

## Synthesis and chiroptical properties of layer-block dendrimers

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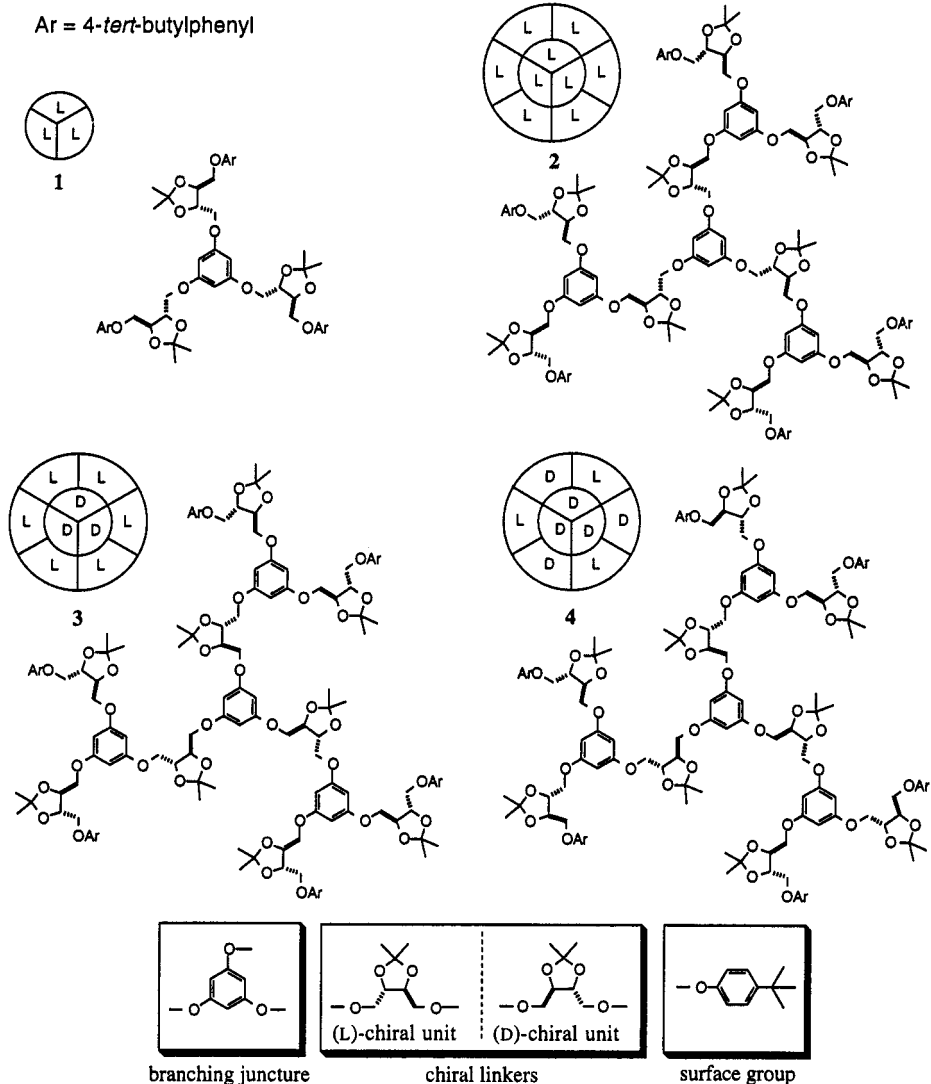
**Abstract:** A series of optically active, tartaric acid-based, monodisperse dendrimers **1 - 4** was prepared. The central core and branching junctures of these dendritic compounds were made up from phloroglucinol units and the surface sectors used were 4-*tert*-butylphenoxy moieties. The optically active elements, which were derivatives of either (D)- or (L)-tartaric acid, served as the chiral linker branches of these dendrimers. For this series of structurally flexible, low generation optically active dendrimers, the observed molar optical rotation was proportional to the number of chiral units residing within the dendritic matrix, with the chiroptical property of the (D)-tartrate unit cancelling that of the (L)-tartrate unit on a one to one mole basis. Circular dichroism studies, however, revealed that this cancellation effect was more effective when both the (D)- and (L)-chirons were situated within the same layer.

### INTRODUCTION

Recent interest in the preparation of optically active dendrimers stemmed from their potential use as chiral hosts for enantiomeric resolutions and as chiral catalysts for asymmetric synthesis (ref. 1). In order to understand the structure-property relationship of a chiral dendrimer, it is necessary to establish the intriguing relationship between the overall chiroptical properties of the dendrimer and the stereo-spatial arrangement of its constituent chiral elements. Homochiral, optically active, structurally defined dendrimers are ideal models for this type of study since the repeating chiral elements are expected to distribute in an orderly manner inside a dendritic matrix. By selecting appropriate chiral elements and placing them in pre-defined positions by either convergent or divergent synthetic methodology, the influence of the three dimensional disposition of these chiral elements on the overall macroscopic chiroptical properties of optically active dendrimers can then be evaluated. Today, the use of optically active, naturally occurring biological molecules such as carbohydrates or amino acids as monomeric units for the construction of chiral bio-active dendrimers has been well exemplified (ref. 2). On the other hand, relatively few studies had been conducted on the preparation of abiotic chiral dendrimers and their structural-chiroptical properties. Some time ago, Newkome reported the synthesis of a series of tryptophane terminated dendritic macromolecules (ref. 3) and showed that the molecular ellipticity of these molecules was proportional to the number of chiral surface groups. Recently, Seebach reported the preparation of optically active dendrimers using (*R*)-3-hydroxybutanoic acid derivatives as the chiral branching junctures (ref. 4). In this particular study, it was discovered that attachment of achiral branches to a chiral centre piece led to a dilution of the overall molar optical rotation of the resulting dendrimers (ref. 4c). On the other hand, Meijer reported that sterically congested dendrimers with multiple optically active units located on the surface sector displayed diminishing optical rotation property (ref. 5). This paper summarizes our independent work on the syntheses and chiroptical property investigations on a series of optically active homo-dendrimers **1 - 2** (ref. 6) and layer-block co-dendrimers **3 - 4** (ref. 7), using optically pure tartrate derivatives as the chiral branches.

### SYNTHESIS

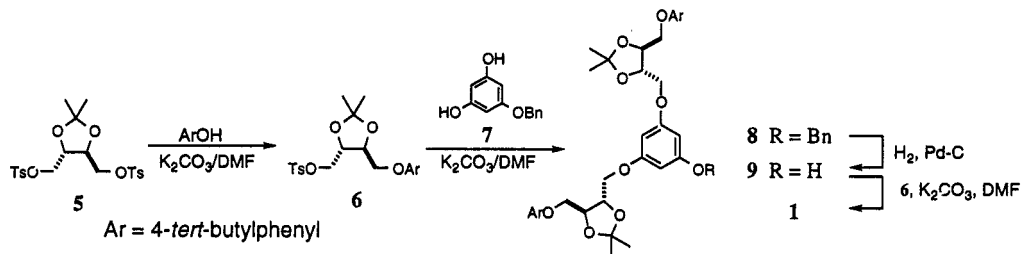
Our chiral dendrimers **1 - 4** utilize phloroglucinols as the branching junctures and 4-*tert*-butylphenoxy moieties as the end groups (Scheme 1). The optically active linkers are made up of either (D)- or (L)-tartrate derived chiral units, because they are inexpensive and readily available in both enantiomeric pure form. The chiral linkers of first two homochiral dendrimers **1** and **2**, comprise of only (L)-tartrate derived units. On the other hand, the layer-block co-dendrimers **3** and **4**, consist of both (D)- and (L)-tartrate derived functionalities as the chiral linkers.



Scheme 1. Architecture of optically active dendrimers

### Syntheses of all (*L*)-tartarate derived chiral dendrimers 1 and 2

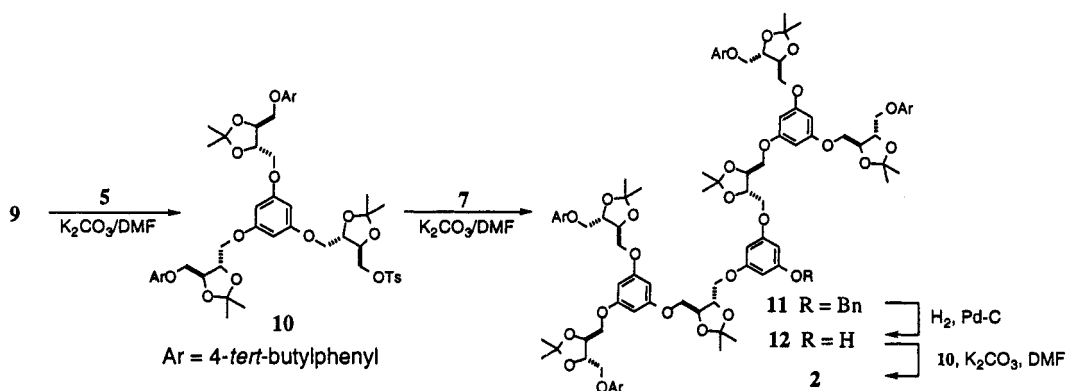
An iterative, convergent approach was employed for the syntheses of chiral dendrimers of the zeroth 1 and the first 2 generation. Treatment of (*2S,3S*)-(-)-1,4-di-*O*-tosyl-2,3-*O*-isopropylidene-*L*-threitol 5 (ref. 8) with 0.5 mol equiv. of 4-*tert*-butylphenol in the presence of potassium carbonate in DMF gave the



Scheme 2. Synthesis of the zeroth generation dendrimer 1

mono-*O*-arylation product **6** in 74% yield together with a small amount of the bis-*O*-arylation compound (Scheme 2). Bis-*O*-alkylation of 5-benzyloxyresorcinol **7** (ref. 9) with 2.1 mol equiv. of **6** under similar condition ( $K_2CO_3$  in DMF,  $100^\circ C$ ) afforded the  $C_2$  symmetric product **8** in 65% yield. The benzyl protecting group was then dismantled by hydrogenolysis ( $H_2$ , 10% Pd on C, EtOH) to give the phenol **9** in 94%. Finally, coupling of **9** ( $K_2CO_3$  in DMF,  $120^\circ C$ ) with an additional mol equiv. of **6** furnished the G0 dendrimer **1** as an oil in 80%. On the other hand, direct tris-*O*-alkylation of phloroglucinol with an excess of the tosylate **6** gave the G0 dendrimer **1** in only 20% yield. This could be due to the poor solubility of the phloroglucinol anion in DMF.

Preparation of the first generation chiral dendrimer **2** could be accomplished by employing a similar reaction sequence (Scheme 3). Thus, mono-*O*-alkylation of the phenol **9** with 3 mol equiv. of the di-*O*-tosylate **5** ( $K_2CO_3$  in DMF,  $100^\circ C$ ) gave the dendritic 'wedge' **10** containing three (*L*)-tartrate derived chiral units in 82% yield. Treatment of 2 mol equiv. of **10** with 5-benzyloxyresorcinol **7** gave the benzyl ether **11** in 70%. Subsequent debenzylation and further *O*-alkylation of the phenol **12** with 1 mol equiv. of **10** afforded the G1 dendrimer **2** as an oil.

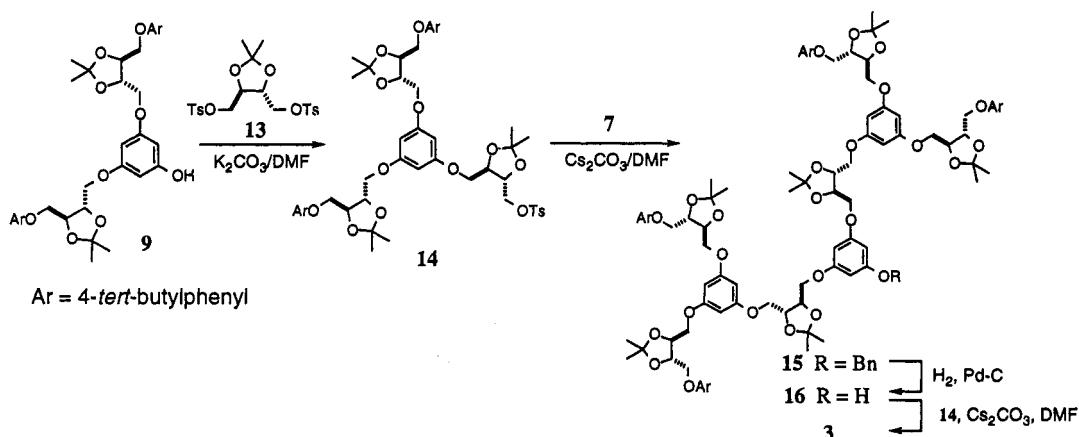


Scheme 3. Synthesis of the first generation dendrimer **2**

The structural identities of these two homochiral dendrimers were confirmed by  $^1H$  and  $^{13}C$  NMR spectroscopy and elemental analyses. Interestingly, the  $^{13}C$  NMR spectrum of G1 **2** was almost identical to that of G0 **1**, except that the relative intensities of each peak was different, suggesting that both the G0 and G1 dendrimers had nearly the same microstructure.

### Syntheses of layer-block chiral dendrimers **3** and **4**

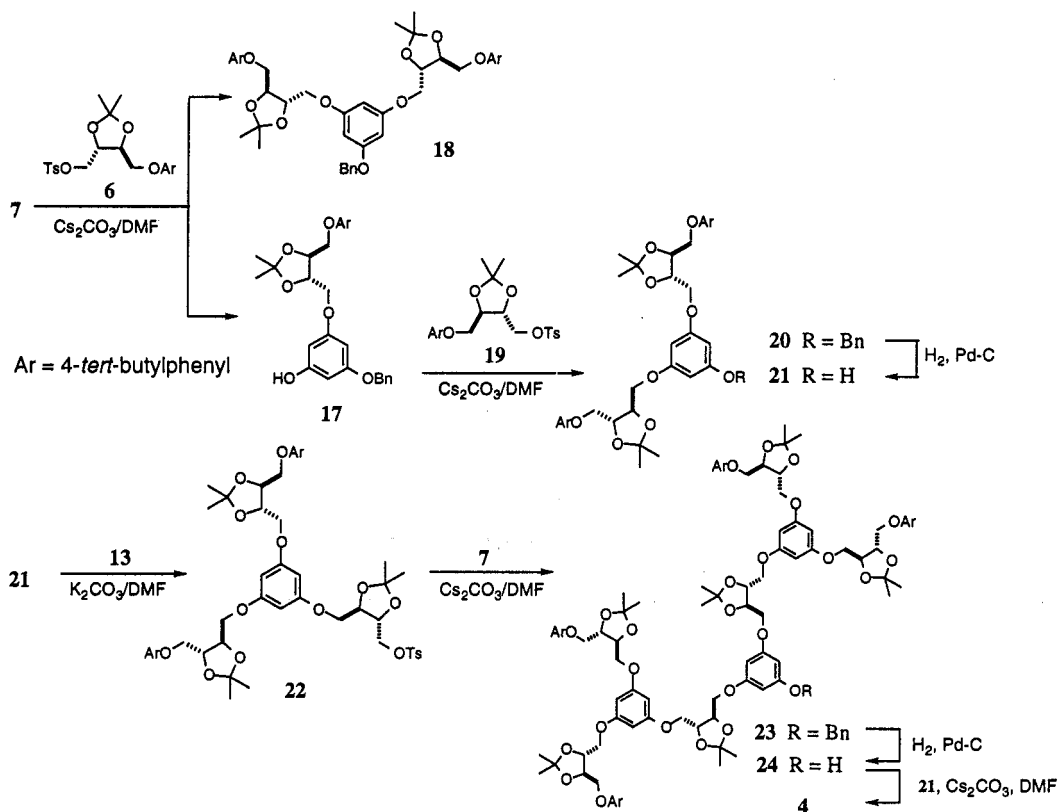
The first layer-block dendrimer **3** has an outer chiral layer made up of six (*L*)-chiral units derived from (*L*)-tartrate acid and an inner chiral layer consisted of three antipodal (*D*)-chiral elements. The synthesis started with the  $C_2$  symmetrical phenol **9** described in the previous section (Scheme 4). Treatment of **9**



Scheme 4. Synthesis of layer-block dendrimer **3**

with 1 mol equiv. of (2*R*,3*R*)-(+)-1,4-di-*O*-tosyl-2,3-*O*-isopropylidene-D-threitol **13** (ref. 10) in the presence of potassium carbonate in DMF gave the layer-block 'wedge' **14** having one (D)- and two (L)-tartrate derived chiral units. Coupling of two mol equiv. of the sector **14** to 5-benzyloxyresorcinol **7** ( $\text{Cs}_2\text{CO}_3$ , DMF) furnished the benzyl ether **15** in 55% yield. Subsequent hydrogenolysis (10% Pd on C, EtOH–EtOAc) followed by attachment of an additional layer-block sector **14** to the resulting phenol **16** gave the first generation layer-block dendrimer **3** in an overall 46% yield as a white foam.

Synthesis of the other layer-block dendrimer **4** proved to be less straight forward (Scheme 5). The bottleneck was the inefficient mono-*O*-alkylation ( $\text{Cs}_2\text{CO}_3$ , DMF) of 5-benzyloxyresorcinol **7** with the tosylate **6** to give the mono-*O*-alkylated product **17**. In all conditions tried, the bis-*O*-alkylated product **18** was always isolated in substantial amounts even when a large excess of **6** was used. We speculated this was due to the poor solubility of the anion of **7** compared to that of **17** in the reaction medium. Thus, as soon as **17** was formed, it underwent further alkylation much quicker than **7**. In the end, we could isolate the desired product **17** in 34% yield together with 28% of the side product **18**. Nevertheless, they were easily separable by silica gel chromatography. Reaction ( $\text{Cs}_2\text{CO}_3$ , DMF) of the phenol **17** with the tosylate **19** (ref. 11) gave the  $\text{C}_{2v}$  symmetrical benzyl ether **20** as a white foam in 89%. After hydrogenolysis, the phenol **21** was reacted with an excess of the (D)-tartrate derived ditosylate **13** to give the dendritic 'wedge' **22** containing two (D)- and one (L)-tartrate derived chiral units. This dendritic 'wedge' was then further transformed to the phenol **24** and finally to the layer-block dendrimer **4** in an overall 14% yield as a white foam following the procedures described for **14**.



Scheme 5. Synthesis of layer-block dendrimer **4**

The structures of these two layer-block dendrimers **3** and **4** were again characterized by their  $^1\text{H}$  and  $^{13}\text{C}$  NMR, mass spectroscopic and elemental analysis. Interestingly, both the  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of **3** and **4** and the all (L)-tartrate derived G1 dendrimer **2** are superimposable. Moreover, in all the diastereomeric G1 dendrimers **2**–**4**, the central as well as the peripheral phloroglucinol ring protons and carbons have nearly identical chemical shift values, suggesting that they have nearly the same microenvironment, irrespective of absolute configurations of the chiral branches around them.

### Chiroptical properties

The optical rotation properties of this novel series of tartrate-based dendrimers were examined by polarimetry studies (Table 1). Two observations were found. Firstly, it was discovered that the molar rotation was proportional to the number of tartrate units in excess inside the dendritic matrix. Secondly, the chiroptical property of the (D)-tartrate unit cancelled that of the (L)-tartrate unit on a one to one basis. As a consequence, dendritic fragments with (D)-tartrate units in excess consistently gave positive optical rotation values and those with excess (L)-units had negative values. Thus, each individual chiral tartaric unit, irrespective of its position inside the dendritic matrix, contributed to the overall molar rotation to the same absolute extent with the sign of rotation depending on its absolute configuration. From this study, it can be concluded that for structurally flexible lower generation dendrimers containing multiple chiral units, the overall macromolecular chiroptical properties of the dendritic molecules can be considered as simple arithmetic sum of all chiroptical properties of its constituent chiral units.

**TABLE 1.** Specific and Molar Rotations of Dendritic Molecules (23°C, D line, CHCl<sub>3</sub>)

Compound	No. of (D)-chiral units	No. of (L)-chiral units	No. of (D)-units in excess <sup>a</sup>	[ $\alpha$ ] <sup>b</sup>	[M] <sup>b</sup>	[M]/chiral unit <sup>c</sup>
1	0	3	-3	-59.6	-569	-190
2	0	9	-9	-69.7	-1769	-197
3	3	6	-3	-16.2	-411	-137
4	6	3	3	+22.8	+579	+193
8	0	2	-2	-55.3	-425	-212
9	0	2	-2	-52.4	-355	-178
10	0	3	-3	-56.0	-547	-182
11	0	6	-6	-60.1	-1096	-183
12	0	6	-6	-57.3	-994	-166
14	1	2	-1	-29.5	-288	-288
15	2	4	-2	-16.7	-304	-152
16	2	4	-2	-21.9	-379	-190
17	0	1	-1	-33.4	-164	-164
20	1	1	0	-2.9	-25	-
21	1	1	0	-3.3	-22	-
22	2	1	1	+7.9	+75	+75
23	4	2	2	+17.6	+314	+157
24	4	2	2	+18.2	+316	+158

<sup>a</sup> Negative values denote (L)-tartrate unit(s) is in excess. <sup>b</sup> In units of 10<sup>-1</sup> deg cm<sup>2</sup> g<sup>-1</sup>. <sup>c</sup> Negative and positive values denote contributions from (L)- and (D)-tartrate unit(s), respectively.

Examination of the circular dichroism (CD) spectra of dendrimers 1 - 4 revealed findings that were not apparent from polarimetry studies (Figure 1). The all (L)-derived dendrimers 1 and 2, showed two negative Cotton effects at 200 and 210 nm, corresponding to the aromatic  $\pi \rightarrow \pi^*$  absorptions of the *tert*-butylphenoxy and the phloroglucinol moieties respectively. As expected, the molar ellipticities of the higher generation G1 dendrimer 2 were consistently larger than those of the G0 dendrimer 1 at both transitions. Dendrimers 2 and 3, having the same chiral environment around the *tert*-butylphenoxy moieties, exhibited roughly the same molar ellipticities at 200 nm. On the other hand, due to the cancellation effect of having both enantiomeric (D)- and (L)-chirons in the same outer layer for layer-block dendrimer 4, this compound showed the smallest Cotton effect at 200 nm. The observed Cotton effect at 210 nm for the different dendrimers needs careful interpretations. If each chiral tartrate unit, irrespective of its positions within the dendrimer, exerts the same absolute chiroptical effect on the phloroglucinol rings, then the total chiroptical effect experienced by the four phloroglucinol rings is equivalent to twelve (L)-units for the all (L)-tartrate derived dendrimer 2, showing the largest negative Cotton effect at 210 nm. Dendrimer 4, on the other hand, has one core phloroglucinol ring surrounded by three (D)-chirons and three peripheral ones surrounded by two (D)- and one (L)-chirons. Due to the exact cancellation effect of having both (D) and (L)-chiral units situated in the same outer layer, the net chiroptical effect for the four phloroglucinol units should be of six (D)-chiral units. As it turned out,

dendrimer **4** showed a positive Cotton effect with a molar ellipticity value half of that of the all (L)-dendrimer **2** at 210 nm. Based on this argument, the phloroglucinol rings of compound **3** should have a net chiral effect of zero. In reality, it still showed a significant absorption at 210 nm. This result suggested that in the layer-block dendrimer **3**, the chiroptical effect of an (L)-chiral unit in the outer shell did not exactly compensate that of a (D)-chiral unit in the inner shell, thus leaving a significant Cotton effect at 210 nm. It was therefore concluded that the chiroptically the outer chiral layer was slightly different from the inner layer.

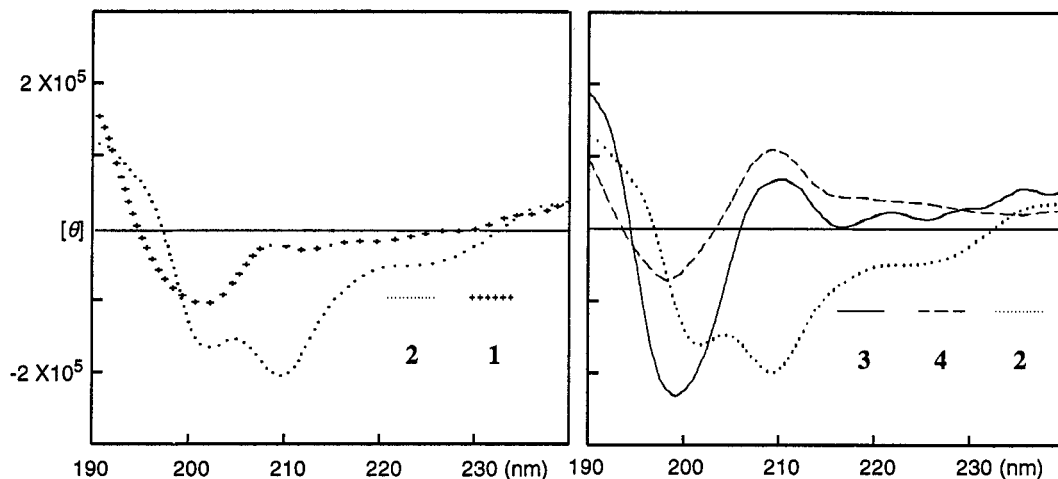


Figure 1. Circular dichroism spectra of dendrimers 1 to 4

#### ACKNOWLEDGMENTS

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#### REFERENCES

- For reviews on dendrimer chemistry, see (a) D. A. Tomalia, A. M. Naylor and W. A. Goddard III. *Angew. Chem. Int. Ed. Engl.* **29**, 138 (1990). (b) D. A. Tomalia and H. D. Durst. *Topics in Current Chemistry* **165**, 193 (1993).
- For examples, see (a) D. N. Posnett, H. McGrath and J. P. Tam. *J. Biol. Chem.* **263**, 1719 (1988). (b) J. P. Tam. *Proc. Natl. Acad. Sci. USA* **85**, 5409 (1988). (c) J. P. Tam and Y.-A. Yu. *Proc. Natl. Acad. Sci. USA* **86**, 9084 (1989). (d) C. Y. Wang, D. J. Looney, M. L. Li, A. M. Walfield, J. Ye, B. Hosein, J. P. Tam and F. Wong-Staal. *Science* **254**, 285 (1991). (e) G. R. Newkome, X. Lin and C. D. Weis. *Tetrahedron: Asymmetry* **2**, 957 (1991). (f) R. H. E. Hudson and M. J. Damha. *J. Am. Chem. Soc.* **115**, 2119 (1993). (g) R. Roy, D. Zanini, S. J. Meunier and A. Romanowska. *J. Chem. Soc., Chem. Commun.* 1869 (1993). (h) J. Shao and J. P. Tam. *J. Am. Chem. Soc.* **117**, 3893 (1995).
- G. R. Newkome, X. Lin and C. D. Weis. *Tetrahedron: Asymmetry* **2**, 957 (1991).
- (a) J.-M. Lapiere, K. Skobridis and D. Seebach. *Helv. Chim. Acta* **76**, 2419 (1993). (b) D. Seebach, J.-M. Lapiere, K. Skobridis and G. Greiveldinger. *Angew. Chem. Int. Ed. Engl.* **33**, 440 (1994). (c) D. Seebach, J.-M. Lapiere, G. Greiveldinger and K. Skobridis. *Helv. Chim. Acta* **77**, 1673 (1994). (d) P. Murer and D. Seebach. *Angew. Chem. Int. Ed. Engl.* **34**, 2116 (1995).
- J. F. G. A. Jansen, H. W. I. Peerlings, E. M. M. de Brabander-Van den Berg and E. W. Meijer. *Angew. Chem. Int. Ed. Engl.* **34**, 1206 (1995).
- (a) H.-F. Chow, L. F. Fok and C. C. Mak. *Tetrahedron Lett.* **35**, 3547 (1994). (b) H.-F. Chow and C. C. Mak. *J. Chem. Soc., Perkin Trans. 1* 2223 (1994).
- C. C. Mak and H.-F. Chow. *Chem. Commun.* 1185 (1996).
- T. Morimoto, M. Chiba and K. Achiwa. *Tetrahedron* **49**, 1793 (1993).
- W. D. Curtis, J. F. Stoddart and G. H. Jones. *J. Chem. Soc., Perkin Trans. 1* 785 (1977).
- Compound **13** was prepared from (D)-tartaric acid by the methods described for its antipode, E. A. Mash, K. A. Nelson, S. van Deusen and S. B. Hemperly. *Org. Synth.* **68**, 92 (1990) and reference 8.
- Compound **18**, the antipode of compound **6**, was prepared from the tosylate **13** and 4-*tert*-butylphenol by the method described for **6**.