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Convergent Synthesis of Internally Branched PAMAM Dendrimers

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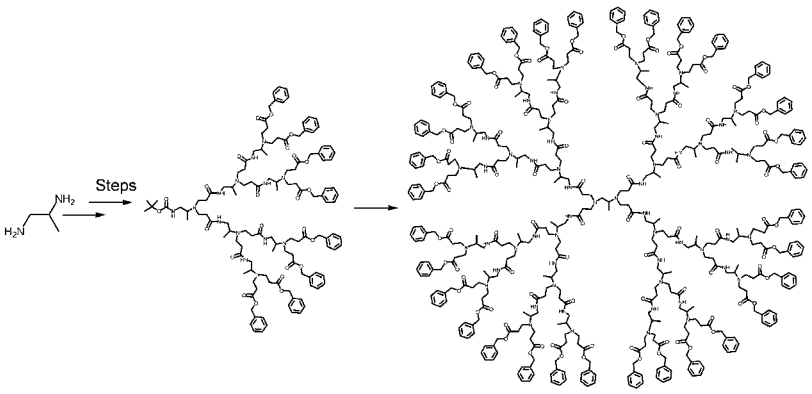
ABSTRACT



A series of aliphatic internally branched poly(amido amine) dendrons and dendrimers has been synthesized. The internal branching unit was 1,2-propanediamine and a series of PAMAM-type dendrons of the types AB_2, AB_4, and AB_8 were built. These were anchored on a core molecule containing four carboxylic acid moieties and the 1,2-propanediamine unit resulted in PAMAM dendrimers with 4, 8, 16, and 32 end groups.

Future applications of dendrimers rely on efficient and practical synthetic procedures. Since the synthesis of the first dendrimers by Vögtle and co-workers in 1978[1] much effort has been put into the synthesis and applications of these aesthetically beautiful macromolecules. Catalysis, drug-delivery systems, molecular encapsulation, molecular light-harvesting, guest−host chemistry, artificial antibodies, and many other exciting applications have been suggested and demonstrated.[2]

The early synthetic efforts in dendrimer synthesis applied the divergent synthesis procedure building the dendrimers from the core by an iterative synthetic procedure. Both major commercially available dendrimers, the poly(propylene amine) dendrimer[3] and the poly(amido amine) dendrimer,[4] were constructed by this procedure. Other types of dendrimers such as Majoral's phosphorus containing dendrimers,[5] Newcome's polyamide dendrimers,[6] and Denkewalter's polylysine dendrimers[7] were products of the divergent approach.

The convergent approach to dendrimer synthesis introduced by Frechet and co-workers revolutionized the synthetic approaches to monodisperse dendrimers.[8] Following Fréchet's poly(aryl ether) dendrons many other types of dendrons and dendrimers have been synthesized using both classical solution phase synthesis and solid-phase synthesis.[9] Building dendrimers via the convergent approach allows for the synthesis of nonsymmetrical dendrimers[10,11] and for specific incorporation of function into the dendrimer interior.[12]

(1) Buhleier, E.; Wehner, W.; Vögtle, F. *Synthesis* **1978**, *2*, 155.
(2) (a) *Topics in Current Chemistry*; Springer-Verlag: Heidelberg; Vols. 197, 210, 212, 217 and 228. (b) Fréchet, J. M. J.; Tomalia, D. A. *Dendrimers and Other Dendritic Polymers*; Wiley Series in Polymer Science; Wiley: New York, 2001. (c) Bosman, A. W.; Janssen, H. M.; Meijer, E. W. *Chem. Rev.* **1999**, *99*, 1665. (d) Hecht, S.; Fréchet, J. M. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 74.
(3) (a) de Brabander-van den Berg, E. M. M.; Meijer, E. W. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1308. (b) Wörner, C.; Mülhaupt, R. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1306.
(4) Tomalia, D. A.; Barker, H.; Dewald, J.; Hall, M.; Kallos, G.; Martin, S.; Roeck, J.; Ryder, J.; Smith, P. *Polym. J.* **1985**, *17*, 117.
(5) (a) Launay, N.; Caminade, A. M.; Majoral, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 3282. (b) Galliot, C.; Prévoté, D.; Caminade, A. M.; Majoral, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 5470.
(6) Newcome, G. R.; Yao, Z.; Baker, G. R.; Gupta, V. K. *J. Org. Chem.* **1985**, *50*, 2003.
(7) Denkewalter, R. G., U.S. Patent 4289872, 1981.
(8) Hawker, C. J.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1990**, *112*, 7638.
(9) Grayson, S. M.; Fréchet, J. M. J. *Chem. Rev.* **2001**, *101*, 3819.

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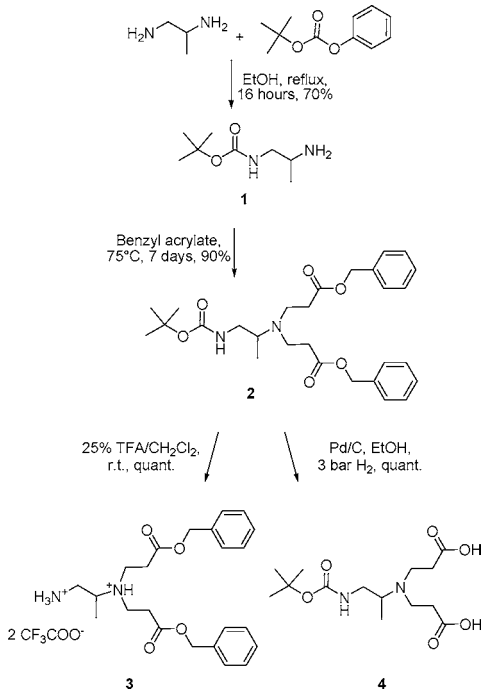
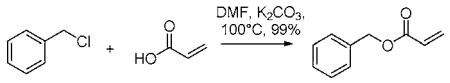
Scheme 1



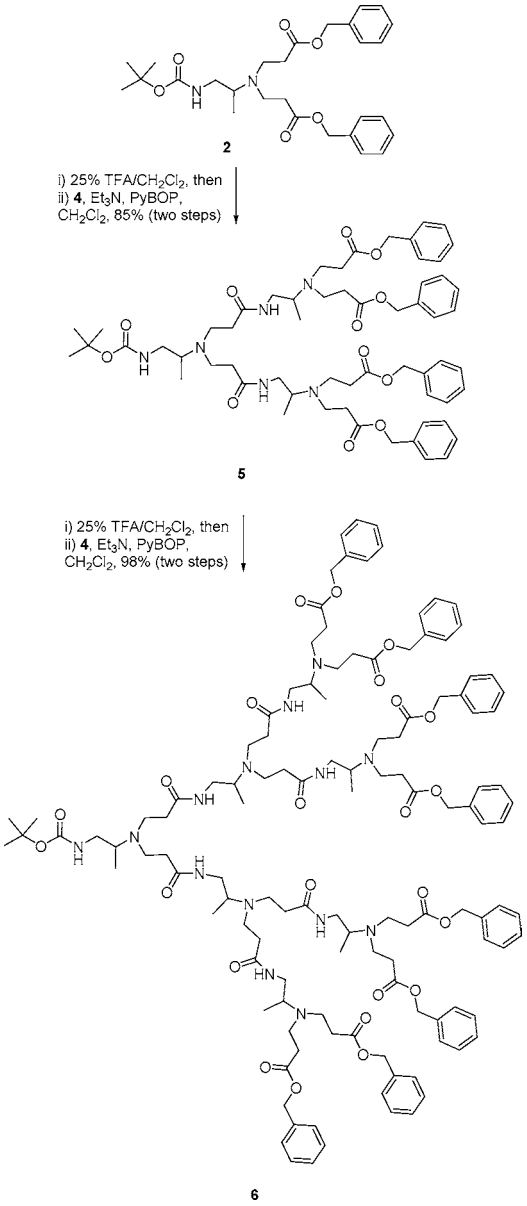
Scheme 2



The synthesis of all-aliphatic poly(amido amine) dendrimers via the convergent approach has presented a significant challenge for solution phase synthesis.[13] A major challenge in the synthesis of nonsymmetrical dendrons with solution phase chemistry is the fact that the use of a large excess of reagents is often not feasible. In the classical PAMAM dendrimer synthesis developed by Tomalia and co-workers, a large excess of both 1,2-ethanediamine and methyl acrylate aided the reactions in going to completion.

Herein we report a convergent regioselective synthesis of a series of nonsymmetrical internally branched PAMAM-type dendrimers using highly effective protection group chemistry in combination with a very efficient peptide coupling reagent.

Scheme 3



The first step in the dendron synthesis was a selective boc protection of 1,2-propanediamine on the amino group located on the primary carbon (Scheme 1). This boc protection proceeded selectively with *tert*-butyl phenyl carbonate as the electrophile in absolute ethanol, and the product was isolated without the use of column chromatography.[14] The boc protected diamine (**1**) was then reacted twice with benzyl acrylate. This reaction was rather sluggish, but performing the reaction neat in an excess of the Michael acceptor at 75 °C for 7 days yielded the desired product (**2**) in 90% yield. This product constitutes the fully orthogonally protected AB_2 wedge. The two carboxylic acid moieties are benzyl protected and the amine is boc protected. The orthogonal deprotection reactions proceeded smoothly by catalytic hydrogenation with

(10) Kremers, J. A.; Meijer, E. W. *J. Org. Chem.* **1994**, *59*, 4262.

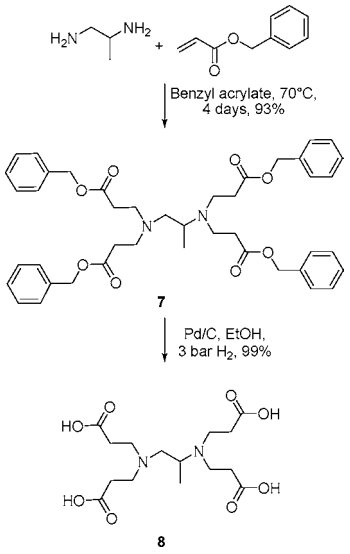
(11) Unsymmetrical PAMAM-type dendrimers have been synthesized by using a divergent/divergent approach: Martin, I. K.; Twyman, L. J. *Tetrahedron Lett.* **2001**, *42*, 1119.

(12) Hecht, S. *J. Polym. Sci. Part A*: *Polym. Chem.* **2003**, *41*, 1047.

(13) Some examples of dendrimers that resemble poly(amido amine) dendrimers synthesized in a convergent manner include: (a) Kim, Y.; Zeng, F.; Zimmerman, S. C. *Chem. Eur. J.* **1999**, *5*, 2133. (b) Kim, C.; Kim, Y. T.; Chang, Y. *J. Am. Chem. Soc.* **2001**, *123*, 5586. (c) Romagnoli, B.; van Baal, I.; Price, D. W.; Harwood, L. M.; Hayes, W. *Eur. J. Org. Chem.* **2004**, 4148. (d) Twyman, L. J.; Beezer, E.; Mitchell, J. C. *Tetrahedron Lett.* **1994**, 4423. (e) Rannard, S.; Davis, N.; McFarland, H. *Polym. Int.* **2000**, 1002. (f) Brouwer, A. J.; Mulders, S. J. E.; Liskamp, R. M. J. *Eur. J. Org. Chem.* **2001**, 1903. (g) Vinogradov, S. A.; Lo, L.-W.; Wilson, D. F. *Chem. Eur. J.* **1999**, *5*, 1338.

(14) Pittelkow, M.; Lewinsky, R.; Christensen, J. B. *Synthesis* **2002**, *15*, 2195.

Scheme 4



Pd/C in ethanol (benzyl groups) and by acidolysis with TFA in CH_2Cl_2 (Boc group).[15] These transformations are shown in Scheme 1.

Isolation of the free amine of the boc deprotected wedge (**3**) was possible by column chromatography on silica with some loss of yield. Distillation of this amine was not possible due to a retro-Michael reaction producing benzyl acrylate. These results prompted us to design a synthesis of the next wedges using the fully protected AB_2 wedge (**2**) as the starting material.

Benzyl acrylate was conveniently synthesized from acrylic acid and benzyl chloride on a large scale (3 mol) in high yield by heating the two components in DMF with K_2CO_3 as the base (Scheme 2). This procedure proved superior to previously described methods with acrylic chloride and benzyl alcohol in our hands.

Thus, the AB_2 wedge (**2**) was deprotected with TFA in CH_2Cl_2 followed by evaporation of all volatiles. This left the TFA salt as described above.

In the synthesis of the fully protected AB_4 dendron (**5**) this salt was converted to the free amine by treatment with Et_3N (in situ) and this was used directly in the coupling reactions with the two carboxylic acid moieties in compound **4**. This reaction sequence is shown in Scheme 3.[16]

The coupling reagent PyBOP[17] was found superior to DCC,[18] TFFH,[19] and a number of other commercially available peptide coupling reagents. An advantage of amide coupling reactions with PyBOP as the coupling reagent was that preactivation of the carboxylic acid was avoided.

Deprotection of the boc protection group from the fully protected AB_4 wedge (**5**) followed by amide coupling to

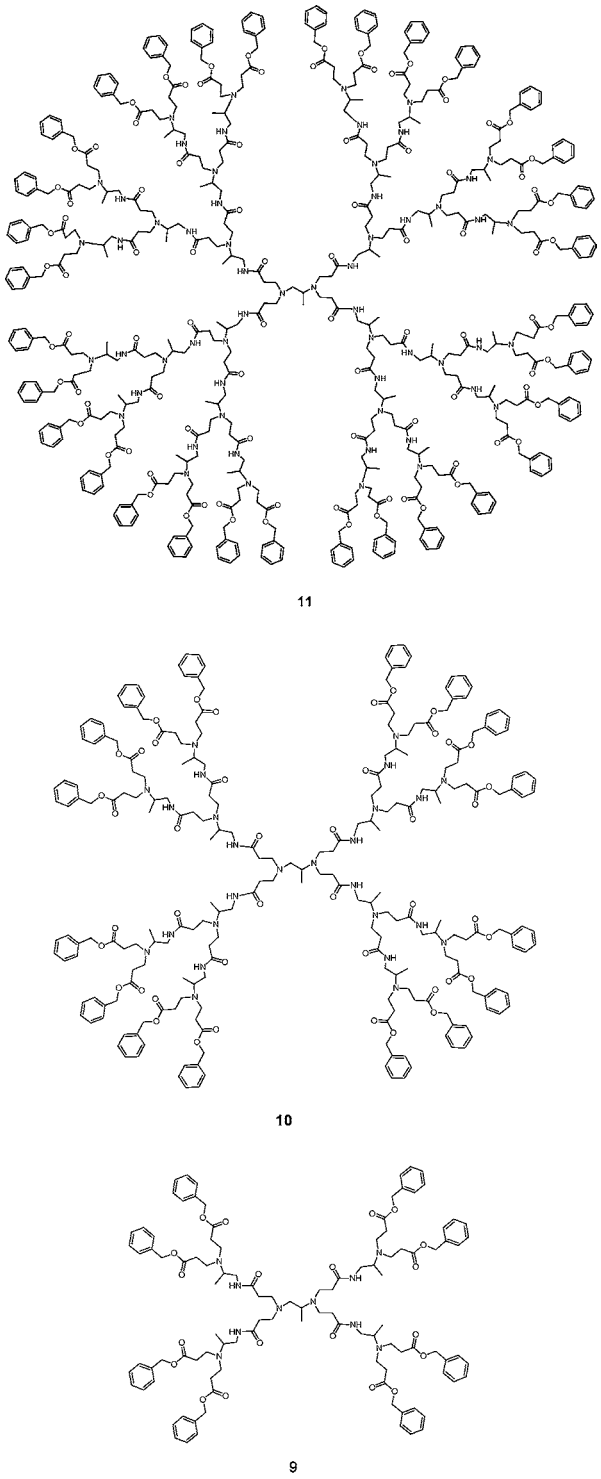


Figure 1. Structure of the dendrimers **9**, **10**, and **11** prepared in 80%, 75%, and 51% yield from **8** and the respective dendrons.

(15) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Chemistry*, 3rd ed.; Wiley: New York, 1999.

(16) General procedure for all amide coupling reactions used in this work: Boc protected amine wedge (1 equiv per carboxylic acid moiety) was treated with 25% TFA in CH_2Cl_2 for 16 h at room temperature. The reaction mixture was evaporated to dryness and dried in vacuo. The resulting amine salt, PyBOP (1.25 equiv per carboxylic acid moiety), and the carboxylic acid were suspended in CH_2Cl_2 and then Et_3N (4 equiv per carboxylic acid) was added at room temperature resulting in a clear solution. This solution was stirred until the reaction was complete. Aqueous workup followed by chromatography on silica or biobeads (SX-1) gave the desired dendrons and dendrimers.

(17) PyBOP: benzotriazole-1-yl-oxy-tris-pyrolidino-phosphinium hexafluorophosphate.

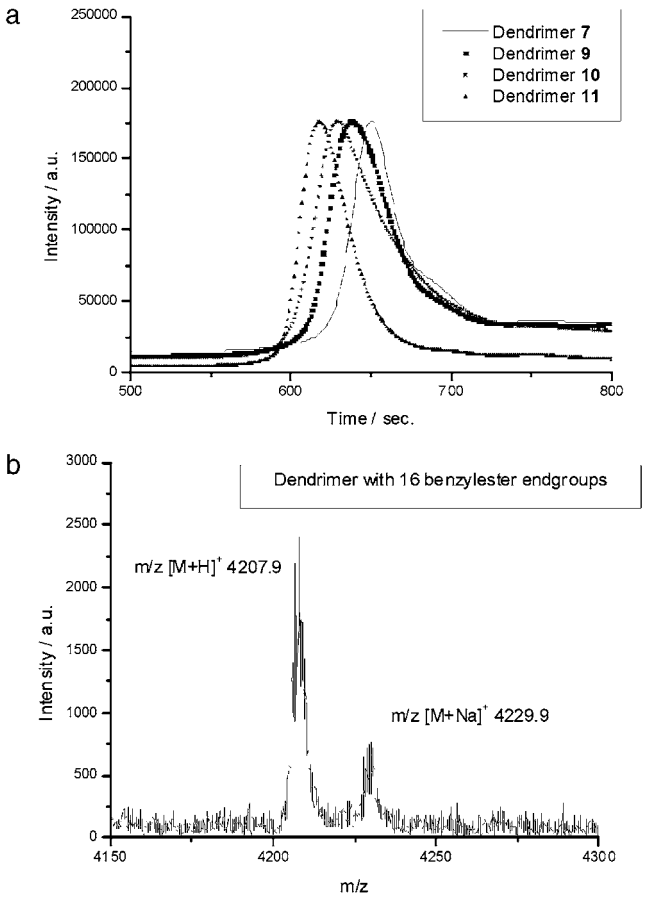


Figure 2. (a) Overlay of SEC of the four dendrimers **7**, **9**, **10**, and **11** and (b) MALDI-MS spectrum of dendrimer **10**.

compound **4** yielded the fully protected AB_8 wedge (**6**) in excellent yield as shown in Scheme 3.

The core of the dendrimer was synthesized by tetraalkylation of 1,2-propanediamine in neat benzyl acrylate. The resulting tetra ester (**7**) was transformed into the corresponding tetra acid by hydrogenolysis, using Pd/C as the catalyst. The synthesis of the core molecule is shown in Scheme 4.

The three PAMAM dendrons (**2**, **5**, and **6**) were anchored to the tetracarboxylic acid core (**8**) by using the deprotection/coupling protocol used for the synthesis of the dendrons. This yielded the series of dendrimers with 8 (**9**), 16 (**10**), and 32 (**11**) benzyl ester end groups as shown in Figure 1.

The yields of the dendrimers upon anchoring of the dendrons to the core drop with each generation presumably due to steric congestion in the vicinity of the core.

The purity of the series of dendrimers was confirmed by SEC, NMR, and MALDI-MS. The MALDI spectrum of the dendrimer with 16 end groups (**10**) and an overlay of the SEC spectra of the various generations of dendrimers are shown in Figure 2. The diasteriomeric and enantiomeric nature of the dendrimers gives rise to relatively broad NMR spectra. This fact does not, however, interfere with the purification of the dendrimers by size exclusion chromatography.

In conclusion, we have presented a novel convergent procedure for the solution phase synthesis of a series of internally branched PAMAM dendrimers.

Acknowledgment. We thank Jeppe Madsen for assistance with the SEC measurements and Kathrine Petersen and Solveig K. Hansen for recording the MALDI-MS.

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

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(18) Dendrimer synthesis has been successful with DCC as the amide coupling reagent: Ashton, P. R.; Hounsell, E. F.; Jayaraman, N.; Nilsen, T. M.; Spencer, N.; Stoddart, J. F.; Young, M. *J. Org. Chem.* **1998**, *63*, 3429.

(19) Dendrimer synthesis has been successful with TFFH as the amide coupling reagent: (a) Ritzen, A.; Frejd, T. *Chem. Commun.* **1999**, *2*, 207. (b) Ritzen, A.; Frejd, T. *Eur. J. Org. Chem.* **2000**, *22*, 3771.