Polycations. II. Chiral Ammonium Dendrimer Synthesis*

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Received 28 August 1997; revised 10 November 1997

ABSTRACT: *The preparation and investigation of chiral cationic dendrimers is described. In these species, cationic sites are provided by quaternary ammonium ion centers derived from the dinitrogen compound 1,4-diazabicyclo[2.2.2]octane (dabco). Stereogenic sites within the dendrimer structures are provided by derivitization of the readily available (S)-1,2,4-butanetriol.* © 1998 John Wiley & Sons, Inc. Heteroatom Chem 9: 485–494, 1998

INTRODUCTION

In the course of our continuing efforts concerning the synthesis of polycationic organic species [1], both dendrimeric and "stringlike" in nature, we have turned to an investigation of the synthesis and characteristics of *chiral* ionic dendrimers. Dendrimers are an intriguing class of compounds that incorporate both the repetitive nature of polymers and a regular branching characteristic reminiscent of fractals.

A number of syntheses of chiral dendrimers have previously been reported. While some of these dendrimers have involved chiral components only at relatively late stages of total elaboration or as part of the terminal functionality, some have incorporated chiral units in the focus site and branching sites. These have involved building blocks based on α-amino acids [2a–g], chiral tris(hydroxymethylmethane) derivatives [2h–j], tetra-differentially substituted pentaerythritol species [2k–l] and the asymmetric dihydroxylation of prochiral alkene monomers [2m]. The present effort is concerned with the synthesis and investigation specifically of chiral *ionic* dendrimers.

In general, dendrimers involve four structural components: (1) a focus site for the divergent branches, (2) branch points, (3) extension units between the focus sites and branch points and between branch points, and (4) a terminal functionality. This is illustrated schematically in Figure 1.

In the prior reported efforts [1b–j] toward the synthesis of cationic dendrimers, the cationic sites (ammonium or phosphonium) were located at the branch points, and substituents attached to the branch points as they were incorporated into the developing dendrimer constituted the extension units; focus sites, as well as branch points, were alkylated or arylated tertiary amines (or phosphines).

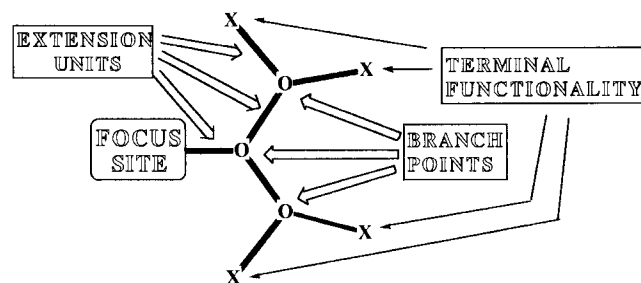In the present effort, cationic (quaternary am-

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FIGURE 1   Four structural components of dendrimers.

monium) sites are incorporated as components of the extension units using 1,4-diazabicyclo[2.2.2]octane (dabco) that is quaternized at both nitrogen centers. *Stereogenic* branch points are provided through the use of derivatives of (S)-1,2,4-butanetriol, the hydroxyls of the 1- and 2-positions serving as reactive sites for elaboration of new branches. Both mono- and bidirectional focus sites have been used in this effort.

RESULTS AND DISCUSSION

Branch Points

Branching sites for the chiral ionic dendrimers were provided through the use of the readily available (S)-1,2,4-butanetriol (**1**). Initial protection of the vicinal diol portion of **1** by acetonide formation followed by substitution of the remaining hydroxyl group by chloride using known procedures [3,4], after purification by column chromatography, yielded the desired intermediate reagent (S)-2,2-dimethyl-4-(2′-chloroethyl)-1,3-dioxolane (**2**). Reaction of **2** with dabco produced (S)-2,2-dimethyl-4-(2′-[″-azonia-4″azabicyclo[2.2.2]octyl]ethyl)-1,3-dioxolane chloride (**3**). The material **3**, which served as the fundamental building block for the chiral ionic dendrimers, was slowly formed as a gummy solid deposited on the flask walls from the ethyl acetate reaction solvent. The material **3**, containing the stereogenic site that would serve as the branch point for dendrimer elaboration, could be harvested before completion of the reaction by decanting the reaction solution and washing the residual deposit with diethyl ether to remove any retained reactants. All stereogenic sites incorporated into the chiral ionic dendrimers described here were derived from **2** in this manner.

Focus Sites

Three focus site units have been used for the construction of the chiral ionic dendrimers reported here. Each of these focus sites were constructed by alkylation of the fundamental building unit **3**. These include the following:

a. a monomethylated focus unit: (S)-2,2-dimethyl-4-(2′-[1″-azonia-4″-methylazoniabicyclo[2.2.2]octyl]ethyl)-1,3-dioxolane dichloride (**4**);

b. a monobenzylated focus unit: benzyl[1-azonia-4-{(S)-3′,4′-dihydroxybutyl-1′-}azoniabicyclo[2.2.2]octane bromide chloride (**5**); and

c. a bidirectional focus unit produced by qua-

ternization of two units of **3** with a 1,4-xylylene unit; 1,4-xylylenebis[1′-azonia-4′-{(S)-3″,4″-dihydroxybutyl-1″-}azoniabicyclo-[2.2.2]octane] dibromide dichloride (**6**).

The structures of these focus units are shown in Figure 2.

Extension Units

In the present approach toward the construction of chiral ionic dendrimers, two significant difficulties are associated with direct introduction of successive branching units without an intervening extension unit. First, all of the core units would first require removal of the acetonide protecting group and conversion of the resultant alcohol functionalities to haloalkyl functionalities to accomplish direct attachment of new building block units. This overall procedure involves two bond-breaking processes at the stereogenic carbon site with the attendant possibility of incomplete retention or inversion of configuration in each step. An approach that avoids *any* bond breaking at the stereogenic site is thereby preferable. Second, direct attachment of building block units through tertiary amine quaternization results in the generation of vicinal diammonium (quaternary) structures, which are extremely susceptible to cleavage [1i].

With these difficulties in mind, extension units were devised that would provide sites for attachment of additional building units (by tertiary amine quaternization) without breaking bonds at the stereogenic carbon sites. After hydrolytic removal of the acetonide linkage of a focus site unit, the resultant vicinal diol is acylated with an ω-halocarboxylic acid
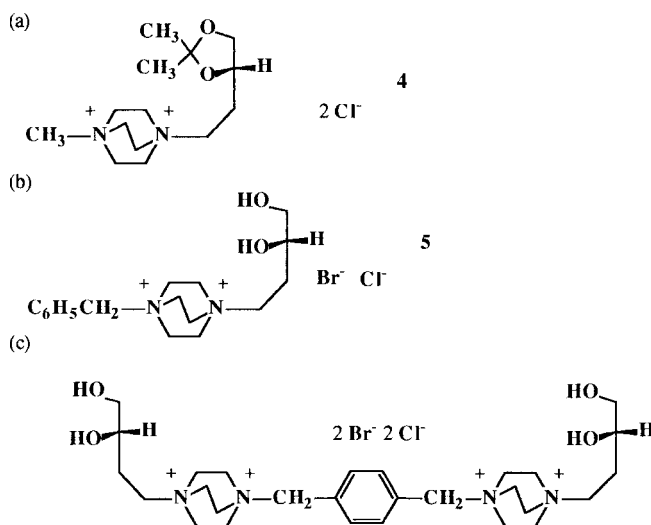

FIGURE 2 Structures of focus site units.

chloride. This avoids breaking any bonds at the stereogenic site and provides both a reasonably (but not totally) unreactive linkage for continued elaboration and reactive sites for alkylation of tertiary amine units that are relatively distant from each other. The reagent of choice for extension unit introduction was 4-chlorobutanoyl chloride. Longer alkyl-chain ω-chloroacyl chlorides would unnecessarily lengthen the distance between cationic sites, while shorter alkyl-chain systems would result in products that are exceedingly reactive by extraneous routes (α-azonia- and β-azoniaesters). The construction of initially functionalized focus unit species such as **7** and **8** derived from **3** with chloroacetyl chloride and 2-chloropropanoyl chloride was successful; however, **7**, being an α-azoniaester, was overly susceptible to hydrolysis and **8**, being a β-azoniaester, partially underwent elimination upon treatment with the tertiary amine reagent **3**.

7

8
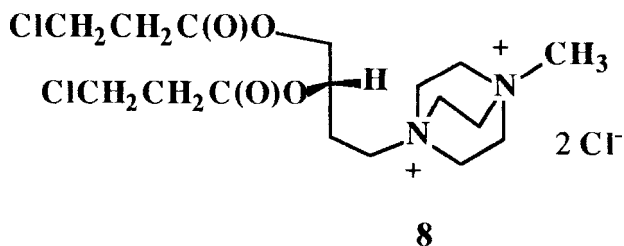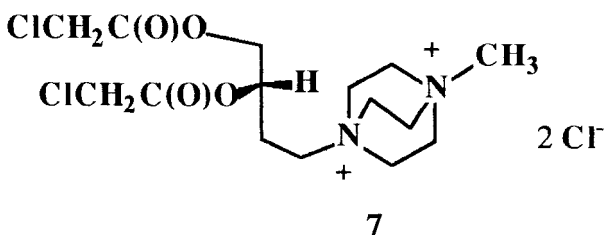
Terminal Functionality

The terminal functionality varies with the stage of elaboration for all of the species generated in this investigation. However, the target materials of elaboration about each of the focus site units have hydroxyl groups as the termini. While all of the materials synthesized herein exhibit significant solubility in water, not unexpectedly those with hydroxyl termini are most soluble, even with extensive elaboration and attendant high molecular mass.

### The Elaboration Process and Dendrimer Characteristics

The fundamental building block **3** was converted to each of the previously noted focus site units **4–6** by reaction with the appropriate organic halide (iodom-

ethane, benzyl chloride, or 1,4-bis(bromomethyl)-benzene, respectively). Because of difficulties associated with mixed iodide salts, the initial preparations of **4** were subjected to ion anion exchange using DOWEX 2 to generate the species with only chloride as the counterion.

The elaboration of dendrimers, particularly those wherein ionic sites are present within the covalent lattice with free-floating counterions, has particular requirements for the types and conditions of reactions employed. All reaction conditions must be relatively mild such that side reactions are virtually nonexistent; any small amount of cleavage of previously generated framework bonds is greatly magnified by the production of dendrimer fragments and the fact that these impurities can be removed only with the greatest difficulty. For example, after the focus units were generated, and after the incorporation of higher generations of branching units, removal of the acetonide protecting groups was accomplished either by treatment with dilute (10^{-4} M) hydrochloric acid, or with a standard cation exchange resin in the H^+ form. Under these mild conditions, no observable cleavage of ester linkages (or any other bond) occurred. As noted previously, the use of shorter extension units produced intermediate species that underwent degradation even under the mildest of conditions. Consequently, the vicinal diols were acylated using an excess of 4-chlorobutanoyl chloride, followed by continued dendrimer elaboration through reaction with **3**. These successive processes were repeated for the introduction of a further generation, ending with acetonide hydrolysis to yield the hydroxy-terminal form of the dendrimer. The process of dendrimer elaboration is illustrated in detail in Scheme 1 for the system based on focus unit **4** and in Scheme 2 for the system based on focus unit **6**.

In certain instances, not all of the hydrogen chloride generated in the reaction of hydroxyl groups with 4-chlorobutanoyl chloride could be removed efficiently under high vacuum. In such instances, as the presence of the acid could inhibit quaternization of the tertiary amine site of **3**, removal of remaining acid by treatment of an aqueous solution of the dendrimer intermediate with potassium carbonate was necessary prior to continued dendrimer elaboration.

Caution must also be taken to ensure complete reaction in a specific manner of all of the terminal sites of intermediate species in dendrimer elaboration. This is accomplished through the use of a significant excess of modifying reagent compared to the dendrimer upon which the operation is performed, keeping in mind the requirement for the complete removal of excess reagent. With the elaboration of
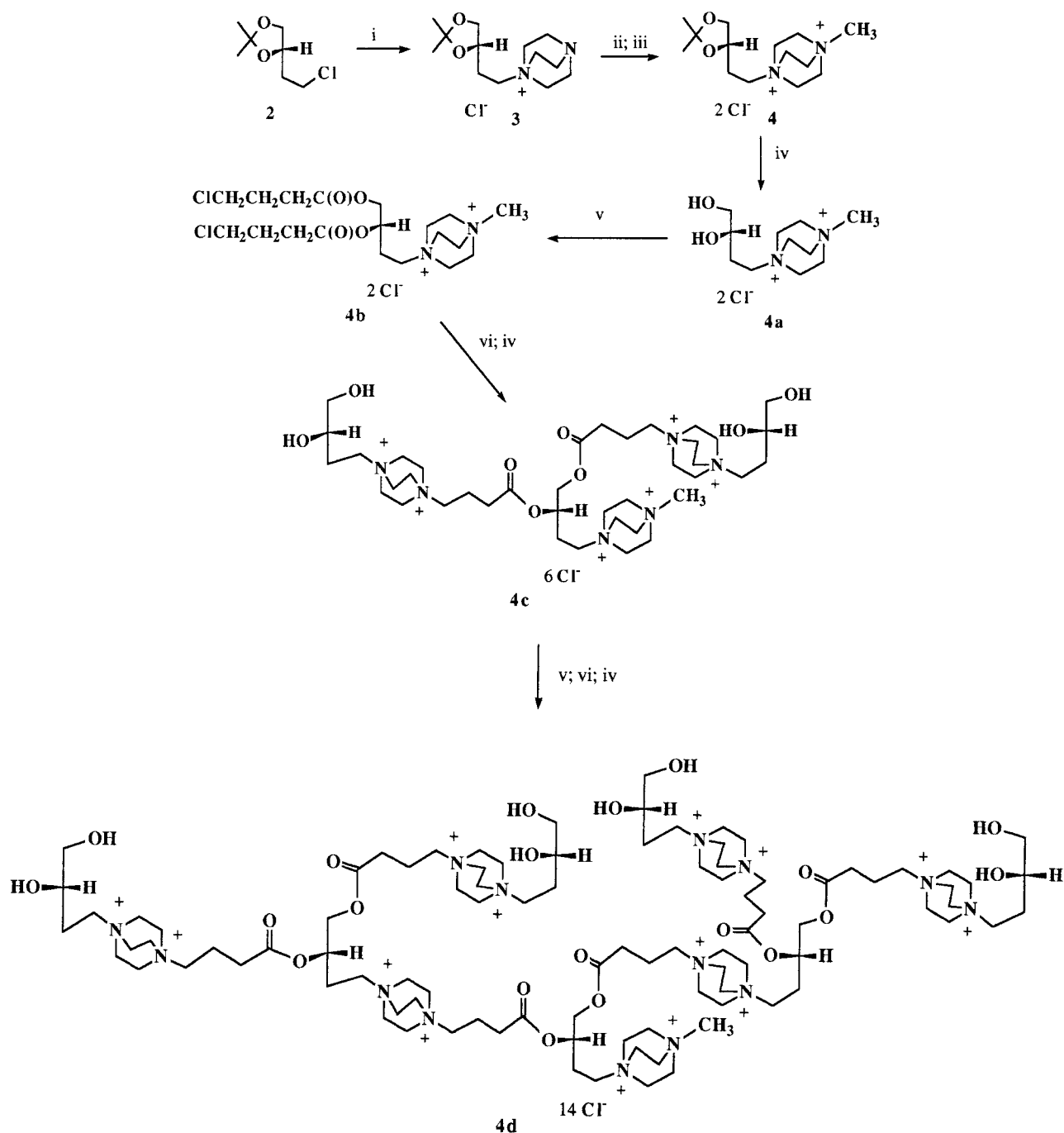
SCHEME 1 (i) dabco; (ii) CH$_3$I; (iii) DOWEX 2 (Cl$^-$); (iv) 10^{-4} M hydrochloric acid; (v) ClCH$_2$CH$_2$CH$_2$C(O)Cl; (vi) **3**.

ionic dendrimers as being performed here, much use is made of differential solubilities for this purpose.

For example, the solubility of **3** compared to other reagents and dendrimer intermediates is a critical factor. The solubility of **3** in ethyl acetate is quite low, being deposited on the flask walls from ethyl acetate solution as it is formed. (Although preparations of **3** were generally performed using a large excess of dabco, this is not absolutely necessary be-

cause of the low solubility of **3** in ethyl acetate and the fact that continued alkylation of **3** with **2** in acetonitrile proceeds only with the greatest difficulty. The reason for the low reactivity of **3** with **2** is not fully understood.) The material **3**, however, is readily soluble in acetonitrile, a solvent in which more highly charged dendrimer construction intermediates exhibit only limited solubility at elevated temperatures. With these characteristics, excess **3** is
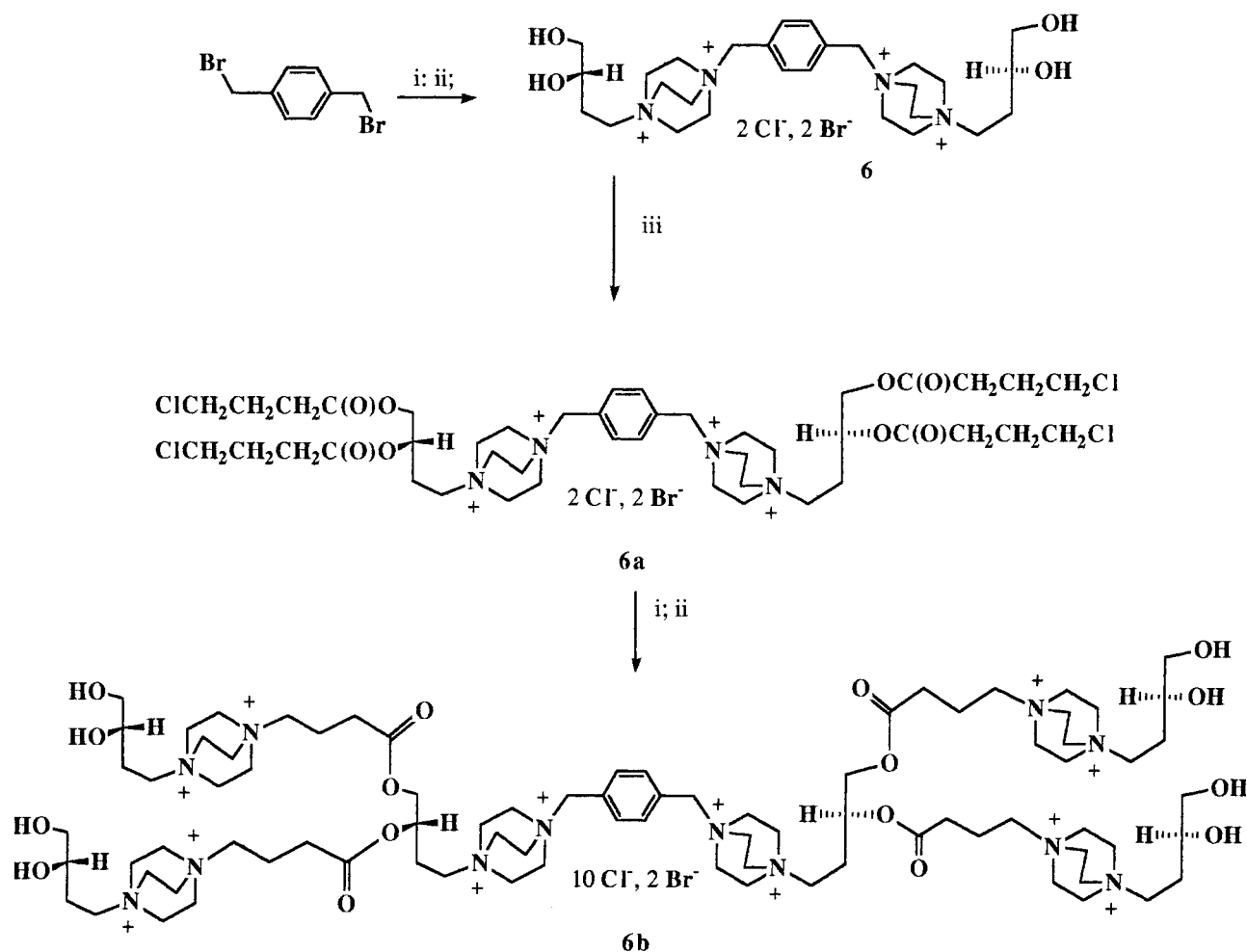
SCHEME 2 (i) **3**; (ii) AMBERLYST™-15 (H⁺); (iii) ClCH₂CH₂CH₂C(O)Cl.

readily removed from elaboration reactions. Similarly, excess of 4-chlorobutanoyl chloride is readily removed by washing with ethyl acetate and diethyl ether, solvents in which the charged dendrimer species are completely insoluble.

Dendrimers based on focus unit **5** were constructed by analogous elaboration procedures as detailed in the Experimental section. The structures of intermediate materials and final dendrimers based on focus unit **5** for which full analytical data and physical characteristics were measured are illustrated in Figure 3.

It might have been expected that optical rotation would have increased progressively with elaboration and introduction of additional stereogenic centers. However, the observed optical rotation using a standard sodium vapor lamp remained low and actually decreased as the elaboration progressed. (Optical rotation data are summarized in Table 1.) Moreover, the species synthesized were inactive in CD measurements, even with UV absorbing chromophores

present. Both of these observations are in accord with the observations on uncharged dendrimers as discussed by Seebach et al. [1j]; the introduction of new stereogenic centers is "diluted" by the simultaneous addition of mass to the species, and, at least at the level of elaboration performed, no conformational chirality is present.

EXPERIMENTAL

General

All chemicals used in syntheses, purification, and comparison analyses were of commercial reagent quality and were used without purification. 2,2-Dimethyl-4-(2′-chloroethyl)1,3-dioxolane (**2**) was prepared as previously reported [4]. All NMR spectra were measured using a Brüker 400 MHz DPX400 instrument, all optical rotations were measured using a Jasco DIP-140 instrument (1 dm cell, aqueous solution with a sodium vapor lamp), and all CD spectra were measured using a Jasco 500C CD/ORD instru-
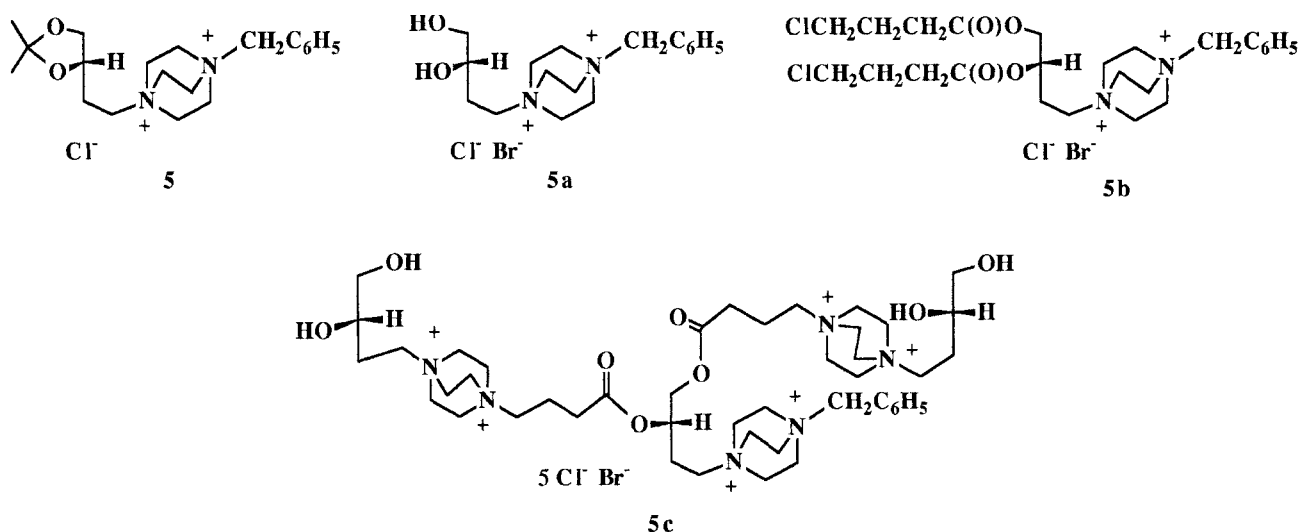
FIGURE 3 Structures of intermediate materials and final dendrimers based on focus unit **5**.

TABLE 1

Compound	Observed $[\alpha]_D$	Concentration (M)
3	−5.58°	0.003
4	−3.82°	0.003
4a	−7.02°	0.003
4b	+9.48°	0.003
4c	+6.42°	0.003
5a	−7.49°	0.0024
5b	+1.77°	0.011
5c	−6.33°	0.0029
6	−5.11°	0.012
6a	−0.53°	0.003
6b	+8.7°	0.0014

All measurements were made in aqueous solution using a sodium vapor lamp.

ment. (All species were inactive in the CD.) Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, NY.

Preparation of (S)-2,2-Dimethyl-4-(2'-{1"-azonia-4"-azabicyclo[2.2.2]octyl}ethyl)-1,3-dioxolane Chloride (3). In a 1 L flask fitted with a magnetic stirrer were placed dabco (80.0 g, 0.713 mol) and 600 mL ethyl acetate. There was then added **2** (26.55 g, 0.161 mol), and the reaction mixture was allowed to stir at ambient temperature for 2 days. A gummy precipitate formed, clinging to the flask walls as well as the bottom, and the first crop of product was isolated by decanting the reaction solution and washing the gummy solid with ethyl acetate followed by diethyl ether and drying under vacuum (dry yield, 6.21 g). (The gummy solid product could be transferred by dissolution in ethanol and evaporation of the sol-

vent.) From the decanted supernatant could be isolated additional crops of product (10.82 g after 4 additional days, 12.05 g after yet an additional 20 days, and 0.35 g after 1 more day). The material **3** thus isolated (29.43 g, 65.8% total yield) exhibited spectra and elemental analyses in accord with the proposed structure. ^{1}H NMR (δ D$_2$O) 1.36 (3H, s), 1.43 (3H, s), 1.99 (2H, m), 3.11 (6H, m), 3.22 (8H, m), 3.67 (1H, m), 4.09 (1H, m), 4.19 (1H, m). ^{13}C NMR (D$_2$O) 111.57, 74.52, 70.85, 63.80, 54.57, 47.29, 28.90, 28.74, 27.23. Anal. C$_{13}$H$_{25}$N$_2$O$_2$Cl requires: C, 56.41%; H, 9.10%. Found: C, 56.54%; H, 8.96%. $[\alpha]_D$ (0.003 M, H$_2$O) = −5.58°.

Preparation of (S)-2,2-Dimethyl-4-(2'-{1"-azonia-4"-methylazoniabicyclo[2.2.2]octyl}ethyl)-1,3-dioxolane Dichloride (4). A solution of **3** (1.52 g, 5.49 mmol) in acetonitrile (15 mL) was placed in a reaction flask fitted with a magnetic stirrer, reflux condenser, and drying tube, and to it was added an excess (2.5 g, 17.6 mmol) of iodomethane. After stirring for 2 hours, the resultant precipitate was collected by filtration with suction through sintered glass and washed with ethyl acetate and diethyl ether. The precipitate was dissolved in water and passed through a bed of DOWEX 2 in the chloride ion form. After evaporation of the water under vacuum, there was isolated an extremely hydroscopic white solid (dry weight 1.13 g, 62.8% yield) that exhibited spectra and elemental analyses in accord with the pentahydrate of the proposed structure **4**. ^{1}H NMR (δ D$_2$O) 1.31 (3H, s), 1.40 (3H, s), 2.14 (2H, m), 3.36 (3H, s), 3.72 (3H, m), 4.02 (12H, br), 4.17 (1H, m), 4.27 (1H, m). ^{13}C NMR (D$_2$O) 110.69, 72.81, 68.54, 62.56, 53.69, 53.01, 51.76, 26.53, 26.35,

24.71. Anal. $C_{14}H_{28}N_2O_2Cl_2 \cdot 5(H_2O)$ requires: C, 40.28%; H, 9.18%. Found: C, 40.17%; H, 9.23%. $[\alpha]_D$ (0.003 M, H_2O) = −3.82°.

Preparation of (S)-1-Methyl-4-(3',4'-dihydroxy-butyl)-1,4-diazoniabicyclo[2.2.2]octane Dichloride (**4a**). The dry acetonide **4** (1.49 g, 4.55 mmol) was added to 10^{-4} M hydrochloric acid (24 mL). The reaction mixture was stirred for 5 hours at ambient temperature after which all volatile materials were removed by freeze drying. The white solid residue (dry weight 1.07 g, 81.7% yield), which was extremely hydroscopic, exhibited spectra and elemental analyses in accord with the nonahydrate of the proposed structure **4a**. ¹H NMR (δ D_2O) 1.94 (2H, dm), 3.28 (3H, s), 3.46 (2H, dm), 3.63 (3H, m), 3.93 (12H, br). ¹³C NMR (D_2O) 67.63, 64.15, 61.94, 53.34, 52.36, 51.56, 24.43. Anal. $C_{11}H_{24}N_2O_2Cl_2 \cdot 9(H_2O)$ requires: C, 29.40%; H, 9.42%. Found: C, 29.02%; H, 9.51%. $[\alpha]_D$ (0.003 M, H_2O) = −7.02°.

Preparation of (S)-1-Methyl-4-(3',4'-di-{4''-chlorobutanoyloxy}butyl)-1,4-diazoniabicyclo[2.2.2]octane Dichloride (**4b**). The diol **4a** (0.95 g, 3.31 mmol) along with acetonitrile (25 mL) was placed in a 100 mL flask fitted with a magnetic stirrer. To it was added an excess of 4-chlorobuanoyl chloride (2.5 g, 17.7 mmol), and the reaction flask was topped with a drying tube. After stirring for 7 days, diethyl ether (50 mL) was added to the clear reaction solution, resulting in the formation of an oily white precipitate. The supernatant was decanted, and the residue was washed/decanted with ethyl acetate (3 × 50 mL) and diethyl ether (2 × 50 mL). The residue was dried under high vacuum to yield a hydroscopic white solid (dry weight 0.79 g, 48.1% yield) that exhibited spectral and elemental analyses in accord with the dihydrate of the proposed structure **4b**. ¹H NMR (δ D_2O) 1.95 (4H, m), 2.15 (2H, m), 2.50 (4H, m), 3.26 (3H, s), 3.49–3.74 (7H, m), 3.96 (14H, br). ¹³C NMR (D_2O) 172.33, 171.93, 66.31, 61.86, 58.74, 50.38, 49.64, 48.46, 42.14, 41.64, 28.37, 28.23, 24.23, 24.11, 20.34. Anal. $C_{19}H_{34}N_2O_4Cl_4 \cdot 2(H_2O)$ requires: C, 36.58%; H, 6.14%. Found: C, 36.57%; H, 5.91%. $[\alpha]_D$ (0.003 M, H_2O) = +9.48°.

Elaboration of the Modified Focus Site **4b** *to the First-Generation Dendrimer* **4c**. In a 100 mL r.b. flask fitted with a magnetic stirrer, heating bath, and reflux condenser were placed **4b** (0.145 g, 0.292 mmol) with acetonitrile (50 mL) and an excess of **3** (0.260 g, 0.939 mmol). The reaction mixture was heated at reflux for 15 hours, after which it was cooled, and the supernatant was decanted. The residue was further washed/decanted with cool aceton-

itrile (3 × 50 mL). To the residue was added hydrochloric acid (10^{-4} M, 25 mL) and the mixture stirred for 4 hours. After this time, all volatile materials were evaporated under high vacuum to give a hydroscopic white solid (dry weight 0.163 g, 58.2% yield) that exhibited spectral and elemental analyses in accord with the dodecahydrate of the proposed structure **4c**. ¹H NMR (δ D_2O) 1.87 (2H, m), 1.98 (4H, m), 2.02 (2H, m), 2.33 (2H, m), 2.55 (4H, m), 3.33 (3H, s), 3.46–3.99 (19H, m), 4.14 (36H, br). ¹³C NMR (D_2O) 173.69, 172.06, 67.57, 62.72, 61.73, 61.54, 60.55, 60.43, 52.21, 51.51, 50.28, 50.22, 50.19, 50.17, 49.83, 44.17, 44.07, 43.57, 43.52, 42.92, 30.27, 30.24, 26.11, 25.99, 24.26, 23.15, 22.22. Anal. $C_{39}H_{76}N_6O_8Cl_6 \cdot 12(H_2O)$ requires: C, 39.49%; H, 8.50%. Found: C, 39.44%; H, 8.10%. $[\alpha]_D$ (0.003 M, H_2O) = +6.42°.

Elaboration of **4c** *to Second-Generation Dendrimer* **4d**. The tetraol **4c** (0.97 g, 1.0 mmol) along with acetonitrile (50 mL) was placed in a 100 mL flask fitted with a magentic stirrer, heating bath, and reflux condenser. To the reaction system was added 4-chlorobutanoyl chloride (1.12 g, 8.0 mmol), the reaction flask was topped with a drying tube, and the reaction mixture was heated at reflux for 2 days. After cooling, the solvent was decanted and the residue washed/decanted with cool ethyl acetate (3 × 50 mL). The residue was dried under high vacuum to yield a hydroscopic white solid. To this material was added acetonitrile (50 mL) and **3** (2.22 g, 8.02 mmol), and the resultant reaction mixture was stirred while heating at reflux for 3 days. After cooling, the supernatant liquid was decanted, and the residue was washed/decanted with cool acetonitrile (3 × 50 mL). To the residue was then added hydrochloric acid (10^{-4} M, 20 mL), and the mixture was stirred for 4 hours at ambient temperature. All volatile materials were then removed by freeze drying to yield a hydroscopic white solid residue (dry weight 0.30 g, 13% yield) that exhibited spectral and elemental analyses in accord with a hydrated form of the proposed structure **4d**. ¹H NMR (δ D_2O) 1.78–2.58 (14H, brm), 2.70–3.23 (12H, brm), 3.28 (3H, s), 3.38–4.22 (143H, br). ¹³C NMR (D_2O) full resolution of signals in the range δ 75–0 could not be attained. However, six signals were present and resolved in the "carboxylate ester" region in accord with the presence of six unique carboxylate carbon sites in **4d**—186.23, 186.14, 186.02, 185.91, 176.50, 163.27. Anal. $C_{95}H_{180}N_{14}O_{20}Cl_{14} \cdot 34(H_2O)$ requires: C, 38.55%; H, 8.50%. Found: C, 38.71%; H, 8.48%.

Preparation of (S)-2,2-Dimethyl-4-(2'-{1''-azonia-4''-benzylazoniabicyclo[2.2.2]octyl}ethyl)-1,3-dioxo-

lane Dichloride (**5**). A solution of **3** (0.500 g, 1.14 mmol) in acetonitrile (50 mL) was placed in a reaction flask fitted with a magnetic stirrer, reflux condenser, and drying tube, and to it was added an excess (0.308 g, 2.21 mmol) of benzyl bromide. After stirring for 12 hours, the resultant precipitate was recovered by suction filtration through sintered glass followed by washing with ethyl acetate (2 × 50 mL) and diethyl ether (2 × 50 mL). After drying under vacuum there was isolated a hydroscopic white solid (dry weight 0.510 g, 74.3% yield) that exhibited spectra and elemental analyses in accord with the monohydrate of the proposed structure **5**. ^{1}H NMR (δ D$_2$O) 1.31 (3H, s), 1.40 (3H, s), 1.97 (2H, m), 3.45–3.71 (3H, m), 3.98 (12H, br), 4.12 (1H, m), 4.24 (1H, m), 4.74 (2H, s), 7.54 (5H, m). ^{13}C NMR (D$_2$O) 132.78, 131.53, 129.55, 124.66, 112.45, 68.83, 68.37, 64.90, 62.75, 51.19, 50.60, 25.12, 25.08, 23.96. Anal. C$_{20}$H$_{32}$N$_2$O$_2$ClBr · (H$_2$O) requires: C, 51.56%; H, 7.36%. Found: C, 51.19%; H, 7.74%.

Preparation of Benzyl[1-azonia-4-{(S)-3',4'-dihydroxybutyl-1'-}azoniabicyclo[2.2.2]octane Bromide Chloride (**5a**). The ketal **5** (0.500 g, 1.12 mmol) was stirred in aqueous solution (25 mL) with AMBERLYST™-15 in the acid form for 2 hours. After removal of the AMBERLYST™-15 by filtration, the volatile materials were evaporated under high vacuum to give a hydroscopic white solid (dry weight 0.323 g, 70.7% yield) that exhibited spectra and elemental analyses in accord with the pentahydrate of the proposed structure **5a**. ^{1}H NMR (δ D$_2$O) 1.89 (2H, dm), 3.47 (2H, m), 3.69 (3H, m), 3.96 (12H, br), 4.74 (2H, s), 7.55 (5H, m). ^{13}C NMR (D$_2$O) 133.32, 131.96, 129.99, 125.12, 69.24, 68.81, 65.35, 63.14, 51.63, 51.04, 25.16. Anal. C$_{17}$H$_{28}$N$_2$O$_2$BrCl · 5(H$_2$O) requires: C, 40.99%; H, 7.69%. Found: C, 40.68%; H, 7.32%. [α]$_D$ (0.0024 M, H$_2$O) = −7.49°.

Preparation of Benzyl[1-azonia-4-{(S)-3',4'-di-(4″-chlorobutanoyloxy)*butyl-1'-}azoniabicyclo-[2.2.2]octane Bromide Chloride* (**5b**). The diol **5a** (0.080 g, 0.20 mmol) along with acetonitrile (30 mL) was placed in a 50 mL flask fitted with a magnetic stirrer. To it was added an excess of 4-chlorobutanoyl chloride (0.050 g, 0.71 mmol) and the reaction flask topped with a drying tube. After stirring for 2 days, diethyl ether (50 mL) was added to the clear reaction solution resulting in the formation of an oily white precipitate. The supernatant was decanted and the residue washed/decanted with ethyl acetate (3 × 50 mL) and diethyl ether (2 × 50 mL). The residue was dried under high vacuum to yield a hydroscopic white solid (dry weight 0.070 g, 56.7% yield) that ex-

hibited spectral and elemental analyses in accord with the octahydrate of the proposed structure **5b**. ^{1}H NMR (δ D$_2$O) 1.98 (4H, m), 2.19 (2H, m), 2.52 (4H, m), 3.50–3.82 (7H, m), 3.94 (14H, br), 4.73 (2H, s), 7.52 (5H, m). ^{13}C NMR (D$_2$O) 175.50, 175.08, 133.28, 131.99, 130.03, 125.14, 69.62, 69.27, 65.04, 61.78, 51.73, 51.02, 31.60, 31.45, 27.44, 27.31, 25.67, 23.56, 23.50. Anal. C$_{25}$H$_{38}$N$_2$O$_4$BrCl$_3$ · 8(H$_2$O) requires: C, 39.46%; H, 7.15%. Found: C, 39.62%; H, 7.02%. [α]$_D$ (0.011 M, H$_2$O) = +1.77°.

Elaboration of the Modified Focus Site **5b** *to the First-Generation Dendrimer* **5c**. In a 100 mL r.b. flask fitted with a magnetic stirrer, heating bath, and reflux condenser were placed **5b** (0.070 g, 0.11 mmol) with acetonitrile (50 mL) and **3** (0.124 g, 0.44 mmol). The reaction mixture was stirred at ambient temperature for 3 days, after which the supernatant was decanted. The residue was further washed/decanted with cool acetonitrile (3 × 50 mL). To the residue was added hydrochloric acid (10^{-4} M, 25 mL), and the mixture was stirred for 4 hours. After this time, all volatile materials were evaporated under high vacuum to give a hydroscopic white solid (dry weight 0.030 g, 26.1% yield) that exhibited spectral and elemental analyses in accord with a hydrated form of the proposed structure **5c**. ^{1}H NMR (δ D$_2$O) 1.77 (2H, m), 1.87 (4H, m), 2.00 (2H, m), 2.31–2.58 (6H, brm), 3.36–3.89 (19H, m), 4.10 (36H, br), 4.53 (2H, s), 7.30 (5H, brm). ^{13}C NMR (D$_2$O) 173.52, 172.44, 131.28, 129.99, 128.02, 124.28, 67.49, 67.26, 66.74, 64.37, 63.04, 62.08, 61.85, 60.89, 59.88, 57.78, 50.07, 49.72, 49.65, 49.51, 49.04, 42.84, 42.32, 41.83, 29.60, 29.46, 28.00, 25.44, 25.32, 23.61, 21.60. Anal. C$_{45}$H$_{80}$N$_6$O$_8$Cl$_6$ · 13(H$_2$O) requires: C, 42.22%; H, 8.35%. Found: C, 42.22%; H, 8.03%. [α]$_D$ (0.0029 M, H$_2$O) = −6.33°.

Preparation of 1,4-Xylylenebis[1'-azonia-4'-{(S)-3',4″-dihydroxybutyl}azoniabicyclo[2.2.2]octane Dibromide Dichloride (**6**). A solution of **3** (8.57 g, 36.0 mmol) in acetonitrile (25 mL) was placed in a reaction flask fitted with a magnetic stirrer, reflux condenser, and drying tube, and to it was added 1,4-bis(bromomethyl)benzene (4.66 g, 17.8 mmol). After stirring for 4 hours, the resultant precipitate was collected by filtration with suction through sintered glass. The recovered solid was stirred in aqueous solution with AMBERLYST™-15 in the acid form. After removal of the AMBERLYST™-15 by filtration, the volatile materials were evaporated under high vacuum, and the resulting solid was washed with ethyl acetate, cold absolute ethanol, and diethyl ether. There was thus isolated a mildly hydroscopic

white solid (dry weight 7.63 g, 57.5% yield) that exhibited spectra and elemental analyses in accord with the trihydrate of the proposed structure **6**. ^{1}H NMR (δ D$_2$O) 1.74–2.00 (4H, m), 3.39–4.14 (34H, brm), 4.81 (4H, s), 7.67 (4H, s). ^{13}C NMR (D$_2$O) 134.55, 128.63, 68.83, 68.16, 65.35, 63.21, 51.67, 51.27, 25.55. Anal. C$_{28}$H$_{50}$N$_4$O$_4$Cl$_2$Br$_2 \cdot$ 3(H$_2$O) requires: C, 42.49%; H, 7.13%. Found: C, 42.40%; H, 7.43%. [α]$_D$ (0.012 *M*, H$_2$O) = $-5.11°$.

Preparation of 1,4-Xylylenebis-[1'-azonia-4'-{(S)-3'',4''-di-[4'' '-chlorobutanoyloxy]butyl}azoniabicyclo-[2.2.2]octane] Tetrachloride (**6a**).   The tetraol **6** (0.50 g, 0.68 mmol) along with acetonitrile (100 mL) was placed in a 250 mL flask fitted with a magnetic stirrer. To it was added an excess of 4-chlorobutanoyl chloride (1.18 g, 8.3 mmol) and the reaction flask topped with a drying tube. After stirring for 4 days, diethyl ether (50 mL) was added to the clear reaction solution resulting in the formation of an oily precipitate. The supernatant was decanted, and the residue was washed/decanted with ethyl acetate (3 × 50 mL) and diethyl ether (2 × 50 mL). There was thus isolated a solid that was dried under high vacuum to yield a hydroscopic off-white solid (dry weight 0.269 g, 34.2% yield) that exhibited spectral properties in accord with the proposed structure **6a**. A sample of this material was dissolved in water and passed through a bed of DOWEX 2 in the chloride ion form. After evaporation of the water under vacuum, there was isolated a solid that exhibited elemental analyses in accord with the pentahydrate of the tetrachloride form of the proposed structure **6a**. ^{1}H NMR (δ D$_2$O) 1.94–2.05 (8H, m), 2.09–2.32 (4H, m), 2.43–2.55 (8H, m), 3.45–4.13 (40H, brm), 4.40 (2H, m), 5.12 (4H, brs), 7.68 (4H, s). ^{13}C NMR (D$_2$O) 173.79, 173.39, 132.84, 126.99, 67.84, 67.76, 63.34, 60.21, 50.03, 49.52, 43.12, 42.50, 29.87, 29.73, 25.79, 25.59, 21.82. Anal. C$_{44}$H$_{70}$N$_4$O$_8$Cl$_8 \cdot$ 5(H$_2$O) requires: C, 45.69%; H, 6.97%. Found: C, 45.96%; H, 7.09%. [α]$_D$ (0.003 *M*, H$_2$O) = $-0.53°$.

Elaboration of the Modified Focus Site **6a** *to the First-Generation Dendrimer* **6b**.   In a 100 mL r.b. flask fitted with a magnetic stirrer, heating bath, and reflux condenser were placed **6a** (dibromide–dichloride form) (0.170 g, 0.147 mmol) with acetonitrile (50 mL) and an excess of **3** (0.184 g, 0.752 mmol). The reaction mixture was stirred for 7 days, after which the supernatant was decanted. The residue was further washed/decanted with cool acetonitrile (3 × 50 mL). To an aqueous solution of the residue was added AMBERLYST™-15 in the acid form, and

the mixture was stirred overnight. After removal of the AMBERLYST™-15 by filtration, the volatile materials were evaporated under high vacuum, and the resulting solid was washed with ethyl acetate and diethyl ether to give an extremely hydroscopic semisolid (dry weight 0.182 g, 58.0% yield) that exhibited spectral and elemental analyses in accord with a hydrated form of the proposed structure **6b**. ^{1}H NMR (δ D$_2$O) 1.88–2.56 (28H, complex), 2.36–4.15 (104H, m), 4.35 (6H, m), 5.09 (4H, brs), 7.68 (4H, s). ^{13}C NMR (D$_2$O) 175.74, 175.68, 135.32, 129.41, 71.58, 71.50, 70.30, 70.21, 68.98, 68.90, 67.14, 64.98, 63.68, 62.69, 52.51, 52.01, 46.22, 45.69, 45.68, 45.62, 45.02, 44.54, 32.37, 32.25, 28.31, 28.25, 26.49, 25.28, 24.34. Anal. C$_{84}$H$_{154}$N$_{12}$O$_{16}$Br$_2$Cl$_{10} \cdot$ 18(H$_2$O) requires: C, 41.57%; H, 7.89%. Found: C, 41.45%; H, 7.62%. [α]$_D$ (0.0014 *M*, H$_2$O) = $+8.7°$.

REFERENCES

[1] (a) J. Fabian, T. October, A. Cherestes, R. Engel, *Synlett,* 1997, 1007; (b) K. Rengan, R. Engel, *Chem. Commun.,* 1990, 1084; (c) K. Rengan, R. Engel, *J. Chem. Soc. Perkin Trans. I,* 1991, 987; (d) R. Engel, K. Rengan, C. Milne, "Cationic Cascade Molecules," *Polym. Prepr., 32,* 1991, 601; (e) R. Engel, "Cascade Molecules," *Polym. News, 17,* 1992, 301; (f) K. Rengan, R. Engel, "Ammonium Cascade Molecules," *J. Chem. Soc. Chem. Commun.,* 1992, 757; (g) R. Engel, K. Rengan, C.-S. Chan, "Phosphorus Cascade Molecules," *Phosphorus and Sulfur, 77,* 1993, 221; (h) R. Engel, K. Rengan, C.-S. Chan, "Cascade Molecules Centered about Phosphorus," *Heteroatom Chem., 4,* 1993, 181; (i) R. Engel, "Ionic Dendrimers and Related Materials," *Adv. Dendritic Macromol., 2,* 1995, 73; (j) A. Cherestes, R. Engel, "Dendrimeric Ion Exchange Materials," *Polymer Commun., 35,* 1994, 3343.
[2] (a) R. G. Denkewalter, J. F. Kolc, W. J. Lukasavage, U.S. Patent 4,410,688 (1979); (b) R. G. Denkewalter, J. F. Kolc, W. J. Lukasavage, U.S. Patent 4,360,646 (1982); (c) R. G. Denkewalter, J. F. Kolc, W. J. Lukasavage, U.S. Patent 4,289,872 (1981); (d) T. M. Chapman, G. L. Hillyer, E. J. Mahan, K. A. Shaffer, *J. Am. Chem. Soc., 116,* 1994, 11195; (e) O. Katzenelson, H. Z. Hel-Or, D. Avnir, *Chem. Eur. J., 2,* 1996, 174; (f) G. R. Newkome, X. Lin, *Macromolecules, 24,* 1991, 1443; (g) L. J. Twyman, A. E. Beezer, J. C. Mitchell, *Tetrahedron Lett., 35,* 1994, 4423; (h) J.-M. Lapierre, K. Skobrides, D. Seebach, *Helv. Chim. Acta, 76,* 1993, 2419; (i) D.

Seebach, J.-M. Lapierre, W. Jaworek, P. Seiler, *Helv. Chim. Acta, 76,* 1993, 459; (j) D. Seebach, J.-M. Lapierre, G. Greiveldinger, K. Skobridis, *Helv. Chim. Acta, 77,* 1994, 1673; (k) J. A. Kremers, E. W. Meijer, *J. Org. Chem., 59,* 1994, 4262; (l) J. A. Kremers, E. W. Meijer, *Macromol. Symp., 98,* 1995, 491; (m) H.-T. Chang, C.-T. Chen, T. Kondo, G. Siuzdak, K. B. Sharpless, *Angew. Chem. Int. Ed. Engl., 35,* 1996, 182.

[3] H. Hayash, K. Nakanishi, C. Brandon, C. Marmur, *J. Am. Chem. Soc., 95,* 1973, 8749.

[4] K.-C. Tang, B. E. Tropp, and R. Engel, *Tetrahedron, 34,* 1978, 2873.