

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.^[1] 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 major quest in dendrimer research has been to find reliable strategies for their efficient construction, especially regarding control of homogeneity, branching patterns, interior cavity size, topology,

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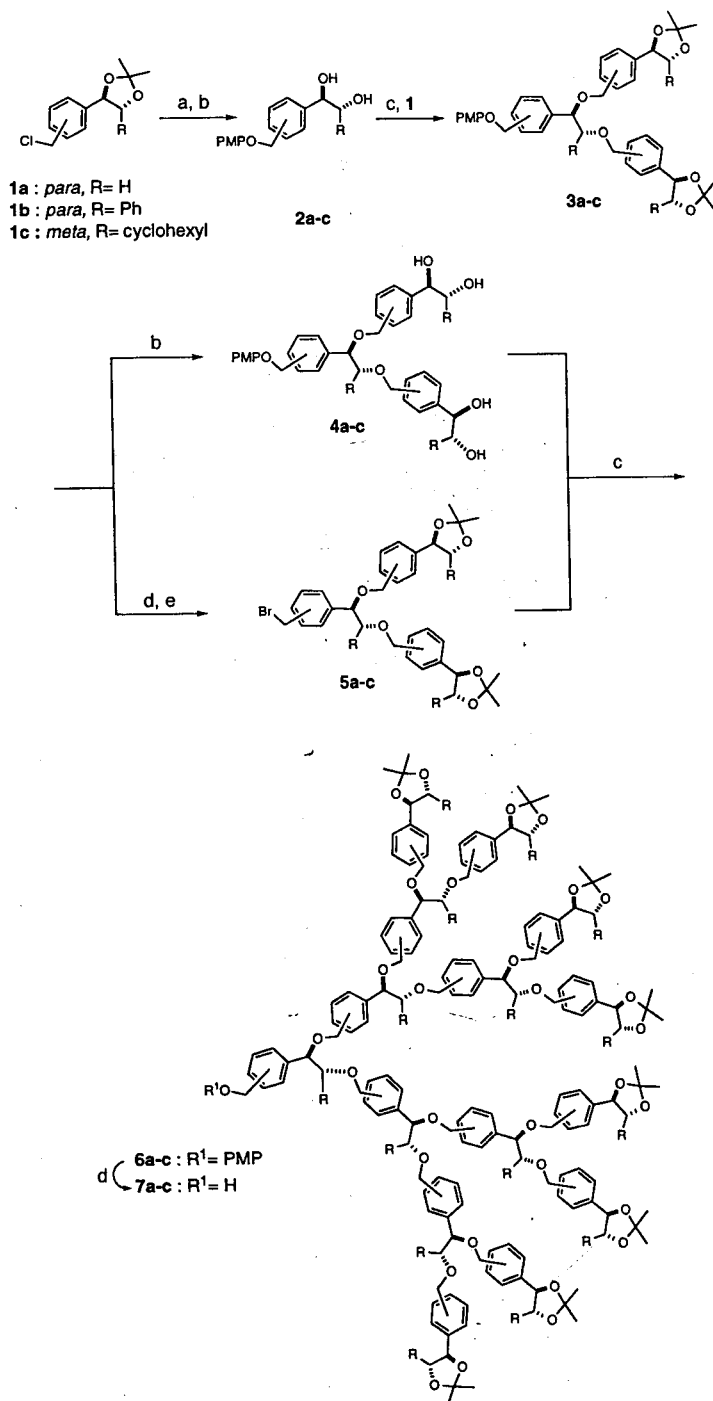
and surface functionality. More recently, following success in the aforementioned areas, the emphasis has shifted toward the elaboration of components with specific functions in both the peripheral and interior domains of the dendrimer.^[2] Nevertheless, relatively few studies have focused on chiral 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^[3] and abiotic cascade molecules.^[4, 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 acetonides **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 mildly 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 benzylic activation 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 K_2CO_3 and a catalytic amount of Bu_4NI under reflux in 2-butanone;^[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.^[10] 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 benzylation technique for the propagation step. Virtually quantitative formation of the bis(acetonides) **3a–c** can be accomplished by simply refluxing the requisite diol and benzylic 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^[8] comprises the repetitive use of a three-reaction sequence for a doubly protected subunit: 1) selective deprotection of the peripheral groups (acetonides), 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 tetraols **4a–c** in yields



Scheme 1. a) $CH_3OC_6H_4OH$, K_2CO_3 , Bu_4NI (5%), 2-butanone, reflux; b) 3 N HCl/CH_3CN (1/10 or 1/3 v/v), room temperature; c) KOH pellets (1.3–3 equiv), toluene, Dean–Stark; d) CAN (2.2–3 equiv), CH_3CN or C_2H_5CN/H_2O (2/1 v/v), $-10^\circ C$ or $0^\circ C$; e) PPh_3 (1.1 equiv), NBS (1.1–1.8 equiv), CH_2Cl_2 , $0^\circ C$.

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 CH_3CN/H_2O at $0^\circ C$ providing the corresponding benzylic alcohol in 93% yield.^[14] However, for ether **4a** removal of the PMP group (95% yield) must be carried out at $-10^\circ C$ 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-

tute for CH_3CN (yield increased from 78 to 92%). Conversion of the resulting benzylic alcohols to the bromides **5a–c** (88–93%) proceeded smoothly upon treatment with PPh_3 and *N*-bromosuccinimide in CH_2Cl_2 at 0°C .^[15] 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.^[16] 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 C_3 -symmetric dendrimers, 1,3,5-benzenetricarbonyl trichloride was coupled directly with benzylic alcohols **7a** ($\text{R} = \text{H}$) and **7b** ($\text{R} = \text{Ph}$) in the presence of 4-dimethylaminopyridine in benzene (Scheme 2). The fourth-

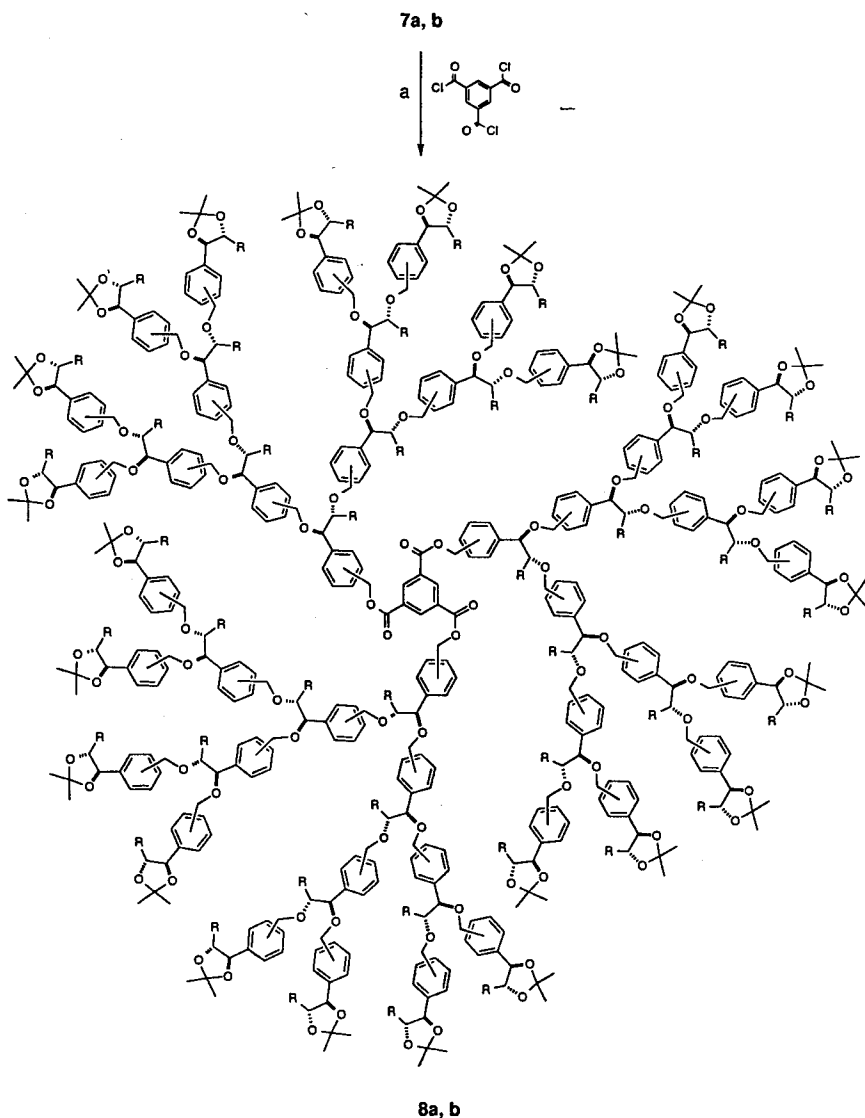
generation dendrimer **8a** with 45 monomer units, 45 stereogenic centers, and a molecular weight of 7929 Da was synthesized in 75% yield (101 mg) at ambient temperature. In contrast, for couplings with **7b**, which has more steric congestion, heating and reflux was required. The corresponding fourth-generation dendrimer **8b** possessing 45 monomer units, 90 stereogenic centers and a molecular weight of 11 354 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 hydrogens in the core unit and the benzylic hydrogens at focal point. For example, in **8b** these two signals appear as singlets at $\delta = 8.9$ 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 spectroscopy (Fig. 1c).

We have developed an efficient approach to chiral polyether dendrimers. The examples described here are C_3 -symmetric dendrimers consisting of 45 chiral monomers and bearing 24 hydroxyl groups in the periphery. Nature uses α -amino acids as 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 antipodal or helical chirality and with a vast array of spacer functions. The directionality (branching pattern) and surface chemistry by simple permutations of the 1,2-diol monomer units. In current research we are exploring the properties of this class of dendrimers for chiral recognition^[17] and for the preparation of C_3 -symmetric dendritic phosphonates 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 under nitrogen atmosphere with tetraol **4a** (74 mg, 1.3 mmol), benzyl bromide **5a** (3.8 g, 6.25 mmol), and 60 mL of toluene. This stirred solution was heated to reflux for 0.5 h, followed by addition of three pellets of KOH (these contain 15 wt.% H_2O , ca. 4.0 mmol, 6.5 mmol). The reaction was monitored by thin-layer chromatography until intermediates were no longer observed; if the reaction seemed too slow in reaching completion, more KOH was added, and the reaction mixture was refluxed an additional hour (approximately 12 h total). After solvent removal in vacuo, the residue was dissolved in 25 mL of CH_2Cl_2 , filtered through Celite, and purified by flash chromatography (3.10 g, 88% yield; $R_f = 0.13$, 2/3 EtOAc/hexane).

8b: A two-necked flask fitted with a Dean-Stark apparatus (filled with molecular sieves) and a condenser was charged with **7b** (211 mg, 0.057 mmol), DMAP (19 mg, 0.15 mmol), and 20 mL of benzene. The resulting solution was stirred and refluxed for 2 h, then cooled to room temperature. 1,3,5-Benzenetricarbonyl trichloride (4.52 mg, 0.017 mmol) was added and the solution refluxed an additional 4 h. Following removal of the solvent in vacuo, flash chromatography (130 mg of **8b** (67% yield; $R_f = 0.63$, 2/3 EtOAc/hexane). (An additional 33 mg (25% yield) of a product ($R_f = 0.13$, 2/3 EtOAc/hexane) resulting from incomplete esterification, the diester carboxylic acid, was recovered—presumably a consequence of trace amounts of water.) ^1H NMR (400 MHz, CDCl_3): $\delta = 8.90$ (s, 3H, $\text{C}_6\text{H}_3(\text{CO}_2\text{CH}_2\text{Ar})_3$), 7.27–7.17 (m, 405H, $45 \times \text{C}_6\text{H}_4 + 45 \times \text{C}_6\text{H}_5$), 5.32 (s, 45H, $\text{C}_6\text{H}_3(\text{CO}_2\text{CH}_2\text{Ar})_3$), 4.70 (s, 48H, methine protons).



Scheme 2. a) DMAP (3 equiv), PhH, room temperature or reflux.

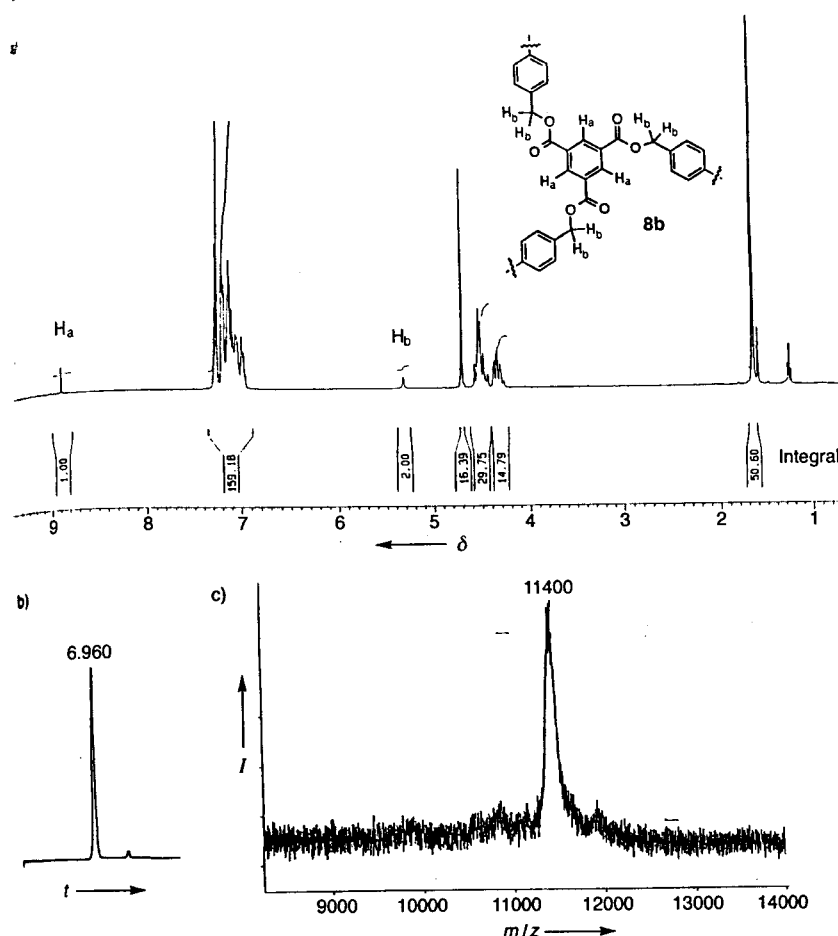


Fig. 1. Characterization of dendrimer **8b**. a) ^1H NMR spectrum (400 MHz, CDCl_3); b) size exclusion chromatogram (Waters Styragel HR 3, 7.8×300 mm, 1 mL min^{-1} , THF); c) MALDI-TOF mass spectrum, resolution $\pm 0.1\%$.

the peripheral shell), 4.57–4.27 (m, 126H, 42 methine protons of the inner layers + $42 \times \text{OCH}_2\text{Ar}$), 1.65 (s, 72H, $\text{C}(\text{CH}_3)_2$), 1.64 (s, 72H, $\text{C}(\text{CH}_3)_2$); ^{13}C NMR (100 MHz, CDCl_3): δ = 164.80 (CO), aromatic quaternary carbons: 138.61, 138.50, 138.44, 138.26, 137.87, 137.80, 137.70, 137.56, 137.49, 136.75, 135.71, 131.25 (core); aromatic methine carbons: 134.54 (core), 128.36, 128.18, 127.87, 127.78, 127.53, 126.98, 126.64, 126.59, 109.25 ($\text{C}(\text{CH}_3)_2$), 85.32, 85.25, 85.03, 84.98, 84.82, 84.65, 70.76, 70.60, 67.19 ($\text{CO}_2\text{CH}_2\text{Ar}$), 27.18 ($\text{C}(\text{CH}_3)_2$), 27.16 ($\text{C}(\text{CH}_3)_2$); IR (KBr): $\tilde{\nu}$ = 3062, 2983, 1729 (CO), 1454, 1371, 1236, 1167, 897, 700 cm^{-1} ; MS (MALDI-TOF) calcd for $\text{C}_{756}\text{H}_{732}\text{O}_{96} + \text{K}$: 11393; found: $11400 \pm 0.1\%$. Anal. calcd for $\text{C}_{756}\text{H}_{732}\text{O}_{96}$: C 79.97, H 6.5; found: C 79.79, H 6.65.

8a: A procedure analogous to that for the synthesis of **7a** was used except the reaction was performed at room temperature (140 mg of **7a** gave 101 mg of **8a**, 75% yield; R_f = 0.4 on aluminum oxide (IB-F), 1/1 EtOAc/hexane). ^1H NMR (400 MHz, CDCl_3): δ = 8.92 (s, 3H, $\text{C}_6\text{H}_5(\text{CO}_2\text{CH}_2\text{Ar})_3$), 7.46–7.25 (m, 180H, $45 \times \text{C}_6\text{H}_4$), 5.39 (s, 6H, $\text{C}_6\text{H}_5(\text{CO}_2\text{CH}_2\text{Ar})_3$), 5.06–5.02 (m, 24H, methine protons of the peripheral shell), 4.72–4.33 (m, 105H, 21 methine protons of the inner layers + $42 \times \text{OCH}_2\text{Ar}$ of all layers), 4.28–4.25 (m, 24H, one methylene proton of the peripheral shell), 3.80–3.51 (m, 42H, both protons from 21 methylene units of the inner layers), 3.68–3.64 (m, 24H, 24 one methylene proton of the peripheral shell), 1.53 (s, 72H, $\text{C}(\text{CH}_3)_2$), 1.47 (s, 72H, $\text{C}(\text{CH}_3)_2$); ^{13}C NMR (100 MHz, CDCl_3): δ = 164.82 (CO), aromatic quaternary carbons: 139.80, 138.59, 138.50, 138.30, 138.27, 138.21, 138.18, 131.23 (core); aromatic methine carbons: 135.10 (core), 128.73, 127.84, 127.82, 127.75, 127.69, 127.39, 127.10, 126.18, 109.66 ($\text{C}(\text{CH}_3)_2$), 80.87, 80.37, 77.66, 75.18, 74.83, 73.29, 73.20, 72.97, 71.62, 71.56, 70.76, 70.55, 70.30, 67.23 ($\text{CO}_2\text{CH}_2\text{Ar}$), 26.60 ($\text{C}(\text{CH}_3)_2$), 25.95 ($\text{C}(\text{CH}_3)_2$); IR (KBr): $\tilde{\nu}$ = 2985, 1729 (CO), 1371, 1221, 1064, 820, 732 cm^{-1} ; MS (MALDI-TOF) calcd for $\text{C}_{486}\text{H}_{552}\text{O}_{96} + \text{Na}$: 7953; found: 7949 $\pm 0.1\%$.

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