ORGANIC
LETTERS

2007
Vol. 9, No. 18
3487−3490

Interplay between Core and Peripheral Chirality in Polyethers

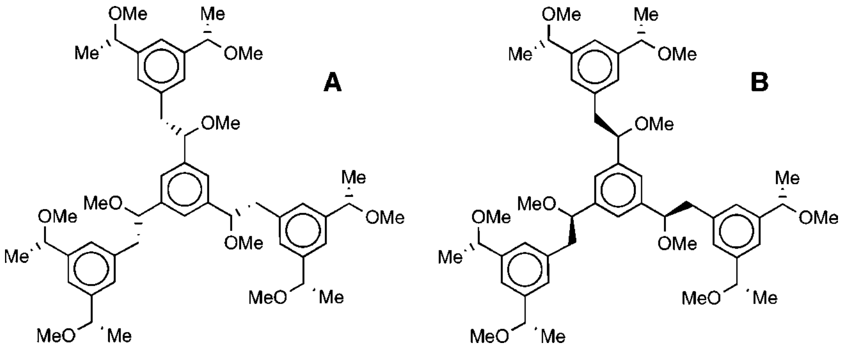
Alice R. E. Brewer,[†] Alex F. Drake,[‡] Susan E. Gibson,*[,§] and Jacob T. Rendell[§]

*Department of Chemistry, Imperial College London, South Kensington Campus,
London SW7 2AZ, UK, Department of Pharmacy, Franklin Wilkins Building,
King's College London, London SE1 9NN, UK, and GDC, NIBR, Novartis Horsham
Research Centre, Wimblehurst Road, Horsham, West Sussex RH12 5AB, UK*

s.gibson@imperial.ac.uk

Received April 20, 2007

ABSTRACT



A chiral-base mediated reaction has been used to synthesise the polyethers illustrated and their enantiomers; CD spectroscopy revealed that the homochiral isomers A may be viewed as a C_3-symmetric arrangement of fixed paddles while the heterochiral isomers B form a C_3-symmetric arrangement of rotating paddles.

A fundamental understanding of how chiral elements can be used to create and control molecular properties is necessary to underpin the full exploitation of macromolecules and supramolecular structures in applications such as catalysis, molecular recognition, drug delivery, and light-emitting and light-harvesting processes.[1] Inherent in this undertaking is the development of techniques that probe the relationship between molecular chirality and molecular properties.[2]

Dendritic-type molecules have for some time been considered good models for disordered and semiordered structures such as polymers, aggregates, clusters, and liquid crystals,[3] and they are increasingly finding applications of their own.[4] With respect to chirality, many types of dendrimers have been explored including dendrimers with a chiral core and achiral branches, dendrimers with chiral peripheral surface groups, and dendrimers with chiral branching units.[5]

To date, however, comparisons of dendritic molecules with a homochiral and heterochiral relationship between chiral elements are rare. In one example, the all L-tartrate-derived homo dendrimer **1** and the heterochiral dendrimer **2** with

---

[†] Novartis Horsham Research Centre.

[‡] King's College London.

[§] Imperial College London.

(1) (a) Hawker, C. J.; Wooley, K. L. *Science* **2005**, *309*, 1200. (b) Darbre, T.; Reymond, J.-L. *Acc. Chem. Res.* **2006**, *39*, 925. (c) Hu, X.; An, Q.; Li, G.; Tao, S.; Liu, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 8145. (d) Ha, C.-S.; Gardella, J. A. *Chem. Rev.* **2005**, *105*, 4205. (e) Lendlein, A.; Jiang, H.; Jünger, O.; Langer, R. *Nature* **2005**, *434*, 879.

(2) Examples of the use of CD spectroscopy to probe chiral polymers and self-assemblies: (a) Satrijo, A.; Meskers, S. C. J.; Swager, T. M. *J. Am. Chem. Soc.* **2006**, *128*, 9030. (b) Nakade, H.; Jordan, B. J.; Xu, H.; Han, G.; Srivastava, S.; Arvizo, R. R.; Cooke, G.; Rotello, V. M. *J. Am. Chem. Soc.* **2006**, *128*, 14924.

(3) Murer, P. K.; Lapierre, J.-M.; Greiveldinger, G.; Seebach, D. *Helv. Chim. Acta* **1997**, *80*, 1648.

(4) For an overview of current commercial applications of dendrimers, see: Helms, B.; Meijer, E. W. *Science* **2006**, *313*, 929.

(5) For a review of chiral dendrimers, see: Romagnoli, B.; Hayes, W. *J. Mater. Chem.* **2002**, *12*, 767.

10.1021/ol070934t CCC: $37.00

six L-tartrate-derived units in the outer layer and three D-chiral units in the inner layer (Figure 1) were compared

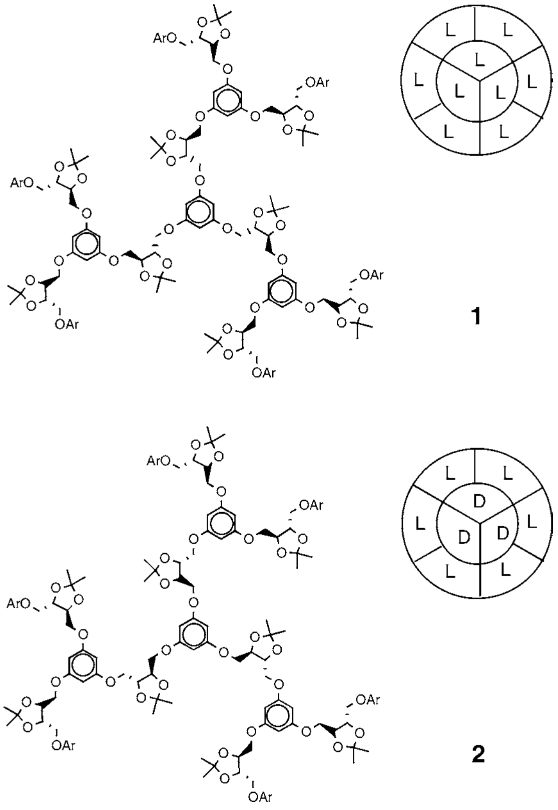


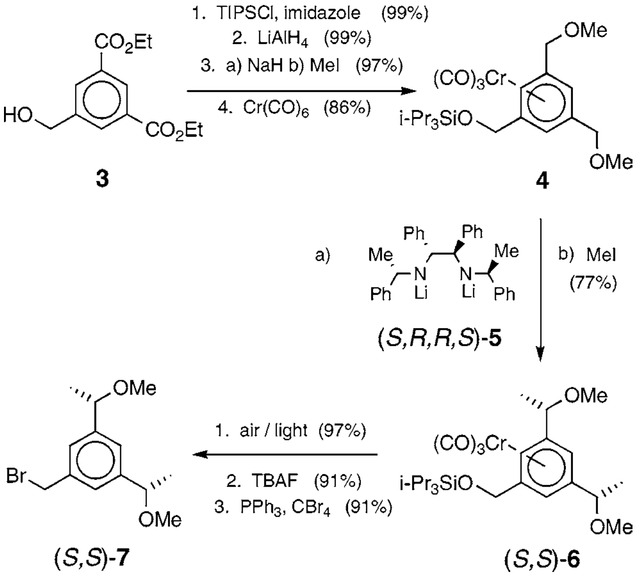
Figure 1. Homochiral dendrimer **1** and heterochiral dendrimer **2**.

by CD spectroscopy. The chiroptical effect of L-chiral units in the outer shell did not completely eliminate that of D-chiral units in the inner shell, and it was concluded that the outer chiral layer was chiroptically slightly different from the inner layer.[6] In a second study, dendrimers prepared from 1,1′-binaphthol units of different configuration and linked by amides were compared. CD and NMR studies revealed differences between the homochiral and heterochiral isomers that suggested that in the homochiral dendrimer the N-H groups of the amides form hydrogen bonds that lead to a different conformation of the molecule than in the heterochiral dendrimer.[7]

We wish to report herein the synthesis of novel polyethers in which the relationship between chirality placed near to the center of the molecule (inner chirality) and chirality placed at its edge (outer chirality) has a significant effect on the properties of the molecule, as revealed by CD spectroscopy. The synthesis draws on a chiral base-mediated reaction that creates multiple stereocenters in a one-pot reaction with high levels of stereochemical control.[8]

At the outset of this study, it was predicted that the asymmetric functionalization of tris ether **8** (Scheme 2) with

Scheme 1. Synthesis of the Electrophile (*S*,*S*)-**7**



bromide (*S*,*S*)-**7** would lead to the homochiral polyether (S_inner,S_outer)-**9** using chiral base (*S*,*R*,*R*,*S*)-**5** and its heterochiral partner (R_inner,S_outer)-**9** using chiral base (*R*,*S*,*S*,*R*)-**5** (Scheme 2). The required bromide, (*S*,*S*)-**7**, was prepared by the route depicted in Scheme 1. Commercially available diethyl 5-(hydroxymethyl)isophthalate **3** was protected as its triisopropylsilyl ether, reduced with lithium aluminum hydride, converted into a dimethyl ether, and complexed with hexacarbonylchromium(0) to give the novel complex **4**. Deprotonation of **4** with 1.5 equiv of the chiral base (*S*,*R*,*R*,*S*)-**5** followed by an iodomethane quench installed the two stereogenic centers destined for the periphery of target molecules **9** in 100% de and 90% ee. Finally, oxidative removal of the tricarbonylchromium(0) unit from (*S*,*S*)-**6** followed by deprotection and bromination of the benzylic alcohol gave the desired electrophile (*S*,*S*)-**7**. [Repetition of the sequence using chiral base (*R*,*S*,*S*,*R*)-**5** gave the enantiomeric bromide (*R*,*R*)-**7** in 48% overall yield from diester **3**.]

With bromide **7** in hand, the readily available tricarbonylchromium(0) complex **8**[8] was deprotonated with 3 equiv of chiral base (*S*,*R*,*R*,*S*)- or (*R*,*S*,*S*,*R*)-**5**, and the electrophile (S,*S*)-**7** was added. Oxidation to remove the chromium led to samples of (S_inner,S_outer)-**9** and (R_inner,S_outer)-**9** (Scheme 2). Repetition of the reactions using electrophile (*R*,*R*)-**7** in conjunction with (*S*,*R*,*R*,*S*)- or (*R*,*S*,*S*,*R*)-**5** gave samples of (S_inner,R_outer)- and (R_inner,R_outer)-**9**, respectively, in 32% and 55% yield.[9] (The NMR spectra of the isomers of **9** indicated impurities of ca. 10%).

As expected, the UV absorption spectra of the four stereoisomers were effectively identical (Figure 2, upper

---

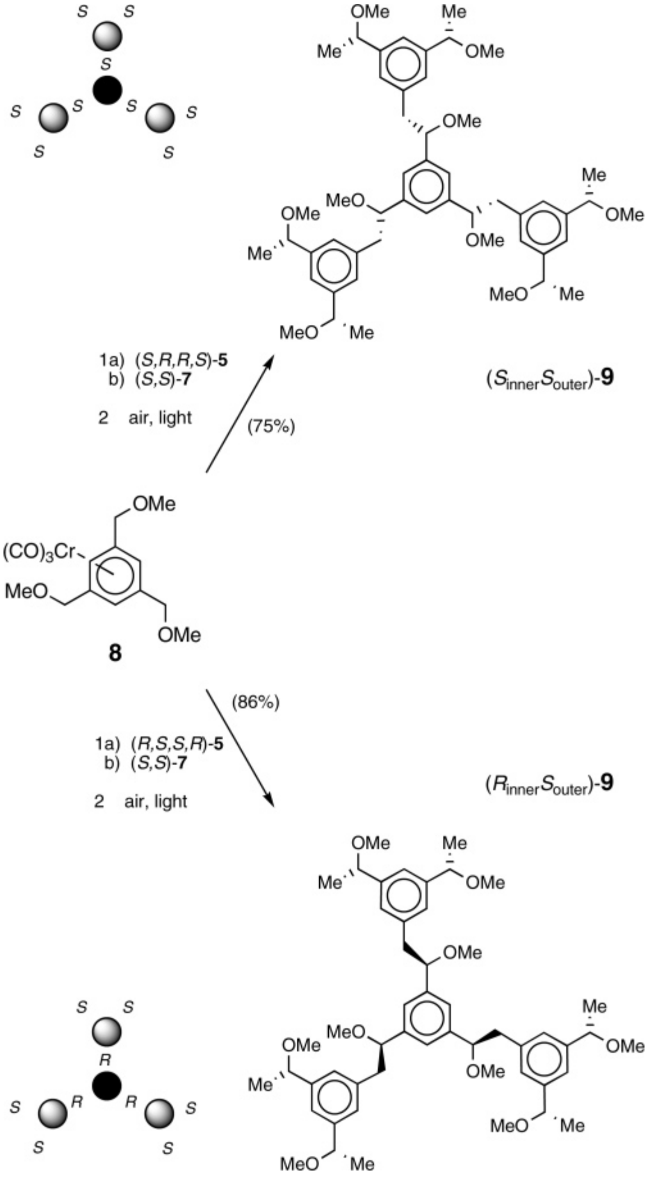
(6) Chow, H.-F.; Mak, C. C. *J. Chem. Soc., Perkin Trans. 1* **1997**, 91.

(7) Lellek, V.; Stibor, I. *J. Mater. Chem.* **2000**, *10*, 1061.

(8) (a) Castaldi, M. P.; Gibson, S. E.; Rudd, M.; White, A. J. P. *Angew. Chem., Int. Ed.* **2005**, *44*, 3432. (b) Castaldi, M. P.; Gibson, S. E.; Rudd, M.; White, A. J. P. *Chem. Eur. J.* **2006**, *12*, 138.

(9) The four stereoisomers of **9** were characterized by mp, ^{1}H NMR, ^{13}C NMR spectroscopy, mass spectrometry, elemental analysis, and UV and CD spectroscopy.

Scheme 2. Synthesis of (S_{inner},S_{outer})-**9** and (R_{inner},S_{outer})-**9**



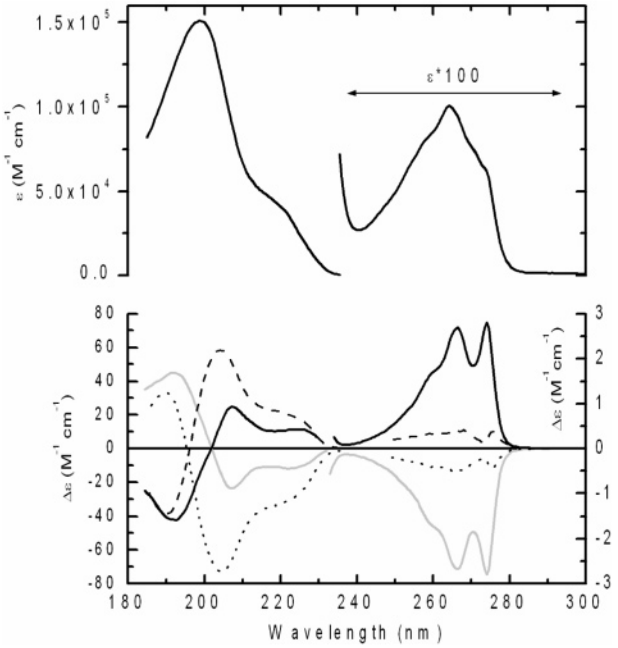


Figure 2. UV spectra of **9** (upper chart) and the CD spectra of ($R_{\text{inner}}R_{\text{outer}}$)-**9** (—), ($S_{\text{inner}}S_{\text{outer}}$)-**9** (—), ($R_{\text{inner}}S_{\text{outer}}$)-**9** (· · ·) and ($S_{\text{inner}}R_{\text{outer}}$)-**9** (- - -) (lower chart).

chart).[10] The classical UV spectrum of the aryl chromophore is observed with the ${}^1L_b$ at 260 nm, the ${}^1L_a$ at 215 nm, and the E transitions around 200 nm. In contrast, the CD spectra differed particularly in the ${}^1L_b$ region (Figure 2, lower chart). The ${}^1L_b$ transition is short axis polarized (see Figure 3), and the CD in this region is sensitive to the freedom of rotation around the long axis of the aryl ring. Thus, the modest magnitude of the CD at 260−275 nm observed for the heterochiral isomers (R_{inner},S_{outer})-**9** and (S_{inner},R_{outer})-**9** is typical of an aryl group free to rotate about its long axis. In contrast the magnitude of the CD in this region observed for the homochiral isomers (R_{inner},R_{outer})-**9** and (S_{inner},S_{outer})-**9** is exceptionally large (>10 times the magnitude generally observed for aryl groups in chiral environments[11]), suggesting that in these isomers rotation about the long axis is severely restricted. Thus, the homochiral isomers can be envisaged as a C_3-symmetric arrangement of fixed paddles on the CD time scale while the heterochiral isomers form a C_3-symmetric arrangement of rotating paddles.

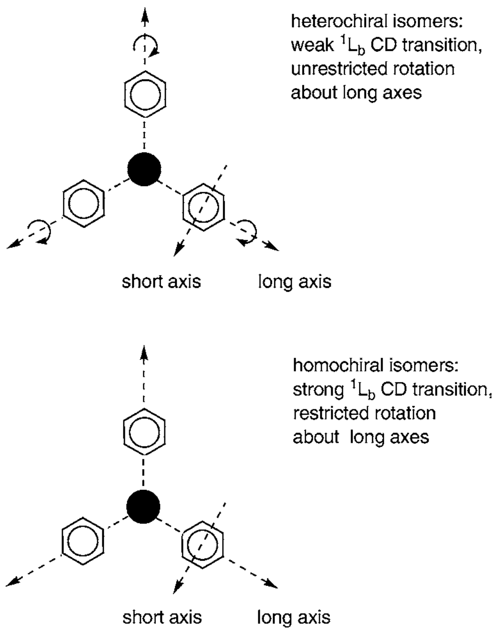


Figure 3. Aryl groups of the heterochiral isomers freely rotate about their long axes while rotation of the aryl groups of the homochiral isomers is restricted.

---

(10) UV and CD spectra were measured in acetonitrile. The pathlength was 1 cm in the near UV and 0.5 mm in the far UV.

In conclusion, we have used a chiral base-mediated reaction to assemble a new class of molecule in which the relationship between chirality located toward the core of the molecule and chirality located around the periphery of the molecule has a significant effect on molecular behavior. The synthesis is modular, versatile, and may be used to synthesize higher generation dendrimers by replacing the iodomethane used in the conversion of complex **4** to complex **6** (Scheme 1) with bromide **7**. It is also amenable to the introduction of functionality such as phosphanes and pyridines[8] and as such should facilitate further understanding and application of the differences between the isomers.

Acknowledgment. We thank Novartis UK Ltd. for generous studentship support (to J.T.R.).

Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL070934T

---

(11) (a) Lightner, D. A.; Gurst, J. E. *Organic Conformational Analysis and Stereochemistry from Circular Dichroism Spectroscopy*; Wiley-VCH: Weinheim, 2000; Chapter 13. (b) Pickard, S. T.; Smith, H. E. *J. Am. Chem. Soc*. **1990**, *112*, 5741.