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Functional Group Diversity in Dendrimers[†]

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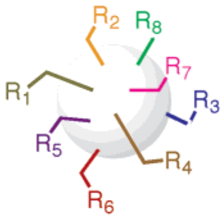
ABSTRACT



A methodology for synthesizing dendrons with different peripheral functionalities is described. The benzyl ether-based dendrons reported here were synthesized using allyl and methoxymethyl ether-based protection–deprotection strategies.

Significant effort has been devoted over the past decade to achieve molecular architectures inspired by Nature.[1] Most biological scaffolds are macromolecular in dimension and exhibit excellent control over size, shape, and functional group displays. Dendrimers belong to a unique class of artificial structural motifs that fit the requirement of controlled size.[2] Due to the globular shape at higher generations, dendrimers have often been referred to as possible globular protein mimics.[3] However, exquisite control of functional group presentations in dendrimers has not been fully explored. Therefore, to further develop dendrimers as potential biomimetics, they should exhibit other important structural features beyond globular conformation and controlled molecular weight.

We have previously described a molecular design based on benzyl ether dendrimers in which functional groups can be directed selectively toward the macromolecular interior.[4] It is equally important that opportunities for diversity among these functional groups are made available. Due to the iterative nature of the dendrimer synthesis, it is easy to imagine varying the functionalities in each layer of the dendrimer. However, the versatility of dendrimers as biomimetics will increase if we gain the ability to vary each of the monomer units within these benzyl ether dendrimers.[5] In this work, we show the synthesis of dendrons up to a third generation in which eight different peripheral units are incorporated. Note that synthesis of a dendrimer, in which each of the peripheral monomers is different, is an indirect demonstration of the ability to vary each of the monomer units within the dendrimer. Therefore, this strategy can be used to generate dendrimers in which every monomer unit is different.

To further our ultimate goal of diversifying functional group placements in our own molecular design,[4] the dendrimers reported herein are benzyl ether-based and convergently[2d,6] assembled. The building blocks used in the

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[†] This paper is dedicated to Professor Jeffrey S. Moore on the occasion of his 40th birthday.

(1) (a) Breslow, R. *Acc. Chem. Res.* **1995**, *28*, 146−153. (b) Cram, D. J. *Nature* **1992**, *356*, 29−36. (c) Rebek, J. *Acc. Chem. Res.* **1999**, *32*, 278−286. (d) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173−180. (e) Hill, D. J.; Mio, M. J.; Prince, R. B.; Hughes, T. S.; Moore, J. S. *Chem. Rev.* **2001**, *101*, 3893−4012. (f) Nowick, J. S. *Acc. Chem. Res.* **1999**, *32*, 287−296.

(2) (a) Newkome, G. R.; Moorefield, C. N.; Vögtle, F. *Dendrimers and Dendrons: Concepts, Syntheses, Applications*; Wiley-VCH: Weinheim, Germany, 2001. (b) Bosman, A. W.; Janssen, H. M.; Meijer, E. W. *Chem. Rev.* **1999**, *99*, 1665−1688. (c) Brunner, H. *J. Organomet. Chem.* **1995**, *500*, 39−46. (d) Grayson, S. M.; Fréchet, J. M. J. *Chem. Rev.* **2001**, *101*, 3819−3868. (e) Fischer, M.; Vögtle, F. *Angew. Chem., Int. Ed.* **1999**, *38*, 884−905. (f) Zeng, F.; Zimmerman, S. C. *Chem. Rev.* **1997**, *97*, 1681−1712.

(3) (a) Smith, D. K.; Diederich, F. *Chem. Eur. J.* **1998**, *4*, 1353−1361 and references therein. (b) Enomoto, M.; Aida, T. *J. Am. Chem. Soc.* **2002**, *124*, 6099−6108.

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(5) For a methodology, involving triazine-based dendrimers, that is capable of differentiating every monomer, see: Zeng, W.; Nowlan, D. T., III; Thomson, L. M.; Lackowski, W. M.; Simanek, E. E. *J. Am. Chem. Soc.* **2001**, *123*, 8914−8922.

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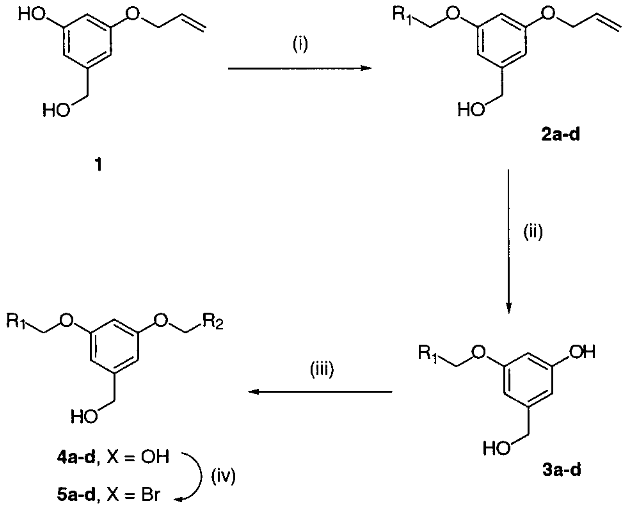
Table 1. Yields for Steps Shown in Scheme 1

	R_1	R_2	step i (% yield)	step ii (% yield)	step iii (% yield)	step iv (% yield)
2−5a	*o*-Me-C_6H_4	*p*-Br-C_6H_4	95	64	95	92
2−5b	*p*-*t*-Bu-C_6H_4	*m*-Cl-C_6H_4	92	67	86	86
2−5c	*m*-Me-C_6H_4	*m*-Br-C_6H_4	84	84	88	88
2−5d	*n*-C_9H_{19}	C_6H_5	82	82	84	82

synthesis of these dendrimers involve AB_2 units. To be able to differentiate each of the monomer units within the dendrimer, only one of the two B functionalities should be reactive. Therefore, we have protected one of the two phenolic groups in 3,5-dihydroxybenzyl alcohol. Utilizing protection−deprotection strategies in dendrimer synthesis increases the number of steps in the assembly. However, we rationalized that the benefits of being able to differentiate each monomer in the dendrimer far outweigh the rather small increase in the number of synthetic steps.

To obtain a G-3 dendron in which all eight functionalities are different, four unsymmetrically substituted G-1 dendrons were synthesized. The repeating unit for the synthesis was 3-allyloxy-5-hydroxybenzyl alcohol (**1**). Treatment of **1** with 1 equiv of benzyl halides or alkyl halides in the presence of potassium carbonate and 18-crown-6 in acetone afforded the monosubstituted products **2a−d** in 82−95% yields (Scheme 1, Table 1). Deprotection of the allyl functionality was carried out with sodium borohydride in the presence of a catalytic amount of $Pd(PPh_3)_4$ to provide products **3a−d** in 64−84% yields (Scheme 1, Table 1).[7] Treatment of **3** with a different set of benzyl bromides afforded products **4a−d** in 84−95% yields (Scheme 1, Table 1). Note that in this reaction sequence, the benzyl bromides that contain a halide moiety in the aryl ring are used as the second electrophile. If these were used in the first step, the allyl deprotection afforded impure product mixtures. We ascribe the impurities to the possible hydrodehalogenation upon treatment with $Pd(PPh_3)_4$ and sodium borohydride.

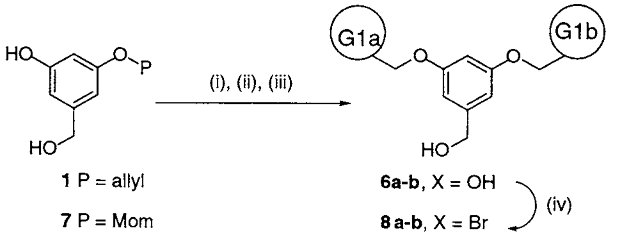
Scheme 1. Assembly of 3-mer Dendrons[a]



[a] (i) R_1CH_2-X, K_2CO_3, 18-crown-6, acetone, reflux; (ii) $Pd(PPh_3)_4$, $NaBH_4$, THF; (iii) R_2CH_2-X, K_2CO_3, 18-crown-6, acetone, reflux; (iv) Ph_3P, NBS, THF.

Treatment of the 3-mer benzyl alcohols **4a−d** with triphenylphosphine and *N*-bromosuccinimide in THF afforded the corresponding bromomethyl compounds **5a−d** in 82−92% yields (Scheme 1, Table 1). This conversion has been previously reported using Ph_3P/CBr_4, Ph_3P/NBS (in DMF), PBr_3, etc.[6,8] In our case, all these protocols provided inconsistent and low yields. However, when attempted in a concentrated solution in THF, our reaction was complete in less than five minutes. We also noticed that the products decomposed if the reaction was allowed to proceed for longer times.

Scheme 2. Synthesis of 7-mer Dendrons[a]



[a] (i) K_2CO_3, 18-crown-6, acetone, reflux, (92% with **5d**, 94% with **5a**); (ii) for P = allyl, $Pd(PPh_3)_4$, $NaBH_4$, THF, 87%; for P = Mom, Dowex® 50W-X8, H^+ form resin, dioxane, H_2O, reflux, 64%; (iii) K_2CO_3, 18-crown-6, acetone, reflux, (89% with **5c**, 92% with **5b**) (iv) Ph_3P, NBS, THF (86% with **6a**, 92% with **6b**).

Sequential treatment of **5d** with **1** followed by the deprotection of the allyl group and treatment with **5c** afforded the 7-mer dendron **6a** in 92, 87, and 89% yields, respectively (Scheme 2). However, coupling of **5a** and **5b** to obtain **6b** using the current synthetic sequence requires subjecting a dendron containing an aryl halide moiety to the palladium-catalyzed deprotection conditions, to which they are incompatible. Therefore, we resorted to an alternate protecting group, MOM-ether. Monoprotected dihydroxybenzyl alcohol

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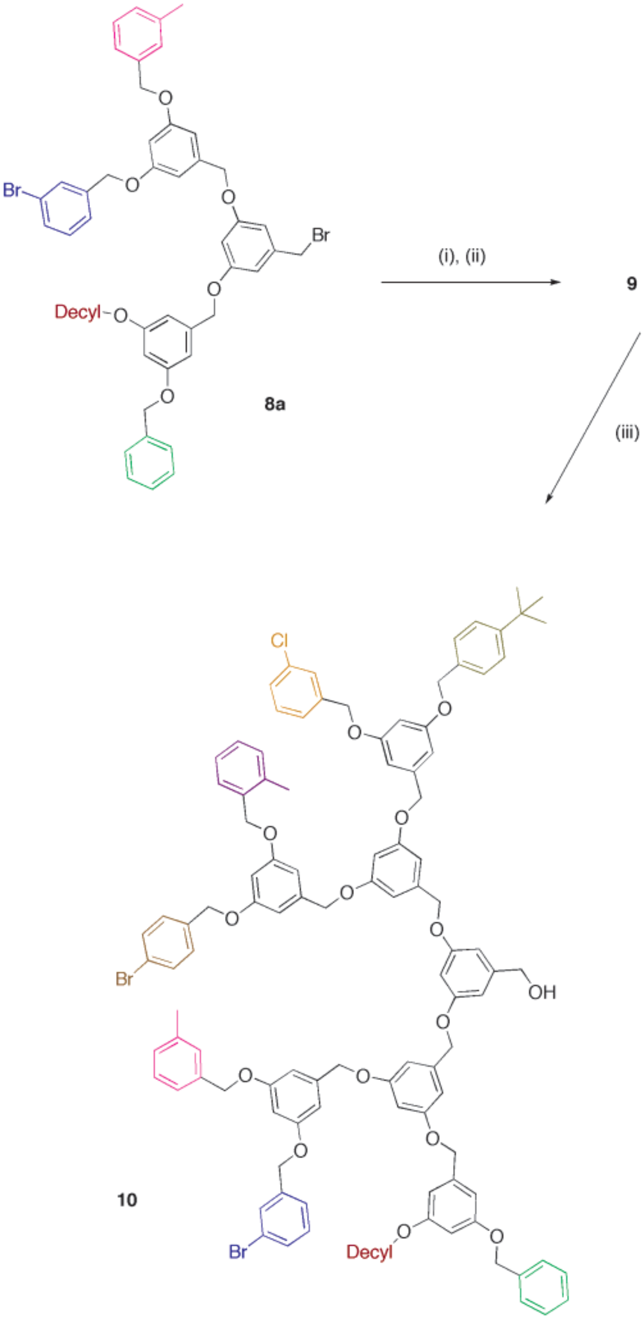
[6] Hawker, C. J.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1990**, *112*, 7638−7647.

[7] For the allyl deprotection methodology, see: Beugelmans, R.; Bourdet, S.; Bigot, A.; Zhu, J. *Tetrahedron Lett.* **1994**, *35*, 4349−4350.

[8] van Bommel, K. J. C.; Metselaar, G. A.; Verboom, W.; Reinhoudt, D. N. *J. Org. Chem.* **2001**, *66*, 5405−5412.

Scheme 3. Synthesis of 15-mer Dendrons[a]



[a] (i) K_2CO_3, 18-crown-6, acetone, reflux, **7**, 80%; (ii) Dowex® 50W-X8, H^+ form resin, methanol/dioxane 1:1, water, reflux, 77%; (iii) K_2CO_3, 18-crown-6, acetone, reflux, **8b**, 79%.

7 was treated with **5a** to afford the monosubstituted product in 94% yield. Deprotection of the MOM-ether using a Dowex resin was achieved in 64% yield. Treatment of the resulting phenol with **5b** afforded the product **6b** in 92% yield (Scheme 2).

Treatment of **6a** and **6b** with Ph_3P and NBS in THF afforded the corresponding bromomethyl compounds **8a** and **8b** in 86 and 92% yields, respectively. Reaction of **8a** with **7**, followed by deprotection of the MOM-ether and treatment with **8b** afforded the 15-mer dendron **10** in 80, 77, and 79% yields, respectively (Scheme 3). Note that all eight peripheral groups in **10** are different from each other.

In summary, we have developed a simple synthetic methodology in which all the monomer units within the dendrimer can be differentiated. We have demonstrated this method by synthesizing a dendron in which all the peripheral groups are different. This approach will open up several opportunities for dendrimers. For example, Schlüter and coworkers have elegantly developed polymers containing dendritic side chains.[9] The current methodology will offer the opportunity to synthesize polymers where dendrimers are main chain components.[10] Also, there have been reports that demonstrate one or two functionalities in the periphery of the dendrimer in a controlled or an uncontrolled fashion.[5,11] The current methodology will offer the opportunity to diversify those functionalities. Meijer, Zimmerman, and Astruc have performed host–guest binding studies based on specific functional groups in the periphery or core.[12] The ability to present different functional groups at the dendrimer surface should significantly further such a repertoire.

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

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