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A Divergent Route to Diversity in Macromolecules

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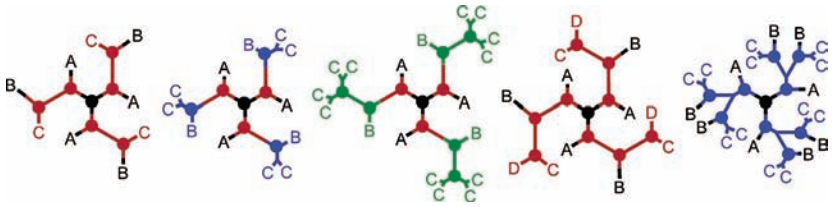
ABSTRACT

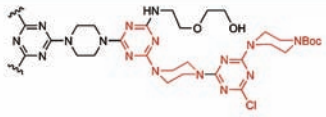
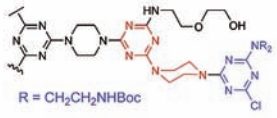
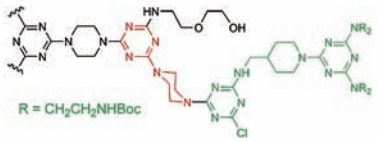


A synthetic route for obtaining functional group diversity in macromolecules is described. The route relies on the differential reactivity of substituted dichlorotriazines. Treatment of a triamine core with substituted dichlorotriazines cleanly yields tris(monochlorotriazines). Subsequent S_NAr reactions with amine nucleophiles bearing the functional group of interest yield diversity. If the substituent on the dichlorotriazine is a protected nucleophile, deprotection of the functionalized core allows for iterative reactions and the synthesis of star, dendritic, and hybrid macromolecules.

Multifunctional molecules are currently being pursued as polymeric therapeutics, and to this end, synthetic efforts are focused on architectures bearing at least three different diversity elements; sites for the conjugation of biocompatible groups (i.e., poly(ethylene glycol)), reporter groups to indicate biodistribution, and pharmacologically active molecules.[1] The syntheses of targets **1**−**3** described herein move us closer to these goals: these scaffolds present the required number of reactive groups including hydroxyls, protected amines, and monochlorotriazines in differing ratios (Table 1). Moreover, the synthetic approach that we describe marries the beneficial aspects of both convergent and divergent routes and represents a divergent synthetic strategy to prepare macromolecules—dendrimers, star polymers, and hybrids thereof—that results in monodisperse, single-chemical entities bearing compositional diversity.[2]

As a divergent[3] synthesis, this strategy has *mole conservation* as its primary advantage over convergent routes.[4] That is, the number of moles of product obtained is equal to the number of moles of initial reagents when perfectly efficient. Additionally, reactions occur on the periphery of the macromolecule during a divergent synthesis, and accordingly, macromolecules of higher generation might be obtained

Table 1. Targets **1**−**3**

cmpd	structure	steps	overall yield[a]	columns
1		4	65%	2
2		4	75%	2
3		4	74%	2

[a] Precluding contributions from the syntheses of **4**−**7**.

(1) Duncan, R. *Nat. Rev. Drug Discov.* **2003**, *2*, 347−360.

(2) For reviews of dendrimer chemistry, see: (a) Fréchet, J. M. J., Tomalia, D. A., Eds. *Dendrimers and other Dendritic Polymers*; John Wiley & Sons, Ltd.: New York, 2001. (b) Grayson, S. M.; Fréchet, J. M. J. *Chem. Rev.* **2001**, *101*, 3819−3868. (c) Tomalia, D. A.; Fréchet, J. M. J. *J. Polym. Sci. Part A: Polym. Chem.* **2002**, *40*, 2719−2728. (d) Fréchet, J. M. J. *J. Polym. Sci., Part A: Polym. Chem.* **2003**, *41*, 3713−3725. (e) Hecht, S. *J. Polym. Sci., Part A: Polym. Chem.* **2003**, *41*, 1047−1058.

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through this route although structural defects common to this strategy would be expected.

The ability to execute exquisite control over the number of unique sites on the surface or interior of the macromolecule is the primary advantage of a convergent synthesis over the divergent approach.[5] Until now, similar degrees of structural complexity could only be obtained through statistical reactions conducted at the surface of the product of a divergent synthesis, although such mixtures hold great promise for application.[6] In addition, and as a result of the repetitive multimerizations (dimerizations for AB_2 systems; trimerizations for AB_3 systems), the number of moles of product resulting from convergent syntheses is reduced by $1/n$ per generation when using common AB_n monomers.

The successful execution of this divergent route to diversity rests in the identification of monomers that have orthogonal or differential reactivity that can be efficiently manipulated in a stepwise manner. To this end, the differential reactivity of triazine trichloride allows for the facile preparation of dichlorotriazine monomers **4**−**6** (Figure 1). These monomers are available in one, two, or four steps in 99%, 92%, and 63% overall yields, respectively, with only a single chromatographic purification required in the last step of the synthesis of **6**.[7] The syntheses of **4**−**6** have been successfully executed on multigram scale. These monomers can be regarded as ABB′, AB_2B', and AB_4B',[8] respectively, and undergo clean, stepwise nucleophilic aromatic substitution (S_NAr) reactions to afford intermediate monochlorotriazine bearing macromolecules.

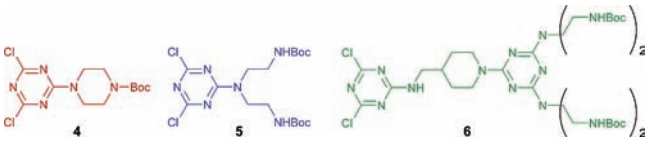
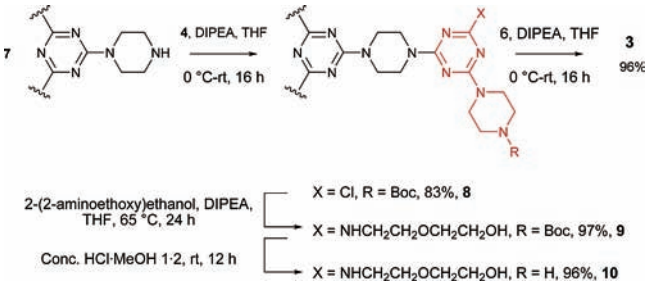


Figure 1. Dichlorotriazines **4**−**6**, available in one, two, or four steps, respectively.

Common to all of the targets described is radial symmetry. That is, the diversity elements incorporated into these macromolecules are common within a generation, but can vary from generation to generation. Throughout, we have chosen aminoethoxyethanol as a diversity element to not only develop an intuition for the physical properties of these targets, but also to determine whether unprotected (latent) hydroxyl groups intended for postsynthetic manipulation interfere with the synthesis (vide infra). Targets **1** and **2** are second generation macromolecules comprising two layers of monomer **4**, and monomers **4** and **5**, respectively. Target **3** is a third generation hybrid comprising monomers **4** and **6**. The use of **6** underscores the opportunity to pursue "hypercore"[9] or "hypermonomer"[10] approaches as has been reported in the dendrimer literature.

Application of this divergent route to diversity to prepare **3** is detailed in Scheme 1. The synthesis commences with a tris(piperazyl)triazine core, **7**, which is available in two steps without chromatography by a modification of previously established protocols.[11] This triamine core is treated with dichlorotriazine **4** for 16 h to yield the first-generation intermediate, **8**, in 83% overall yield. Subsequent treatment of **8** with excess 2-(2-aminoethoxy)ethanol affords the functionalized intermediate, **9**, in greater than 97% isolated yield. Extraction with water removes the excess amine. Purity

Scheme 1. Divergent Syntheis of **3**



(3) (a) Buhleier, E.; Wehner, W.; Voegtle, F. *Synthesis* **1978**, 155−158. (b) Newkome, G. R.; Yao, Z.; Baker, G. R.; Gupta, V. K. *J. Org. Chem.* **1985**, *50*, 2003−2044. (c) Newkome, G. R.; Yao, Z.; Baker, G. R.; Gupta, V. K.; Russo, P. S.; Saunders, M. J. *J. Am. Chem. Soc.* **1986**, *108*, 849−850. (d) Newkome, G. R.; Baker, G. R.; Saunders, M. J.; Russo, P. S.; Gupta, V. K.; Yao, Z.; Miller, J. E.; Bouilliona, K. *J. Chem. Soc., Chem. Commun.* **1986**, 752−753. (e) Tomalia, D. A.; Baker, H.; Dewald, J.; Hall, M.; Kallos, G.; Martin, S.; Roeck, J.; Ryder, J.; Smith, P. *Macromolecules*, **1986**, *19*, 2466−2468.

(4) Hawker, C. J.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1990**, *112*, 7638−7647.

(5) (a) Freeman, A. W.; Chrisstoffels, L. A. J.; Fréchet, J. M. J. *J. Org. Chem.* **2000**, *65*, 7612−7617. (b) Sivanandan, K.; Vutukuri, D.; Thayumanavan, S. *Org. Lett.* **2002**, *4*, 3751−3753. (c) Douat-Casassus, C.; Darbre, T.; Reymond, J.-L. *J. Am. Chem. Soc.* **2004**, *126*, 7817−7826. (d) Brouwer, A. J.; Liskamp, R. M. J. *Eur. J. Org. Chem.* **2005**, 487−495. (e) Zhang, W.; Nowlan, D. T., III; Thomson, L. M.; Lackowski, W. M.; Simanek, E. E. *J. Am. Chem. Soc.* **2001**, *123*, 8914−8922. In addition, synergistic divergent/convergent syntheses have provide dendrimers with orthogonal groups. See: (f) Grayson, S. M.; Fréchet, J. M. J. *Org. Lett.* **2002**, *4*, 3171−3174. (g) Gillies, E. R.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **2002**, *124*, 14137−14146. (h) Furuta, P.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **2003**, *125*, 13173−13181. (i) Ropponen, J.; Nummelin, S.; Rissanen, K. *Org. Lett.* **2004**, *6*, 2495−2497. (j) Steffensen, M. B.; Simanek, E. E. *Angew. Chem., Int. Ed.* **2004**, *43*, 5178−5180. (k) Lim, J.; Simanek, E. E. *Mol. Pharm.* **2005**, *2*, 273−277.

(6) Statistical mixtures of products or functional group placements in a dendrimer have been prepared in a divergent fashion, particularly using PAMAM polymers. For examples of this chemistry used in biologically relevant cases, see: (a) Stiriba, S.-E.; Frey, H.; Haag, R. *Angew. Chem, Int. Ed.* **2002**, *41*, 1329−1334. (b) Kukowska-Latallo, J. F.; Candido, K. A.; Cao, Z.; Nigavekar, S. S.; Majoros, I. J.; Thomas, T. P.; Balogh, Lajos P.; Khan, M. K.; Baker, J. R., Jr. *Cancer Res.* **2005**, *65*, 5317−5324. (c) Venditto, V. J.; Regino, C. A. S.; Brechbiel, M. W. *Mol. Pharm.* **2005**, *2*, 302−311. (d) Wolfenden, M. L.; Cloninger, M. J. *J. Am. Chem. Soc.* **2005**, *127*, 12168−12169.

(7) Efforts to optimize the synthesis of **6** (and its single problematic step, 68% yield) are ongoing.

(8) Monomers **4**−**6** can be regarded as ABB′, AB_2B', and AB_4B', respectively, where A is the first chloride displaced via nucleophilic aromatic substitution, B′ is the second chloride to be displaced, and B represents the Boc-protected amines.

(9) Wooley, K. L.; Hawker, C. J.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1991**, *113*, 4252−4261.

(10) (a) Gilat, S. L.; Adronov, A.; Fréchet, J. M. J. *J. Org. Chem.* **1999**, *64*, 7474−7484. (b) Abramov, M. A.; Shukla, R.; Amabilino, D. B.; Dehaen, W. *J. Org. Chem.* **2002**, *67*, 1004−1007.

(11) Chen, H.-T.; Neerman, M. F.; Parrish, A. R.; Simanek, E. E. *J. Am. Chem. Soc.* **2004**, *126*, 10044−10048.

was assessed by thin-layer chromatography (TLC), NMR spectroscopy, and mass spectrometry. A single species was observed in the mass spectrum corresponding to the expected isotope ratio for M + H^+, M + Na^+, and M + K^+. NMR spectroscopy corroborated this assignment; disappearance of the peak at 169 ppm in the $^{13}C\{^1H\}$ NMR spectrum is consistent with complete substitution of the monochlorotriazine derivative.

Intermediate **10** is common to targets **1**, **2**, **3**, and **11** (Figure 3) and is achieved by deprotection of **9** with methanolic HCl, washing the aqueous layer with CH_2Cl_2 and then isolating the product from the aqueous phase by removing the water using rotary evaporation. Mass spectrometry is useful for monitoring the extent of deprotection. Subsequently, the hydrochloride salt of **10** was treated with **6** in the presence of excess base to prepare **3**. This synthesis proceeds with modest reaction times (ca. 16 h) at room temperature to provide gram quantities of product in 96% isolated yield. Chromatographic purification is required to separate **3** from excess **6**. Mass spectrometry suggests that **10** is the only polymeric product in the crude reaction mixture, which is readily removed by extraction of a dichloromethane solution with water.

Admittedly, assigning purity to polymeric materials is challenging due to the degenerate signals in the NMR spectra, as well as ambiguities inherent to reliance on mass spectrometry. Regardless, we are confident that the purity of these molecules is consistent with the high standards associated with small-molecule organic synthesis. This supposition is further supported by significant polarity differences between reagents and products in TLC experiments. However, the best evidence for purity rests in our ability to isolate and characterize the expected side products that arise due to incomplete or over-reaction (Figure 2).

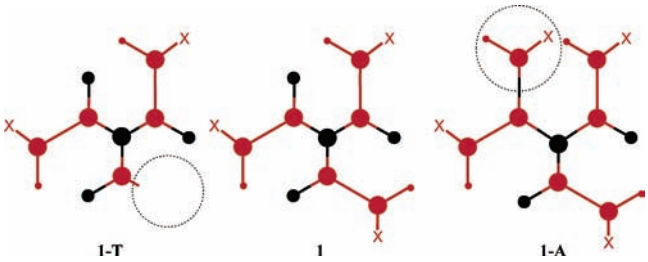


Figure 2. Depiction of impurities that are detected by mass spectrometry before purification (**1-T** is the *t*runcated impurity and **1-A** is the desired product with an *a*dditional dichlorotriazine unit obtained by substitution on a latent appended hydroxyl group).

While this strategy affords macromolecules for diverse applications, we are aware of potential limitations. For example, the syntheses of targets **11** and **12** are complicated by solubility issues (Figure 3). Previous experience has shown that the presentation of hydrogen-bond donating groups leads to aggregation in triazine macromolecules.[12] Following deprotection of the penultimate intermediates, the products are only soluble in water or methanol. As a result, while small quantities of each material are available, alternatives to the pendant hydroxyls will likely be required in order to match the synthetic efficiencies for **1**−**3**, all of which are available in 4 steps in ∼70% overall yield with only two chromatographic separations required.

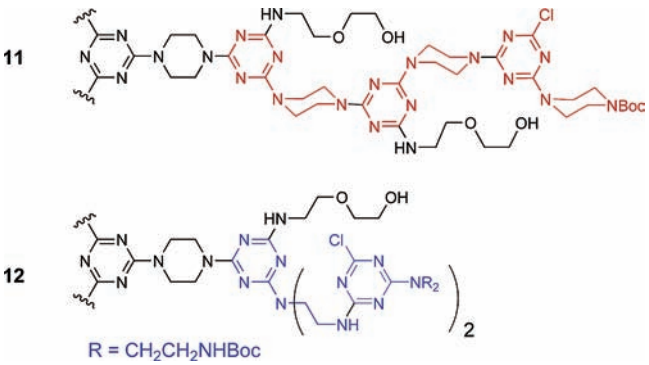


Figure 3. Targets **11** and **12** suffer solubility challenges, attributed in part, to the presence of hydrogen-bond donors.

These manipulations may be performed to provide gram quantities of material without any care given to humidity or inert atmospheres. Results from the manipulation of the orthogonal functional groups, as well as synthetic studies addressing generality will be reported in due course.

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Supporting Information Available: Experimental and characterization details and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Zhang, W.; Gonzalez, S. O.; Simanek, E. E. *Macromolecules* **2002**, *35*, 9015−9021.