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Synthesis and application of amino alcohol imides as NMR solvating agents for chiral discrimination of carboxylic acids

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ABSTRACT

A series of amino alcohol imides **2**–**8** have been synthesized from commercially available starting materials by regioselective ring opening reaction of epoxides with chiral amines. Compounds **2**–**8** were tested as chiral solvating agents (CSAs) for enantiomeric discrimination of biological important carboxylic acids. C_2-Symmetric (*S*,*R*,*R*,*S*)-**3** was found to be a satisfactory CSA for mandelic acid with $\Delta\Delta\delta$ of 24.8 Hz. CSA (*S*,*S*)-**5** exhibited the best enantiomeric discrimination for α-phenyl-α-methoxyacetic acid with $\Delta\Delta\delta$ of 32 Hz. Enantiomeric differentiated values found for mandelic acid, *o*-chloro mandelic acid, ibuprofen and naproxen are 7.2, 4.4, 2 and 3 Hz respectively.

1. Introduction

Chiral recognition has received considerable attention due to the significant importance of chirality in biology. It is very important to check or ascertain the enantiomeric composition and absolute configuration of chiral molecules. Ever growing requirement for enantiopure molecules in the pharmaceutical industries and the consequent demand for asymmetric synthesis impose the necessity for exploring simple, easy to use, cost effective and reliable techniques for testing of enantiopurity.[1] Among the various methods, NMR spectroscopy has the advantages of easy performance and accessibility with no need for special equipment apart from the common NMR spectrometers.[2]

Chiral carboxylic acids are basic building blocks of natural products and drug molecules as well as versatile functional synthons.[3] Due to their importance in biological systems and usefulness as a source of chirality in organic synthesis, the chiral recognition of carboxylic acids by artificial receptors is of critical importance in the preparation, separation, and analysis of enantiomers. Dioxocyclens,[4] macrocyclic dioxopolyamines,[5] proline derivatives,[6] amines,[7] amine and amide functionalized macrocycles,[8] aminonaphthols or amino alcohols,[9] calixarene[10] have been designed and used for enantiodiscrimination of chiral carboxylic acids.

Nowadays, world regulatory authorities such as U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) impose that the control of enantiomeric purities is crucial for the commercialization of drug substances with chiral properties.[11] Therefore, the development of new CSAs continues to be an active area research and several types of CSAs have been proposed, from very simple chiral organic molecules to supramolecular or multiselector systems.[12] In the present study we report the synthesis of chiral amino alcohol imides and their applications as CSAs for enantio discrimination of carboxylic acids by NMR spectroscopy. For this purpose, amino alcohol imides **3**–**8** were synthesized by regioselective ring opening reaction of (*R*)-*N*-(2,3-epoxypropyl) phthalimide with appropriate chiral amines (Schemes 1 and 2).

2. Results and discussions

The basic unit amino alcohol imide functionality was created by the regioselective ring opening reaction of (*R*)-*N*-(2,3-epoxypropyl) phthalimide with various chiral amines. We chose this system due to the simplicity of its preparation from readily available substances and connected with three functional groups of hydroxyl, secondary or tertiary amine and imide groups which are closely to the stereocenters. Herein we planned to make different derivatives of enantiomerically pure *N*,*N*′-dibenzyl-1,2-diamnocyclohexane **1** which is used as many asymmetric reactions as a catalyst.[13] Therefore, C_2-symmetric compound (*R*,*R*,*R*,*R*)-**2** with secondary amine alcohol functionality was prepared by reaction of (*R*,*R*)-**1** with (*R*)-styrene oxide to give a tertiary amino alcohol which was then debenzylated to give (*R*,*R*,*R*,*R*)-**2** in 71.7% yield. C_2-symmetric (*S*,*R*,*R*,*S*)-**3** with tertiary amine functionality was easily prepared by regioselective ring opening of (*R*)-*N*-(2,3-epoxypropyl)phthalimide with chiral amine (*R*,*R*)-**1** in high yield (70%).

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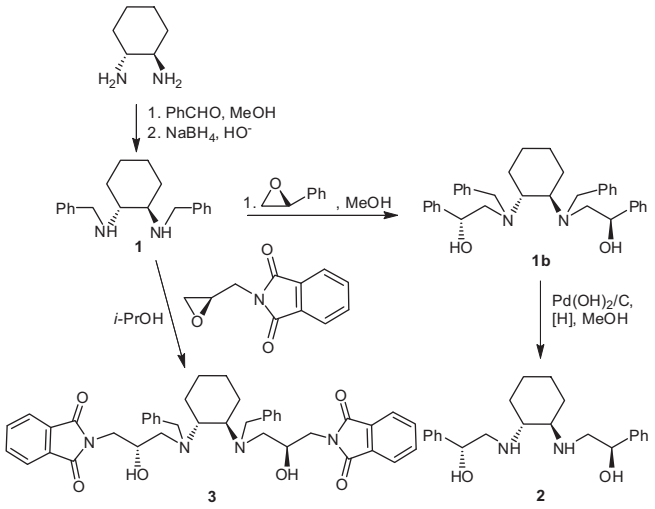
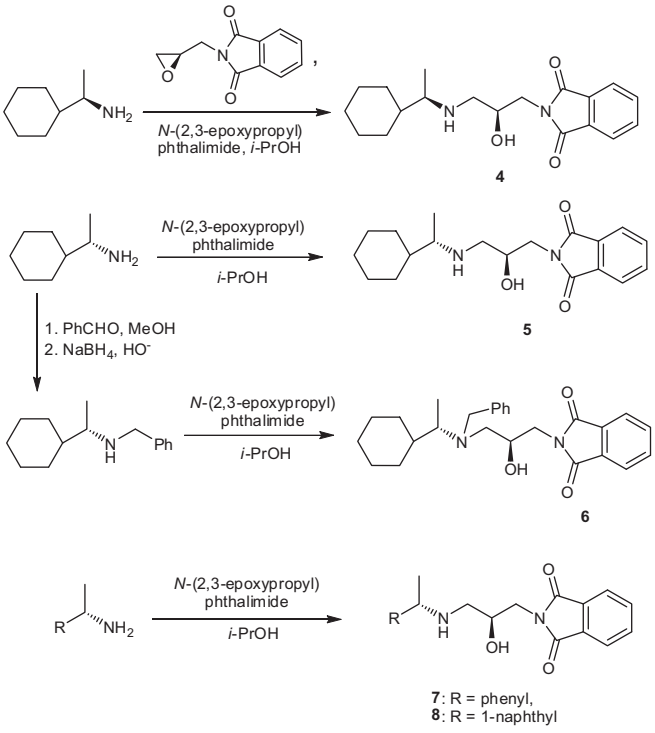


Scheme 1. Synthesis of amino alcohol (*R*,*R*,*R*,*R*)-**2** and amino alcohol imid (*S*,*R*,*R*,*S*)-**3**.



Scheme 2. Synthesis of amino alcohol imides **4**–**8**.

Chiral compound (*R*,*S*)-**4** and (*S*,*S*)-**5** were prepared by the ring opening reaction of (*R*)-*N*-(2,3-epoxypropyl)phthalimide with (*R*)- and (*S*)-cyclohexylethylamine in 68% and 73% yield respectively. We next tried to block the N–H functionality of (*S*,*S*)-**5** in order to see the effect of tertiary amine and/or hydroxyl and imide groups on chiral solvating process. With this aim (*S*)-α-cyclohexylethylamine was condensed with benzaldehyde to the imine intermediate and then reduced to form benzylated product which was then converted to the (*S*,*S*)-**6** by using (*R*)-*N*-(2,3-epoxypropyl)phthalimide with excellent conversion (Scheme 2). Extended studies were focused on the introducing aromatic substituents to this system. Therefore, (*S*)-α-phenylethylamine and (*S*)-1-(1-naphthyl) ethylamine were treated with (*R*)-*N*-(2,3-epoxypropyl)phthalimide to give (*S*,*S*)-**7** and (*S*,*S*)-**8** in high yields (Scheme 2).

Amino alcohol and amino alcohol imide functionalized **2**–**8** molecules were used as potential CSAs for enantio discrimination of mandelic acid (**A**), *o*-chloromandelic acid (**B**), α-phenyl-α-methoxyacetic acid (**C**), ibuprofen (**D**) and naproxen (**E**) as analytes in ^{1}H NMR spectroscopy (Fig. 1). The results obtained by this work are as follows:

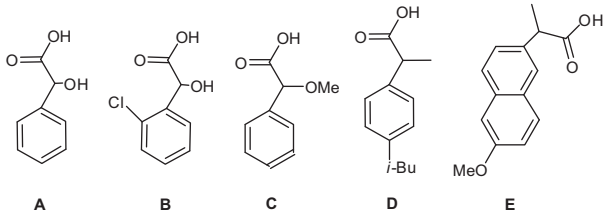


Figure 1. Structure of analytes used herein.

Amino alcohol (*R*,*R*,*R*,*R*)-**2** with secondary alcohol and amine functionality shifted the signal C-α-H of analytes to the high magnetic field (0.02–0.3 ppm) and exhibited low enantiomeric discriminations. The best differentiated value was obtained in the case of mandelic acid with $\Delta\Delta\delta$ of 10 Hz (Table 1). C_2-Symmetric amino alcohol imide (*S*,*R*,*R*,*S*)-**3** was found to be the best reagent for enantio discrimination of mandelic acid with $\Delta\Delta\delta$ of 24.8 Hz. The values for α-phenyl-α-methoxyacetic acid and *o*-chloromandelic acid were found to be 16.6 and 8 Hz respectively (Table 1). Therefore, we have shown the practically applicable of the (*S*,*R*,*R*,*S*)-**3** as a good CSA for the measurement of mandelic acid as a model analyte (Fig. 2).

We have also tried to get a deeper knowledge about inclusion complexes formed in solution. Therefore, we focused on the species formed between (*S*,*R*,*R*,*S*)-**3** and analyte **A**. Job plots for both mandelic acid's enantiomers indicate 1:1 CSA/A stoichiometry (Fig. 3).

Amino alcohol amide (*R*,*S*)-**4** which derived from (*R*)-α-cyclohexylethylamine was showed a good enantiomeric discrimination towards mandelic acid, *o*-chloro mandelic acid and α-phenyl-α-methoxyacetic acid with $\Delta\Delta\delta$ of 8.8, 6.4 and 3.6 Hz respectively.

Amino alcohol amide (*S*,*S*)-**5** which derived from (*S*)-α-cyclohexylethylamine was also exhibit a good enantiomeric discrimination towards all of the analtytes. The best enantio differentiated value was found to be for α-phenyl-α-methoxyacetic acid with $\Delta\Delta\delta$ of 32 Hz. Enantiomeric differentiated values found for mandelic acid, *o*-chloro mandelic, ibuprofen and naproxen are 7.2, 4.4, 2.0 and 3.0 Hz respectively. It is indicate that the *S* configuration of amine has a broad enantio discrimination ability than the (*R*,*S*)-**4** by creation of better pocket sides to binding with one of enantiomer of chiral acids. Additionally, it can be stated that polar group of stereogenic center causes strong hydrogen bonding, dipol–dipol interaction to enantio discrimination of mandelic acid or its derivatives when compared with ibuprofen and naproxen.

Reasonable CSA activity of (*S*,*S*)-**5** lead us to prepare samples of different enantiomeric purity (0–100%) of α-phenyl-α-methoxyacetic acid and it showed a satisfactory experimentally enantiomeric discrimination (Fig. 4).

Amino alcohol imide (*S*,*S*)-**6** as a *N*-benzyl derivative of (*S*,*S*)-**5** exhibit low enantio differentiated values. It showed discrimination ability towards only mandelic acid, *o*-chloro mandelic acid with $\Delta\Delta\delta$ of 2.4 and 3 Hz respectively (Table 2). This is indicate that secondary amine functionality of (*S*,*R*)-**5** play an important rule on enantiomeric recognition via hydrogen bonding. The better CSA ability of (*S*,*R*,*R*,*S*)-**3** with tertiary amine functionality can be attributed to its symmetry and less flexibility properties when compared with (*S*,*R*)-**6**. Surprisingly, it was found that amino alcohol imide (*S*,*R*)-**7** and (*S*,*R*)-**8** which are bearing phenyl and naphthyl

Table 1
Induced shifts (Δδ, ppm) and splitting (ΔΔδ, ppm) for the signal of the carboxylic acids **A**–**E** in the presence of CSA **2**–**5** (400 MHz, 20 mM in $CDCl_3$ at 25 °C)

	Acid	Signal	CSA							
			2		**3**		**4**		**5**	
			Δδ[a]	ΔΔδ[b]	Δδ[a]	ΔΔδ[b]	Δδ[a]	ΔΔδ[b]	Δδ[a]	ΔΔδ[b]
1	A	CαH	−0.300	10	−0.513	24.8	0.489	8.8	−0.474	7.2
2	B	CαH	−0.247	4.4	−0.514	8.0	−0.456	5.6	−0.452	4.4
3	C	CαH	−0.002	0.0	−0.164	16.8	−0.242	3.6	−1.117	32.0
4	D	CαH	0.015	0.8	−0.020	0.0	−0.384	1.2	−0.147	2.0
5	E	CαH	−0.013	0.0	−0.045	0.0	−0.236	3.2	−0.110	2.4

[a] Averaged between signals (ppm) from both enantiomers.
[b] ΔΔδ: Hz.

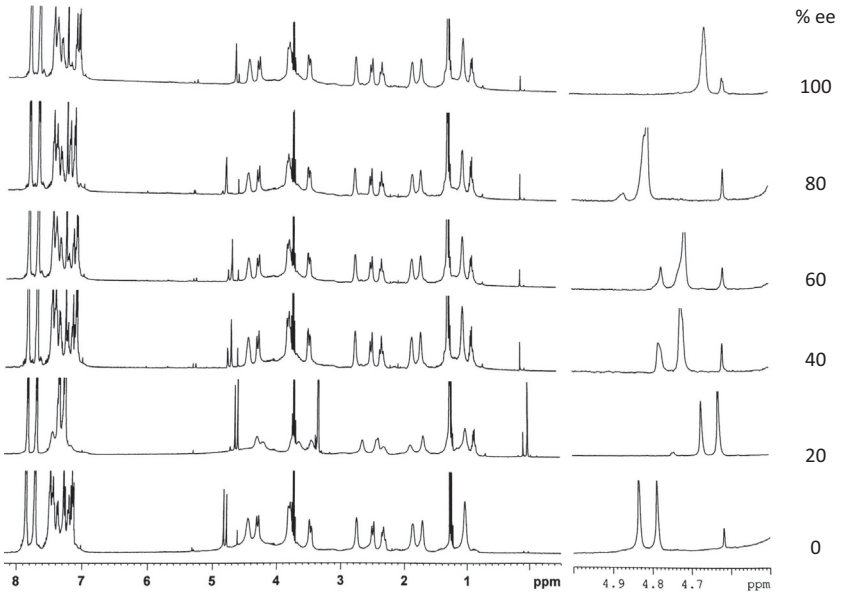


Figure 2. ^{1}H NMR spectra of (±)-mandelic acid (A) of various ratios of optical purity (0–100% ee) in the presence of (*S*,*R*,*R*,*S*)-**3** [1:2 equiv of (*S*,*R*,*R*,*S*)-**3**/A].

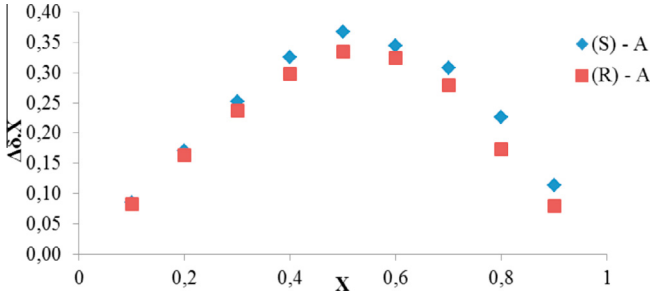


Figure 3. Job plots for (*S*)- and (*R*)-**A** with CSA (*S*,*R*,*R*,*S*)-**3**.

substituents exhibit any significant enantiomeric discriminations with all of the analytes. This is may be due to the lower polarity and planar shape of side arm of (*S*,*S*)-**7** and (*S*,*S*)-**8** is not sufficient driving force to form relative stable inclusion complexes.

3. Conclusion

In conclusion, we have synthesized novel an amino alcohol and six amino alcohol imide functionalized compounds (**3**–**8**) by regioselective ring opening of terminal epoxides. Their enantiodiscriminating abilities for carboxylic acids have been investigated by ^{1}H NMR spectroscopy. Chiral amino alcohol imids (*S*,*R*,*R*,*S*)-**3** and (*S*,*S*)-**5** were discovered to exhibit good enantio discrimination towards mandelic and α-phenyl-α-methoxyacetic acids respectively, indicating the possible use of these compounds as potential CSAs. The results indicate that not only class of chiral amine but also both polarity and chiral environment of reagent and analyte are effective in the chiral discrimination in ^{1}H NMR analysis.

4. Materials and methods

4.1. Apparatus and chemicals

Melting points were determined with GALLENKAMP Model apparatus with open capillaries. Infrared spectra were recorded on a MİDAC-FTIR Model 1700 spectrophotometer. The Elemental analyses were obtained with CARLO-ERBA Model 1108 apparatus. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on BRUKER DPX-400 high performance digital FT-NMR spectrometer, with tetramethylsilane as the internal standard solutions in deuteriochloroform. Optical rotations were recorded using PERKIN ELMER Model 341 polarimeter. All chemicals were purchased from Sigma Aldrich and Merck and reagent grade unless otherwise specified.

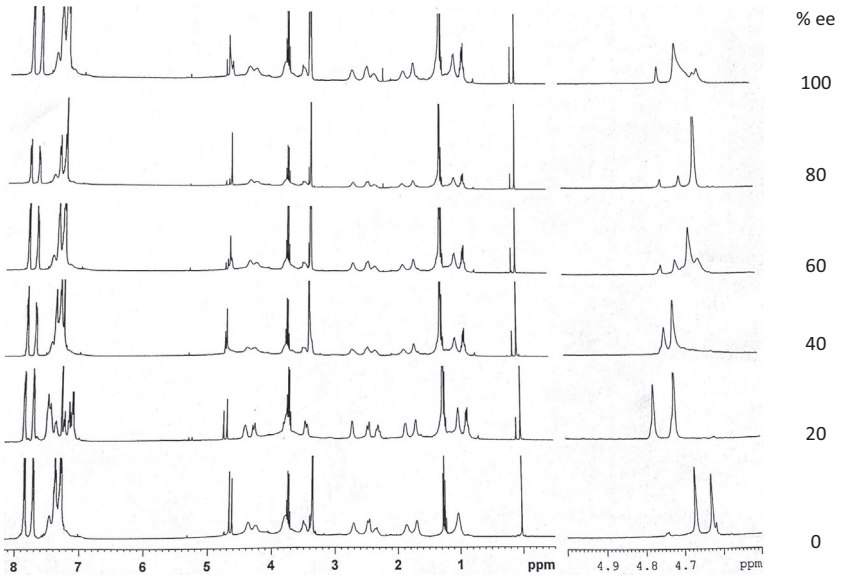


Figure 4. ^{1}H NMR spectra of (±)-α-phenyl-α-methoxyacetic acid (**C**) of various ratios of optical purity (0–100% ee) in the presence of (*S*,*S*)-**5**. [1:1 equiv of (*S*,*S*)-**5**/**C**].

Table 2
Induced shifts (Δδ, ppm) and splitting (ΔΔδ, ppm) for the signal of the carboxylic acids **A**–**E** in the presence of CSA **6**–**8** (400 MHz, 20 mM in $CDCl_3$ at 25 °C)

	Acid	Signal	CSA					
			6		**7**		**8**	
			Δδ[a]	ΔΔδ[b]	Δδ[a]	ΔΔδ[b]	Δδ[a]	ΔΔδ[b]
6	A	CαH	−0.153	2.4	−0.136	7.6	−0.006	0.0
7	B	CαH	−0.167	3.0	−0.173	0.0	0.015	0.0
8	C	CαH	−0.007	0.0	−0.059	0.0	0.002	0.0
9	D	CαH	−0.067	0.0	−0.093	0.0	−0.002	0.0
10	E	CαH	−0.007	0.0	−0.166	2.2	0.013	0.0

[a] Averaged between signals from both enantiomers.
[b] ΔΔδ: Hz.

4.2. Synthesis

4.2.1. (1*R*,2*R*)-Bis[(*R*)-2-hydroxy(2-phenyl)ethyl]-1,2-diaminocyclohexane 2

Compounds **1** and **1b** were synthesized starting from chiral 1,2-diaminocyclohexane as described in previously report.[14] $Pd(OH)_2$/C (20%, 75 mg) was added in one portion to a solution of the appropriate compound **1b** (400 mg, 0.75 mmol) in methanol (2 mL) as described previously report.[15] The mixture was stirred under hydrogen and the reaction was monitored by TLC. Sodium carbonate (80 mg, 0.75 mmol) was added and stirred for 1 h by the completion of the reaction. The solution was filtrated and washed with methanol, then concentrated in vacuum. The crude product was purified by flash chromatography on silica gel H:EtOAc:EtOH:TEA (4:1:1:0.5 as eluent) to give 190 mg 71.7% of compound **2** as a viscous oil. $[\alpha]_D^{20} = -52.2°$ (c = 1, $CHCl_3$). IR (KBr): 3346, 3250, 3057, 3030, 2926, 2860, 1493, 1453, 1348, 1310, 1195, 1139, 1056, 924, 893, 854, 791, 756, 701 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 7.41–7.27 (m, 10H), 4.55 (dd, J = 4, J = 8.12 Hz, 2H), 2.90–2.71(m, 8H), 2.32–2.27 (m, 2H), 2.12–1.99 (m, 2H), 1.38–1.37 (m, 2H); 1.28–1.05 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ: 142.55, 128.39, 127.48, 125.90, 72.00, 60.32, 53.84, 31.87, 25.01. Anal. Calcd for $C_{22}H_{30}N_2O_2$: C, 74.57; H, 8.47; N, 7.90. Found: C, 74.89; H, 8.36; N, 7.82.

4.2.2. General procedure for the synthesis of compounds 3–7

Compounds **3**–**7** have been synthesized using a procedure originally reported by Roehrig et al.[16] Chiral amine or amino alcohol (0.6 mmol, 1.2 equiv) in 10 mL isopropanol was added to the solution of (*R*)-*N*-(2,3-epoxypropyl)phthalimide (102 mg, 0.50 mmol) in 10 mL of isopropanol at in an ice bath and stirred for 1 h. then refluxed for 12 h. The reaction monitored by TLC. Solvent was removed by rotary evaporator under reduced pressure after completion of the reaction.

4.2.3. *N*,*N*′-Dibenzyl-*N*,*N*′-bis[(*S*)-2-hydroxy-3-phtalimido]-(1*R*,2*R*)-1,2-diaminocyclo-hexane 3

Compound (*S*,*R*,*R*,*S*)-**3** was synthesized by reacting (*R*)-*N*-(2,3-epoxypropyl)phthalimide (2.04 g, 5 mmol) and **1** (0.73 g, 5 mmol) as the method described above. Solvent was removed under reduced pressure by completion of the reaction and the crude product was purified by crystallization with MeOH to give 2.45 g 70% as a white crystals. Mp: 164–165 °C, $[\alpha]_D^{20} = -14.2°$ (c = 1, $CHCl_3$). IR (KBr): 3434.6, 3384.5, 3332.4, 3053.75, 2931.3, 2859.9, 1771.3, 1709.6, 1612.2, 1434.97, 1393.3, 1147.4, 1083.8, 1011.5, 842.7, 626.0, 619.0 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 7.84 (d, J = 2.4 Hz, 2H); 7.713 (d, J = 2.8 Hz, 2H); 7.468–7335 (m, 10H); 4.34–3.27 (m, 10H); 2.86–2.14 (m, 6H); 1.69–1.67 (m, 6H); 1.05 (m, 4H). ^{13}C NMR (100 MHz $CDCl_3$, ppm) δ: 168.33, 138.08, 133.80, 132.17, 128.33, 127.35, 123.24, 66.58, 58.86, 56.28, 53.08, 42.21, 25.40, 23.76. Anal. Calcd for $C_{42}H_{44}N_4O_6$: C, 72.0; H, 6.28; N, 8.0. Found: C, 71.58; H, 6.12; N, 7.78.

4.2.4. 2-[(2*S*)-2-Hydroxy-3-[[(1*R*)-α-cyclohexylethyl]amino] propyl]isoindoline-1,3-dione 4

Compound **4** was synthesized by reacting (*R*)-*N*-(2,3-epoxypropyl)phthalimide (767 mg, 3.77 mmol) and (*R*)-α-cyclohexylethylamine (0.4 g, 3.15 mmol) as usual manner. Solvent was removed under reduced pressure by completion of the reaction and the crude product was purified by flash chromatography on silica gel with *n*-hexane:EtOAc (1:4 as eluent) to give 0.707 mg 68% yield as white powder crystals. Mp 136–138 °C, $[\alpha]_D^{20} = 14°$ (c = 1, $CHCl_3$). IR (KBr): 3460.7, 3453.6, 3319.8, 3262.9, 3032.5, 2911.0, 2848.3, 2760.6, 2697.9, 1769.3, 1709.6, 1439.6, 1393.3, 1318.1, 1163.8, 1112.74, 1094.42, 1024.0, 898.9, 836.9, 789.7, 717.7 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: ^{1}H NMR ($CDCl_3$): 7.88–7.86 (m, 2H); 7.75–7.73 (m, 2H); 4.04–4.01 (m, 1H); AB system; A part:

3.808 (dd, J = 24.8 Hz, J = 13.6 Hz, –CH_2–, 1H); B part: 3.793 (dd, J = 23.2 Hz, J = 14 Hz, –CH_2–, 1H); 2.83 (dd, J = 9.2 Hz, J = 3.2 Hz, 1H); 2.69 (dd, 12.4 Hz, 7.2 Hz, 1H); 2.572–2.542 (m, 1H): 1.77–1.69 (m, 5H); 1.26–1.01 (m, 9H). ^{13}C NMR (100 MHz $CDCl_3$, ppm) δ: 168.64, 134.07, 132.03, 123.41, 66.99, 58.19, 49.38, 42.24, 41.60, 29.61, 28.20, 26.54, 26.40, 26.29, 16.29. Anal. Calcd for $C_{19}H_{26}N_2O_3$: C: 69.09, H: 7.87; N: 8.48. Found: C, 68.87; H, 7.69; N, 7.79.

4.2.5. 2-[(2*S*)-2-Hydroxy-3-[[(1*S*)-α-cyclohexylethyl]amino] propyl]isoindoline-1,3-dione 5

Compound **5** was synthesized by reacting (*R*)-*N*-(2,3-epoxypropyl)phthalimide (767 mg 3.77 mmol) and (*S*)-α-cyclohexylethylamine (0.4 g, 3.15 mmol) as usual manner. Solvent was removed under reduced pressure by completion of the reaction and the crude product was purified by flash chromatography on silica gel with *n*-hexane:EtOAc (3:2 as eluent) to give 0.76 mg 73.07% of **5** as viscous oil. $[\alpha]_D^{20}$ = +7.2° (c = 1, $CHCl_3$). IR (KBr): 3386.5, 3380.5, 3378, 3156.29, 3142.3, 3130.4, 3125.5, 2918.75, 2850.3, 1710.65, 1614.14, 1429.0, 1394.29, 1329.69, 1189.8, 1127.2, 1087.67, 1029.8, 982.5, 917.0, 722.2 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 7.86–7.71 (m, 4H); 3.96–3.93 (m, 1H); AB system; A part: 3.78 (dd, J = 22.8 Hz, 17.6 Hz, –CH_2–, 1H); B part: 3.76 (dd, J = 21.2 Hz, J = 14 Hz, –CH_2–, 1H); 3.103 (m, 2H): 2.86 (dd, J = 12.4 Hz, J = 4 Hz. 1H); 2.536–2.449 (m, 1H); 1.75–1.65 (m, 5H); 1.22–0.98 (m, 10H). ^{13}C NMR (100 MHz $CDCl_3$, ppm) δ: 168.64, 134.01, 132.02, 123.35, 67.98, 58.45, 50.20, 42.69, 41.89, 29.75, 27.95, 26.66, 26.54, 26.40, 16.93. Anal. Calcd for $C_{19}H_{26}N_2O_3$: C, 69.09; H, 7.87; N, 8.48. Found: C, 68.72; H, 7.62; N, 7.92.

4.2.6. 2-[(2*S*)-2-Hydroxy-3-[*N*-benzyl-[(1*S*)-α-cyclohexylethyl] amino]propyl]isoindol-ine-1,3-dione 6

(*S*)-*N*-Benzyl-α-cyclohexylethylamine was prepared as a precursor of compound **6**. Therefore, (*S*)-α-cyclohexylethylamine (1 mL, 6.82 mmol) was benzylated to give 1.42 g 96% of (*S*)-*N*-benzyl-α-cyclohexylethylamine according to the literature method.[15] IR (KBr): 3321.8, 3161.7, 3067.2, 2940.12, 1643.9, 1582.3, 1483.0, 1431.9, 1378.8, 1332.8, 1224.5, 1189.8, 1068.3, 981.6, 838.8 (cm^{-1}). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 7.38–7.29 (m, 5H), 3.89 (d, 1H, J = 13.2 Hz), 3.75 (d, J = 13.2 Hz, 1H), 2.58–2.51 (m, 1H), 1.82–1.71 (m, 6H), 1.44–1.14 (m, 4H), 1.09–1.01 (m, 5H). ^{13}C NMR (100 MHz $CDCl_3$, ppm) δ: 141.16, 128.34, 128.12, 126.75, 57.12, 51.62, 43.02, 29.89, 28.13, 26.84, 26.72, 26.59, 16.79). Compound **6** was prepared by using (*R*)-*N*-(2,3-epoxypropyl)phthalimide (0.655 mg, 3.77 mmol) and (*S*)-*N*-benzyl-α-cyclohexylethylamine (0.7 g, 3.22 mmol) as usual manner. Solvent was removed under reduced pressure by completion of the reaction and the crude product was purified by flash chromatography on silica gel with *n*-hexane:EtOAc (2:1 as eluent) to give compound **6** as viscous oil (1.05 g, 77.66%). $[\alpha]_D^{20}$ = +9.8° (c = 1, $CHCl_3$). IR (KBr): 3564, 3514, 3476, 3434, 3086, 2913, 2859, 1772, 1712, 1611, 1429, 1393, 1327, 1262, 1151, 1086, 1027, 960, 722 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 7.78–7.76 (m, 2H); 7.76–7.63 (m, 2H); 7.31–7.16 (m, 5H); 3.85–3.76 (m, 2H): 3.70–3.69 (m, 1H); 3.47–3.35 (m, 2H): 3.17 (s, 1H); 2.61–2.23 (m, 4H); 1.73–1.64 (m, 4H); 1.23–1.14(m, 1H). ^{13}C NMR (100 MHz $CDCl_3$, ppm) δ: 168.57, 140.08, 133.88, 132.03, 129.10, 128.29, 126.98, 123.20, 68.29, 61.89, 55.79, 54.78, 42.71, 41.08, 31.45, 30.54, 26.57, 26.48, 26.33, 11.09. Anal. Calcd for $C_{26}H_{32}N_2O_3$: C, 74.28; H, 7.62; N, 6.66. Found: C, 74.86; H, 7.29; N, 7.41.

4.2.7. 2-[(2*S*)-2-Hydroxy-3-[[(1*S*)-α-phenylethyl]amino]propyl] isoindoline-1,3-dione 7

Compound **7** was synthesized by reacting (*R*)-*N*-(2,3-epoxypropyl)phthalimide (500 mg, 2.46 mmol) and (*S*)-α-phenylethylamine (298 mg, 2.46 mmol) as usual manner. Crude product was purified by flash chromatography on silica gel with *n*-hexane:EtOAc:TEA (1:0.5:0.1 as eluent) to afford pure compound **6** (612 mg, 76.69%) as a viscous oil. $[\alpha]_D^{20}$ = 10.7° (c = 1, $CHCl_3$). IR (KBr): 3264, 2921, 2851, 1773, 1714, 1566, 1463, 1395, 1085, 1023, 918, 627 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 7.84–7.81 (m, 2H); 7.72–7.69 (m, 2H); 7.31–7.22 (m, 5H); 3.912–3.87 (m, 1H); 3.807–3.689 (m, 3H); 2.71 (br s, 1H); 2.62–2.56 (m, 2H); 1.39–1.26 (m, 5H). ^{13}C NMR (100 MHz $CDCl_3$, ppm) δ: 168.70, 145.14, 134.05, 131.98, 128.53, 127.08, 126.57, 123.37, 68.47, 58.52, 50.50, 42.00, 24.14. Anal. Calcd for $C_{19}H_{20}N_2O_3$: C, 70.37; H, 6.17; N, 8.64. Found: C, 70.56; H: 6.10; N, 8.54.

4.2.8. 2-[(2*S*)-2-Hydroxy-3-[[(1*S*)-1-naphthylethyl]amino] propyl]isoindoline-1,3-dione 8

Compound **8** was synthesized by reacting (*R*)-*N*-(2,3-epoxypropyl)phthalimide (528 mg 2.6 mmol) and (*S*)-1-(1-naphthyl)ethylamine (442.45 mg, 2.6 mmol) as usual manner. Solvent was removed under reduced pressure by completion of the reaction and the crude product was purified by flash chromatography on silica gel with *n*-hexane:EtOH (4:1 as eluent) to give pure compound **6** (698 mg, 72%) as a white solid. Mp 249–250 °C, $[\alpha]_D^{20}$ = +16.9° (c = 0.5, DMSO). IR (KBr): 3492, 3468, 3421, 3352, 3290.9, 3051.8, 2952.5, 2843.5, 2796.3, 2689.2, 2622.7, 2526.3, 1773.2, 1711.5, 1588.1, 1433.8, 1395.2, 1345.1, 1296.9, 1092.5, 1008.6, 964.2, 801.3, 779.1, 723.2 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 9.78 (br s, 1H); 9.08 (br s, 1H): 8.20–8.18 (m, 1H); 8.00–7.56 (m, 8H); 5.86 (s, 1H); 5.36 (s, 1H); 4.20 (s, 1H); 3.57–3.12 (m, 3H); 2.67 (s, 1H): 2.47 (s, 1H); 1.68–1.67 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz $CDCl_3$, ppm) δ: 168.28, 134.81, 134.10, 133.80, 132.12, 130.83, 129.37, 127.41, 126.60, 126.60, 124.74, 123.50, 122.96, 64.36, 52.76, 49.40, 41.97, 20.55. Anal. Calcd for $C_{23}H_{22}N_2O_3$: C, 73.80; H, 5.88; N, 7.49. Found: C, 73.36; H: 6.10; N, 7.84.

4.2.9. Evaluation of the stoichiometric ratio of the (*S*,*R*,*R*,*S*)-3 and mandelic acid complexes (Job plots)

The stoichiometry of the complexes between (*S*,*R*,*R*,*S*)-**3** and enantiomers of mandelic acid were clarified by Job plot.[17] Therefore, equimolar amounts of CSA and analytes were dissolved in $CDCl_3$. The solution distributed among nine NMR tubes that molar reaction of that solutions was kept from 0.1 to 0.9. Chemical shifts differences ($\Delta\delta$) C-α-H of mandelic acid was determined. Mol fraction (X) of these nine tubes plotted against X. ($\Delta\delta$) itself.

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