Asymmetric Dihydroxylation Enables Rapid Construction of Chiral Dendrimers Based on 1,2-Diols**

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Research in dendrimers is a rapidly expanding area at the interface between conventional organic chemistry and polymer science. These macromolecules consist of a polyfunctional central core covalently linked to layers of repeating units bearing functionalized branches, leading to structures with a discrete number of generations and functional end groups. The quest in dendrimer research has been to find reliable strategies for their efficient construction, especially regarding control of homogeneity, branching patterns, interior cavity size, topological features, and surface chemistry.

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and surface functionality. More recently, following success in the aforementioned areas, the emphasis has shifted toward the elaboration of components with specific functions in both the peripheral and interior domains of the dendrimer.[21] Nevertheless, relatively few studies have focused on chiral dendrimers. Most of those cases involve the use and derivatization of chiral pool materials such as nucleotides, amino acids, and tartaric acid as building blocks or as terminal groups for the construction of biopolymers[23] and abiotic cascade molecules.[5] The Seebach group has done the pioneering work in the synthesis of chiral starburst dendrimers.[6]

Interest in applications of the asymmetric dihydroxylation process attracted us to this field. The primary goal was to introduce chiral cavities into these materials, creating the potential for asymmetric catalysis, chiral recognition, and resolution. Since two stereogenic centers can be created in the asymmetric dihydroxylation (AD) of prochiral olefins,[7] we sought to utilize these readily available 1,2-diols as branch units for the construction of chiral dendrimers, in which the hydroxyl groups provide the covalent linkage points. Here we describe our initial results on the assembly of chiral polyether dendrimers by a "double exponential dendrimer growth" approach.[8]

On the basis of several considerations, three functionalized acetones 1a–c with various R substituents in the acetonide and the chloromethyl group in different positions on the aromatic ring were chosen as chiral monomer units. First, these chiral isopropylidene ketals can be readily prepared in enantiomerically pure form by the AD of appropriate 3- or 4-chloromethylphenyl alkenes. Second, the acetonide protecting group can be removed under mild acidic conditions and also greatly simplifies spectroscopic analysis. Third, the aromatic spacer reduces steric congestion, enabling propagation to higher generations, and also bears the functionality for anchoring to the central core. Of special importance in this latter role is the benzyl group facilitating the Williamson ether couplings.

To efficiently employ the alternative double exponential approach, judicious selection of a focal protective group compatible with both stages of propagation was essential. We chose the p-methoxyphenyl (PMP) ether group due to its stability under both basic (etherification) and acidic (hydrolysis) reaction conditions. The PMP ether functionality was installed at the focal site of 1a–c by reaction with 4-hydroxyanisole in the presence of K2CO3 and a catalytic amount of Bu4NI under reflux in 2-butanol;[9] quantitative yields were obtained in all cases. The masked diol functionality of the resulting PMP ether was released by exposure to 3 N hydrochloric acid in acetonitrile at ambient temperature.[11] The corresponding 1,2-diols 2a–c, each prepared in greater than 95% yield, were then subjected to double etherification with the individual benzylic chlorides 1a–c. Instead of the commonly employed Williamson etherification conditions (NaH/THF or DMF), we took advantage of a KOH/toluene-based benzylendihydroxylation technique for the propagation step. Virtually quantitative formation of the bis(acetonides) 3a–c can be accomplished by simply refluxing the requisite diol and benzyl chloride in toluene in the presence of KOH pellets with concomitant azeotropic removal of water.[11, 12]

The double exponential dendrimer growth process[13] pioneered by Moore and co-workers[9] comprises the repetitive use of a three-reaction sequence for a doubly protected subunit: 1) selective deprotection of the peripheral groups (acetones), 2) selective unmasking and functionalization of the focal group (PMP), and 3) coupling of these two components. Hydrolysis of the common intermediates 3a–c under conditions similar to those described previously provided tetrads 4a–c in yields ranging from 70% (R = cyclohexyl) to 97% (R = H, Ph). The PMP group in 3b (R = Ph) was cleaved oxidatively by cerium ammonium nitrate (CAN) in CH3CN/H2O at 0 °C providing the corresponding benzyl alcohol in 93% yield.[14] However, for ether 4a removal of the PMP group (95% yield) must be carried out at −10 °C to prevent concomitant hydrolysis of the peripheral acetonides, which are more sensitive in this less substituted series. To overcome the problem associated with the low solubility of 3c (R = cyclohexyl) in the solvent system employed, propionitrile was ultimately found to be the best substi-
stitute for CH₃CN (yield increased from 78 to 92%). Conversion of the resulting benzylic alcohols to the bromides 5a–c (88–93%) proceeded smoothly upon treatment with PPh₃ and N-bromosuccinimide in CH₂Cl₂ at 0 °C. In the final stage, the second-generation tetraols 4a–c were propagated to the fourth-generation monodendrons 6a–c by the KOH/toluene-mediated coupling with the respective benzylic bromides 5a–c. These exhaustive, fourfold etherifications provided 6a–c, which have eight end groups, in good yields ranging from 88 to 93%. Electrospray and/or FAB mass spectral analyses of these monodendrons exhibited no signs of products with defects that would arise from incomplete branches, thus demonstrating the overall efficiency of this approach.

After the final coupling the PMP group was removed by our modified oxidative cleavage conditions without overoxidation of the resulting alcohol. The fourth-generation benzylic alcohols 7a–c were thus obtained in yields of 84 to 89%. A variety of chiral dendrimers can be constructed by anchoring these chiral dendritic components onto a polyfunctional molecular core. As a model for the synthesis of C₄-symmetric dendrimers, 1,3,5-benzenetricarbonyl trichloride was coupled directly with benzylic alcohols 7a (R = H) and 7b (R = Ph) in the presence of 4-dimethylaminopyridine in benzene (Scheme 2). The fourth-
generation dendrimer 8a with 45 monomer units, 45 stereocenters, and a molecular weight of 7929 Da was synthesized with a 75% yield (101 mg) at ambient temperature. In contrast, for couplings with 7b, which has more steric congestion, heating reflux was required. The corresponding fourth-generation dendrimer 8b possessing 45 monomer units, 90 stereogenic centers, and a molecular weight of 11354 Da was obtained in 67% yield (130 mg). Important features allowing us to confirm unambiguously the structural integrity and identity of this type of dendrimer are the characteristic ¹H NMR shifts of the aromatic protons in the core unit and the benzylic protons at the focal point. For example, in 8b these signals appear as singlets at δ = 8.9 and 5.3, respectively, in a ratio of 1:1 (Fig. 1a). Further confirmation of structure and purity was obtained by size exclusion chromatography (Fig. 1b) and MALDI-TOF mass spectrometry (Fig. 1c).

We have developed an efficient approach to chiral poly-
dendrimers. The examples described here are C₄-symmetric dendrimers consisting of 45 chiral monomers and bearing 290 tetronic groups in the periphery. Nature uses a-amino acids in fundamental repeat units for protein synthesis; this asymmetric dihydroxylation methodology for dendrimers may offer an abiotic counterpart, holding promise for the construction of chiral macromolecules of either amphi-
and with a vast array of spacer functionality, directionality (branching pattern), and surface chemistry by simple permutations of the 1,2-diol monomer units. Current research we are exploring properties of this class of dendrimeric chiral recognition and for the preparation of C₄-symmetric dendritic porphyrins as potential ligands for transition metal catalyzed asymmetric transformations.

**Experimental Procedure**

6a: A single-necked flask fitted with a Dean–Stark apparatus and a magnetic stir bar was charged with a nitrogen atmosphere with tetraol 4a (7b, 1.3 mmol), benzyl bromide 5a (3.8 g, 6.25 mmol), and 60 mL of toluene. The reaction mixture was heated to reflux for 0.5 h, followed by addition of KOH (these contain 15 wtr. % H₂O, ca. 4 g, 6.5 mmol). The reaction was monitored by thin-layer chromatography until intermediates were no longer observed; if the reaction seemed too slow in reaction completion, more KOH was added, and the reaction mixture was refluxed an additional 2 h (approximately 2 h total). After solvent removal in vacuo, the residue was dissolved in 25 mL of CH₂Cl₂, filtered through Celite, and purified by flash chromatography (310 g, 88% yield; Rf = 0.13, 2/3 EtOAc/hexane).

8b: A two-necked flask fitted with a Dean–Stark (filled with molecular sieves) and a condenser charged with 7b (211 mg, 0.057 mmol), DMSO (19 mg, 0.15 mmol), and 20 mL of benzene. The stirring solution was stirred and refluxed for 2 h, cooled to room temperature, and filtered through Celite. The reaction mixture was filtered through Celite and purified by flash chromatography (80 mg of 8b (67% yield; Rf = 0.63, 2/3 EtOAc/hexane). (An additional 33 mg (25%) of a product Rf = 0.13, 2/3 EtOAc/hexane) resulted from incomplete esterification, the diester carbonate, was recovered—presumably a consequence of reaction with trace amounts of water.)

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COMMUNICATIONS


8) A similar achiral approach has been reported recently and was named “double exponential dendrimer growth”, by the authors: T. Kawaguichi, K. L. Walker, C. L. Wilkins, J. Am. Chem. Soc. 1995, 117, 2159.


11) This unusual process harkens back to the old days of sugar chemistry in Germany [12]. However, its use here requires comment since the best modern conditions for either formation (NaH, DMF, cat. R-Ni) fail in these systems due to formation of insoluble alkoxides. Furthermore, for the perbenzylolation of smaller, less oxygenated polysilanes (e.g. pentaerythritol and methyl glycoptene) the present Zemplén conditions [12a] are much poorer (i.e. deliver a lot of the expected ArCl(CH$_2$)$_3$Cl by-product) than the NaH/DMF conditions (H.-T. Chang, K. B. Sharpless, unpublished results). We believe that the large polystyrene polymers in this study cover the surface of the solid KOH and serve as solid/liquid phase-transfer catalysts, such that the ArCH$_2$X$_3$ species is denoted access to hydroxide ion. Whatever the explanation, the Zemplén etherification procedure is uniquely effective for construction of these polystyrene dendrimers.


15) Bromination of the benzylil alcohol 6a-c was less satisfactory using the Fréchet protocol (Pd$_4$H$_8$(Cl)$_{11}$) for dendritic polyaryl synthesis owing to competitive depletion of the acetone functionality [15e]. c) J. C. Hawker, J. M. J. Fréchet, J. Am. Chem. Soc. 1990, 112, 7638; b) K. C. Nicolau, C. A. Veale, S. E. Webber, H. Katerinopoulos, ibid. 1985, 107, 7515; c) H. Hayashi, K. Nakanishi, C. Brandon, J. Marmur, ibid. 1973, 92, 8749.

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[16] Oxidation of benzyl alcohols to aldehydes by CAN has been reported; W.S. Trahanovsky, L. Young, J. Chem. Soc. 1965, 5777.

[17] Since this type of dendrimer has unsymmetrical branch cells leading to surfaces with higher fractal dimensions [1a, 3a, 17a–c], it could possibly provide a chiral environment. a) B. B. Mandelbrot, Fractals: Form, Chance and Dimensions, Freeman, New York, 1977; The Fractal Geometry of Nature, Freeman, New York, 1982; b) H. H. Kaye: A Random Walk Through Fractal Dimensions, VCH, Weinheim, New York, 1989; c) A. B. Blumen, H. Sörrer, Angew. Chem. 1990, 102, 158; Angew. Chem. Int. Ed. Engl. 1990, 29, 113. One preliminary investigation of these dendrimers’ properties examined the relationship of the optical rotation with generation numbers on the styrene-based dendrons and of dendrimer 8. We found that the molar optical rotation is approximately proportional to the number of repeat units. Hence, the molar optical rotation of the PMP-acetamide-protected dendrons per repeat unit is as follows: 1st generation, $\beta143^\circ$ (molar rotation, $\alpha143^\circ$); 1 unit; $\alpha145.6^\circ$ (c = 3.0 in CHCl$_3$); 2nd generation, $\alpha165^\circ$ (molar rotation, $\alpha495^\circ$); 3 units; $\alpha75.6^\circ$ (c = 1.0 in CHCl$_3$); 3rd generation, $\alpha156^\circ$ (molar rotation, $\alpha1095^\circ$); 7 units; $\alpha82.0^\circ$ (c = 13.6 in CHCl$_3$); 4th generation, $\alpha189^\circ$ (molar rotation, $\alpha2836^\circ$); 15 units; $\alpha105.2^\circ$ (c = 4.25 in CHCl$_3$) and dendrimer 8, $\alpha163^\circ$ (molar rotation, $\alpha7345^\circ$); 45 units; $\alpha92.7^\circ$ (c = 0.8 in CHCl$_3$).