35g, 82%) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.65-3.46 (m, 222H, C**H**$_2$OC**H**$_2$C**H**$_2$OC**H**$_2$C**H**$_2$OC**H**$_2$, C_3N_3-NHC**H**$_2$CH$_2$CH$_2$O), 3.21 (br m, 16H, BocNHC**H**$_2$), 2.0 (m, 2H, NH$_2$C**H**$_2$CH$_2$CH$_2$O) 1.84-1.73 (m, 60H, OCH$_2$C**H**$_2$CH$_2$), 1.43 (s, 72H, C(C**H**$_3$)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.11 (**C**$_3$N$_3$), 157.0 (**C**O), 79.32 (**C**(CH$_3$)$_3$), 70.96 (O**C**H$_2$**C**H$_2$O), 70.66 (two lines, O**C**H$_2$**C**H$_2$O), 69.94 (CH$_2$CH$_2$**C**H$_2$O), 69.51 (CH$_2$CH$_2$**C**H$_2$O), 38.73 (NH$_2$**C**H$_2$CH$_2$CH$_2$O), 38.73 (**C**H$_2$CH$_2$CH$_2$O), 38.56 (**C**H$_2$CH$_2$CH$_2$O), not found (NH$_2$CH$_2$**C**H$_2$CH$_2$O), not found (NHCH$_2$**C**H$_2$CH$_2$O), 28.63 (C(**C**H$_3$)$_3$); MS (ESI-TOF) calcd for $C_{211}H_{403}N_{51}O_{61}$ 4628.0001, found 4632.2038$(M + H)^+$.

Compound 7. Compound **6** (1.05 g, 0.228 mmol) was added to a solution of cyanuric chloride (0.019 g, 0.104 mmol) in THF (2.3 mL), afterwards DIPEA was added dropwise (0.084 mL, 0.487 mmol). The solution was stirred for 2 minutes in order to allow reagents to mix. Then, the solution was irradiated in the microwave while stirring (CEM SP Discovery) for 10 minutes at 60ºC using dynamic mode. The crude product was purified twice by automated chromatography. The solvent system (in column volumes) used was the following: 1 CV (100% DCM to 95:5 DCM:MeOH), 14CV (95:5 DCM:MeOH), 10CV (90:10 DCM:MeOH), 10CV (85:15 DCM:MeOH), 15CV (80:20 DCM:MeOH) to give **7** (1.49g, 70%) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.64-3.42 (m, 448H, C**H**$_2$OC**H**$_2$C**H**$_2$OC**H**$_2$C**H**$_2$OC**H**$_2$, C_3N_3-NHC**H**$_2$CH$_2$CH$_2$O), 3.21 (br m, 32H, BocNHC**H**$_2$), 1.83-1.74 (m, 120H, OCH$_2$C**H**$_2$CH$_2$), 1.44 (s, 144H, C(C**H**$_3$)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.04 (**C**$_3$N$_3$), 154.36 (**C**O), 80.05(**C**(CH$_3$)$_3$), 70.98 (O**C**H$_2$**C**H$_2$O), 70.61 (two lines, O**C**H$_2$**C**H$_2$O), 69.94 (CH$_2$CH$_2$**C**H$_2$O), 69.64 (CH$_2$CH$_2$**C**H$_2$O), 38.73 (**C**H$_2$CH$_2$CH$_2$O), 38.30(**C**H$_2$CH$_2$CH$_2$O), 29.84 (NHCH$_2$**C**H$_2$CH$_2$O), 28.62 (C(**C**H$_3$)$_3$); MS (ESI-TOF) calcd for $C_{425}H_{804}ClN_{105}O_{122}$ 9366.9625, found 9374.7207$(M + H)^+$.

Compound 8. A solution of propargylamine (0.136 g, 2.48 mmol), **1** (0.492 g, 0.248 mmol), and Cs_2CO_3 (0.242 g, 0.741 mmol) in dioxane (2.5 mL) was stirred for 2 minutes. Then, the solution was irradiated in the microwave while stirring for three periods of 30 minutes at 95ºC using dynamic mode. In each extra period were added 10 equivalents more of propargylamine (0.408g, 7.44 mmol) to give a total of 30 equivalents in the final solution. Afterwards, the reaction mixtures was 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 product was purified by silica gel chromatography (DCM:MeOH 10:1) to give **8** (0.46 g, 93%) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.16 (br, 2H, HC≡CC**H**$_2$), 3.65-3.43 (m, 88H, C**H**$_2$OC**H**$_2$C**H**$_2$OC**H**$_2$C**H**$_2$OC**H**$_2$, C_3N_3-NHC**H**$_2$CH$_2$CH$_2$O), 3.21 (br m, 8H, BocNHC**H**$_2$), 2.23 (br, 1H, **H**C≡CCH$_2$), 1.85-1.73 (m, 24H, OCH$_2$C**H**$_2$CH$_2$), 1.43 (s, 36H, C(C**H**$_3$)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.59 (br, **C**$_3$N$_3$), 156.98 (**C**O), 81.85 (HC≡**C**CH$_2$), 79.32 (**C**(CH$_3$)$_3$), 70.7 (H**C**≡CCH$_2$), 70.96 (O**C**H$_2$**C**H$_2$O), 69.95 (O**C**H$_2$**C**H$_2$O), 69.93 (O**C**H$_2$**C**H$_2$O) 69.67 (CH$_2$CH$_2$**C**H$_2$O), 69.56 (CH$_2$CH$_2$**C**H$_2$O), 38.71 (**C**H$_2$CH$_2$CH$_2$O), 38.35 (**C**H$_2$CH$_2$CH$_2$O), not found (HC≡**C**CH$_2$), 28.61 (NHCH$_2$**C**H$_2$CH$_2$O), 28.4 (C(**C**H$_3$)$_3$); MS (ESI-TOF) calcd for $C_{92}H_{172}N_{22}O_{26}$ 2001.2813, found 2002.2499 $(M + H)^+$.

Compound 9. A solution of **8** (0.800 g, 0.4 mmol) in concentrated HCl (1.5 mL) and methanol (3 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 under vacuum. The residue was dissolved in chloroform, washed with 5 M NaOH (aq), dried over $MgSO_4$, filtered, and evaporated under vacuum to give **9** (0.640 g, quantitative) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.21 (br, 2H, HC≡CC**H**$_2$), 3.69-3.47 (m, 88H, C**H**$_2$OC**H**$_2$C**H**$_2$OC**H**$_2$C**H**$_2$OC**H**$_2$, C_3N_3-NHC**H**$_2$CH$_2$CH$_2$O), 2.85 (br, 8H, OCH$_2$CH$_2$C**H**$_2$NH$_2$), 2.30 (br, 1H, **H**C≡CCH$_2$), 1.87-1.76 (m, 24H, OCH$_2$C**H**$_2$CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.89 (**C**$_3$N$_3$), 70.84 (HC≡**C**CH$_2$), 70.80 (H**C**≡CCH$_2$, O**C**H$_2$**C**H$_2$O), 70.46 (O**C**H$_2$**C**H$_2$O), 70.39 (O**C**H$_2$**C**H$_2$O) 69.63 (CH$_2$CH$_2$**C**H$_2$O), 69.49 (two lines, CH$_2$CH$_2$**C**H$_2$O), 39.63 (**C**H$_2$CH$_2$CH$_2$O), 38.08 (**C**H$_2$CH$_2$CH$_2$O), 33.33 (OCH$_2$**C**H$_2$CH$_2$NH$_2$), 30.13 (HC≡**C**CH$_2$), 29.67 (NHCH$_2$**C**H$_2$CH$_2$O); MS (ESI-TOF) calcd for $C_{72}H_{140}N_{22}O_{18}$ 1601.0716, found 1602.0498 $(M + H)^+$.

Compound 10. A solution of propargylamine (0.0125 g, 0.2245 mmol), **5** (0.100 g, 0.022 mmol), and Cs_2CO_3 (0.022g, 0.066 mmol) in dioxane (0.3 mL) was stirred for 2 minutes. Then, the solution was irradiated in the microwave while stirring (CEM SP Discovery) for three periods of 30 minutes at 95ºC using dynamic mode. In each extra period were added 10 equivalents more of propargylamine (0.0375g, 0.6735mmol) to give a total of 30 equivalents in the final solution 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 product was purified by silica gel chromatography (DCM:MeOH 10:1 to DCM:MeOH 7:1) to give **10** (0.093 g, 93%) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.16 (br, 2H, HC≡CC**H**$_2$), 3.64-3.43

(m, 102H, C**H**$_2$OC**H**$_2$C**H**$_2$OC**H**$_2$C**H**$_2$OC**H**$_2$, C_3N_3-NHC**H**$_2$CH$_2$CH$_2$O), 3.21 (br m, 16H, BocNHC**H**$_2$), 2.25 (br, 1H, **H**C≡CCH$_2$), 1.82-1.73 (m, 56H, OCH$_2$C**H**$_2$CH$_2$), 1.43 (s, 72H, C(C**H**$_3$)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.82 (br, **C**$_3$N$_3$), 157.03 (**C**O), not found (HC≡**C**CH$_2$), 79.34 (**C**(CH$_3$)$_3$), 70.7 (H**C**≡CCH$_2$), 70.96 (O**C**H$_2$**C**H$_2$O), 69.95 (O**C**H$_2$**C**H$_2$O), 69.93 (O**C**H$_2$**C**H$_2$O) 69.67 (CH$_2$CH$_2$**C**H$_2$O), 69.56 (CH$_2$CH$_2$**C**H$_2$O), 38.78 (**C**H$_2$CH$_2$CH$_2$O), 38.40 (**C**H$_2$CH$_2$CH$_2$O), not found (HC≡**C**CH$_2$), 29.85 (NHCH$_2$**C**H$_2$CH$_2$O), 28.65 (C(**C**H$_3$)$_3$); MS (ESI-TOF) calcd for $C_{204}H_{348}N_{50}O_{58}$ 4462.8636 found 4464.9714 $(M + H)^+$.

Compound 11. A solution of **10** (0.093 g, 0.020 mmol) in concentrated HCl (0.5 mL) and methanol (1 mL) was stirred for 1 min at room temperature and then was irradiated in the microwave while stirring (CEM SP Discovery) for two periods of 3 minutes at 60ºC using dynamic mode and then evaporated under vacuum. The residue was dissolved in chloroform, washed with 5 M NaOH (aq), dried over $MgSO_4$, filtered, and evaporated under vacuum to give **11** (0.075 g, quantitative) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.14 (br, 2H, HC≡CC**H**$_2$), 3.62-3.40 (m, 102H, C**H**$_2$OC**H**$_2$C**H**$_2$OC**H**$_2$C**H**$_2$OC**H**$_2$, C_3N_3-NHC**H**$_2$CH$_2$CH$_2$O), 2.77 (br, 16H, OCH$_2$CH$_2$C**H**$_2$NH$_2$), 2.21 (br, 1H, **H**C≡CCH$_2$), 1.80-1.68 (m, 56H, OCH$_2$C**H**$_2$CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.94 (**C**$_3$N$_3$), 81.1 (HC≡**C**CH$_2$), not found (H**C**≡CCH$_2$, O**C**H$_2$**C**H$_2$O), 70.88 (O**C**H$_2$**C**H$_2$O), 70.49 (two lines, O**C**H$_2$**C**H$_2$O) 69.66 (CH$_2$CH$_2$**C**H$_2$O), 69.48 (two lines, CH$_2$CH$_2$**C**H$_2$O), 39.63 (**C**H$_2$CH$_2$CH$_2$O), 38.13 (**C**H$_2$CH$_2$CH$_2$O), 33.44 (OCH$_2$**C**H$_2$CH$_2$NH$_2$), not found (HC≡**C**CH$_2$), 29.7 (NHCH$_2$**C**H$_2$CH$_2$O); MS (ESI-TOF) calcd for $C_{164}H_{320}N_{50}O_{42}$ 3662.4441, found 3664.5145 $(M + H)^+$.

Compound 12. A solution of propargylamine (0.0076 g, 0.0137 mmol), **7** (0.128 g, 0.0137 mmol), and Cs_2CO_3 (0.0145g, 0.041 mmol) in dioxane (0.2 mL) was stirred for 2 minutes. Then, the solution was irradiated in the microwave while stirring for three periods of 30 minutes at 95ºC using dynamic mode. In each extra period were added 10 equivalents more of propargylamine (0.023 g, .041 mmol) to give a total of 30 equivalents in the final solution 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 product was purified by silica gel chromatography (DCM:MeOH 10:1 to DCM:MeOH 7:1) to give **12** (0.087 g, 68%) as a clear wax. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.05 (br, 2H, HC≡CC**H**$_2$), 3.51-3.29 (m, 448H, C**H**$_2$OC**H**$_2$C**H**$_2$OC**H**$_2$C**H**$_2$OC**H**$_2$, C_3N_3-NHC**H**$_2$CH$_2$CH$_2$O), 3.08 (br m, 32H, BocNHC**H**$_2$), 2.17 (br, 1H, **H**C≡CCH$_2$), 1.69-1.60 (m, 120H, OCH$_2$C**H**$_2$CH$_2$), 1.31 (s, 144H, C(C**H**$_3$)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7 (**C**$_3$N$_3$), 155.9 (**C**O), 81.1 (not found, HC≡**C**CH$_2$), 78.6 (**C**(CH$_3$)$_3$), 70.5 (not found, H**C**≡CCH$_2$), 70.4 (O**C**H$_2$**C**H$_2$O), 70.0 (two lines, O**C**H$_2$**C**H$_2$O), 69.3 (CH$_2$CH$_2$**C**H$_2$O), 69.1 (CH$_2$CH$_2$**C**H$_2$O), 69.0 (CH$_2$CH$_2$**C**H$_2$O), 38.3 (**C**H$_2$CH$_2$CH$_2$O), 37.8 (**C**H$_2$CH$_2$CH$_2$O), 30.1 (not found, HC≡**C**CH$_2$), 29.5 (NHCH$_2$**C**H$_2$CH$_2$O), 28.3 (C(**C**H$_3$)$_3$); MS (ESI-TOF) calcd for $C_{428}H_{808}N_{106}O_{122}$ 9386.03, found 9392.20 $(M + H)^+$.

Compound 13. A solution of **12** (0.087 g, 0.009 mmol) in concentrated HCl (0.5 mL) and methanol (1 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 under vacuum. The residue was dissolved in chloroform, washed with 5 M NaOH (aq), dried over $MgSO_4$, filtered, and evaporated under vacuum to give **13** (0.070 g, quantitative) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.12 (br, 2H, HC≡CC**H**$_2$), 3.60-3.38 (m, 448H, C**H**$_2$OC**H**$_2$C**H**$_2$OC**H**$_2$C**H**$_2$OC**H**$_2$, C_3N_3-NHC**H**$_2$CH$_2$CH$_2$O), 2.78 (br, 32H, OCH$_2$CH$_2$C**H**$_2$NH$_2$), 2.22 (br, 1H, **H**C≡CCH$_2$), 1.78-1.69 (m, 120H, OCH$_2$C**H**$_2$CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1 (**C**$_3$N$_3$), 81.1 (not found, HC≡**C**CH$_2$), 70.6 (O**C**H$_2$**C**H$_2$O), 70.5 (H**C**≡CCH$_2$), 70.3 (O**C**H$_2$**C**H$_2$O), 70.2 (O**C**H$_2$**C**H$_2$O) 69.5 (CH$_2$CH$_2$**C**H$_2$O), 69.4 (CH$_2$CH$_2$**C**H$_2$O), 69.3 (CH$_2$CH$_2$**C**H$_2$O), 39.6 (**C**H$_2$CH$_2$CH$_2$O), 38.1 (**C**H$_2$CH$_2$CH$_2$O), 32.9 (OCH$_2$**C**H$_2$CH$_2$NH$_2$), 30.1 (not found, HC≡**C**CH$_2$), 29.7 (NHCH$_2$**C**H$_2$CH$_2$O); MS (ESI-TOF) calcd for $C_{348}H_{680}N_{106}O_{90}$ 7785.19, found 7790.0851 $(M + H)^+$.

Compound 14. To a mixture of **3** (150 mg, 0.075 mmol) and 4-(2-azidoethyl)phenol (19 mg, 0.074 mmol) in *t*-butanol (0.8 mL), a solutions of $CuSO_4$⋅5H_2O (4.5 mg, 0.019 mmol) in water (0.3 mL) followed by sodium-L-ascorbate (18 mg, 0.09mmol) were added at room temperature and stirred for 4h. Then, the solution was diluted with dichloromethane (20 mL) and washed three times with 1mM EDTA (20 mL), brine, dried over $MgSO_4$ and concentrated. The crude product was purified by column chromatography (DCM:MeOH 97:3 to DCM:MeOH 9:1; to give **14** as a white wax (132 mg, 81 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (s, 1H, from triazole), 6.79-6.77 (d, J = 7.2, 2H, HO-C-C**H**=CH-C), 6.72-6.7 (d, J = 8.0, 2H, HO-C-CH=C**H**-C), 4.48-4.47 (t, J = 6.1, 2H, NH-C**H**$_2$-triazole), 3.65-3.43 (m, 88H, C**H**$_2$OC**H**$_2$C**H**$_2$OC**H**$_2$C**H**$_2$OC**H**$_2$, C_3N_3-NHC**H**$_2$CH$_2$CH$_2$O), 3.21 (br, m, 8H, BocNHC**H**$_2$), 3.04 (m, 2H, triazole-N-C**H**$_2$-CH$_2$-phenol),1.83-1.70 (m, 24H, OCH$_2$C**H**$_2$CH$_2$), 1.44 (s, 36H, C(C**H**$_3$)$_3$); ^{13}C NMR (100 MHz, CDCl3) δ 164.75 (**C**$_3$N$_3$), 164.69 (**C**$_3$N$_3$), 156.05 (**C**O), 145.6 (HO-**C**), 129.9 (CH2C=**C**H-CH=CH-C-OH), 127.77 (CH2**C**=CH-CH=CH-C-OH), 122.61 (**C**H from triazole), 115.84 (CH2C=CH-CH=**C**H-C-OH), 78.7 (**C**(CH$_3$)$_3$), 70.5 (O**C**H$_2$**C**H$_2$O), 70.2 (two lines, O**C**H$_2$**C**H$_2$O), 69.5 (CH$_2$CH$_2$**C**H$_2$O), 69.3 (CH$_2$CH$_2$**C**H$_2$O), 51.83 (phenol-CH$_2$**C**H$_2$-Triazole), 38.38 (**C**H$_2$CH$_2$CH$_2$O), 38.1 (**C**H$_2$CH$_2$CH$_2$O), 35.83 (phenol-**C**H$_2$CH$_2$-Triazole),29.53 (NHCH$_2$**C**H$_2$CH$_2$O), 28.40 (C(**C**H$_3$)$_3$); MS (ESI-TOF) calcd for $C_{100}H_{181}N_{25}O_{27}$ 2164.36, found 2165.66 $(M + H)^+$.

Conclusions

Microwave-assisted reactions are readily applied to the convergent synthesis of triazine dendrimers up to generation 3. Success derives from both the controlled disubstitution of cyanuric chloride and the efficient substitution of the resulting monochlorotriazine. Microwave irradiation also promotes BOC-deprotection of peripheral amines. In aggregate, small generation triazine dendrimers are now rapidly accessible at gram scales. The choice of linking diamine, the PEG-like 4,7,10-trioxa-1,13-tridecanediamine, contributes to the solubility of these materials in organic solvent when protected, and in water upon removal of the BOC groups. The limitations of this chemistry to larger generation dendrimers is currently being explored: simply extending reaction times does not yield satisfactory results. Our immediate needs for high generation dendrimers still require traditional thermal conditions which are now aided directly by the rapid, microwave-assisted synthesis of the macromonomer and G3 starting material.

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Notes and references

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TOC GRAPHIC FOR:

Rapid, Semi-automated Convergent Synthesis of Low Generation Triazine Dendrimers using Microwave Assisted Reactions

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