Tetrahedron 64 (2008) 7709–7717

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Cycloalkane-1,2-diamine derivatives as chiral solvating agents. Study of the structural variables controlling the NMR enantiodiscrimination of chiral carboxylic acids

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ARTICLE INFO

Article history:
Received 1 April 2008
Received in revised form 9 June 2008
Accepted 9 June 2008
Available online 12 June 2008

Keywords:
Chiral solvating agent (CSA)
NMR
Anion recognition
Pincer
Enantiodiscrimination

ABSTRACT

A family of pincer-like receptors (**2**–**5**) has been synthesized and tested for the NMR enantiodiscrimination (CSA) of chiral carboxylic acids. Starting from a previous design (**1**), different structural variables have been mapped on the receptor frame. The splitting of the signals of the acids upon the addition of the CSAs largely depends on these structural variables. Thus, we concluded that the C_2 symmetrical pyridine-2,6-biscarboxamide moiety is a key structural feature for the efficiency of the CSA. Structural studies by NMR and molecular modeling showed that this moiety promotes the U-shape-folded pincer-like conformation by intramolecular H-bonds. On the other hand, we also observed that the cyclohexane-1,2-diamine derivative **5** is a more versatile CSA than its cyclopentane analogue **1**, as **5** shows a better performance for more structurally different acids. However, the original cyclopentane derivative (**1**) remained the best for the arylpropionic acids. Finally, combination of NMR and modeling studies allowed us to propose a reasonable model for the interaction and, accordingly, for the observed NMR enantiodiscrimination.

1. Introduction

The development of more efficient methods for the easy and fast measurement of the enantiomeric excess (ee) of a chiral organic molecule[1] is an area of increasing interest due to the importance that chirality has in biological and pharmaceutical chemistry. Among other spectroscopic and chromatographic 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, this technique requires the modification of the substrate with a chiral auxiliary, which would convert the mixture of enantiomers into a mixture of diastereomeric molecular (covalent, chiral derivatizing agents, CDA) or supramolecular (non-covalent, chiral solvating agents, CSA) complexes.[3] Ideally, these diastereomeric species will show chemical shift non-equivalence of some of their NMR signals, allowing the determination of the enantiomeric composition of the substrate by the direct integration of these bands.[4] The advantage of using the non-covalent chiral solvating agents relies on the possibility of carrying out the experiment in situ, without purification steps.[5] Besides, the starting chiral materials, analyte and CSA, could be easily recovered after the measurement. There are several CSAs described in the literature for amines,[6] amides,[7] alcohols,[8] ammonium salts,[9] phosphorous-containing molecules,[10] and aromatic compounds.[11] However, despite the increasing number of papers describing CSAs for carboxylic acids,[12] useful receptors for the pharmacologically active arylpropionic acids are very scarce.[13]

Within our current research project devoted to the preparation of new receptors for the molecular recognition of chiral carboxylic acids[14] and taking advantage of our chemoenzymatic methodologies for the preparation of enantiopure forms of both *trans*-cyclopentane-1,2-diamine[15] and *trans*-cyclohexane-1,2-diamine[16] derivatives, we envisioned to implement these chiral moieties in a family of new semi-rigid C_2 symmetrical receptors, and to test their abilities as CSAs for carboxylic acids. Additionally, we have made an effort to understand the structural basis responsible for the different behavior of all the receptors.

2. Results and discussion

2.1. Design and syntheses of the receptors 2–5

Starting from the pincer-like receptor **1**,[17] and taking into account our previously reported results, we envisioned to carry out

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doi:10.1016/j.tet.2008.06.031

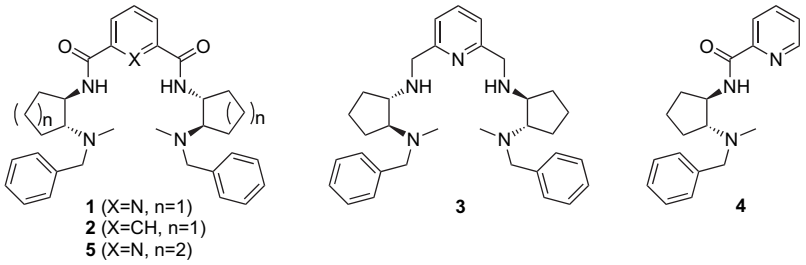


Figure 1. Structures of the previous receptor (**1**) and those prepared and studied in this work (**2**–**5**).

successive structural changes (**2**–**5**) in order to check their effect on the NMR chiral discrimination properties (Fig. 1).

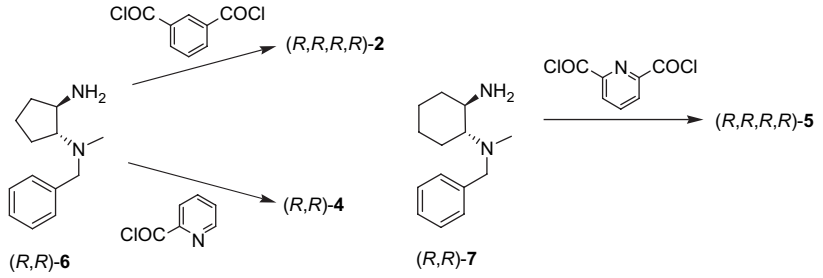
The first question to be answered is the importance of the pincer conformation for the CSA ability. For this U-shape geometry, a pyridine-2,6-biscarboxamide moiety is necessary,[18] the pincer conformation being fitted by two H-bonds formed between the NH groups and the pyridine nitrogen. Thus, in order to check this aspect, we planned the synthesis of the receptor **2** incorporating a benzene-1,3-biscarboxamide and receptor **4**, which can be considered as 'one half' of the pincer structure. Both compounds **2** and **4** were prepared in high yields from the enantiopure diamine (*R*,*R*)-**6** which is indicated in Scheme 1.

Another important structural feature of the pincer is the chiral moiety. In order to study the effect of this fragment, we also synthesized the receptor **5**, in which the size of the carbocycle of the starting chiral diamine has been increased by one methylene group. Therefore, we could also compare the performance of the cyclohexane and cyclopentanediamine moieties. Thus, the receptor **5** was readily synthesized by coupling of the diamine (*R*,*R*)-**7**[16] with 0.5 equiv of 2,6-bis(chlorocarbonyl)pyridine in 90% yield (Scheme 1).

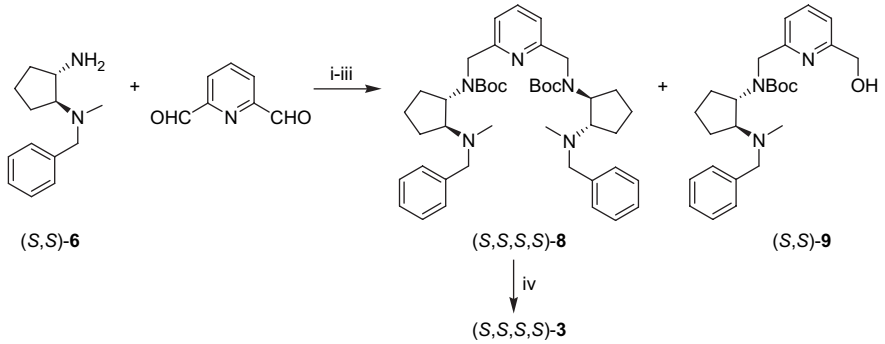
On the other hand, compound **3** lacks the amide bond, retaining the nitrogen atoms as secondary amino groups. In the presence of the racemic acid, protonation could take place in these nitrogen atoms thus favoring H-bonds with the pyridinic nitrogen and the U-shape conformation. This receptor was prepared by reductive amination of the diamine (*S*,*S*)-**6** with 2,6-pyridinedicarboxaldehyde (Scheme 2). However, in this process two compounds with similar chromatographic retention factors were produced: the polyamine **3** and an amino alcohol resulting from the monoamination of the dialdehyde and subsequent reduction of both imino and carbonyl groups. In order to facilitate the isolation of **3**, the compound was derivatized with $(Boc)_2O$ and the resulting new mixture formed by **8** and **9** easily separated by flash chromatography. After the Boc groups of **8** were removed by acid treatment, the desired C_2 symmetric compound **3** was isolated in 55% overall yield.

2.2. NMR enantiodiscrimination studies

We tested the abilities of receptors **2**–**5** as CSAs for several chiral carboxylic acids (**10**–**20** in Fig. 2) bearing different residues attached to the stereogenic center. The experiments were carried out by mixing equimolecular amounts of the corresponding receptor and the racemic acid in $CDCl_3$ (10 mM). Immediately after each addition, ^1H NMR spectrum was acquired in a 300 MHz spectrometer at room temperature. Table 1 shows the spectra of some acids in the presence of receptor **2**–**5**. In addition, Table 2 shows the values for the induced chemical shifts ($\Delta\delta$) on the signals of all the carboxylic acids after the addition of **2**–**5**, as well as the splitting



Scheme 1. Synthesis of receptors **2**, **4**, and **5**.



Scheme 2. Reagents and conditions: (i) $MgSO_4$, MeOH, 25 °C; (ii) $NaBH_4$, MeOH, 0 °C; (iii) $(Boc)_2O$, CH_2Cl_2; (iv) 3 N aq HCl, 25 °C, 55% overall yield.

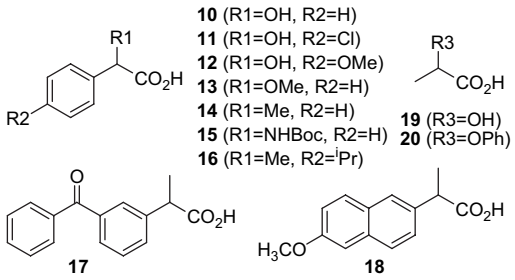


Figure 2. Structures of the carboxylic acids studied.

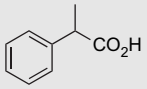
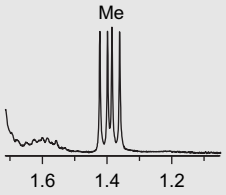
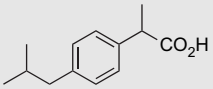
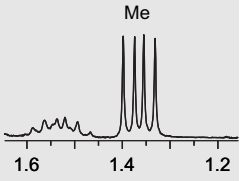
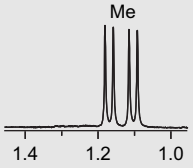
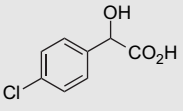
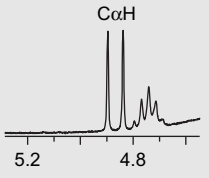
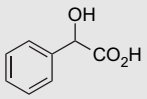
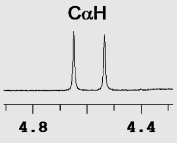
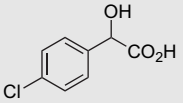
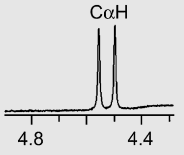
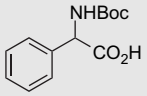
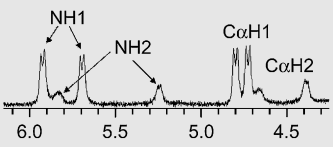
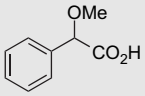
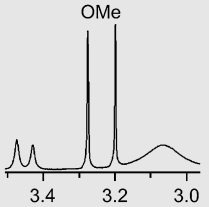
between signals corresponding to each enantiomer of the acids ($\Delta\Delta\delta$). For the sake of an easier comparison, values previously obtained with receptor **1** are also displayed in Table 2, and selected representative splitting values for **1**–**5** are plotted in Figure 3. As a general trend, the signals of the CαH protons of the acids move upfield ($\Delta\delta<0$), implying a deprotonation of the carboxylic group, which is more efficient for the stronger mandelic type acids such as those indicated by the higher chemical shifts variations. Additionally, other signals from the substrates also move upfield, suggesting a shielding effect of the aromatic groups of the receptors over the protons of the substrates. Only NH protons from *N*-Boc-phenylglycine (**15**, entries 12 and 13 in Table 2) resonate at lower field upon the addition of the receptors, which can be interpreted as the establishment of a stronger intramolecular hydrogen bond with the carboxylate anion than that with the carboxylic function.

Regarding the NMR enantiodiscrimination, some important differences must be pointed out. The pyridine-2,6-biscarboxamide moiety led, in general, to the largest splitting values. This trend can be easily checked if the splitting produced by receptors **1** and **2** are compared. Thus, the derivative **2** was much less efficient for the selected acids. On the other hand, the polyamine receptor **3** showed a very good peak resolution for lactic acid **19** (Tables 1 and 2) although, for the most of examples, it produced large line broadening and smaller splitting. This observation suggested the involvement of a mixture of different conformations as a consequence of the less rigidity of the cavity of **3** (due to the change of carbonyl by methylenic units) as well as by the presence of two different basic nitrogens susceptible to be protonated. In contrast, the co-planarity between the aromatic pyridine and both amide groups in **1** leads to the more rigid pincer-like conformation, which is stabilized by intramolecular H-bonds. This conformation would favor the NMR enantiodiscrimination within the supramolecular receptor–substrate complexes (see below). The elimination of one half of the pincer biting cavity drastically reduced the splitting for most of the acids (compare receptors **1** and **4**), thus supporting the importance of the mentioned cavity. Only for two substrates (**12** and **15**) bearing an H-bonding donor at Cα, the receptor **4** behaves more efficiently than the original one **1**.

On the other hand, we have found that substitution of the cyclopentane moiety by a cyclohexane ring leads to a more versatile CSA, with a broader applicability. Thus, receptor **5** showed a $\Delta\Delta\delta\geq0.04$ ppm for at least one of the signals of any of the substrates. This CSA works with acids having either H-bonding or aromatic groups on Cα. However, the initial receptor **1** still remained more suitable than **5** for the arylpropionic acids (**14**, **16**–**18**). Thus, we could get splitting of the signals of $\Delta\Delta\delta\geq0.05$ ppm for all the tested acids, by choosing the addition of either **1** or **5**.

We have also demonstrated the practical applicability of the best of our receptors (**5**) for the measurement of the ee of carboxylic acids, using **13** as a model compound. Samples containing different proportions of both enantiomers of **13** were prepared and analyzed

Table 1
Partial ^{1}H NMR spectra[a] of selected racemic acids in the presence of receptors **2**–**5**

Receptor	Carboxylic acid	Spectrum	Receptor	Carboxylic acid	Spectrum
2			**2**		
3			**4**		
5			**5**		
5			**5**		

[a] Frequency: 300 MHz, 10 mM in $CDCl_3$.

Table 2
Induced shift (Δδ, ppm) and splitting (ΔΔδ, ppm) for the signals of the carboxylic acids **10**–**20** in the presence of receptors **1**–**5** (300 MHz, 10 mM in $CDCl_3$)

	Acid	Signal	Receptor									
			1[a]		**2**		**3**		**4**		**5**	
			Δδ[b]	ΔΔδ	Δδ[b]	ΔΔδ	Δδ[b]	ΔΔδ	Δδ[b]	ΔΔδ	Δδ[b]	ΔΔδ
1	**10**	CαH	−0.54	0.02	n.m.[c]	n.m.[c]	−0.55	0.01	−0.35	0.04	−0.60	0.12
2	**11**	CαH	−0.57	0.06	−0.71	0.01	−0.70	0.01	−0.51	0.06	−0.58	0.05
3	**12**	CαH	−0.40	—	n.m.[c]	n.m.[c]	−0.50	—	−0.33	0.05	−0.75	0.13
4	**12**	OMe	−0.03	0.01	n.m.[c]	n.m.[c]	−0.09	0.03	−0.01	—	−0.05	0.01
5	**12**	ArH	−0.06	0.05	n.m.[c]	n.m.[c]	−0.13	0.02	—	—	−0.09	0.03
6	**13**	CαH	−0.27	—	−0.29	0.01	—	—	−0.08	0.01	−0.27	0.04
7	**13**	OMe	−0.18	0.09	−0.25	<0.01	−0.21	0.02	−0.04	0.01	−0.19	0.08
8	**14**	CαH	−0.15	0.01	−0.17	—	−0.22	—	−0.05	—	−0.10	—
9	**14**	Me	−0.14	0.08	−0.14	0.05	−0.12	—	−0.01	0.02	−0.06	0.04
10	**15**	CαH1[d]	−0.22	0.01	n.m.[c]	n.m.[c]	−0.34	0.04	−0.07	0.05	−0.36	0.07
11	**15**	CαH2[d]	—	—	n.m.[c]	n.m.[c]	−0.50	—	−0.27	—	−0.62	0.30
12	**15**	NH1[d]	0.42	0.06	n.m.[c]	n.m.[c]	0.47	0.04	0.52	0.10	0.32	0.22
13	**15**	NH2[d]	0.10	—	n.m.[c]	n.m.[c]	0.58	0.05	0.56	—	0.21	0.69
14	**16**	CαH	—	—	−0.16	—	−0.24	—	−0.04	—	−0.02	—
15	**16**	Me	−0.12	0.09	−0.07	0.04	−0.17	0.01	−0.06	0.02	−0.05	0.04
16	**17**	CαH	−0.20	—	−0.22	—	—	—	−0.11	—	−0.06	—
17	**17**	Me	−0.16	0.09	−0.18	0.04	−0.22	—	−0.04	—	−0.09	0.04
18	**18**	CαH	−0.31	—	n.m.[c]	n.m.[c]	−0.28	—	—	—	−0.30	—
19	**18**	Me	−0.28	0.08	n.m.[c]	n.m.[c]	—	<0.01	−0.01	—	−0.05	0.04
20	**19**	CαH	—	—	n.m.[c]	n.m.[c]	—	—	−0.35	—	−0.68	—
21	**19**	Me	−0.35	0.02	n.m.[c]	n.m.[c]	−0.41	0.07	−0.17	0.02	−0.39	0.07
22	**20**	CαH	−0.23	—	n.m.[c]	n.m.[c]	−0.43	—	−0.06	0.02	−0.23	—
23	**20**	Me	−0.20	0.04	n.m.[c]	n.m.[c]	−0.19	0.02	−0.09	—	−0.25	0.05

[a] Taken from Ref. 17.
[b] Averaged between signals from both enantiomers.
[c] n.m.=not measured.
[d] The numbers 1 and 2 correspond to the presence of two rotamers in the carbamate bond.

with **5** as a CSA (Fig. 4), rendering an excellent linear response correlation (R^2=0.9989). Moreover, samples containing 97.0, 98.0, and 99.0% ee were carefully prepared and analyzed with receptor **5** at 500 MHz. They showed 96.5, 98.0, and 98.6% ee, respectively, which rendered a ~0.5% error in the determination of ees within the most conflictive range. Therefore, both **1** and **5** have shown to be useful CSAs for carboxylic acids, being the practical applicability of either **1** or **5** dependent on the acid structure.

2.3. Structural studies in solution

Considering the obtained results, two main structural features are especially important for this family of receptors: the pyridine-2,6-biscarboxamide unit and the size of the cycloalkanediamine. With the aim of proposing an explanation for these facts, we have studied the solution structures of receptors **2** and **5** by NMR and molecular modeling. Regarding compound **2**, a full set of 1D NOESY experiments (Fig. 5) showed that the receptor exists as a mixture of cis/trans dispositions of the isophthalamide moiety. For instance,

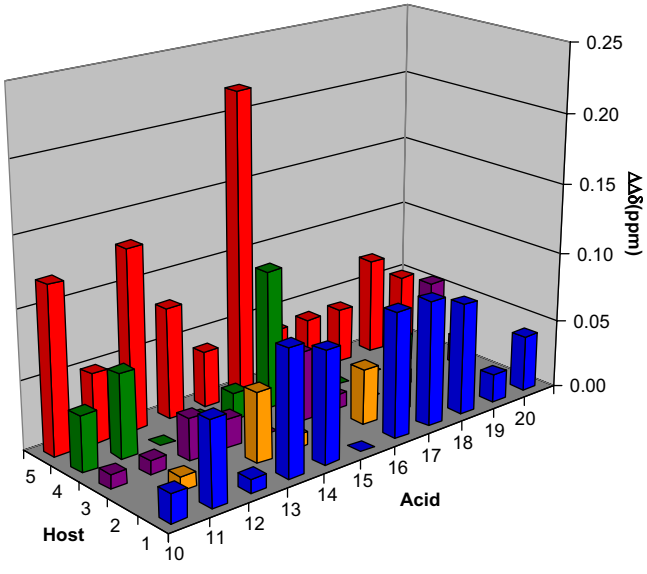


Figure 3. Plot of the splitting (ΔΔδ, ppm) observed by selected proton signals of **10**–**20** upon the addition of the receptors **1**–**5**. The proton signals used in this plot were those showing the largest splitting for every compound.

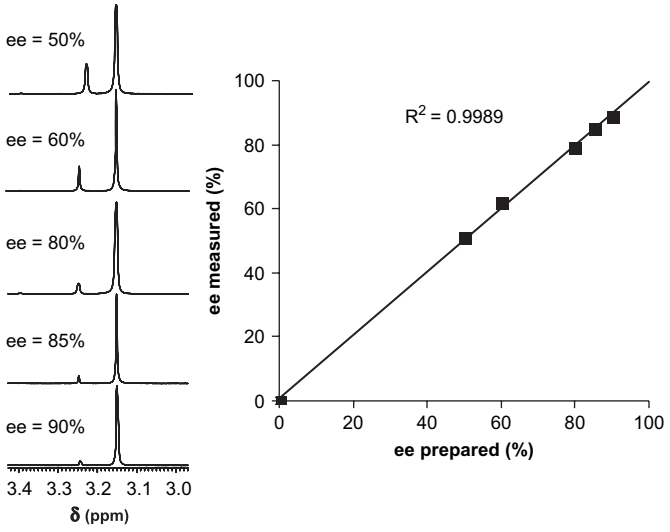


Figure 4. A selected region of the 300 MHz ^{1}H NMR spectra of (*R*)-**13** (20 mM) with different enantiomeric purities in the presence of (*R*,*R*,*R*,*R*)-**5** (20 mM) and correlation between theoretical and observed % ee values.

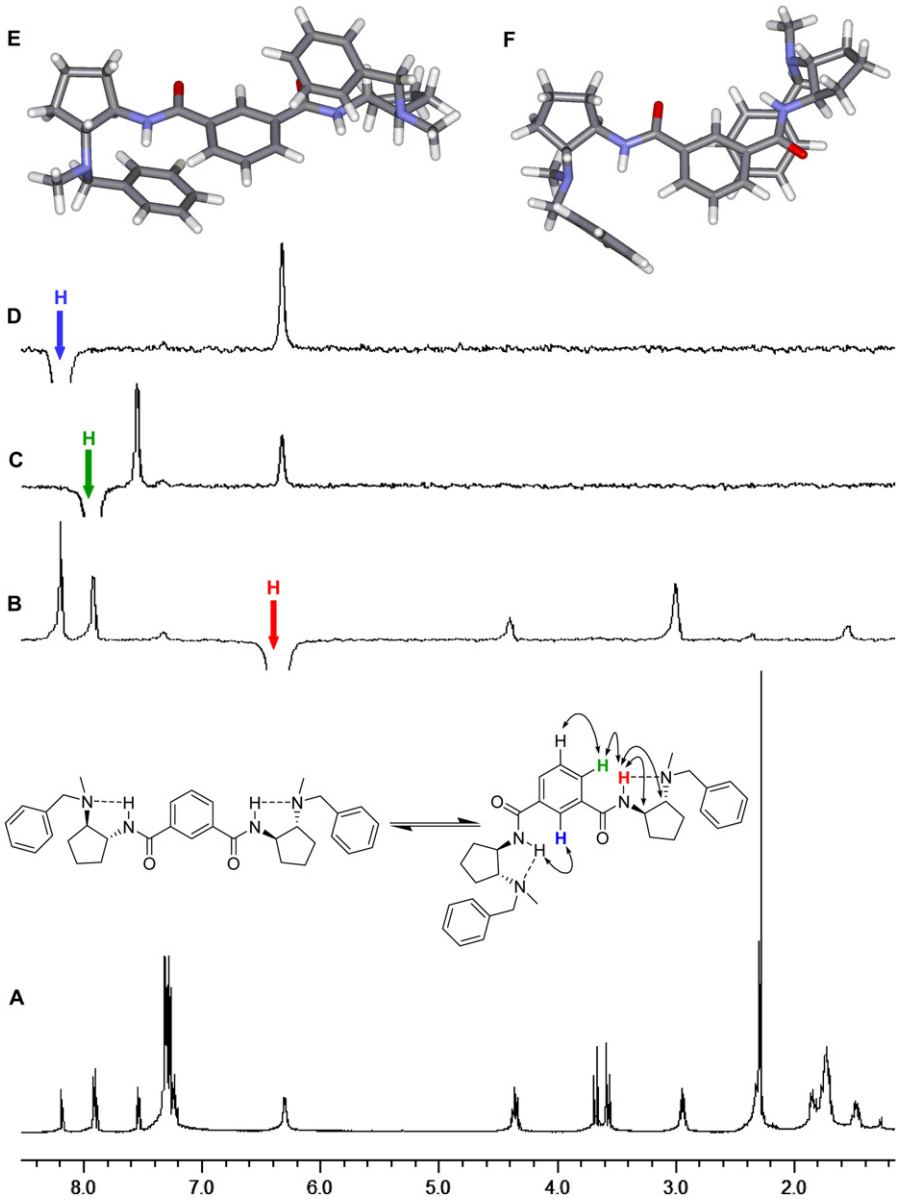


Figure 5. Solution conformational analysis of compound **2**: (A) ^{1}H NMR spectrum (500 MHz, 10 mM in $CDCl_3$) and selected 1D NOESY traces upon irradiation on proton signals of (B) amide NH (red), (C) 4/6-positions (green) or (D) 2-position (blue) of the isophthalamide moiety. (E) Global minimum obtained by Monte Carlo MMFF calculations. (F) Second lowest minimum.

irradiation of amide NH proton (Fig. 5B) produced NOE enhancements on the aromatic protons at *ortho* positions to the carbonyl groups (positions 2 and 4/6). This observation was further confirmed by the irradiation of either 4/6 (Fig. 5C) or 2 (Fig. 5D) proton nuclei. Interestingly, Monte Carlo conformational searches rendered the all trans conformation of the isophthalamide moiety as the most stable one (Fig. 5E), with a small participation of the trans/cis conformation (Fig. 5F). Thus, in this case, the U-shaped pincer conformation is highly disfavored, in contraposition with the initial receptor **1**. This situation could account for the less efficient NMR enantiodiscrimination observed here and highlight the structural importance of the pyridine nitrogen.

With respect to the solution conformation of receptor **5**, the analysis of their 2D NOESY spectra (Fig. 6A) showed cross-peaks between the amide NH and the protons of the benzyl (CH_2 and H*ortho*) and methylgroups but not with the protons of the pyridine moiety. This implies a U-shape-folded pincer-like conformation in solution. In addition, Monte Carlo conformational searches also rendered a folded geometry as the global minimum, which displays bifurcated H-bonds between NH amide protons and both pyridine and aliphatic amine nitrogen atoms. Moreover, the angles imposed by the cyclohexane moieties produced steric repulsions between the two equivalent methylamino groups, leading to a slight distortion from the ideal C_2 symmetry in the global minimum (Fig. 6B). The second lowest minimum is the C_2 symmetrical one (Fig. 6C), being only 0.1 kcal/mol higher in energy and supporting their coexistence in solution at room temperature. The overall effect is a slightly more flexible pincer conformation for **5** than for **1**, which could explain the more efficient capability of the receptor **5** to accommodate to the carboxylic acids.

We have also tried to get a deeper knowledge about the supramolecular species formed in solution. With this aim, we focused on the complexes formed between (*R*,*R*,*R*,*R*)-**5** and **13**. Job plots for both enantiomers of the acid rendered a 1:2 CSA/acid stoichiometry (Fig. 7). For this reason, to carry out the following ^{1}H NMR experiments, a sample 20 mM for the racemic acid **13** and 10 mM for the

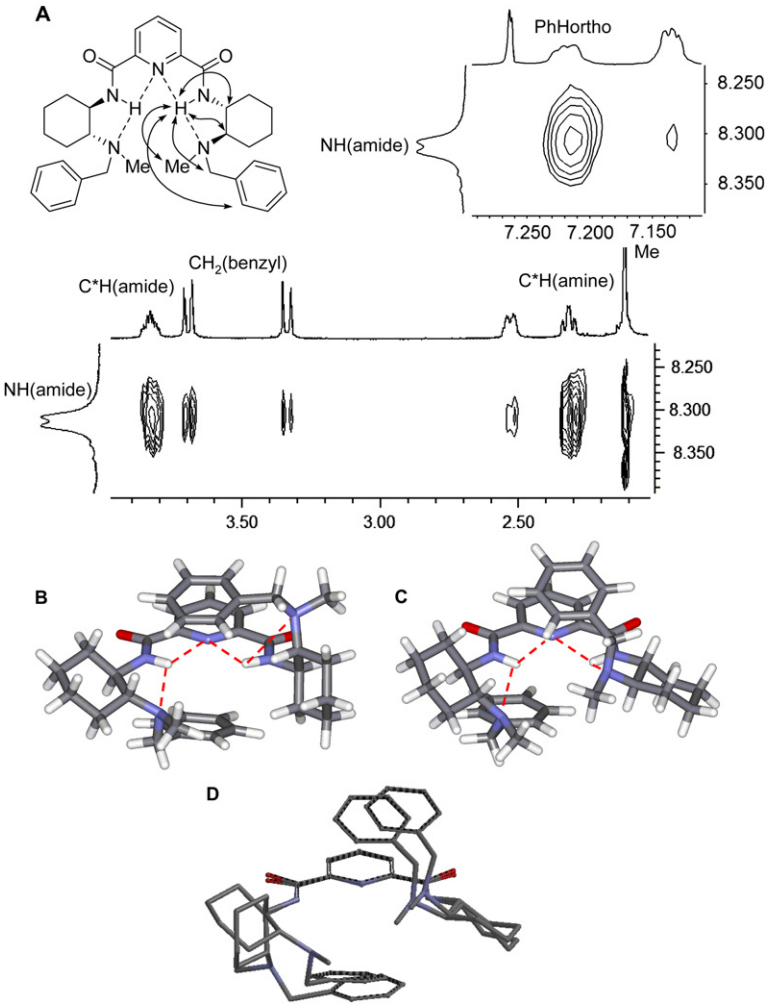


Figure 6. (A) Selected regions of the 2D NOESY spectra (500 MHz, 10 mM in $CDCl_3$) of **5** showing the cross-peaks implicating the amide NH proton (also shown in the structure by double-headed arrows). (B) Global minimum obtained by Monte Carlo MMFF calculations. (C) Second lowest minimum. (D) Superposition of (B) and (C).

receptor was prepared. As it was expected, the addition of *rac*-**13** over (*R*,*R*,*R*,*R*)-**5** causes a deshielding of its proton signals close to the amino group (0.17 and 0.89 ppm for NMe and chiral NCH, respectively) as well as those close to the amide group (0.95 and 0.32 ppm for amide N*H* and C*H*, respectively). These data support the proton transference from the acid to the receptor and the formation of a strong carboxylate–amide hydrogen bond. Concomitantly, protons 3 and 4 of the pyridine moiety moved upfield (0.18 and 0.08 ppm, respectively) suggesting a π–π interaction between **5** and **13**. An additional proof for the formation of the supramolecular complexes was obtained by 1D ROESY experiments (Fig. 8). Irradiation of protons at positions 3/5 of the pyridine ring of **5** yielded small intermolecular ROEs on OMe and aromatic protons of **13**, suggesting the co-existence of different orientations between them (Fig. 8A).

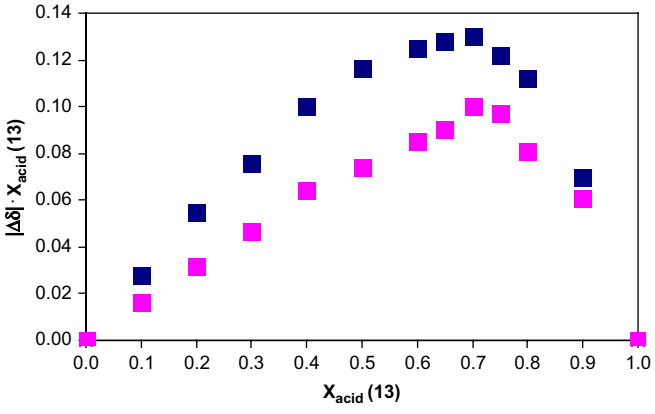


Figure 7. Job plots for (*R*,*R*,*R*,*R*)-**5** and either (*S*)-**13** (magenta) or (*R*)-**13** (blue).

Molecular modeling was also undertaken with all the possible stereoisomeric combinations of two molecules of **13** and one of (*R*,*R*,*R*,*R*)-**5** (Fig. 8B–D). We obtained several energetically close local minima, displaying different dispositions between receptor and substrates, in a good agreement with NMR data. However, some general trends can be extracted from the 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 **5**. Additionally, the phenyl group of the substrate tends to set parallel on top of the pyridine of the pincer (inter-ring distance ~3.7 Å). This disposition is favored for (*S*)-**13** (Fig. 8B), while for (*R*)-**13** the steric hindrance with cyclohexane moiety forces the acid to rotate ~180° to the opposite disposition (Fig. 8C). Both diastereomeric conformations would locate the OMe group toward the benzyl sidearm of **5**, but a bit closer in the case of (*R*)-**13**. These facts agree with the observed shielding of the OMe signals, being slightly larger for (*R*)-**13**. Overall, the global picture for **5** is very similar to that found for **1**,

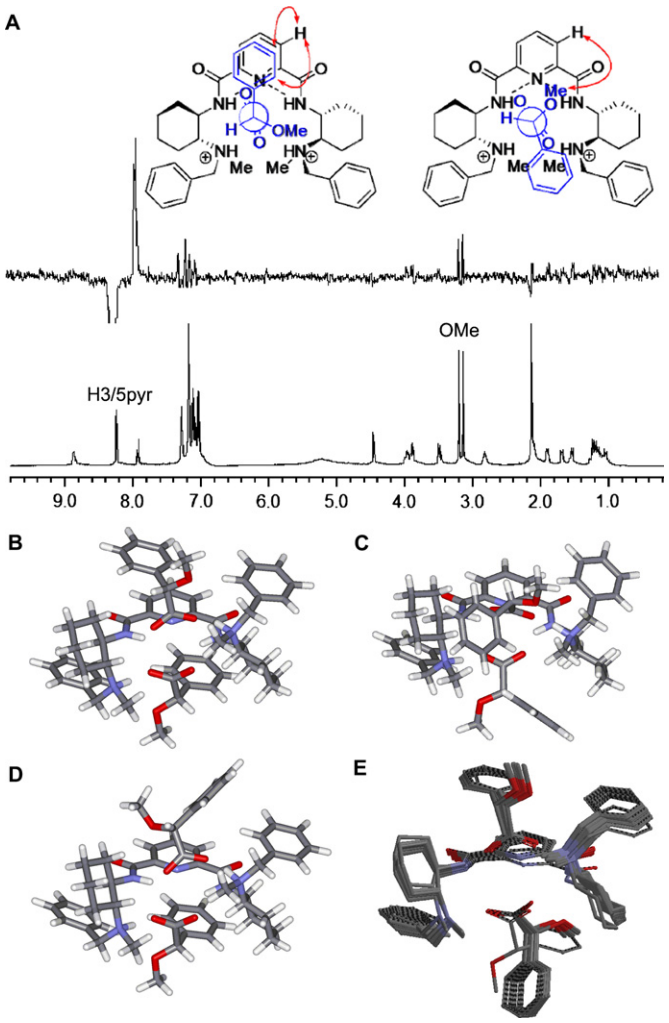


Figure 8. (A) ^{1}H NMR (lower trace) and 1D ROESY (upper trace) spectra upon irradiation of the 3/5 pyridine protons in a sample containing a 1:2 mixture of (*R,R,R,R*)-**5**/*rac*-**13** with the schematic representation of the possible orientations between them, with observed ROEs in red arrows. Optimized structures (global minima) of the corresponding supramolecular complexes with (B) two molecules of (*S*)-**13**, (C) two molecules of (*R*)-**13** and (D) (*R*)-**13**+(*S*)-**13**. (E) Superposition of the energetically accessible local minima of (B).

although the analysis of the conformational ensemble suggests that complexes with **5** are more flexible (a larger number of energetically accessible minima from a Boltzmann distribution, Fig. 8D), like the receptor itself. This observation could explain the somehow higher versatility of **5** versus **1**, as the pincer cavity can be easier adapted to the size and shape of the substrate.

3. Conclusions

In this paper, a family of pincer-like nitrogen-containing receptors (**2**–**5**) have been synthesized and tested as CSA for different chiral carboxylic acids. Their structural variables have been mapped in order to understand their effects on the NMR enantiodiscrimination. Thus, we have found that the pyridine-2,6-biscarboxamide moiety is very important for the efficiency of these compounds as CSA. This fact is closely related to the propensity of this substructure to promote a U-shape-folded pincer-like conformation, as demonstrated by NMR and molecular modeling studies of the receptors **2** and **5**. Thus, compounds lacking either the pyridine nitrogen (**2**), or the amide functionality (**3**), or one chiral arm of the pincer cavity (**4**) produced, in general, lower splitting than the original CSA (**1**). On the other hand, the effect of the chiral diamine moiety has been also studied comparing the cyclopentane (**1**) and the cyclohexane (**5**) derivatives. The cyclohexane compound (**5**) showed to be more versatile than **1**, as it produced good splitting ($\Delta\Delta\delta \geq 0.04$ ppm) for all the acids. Overall, the use of either **1** or **5** would cover quite structurally different chiral carboxylic acids, and they can be considered complementary in that sense. Finally, a deep NMR and modeling study of the supramolecular complexes for one example allowed us to propose a model for the interaction. These studies revealed a proton transference from the acid to the receptor toward the formation of a 1:2 CSA/acid complex. Besides, the key roles played by intermolecular H-bonding (implicating both amide and ammonium NH) and π–π interactions were also highlighted.

4. Experimental section

4.1. Synthesis of receptor (*R,R,R,R*)-2

The enantiopure diamine (*R,R*)-**6** (2.4 mmol) and isophthaloyl dichloride (1.2 mmol) were dissolved in 18 mL of dry CH_2Cl_2 under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 4 h after which the mixture was extracted with 3 N aqueous NaOH. The organic layer was dried and evaporated, and the product was purified by flash chromatography using ethyl acetate/methanol mixtures. Yield: 90%; mp 30–32 °C; $[\alpha]_D^{20}$ +78.7 (*c* 0.52, $CHCl_3$) >99% ee; R_f (MeOH/AcOEt 1:6) 0.27; IR (cm^{-1}) 3244, 1636; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.33–1.50 (m, 2H), 1.50–1.90 (m, 8H), 2.06–2.34 [m+s, (2×CH+CH_3), 8H], 2.90 (q, ^{3}J=7.8 Hz, 2H), AB quartet (δ_A=3.51, δ_B=3.60, J_{AB}=13.3 Hz, 4H), 4.31 (q, ^{3}J=7.7 Hz, 2H), 6.4 (d, ^{3}J=6.7 Hz, 2NH), 7.12–7.35 (m, 10H), 7.46 (t, ^{3}J=7.6 Hz, 1H), 7.86 (d, ^{3}J=7.8 Hz, 2H), 8.15 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ (ppm): 21.2 (CH_2), 23.5 (CH_2), 31.5 (CH_2), 37.9 (CH_3), 52.5 (CH), 59.1 (CH_2), 69.9 (CH), 125.2 (CH), 126.9 (CH), 128.2 (CH), 128.7 (CH), 129.7 (CH), 135.0 (C), 139.5 (C), 166.3 (C); ESI-MS (*m*/*z*): 539 [(M+1)$^+$, 15]. Anal. Calcd for: ($C_{34}H_{42}N_4O_2$) C, 75.80; H, 7.86; N, 10.40. Found C, 75.67; H, 8.06; N, 10.28.

4.2. Synthesis of (*S,S,S,S*)-3

Enantiopure diamine (*S,S*)-**6** (1.8 mmol) was dissolved in 20 mL of MeOH and $MgSO_4$ (0.39 g) and pyridine-2,6-dicarboxaldehyde (0.90 mmol) were added. The reaction mixture was stirred at room temperature overnight. After filtration of the solid, the solution was cooled to 0 °C and $NaBH_4$ (3.6 mmol) slowly added in portions. After 12 h, the excess $NaBH_4$ was destroyed by addition of 3 N aqueous HCl and the solution evaporated to dryness. Aqueous NaOH (3 N) was added (15 mL) and extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were washed with brine (10 mL), dried with Na_2SO_4, and evaporated under reduced pressure. The resulting crude was dissolved in CH_2Cl_2 (10 mL) and treated with di-*tert*-butyl dicarbonate (2.0 mmol). After 7 h of stirring, the mixture was evaporated to dryness giving a mixture of **8** and **9**. Then, further purification by flash chromatography (ethyl acetate/hexane mixtures) allowed to isolate (*S,S,S,S*)-**8** as the sole product. Yield: 60%; yellow oil; $[\alpha]_D^{20}$ +33.0 (*c* 0.50, $CHCl_3$) >99% ee; R_f (Hex/AcOEt 1:1) 0.51; IR (cm^{-1}) 1681; ^{1}H NMR ($CDCl_3$, 300 MHz) and ^{13}C NMR ($CDCl_3$, 75.5 MHz) spectra: a complex mixture of rotamers was observed, the analyses of both spectra being very difficult; ESI-MS (*m*/*z*): 712 [(M+1)$^+$, 70]. Anal. Calcd for ($C_{43}H_{61}N_5O_4$): C, 72.54; H, 8.64; N, 9.84. Found C, 72.75; H, 8.46; N, 10.03.

(*S,S,S,S*)-**8** (0.40 mmol) was hydrolyzed with 3 N aqueous HCl (10 mL) at room temperature. Then, the solution was basified with pellets of NaOH and extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were washed with brine (10 mL), dried with Na_2SO_4, and evaporated under reduced pressure to yield (*S,S,S,S*)-**3**

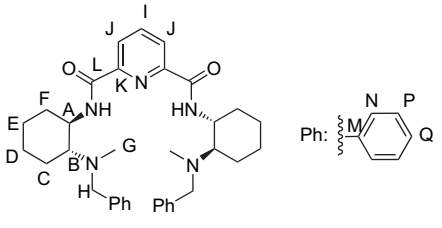
in state of purity. Yield: 92%; yellow oil; $[\alpha]_D^{20}$ +73.5 (*c* 0.60, $CHCl_3$) >99% ee; R_f (MeOH) 0.16; IR (cm^{-1}) 3385, 2952; ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.14–1.96 (m, 12H), 2.09 (s, 6H), AB quartet (δ_A=3.45, δ_B=3.53, J_{AB}=13.3 Hz, 4H), AB quartet (δ_A=3.83, δ_B=3.93, J_{AB}=14.4 Hz, 4H), 7.00–7.36 (m, 12H), 7.50 (t, ^3J=7.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ (ppm): 21.5 (CH_2), 22.8 (CH_2), 30.7 (CH_2), 37.9 (CH_3), 53.7 (CH), 59.3 (CH_2), 66.1 (CH), 71.3 (CH), 120.2 (CH), 126.7 (CH), 128.1 (CH), 128.6 (CH), 136.5 (CH), 139.7 (C), 159.2 (C); ESI-MS (*m*/*z*): 512 [$(M+1)^+$, 100]. Anal. Calcd for ($C_{33}H_{45}N_5$): C, 77.45; H, 8.86; N, 13.69. Found C, 77.32; H, 8.95; N, 13.57.

4.3. Synthesis of (*R*,*R*)-4

Receptor (*R*,*R*)-**4** was prepared following the procedure described for (*R*,*R*,*R*,*R*)-**2**, by mixing 0.5 mmol of the enantiopure diamine (*R*,*R*)-**6** and 0.70 mL (0.70 mmol) of a 1 M solution of picolinoyl chloride in CH_2Cl_2 (this acid chloride was previously prepared by refluxing picolinic acid in thionyl chloride for 1 h). Yield: 75%; yellow oil; $[\alpha]_D^{20}$ −43.9 (*c* 0.50, $CHCl_3$) >99% ee; R_f (MeOH/AcOEt 4:1) 0.51; IR (cm^{-1}) 3380, 1666; ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.44–1.98 (m, 5H), 2.15–2.34 [m+s, (CH_3+CH), 4H], 3.01 (q, ^3J=7.8 Hz, 1H), AB quartet (δ_A=3.44, δ_B=3.78, J_{AB}=13.3 Hz, 2H), 4.44 (q, ^3J=7.8 Hz, 1H), 7.16–7.42 (m, 5H), 7.41 (ddd, ^3J=7.7 Hz, ^3J=4.8 Hz and ^4J=1.3 Hz 1H), 7.83 (dt, ^3J=7.7 Hz and ^4J=1.6 Hz, 1H), 8.14 (d, ^3J=7.8 Hz, NH), 8.21 (d, ^3J=7.7 Hz, 1H), 8.55 (ddd, ^3J=4.8 Hz, ^4J=1.6 Hz, and ^5J=1.0 Hz 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ (ppm): 21.6 (CH_2), 25.3 (CH_2), 32.0 (CH_2), 38.0 (CH_3), 57.7 (CH), 59.3 (CH_2), 70.5 (CH), 122.0 (CH), 125.9 (CH), 126.7 (CH), 128.1 (CH), 128.7 (CH), 137.2 (CH), 139.5 (C), 147.9 (CH), 150.0 (C), 163.7 (C); ESI-MS (*m*/*z*): 310 [$(M+1)^+$, 100]. Anal. Calcd for: ($C_{19}H_{23}NO$) C, 73.76; H, 7.49; N, 13.58. Found C, 73.56; H, 7.69; N, 13.48.

4.4. Synthesis of (*R*,*R*,*R*,*R*)-5

It was prepared following the procedure described for (*R*,*R*,*R*,*R*)-**2**, but employing the enantiopure diamine (*R*,*R*)-**7** and 2,6-bis-(chlorocarbonyl)pyridine. Yield: 86%; mp 57–58 °C; $[\alpha]_D^{20}$ −195.0 (*c* 0.50, $CHCl_3$) >99% ee; R_f (MeOH/AcOEt 1:6) 0.20; IR (cm^{-1}) 3397, 1654; ^1H NMR ($CDCl_3$, 600 MHz) δ (ppm): 1.04 (dq, $^3J_{Fax,Feq}$=3.0 Hz, $^2J_{Fax,Feq}$=$^3J_{Fax,Aax}$=$^3J_{Fax,Eax}$=13.0 Hz, 2H_{Fax}), 1.10 (tq, $^3J_{Dax,Cec}$=$^3J_{Dax,Eeq}$=3.4 Hz, $^3J_{Dax,Eax}$=$^3J_{Dax,Cax}$=$^2J_{Dax,Deq}$=13.0 Hz, 2H_{Dax}), 1.33 (dq, $^3J_{Cax,Deq}$=3.4 Hz, $^3J_{Cax,Dax}$=$^3J_{Cax,Bax}$=$^2J_{Cax,Ceq}$=12.2 Hz, 2H_{Cax}), 1.38 (tt, $^3J_{Eax,Deq}$=$^3J_{Eax,Feq}$=3.6 Hz, $^3J_{Eax,Dax}$=$^3J_{Eax,Fax}$=$^2J_{Eax,Eeq}$=13.2 Hz, 2H_{Eax}), 1.67 (d, $^2J_{Eeq,Eax}$=13.7 Hz, 2H_{Eeq}), 1.83 (d, $^2J_{Deq,Dax}$=13.0 Hz, 2H_{Deq}), 1.93 (d, $^2J_{Ceq,Cax}$=12.2 Hz, 2H_{Ceq}), 2.22 (s, 6H), 2.33 (dt, $^3J_{Bax,Ceq}$=3.0 Hz, $^3J_{Bax,Cax}$=12.2 Hz, 2H_{Bax}), 2.56 (d, $^2J_{Feq,Fax}$=12.2 Hz, 2H_{Feq}), AB system (δ_A=3.40, δ_B=3.81, $J_{A,B}$=14.3 Hz, 4H_H), 3.83 (quintet, ^3J=5.4 Hz, 2H_A), 7.16–7.44 (m, 10H), 8.04 (t, ^3J=6.4 Hz, 1H_I), 8.30 (d, ^3J=4.8 Hz, 2NH), 8.4 (d, ^3J=7.8 Hz, 2HI_J); ^{13}C NMR ($CDCl_3$, 151 MHz) δ (ppm): 23.0 (CH_2), 24.7 (CH_2), 25.3 (CH_2), 32.5 (CH_2), 37.0 (CH_3), 51.1 (CH), 56.6 (CH_2), 66.6 (CH), 124.7 (CH), 126.7 (CH), 128.1 (CH), 128.4 (CH), 138.8 (CH), 139.7 (C), 148.9 (C), 163.3 (C); ESI-MS (*m*/*z*): 568 [$(M+1)^+$, 100]. Anal. Calcd for: ($C_{36}H_{45}N_5O_2$) C, 74.04; H, 7.99; N, 12.33. Found C, 73.94; H, 8.19; N, 12.13.



(*R*,*R*,*R*,*R*)-**5**

4.5. Molecular modeling

To obtain the minima of energy by molecular modeling, the *conformer distribution calculation* option available in Spartan 04 was used.[19] With this option, an exhaustive Monte Carlo search without constraints was performed for every structure. The torsion angles were randomly varied and the obtained structures fully optimized using the MMFF force field. Thus, 100 minima of energy within an energy gap of 10 kcal/mol were generated. These structures were analyzed and ordered considering the relative energy, being the repeated geometries eliminated. For the receptors alone, the two lowest energy local minima are shown. For the supramolecular complexes, this calculation was performed for every stereoisomeric complex obtained by combination of one molecule of (*R*,*R*,*R*,*R*)-**5** and either two of (*R*)-**13**, one (*R*) and one (*S*)-**13** or two (*S*)-**13**.

Acknowledgements

Financial support from the Spanish M.E.C. (CTQ2007-61126) is gratefully acknowledged.

References and notes

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) Wenzel, T. J. *Discrimination of Chiral Compounds Using NMR Spectroscopy*; John Wiley and Sons: Hoboken, NJ, 2007; (b) Ucello-Barretta, G.; Baklzano, F.; Salvadori, P. *Curr. Pharm. Des.* **2006**, *12*, 4023; (c) Seco, J. M.; Quiñoá, E.; Riguera, R. *Chem. Rev.* **2004**, *104*, 17; (d) Wenzel, T. J.; Wilcox, J. D. *Chirality* **2003**, *15*, 256; (e) 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. Ema, T.; Tanida, D.; Sakai, T. *J. Am. Chem. Soc.* **2007**, *129*, 10591.
5. 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.
6. (a) Lovely, A. E.; Wenzel, T. J. *Tetrahedron: Asymmetry* **2006**, *17*, 2642; (b) Ema, T.; Ouchi, N.; Doi, T.; Korenaga, T.; Sakai, T. *Org. Lett.* **2005**, *4*, 3985; (c) Pazos, Y.; Leiro, V.; Seco, J. M.; Quiñoá, E.; Riguera, R. *Tetrahedron: Asymmetry* **2004**, *15*, 1825; (d) Omata, K.; Aoyagi, S.; Kabuto, K. *Tetrahedron: Asymmetry* **2004**, *15*, 2351; (e) Menezes, P. H.; Gonçalves, S. M. C.; Hallwass, F.; Silva, R. O.; Bieber, L. W.; Simas, A. M. *Org. Lett.* **2003**, *5*, 1601; (f) Hirose, T.; Naito, K.; Shitara, H.; Nohira, H.; Baldwin, B. W. *Tetrahedron: Asymmetry* **2001**, *12*, 375.
7. (a) Ucello-Barreta, G.; Berni, M. G.; Balzano, F. *Tetrahedron: Asymmetry* **2007**, *18*, 2565; (b) Uccello-Barretta, G.; Nazzi, S.; Balzano, F.; Levkin, P. A.; Schurig, V.; Salvadori, P. *Eur. J. Org. Chem.* **2007**, 3219.
8. (a) Tanaka, K.; Fukuda, N.; Fujiwara, T. *Tetrahedron: Asymmetry* **2007**, *18*, 2657; (b) Abid, M.; Török, B. *Tetrahedron: Asymmetry* **2005**, *16*, 1547; (c) Maly, A.; Lejczak, B.; Kafarski, P. *Tetrahedron: Asymmetry* **2003**, *14*, 1019.
9. (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.
10. (a) Ma, F.; Shen, X.; Ou-Yang, J.; Deng, Z.; Zhang, C. *Tetrahedron: Asymmetry* **2008**, *19*, 31; (b) Li, Y.; Raushel, F. M. *Tetrahedron: Asymmetry* **2007**, *18*, 1391.
11. (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.
12. (a) Wang, W.; Ma, F.; Shen, X.; Zhang, C. *Tetrahedron: Asymmetry* **2007**, *18*, 832; (b) Ma, F.; Shen, X.; Zhang, C. *Org. Lett.* **2007**, *9*, 125; (c) Ema, T.; Tanida, D.; Sakai, T. *Org. Lett.* **2006**, *8*, 3773; (d) González-Álvarez, A.; Alfonso, I.; Gotor, V. *Tetrahedron Lett.* **2006**, *47*, 6397; (e) Cuevas, F.; Ballester, P.; Pericás, M. A. *Org. Lett.* **2005**, *7*, 5485; (f) Yang, D.; Li, X.; Fan, Y.-F.; Zhang, D.-W. *J. Am. Chem. Soc.* **2005**, *127*, 7996; (g) Zheng, Y. S.; Zhang, C. *Org. Lett.* **2004**, *6*, 1189; (h) Yang, X.; Wu, X.; Fang, M.; Yuan, Q.; Fu, E. *Tetrahedron: Asymmetry* **2004**, *15*, 2491; (i) Port, A.; Virgili, A.; Alvarez-Larena, A.; Piniella, J. F. *Tetrahedron: Asymmetry* **2000**, *11*, 3747; (j) Bilz, A.; Store, T.; Helmchen, G. *Tetrahedron: Asymmetry* **1997**, *8*, 3999.
13. Yang, X.; Wang, G.; Zhong, Z.; Wu, X.; Fu, E. *Tetrahedron: Asymmetry* **2006**, *17*, 916.
14. (a) González-Álvarez, A.; Alfonso, I.; Díaz, P.; García-España, E.; Gotor-Fernández, V.; Gotor, V. *J. Org. Chem.* **2008**, *73*, 374; (b) González-Álvarez, A.; Alfonso,

I.; Díaz, P.; García-España, E.; Gotor, V. *Chem. Commun.* **2006**, 1227; (c) Alfonso, I.; Dietrich, B.; Rebolledo, F.; Gotor, V.; Lehn, J.-M. *Helv. Chim. Acta* **2001**, *84*, 280; (d) Alfonso, I.; Rebolledo, F.; Gotor, V. *Chem.—Eur. J.* **2000**, *6*, 3331.
15. (a) González-Sabín, J.; Gotor, V.; Rebolledo, F. *J. Org. Chem.* **2007**, *72*, 1309; (b) Luna, A.; Alfonso, I.; Gotor, V. *Org. Lett.* **2002**, *4*, 3627.
16. González-Sabín, J.; Rebolledo, F.; Gotor, V. *Chem.—Eur. J.* **2004**, *10*, 5788.
17. Peña, C.; González-Sabín, J.; Alfonso, I.; Rebolledo, F.; Gotor, V. *Tetrahedron: Asymmetry* **2007**, *18*, 1981.
18. Gale, P. A.; Garric, J.; Light, M. E.; McNally, B. A.; Smith, B. D. *Chem. Commun.* **2007**, 1736 and references cited therein.
19. Wavefunction, Inc. Irvine, CA. For MMFF force field calculations, see: Halgren, T. A. *J. Comput. Chem.* **1996**, *17*, 490 and following papers in this issue.