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An excellent new resolving agent for the diastereomeric resolution of *rac*-mandelic acid

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ABSTRACT

Chiral mandelic acid (*S*)-**1**, which is an important precursor for stereoselective transformations and a versatile intermediate for pharmaceuticals, was resolved with the Pope and Peachey method. Enantiopure 1-amino-3-phenoxypropan-2-ol (*S*)-**2**, a key intermediate for pharmaceuticals, was used to resolve *rac*-mandelic acid *rac*-**1** successfully for the first time. The less soluble salt (*S*)-**1**·(*S*)-**2**·H_2O could be obtained in 77% yield and 98% de (*E* 75%) using (*S*)-**2** and LiOH in water. The crystal structure of the less soluble salt (*S*)-**1**·(*S*)-**2**·H_2O showed that the water molecule played a key role in forming the crystals.

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1. Introduction

Enantiopure mandelic acid (*S*)-**1** and its derivatives are important organic molecules, which can be utilized as important precursors for the introduction of a stereogenic center in stereoselective transformations.[1,2] They are also versatile intermediates for pharmaceuticals[3] and resolving agents.[4]

Several methods for obtaining enantiopure **1** have been developed to date; these include (i) asymmetric synthesis via metal catalysts or organic catalysts;[5] (ii) enzymatic or biomimetic methods;[6] and (iii) diastereomeric resolution.[7] With methods (i) and (ii), (*S*)-**1** can be obtained in high enantiopurity and good yield. However, scalable processes for industrial synthesis are few, because the price of the chiral ligands and catalysts is high. The diastereomeric resolution of racemic mixtures remains an economical and frequently used procedure in the chemical and pharmaceutical industries, since the resolving agent is recyclable and it is generally simple, clean, and easy to scale up to an industrial scale.[8]

For the diastereomeric resolution of *rac*-**1**, a number of chiral resolving agents have been described, which include cinchonine,[7a] (−)-ephedrine,[7b] (−)-2-aminobutan-1-ol,[7c] (+)-1-phenylethylamine,[7d] and (−)-phenylglycine butyl ester.[7e] The uses of alkaloids and (−)-2-aminobutan-1-ol are limited due to their cost. (+)-1-Phenylethylamine and (−)-phenylglycine butyl ester are relatively inexpensive. However, the diastereomeric salt needed to be recrystallized 3 times or more to obtain high enantiomeric purity. Thus searching for new more efficient resolving agents, which are inexpensive or easy to synthesize, is necessary.

Enantiopure aryloxypropylamine with an amino group, an aromatic ring, and a hydroxy group, appears to be a good candidate for chiral discrimination, which is easy to synthesize.[9] In our previous work, aryloxypropylamine could be kinetically resolved by a C-12 higher carbon sugar.[10] This method was used for the preparation of the enantiomerically pure β-blockers (*S*)-Betaxolol and (*S*)-Metoprolol.[11] Since the use of aryloxypropylamine as a resolving agent has not been reported, the resolution of *rac*-**1** with aryloxypropylamines was investigated.

2. Results and discussion

2.1. Traditional resolution

In order to determine the most suitable resolving agent for *rac*-**1**, three aryloxypropylamines were examined: (*S*)-**2**, (*S*)-**3** [*N*-methyl-substituted (*S*)-**2**], and (*S*)-**4** [*N*-ethyl-substituted (*S*)-**2**] (Fig. 1). The resolving solvent was chosen from water, methanol,

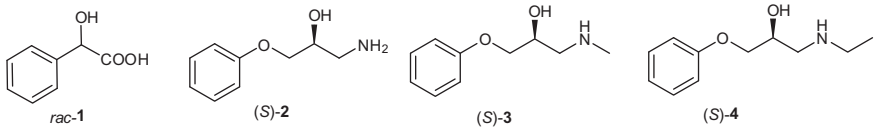

Figure 1. Structures of *rac*-**1** and resolving agents (*S*)-**2**, (*S*)-**3**, and (*S*)-**4**.

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Table 1
Traditional resolution of *rac*-**1** with (*S*)-**2**, (*S*)-**3**, and (*S*)-**4**

Entry	Resolving agent[a]	Solvent	Absolute configuration	Yield[b] (%)	de[c] (%)	*E*[d] (%)
1	(*S*)-**2**	Water	(*S*)	109	65	71
2		Methanol	(*S*)	120	57	68
3		Ethanol	(*S*)	132	50	66
4		Ethyl acetate	(*S*)	167	23	38
5	(*S*)-**3**	Water	(*S*)	62	87	54
6		Methanol	(*S*)	77	77	59
7		Ethanol	(*S*)	84	70	59
8		Ethyl acetate	(*S*)	113	63	71
9	(*S*)-**4**	Water	(*S*)	5	12	0.6
10		Methanol	(*S*)	12	5	0.6
11		Ethanol	(*S*)	10	5	0.5
12		Ethyl acetate	(*S*)	10	3	0.3

[a] Molar ratio of resolving agent to *rac*-**1** was 1.0, concentration of *rac*-**1** was 152 mg/mL.
[b] Based on half the amount of *rac*-**1** used.
[c] de of the salt was determined by ee of acid **1** liberated from the salt.
[d] Resolution efficiency *E*(%) = yield (%) × de (%).

ethanol, and ethyl acetate and the volume was 1 mL. The experimental results are summarized in Table 1.

We found that (*S*)-**2**, (*S*)-**3**, and (*S*)-**4** all gave precipitation. In protic solvents, (*S*)-**2** showed good resolution efficiency (*E* = 66–71%, Table 1, entries 1–3), (*S*)-**3** moderate (*E* = 54–59%, Table 1, entries 5–7), and (*S*)-**4** poor (*E* = 0.6%, Table 1, entries 9–11). While in an aprotic solvent, (*S*)-**3** showed the best result (Table 1, entry 8) it was found that compound (*S*)-**2** in water gave the same resolution efficiency (*E* 71%) as (*S*)-**3** in ethyl acetate (Table 1, entries 1 and 8). From an environmental and industrial point, water was the most suitable resolving solvent. Therefore, the resolution of *rac*-**1** with (*S*)-**2** in water was optimized in detail. In order to improve the resolution efficiency, the ratio of (*S*)-**2** to *rac*-**1** was next examined; the experimental results are shown in Table 2.

As shown in Table 2, if the ratio was less or more than 1.0, the resolution was poor. When the ratio was less, the yield and enantiomeric purity both decreased with the ratio (Table 2, entries 2–4). When the ratio was 0.5, two diastereomeric salts deposited simultaneously (Table 2, entry 4). The best resolution was obtained when the ratio of (*S*)-**2** to *rac*-**1** was 1.0 (Table 2, entry 2). However, the resolution efficiency was relatively low with traditional resolution (109% yield, 65% de). Therefore, a Pope and Peachey resolution was carried out in order to improve the resolution efficiency.

Table 2
Effect of molar ratio of (*S*)-**2** in water

Entry	Ratio of (*S*)-**2** to *rac*-**1**[a]	Yield[b] (%)	de[c] (%)	*E*[d] (%)
1	1.2	91	15	14
2	1.0	109	65	71
3	0.7	104	18	19
4	0.5	95	0	0

[a] Concentration of *rac*-**1** was 152 mg/mL.
[b] Based on half the amount of *rac*-**1** used.
[c] de of the salt was based on ee of acid **1** liberated from the salt.
[d] Resolution efficiency *E*(%) = yield (%) × de (%).

2.2. Optimization of the resolution conditions based on the Pope and Peachey method

Pope and Peachey have shown that resolutions can be made more effective by incorporating an achiral reagent in the resolution when the solubility differences between the two diastereomeric salts are relatively small. The achiral reagent competes with the resolving agent for the enantiomers in the racemic mixture. In the perfect case, the achiral reagent reacts completely with one enantiomer and the resolving agent reacts completely with the other.[12] The role of the achiral reagent is to form highly soluble salts with the enantiomer remaining in the solution.

As a supplementary base, four types of bases were examined: LiOH, NaOH, KOH, and Et_2NH (DEA). The molar ratio of the base to *rac*-**1** was set at 0.2 and the results are summarized in Table 3.

It was found that the addition of a base led to a decrease in the yield (Table 3, entries 1–4 vs Table 2, entry 2). Among the bases examined, LiOH and NaOH were extremely efficient as supplementary bases for obtaining higher resolution efficiency compared with a traditional resolution (Table 3, entries 1, 2 vs Table 2, entry 2). Comparing LiOH and NaOH, LiOH was found to be better because it afforded a higher yield (Table 3, entry 1 vs 2) and as a result, the best supplementary base was LiOH.

In order to determine the content of LiOH, the molar ratio of LiOH to *rac*-**1** was examined. The experimental results are shown in Table 4.

Table 3
Optimization of the resolution of *rac*-**1** with the Pope and Peachey method

Entry	Ratio of (*S*)-**2** to *rac*-**1**[a]	Supplementary base		Yield[b] (%)	de[c] (%)	*E*[d] (%)
		Base	Ratio to *rac*-**1**			
1	0.8	LiOH	0.2	99	85	84
2	0.8	NaOH	0.2	85	86	73
3	0.8	KOH	0.2	107	18	19
4	0.8	DEA	0.2	91	28	25

[a] Concentration of *rac*-**1** was 152 mg/mL.
[b] Based on half the amount of *rac*-**1** used.
[c] de was based on ee of acid **1** liberated from the salt.
[d] Resolution efficiency *E*(%) = yield (%) × de (%).

Table 4
Effect of molar ratio of LiOH

Entry	Ratio of (*S*)-**2** to *rac*-**1**[a]	Ratio of LiOH to *rac*-**1**	Yield[b] (%)	de[c] (%)	*E*[d] (%)
1	0.7	0.3	92	83	76
2	0.8	0.2	99	85	84
3	0.9	0.1	104	82	85
4	0.95	0.05	125	20	25

[a] Concentration of *rac*-**1** was 152 mg/mL.
[b] Based on half the amount of *rac*-**1** used.
[c] de of the salt was based on ee of acid **1** liberated from the salt.
[d] Resolution efficiency *E*(%) = yield (%) × de (%).

As shown in Table 4, it was found that a decrease in the ratio of LiOH led to an increase in the resolution yield (Table 4, entries 1–4). When the LiOH molar ratio was between 0.1 and 0.3, the enantiomeric purity of the diastereomeric salt remained at a higher level (82–85% de). Once the LiOH molar ratio decreased to 0.05, the enantiomeric purity greatly decreased (20% de). As a result, it was found that the highest resolution efficiency (*E* 85%) could be obtained when the content of LiOH was 0.1 (Table 4, entry 3). However, the enantiomeric purity of the diastereomeric salt (82% de) was relatively low, and so multiple salt recrystallization could not be avoided. The resolution was further optimized by adjusting the substrate concentration. The experimental results are summarized in Table 5.

Table 5
Effect of substrate concentration in water

Entry	Substrate concentration (mg/mL)[a]	Yield[b] (%)	de[c] (%)	*E*[d] (%)
1	152	104	82	85
2	100	93	86	80
3[e]	76	76	98	74
4[f]	76	77	98	75

[a] *rac*-**1** concentration.
[b] Based on half the amount of *rac*-**1** used.
[c] de was based on ee of acid **1** liberated from the salt.
[d] Resolution efficiency *E*(%) = yield (%) × de(%).
[e] The content of *rac*-**1** was 152 mg (1 mmol).
[f] The content of *rac*-**1** was 30 g (197 mmol).

As can be seen from Table 5, decreasing the concentration caused the yield to decrease and the enantiomeric purity to increase (Table 5, entries 1–3). When the substrate concentration was 76 mg/mL and the molar ratio of *rac*-**1**/(*S*)-**2**/LiOH was 1.0/0.9/0.1, the diastereomeric salt could be obtained in 98% de and 77% yield (Table 5, entry 4). On the other hand, when the resolution of *rac*-**1** was scaled up from the milligram to the gram scale, a good resolution could still be obtained (Table 5, entry 3 vs 4).

2.3. Crystal structure of the less soluble salt

For a better interpretation of the chiral recognition of (*S*)-**2**, we focused on the crystal structure of the less soluble salt. The less soluble salt was a colorless rod and crystallized in orthorhombic $P2_12_12_1$ space group, the unit cell consisted of four (*S*)-**1**, four (*S*)-**2**, and four H_2O molecules. The atomic-numbering of the less soluble salt (*S*)-**1**·(*S*)-**2**·H_2O[13] is shown in Figure 2.

It is generally believed that the pattern of hydrogen-bonding as well as the CH/π interaction accounts for the chiral discrimination.[14] Therefore, special attention was paid to the hydrogen-bonding network and CH/π interactions in the crystal structure.

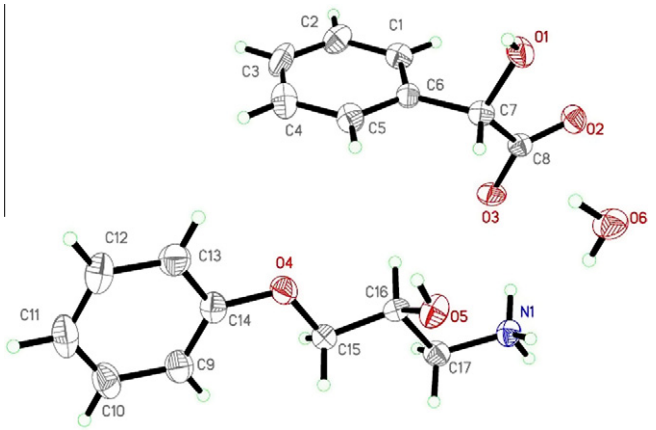

Figure 2. Atomic-numbering molecule schemes of the less soluble salt (*S*)-**1**·(*S*)-**2**·H_2O.

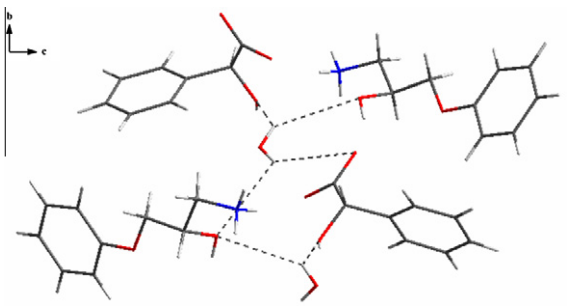

Figure 3. Crystal structure of (*S*)-**1**·(*S*)-**2**·H_2O. The hydrogen-bonding pattern viewed along the *a*-axis. The dotted lines represent hydrogen bonds.

In the crystal packing of (*S*)-**1**·(*S*)-**2**·H_2O, water molecules participated in the hydrogen-bonding network formation which worked as connectors between the amine and the acidic molecules (Fig. 3). Amine, acid, and water molecules were arranged in an orderly manner, resulting in the formation of the 2_1 column parallel to the *b*-axis (Fig. 4). Due to the hydrogen bonds, the 2_1 column extended infinitely along the *b*-axis and the columns were interlinked along the *a*-axis (Fig. 4). Thus, the crystal of the less soluble salt (*S*)-**1**·(*S*)-**2**·H_2O was formed. In the crystal packing, the water molecule played an important role for the chiral discrimination, and was essential in forming the salt crystals.

In the crystal packing of (*S*)-**1**·(*S*)-**2**·H_2O, the CH/π interaction between the benzene rings of the acid and the amine was found. It also played an important role in the crystal packing. On one hand, the CH/π interaction participated in the formation of the 2_1 columns, while on the other, it also interlinked the 2_1 columns along the *b*-axis (Fig. 5). In addition to the hydrogen-bonding, the

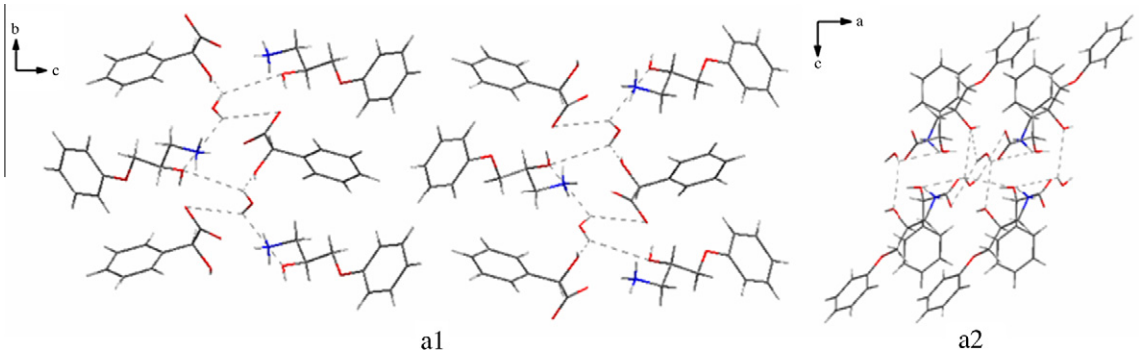

Figure 4. Crystal structure of (*S*)-**1**·(*S*)-**2**·H_2O. **a1** Two 2_1 columns viewed along *a*-axis. **a2** Two 2_1 columns viewed along *b*-axis. The dotted lines represent hydrogen bonds.

CH/π interaction also helped with the stability of the salt (*S*)-**1**·(*S*)-**2**·H_2O.

3. Conclusion

Enantiopure 1-amino-3-phenoxypropan-2-ol (*S*)-**2**, a new resolving agent, has been used to resolve *rac*-**1** with good chiral-recognition ability and high resolution efficiency. A new resolution process for *rac*-**1** based on the Pope and Peachey method has been established. Compound (*S*)-**2**, LiOH, and water were found to be a suitable resolving agent, supplementary base, and solvent, respectively. When *rac*-**1**/(*S*)-**2**/LiOH was 1.0/0.9/0.1, the less soluble salt (*S*)-**1**·(*S*)-**2**·H_2O was obtained in 77% yield and 98% de (*E* 75%). A water molecule was found to play a key role in forming the less soluble salt crystals. In the crystal of (*S*)-**1**·(*S*)-**2**·H_2O, the hydrogen-bonding and CH/π interactions aided the stability of the salt.

4. Experimental

4.1. General

Compound *rac*-**1** was purchased from Sinopharm Chemical Reagent Co., Ltd, the resolving agents (*S*)-**2**, (*S*)-**3**, and (*S*)-**4** were synthesized according to the reported method[10] and determined by NMR and HPLC. ^1H NMR and ^{13}C NMR were recorded at 400 MHz and 100 MHz on a Bruke Avance II, and spectroscopic data are reported in ppm relative to tetramethylsilane (TMS) as the internal standard. IR spectra were measured on a JASCO FT/IR-230 spec-

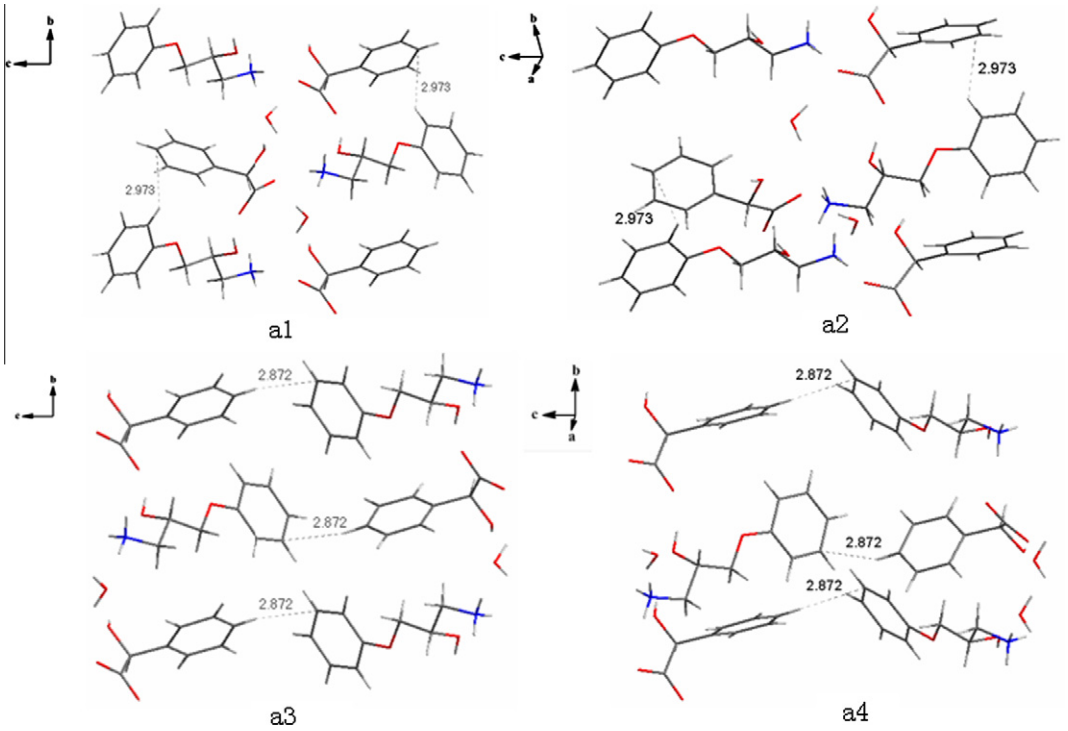

Figure 5. Crystal structure of (*S*)-**1**·(*S*)-**2**·H_2O. **a1** CH/π interaction in one 2_1 column viewed along the *a*-axis. **a2** CH/π interaction in one 2_1 column viewed from a certain angle. **a3** CH/π interaction between two 2_1 columns viewed along the *a*-axis. **a4** CH/π interaction between two 2_1 columns viewed from a certain angle. The dotted lines indicate short CH/π distances D_{atm} (Å).

trometer in KBr pellets. Melting points were obtained on a YAMATO apparatus MLDEL MP-21.

4.2. Preparation of resolving agents (*S*)-2, (*S*)-3, and (*S*)-4

Phenol (32 g, 0.34 mol) was added to the mixture of (*S*)-epichlorohydrin (265 mL, 3.4 mol, 10 equiv) and K_2CO_3 (61 g, 0.44 mol, 1.3 equiv). The mixture was kept at 110 °C for 2–3 h followed by filtration and concentrated under vacuum. The residue (50 g, 0.33 mol) was added dropwise into excess ammonia water (2500 mL, 3.3 mol) for 24 h at room temperature. Next the mixture was filtered and the solution was evaporated under vacuum. The residue was recrystallized with ethyl acetate (2 × 80 mL) to give the precipitate (*S*)-**2** (39.7 g, 0.24 mol, yield: 72%).

(*S*)-**2**. Yield: 72%; mp: 102–110 °C; IR (KBr) cm^{-1}: 3375, 3074, 3063, 3008, 2965, 2936, 2841, 1593, 1509, 1465, 1450, 1346, 1331, 1295, 1258, 1231, 1188, 1125, 1054, 1025, 913, 860, 826, 778, 747; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33–7.28 (m, 2H), 7.01–6.93 (m, 3H), 4.17-4.11 (m, 1H), 4.04–4.02 (m, 2H), 2.95 (dd, *J* = 12.0, 4.0 Hz, 1H), 2.89 (dd, *J* = 12.4, 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 158.55, 129.53, 121.19, 114.57, 70.25, 68.77, 51.86. HRMS (ESI) calcd for $C_9H_{13}NO_2$ $[M+H]^+$: 168.1025, found 168.1031. The ee value of (*S*)-**2** was determined by HPLC on Lux Cellulose-1 (4.6 mm × 250 mm I.D., 3 μm, Phenomenex) (hexane/ethanol = 50:50 with 0.2% diethylamine, 0.8 mL/min), UV 224 nm, $t_{(R)\text{-}\mathbf{2}}$ = 6.10 min, $t_{(S)\text{-}\mathbf{2}}$ = 11.67 min. $[\alpha]_D^{24} = -10.5$ (*c* 1.0, ethanol).

(*S*)-**3** was prepared using the same method as (*S*)-**2**. (*S*)-**3**. Yield:76%; mp: 36–46 °C; IR (KBr) cm^{-1}:3322, 3104, 3068, 3038, 2970, 2944, 2926, 2865, 2804, 1598, 1586, 1496, 1480, 1449, 1437, 1351, 1304, 1247, 1173, 1148, 1127, 1082, 1035, 969, 927, 910, 826, 813, 761, 690; ^1H NMR (400 MHz, $CDCl_3$) *δ* 7.33–7.28 (m, 2H), 7.00–6.93 (m, 3H), 4.14–4.09 (m, 1H), 4.02–4.01 (m, 2H), 2.85 (dd, *J* = 12.0, 4.0 Hz, 1H), 2.79 (dd, *J* = 12.0, 7.2 Hz, 1H), 2.51 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 158.64, 129.50, 121.07, 114.54, 70.37, 68.11, 53.90, 36.41. HRMS (ESI) calcd for $C_{10}H_{15}NO_2$ $[M+H]^+$: 182.1181, found 182.1180. The ee value of (*S*)-**3** was determined by HPLC on Lux Cellulose-1 (4.6 mm × 250 mm I.D., 3 μm, Phenomenex) (hexane/ethanol = 50:50 with 0.2% diethylamine, 0.8 mL/min), UV 224 nm, $t_{(R)\text{-}\mathbf{3}}$ = 5.11 min, $t_{(S)\text{-}\mathbf{3}}$ = 6.49 min. $[\alpha]_D^{25} = -16.0$ (*c* 1.0, ethanol).

(*S*)-**4** was prepared using the same method as (*S*)-**2**. (*S*)-**4**. Yield: 87%; mp: 83–87 °C; IR (KBr) cm^{-1}: 3315, 3051, 2969, 2925, 2868, 2837, 1598, 1584, 1491, 1447, 1380, 1333, 1296, 1241, 1173, 1147, 1109, 1085, 1034, 1018, 894, 846, 813, 761, 697; ^1H NMR (400 MHz, $CDCl_3$) *δ* 7.33–7.28 (m, 2H), 7.00–6.93 (m, 3H), 4.12–4.06 (m, 1H), 4.00 (d, *J* = 5.2 Hz, 2H), 2.90 (dd, *J* = 12.0, 4.0 Hz, 1H), 2.82–2.69 (m, 3H), 2.48 (s, 2H), 1.16 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 158.69, 129.48, 121.03, 114.57, 70.48, 68.33, 51.66, 44.12, 15.35. HRMS (ESI) calcd for $C_{11}H_{17}NO_2$ $[M+H]^+$: 196.1338, found 196.1335. The ee value of (*S*)-**4** was determined by HPLC on Lux Cellulose-1 (4.6 mm × 250 mm I.D., 3 μm, Phenomenex) (hexane/ethanol = 50:50 with 0.2% diethylamine, 0.8 mL/min), UV 224 nm, $t_{(R)\text{-}\mathbf{4}}$ = 4.45 min, $t_{(S)\text{-}\mathbf{4}}$ = 6.86 min. $[\alpha]_D^{19} = -13.0$ (*c* 1.0, ethanol).

4.3. Preparation of the less soluble salt

The traditional resolution procedure is as follows (Table 2, entry 2): to a 5 mL flask were added *rac*-**1** (152 mg, 1 mmol), (*S*)-**2** (167 mg, 1 mmol), and water (1 mL). The solution was then kept at 70 °C for 0.5 h. Next, the solution was gradually cooled to 25 °C and kept for 12 h. The precipitate was filtered off and washed with cooled water (0.3 mL) to afford (*S*)-**1**·(*S*)-**2**·H_2O (183 mg, 0.54 mmol, yield 109%, 65% de, *E* 71%).

The Pope and Peachey resolution procedure is as follows (Table 5, entry 3): to a 5 mL flask were added *rac*-**1** (152 mg, 1 mmol), (*S*)-**2** (150 mg, 0.9 mmol), LiOH (2.4 mg, 0.1 mmol), and water (1 mL). The solution was then kept at 70 °C for 0.5 h. The solution was gradually cooled to 25 °C and kept for 12 h. The precipitate was filtered and washed with cooled water (3 × 0.3 mL) to afford (*S*)-**1**·(*S*)-**2**·H_2O (128 mg, 0.38 mmol, yield 76%, 98% de, *E* 74%).

(*S*)-**1**·(*S*)-**2**·H_2O: mp: 127–129 °C; IR (KBr) cm^{-1}: 3489, 3414, 3230, 3065, 2925, 1611, 1596, 1583, 1496, 1457, 1421, 1339, 1293, 1266, 1248, 1235, 1182, 1082, 1058, 972, 753, 703, 693, 531, 517; ^1H NMR (400 MHz, DMSO) *δ* 7.39–7.37 (d, *J* = 7.6 Hz, 2H), 7.32–7.22 (m, 4H), 7.18–7.15 (m, 1H), 6.97–6.93 (m, 3H), 4.58 (s, 1H), 4.04–4.02 (m, 1H), 3.96–3.89 (m, 2H), 3.00 (dd, *J* = 12.8, 3.2 Hz, 1H), 2.79 (dd, *J* = 12.8, 8.8 Hz, 1H). ^{13}C NMR (100 MHz, DMSO) *δ* 175.77, 158.78, 143.95, 129.96, 127.87, 126.76, 126.63, 121.19, 114.93, 73.97, 70.00, 66.43, 42.39. $[\alpha]_D^{23} = +27.0$ (*c* 1.0, ethanol).

4.4. Preparation of (*S*)-1 from the less soluble salt

The crystal (*S*)-**1**·(*S*)-**2**·H_2O (100 mg, 0.31 mmol) was dissolved in H_2O (5 mL) and diluted with HCl (1 M, 0.94 mL). The mixture was extracted by ethyl acetate (3 × 5 mL) and dried over anhydrous Na_2SO_4. The solution was concentrated under reduced pressure to give (*S*)-**1** (45 mg, 0.30 mmol). The ee value of (*S*)-**1** was determined by HPLC on Lux Cellulose-1 (4.6 mm × 250 mm I.D., 3 μm, Phenomenex) (hexane/ethanol = 90:10 with 0.15% trifluoroacetic acid, 0.8 mL/min), UV 210 nm, $t_{(S)\text{-}\mathbf{1}}$ = 9.67 min, $t_{(R)\text{-}\mathbf{1}}$ = 12.19 min.

Acknowledgments

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