ORGANIC LETTERS

2001
Vol. 3, No. 12
1961−1964

# Toward Globular Macromolecules with Functionalized Interiors: Design and Synthesis of Dendrons with an Interesting Twist

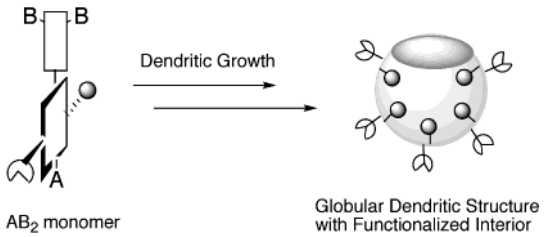
**Pandi Bharathi, Hongda Zhao, and S. Thayumanavan***

*Department of Chemistry, Tulane University, New Orleans, Louisiana 70118*

*thai@tulane.edu*

**Received May 3, 2001**

## ABSTRACT




**Design and synthesis of a novel class of monodendrons, in which the functional units can potentially be directed toward the concave interiors of dendrimers, are described. The key feature of the design is the placement of the amphiphilic and the $AB_2$ functional groups in orthogonal planes.**

The concave nature of the binding sites in enzymes and nucleic acids has long inspired chemists to design new host materials with recognition sites at their concave face.[1] The globular architecture of dendrimers[2] presents a new scaffold for such recognition possibilities. In fact, dendrimers have often been referred to as possible globular protein mimics.[3] However, to fully realize dendritic structures as potential biological mimics, the ability to incorporate additional structural features is needed. Arguably, the most important of these structural requirements is the ability to selectively functionalize the concave interiors of these macromolecules, i.e., selectively direct functional groups toward the interior of the globular dendrimer. The difficulty in meeting this structural requisite arises from the flexible nature of the backbone in a globular dendrimer. In molecules with flexible backbone, attaining conformational control over the orientation of the functional groups is nontrivial. A promising approach to achieving such control involves rendering these macromolecules amphiphilic. The amphiphilicity and globular shape of dendrimers have been combined previously, and they have been shown to exhibit useful properties.[4] In these

(1) (a) Cram, D. J. *Nature* **1992**, *356*, 29. (b) Breslow, R.; Dong, S. D. *Chem. Rev.* **1998**, *98*, 1997. (c) Breslow, R. *Acc. Chem. Res.* **1995**, *28*, 146. (d) Conn, M. M.; Rebek, J. *Chem. Rev.* **1997**, *97*, 1647. (e) Jasat, A.; Sherman, J. C. *Chem. Rev.* **1999**, *99*, 931. (f) Rowan, A. E.; Elemans, J. A. A. W.; Nolte, R. J. M. *Acc. Chem. Res.* **1999**, *32*, 995. (g) Wulff, G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1812.

(2) (a) Fréchet, J. M. J. *Science* **1994**, *263*, 1710. (b) Newkome, G. R.; Moorefield, C. N.; Vögtle, F. *Dendritic Molecules. Concepts, Synthesis, Perspectives*; VCH: Weinheim, 1996. (c) Tomalia, D. A.; Naylor, A. M.; Goddard, W. A., III. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 138. (d) Tomalia, D. A. *Adv. Mater.* **1994**, *6*, 529. (e) Bosman, A. W.; Janssen, H. M.; Meijer, E. W. *Chem. Rev.* **1999**, *99*, 1665. (f) Fischer, M.; Vögtle, F. *Angew. Chem., Int. Ed.* **1999**, *38*, 884. (g) Frey, H. *Angew. Chem., Int. Ed.* **1998**, *37*, 2193. (h) Matthews, O. A.; Shipway, A. N.; Stoddart, J. F. *Prog. Polym. Sci.* **1998**, *23*, 1. (i) Moore, J. S. *Acc. Chem. Res.* **1997**, *30*, 402. (j) Newkome, G. R.; He, E.; Moorefield, C. N. *Chem. Rev.* **1999**, *99*, 1689. (k) Zeng, F.; Zimmerman, S. C. *Chem. Rev.* **1997**, *97*, 1681. (l)Percec, V.; Cho, W. D.; Ungar, G. *J. Am. Chem. Soc.* **2000**, *122*, 10273 and references therein.

(3) Smith, D. K.; Diederich, F. *Chem. Eur. J.* **1998**, *4*, 1353.

(4) (a) Newkome, G. R.; Moorefield, C. N.; Baker, G. R.; Saunders, M. J.; Grossman, S. H. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1178. (b) Hawker, C. J.; Wooley, K. L.; Fréchet, J. M. J. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1287. (c) Jansen, J. F. G. A.; Berg, E. M. M. d. B.-v. d.; Meijer, E. W. *Science* **1994**, *266*, 1226. (d) Jansen, J. F. G. A.; Meijer, E. W.; Berg, E. M. M. d. B.-v. d. *J. Am. Chem. Soc.* **1995**, *117*, 4417. (e) Baars, M. W. P. L.; Kleppinger, R.; Koch, M. H. J.; Yeu, S.-L.; Meijer, E. W.

10.1021/ol016064b CCC: $20.00 
**Published on Web 05/15/2001**

cases, however, since the amphiphilicity is the result of the difference in hydrophilicity between the macromolecular backbone and the peripheral moieties, the functional groups are not necessarily directed toward the interior of the globular macromolecules (cartoon **A**, Figure 1).

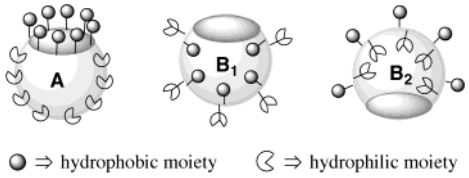



**Figure 1.** Schematic representation of amphiphilic dendrimers. **A**: amphiphilic dendrimers with peripheral functionalities (previously reported in the literature). $\mathbf{B}_1$: the facially amphiphilic dendrimers in a polar media. $\mathbf{B}_2$: the facially amphiphilic dendrimers in a nonpolar media.

Herein, we present a novel design that potentially directs functional groups selectively into the concave interior of the dendrimer. In this design, the dendrimers are uniformly amphiphilic over the entire globular surface, i.e., when the convex face of the dendrimer is hydrophilic, the concave face will be hydrophobic and vice versa. A two-dimensional schematic representation is shown by the structures **B** in Figure 1. The nature of the functional group directed toward the concave interior of the dendrimer will be driven by solvophobic interactions. In this design, the inherent flexibility of the dendritic backbone can be expected to yield two solvent-dependent conformations ($\mathbf{B}_1$ and $\mathbf{B}_2$). In polar media, the hydrophilic moieties would be on the convex face due to favorable surface contacts with the solvent. Because of the facial amphiphilicity of the dendrimer, the hydrophobic moieties would be directed toward the concave face (conformation $\mathbf{B}_1$). Similarly, conformation $\mathbf{B}_2$ should result in a nonpolar media. Such macromolecular architectures are reminiscent of the class of small molecules that have been named facial amphiphiles.[5]

Our design involves a monomer unit that has the $AB_2$ functional groups for the dendrimer growth and the amphiphilic functional groups in orthogonal planes (see Figure 2). Also, the hydrophobic and hydrophilic components are

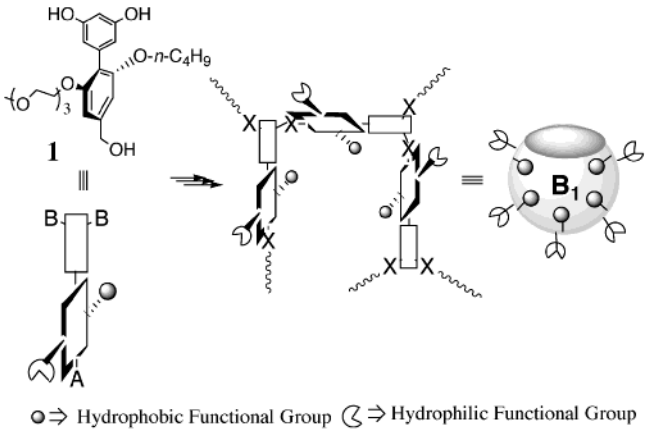



**Figure 2.** Representation of the monomer unit with $AB_2$ units and amphiphilic units in orthogonal planes.

placed on opposite sides of the plane containing the $AB_2$ moieties. Such relative placement of the functional groups dictates that the amphiphilic moieties are in a plane perpendicular to that of the macromolecular backbone upon assembly of the dendrimer. The geometric arrangement of the dendrimer also dictates that the hydrophobic and the hydrophilic functionalities are in opposite faces of the globular dendrimer, and thus structures **B** should result. A monomer unit that satisfies these structural requirements is represented by the biphenyl molecule **1** in Figure 2, in which the hydrophilic unit is a triethylene glycol monomethyl ether (TEG) moiety and the hydrophobic unit is an *n*-butyl group. The $AB_2$ functionalities are the two phenolic and one hydroxymethyl groups in **1**. The key feature in the relative placement of these functionalities is the *para* connectivity between the biphenyl linkage and the hydroxymethyl substituent. Because of this structural motif, the relative geometry of the two phenolic groups and the hydroxymethyl moiety in **1** is similar to that of 3,5-dihydroxybenzyl alcohol (the classical Fréchet-type monomer[6]), and this geometry is independent of the extent of the atropisomeric twist between the aryl groups. Therefore, the globular features observed with Fréchet's benzyl ether dendrimers are also anticipated in the current design. It also should be noted that the twist between the two aryl rings would dictate the *n*-butyl and the TEG moieties to be in a plane perpendicular to the dihydroxybenzyl alcohol plane (Figure 2).[7] Since these functionalities are at the *ortho* positions to the biphenyl linkage, they are situated at the opposite faces of the dihydroxybenzyl alcohol plane. These features will render the dendrimers facially amphiphilic.

The key step in the synthesis of the target monomer **1** is making the biaryl bond. Since it has been shown that Suzuki coupling affords reasonably good yields in the syntheses of hindered biaryls,[8] this was the reaction of choice for the synthesis of **1**. Thus, the biaryl compound **1** was synthesized

*Angew. Chem., Int. Ed.* **2000**, *39*, 1285. (f) Watkins, D. M.; Sayed-Sweet, Y.; Klimash, J. W.; Turro, N. J.; Tomalia, D. A. *Langmuir* **1997**, *13*, 3136. (g) Cooper, A. I.; Londono, J. D.; Wignall, G.; McClain, J. B.; Samulski, E. T.; Lin, J. S.; Dobrynin, A.; Rubinstein, M.; Burke, A. L. C.; Fréchet, J. M. J.; DeSimone, J. M. *Nature* **1997**, *389*, 368. (h) Pan, Y.; Ford, W. T. *Macromolecules* **2000**, *33*, 3731. (i) Chen, W.; Tomalia, D. A.; Thomas, J. L. *Macromolecules* **2000**, *33*, 9169. (j) Crooks, R. M.; Zhao, M.; Sun, L.; Chechik, V.; Yeung, L. K. *Acc. Chem. Res.* **2001**, *34*, 181.

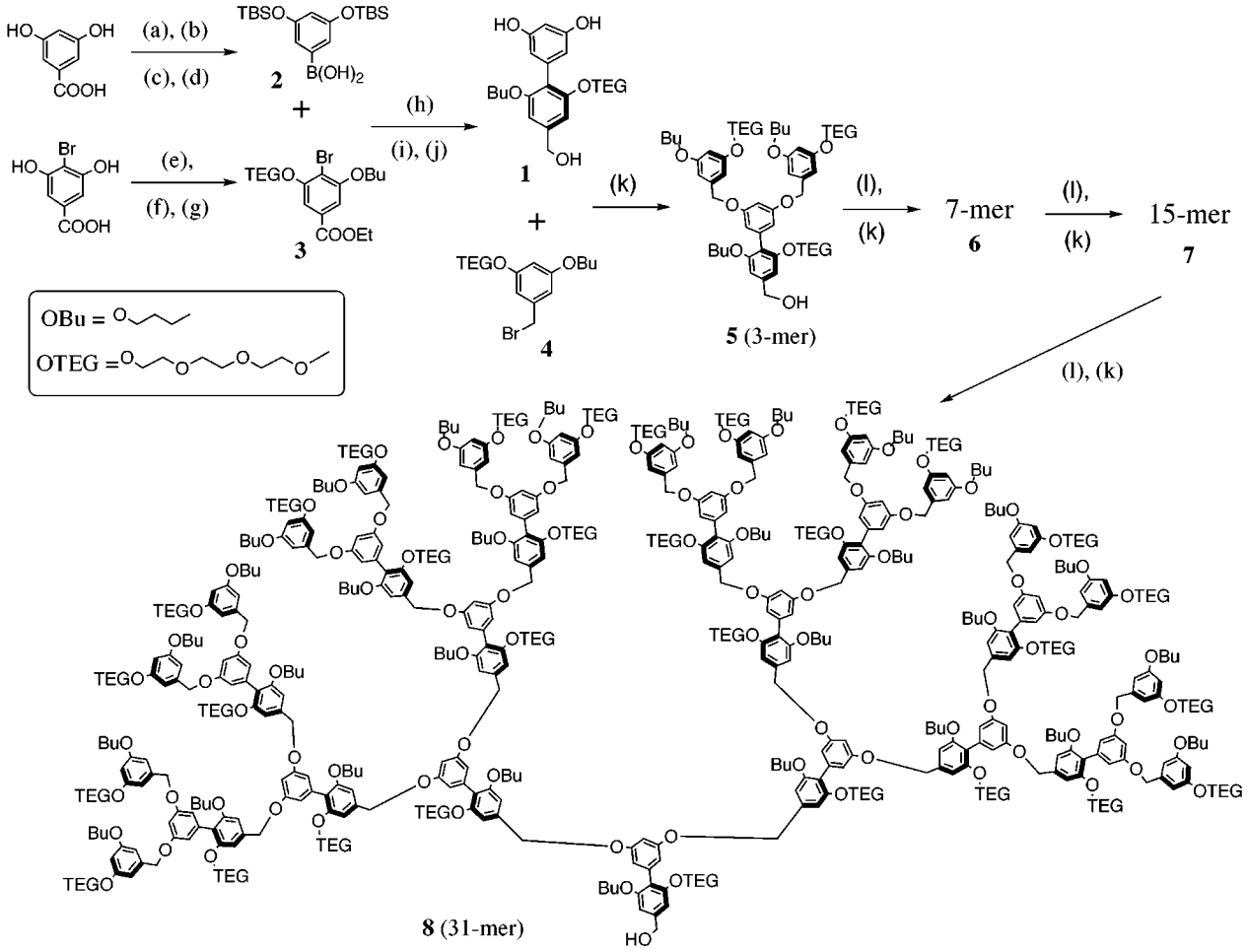
(5) (a) Cheng, Y.; Ho, D. M.; Gottlieb, C. R.; Kahne, D. *J. Am. Chem. Soc.* **1992**, *114*, 7319. (b) Venkatesan, P.; Cheng, Y.; Kahne, D. *J. Am. Chem. Soc.* **1994**, *116*, 6955. (c) McQuade, D. T.; Barrett, D. G.; Desper, J. M.; Hayashi, R. K.; Gellman, S. H. *J. Am. Chem. Soc.* **1995**, *117*, 4862. (d) Janout, V.; Lanier, M.; Regen, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 640.

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

(7) We note that the biphenyl linkage in **1** does not necessarily result in a 90° twist. With a crude modeling study using Chem-3D, we noticed a twist of about 60° for the monomer **1**. This twist is sufficient for our goal of placing functionality toward dendritic interiors.

(8) (a) Hoye, T. R.; Chen, M. *J. Org. Chem.* **1996**, *61*, 7940. (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

**Scheme 1.** Synthesis of the Monodendrons[a]




[a] (a) TBS-Cl, imidazole, DMF, 81%; (b) $SOCl_2$, catalytic $Me_3N{\cdot}HCl$; (c) catalytic AIBN, 2-mercaptopyridine-*N*-oxide sodium salt, $CBrCl_3$, 62%; (d) (i) *t*-BuLi, (ii) $B(OMe)_3$, (iii) aqueous $NH_4Cl$; (e) catalytic $H_2SO_4$, EtOH, 95%; (f) $K_2CO_3$, 18-crown-6, acetone, Bu−I (0.8 equiv), 46%; (g) $K_2CO_3$, 18-crown-6, acetone, TEG-OTs, 92%; (h) catalytic $Pd(PPh_3)_4$, $K_3PO_4$, DME, reflux, 45%; (i) $LiBH_4$, THF, 88%; (j) TBAF, THF, 91%; (k) $K_2CO_3$ **1**, 18-crown-6, THF; (l) $Ph_3P$, $CBr_4$ (**5** 72% from **4**; **6** 61% from **5**; **7** 21% from **6**; **8** 39% from **7**).

using palladium-catalyzed coupling of aryl boronic acid **2** with bromoarene **3** in DME in the presence of potassium phosphate to afford the corresponding biphenyl compound in 45% yield.[9] This product's ester moiety was reduced, and the TBS groups were deprotected to afford product **1** (Scheme 1).

Compounds **2** and **3** were synthesized from 3,5-dihydroxybenzoic acid and 4-bromo-3,5-dihydroxybenzoic acid, respectively, as shown in Scheme 1. The hydroxy groups of 3,5-dihydroxybenzoic acid were protected with TBS groups. The resulting ester was treated with 1 equiv of thionyl chloride in the presence of a catalytic amount of $Me_3N{\cdot}HCl$ to afford the corresponding acid chloride, which was then converted to a bromide moiety using a literature procedure.[10] Product **3** was synthesized from 4-bromo-3,5-dihydroxybenzoic acid by converting the acid to an ester, followed by sequential alkylations of the phenolic groups.

Note that any biphenyl twist in the peripheral monomer units will not serve the purpose of directing functionality. The orientation of the peripheral moieties has to arise solely from solvophobic interactions. Therefore, compound **4** with the hydrophobic *n*-butyl group and a hydrophilic TEG group was synthesized as the peripheral monomer.[11] Treatment of **4** with **1** in the presence of potassium carbonate and 18-crown-6 afforded the 3-mer monodendron **5** in 72% yield. The hydroxymethyl group at the focal point of **5** was converted to a bromomethyl moiety using triphenylphosphine and carbon tetrabromide. These two steps were repeated to obtain the monodendrons **6**−**8** as shown in Scheme 1.[6,11]

The assembled dendritic structures were characterized by NMR and matrix-assisted laser-desorption time-of-flight (MALDI-ToF) mass spectrometry. The NMR spectra of all the dendritic structures were consistent with the structures

(9) Suzuki coupling was attempted with various bases and solvents to optimize the yield. For a study that shows that the nature of the base significantly affects the yields, see: Griffiths, C.; Leadbeater, N. E. *Tetrahedron Lett.* **2000**, *41*, 2487−2490.

(10) Dol, G. C.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Eur. J. Org. Chem.* **1998**, 359−364.

(11) See Supporting Information for the experimental details.

shown. The $^1$H NMR shift of the methylene group of the hydroxymethyl focal point was a useful tool in the characterizations. The chemical shift of this group was consistently around 4.6 ppm, whereas the other methylene groups of benzyl ethers appeared around 5.0 ppm. The relative integration between these two areas was a useful diagnostic tool for characterizing the generation of the dendrons. Also, the chemical shift of the methylene group at the focal point changed to 4.4 ppm upon conversion of the hydroxymethyl group to the bromomethyl moiety. The possibility of alkylating just one of the two phenolic groups in **1** creates difficulties in unambiguously assigning the structures of these dendrons by NMR, because the differences in relative integration of the $^1$H NMR peaks between this possibility and the expected monodendrons are small. However, MALDI-ToF mass spectra confirmed the structures of **6**−**8**, with no peaks for the corresponding monosubstituted dendrons [**6** $m/z$ = 2635.8 ($M + Na^+$ calcd for $C_{144}H_{210}O_{42}$ 2636.2); **7** $m/z$ = 5662.4 ($M + Na^+$ calcd for $C_{312}H_{450}O_{90}$ 5662.9); **8** $m/z$ = 11 695.0 ($M^+$ calcd for $C_{648}H_{930}O_{186}$ 11696.2)]. The purity of these dendrons was also analyzed using gel permeation chromatography, and we found single peak for each of the monodendrons.

In summary, we have designed and synthesized amphiphilic dendrons in which each repeating unit has hydrophobic and hydrophilic functionalities. By exploiting the atropisomeric structural motif presented by biphenyls, these amphiphilic groups are putatively placed at the opposing sides of the plane of the dendritic growth. Thus, these custom-designed dendrons should have either the hydrophobic or the hydrophilic functional groups selectively directed toward the concave interiors of the dendrimer, depending on the polarity of the solvent. While this relative placement of functionalities is reasonable from a solvophobic standpoint and from the fact that nature provides examples in the form of amphiphilic globular proteins,[12] the supramolecular placement of these moieties needs to be confirmed. Experiments to investigate these structural details are currently underway in our laboratories.

**Acknowledgment.** This paper is dedicated to Professor Seth R. Marder on the occasion of his 40th birthday. We are grateful to Tulane University for support of this work. We thank Ms. Jessica Simons for assistance with the synthesis of some of the earlier substrates.

**Supporting Information Available:** Synthetic procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL016064B

(12) For an example, see: Xu, Z.; Bernlohr, D. A.; Banaszak, L. J. *J. Biol. Chem.* **1993**, *268*, 7874−7884.