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Optical Resolution of a 1,5-Benzothiazepine Derivative, a Synthetic Intermediate of Diltiazem, by Preferential Crystallization and Diastereomeric Salt Formation

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Practical preparation methods of an optically active intermediate of diltiazem, (+)-(2*S*,3*S*)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-3-hydroxy-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one [(+)-7], have been developed by the use of physicochemical and chemical resolutions. 1) The salt of (±)-7 with 3-amino-4-hydroxybenzenesulfonic acid (AHS), was found to exist as a conglomerate and could be reproducibly resolved into (+)-7·AHS and (−)-7·AHS of 94—98% ee by a preferential crystallization procedure. 2) (+)-(1*R*)-3-Bromocamphor-9-sulfonic acid [(+)-BCS] was found to be an efficient resolving agent for (±)-7 and the diastereomeric resolution provided (+)-7·(+)-BCS·$2H_2O$ salt in >43% yield and >97% ee by fractional crystallization. It is presumed that the crystal water of (+)-7·(+)-BCS·$2H_2O$ plays an important role in the selective crystallization during this efficient resolution.

Key words diltiazem; optical resolution; preferential crystallization; diastereomeric salt

Diltiazem (+)-**8**,[1] a representative calcium channel blocker, is used throughout the world to treat angina pectoris, hypertension, and several other disorders. Among the four possible stereoisomers of diltiazem, only the (+)-(2*S*,3*S*)-isomer exhibits potent coronary vasodilating activity. Therefore, diltiazem has been developed and marketed as a single isomer.

In order to obtain the desired optical isomer, various methods[2–5] including resolution have been developed (Chart 1). Industrially, diltiazem was once manufactured through a diastereomeric resolution[3d] of its intermediate (±)-**4** with L-lysine. Although this resolution itself was very efficient, a simpler and more economical process was required to reduce the production cost of diltiazem. Recently, an enzymatic preparation[4e] of an intermediate, methyl (−)-(2*R*,3*S*)-3-(4-methoxyphenyl)glycidate [(−)-**2**], has

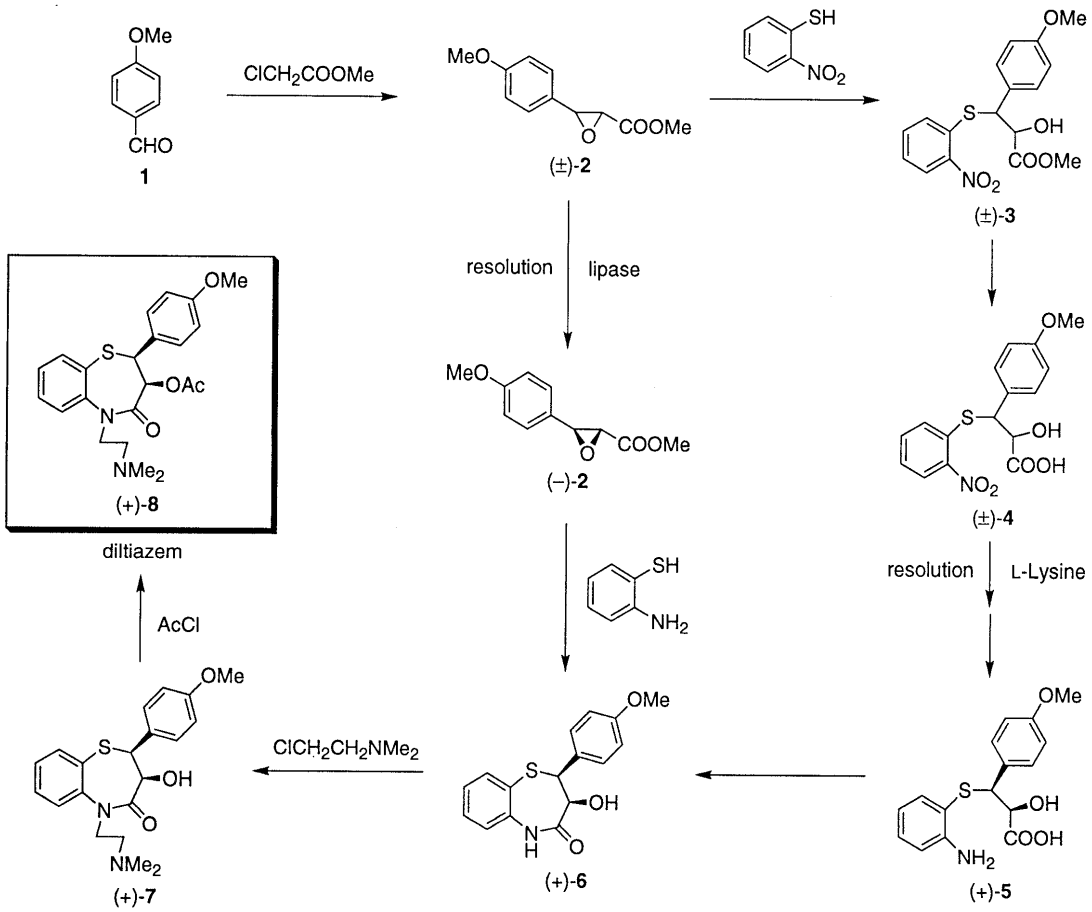

Chart 1

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been utilized in industrial production. Even this simple and economical method suffers the inevitable disadvantage that more than half of (±)-**2** is hydrolyzed and discarded. While (−)-**2** is a good raw material, more efficient preparation is very difficult, whether by enzymatic processes,[4a−c] by classical resolution[3f] including the recycling of undesired (+)-**2**, or by asymmetric syntheses.[5a−f]

As an alternative, we focused on a 1,5-benzothiazepine derivative (±)-**7**, because it can be easily prepared according to the above synthetic route by using racemic (±)-**2**. If both the efficient resolution of (±)-**7** and the recycling of the undesired (−)-**7** are possible, it is expected to be a promising alternative approach to obtain chiral diltiazem. The present paper reports an investigation of practical resolution procedures for (±)-**7** by preferential crystallization and diastereomer formation.

Results and Discussion

The syntheses of racemic and optically active **7** were performed by the method[6,7] outlined in Chart 1: racemic **2**, prepared by Darzens reaction of *p*-anisaldehyde **1** with methyl chloroacetate, was treated with 2-aminothiophenol followed by ring closure reaction to give the 1,5-benzothiazepine derivative (±)-**6**. Successive *N*-alkylation of (±)-**6** with 2-dimethylaminoethyl chloride readily provided (±)-**7** in 52% overall yield from **1**. Similarly, (+)-**7** was prepared through an enzymatic resolution[4e] of (±)-**2** in 25% overall yield.

Preferential Crystallization Procedure The separation of two enantiomers by preferential crystallization is a suitable procedure for use on an industrial scale, since it can be easily achieved by seeding a small amount of crystals of one enantiomer in a supersaturated racemic solution.[8] Some synthetic intermediates of diltiazem were resolved by preferential crystallization.[2] However, to our knowledge, the resolution of (±)-**7** by this method has not yet been reported, and thus we attempted it.

Table 1. Properties of **7**·NSA and **7**·AHS Salts

	mp (°C)	Solubility[a] (g/100 ml)		IR spectrum
		25 °C	40 °C	
(±)-**7**·NSA	136—138	17.90 (A)	—	Identical
(+)-**7**·NSA	142—144	9.26 (A)	—	
(±)-**7**·AHS	134—137	1.19 (B)	2.09 (B)	Identical
(+)-**7**·AHS	138—141	0.83 (B)	1.21 (B)	

a) Solvent: A (w/w) = DMF/H_2O (1/1), B = H_2O.

First, the possibility of resolution of (±)-**7** by preferential crystallization according to the standard screening method[8] was examined by comparing the melting point and infrared (IR) spectrum of (±)-**7** with those of (+)-**7**. Unfortunately, crystalline (±)-**7** itself did not exist as a conglomerate appropriate for this resolution, and we therefore sought conglomerate crystalline salts of (±)-**7** with achiral acids.

A wide variety of mineral, carboxylic, and sulfonic acids were each added to (±)- and (+)-**7**, dissolved in appropriate solvents, and allowed to crystallize. Seventeen salt pairs of (±)- and (+)-**7** were crystallized. Their physicochemical properties were examined and the salts of (±)-**7** with 1-naphthalenesulfonic acid (NSA) and 3-amino-4-hydroxybenzenesulfonic acid (AHS) were found to satisfy the requirements (Table 1).

Next, a supersaturated solution of (±)-**7**·NSA in 50% *N*,*N*-dimethylformamide (DMF)/H_2O was prepared and resolution was attempted by seeding (+)- or (−)-**7**·NSA alternately. Although the first trial was successful, the sequence of alternate crystallizations of the two enantiomers failed.

On the other hand, a supersaturated solution of (±)-**7**·AHS in water was seeded with crystals of (+)-**7**·AHS and stirred at 40 °C for 7 h to give the (+)-salt. As shown in Table 2, alternate seeding of the (−)- or (+)-salt provided the corresponding salts of 94—98% ee. The optical purity of these salts was sufficiently high, but the degree of resolution was a little low. As a tool for raising the enantiomer yield, it might be useful to increase the supersaturation degree, for example, by addition of other acids[9] or salts.[10]

The subsequent decomposition of these salts with an alkali solution readily provided (+)- and (−)-**7** in high yield and high optical purity.

Diastereomeric Salt Procedure There are various res-

Table 2. Successive Alternate Resolution of (±)-**7**·AHS by Preferential Crystallization[a]

Run	Amount of (±)-**7**·AHS added (g)	Composition of the solution		Crystallization conditions		Separated crystals		Degree of resolution[d] (%) (R)
		(±)-**7**·AHS (g) (A)	Excess (+)- or (−)-**7**·AHS[b] (g) (B)	Temperature (°C)	Time (h)	Yield (g) (C)	Ee[c] (%) (D)	
1	—	5.02	0.25 (+)	40	7	0.49 (+)	97.1	7.8
2	0.42	5.02	0.20 (−)	40	5	0.40 (−)	96.3	6.2
3	0.31	5.02	0.16 (+)	40	3	0.29 (+)	97.6	3.7
4	0.20	5.02	0.09 (−)	40	4	0.22 (−)	97.3	3.7
5	0.17	5.02	0.09 (+)	40	6	0.22 (+)	98.2	3.8
6	0.21	5.02	0.10 (−)	40	6	0.23 (−)	97.6	3.8
7	0.19	5.02	0.09 (+)	40	8	0.25 (+)	97.8	5.0
8	0.24	5.02	0.12 (−)	40	7	0.28 (−)	97.2	4.9
9	0.26	5.02	0.12 (+)	40	9	0.29 (+)	93.7	4.8
10	0.27	5.02	0.12 (−)	40	8	0.31 (−)	95.2	5.8

a) Resolutions were carried out on a 160 ml scale by the use of 0.03 g of seed crystals. *b*) Values were calculated from analysis of separated crystals. *c*) Determined by HPLC analysis (Chiralcel OD). *d*) R = (C·D/100 − B − 0.03)·(2/A)·100.

Table 3. Diastereomeric Resolution of (±)-7 with Various Resolving Agents

Run	Chiral resolving agent	Solvent	Diastereomeric salt isolated yield (%)[a]	Ratio of isomer 7[b]	
				(−)-7	(+)-7
1	L-Tartaric acid	$MeOH/H_2O$	62	50	50
2	*N*-Acetyl-(D)-valine	AcOEt	70	50	50
3	(−)-Menthoxyacetic acid	MeOH	73	50	50
4	*N*-Acetyl-(L)-isoleucine	AcOEt/MeOH	65	49	51
5	*N*-Acetyl-(L)-asparagine	MeCN/MeOH	63	50	50
6	(+)-(*S*)-2-(6-Methoxy-2-naphthyl)propionic acid	$MeOH/H_2O$	43	50	50
7	(+)-(1*S*)-3-Bromocamphor-10-sulfonic acid	MeCN/MeOH	46	50	50
8	(+)-(1*R*)-3-Bromocamphor-9-sulfonic acid	$MeOH/H_2O$	34	4	96

a) Based on (±)-**7**. *b*) Determined by HPLC analysis (Chiralcel OD).

Table 4. Diastereomeric Resolution of (±)-7 with (+)-BCS

Run	(+)-BCS Molar ratio[a]	Fractional crystallization			(+)-7·(+)-BCS·$2H_2O$	
		Solvent	Temperature (°C)	Time (h)	Yield (%)[b]	Ee (%)[d]
1	1.0	$MeOH/H_2O$	25	2	46.9	97.8
(recrystallization)		$EtOH/H_2O$	5	2	43.5 (92.7)[c]	99.9
2	0.6	$MeOH/H_2O$	25	2	43.6	97.0
(recrystallization)		$EtOH/H_2O$	5	2	41.3 (94.7)[c]	99.7

a) Equivalent to (±)-7. *b*) Based on (±)-7. *c*) Recrystallization yield. *d*) Ee of (+)-7, determined by HPLC analysis (Chiralcel OD).

olution methods for separating racemic substances into their enantiomers,[8] among which diastereomeric salt formation is a practical one. Many diastereomeric resolutions of diltiazem intermediates have been reported.[3] As for (±)-**7**, Inoue *et al.* reported a diastereomeric procedure using (+)-10-camphorsulfonic acid as a resolving agent.[3a] However, this resolution required repeated crystallization of the diastereomeric salt to obtain optically pure (+)-**7**. We therefore sought a more effective resolving agent for (±)-**7**.

Small-scale resolutions of (±)-**7** were performed through diastereomeric salt formation with various acidic resolving agents, and eight of these formed crystalline diastereomeric salts. Most of these salts were unresolved, but (+)-(1*R*)-3-bromocamphor-9-sulfonic acid [(+)-BCS][11] was an efficient resolving agent for (±)-**7** (Table 3). Furthermore, we examined the resolution conditions, that is, the kind and quantity of the solvents, the temperature and the time of the crystallization, and the molar ratio of (+)-BCS (Table 4). Under the optimum conditions, (±)-**7** could be resolved into less soluble (+)-**7**·(+)-BCS·$2H_2O$ in up to 43% yield and 97% ee by using only 0.6 eq of (+)-BCS. After recrystallization, the salt was quantitatively converted to optically pure (+)-**7** by decomposition with alkaline solution. Moreover, (+)-BCS could be easily recovered from the mother liquor by using an ionic resin column.

We examined the reason for this highly selective crystallization by comparison of the physicochemical properties of the diastereomeric salt pair.[12] In Table 5, the melting point, the enthalpy of fusion, the solubility, and the optical rotation of the more soluble (−)-**7**·(+)-BCS are compared with those of the less soluble (+)-**7**·(+)-BCS·$2H_2O$. Surprisingly, the solubility ratio of the two salts is only 2 times, which seems to be insufficient for the highest resolution efficiency. This prompted us to perform detailed thermal analyses of both salts (Fig. 1). In the differential scanning calorimetry (DSC) analyses, (−)-**7**·(+)-BCS showed a single endothermic peak due to fusion with a maximum at 235.3 °C, immediately accompanied by decomposition. In contrast, (+)-**7**·(+)-BCS·$2H_2O$ has two peaks with maxima at about 50 °C and 154.6 °C. The former peak corresponds to crystal water, which was identified as two molecules of water by thermogravimetry (TG) and elemental analysis. The crystal water of (+)-**7**·(+)-BCS·$2H_2O$ was slowly lost at room temperature in dry N_2 gas, and conversely, the dehydrated salt was easily transformed into the dihydrated salt upon exposure to a humid atmosphere. This characteristic water of solvation observed in the less soluble (+)-**7**·(+)-BCS·$2H_2O$, does not exist in the more soluble (−)-**7**·(+)-BCS. In diastereomeric resolution methods, it is empirically known that solvation occasionally has a marked influence on the efficiency of resolution.[8,13] This crystal water, which is related to the formation of thermodynamically more stable crystals, presumably plays an important role in selective crystallization. Comparison of the X-ray crystal structures of the diastereomeric salt pair should be informative.

Table 5. Properties of (−)-**7**·(+)-BCS and (+)-**7**·(+)-BCS·$2H_2O$

Diastereomeric salt	mp[a] (°C)	ΔH^f[a] (kJ mol^{-1})	Solubility[c] (g/100 g solv.)	$[\alpha]_D^{25}$ (c=1.0, MeOH)
(−)-**7**·(+)-BCS	235	49	0.99 (A) 1.63 (B)	−25.0°
(+)-**7**·(+)-BCS·$2H_2O$	50, 154[b]	68, 40[b]	0.47 (A) 0.73 (B)	+112.2°

a) DSC method, mp: temperature of top peak of fusion, ΔH^f: enthalpy of fusion. *b*) Two peaks. *c*) 25°C, solvent A = H_2O, B (v/v) = H_2O/MeOH (7/3).

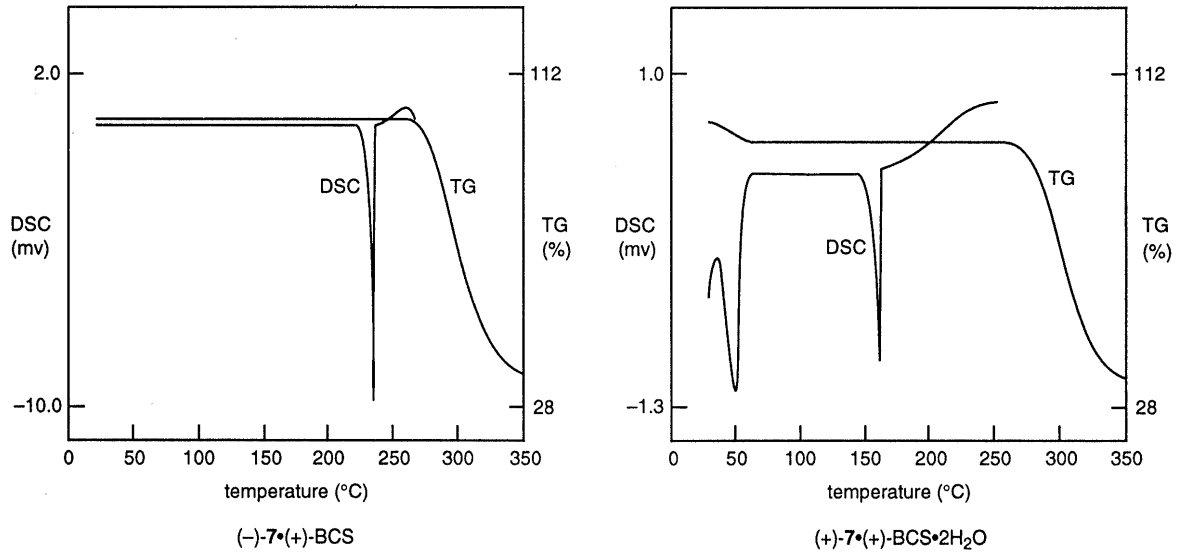

Fig. 1. DSC and TG Curves of (−)-7·(+)-BCS and (+)-7·(+)-BCS·$2H_2O$

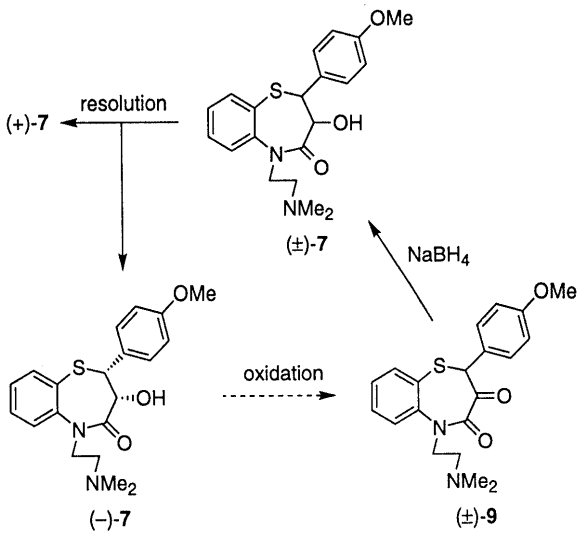

Chart 2

Conclusion

We have developed two effective resolution methods for the diltiazem intermediate (±)-7. With respect to the preferential crystallization procedure, the ee % obtained at each step is very high, the cost of AHS is low, and the solvent is water. It should be straightforward to automate this procedure. On the other hand, although the yield and the optical purity of the diastereomeric salt procedure are excellent, this method requires the expensive chiral resolving agent (+)-BCS. The preferential crystallization procedure seems more promising for practical diltiazem synthesis. At present, a tool for recycling the unwanted enantiomer (−)-7 (Chart 2) is under investigation, and if this proves possible, it would make this procedure more economical.

Experimental

Melting points are uncorrected. Optical rotations were measured on a Perkin Elmer Model 243 polarimeter. IR spectra were recorded on a Perkin Elmer 1600 series FT-IR. ^{1}H-NMR spectra were measured at 200 MHz on a Bruker AC-200 instrument and chemical shifts are reported relative to tetramethylsilane (TMS). Elemental analyses were performed on a Perkin Elmer 2400 CHN analyzer. DSC and TG were performed on a Shimadzu DSC-50 and a Shimadzu TGA-50 by raising the temperature at 5 °C per min under N_2. All of the solvents and reagents were commercial products used without further purification. Analytical TLC was performed on E. Merck precoated Silica gel 60 F_{254} plates. The optical purity of **7** was analyzed by chiral HPLC [column: Daicel Chiralcel OD 4.6×250 mm; mobile phase: *n*-hexane–EtOH–diethylamine=85:15:0.1; flow rate: 0.5 ml/min; detection: UV 254 nm; temperature: 35 °C; t_R: (−)-**7** 14 min, (+)-**7** 16 min].

Methyl (±)-(2*RS*,3*SR*)-3-(4-Methoxyphenyl)glycidate [(±)-2] A mixture of *p*-anisaldehyde (450 g, 3.31 mol) and methyl chloroacetate (534 g, 4.92 mol) was added to 24 wt. % sodium methoxide solution in MeOH (1320 ml, 5.48 mol) over 4.5 h at 0 °C and stirring was continued for a further 4 h. The reaction mixture was poured into a solution of AcOH (60 g, 1.0 mol) in water (7500 ml) over 20 min at 0 °C. The whole was stirred for 1 h, then precipitated crystals were collected by filtration, and washed with cold water and cold MeOH to give a crude product, which was recrystallized from hot MeOH (400 ml) to yield (±)-**2** (551 g, 80.0%): mp 69—71 °C; IR (KBr) cm^{-1}: 1730, 1520, 1310, 1250; ^{1}H-NMR (DMSO-d_6) δ: 3.73 (s, 3H), 3.76 (s, 3H), 3.82 (d, 1H, J=1.9 Hz), 4.10 (d, 1H, J=1.9 Hz), 6.94 (d, 2H, J=10 Hz), 7.29 (d, 2H, J=10 Hz).

Methyl (−)-(2*R*,3*S*)-3-(4-Methoxyphenyl)glycidate [(−)-2] Compound (−)-**2** was prepared by resolving (±)-**2** according to a reported procedure[4e]: mp 87—88 °C; $[\alpha]_D^{20}$ = −207.1° (c=1.0, MeOH); IR (KBr) cm^{-1}: 1750, 1520, 1450, 1210. The ^{1}H-NMR spectrum of the product was identical with that of (±)-**2**.

(±)-(2*RS*,3*RS*)-2,3-Dihydro-3-hydroxy-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one [(±)-6] A solution of (±)-**2** (260.3 g, 1.25 mol) and 28% aqueous $FeCl_3 \cdot 6H_2O$ (1 drop) in chlorobenzene (1270 ml) was heated to 80—85 °C. 2-Aminothiophenol (164.3 g, 1.31 mol) was added over 30 min, and the resulting mixture was stirred for 45 min at 115 °C. Methanesulfonic acid (4.8 g, 0.05 mol) was added, and the solution was refluxed for 8 h while chlorobenzene was distilled off (the amount of distilled chlorobenzene: 570 ml). The mixture was stirred for 14 h under cooling, and precipitated crystals were collected by filtration and washed with chlorobenzene to give a crude product. The product was refluxed for 2 h in MeOH (1500 ml), cooled to room temperature, and filtered to give pure (±)-**6** (260 g, 69.0%): mp 170—172 °C; IR (KBr) cm^{-1}: 1680, 1510, 1475, 1250; ^{1}H-NMR (DMSO-d_6) δ: 3.76 (s, 3H), 4.29 (dd, 1H, J=6.4, 6.6 Hz), 4.74 (d, 1H, J=6.4 Hz), 5.05 (d, 1H, J=6.6 Hz), 6.87—7.62 (m, 8H), 10.31 (s, 1H).

(+)-(2*S*,3*S*)-2,3-Dihydro-3-hydroxy-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one [(+)-6] Compound (+)-**6** was prepared from (−)-**2** according to the above procedure: mp 202—204 °C; $[\alpha]_D^{20}$ = +114.0° (c=0.5, DMF); IR (KBr) cm^{-1}: 1680, 1510, 1475, 1250. The ^{1}H-NMR spectrum of the product was identical with that of (±)-**6**.

(±)-(2*RS*,3*RS*)-5-[2-(Dimethylamino)ethyl]-2,3-dihydro-3-hydroxy-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one [(±)-7] A modified literature procedure[7] was used to prepare (±)-**7**. A mixture of (±)-**6** (106.3 g, 0.353 mol), 2-(dimethylamino)ethyl chloride hydrochloride (55.9 g, 0.388 mol), anhydrous K_2CO_3 (107.2 g, 0.776 mol), AcOEt(860

ml), and water (18.9 g) was refluxed for 8 h. The reaction mixture was cooled to room temperature, washed with water, and concentrated under reduced pressure. The residue was dissolved in 2-PrOH (276 ml) under heating, filtered, and cooled in an ice bath for 2 h with stirring. Precipitated crystals were collected by filtration, washed with 2-PrOH (100 ml), and dried at 60 °C to give (±)-**7** (123.4 g, 93.9%): mp 106—108 °C; IR (KBr) cm^{-1}: 2830, 1665, 1510, 1250; ^{1}H-NMR (DMSO-d_6) δ: 2.14 (s, 6H), 2.22—2.35 (m, 1H), 2.49—2.62 (m, 1H), 3.63—3.76 (m, 1H), 3.76 (s, 3H), 4.20 (t, 1H, J=7.3 Hz), 4.26—4.41 (m, 1H), 4.50 (d, 1H, J=7.3 Hz), 4.89 (d, 1H, J=7.3 Hz), 6.87—7.70 (m, 8H).

(+)-(2*S*,3*S*)-5-[2-(Dimethylamino)ethyl]-2,3-dihydro-3-hydroxy-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one [(+)-7] Compound (+)-**7** was prepared from (+)-**6** according to the above procedure: mp 84—86 °C; $[\alpha]_D^{25}$ = +172.1° (c=1.0, MeOH); IR (KBr) cm^{-1}: 2825, 1670, 1510, 1475, 1250. The ^{1}H-NMR spectrum of the product was identical with that of (±)-**7**.

Optical Resolution of (±)-7 by Preferential Crystallization Procedure. Search for Conglomerate Salts of (+)-7 The achiral acid (1.1 mmol) was added to each of (±)-**7** (0.373 g, 1.0 mmol) and (+)-**7** (0.373 g, 1.0 mmol), and the mixture was dissolved in a small amount of various solvents under heating, and allowed to stand at room temperature. Crystallized salt pairs of (±)- and (+)-**7** were collected by filtration and dried at 50 °C under reduced pressure. Melting points, solubilities, and IR spectra of both salts were compared. The two salts of (±)-**7** with NSA and AHS satisfied the requirements for a conglomerate (Table 1).

(±)-(2*RS*,3*RS*)-5-[2-(Dimethylamino)ethyl]-2,3-dihydro-3-hydroxy-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one·3-Amino-4-hydroxybenzenesulfonate [(±)-7·AHS] (±)-**7** (7.46 g, 0.02 mol) and 95% AHS (4.38 g, 0.022 mol) were dissolved in a mixture of MeOH (16 ml) and water (64 ml) under heating, and the whole was allowed to stand at 5 °C for 20 h. Precipitated crystals were collected by filtration, washed with cold water, and dried at 50 °C to give the desired product (±)-**7**·AHS (10.42 g, 92.8%): mp 134—137 °C; IR (KBr) cm^{-1}: 1505, 1245, 1170, 1020; ^{1}H-NMR (DMSO-d_6) δ: 2.81 (s, 6H), 3.05—3.20 (m, 2H), 3.76 (s, 3H), 3.94—4.10 (m, 1H), 4.24 (t, 1H, J=6.8 Hz), 4.35—4.55 (m, 1H), 4.83 (d, 1H, J=6.6 Hz), 4.92 (d, 1H, J=7.2 Hz), 6.52—7.75 (m, 11H).

(+)-(2*S*,3*S*)-5-[2-(Dimethylamino)ethyl]-2,3-dihydro-3-hydroxy-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one·3-Amino-4-hydroxybenzenesulfonate [(+)-7·AHS] (+)-**7**·AHS was prepared from (+)-**7** according to the above procedure: mp 138—141 °C; $[\alpha]_D^{25}$ = +87.3° (c=1.0, MeOH). The IR and ^{1}H-NMR spectra of the product were identical with those of (±)-**7**·AHS.

Optical Resolution of (±)-7·AHS by Preferential Crystallization A) (±)-**7**·AHS (5.02 g) and (+)-**7**·AHS (0.25 g) were dissolved in water (160 g) under heating. After cooling to 40 °C, crystals of (+)-**7**·AHS (0.03 g) were seeded in the solution. The mixture was stirred for 7 h and the precipitated crystals were collected by filtration. The filtered crystals were washed with cold water and dried at 50 °C to give (+)-**7**·AHS (0.49 g): mp 138—141 °C; $[\alpha]_D^{25}$ = +86.0° (c=1.0, MeOH); optical purity 97.1% ee. The IR and ^{1}H-NMR spectra of the product were identical with those of (±)-**7**·AHS.

B) (±)-**7**·AHS (0.42 g) was added to the mother liquor (adjusted to 160 g) obtained in the above-mentioned step (A), and the mixture was dissolved under heating. After cooling to 40 °C, crystals of (−)-**7**·AHS[14] (0.03 g) were seeded in the solution. The mixture was stirred for 5 h and the precipitated crystals were collected by filtration. The filtered crystals were washed with cold water and dried at 50 °C to give (−)-**7**·AHS (0.40 g): mp 138—141 °C; $[\alpha]_D^{25}$ = −83.2° (c=1.0, MeOH); optical purity 96.3% ee. The IR and ^{1}H-NMR spectra of the product were identical with those of (±)-**7**·AHS. Subsequently, optically active (+)-**7**·AHS and (−)-**7**·AHS were obtained by repeated resolution (10 times) in the same manner as described above (Table 2).

Preparation of (+)-7 and (−)-7 (+)-**7**·AHS (0.56 g, 1 mmol, 97.8% ee) was dissolved in water (30 ml) under heating and to this solution, $NaHCO_3$ (0.09 g, 1.1 mmol) was added. The mixture was extracted with AcOEt. The extract was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure to give (+)-**7** (0.35 g, 93%): mp 84—86 °C; $[\alpha]_D^{25}$ = +166.1° (c=1.0, MeOH); optical purity 98.0% ee. The IR and ^{1}H-NMR spectra of the product were identical with those of authentic (+)-**7**.

(−)-**7**·AHS (0.87 g, 1.55 mmol, 97.4% ee) was recrystallized from hot water (10 ml). The recrystallized salt (0.66 g, 1.18 mmol, 100% ee) was treated according to the above procedure to give (−)-**7** (0.40 g, 91%): mp 81—84 °C; $[\alpha]_D^{20}$ = −170.5° (c=1.0, MeOH); optical purity 100% ee. The IR and ^{1}H-NMR spectra of the product were identical with those of authentic (+)-**7**.

Optical Resolution of (±)-7 by Diastereomeric Salt Procedure. Search of Resolving Agents for (±)-7 (±)-**7** (0.2 g, 0.54 mmol) and an acidic resolving agent (0.54 mmol) were dissolved in a small amount of various solvents under heating and the whole was allowed to stand at room temperature. Precipitated crystals were collected by filtration and dried at 50 °C under reduced pressure. Resolution ratios of the obtained diastereomeric salts were analyzed by chiral HPLC. The results are summarized in Table 3.

Optical Resolution of (±)-7 with (+)-BCS (±)-**7** (2.0 g, 5.37 mmol) and (+)-BCS ammonium salt (1.06 g, 3.23 mmol) were dissolved in a mixture of water (20 ml), MeOH (6.4 ml), and 6 N HCl (0.36 ml, 2.2 mmol) under heating, and the mixture was stirred at 25 °C for 2 h. Precipitated crystals were collected by filtration and dried at 50 °C under reduced pressure to give crude (+)-**7**·(+)-BCS·$2H_2O$ (1.69 g, 43.6%, 97.0% ee). The crude salt (1.58 g, 2.19 mmol) was recrystallized from a mixture of water (15 ml) and EtOH (0.5 ml) to give purified (+)-**7**·(+)-BCS·$2H_2O$ (1.49 g, 94.7%, 99.7% ee): mp 147—149 °C; $[\alpha]_D^{25}$ = +112.2° (c=1.0, MeOH); IR (KBr) cm^{-1}: 3455, 1755, 1665, 1515, 1475; ^{1}H-NMR (DMSO-d_6) δ: 0.82 (s, 3H), 1.09 (s, 3H), 1.12—1.24 (m, 1H), 1.67—1.89 (m, 2H), 2.06—2.15 (m, 1H), 2.38 (d, 1H, J=14.0 Hz), 2.86 (s, 7H), 3.00 (t, 1H, J=4.2 Hz), 3.13—3.46 (m, 4H), 3.76 (s, 3H), 3.97—4.11 (m, 1H), 4.25 (d, 1H, J=7.3 Hz), 4.37—4.52 (m, 1H), 4.90—4.99 (m, 3H), 6.89 (d, 2H, J=8.7 Hz), 7.33—7.76 (m, 6H), 9.53 (s, 1H)

Preparation of (+)-7 The recrystallized (+)-**7**·(+)-BCS·$2H_2O$ (1.44 g, 2.0 mmol, 99.7% ee) was suspended in water (60 ml) and to this solution, $NaHCO_3$ (0.18 g, 2.2 mmol) was added. The mixture was extracted with AcOEt. The extract was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure to give (+)-**7** (0.70 g, 94.0%): mp 86—88 °C; $[\alpha]_D^{25}$ = +170.8° (c=1.0, MeOH); optical purity 100% ee. The IR and ^{1}H-NMR spectra of the product were identical with those of authentic (+)-**7**.

Preparation of (−)-(2*R*,3*R*)-5-[2-(Dimethylamino)ethyl]-2,3-dihydro-3-hydroxy-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one·(+)-(1*R*)-3-Bromocamphor-9-sulfonate [(−)-7·(+)-BCS] (−)-**7** (0.30 g, 0.81 mmol) was dissolved in 22.9 wt% aqueous (+)-BCS (1.12 g, 0.82 mmol) under heating and the solution was concentrated under reduced pressure. The residue was allowed to stand overnight at room temperature. Precipitated crystals were triturated in acetonitrile, collected by filtration, and dried at 40 °C to give (−)-**7**·(+)-BCS (0.41 g, 74.5%): mp 223—225 °C; $[\alpha]_D^{25}$ = −25.0° (c=1.0, MeOH); IR (KBr) cm^{-1}: 1755, 1665, 1510, 1475; ^{1}H-NMR (DMSO-d_6) δ: 0.81 (s, 3H), 1.08 (s, 3H), 1.12—1.24 (m, 1H), 1.67—1.88 (m, 2H), 2.05—2.20 (m, 1H), 2.36 (d, 1H, J=14.0 Hz), 2.85 (m, 7H), 3.00 (t, 1H, J=4.2 Hz), 3.13—3.46 (m, 4H), 3.76 (s, 3H), 3.97—4.11 (m, 1H), 4.25 (d, 1H, J=7.3 Hz), 4.37—4.52 (m, 1H), 4.90—4.99 (m, 3H), 6.89 (d, 2H J=8.7 Hz), 7.33—7.76 (m, 6H), 9.50 (s, 1H).

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