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Practical continuous resolution of α-amino-ε-caprolactam by diastereomeric salt formation using a single resolving agent with a solvent switch method

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Abstract—A practical procedure for the continuous resolution of (*R*)-(+)- and (*S*)-(−)-α-amino-ε-caprolactams **1** from the racemate by diastereomeric salt formation has been developed using a single naturally-based resolving agent, *N*-tosyl-(*S*)-phenylalanine **5**, together with a simple solvent switch method. The (*S*)-**1**·(*S*)-**5**·H_2O salt (30%, 93% de, *E* 56%) was obtained by crystallization from MeOH, while the (*R*)-**1**·(*S*)-**5** salt (41%, 92% de, *E* 75%) was crystallized from the 2-propanol: water (89:11) of the condensate of the mother liquor after the first crystallization. The (*R*)-**1** hydrochloride was efficiently prepared from the crude salt without further purification with high enantiomeric purity in >99.9% ee and 36% yield versus (*RS*)-**1**.

1. Introduction

Enantiopure α-amino-ε-caprolactam **1** is used not only as a synthetic intermediate for pharmaceuticals,[1] but also as a key intermediate for the production of enantiopure lysine.[2] Various resolution procedures for (*S*)-**1** aimed at an industrial-scale production of (*S*)-lysine (L-form) have been devised such as an enantiomeric resolution via a diastereomeric salt formation using L-amino acid derivatives[3] and L-tartaric acid,[4] and the preferential crystallization of a nickel complex,[5] amino acid salt[6] and inorganic acid salts.[7] Enzymatic resolution has also been well documented.[2,8] Similarly, to obtain (*R*)-**1**, low-yield preferential crystallization or resolution via diastereomeric salt formation using the costly unnatural D-amino acid derivative as the resolving agent must be employed. To find a cost effective resolution procedure for obtaining (*R*)-**1**, we reexamined a resolution of (*RS*)-**1** by diastereomeric salt formation. As a result, we found that the configuration of the excess enantiomer in the diastereomeric salt is variable depending on the dielectric constant (ε) of solvent used in the resolution process. No other physical and chemical constants of the solvents correlated to the configuration, enantiomeric excess, yield or resolution efficiency. Based on this finding, we contrived a practical resolution process to afford respective diastereomeric salts containing (*S*)- or (*R*)-**1** by using only one naturally-based resolving agent along with a simple solvent switch. Similar resolution processes along with solvent switch have been reported by Nohira et al for the resolution of racemic 1-phenyl- 2-(*p*-tolyl)-ethylamine[9] and α-2-(*p*-methoxyphenyl)- 3-acetoxy-5-(-dimethylaminoethyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one[10] with enantiopure mandelic acid as the resolving agent. To our best knowledge, a significant role of the dielectric constant (ε) of solvent used in the resolution process has not been described to date.

Herein we report a practical procedure for the continuous resolution of (*R*)- and (*S*)-α-amino-ε-caprolactams **1** production with *N*-tosyl-(*S*)-phenylalanine **5** as a resolving agent and a simple solvent switch.

2. Results and discussion

To find the most suitable resolving agent for (*RS*)-**1**, commercially available acidic resolving agents such as L-tartaric acid **2**, di-*p*-toluoyl-D-tartaric acid **3**, dibenzoyl-D-tartaric acid **4**, *N*-tosyl-(*S*)-phenylalanine **5**, *N*-tosyl-(*S*)-alanine **6**, (*S*)-mandelic acid **7** and

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(*S*)-2-methoxy-2-phenylacetic acid **8** were examined using methanol as a solvent. The results are summarized in Table 1. The resolving agent (*S*)-**5** showed the highest resolution efficiency (*E*)[11] (93% de (diastereomeric excess),[12] *E* 60%, Table 1, entry 4), whereas (*S*)-**6** and (*R*)-**7** gave poor results (*E* 16% and 6%, Table 1, entries 5 and 6, respectively). Other resolving agents L-**2**, D-**3**, D-**4** and (*S*)-**8** did not afford any crystals at all (Table 1, entries 1, 2, 3 and 7) (Fig. 1).

Next, resolution conditions were optimized with (*S*)-**5** as a resolving agent in various alcohol solvents and water, and the results are summarized in Table 2. As a result, we found that the configuration of the enantiomer of **1** enriched in the salt deposited by the resolution procedure is variable depending on the dielectric constant (ε) of the solvent used. Namely, the (*S*)-**1**·(*S*)-**5** diastereomeric salt was obtained from the solvents having a dielectric constant (ε) between 29 and 58 (Table 2, entries 4–8), whereas the (*R*)-**1**·(*S*)-**5** diastereomeric salt was obtained from the solvents having a dielectric constant of lower than 25 or higher than 63 (Table 2, entries 1–3 and 9–11), albeit the low diastereomeric purity. Determination of the water content by the Karl Fischer method, elemental and X-ray crystal structure analyses, confirmed that the (*S*)-**1**·(*S*)-**5** salt was monohydrated containing 0.5 equiv. of adhered water, whereas no water was detected in the (*R*)-**1**·(*S*)-**5** salt.[13] Crystal structures of the salts determined by the X-ray crystal structure analysis are shown

Table 1. Resolution of (*RS*)-**1** with various resolving agents

Entry	Resolving agent[a]	Solvent/(*RS*)-**1** ratio (w/w)[b]	Yield[c] %	Diastereomeric excess % de	Resolution efficiency (*E*)[d] %	Absolute configuration
1	L-**2**	4	Not crystallized			
2	D-**3**	10	Oil			
3	D-**4**	2.5	Not crystallized			
4	(*S*)-**5**	10	32	93	60	S
5	(*S*)-**6**	25	54	29	16	*R*
6	(*S*)-**7**	12	90	7	6	*R*
7	(*S*)-**8**	10	Oil			

Resolving agent: L-**2**, L-tartaric acid; D-**3**, D-ditoluoyltartaric acid; D-**4**, D-dibenzoyltartaric acid; (*S*)-**5**, *N*-tosyl-(*S*)-phenylalanine; (*S*)-**6**, *N*-tosyl-(*S*)-alanine; (*S*)-**7**, (*S*)-mandelic acid; (*S*)-**8**, (*S*)-2-methoxy-2-phenylacetic acid.

[a] Resolving agent/(*RS*)-**1** = 1.0 (molar ratio).

[b] Solvent = MeOH.

[c] Yield: calculated based on (*RS*)-**1**.

[d] Resolution efficiency = yield(%)×2×diastereomeric purity(% de)/100.

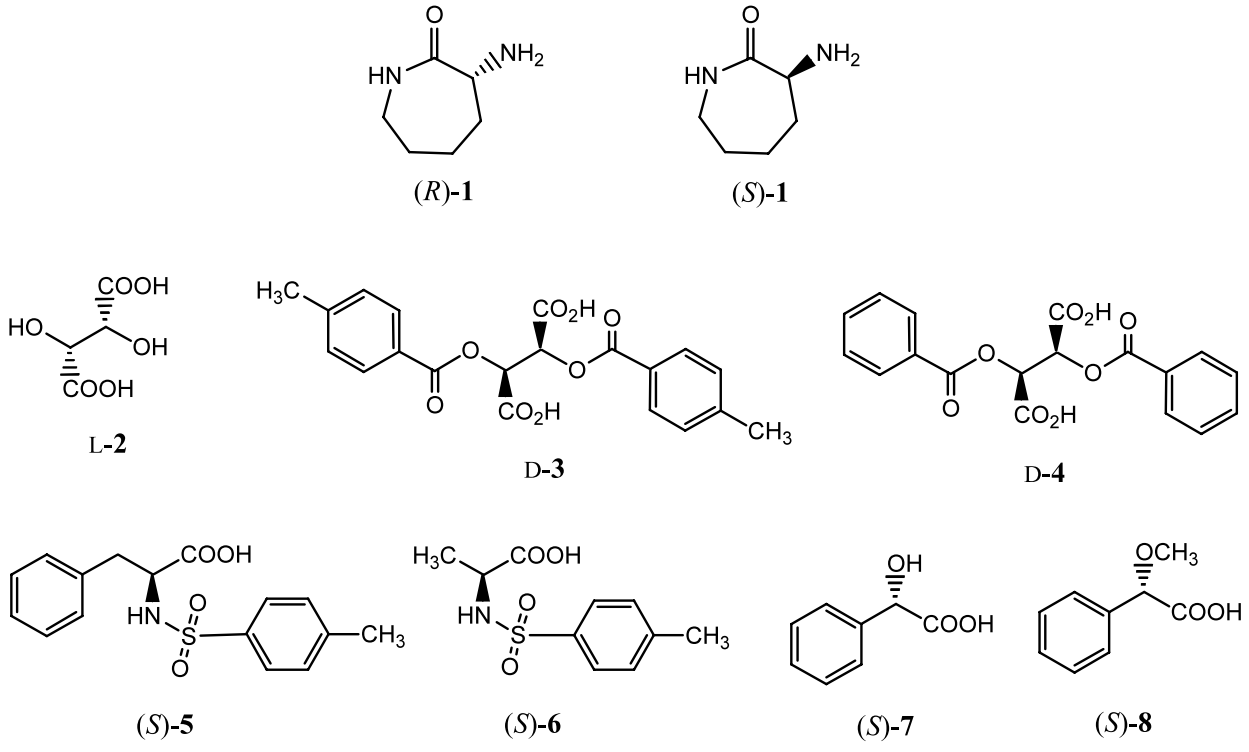

Figure 1.

Table 2. Resolution of (*RS*)-**1** with (*S*)-**5** in alcohol-water solvents[a]

Entry	Solvent[b]	Dielectric constant[c] (ε)	Solvent/(*RS*)-**1** ratio (w/w)	Yield[d] %	Diastereomeric excess % de	Resolution efficiency (*E*) %	Absolute configuration
1	2-PrOH	18	50	64	32	41	*R*
2	EtOH	24	32	68	7	10	*R*
3	89% 2-PrOH	25	11	59	29	34	*R*
4	90% EtOH	29	15	60	10	12	*S*
5	MeOH	33	10	30	93	56	*S*
6	81% EtOH	34	12	24	99	48	*S*
7	60% MeOH	51	11	9	95	17	*S*
8	45% MeOH	58	8	48	3	3	*S*
9	35% MeOH	63	6	16	13	4	*R*
10	10% MeOH	74	19	37	35	26	*R*
11	Water	78	18	30	28	17	*R*

[a] Resolving agent (*S*)-**5**/(*RS*)-**1** = 1.0 (molar ratio).
[b] Mixed solvents are indicated with alcohol contents in weight.
[c] Dielectric constant (ε) for a mixed solvent is the weighted average value calculated from those of pure solvents.
[d] Yield: calculated based on (*RS*)-**1**.

in Figure 2. These results led us to consider continuous resolution by a simple solvent switch using (*S*)-**5** as the resolving agent because the resolution of one enantiomer-enriched sample usually gives a much better result than that of the racemic sample as a starting material. MeOH was the best solvent for the first resolution to obtain the (*S*)-**1**·(*S*)-**5**·H_2O salt, although 89% 2-PrOH (2-propanol:water = 89:11, weight ratio) was suited for the second resolution to obtain (*R*)-**1**·(*S*)-**5** salt.

After the (*S*)-**1**·(*S*)-**5**·H_2O salt [30% yield versus (*RS*)-**1**, 93% de, *E* 56%, Table 3, entry 1] was collected by

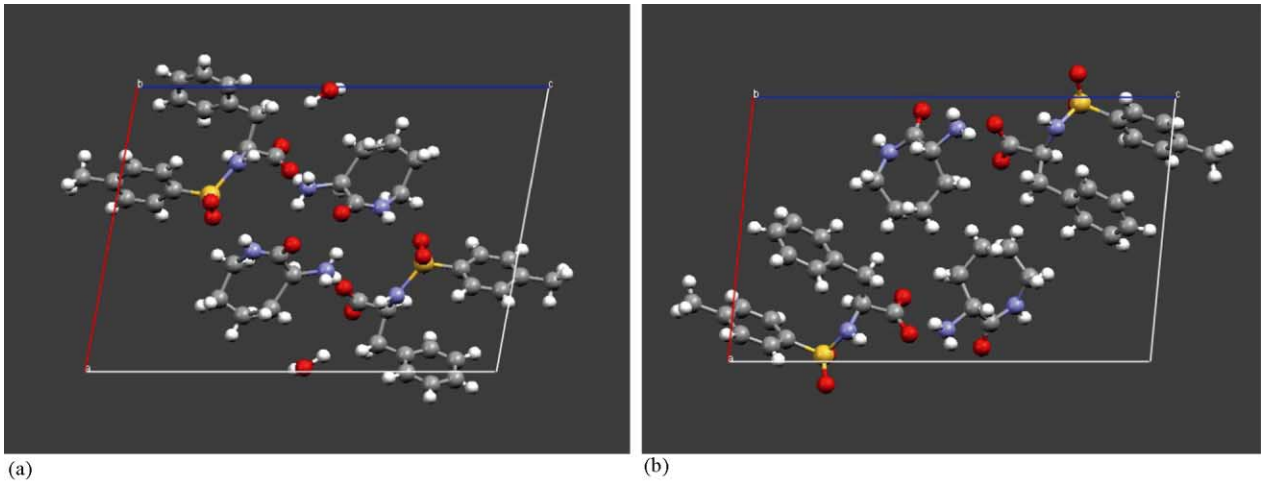

Figure 2. Crystal structures of (a) (*S*)-**1**·(*S*)-**5**·H_2O salt and (b) (*R*)-**1**·(*S*)-**5** salt viewed from the 2_1-columns.

Table 3. Resolution of (*RS*)-**1** with (*S*)-**5** by the solvent switch method[a]

	1st resolution (*RS*)-**1** from MeOH[b]				2nd resolution (*R*)-enriched **1** from 89% 2-PrOH[c]		
Entry	Yield[d] %	Diastereomeric purity % de	Resolution efficiency[d] *E*1, %	Mother liquor % de	Yield[d] %	Diastereomeric purity % de	Resolution efficiency[d] *E*2, %
1	30	93	56	40	41	93	75
2	30	91	55	40	42	91	76
3	29	93	54	40	41	92	75
4	29	90	52	40	41	94	77
5	28	99	55	41	43	92	79

[a] Resolving agent (*S*)-**5**/(*RS*)-**1** = 1.0 (molar ratio).
[b] MeOH/(*RS*)-**1** = 10/1 10 (weight ratio).
[c] 89% 2-PrOH/(*S*)-enriched **1** contained in the mother liquor of the first resolution = 11/1 (weight ratio).
[d] Yields and resolution efficiencies were calculated based on (*RS*)-**1** used in the first resolution.

filtration in the first resolution of (*RS*)-**1** with (*S*)-**5** from MeOH, an equimolar mixture of (*R*)-enriched **1** (40% de) and (*S*)-**5** was recovered as a condensate by evaporating the mother liquor of the first resolution, and 89% 2-PrOH was added. The mixture was heated to dissolve the condensate and gradually cooled to crystallize the salt. The (*R*)-**1**·(*S*)-**5** salt was obtained in high resolution efficiency [41% yield versus (*RS*)-**1**, 93% de, *E* 75%, Table 3, entry 1]. The resolution processes were repeated and quite reproducible results were obtained (1st resolution: 29–31% yield, 91–93% de, *E* 54–56%; 2nd resolution: 41–42% yield, 91–94% de, *E* 75–77%, Table 3, entries 2–5).

The diastereomeric excess (de) of the crude salts, (*S*)-**1**·(*S*)-**5**·H_2O and (*R*)-**1**·(*S*)-**5**, could be easily improved by recrystallization once more from MeOH and 89% 2-PrOH, respectively, to afford the pure salt with more than 99% de. Alternatively, the crude salt was treated with 35% HCl (1.5 equiv. to the salt) in EtOH (EtOH/salt = 14.5 w/w) and the resulting crystallized hydrochlorides were collected by filtration to give (*R*)-**1**·HCl in 36% yield versus (*RS*)-**1** with more than 99.9% ee.

3. Conclusion

In the resolution process of (*RS*)-α-amino-ε-caprolactam **1** with *N*-tosyl-(*S*)-phenylalanine **5**, it was found that the configuration of the excess enantiomer in the diastereomeric salt is variable depending on the dielectric constant (ε) of solvent used. Based on the finding, we could develop the practical resolution procedure for (*R*)- and (*S*)-α-amino-ε-caprolactam **1** production by diastereomeric salt formation using only one naturally-based resolving agent (*S*)-**5** with a simple solvent switch method. Enantiopure **1** was obtained as a hydrochloride by treatment of the respective crude diastereomeric salt with hydrochloric acid.

4. Experimental

4.1. General

(*RS*)-**1** was obtained from Ajinomoto Co., Inc. and used without any purification. *N*-tosyl-(*S*)-phenylalanine **5** (>99.5% ee),[14] (*S*)-mandelic acid **7** (>99.5% ee) and (*S*)-2-methoxy-2-phenylacetic acid **8** (>99.5% ee) were made of Yamakawa Chemical (Tokyo). Other reagents were purchased from Junsei Chemical, unless otherwise indicated.

^{1}H NMR spectra were recorded on a JEOL JNM-ECP400 spectrometer in DMSO-d_6 with Me_4Si as an internal reference. IR spectra were measured on a JASCO IR-700 spectrometer using KBr pellets. Optical rotations were measured on a JASCO DIP-370 polarimeter with a circular temperature control unit. High-performance liquid chromatography was performed by a JASCO Intelligent HPLC system equipped with a 875-UV detector. Melting points were determined with a YAMATO MP-21 instrument and uncorrected. Water contents in the salts were measured by the Karl Fischer method with a HIRANUMA Aquacounter AQV-5.

4.2. Determination of enantiomeric and diastereomeric purities

The enantiomeric purity of **1** and the diastereomeric purity of the salts, (*S*)-**1**·(*S*)-**5**·H_2O and (*R*)-**1**·(*S*)-**5**, were directly determined by HPLC using a SUMICHIRAL OA-5000 column (ID 4.6 mm×150 mm). Analytical conditions for the HPLC were as follows; 1 mM $CuSO_4$ aq. solution, 0.5 mL/min, 20°C, detected at 254 nm; injection sample 10 μL (10 mg/10 mL), Retention times: the (*S*)-enantiomer 9.8 min, the (*R*)-enantiomer 12.1 min. In the analysis of the diastereomeric purity of the salt, the peaks of (*S*)-**5** were not observed; the column was washed after analysis by pushing out (*S*)-**5** with a mixture of 2 mM $CuSO_4$ aq. soln and methanol (70:30).

4.3. Preparation of (*S*)-1·(*S*)-5·H_2O salt

A typical experimental procedure is as follows: To a 1000 mL flask were added (*RS*)-**1** (50 g, 390 mmol), (*S*)-**5** (124.6 g, 390 mmol) and methanol (500 g), and the mixture was stirred and heated up to about 55°C to give a clear solution. The solution was then gradually cooled, seeded (2 mg) at 48°C, kept for 1 h at 36–38°C (corresponding to the crystallization temperature), and then cooled again to 20°C. After aging the suspension at the temperature for 1 h, the crystals were filtered off and washed twice with methanol (20 mL in total) to afford the crude (*S*)-**1**·(*S*)-**5**·H_2O salt (52.6 g, 113 mmol, 29% yield, 93% de, *E* 54%). Analytical data for the recrystallized salt are as follows.

(*S*)-**1**·(*S*)-**5**·H_2O (additional 0.5 equiv. amount of water is contained because the salt was highly hygroscopic): $[\alpha]_D^{22}$ +20.7 (*c* 0.104, EtOH); >99.9% de; mp 101.5–107.5°C, 160.5–162.0°C; IR (KBr) cm^{-1}: 3598, 3424, 3312, 3194, 3024, 2924, 2858, 1665, 1596, 1472, 1385, 1303, 1157, 1097, 555; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.11–8.01 (m, 1H), 7.57 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H), 7.17–7.12 (m, 5H), 3.92 (d, J = 11.2 Hz, 1H), 3.40 (t, J = 5.2 Hz, 1H), 3.15–3.09 (m, 2H), 2.95 (dd, J = 5.2, 13.2 Hz, 1H), 2.88 (dd, J = 5.2 Hz, 13.2 Hz, 1H), 2.36 (s, 3H), 1.89–1.81 (m, 2H), 1.75–1.72 (m, 1H), 1.62–1.40 (m, 2H), 1.25–1.19 (m, 1H); Water content (KF): calcd for 1.5 equiv.: 5.70%. found: 5.81%. Anal. calcd for $C_{22}H_{29}N_3O_5S$·1.5 H_2O: C, 55.23; H, 6.68; N, 8.99; S, 6.86. Found C, 55.59; H, 6.48; N, 8.87; S, 6.88.

4.4. Preparation of (*R*)-1·(*S*)-5 salt

The mother liquor obtained after the first resolution described above was evaporated to dryness giving a condensate (122.3 g; 40% de). To the condensate was added 2-propanol (333 g) and water (41 g), the slurry was transferred to a 500 mL flask. The mixture was

stirred and heated up to about 75°C to give a clear solution. The solution was then gradually cooled, seeded (2 mg) at 66°C, kept for 1 h at 62–64°C (corresponding to the crystallization temperature), and then cooled again to 20°C. After aging the suspension at the temperature for one hour, the crystals were filtered off and washed twice with 89% 2-propanol (20 mL in total) to afford the crude (*R*)-**1**·(*S*)-**5** salt (71.4g, 160 mmol, 41% yield, 92% de, *E* 75%). Analytical data for the recrystallized salt are as follows.

(*R*)-**1**·(*S*)-**5**: $[\alpha]_D^{22}$ +30.5 (*c* 0.106, EtOH); 98.9% de; mp 180.5–183.5°C; IR (KBr) cm^{-1}: 3338, 3264, 2930, 2856, 1692, 1613, 1562, 1381, 1315, 1152, 661; ^1H NMR (DMSO-d_6, 400 MHz): δ 8.11-8.08 (m, 1H), 7.57 (d, $J=8.4$ Hz, 2H), 7.30 (d, $J=8.4$ Hz, 2H), 7.19–7.10 (m, 5H), 3.92 (d, $J=11.2$ Hz, 1H), 3.40 (t, $J=5.2$ Hz, 1H), 3.16-3.02 (m, 2H), 2.95 (dd, $J=5.2$, 13.6 Hz, 1H), 2.88 (dd, $J=5.2$ Hz, 13.6 Hz, 1H), 2.36 (s, 3H), 1.88–1.81 (m, 2H), 1.75–1.71 (m, 1H), 1.58–1.43 (m, 2H), 1.25-1.18 (m, 1H). Anal. calcd for $C_{22}H_{29}N_3O_5S$: C, 59.05; H, 6.53; N, 9.39; S, 7.16. Found C, 59.14; H, 6.53; N, 9.43; S, 7.12.

4.5. Preparation of (*R*)-1·HCl

To the 300 mL flask was added the crude (*R*)-**1**·(*S*)-**5** salt (10 g, 92% de) and water (100 g) and heated to dissolve (60°C). To the dissolved mixture was added 35% HCl (5.4 g; 52 mmol) dropwise (pH<1), and heat to 80°C and kept the temperature for 1 h. After aging the slurry, the mixture was cooled to 20°C and kept for 1 h, and then the crystals were filtered off and washed with water to recover the resolving agent (*S*)-**5** (7.0 g, recovery 98%). In order to remove a trace of (*S*)-**5** in the filtrate, to the filtrate was added 30% NaOH (6.5 g, 49 mmol, pH 10.5) and activated carbon (AC, 0.1 g), the mixture was stirred for 1 h, and then AC was filtered off. The filtrate was evaporated to dryness and ethanol was added to crystallize NaCl. After stirring at 50°C for a half hour, NaCl is filtered off while keeping the temperature (2.5 g). To the filtrate was added ethanol (41.5 g) and 35% HCl (3.5 g, 34 mmol), and the mixture was heated to 50°C. After aging at the temperature, the mixture is cooled to 25°C and filtered after aging for 1 h to afford (*R*)-**1**·HCl (3.2 g, 36% yield versus (*RS*)-**1**, >99.9% ee).

(*R*)-**1**·HCl: $[\alpha]_D^{22}$ +10.2 (*c* 0.106, EtOH), $[\alpha]_D^{25}$ +26.5 (*c* 4.01, 1N HCl) [lit.[15] $[\alpha]_D^{25}$ +26.4 (*c* 4, 1N HCl)]; mp 292–294°C (dec.).

(*R*)-**1**·HCl could be obtained directly from the mother liquor of the first crystallization by the same procedure applied for the (*R*)-**1**·(*S*)-**5** salt described above. However, the yield became quite lower than the process via (*R*)-**1**·(*S*)-**5** salt crystallization from 89% 2-propanol [19% versus (*RS*)-**1**, 99.4% ee].

4.6. X-Ray crystal structure analysis

(*S*)-**1**·(*S*)-**5**·H_2O salt: A colorless chip single crystal of (*S*)-**1**·(*S*)-**5**·H_2O salt (0.40×0.07×0.04 mm) was grown from the recrystallization conditions (MeOH) indicated above using recrystallized salt crystals (>99.9% de). The X-ray intensities were measured up to $2\theta_{max}=67.6°$ with graphite monochromated CuK_α radiation ($\lambda=1.5419$ Å) (Rigaku) at 293 K.

$C_{22}H_{31}N_3O_6S$; formula weight 465.56; monoclinic, $P2_1(\#4)$, $a=12.726(2)$, $b=5.3317(5)$, $c=17.901(2)$, $\beta=100.395(4)$, $V=1195.0(3)$, $Z=2$, $D_{calcd}=1.294$, $R=0.075$; $Rw=0.125$. Number of reflections measured = total 3912; unique: 2555. Crystallographic data (excluding structure factors) for the structure have been deposited with the Cambridge Crystallographic Data Centre as a supplementary publication number CCDC 220041.

(*R*)-**1**·(*S*)-**5** salt: A colorless platelet single crystal of (*R*)-**1**·(*S*)-**5** salt (0.40×0.15×0.03 mm) was grown from the recrystallization conditions (89% 2-propanol) indicated above using recrystallized salt crystals (>98.9% de). The X-ray intensities were measured up to $2\theta_{max}=68.2°$ with graphite monochromated CuK_α radiation ($\lambda=1.5419$ Å) (Rigaku) at 293 K.

$C_{22}H_{29}N_3O_6S$; formula weight 447.55; monoclinic, $P2_1$ ($\#4$), $a=11.2302(4)$, $b=5.5390(2)$, $c=17.850(1)$, $\beta=95.444(2)$, $V=1150.4(1)$, $Z=2$, $D_{calcd}=1.345$, $R=0.035$, $Rw=0.077$. Number of reflections measured = total 3851; unique: 1561. Crystallographic data (excluding structure factors) for this structure have been deposited with the Cambridge Crystallographic Data Centre as a supplementary publication number CCDC 220042.

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11. Resolution efficiency (*E*, %) = yield(%)×diastereomeric purity(% de)×2/100.
12. Diastereomeric excess (% de) = [A-B]X100/(A+B), where A and B are both diastereomers.
13. Water contents of both salts were determined by Karl Fischer method, and 5.81 and 0.12% of water were detected for (*S*)-**1**·(*S*)-**5** and (*R*)-**1**·(*S*)-**5**, respectively. These results revealed that the (*S*)-**1**·(*S*)-**5** salt contains 1.5 equiv. of water and the elemental analysis followed the results. However, the X-ray crystal structure analyses revealed that the (*S*)-**1**·(*S*)-**5** salt was monohydrated. These results indicated that (*S*)-**1**·(*S*)-**5** salt crystals are containing one equivalent water as a component of the crystal structure and the rest of 0.5 equiv. water are existed as adhered water to the crystals. The water detected in the salt crystallized from water-free solvent such as MeOH, EtOH, etc. was introduced from the starting material (*RS*)-**1** (containing 3.7% of water).
14. (*S*)-**5**: White solid, >99.9% ee, CP 99.9%, mp 164.5°C (lit.: 161–163°C, Kinugasa, M.; Harada, T.; Egusa, T.; Fijita, K.; Oku, A. *Bull. Chem. Soc. Jpn.* **1996**, 3639); $[\alpha]_D^{20}$ +1.0 (*c* 4.0, MeOH) (lit.: $[\alpha]_D$ +1.1 (*c* 4, MeOH), Sakota; Koine; Okita, *Nippon Kagaku Zasshi* 1969, *90*, 77; *Chem. Abstr.* 70: 115517 (1968)).
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