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Ring-expanded chiral rhombamine macrocycles for efficient NMR enantiodiscrimination of carboxylic acid derivatives

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ABSTRACT

Novel 46-membered chiral rhombamine macrocycles (*R*,*R*,*R*,*R*)-**8a** and **8b** were synthesized by [2+2] cyclocondensation reactions of (*R*,*R*)-1,2-diaminocyclohexane with the corresponding dialdehydes and subsequent reduction with $NaBH_4$. The X-ray crystal structure of 1:4 dioxane complex with (*R*,*R*,*R*,*R*)-**8a** indicated a rhombus conformation of the chiral macrocycle. Compounds (*R*,*R*,*R*,*R*)-**8a** and **8b** were tested as chiral shift reagents for a wide range of α-substituted carboxylic acids and amino acid derivatives. Enantiodiscrimination of ^1H NMR signals was observed with $\Delta\Delta\delta$ values of up to 0.214 ppm.

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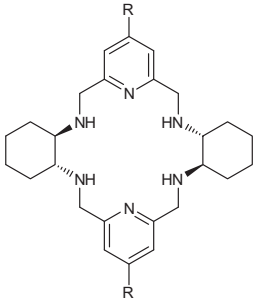
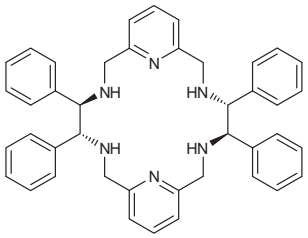
1. Introduction

The use of chiral shift reagents for NMR spectroscopy is one of the most convenient methods for achieving the rapid determination of the enantiomeric excess (ee) of a chiral compound.[1] This method has the advantage of simple implementation without the need for chiral derivatization of the analyte. A wide variety of chiral shift reagents, such as lanthanide complexes, crown ethers, cyclodextrins, and porphyrins, have been developed.[2] However, reports on chiral macrocyclic compounds as efficient chiral shift reagents remain scarce.[3] For example, teraazapyridinophanes **1**–**3**[4] and the aza-crown macrocycle **4**[5] have been reported as chiral shift reagents for carboxylic acids; however, these compounds show enantiodiscrimination for only a limited number of carboxylic acids. We and Gawronski have reported on chiral triangleamines **5a**[6a] and **5b**[6b,c] as chiral shift reagents for secondary alcohols, cyanohydrins, propargylic alcohols, and some carboxylic acids. Better results for the enantiodiscrimination of carboxylic acid derivatives have been obtained by using phenolic hexaazamacrocycle **6**[7] and 30-membered chiral rhombamine macrocyle **7**.[8] In the latter case, four benzene moieties are involved in the CH–π interactions between the host and guest molecules. Herein we report the synthesis of ring-expanded 46-membered chiral rhombamine macrocyles **8a** and **8b** with eight benzene moieties and their successful application as chiral NMR shift reagents for a wide range of carboxylic acids and amino acid derivatives.



1a: R = H
1b: R = OCH_2Ph



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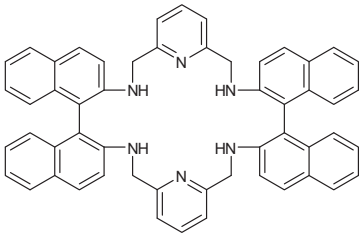

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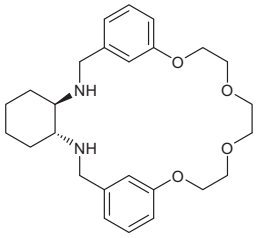

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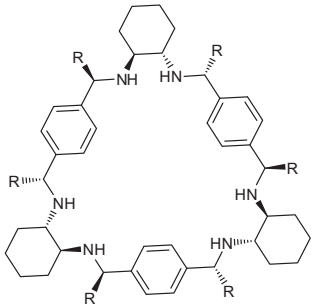
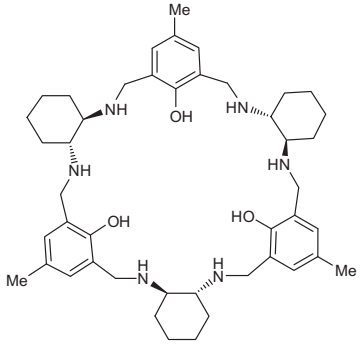


5a: R = H
5b: R = Ph



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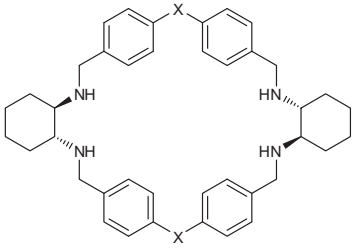
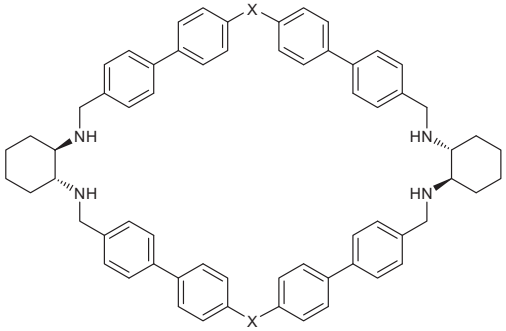
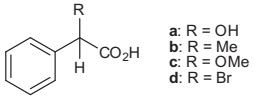


7a: X = CH_2
7b: X = O



8a: X = CH_2
8b: X = O



a: R = OH
b: R = Me
c: R = OMe
d: R = Br

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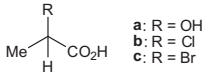

a: R = OH
b: R = Cl
c: R = Br

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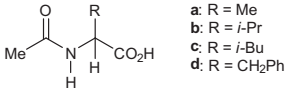

a: R = Me
b: R = *i*-Pr
c: R = *i*-Bu
d: R = CH_2Ph

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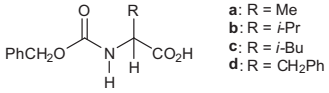

a: R = Me
b: R = *i*-Pr
c: R = *i*-Bu
d: R = CH_2Ph

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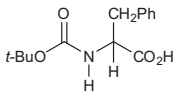

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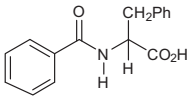

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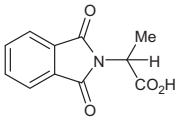

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2. Results and discussion

The novel chiral rhombamine macrocyles **8a** and **8b** were synthesized by treating enantiomerically pure (*R*,*R*)-1,2-cyclohexanediamine with the corresponding dialdehydes followed by $NaBH_4$ reduction of the intermediate [2+2] macrocyclic imines, according to a similar procedure to that employed for the preparation of compounds **7a** and **7b**. The identities of **8a** and **8b** were confirmed by electrospray ionization-mass spectrometry and NMR analysis. The structure of (*R*,*R*,*R*,*R*)-**8a** was determined by X-ray crystal structure analysis. Compound (*R*,*R*,*R*,*R*)-**8a** crystallized in the triclinic space group *P*1 and *Z* = 1. The asymmetric unit contained

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