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The novel macrocyclic compounds as chiral solvating agents for determination of enantiomeric excess of carboxylic acids

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ABSTRACT

The novel macrocyclic compounds **1**–**8** and acyclic compound **9** were designed and synthesized. ^{1}H NMR studies demonstrated that **1** and **2** were the best chiral solvating agents, and are effective for the determination of the enantiomeric excess of a wide range of α-chiral carboxylic acids. Large non-equivalent chemical shifts (up to 411.2 Hz) can be achieved in the presence of **1** and **2**. Quantitative analyses of a series of mandelic acids with different enantiomeric purities demonstrate that **1** and **2** are excellent chiral solvating agents for carboxylic acids.

1. Introduction

Due to the importance of chiral species in biological and pharmaceutical chemistry,[1] rapid and convenient analytical procedures to determine the enantiomeric excess of chiral products are required. Among the various available methods, NMR spectroscopy, using milligram level amount of analyte and less than 1 mL of deuterated solvent, might be a facile and environmentally benign tool.[2] This technique requires an effective chiral additive to combine with the sample to form diastereomeric species, which need to appear different in some of their NMR signals.[2] The chiral additive is generally divided into chiral derivating agent (CDA), chiral solvating agent (CSA, including chiral NMR solvent), and chiral lanthanide shift reagent (CLSR).[2b,c]

Based on the great success of the classical CDA methoxytrifluoromethylphenylacetic acid (MTPA) and methoxyphenylacetic acid (MPA) originally proposed by Mosher[3] and Trost,[4] a wide variety of new and efficient CDAs have been developed that can be applied to diverse kinds of compounds.[2] However, additional synthetic efforts[5] and the fact that neither analyte nor CDA could be recovered after examination are disadvantages of this method. The use of CSA was first reported by Pirkle.[6] This method, which just requires the mixing of the CSA and the sample in an NMR tube and recording the spectra, is quick and simple to perform. However, the difference in chemical shift induced by a CSA, from a comparison of this induced by CDA in many cases, is generally too small to realize baseline resolution. Thus, the development of new and effective CSAs is still under research.

Carboxylic acids are frequently found in Nature as optically active compounds with the stereogenic center at the α-position, and general approaches for the determination of enantiomeric excess[7] for these systems are rare.[2] Herein, we attempted to search for a highly powerful CSA that would be suitable for the determination of this enantiomeric excess of carboxylic acids.

2. Results and discussion

2.1. Molecular design

Theoretically, a chiral solvating agent should form stable complexes with the enantiomers in question, and should also possess strongly anisotropic group. Thus, the structure of the diastereomeric complex should be well suited to produce selective shielding effects on the protons of the substrate moiety. Chiral macrocyclic compounds have been recognized as successful and promising chiral selectors for molecular recognition, mainly because of their inherent reduced flexibility and complexation ability.[8] A complex based on a salt bridge is obviously more stable than that via an ordinary hydrogen bond. Taking this into account, we designed macrocyclic compounds **1**–**8** (Fig. 1) to investigate their chiral discrimination ability toward α-chiral carboxylic acids. The acyclic compound **9** was also designed to investigate the importance of macrocyclic structures. These compounds are easily synthesized and have wide detection windows to avoid NMR signal overlapping (see Figs. 2 and 3).

Compounds **1**–**9** can be synthesized shown in Scheme 1, in a similar manner to that previously reported by us.[7e,9] First, a Mannich reaction was carried out, using an amine, β-naphthol, and dialdehyde as starting materials, to yield the aminonaphthol. Then, coupling of the aminonaphthol with the corresponding halogenoalkane led to the formation of the target molecules **1**–**9** in high

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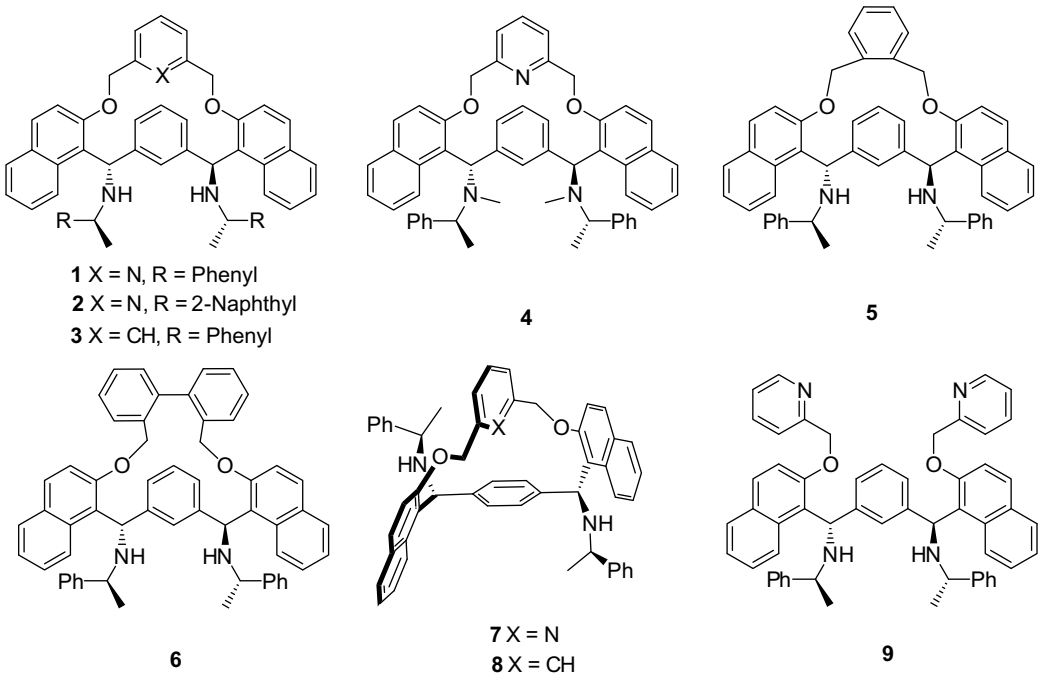


Figure 1. Chemical structures of compounds **1–9**.

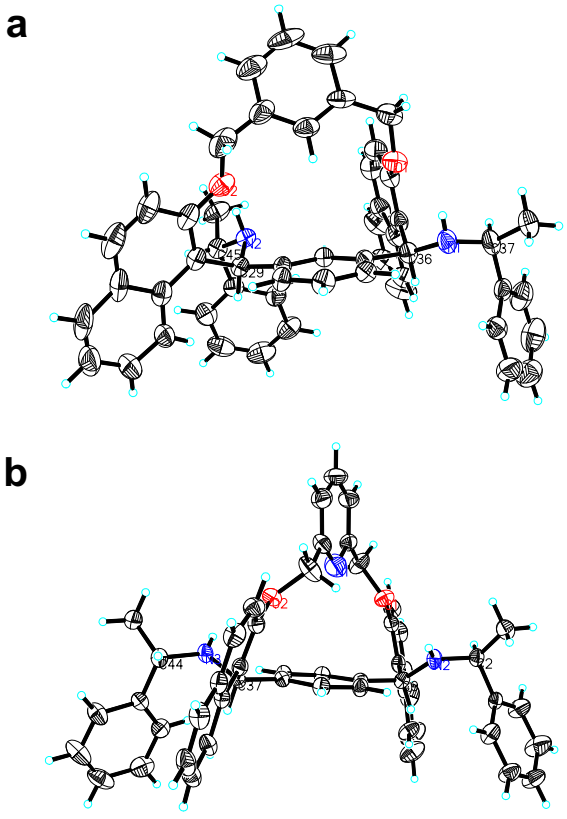


Figure 2. X-ray structures of new compounds **3** (a) and **7** (b).

yield. The sizes of macrocyclic compounds **1–3** and **7** were confirmed by X-ray diffraction,[10] and the molecular weights of **4–6** and **8** are confirmed by HRMS method. All the stereogenic centers of **1–9** all have (*S*)-configurations when the chiral sources, the amines, are the (*S*)-isomers.

2.2. Determination of the enantiomeric excess of α-chiral acids

To evaluate the chiral discrimination abilities of compounds **1–9**, we measured ^{1}H NMR spectra for 1:1 mixtures of **1–9** and mandelic acid **21** in $CDCl_3$. The results are summarized in Table 1. Although the structures of the CSAs **1–9** are similar, the chiral discrimination abilities of them toward mandelic acid are obviously different. The CSAs **1–2** are superior to CSAs **3–9**. From a comparison of the chemical shift non-equivalences ($\Delta\Delta\delta$), it appears that the change of the pyridine ring (CSAs **1** and **7**) to benzene (CSAs **3** and **8**) causes a significant decrease in chiral discrimination ability. The secondary amino moiety in the CSA is also very important (comparing CSA **1** and CSA **4**). It should be noted that the macrocyclic compounds derived from *p*-benzenedialdehydes **7** and **8** show less chiral discriminating ability than those derived from *m*-benzenedialdehydes **1** and **3**, and the acyclic compound **9** is ineffective.

The large non-equivalent chemical shifts of mandelic acid in the presence of **1** and **2** inspired us to explore the enantiomeric discriminating abilities of **1** and **2** with those of other α-chiral carboxylic acids (the $\Delta\Delta\delta$ inducted by **5** and **6** were also larger or similar to most of the reported CSAs,[7] but they are obviously less effective than that of **1** and **2**). A wide variety of α-chiral carboxylic acids, including some derivatives of mandelic acids, α-halo acids, α-alkyl acid, some derivatives of α-amino acids, etc., **21–40**, were chosen as guests to screen the potential of **1** and **2** as a CSA by using the ^{1}H NMR method. The results are summarized in Table 2.

As shown in Table 2, in the presence of CSAs **1** and/or **2**, the chemical shift non-equivalences of at least one of the protons of the selected acids are large enough to give baseline resolution on a 500 MHz NMR instrument at 25 °C. Good enantiomeric discrimination is seen in many cases [$\Delta\Delta\delta$ >0.10 ppm for all the acids except **26** (in the presence of CSA **1**), **29**, **38** (in the presence of CSA **2**), and **40**, $\Delta\Delta\delta$ >0.30 ppm for **21–25**, **34**, **36**], where the degrees of the chemical shift differences are even comparable to those reported for diastereomeric compounds covalently linked by chiral derivating agents.[2] In some cases, the $\Delta\Delta\delta$ are up to 0.80 ppm (411.2 Hz for **22** in the presence of **2**, 406.4 Hz for **24** in the pres-

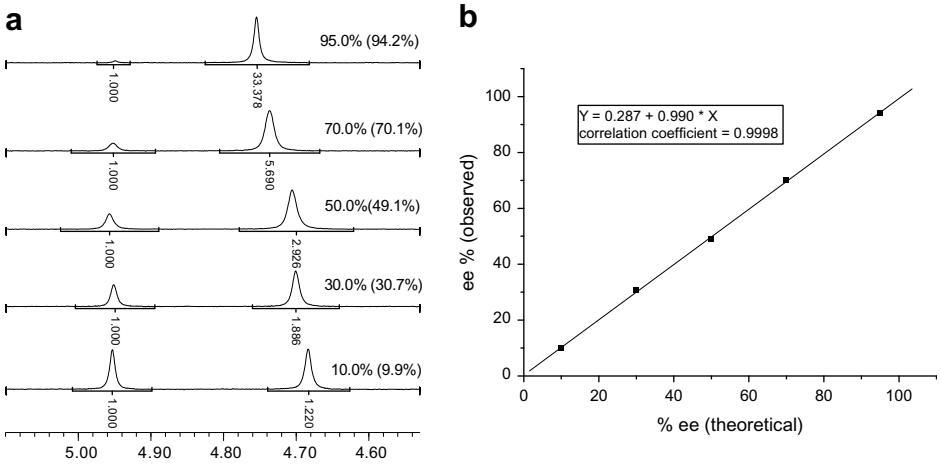
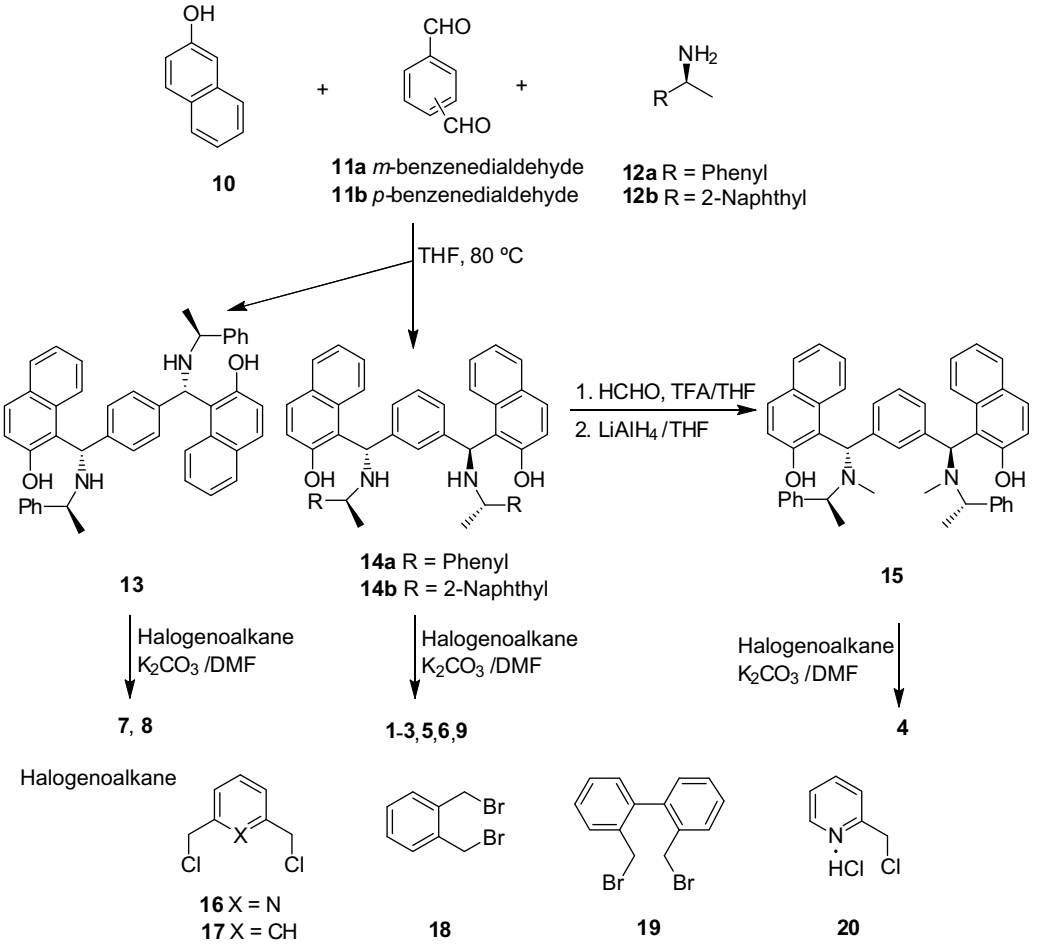


Figure 3. (a) A selected region of ^{1}H NMR of **21** (10 mM) with various enantiomeric purities in the presence of **1** (2 mM) in $CDCl_3$ (3% volume of MeOD-d_4 was added to eliminate the broad signal of the active protons) at 25 °C. Observed % ee values calculated from the integrals are indicated in the parentheses. (b) Correlation between the theoretical and observed % ee values.



Scheme 1. Synthesis of compounds **1**–**9**.

ence of **1**). In the case of **22**, even 0.25 equiv of **1** is enough to afford excellent separation (387.8 Hz for α-proton, 38.0 Hz for OCH_3) When 1 equiv of **1** was used, the $\Delta\Delta\delta$ were 399.1 Hz and 93.4 Hz, however, the α-proton and OCH_3 of (*R*)-**22** overlapped. It should be noted that, in many cases, the protons far from the stereogenic center, such as OCH_3 in **22** and CH_3(Ts) in **36**–**40**, can also be split completely in the presence of **1** and/or **2**. Although α-chloropropanoic acid **29** could not be differentiated by **1** at 25 °C, the signal of the CH_3 can display a baseline separation at 0 °C (Table 2).

The absolute configuration assignment ability of **1** and **2** was also investigated, using enantiomerically enriched acids. Unfortunately, as shown in Table 2, the correlation of the change in chemical shifts seems ambiguous.

Table 1
Measurement of ^{1}H chemical shift non-equivalences ($\Delta\Delta\delta$) of the α-proton of mandelic acid **21** in the presence of CSAs **1**–**9** by ^{1}H NMR spectroscopy (500 MHz) in $CDCl_3$ at 25 °C[a]

CSA	1	2	3	4	5	6	7	8	9
$\Delta\Delta\delta$ (ppm)	0.63	0.52	0.04	0.02	0.11	0.11	0.05	0.00	0.00

[a] All samples are prepared by mixing 1 equiv of mandelic acid **21** and CSA in NMR tubes, all the final concentrations are 10 mM in 0.5 mL of $CDCl_3$.

From a comparison of the chemical shift non-equivalences of mandelic acid analogues (**21**–**24**) and other phenylacetic acid derivatives **25**–**27** (Table 2), it appears that the acids with hydrogen bond donors gave better results, suggesting that the formation of the hydrogen bond between the α-hydroxyl and the CSA also plays an important role in the chiral discrimination. Similar result can also be found with **28**–**30**. From Table 1, it can be seen that the CSA containing pyridine ring (CSAs **1** and **7**) shows a better chiral discrimination ability than that without pyridine ring (CSAs **3** and **8**), probably due to the nitrogen atom in the pyridine being a hydrogen bond accepter.

In order to investigate the importance of the additional hydrogen bond between the donors, an experiment was carried out, using **1**–**3**, **5**, and **6** as a CSA, and **25** and **27** as guests. These two guests have no hydrogen bond donors except for the carboxyl group, and may have the same interactions with the CSA. As shown in Table 3, the chiral discrimination ability of CSA **1** and **2** is superior to that of the other three, which means this ability is decided not by the additional hydrogen bond, but by the stereostructure of the CSA itself.

To explore the quantitative analysis ability of **1** and **2** as a CSA, five samples containing mandelic acid **21** with 10%, 30%, 50%, 70%, and 95% ee were prepared, and the enantiomeric compositions were determined by the ^{1}H NMR method in the presence of 0.2 equiv of **1** and **2**. The results, which were calculated based on the integrations of the NMR signals, are within ±1% of the actual enantiopurity of the samples. We also confirmed a linear correlation between the theoretical (y) and observed %ee values (x). The equation (for **1**, $y = 0.990x + 0.287$, correlation coefficient = 0.9998; for **2**, $y = 0.993x + 0.272$, correlation coefficient = 0.9999) demonstrates the high accuracy of this method.

The stoichiometry was determined according to Job's method of continuous variation.[11] The Job plots of $\Delta\delta X$ versus the mole fraction (X) of (*R*)- or (*S*)-**21** in the mixture were obtained, which showed maxima at $X = 0.67$ (see Fig. 4). This indicates that **1** or **2** forms a '1:2' complex with (*R*)-**21** or (*S*)-**21**. Probably the acid interacts with the two aliphatic nitrogen atoms of **1** or **2**.

The C=O stretch (1718 cm^{-1} for mandelic acid) disappeared in the IR spectra of a 1:1 mixture of **1** and mandelic acid, and the observed intensities got stronger at 1622 cm^{-1} and 1597 cm^{-1} (the COO^- stretch and the aromatic ring stretch), which demonstrated that the carboxyl of the acid was ionized.

We also performed the NOESY spectra of a mixture of **1** and an acid such as **21**, **26**, **39**, and phenylacetic acid. Unfortunately, we failed to observe the intermolecular NOEs in the 2D NOESY spectra to obtain more structure information of the complexes.

2.3. Important factors (experimental conditions) for chiral discrimination in NMR

Chiral solvating agents form diastereoisomeric complexes, which may appear differently in some of their NMR signals, with analytes via rapidly reversible equilibria in competition with the bulk solvent.[2c]

$$S_{CSA} + 2R_{Acid} \overset{K_B}{\rightleftharpoons} S_{CSA} \cdot 2R_{Acid}$$

$$S_{CSA} + 2S_{Acid} \overset{K_B}{\rightleftharpoons} S_{CSA} \cdot 2S_{Acid}$$

The exchange between the free analyte and the complex is rapid on the NMR timescale, and the observed chemical shift is the mole fraction weighted average of the shifts observed in the free and complexed molecules. Thus, the chemical shift non-equivalence is the result of two causes; the distinct chemical shifts and the different stabilities of the complexes. The experimental conditions, which affect these two causes and the fractional populations of free acid, will also affect the chemical shift non-equivalence.

2.4. Solvent

We have demonstrated that non-equivalent chemical shifts decrease upon addition of polar solvents, such as acetone, methanol, and DMSO.[7e] Polar solvents will decrease the formation of the complex by destroying the hydrogen bonds between the CSA and the acid. Therefore, the less polar and inexpensive solvent, $CDCl_3$ is preferred. Sometimes, the addition of a small amount of CD_3OD is advised to obtain a better solubility or to eliminate the broad signal of the active protons ('methanol-exchange', the residual active protons' peak is sharp, with a chemical shift changeably at 2.0–3.5 ppm when 1–10% volume of methanol-d_4 is used, see Fig. 5).

2.5. Ratio of CSA to acid

Upon the addition of the CSA, more and more complex forms while the fractional populations of free acid decrease, leading to an increase in the non-equivalent chemical shift (see Fig. 6).

As shown in Figure 6, upon gradual addition of **1**, the difference between the chemical shifts of the α-protons of (*R*) and (*S*)-**26** increases from 28.3 Hz (**1**:**26** = 1:5) to 59.0 Hz at a molar ratio of 2:1 (the $\Delta\Delta\delta$ of the methyl of **26** also gradually increases from 21.8 Hz to 83.6 Hz). However, for acid **21**, a maximum $\Delta\Delta\delta$ appeared when the molar ratio of **1**–**21** was 1: 2.[7e] This can be explained by that the stronger acid **21** forms a salt through complete proton transfer (K is very large), while the weaker acid **26** forms a salt with **1** through partial proton transfer (K is smaller) in the non-polar solvent. For acid **21**, when the molar ratio of **1**–**21** is smaller than 1:2, the residual free **21** decreases as **1** increases; when the molar ratio is 1:2, **21** and **1** transfer to the 1:2 complex completely and the $\Delta\delta$ increases to the $\Delta\delta$(max); when the molar ratio is larger than 1:2, some 1:1 complex may form, meaning the system is more complicated and a change of $\Delta\Delta\delta$ is harder to expect. For a weaker acid, such as **26**, upon the addition of **1**, the residual free **26** decreases, but always exists, thus the $\Delta\Delta\delta$ keeps increasing.

Generally, a molar ratio of CSA to analyte between 1:2 and 1:1 is advised. In this paper, the typical conditions involve a 1:1 mole ratio.

2.6. Concentrations

According to the theory of chemical equilibrium, upon increasing the concentration, the mole fraction of the reactants decreases for a combination reaction. So, it can be predicted that the fractional population of free acid is smaller and the $\Delta\Delta\delta$ is larger at a larger concentration, which is supported by experiments (see Fig. 7).

For stronger acids, such as **21**, the concentration does not obviously affect the $\Delta\Delta\delta$. When the concentration increased from 1 mM to 100 mM, the non-equivalent chemical shift increased by only 21.3 Hz, from 279.7 Hz to 301.0 Hz. Due to the fact that the forward reaction of salt formation chemical equilibrium has gone

Table 2
Measurement of ^{1}H chemical shift non-equivalences ($\Delta\Delta\delta$) of the acids **21**–**40** in the presence of CSAs **1**–**2** by ^{1}H NMR spectroscopy (500 MHz) in $CDCl_3$[a]

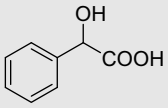
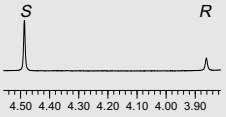
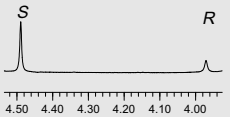
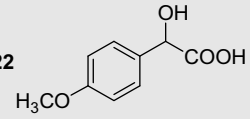
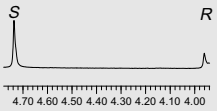
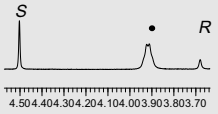
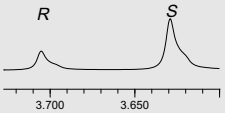
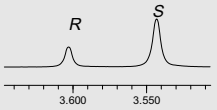
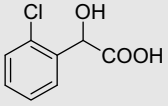
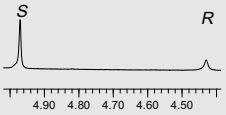
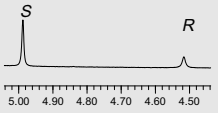
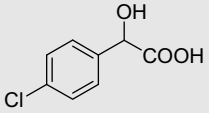
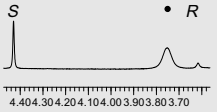
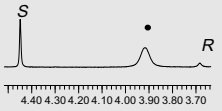
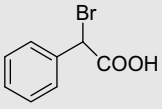
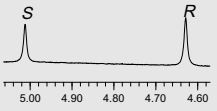
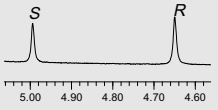
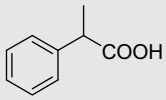
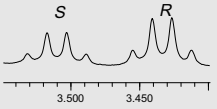
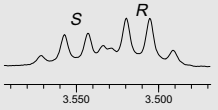
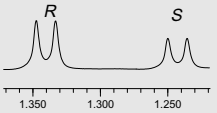
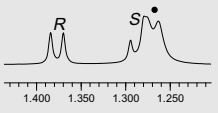
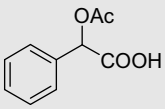
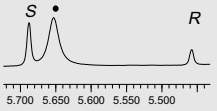
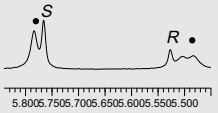
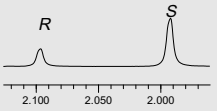
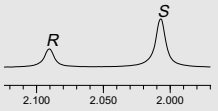
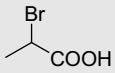
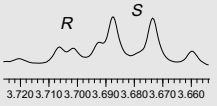
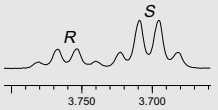
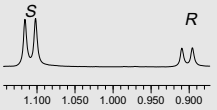
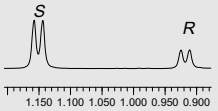
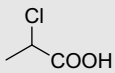
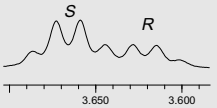
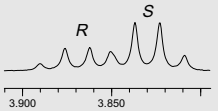
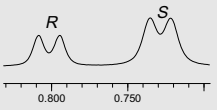
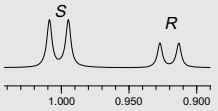
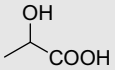
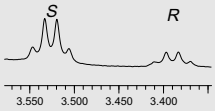
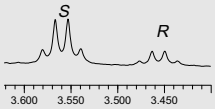
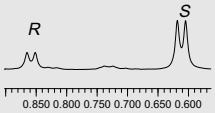
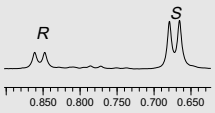
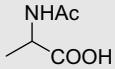
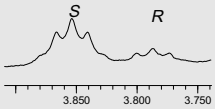
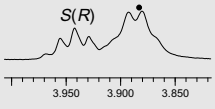
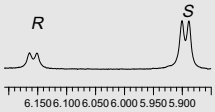
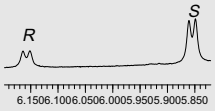
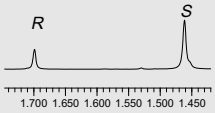
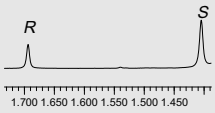
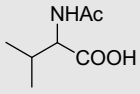
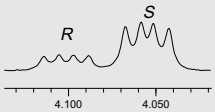
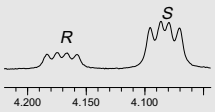
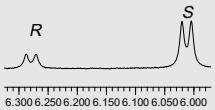
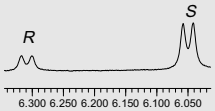
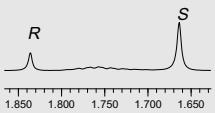
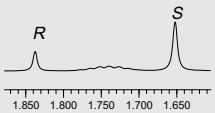
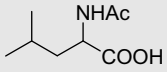
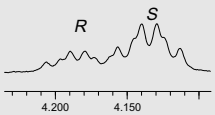
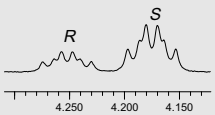
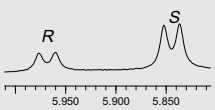
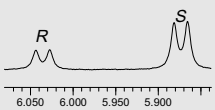
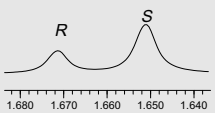
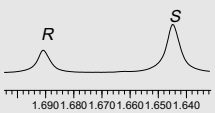
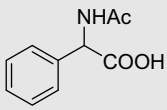
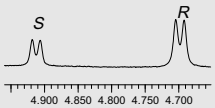
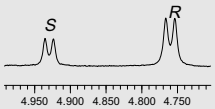
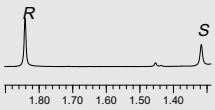
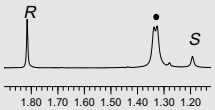
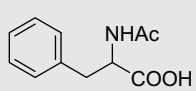
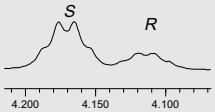
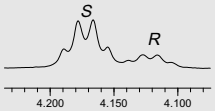
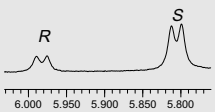
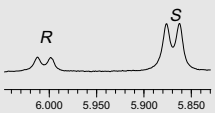
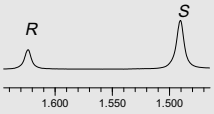
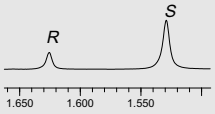
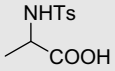
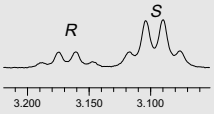
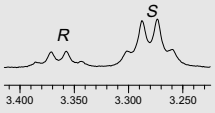
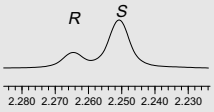
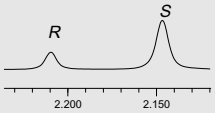
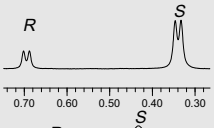
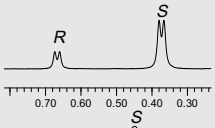
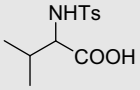
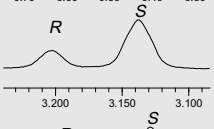
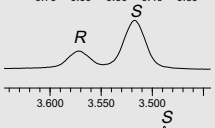
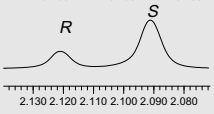
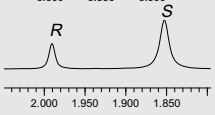
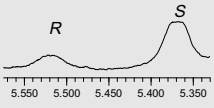
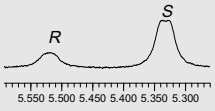
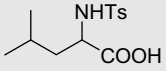
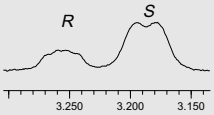
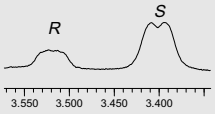
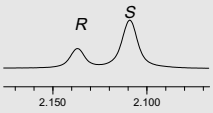
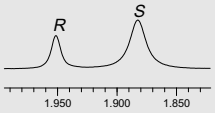
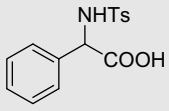
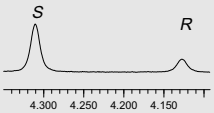
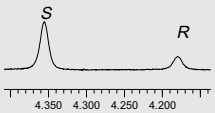
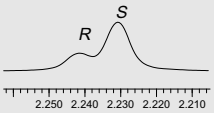
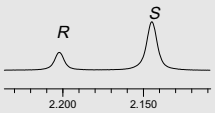
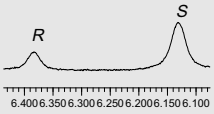
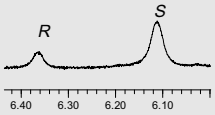
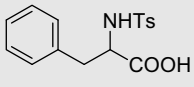
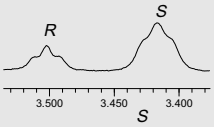
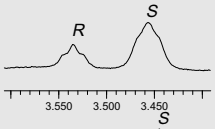
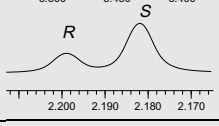
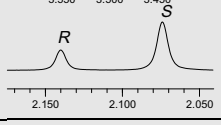
Acid	Proton	CSA **1**		CSA **2**	
		$\Delta\Delta\delta$ (ppm)	Spectra	$\Delta\Delta\delta$ (ppm)	Spectra
21 	α-H	0.63		0.52	
22 	α-H	0.78[b]		0.82	
	OCH_3	0.08[b]		0.06	
23 	α-H	0.54		0.47	
24 	α-H	0.81		0.77	
25 	α-H	0.38		0.34	
26 	α-H	0.08		0.04	
	CH_3	0.10		0.09	
27 	α-H	0.23		0.24[e]	
	$COCH_3$	0.10		0.08	
28 	α-H	0.02		0.06	
	CH_3	0.21		0.23	
29 	α-H	0.04[c]		0.04[e]	
	CH_3	0.07[c]		0.06	

Table 2 (*continued*)

Acid	Proton	CSA **1**		CSA **2**	
		ΔΔδ (ppm)	Spectra	ΔΔδ (ppm)	Spectra
30 	α-H	0.14		0.10	
	CH_3	0.25		0.18	
31 	α-H	0.07[d]		0.00	
	NH	0.26		0.30	
	$COCH_3$	0.24		0.29	
32 	α-H	0.05		0.09	
	NH	0.27		0.29	
	$COCH_3$	0.17		0.19	
33 	α-H	0.05		0.08	
	NH	0.12		0.16	
	$COCH_3$	0.02		0.05	
34 	α-H	0.21		0.17	
	$COCH_3$	0.52		0.62	
35 	α-H	0.06[d]		0.05[f]	
	NH	0.18		0.14	

(*continued on next page*)

Table 2 (*continued*)

Acid	Proton	CSA **1**		CSA **2**	
		ΔΔδ (ppm)	Spectra	ΔΔδ (ppm)	Spectra
	$COCH_3$	0.13		0.10	
36 	α-H	0.07		0.04	
	CH_3(Ts)	0.01		0.06	
	$CHCH_3$	0.36		0.29	
37 	α-H	0.06		0.06[e]	
	CH_3(Ts)	0.03		0.14	
	NH	0.16		0.18	
38 	α-H	0.07		0.11[e]	
	CH_3(Ts)	0.03		0.07	
39 	α-H	0.18		0.18	
	CH_3(Ts)	0.01		0.06	
	NH	0.25		0.25	
40 	α-H	0.09		0.08	
	CH_3(Ts)	0.02		0.07	

[a] Typical conditions: concentration of the acid and the CSA is 10 mM (1:1) in 0.5 mL of $CDCl_3$, and the spectra are recorded at 25 °C, unless otherwise indicated. The *R* and *S* in the spectra, respectively, represent the signals of (*R*) and (*S*) isomers, and the dots represent the signals of the CSA.

[b] 0.25 equiv of CSA is used.

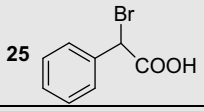
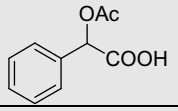
[c] The spectra are recorded at 0 °C.

[d] 2 equiv of CSA is used.

[e] 0.5 equiv of CSA is used.

[f] 5 equiv of CSA is used.

Table 3
Measurement of the ^{1}H chemical shift non-equivalences ($\Delta\Delta\delta$) of the acids **25** and **27** in the presence of CSAs **1**–**3**, **5**–**6** by ^{1}H NMR spectroscopy (500 MHz) in $CDCl_3$[a]

CSA	**25** 	**27** 	
	$\Delta\Delta\delta(\alpha)$ (ppm)	$\Delta\Delta\delta(\alpha)$ (ppm)	$\Delta\Delta\delta(CH_3)$ (ppm)
1	0.38	0.23	0.10
2	0.34	0.24	0.08
3	0.02	0.00	0.09
5	0.11	0.04	0.03
6	0.03	0.01	0.04

[a] Typical conditions: concentration of the acid and the CSA is 10 mM (1:1) in 0.5 mL of $CDCl_3$, and the spectra are recorded at 25 °C.

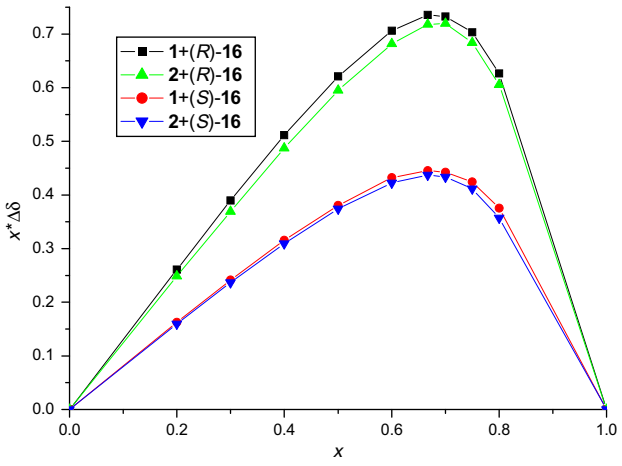


Figure 4. Job plots for the complexation of CSAs **1** and **2** with acid (*R*)-**21** and (*S*)-**21**. (X = [acid]/([CSA] + [acid]), $\Delta\delta$ = variation of the chemical shift of the α-proton of **21**).

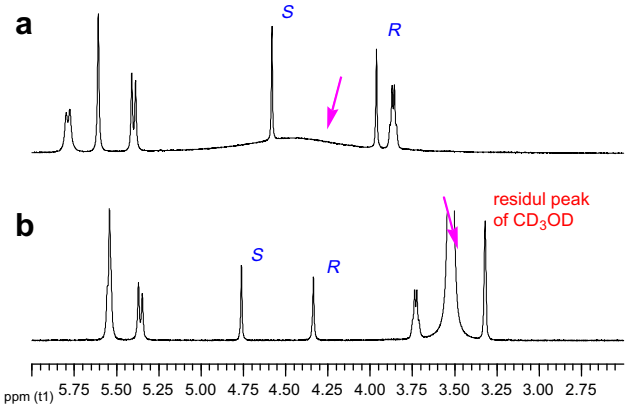


Figure 5. The overlaid ^{1}H NMR spectra (500 MHz) of the 1:2 mixture of **1** and **21** in various deuterated solvents. (a) $CDCl_3$, (b) $CDCl_3/CD_3OD$ (10%). *R* and *S* stand for the α-protons of corresponding mandelic acid **21**, the arrows indicate the residual active protons' peak.

nearly to completion, the concentration has less effect on the mole fraction of the reactant.

The advised concentration is 10 mM (1 mg of analyte with molecular weight of 200 and about 4 mg of CSA in 0.5 mL of solvent).

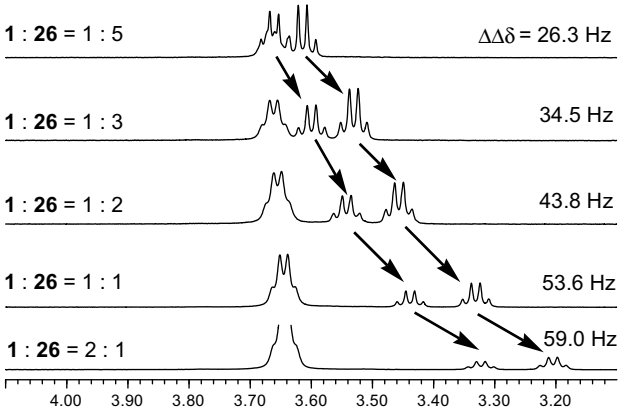


Figure 6. Mole ratio variation of $\Delta\Delta\delta$ for **26** in the presence of CSA **1**. The concentration of **26** is 20 mM in $CDCl_3$ unchangeable.

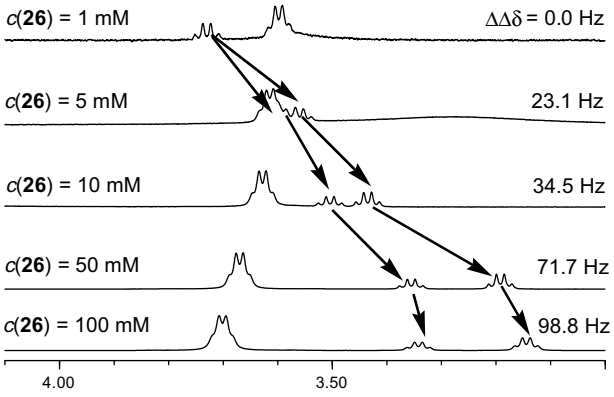


Figure 7. Concentrations variation of $\Delta\Delta\delta$ for **26** in the presence of CSA **1**. The mole ratio of **1**–**26** is 1:1, unchangeable.

2.7. Temperature

As the temperature is lowered, the chemical equilibrium goes forwards because salt formation reaction is generally an exothermic reaction. So the fractional population of free acid decreases. Additionally, there will be a preferential population of specific lower energy conformations at lower temperatures, which means the distinct chemical shifts of the complex are also larger. These two factors make the $\Delta\Delta\delta$ larger at lower temperatures. A linear dependence of the $\Delta\Delta\delta$ of **26** with temperature in the range 253–293 K is observed (see Fig. 8).[12]

Lowering the temperature is a useful method for systems where $\Delta\Delta\delta$ may be very small at room temperature.[7c] However, there is still a risk of signal broadening, because the rate of exchange between the free and bound states may decrease to the intermediate rate of the ^{1}H NMR timescale. For example, the signals of **29** and **1** broaden when the temperature is lower than 253 K (see Fig. 9).

Fortunately, the excellent CSA, **1** and **2**, can distinguish between most of the acids at room temperature, and is the advised experimental conditions.

Theoretically, the $\Delta\Delta\delta$ is a complex function of solvating agent and analyte structures, temperature, concentrations of CSA and analyte, etc., so the variation of $\Delta\Delta\delta$ is hard to predict. However, the experimental results demonstrate that the discrimination ability of **1** and **2** can be increased by increasing the concentration and molar ratio of CSA to analyte, using a less polar solvent and by lowering the temperature.

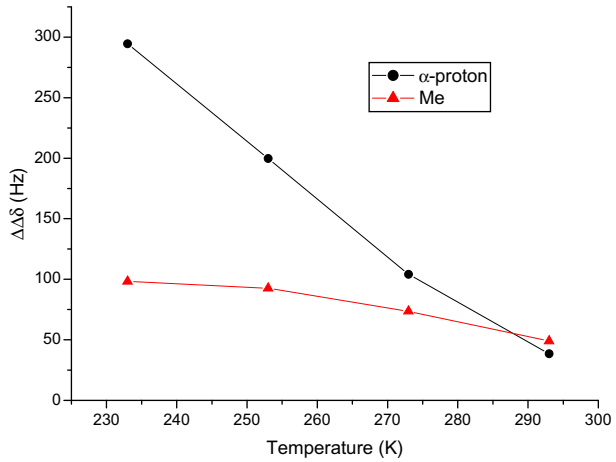


Figure 8. Temperature variation of ΔΔδ for **26** in the presence of CSA **1**.

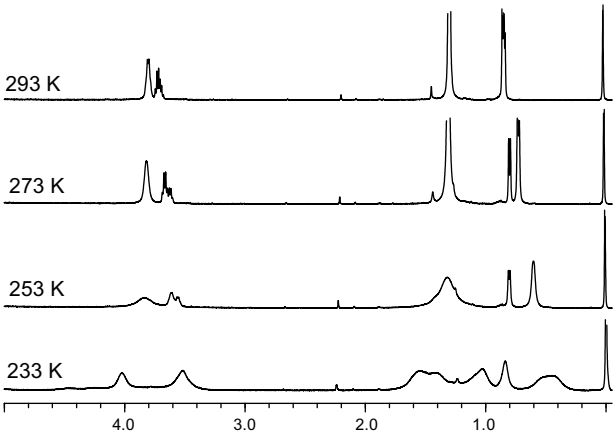


Figure 9. Temperature variation of ΔΔδ for **29** in the presence of CSA **1**.

3. Conclusion

In conclusion, the macrocyclic compounds **1** and **2** have been synthesized conveniently and effectively, and have been proved to be effective chiral solvating agents for the determination of the enantiomeric excess of α-chiral carboxylic acids by ^{1}H NMR spectroscopy.

4. Experimental

4.1. General

IR spectra were obtained on a Nicolet 360 Avatar IR spectrometer as KBr pellets. NMR spectra were recorded on Avance 500 Bruker spectrometer at 500 MHz for ^{1}H, 125 MHz for ^{13}C. Mass spectra were recorded on Trace MS 2000-Mass Spectrometer using the EI technique. HRMS was recorded on Micromass GCT–MS using the EI technique. Elemental analysis was performed on Vario E1 elemental analyzer. Optical rotations were measured with a Perkin–Elmer Model 343 polarimeter using the sodium D line at 589 nm.

Aminonaphthols **13**–**15**[9] and macrocyclic compound **1**–**2**[7e,9a] were prepared according to our previously reported methods.

4.2. General procedures for synthesis of macrocyclic compounds 1–8

A mixture of (3 mmol) aminonaphthol, halogenoalkane (3 mmol), and 4.14 g (30 mmol) K_2CO_3 in 60 mL dry DMF was stirred at room temperature for 36 h. Then it was poured into 150 mL water and extracted with toluene (20 mL × 3), washed with water (20 mL) and brine (20 mL). The organic phase was dried with Na_2SO_4, filtrated, concentrated, and purified by flash chromatography.

4.2.1. (12*S*,18*S*)-*N*12,*N*18-Bis[(1*S*)-1-phenylethyl]-{2*H*,8*H*,12*H*,18*H*-(3,7),(13,17)-dimetheno-dinaphtho[2,1-*j*:1′,2′-*s*][1,9]-dioxacycloeicosin-12,18-diamine} (*S*,*S*,*S*,*S*)-3

Mp 172–174 °C. $[\alpha]_D^{20} = +19.6$ (*c* 0.23, THF). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ: 1.03 (d, *J* = 5.9 Hz, 6H), 2.88 (s, 2H), 3.57 (q, *J* = 6.2 Hz, 4H), 5.09 (d, *J* = 12.0 Hz, 2H), 5.20 (d, *J* = 12.1 Hz, 2H), 5.38 (s, 1H), 6.63 (s, 1H), 6.95–7.06 (m, 4H), 7.08–7.10 (m, 5H), 7.13–7.16 (m, 4H), 7.28 (d, *J* = 9.0 Hz, 2H), 7.35–7.39 (m, 7H), 7.56 (s, 1H), 7.60 (s, 2H), 7.86–7.89 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ: 25.7, 55.5, 55.7, 69.7, 114.3, 123.0, 123.5, 123.8, 125.9, 126.3, 126.5, 126.6, 127.0, 127.2, 128.0, 128.1, 128.5, 128.8, 128.9, 134.6, 137.8, 144.8, 146.5, 154.1. IR (KBr): 3449, 3056, 3024, 1622, 1594, 1513, 1251, 1219 cm^{-1}; MS (EI): 730 (M^+); EA for $C_{52}H_{46}N_2O_2$: Calcd C, 85.45; H, 6.34; N, 3.83. Found: C, 85.56; H, 6.38; N, 3.90. Crystallographic data have been deposited at the Cambridge Crystallographic Data Center (CCDC) under accession number 614 540.

4.2.2. (12*S*,18*S*)-*N*12,*N*18-Dimethyl-*N*12,*N*18-bis[(1*S*)-1-phenylethyl]-{2*H*,8*H*,12*H*,18*H*-13,17-metheno-3,7-nitrilo-dinaphtho[2,1-*j*:1′,2′-*s*][1,9]dioxacycloeicosin-12,18-diamine}(*S*,*S*,*S*,*S*)-4

Mp 164–166 °C. $[\alpha]_D^{20} = +349.0$ (*c* 0.67, THF). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ: 1.14 (d, *J* = 5.7 Hz, 6H), 1.90 (s, 6H), 3.96 (q, *J* = 6.4 Hz, 2H), 5.31 (d, *J* = 10.1 Hz, 2H), 5.36 (d, *J* = 10.1 Hz, 2H), 6.11 (s, 2H), 7.10 (t, *J* = 7.7 Hz, 2H), 7.18 t, *J* = 7.1 Hz, 2H), 7.27 (t, *J* = 7.3 Hz, 4H), 7.31–7.38 (m, 6H), 7.42 (t, *J* = 10.9 Hz, 2H), 7.50 (t, *J* = 7.1 Hz, 2H), 7.74 (d, *J* = 8.5 Hz, 2H), 7.80 (d, *J* = 7.2 Hz, 2H), 7.89 (t, *J* = 7.6 Hz, 2H), 8.48 (s, 1H), 9.77 (d, *J* = 8.63 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ: 33.3, 33.6, 55.9, 64.4, 72.7, 114.1, 115.3, 122.3, 123.7, 124.9, 125.7, 126.0, 126.4, 127.2, 127.6, 127.8, 128.1, 128.2, 128.9, 130.2, 131.9, 133.2, 137.2, 143.4, 153.9, 156.4. IR (KBr): 3444, 3055, 1622, 1595, 1508, 1264, 1240 cm^{-1}; HRMS (EI): for $C_{53}H_{49}N_3O_2$ calcd 759.3825, found 759.3834 (M^+); EA for $C_{53}H_{49}N_3O_2$: Calcd C, 83.76; H, 6.50; N, 5.53. Found: C, 83.40; H, 6.74; N, 5.18.

4.2.3. (9*S*,15*S*)-*N*9,*N*15-Bis[(1*S*)-1-phenylethyl]-{2*H*,5*H*,9*H*,15*H*-10,14-metheno-benzo[*c*]-dinaphtho[2,1-*g*:1′,2′-*p*][1,5]-dioxacycloheptadecin-9,15-diamine} (*S*,*S*,*S*,*S*)-5

Mp 183–186 °C. $[\alpha]_D^{20} = -2.1$ (*c* 0.63, THF). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ: 1.22 (d, *J* = 5.9 Hz, 6H), 3.60 (q, *J* = 6.4 Hz, 2H), 4.93 (br, 2H), 5.04 (br, 2H), 5.57 (br, 2H), 6.95 (t, *J* = 7.0 Hz, 1H), 7.08 (d, *J* = 6.8 Hz, 4H), 7.23–7.24 (m, 6H), 7.34–7.36 (m, 8H), 7.41 (d, *J* = 8.9 Hz, 2H), 7.63 (s, 1H), 7.78 (d, *J* = 7.7 Hz, 4H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ: 25.1, 55.7, 56.4, 69.9, 115.9, 123.7, 125.3, 125.9, 126.6, 127.1, 127.5, 128.2, 128.4, 128.7, 129.1, 130.3, 133.7, 135.3, 144.2, 146.0, 154.7. IR (KBr): 3450, 3059, 3025, 1620, 1592, 1510, 1266, 1231, 1208 cm^{-1}; HRMS (EI): for $C_{52}H_{46}N_2O_2$ calcd 730.3559, found 730.3569 (M^+); EA for $C_{52}H_{46}N_2O_2$: Calcd C, 85.45; H, 6.34; N, 3.83. Found: C, 85.55; H, 5.92; N, 3.67.

4.2.4. (11*S*,17*S*)-*N*11,*N*17-Bis[(1*S*)-1-phenylethyl]-{2*H*,7*H*,11*H*,17*H*-12,16-metheno-dibenzo[*c*:*e*]-dinaphtho[2,1-*i*:1′,2′-*r*][1,8]dioxacyclononadecin-11,17-diamine} (*S*,*S*,*S*,*S*)-6

Mp 148–150 °C. $[\alpha]_D^{20} = -62.4$ (*c* 0.90, THF). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ: 1.11 (d, *J* = 6.4 Hz, 6H), 2.79 (s, 2H), 3.60 (q, *J* = 6.2 Hz, 2H), 4.13 (d, *J* = 13.0 Hz, 2H), 4.69 (d, *J* = 13.0 Hz, 2H), 5.31 (s, 2H), 6.68 (t, *J* = 7.3 Hz, 1H), 6.96 (d, *J* = 6.7 Hz, 2H), 7.07

(d, J = 7.2 Hz, 4H), 7.10–7.13 (m, 6H), 7.15 (d, J = 7.0 Hz, 2H), 7.19 (d, J = 8.9 Hz, 2H), 7.43–7.32 (m, 7H), 7.47 (t, J = 7.5 Hz, 2H), 7.58 (d, J = 8.5 Hz, 2H), 7.64 (d, J = 7.5 Hz, 2H), 7.80 (d, J = 8.9 Hz, 2H), 7.85 (d, J = 7.9 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ: 25.9, 55.1, 55.5, 70.3, 117.4, 123.2, 123.9, 124.0, 124.9, 126.5, 126.6, 126.9, 127.2, 127.4, 128.0, 128.1, 128.4, 129.0, 129.1, 129.3, 134.4, 135.4, 137.9, 144.7, 146.4, 155.4. IR (KBr): 3448, 3059, 3024, 1622, 1595, 1512, 1252, 1222 cm^{-1}; HRMS (EI): for $C_{58}H_{50}N_2O_2$ calcd 806.3872, found 806.3883 (M^+); EA for $C_{58}H_{50}N_2O_2$: Calcd C, 86.32; H, 6.24; N, 3.47. Found: C, 85.99; H, 6.40; N, 3.16.

4.2.5. (12*S*,17*S*)-*N*12,*N*17-Bis[(1*S*)-1-phenylethyl]-{2*H*,8*H*,12*H*,17*H*-3,7-nitrilo-13,16-etheno-dinaphtho[2,1-*j*:1′,2′-*r*][1,9] dioxacyclonondecin-12,17-diamine} (*S*,*S*,*S*,*S*)-7

Mp 297–298 °C. $[\alpha]_D^{20} = +247.7$ (c 0.26, THF). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ: 1.26 (d, J = 6.3 Hz, 6H), 3.08 (br, 2H), 3.59 (q, J = 6.4 Hz, 2H), 4.96 (br, 2H), 5.19 (br, 2H), 5.27 (br, 2H), 6.08 (br, 1H), 7.28–7.02 (m, 12H), 7.47–7.34 (m, 5H), 7.53 (br, 2H), 7.61 (br, 2H), 7.89 (d, J = 7.8 Hz, 2H), 7.94 (d, J = 8.3 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ: 26.0, 55.0, 55.6, 72.7, 116.8, 121.8, 123.3, 124.1, 125.5, 126.6, 126.7, 127.2, 128.1, 128.4, 129.0, 129.4, 134.6, 136.6, 142.0, 146.4, 155.4. IR (KBr): 3440, 3062, 3023, 1621, 1593, 1509, 1253, 1213 cm^{-1}; HRMS (EI): for $C_{51}H_{45}N_3O_2$ calcd 731.3512, found 731.3520 (M^+); EA for $C_{51}H_{45}N_3O_2$: Calcd C, 83.69; H, 6.20; N, 5.74. Found: C, 83.12; H, 6.27; N, 5.70. Crystallographic data have been deposited at the Cambridge Crystallographic Data Center (CCDC) under accession number 617 797.

4.2.6. (12*S*,17*S*)-*N*12,*N*17-Bis[(1S)-1-phenylethyl]-{2*H*,8*H*,12*H*,17*H*-3,7-metheno-13,16-etheno-dinaphtho[2,1-*j*:1′,2′-*r*] [1,9]dioxacyclonondecin-12,17-diamine} (*S*,*S*,*S*,*S*)-8

Mp 176–178 °C. $[\alpha]_D^{20} = -62.2$ (c 0.36, THF). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ: 1.15 (d, J = 6.4 Hz, 6H), 3.58 (q, J = 6.29 Hz, 2H), 4.96 (d, J = 11.7 Hz, 2H), 5.27 (d, J = 11.7 Hz, 2H), 5.57 (s, 2H), 5.74 (s, 1H), 6.76 (br, 2H), 7.28–7.20 (m, 8H), 7.36–7.29 (m, 7H), 7.38 (d, J = 7.6 Hz, 2H), 7.42 (d, J = 9.2 Hz, 2H), 7.57 (d, J = 8.7 Hz, 2H), 7.87 (d, J = 8.6 Hz, 4H), 7.92 (br, 2H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ: 26.1, 54.9, 55.6, 70.6, 115.0, 123.1, 123.7, 126.3, 126.5, 126.7, 126.8, 127.3, 127.8, 128.2, 128.4, 128.8, 128.9, 134.3, 137.3, 142.5, 146.5, 154.2. IR (KBr): 3441, 3056, 3025, 1622, 1593, 1513, 1252, 1224 cm^{-1}; HRMS (EI): for $C_{52}H_{46}N_2O_2$ calcd 730.3559, found 730.3567 (M^+); EA for $C_{52}H_{46}N_2O_2$: Calcd C, 85.45; H, 6.34; N, 3.83. Found: C, 85.14; H, 6.38; N, 3.72.

4.3. Synthesis of acyclic compound 9

A mixture of (0.628 g, 1 mmol) aminonaphthol **14a**, 2-chloromethylpyridine hydrochloride **20** (0.489 g, 3 mmol) and K_2CO_3 (1.38 g 10 mmol) in 20 mL dry DMF was stirred at room temperature for 8 h. Then it was poured into 60 mL water and extracted with toluene (20 mL × 3), and washed with water (20 mL) and brine (20 mL). The organic phase was dried over Na_2SO_4, filtrated, concentrated and purified by flash chromatography (acetone–petroleum ether = 1: 4) (0.74 g, 91.4% yield).

4.3.1. (1*S*,1′*S*)-*N*,*N*′-((1*S*,1′*S*)-1,3-Phenylenebis((2-(pyridin-2-ylmethoxy)naphthalen-1-yl)methylene))bis(1-phenylethanamine) (*S*,*S*,*S*,*S*)-9

Mp 161–162 °C. $[\alpha]_D^{20} = -54.1$ (c 0.61, THF). ^{1}H NMR (500 MHz, $CDCl_3$/CF_3COOD-10%, ppm): δ: 1.65 (d, J = 6.8 Hz, 6H), 4.15 (q, J = 6.6 Hz, 2H), 5.20 (d, J = 15.5 Hz, 2H), 5.47 (d, J = 15.5 Hz, 2H), 5.87 (s, 2H), 6.77–6.70 (m, 2H), 6.79 (d, J = 7.5 Hz, 4H), 7.01 (t, J = 7.5 Hz, 2H), 7.18–7.08 (m, 6H), 7.27–7.30 (m, 2H), 7.42 (t, J = 7.7 Hz, 2H), 7.44 (d, J = 7.2 Hz, 1H), 7.62 (d, J = 7.7 Hz, 2H), 7.87 (d, J = 8.2 Hz, 2H), 7.95 (t, J = 8.0 Hz, 2H), 7.96 (d, J = 3.7 Hz, 1H), 8.34 (t, J = 7.9 Hz, 2H), 8.80 (d, J = 5.6 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$/CF_3COOD-10%, ppm) δ: 20.2, 56.5, 59.2, 67.1, 113.5, 114.9, 120.5, 125.4, 125.5, 126.9, 127.5, 128.9, 129.4, 129.4, 130.1, 130.4, 131.3, 132.9, 133.9, 136.4, 141.8, 147.5, 150.3, 153.3. IR (KBr): 3441, 3059, 3025, 1623, 1593, 1513, 1263, 1245 cm^{-1}; MS (EI): 810 (M^+); EA for $C_{56}H_{50}N_4O_2$: Calcd C, 82.93; H, 6.21; N, 6.91. Found: C, 83.16; H, 6.56; N, 6.10.

4.4. Determination of the stoichiometry by ^{1}H NMR titrations (job plots)

The CSAs **1** and **2**, (*R*)- and (*S*)-mandelic acid were separately dissolved in $CDCl_3$ with a concentration of 10 mM. These solutions were distributed among 10 NMR tubes, with various amounts of CSA **1** or **2** and acid [(*R*)- or (*S*)-mandelic acid], so that the total concentration of CSA and acid was 10 mM, and the molar ratio of the CSA to the acid in the 10 tubes was 0, 0.25, 0.33, 0.43, 0.50, 0.67, 1.00, 1.50, 2.33, 4.00. The ^{1}H NMR spectrum of each sample was recorded on a 500 MHz spectrometer. All recorded Job plots were found to exhibit maxima at 0.67. This indicates that **1** and **2** form 1:2 complexes with the mandelic acids.

4.5. Study of the discrimination ability of CSAs 1–2 towards various acids 21–40

The CSAs **1** and **2**, and the acids were separately dissolved in $CDCl_3$ with a concentration of 20 mM. Then, 0.25 mL of **1** or **2** and 0.25 mL acid were added to NMR tubes, so that the total volume was 0.5 mL and concentration of CSA and acid was 10 mM. For some less soluble acids, such as **31**–**40**, 1 equiv a CSA and 1 equiv of acid were mixed, to which $CDCl_3$ was added, and the concentration was adjusted to 10 mM. The ^{1}H NMR spectrum of each sample was recorded on a 500 MHz spectrometer.

4.6. Determination of enantiomeric purity of mandelic acid

Five samples containing mandelic acid with 10%, 30%, 50%, 70%, and 95% ee, respectively (all samples were prepared by adding 0.2 equiv (not exactly) of CSA **1** or **2** in the solutions of mandelic acid (final concentration was 10 mM in $CDCl_3$), 3% volume of MeOD was added to eliminate the broad signal of active protons) were prepared and their spectra were recorded on a 500 MHz spectrometer. The results were calculated based on the integrations of the NMR signals of α-H of mandelic acid isomers.

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10. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 614 539 for **1**, 652 314 for **2**, 614 540 for **3**, 617 797 for **7**. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223–336033 or e-mail:deposit@ccdc.cam.ac.uk].
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