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Enantiomeric discrimination of α-hydroxy acids and *N*-Ts-α-amino acids by ^{1}H NMR spectroscopy

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ABSTRACT

A new kind of chiral compounds with multiple amino, amido and phenolic hydroxy groups has been synthesized from D-phenylalanine and D-phenylglycine, respectively. The enantiomeric discriminations of α-hydroxy acids and *N*-Ts-α-amino acids have been finished in the presence of the above chiral compounds as chiral solvating agents by ^{1}H NMR spectroscopy. The results show that the chiral compounds are highly effective and practical chiral solvating agents towards α-hydroxy acids and *N*-Ts-α-amino acids.

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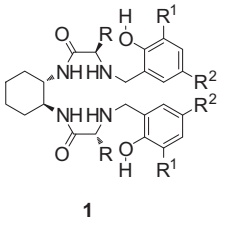
Determination of enantiomers, assignment of absolute configuration and analysis of enantiomeric excess are significant, indispensable and basic data to a chiral compound in biology, pharmaceutical chemistry and asymmetric catalysis.[1] Therefore, many methods and techniques, such as HPLC,[2] NMR,[3] UV/Vis[4] and fluorescence spectroscopy,[5] have been developed to meet these demands. Among them, NMR technology has some distinctive advantages and features, such as less sampling amount, less environmental pollution, convenient procedure and high accuracy.[6] Thus, various chiral shift reagents (CSRs) and chiral solvating agents (CSAs), such as lanthanide complexes,[7] cyclodextrins,[8] crown ethers,[9] porphyrins,[10] calixarenes[11] and others,[12] have been designed and utilized for this purpose by NMR spectroscopy. In recent decades, design and synthesis of more effective chiral auxiliaries with the unique architecture have fascinated many chemists for chiral molecular recognition by ^{1}H NMR spectroscopy.[13] Herein, we report the highly facile and effective synthesis for chiral compounds **1a**–**1h** with multiple amino, amide and phenolic hydroxyl groups as chiral solvating agents to discriminate enantiomers of α-hydroxy acids and *N*-Ts-α-amino acids by ^{1}H NMR spectroscopy.

Chiral compounds **1a**–**1h** with multiple binding sites have been synthesized from (1*S*,2*S*)-(+)-1,2-diaminocyclohexane and D-phenylalanine or D-phenylglycine as chiral sources for enantiomeric discrimination towards α-hydroxy acids and *N*-Ts-α-amino acids. Their chemical structures are shown in Figure 1.



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1a: R = Bn, R^1 = H, R^2 = H
1b: R = Bn, R^1 = H, R^2 = Cl
1c: R = Bn, R^1 = Br, R^2 = Br
1d: R = Bn, R^1 = H, R^2 = OCH_3
1e: R = Ph, R^1 = H, R^2 = H
1f: R = Ph, R^1 = H, R^2 = Cl
1g: R = Ph, R^1 = H, R^2 = Br
1h: R = Ph, R^1 = H, R^2 = OCH_3

Figure 1. Chemical structures of chiral compounds **1a**–**1h**.

As shown in Figure 1, molecular structures of **1a**–**1h** contain some polar functional groups, such as amino, amide and phenolic hydroxyl groups, which can easily form hydrogen-bonding interaction with some matched guests. These structural features of **1a**–**1h** will be helpful to improve capability to discriminate enantiomers of α-hydroxy acids and *N*-Ts-α-amino acids by ^{1}H NMR spectroscopy.

N-Boc-protected D-phenylalanine and D-phenylglycine were prepared based on the reported literature.[14] The coupling reaction of **3** with (1*S*,2*S*)-(+)-1,2-diaminocyclohexane was carried out in the presence of *N*,*N*′-dicyclohexylcarbodiimide (DCC) at ice-salt bath under nitrogen atmosphere. The crude products were purified by column chromatography on silica gel to afford pure compounds **4a** and **4b** (**4a**: R = Bn, **4b**: R = Ph) in 68% and 70% yields, respectively. Chiral diamines **5a** and **5b** (**5a**: R = Bn, **5b**: R = Ph) were obtained by deprotection of *N*-Boc-protected diamide **4** in trifluoroacetic acid (TFA).[15] The crude product was used in the next step without further purification (Scheme 1).

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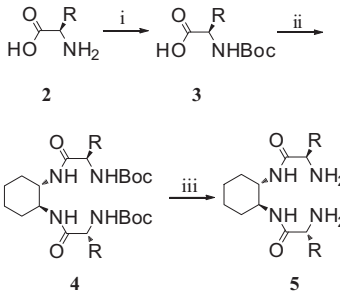
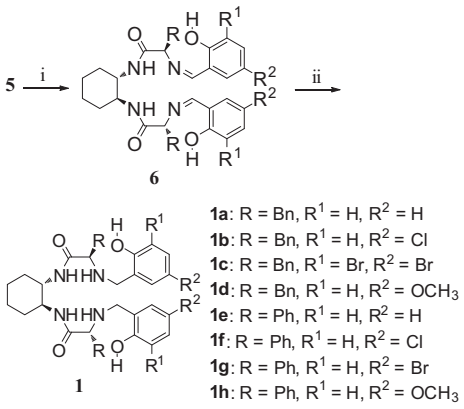


Scheme 1. Synthesis of chiral compounds **4** and **5**. Reagents and conditions: (i) $(Boc)_2O$, NaOH (1 M), isopropanol; (ii) (1*S*,2*S*)-(+)-1,2-diamino-cyclohexane, DCC, EtOAc, ice-salt bath to rt, N_2; (iii) TFA, CH_2Cl_2, N_2.



Scheme 2. Synthesis of chiral compounds **1a**–**1h**. Reagents and conditions: (i) salicylaldehyde or its derivatives, MeOH, reflux, N_2; (ii) $NaBH_4$, MeOH/PhMe.

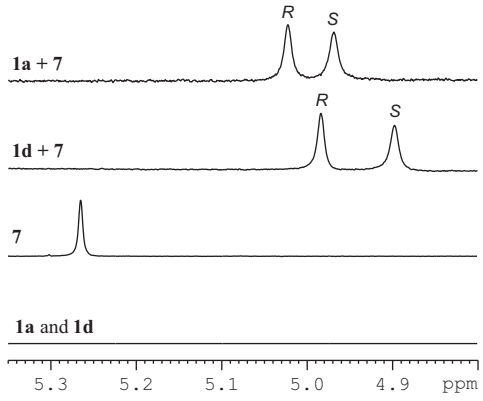


Figure 2. Overlaid ^1H NMR spectra of free **1a** and **1d**, free (±)-**7**, (±)-**7** with **1a** and **1d**, respectively.

Condensation reactions of **5** with salicylaldehyde and its derivatives were performed to afford chiral diimines **6a**–**6h**, respectively.[15] Chiral compounds **1a**–**1h** were obtained by reductive reaction in the presence of $NaBH_4$.[16] They were purified by column chromatography on silica gel to afford **1a**–**1h** in 55–75% isolated yields (Scheme 2).

To explore enantiomeric discriminating capability of **1a**–**1h** as CSAs towards α-hydroxy acids and *N*-Ts-α-amino acids by ^1H NMR spectroscopy, (±)-mandelic acid **7** was first used as a guest in the presence of **1a** and **1d**, respectively. Their ^1H NMR spectra show that the single peak of α-H of (±)-**7** was split into two equal-intensity peaks with well-resolved signals. The nonequivalent chemical shifts ($\Delta\Delta\delta$) of α-H of (±)-**7** were given to be 0.0540 and 0.0862 ppm, respectively. Then, the assignments of

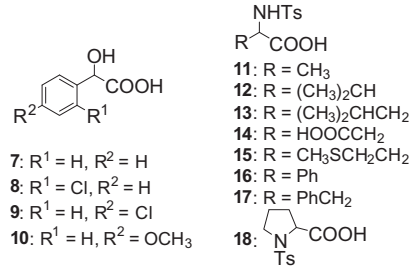


Figure 3. Structures of α-hydroxy acids and *N*-Ts-α-amino acids.

(*R*)- and (*S*)-enantiomers of (±)-**7** were clearly determined by integral change of α-H signals of (*S*)-enantiomer when (*S*)-**7** was added to 1:1 mixture of (±)-**7** with **1a** and **1d**, respectively. Their overlaid ^1H NMR spectra are shown in Figure 2.

Based on the above results, in order to further examine enantiomeric discriminating capability of **1a**–**1h** as CSAs, the following α-hydroxy acids and *N*-Ts-α-amino acids were used as guests. Their chemical structures are shown in Figure 3.

First, ^1H NMR spectra of α-hydroxy acids (±)-**7**–**10** were recorded in the presence of **1a**–**1h** as CSAs, respectively. Among them, enantiomers of most guests can be discriminated by **1a**–**1h** as CSAs. The nonequivalent chemical shifts ($\Delta\Delta\delta$) of α-H of (±)-**7**–**10** and protons of OCH_3 group of (±)-**10** were observed except (±)-**7**, (±)-**9** and (±)-**10** in the presence of **1b**, (±)-**8** and (±)-**9** in the presence of **1c** and **1f** and (±)-**9** in the presence of **1d** and **1e**, respectively. After (*S*)- or (*R*)-enantiomer of (±)-**7**–**10** was added to the above 1:1 mixture of the discriminated guest with the corresponding CSA, respectively, their ^1H NMR spectra were recorded again at the same condition. The assignment of the (*S*)- and (*R*)-enantiomers was determined by the integral change of the corresponding proton signals. Their chemical shift nonequivalences ($\Delta\Delta\delta$, ppm) are summarized in Table 1.

To further explore enantiomeric discriminating capability of **1a**–**1h** as CSAs, ^1H NMR spectra of *N*-Ts-α-amino acids (±)-**11**–**18** were measured in the presence of **1a**–**1h**, respectively. The nonequivalent chemical shifts of the two enantiomers of most guests can be obviously observed by ^1H NMR signals by their corresponding protons. After adding the (*S*)- or (*R*)-enantiomer of (±)-**11**–**18** to the 1:1 mixture of the discriminated enantiomers with **1a**–**1h**, respectively, their ^1H NMR spectra were measured again under the same condition. The assignment of most (*S*)- and (*R*)-enantiomers was clearly determined by change of integration of the signals of the corresponding proton. These discriminating results indicate that **1a**–**1h** are effective chiral solvating agents towards the above guests. The chemical shift nonequivalences ($\Delta\Delta\delta$, ppm) are shown in Table 2.

A highly effective chiral solvating agent can not only discriminate a pair of enantiomers, but also have its practicalities in some ways, for example, determination of enantiomeric excess (ee%) of a chiral compound. Herein, to examine the practical applicability of CSAs **1a**–**1h**, all the samples of **7** with 90%, 70%, 50%, 30%, 10%, 0%, −10%, −30%, −50%, −70% and −90% ee were prepared in the presence of **1a** for evaluating their enantiomeric excesses by ^1H NMR spectroscopy. ^1H NMR spectra of all samples were recorded and their enantiomeric excesses were calculated based on the integration of ^1H NMR signals of α-H of (*R*)-**7** and (*S*)-**7**. The results are shown in Figure 4.

The above results indicate that the enantiomeric excesses of **7** with different optical compositions were determined in high accuracy in the presence of **1a** by ^1H NMR spectroscopy ($y = 0.9996x - 0.1440$, correction coefficient = 0.9999). The linear correction between the theoretical (x) and observed ee % (y) is shown in Figure 5.

Table 1
Measurements of chemical shift nonequivalences ($\Delta\Delta\delta$, ppm) of guests (±)-**7**–**10** (10×10^{-3} M) in the presence of **1a**–**1h** (10×10^{-3} M) as CSAs by ^{1}H NMR spectroscopy (400 MHz) in $CDCl_3$ at room temperature, respectively[a]

Entry	CSA	Guest	Proton	$\Delta\Delta\delta$[b]	Entry	CSA	Guest	Proton	$\Delta\Delta\delta$[b]
1	**1a**	**7**	α-H	0.0540	13	**1h**	**8**	α-H	0.0670
2	**1c**	**7**	α-H	0.0056[c]	14	**1a**	**9**	α-H	0.0163
3	**1d**	**7**	α-H	0.0862	15	**1g**	**9**	α-H	0.0191[c]
4	**1e**	**7**	α-H	0.0297	16	**1h**	**9**	α-H	0.0149
5	**1f**	**7**	α-H	0.0139	17	**1a**	**10**	α-H	0.0476
6	**1g**	**7**	α-H	0.0132[c]	18	**1c**	**10**	OCH_3	0.0075
7	**1h**	**7**	α-H	0.0488	19	**1d**	**10**	α-H	0.0721
8	**1a**	**8**	α-H	0.0526	20	**1e**	**10**	α-H	0.0242
9	**1b**	**8**	α-H	0.0299	21	**1f**	**10**	OCH_3	0.0037
10	**1d**	**8**	α-H	0.0796	22	**1g**	**10**	α-H	0.0089[c]
11	**1e**	**8**	α-H	0.0482	23	**1h**	**10**	OCH_3	0.0139
12	**1g**	**8**	α-H	0.0191[c]				α-H	0.0459

[a] $\Delta\Delta\delta = \Delta\delta_R - \Delta\delta_S$; $\Delta\delta_R = \delta_R - \delta_{free}$; $\Delta\delta_S = \delta_S - \delta_{free}$.
[b] $\Delta\Delta\delta$ of the corresponding protons of guests (H:G = 1:1).
[c] Guest (5×10^{-3} M), host (5×10^{-3} M) $CHCl_3/CD_3OD$ (5%).

Table 2
Measurements of chemical shift nonequivalences ($\Delta\Delta\delta$, ppm) of guests (±)-**11**–**18** (10×10^{-3} M) in the presence of **1a**–**1h** (10×10^{-3} M) as CSAs by ^{1}H NMR spectroscopy (400 MHz) in $CDCl_3$ at room temperature[a]

Entry	CSA	Guest	Proton	$\Delta\Delta\delta$[b]	Entry	CSA	Guest	Proton	$\Delta\Delta\delta$[b]
1	**1a**	**11**	PhCH_3	0.0079				PhCH_3	0.0082[d]
2	**1e**	**11**	CH_3	0.0456	20	**1d**	**15**	SCH_3	0.0191
3	**1f**	**11**	CH_3	0.0303				PhCH_3	0.0162[d]
			PhCH_3	0.0074	21	**1e**	**15**	SCH_3	0.0316
4	**1g**	**11**	CH_3	0.0117[c]	22	**1f**	**15**	SCH_3	0.0271
5	**1h**	**11**	CH_3	0.0357	23	**1a**	**16**	α-H	0.0521
			PhCH_3	0.0073	24	**1b**	**16**	PhCH_3	0.0075
6	**1a**	**12**	PhCH_3	0.0170[d]				α-H	0.0067
7	**1b**	**12**	PhCH_3	0.0134[d]	25	**1c**	**16**	PhCH_3	0.0071
8	**1d**	**12**	CH_3	0.0569				α-H	0.0283
			PhCH_3	0.0076	26	**1d**	**16**	α-H	0.0195
			Ts*NH*	0.1480	27	**1e**	**16**	PhCH_3	0.0161
9	**1f**	**12**	CH_3	0.0180[d]				α-H	0.0870
			CH_3	0.0284	28	**1f**	**16**	PhCH_3	0.0248
10	**1c**	**13**	PhCH_3	0.0052				α-H	0.1261
11	**1d**	**13**	CH_3	0.0421	29	**1g**	**16**	PhCH_3	0.0165
			CH_3	00285				α-H	0.0497
			PhCH_3	0.0102[d]	30	**1h**	**16**	PhCH_3	0.0253
12	**1e**	**13**	CH_3	0.0167				α-H	0.1231
			CH_3	0.0103	31	**1a**	**17**	PhCH_3	0.0071
13	**1f**	**13**	CH_3	0.0074	32	**1d**	**17**	PhCH_3	0.0172
			CH_3	0.0172	33	**1e**	**17**	PhCH_3	0.0107
14	**1g**	**13**	CH_3	0.0061	34	**1f**	**17**	PhCH_3	0.0150
15	**1h**	**13**	CH_3	0.0168				α-H	0.1194
			CH_3	0.0157	35	**1g**	**17**	PhCH_3	0.0095
16	**1d**	**14**	PhCH_3	0.0225[c]				α-H	0.1164
17	**1a**	**15**	SCH_3	0.0154	36	**1a**	**18**	PhCH_3	0.0026
			PhCH_3	0.0152[d]				α-H	0.0292
18	**1b**	**15**	SCH_3	0.0195	37	**1b**	**18**	α-H	0.0216
			PhCH_3	0.0052	38	**1d**	**18**	PhCH_3	0.0075
19	**1c**	**15**	SCH_3	0.0126	39	**1f**	**18**	α-H	0.0411

[a] $\Delta\Delta\delta = \Delta\delta_R - \Delta\delta_S$; $\Delta\delta_R = \delta_R - \delta_{free}$; $\Delta\delta_S = \delta_S - \delta_{free}$.
[b] $\Delta\Delta\delta$ of the corresponding protons of guests (H:G = 1:1).
[c] Guest (5×10^{-3} M), host (5×10^{-3} M) $CHCl_3/CD_3OD$ (5%).
[d] Nonequivalent chemical shifts were given by adding (*S*)-enantiomer to the mixture of (±)-guest and host.

To study effect of concentration in the process of enantiomeric discrimination, ^{1}H NMR spectra of (±)-**7** at various concentrations were recorded in the presence of **1a**. As the concentration increases, nonequivalent chemical shifts of α-H of (±)-**7** were found to be increasing until a maximum value ($\Delta\Delta\delta$, 25.44 Hz) was observed at 30 mM. Then, nonequivalent chemical shifts of α-H of (±)-**7** were observed to trend downward gradually. Based on general requirement for concentration in ^{1}H NMR spectroscopy and slight change of nonequivalent chemical shifts of α-H of (±)-**7** between concentration of 10 and 30 mM, concentration of 10 mM was used for the enantiomeric discrimination. The overlaid ^{1}H NMR spectra of various concentrations of (±)-**7** in the presence of **1a** are shown in Figure 6.

In order to investigate solvent effect on enantiomeric discrimination, ^{1}H NMR spectra of (±)-**7** were measured in the presence of **1a** in different deuterated solvents, such as free $CDCl_3$, $CDCl_3$ containing 10% benzene-d_6, acetone-d_6, methanol-d_4 and DMSO-d_6, respectively. The results indicate that deuterated solvents with strong polar functional group may participate more actively in the process of enantiomeric discrimination so as to result in weakening or losing of discriminating capability of **1a**. Obviously, chloroform-*d* is more suitable for the enantiomeric discrimination by ^{1}H NMR spectroscopy. The detailed results are shown in Table 3.

Moreover, upon addition of CSA **1a**, nonequivalent chemical shifts ($\Delta\Delta\delta$) of α-H of (±)-**7** were found to be increasing gradually from 12.32 to 21.96 Hz. But, with the continued addition of **1a**,

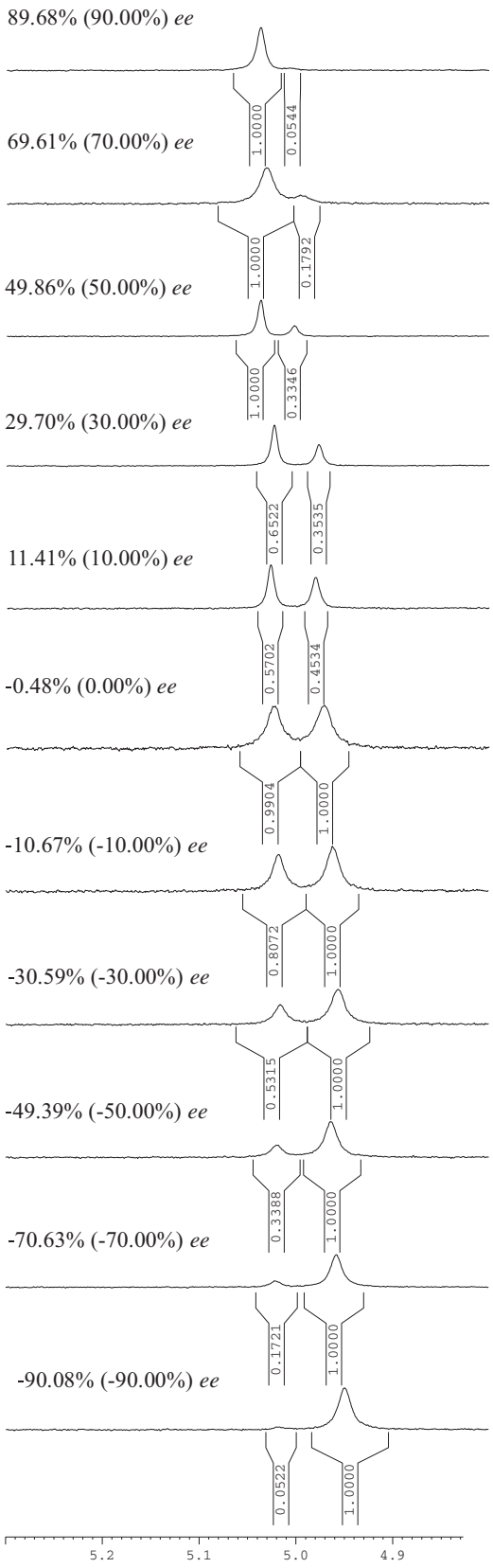


Figure 4. Determination of enantiomeric excesses of **7** (ee% = *R*% − *S*%), the *R* and *S* stand for α-H of enantiomers of (±)-**7** in the presence of equal amounts of **1a**.

nonequivalent chemical shifts of α-H of (±)-**7** were given a small change (2.56 Hz) from 1:1 (19.40 Hz) to 3:1 (21.96 Hz) molar ratio of **1a** with (±)-**7**. The 1:1 molar ratio of host with guest was used

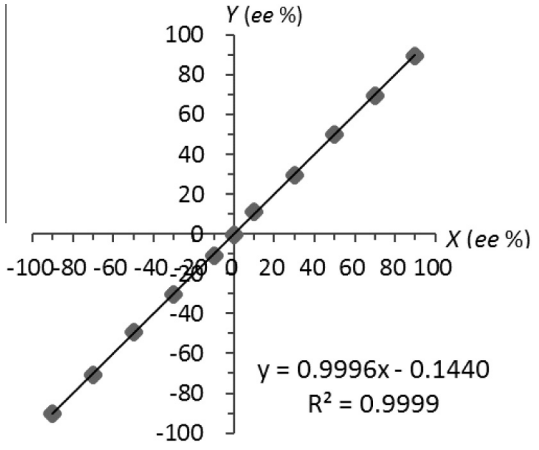


Figure 5. Linear correlation between theoretical ee values (*X*) and observed ee values (*Y*) of **7** in the presence of equal amounts of **1a**.

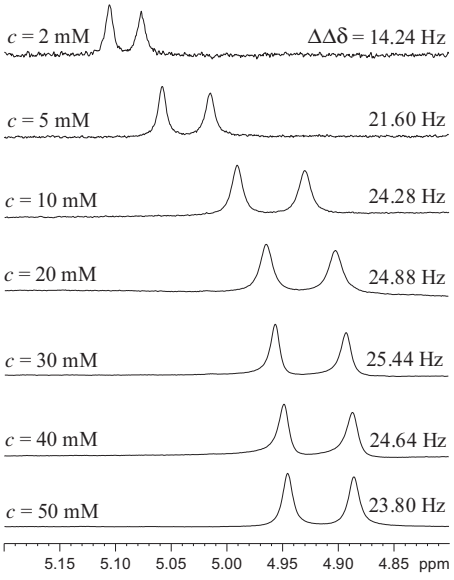


Figure 6. Overlaid ^{1}H NMR spectra of various concentrations of (±)-**7** in the presence of **1a**. The mole ratio of **1a** and (±)-**7** is 1:1, unchangeable.

Table 3
Measurements of chemical shift nonequivalences (ΔΔδ, Hz) of α-H of (±)-**7** in the presence of **1a** by ^{1}H NMR spectroscopy in different deuterated solvents at room temperature[a]

Entry	Solvent	ΔΔδ (Hz)
1	$CDCl_3$	21.60
2	$CDCl_3/C_6D_6$ (10%)	20.28
3	$CDCl_3/CD_3COCD_3$ (10%)	6.68
4	$CDCl_3/CD_3OD$ (10%)	0.00
5	$CDCl_3$/DMSO-d_6 (10%)	0.00

[a] The concentration of **1a** and (±)-**7** is 10 mM (1:1) in 0.5 mL of various deuterated solvents in NMR tubes, respectively.

for enantiomeric discrimination. The overlaid ^{1}H NMR spectra of (±)-**7** and **1a** with the different molar ratio are shown in Figure 7.

Finally, Job plots of (±)-**7** were performed in the presence of **1a** with a total concentration of 10 mM. A maximum of $X{\cdot}\Delta\delta$ of (±)-**7** was observed at $X = 0.5$ when molar ratio of (±)-**7** versus **1a** was 1:1. The result indicates that CSA **1a** can bind two enantiomers of (±)-**7** to form a complex with 1:1 molar ratio. In theory, three

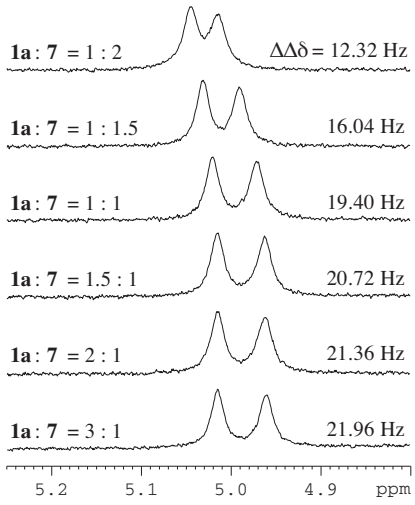


Figure 7. Overlaid ^{1}H NMR spectra of the various molar ratios of (±)-**7** with **1a**. The concentration of (±)-**7** is 5 mM in $CDCl_3$, unchangeable.

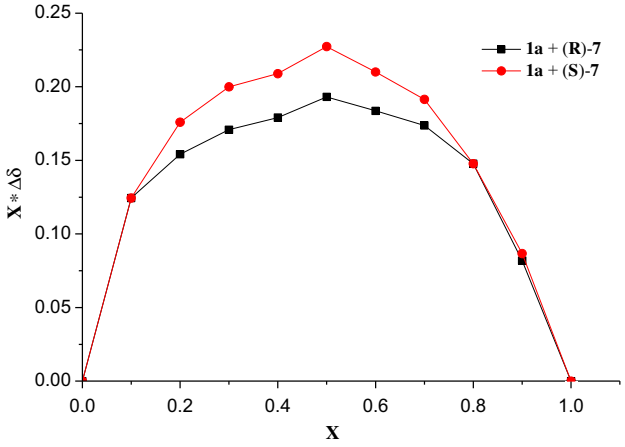


Figure 8. Job plots for complexation of (*R*)- and (*S*)-**7** with **1a**. Δδ standing for chemical shift change of α-H of (*R*)- and (*S*)-**7** in the presence of **1a**. *X* standing for the mole fraction of (±)-**7**, (*X* = [(±)-**7**]/([(±)-**7**] + [**1a**])).

kinds of complexes (*R*)/(*R*)-, (*S*)/(*S*)- and (*R*)/(*S*)-**7** with **1a** should be generated based on the Job plots. However, only two sets of ^{1}H NMR signals of α-H of (*R*)/(*R*)- and (*S*)/(*S*)-7 were obtained in the presence of **1a**. The results may be due to a faster exchange over NMR timescale among the free guest, host and their complexes.[14] The Job plot of (*R*)- and (*S*)-**7** in the presence of **1a** is shown in Figure 8.

In conclusion, chiral compounds **1a**–**1h** with multiple binding sites have been efficiently synthesized for enantiomeric discrimination as chiral solvent agents. Their enantiomeric discriminating capability was examined towards α-hydroxy acids and *N*-Ts-α-amino acids by ^{1}H NMR spectroscopy. The results show that chiral compounds **1a**–**1h** are highly effective and practical chiral solvating agents towards the above guests.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.10.060.

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