Pergamon

Tetrahedron Letters 39 (1998) 1701–1704

TETRAHEDRON
LETTERS

Synthesis of Optically Active Chiral Shell Dendrons

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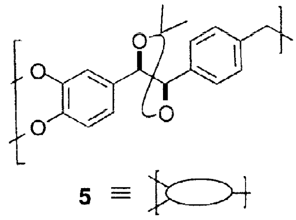
Received 12 November 1997; revised 6 January 1998; accepted 8 January 1998

Abstract: We present the preparation of a series of chiral dendrons, in which chiral subunits are placed in individual generational shells at increasing distances from the focal point, by a combination of convergent and divergent dendrimer synthesis methods. Analysis of chiroptical data suggests that these dendrons do not possess conformational order in solution. © 1998 Elsevier Science Ltd. All rights reserved.

Interest in chiral dendritic structures has increased in recent years because of their potential as supports for asymmetric catalysis and stereoselective recognition. In addition, attention has been paid to the effect of chiral subunits on the conformational order of dendritic structures, the fractal nature of dendritic surfaces, and the connection between microscopic and macroscopic chirality.[1] Reported chiral dendritic structures have included molecules with (a) a chiral core,[2,3] (b) chiral terminal units,[4,5] (c) chiral branching units,[6-9] and (d) combinations thereof, yet there have been no reports of chiral branching units isolated within individual generational shells of a dendrimer. The isolation of chiral units at different positions within dendritic structures would allow the study of the effect of subunit position on dendrimer conformation, catalytic activity, and clathration ability. As part of our program to develop strategies for the incorporation of asymmetric units into dendrimers,[10-13] we present here the preparation of a series of dendritic molecules **1-4** where a generational shell of chiral subunits is placed at varying distances from the focal point of the dendron (Scheme 1). The chiral subunits (**5**) are derivatives of (*R*,*R*)-hydrobenzoin and have been reported previously.[11,14] The achiral branching units are 3,5-substituted benzyl aryl ethers.[15]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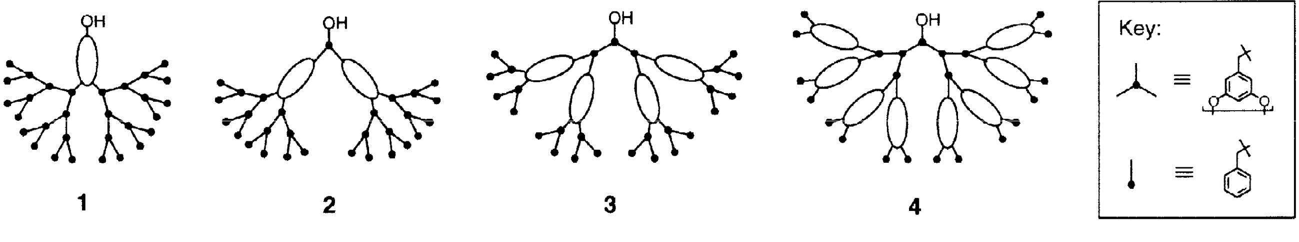
Synthesis of first- and second-shell chiral dendrons **1** and **2** followed a convergent approach (Scheme

Scheme 1. Fourth generation dendrons with chiral shells based on hydrobenzoin-derived subunit **5**.



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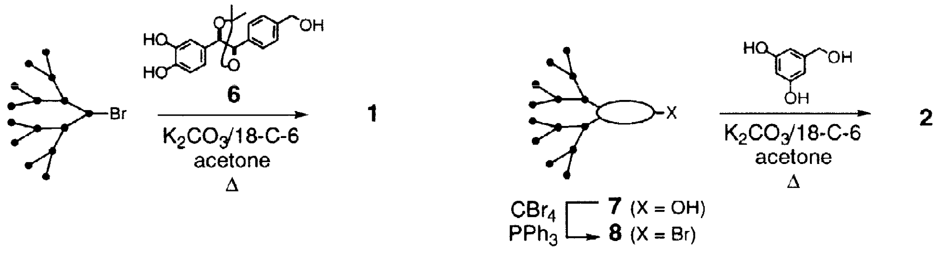
PII: S0040-4039(98)00135-X

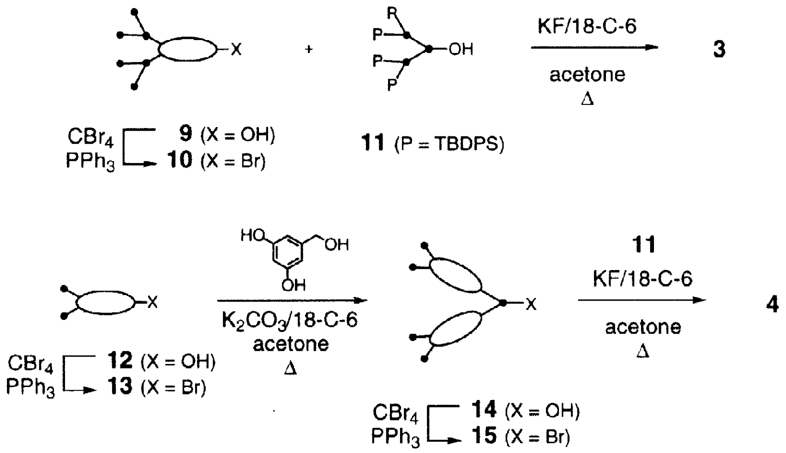
Scheme 2. Synthesis of First- and Second-Shell Chiral Dendrons **1** and **2**.



2). Dialkylation of chiral diphenol **6**[14] with a third generation dendritic bromide of the Fréchet type[15] ([G3]Br) provided first-shell chiral dendron **1** (85%). To prepare second-shell chiral dendron **2**, dendritic alcohol **7** was first obtained from [G2]Br and **6** in 89% yield (K_2CO_3/18-crown-6/acetone). Alcohol **7** was then converted to bromide **8** (CBr_4/PPh_3, 86%) which was allowed to react with 3,5-dihydroxybenzyl alcohol to yield chiral second-shell dendron **2** (92%).

Chiral third- and fourth-shell dendrons **3** and **4** were prepared by a combination of convergent and divergent techniques as pioneered by L'abbé et al (Scheme 3). Alcohol **9**, prepared from [G1]Br and **6** (93%), was converted to bromide **10** (CBr_4/PPh_3, 95%) and then allowed to react with tetrakis(*tert*-butyldiphenylsilyl)-protected dendron **11**[16] in the presence of potassium fluoride and 18-crown-6 in acetone to yield **3** (75%). Fourth-shell chiral dendron **4** was prepared in a similar manner (eq 2). Alcohol **12**[14] was converted to bromide **13** (92%) and then coupled to 3,5-dihydroxy benzyl alcohol to give second generation dendron **14** (49%). Subsequent bromination yielded **15** (CBr_4/PPh_3, 86%) which was used to provide **4** (70%), again by the method of L'abbé.[16]

Scheme 3. Synthesis of Third- and Fourth-Shell Chiral Dendrons **3** and **4**.



All dendrons are colorless glasses which are readily soluble in common organic solvents (acetone, ether, CH_2Cl_2, ethyl acetate). Structural characterization was carried out principally by ^1H and ^{13}C NMR spectroscopy and combustion analysis.[17] In addition, mass spectrometry data (MALDI-TOF) confirms the expected molecular masses for all dendrons reported (Table 1).

We have demonstrated in previous reports that it possible to gain information on the conformation of chiral dendrimers by comparing the chiroptical properties of several dendrimers of similar structure with appropriate low-molecular-weight model compounds.[11-13,18,19] The chiroptical data for dendrons **1-4**, **7**, **9**, and

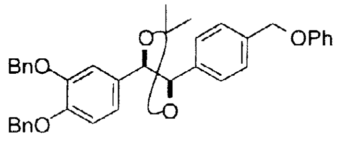
Table 1. Chiroptical[a] and Mass Spectral Data for the Reported Dendrons.

Compound	No. of Chiral Units	FW	$[\alpha]_D^{26}$ [b]	$[\Phi]_D$ [c]	$[\Phi]_D/n$ [d]	Mass Spec.[e] (M+Na)	(M+K)
1	1	3468.08	+17.3	+600	+600	3496.0	3507.1
2	2	3644.29	+41.6	+1516	+758	3670.5	3684.7
3	4	3996.72	+77.9	+3113	+778	4021.9	4037.4
4	8	4701.58	+123	+5783	+723	4728.1	4705.4[f]
7	1	1770.09	+36.0	+637	+637	1795.5	1811.7
9	1	921.10	+65.8	+606	+606	945.5	962.2
12	1	496.60	+119	+591	+591	—[g]	—[g]

[a] All rotations measured in CH_2Cl_2. [b] Specific rotation (10^{-1} deg cm^2 g^{-1}). [c] Molar rotation (10 deg cm^2 mol^{-1}). [d] Number of chiral units = n. [e] MALDI-TOF data. [f] M+H. [g] See reference 14.

12 is presented in Table 1. Note that dendrons **12**, **9**, **7**, and **1**, in that order, constitute a series of structures in which achiral dendritic fragments of increasing size are attached to a chiral focal subunit. From the chiroptical data of these dendrons we can establish that the chiral focal subunit appears to have no increased influence on the molar optical activity of the dendrons as the attached achiral wedges increase in size. The molar optical rotation per chiral unit ($[\Phi]_D/n$) of these dendrons varies only ± 4% from the median value of +614. This also implies that the conformational equilibria of the chiral subunits are similar in all four dendrons.[18] However, as the chiral units proceed from the focal point (dendron **1**) to shells further into the interior of the dendron (dendrons **2** → **4**), an immediate increase is seen in the $[\Phi]_D/n$ value which seems to saturate. The $[\Phi]_D/n$ values of second-, third- and fourth-shell chiral dendrons **2-4** are approximately 26% greater, on average, than that of first-shell dendron (**1**). That the chiral unit has a larger effect on the optical rotatory power of the molecule when it is not placed near the periphery of the dendron suggests conformational order in dendrons **2-4**.

However, slight changes in constitution, rather than conformation, could also be responsible for the observed changes in optical activity. As we illustrated in a chiroptical study of dendrons consisting of solely chiral units,[11] subunits closer to the core of a dendrimer—or focal point of a dendron—are different in constitution than subunits in other regions of the structure (interior, periphery), and can, therefore, have dramatically different optical activities. Accordingly, while the chiral subunits of **1**, **7**, **9**, and **12** are extremely similar to each other in surrounding constitution, being directly adjacent to the focal hydroxyl group, they are constitutionally dissimilar to those in dendrons **2-4**, which are more remote from the focal hydroxyl group. To examine the effect of this constitutional difference, we prepared compound **16**, which differs from **12** only in the replacement of a proton with a phenyl group at the focal point. The $[\Phi]_D$ value of **16**, +767, in contrast with that of **12** (+591), strongly suggests that the difference in $[\Phi]_D/n$ values between first-shell chiral dendron **1** and second-, third- and fourth-shell chiral dendrons **2-4** is based solely on constitutional changes in the dendritic structure and not conformational order.



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The incorporation of these dendrons into dendrimers and further investigation of the effect of chiral dendrimer subunits on macromolecular asymmetry are ongoing efforts in our laboratory.

Acknowledgment. We are grateful to the National Science Foundation (DMR-9702123) and the Petroleum Research Fund (29720-G7), administered by the American Chemical Society, for support of this research. We thank Mu-Jen Wu for assistance in the preparation of compounds **6** and **12**.

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(17) Selected data: **1**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.11 (m, 84H), 6.80-6.43 (m, 45H), 4.99 (s, 2H), 4.97 (s, 2H), 4.90 (s, 32H), 4.79 (s, 16H), 4.73 (s, 8H) 4.61 (d, *J* = 8.4 Hz, 1H), 4.55 (d, *J* = 8.4 Hz, 1H), 4.54 (s, 2H), 1.58 (s, 6H). Anal. Calcd for $C_{228}H_{200}O_{33}$: C, 78.95; H, 5.82. Found: C, 78.34; H 5.95. **2**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.13 (m, 84H), 6.78-6.42 (m, 45H), 5.02-4.99 (m, 10H), 4.91 (s, 16H), 4.89 (s, 16H), 4.79 (s, 8H), 4.77 (s, 8H), 4.64 (d, *J* = 8.5 Hz, 2H), 4.59 (d, *J* = 8.54 Hz, 2H), 4.46 (d, *J* = 5.8 Hz, 2H), 1.59 (s, 6H). Anal. Calcd for $C_{239}H_{212}O_{35}$: C, 78.76; H, 5.87. Found: C, 78.70; H 5.97. **3**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.13 (m, 96H), 6.85-6.78 (m, 12H), 6.67-6.44 (m, 33H), 5.03 (d, *J* = 12.2 Hz, 4H), 5.02 (s, 8H), 4.98 (d, *J* = 12.2 Hz, 4H), 4.91 (s, 8H), 4.88 (s, 20H), 4.86 (s, 16H), 4.63 (d, *J* = 8.5 Hz, 4H), 4.57 (d, *J* = 8.5 Hz, 4H), 4.49 (d, *J* = 6.0 Hz, 2H), 1.60 (s, 12H), 1.59 (s, 12H). Anal. Calcd for $C_{261}H_{236}O_{39}$: C, 78.43; H, 5.95. Found: C, 78.53; H 6.03. **4**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.20 (m, 112H), 6.63-6.43 (m, 45H), 4.94 (s, 16H), 4.92 (s, 4H), 4.91 (s, 32H), 4.88 (s, 8H), 4.68 (d, *J* = 8.4 Hz, 8H), 4.61 (d, *J* = 8.4 Hz, 8H), 4.49 (d,*J* = 6.0 Hz, 2H), 1.61 (s, 24H), 1.59 (s, 24H). Anal. Calcd for $C_{305}H_{284}O_{47}$: C, 77.91; H, 6.09. Found: C, 77.49; H 6.15. **7**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.13 (m, 44H), 6.83-6.43 (m, 21H), 5.05 (s, 2H), 5.01 (d, *J* = 7.6 Hz, 2H), 4.93 (s, 8H), 4.92 (s, 8H), 4.81 (s, 4H), 4.79 (s, 4H), 4.63 (d, *J* = 8.4 Hz, 1H), 4.57 (d, *J* = 5.8 Hz, 2H), 4.56 (d, *J* = 8.4 Hz, 1H), 1.60 (s, 6H). Anal. Calcd for $C_{116}H_{104}O_{17}$: C, 78.70; H, 5.93. Found: C, 78.92; H 6.03. **9**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.13 (m, 24H), 6.84-6.70 (m, 3H), 6.68 (d, *J* = 2.2 Hz, 2H), 6.65 (d, *J* = 2.2 Hz, 2H), 6.48 (t, *J* = 2.2 Hz, 1H), 6.47 (t, *J* = 2.2 Hz, 1H), 5.06 (s, 2H), 5.04 (d, *J* = 12.6 Hz, 1H), 5.49 (d, *J* = 12.6 Hz, 1H), 4.91 (s, 4H), 4.90 (s, 4H), 4.63 (d, *J* = 8.5 Hz, 1H), 4.60 (d, *J* = 6.0 Hz, 2H), 4.57 (d, *J* = 8.6 Hz, 1H), 1.62 (s, 3H), 1.60 (s, 3H). Anal. Calcd for $C_{60}H_{56}O_9$: C, 78.23; H, 6.13. Found: C, 78.34; H 6.16.

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