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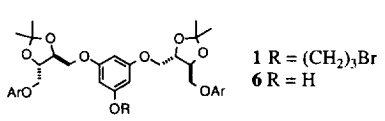
Facile Preparation of Optically Active Dendritic Fragments Containing Multiple Tartrate-derived Chiral Units

Hak-Fun Chow* and Chi Ching Mak

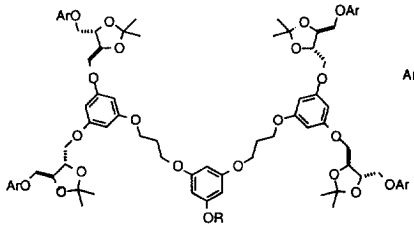
Department of Chemistry, The Chinese University of Hong Kong,
Shatin, N.T., HONG KONG

Abstract: The synthesis of a series of (L)-tartrate-derived optically active, homochiral, dendritic fragments **1** - **5** by an iterative, convergent approach was reported. The chiroptical property of these chiral fragments was directly proportional to the number of chiral units.

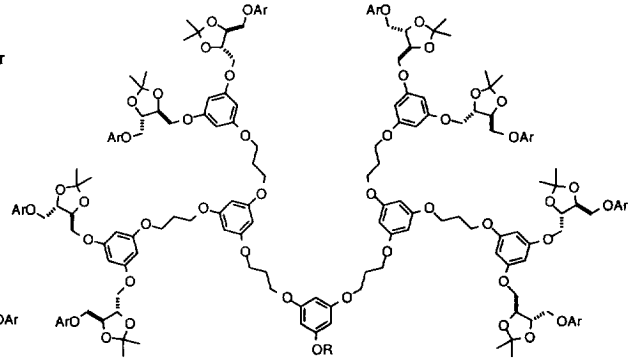
Dendrimer chemistry[1] has emerged as a rapidly growing research area serving as the bridge between conventional organic chemistry and polymer science. With our increasing ability to precisely control the disposition of functional components in pre-defined locations within a hyperbranched polymer matrix, structurally defined functional dendritic molecules with interesting properties can now be prepared.[2] Within this subject area, of notable interest are the preparation of dendrimers with multiple chiral units and their utilization as asymmetric catalysts, chiral auxiliaries, chiral hosts for asymmetric recognition and resolution.[3] Today, the use of optically active, naturally occurring biological molecules such as carbohydrates and amino acids as monomeric units for the construction of bio-dendrimers has been well exemplified.[4] On the other hand, relatively few studies had been conducted on the preparation of abiotic chiral dendrimers.[5] We recently reported the facile construction of a series of acid/basic and redox stable polyether based dendritic fragments[6] and demonstrated that they were useful building blocks for functional dendrimers.[7] Here we reported the synthesis of a series of chiral dendritic fragments **1** - **5** bearing electrophilic bromide or nucleophilic phenol functionalities. The chiral elements are derivatives of (L)-tartrate, and are located near the peripheral sector, serving as chiral linkers between the surface 4-*tert*-butylphenyl and branching phloroglucinol moieties.



1 R = $(CH_2)_3Br$
6 R = H



2 R = $(CH_2)_3Br$, **4** R = H, **7** R = Bn



3 R = $(CH_2)_3Br$, **5** R = H, **8** R = Bn

Ar = 4-*tert*-butylphenyl

A three step iterative cycle was employed for the synthesis of these chiral dendritic fragments. The starting material was the known optically active first generation[8] phenol **6**[5c] (G1-OH) with two chiral (L)-tartrate derived units. Mono-*O*-alkylation of **6** with 10 equivalents of 1,3-dibromopropane (K_2CO_3, acetone, 56°C, 10 h) afforded the bromide **1** (G1-Br) as an oil in 89% yield. Bis-*O*-alkylation of 5-benzyloxyresorcinol[9] with 2 equivalents of **1** (K_2CO_3, acetone, 56°C, 38 h) furnished the benzyl ether of the second generation **7** (G2-OBn) in 81% yield. Hydrogenolysis of the benzyl protective group (H_2, 10% Pd on C, ethyl acetate-ethyl alcohol) gave the phenol **4** (G2-OH) with four chiral (L)-tartrate derived units as a white glassy substance in 86% yield. This series of reactions completed the first iterative synthetic cycle.

The synthesis of the second generation dendritic bromide **2** (G2-Br) went uneventfully. This compound could be obtained in 80% yield from the phenol **4** (G2-OH) under similar reaction conditions (10 eq. 1,3-dibromopropane, K_2CO_3, acetone, 56°C, 10 h). Bis-*O*-alkylation of 5-benzyloxyresorcinol with 2 equivalent of **2** (K_2CO_3, acetone, 56°C, 72 h) afforded the benzyl ether of the third generation **8** (G3-OBn) in 63% yield. Hydrogenolysis of the benzyl moiety (H_2, 10% Pd on C, ethyl acetate-ethyl alcohol) gave phenol **5** (G3-OH) with eight chiral (L)-tartrate derived units as a white foam in 73% yield. Final attachment of the bromopropyl moiety onto the phenol **5** (10 eq. 1,3-dibromopropane, K_2CO_3, acetone, 56°C, 10 h) afforded the third generation bromide **3** in 70% yield.

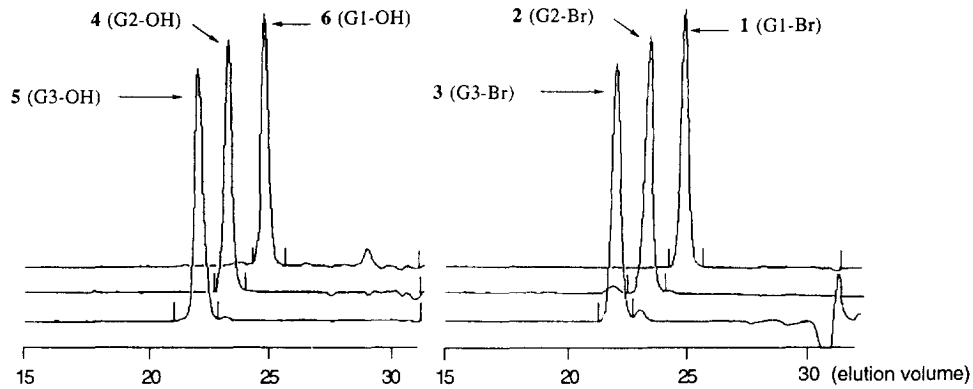


Figure 1. Gel permeation chromatogram of chiral dendritic fragments (Waters HR1, HR2 and HR4 columns in serial; temperature: 40°C; solvent: THF; flow rate: 1.0 ml/min)

The structural identities of these chiral dendrimers were confirmed by ^1H and ^{13}C-NMR spectroscopy and elemental analysis.[10] The purity of the products could also be determined by gel permeation chromatographic (GPC) analysis (Figure 1). Using narrow-dispersity polystyrenes as the calibration standards, the polydispersity of the dendritic bromides and phenols **1** - **5** obtained was around 1.01 – 1.02 (Table 1). The GPC measured weight-average molecular weights M_w, however, were slightly higher than the theoretical M_{calcd} values.

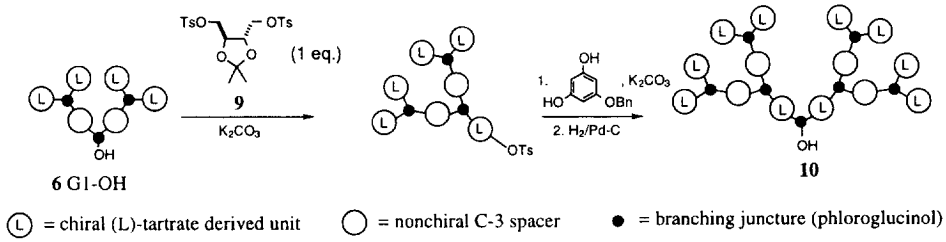
Inspection of the optical rotational properties of these dendritic fragments revealed that the specific rotations $[\alpha]_D$ remained essentially the same, while the molar rotations $[M]_D$ were directly proportional to the number of chiral (L)-tartrate units. This observation was consistent with the findings reported earlier by us,[5c] further confirming that these chiral units acting as independent, non-interacting moieties. It was, however, noticed that

Table 1. Optical activity and gel permeation chromatography data for the dendritic fragments

Compound	No. of chiral units	$[\alpha]_D^{21}$ (in CH_2Cl_2)	$[M]_D$	$[M]$/chiral unit	M_{calcd}	M_n	M_w	M_w/M_n
1 (G1-Br)	2	-29.8	-238	-119	800	766	773	1.01
2 (G2-Br)	4	-38.9	-655	-164	1685	1904	1929	1.01
3 (G3-Br)	8	-28.6	-988	-124	3455	4109	4173	1.02
4 (G2-OH)	4	-30.9	-483	-121	1564	1906	1927	1.01
5 (G3-OH)	8	-35.2	-1174	-147	3334	4032	4101	1.02
6 (G1-OH)	2	-20.0	-136	-67	679	760	767	1.01
7 (G2-OBn)	4	-38.2	-632	-158	1654	1916	1938	1.01
8 (G3-OBn)	8	-36.4	-1246	-156	3424	4080	4160	1.02

compound **6** (G1-OH) had a much lower specific rotational value, for reasons which were not apparent in this study.

Although the chiral elements reported in this series of dendritic fragments are located near the peripheral, it is possible to introduce chiral units in the interior domain of these dendritic molecules (Scheme 1). For example, if one uses chiral (2*S*,3*S*)-(–)-1,4-di-*O*-tosyl-2,3-*O*-isopropylidene-(L)-threitol **9**[11] in place of the optically inactive 1,3-dibromopropane as the linker and reacts it with phenol **6** (G1-OH), the resulting chiral dendritic fragment **10** after further elaboration will have chiral units situated both in the exterior and interior regions. Moreover, one could also use the antipode of **9** to generate chiral dendritic molecules containing both (D)- and (L)-tartrate units. Hence, our synthetic route could be used to synthesize a wide range of chiral dendritic fragments with the chiral units deposited at desired positions inside a dendritic network. Most importantly, the bromo and phenol functionalities in these target dendritic fragments serve as the anchoring points for them to attach to different chemical structures and to investigate the physico-chemical properties of these interesting class of optically active functional dendrimers.



Scheme 1. Schematic diagram for the synthesis of alternative chiral dendritic fragment

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References and Notes

1. For a recent review, see Tomalia, D. A.; Durst, H. D. *Topics in Current Chemistry* **1993**, *165*, 193 - 313.

2. Issberner, J.; Moors, R.; Vögtle, F. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2413 - 2420.
3. (a) Brunner, H.; Altmann, S. *Chem. Ber.* **1994**, *127*, 2285 - 2296; (b) Brunner, H. *J. Organomet. Chem.* **1995**, *500*, 39 - 46; (c) Bolm, C.; Derrien, N.; Seger, A. *Synlett* **1996**, 387 - 388.
4. (a) Posnett, D. N.; McGrath, H.; Tam, J. P. *J. Biol. Chem.* **1988**, *263*, 1719 - 1725; (b) Tam, J. P. *Proc. Natl. Acad. Sci. USA* **1988**, *85*, 5409 - 5413; (c) Tam, J. P.; Lu, Y.-A. *Proc. Natl. Acad. Sci. USA* **1989**, *86*, 9084 - 9088; (d) Wang, C. Y.; Looney, D. J.; Li, M. L.; Walfield, A. M.; Ye, J.; Hosein, B.; Tam, J. P.; Wong-Staal, F. *Science* **1991**, *254*, 285 - 288; (e) Hudson, R. H. E.; Damha, M. J. *J. Am. Chem. Soc.* **1993**, *115*, 2119 - 2124; (f) Roy, R.; Zanini, D.; Meunier, S. J.; Romanowska, A. *J. Chem. Soc., Chem. Commun.* **1993**, 1869 - 1872; (g) Shao, J.; Tam, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 3893 - 3899; (h) Jansen, J. F. G. A.; Peerlings, H. W. I.; de Brabander-Van den Berg, E. M. M.; Meijer, E. W. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1206 - 1209.
5. (a) Newkome, G. R.; Lin, X.; Weis, C. D. *Tetrahedron: Asymmetry* **1991**, *2*, 957 - 960; (b) Seebach, D.; Lapierre, J.-M.; Skobridis, K.; Greiveldinger, G. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 440 - 442; (c) Chow, H.-F.; Fok, L. F.; Mak, C. C. *Tetrahedron Lett.* **1994**, *35*, 3547 - 3550; (d) Twyman, L. J.; Beezer, A. E.; Michell, J. C. *Tetrahedron Lett.* **1994**, *35*, 4423 - 4426; (e) Murer, P.; Seebach, D. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2116 - 2119; (f) Chang, H.-T.; Chen, C.-T.; Kondo, T.; Siuzdak, G.; Sharpless, K. B. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 182 - 186.
6. (a) Chow, H.-F., Chan, I. Y.-K.; Mak, C. C. *Tetrahedron Lett.* **1995**, *36*, 8633 - 8636; (b) Chow, H.-F.; Chan, I. Y.-K.; Mak, C. C.; Ng, M.-K. *Tetrahedron* **1996**, *52*, 4277 - 4290.
7. Chow, H.-F.; Chan, I. Y.-K.; Chan, D. T. W.; Kwok, R. W. M. *Chem. Eur. J.* accepted for publication.
8. The notation described by Fréchet was adopted, see Hawker, C. J.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1990**, *112*, 7638 - 7647.
9. Curtis, W. D.; Stoddart, J. F.; Jones, G. H. *J. Chem. Soc., Perkin Trans. 1* **1977**, 785 - 788.
10. Selected spectroscopic data: **1**: ^{1}H-NMR (δ, $CDCl_3$): 7.29 (d, J = 8.4 Hz, 4 H; ArH), 6.86 (d, J = 8.6 Hz, 4 H; ArH), 6.17 (s, 1 H), 6.15 (s, 2 H), 4.35 - 4.25 (m, 4 H), 4.25 - 4.05 (m, 8 H), 4.01 (t, J = 5.3 Hz, 2 H), 3.53 (t, J = 6.1 Hz, 2 H; CH_2Br), 2.23 (quin, J = 5.8 Hz, 2 H), 1.49 (s, 12 H; 4 Me), 1.28 (s, 18 H; 2 *t*-Bu). **2**: ^{1}H-NMR (δ, $CDCl_3$): 7.29 (d, J = 8.8 Hz, 8 H; ArH), 6.86 (d, J = 8.9 Hz, 8 H; ArH), 6.14 (s, 6 H), 6.08 (s, 3 H), 4.38 - 4.28 (m, 8 H), 4.20 - 4.00 (m, 26 H), 3.56 (t, J = 6.5 Hz, 2 H; CH_2Br), 2.24 (quin, J = 6.2 Hz, 2 H), 2.19 (quin, J = 5.9 Hz, 4 H), 1.49 (s, 24 H; 8 Me), 1.28 (s, 36 H; 4 *t*-Bu). **3**: ^{1}H-NMR (δ, $CDCl_3$): 7.29 (d, J = 8.8 Hz, 16 H; ArH), 6.86 (d, J = 8.8 Hz, 16 H; ArH), 6.15 (s, 12 H), 6.09 (s, 9 H), 4.40 - 4.20 (m, 16 H), 4.20 - 3.85 (m, 58 H), 3.54 (t, J = 6.4 Hz, 2 H; CH_2Br), 2.30 - 2.10 (m, 14 H), 1.44 (s, 48 H; 16 Me), 1.28 (s, 72 H; 8 *t*-Bu). **4**: ^{1}H-NMR (δ, $CDCl_3$): 7.29 (d, J = 8.8 Hz, 8 H; ArH), 6.86 (d, J = 8.8 Hz, 8 H; ArH), 6.15 (s, 6 H), 6.05 (s, 1 H), 6.02 (s, 2 H), 5.50 - 5.35 (brs, 1 H; OH), 4.38 - 4.28 (m, 8 H), 4.21 - 4.01 (m, 24 H), 2.17 (quin, J = 5.8 Hz, 4 H), 1.49 (s, 24 H; 8 Me), 1.28 (s, 36 H; 4 *t*-Bu). **5**: ^{1}H-NMR (δ, $CDCl_3$, OH not observed): 7.28 (d, J = 8.8 Hz, 16 H; ArH), 6.86 (d, J = 8.9 Hz, 16 H; ArH), 6.14 (m, 12 H), 6.08 (s, 6 H), 6.05 - 5.95 (m, 3 H), 4.40 - 4.25 (m, 16 H), 4.25 - 3.95 (m, 56 H), 2.30 - 2.10 (m, 12 H), 1.48 (s, 48 H; 16 Me), 1.28 (s, 72 H; 8 *t*-Bu).
11. Morimoto, T.; Chiba, M.; Achiwa, K. *Tetrahedron* **1993**, *49*, 1793 - 1806.

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