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Tetrahedron: *Asymmetry* 18 (2007) 1981–1985

Tetrahedron: *Asymmetry*

New pincer-like receptor derived from *trans*-cyclopentane-1,2-diamine as a chiral shift reagent for carboxylic acids

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Received 24 July 2007; accepted 16 August 2007

Abstract—A new pincer-like enantiopure receptor bearing two (1*R*,2*R*)-cyclopentane-1,2-diamine moieties has been synthesized and tested as a chiral shift reagent (CSR) for different carboxylic acids. This CSR is efficient for those acids bearing an aromatic group attached to Cα, especially for arylpropionic acids. A full structural study of the diastereomeric supramolecular complexes has allowed us to propose a reasonable model for the interaction.

1. Introduction

Due to the importance of chirality in pharmaceutical and biological chemistry, there is an increasing academic and industrial interest in the development of new, efficient methods for the easy and fast measurement of the enantiomeric excess (ee) of chiral organic molecules.[1] Among other techniques, NMR spectroscopy has the advantages of easy performance and accessibility,[2] with no need for special equipment apart from the common NMR spectrometers. However, as enantiomers cannot be distinguished in an achiral environment, this technique requires modification of the analyte with a chiral shift reagent (CSR), which would convert the mixture of enantiomers into a mixture of diastereomeric molecular or supramolecular complexes.[3] The advantages of using non-covalent CSRs rely on the possibility of carrying out the experiment in situ,[4] and recovering the starting chiral materials after the measurement. In the recent literature, several non-covalent CSRs for amines,[5] alcohols,[6] ammonium salts,[7] and aromatic compounds[8] have been reported. However, despite the increasing number of papers describing CSRs for carboxylic acids,[9] useful receptors for the pharmacologically active arylpropionic acids remain very scarce.[10]

2. Results and discussion

On the other hand, we and others have recently developed synthetic approaches toward enantiopure derivatives of *trans*-cyclopentane-1,2-diamine.[11] Applications of this diamine remain almost unexplored due to the limited availability of both enantiomers.[12] In connection with our ongoing interest in expanding the use of this system and taking advantage of our chemoenzymatic methodologies, we envisioned the preparation of a semi-rigid C_2 symmetrical receptor,[13] as a CSR for carboxylic acids. Thus, conventional hydrolysis (Scheme 1) of enantiopure (*R*,*R*)-**1**,[11a] followed by the coupling with 0.5 equiv of 2,6-bis(chlorocarbonyl)pyridine, led to (*R*,*R*,*R*,*R*)-**3**.

We selected the pyridine-2,6-biscarboxamide linker in order to stabilize a pincer-like conformation, favoring interaction with the substrate.[14] Accordingly, 1D NOESY irradiation of the amide NH yielded NOEs on protons of both benzyl and methyl substituents on the amino group, in good agreement with the major presence of the intended conformation in solution (Fig. 1).

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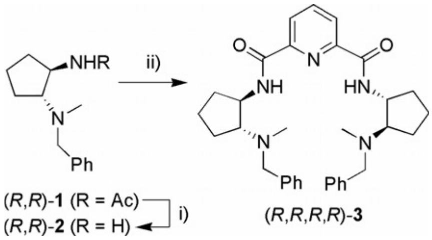
doi:10.1016/j.tetasy.2007.08.021



Scheme 1. Synthesis of (*R*,*R*,*R*,*R*)-**3**: (i) 6 M HCl, then NaOH and extraction (80%); (ii) 2,6-bis(chlorocarbonyl)pyridine (0.5 equiv) in CH_2Cl_2 (85%).

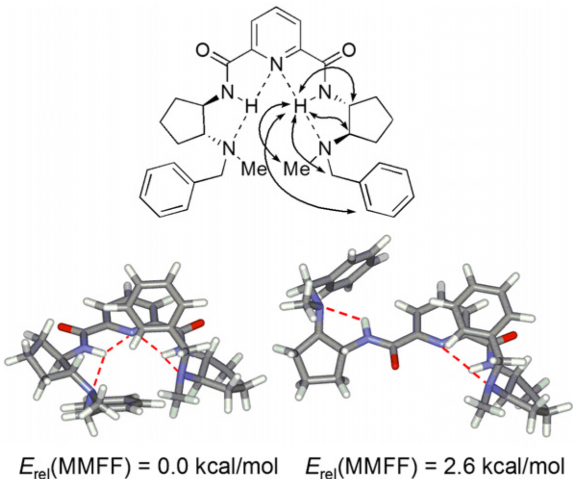


Figure 1. Selected NOEs observed upon irradiation of the amide proton signal (up) and local minima obtained by a Monte Carlo conformational search with relative energies (down).

Moreover, Monte Carlo conformational searches also rendered this folded geometry as the global minimum, which displays bifurcated H-bonds implicating amide protons and both pyridine and aliphatic amine nitrogen atoms (Fig. 1). Breaking of only one of these H-bonds led to a rotation of one of the cyclopentylamide moieties and to a large destabilization of the molecule. All of these results are in perfect agreement with the NMR data (Fig. 1). Once we had confirmed the success of the structural design of (*R*,*R*,*R*,*R*)-**3**, we tested its ability as CSR for several chiral carboxylic acids **4**–**14** (Fig. 2) bearing different residues attached to the stereogenic centre. The experiments were carried out by mixing equimolecular amounts of (*R*,*R*,*R*,*R*)-**3** and racemic acids **4**–**14** in $CDCl_3$ (20 mM). Immediately after each addition, ^1H NMR spectrum was acquired on a 300 MHz spectrometer at room temperature (Fig. 3). Table 1 shows values for the induced chemical shifts ($\Delta\delta$) on the signals of the carboxylic acids after the addition of **3**, as well as the splitting between signals corresponding to each enantiomer of the acids ($\Delta\Delta\delta$). As a general trend, the signals from the acids move upfield ($\Delta\delta < 0$), suggesting a deprotonation of the carboxylic group. Only NH protons from *N*-Boc-phenylglycine **9** (Table 1, entries 11 and 12) resonate at lower field ($\Delta\delta = 0.42$ and 0.10 ppm) upon the addition of receptor **3**, which can be interpreted as the establishment of a

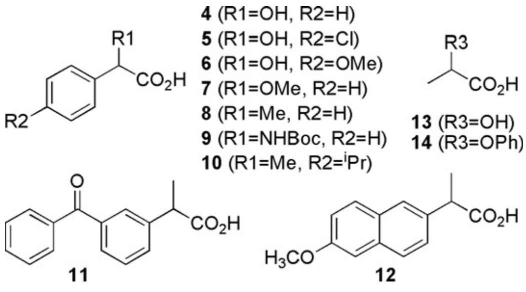


Figure 2. Structures of the carboxylic acids studied.

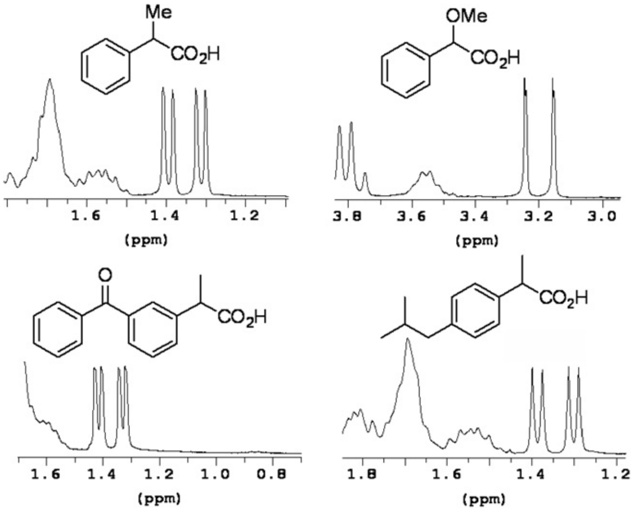


Figure 3. Partial ^1H NMR spectra ($CDCl_3$, 300 MHz) of selected α-arylcarboxylic acids after the addition of 1 equiv of (*R*,*R*,*R*,*R*)-**3**, showing the splitting of signals corresponding to the groups (Me or OMe) attached to Cα.

Table 1. Induced shift ($\Delta\delta$) and splitting ($\Delta\Delta\delta$) for the formation of diastereomeric complexes between (*R*,*R*,*R*,*R*)-**3** and different carboxylic acids (300 MHz, 20 mM in $CDCl_3$)

Entry	Acid	Signal	$\Delta\delta$ (ppm)[a]	$\Delta\Delta\delta$ (ppm)	$\Delta\Delta\delta$ (Hz)
1	**4**	CαH	−0.54	0.02	5.2
2	**5**	CαH	−0.57	0.06	16.7
3	**6**	CαH	−0.40	—	—
4	**6**	OMe	−0.03	0.01	3.0
5	**6**	ArH	−0.06	0.05	15.7
6	**7**	CαH	−0.27	—	—
7	**7**	OMe	−0.18	0.09	26.6
8	**8**	CαH	−0.15	0.01	3.5
9	**8**	Me	−0.14	0.08	24.7
10	**9**	CαH	−0.22	0.01	3.0
11	**9**	NH(1)[b]	0.42	0.06	17.0
12	**9**	NH(2)[b]	0.10	—	—
13	**10**	Me	−0.12	0.09	25.8
14	**11**	CαH	−0.20	—	—
15	**11**	Me	−0.16	0.09	25.7
16	**12**	CαH	−0.31	—	–
17	**12**	Me	−0.28	0.08	25.1
18	**13**	Me	−0.35	0.02	6.2
19	**14**	CαH	−0.23	—	—
20	**14**	Me	−0.20	0.04	11.4

[a] Averaged between signals from both enantiomers.

[b] See Ref. 15.

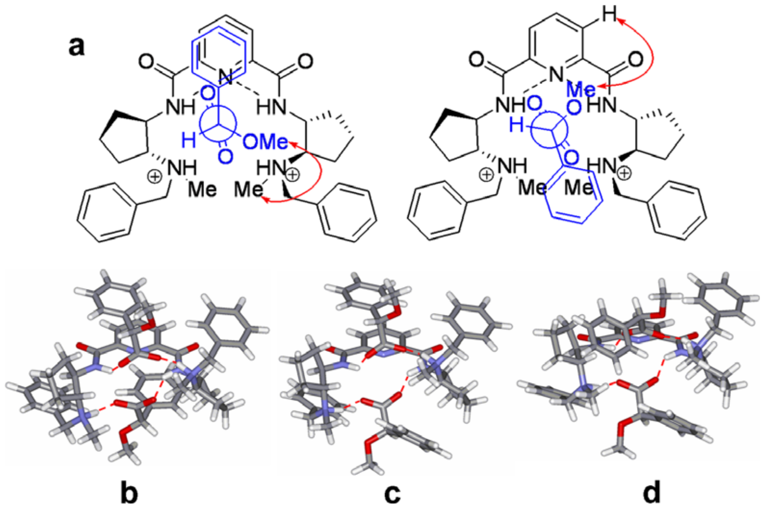


Figure 4. Schematic representation of the possible orientations between (*R*,*R*,*R*,*R*)-**3** and **7** (a) with observed ROEs in red arrows and optimized structures of the corresponding supramolecular complexes with (b) 2 molecules of (*S*)-**7**, (c) (*R*)-**7** + (*S*)-**7** and (d) 2 molecules of (*R*)-**7**.

stronger intramolecular hydrogen bond with the carboxylate anion than that with the carboxylic acid function.

Regarding the NMR enantiodiscrimination, compound **3** produced splitting of most of the examined examples, being successful for the α-arylsubstituted acids, especially for compounds **10**–**12** (entries 13–17), which have activity as non-steroidal antiinflammatory drugs.[16] Interestingly, the splitting is larger for protons of the residues attached to the stereogenic centre (Fig. 3) than for the CαH itself.

Once the efficacy of **3** as CSR was demonstrated, we tried to gain a deeper knowledge about the supramolecular species formed in solution. With this aim, we focused on the complexes formed between (*R*,*R*,*R*,*R*)-**3** and **7**. Job Plots for both enantiomers of the acid rendered 1:2 CSR–acid stoichiometry. Additional ^{1}H NMR titration of (*R*,*R*,*R*,*R*)-**3** with each enantiomer of **7** showed that the observed anisochrony comes from the different chemical shifts of the diastereomeric complexes and not from differences in their stabilities. On the other hand, the addition of 2 equivalents of *rac*-**7** over (*R*,*R*,*R*,*R*)-**3** de-shielded the receptor ^{1}H NMR signals close to the amino group (0.13 and 0.99 ppm for N*Me* and chiral NC*H*, respectively) as well as those close to the amide group (1.36 and 0.23 ppm for amide N*H* and C*H*, respectively). These data support the proton transference from the acid to the CSR and the formation of a strong carboxylate–amide hydrogen bond. Concomitantly, protons from the pyridine moiety moved upfield (0.13 and 0.08 ppm), suggesting a π–π interaction between **3** and **7**. This contact could explain better CSR ability with acids bearing aromatic groups. An additional proof for the formation of supramolecular complexes was obtained by 1D ROESY experiments (Fig. 4a). Irradiation of either the NMe or pyridine protons of **3** yielded small intermolecular ROEs on OMe protons of **7**, suggesting the co-existence of different orientations between them.

Molecular modelling was also undertaken with all the possible stereoisomeric combinations of two molecules of **7** and one of (*R*,*R*,*R*,*R*)-**3** (Fig. 4b–d). We obtained several energetically close local minima, displaying different dispositions between the receptor and substrate, in good agreement with NMR data. However, some general trends could be extracted from analysis of the obtained structural ensembles. All the minima set the substrates on both faces of the receptor with the carboxylate groups pointing to the cavity of the pincer, thus forming strong H-bonds with both ammonium and amide groups of the CSR. Additionally, the phenyl group of the substrate tends to sit parallel on top of the pyridine of the CSR (inter-ring distance ~3.7 Å). This disposition is favored for (*S*)-**7** (Fig. 4b), while for (*R*)-**7** the steric hindrance with the cyclopentane moiety forces the acid to rotate ~180° to the opposite disposition (Fig. 4d). Both diastereomeric conformations would locate the OMe group towards the benzyl sidearm of **3**, but a bit closer in the case of (*R*)-**7**. These facts agree with the observed shielding of the OMe signals, being slightly larger for (*R*)-**7**.

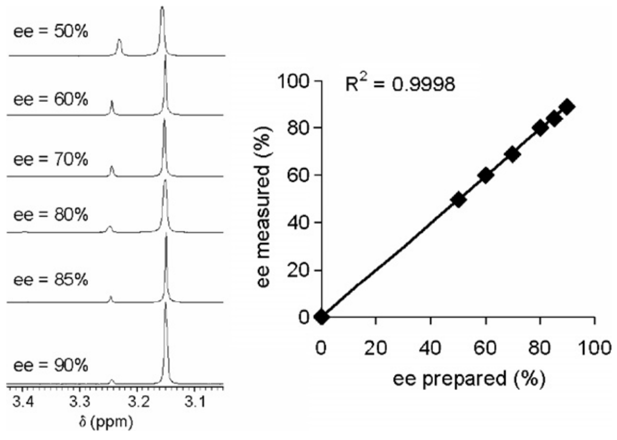


Figure 5. Selected region of the 300 MHz ^{1}H NMR spectra of (*R*)-**7** with different enantiomeric purities (20 mM) in the presence of 0.5 equiv of (*R*,*R*,*R*,*R*)-**3** and correlation between theoretical and observed % ee values.

Finally, we have also demonstrated the practical applicability of our method for the measurement of the ee of carboxylic acids, with **7** as a model compound. Samples containing different proportions of both enantiomers of **7** were prepared and analyzed with our CSR (Fig. 5), rendering an excellent linear response correlation ($R^2 = 0.9998$).

3. Conclusion

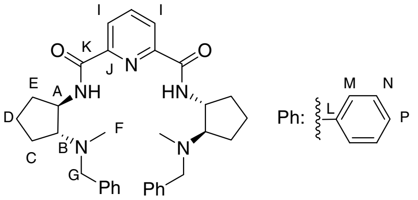
In conclusion, a new pincer-like receptor **3** derived from *trans*-cyclopentane-1,2-diamine has shown to be an efficient CSR for the fast and easy determination of the ee of carboxylic acids, especially for those bearing an aromatic group in the α-position. A deeper study of one of the systems has allowed us to characterize the supramolecular complexes formed and to identify the key interactions for the NMR enantiodiscrimination. Related CSRs are currently under study and will be published in due course.

4. Experimental

4.1. Synthesis of (*R*,*R*,*R*,*R*)-3

Starting from enantiopure (*R*,*R*)-**1**,[11a] in a flask containing 3.7 mmol of the acetamide (*R*,*R*)-**1**, 45 ml of 6 M HCl was added. The mixture was heated at reflux until total consumption of the starting material. The reaction mixture was then cooled and solid NaOH was added to basic pH. The aqueous phase was extracted with CH_2Cl_2 (4 × 15 ml), the organic phases were collected, dried and evaporated to give rise to (*R*,*R*)-**1**, pure enough for the next step (80% yield).

Diamine (*R*,*R*)-**2** (2.4 mmol) was dissolved in 18 ml of dry CH_2Cl_2 and 2,6-bis(chlorocarbonyl)pyridine (1.2 mmol) was added. The reaction mixture was stirred at room temperature for 4 h, after which the mixture was extracted with 3 M aqueous NaOH. The organic layers were dried and evaporated, and the product was purified by flash chromatography (75%).



(*R*,*R*,*R*,*R*)-**3**

$[\alpha]_D^{20} = -146.9$ (*c* 0.85, $CHCl_3$). R_f (MeOH–AcOEt 1:6) 0.20; IR (cm^{-1}) 3318, 1660. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.34–1.56 (m, 2H), 1.56–1.84 (m, 8H), 2.15–2.34 [m+s, ($2 \times CH_3 + CH$) 8H], 2.94 (*c*, $^3J = 8.3$ Hz, $2H_B$), AB quartet ($\delta_A = 3.51$, $\delta_B = 3.67$, $J_{AB} = 13.4$ Hz, $4H_G$), 4.34 (q, $^3J = 8.1$ Hz, $2H_A$), 7.11–7.35 (m, $10H_{M,N,P}$), 7.85 (d, $^3J = 7.2$ Hz, 2NH), 8.07 (t, $^3J = 8.0$ Hz, $1H_H$), 8.4 (d, $^3J = 7.8$ Hz, $2H_I$). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ (ppm): 21.0 (CH_2), 23.4 (CH_2), 31.2 (CH_2), 38.1 $(CH_3)_F$, 51.9 $(CH)_A$, 58.5 $(CH_2)_G$, 70.5 $(CH)_B$, 124.8 $(CH)_I$, 126.9 $(CH)_P$, 128.2 $(CH)_N$, 128.5 $(CH)_M$, 138.9 $(CH)_H$, 139.3 $(C)_L$, 148.9 $(C)_J$, 163.3 $(C)_K$. ESI-MS (*m*/*z*): 540 [$(M+1)^+$, 100]. Anal. Calcd for $C_{34}H_{41}N_5O_2$: C, 73.44; H, 7.66; N, 12.98. Found: C, 73.33; H, 7.89; N, 12.87.

Acknowledgements

Financial support from the Spanish M.E.C. (CTQ-2004-04185) is gratefully acknowledged. We also thank the personal support rendered to I.A. (Ramon y Cajal program, M.E.C.).

References

1. (a) Vespalec, R.; Boceck, P. *Chem. Rev.* **2000**, *100*, 3715; (b) Schuric, V.; Nowotny, A. P. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 939; (c) Pirkle, W. H.; Bocek, P. *Chem. Rev.* **1989**, *89*, 347.
2. (a) Ucello-Barretta, G.; Baklzano, F.; Salvadori, P. *Curr. Pharm. Design* **2006**, *12*, 4023; (b) Seco, J. M.; Quiñoá, E.; Riguera, R. *Chem. Rev.* **2004**, *104*, 17; (c) Wenzel, T. J.; Wilcox, J. D. *Chirality* **2003**, *15*, 256; (d) Parker, D. *Chem. Rev.* **1991**, *91*, 1441.
3. (a) Uccello-Barretta, G.; Balzano, F.; Sicoli, G.; Scarselli, A.; Salvadori, P. *Eur. J. Org. Chem.* **2005**, 5349; (b) Uccello-Barretta, G.; Balzano, F.; Martinelli, J.; Berni, M. G.; Villani, C.; Gasparrini, F. *Tetrahedron: Asymmetry* **2005**, *16*, 3746.
4. For recent examples of in situ covalent CSRs which do not require additional purification steps, see: (a) Pérez-Fuertes, Y.; Kelly, A. M.; Johnson, A. L.; Arimori, S.; Bull, S. D.; James, T. D. *Org. Lett.* **2006**, *8*, 609; (b) Chin, J.; Kim, D. C.; Kim, H.-J.; Panosyan, F. B.; Kim, K. M. *Org. Lett.* **2004**, *6*, 2591.
5. (a) Ema, T.; Ouchi, N.; Doi, T.; Korenaga, T.; Sakai, T. *Org. Lett.* **2005**, *4*, 3985; (b) Pazos, Y.; Leiro, V.; Seco, J. M.; Quiñoá, E.; Riguera, R. *Tetrahedron: Asymmetry* **2004**, *15*, 1825; (c) Omata, K.; Aoyagi, S.; Kabuto, K. *Tetrahedron: Asymmetry* **2004**, *15*, 2351; (d) Menezes, P. H.; Gonçalves, S. M. C.; Hallwass, F.; Silva, R. O.; Bieber, L. W.; Simas, A. M. *Org. Lett.* **2003**, *5*, 1601; (e) Hirose, T.; Naito, K.; Shitara, H.; Nohira, H.; Baldwin, B. W. *Tetrahedron: Asymmetry* **2001**, *12*, 375.
6. (a) Abid, M.; Török, B. *Tetrahedron: Asymmetry* **2005**, *16*, 1547; (b) Maly, A.; Lejczak, B.; Kafarski, P. *Tetrahedron: Asymmetry* **2003**, *14*, 1019.
7. (a) Nakatsuji, Y.; Nakahara, Y.; Muramatsu, A.; Kida, T.; Akashi, M. *Tetrahedron Lett.* **2005**, *46*, 4331; (b) Lacour, J.; Vial, L.; Herse, C. *Org. Lett.* **2002**, *4*, 1351.
8. (a) Bergman, S. D.; Frantz, R.; Gut, D.; Kol, M.; Lacour, J. *Chem. Commun.* **2006**, 850; (b) Dignam, C. F.; Zopf, J. J.; Richards, C. J.; Wenzel, T. J. *J. Org. Chem.* **2005**, *70*, 8071; (c) Dignam, C. F.; Richards, C. J.; Zopf, J. J.; Wacker, L. S.; Wenzel, T. J. *Org. Lett.* **2005**, *7*, 1773; (d) Hebbe, V.; Londez, A.; Goujon-Ginglinger, C.; Meyer, F.; Uziel, J.; Jugé, S.; Lacour, J. *Tetrahedron Lett.* **2003**, *44*, 2467; (e) Planas, J. G.; Prim, D.; Rose, E.; Rose-Munch, F.; Monchaud, D.; Lacour, J. *Organometallics* **2001**, *20*, 4107; (f) Lacour, J.; Ginglinger,

C.; Favarger, F.; Torche-Haldimann, S. *Chem. Commun.* **1997**, 2285.

9. (a) Ma, F.; Shen, X.; Zhang, C. *Org. Lett.* **2007**, *9*, 125; (b) Ema, T.; Tanida, D.; Sakai, T. *Org. Lett.* **2006**, *8*, 3773; (c) González-Álvarez, A.; Alfonso, I.; Gotor, V. *Tetrahedron Lett.* **2006**, *47*, 6397; (d) Cuevas, F.; Ballester, P.; Pericás, M. A. *Org. Lett.* **2005**, *7*, 5485; (e) Yang, D.; Li, X.; Fan, Y.-F.; Zhang, D.-W. *J. Am. Chem. Soc.* **2005**, *127*, 7996; (f) Zheng, Y. S.; Zhang, C. *Org. Lett.* **2004**, *6*, 1189–1192; (g) Yang, X.; Wu, X.; Fang, M.; Yuan, Q.; Fu, E. *Tetrahedron: Asymmetry* **2004**, *15*, 2491; (h) Port, A.; Virgili, A.; Álvarez-Larena, A.; Piniella, J. F. *Tetrahedron: Asymmetry* **2000**, *11*, 3747.
10. Yang, X.; Wang, G.; Zhong, Z.; Wu, X.; Fu, E. *Tetrahedron: Asymmetry* **2006**, *17*, 916.
11. (a) González-Sabín, J.; Gotor, V.; Rebolledo, F. *J. Org. Chem.* **2007**, *72*, 1309; (b) Xu, Q.; Appella, D. H. *J. Org. Chem.* **2006**, *71*, 8655; (c) Luna, A.; Alfonso, I.; Gotor, V. *Org. Lett.* **2002**, *4*, 3627.
12. (a) Toftlund, H.; Pedersen, E. *Acta Chem. Scand.* **1972**, *26*, 4019; (b) Daly, A. M.; Gilheany, D. G. *Tetrahedron: Asymmetry* **2003**, *14*, 127.
13. For receptors of chiral carboxylic acids from our research group (a) González-Álvarez, A.; Alfonso, I.; Díaz, P.; García-España, E.; Gotor, V. *Chem. Commun.* **2006**, 1227; (b) Alfonso, I.; Dietrich, B.; Rebolledo, F.; Gotor, V.; Lehn, J.-M. *Helv. Chim. Acta* **2001**, *84*, 280; (c) Alfonso, I.; Rebolledo, F.; Gotor, V. *Chem. Eur. J.* **2000**, *6*, 3331.
14. Gale, P. A.; Garric, J.; Light, M. E.; McNally, B. A.; Smith, B. D. *Chem. Commun.* **2007**, 1736, and references cited therein.
15. The presence of the CSR also affects the proportion of rotamers in the carbamate bond of **9**.
16. Evans, A. M. *J. Clin. Pharmacol.* **1996**, *36*, 7.