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Lecture Transcripts

(*S*)-3-Methyl-2-phenylbutylamine, a Versatile Agent to Resolve Chiral, Racemic Carboxylic Acids[1]

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Abstract:

(*S*)-Ibuprofen 2, (*S*)-ketoprofen 3, and (*S*)-naproxen 4 are all obtained by optical resolution of the respective racemates with (*S*)-3-methyl-2-phenylbutylamine (PBA) 1: (*S*)-2, 98.7% ee, 39.8% yield; (*S*)-3, 99.4% ee, 36.7% yield; (*S*)-4, 99.2% ee, 35.1% yield. (*S*)-PBA 1 is also useful in resolving other racemic carboxylic acids of pharmaceutical importance; (*R*)-2-hydroxy-4-phenylbutanoic acid (HPBA) 5, a key intermediate for ACE inhibitors such as benazapril 7, and (*S*)-2-benzylsuccinic acid (BSA) 6, a key intermediate for hypoglycemic KAD-1229 8, are obtained in 99% ee and 34.4% yield, and in 99% ee and 32.2% yield, respectively.

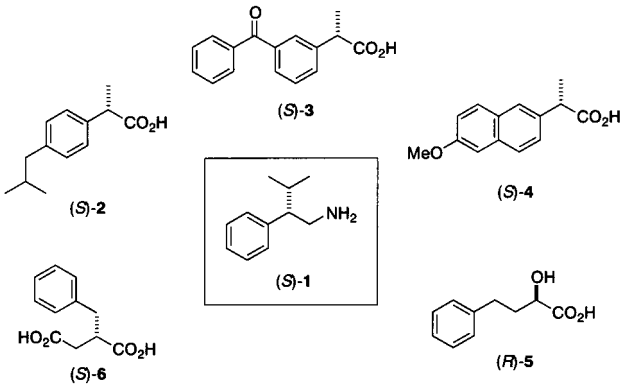

Figure 1. **Structures of (*S*)-PBA 1 and the carboxylic acid enantiomers 2−6 resolved by (*S*)-1.**

Introduction

Optical resolution still represents a practical method to produce single enantiomers on an industrial scale, notwithstanding the recent great progress in both chemocatalytic and biocatalytic asymmetric synthesis.[2] However, the diversity of resolving agents has not expanded as widely as that of chiral catalysts.[3] In this communication, we introduce a new resolving agent of the β-alkyl-β-phenethylamine type, (*S*)-3-methyl-2-phenylbutylamine (PBA) **1** (Figure 1),[4,5] and demonstrate its versatility through select case studies. Carboxylic acid enantiomers that have been resolved by (*S*)-PBA **1** are as follows: (*S*)-ibuprofen **2**, (*S*)-ketoprofen **3**, (*S*)-naproxen **4**, (*R*)-2-hydroxy-4-phenylbutanoic acid (HPBA) **5**, and (*S*)-2-benzylsuccinic acid (BSA) **6** (Figure 1).

Results and Discussion

Early in the 1990s when we commenced an optical resolution program featuring (*S*)-PBA **1**, a racemic switch of Profen NSAIDs (nonsteroidal antiinflammatory drugs of the α-arylpropionic acid type) was in such vogue that various chiral technologies were developed to synthesize selectively their (*S*)-isomers in which the inhibitory activity against cyclooxygenases exclusively resided.[6] The enantioselective approaches covered optical resolution via diastereomeric salt

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(2) For a comprehensive review from an industrial viewpoint see: *Handbook of CHIRAL CHEMICALS*; Ager, D. J., Ed.; Marcel Dekker: New York, 1999.

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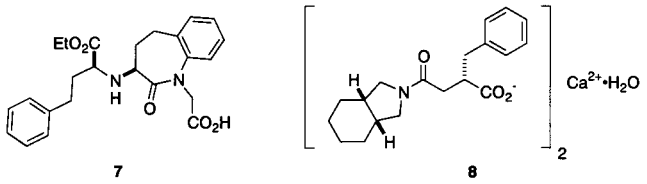


7 8

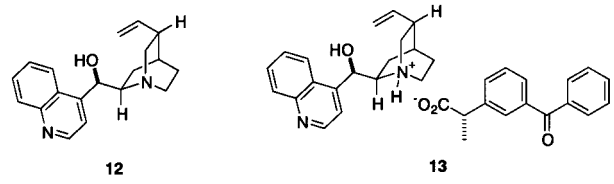
Figure 2. **Structures of benazapril 7 and KAD-1229 8.**

formation for (*S*)-ibuprofen **2**,[6,7] (*S*)-ketoprofen **3**,[8] and (*S*)-naproxen **4**;[6,9a,b] enzymatic kinetic resolution for (*S*)-**2**[6,7] and (*S*)-**4**;[6,9a,b] and asymmetric synthesis for (*S*)-**2**[6,7] and (*S*)-**4**.[6,9]

Although the pharmaceutical industry's enthusiasm for the profen-racemic switch soon diminished,[6] the process development of single-enantiomer drugs has remained a major technological concern. In fact, (*R*)-HPBA **5**, a key intermediate for antihypertensive ACE (angiotensin II converting enzyme) inhibitors such as benazapril **7** (Figure 2),[10] has drawn a wide range of synthetic challenges: asymmetric synthesis[11a] and enzymatic kinetic resolution.[11b,c] In addition, (*S*)-BSA **6** is employed as a key intermediate for hypoglycemic KAD-1229 **8** (Figure 2),[12] while it has represented a target for enantioselective synthesis via catalytic asymmetric hydrogenation[13a] since its first optical resolution reported more than 50 years ago.[13b]

Hence, we have attempted to apply (*S*)-PBA **1** to the optical resolution of (±)-**2**, (±)-**3**, (±)-**4**, (±)-**5**, and (±)-**6**, and each successful result is discussed below.

(*S*)-Ibuprofen 2. (±)-Ibuprofen **2** (1.0 equiv) was combined with (*S*)-**1** (0.5 equiv) in an aqueous solution of KOH (0.5 equiv), and the resulting solution was heated at reflux. When the solution was allowed to cool to ambient temperature, the diastereomeric salt **9** precipitated in 47.0% yield based on the whole amount of (±)-**2** (Scheme 1), and the salt was shown to contain (*S*)-**2** of 85.0% ee by chiral HPLC analysis (Daicel Chiralcel OJ). Its single recrystallization from 6.25:1 MeOH−H_2O increased the optical purity of (*S*)-**2** contained in the salt up to 98.7% ee as determined by the chiral HPLC analysis. The purified salt **9** obtained in 86.8% yield was treated with 2.0 M NaOH aqueous solution to liberate the free acid (*S*)-**2** of 98.7% ee in 97.6% yield [39.8% overall yield from (±)-**2**].



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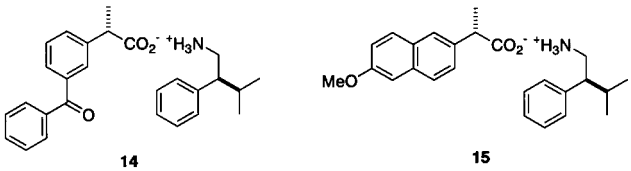
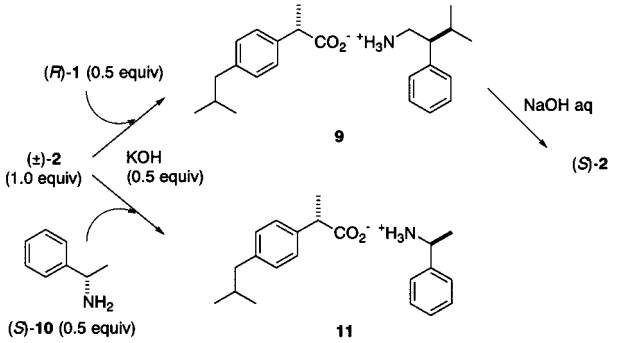


14 15

Figure 3. **Structures of (−)-cinchonidine 12 and diastereomeric salts 13−15.**

Scheme 1. **Optical resolution of (±)-ibuprofen 2**



For the purpose of comparison, (±)-ibuprofen **2** was resolved by (*S*)-α-phenethylamine **10** under the same conditions as described above (Scheme 1), which were identical to those disclosed in the patent literature.[7a] To obtain the diastereomeric salt **11** containing (*S*)-**2** of 98.7% ee, recrystallization had to be repeated as many as three times, giving the purified **11** in 21.7% overall yield. These results have clearly demonstrated that (*S*)-**1** is twice as efficient as (*S*)-**10** in resolving (±)-ibuprofen **2** into its (*S*)-enantiomer.

(*S*)-Ketoprofen 3. It was reported in the patent literature[8] that (±)-ketoprofen **3** was resolved by (−)-cinchonidine **12** as follows (Figure 3): (±)-Ketoprofen **3** (1.0 equiv) was combined with **12** (1.0 equiv) in methyl isobutyl ketone (MIBK).[8b] After the precipitated diastereomeric salt **13** was recrystallized once from MIBK, (*S*)-**3** of 76.5% ee was liberated in 33.2% overall yield.

On the basis of this precedent, the diastereomeric salt formation between (*S*)-**3** and (S)-**1** was initially attempted in MIBK. When (±)-**3** (1.0 equiv) was combined with (*S*)-**1** (0.6 equiv) in MIBK, the diastereomeric salt **14** precipitated preferentially (Figure 3). After its single recrystallization, the free acid (*S*)-**3** was liberated in 36% overall yield, and its optical purity was determined to be 99.2% ee by chiral HPLC analysis (Waters Opti Pak TA).

Next, each experimental parameter was explored to maximize the resolution efficiency. As a result, wet *tert*-butyl ether (MTBE) turned out to be the crystallization solvent of choice. Under the optimized conditions, (±)-**3** (1.0 equiv) was combined with (*S*)-**1** (0.5 equiv) in MTBE

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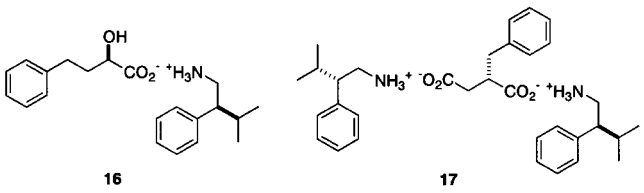

16 17

Figure 4. **Structures of diastereomeric salts 16 and 17.**

containing 12.5% (w/w) water [half weight of (±)-**3**], and the diastereomeric salt **14** precipitated preferentially in 37.7% yield. The chiral HPLC analysis showed that the salt contained (*S*)-**3** of 99.1% ee. Without further purification, it was treated with HCl aqueous solution to give the free acid (*S*)-**3** in 99.4% ee and 36.7% overall yield from (±)-**3**.

(*S*)-Naproxen 4. (±)-Naproxen **4** had been resolved into its (*S*)-enantiomer by (−)-cinchonidine **12** as reported in the review article.[9b] Encouraged by this precedent and our successful experience in replacing **12** with (*S*)-PBA **1** in the optical resolution of (±)-ketoprofen **3**, we undertook the optical resolution of (±)-**4** by (*S*)-**1**.

When (±)-**4** (1.0 equiv) was combined with (*S*)-**1** (0.51 equiv) in 2-propanol (IPA), the diastereomeric salt **15** precipitated preferentially in 43% yield (Figure 3), and the optical purity of (*S*)-**4** contained in the salt was determined to be 86.5% ee by chiral HPLC analysis [Daicel Crownpak CR (+)]. After single recrystallization from MeOH, the purified salt **15** was treated with 1.0 M HCl aqueous solution to liberate the free acid (*S*)-**4** in 99.2% ee and 35.1% overall yield from (±)-**4**.

(*R*)-HPBA 5. (±)-HPBA **5** was best resolved by (*S*)-**1** in a water-immiscible organic solvent that contained a controlled amount of H_2O, as was the case with the optimum conditions to resolve (±)-ketoprofen **3** by (*S*)-**1**. When (±)-**5** (1.0 equiv) was combined with (*S*)-**1** (1.0 equiv) in warm toluene (PhMe) containing 1.2% (w/w) water, the diastereomeric salt **16** precipitated preferentially in 37.5% yield (Figure 4), and the optical purity of (*R*)-**5** contained in the salt was determined to be 94.5% ee by chiral HPLC analysis (Daicel Crownpak OD). After single recrystallization from PhMe containing 1.2% (w/w) water, the optical purity of (*R*)-**5** contained in the purified **16** was increased up to 99.0% ee as determined by the chiral HPLC analysis. The purified salt **16** obtained in 93.4% yield was treated with dilute NaOH aqueous solution. After extracting the free base (*S*)-**1** into PhMe, the aqueous layer was acidified to pH < 2 with concentrated HCl to allow the free acid (*R*)-**5** to precipitate in 99.0% ee in 98.1% yield [34.4% overall yield from (±)-**5**].

(*S*)-BSA 6. (±)-BSA **6** being a dibasic acid, (S)-**1** would be required in 4 equiv based on (*S*)-**6**, if the whole amount of (±)-**6** were to be neutralized in forming diastereomeric salt **17** (Figure 4), which always precipitated preferentially and independently of the ratio of (S)-**1** to (±)-**6**. Thus, to save the loading of (S)-**1**, we attempted to neutralize the unwanted (*R*)-isomer with an achiral inorganic base.

After extensive experimentation, the economy of the resolving agent was realized without compromising the resolution efficiency as follows: When (±)-**6** (1.0 equiv) was combined with (*S*)-**1** (1.3 equiv) in an aqueous solution of NaOH (0.7 equiv), the diastereomeric salt **17** precipitated preferentially in 37.5% yield. The optical purity of (*S*)-**6** contained in the salt was determined to be 93.8% ee by chiral HPLC analysis (Daicel Chiralcel OD). After single recrystallization from water, the optical purity of (*S*)-**6** contained in the purified salt was increased up to 99.9% ee as shown by the chiral HPLC. The purified salt **17** obtained in 86.8% yield was treated with NaOH aqueous solution, and the free base (*S*)-**1** was extracted into PhMe. The remaining aqueous mixture was then acidified with concentrated HCl to allow the free acid (*S*)-**6** to precipitate in not less than 99.0% ee and 98.8% yield [32.2% overall yield from (±)-**6**].

Table 1. **Optical resolution with (*S*)-PBA 1**

acid resolved	ratio[a]	yield (%)[b]	no.[c]	ee (%)[d]	E[e]
2	0.50	39.8	1	98.7	39.4
3	0.50	36.7	0	99.4	36.5
4	0.51	35.1	1	99.2	34.8
5	1.0	34.4	1	99.0	34.1
6	1.3	32.2	1	99.0	31.8

[a] A molar ratio of (*S*)-**1** to each racemic acid. [b] Overall yield (%) of the resolved acid based on the whole amount of racemic acid. [c] Number of recrystallization times. [d] Optical purity (% ee) of the resolved acid. [e] E = yield (%)[b] × ee (%)[d]/100.

Conclusions

As summarized in Table 1, (*S*)-ibuprofen **2**, (*S*)-ketoprofen **3**, (*S*)-naproxen **4**, (*R*)-HPBA **5**, and (*S*)-BSA **6** were all obtained successfully via optical resolution of the respective racemates by the use of SPBA **1** as the sole resolving agent.

The comments worth making are as follows: (1) in each case, high-resolution efficiency has been achieved as shown by $E > 30$,[14] where E = yield (%) × ee (%)/100 with the maximum value set as 50; (2) single recrystallization would often suffice to obtain the carboxylic acid enantiomer of not less than 99% ee; (3) when the diastereomeric salt formation or recrystallization is run in water-immiscible organic solvent, inclusion of a controlled amount of water should be beneficial; (4) the loading of (*S*)-PBA **1** should be saved by selective neutralization of the unwanted enantiomer with an achiral inorganic base, such as KOH and NaOH.

Experimental Section

Melting points were measured on an Electrothermal 1A8104 melting point apparatus and uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, on a Varian UNITY-400 spectrometer in a $CDCl_3$ or DMSO-d_6 solution with tetramethylsilane as an internal standard. FT-IR spectra were recorded on a Perkin-Elmer 1600 spectrometer. Mass spectra were recorded on a Hitachi M-8000 mass spectrometer (ESI). Elemental analyses were performed on an Elementar vario EL analyzer. Optical rotations were measured on a Horiba SEPA-200 polarimeter.

1. Optical Resolution of (±)-Ibuprofen 2 by (*S*)-PBA 1. 1.1. (*S*)-3-Methyl-2-phenylbutylammonium (*S*)-2-(4-Isobutylphenyl)propionate 9. After a solution of (±)-**2** (51.5

(14) The optical resolution of (±)-**2** by (*S*)-**1** is now being practiced on an industrial scale with a slight modification to supply (*S*)-**2** to the pharmaceutical market.

g, 250 mmol) and KOH (85%, 8.25 g, 125 mmol) in H_2O (250 mL) was stirred and heated at reflux, (*S*)-**1** (20.4 g, 125 mmol) was added dropwise over 20 min. After the heating was continued at a refluxing temperature for 20 min, the mixture was allowed to cool to ambient temperature. The precipitated solids were collected by filtration at ambient temperature, washed with ice-chilled water, and dried in vacuo to give crude **9** [43.4 g; 94.0% yield based on (*S*)-**1**, 47.0% yield based on the whole amount of (±)-**2**], which contained (*S*)-**2** of 85% ee {$[\alpha]^{25}_D$ +50.1 (*c* 1.0, MeOH)} as determined by HPLC [Chiralcel OJ (Daicel) 4.6 mmϕ × 250 mm; *n*-hexane:IPA:trifluoroacetic acid (TFA) (100:0.8:0.1), 1.3 mL/min, 25 °C; 254 nm; after 5% HCl aqueous solution (5.0 mL) was added to the crude salt **9** (50 mg), the mixture was extracted with *n*-hexane (5.0 mL), and 10 μL of the *n*-hexane solution was injected; t_R 18.5 min for (*S*)-**2**, 26.6 min for (*R*)-**2**]. The solids thus obtained (40 g) were recrystallized from MeOH (250 mL) and H_2O (40 mL) to give purified **9** [34.7 g, 86.8% yield; 40.8% overall yield based on the whole amount of (±)-**2**], and the optical purity of (*S*)-**2** contained in it was 98.7% ee {$[\alpha]^{25}_D$ +59.1 (*c* 1.0, MeOH)} as determined by the HPLC method described above; purified **9**: mp 170−171 °C; $[\alpha]^{25}_D$ −10.1 (*c* 1.06, EtOH); IR ν (KBr) 2964 (s), 2875 (m), 2665 (w), 2200 (w), 1637 (s),1549 (s), 1454 (s), 1384 (m), 1288 (s), 1217 (m), 1176 (m), 1062 (m), 881 (m), 845 (m), 791 (m), 706 (m), 580 (w) cm^{-1}. Anal. calcd for $C_{24}H_{35}NO_2$: C, 78.00; H, 9.55; N, 3.79; found: C, 77.9; H, 9.4; N, 3.7.

1.2. (*S*)-Ibuprofen 2. To the purified **9** (17.5 g, 41.8 mmol) was added 1.0 M NaOH aqueous solution (52 mL). After the mixture was extracted with diisopropyl ether (IPE; 30 mL × 2) to recover (*S*)-**1**, the aqueous layer was acidified with 3.0 M HCl aqueous solution (30 mL) and extracted with IPE (30 mL × 3). The combined IPE extracts were dried ($MgSO_4$) and concentrated in vacuo to give (*S*)-**2** as a colorless oil (8.41 g, 97.6%), which solidified spontaneously on standing at ambient temperature; its optical purity was determined to be 98.7% ee by the HPLC method described above in which 10 μL of a solution of (*S*)-**2** (10 mg) in *n*-hexane (2.0 mL) was injected: mp 52−53 °C [lit.:[7a] mp 40−48 °C for 99% pure (*S*)-**2**]; $[\alpha]^{25}_D$ +59.0 (*c* 1.0, MeOH) {lit.:[7a] $[\alpha]_D$ +56 for (*S*)-**2** of 99% purity}. IR ν (KBr) 2976 (m), 2638 (w), 1706 (s), 1510(s), 1467 (s), 1417 (s), 1381 (m), 1283 (s), 1228 (m), 1184 (m), 1053 (m), 945 (m), 866 (m), 779 (m), 655 (m), 590 (m), 428 (m) cm^{-1}; ^{1}H NMR δ ($CDCl_3$) 7.21 (d, J = 8.0 Hz, 2H), 7.09 (d, J = 8.0 Hz, 2H), 3.70 (q, J = 7.2 Hz, 1H), 2.44(d, J = 6.8 Hz, 2H), 1.95−1.75 (m, 1H), 1.49 (d, J = 7.2 Hz, 3H), 0.89(d, J = 7.2 Hz, 6H); MS *m*/*z* 205 {$[M - H]^-$}.

2. Optical Resolution of (±)-Ketoprofen 3 by (*S*)-PBA 1. 2.1. (*S*)-3-Methyl-2-phenylbutylammonium (*S*)-2-(3-Benzoylphenyl)propionate 14. To a stirred solution of (±)-**3** (1.20 kg, 4.72 mol) in MTBE (4.80 L) was added H_2O (600 g), and the mixture was warmed to 50−55 °C, during which it became homogeneous with increasing temperature. To this solution was added (*S*)-**1** (388 g, 2.38 mol) dropwise at the same range of temperature over 30 min. The mixture was allowed to cool to 35 °C, during which solids started to precipitate. After the mixture was warmed to 50 °C, it was allowed to cool to 40 °C, and warmed again up to 45 °C. After the mixture was allowed to cool to 10 °C over 1 h, the stirring was continued at 5−10 °C for 1 h. The precipitated solids were collected by filtration, washed with ice-chilled MTBE (1.0 L × 3), and dried in vacuo to give **14** [741 g, 37.7% based on the whole amount of (±)-**3**], which contained (*S*)-**3** of 99.1% ee as determined by HPLC [Opti Pak TA (Waters) 3.9 mmϕ × 300 mm; *n*-hexane:IPA:TFA (92:8:0.3), 1.0 mL/min, ambient temperature; 255 nm; after 5% HCl aqueous solution (5.0 mL) was added to **14** (50 mg), the mixture was extracted with *n*-hexane (5.0 mL), and 10 μL of the *n*-hexane solution was injected; t_R 20.3 min for (*S*)-**3**, 14.7 min for (*R*)-**3**]; **14**: mp 131.0−132.0 °C; $[\alpha]^{25}_D$ +10.2 (*c* 1.0, EtOH); IR ν (KBr) 2978 (m), 2962 (m), 2929 (m), 1647 (s), 1636 (s), 1552 (s), 1533 (s), 1387 (s), 1319 (m), 1281 (m), 1246 (m), 710 (s) cm^{-1}. Anal. calcd for $C_{27}H_{31}NO_3$: C, 77.67; H, 7.48; N, 3.35; found: C, 77.5; H, 7.4; N, 3.3.

2.2. (*S*)-Ketoprofen 3. The diastereomeric salt **14** thus obtained (720 g, 1.72 mol) was poured into a stirred 4% (w/v) HCl aqueous solution (2.28 kg), and the mixture was made homogeneous by warming up to 50 °C. The stirred mixture was allowed to cool to 15 °C, during which solids started to precipitate. After H_2O (0.79 L) was added at the same temperature, the mixture was allowed to cool to 10 °C, and the stirring was continued at 5−10 °C for 2 h. The precipitated solids were collected by filtration, washed with H_2O (1.0 L × 3), and dried in vacuo to give (*S*)-**3** as a white powder (431 g, 98.3%), the optical purity of which was determined to be 99.4% ee by the HPLC method described above in which 5 μL of a solution of (*S*)-**3** (10 mg) in IPA (20 mL) was injected: mp 76.8−77.4 °C [lit.:[8a] mp 73.2−74.7 °C for (*S*)-**3** of 97% ee]; $[\alpha]^{25}_D$ +46.3 (*c* 1.0, MeOH) {lit.:[8a] $[\alpha]_D$ +54.3 for (*S*)-**3** of 97% ee}; IR ν (KBr) 3211 (m), 2982 (m), 2941 (m), 2879 (m), 1728 (v s), 1687 (m), 1655 (s), 1284 (m), 1173 (m), 1157 (m), 829 (m), 716 (m), 700 (m) cm^{-1}; ^{1}H NMR δ ($CDCl_3$) 1.56 (3H, d, J = 7.2 Hz), 3.83 (1H, q, J = 7.2 Hz), 7.45 (1H, t, J = 8.0 Hz), 7.47 (2H, t, J = 8.0 Hz), 7.56 (1H, t, J = 8.0 Hz), 7.59 (1H, t, J = 8.0 Hz), 7.69 (1H, t, J = 8.0 Hz), 7.78 (1H, s), 7.79 (2H, d, J = 8.0 Hz), 9.00−12.00 (1H, br s); MS *m*/*z* 253 {$[M - H]^-$}.

3. Optical Resolution of (±)-Naproxen 4 by (*S*)-PBA 1. 3.1. (*S*)-3-Methyl-2-phenylbutylammonium (*S*)-2-(6-Methoxy-2-naphthyl)propionate 15. A mixture of (±)-naproxen **4** (10.0 g, 43.4 mmol) and IPA (120 mL) was stirred and warmed until it became homogeneous, and the resulting solution was further heated to 70 °C. After (*S*)-**1** (3.63 g, 22.2 mmol) was added dropwise, the mixture was allowed to cool to 30 °C over 1 h. The precipitated solids were collected by filtration, washed with IPA (15 mL), and dried to give crude **15** [7.35 g, 43.0% yield based on the whole amount of (±)-**4**], which contained (*S*)-**4** of 86.5% ee as determined by HPLC [Optipak-TA (Waters), 3.9 mmϕ × 300 mm; *n*-hexane:IPA:TFA (75:25:0.3), 0.8 mL/min, ambient temperature; 254 nm; 1.0 M HCl aqueous solution (1.0 mL) was added to the crude **15** (20 mg), and the mixture

was extracted with AcOEt (1.0 mL). A portion (0.5 mL) of the AcOEt extract was concentrated in vacuo to give a solid residue. After this was dissolved in IPA (1.0 mL), 10 μL of the IPA solution was injected; t_R 11.1 min for (*S*)-**4**, 13.0 min for (*R*)-**4**]. To 7.30 g (18.6 mmol) of the crude **15** was added MeOH (80 mL), and the mixture was stirred and warmed until it became homogeneous. After the stirred mixture was allowed to cool to 16 °C, the precipitated solids were collected by filtration, washed with MeOH (10 mL), and dried in vacuo to give purified **15** (6.20 g, 84.9%); the optical purity of (*S*)-**4** contained in it was determined to be 99.2% ee by the HPLC method described above; purified **15**: mp 184−185 °C; $[\alpha]^{25}_D$ −14.0 (*c* 0.96, MeOH); IR ν (KBr) 2956 (m), 2654 (w), 2179 (w), 1634 (s), 1605 (s), 1541 (m), 1392 (s), 1261 (s), 1211 (m), 1161 (m), 1032 (m), 928 (m), 854 (m), 812 (m), 708 (m), 671 (m), 471 (m) cm^{-1}. Anal. calcd for $C_{25}H_{31}NO_3$: C, 76.30; H, 7.94; N, 3.56; found: C, 76.2; H, 7.9; N, 3.5.

3.2. (*S*)-Naproxen 4. To the purified **15** (6.16 g, 15.7 mmol) was added 1.0 M HCl aqueous solution (20 mL) with stirring. The mixture was extracted with AcOEt, and the AcOEt extracts were washed with H_2O and concentrated in vacuo. The solid residue was suspended in *n*-hexane (10 mL), and the resulting heterogeneous mixture was stirred vigorously. The solids were collected by filtration and dried to give free acid (*S*)-**4** as a white powder (3.48 g, 96.3%), the optical purity of which was 99.2% ee as determined by the HPLC method described above in which 10 μL of a solution of (*S*)-**4** (5 mg) in IPA (1.0 mL) was injected: mp 152−154 °C (lit.:[9c] mp 154−155 °C); $[\alpha]^{20}_D$ +68.3 (*c* 1.0, $CHCl_3$) {lit.:[9c] $[\alpha]^{20}_D$ +68.5 (*c* 1.0, $CHCl_3$)}; IR ν (KBr) 3192 (w), 2962 (m), 2940 (m), 1927 (m), 1728 (s), 1684 (s), 1605 (s), 1506 (m), 1454 (m), 1395 (s), 1265 (s), 1229 (m), 1176 (m), 1028 (m), 864 (m), 820 (m), 673 (m), 484 (m) cm^{-1}; ^{1}H NMR δ ($CDCl_3$) 7.71−7.67 (m, 3H), 7.41 (dd, J = 2.0, 8.4 Hz, 1H), 7.13 (dd, J = 2.8, 8.8 Hz, 1H), 7.11 (d, J = 2.4 Hz, 1H), 3.91 (s, 3H), 3.88 (q, J = 7.2 Hz, 1H), 1.58 (d, J = 7. 2 Hz, 3H); MS *m*/*z* 229 {[M − H]$^-$}.

4. Optical Resolution of (±)-HPBA 5 by (*S*)-PBA 1. 4.1. (*S*)-3-Methyl-2-phenylbutylammonium (*R*)-2-Hydroxy-4-phenylbutanoate 16. After a stirred mixture of (±)-**5** (86.6 g, 0.48 mol), H_2O (3.5 g), and PhMe (300 g) was warmed to 60 °C, (*S*)-**1** (78.4 g, 0.48 mol) was added dropwise at the same temperature. The resulting solution was allowed to cool to 37 °C slowly and was seeded with **16** (99% ee for (*R*)-**5**; 0.01 g). After the mixture was allowed cool to 10 °C slowly, the precipitated solids were collected by filtration, washed with PhMe (121 g), and dried in vacuo to give crude **16** (61.9 g, 37.5%), which was shown to contain (*R*)-**5** of 94.5% ee by HPLC [Chiralcel OD (Daicel) 4.6 mmϕ × 250 mm; *n*-hexane:IPA:TFA (95:5:0.3), 1.0 mL/min, ambient temperature; 254 nm; after 1.0 M HCl aqueous solution (1.0 mL) was added to the crude **16** (20 mg), the mixture was extracted with ether (1.0 mL), and 10 μL of the ethereal extract was injected; t_R 16.1 min for (*R*)-**5**, 13.7 min for (*S*)-**5**]; crude **16**: mp 119.1 °C. The crude **16** (61.9 g, 0.18 mol) thus obtained was added to a stirred mixture of PhMe (214 g) and H_2O (2.5 g) in one portion. The mixture was stirred and heated to 60 °C where it became homogeneous. After the solution was allowed to cool to 10 °C slowly, the precipitated solids were collected by filtration, washed with PhMe (43.3 g), and dried in vacuo to give purified **16** as a white powder (57.8 g, 93.4%); the optical purity of (*R*)-**5** contained in it was 99.0% ee as determined by the HPLC method described above; purified **16**: mp 120.3 °C; $[\alpha]^{25}_D$ −1.63 (*c* 1.04, MeOH); IR ν (KBr) 3573 (s), 3025 (s), 2965 (s), 2906 (s), 2162 (w), 1639 (s), 1532 (s), 1493 (s), 1454 (s), 1408 (s), 1386 (m), 1300 (m), 1242 (m), 1095 (m), 1063 (s), 1030 (m), 919 (m), 703 (s) cm^{-1}. Anal. calcd for $C_{21}H_{29}NO_3$: C, 73.44; H, 8.51; N, 4.08; found: C, 73.3; H, 8.4; N, 4.0.

4.2. (*R*)-2-Hydroxy-4-phenylbutanoic acid (HPBA) 5. To the purified **16** (57.8 g, 0.17 mol) was added 2.9% NaOH aqueous solution (277 g), and the mixture was extracted with PhMe (52 g × 3) to recover (*S*)-**1**. After the aqueous layer was acidified to pH < 2 with concentrated HCl, the precipitated solids were collected by filtration and dried in vacuo to give free acid (*R*)-**5** as a white powder (29.7 g, 98.1%), the optical purity of which was determined to be 99.0% ee by the HPLC method described above in which 10 μL of a solution of (*R*)-**5** (about 6 mg) in IPA (2.0 mL) was injected: mp 116−118 °C (lit.:[11c] mp 113.3 °C); $[\alpha]^{20}_D$ −9.11. (*c* 2.70, EtOH) {lit.:[11c] $[\alpha]^{25}_D$ −8.3 (*c* 3.0, EtOH)}; IR ν (KBr) 3460 (s), 2928 (m), 2582 (w), 1732 (s), 1497 (s), 1454 (s), 1240 (m), 1173 (m), 1097 (m), 864 (m), 743 (m), 696 (m) cm^{-1}; ^{1}H NMR δ ($CDCl_3$) 7.35−7.15 (m, 5H), 6.20−5.60 (br s, 1H), 4.26 (dd, J = 4.0 Hz, 8.0 Hz, 1H), 2.79 (t, J = 8.0 Hz, 2H), 2.20−2.13 (m, 1H), 2.05−1.98(m, 1H); MS *m*/*z* 179 {[M − H]$^-$}.

5. Optical Resolution of (±)-BSA 6 by (*S*)-PBA 1. 5.1. Bis[(*S*)-3-methyl-2-phenylbutylammonium] (*S*)-2-Benzylsuccinate 17. To a stirred solution of (±)-**6** (1.30 kg, 6.24 mol) in H_2O (6.30 kg) was added 48% aqueous solution of NaOH (364 g, 4.37 mol) dropwise. After the stirred solution was warmed to 40 °C, (*S*)-**1** (1.32 kg, 8.11 mol) was added dropwise at the same temperature. After the stirred mixture was heated to 59 °C, it was allowed to cool to 50 °C, where the solution was seeded with **17** (1.0 g). After the stirring was continued at 50 °C for 1 h, the solution was allowed to cool to 35 °C, and it was kept at the same temperature for 1 h. The precipitated solids were collected by filtration at the same temperature, washed with H_2O (3.25 kg), and air-dried at 50 °C for 15 h to give **17** as a white powder [1.25 kg, 37.5% yield based on the whole amount of (±)-**6**], which contained (*S*)-**6** of 93.8% ee as determined by HPLC [Chiralcel OJ (Daicel) 4.6 mmϕ × 250 mm; *n*-hexane:IPA:TFA (95:5:0.3), 1.0 mL/min, ambient temperature; 220 nm; 1.0 M HCl aqueous solution (1.0 mL) was added to the crude **17** (10 mg), and the mixture was extracted with ether (0.5 mL). After the ethereal extract was concentrated in vacuo, the residue was dissolved in *n*-hexane (1.0 mL), and 10 μL of the *n*-hexane solution was injected; t_R 18.0 min for (*S*)-**6**, 15.3 min for (*R*)-**6**]. To the crude salt **17** (1.15 kg, 2.15 mol) was added H_2O (3.45 kg), and the mixture was stirred and heated to 80 °C where it became homogeneous. The stirred mixture was then allowed to cool to 72 °C, where it was

seeded with **17** (0.50 g). After the stirring was continued at the same temperature for 1 h, the mixture was allowed to cool to 10 °C slowly. The precipitated solids were collected by filtration and air-dried at 50 °C for 15 h to give purified **17** as a white powder (998 g, 86.8%), the optical purity of which was determined to be 99.9% ee by the HPLC method described above; purified **17**: mp 146.1−146.9 °C; $[\alpha]^{25}_{D}$ −23.3 (*c* 1.0, EtOH); IR *ν* (KBr) 2964 (s), 2785 (s), 2687 (s), 1630 (m), 1524 (s), 1452 (m), 1379 (s), 1198 (m), 766 (m), 698 (s), 654 (m), 544 (m) cm^{-1}. Anal. calcd for $C_{33}H_{46}N_2O_4$: C, 74.12; H, 8.67; N, 5.24; found: C, 74.1; H, 8.5; N, 5.1.

5.2. (*S*)-2-Benzylsuccinic Acid (BSA) 6. To a stirred mixture of the purified **17** (950 g, 1.78 mol) and H_2O (1.37 kg) was added 48% NaOH aqueous solution (343 g). After the layers were separated, the aqueous layer was extracted with PhMe (1.25 kg × 1; 625 g × 1) to recover (*S*)-**1**. To the aqueous layer was added concentrated HCl (586 g) with stirring at ambient temperature, and the stirred mixture was cooled to 5 °C. After the stirring was continued at the same temperature for 1 h, the precipitated solids were collected by filtration, washed with H_2O (700 mL), and air-dried at 50 °C for 48 h to give (*S*)-**6** as a white powder (366 g, 98.8%), the optical purity of which was determined to be 99.0% ee by the HPLC method described above: mp 162.0−163.8 °C; $[\alpha]^{25}_{D}$ −27.1 (*c* 1.5, AcOEt) {lit.:[13b] $[\alpha]^{22}_{D}$ −27.3 (*c* 1.46, AcOEt)}; IR *ν* (KBr) 3029 (m), 1712 (s), 1454 (m), 1434 (m), 1293 (m), 1239 (m), 1199 (m), 1153 (m), 944 (m), 761 (m), 705 (m) cm^{-1}; ^{1}H NMR *δ* (DMSO-d_6) 2.24 (dd, J = 17.0 Hz, J = 4.2 Hz, 1 H), 2.42 (dd, J = 17.0 Hz, J = 8.6 Hz, 1H), 2.73 (dd, J = 15.4 Hz, J = 9.8 Hz, 1H), 2.80−3.00 (m, 2 H), 7.16−7.23 (m, 3 H), 7.26−7.31 (m, 2H), 12.1−12.5 (br. s, 2 H); ^{13}C NMR (DMSO-d_6) *δ* 34.6, 36.7, 42.2, 126.1, 128.0, 128.7, 138.5, 172.6, 174.8; MS *m*/*z* 207 {$[M - H]^-$}, 163 {$[M - CO_2H]^-$}.

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