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# Unusual asymmetric oxidation of sulfide; the diastereoselective oxidation of prochiral sulfide-chiral acid salt with hydrogen peroxide without metal

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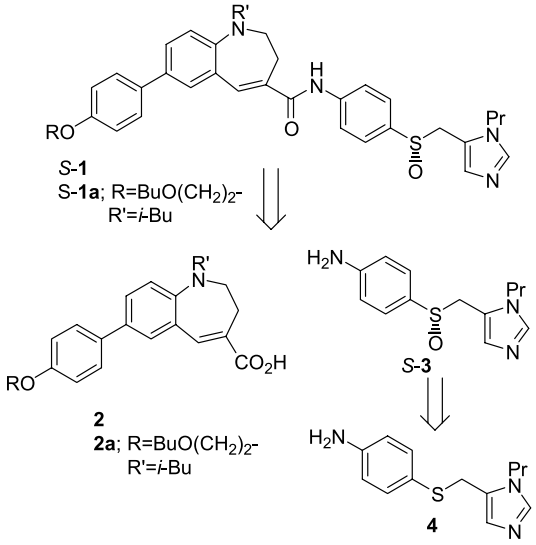
**Abstract**—The sulfide **4** was treated with chiral acid in a mixture of toluene and methyl *iso*-butylketone to precipitate the salt, which reacted with 30% $H_2O_2$ for 3 weeks at rt. The resulting crystals were collected followed by recrystallization to give the salt of enantiometrically pure sulfoxide and chiral acid **7** in 72% yield and 98.1% de, which was led to chiral sulfoxide *S*-**3** after neutralization. Sulfoxide *S*-**3** was led to *S*-**1a** as the candidate for an orally active HIV-1 therapeutic agent.


## 1. Introduction

Over the past three decades, many asymmetric synthetic methods have been developed in the pharmaceutical and agricultural industries because of switching to chiral compounds from racemic compounds.[1] For asymmetric oxidation, especially for enantioselective oxidation of sulfide, there have been many reports because of the increasing use of chiral sulfoxides both as biological products[2] and chiral auxiliaries.[3] Although the asymmetric oxidation of prochiral sulfides with chiral metal complexes such as Ti/diol, V, Ti and Mn/salen, and V-Schiff bases are generally used,[4] the Kagan method and its improvements are mainly used in preparations for a large scale.[5] However, these preparations have some drawbacks: (1) difficulty in removing or recovering the expensive auxiliaries, and (2) metals remaining in drug substances.

Recently, Seto et al. have reported that benzazepines having the chiral sulfoxide moiety *S*-**1** could be candidates for an orally active HIV-1 therapeutic agent, showing CCR5 antagonist activities.[6] In an early synthesis, *S*-**1** was prepared by the separation of *rac*-**1** using a chiral column by HPLC.[7] Therefore, the preparation of *S*-**1** amerable a large scale was required to support pharmacological and toxicological evaluations. To accomplish this goal, sulfide **4** was enantiometrically oxidated to give *S*-**3**, which led to *S*-**1** (Scheme 1).




**Scheme 1.**

## 2. Results and discussion

First, the preparation of *S*-**3** was conducted using the optical resolution of *rac*-**3**, which was produced by the alkylation of

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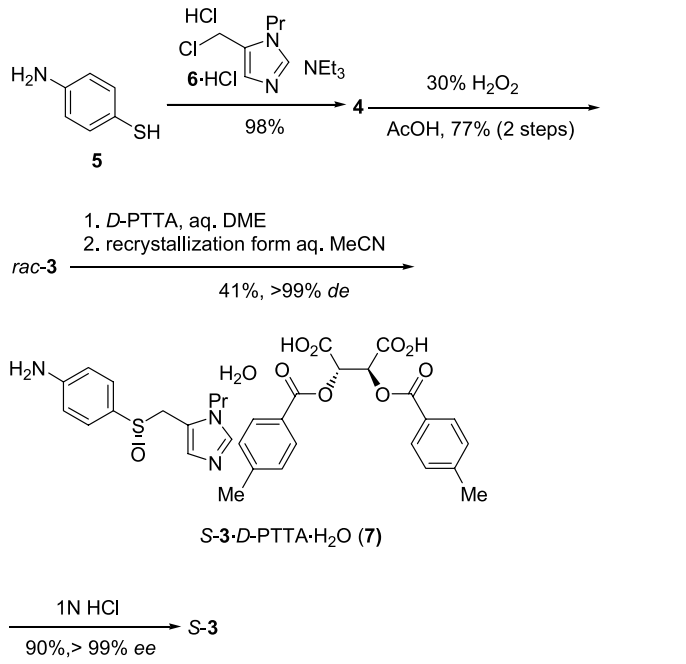



**Scheme 2.**

4-aminothiophenol **5** with 5-(chloromethyl)-1-propyl-1*H*-imidazole hydrochloride **6**·HCl[6a] and triethylamine in aqueous 2-propanol followed by the oxidation with 30% $H_2O_2$ in AcOH in 77% yield (2 steps) as shown in Scheme 2. Di-*p*-toluoyl-D-tartaric acid (D-PTTA) was found as a suitable acid of optical resolution by the screening of various acids. The optical resolution of *rac*-**3** was carried out with D-PTTA in aqueous 1,2-dimethoxyethane (DME) followed by recrystallization from aqueous MeCN to give *S*-**3**·D-PTTA monohydrate (**7**) in 41% yield and >99% de, which gave *S*-**3** in 90% yield and >99% ee after neutralization. The absolute configuration of **7** was determined by X-ray crystallographic analysis (Fig. 1).[8]

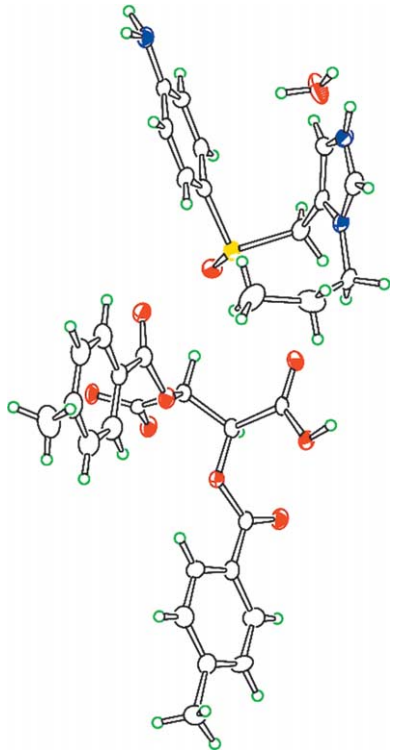
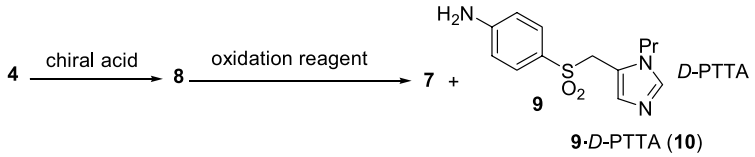


**Figure 1.** Molecular structure of **7**.

Next, the diastereoselective oxidation of the derivatives led from **4** was carried out. Namely, prochiral sulfide **4** yielded **8** by the salt formation with chiral acid, which was reacted with the oxidation reagent to afford the asymmetric oxidation (Table 1). Initially, D-PTTA as a chiral acid and 30% $H_2O_2$ as an oxidation reagent were chosen. The treatment of **4** was carried out with an equivalent of D-PTTA in methyl *iso*-butylketone (MIBK) to precipitate the salt of **4** and D-PTTA. Subsequently, 3 equiv of 30% $H_2O_2$ was added to the resulting mixture, and the suspension was stirred at rt for 24 h (Table 1). Surprisingly, the oxidation afforded the diastereoselective reaction, giving **7** in 42% conversion and 52% de, and sulfone **9** was not detected, while the reaction mixture was kept in suspension (run 1).[9] This result showed that the reaction of **8** with 30% $H_2O_2$ asymmetrically afforded the oxidation of sulfide, giving **7**, however, not the kinetic resolution of racemic sulfoxide to sulfone. Increasing the equivalent of $H_2O_2$ to 5 did not affect the conversion or diastereoselectivity (run 2). When *m*-chlorobenzoic peracid (*m*CPBA) was used, the oxidation afforded the diastereoselectivity, however, giving a large amount of sulfone **9** (run 3). A variety of solvents were also examined. The reactions in $CH_2Cl_2$ or toluene showed almost the same diastereoselectivities as that in MIBK, and gave an increased conversion (runs 4 and 5). The use of 2-propanol decreased both the conversion and diastereoselectivity (run 6). Mixed solvent, for instance, $CH_2Cl_2$/toluene and MIBK/toluene, increased the diastereoselectivity (runs 7 and 8). Using the conditions of run 8, **4** were reacted for 8 days at rt to give 92% conversion and 68% de (run 9). After the reaction was continued for 3 weeks, the resulting solid was filtered off followed by recrystallization from aqueous MeCN, giving **7** in 72% yield and 98.1% de (Scheme 3). On the other hand, the solution of **4** dissolved in a large amount of MIBK and toluene was reacted with 30% $H_2O_2$, showing lower selectivity (4% de, run 10). From these results, it was considered that the steric formation of **8** was held by deposition from the solution, which reacted heterogenously with $H_2O_2$ to afford the asymmetric oxidation. Moreover, the practical preparation was studied. After the reaction of **5** with **6**·HCl was completed, **4** was extracted with MIBK, and a solution of D-PTTA in toluene and 30% $H_2O_2$ were added to the solution. The mixture was stirred for 24 h at rt to give **7** in 60% conversion and 70% de. Subsequently, the addition of methanol to the reaction mixture followed by stirring for 8 h at 50 °C gave 98.5% conversion and 42% de, which was led to diastereometrically pure **7** (98.2% de) in 53% yield (2 steps) after the crystallization from the reaction solution.

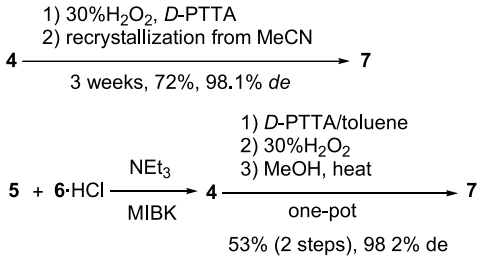
Chiral sulfoxide *S*-**3** led to *S*-**1a** as one of the biologically active products (Scheme 4). In the previous report, **2a** was prepared in 3% from starting material using 10 steps.[6] We already reported the efficient synthesis of benzazepines.[11] According to our procedure, the synthesis of **2a** was carried out. The hydrolysis of 1-isobutylpyrrolidin-2-one with aqueous MsOH followed by neutralization and anilination of **11** gave butyric acid **12** in one-pot. After workup, **12** was

**Table 1**. Oxidation of **4** with D-PTTA[a]

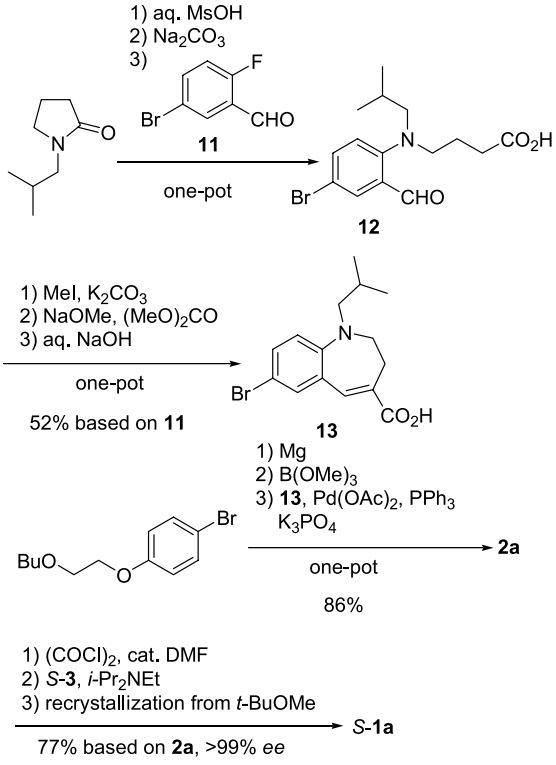



| Entry | Solvent (v/w) | Chiral acid | Reagent (eq) | Conditions | Conversion (%) | | |
|---|---|---|---|---|---|---|---|
| | | | | | **7** | **10** | de (%)[b] |
| 1 | MIBK (25) | D-PTTA | 30% $H_2O_2$ (3) | rt, 24 h | 42 | — | 52 |
| 2 | MIBK (25) | D-PTTA | 30% $H_2O_2$ (5) | rt, 24 h | 48 | — | 47 |
| 3 | MIBK (25) | D-PTTA | *m*CPBA (1.1) | rt, 24 h | 31 | 41 | 47 |
| 4 | $CH_2Cl_2$ (50) | D-PTTA | 30% $H_2O_2$ (3) | rt, 24 h | 68 | — | 49 |
| 5 | Toluene (50) | D-PTTA | 30% $H_2O_2$ (3) | rt, 24 h | 75 | 3 | 42 |
| 6 | 2-Propanol (50) | D-PTTA | 30% $H_2O_2$ (3) | rt, 24 h | 11 | — | 28 |
| 7 | $CH_2Cl_2$ (20)/toluene (40) | D-PTTA | 30% $H_2O_2$ (3) | rt, 24 h | 64 | 1 | 66 |
| 8 | MIBK (25)/toluene (25) | D-PTTA | 30% $H_2O_2$ (3) | rt, 24 h | 40 | — | 76 |
| 9 | MIBK (25)/toluene (25) | D-PTTA | 30% $H_2O_2$ (3) | rt, 8 days | 92 | 5 | 68 |
| 10[c] | MIBK (1000)/toluene (1000) | D-PTTA | 30% $H_2O_2$ (3) | rt, 3 days | 5 | — | 4 |

[a] To a mixture of **4** (99 mg, 0.4 mmol), D-PTTA (150 mg, 0.4 mmol) and solvent was added oxidation reagent (0.14 g, 1.2 mmol), and the suspension was stirred at rt.
[b] Determined by HPLC on a Daicel Chiralcel OD (85/15 *n*-hexane/ethanol).
[c] The reaction mixture was solution.




**Scheme 3.**




**Scheme 4.**

used in the next step without purification. Compound **12** was esterified with MeI and $K_2CO_3$, which was treated with the combination of NaOMe and dimethyl carbonate followed by hydrolysis to give **13** in 52% Yield (2 steps, one-pot). The Suzuki–Miyaura reaction of **13** with boronate complex led from aryl bromide gave **2a** in 86% yield. The treatment of carboxylic acid **2a** with 1.1 equiv of oxalyl chloride and a catalystic amount of DMF in THF, followed by amidation with 1.3 equiv of *S*-**3** and 3.5 equiv of *i*-$Pr_2$NEt, gave crude *S*-**1a** without the Pummerer rearrangement. Crude *S*-**1a** was recrystallized from *t*-BuOMe to give high quality *S*-**1a** (purity >99%, >99% *ee*) as a solvate of *t*-BuOMe in 77% yield (Scheme 5).[10]

## 3. Conclusion

A new type of asymmetric sulfoxidation has been developed. Treatment of prochiral sulfide **4** having imidazole moiety with tartaric acid derivative led to imidazole-sulfide having the chiral moiety, which was reacted with $H_2O_2$ to afford diastereometrically oxidation. Subsequently, the de of the resulting diastereomer sulfoxide **7** was increased by recrystallization, which was converted to high enantiometrically pure sulfoxide *S*-**3** after neutralization. For the procedure described here, it was easy to recover the tartaric acid derivative as an auxiliary, and this synthesis perfectly prevented contamination by metal.

## 4. Experimental

### 4.1. General

Melting points were recorded on a Büchi B-540 micro melting apparatus and were uncorrected. Optical rotation values were recorded on a JASCO DIP-370 polarimeter under standard conditions. IR spectra were recorded on a Horiba FT-210 spectrophotometer, and absorptions are reported in $cm^{-1}$. $^1H$ NMR (300 MHz) and $^{13}C$ NMR

(75.5 MHz) spectra were recorded on a Bruker DPX-300 spectrometer at ambient temperature. $^1$H NMR spectra are reported as follows: Chemical shifts in ppm downfield from tetramethylsilane as an internal standard, multiplicity (s = singlet, d = doublet, t = triplet and m = mutiplet), coupling constants spectra (Hz) and integration. $^{13}$C NMR spectra recorded in ppm relative to the central line for $CDCl_3$ at 77 ppm, DMSO-$d_6$ at 39.7 ppm, and $CD_3OD$ at 49.0 ppm. The column chromatography was performed on Chromatorex (Fuji Silysia Chemical Ltd). Elemental analyses were performed at Takeda Analytical Research Laboratories, Ltd.

**4.1.1. 4-{[(1-Propyl-1*H*-imidazol-5-yl)methyl]thio}phenylamine (4).** The solution of **6**·HCl (3.90 g, 20 mmol) and water (2.5 mL) was added to a suspension of 4-aminothiophenol (**5**, 2.56 g, 20 mmol), $NEt_3$ (5.5 mL, 40 mmol) and 2-propanol (10 mL) at −10 to 0 °C, and stirred for 1 h. Water was added to a reaction mixture, and the remaining solution was extracted with methyl *iso*-butylketone (MIBK). The organic layer was washed with brine, dried with $Na_2SO_4$ and concentrated in vacuo. The resulting residue was purified by chromatography on silica-gel with AcOEt to give **4** as a white crystalline (4.85 g, yield 98%). Mp 49–51 °C. $^1$H NMR ($CDCl_3$): $\delta$ 0.96 (3H, t, $J$ = 7.3 Hz), 1.76–1.88 (2H, m), 3.76 (2H, br s), 3.86–3.92 (4H, m), 6.54–6.59 (2H, m), 6.64 (1H, s), 7.06–7.11 (2H, m), 7.42 (1H, s). $^{13}$C NMR ($CDCl_3$): $\delta$ 11.0, 24.0, 30.6, 46.3, 115.2, 121.0, 126.9, 128.8, 135.3, 137.5, 146.9. IR (KBr): 1633, 1600, 1496. Anal. Calcd for $C_{13}H_{17}N_3S\cdot 0.1H_2O$: C, 62.67; H, 6.96; N, 16.86. Found: C, 62.74; H, 6.83; N, 16.77.

**4.1.2. (*S*)-4-{[(1-Propyl-1*H*-imidazol-5-yl)methyl]sulfinyl}phenylammonium (2*S*,3*S*)-2,3-bis-[(4-methylbenzoyl)oxy]-butenoate hydrate (7) using asymmetric oxidation.** The solution of **4** (1.24 g, 5.0 mmol) and MIBK (15 mL) was added to a solution of D-PTTA (1.94 g, 5.0 mmol), MIBK (15 mL) and toluene (30 mL) at rt. Subsequently, 30% $H_2O_2$ (1.73 g, 15.0 mmol) were added to the resulting suspension, and stirred for 3 weeks. The resulting solid was collected by filtration and recrystallized from a mixture of MeCN (9 mL) and water (9 mL) to give **7** as a white crystalline (2.4 g, yield 72%, 98.1% de). $[\alpha]_D^{25} = -31.5$ ($c$ 1.014, MeOH). Mp 140–141 °C. $^1$H NMR ($CD_3OD$): $\delta$ 0.89 (3H, t, $J$ = 7.41 Hz), 1.70–1.77 (2H, m), 2.40 (6H, s), 3.82 (2H, t, $J$ = 7.53 Hz), 4.18–4.38 (2H, m), 5.90 (2H, s), 6.7–6.74 (2H, m), 7.01 (1H, s), 7.18–7.14 (2H, m), 7.28–7.31 (4H, m), 7.98–8.00 (4H, m), 8.46 (1H, d, $J$ = 1.2 Hz). $^{13}$C NMR ($CD_3OD$): $\delta$ 11.0, 21.7, 24.3, 50.6, 74.4, 115.4, 124.4, 126.7, 127.4, 128.1, 130.2, 131.0, 137.6, 145.6, 154.2, 167.2, 171.0. IR (KBr): 1708, 1592. Anal. Calcd for $C_{33}H_{35}N_3O_9S$: C, 61.00; H, 5.43; N, 6.47. Found: C, 59.26; H, 5.67; N, 6.18. HPLC conditions: column, Chiralcel OD, mobile phase: *n*-hexane/2-propanol (85/15), flow rate: 1.0 mL/min, detection: UV (277 nm), column temp.: 35 °C, retention time; 19.9 (substrate), 22.2 (*R*-product), 24.7 (sulfone product) and 28.5 (*S*-product) min.

**4.1.3. Practical preparation of 7.** The solution of **6**·HCl (3.90 g, 20 mmol) and water (2.5 mL) was added to a suspension of **5** (2.56 g, 20 mmol), $NEt_3$ (5.5 mL, 40 mmol) and 2-propanol (10 mL) at −15 to −10 °C, and stirred for 1 h. Water was added to a reaction mixture, and the remaining solution was extracted with methyl *iso*-butylketone (MIBK). The organic layer was washed with brine, dried with $Na_2SO_4$ and concentrated in vacuo. To the resulting residue were added MIBK (30 mL), D-PTTA (7.7 g, 20 mmol) in toluene/MIBK (90 mL/60 mL) and water (3.6 mL), and the mixture was stirred for 2 h at rt. Subsequently, 30% $H_2O_2$ (6.8 g, 60 mmol) were added to the resulting suspension, and stirred for 24 h. Methanol (30 mL) was added to the mixture, and the mixture was stirred for 8 h at 50 °C. Water (30 mL) was added to the reaction mixture, and the mixture was stirred for 5 h at rt. The resulting solid was collected by filtration to give **7** as a white crystalline (7.1 g, yield 53%, 98.2% de).

**4.1.4. 4-{[(1-Propyl-1*H*-imidazol-5-yl)methyl]sulfinyl}-phenylamine (*rac*-3).** The solution of **6**·HCl (0.78 g, 4.0 mmol) and water (0.5 mL) was added to a suspension of **5** (0.46 g, 3.64 mmol), $NEt_3$ (1.1 mL, 8.0 mmol) and MeOH (2 mL) at 0–5 °C, and stirred for 1 h. After warmed to rt, AcOH (1 mL) and 30% $H_2O_2$ (0.62 g, 5.46 mmol) were added to the resulting mixture, and stirred for 17 h. Sodium sulfite and 6 N NaOH (3 mL) were added to a reaction mixture at 0 °C, and stirred for 1 h. The remaining solution was extracted with a mixture of AcOEt and 2-propanol. The organic layer was washed with brine, dried with $Na_2SO_4$ and concentrated in vacuo. To the resulting residue was added AcOEt (4 mL), and stirred for 1 h at rt. The resulting solid was collected by filtration to give *rac*-**3** monohydrate as a white crystalline (0.73 g, yield 71% from **5**). Mp 145–146 °C. $^1$H NMR ($CDCl_3$): $\delta$ 0.90 (3H, t, $J$ = 7.4 Hz), 1.69–1.78 (2H, m), 3.60–3.80 (2H, m), 3.97–4.08 (4H, m), 6.61 (1H, s), 6.67–6.72 (2H, m), 7.15–7.20 (2H, m), 7.44 (1H, s). $^{13}$C NMR ($CDCl_3$): $\delta$ 11.1, 24.0, 46.5, 52.4, 114.7, 120.0, 126.2, 129.7, 131.3, 138.4, 149.9. IR (KBr): 3214, 1650, 1596, 1500. Anal. Calcd for $C_{13}H_{17}N_3OS$: C, 59.29; H, 6.51; N, 15.96. Found: C, 59.19; H, 6.63; N, 15.84.

**4.1.5. Synthesis of 7 using optical resolution.** To a solution of D-PTTA (14.7 g, 38.0 mmol), *rac*-**3** (10.0 g, 38.0 mmol) and DME (90 mL) was added water (90 mL) at rt, and stirred for 14 h. The resulting solid was collected by filtration and recrystallized from a mixture of MeCN (70 mL) and water (70 mL) to give **7** as a white crystalline (10.5 g, yield 41%, >99% de).

**4.1.6. (*S*)-4-{[(1-Propyl-1*H*-imidazol-5-yl)methyl]sulfinyl}phenylamine (*S*-3).** The suspension of **7** (2.7 g, 4.0 mmol, 99% de) and AcOEt (10 mL) was adjusted to below pH = 3 with 1 N HCl, and separated. The aqueous layer was adjusted to pH = 10 with 25% $Na_2CO_3$ solution, extracted with a mixture of AcOEt and 2-propanol (4:1, 15 mL × 3). The organic layer was washed with brine, dried with $Na_2SO_4$ and concentrated in vacuo. The resulting residue was triturated with AcOEt and collected by filtration to give *S*-**3** as a white crystalline (0.79 g, 99% ee, yield 79%). $[\alpha]_D^{25} = -167.2$ ($c$ 1.018, MeOH). Mp 141–142 °C. $^1$H NMR ($CDCl_3$): $\delta$ 0.90 (3H, t, $J$ = 7.4 Hz), 1.69–1.79 (2H, m), 3.72–3.77 (2H, m), 3.97–4.08 (4H, m), 6.61 (1H, s), 6.60–6.71 (2H, m), 7.15–7.27 (2H, m), 7.44 (1H, s). $^{13}$C NMR ($CDCl_3$): $\delta$ 11.1, 24.0, 46.5, 52.4, 114.7, 120.0, 126.2, 129.7, 131.3, 138.4, 149.9. IR (KBr): 3156, 1633, 1592,

1500. Anal. Calcd for $C_{13}H_{17}N_3OS$: C, 59.29; H, 6.51; N, 15.96. Found: C, 59.30; H, 6.60; N, 15.96.

**4.1.7. 7-Bromo-1-isobuthyl-1-2,3-dihydro-1*H*-1-benzazepine-4-carboxylic acid (13).** A solution of 1-isobutylpyrrolidin-2-one (28.0 g, 0.2 mol) in a mixture of MsOH (26 mL, 0.8 mol) and water (66 mL) was refluxed for 24 h. After the solution was cooled to rt, $Na_2CO_3$ (84.8 g, 0.8 mol) and water (30 mL) were added, and the mixture was stirred for 1 h. After addition of DMSO (30 mL) to the resulting mixture, a solution of **11** (12.2 g, 0.06 mol) in DMSO (66 mL) was added dropwise to the whole mixture under refluxing conditions. The mixture was refluxed for 9 h. After it was cooled to 30 °C, the mixture was treated with 6 N HCl until the pH was adjusted to 3 and extracted with AcOEt. The organic layer was washed with brine. The organic layer was extracted with 1 N NaOH. The aqueous layer was treated with 6 N HCl until the pH was adjusted to 3 and extracted with AcOEt. The organic layer was concentrated in vacuo to give crude **12** as a brown oil, which was used directly in further reactions without purification.

To a solution of crude **12** and $K_2CO_3$ (9.1 g, 0.066 mol) in DMF (50 mL) was added dropwise a solution of MeI (10.2 g, 0.072 mol) in DMF (10 mL) at rt, and the mixture was stirred for 1 h. After addition of dimethyl carbonate (120 mL) to the mixture, 28% NaOMe in MeOH (27.8 g, 0.144 mol) was added and the whole mixture was stirred for 1 h at 60 °C. After the mixture was cooled to 5 °C, 2 N HCl (100 mL) was added, and the whole mixture was concentrated in vacuo and extracted with toluene. The organic layer was washed successively with 1 N NaOH, brine and water, and concentrated in vacuo. To the resulting residue were THF (85 mL), MeOH (85 mL) and 1 N NaOH (120 mL, 0.12 mol), and the mixture was stirred for 1.5 h at 50 °C. After the mixture was concentrated in vacuo, the resulting solution was washed with toluene. The aqueous layer was treated with 6 N HCl until the pH was adjusted to 3 and extracted with AcOEt. The organic layer was washed with brine, and concentrated in vacuo. The residue was dissolved in MeOH (45 mL) at 60 °C, and water (9 mL) was added dropwise to the solution. The mixture was stirred for 8 h at rt, and stirred for 1 h at 0–5 °C. The resulting solid was collected by filtration and washed with a mixture of MeOH (15 mL) and water (15 mL) to give **13** as a yellow crystalline powder (10.1 g, yield 52% from **11**): Mp 144–145 °C. $^1$H NMR ($CDCl_3$): $\delta$ 0.91 (6H, d, $J$=6.60 Hz), 1.90–2.25 (1H, m), 2.75–2.85 (2H, m), 3.12 (2H, d, $J$=7.35 Hz), 3.20–3.30 (2H, m), 6.72 (1H, d, $J$=8.97 Hz), 7.20–7.30 (1H, m), 7.44 (1H, s), 7.70 (1H, s). $^{13}$C NMR ($CDCl_3$): $\delta$ 20.3, 26.5, 32.5, 51.9, 61.8, 109.6, 117.6, 124.1, 128.9, 132.5, 138.6, 140.9, 151.2, 173.6. IR (KBr): 1677, 1614, 1490. Anal. Calcd for $C_{15}H_{18}NO_2Br$: C, 55.57; H, 5.60; N, 4.32. Found: C, 55.52; H, 5.59; N, 4.13.

**4.1.8. 7-[4-(2-Butoxyethoxy)phenyl]-1-isobuthyl-2,3-dihydro-1*H*−1-benzazepine-4-carboxylic acid (2a).** Under an argon atmosphere, to a suspension of magnesium (2.25 g, 92 mmol) in THF (140 mL) was added dropwise a solution of 1-bromo-4-(2-butoxyethoxy)benzene (24.6 g, 90 mmol) in THF (40 mL) under refluxing conditions and the whole mixture was refluxed for 1 h. After the mixture was cooled to −10 °C, a solution of trimethylborate (10.0 mL, 90 mmol) in THF (40 mL) was added dropwise and the resulting mixture was stirred for 1 h at the same temperature. After the mixture was warmed to rt, $Pd(OAc)_2$ (27 mg, 0.12 mmol) and $PPh_3$ (126 mg, 0.048 mmol) were added and the whole mixture was stirred for 0.5 h at the same temperature. Next, **13** (19.4 g, 60 mmol) and a solution of $K_3PO_4$ (79.6 g, 375 mmol) in water (100 mL) were added, and the mixture was refluxed for 2 h. After it was cooled to rt, 3 N HCl was added and the mixture was separated. The aqueous layer was extracted with toluene. The organic layer was washed successively with 2 N NaOH and brine. Activated charcoal (2 g) and tri-*n*-butylphosphine (2 mL) were added to the organic layer and the mixture was stirred for 0.5 h. The charcoal was filtered off and washed with toluene. The filtrate and washing were combined and concentrated in vacuo. The residue was dissolved in *i*-$Pr_2O$ under refluxing conditions. After it was cooled to 0 °C, the mixture was stirred for 1 h at the same temperature. The resulting solid was collected by filtration and washed with cold *i*-$Pr_2O$ to give crude **2a** (23.7 g) as a yellow crystalline powder. Crude **2a** (2.0 g) was dissolved in 2-propanol (10 mL) under refluxing conditions, and tri-*n*-butylphosphine (0.2 mL) was added to the solution. After it was cooled to 0 °C, the mixture was stirred for 1 h at the same temperature. The resulting solid was collected by filtration and washed with cold 2-propanol to give crude **2a** as a yellow crystalline powder (1.9 g, yield 86%): Mp 126–127 °C. $^1$H NMR ($CDCl_3$): $\delta$ 0.91–1.10 (9H, m), 1.35–1.50 (2H, m), 1.55–1.70 (2H, m), 2.00–2.15 (1H, m), 2.85–2.90 (2H, m), 3.20 (2H, d, $J$=7.30 Hz), 3.30–3.35 (2H, m), 3.58 (2H, d, $J$=6.66 Hz), 3.803.85 (2H, m), 4.15–4.20 (2H, m), 6.92 (1H, d, $J$=8.75 Hz), 7.01 (2H, d, $J$=8.75 Hz), 7.40–7.55 (4H, m), 7.91 (1H, s). $^{13}$C NMR ($CDCl_3$): $\delta$ 13.8, 19.2, 20.4, 26.6, 31.7, 32.6, 52.0, 61.8, 67.5, 69.2, 71.4, 115.0, 116.2, 122.5, 127.2, 127.8, 128.4, 130.6, 133.0, 134.9, 142.5, 151.1, 157.8, 173.7. IR (KBr): 1668, 1608, 1500. Anal. Calcd for $C_{27}H_{35}NO_4$: C, 74.11; H, 8.06; N, 3.20. Found: C, 74.18; H, 8.33; N, 2.95.

**4.1.9. 7-[4-(2-Butoxyethoxy)phenyl]-1-isobuthyl-1-*N*-(4-{[(1-propyl-1*H*-imidazol-5-yl)methyl]-(*S*)-sulfinyl}-phenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxamide (*S*-1a).** The suspension of **7** (5.0 g, 7.5 mmol, >99% de) and AcOEt (15 mL) was adjusted to below pH=3 with 1 N HCl, and separated. The aqueous layer was adjusted to pH=9 with 25% $K_2CO_3$ solution, extracted with a mixture of AcOEt and 2-propanol. The organic layer was washed with brine, dried with $Mg_2SO_4$ and concentrated in vacuo to give *S*-**3**. Oxalyl chloride (0.56 mL, 6.4 mmol) was dropped to a solution of **2a** (2.56 g, 5.9 mmol), DMF (1 drop) and THF (8 mL) at 0–5 °C, and stirred for 1 h. The resulting acid chloride was dropped to a mixture of *S*-**3**, $NEt_3$ (2.9 mL, 20.8 mmol) and THF (18 mL) below 10 °C and stirred for 1 h. Water was added to the reaction mixture, which was separated and extracted with AcOEt. The organic solution was washed with 10% acetic acid, 7% $NaHCO_3$ aqueous solution, and 10% NaCl aqueous solution. Activated carbon (0.4 g), silica-gel (4 g) and $Na_2SO_4$ (2 g) were added to an organic solution, and stirred for 10 min. Solid was filtered off, and the mother solution was concentrated in vacuo. The resulting residue was crystallized from a mixture of *t*-BuOMe (20 mL) and water (9 mL), and recrystallized

from a mixture of *t*-BuOMe (31 mL) and EtOH (3 mL) to give *S*-**1a** as a yellow solid (3.5 g as the solvate of *t*-BuOMe, >99%*ee*, yield 78%). All analytical data of *S*-**1a** were determined as the solvate of *t*-BuOMe. $[\alpha]_D^{25} = -117.1$ (*c* 1.013, MeOH). Mp 94–96 °C. $^1$H NMR ($CDCl_3$): $\delta$ 0.84–0.97 (12H, m), 1.19 (9H, s), 1.28–1.42 (2H, m), 1.53–1.75 (4H, m), 2.02–2.11 (1H, m), 2.88–2.94 (2H, m), 3.17–3.21 (2H, m), 3.21 (3H, s), 3.33–3.37 (2H, m), 3.53 (2H, t, $J$= 6.6 Hz), 3.71–3.81 (4H, m), 3.95–4.10 (2H, m), 4.13–4.16 (2H, m), 6.55 (1H, s), 6.90–6.98 (3H, m), 7.32 (2H, d, $J$= 8.7 Hz), 7.43–7.47 (5H, m), 7.75 (2H, d, $J$=8.7 Hz), 8.32 (1H, s). $^{13}$C NMR ($CDCl_3$): $\delta$ 11.1, 13.9, 19.2, 20.5, 24.0, 26.7, 27.0, 31.7, 33.3, 46.6, 49.4, 52.0, 52.1, 61.7, 67.6, 69.1, 71.4, 72.8, 115.0, 116.3, 119.7, 120.1, 122.8, 125.3, 127.2, 127.8, 130.8, 131.3, 133.0, 133.6, 134.0, 136.0, 136.3, 138.6, 141.9, 150.7, 157.9, 168.3. IR (KBr): 2956, 1654, 1498, 1241. Anal. Calcd for $C_{40}H_{50}N_4O_4S \cdot C_5H_{12}O$: C, 70.10; H, 8.10; N, 7.27. Found: C, 69.82; H, 8.01; N, 7.31. HPLC conditions: column, Chiralcel OJ-R, mobile phase: 0.05 M $KH_2PO_4$/MeCN/MeOH (40/50/10), flow rate: 1.0 mL/min, detection: UV (295 nm), column temp.: 35 °C, retention time; 11.5 (*S*-product) and 14.1 (*R*-product) min.

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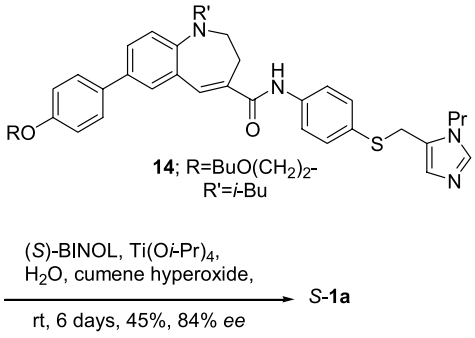
7. The asymmetric synthesis of *S*-**1a** as shown in Scheme 5 was also reported.[6a]




**Scheme 5.**

8. Crystallographic data have been deposited with the Cambridge Crystallographic Data Center (CCDC 249650). Copies of data can be obtained free of charge via www.ccdc.cam.ac.uk/.
9. The reaction of **4** with an equivalent of (*R*)-1, 1′-binaphthyl-2,2′-diyl hydrogenphosphate and 3 equivalents of 30% $H_2O_2$ in $CH_2Cl_2$ for 24 h at rt gave the salt of *R*-3 and (*R*)-1, 1′-binaphthyl-2,2′-diyl hydrogenphosphate in 51% conversion and 31% de.
10. In a previous report[6], *S*-**1a** was isolated as a solvate of AcOEt.
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