ORGANIC LETTERS

2006
Vol. 8, No. 21
4679−4682

Macrocyclic Chiral Receptors toward Enantioselective Recognition of Naproxen

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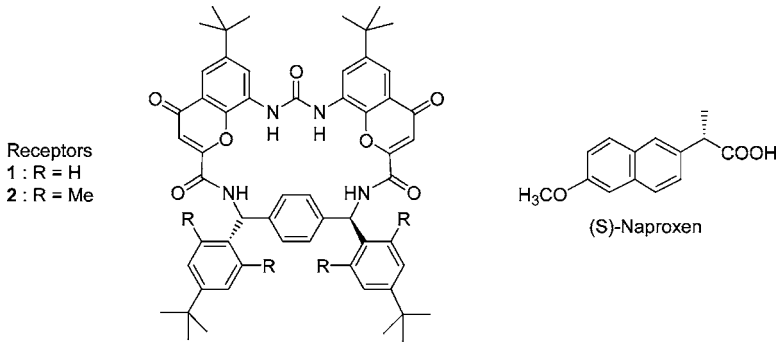
Received June 20, 2006

ABSTRACT



A macrocyclic receptor based on a bischromenylurea and an α,α′-(*o*,*o*′-dialkyl)diphenyl-*p*-xylylenediamine spacer provides a C_2 chiral cavity to associate carboxylates by H-bonds. The extent of the selectivity obtained for the racemic receptor 2 and enantiomerically pure (*S*)-naproxen is 7.2:1. Steric repulsions close to the cavity are decisive for the chiral selectivity.

Within the field of molecular recognition, there is great interest in the development of macrocyclic systems for the chiral discrimination of biologically active molecules. The recognition of enantiomers of naproxen [2-(6-methoxynaphth-2-yl)propionic acid], a nonsteriodal antiinflammatory drug (NSAID),[1] remains a challenging task. The (*S*)-enantiomer of this α-arylpropionic acid is more interesting because of its greater pharmacological activity in comparison with the (*R*)-isomer.[2]

The chiral recognition of this kind of guest involves certain special difficulties because both enantiomers differ only in the disposition of a small methyl group and a hydrogen atom at the steric center. Therefore, the chirality associated with the α position of the carboxylate could be exploited with complementary shaped hosts with precise topology selecting between the sizes of both methyl and hydrogen groups.

Several synthetic receptors have already been shown to associate naproxen.[3] Besides these, chiral receptors focused on the resolution of this substrate have also been synthesized. As far as we know, however, even though the formation of the two diastereomeric complexes has been observed, enantioselectivities lower than 1.3 in solution or 2.25 in chiral stationary phases have been reported.

A combination of geometrically well-defined cleft-type hosts, to complex the carboxylate function by efficient

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(2) (a) Harrison, I. T.; Lewis, B.; Nelson, P.; Rooks, W.; Roszkowski, A.; Tomolonis, A.; Fried, J. H. *J. Med. Chem.* **1970**, *13*, 203−205. (b) Agranat, I.; Caner, H.; Caldwell, J. *Nat. Rev. Drug Discovery* **2002**, *1*, 753−768.

10.1021/ol061505i CCC: $33.50
Published on Web 09/20/2006

hydrogen bonds, with appropriate alkyl substituents, to introduce steric interaction near the guest's stereogenic center, could be useful in the resolution of the racemic mixture.

Receptors based on a bischromenylurea skeleton have shown good results in the association of the carboxylate group[4] owing to four efficient hydrogen bonds for syn and anti lone pairs of the oxoanion.

Taking into account these observations, we searched for suitable spacers able to close a macrocycle[5] to restrict the host conformation, by bridging the gap between the two-chromenone binding arms with amide functions as H-bond donors.

Initially, it was observed that a spacer of xylylenediamine was appropriate to achieve the desired macrocycle. The para-substituted isomer is a better spacer than the meta-substituted one.[6] Accordingly, the use as a spacer of a bulkier *p*-xylylenediamine substituted by two α,α′-phenyl rings (Figure 1) should introduce steric hindrance close to the cavity.

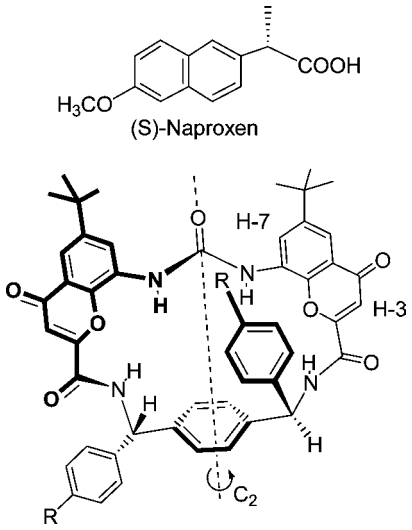
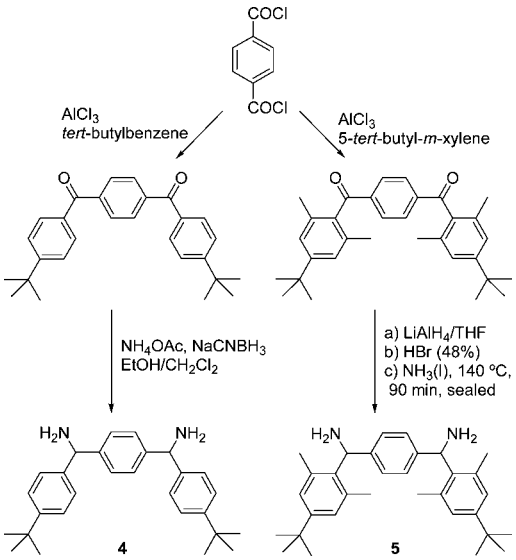


Figure 1. Guest (*S*)-naproxen and C_2 chiral cavity of hosts for associate carboxylates by hydrogen bonds.

Each receptor enantiomer includes a C_2 symmetry axis, offering a chiral cavity for the association (Figure 1). The steric effects between the peripheral phenyl rings of the host and the guest could produce the selective binding of one of the enantiomers of a racemic mixture.

Preparation of new receptors was carried out from dicarboxyethyl bischromenylurea[4a,b] **3** (Scheme 1) and the required

Scheme 1. Preparation of Diamines



diamines. *p*,*p*′-Bis-*tert*-butylphenyl-*p*-xylylenediamine (**4**) was obtained by reductive amination of the dicarbonyl compound formed by acylation of *tert*-butylbenzene with terephthaloyl dichloride (Scheme 1). The *tert*-butyl groups, not involved in the chiral cavity, were introduced to improve solubility.

The synthesis of the designed macrocyclic receptors is depicted in Scheme 2. Hydrolysis of ethoxycarbonyl amino chromenone **3**[4a] gave a dicarboxylic acid, whose bistriethylammonium salt was derivatized with pivaloyl chloride. The coupling with the diamine **4** in high-dilution conditions afforded the desired macrocyclic receptor **1** in 29% yield.

^{1}H NMR competitive experiments[7] with receptor **1** were undertaken to check the chiral recognition properties of the racemic receptors (the meso form was separated by crystallization in ethyl acetate/methanol, mp = 294−296 °C; racemate, mp = 268−270 °C). The titrations were carried

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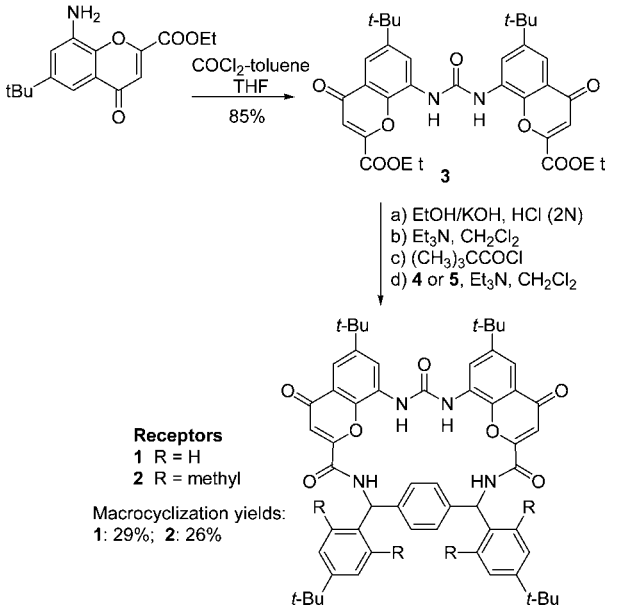
(6) Conventional NMR titrations of the *p*-xylylenediamine receptor **1** show $K_{ass} = 6 \times 10^5$ and 2×10^4 M^{-1} (DMSO-d_6) with the guests tetraethylammonium acetate and benzoate, respectively. A similar macrocycle with a smaller cavity was made with *m*-xylylenediamine as a spacer; the K_{ass}'s in this case were reduced to 2×10^4 and 3.6×10^3 M^{-1}, respectively. When naproxenate was used as a guest, the K_{ass} value was also one order higher with the former receptor ($K_{ass} = 8.8 \times 10^4$ M^{-1}) over the latter ($K_{ass} = 6.6 \times 10^3$ M^{-1}) because the larger cavity size of receptor **1** is more appropriate for complexing a carboxylate function.

(7) (a) Fielding, L. *Tetrahedron* **2000**, *56*, 6151−6170. (b) Whitlock, B. J.; Whitlock, H. W. *J. Am. Chem. Soc.* **1990**, *112*, 3910−3915.

Scheme 2. Synthesis of Receptors **1** and **2**



out adding small amounts of the guest to the receptor solution. Thus, small amounts of the tetraethylammonium salt of enantiomerically pure *S*-naproxen were added to the racemic receptor **1** in DMSO-d_6. Because diastereomeric complexes show different ^{1}H NMR chemical shifts, the formation of the complexes with each enantiomer afforded splitting of the ^{1}H NMR host **1** signals. These are proportional to the ratio between a receptor forming a complex and a free receptor in solution. Plots of the chemical shifts of the protons (H-7 and H-3, respectively) of chromenone with respect to each other in the diastereomeric complexes and treatment with a curve-fitting program provided a K_{ass} ratio between both enantiomeric receptors with only slight chiral discrimination (ratio 1.2:1). However, this suggests that the formation of an enantioselective receptor should be possible by incorporating features that promote or block one of the binding modes.

Analysis of CPK models revealed that the introduction of alkyl substituents in ortho positions in the peripheral phenyl rings restricts the rotation of the $C_{aryl}-C_{amide}$ single bonds, freezing the degrees of freedom of the macrocycle. Thus, receptor **2** sets methyl groups at positions 2 and 6 of these phenyl rings, which are located near the steric center of the guest in the complex. The required diamine **5** was prepared (Scheme 1). In this case, reductive amination was not possible because the carbonyl functions were too sterically hindered;[8] therefore, the carbonyl groups were reduced to hydroxyl functions, substituted by bromide, and transformed into amine groups. The macrocyclization step yielded 26% of receptor **2**.

The **2**-*meso* form was isolated by crystallization in chloroform−methanol as a solid with a mp > 300 °C (decompose), whereas the racemate has a mp = 244−245 °C.

(8) (a) Lane, C. F. *Synthesis* **1975**, 135−146. (b) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897−2904.

2-*meso* and tetraethylammonium acetate establish a complex with $K_{ass} = 6.0 \times 10^4$ M^{-1} (DMSO-d_6), whereas the complex with the naproxenate salt has a $K_{ass} = 4.2 \times 10^3$ M^{-1} (DMSO-d_6).

The structure of the acetate complex was established through X-ray diffraction studies[9] (Figure 2). The carboxylate

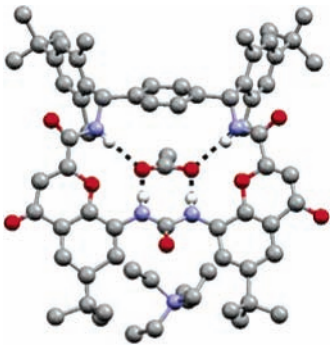


Figure 2. X-ray crystal structure of the **2**-*meso* and tetraethylammonium acetate complex. Four hydrogen bonds bind the carboxylate.

ion is bound by four hydrogen bonds. The oxoanion lies almost in the plane of the cavity. One of the oxygens of the anion is almost symmetrically located (1.99 and 2.01 Å) between the urea and amide H-bond donors, but the other one is somewhat asymmetrically disposed (1.86 and 2.16 Å) due to the total lack of planarity of the structure.

Unfortunately, all our attempts to obtain single crystals for X-ray analysis of any of the complexes with the naproxenate salt failed.

The enantioselective complexation of (*S*)-naproxenate with racemic mixture **2** led to two diastereomeric complexes. A remarkable unfolding of the signal of the H-7 chromenone (from 8.99 for the free receptor to 8.82 and 8.91 ppm in the complexed forms) and the protons of chiral centers (from 6.65 for the free receptor to 6.35 and 6.43 ppm in the complexed form) was observed. Also, a downfield shift and broadening of the N−H signals and a low-field shift of the H-3 of chromenone (0.20 ppm) occurred.

A good enantiomeric recognition of 7.2 was obtained with racemic receptor **2** and (*S*)-naproxen salt in competitive experiments.

According to molecular mechanics calculations, the (*R*,*R*)-**2**−(*S*)-naproxenate (Figure 3) must be the most stable complex [the calculated energy differences[10] between the (*S*,*S*)-**2**−(*S*)-naproxenate and the (*S*,*S*)-**2**−(*R*)-naproxenate range from 0.5 kcal/mol (MM2) to 3 kcal/mol (MMFF), in

(9) Crystallographic data (excluding structure factors) have been deposited at the Cambridge Crystallographic Data Centre as Supporting Information no. CCDC-275962.

(10) Monte Carlo searches for both complexes (using MM2, MM3, and MMFF as force fields) were run on Silicon Graphics workstations using Macromodel. The resulting minimum-energy conformations were subjected to 300 ps molecular dynamics at 600 K (temperature at which the complexes did not break apart) and sampled the guest conformational and rotational space. The sampled conformations were finally energy minimized.

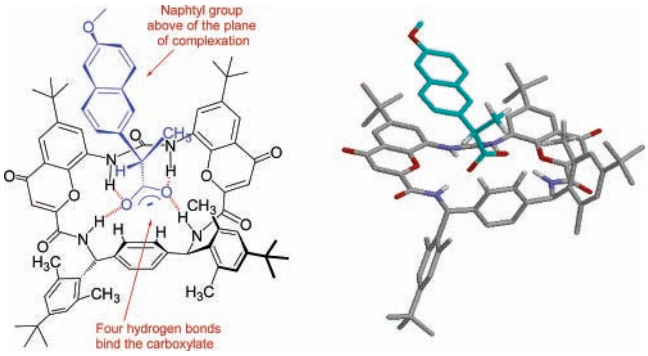


Figure 3. Lowest-energy conformation proposed for the complex between receptor (*R*,*R*)-**2** and (*S*)-tetraethylammonium naproxenate. It displays a geometry in which the interactions between the proton and methyl group of the guest and the 2,6-dimethyl-*tert*-butylphenyl peripheral groups are minimized.

good qualitative agreement with the experimentally measured 1.4 kcal/mol] with favorable interactions between the host and guest methyl groups.

Using the reciprocity principle[3g] in chiral recognition, a single enantiomer of receptor **2** would have the same selectivity for enantiomers of naproxen. To the best of our knowledge, this could be the highest chiral recognition reported for naproxen.

The relatively large effect on chiral affinity observed by us may be attributed to the framework of receptor **2**, having a rigid and hindered cavity where host−guest binding takes place without disturbing the required complementary geometry. Steric repulsion close to the cavity seems to be decisive for the chiral selectivity.

Efforts to attain the resolution of racemic receptor **2** are in progress. Also, binding studies with related guests such as ibuprofen and ketoprofen are now under way in our laboratory and will be reported in due course.

Acknowledgment. We thank Anna Lithgow for the 400 MHz NMR spectra and César Raposo for the mass spectra (Nuclear Magnetic Resonance and Mass Spectrometry Services, Salamanca University). This work was financially supported by "Ministerio de Ciencia y Tecnología" (MCYT Grant No. BQU-2002-00676) and JCyL (SA 053/03). We also thank the M.E.C. for two fellowships (S.G. and M.B.J.; Department of Organic Chemistry, Salamanca University).

Supporting Information Available: Experimental details and characterization data of receptors **1** and **2** and intermediate compounds, details concerning the determination of the relative binding constants, and a summary of the crystallographic data of the complex between receptor **2**-*meso* and tetraethylammonium acetate. This material is available free of charge via the Internet at http://pubs.acs.org.

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