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An Approach to Highly Functionalized Dendrimers From Chiral, Non-Racemic Synthetic Monomers

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Abstract: An approach to dendrimers with highly functional interiors constructed from chiral, non-racemic hydrobenzoin monomer units is presented. An optically pure monomer unit is prepared using asymmetric dihydroxylation (AD) and a representative dendrimer is constructed by a convergent growth strategy.

Dendrimers[1] possess structural characteristics which make them attractive candidates for chemical sensor applications. These characteristics include a distinct exterior which can be modified to impart various solubility and blending properties to the material, as well as a distinct interior, which can be modified based on the linking architecture used in construction.[2] In many cases the interior and exterior of the dendrimer can be modified independently, potentially imparting a wide range of properties to the resultant material.[3,4] Despite this, relatively few reports have focused on the interior of a dendrimer as an active site.[5] The larger portion of the research in the dendrimer field has focused on the utilization of the exterior of the dendrimer for anchoring various active residues, while keeping the interior rather devoid of active functionality.[6,7]

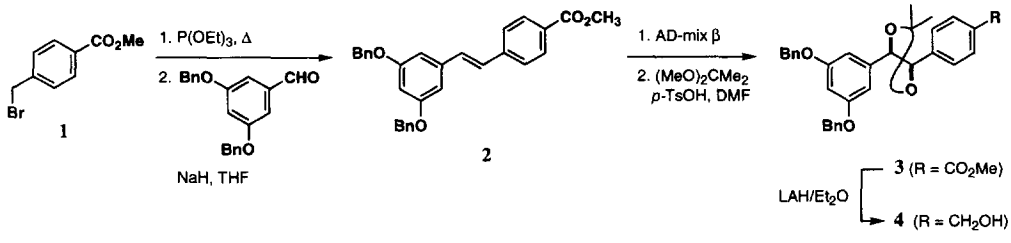
We are currently attempting to systematically vary the monomeric subunits of particular dendritic structural classes to obtain materials with interior cavities of different size, shape, and functionality. Through rational design, we intend to synthesize materials which will selectively recognize small molecules based on their shape and functionality and potentially orient subtrates for directed approach to catalytic sites within the interior of the dendrimer. For a dendrimer to have any selectivity with regards to shape and functionality, however, it must possess both structural sub-units with well-defined topology, as well as interior moieties capable of interacting strongly with guest molecules. The dendritic materials we have targeted consist of: (1) chiral, non-racemic sub-units in the interior for shape selectivity, and (2) active functionality, such as hydroxyl or amino groups, capable of engaging in hydrogen bonding with encapsulated guest molecules. Potential applications for these materials include stationary phases for chiral chromatographic separations, detectors for various small molecules in either a biological or abiotic setting, and selective absorbents.

Several workers have introduced chirality into dendritic structures. The earliest example was provided by Newkome, who modified an amine-terminated dendrimer with tryptophane residues.[8] Other efforts include the use of nucleic acids,[9] amino acids,[10-13] tartrates,[14] and chiral triols derived from the natural biopolymer poly[(R)-3-hydroxybutanoate][15] as either surface or structural units. In these dendrimers the source of chirality is naturally derived. Only the recent work of Sharpless, a series of polyether dendrimers

up to the 4th generation,[16] utilizes monomeric units from asymmetric synthesis. Despite these reports, only those structures reported by Mitchell[10] and Chapman[11] possess moieties (amide linkages) capable of providing strong enthalpic contributions to guest binding. In addition, few dendrimers have the available functionality to anchor well-defined transition-metal moieties for asymmetric catalysis.[5-7,17] In this preliminary communication, we report an approach to a family of dendrimers constructed from chiral, non-racemic hydrobenzoin monomers obtained from catalytic asymmetric synthesis.

Our approach to dendrimers with highly functionalized interior cavities constructed from enantiopure monomeric sub-units currently utilizes the powerful Sharpless Asymmetric Dihydroxylation (AD)[18] to introduce asymmetric functionality into our monomers. Stilbene derivative **2**, prepared by a Horner-Emmons modified Wittig reaction in >95% yield, is a prototypical precursor for a class of dendritic hydrobenzoin materials. Asymmetric dihydroxylation, acetonide protection, and LAH reduction of the benzoate ester yields hydrobenzoin derivative **4** in 56% overall yield from **2** (4 steps).[19] Benzyl alcohol **4** is primed for dendrimer construction by the convergent method developed by Hawker and Fréchet.[20]

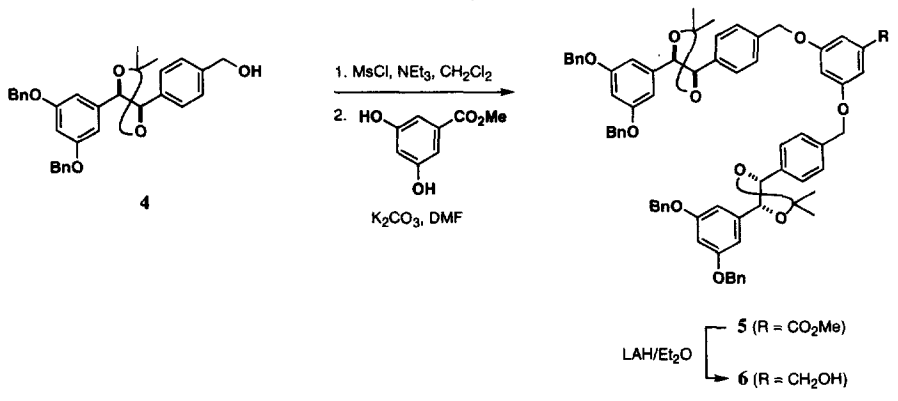
Scheme 1



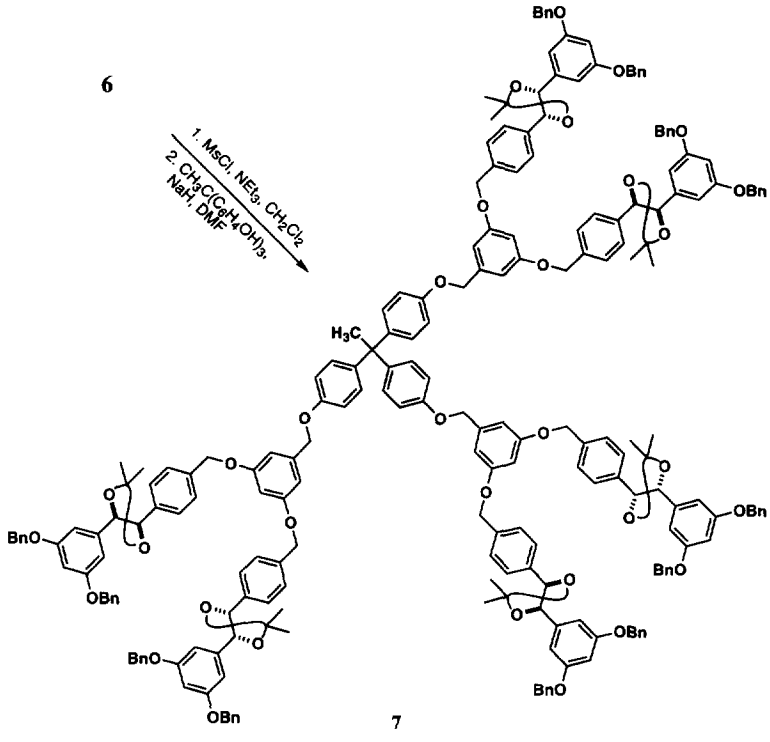
We have found that a modification of this method is necessary to retain the integrity of our acetonide groups. Rather that a benzylic bromide leaving group, we are currently employing sulfonate esters in the coupling reactions (Scheme 2). Mesylation of **4** proceeds in excellent yields (>90%). Coupling of two equiv. **4** to branching unit methyl 3,5-dihydroxybenzoate proceeds in moderate yield (47%) but has yet to be optimized. Similar procedures are followed in the subsequent reduction, mesylation, and coupling reactions to yield dendrimer **7** (94% pure by normal phase HPLC, Schemes 2 and 3).

Characterization by ^{13}C NMR spectroscopy is extremely useful with relatively small molecules such as **5** and **7**. We are able to determine the necessary structural symmetry in both monodendron **5** (exhibits 25

Scheme 2



Scheme 3



inequivalent peaks) and dendrimer **7** (exhibits 30 inequivalent peaks) from their respective ^{13}C NMR spectra. Assignment was straightforward and consistent with the expected structures.[21] Further characterization of **7** was carried out by gel permeation chromatography (GPC). The GPC trace of **7** (Figure 1) indicates a monomodal and extremely narrow weight distribution (PDI 1.08), but cannot tell us if we have relatively small defects in the dendrimer structure. We are currently obtaining mass spectral data as further characterization of these materials.

Modeling studies suggest that monodendrons of type **6** prefer a helical conformation. Monte Carlo conformational searches (Macromodel 3.5a) have been carried out on an analogue of monodendron **6** (methyl groups replacing the benzyl groups). Convergence was found on a series of low-energy structures which all have a similar helical conformation. All but one of the structures within 1 kcal of the global minimum have this same helical twist. Optical rotation studies on monodendron **6** and dendrimer **7** are underway.[22]

We have presented and demonstrated the viability of an approach to chiral dendrimers constructed from enantiomerically pure hydrobenzoin units. In addition to continued synthetic efforts, future work includes a thorough investigation of the chiroptical properties of these materials

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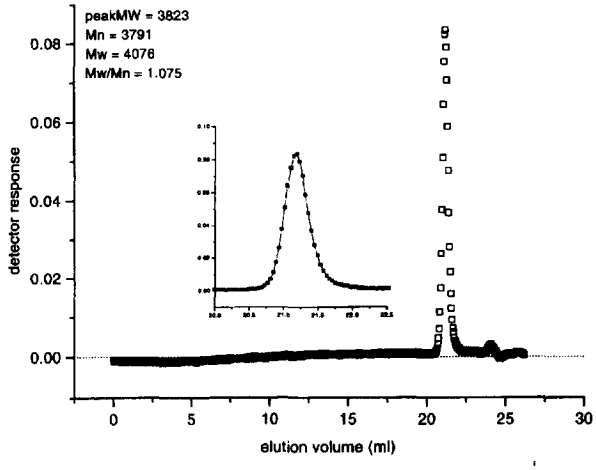

Figure 1. GPC trace of dendrimer **7**. Analysis was performed in THF on Phenomenex SEC columns (10^3 Å and 10^4 Å columns in series) with refractive index detection. Calibration was performed with monodisperse polystyrene standards.

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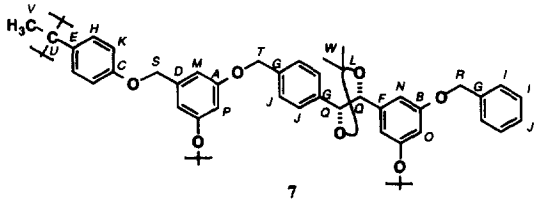
(21) (Selected spectral data for **5**: ^{13}C NMR ($CDCl_3$) δ 166.65 (A), 159.96 (B), 159.74 (C), 139.33 (D), 136.90 (E), 136.78 (E), 136.54 (E), 132.10 (F), 128.54 (G), 127.96 (H), 127.55 (H), 127.48 (G), 127.03 (H), 109.50 (I), 108.38 (J), 107.27 (K), 105.87 (L), 101.99 (M), 85.18 (L), 84.84 (L), 70.10 (O), 69.99 (P), 52.19 (Q), 27.15 (R), 27.10 (R). **7**: ^{13}C NMR ($CDCl_3$) δ 160.11 (A), 159.96 (B), 156.81 (C), 142.09 (D), 139.60 (E), 139.36 (F), 136.86 (G), 136.81 (G), 136.79 (G), 129.65 (H), 128.54 (I), 127.96 (J), 127.57 (J), 127.49 (I), 127.01 (J), 113.99 (K), 109.49 (L), 106.47 (M), 105.86 (N), 101.99 (O), 101.52 (P), 85.19 (Q), 84.87 (Q), 70.09 (R), 69.91 (S), 69.84 (T), 50.69 (U), 29.68 (V), 27.17 (W), 27.11 (W).



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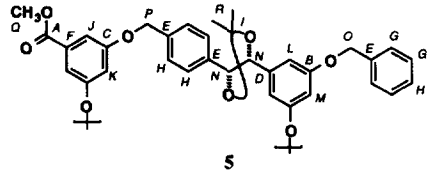

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