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Synthesis and chiroptical properties of amphiphilic dendrimers based on 2,3-dihydroxybenzyl alcohol

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This paper is dedicated to the memory of Willie W. Hsu

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Abstract—The syntheses and chiroptical properties of amphiphilic dendrimers based on 2,3-dihydroxybenzyl alcohol up to the third generation are described. Water-solubility is imparted to the dendrimers using a selective palladium-catalyzed deprotection of allyl ester terminal groups. Circular dichroism studies indicate that a transfer of chirality from the central core to the achiral branch segments does not occur in any of the dendrimers in THF. However, a temperature-dependent Cotton effect associated with the 2,3-dialkoxybenzyl ether branching subunit appears at the first generation in water consistent with a transfer of chirality from the chiral core to the dendrons. This effect disappears at the second and third generations suggesting greater conformational flexibility at higher dendrimer generation. The increased flexibility at higher dendrimer generation is rationalized by a decrease in hydrophobic compression at higher dendrimer generation. This work highlights the effect of asymmetric branching and solvent-induced compression in restricting the conformational mobility of dendrimers. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Dendrimers are highly branched macromolecules that are typically constructed using symmetrically branched monomers to facilitate growth to high molecular weight materials.[1] Many of these systems maintain a relatively flexible structure that permits highly dynamic conformational equilibria to exist in the branch segments.[2] This flexibility severely impedes the ability to create higher levels of conformational order in these molecules.[3,4] For example, attempts to induce stable chiral conformations in dendrimers constructed with enantiomerically pure subunits have been unsuccessful for many of the relatively flexible systems that have been studied.[5] Similarly, Meijer observed that an enantiomerically pure dendrimer constructed using three constitutionally different dendrons attached to a central carbon atom exhibited no optical activity when flexible 3,5-branched polyarylether dendrons were employed;[6] however, restricting conformational mobility by employing 2,6-branched polyarylether dendrons permitted the expression of a small temperature-dependent optical rotation.[7] Theoretical[8] and experimental[9] studies suggest that the molecular dimensions of dendrimers expand in good solvents and collapse in poor solvents. Therefore, conformational order should be maximal in poor solvents such as water due to a hydrophobic effect that compresses the dendrimer structure.[10] Most chiroptical studies on chiral dendrimers have been conducted in good solvents that induce a fully expanded conformation with maximum flexibility.[11] Recently, we observed that chiral, amphiphilic dendrimers constructed with symmetrically branched monomers based on 3,5-dihydroxybenzyl alcohol experienced significant aggregation in water that perturbed the conformational equilibria of the dendrons and increased the steric effect of the dendrons on the chiral central core.[12] Chiral conformational order was not present in the dendrons of these symmetrically branched systems. The purpose of this work is to determine the effect of water[13] on the conformational properties of dendrimers constructed with unsymmetrically branched dendrons based on 2,3-dihydroxybenzyl alcohol to restrict mobility and to create a potential in a dendritic wedge to coil helically toward the focal point upon compression in aqueous medium.[14]

2. Results and discussion

2.1. Dendron synthesis

Unsymmetrically branched polyarylether dendrons based on 2,3-dihydroxybenzyl alcohol were prepared in a convergent manner from 2,3-dihydroxybenzaldehyde.[14] Generational growth was achieved by convergent O-alkylation of 2,3-dihydroxybenzaldehyde with the dendron monobromides and focal point activation occurred by a subsequent reduction/bromination sequence (Scheme 1). In order to create a hydrophilic periphery, allyl ester groups were chosen as terminal groups because of the potential to

Keywords: dendrimers; dihydroxybenzyl alcohol; chiroptical properties.

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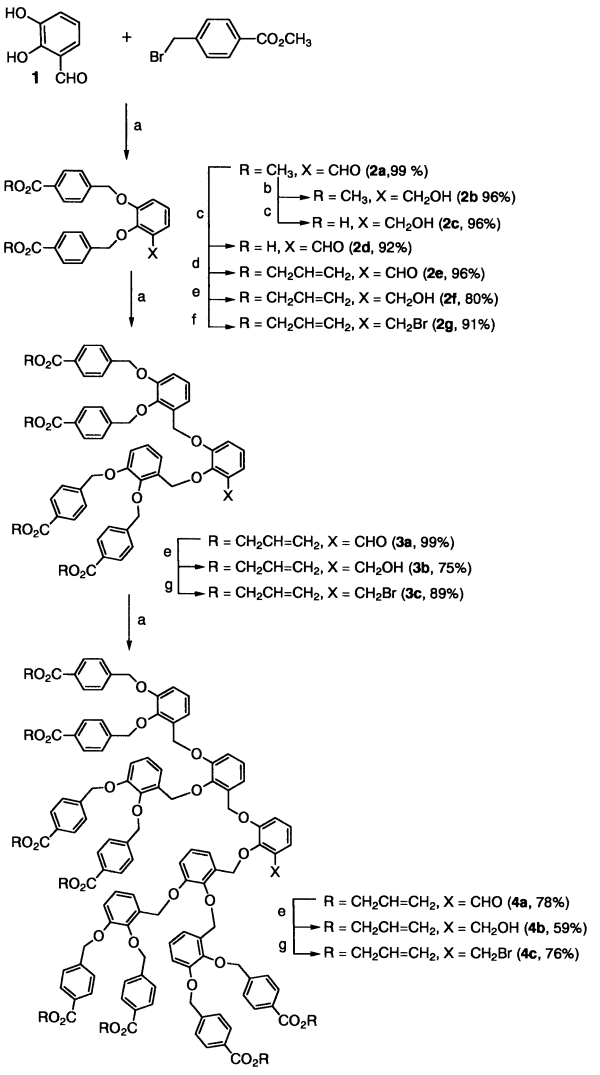
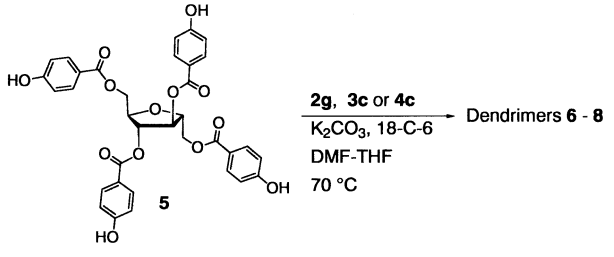


Scheme 1. Dendron synthesis. (a) **1**, K_2CO_3, 18-C-6, DMF–THF, 70°C. (b) $NaBH_4$, CH_3OH, reflux. (c) NaOH, THF–H_2O. (d) $H_2C{=}CHCH_2Br$, K_2CO_3, 18-C-6, DMF–THF, 70°C. (e) Diisobutylaluminum hydride, THF, −78°C. (f) PBr_3, CH_2Cl_2. (g) CBr_4, PPh_3, THF.

liberate hydrophilic carboxylate groups upon palladium-catalyzed deprotection.[15] We have previously found this deprotection method to be effective in exhaustively deprotecting the periphery of the 3,5-branched analogs of these dendrimers because the solubility of partially hydrolyzed intermediates is maintained throughout the course of the hydrolysis.[12] This method also permits the peripheral esters to be deprotected under conditions that do not effect hydrolysis of ester linkages that will be employed to link



Scheme 2. Dendrimer synthesis.

Table 1. GPC data (polystyrene-equivalent molecular weights) of 2,3- and 3,5-branched dendrimers

3,5-Branched	M_W (calcd)	M_W	M_n
$(AllylO_2C)_8$[G-1]–dendrimer	2526	2407	2095
$(AllylO_2C)_{16}$[G-2]–dendrimer	4897	4951	4711
$(AllylO_2C)_{32}$[G-3]–dendrimer	9638	9614	9264
2,3-Branched			
$(AllylO_2C)_8$[G-1]–dendrimer	2526	2533	2522
$(AllylO_2C)_{16}$[G-2]–dendrimer	4897	4149	4118
$(AllylO_2C)_{32}$[G-3]–dendrimer	9638	6524	6467

the central core to the dendrons. Accordingly, 2,3-dihydroxybenzaldehyde was treated with methyl 4-bromomethylbenzoate in the presence of potassium carbonate and 18-C-6 in THF–DMF (4:1) at 70°C affording **2a** in 99% yield (Scheme 1). Initial attempts to install the allyl esters by transesterification of **2a** with sodium allyloxide in THF afforded low yields of **2e** contaminated by small amounts of inseparable methyl esters. Extended reaction times led to decomposition and decreased yields. Consequently, the methyl esters of **2a** were exhaustively hydrolyzed with sodium hydroxide in THF–H_2O at 65°C affording diacid **2d** in 92% yield. Subsequent deprotonation of **2d** with K_2CO_3 and alkylation with allyl bromide afforded 96% yield of bis-allyl ester **2e** without any contamination by materials containing methyl esters. Subsequent reduction of the focal aldehyde using $NaBH_4$ in methanol was unreliable due to the tendency of allyl esters to undergo transesterification in methanol. Similarly, the poor solubility $NaBH_4$ in THF caused reduction in this solvent to be slow and difficult to reproduce. Reduction with diisobutylaluminum hydride (DIBAL-H) in THF at −78°C produced the focal alcohol (**2f**) in a reproducible 80% yield. Conversion to the bromide was achieved at the first generation by exposure to phosphorous tribromide in CH_2Cl_2; however, at later generations, this reagent caused cleavage of the benzylic linkages.[14] Therefore, at the second and third generations, CBr_4/PPh_3 was used to install the focal bromide without benzylic cleavage. Growth to the second and third generation dendrons proceeded by iterative repetition of these steps as shown in Scheme 1.

2.2. Dendrimer synthesis and deprotection

1,3,4,6-tetra-*O*-(4-hydroxybenzoyl)-2,5-anhydro-D-mannitol, **5**,[16] was used as a tetrafunctional central core wherein convergent dendron attachment occurred by O-alkylation of the phenolic hydroxyl groups of the central core unit (Scheme 2). Accordingly, *tetra*-alkylation of the central core, **5**, with the first $(allylO_2C)_2$[G-1]–CH_2Br, **2g**), second $(allylO_2C)_4$[G-2]–CH_2Br, **3c**) and third $(allylO_2C)_8$[G-3]–CH_2Br, **4c**) generation dendron monobromides was accomplished using K_2CO_3/18-C-6 in THF–DMF (4:1) at 70°C. Purification over silica gel afforded monodisperse dendrimers with molecular weights of 2526 (**6a**, 79%), 4897 (**7a**, 46%) and 9638 (**8a**, 51%) with 8, 16 and 32 terminal allyl esters, respectively. GPC analysis indicated that the dendrimers were monodisperse; however, the polystyrene-equivalent molecular weights were significantly lower than the theoretical molecular weights of these dendrimers and the polystyrene-equivalent weights of the analogous 3,5-branched dendrimers[12] (Table 1). The significantly

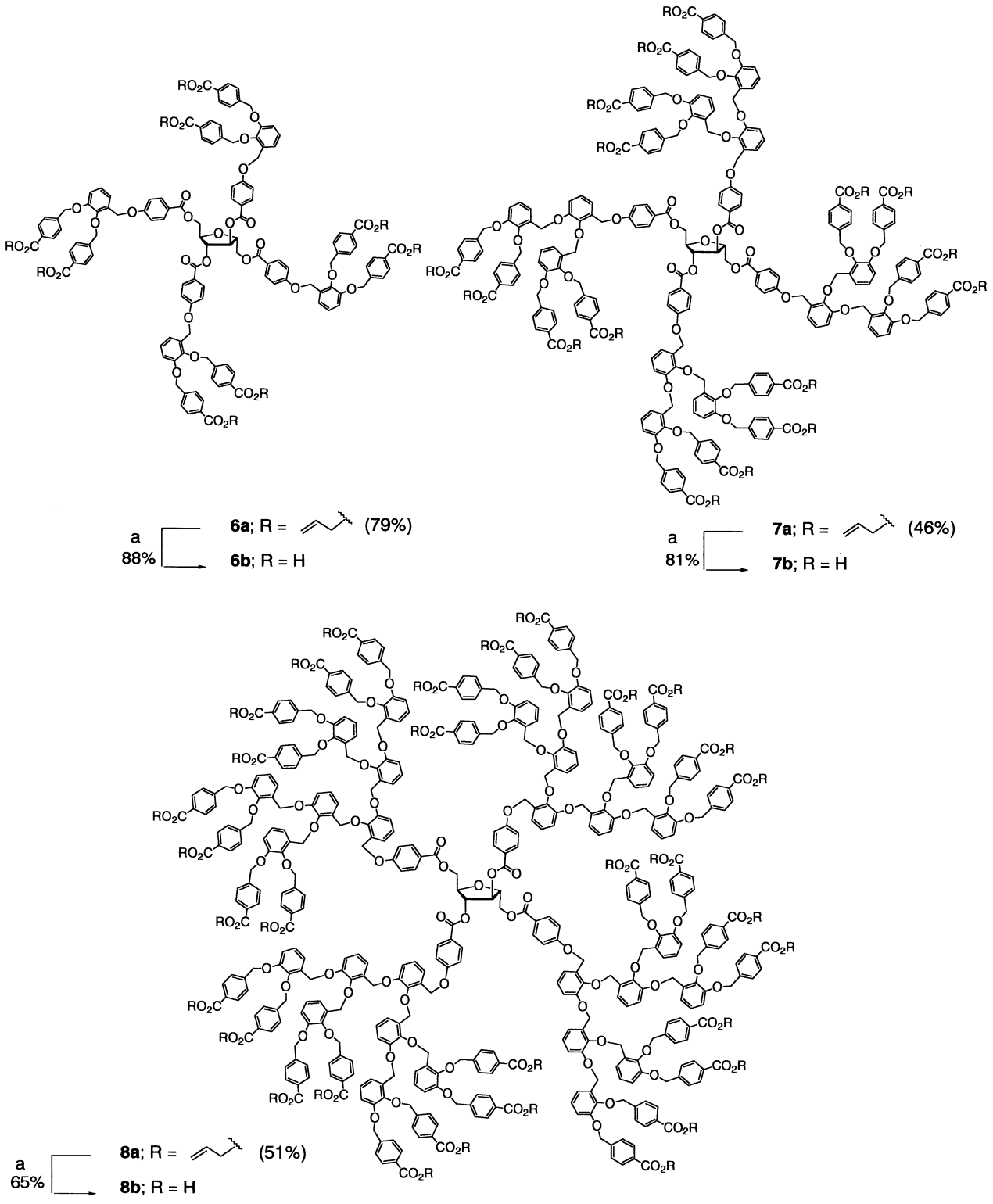


Figure 1. Unsymmetrically branched amphiphilic dendrimers. (a) 2.5 mol% $Pd_2(dba)_3CHCl_3$–25 mol% PPh_3, 1.2 M $HCO_2H/(C_4H_9)_3N$ (1:1) in THF, 50°C.

lower molecular weights observed for the isomeric 2,3-branched dendrimers relative to the 3,5-branched architecture is consistent with a more compact dendrimer conformation. MALDI-TOF mass spectrometry revealed molecular ions consistent with the expected molecular weights. Deprotection of the allyl esters of **6a**–**8a** was effected by exposure to 2.5 mol% $Pd_2(dba)_3CHCl_3$–25 mol% PPh_3 and excess $HCO_2H/(C_4H_9)_3N$ (1:1) in THF at 50°C for 12 h (Fig. 1). This process exhaustively deprotected the dendrimer periphery affording amphiphilic dendrimers **6b**–**8b** in high yields. Negative ion electrospray mass spectrometry displayed ions at $(M-1H)/e=2229$ for **6b** and $(M-3H)/3e=1417$ for **7b**; however, we have been unable to observe distinct ions with dendrimer **8b**.

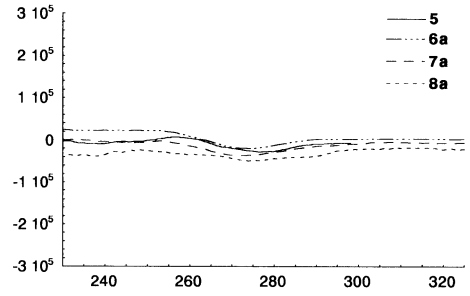


Figure 2. CD spectra of central core **5** and allyl ester terminated dendrimers **6a**–**8a** in THF at 25°C.

2.3. Circular dichroism studies

Circular dichroic spectra were recorded for **5** and dendrimers **6**–**8** to determine the effect of the chiral core on the conformational equilibria of the achiral dendrons as a function of dendrimer generation and solvent quality. In THF, the chiral central core, **5**, and the allyl ester terminated dendrimers, **6a**–**8a**, exhibited very weak excitonic couplets associated with a transition at 262 nm of the 4-alkoxybenzoate linker present at the central core (Fig. 2). A similarly weak couplet was observed in the CD spectra of the carboxylate-terminated dendrimers, **6b**–**8b**, in THF (Fig. 3). The CD spectra depicted in Figs. 2 and 3 were not sensitive to temperature. Consequently, the achiral dendrons were not contributing to the observed chiroptical properties suggesting a lack of chiral conformational order in the branch segments of dendrimers **6a/b**–**8a/b** in organic solvents.

The CD spectra of **5** and **6b**–**8b** were recorded in water (pH 9.0, phosphate) in order to determine whether hydrophobic compression of these unsymmetrically branched dendrimers would facilitate the transfer of chirality from the central core to the achiral dendrons more effectively than observed for analogous 3,5-branched polyarylether dendrimers. In the 3,5-branched systems, the intensity of all the CD spectra were significantly reduced in water relative to THF due to a putative collapse of the dendrimer structure in water; however, no conformational order in the dendritic branches was apparent by CD spectroscopy.[17] Interestingly, in aqueous medium, **5** and **7b**–**8b** exhibited flat lines in the CD spectra similar to the spectra of the 3,5-branched systems (Fig. 4).[12] An intense Cotton effect (CE) at ca.

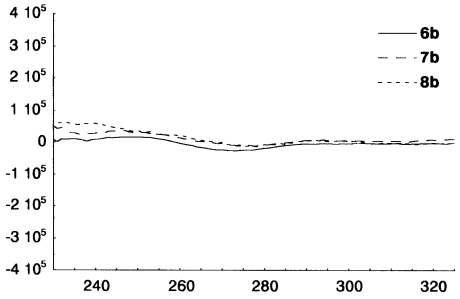


Figure 3. CD spectra of carboxylic acid terminated dendrimers **6b**–**8b** in THF.

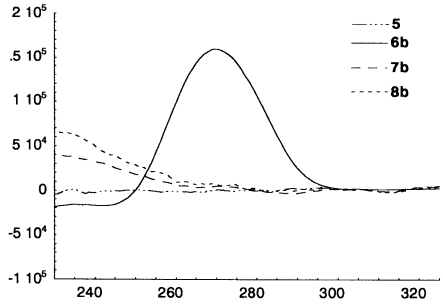


Figure 4. CD spectra of central core **5** and carboxylic acid terminated dendrimers **6b**–**8b** in water (pH 9, phosphate).

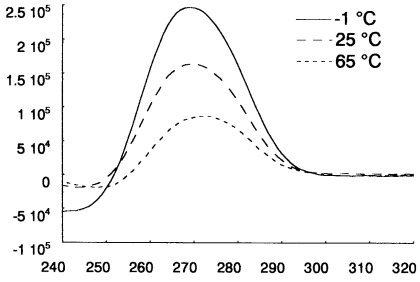


Figure 5. CD spectrum of **6b** in water (pH 9, phosphate) as a function of temperature.

272 nm was observed for the first generation dendrimer, **6b**, in water that was absent in THF. Further, decreasing the temperature to −1°C doubled the intensity of the CE while increasing the temperature to 65°C significantly reduced the intensity of the CE (Fig. 5). This temperature dependence is consistent with a conformational origin of the peak.

Inspection of the ultraviolet spectrum shown in Fig. 6 suggests that this CE arises from a transition of the 2,3-dialkoxybenzyl ether chromophore present in the branch segments of the dendrimer. Dendrimer **6b** displayed a UV spectrum in water (pH 9, phosphate) having two overlapping transitions at approximately 262 and 275 nm. Comparison of the spectra of dendrimer **6b**, central core **5** and $(HO_2C)_2$[G-1]–CH_2OH (**2c**)[18] indicate that the peak at 262 nm is due to a transition of the 4-alkoxybenzoate linkage because, although present in **6b** and **5**, this transition is not present in the spectrum of **2c**. The peak at approximately 275 nm is responsible for the CE observed in the CD spectrum of dendrimer **6b** in water. Comparison of UV

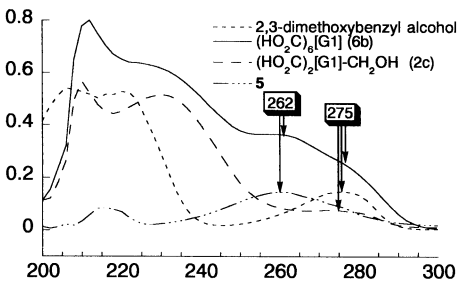


Figure 6. UV spectra of 2,3-dimethoxybenzyl alcohol, **2c** and **6b** in H_2O (pH 9, phosphate) and central core **5** in THF.

spectra of dendrimer **6b** and dendron **2c** indicates that the 2,3-dialkoxybenzyl ether linkage in the dendritic wedge of the dendrimer gives rise to this transition and is responsible for the CE observed in the CD spectrum. The UV spectrum of 2,3-dimethoxybenzyl alcohol, measured in water, also exhibited a transition at 275 nm consistent with this assignment.

Therefore, we can conclude that a conformational change occurs in water that induces a circular dichroism in the 2,3-dialkoxybenzyl subunit present in the dendritic wedges of **6b**. This CE indicates that the chirality of the central core was transferred to the achiral branch segments of the dendrimer in aqueous media. The induction of chirality into the dendrons disappears at the second (**7b**) and third (**8b**) generations and for all the dendrimers in a nonaqueous solvent. The absence of induced chirality in the dendritic wedges at higher dendrimer generation suggests that greater conformational freedom exists in these systems. We have previously observed that analogous 3,5-branched dendrimers in aqueous medium experience a generation-dependent aggregation that decreased with increasing dendrimer generation as evidenced by multi-angle laser light scattering studies (MALLS). This aggregation behavior could be rationalized by increased water compatibility, indicated by MALLS, that is induced by the development of a more globular morphology at higher generations.[12] Consequently, the increased conformational mobility at higher dendrimer generations can be rationalized by the decreasing hydrophobic compression that occurs as the dendrimers become more compatible with the aqueous phase at higher dendrimer generation. These observations highlight the importance of an unsymmetrically branched repeat unit and solvent-induced compression in restricting the conformational mobility in dendrimers.

3. Conclusion

A convenient synthesis of chiral, amphiphilic dendrimers up to the third generation based on an unsymmetrically branched subunit, 2,3-dihydroxybenzyl alcohol, has been described. GPC analysis indicates that these materials are much more compact than the analogous 3,5-branched dendrimers as a consequence of the 2,3-branching pattern. Although these dendrimers are highly flexible, this work underscores the importance of the hydrophobic effect in increasing structural rigidity. At the first dendrimer generation in water, the chirality of the central core is transferred to the 2,3-dihydroxybenzyl linkage of the dendron as indicated by the appearance of a CE upon dissolving in water. Since we have not previously observed this effect for the analogous 3,5-branched systems, the unsymmetric branching appears to be requisite in creating this local chirality in the dendron. The chirality is localized to this chromophore and does not extend further into the dendrons at higher generations presumably due to a decreasing hydrophobic effect at higher dendrimer generation. Therefore, we can conclude that unsymmetrical dendron branching and hydrophobic collapse in water contributes to chirality transfer, but to achieve more extensive conformational order will require significantly more rigid dendrimer scaffolds in conjunction with these effects.

4. Experimental

4.1. General

Melting points were determined in open capillaries and are uncorrected. ^{1}H NMR spectra were recorded at 250, 400, 500 or 600 MHz and ^{13}C NMR spectra at 100 or 125 MHz. EI or FAB mass spectra were recorded at The Ohio State University Chemical Instrument Center. MALDI-TOF spectrometry was performed using 2,5-dihydroxybenzoic acid or 3-indoleacrylic acid as the matrix in tetrahydrofuran (THF). Circular dichroism (CD) measurements were carried out on an Aviv 202 CD spectrometer, using optical grade solvents and quartz glass cuvettes with a 10 mm path length. All reactions were performed under an argon or nitrogen atmosphere. Dimethylformamide (DMF) was dried by distillation from barium oxide or magnesium sulfate; THF was distilled from sodium/benzophenone ketyl and dichloromethane was distilled from calcium hydride. Chromatographic separations were performed on silica gel 60 (230–400 mesh, 60 Å) using the indicated solvents.

4.1.1. $(CH_3O_2C)_2$[G-1]–CHO (2a). Methyl 4-bromomethylbenzoate (17.41 g, 76.0 mmol), 2,3-dihydroxybenzaldehyde (5.00 g, 36.2 mmol), potassium carbonate (25.02 g, 181.0 mmol) and 18-C-6 (1.90 g, 7.2 mmol) were sequentially dissolved in a dry 4:1 THF/DMF (181.0 mL). After heating the reaction mixture at 70°C for 10 min, the solvent was removed over 20–30 min under vacuum (60 mmHg). If necessary, this process was repeated by adding an aliquot of solvent followed by removal, until the reaction was complete by TLC. The resultant residue was then partitioned between water (200 mL) and CH_2Cl_2 (200 mL) and the organic layer was washed with water (2×100 mL) and saturated NaCl (2×100 mL) then dried over $MgSO_4$. Concentration of the CH_2Cl_2 layer afforded **2a** as an off-white powder (15.5 g, 35.7 mmol, 99%). Mp=125–126°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.91 (s, 3H), 3.92 (s, 3H), 5.20 (s, 2H), 5.24 (s, 2H), 7.12 (t, J=7.92 Hz, 1H), 7.21 (dd, J=8.07, 1.59 Hz, 1H), 7.39 (d, J=8.46 Hz, 2H), 7.41 (obscured d, 1H), 7.48 (d, J=8.16 Hz, 2H), 7.99 (d, J=8.22 Hz, 2H), 8.04 (d, J=8.25 Hz, 2H), 10.31 (s, 1H). ^{13}C NMR (ppm) (75 MHz, $CDCl_3$) 52.0, 52.1, 70.6, 75.6, 119.9, 120.2, 124.4, 127.0, 127.8, 129.7, 129.9, 130.0, 130.5, 141.1, 141.3, 151.0, 151.5, 166.5, 189.6. Anal. calcd for $C_{25}H_{22}O_7$: C, 69.12; H, 5.10. Found: C, 69.09; H, 5.10.

4.1.2. $(CH_3O_2C)_2$[G-1]–CH_2OH (2b). A suspension of $(CH_3O_2C)_2$[G-1]–CHO, **2a**, (11.75 g, 27.0 mmol) in methanol (135.0 mL) was stirred at reflux under nitrogen for 10 min, whereupon the addition of sodium borohydride (1.12 g, 29.7 mmol) resulted in a homogeneous mixture. After 3 h, the mixture was allowed to cool to room temperature and 0.1 M NaOH (150 mL) was added. This mixture was stirred for 5 min and then partitioned between CH_2Cl_2 (150 mL) and water (150 mL). The aqueous layer was extracted with CH_2Cl_2 (2×100 mL) and the combined organic layers were dried over $MgSO_4$. Concentration of the CH_2Cl_2 layer afforded **2b** as a tan solid (11.32 g, 25.93 mmol, 96%). Mp=88–90°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.88 (s, 3H), 3.90 (s, 3H), 4.63 (s, 2H), 5.12 (s, 2H), 5.13 (s, 2H), 6.91 (dd, J=7.50, 2.08 Hz, 1H),

6.92–7.07 (m, 2H), 7.44 (d, J=8.06 Hz, 2H), 7.45 (d, J=7.94 Hz, 2H), 7.97 (d, J=8.34 Hz, 2H), 8.00 (d, J=8.38 Hz, 2H). ^{13}C NMR (ppm) (75 MHz, $CDCl_3$) 52.0, 52.0, 61.0, 70.3, 74.4, 113.9, 121.4, 124.4, 126.9, 127.6, 129.6, 129.8, 135.2, 141.8, 142.5, 145.9, 151.2, 166.5, 166.6. Anal. calcd for $C_{25}H_{24}O_7$: C, 68.80; H, 5.54. Found: C, 68.68; H, 5.50.

4.1.3. (HO_2C)$_2$[G-1]–CH_2OH (2c). (CH_3O_2C)$_2$[G-1]–CH_2OH (**2b**) (14.59 g, 33.4 mmol) was dissolved in THF (100 mL) to which NaOH (3.42 g, 85.5 mmol) in water (100 mL) was added. The reaction was heated at reflux for 14 h. The reaction was cooled to ambient temperature, diluted with water (75 mL), and acidified to pH 1 with HCl 1.2N. The resulting milky solution was cooled to −4°C for 3 h and a white solid was isolated by filtration. The solid was dried over phosphorous pentoxide under vacuum (0.3 mmHg) for several days to afford a white solid (13.01 g, 31.8 mmol, 96%). Mp=218–225°C (water). ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.52 (s, 2H), 5.10 (s, 2H), 5.25 (s, 2H), 7.03–7.11 (m, 3H), 7.54 (d, J=8.2 Hz, 2H), 7.58 (d, J=8.2 Hz, 2H), 7.93 (d, J=7.9 Hz, 2H), 7.97 (d, J=9.4 Hz, 2H), 12.95 (bs, 2H). ^{13}C NMR (ppm) (400 MHz, DMSO-d_6) 58.4, 69.7, 73.9, 113.2, 120.6, 124.4, 127.7, 128.2, 129.6, 129.8, 130.5, 130.5, 136.8, 142.5, 143.0, 144.9, 151.2, 167.4, 167.5. IR (film): 3407, 1692 cm^{-1} MS for $C_{23}H_{20}O_7Na$ (M+Na) (Q-TOF Electrospray MS) calcd 431.1107; obsd 431.1111.

4.1.4. (HO_2C)$_2$[G-1]–CHO (2d). (CH_3O_2C)$_2$[G-1]–CHO (**2a**) (9.28 g, 21 mmol) was suspended in THF (35 mL) and 2 M NaOH (aq.) (25 mL). THF (50 mL) and water (50 mL) were added to dissolve the solid and the resulting homogeneous solution was heated at reflux for 5 h. The reaction mixture was cooled to ambient temperature, diluted with water (50 mL), and acidified to pH 1 with 1.2N HCl (aq.). The solid was isolated by filtration and the resulting filtrate was rinsed with cold water, cold diethyl ether, and dried over phosphorous pentoxide under vacuum (0.3 mmHg) affording **2d** as a white solid (7.81 g, 19 mmol, 92%). Mp=257–262°C (dec.) (H_2O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.26 (s, 2H), 5.33 (s, 2H), 7.22 (t, J=7.8 Hz, 1H), 7.29 (d, J=7.4 Hz, 1H), 7.51 (d, J=7.8 Hz, 3H), 7.61 (d, J=7.8 Hz, 2H), 7.90 (d, J=7.8 Hz, 2H), 7.97 (d, J=7.8 Hz, 2H), 10.19 (s, 1H), 13.00 (bs, 2H). ^{13}C NMR (ppm) (100 MHz, DMSO-d_6) 70.1, 75.3, 119.4, 120.6, 125.1, 127.9, 128.8, 129.7, 129.9, 130.2, 130.8, 130.9, 141.7, 141.8, 150.8, 152.1, 167.4, 190.1. IR (film): 3416, 1683 cm^{-1}. MS for $C_{23}H_{18}O_7Na$ (M+Na) (Q-TOF Electrospray MS) calcd 429.09; obsd 429.1. Anal. calcd for $C_{23}H_{18}O_7$: C, 67.98; H, 4.46. Found: C, 67.89; H, 4.62.

4.1.5. ($AllylO_2C$)$_2$[G-1]–CHO (2e). (HO_2C)$_2$G-1-CHO (**2d**) (2.53 g, 6.23 mmol), K_2CO_3 (3.44 g, 24.9 mmol), and 18-C-6 (0.17 g, 0.64 mmol) were dissolved in THF/DMF 4:1 (50 mL) and allyl bromide (1.5 mL, 2.1 g, 17 mmol) was added. After heating the mixture at reflux for 18 h, the mixture was cooled to ambient temperature, the solvent removed in vacuo. The resulting residue was partitioned between dichloromethane (150 mL) and water (100 mL) and the aqueous phase was washed with dichloromethane (3×100 mL). The combined organic layers were then dried over $MgSO_4$, filtered and the concentrated in vacuo to a yellow solid. Purification by flash chromatography (SiO_2) (0→5% CH_2Cl_2/diethyl ether) affording a white solid (2.89 g, 5.95 mmol, 96%). Mp=69–72°C (CH_2Cl_2/diethyl ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.83 (m, 4H), 5.22 (s, 2H), 5.26 (s, 2H), 5.29 (dt, J=9.44, 1.0 Hz, 1H), 5.42 (dt, J=17.2, 1.3 Hz, 1H), 6.03 (m, 2H), 7.14 (t, J=8.0 Hz, 1H), 7.21 (d, J=8.0 Hz, 1H), 7.43 (m, 3H), 7.51 (d, J=8.2 Hz, 2H), 8.03 (d, J=8.2 Hz, 2H), 8.08 (d, J=8.2 Hz, 2H), 10.31 (s, 1H). ^{13}C NMR (ppm) (100 MHz, $CDCl_3$) 66.1, 66.2, 71.1, 76.1, 118.7, 118.8, 120.4, 120.7, 124.9, 127.5, 128.4, 130.4, 130.5, 130.6, 130.8, 132.6, 132.6, 141.7, 141.9, 151.7, 152.2, 166.2, 166.2, 190.1. IR (neat film): 1726, 1678 cm^{-1}. MS for $C_{29}H_{26}O_7Na$ (Electrospray) (M+Na) calcd 509.2; obsd 509.2. Anal. calcd for $C_{29}H_{26}O_7$: C, 71.59; H, 5.39. Found: C, 71.36, H, 5.46.

4.1.6. ($AllylO_2C$)$_2$[G-1]–CH_2OH (2f). ($AllylO_2C$)$_2$[G-1]–CHO (**2e**) (2.77 g, 5.70 mmol) was dissolved in dry THF (15 mL) and cooled to −78°C, whereupon diisobutylaluminum hydride (DIBAL-H) (7.9 mL, 7.9 mmol, 1 M in hexanes) was added dropwise via syringe. After 10 min, aqueous saturated ammonium chloride (20 mL) was carefully added and the mixture was warmed up to ambient temperature. The mixture was then partitioned between saturated aqueous sodium bicarbonate (14 mL) and CH_2Cl_2 (46 mL). The organic layer was extracted further with CH_2Cl_2 (4×50 mL) and the combined organic layers were washed with brine (75 mL), dried ($MgSO_4$), and the solvent was removed in vacuo. Purification by flash chromatography (SiO_2) (95:5 CH_2Cl_2/diethyl ether) afforded **2f** as a white solid (2.22 g, 4.55 mmol, 80%). Mp=63–66°C (CH_2Cl_2/diethyl ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.63 (s, 2H), 4.83 (bs, 4H), 5.17 (s, 2H), 5.19 (s, 2H), 5.29 (d, J=10.4 Hz, 2H), 5.42 (d, J=17.1 Hz, 2H), 6.05 (m, 2H), 6.98 (t, J=7.7 Hz, 2H), 7.05 (d, J=7.8 Hz, 1H), 7.46–7.51 (m, 4H), 8.03–8.08 (m, 4H). ^{13}C NMR (ppm) (100 MHz, $CDCl_3$) 60.6, 64.7, 64.8, 69.5, 73.6, 113.2, 117.4, 117.5, 120.7, 123.6, 126.1, 126.9, 129.0, 129.1, 131.3, 131.3, 134.3, 141.0, 141.7, 145.1, 150.4, 165.0, 165.1. IR (dry film): 3340, 1714 cm^{-1}. HRMS (EI) for $C_{29}H_{28}O_7$ calcd 488.1835; obsd 488.1841. Anal. calcd for $C_{29}H_{28}O_7$: C, 71.30; H, 5.78; Found: C, 71.54, H, 5.61.

4.1.7. ($AllylO_2C$)$_2$[G-1]–CH_2Br (2g). ($AllylO_2C$)$_2$[G-1]–CH_2OH (**2f**) (2.34 g, 4.79 mmol) was dissolved in CH_2Cl_2 (4 mL) at 0°C, and phosphorous tribromide (228 μL, 0.65 g, 2.39 mmol) was added. After 1.5 h, the solvent was evaporated to dryness and the residue was partitioned between CH_2Cl_2 (50 mL) and water (50 mL). The aqueous layer was washed with CH_2Cl_2 (3×50 mL) and the combined organic layers were dried ($MgSO_4$), concentrated in vacuo and purified by flash chromatography (SiO_2) (CH_2Cl_2) affording **2g** as a white solid (2.40 g, 4.36 mmol, 91%). Mp=69–77°C (CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.53 (s, 2H), 4.84 (bs 4H), 5.18 (s, 2H), 5.26 (s, 2H), 5.35 (d, J=10.4 Hz, 2H), 5.42 (d, J=16.4 Hz, 2H), 6.05 (m, 2H), 6.94 (dd, J=7.11, 2.5 Hz, 1H), 7.02 (t, J=7.10 Hz, 2H), 7.49 (d, J=8.1 Hz, 2H), 7.54 (d, J=8.1 Hz, 2H), 8.06 (d, J=8.2 Hz, 2H), 8.10 (d, J=8.2 Hz, 2H). ^{13}C NMR (ppm) (100 MHz, $CDCl_3$) 66.0, 66.1, 70.8, 74.4, 115.2, 118.7, 118.8, 123.8, 125.0, 127.4, 128.1, 128.3, 130.1, 130.3, 130.3, 130.4, 132.6, 132.7, 132.9, 142.1, 143.1, 146.9, 152.1, 166.3, 166.5. IR (neat film): 1721 cm^{-1}. HRMS

(EI) for $C_{29}H_{27}BrO_6$ (M) calcd 550.0991; obsd 550.0993. Anal. calcd for $C_{29}H_{27}BrO_6$: C, 63.17; H, 4.94; Br, 14.49. Found: C, 63.01; H, 4.92; Br, 14.36.

4.1.8. (AllylO$_2$C)$_4$[G-2]–CHO (3a). (AllylO$_2$C)$_2$[G-1]–CH_2Br (**2g**) (3.65 g, 6.62 mmol), was converted to (Allyl $O_2C)_4$-[G-2]–CHO (**3a**) using 2,3-dihydroxybenzaldehyde (0.46 g, 3.35 mmol), K_2CO_3 (3.36 g, 24.3 mmol) and 18-C-6 (0.11 g, 0.40 mmol) in THF (5 mL) and DMF (1.5 mL) as described for **2a**. Purification by flash chromatography (SiO_2) (95:5 CH_2Cl_2/diethyl ether) afforded **3a** as a white solid (3.36 g, 3.12 mmol, 99%). Mp=100–105°C (CH_2Cl_2/diethyl ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.80–4.84 (m, 8H), 5.00 (s, 2H), 5.04 (s, 2H), 5.14 (bs, 4H), 5.19 (bs, 4H), 5.28 (m, 4H), 5.42 (m, 4H), 5.98–6.08 (m, 4H), 6.95–7.06 (m, 8H), 7.31–7.50 (m, 9H), 7.91–7.97 (m, 4H), 8.03–8.07 (m, 4H), 10.18 (s, 1H). ^{13}C NMR (ppm) (100 MHz, $CDCl_3$) 65.4, 65.4, 66.2, 70.2, 70.3, 71.2, 74.2, 74.4, 114.2, 118.0, 118.1, 118.2, 119.5, 121.5, 124.0, 124.2, 124.4, 126.8, 127.2, 127.6, 129.5, 129.6, 129.8, 129.8, 130.3, 130.8, 132.0, 141.7, 142.4, 142.5, 151.2, 165.7, 190.2. IR (neat film): 1720, 1687 cm^{-1}. MS for $C_{65}H_{58}O_{15}K$ (MALDI-TOF) (M+K) calcd 1117.4; obsd 1117.3. Anal. calcd for $C_{65}H_{58}O_{15}$: C, 72.34; H, 5.42; Found: C, 72.44, H, 5.42.

4.1.9. (AllylO$_2$C)$_4$[G-2]–CH$_2$OH (3b). (AllylO$_2$C)$_4$[G-2]–CHO (**3a**) (3.36 g, 3.11 mmol) was converted to (Allyl $O_2C)_4$[G-2]–CH_2OH (**3b**) using DIBAL-H (4.5 mL, 4.5 mmol, 1 M in hexanes) in THF (11 mL) at −78°C for 2 h as described for **2f**. Purification by flash chromatography (SiO_2) (95:5 CH_2Cl_2/diethyl ether) afforded **3b** as a white solid (2.51 g, 2.32 mmol, 75%). Mp=85–90°C (CH_2Cl_2/diethyl ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.89 (bs, 1H), 4.51 (s, 2H), 4.79–4.84 (m, 8H), 5.04 (bd, 4H), 5.11 (s, 2H), 5.12 (s, 2H), 5.15 (s, 2H), 5.17 (s, 2H), 5.26–5.31 (m, 4H), 5.37–5.39 (m, 2H), 5.42–5.44 (m, 2H), 5.92–6.10 (m, 4H), 6.82–7.08 (m, 9H), 7.35 (d, J=8.2 Hz, 2H), 7.39 (d, J=8.2 Hz, 2H), 7.43 (d, J=8.2 Hz, 2H), 7.47 (d, J=8.2 Hz, 2H), 7.92 (d, J=8.2 Hz, 2H), 7.95 (d, J=8.2 Hz, 2H), 8.02 (d, J=8.2 Hz, 2H), 8.05 (d, J=8.2 Hz, 2H). ^{13}C NMR (ppm) (100 MHz, $CDCl_3$) 62.0, 65.9, 66.0, 66.1, 66.5, 70.5, 70.8, 70.9, 74.9, 75.0, 114.3, 114.7, 115.0, 118.6, 118.6, 118.7, 118.7, 121.6, 123.4, 124.6, 124.8, 124.8, 127.4, 127.4, 128.2, 127.8, 127.9, 130.1, 130.1, 130.2, 130.3, 130.4, 130.4, 131.9 132.5, 132.6, 132.6, 132.7, 132.7, 135.6, 142.3, 142.3, 143.1, 143.2, 146.4, 151.8, 152.0, 166.3, 166.4. IR (neat film): 3329, 1721 cm^{-1}. MS for $C_{65}H_{60}O_{15}Na$ (MALDI-TOF) (M+Na) calcd 1103.4; obsd 1103.0. Anal. calcd for $C_{65}H_{60}O_{15}$: C, 72.21; H, 5.59. Found: C, 72.32, H, 5.49.

4.1.10. (AllylO$_2$C)$_4$[G-2]–CH$_2$Br (3c). Carbon tetrabromide (CBr_4) (1.53 g, 4.63 mmol) and triphenylphosphine (1.21 g, 4.61 mmol) were added to a solution of (allylO$_2$C)$_4$[G-2]–CH_2OH (**3b**) (2.50 g, 2.31 mmol) in THF (12.5 mL). After 5 min at room temperature, the mixture was partitioned between water (20 mL) and CH_2Cl_2 (50 mL). The aqueous phase was extracted with CH_2Cl_2 (4×50 mL) and the combined organic phases were dried ($MgSO_4$), and concentrated in vacuo. Purification by flash chromatography (SiO_2) (50⟶100% CH_2Cl_2/hexanes) affording **3c** as a white solid (2.35 g, 2.05 mmol, 89%). Mp=70–81°C (CH_2Cl_2/diethyl ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.45 (s, 2H), 4.79–4.84 (m, 8H), 5.03 (s, 2H), 5.07 (s, 2H), 5.10 (s, 2H), 5.15 (s, 2H), 5.16 (s, 2H), 5.22 (s, 2H), 5.25–5.31 (m, 4H), 5.37–5.45 (m, 4H), 5.91–6.10 (m, 4H), 6.82 (dd, J=2.9 Hz, 6.7 Hz, 1H), 6.87–7.04 (m, 7H), 7.17 (d, J=6.78 Hz, 1H), 7.38 (d, J=8.1 Hz, 2H), 7.40 (d, J=8.2 Hz, 2H), 7.45 (d, J=8.2 Hz, 2H), 7.49 (d, J=8.2 Hz, 2H), 7.90 (d, J=8.2 Hz, 2H), 7.95 (d, J=8.2 Hz, 2H), 7.99 (d, J=8.4 Hz, 2H), 8.02 (d, J=8.4 Hz, 2H). ^{13}C NMR (ppm) (100 MHz, $CDCl_3$) 28.9, 53.9, 65.9, 66.0, 66.1, 66.1, 66.6, 70.3, 70.8, 74.9, 75.0, 114.7, 118.6, 118.6, 118.7, 118.7, 127.4, 127.4, 127.9, 128.2, 130.0, 130.2, 130.2, 130.3, 130.3, 130.4, 132.7, 132.7, 132.7, 132.7, 132.7, 142.4, 142.5, 143.1, 143.5, 146.6, 151.8, 152.3, 166.3, 166.3, 166.3, 166.4. IR (dry film): 1720 cm^{-1}. MS for $C_{65}H_{59}BrO_{14}K$ (M+K) (MALDI-TOF) calcd 1183.18; obsd 1184.5. Anal. calcd for $C_{65}H_{59}BrO_{14}$: C, 68.24; H, 5.20. Found: C, 68.00, H, 5.32.

4.1.11. (AllylO$_2$C)$_8$[G-3]–CHO (4a). (AllylO$_2$C)$_4$[G-2-]CH_2Br (**3c**) (0.90 g, 0.79 mmol), was converted to (allyl $O_2C)_8$[G-3]–CHO (**4a**) using 2,3-dihydroxybenzaldehyde (0.056 g, 0.4 mmol), K_2CO_3 (0.48 g, 3.5 mmol) and 18-C-6 (11 mg, 0.04 mmol) in THF (4 mL) and DMF (1 mL) as described for **2a**. Purification by flash chromatography (SiO_2) (95:5 CH_2Cl_2/diethyl ether) affording **4a** as a white solid (0.69 g, 0.3 mmol, 78%). Mp=105–110°C (CH_2Cl_2/diethyl ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.75 (bd, 2H), 4.77 (bd, 2H), 4.78–4.84 (m, 12H), 4.89 (s, 2H), 4.95 (s, 2H), 4.97 (s, 2H), 5.03 (s, 4H), 5.05 (s, 2H), 5.06 (s, 2H), 5.08 (s, 2H), 5.09 (s, 2H), 5.11 (s, 4H), 5.14 (s, 4H), 5.15 (s, 2H), 5.24–5.31 (m, 8H), 5.38–5.43 (m, 8H), 5.95–6.09 (m, 8H), 6.76–7.05 (m, 21H), 7.21–7.30 (m, 4H), 7.37–7.43 (m, 8H), 7.46–7.49 (m, 4H), 7.87–8.20 (m, 8H), 7.81–8.31 (m, 4H), 10.1 (s, 1H). ^{13}C NMR (ppm) (100 MHz, $CDCl_3$) 65.9, 66.0, 66.0, 66.0, 66.5, 70.6, 70.7, 70.8, 71.9, 74.7, 74.8, 74.9, 114.5, 118.6, 118.7, 118.7, 118.7, 127.4, 127.4, 127.7, 127.7, 128.2, 130.0, 130.0, 130.2, 130.3, 130.3, 130.4, 132.7, 132.7, 132.7, 132.7, 142.3, 142.3, 143.1, 143.2, 146.2, 151.8, 151.8, 166.3, 166.3, 190.9. IR (neat film): 1720 cm^{-1}. MS for $C_{137}H_{122}O_{31}Na$ (M+Na) (MALDI-TOF) calcd 2287.4; obsd 2287.4. Anal. calcd for $C_{137}H_{122}O_{31}$: C, 72.67; H, 5.43. Found: C, 72.49, H, 5.39.

4.1.12. (AllylO$_2$C)$_8$[G-3]–CH$_2$OH (4b). (AllylO$_2$C)$_8$[G-3]–CHO (**4a**) (0.68 g, 0.3 mmol) was converted to (allylO$_2$C)$_8$[G-3]–CH_2OH (**4b**) using DIBAL-H (0.4 mL, 0.4 mmol, 1 M in hexanes) in THF (2.8 mL) at −78°C for 30 min as described for **2f**. Purification by flash chromatography (SiO_2) (0⟶5% diethyl ether/CH_2Cl_2) affording **4b** a white glass (0.41 g, 0.18 mmol, 59%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.46 (s, 2H), 4.77–4.83 (m, 16H), 4.91 (s, 2H), 4.96 (s, 2H), 4.98 (s, 2H), 5.04 (s, 2H), 5.07 (m, 20H), 5.21–5.29 (m, 8H), 5.31–548 (m, 8H), 5.96–6.10 (m, 8H), 6.70 (m, 1H), 6.82–7.15 (m, 20H), 7.27 (d, J=8.47 Hz, 2H), 7.31 (d, J=8.17 Hz, 2H), 7.38–7.43 (m, 8H), 7.47 (d, J=8.2 Hz, 2H), 7.51 (d, J=8.2 Hz, 2H), 7.83–7.85 (m, 4H), 7.91–8.01 (m, 8H), 8.06 (m, 4H). ^{13}C NMR (ppm) (100 MHz, $CDCl_3$) 61.7, 65.9, 65.9, 656.0, 66.0, 66.4, 70.4, 70.5, 70.7, 70.8, 74.8, 74.9, 114.5, 118.6, 118.6, 118.7, 124.6, 124.8, 127.3, 127.4, 127.7, 127.7, 128.1, 129.9, 130.0, 130.2, 130.3, 130.3, 130.4, 131.8,

132.4, 132.6, 142.3, 142.4, 143.1, 143.3, 146.6, 151.6, 151.8, 166.3, 166.4. IR (neat film): 2923, 1719 cm^{-1}. MS for $C_{137}H_{124}O_{31}Na$ (M+Na) (MALDI-TOF) calcd 2289.42; obsd 2289.9. Anal. calcd for $C_{137}H_{124}O_{31}$: C, 72.60; H, 5.51. Found: C, 72.45; H, 5.49.

4.1.13. (AllylO$_2$C)$_8$[G-3]–CH$_2$Br (4c). (AllylO$_2$C)$_8$[G-3]–CH_2OH (0.38 g, 0.17 mmol) was converted to (allylO$_2$C)$_8$ [G-3]–CH_2Br (**4c**) using CBr_4 (0.17 g, 0.5 mmol) and triphenylphosphine (0.14 g, 0.5 mmol) in THF (2 mL) as described for **3c**. Purification by flash chromatography (SiO_2) (50⟶100% CH_2Cl_2/hexanes) afforded **4c** as a clear glass (0.30 g, 0.13 mmol, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.37 (s, 2H), 4.74–4.82 (m, 16H), 4.89 (s, 2H), 4.91 (s, 4H), 5.00 (s, 2H), 5.02–5.12 (m, 20H), 5.22–5.28 (m, 8H), 5.33–5.44 (m, 8H), 5.93–6.07 (m, 8H), 6.64 (d, J=7.9 Hz, 1H), 6.76–7.15 (m, 20H), 7.23–7.45 (m, 16H), 7.9–8.2 (m, 16H). ^{13}C NMR (ppm) (100 MHz, $CDCl_3$) 29.1, 65.9, 65.9, 66.0, 66.0, 66.1, 66.2, 66.5, 70.5, 70.6, 70.7, 70.7, 74.7, 74.8, 74.9, 114.7, 118.6, 118.7, 118.7, 118.7, 127.4, 127.4, 127.5, 127.7, 128.2, 130.0, 130.0, 130.1, 130.2, 130.3, 130.3, 130.4, 132.7, 132.7, 132.7, 142.4, 142.4, 143.2, 143.2, 151.8, 151.8, 151.8, 166.3, 166.3, 166.3, 166.4. IR (neat film): 1721 cm^{-1}. MS for $C_{137}H_{123}BrO_{30}Na$ (M+Na) (MALDI-TOF) calcd 2351.7; obsd 2351.0. Anal. calcd for $C_{137}H_{123}BrO_{30}$: C, 70.64; H, 5.32; Found: C, 70.39, H, 5.31.

4.1.14. (AllylO$_2$C)$_8$[G-1]–dendrimer (6a). (AllylO$_2$C)$_2$ [G-1]–CH_2Br (**2g**) (207 mg, 0.38 mmol), **5** (54.6 mg, 0.085 mmol), finely powdered K_2CO_3 (140 mg, 1.01 mmol), and 18-C-6 (10.4 mg, 0.039 mmol) were dispersed in 4:1 THF/DMF (1.0 mL) and heated to 70°C. After 14 h, the solvent was removed in vacuo, and the resultant residue was partitioned between CH_2Cl_2 (5 mL), and water (5 mL). The aqueous phase was then separated and extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo producing a white solid. Purification by flash chromatography (SiO_2) (5% diethyl ether/CH_2Cl_2) afforded **6a** as a white solid (169 mg, 0.067 mmol, 79%). Mp=52–60°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.71 (bs, 6H), 4.74–4.83 (m, 16H), 5.04 (d, J=10.8 Hz, 8H), 5.14–5.17 (m, 16H), 5.24–5.30 (m, 8H), 5.35–5.43 (m, 8H), 5.73 (s, 2H), 5.96–6.09 (m, 8H), 6.84 (d, J=8.6 Hz, 4H), 6.89 (d, J=8.6 Hz, 4H), 6.96–7.03 (m, 12H), 7.41–7.37 (m, 8H), 7.48–7.51 (m, 8H), 7.94–7.98 (m, 12H), 8.01–8.07 (m, 12H). ^{13}C NMR (ppm) (100 MHz, $CDCl_3$) 64.2, 65.8, 65.9, 66.0, 66.1, 70.8, 75.1, 79.8, 82.54, 114.7, 114.9, 118.6, 118.8, 122.0, 122.3, 122.8, 125.0, 127.4, 128.2, 130.2, 130.3, 130.4, 131.1, 131.2, 132.3, 132.4, 132.6, 132.6, 142.3, 142.9, 146.5, 151.9, 162.9, 163.3, 165.7, 166.3. IR (neat film): 1718 cm^{-1}. MS for $C_{150}H_{132}O_{137}Na$ (M+Na) (MALDI-TOF) calcd 2547.8; obsd 2546.2. Anal. calcd for $C_{150}H_{132}O_{37}$: C, 71.30; H, 5.27; Found: C, 70.95, H, 5.35.

4.1.15. (HO$_2$C)$_8$[G-1]–dendrimer (6b). $Pd_2(dba)_3$·$CHCl_3$ (24.7 mg, 0.024 mmol) and triphenylphosphine (62.8 mg, 0.239 mmol) were mixed in THF (2.2 mL) and stirred at ambient temperature until the solution became bright yellow and homogeneous (ca. 5 min). (AllylO$_2$C)$_8$[G-1]–dendrimer **6a** (0.13 g, 0.051 mmol) was dissolved in a portion of this solution (0.58 mL, 0.0059 mmol,) and 1 mL of a pre-formed 1.2 M solution of N(C_4H_9)$_3$/HCO_2H (1:1) in THF. The mixture was then heated to 55°C for 20 h and the solvent was removed in vacuo. The oily residue was dissolved in CH_2Cl_2 (10 mL) and washed with water (10 mL). The CH_2Cl_2 layer was concentrated in vacuo and the resultant yellow solid was dissolved in 20 mL of 5% aqueous $NaHCO_3$ and washed with 20 mL diethyl ether. The aqueous layer was diluted to 50 mL with water and acidified with concentrated hydrochloric acid to pH 2 causing a precipitate to form which was filtered, washed with two portions of deionized water (10 mL) and dried for 12 h in a vacuum dessicator (0.1 mmHg) over P_2O_5 affording dendrimer **6b** as a white solid (0.1005 g, 0.045 mmol, 88%). Mp=167–174°C (water). ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.20–4.66 (m, 6H), 5.05–5.10 (m, 16H), 5.24–5.26 (m, 8H), 5.64 (s, 2H), 6.82–7.15 (m, 20H), 7.39–7.43 (m, 8H), 7.55–7.58 (m, 8H), 7.75–7.95 (m, 24H), 12.94 (bs, 8H). ^{13}C NMR (ppm) (100 MHz, DMSO-d_6) 59.7, 65.2, 71.1, 75.2, 80.9, 82.7, 116.2, 116.3, 122.9, 123.3, 123.4, 126.0, 129.0, 129.0, 129.1, 129.5, 129.5, 130.9, 130.9, 130.9, 131.1, 131.8, 131.9, 131.9, 133.0, 133.3, 143.5, 143.9, 147.3, 147.4, 152.9, 163.9, 164.2, 166.4, 166.8, 168.4, 168.6, 168.7, 168.7. IR (neat film): 2966, 1718 cm^{-1}. HRMS for $C_{126}H_{100}O_{37}Na$ (M+Na) (electrospray) calcd 2229.1555; obsd 2229.3063.

4.1.16. (AllylO$_2$C)$_{16}$[G-2]–dendrimer (7a). (AllylO$_2$C)$_4$ [G-2]–CH_2Br (**3c**) (0.67 g, 0.58 mmol) was converted to (AllylO$_2$C)$_{16}$[G-2]–dendrimer (**7a**) using **5** (87.5 mg, 0.135 mmol), freshly powdered K_2CO_3 (0.15 g, 1.1 mmol), 18-C-6 (8.3 mg, 0.031 mmol) in 3:1 THF/DMF (12 mL) at 70°C for 14 h as described for dendrimer **6a**. Purification by flash chromatography (SiO_2) (5% diethyl ether/CH_2Cl_2) afforded **7a** as white solid (0.30 g, 0.062 mmol, 46%). Mp=47–57°C (CH_2Cl_2/diethyl ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.64 (bs, 6H), 4.79 (m, 32H), 4.89–5.2 (m, 56H), 5.23–5.43 (m, 32H), 5.64 (s, 2H), 5.93–6.09 (m, 16H), 6.65–7.05 (m, 36H), 7.26–7.48 (m, 40H), 7.82–8.05 (m, 40H). ^{13}C NMR (ppm) (100 MHz, $CDCl_3$) 65.9, 66.0, 66.0, 66.0, 66.4, 70.6, 70.7, 70.8, 74.7, 74.9, 114.5, 114.8, 118.6, 118.7, 118.7, 118.7, 124.9, 127.4, 127.4, 127.7, 128.2, 130.0, 130.1, 130.2, 130.3, 130.4, 131.8, 132.6, 132.6, 132.7, 132.7, 142.3, 143.1, 143.3, 146.6, 151.8, 152.1, 166.2, 166.3. IR (neat film): 1720 cm^{-1}. MS for $C_{294}H_{260}O_{69}Na$ (M+Na) (MALDI-TOF) calcd 4920.07; obsd 4918.2. Anal. calcd for $C_{294}H_{260}O_{69}$: C, 72.11; H, 5.35. Found: C, 72.27, H, 5.32.

4.1.17. (HO$_2$C)$_{16}$[G-2]–dendrimer (7b). (AllylO$_2$C)$_{16}$ [G-2]–dendrimer (**7a**) (210 mg, 0.043 mmol) was converted to (HO$_2$C)$_{16}$[G-2]–dendrimer (**7b**) (148 mg, 0.035 mmol, 81%) as a white solid as described for **6b**. Mp=151–172°C (water). ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.63–4.68 (m, 6H), 4.94–5.33 (m, 56H), 5.66 (s, 2H), 6.73–7.17 (m, 44H), 7.35–7.61 (m, 32H), 7.82–8.23 (m, 40H), 12.96 (bs, 16H). ^{13}C NMR (ppm) (100 MHz, DMSO-d_6) 65.7, 70.6, 70.7, 74.9, 75.0, 115.3, 115.6, 115.7, 122.3, 122.8, 125.3, 125.5, 128.5, 128.5, 128.6, 129.0, 130.4, 130.5, 130.6, 130.7, 131.2, 131.3, 131.4, 131.4, 132.0, 132.7, 132.8, 143.0, 143.1, 143.5, 146.6, 147.0, 152.2, 152.4, 152.6, 163.7, 166.3, 168.3. IR (neat film): 2975, 1690 cm^{-1}. MS for $C_{2\ 4\ 6}H_{193}O_{69}$ (M−3H/3e) (Q-TOF electrospray) calcd 1417.71; obsd 1418.45.

4.1.18. (AllylO_2C)$_{16}$[G-3]–dendrimer (8a). (AllylO_2C)$_8$[G-3]–CH_2Br (**4c**) (150 mg, 0.065 mmol) was converted to (AllylO_2C)$_{16}$[G-3]–dendrimer (**8a**) using **5** (10.3 mg, 0.016 mmol), freshly powdered K_2CO_3 (20 mg, 0.15 mmol), 18-C-6 (11 mg, 0.042 mmol) in 3:1 THF/DMF (2 mL) at 70°C for 14 h as described for dendrimer **6a**. Purification by flash chromatography (SiO_2) (0⟶10% diethyl ether/$CHCl_3$) afforded **8a** as white solid (77 mg, 8.0 μmol, 51%). Mp=50–90°C ($CHCl_3$/diethyl ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.63 (bs, 6H), 4.71–4.84 (m, 64H), 4.94–5.19 (m, 120H), 5.20–5.44 (m, 64H), 5.63 (bs, 2H), 5.97–6.10 (m, 32H), 6.71–7.04 (m, 92H), 7.20–7.41 (m, 64H), 7.75–8.05 (m, 72H). ^{13}C NMR (ppm) (100 MHz, $CDCl_3$) 65.8, 65.9, 66.0, 66.0, 66.0, 66.8, 70.5, 70.6, 70.7, 74.8, 114.4, 118.5, 118.6, 118.6, 118.7, 118.7, 127.3, 127.4, 127.6, 127.7, 128.1, 128.1, 129.9, 130.0, 130.1, 130.2, 130.3, 130.4, 131.8, 132.6, 142.3, 142.4, 143.1, 143.4, 146.2, 151.8, 151.9, 166.3. IR (neat film): 1722 cm^{-1}. MS for $C_{582}H_{516}O_{133}Na$ (M+Na) (MALDI-TOF) calcd 9661.14; obsd 9664.9. Anal. calcd for $C_{582}H_{516}O_{133}$: C, 72.53; H, 5.40. Found: C, 72.20, H, 5.40.

4.1.19. (HO_2C)$_{32}$[G-3]–dendrimer (8b). (AllylO_2C)$_{16}$[G-3]–dendrimer (**8a**) (63 mg, 6.5 μmol) was converted to (HO_2C)$_{32}$[G-3]–dendrimer (**8b**) (0.035 g, 4.19 μmol, 65%) as a waxy white solid as described for **6b**. Mp=165–180°C (water). ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.53–4.58 (m, 6H), 4.76–5.22 (m, 120H), 5.59 (s, 2H), 6.82–7.23 (m, 92H), 7.32–7.55 (m, 64H), 7.67–8.17(m, 72H), 12.88 (bs, 32H). ^{13}C NMR (ppm) (100 MHz, DMSO-d_6) 65.3, 65.8, 69.7, 74.1, 113.9, 114.1, 114.5, 124.4, 124.6, 127.5, 127.7, 127.7, 127.7, 128.1, 129.4, 129.5, 129.6, 129.7, 129.8, 130.3, 130.4, 130.5, 131.2, 131.8, 142.2, 142.7, 145.6, 151.4, 151.4, 151.5, 151.6, 167.4. IR (neat film): 2972, 1691 cm^{-1}.

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References

1. (a) Newkome, G. R.; Moorefield, C. N.; Vögtle, F. *Dendritic Molecules—Concepts–Synthesis–Perspectives*; VCH: New York, 1996. (b) *Dendrimers*, Vogtle, F., Ed.; *Top. Curr. Chem.*, Springer: New York, 1998. (c) *Dendrimers II. Architecture, Nanostructure and Supramolecular Chemistry*, Vogtle, F., Ed.; *Top. Curr. Chem.*, Springer: New York, 2000. (d) *Dendrimers III. Design, Dimension, Function*, Vogtle, F., Ed.; *Top. Curr. Chem.*, Springer: New York, 2001.
2. (a) Mourey, T. H.; Turner, S. R.; Rubinstein, M.; Frechet, J. M. J.; Hawker, C. J.; Wooley, K. L. *Macromolecules* **1992**, *25*, 2401. (b) Wooley, K. L.; Klug, C. A.; Tasaki, K.; Schaefer, J. *J. Am. Chem. Soc.* **1997**, *119*, 53. (c) De Backer, S.; Prinzie, Y.; Verheijen, W.; Smet, M.; Desmedt, K.; Dehaen, W.; De Schryver, F. C. *J. Phys. Chem. A* **1998**, *102*, 5451. (d) Gorman, C. B.; Hager, M. W.; Parkhurst, B. L.; Smith, J. C. *Macromolecules* **1998**, *31*, 815. (e) Topp, A.; Bauer, B. J.; Tomalia, D. A.; Amis, E. J. *Macromolecules* **1999**, *32*, 7232. (f) Kao, H.-M.; Stefanescu, A. D.; Wooley, K. L.; Schaefer, J. *Macromolecules* **2000**, *33*, 6214. (g) Naidoo, K. J.; Hughes, S. J.; Moss, J. R. *Macromolecules* **1999**, *32*, 331.
3. Bosman, A. W.; Janssen, H. M.; Meijer, E. W. *Chem. Rev.* **1999**, *99*, 1665.
4. For an example of a dynamically ordered dendrimer see: (a) Huang, B.; Parquette, J. R. *J. Am. Chem. Soc.* **2001**, *123*, 2689. (b) Recker, J.; Tomcik, D. J.; Parquette, J. R. *J. Am. Chem. Soc.* **2000**, *122*, 10298.
5. For some reviews of chiral dendrimers, see: (a) Seebach, D.; Rheiner, P. B.; Greiveldinger, G.; Butz, T.; Sellner, H. *Top. Curr. Chem.* **1998**, *197*, 125. (b) Peerlings, H. W. I.; Meijer, E. W. *Chem. Eur. J.* **1997**, *3*, 1563. (c) Thomas, C. W.; Tor, Y. *Chirality* **1998**, *10*, 53. For some recent examples, see: (d) Gong, L.-Z.; Hu, Q.-S.; Pu, L. *J. Org. Chem.* **2001**, *66*, 2358. (e) Reuter, C.; Pawlitzki, G.; Worsdorfer, U.; Plevoets, M.; Mohry, A.; Kubota, T.; Okamoto, Y.; Vogtle, F. *Eur. J. Org. Chem.* **2000**, 3059. (f) Turrin, C.-O.; Chiffre, J.; Daran, J.-C.; de Montauzon, D.; Caminade, A.-M.; Manoury, E.; Balavoine, G.; Majoral, J.-P. *Tetrahedron* **2001**, *57*, 2521.
6. (a) Kremers, J. A.; Meijer, E. W. *J. Org. Chem.* **1994**, *59*, 4262. (b) Peerlings, H. W. I.; Strunk, M. P.; Meijer, E. W. *Chirality* **1998**, *10*, 46. (c) Rosini, C.; Superchi, S.; Peerlings, H. W. I.; Meijer, E. W. *Eur. J. Org. Chem.* **2000**, 61.
7. Peerlings, H. W. I.; Trimbach, D. C.; Meijer, E. W. *Chem. Commun.* **1998**, 497.
8. (a) Murat, M.; Grest, G. S. *Macromolecules* **1996**, *29*, 1278. (b) Welch, P.; Muthukumar, M. *Macromolecules* **1998**, *31*, 5892.
9. (a) De Backer, S.; Prinzie, Y.; Verheijen, W.; Smet, M.; Desmedt, K.; Dehaen, W.; De Schryver, F. C. *J. Phys. Chem. A* **1998**, *102*, 5451. (b) Gitsov, I.; Frechet, J. M. J. *J. Am. Chem. Soc.* **1996**, *118*, 3785. (c) Stechemesser, S.; Eimer, W. *Macromolecules* **1997**, *30*, 2204. (d) Topp, A.; Bauer, B. J.; Tomalia, D. A.; Amis, E. J. *Macromolecules* **1999**, *32*, 7232.
10. Naylor, A. M.; Goddard, W. A. I.; Kiefer, G. E.; Tomalia, D. A. *J. Am. Chem. Soc.* **1989**, *111*, 2339. For an example of a dendrimer that folds in a solvent-dependent manner, see Ref. 4.
11. Seebach observed a variation in the sign and shape of the CD spectra with dendrimer generation that occurred in a poor solvent, acetonitrile, but not in a good solvent such as dichloromethane. Murer, P.; Seebach, D. *Helv. Chim. Acta* **1998**, *81*, 603.
12. Laufersweiler, M. J.; Rohde, J. M.; Chaumette, J-L.; Sarazin, D.; Parquette, J. R. *J. Org. Chem.* **2001**, *66*, 6440.
13. For examples of chiral, water-soluble dendrimers, see: (a) Schmitzer, A.; Perez, E.; Rico-Lattes, I.; Lattes, A. *Tetrahedron Lett.* **1999**, *40*, 2947. (b) Schmitzer, A.; Perez, E.; Rico-Lattes, I.; Lattes, A.; Rosca, S. *Langmuir* **1999**, *15*, 4397. (c) Ritzen, A.; Frejd, T. *Eur. J. Org. Chem.* **2000**, 3771. (d) Rico-Lattes, I.; Schmitzer, A.; Perez, E.; Lattes, A. *Chirality* **2001**, *13*, 24.
14. For a preliminary communication of this work, see: Weintraub, J. G.; Parquette, J. R. *J. Org. Chem.* **1999**, *64*, 3796.
15. Hayakawa, Y.; Wakabayashi, S.; Kato, H.; Noyori, R. *J. Am. Chem. Soc.* **1990**, *112*, 1691.
16. See Ref. 12 and Rohde, J. M.; Parquette, J. R. *Tetrahedron Lett.* **1998**, *39*, 9161.

17. We have observed a decrease in CD intensity and optical rotation in analogous 3,5-branched dendrimers. This decrease was corollated with an increasing steric effect that perturbs the conformational equilibrium of the central core rather than contributions from chiral conformations in the branch segments. See Chaumette, J.-L.; Laufersweiler, M. J.; Parquette, J. R. *J. Org. Chem.* **1998**, *12*, 16.
18. Prepared by reduction of **2a** with $NaBH_4$ followed by hydrolysis of the methyl esters with sodium hydroxide.