Zuschriften

Die Synthese von Dendrimeren mit bis zu sechs verschiedenen Funktionalitäten durch ein mehrstufiges Eintopfverfahren auf der Grundlage selektiver Schutzgruppenoperationen beschreiben E. E. Simanek und M. B. Steffensen in ihrer Zuschrift auf den folgenden Seiten.

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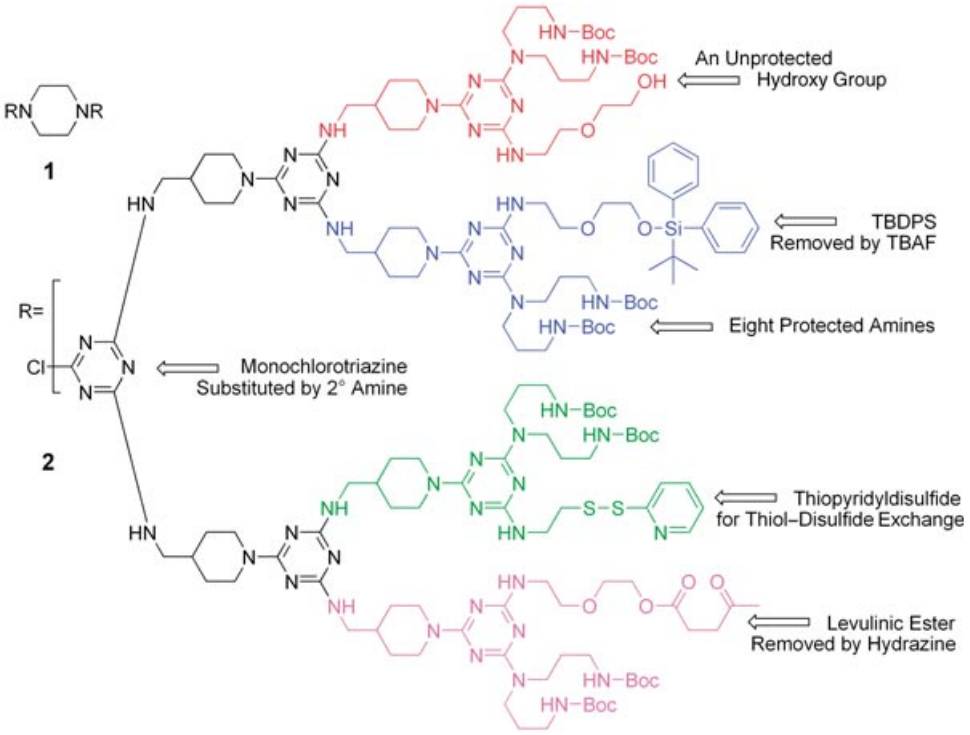
Dendrimer Synthesis

Synthesis and Manipulation of Orthogonally Protected Dendrimers: Building Blocks for Library Synthesis**

*Mackay B. Steffensen and Eric E. Simanek**

Even when reduced to trivial manipulations, the synthesis of dendrimers still remains laborious[1] with few exceptions—notably, one-pot syntheses.[2] As applications are pursued for these architectures, the need to execute structure–property relationships only further increases the burden of synthesis. Not surprisingly, the number of reports of libraries of dendrimers are exceedingly few, and in many cases these libraries are the result of substoichiometric (with respect to the number of reactive surface groups) and statistical reactions at the periphery to yield cocktails of molecules as opposed to single-molecule chemical entities.[3] We and others interested in these architectures have continued to pursue the preparations of versatile targets that are amenable to post-synthetic substoichiometric manipulation.[4] In our hands, the targets reported here (**1** and **2**) are the building blocks of drug-delivery vehicles,[5] while in other hands they may be the basis for novel materials such as poly(block) polymers or other novel materials.[6] Here, we describe the synthesis of these molecules and their manipulation upon selective removal of protecting groups.

Dendrimers **1** and **2** have five and six groups for manipulation, respectively:[7] the free hydroxy group(s) are readily acylated; the levulinic acid ester (Lev) can be unmasked using hydrazine;[8] the *tert*-butyldiphenylsilyl (TBDPS, $C_4H_9SiPh_2$) ether can be removed using tetrabutylammonium fluoride;[9] the thiopyridyl group (PyrS) can participate in thiol–disulfide exchange reactions with free thiols or be removed with dithiothreitol and subsequently alkylated or acylated;[10] the *tert*-butyloxycarbonate groups (Boc: C_4H_9OCO) can be removed with trifluoroacetic acid or formic acid;[11] and the monochlorotriazine of **2** can be treated with a variety of amine nucleophiles.[12] Here, we describe the synthesis of these targets and establish that selective deprotection and subsequent reaction can be effected.



The convergent synthesis of these molecules proceeds in a highly efficient manner. Of the four building blocks used (**4**–**7**, Scheme 1; each indicated with a different color), three (**4**–**6**) originate from a common intermediate (**3**) and are available in yields exceeding 90%. The selective substitution of the triazine ring reduces the synthesis of these dendrimers to a trivial procedure. The use of diamines that react chemoselectively with monochlorotriazines obviates the need for protecting groups or great excesses of reagents.[12]

Intermediate **3** is obtained in quantitative yields by treating the bisprotected triamine[11] with cyanuric chloride followed by the addition of 2-(2-aminoethoxy)ethanol in the same pot. This protocol is commonly executed on a 10-gram scale. The synthesis of **6**–**8** from the common intermediate **3** proceeds cleanly, starting with protection of the alcohol using TBDPSCl to yield **4** or esterification using levulinic acid and DCC to yield **5**. These reactions are routinely run on a 5-g scale and the products are easily purified by chromatography on silica gel. The secondary amine of 4-aminomethylpiperidine (4-AMP) reacts more than 20 times faster than the primary amine to provide the building blocks **6**–**8** in greater than 90% overall yield.[12]

[*] M. B. Steffensen, Dr. E. E. Simanek
Texas A&M University
Department of Chemistry
College Station, TX 77843-3255 (USA)
Fax: (+1) 979-845-9452
E-mail: simanek@tamu.edu

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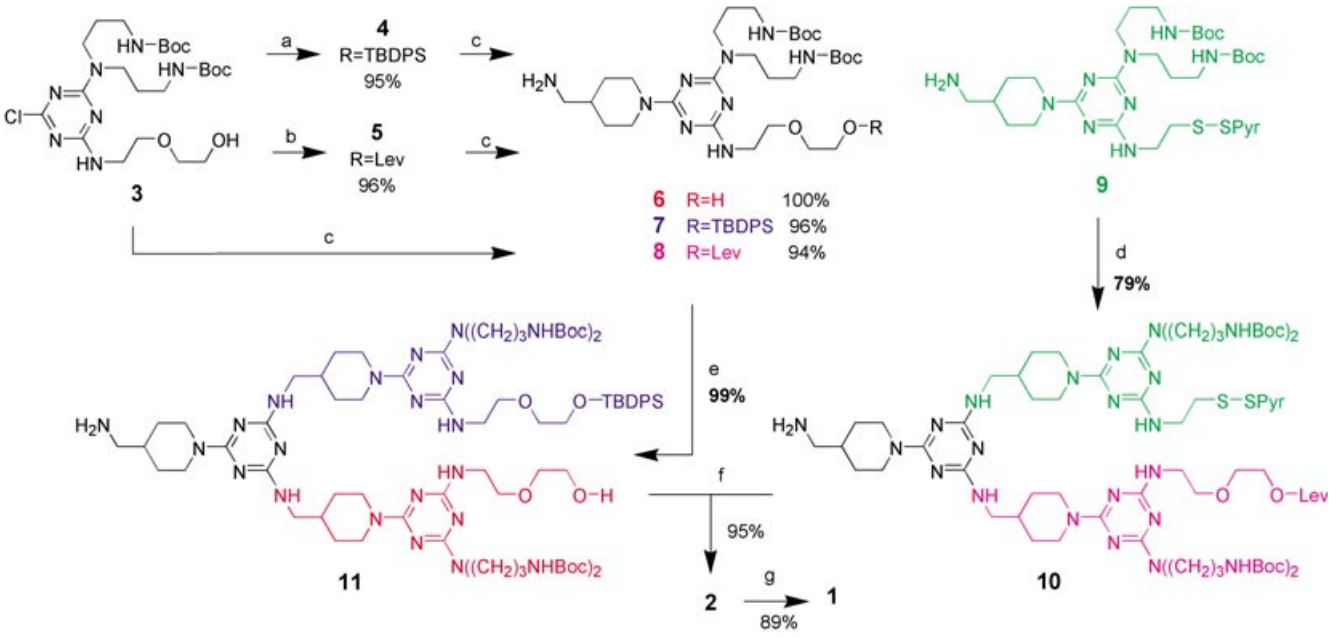

Scheme 1. Synthesis of **1** and **2.** Reagents and conditions: a) TBDPSCl, imidazole, THF, RT, 8 h; b) levulinic acid, DCC, DMAP, THF, RT, 8 h; c) 4-AMP, THF, RT, 8 h; d) **7**+$C_3N_3Cl_3$, DIEA, THF, 0 °C, 2 h; then **6**, RT, 24 h; then 4-AMP, RT, 18 h; e) $C_3N_3Cl_3$, DIEA, THF, 0 °C, 2 h; then **8**, RT, 18 h; then 4-AMP, RT, 18 h; f) **11**+$C_3N_3Cl_3$, DIEA, THF, 0 °C, 2 h; then **6**, RT, 18 h; g) piperazine, THF, 0 °C, 20 h, extraction, then **2**, RT, 10 days. DIEA = diisopropylethylamine, DCC = dicyclohexylcarbodiimide, DMAP = 4-dimethylaminopyridine, 4-AMP = 4-aminomethylpiperidine.

The preparation of the fourth building block (**9**) occurs in a single-pot reaction that commences with monosubstitution of cyanuric chloride with 2-pyridyldithioethylamine (PDA), followed by addition of the bisprotected triamine, and concluding with the addition of 4-AMP. The overall yield for this reaction sequence is 93%, with the final product isolated by chromatography. Synthesis of **10** occurs in a single-pot procedure that relies on first treating **9** with cyanuric chloride, then **8**, and concluding with addition of 4-AMP. This series of manipulations provides **10** in only 79% yield. The uncharacteristically low yield for this series of reactions is presumably a consequence of the condensation of the keto group of the levulinic ester with the free primary amine upon workup. Signals corresponding to the dimerization of **10** minus the loss of water appear in the mass spectra.

The synthesis of **11** proceeds in a manner similar to that of **10**. This reaction is illustrative of the ease at which these multistep, one-pot reactions can be monitored by thin-layer chromatography (TLC). Addition of cyanuric chloride to a solution of **7** ($R_f = 0.3$ in 9:1 CH_2Cl_2:CH_3OH) at 0 °C results in the dichlorotriazine intermediate forming rapidly to give a single new spot by TLC ($R_f = 0.6$ in 9:1 CH_2Cl_2:CH_3OH). After addition of **6** and consumption of the dichlorotriazine, a single spot is again visible by TLC ($R_f = 0.4$ in 9:1 CH_2Cl_2:CH_3OH) which corresponds to the monochlorotriazine. The final reaction with 4-AMP gives **11**, a material that has an R_f value of 0.25 (9:1 CH_2Cl_2:CH_3OH) because of the presence of a free primary amine. Intermediate **11** is obtained in 99% yield.

To obtain **2**, intermediate **11** is treated sequentially with cyanuric chloride and then **10**. Overall, a total of 18 reactions are involved in the synthesis. The longest continuous reaction sequence is only five reactions and provides **2** in 80% overall yield. This route has been executed to produce more than 10 g of **2**. (The route with the lowest yield commences with **9** and produces **2** in three steps and 70% overall yield.) Dendrimer **1** could be obtained by dimerizing **2** with piperazine, but to avoid errors that could arise in the stoichiometry of the reactants as a result of the substantial differences in the molecular weight of **2** and piperazine, we adopt a two-step procedure.[13] Initially, **2** is treated with an excess of piperazine. The excess piperazine is then removed and the remaining material is treated with **1**. The process proceeds in 89% overall yield and the product is purified by chromatography on silica gel.

We evaluated the selective manipulation and deprotection of these scaffolds using **2** (Scheme 2). In short, nucleophilic aromatic substitution with amino acid derivatives can be executed to yield **12.** The free hydroxy group of **12** is amenable to modification with a chloroformate group to yield carbonate **13.** The propargyloxycarbonyl (Poc) group can serve as either a protecting group[13] or a reagent for click chemistry.[14] Selective deprotection of the silyl ether is achieved with tetrabutylammonium fluoride to yield **14**. Cleavage of the levulinic acid ester is facilitated with hydrazine to yield **15**. The pyridyl disulfide group on **1** was cleaved with dithiothreitol before coupling with the commercially available biotin-PDA (an activated biotin–disulfide conjugate) to form disulfide **16**. Triscarboxylethylphosphane reduced the disulfide with concommitent removal of the Poc group. The generality of this reaction is unclear as previous methods for removal of the Poc group typically required heterogeneous solutions of tetrathiomolybdate.[13c] Excess hydrazine can also lead to loss of the Poc group.

Targets **1** and **2** represent useful building blocks for the preparation of dendrimer libraries for diverse purposes.

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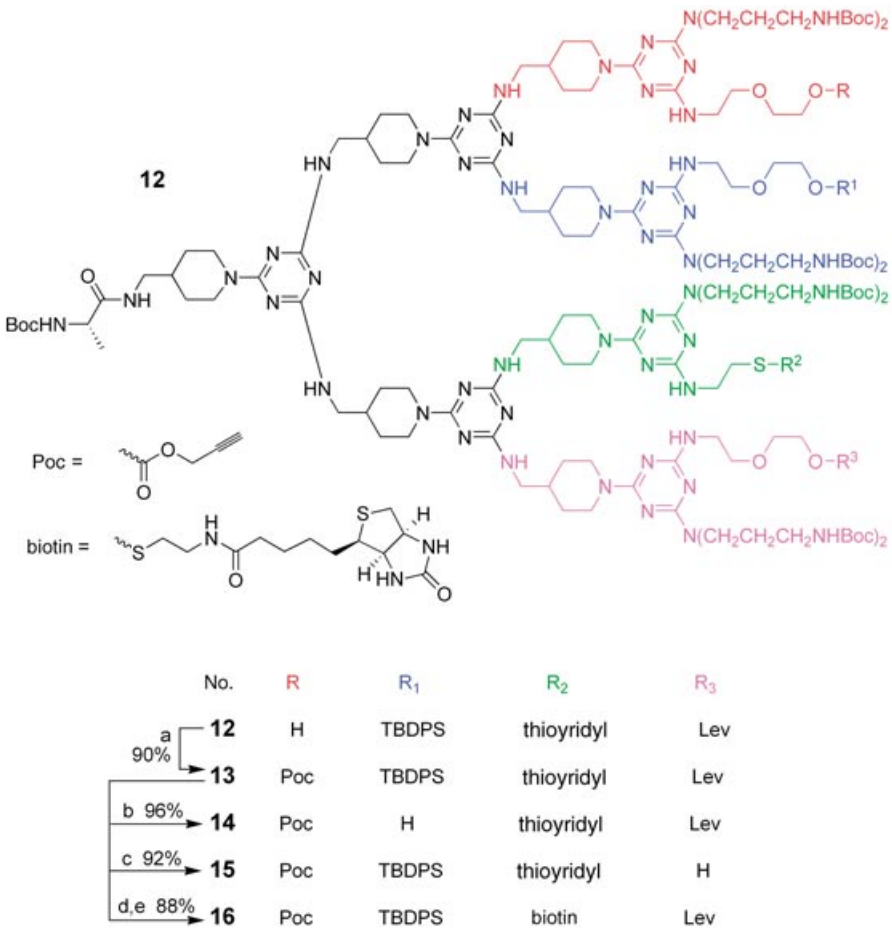

No.	R	R_1	R_2	R_3
12	H	TBDPS	thioyridyl	Lev
13	Poc	TBDPS	thioyridyl	Lev
14	Poc	H	thioyridyl	Lev
15	Poc	TBDPS	thioyridyl	H
16	Poc	TBDPS	biotin	Lev

a 90% → 13; b 96% → 14; c 92% → 15; d,e 88% → 16

Scheme 2. Manipulation of the core. Reagents and conditions: a) propargylchloroformate, pyridine, THF, RT, 2 h; b) TBAF, THF, RT, 4 h; c) hydrazine, THF, RT, 2 h; d) DTT, CH_2Cl_2, RT, 2 h; e) biotin-PDA, DMF, RT, 2 h. Boc-Ala-4-Amp: see Supporting Information for preparation, TBAF = tetrabutylammonium fluoride, DTT = dithiothreitol, biotin-PDA = biotin-pyridyldithioethylamine.

These molecules suffer the limitation that the deprotection steps occur in yields of about 90% and release the protecting group as a by-product into solution, thus necessitating purification. The incorporation of these groups onto a solid support, a current aim of our research, addresses these limitations. We refer to these dendrimers as molecular fruit-salad trees, the nanoscale variant of a tree produced by grafting branches that yield different fruits on a common trunk.[15] Further studies on these architectures will be reported in due course.

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[1] a) S. M. Grayson, J. M. J. Fréchet, *Chem. Rev.* **2001**, *101*, 3819–3867; b) G. R. Newkome, F. Vögtle, C. N. Moorefield, *Dendrimers and Dendrons: Concepts, Syntheses, Applications*, VCH, New York, **2001**; c) J. M. J. Frèchet, D. A. Tomalia, *Dendrimers and Other Dendritic Polymers*, Wiley, New York, **2002**.

[2] a) M. Okaniwa, K. Takeuchi, M. Asai, M. Ueda, *Macromolecules* **2002**, *35*, 6232–6238; b) S. P. Rannard, N. J. Davis, *J. Am. Chem. Soc.* **2000**, *122*, 11729—11770.

[3] a) P. Singh, *Bioconjugate Chem.* **1998**, *9*, 54–63; b) G. R. Newkome, C. D. Weis, C. N. Moorefield, G. R. Baker, B. J. Childs, J. Epperson, *Angew. Chem.* **1998**, *110*, 318–321; *Angew. Chem. Int. Ed.* **1998**, *37*, 307–310; c) G. R. Newkome, B. J. Childs, M. J. Rourk, G. R. Baker, C. N. Moorefield, *Biotechnol. Bioeng.* **1999**, *61*, 243–253; d) J. R. Baker, A. Quintana, L. Piehler, M. Banazak-Holl, D. Tomalia, E. Raczka, *Biomed. Microdevices* **2001**, *3*, 61–69.

[4] a) W. Zhang, D. T. Nowlan III, L. M. Thomson, W. M. Lackowski, E. E. Simanek, *J. Am. Chem. Soc.* **2001**, *123*, 8914–8922; b) Z. Bo, A. Schäfer, P. Franke, A. D. Schlüter, *Org. Lett.* **2000**, *2*, 1645–1648; c) H.-F. Chow, C.-F. Leung, K.-W. Wong, L. Xi, *Angew. Chem.* **2003**, *115*, 5069–5073; *Angew. Chem. Int. Ed.* **2003**, *42*, 4919–4923; d) S. Li, M. L. Szalai, R. M. Kevwitch, D. V. McGrath, *J. Am. Chem. Soc.* **2003**, *125*, 10516–10517; e) K. L. Wooley, C. J. Hawker, J. M. J. Fréchet, *J. Chem. Soc. Perkin Trans. 1* **1991**, 1059–1076; f) W. Zhang, S. E. Tichy, L. M. Pérez, G. Maria, P. A. Lindahl, E. E. Simanek, *J. Am. Chem. Soc.* **2003**, *125*, 5086–5094.

[5] a) S.-E. Stiriba, H. Frey, R. Haag, *Angew. Chem.* **2002**, *114*, 1385–1390; *Angew. Chem. Int. Ed.* **2002**, *41*, 1329–1334; b) F. Aulenta, W. Hayes, S. Rannard, *Eur. Polym. J.* **2003**, *39*, 1741–1771; c) M. J. Cloninger, *Curr. Opin. Chem. Biol.* **2002**, *6*, 742–748; d) R. Esfand, D. A. Tomalia, *Drug Discovery Today* **2001**, *6*, 427–436; e) A. K. Patri, I. J. Majoros, J. R. Baker, Jr., *Curr. Opin. Chem. Biol.* **2002**, *6*, 466–471.

[6] Materials are available in limited supply to other investigators by contacting Professor Simanek.

[7] Inspiration from: C.-H. Wong, X.-S. Ye, Z. Zhang, *J. Am. Chem. Soc.* **1998**, *120*, 7137–7138.

[8] a) J. H. van Boom, P. M. J. Burgers, *Tetrahedron Lett.* **1976**, *17*, 4875–4878; b) N. Jeker, C. Tamm, *Helv. Chim. Acta* **1984**, *67*, 190.

[9] S. Hanessian, P. Lavallee, *Can. J. Chem.* **1977**, *55*, 562–565.

[10] J. Connor, A. J. Schroit, *Biochemistry* **1988**, *27*, 848–851.

[11] D. A. Westerberg, P. L. Carney, P. E. Rogers, S. J. Kline, D. K. Johnson, *J. Med. Chem.* **1989**, *32*, 236–243.

[12] M. B. Steffensen, E. E. Simanek, *Org. Lett.* **2003**, *5*, 2359–2361.

[13] a) S. Sinha, P. Ilankumaran, S. Chandrasekaran, *Tetrahedron Lett.* **1999**, *40*, 771–774; b) R. G. Bhat, S. Sinha, S. Chandrasekaran, *Chem. Commun.* **2002**, 812–813; c) P. R. Sridhar, S. Chandrasekaran, *Org. Lett.* **2002**, *4*, 4731–4733.

[14] H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem.* **2001**, *113*, 2056–2075; *Angew. Chem. Int. Ed.* **2001**, *40*, 2004–2021.

[15] Fruit-salad trees are commercially available: http://www.fruitsaladtrees.com/.

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