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Optically active macrocyclic hexaazapyridinophanes decorated at the periphery: synthesis and applications in the NMR enantiodiscrimination of carboxylic acids

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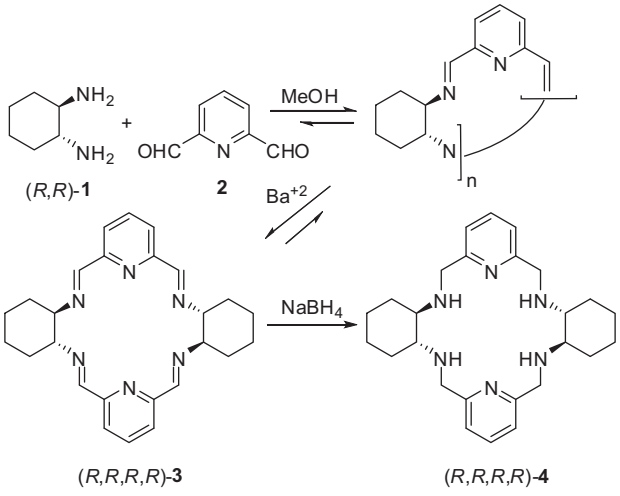
ABSTRACT

A family of pyridine based dialdehydes has been efficiently prepared starting from chelidamic acid by chemical modification of its 4-hydroxyl group. The condensation of these dialdehydes with commercially available (1*R*,2*R*)-(−)-cyclohexane-1,2-diamine in the presence of Ba^{2+} template led, after the in situ reduction, to the synthesis of a family of enantiopure hexaazapyridinophanes substituted at the periphery. These new receptors have been used as chiral shift agents towards different carboxylic acids. Good splitting of the carboxylic acid NMR signals (up to $\Delta\Delta\delta$=0.13 ppm) were observed using substoichiometrical amount of the receptor.

1. Introduction

Optically active polyazamacrocycles are important compounds in organic,[1] supramolecular,[2] medicinal[3] and bioorganic[4] chemistry. Additionally, these structures have shown extraordinary properties for the molecular recognition of cationic[5] and anionic species,[6] and have been widely used as chiral solvating agents (CSAs) for the fast and accurate determination of enantiomeric excesses in combination with NMR spectroscopy.[7] Among the described non-racemic chiral polyazamacrocycles, those bearing *trans*-cyclohexane-1,2-diamine as the chiral reporter are especially useful due to the structural peculiarities of this moiety.[8] However, the syntheses of these systems are not trivial, due to the low yields usually associated to the key macrocyclization step.

Previous studies in our research group showed that a Dynamic Combinatorial Library (DCL) of oligoimines was formed when an equimolecular amount of (1*R*,2*R*)-diaminocyclohexane (**1**) and pyridine-2,6-dicarboxaldehyde (**2**) were mixed in methanol.[9] Different metallic templates were added to the reaction media, observing that the addition of Ba^{+2} led exclusively to the dimeric cyclic imine **3**, which was subsequently reduced with $NaBH_4$ allowing the synthesis of the hexaazamacrocycle **4** in high purity after a simple extraction (Scheme 1).



Scheme 1. Effect of the Ba^{+2} template on the DCL of oligoimines and synthesis of polyamine **4**.

The polyamine **4** has been successfully employed as chiral solvating agent for carboxylic acids[10] and as a highly enantioselective receptor for dicarboxylates in aqueous solution.[11] Following our

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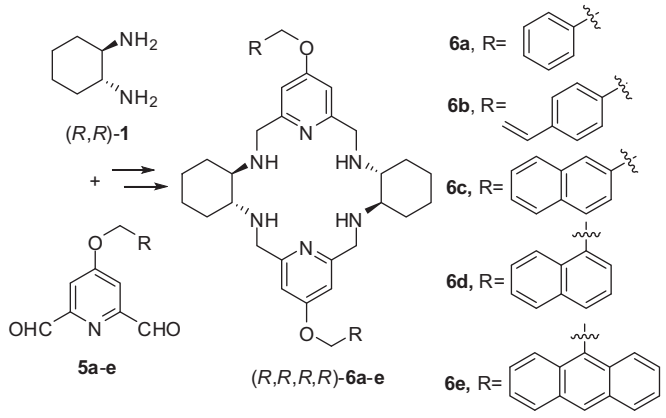
research work in macrocyclic chemistry,[10–12] we decided to expand the chemical diversity of these systems by structural modifications at the periphery of the macrocyclic core of **4**. These modifications could tune the properties of the obtained molecules in terms of solubility, binding abilities or catalytic activities, without altering the structural characteristics of the central chiral macrocyclic core. Accordingly, we envisioned the synthesis of macrocycles **6a**–**e** with different arylmethoxy substituents in the 4-position of the pyridine ring, such as benzyloxy, (4-ethenylbenzyl)oxy, 1-naphthylmethoxy, 2-naphthylmethoxy and 9-anthracenylmethoxy (Scheme 2). Some naphthalene derivatives could display interesting properties as ligands in asymmetric synthesis,[13] in chiral chromatographic separations of amino acids[14] and enantioselective sensing.[15] On the other hand, chiral anthracene derivatives have been used in cycloaddition reactions[16] and as templates for asymmetric Diels–Alder/retro Diels–Alder reactions.[17]



Scheme 2. Proposed polyazamacrocycles **6a**–**e**.

2. Results and discussion

2.1. Design and synthesis of dialdehydes

Since we intended to make modifications at the periphery of the compounds without altering the macrocyclic frame properties, we initially studied the expected effect of the substitution at the 4-position of the pyridine. To do that, we performed in silico conformational analysis by Monte Carlo simulations on the proposed macrocycles. Interestingly, superposition of the obtained local minima suggested the free movement of the substituents at the periphery, without altering the twisted helical highly chiral macrocyclic core (Fig. 1).

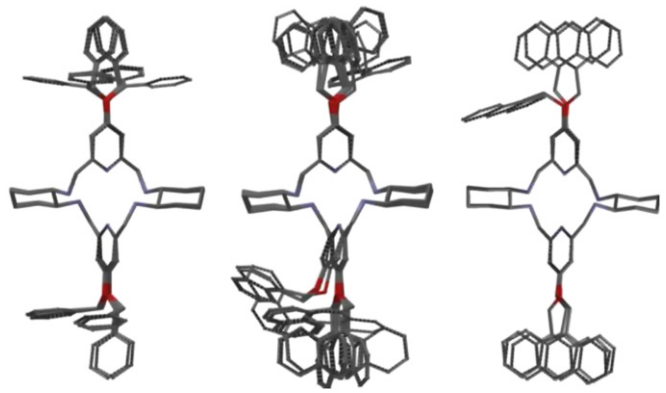
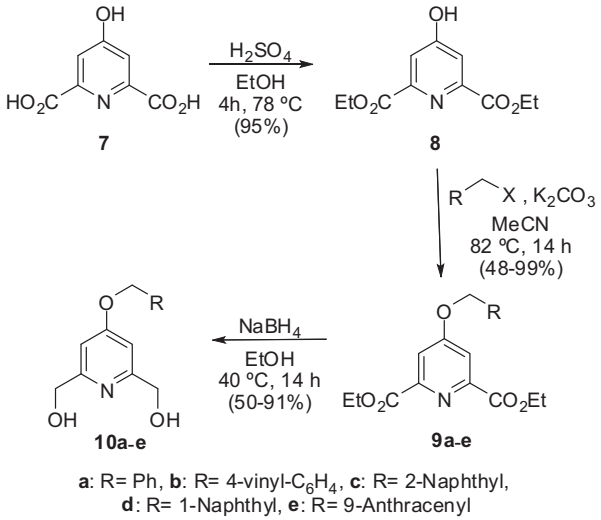


Figure 1. Superposition of the energetically accessible conformational local minima (Monte Carlo searches followed by MMFF minimizations) obtained for **6a** (left), **6d** (middle) and **6e** (right). Hydrogen atoms have been omitted for clarity.

This theoretical analysis encouraged us to endeavour the preparation of these macrocyclic compounds. First of all, an efficient route for the syntheses of the 4-substituted pyridin-2,6-dicarboxaldehydes **5a**–**e** was necessary (Scheme 3). In this manner, chelidamic acid (**7**) was used as starting material for the preparation of diethyl 4-hydroxypyridine-2,6-dicarboxylate (**8**) through chemical esterification of **7** with ethanol in acidic media as described by Chauvin, obtaining diester **8** in 95% isolated yield.[18]



Scheme 3. Chemical synthesis of diols **10a**–**e** from commercially available chelidamic acid.

The hydroxyl group at the 4-position allowed us to introduce different functionalities by simple treatment of **8** with potassium carbonate and the corresponding arylmethyl halides. In this way, the *O*-alkylated diesters **9a**–**d** were obtained with excellent isolated yields while **9e** was obtained in 48% yield as some none-identified by-products were observed (Table 1). Next, the subsequent reduction of diesters **9a**–**e** with sodium borohydride in ethanol,[19] afforded diols **10a**–**e** in moderate to excellent isolated yields.

Table 1
Isolated yields for the alkylation, reduction and oxidation steps

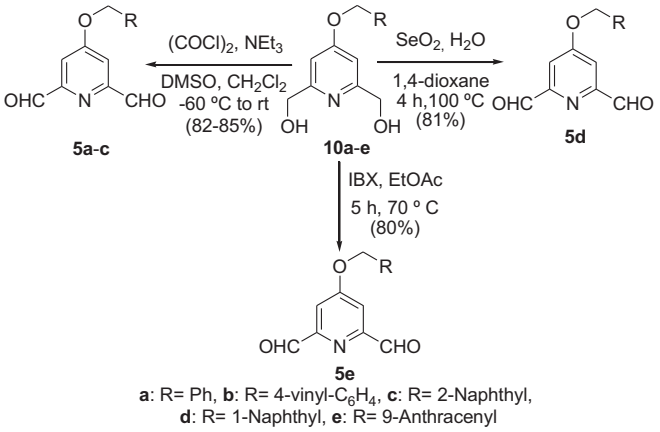
Entry	R	X	**9**[a] (%)	**10**[b] (%)	**5**[a] (%)
1	Ph (**a**)	Br	98	91	82
2	4-Vinyl/C_6H_4 (**b**)	Cl	95	88	85
3	2-Naphthyl (**c**)	Br	99	84	83
4	1-Naphthyl (**d**)	Cl	90	69	81
5	9-Anthracenyl (**e**)	Cl	48	50	80

[a] Isolated yield after flash chromatography.
[b] Isolated yield after extraction.

The corresponding diols were subjected to Swern oxidation conditions,[19] obtaining the dialdehydes **5a**–**c** in good isolated yields. Unfortunately, no product was detected in the case of **5d**,**e** due to the poor solubility of the diols **10d**,**e** at −60 °C in CH_2Cl_2. For that reason, different oxidation procedures were tried to overcome this limitation (Scheme 4). Thus, the oxidation of **10d**,**e** with SeO_2 at 100 °C[20] allowed us to prepare the dialdehyde **5d** in 81% yield, however many side products were observed in the oxidation of **10e**. Finally, the oxidation of **10e** was attempted with IBX (2-iodoxybenzoic acid) in ethyl acetate[21] at 70 °C, allowing the preparation of **5e** in 80% yield.

2.2. Generation of the library and templated synthesis of the dimeric macrocycles

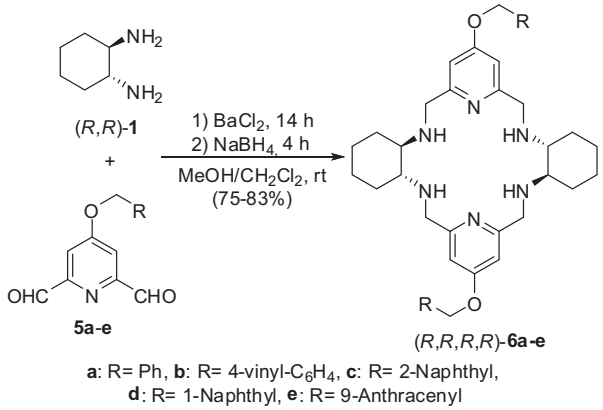
Once we had developed an efficient synthetic procedure for the dialdehydes **5a**–**e**, we tried to build the corresponding dynamic



Scheme 4. Chemical synthesis of dialdehydes **5a**–**e** from diols **10a**–**e**.

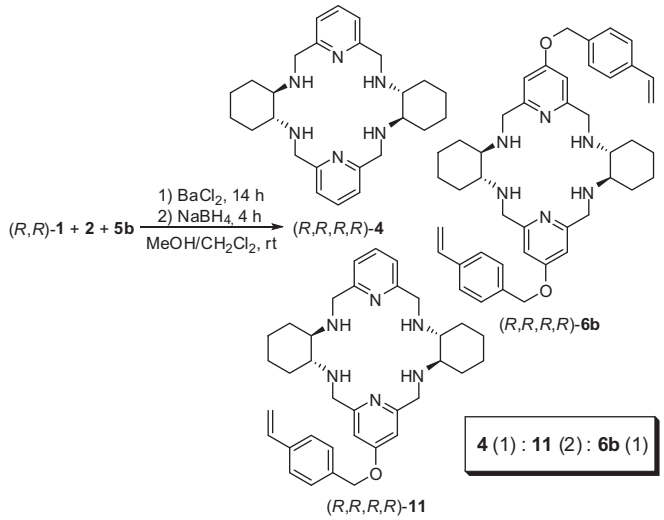
mixtures of oligoimines (DCL) by mixing each dialdehyde **5a**–**e** with an equimolecular amount of (1*R*,2*R*)-diaminocyclohexane (**1**) in methanol. Unfortunately, under these conditions for all the dialdehydes **5a**–**e**, the formation of a precipitate was observed. This behaviour is undesirable for taking advantage of the templation effect, since this requires the system to operate under thermodynamic control, and precipitation should produce a kinetic trapping process. This would imply that the different members of the library cannot interconvert through a chemical reversible process, and thus, the formation of a true DCL of oligoimines is not possible. This limitation was overcome by using a 1:1 mixture of methanol and CH_2Cl_2 as solvent, because in these conditions we did not observe any precipitate.

Based on the previous experience in our research group,[9] the dimeric cyclic imine host was obtained by simply adding the metallic template Ba^{+2} to the reaction vessel. Then, the equilibrium mixture was frozen by the in situ reduction of the dimeric cyclic imine with $NaBH_4$, leading to the desired macrocycles **6a**–**e** as unique products with high isolated yields (75–83%) and purity after an extraction procedure (Scheme 5). All the macrocycles showed their ^1H and ^{13}C NMR spectra in agreement with the expected D_2 symmetry of the molecules, and their corresponding dimeric nature was unambiguously proved by ESI mass spectrometry.



Scheme 5. Barium-templated syntheses of the azamacrocyclic receptors (*R*,*R*,*R*,*R*)-**6a**–**e**.

The yields of **6a**–**e** were very good and similar to the originally obtained for the synthesis of **4**,[9] lacking the substitution at position 4. This observation suggested no effect of the substitution at that position in the templated reaction. In order to confirm that hypothesis we designed a competition experiment, by performing the templated reaction process with an equimolecular ratio of two different dialdehydes (**2** and **5b**, Scheme 6). The analysis of the ESI-MS spectrum



Scheme 6. Effect of the substitution at 4-position of the pyridine on the templated effect.

of the crude reaction, after reduction, showed the peaks at *m*/*z* 435.3, 567.3 and 699.4 corresponding to the $[M+H]^+$ species of **4**, **11** and **6b**. These mass peaks showed an approximate relative intensity of 1:2:1 (see Supplementary data). This molar ratio was additionally confirmed by the analysis of the ^1H NMR spectrum. Since this ratio corresponds to the statistical proportion of the macrocyclic dimers, we finally concluded that the substitution at the 4-position of the pyridine did not substantially perturb the template effect.

2.3. Role of chiral polyazamacrocycles (*R*,*R*,*R*,*R*)-6a–e as chiral shift agents: NMR enantiodiscrimination studies

Afterwards, the enantiodiscrimination ability of the optically active receptors **6a**,**c**–**e** was tested as CSAs for different mandelic acids **12a**–**c** and lactic acid **12d** (Fig. 2). The experiments were carried out in an NMR tube by mixing each macrocycle (*R*,*R*,*R*,*R*)-**6a**, **c**–**e** and the corresponding racemic carboxylic acid in $CDCl_3$ (20 mM).

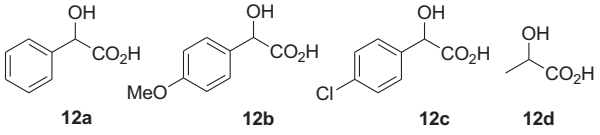


Figure 2. Selected carboxylic acids.

All the experiments were performed immediately after each addition and recorded in a 300 MHz spectrometer at room temperature (Fig. 3). Different molar proportions of receptor (*R*,*R*,*R*,*R*)-**6a** versus mandelic acid **12a** were analyzed (Table 2). The highest values of induced chemical shift ($\Delta\delta$) and splitting between the signals corresponding to each enantiomer of **12a** ($\Delta\Delta\delta$) were achieved with a 1:4 ratio (receptor/substrate). A similar behaviour was observed for **6c**–**e** (data not shown).

Table 2
Optimization of the receptor:acid ratio

Entry	Molar ratio (**6a**/**12a**)	$\Delta\delta$[a]	$\Delta\Delta\delta$
1	1:8	−0.22	0.07
2	1:4	−0.37	0.12
3	1:1	−0.18	0.03

[a] Averaged between signals from both enantiomers.

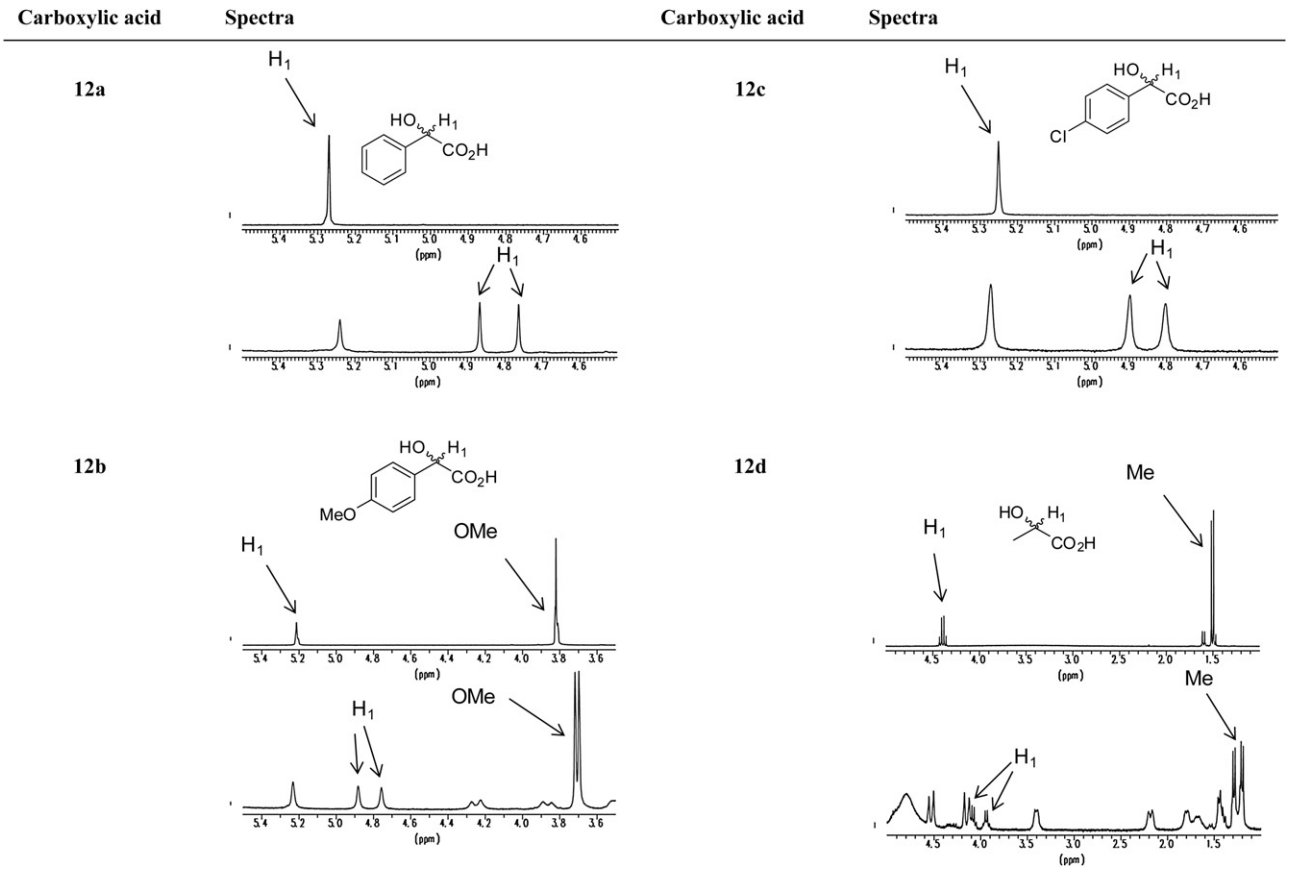


Figure 3. Partial NMR spectra of selected acids **12a**–**d** in the absence (upper trace) and in the presence (lower trace) of the receptor **6c** (300 MHz, 20 mM in $CDCl_3$ at rt).

Table 3 shows the values of ($\Delta\delta$) on the signal of the carboxylic acids **12a**–**d** after the addition of **4**, **6a**,**c**–**e** with a 1:4 ratio (receptor/substrate), as well as ($\Delta\Delta\delta$). Good baseline resolution for an accurate integration of the splitting signals was observed for the α-hydroxy-

Table 3
Selected chemical induced shift ($\Delta\delta$) and splitting ($\Delta\Delta\delta$) measured in ppm for diastereomeric complexes formed between (*R*,*R*,*R*,*R*)-**4**, (*R*,*R*,*R*,*R*)-**6a**,**c**–**e** and different carboxylic acids (**12a**–**d**) (1:4 M ratio) measured by NMR (300 MHz, 20 mM in $CDCl_3$, rt)

Entry	Acid	Signal	Receptor									
			4[b]		**6a**		**6c**		**6d**		**6e**	
			$\Delta\delta$[a]	$\Delta\Delta\delta$	$\Delta\delta$[a]	$\Delta\Delta\delta$	$\Delta\delta$[a]	$\Delta\Delta\delta$	$\Delta\delta$[a]	$\Delta\Delta\delta$	$\Delta\delta$[a]	$\Delta\Delta\delta$
1	**12a**	CαH	−0.59	0.13	−0.37	0.12	−0.38	0.11	−0.35	0.12	−0.28	0.08
2	**12b**	CαH	−0.57	0.19	−0.39	0.12	−0.41	0.13	−0.40	0.12	−0.35	0.08
3	**12b**	OMe	−0.06	0.02	−0.08	0.02	−0.11	0.02	−0.12	0.02	−0.17	0.02
4	**12c**	CαH	−0.60	0.15	−0.44	0.10	−0.41	0.10	−0.44	0.09	−0.37	0.05
5	**12d**	CαH	−0.47	0.20	−0.37	0.12	−0.38	0.14	−0.35	0.12	−0.28	0.08
6	**12d**	Me	−0.33	0.08	−0.24	0.07	−0.26	0.09	−0.22	0.06	−0.18	0.04

[a] Averaged between signals from both enantiomers.
[b] Experiments involving macrocycle **4** were previously described in Ref. 10.

carboxylic acids with the receptors **4**, **6a**,**c**–**e**. Interestingly, enantiodiscrimination was also observed for the OMe signal of **12b**, which is far away from the stereocentre (Table 3 and Fig. 3). Additionally, the good splitting observed for lactic acid (**12d**) demonstrates that the presence of aromatic rings is not necessary for an efficient signal separation. On the hand, the comparison between the ligands showed that very similar values of ($\Delta\Delta\delta$) were obtained for the receptors (*R*,*R*,*R*,*R*)-**6a**,**c**–**e**, however, in general better separations were observed for the previously reported macrocycle (*R*,*R*,*R*,*R*)-**4**.

Other remarkable features of the analysis recorded in Table 3 and Figure 3 should be commented. First of all, an up-field shift was observed for the signals of the acids, which suggested the deprotonation of the carboxylic group. Concomitantly, the signals of the receptor moved downfield, which clearly indicated a proton transfer from the acid to the receptor, leading to the formation of diastereomeric salts. On the other hand, we have observed for all the examples that the optimal signal separation was obtained with a very low ratio of the polyamine receptor (0.25 M equivalents with respect to the acid). However, the splitting disappeared when an excess of the receptor was added.

These results are in agreement with the formation of multimolecular complexes. Job's plot analysis has been performed separately for each enantiomer in order to determine the stoichiometry of the corresponding complexes. The experiments showed an ideal 1:4 (receptor/acid) stoichiometry for both enantiomers of mandelic acid (Fig. 4). Besides, the Job's plot showed that the chemical induced shifts are identical for both enantiomers at larger proportions of the receptor (mole fraction of the acid $\leq$0.4). The maxima of the Job's plots of both enantiomers of the acid also fit with the maximum splitting of the signals. This is strongly consistent with the CSA experiments performed with the racemic mixture of the acids.

The formation of complexes with multiple stoichiometries precluded the deep analysis of the binding interactions. However, in order to illustrate the experimental data, we performed molecular modelling calculations with the diastereomeric salts formed by the tetraprotonated form of the receptor (*R*,*R*,*R*,*R*)-**6c** and four molecules of both enantiomers of mandelic carboxylate (**12a**). The minimized geometries were obtained by the exhaustive Monte Carlo conformational searches with MMFF minimizations, as implemented in Spartan '06. The structures for the corresponding global minima are shown in Figure 5. The analysis showed that the receptor **6c** is able to bind four molecules of **12a**, two of them at

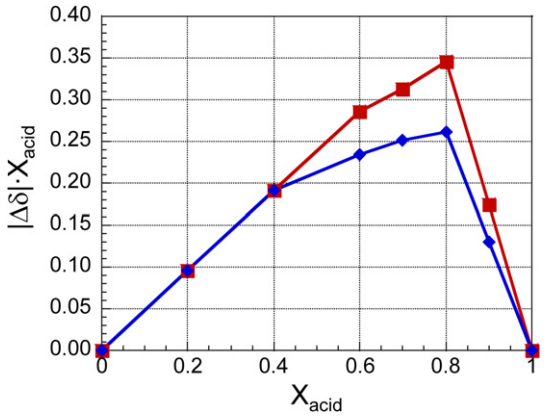


Figure 4. Job's plot obtained for (*R*,*R*,*R*,*R*)-**6c** and (*R*)-**12a** (red) and (*S*)-**12a** (blue) [X=molar fraction of **12a**, Δδ=chemical shift change of (*R*)-**12a** and (*S*)-**12a**]. The signal corresponding to the Cα*H* proton of **12a** was used in both cases.

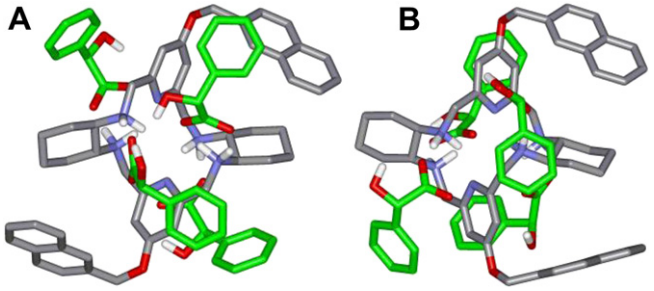


Figure 5. Minimized geometries for the supramolecular complexes formed by receptor (*R*,*R*,*R*,*R*)-**6c** and four molecules of (A) (*R*)-**12a** or (B) (*S*)-**12a**. For the sake of clarity, non-polar hydrogen atoms have been omitted and the carbon atoms of the mandelic carboxylate molecules are shown in bright green colour.

each face of the macrocyclic ring. Despite the main binding interactions are the electrostatic carboxylate ammonium contacts, other H-bonding and aryl–aryl interactions were found. Interestingly, the complex with (*R*)-**12a** is more stable and more symmetrical than that with the (*S*) enantiomer. A combination of these two facts (different energies and geometries) could be the source of the enantiodiscrimination observed in the NMR spectra.

3. Conclusions

In conclusion, the synthesis of a family of chiral hexaazapyridinophanes has been carried out in high yields (75–83%) by a templated one-pot two-steps process, starting from (*R*,*R*)-cyclohexane-1,2-diamine and different 4-substituted-2,6-pyridinedicarboxaldehydes. These dialdehydes were prepared from chelidamic acid in four steps rendering low to good overall yields (19–71%). The macrocyclic polyamines have shown good efficiencies as CSAs for α-hydroxycarboxylic acids. The experimental data revealed the formation of 1:4 (receptor/acid) supramolecular complexes, which allowed the use of substoichiometric proportions of the receptors for a suitable signal separation in the NMR spectra.

4. Experimental section

4.1. General

Chemical reagents were purchased from different commercial sources and used without further purification. Solvents were distilled over an adequate desiccant under nitrogen. Flash chromatography was performed using silica gel 60 (230–240 mesh). Melting points were taken on samples in open capillary tubes and are uncorrected. IR spectra were recorded using KBr pellets. ^{1}H, ^{13}C NMR and DEPT were obtained using a Brüker NAV-300 spectrometer (^{1}H, 300.13 MHz and ^{13}C, 75.5 MHz). The chemical shifts are given in delta values (δ, ppm) and the coupling constants (*J*) in hertz (Hz). ESI$^+$ experiments were carried out using a liquid chromatograph mass detector to record mass spectra (MS). High resolution mass experiments (HRMS) were measured by ESI$^+$ and carried out with a Bruker Micro TofQ. Measurements of the optical rotations were done in a Perkin–Elmer 241 polarimeter. The molecular modelling studies were performed with Spartan '06 software (Version 1.1.2). Monte Carlo conformational searches were carried out with MMFF force field minimizations. Thus, over 10,000 structures were generated and minimized with the MMFF force field. The obtained minima were ordered attending to their relative stabilities and the global minimum was thus located and identified. For the superposition of the accessible local minima, we calculated the Boltzmann distribution from the computed relative energies of the conformers, and those showing a proportion ≥1% were aligned using the tools available in the same software.

*4.1.1. Synthesis of diethyl 4-(benzyloxy)pyridine-2,6-dicarboxylate (**9a**).* Over a solution of **8** (500 mg, 2.1 mmol) in dry acetonitrile (16 mL) were successively added K_2CO_3 (462 mg, 3.3 mmol) and benzyl bromide (246 μL, 2.1 mmol). The resulting solution was stirred at 82 °C during 14 h. Then the reaction was stopped by filtration of K_2CO_3, and the solvent was removed under reduced pressure. Reaction crude was purified by flash chromatography (1% MeOH/CH_2Cl_2). White solid. Yield: 98%; mp 75–76 °C (MeOH/CH_2Cl_2); R_f (1% MeOH/CH_2Cl_2): 0.26; IR (cm^{-1}) 3025, 2936, 1715, 1546, 1121, 1032; ^{1}H NMR ($CDCl_3$, 300.13 MHz): δ 1.42 (t, $^3J_{HH}$=7.0 Hz, 6H), 4.40 (q, $^3J_{HH}$=7.1 Hz, 4H), 5.19 (s, 2H), 7.33–7.41 (m, 5H), 7.83 (s, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 13.9 ($2CH_3$), 62.1 ($2CH_2$), 70.5 (CH_2), 114.4 (2CH), 127.5 (2CH), 128.5 (CH), 128.6 (2CH), 134.5 (C), 150.0 (C), 164.4 (2C), 166.3 (2C); MS (ESI$^+$, *m*/*z*): 330 [(M+H)$^+$, 100%]; HRMS (ESI)$^+$ calcd for $C_{18}H_{20}NO_5$ (M+H)$^+$: 330.1336; found 330.1331.

*4.1.2. Synthesis of diethyl 4-[(4-ethenylbenzyl)oxy]pyridine-2,6-dicarboxylate (**9b**).* We used the same procedure as for **9a**, but using 1-(chloromethyl)-4-ethenylbenzene. White solid. Yield: 95%; mp 77–78 °C (MeOH/CH_2Cl_2); R_f (1% MeOH/CH_2Cl_2): 0.28; IR (cm^{-1}) 3036, 3025, 2936, 1725, 1536, 1523, 1243, 1101; ^{1}H NMR ($CDCl_3$, 300.13 MHz): δ 1.38 (t, $^3J_{HH}$=7.1 Hz, 6H), 4.38 (q, $^3J_{HH}$=7.1 Hz, 4H), 5.14 (s, 2H), 5.21 (d, $^3J_{HH\ (cis)}$=11.0 Hz, 1H), 5.67 (d, $^3J_{HH\ (trans)}$=17.5 Hz, 1H), 6.57–6.67 (dd, $^3J_{HH\ (trans)}$=17.5 Hz, $^3J_{HH\ (cis)}$=11.0 Hz, 1H), AB system (δ_A=7.32 δ_B=7.38, $^3J_{HH}$=8.0 Hz, 4H), 7.83 (s, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 13.9 ($2CH_3$), 62.0 ($2CH_2$), 70.2 (CH_2), 114.2 (2CH), 114.3 (CH_2), 126.3 (2CH), 127.7 (2CH), 133.4 (C), 135.8 (CH), 137.7 (C), 149.9 (C), 164.3 (2C), 166.2 (2C); MS (ESI$^+$, *m*/*z*): 356 [(M+H)$^+$, 100%]. HRMS (ESI)$^+$ calcd for $C_{20}H_{22}NO_5$ (M+H)$^+$: 356.1492; found 356.1498.

*4.1.3. Synthesis of diethyl 4-(naphthalen-2-ylmethoxy)pyridine-2,6-dicarboxylate (**9c**).* We used the same procedure as for **9a**, but using 2-(bromomethyl)naphthalene. White solid. Yield: 99%; mp 121–122 °C (MeOH/CH_2Cl_2); R_f (1% MeOH/CH_2Cl_2): 0.25; IR (cm^{-1}) 3021, 2987, 1722, 1532, 1520, 1114, 1043; ^{1}H NMR ($CDCl_3$, 300.13 MHz): δ 1.44 (t, $^3J_{HH}$=6.9 Hz, 6H), 4.44 (t, $^3J_{HH}$=7.0 Hz, 4H), 5.37 (s, 2H), 7.50–7.54 (m, 3H), 7.84–7.92 (m, 6H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 14.0 ($2CH_3$), 62.2 ($2CH_2$), 70.7 (CH_2), 114.5 (2CH), 124.5 (CH), 126.4 (2CH), 126.8 (CH), 127.6 (CH), 127.9 (CH), 128.6 (CH), 132.0 (C), 133.0 (C), 133.1 (C), 150.0 (C), 164.4 (2C), 166.3 (2C); MS (ESI$^+$, *m*/*z*): 380 [(M+H)$^+$, 100%]. HRMS (ESI)$^+$ calcd for $C_{22}H_{22}NO_5$ (M+H)$^+$: 380.1492; found 380.1477.

*4.1.4. Synthesis of diethyl 4-(naphthalen-1-ylmethoxy)pyridine-2,6-dicarboxylate (**9d**).* We used the same procedure as **9a**, but using

1-(chloromethyl)naphthalene. White solid. Yield: 90%; mp 138–139 °C (MeOH/CH_2Cl_2); R_f (1% MeOH/CH_2Cl_2): 0.25; IR (cm^{-1}) 3016, 2955, 1724, 1531, 1518, 1110, 1033; ^1H NMR ($CDCl_3$, 300.13 MHz): δ 1.44 (t, $^3J_{HH}$=6.8 Hz, 6H), 4.45 (t, $^3J_{HH}$=6.8 Hz, 4H), 5.62 (s, 2H), 7.47–7.60 (m, 4H), 7.84–7.92 (m, 5H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 14.0 ($2CH_3$), 62.3 ($2CH_2$), 69.2 (CH_2), 114.5 (2CH), 123.1 (CH), 125.1 (CH), 126.0 (CH), 126.7 (CH), 127.1 (CH), 128.7 (CH), 129.7 (CH), 130.0 (C), 131.2 (C), 133.6 (C), 150.0 (C), 164.4 (2C), 165.3 (2C); MS (ESI^+, *m*/*z*): 380 [$(M+H)^+$, 100%]. HRMS $(ESI)^+$ calcd for $C_{22}H_{22}NO_5$ $(M+H)^+$: 380.1492; found 380.1483.

*4.1.5. Synthesis of diethyl 4-(anthracen-9-yl)pyridine-2,6-dicarboxylate (**9e**).* We used the same procedure as for **9a**, but using 9-(chloromethyl)anthracene. White solid. Yield: 48%; mp 177–178 °C (MeOH/CH_2Cl_2); R_f (1% MeOH/CH_2Cl_2): 0.25; IR (cm^{-1}) 3025, 2932, 2843, 1724, 1531, 1441, 1518, 1110, 1033; ^1H NMR ($CDCl_3$, 300.13 MHz): δ 1.42 (t, $^3J_{HH}$=7.0 Hz, 6H), 4.46 (t, $^3J_{HH}$=6.8 Hz, 4H), 5.88 (s, 2H), 7.43–7.56 (m, 4H), 7.96 (s, 2H), 7.98 (d, $^3J_{HH}$=8.6 Hz, 2H), 8.10 (d, $^3J_{HH}$=8.4 Hz, 2H), 8.43 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 13.9 ($2CH_3$), 62.1 ($2CH_2$), 63.1 (CH_2), 114.2 (2CH), 123.0 (2CH), 124.2 (2CH), 124.8 (2CH), 126.6 (2C), 128.9 (2CH), 129.4 (CH), 130.6 (2C), 131.0 (C), 150.0 (C), 164.4 (2C), 166.6 (2C); MS (ESI^+, *m*/*z*): 430 [$(M+H)^+$, 100%]. HRMS $(ESI)^+$ calcd for $C_{26}H_{24}NO_5$ $(M+H)^+$: 430.1654; found 430.1634.

*4.1.6. Synthesis of [4-(benzyloxy)pyridine-2,6-diyl]dimethanol (**10a**).* Over a solution of **9a** (329 mg, 1.0 mmol) in dry EtOH (20 mL) was carefully added $NaBH_4$ (238 mg, 6.0 mmol). The resulting solution was stirred at 40 °C for 14 h, then the reaction was quenched adding H_2O (25 mL). The mixture was extracted with EtOAc (3×40 mL), organic phases were combined, dried over Na_2SO_4, filtered under vacuum and evaporated to dryness. White solid. Yield: 91%; mp 298 °C (dec.) (ethyl acetate); R_f (7% MeOH/CH_2Cl_2): 0.20; IR (cm^{-1}) 3115, 3025, 2987, 1545, 1432, 1321, 1211; ^1H NMR (CD_3OD, 300.13 MHz): δ 4.81 (s, 4H), 5.37 (s, 2H), 7.23 (s, 2H), 7.51–7.64 (m, 5H); ^{13}C NMR (CD_3OD, 75.5 MHz): δ 66.5 ($2CH_2$), 72.2 (CH_2), 108.0 (2CH), 130.0 (2CH), 130.5 (CH), 130.9 (2CH), 138.8 (C), 164.9 (2C), 170.0 (C); MS (ESI^+, *m*/*z*): 246 [$(M+H)^+$, 100%], 184 [$(M-60)^+$, 10%]. HRMS $(ESI)^+$ calcd for $C_{14}H_{16}NO_3$ $(M+H)^+$: 246.1125; found 246.1129.

*4.1.7. Synthesis of {4-[(4-ethenylbenzyl)oxy]pyridine-2,6-diyl}dimethanol (**10b**).* We used the same procedure as for **10a**, but using **9b**. White solid. Yield: 88%; mp 245 °C (dec.) (ethyl acetate); R_f (7% MeOH/CH_2Cl_2): 0.22; IR (cm^{-1}) 3100, 3025, 3017, 2930, 1535, 1399, 1311, 1113; ^1H NMR (DMSO-d_6, 300.13 MHz): δ 4.47 (s, 4H), 5.19 (s, 2H), 5.27 (d, $^3J_{HH\ (cis)}$=10.9 Hz, 1H), 5.39 (br s, 2H), 5.85 (d, $^3J_{HH\ (trans)}$=17.7 Hz, 1H), 6.74 (dd, $^3J_{HH\ (trans)}$=17.6 Hz, $^3J_{HH\ (cis)}$=10.9 Hz, 1H), 6.94 (s, 2H), AB system (δ_A=7.42 δ_B=7.51, $^3J_{HH}$=8.1 Hz, 4H); ^{13}C NMR (DMSO-d_6, 75.5 MHz): δ 64.0 ($2CH_2$), 68.8 (CH_2), 104.7 (2CH), 114.6 (CH_2), 126.3 (2CH), 127.9 (2CH), 136.0 (C), 136.2 (CH), 136.9 (C), 163.0 (2C), 165.7 (C); MS (ESI^+, *m*/*z*): 272 [$(M+H)^+$, 100%]. HRMS $(ESI)^+$ calcd for $C_{16}H_{18}NO_3$ $(M+H)^+$: 272.1281; found 272.1281.

*4.1.8. Synthesis of [4-(naphthalen-2-ylmethoxy)pyridine-2,6-diyl]dimethanol (**10c**).* We used the same procedure as for **10a**, but using **9c**. White solid. Yield: 84%; mp 260 °C (dec.) (ethyl acetate); R_f (7% MeOH/CH_2Cl_2): 0.24; IR (cm^{-1}) 3029, 3020, 2921, 1530, 1322, 1112; ^1H NMR (DMSO-d_6, 300.13 MHz): δ 4.47 (s, 4H), 5.34–5.38 (m, 4H), 7.00 (s, 2H), 7.52–7.60 (m, 3H), 7.92–7.99 (m, 4H); ^{13}C NMR (DMSO-d_6, 75.5 MHz): δ 64.0 ($2CH_2$), 69.1 (CH_2), 104.7 (2CH), 125.6 (CH), 126.2 (2CH), 126.4 (CH), 127.6 (CH), 127.8 (CH), 128.1 (CH), 132.6 (C), 132.8 (C), 134.0 (C), 163.0 (2C), 165.8 (C); MS (ESI^+, *m*/*z*): 296 [$(M+H)^+$, 100%]. HRMS $(ESI)^+$ calcd for $C_{18}H_{18}NO_3$ $(M+H)^+$: 296.1281; found 296.1270.

*4.1.9. Synthesis of [4-(naphthalen-1-ylmethoxy)pyridine-2,6-diyl]dimethanol (**10d**).* We used the same procedure as for **10a**, but using **9d**. White solid. Yield: 69%; mp 265 °C (dec.) (ethyl acetate); R_f (7% MeOH/CH_2Cl_2): 0.24; IR (cm^{-1}) 3029, 3020, 2921, 1530, 1322, 1112; ^1H NMR (DMSO-d_6, 300.13 MHz): δ 4.49 (s, 4H), 5.38 (br s, 2H), 5.65 (s, 2H), 7.03 (s, 2H), 7.52–7.69 (m, 4H), 7.95–8.08 (m, 3H); ^{13}C NMR (DMSO-d_6, 75.5 MHz): δ 64.0 ($2CH_2$), 67.7 (CH_2), 104.8 (2CH), 123.8 (CH), 125.4 (2CH), 126.1 (CH), 126.9 (CH), 128.5 (CH), 128.9 (CH), 131.1 (C), 131.8 (C), 133.3 (C), 163.1 (2C), 165.8 (C); MS (ESI^+, *m*/*z*): 296 [$(M+H)^+$, 100%]. HRMS $(ESI)^+$ calcd for $C_{18}H_{18}NO_3$ $(M+H)^+$: 296.1281; found 296.1283.

*4.1.10. Synthesis of [4-(anthracen-9-ylmethoxy)pyridine-2,6-diyl]dimethanol (**10e**).* We used the same procedure as for **10a**, but using **9e**. White solid. Yield: 50%; mp 267 °C (dec.) (ethyl acetate); R_f (7% MeOH/CH_2Cl_2): 0.24; IR (cm^{-1}) 3042, 3065, 2977, 1533, 1475, 1345, 1113; ^1H NMR (DMSO-d_6, 300.13 MHz): δ 4.53 (s, 4H), 5.38 (br s, 2H), 6.14 (s, 2H), 7.11 (s, 2H), 7.54–7.63 (m, 4H), 8.15 (d, $^3J_{HH}$=8.3 Hz, 2H), 8.31 (d, $^3J_{HH}$=8.2 Hz, 2H), 8.74 (s, 1H); ^{13}C NMR (DMSO-d_6, 75.5 MHz): δ 62.1 ($2CH_2$), 64.0 (CH_2), 104.8 (2CH), 124.0 (2CH), 125.3 (2CH), 126.5 (2C), 126.9 (2CH), 129.0 (3CH), 130.5 (2C), 131.0 (C), 163.0 (2C), 166.1 (C); MS (ESI^+, *m*/*z*): 346 [$(M+H)^+$, 50%], 184 [$(M-162)^+$, 100%]. HRMS $(ESI)^+$ calcd for $C_{22}H_{20}NO_3$ $(M+H)^+$: 346.1438; found 346.1439.

*4.1.11. Synthesis of 4-(benzyloxy)pyridine-2,6-dicarboxaldehyde (**5a**).* A solution of oxalyl chloride (400 μL, 4.4 mmol) in CH_2Cl_2 (23 mL) was cooled to −60 °C in a 100 mL flask fitted with a $CaSO_4$ drying tube. Then DMSO (494 μL, 2.0 mmol) in CH_2Cl_2 (5.8 mL) was added dropwise to this solution. The resulting mixture was stirred for 5 min and then a solution of diol **10a** (2.0 mmol, 490 mg) in CH_2Cl_2/DMSO (3:1, 20 mL) was added dropwise. Stirring was continued for 15 min at −60 °C, after which Et_3N (2.8 mL, 20.0 mmol) was added and the reaction mixture was allowed to warm up to room temperature. Reaction was quenched adding H_2O (60 mL) and the aqueous layer was extracted with CH_2Cl_2 (3×60 mL), organic phases were combined, dried over Na_2SO_4, filtered under vacuum and evaporated to dryness. The crude product was purified by flash chromatography (20% EtOAc/hexane). White solid. Yield: 82%; mp 107–108 °C (ethyl acetate/hexane); R_f (20% EtOAc/hexane): 0.23; IR (cm^{-1}) 2936, 1725, 1422, 1315, 1221; ^1H NMR ($CDCl_3$, 300.13 MHz): δ 5.24 (s, 2H), 7.42–7.44 (m, 5H), 7.71 (s, 2H), 10.1 (s, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 70.8 (CH_2), 111.6 (2CH), 127.5 (2CH), 128.7 (CH), 128.8 (2CH), 134.4 (C), 154.7 (2C), 166.5 (C), 192.1 (2CH); MS (ESI^+, *m*/*z*): 242 [$(M+H)^+$, 100%]. HRMS $(ESI)^+$ calcd for $C_{14}H_{12}NO_3$ $(M+H)^+$: 242.0812; found 242.0803.

*4.1.12. Synthesis of 4-[(4-ethenylbenzyl)oxy]pyridine-2,6- dicarboxaldehyde (**5b**).* We used the same procedure as for **5a**, but using **10b**. White solid. Yield: 85%; mp 80–82 °C (ethyl acetate/hexane); R_f (20% EtOAc/hexane): 0.25; IR (cm^{-1}) 2923, 1722, 1563, 1432, 1399, 1315, 1221; ^1H NMR ($CDCl_3$, 300.13 MHz): δ 5.20 (s, 2H), 5.27 (d, $^3J_{HH\ (cis)}$=11.0 Hz, 1H), 5.75 (d, $^3J_{HH\ (trans)}$=17.6 Hz, 1H), 6.68 (dd, $^3J_{HH\ (trans)}$=17.6 Hz, $^3J_{HH\ (cis)}$=10.9 Hz 1H), AB system (δ_A=7.33 δ_B=7.44, $^3J_{HH}$=8.5 Hz, 4H), 7.68 (s, 2H), 10.1 (s, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 70.4 (CH_2), 111.5 (2CH), 114.6 (CH_2), 126.5 (2CH), 127.7 (2CH), 133.7 (C), 135.9 (CH), 137.9 (C), 154.6 (2C), 166.4 (C), 192.0 (2C); MS (ESI^+, *m*/*z*): 300 [$(M+33)^+$, 100%], 268 [$(M+H)^+$, 25%]. HRMS $(ESI)^+$ calcd for $C_{16}H_{13}NNaO_3$ $(M+Na)^+$: 290.0788; found 290.0779.

*4.1.13. Synthesis of 4-(naphthalen-2-ylmethoxy)pyridine-2,6-dicarboxaldehyde (**5c**).* We used the same procedure as for **5a**, but using **10c**. White solid. Yield: 83%; mp 149–151 °C (ethyl acetate/hexane); R_f (20% EtOAc/hexane): 0.25; IR (cm^{-1}) 2972, 1720, 1523, 1444, 1351, 1227; ^1H NMR ($CDCl_3$, 300.13 MHz): δ 5.40 (s, 2H), 7.49–7.54 (m, 3H), 7.76 (s, 2H), 7.85–7.92 (m, 4H), 10.1 (s, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 70.9 (CH_2), 111.7 (2CH), 124.8 (CH), 126.5

(2CH), 126.7 (CH), 127.7 (CH), 127.9 (CH), 128.8 (CH), 131.8 (C), 133.0 (C), 133.1 (C), 154.7 (2C), 166.5 (C), 192.2 (2C); MS (ESI^+, *m*/*z*): 354 [$(M+62)^+$, 50%], 292 [$(M+H)^+$, 100%]. HRMS $(ESI)^+$ calcd for $C_{18}H_{13}NNaO_3$ $(M+Na)^+$: 314.0788; found 314.0776.

*4.1.14. Synthesis of 4-(naphthalen-1-ylmethoxy)pyridine-2,6-dicarboxaldehyde (**5d**).* Over a solution of **10d** (200 mg, 0.67 mmol) in 1,4-dioxane (10 mL) were successively added H_2O (75 μL) and SeO_2 (225 mg, 2.0 mmol). The resulting solution was stirred at 100 °C for 4 h, and then the reaction quenched by filtration of the suspended solid. Solvent was evaporated under reduced pressure, obtaining a reaction crude that was purified by flash chromatography (20% EtOAc/hexane). White solid. Yield: 81%; mp 157–161 °C (ethyl acetate/hexane); R_f (20% EtOAc/hexane): 0.26; IR (cm^{-1}) 2975, 1731, 1543, 1422, 1375, 1224; ^1H NMR (DMSO-d_6, 300.13 MHz): δ 5.87 (s, 2H), 7.52–7.75 (m, 4H), 7.87 (s, 2H), 7.96–8.15 (m, 3H), 10.1 (s, 2H); ^{13}C NMR (DMSO-d_6, 75.5 MHz): δ 69.1 (CH_2), 112.2 (2CH), 123.6 (CH), 125.3 (2CH), 126.0 (CH), 126.7 (CH), 128.4 (CH), 128.8 (CH), 131.0 (C), 132.1 (C), 154.6 (2C), 167.1 (C), 192.5 (2C); MS (ESI^+, *m*/*z*): 292 [$(M+H)^+$, 100%]. HRMS $(ESI)^+$ calcd for $C_{18}H_{13}NNaO_3$ $(M+Na)^+$: 314.0788; found 314.0782.

*4.1.15. Synthesis of 4-(anthracen-9-ylmethoxy)pyridine-2,6- dicarboxaldehyde (**5e**).* Over a solution of **10e** (320 mg, 0.9 mmol) in EtOAc (70 mL) was added IBX (1.5 g, 3.8 mmol). The resulting solution was stirred at 70 °C for 5 h, and then the reaction quenched by filtration of the precipitated solid. Solvent was evaporated under reduced pressure, obtaining a reaction crude that was purified by flash chromatography (20% EtOAc/hexane). Yellowish solid. Yield: 80%; mp 157–161 °C (ethyl acetate/hexane); R_f (20% EtOAc/hexane): 0.24; IR (cm^{-1}) 2972, 1731, 1573, 1442, 1310, 1218; ^1H NMR ($CDCl_3$, 300.13 MHz): δ 6.13 (s, 2H), 7.49–7.63 (m, 4H), 7.87 (s, 2H), 8.09 (d, $^3J_{HH}$=8.1 Hz, 2H), 8.21 (d, $^3J_{HH}$=8.2 Hz, 2H), 8.61 (s, 1H), 10.1 (s, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 63.9 (CH_2), 111.7 (2CH), 123.1 (2CH), 124.2 (2C), 125.2 (2CH), 127.1 (2CH), 129.3 (2CH), 129.9 (CH), 130.9 (2C), 131.3 (C), 154.9 (2C), 167.0 (C), 192.1 (2C); MS (ESI^+, *m*/*z*): 342 [$(M+H)^+$, 100%]. HRMS $(ESI)^+$ calcd for $C_{22}H_{15}NNaO_3$ $(M+Na)^+$: 364.0944; found 364.0961.

*4.1.16. Synthesis of (R,R,R,R)-4-(benzyloxy) dimer (**6a**).* Over a solution of (1*R*,2*R*)-(−)-cyclohexane-1,2-diamine (45 mg, 0.39 mmol) in CH_2Cl_2/MeOH (1:1, 8 mL), was added **5a** (94 mg, 0.39 mmol) and the solution was stirred for 15 min at room temperature. Then $BaCl_2$ (146 mg, 0.60 mmol) was added and the resulting mixture stirred for additional 14 h. Then the solution was cooled 0 °C, and $NaBH_4$ (64 mg, 1.70 mmol) was carefully added. The resulting white suspension was stirred for 4 h at room temperature, quenching the reaction with concentrated HCl (0.5 mL). The mixture was basified with NaOH 4 N (10 mL) and extracted with CH_2Cl_2 (3×10 mL), organic phases were combined, dried over Na_2SO_4, filtered under vacuum and evaporated to dryness, isolating **6a**. White solid. Yield: 79%; mp 99–101 °C (CH_2Cl_2); R_f (5% NH_3/MeOH): 0.12; $[\alpha]_D^{20}$ −38.5 (*c* 0.5, CH_2Cl_2); IR (cm^{-1}) 3400, 2950, 1600, 1435; ^1H NMR ($CDCl_3$, 300.13 MHz): δ 0.98–1.13 (m, 8H), 1.55–1.63 (m, 4H), 1.99–2.09 (m, 8H), 3.10–3.63 (br s, 4H, NH), AB system (δ_A=3.72 δ_B=4.07, $^2J_{HH}$=15.8 Hz, 8H), 5.01–5.11 (m, 4H), 6.66 (s, 4H), 7.31–7.43 (m, 10H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 24.5 (CH_2), 32.4 (CH_2), 51.2 (CH_2), 59.0 (CH), 69.8 (CH_2), 107.8 (CH), 127.5 (CH), 128.3 (CH), 128.6 (CH), 135.6 (C), 161.4 (C), 165.4 (C); MS (ESI^+, *m*/*z*): 647 [$(M+H)^+$, 100%]. HRMS $(ESI)^+$ calcd for $C_{40}H_{51}N_6O_2$ $(M+H)^+$: 647.4068; found 647.4083.

*4.1.17. Synthesis of (R,R,R,R)-4-[(4-ethenylbenzyl)oxy] dimer (**6b**).* We used the same procedure as for **6a**, but using **5b**. White solid. Yield: 85%; mp 105–106 °C (CH_2Cl_2); R_f (5% NH_3/MeOH): 0.12; $[\alpha]_D^{20}$ −27.5 (*c* 1.0, CH_2Cl_2); IR (cm^{-1}) 3400, 2950, 1600, 1435; ^1H NMR ($CDCl_3$, 300.13 MHz): δ 0.99–1.12 (m, 8H), 1.55–1.65 (m, 4H), 2.00–2.09 (m, 8H), 3.10–3.63 (br s, 4H, NH), AB system (δ_A=3.68 δ_B=4.02, $^2J_{HH}$=15.5 Hz), AB system (δ_A=5.05 δ_B=5.09, $^2J_{HH}$=11.9 Hz), 5.29 (d, $^3J_{HH\ (cis)}$=10.4 Hz, 2H), 5.79 (d, $^3J_{HH\ (trans)}$=17.6 Hz, 2H), 6.63 (s, 4H), 6.74 (dd, $^3J_{HH\ (trans)}$=17.6 Hz, $^3J_{HH\ (cis)}$=10.4 Hz, 2H), AB system (δ_A=7.36 δ_B=7.44, $^3J_{HH}$=8.0 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 24.5 (CH_2), 32.7 (CH_2), 51.4 (CH_2), 58.9 (CH), 69.5 (CH_2), 107.6 (CH), 126.4 (CH), 127.7 (CH), 135.1 (C), 136.1 (CH), 137.6 (C), 161.8 (C), 165.5 (C); MS (ESI^+, *m*/*z*): 699 [$(M+H)^+$, 100%]. HRMS $(ESI)^+$ calcd for $C_{44}H_{55}N_6O_2$ $(M+H)^+$: 699.4381; found 699.4373.

*4.1.18. Synthesis of (R,R,R,R)-4-(naphthalen-2-ylmethoxy) dimer (**6c**).* We used the same procedure as for **6a**, but using **5c**. White solid. Yield: 81%; mp 107–109 °C (CH_2Cl_2); R_f (5% NH_3/MeOH): 0.11; $[\alpha]_D^{20}$ −19.5 (*c* 1, CH_2Cl_2); IR (cm^{-1}) 3404, 2953, 1645, 1443; ^1H NMR ($CDCl_3$, 300.13 MHz): δ 0.96–1.13 (m, 8H), 1.53–1.64 (m, 4H), 1.98–2.09 (m, 8H), 3.10–3.63 (br s, 4H, NH), AB system (δ_A=3.71 δ_B=4.06, $^2J_{HH}$=15.5 Hz), 3.83–3.87 (br s, 4H, NH), 5.19–5.29 (m, 4H), 6.68 (s, 4H), 7.45–7.51 (m, 6H), 7.81–7.89 (m, 8H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 24.5 (CH_2), 32.5 (CH_2), 51.3 (CH_2), 58.9 (CH), 69.8 (CH_2), 107.7 (CH), 124.9 (CH), 126.1 (CH), 126.2 (CH), 126.4 (CH), 127.6 (CH), 127.8 (CH), 128.4 (CH), 133.0 (2C), 133.1 (C); MS (ESI^+, *m*/*z*): 747 [$(M+H)^+$, 100%]. HRMS $(ESI)^+$ calcd for $C_{48}H_{55}N_6O_2$ $(M+H)^+$: 747.4381; found 747.4405.

*4.1.19. Synthesis of (R,R,R,R)-4-(naphthalen-1-ylmethoxy) dimer (**6d**).* We used the same procedure as for **6a**, but using **5d**. White solid. Yield: 75%; mp 105–107 °C (CH_2Cl_2); R_f (5% NH_3/MeOH): 0.12; $[\alpha]_D^{20}$ −44.7 (*c* 0.4, CH_2Cl_2); IR (cm^{-1}) 3403, 2955, 1625, 1525, 1445; ^1H NMR ($CDCl_3$, 300.13 MHz): δ 0.96–1.13 (m, 8H), 1.53–1.64 (m, 4H), 1.98–2.09 (m, 8H), 3.10–3.63 (br s, 4H, NH), AB system (δ_A=3.74 δ_B=4.11, $^2J_{HH}$=15.5 Hz), 3.83–3.87 (br s, 4H, NH), 5.45–5.59 (m, 4H), 6.73 (s, 4H), 7.47–7.60 (m, 8H), 7.86–8.01 (m, 6H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 24.5 (CH_2), 32.5 (CH_2), 51.3 (CH_2), 59.0 (CH), 68.3 (CH_2), 107.7 (CH), 123.3 (CH), 125.2 (CH), 126.0 (CH), 126.6 (CH), 126.7 (CH), 128.7 (CH), 129.3 (CH), 130.9 (C), 131.3 (C), 133.7 (C), 161.5 (C), 165.7 (C); MS (ESI^+, *m*/*zm*/*z*): 747 [$(M+H)^+$, 100%]. HRMS $(ESI)^+$ calcd for $C_{48}H_{55}N_6O_2$ $(M+H)^+$: 747.4381; found 747.4366.

*4.1.20. Synthesis of (R,R,R,R)-4-(anthracen-9-ylmethoxy) dimer (**6e**).* We used the same procedure as for **6a**, but using **5e**. Yellowish solid. Yield: 83%; mp 127–129 °C (CH_2Cl_2); R_f (5% NH_3/MeOH): 0.12; $[\alpha]_D^{20}$ −20.1 (*c* 0.25, CH_2Cl_2); IR (cm^{-1}) 3410, 3401, 2975, 1634, 1501, 1440; ^1H NMR ($CDCl_3$, 300.13 MHz): δ 0.98–1.13 (m, 8H), 1.55–1.63 (m, 4H), 1.99–2.09 (m, 8H), 3.50–4.101 (br s, 4H, NH), AB system (δ_A=3.80 δ_B=4.15, $^2J_{HH}$=15.8 Hz), 5.86–5.94 (m, 4H), 6.81 (s, 4H), 7.49–7.58 (m, 8H), 8.08 (d, $^3J_{HH}$=8.2 Hz, 4H), 8.19 (d, $^2J_{HH}$=8.1 Hz, 4H), 8.55 (s, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 24.3 (CH_2), 31.6 (CH_2), 50.9 (CH_2), 59.1 (CH), 62.5 (CH_2), 108.0 (CH), 123.9 (CH), 124.1 (C), 125.3 (CH), 127.1 (CH), 129.4 (CH), 129.7 (CH), 130.9 (C), 131.3 (C), 160.4 (C), 161.7 (C); MS (ESI^+, *m*/*z*): 847 [$(M+H)^+$, 100%]. HRMS $(ESI)^+$ calcd for $C_{56}H_{59}N_6O_2$ $(M+H)^+$: 847.4694; found 847.4668.

4.1.21. Study of the 4-position effect on the templated step. Over a solution of (1*R*,2*R*)-(−)-cyclohexane-1,2-diamine (61 mg, 0.50 mmol) in CH_2Cl_2/MeOH (1:1, 10 mL), were added **2** (34 mg, 0.25 mmol) and **5b** (67 mg, 0.25 mmol) and the solution was stirred for 15 min at room temperature. Then $BaCl_2$ (195 mg, 0.80 mmol) was added and the resulting mixture stirred for additional 14 h. Then the solution was cooled down to 0 °C, and $NaBH_4$ (80 mg, 2.13 mmol) was carefully added. The resulting white suspension was stirred for 4 h at room temperature, quenching the reaction with concentrated HCl (1.0 mL). The mixture was basified with NaOH 4 N (15 mL) and extracted with CH_2Cl_2 (3×10 mL), organic phases were combined, dried over Na_2SO_4, filtered under vacuum

and evaporated to dryness, isolating the statistical mixture of **4** (1)/**11** (2)/**6b** (1).

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Supplementary data

Copies of the ^{1}H and ^{13}C NMR spectra are available in the Electronic Supporting Information. Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.06.009. These data include MOL files and InChIKeys of the most important compounds described in this article.

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