# Synthesis of Unsymmetrically Branched Dendrimeric Wedges up to the Fourth Generation Based on 2,3-Dihydroxybenzyl Alcohol

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Dendrimers, in contrast to linear polymers, maintain a highly branched primary structure that creates a spherical morphology with internal cavities and a densely packed surface at higher generations.[1] These structural characteristics are expected to be useful in designing highly ordered materials for applications in molecular recognition and catalysis.[2] Symmetrically branched subunits are commonly employed to facilitate generational growth by minimizing steric interactions that develop as the dendrimer grows in size. This approach permits synthetic access to high molecular weight materials; however many of these systems appear to maintain a relatively flexible structure so that conformational rigidity can be observed only at high molecular weights. Moreover, several theoretical[3] and experimental[4] studies suggest that significant inward folding of the chain termini occurs in these systems, resulting in a density maximum near the core rather than at the periphery. As a consequence of this conformational mobility, Meijer observed that an enantiomerically pure dendrimer constructed using three constitutionally different wedges attached to a central carbon atom exhibited no optical activity.[5] However, attachment of "backfolding" wedges to restrict flexibility in the branch segments permitted the expression of a small temperature-dependent optical rotation.[6] The presence of stable chiral conformations in dendrimers constructed with enantiomerically pure subunits appears to be uncommon in many of the relatively flexible systems that have been studied.[7−9] Therefore, to restrict mobility and create the potential in a dendritic wedge to coil helically toward the focal point, we modified the symmetrical 3,5-disubstitution pattern of a Fréchet-type wedge to an unsymmetrical 2,3-branched pattern.[10] We describe herein the synthesis of unsymmetrically branched dendrons based on 2,3-dihydroxybenzyl alcohol.

The synthesis progressed in a convergent fashion starting with 2,3-dihydroxybenzaldehyde, **1**, as the branching subunit (Scheme 1). Generational growth was accomplished by O-alkylation of the phenolic hydroxyl groups, and focal point activation was achieved by a reduction/bromination sequence on the focal aldehyde. Because our intention was to develop a method to construct amphiphilic dendrimers with the 2,3-branching pattern, potentially hydrophilic methyl esters were introduced in the first step; these groups ultimately become the termini of the dendrimer. Accordingly, treatment of **1** with methyl-4-bromomethylbenzoate in the presence of potassium carbonate and 18-C-6 in THF−DMF (4:1) at 70 °C afforded the first-generation dendron $(CH_3O_2C)_2$-[G-1]-CHO, **2a**. We found that alkylation occurred most effectively by removing the solvent at ca. 60 mmHg during the course of the reaction. In this manner, the reaction proceeded to completion in 30−60 min, affording pure **2a** in 99% yield without the need for chromatographic purification. Consequently, this protocol was employed to increase the rate of the alkylation step for each ensuing generation. Subsequent reduction of the aldehyde with $NaBH_4$ in refluxing methanol generated the corresponding alcohol $(CH_3O_2C)_2$-[G-1]-OH, **2b**. Conversion to the bromide, **2c**, was accomplished by exposure of the alcohol to $PBr_3$ in $CH_2Cl_2$ at 0 °C. Reaction of 2 equiv of **2c** with **1** as above gave the second-generation aldehyde $(CH_3O_2C)_4$-[G-2]-CHO, **3a**. Although the first-generation materials (**2a**−**c**) were quite soluble in $CH_2Cl_2$, THF, and methanol, beginning with the second generation, the dendrons exhibited poor solubility in methanol and were only sparingly soluble in THF.[11] Therefore, reduction of **3a** with $NaBH_4$ in THF at reflux provided unreliable yields. Performing the reduction in $CH_2Cl_2$ using $BH_3$−THF circumvented the problems associated with solubility and reproducibly provided alcohol **3b** in $\geq$85% yield. Surprisingly, bromination of second-generation alcohol **3b** with $PBr_3$ generated significant amounts of the first-generation bromide **2c** as a side product as a result of selective cleavage of the more electron-rich inner shell benzyl linkages. Fortuitously, recourse to a $CBr_4/PPh_3$ bromination method furnished bromide **3c** without significant cleavage of the benzylic linkages. Subsequent condensation of **3c** with **1** gave third-generation aldehyde $(CH_3O_2C)_8$-[G-3]-CHO **4a** in $\geq$99% yield. Reduction of **4a** to alcohol $(CH_3O_2C)_8$-[G-3]-OH **4b** was similarly accomplished using $BH_3$−$S(CH_3)_2$ in $CH_2Cl_2$. Focal activation of **4b** with $CBr_4/PPh_3$ and alkylation with **1** provided the fourth-generation dendron $(CH_3O_2C)_{16}$-[G-4]-CHO, **5**, in 98% yield.[12]

The synthesis of these desymmetrized analogues of the 3,5-branched Fréchet-type dendrons affords a capability to explore the effect of monomer structure on the global morphology of the dendrimers. The lack of symmetry of these materials is apparent in the 500 MHz $^1$H NMR spectrum of third-generation aldehyde **4a**, in which both the benzylic methylene and methyl ester proton resonances appear as partially resolved singlets (Figure 1). Furthermore, inspection of the lowest energy conformer of **3b** suggests that the

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(10) For synthesis of 3,5-branched polyether dendrimers, see: (a) Fréchet, J. M. J.; Hawker, C. J.; Wooley, K. L. *J. Macromol. Sci., Pure Appl. Chem.* **1994**, *A31*(11), 1627. (b) Hawker, C. J.; Wooley, K. L.; Fréchet, J. M. J. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1287.

(11) This is in contrast to dendritic wedges based on 3,5-dihydroxybenzyl alcohol, which exhibit good solubility in THF from generation one to four. (see ref 10b).

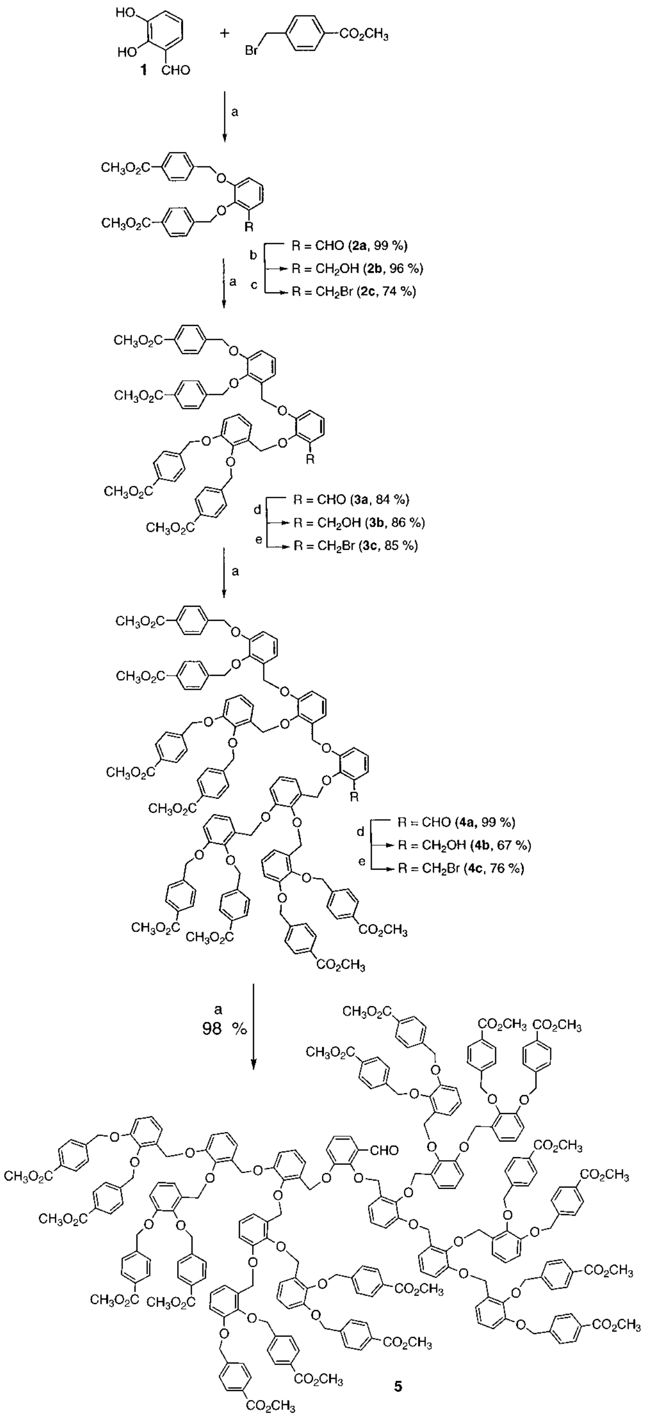
(12) Molecular weights for **3**−**5**, determined by MALDI-TOF, were consistent with the expected structures (see Supporting Information).

(13) The lowest energy conformation was generated by employing a Monte Carlo conformational search using the MM2* force field and the GB/SA model for $CHCl_3$ implemented on Macromodel 5.0. This afforded a single conformation within 1 kcal/mol of the global energy minimum.

(14) For a comparison of the hydrodynamic volumes of 3,5-branched polyaryl ether dendrons with their exact linear analogues, see: Hawker, C. J.; Malmström, E. E.; Frank, C. W.; Kampf, J. P. *J. Am. Chem. Soc.* **1997**, *119*, 9903.

10.1021/jo990438l CCC: $18.00

**Scheme 1. Synthesis of Dendrons**[a]



[a] **Key.** (a) **1**, $K_2CO_3$, 18-C-6, DMF-THF, 70°C. (b) $NaBH_4$ , MeOH (c) $PBr_3$ , $CH_2Cl_2$. (d) $BH_3$, $CH_2Cl_2$. (e) $CBr_4/PPh_3$, THF.

unsymmetrical branching pattern of these wedges may force the terminal groups to coil around the focal point of the wedge (Figure 2).[13] This coiling effect would be expected to create a more compact globular morphology than would be present in the corresponding 3,5-branched isomers. Accordingly, the molecular weights of dendrons **2**−**5**, determined by GPC, were lower than those determined for the analogous 3,5-branched dendrons at all four generations (Table 1).[14] However, the disparity between the polystyrene-equivalent molecular weights of the 2,3- and 3,5-branched systems at a particular generation remained constant up to the fourth generation. Because the dendrons are isomeric with the Fréchet-type dendrons, the differences in GPC retention volumes at each generation are due to the more compact structures of **2**−**5**.

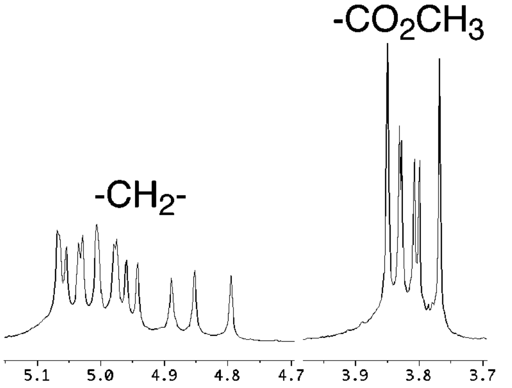


**Figure 1.** Selected regions of the 500 MHz $^1H$ NMR spectrum of **4a** in $CDCl_3$.

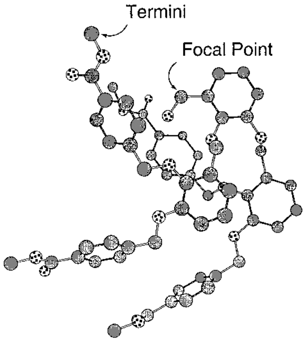


**Figure 2.** Lowest energy conformer of $(CH_3O_2C)_4$-[G-2]-OH, **3b**.

**Table 1. GPC Data of 2,3- and 3,5-Branched Dendrons**[a]

| | $MW_c$[b] | $MW_p$[c] | $M_w$ | $M_n$ |
|---|---|---|---|---|
| 3,5-branched | | | | |
| $(CO_2CH_3)_2$-[G1]-OH | 436 | 467 | 432 | 415 |
| $(CO_2CH_3)_4$-[G2]-OH | 977 | 1274 | 1255 | 1247 |
| $(CO_2CH_3)_8$-[G3]-OH | 2058 | 1997 | 2092 | 1960 |
| $(CO_2CH_3)_{16}$-[G4]-OH | 4220 | 4221 | 4017 | 3934 |
| 2,3-branched | | | | |
| $(CO_2CH_3)_2$-[G1]-OH | 436 | 342 | 284 | 261 |
| $(CO_2CH_3)_4$-[G2]-OH | 977 | 836 | 768 | 747 |
| $(CO_2CH_3)_8$-[G3]-OH | 2058 | 1608 | 1586 | 1526 |
| $(CO_2CH_3)_{16}$-[G4]-CHO | 4218 | 3574 | 3634 | 3547 |

[a] Polystyrene-equivalent molecular weights. [b] Calculated MW. [c] Molecular weight at peak of GPC trace.

In conclusion, we have described a convenient synthesis of unsymmetrically branched wedges with potentially hydrophilic termini for application to dendrimer synthesis. Each generational growth step proceeds with high efficiency up to the fourth generation, and the synthesis should be amenable to large-scale preparation of these materials. The construction of amphiphilic dendrimers from these wedges is currently in progress.

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**Supporting Information Available:** Full experimental procedures and analytical data for dendrons **2**−**5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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