

Synthesis of dendrimers with multifunctional periphery using an ABB' monomer†

Dharma Rao Vutukuri, Kulandaivelu Sivanandan and S. Thayumanavan*

Department of Chemistry, Tulane University, New Orleans, LA 70118, USA. E-mail: thai@tulane.edu;
Fax: +1-504-865-5596

Received (in Columbia, MO, USA) 5th December 2002, Accepted 4th February 2003

First published as an Advance Article on the web 21st February 2003

A new methodology using an ABB' monomer for synthesizing dendrons with multiple functionalities in the periphery is described.

Despite the fact that proteins are macromolecular in nature, most approaches toward mimicking proteins are small-molecule based.¹ More recently, polymeric scaffolds have been used for achieving biomimetic functions.² In general, highly desirable features in biomimetic structures are control and diversity in functional group presentations. Despite the advances in living polymerizations, synthetic linear polymers have not yet achieved the control or the diversity in functional group display offered in biomacromolecules. Dendrimers are unique macromolecules in this respect, since they can be achieved with excellent control of molecular weight and shape.³ However, only a few reports on presenting a variety of functional groups on a single dendrimer surface are available.

Diversity in functional group incorporations in dendrimers can be approached in an uncontrolled⁴ or a controlled fashion.^{5–7} Three different methods of incorporating functional groups in a controlled fashion have been reported recently in the literature: (i) stepwise incorporation of functionalities onto an AB₂ monomer unit, where the desired monosubstituted product and the disubstituted byproduct are obtained in statistical yields;⁵ (ii) incorporation of three different molecules on to a common core unit, where the different reactivities of di-, mono-, and unsubstituted cyanuric chloride are utilized;⁶ (iii) stepwise incorporation of two different functional groups on an AB₂ monomer, in which one of the B units is protected in the first step. The second functional group is incorporated following deprotection of the B moiety.⁷ A complementary and perhaps a more versatile approach is to use an ABB' monomer instead of the AB₂ monomer. In this paper, we present our efforts in this direction.

We prefer the third method among the ones mentioned above, since our long-term goal is to combine our approaches to diversifying functional groups with our strategy to spatially control functional group presentations in the dendritic interior.⁸ The protection–deprotection method mentioned above is high-yielding; however, this approach can be time-consuming. Therefore, we envisioned that a more effective strategy would be to build an ABB' building block, in which both B and B' units could react with A. Also, the reactivity of B with A is much better than the reactivity of B' with A. This approach is schematically represented in Fig. 1.

The repeating unit of choice is ethyl 3-hydroxy-5-(hydroxymethyl)benzoate (**1**), in which the phenolic moiety is more reactive than the hydroxyalkyl group towards electrophiles such as alkyl halides under mildly basic conditions. Thus, in structure **1**, the phenolic moiety is B; the hydroxyalkyl moiety is B'; the ester moiety is A_p, *i.e.*, the masked form of A. Accordingly, the monomer **1** was treated with potassium carbonate and exactly one equivalent of 3-bromobenzyl bromide in THF in the presence of 18-crown-6 to afford the monosubstituted product **2a**. The reaction was monitored by TLC. Upon completion,

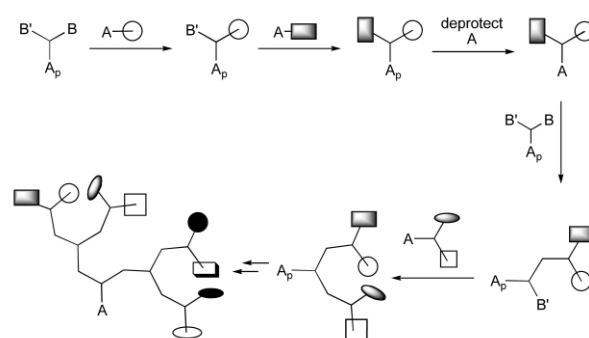
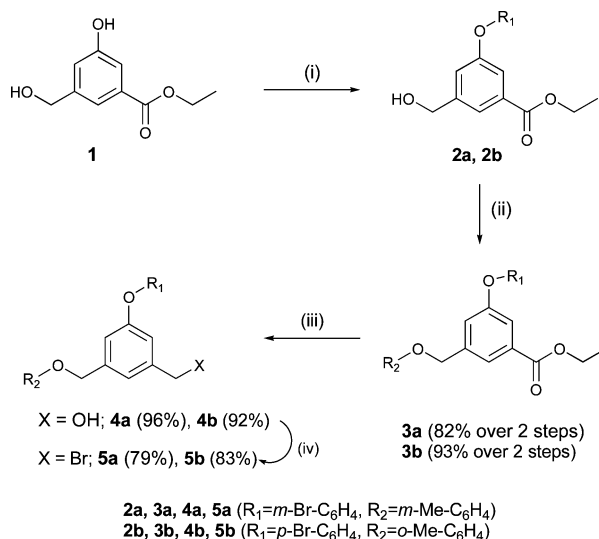


Fig. 1 Schematic representation of the synthetic strategy for achieving a differentially functionalized second generation monodendron. The functionality B is more reactive with A than is B'. Different shapes and shades represent differentially functionalized monomers.

3-methylbenzyl bromide was added as the second electrophile followed by sodium hydride. The resultant reaction mixture was stirred at ambient temperature for one hour to afford the 3-mer dendron **3a** in 82% overall yield as shown in Scheme 1. The substitution at the phenolic position in the first step was confirmed using ¹H NMR of the crude reaction mixture containing **2a**. A similar reaction of **1** with 4-bromobenzyl bromide as the first electrophile and 2-methylbenzyl bromide as the second electrophile afforded the 3-mer dendron **3b** in 93% overall yield. It is crucial to add exactly one equivalent of the first electrophile in the above reaction in order to obtain the products **3** in their pure form. The esters **3a** and **3b** were reduced using H₃B·SMe₂ to afford the corresponding benzyl alcohols **4a** and **4b** in 96% and 92% yields respectively. Conversion of the hydroxymethyl moiety to a bromomethyl group was achieved in

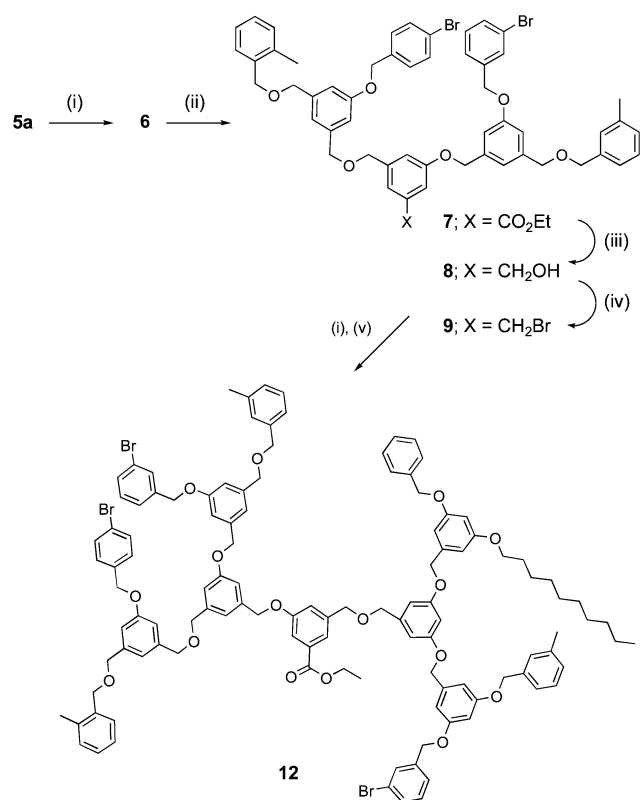


Scheme 1 Synthesis of 3-mer dendrons. (i) R₁X, K₂CO₃, 18-crown-6, THF, reflux; (ii) R₂X, NaH, rt; (iii) BH₃·Me₂S, THF, reflux; (iv) PPh₃, NBS, THF, rt.

† Electronic supplementary information (ESI) available: experimental details. See <http://www.rsc.org/suppdata/cc/b2/b212206p/>

79% and 83% yields to afford **5a** and **5b** respectively (Scheme 1).

The synthesis of 7-mer dendron from 3-mer dendrons **5a** and **5b** was achieved by a two-step sequence. Treatment of the 3-mer benzylic bromide **5a** with **1** afforded the phenol substituted product **6** in 82% isolated yield (Scheme 2 and Fig. 2). Compound **6** was then treated with sodium hydride followed by **5b** to afford the 7-mer dendron **7** in 77% yield. It should be noted that the synthesis of the dendron **7** was carried out in two steps, instead of the one-pot protocol above. This is mainly due to the small amount of inseparable impurity observed in the product mixture. This impurity is attributed to the possible inexact addition of the first electrophile in the one-pot protocol. The ester moiety of **7** was reduced to a hydroxymethyl group **8**, which was then converted to the corresponding bromomethyl moiety **9** in 82% and 88% yields, respectively, as outlined in Scheme 2. Reaction of **9** with **1** in the presence of potassium carbonate afforded the corresponding monosubstituted dendron **10** (structure not shown) in 82% yield. Treatment of this dendron with a previously reported⁷ 7-mer dendron **11** (Fig. 2)



Scheme 2 Synthesis of 7-mer and 15-mer dendrons. (i) K_2CO_3 , 18-crown-6, **1**, THF, reflux, 82%; (ii) NaH, 18-crown-6, **5b**, THF, rt, 77%; (iii) $BH_3 \cdot Me_2S$, THF, reflux, 82%; (iv) PPh_3 , NBS, THF, rt, 88%; (v) NaH, 18-crown-6, **11**, THF, rt, 72%.

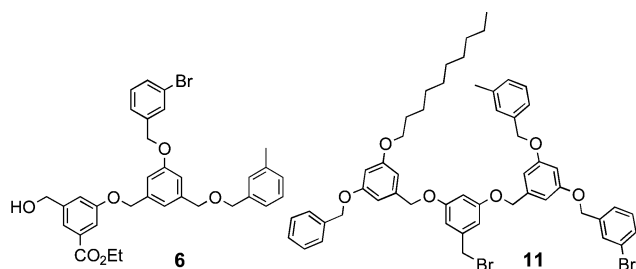


Fig. 2 Structures of dendrons **6** and **11**.

in the presence of sodium hydride afforded the 15-mer dendron **12** in 72% yield (Scheme 2). Six out of the eight peripheral units in dendron **12** are different from each other. Note that if a different dendron were used in place of **11**, a dendritic macromolecule where all the eight peripheral units are different from each other would be obtained.

In summary, a new methodology for the syntheses of dendrons up to a 15-mer (third generation) with different functional groups in the periphery is described. The methodology takes advantage of the different reactivities of two different functional groups with an electrophile in a new ABB' monomer. It should be noted that the ability to vary the monomer units in the periphery of a dendrimer in a highly controlled fashion is an indirect demonstration of the ability to vary each monomer unit within the dendrimer. The possible diversity of functional group presentations in dendrimers arising from this methodology should expand the opportunities for use of these macromolecules in biomimetics,⁹ new polymer architectures,^{5c,10} molecular recognition,¹¹ and catalysis.¹²

This work is supported by the NIGMS of the National Institutes of Health (R01 GM065255-01). ST is a Cottrell Scholar of the Research Corporation and NSF-Career (NSF-CHE-0134972) awardee.

Notes and references

- (a) D. J. Cram, *Nature*, 1992, **356**, 29; (b) R. Breslow, *Acc. Chem. Res.*, 1995, **28**, 146; (c) J. Rebek, *Acc. Chem. Res.*, 1999, **32**, 278.
- (a) L. Liu and R. Breslow, *J. Am. Chem. Soc.*, 2002, **124**, 4978; (b) L. Liu, M. Rozenman and R. Breslow, *J. Am. Chem. Soc.*, 2002, **124**, 12660.
- (a) G. R. Newkome, C. N. Moorefield and F. Vögtle, *Dendrimers and Dendrons: Concepts, Syntheses, Applications*, Wiley-VCH, Weinheim, Germany, 2001; (b) A. W. Bosman, H. M. Janssen and E. W. Meijer, *Chem. Rev.*, 1999, **99**, 1665; (c) S. M. Grayson and J. M. J. Fréchet, *Chem. Rev.*, 2001, **101**, 3819; (d) M. Fischer and F. Vögtle, *Angew. Chem., Int. Ed.*, 1999, **38**, 884; (e) F. Zeng and S. C. Zimmerman, *Chem. Rev.*, 1997, **97**, 1681.
- G. R. Newkome, C. D. Weis, C. N. Moorefield, G. R. Baker, B. J. Childs and J. Epperson, *Angew. Chem., Int. Ed.*, 1998, **37**, 307.
- (a) K. L. Wooley, C. J. Hawker and J. M. J. Fréchet, *J. Chem. Soc., Perkin Trans. 1*, 1991, 1059; (b) Z. Bo, A. Schäfer, P. Franke and A. D. Schlüter, *Org. Lett.*, 2000, **2**, 1645; (c) R. N. Ganesh, J. Shraberg, P. G. Sheridan and S. Thayumanavan, *Tetrahedron Lett.*, 2002, **43**, 7217.
- W. Zeng, D. T. Nowlan III, L. M. Thomson, W. M. Lackowski and E. E. Simanek, *J. Am. Chem. Soc.*, 2001, **123**, 8914.
- (a) K. Sivanandan, D. Vutukuri and S. Thayumanavan, *Org. Lett.*, 2002, **4**, 3751; (b) D. Vutukuri, P. Bharathi, Z. Yu, K. Rajasekaran, M.-H. Tran and S. Thayumanavan, *J. Org. Chem.*, 2003, **68**, 1146.
- P. Bharathi, H. Zhao and S. Thayumanavan, *Org. Lett.*, 2001, **3**, 1961.
- D. K. Smith and F. Diederich, *Chem. Eur. J.*, 1998, **4**, 1353 and references therein.
- (a) Z. Bo, J. P. Rabe and A. D. Schlüter, *Angew. Chem., Int. Ed.*, 1999, **38**, 2370; (b) B. Karakaya, W. Claussen, K. Gessler, W. Saenger and A.-D. Schlüter, *J. Am. Chem. Soc.*, 1997, **119**, 3296; (c) W. Stocker, B. L. Schürmann, J. P. Rabe, S. Förster, P. Linder, I. Neubert and A. D. Schlüter, *Adv. Mater.*, 1998, **10**, 793.
- (a) S. C. Zimmerman, Y. Wang, P. Bharathi and J. S. Moore, *J. Am. Chem. Soc.*, 1998, **120**, 2172; (b) S. C. Zimmerman, F. Zeng, D. E. C. Reichert and S. V. Kolotuchin, *Science*, 1996, **271**, 1095; (c) M. W. P. L. Baars, A. J. Karlsson, V. Sorokin, B. F. W. de Waal and E. W. Meijer, *Angew. Chem., Int. Ed.*, 2000, **39**, 4262; (d) D. de Groot, B. F. M. de Waal, J. N. H. Reek, A. P. H. J. Schenning, P. C. J. Kamer, E. W. Meijer and P. W. N. M. van Leeuwen, *J. Am. Chem. Soc.*, 2001, **123**, 8453; (e) C. Valério, J. L. Fillaut, J. Ruiz, J. Guittard, J. C. Blais and D. Astruc, *J. Am. Chem. Soc.*, 1997, **119**, 2588.
- (a) J. W. J. Knapen, A. W. van der Made, J. C. de Wilde, P. W. N. M. van Leeuwen, P. Wijkens, D. M. Grove and G. van Koten, *Nature*, 1994, **372**, 659; (b) M. E. Piotti, R. Bond, C. J. Hawker and J. M. J. Fréchet, *J. Am. Chem. Soc.*, 1999, **121**, 9471.