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AN EFFICIENT SYNTHESIS OF OPTICAL ISOMERS OF VASOPRESSIN V_2 RECEPTOR ANTAGONIST OPC-41061 BY LIPASE-CATALYZED ENANTIOSELECTIVE TRANSESTERIFICATION

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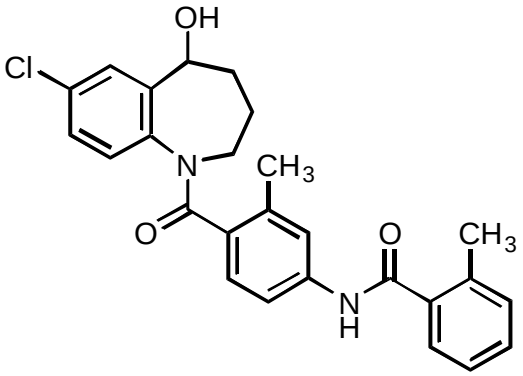
Abstract - The optically active enantiomers of 7-chloro-5-hydroxy-1-[2-methyl-4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine (OPC-41061, **1**) were enantioselectively synthesized. The chiral acetate ((*R*)-(–)-**3**) and the chiral alcohol ((*S*)-(+)-**2**) were prepared *via* the resolution of the racemic alcohol ((±)-**2**) using the lipase-mediated transesterification with vinyl acetate. Compounds ((*R*)-(–)-**3**) and **(**(*S*)-(+)-**2**) were converted to optically active **1**.

INTRODUCTION

The benzazepine derivative 7-chloro-5-hydroxy-1-[2-methyl-4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine (OPC-41061, **1**)[1] is a new vasopressin V_2 receptor antagonist and is now under clinical trial as a novel aquaretic agent. This compound has an asymmetric carbon at the 5-position of the benzazepine ring. In order to clarify the mechanism of action and the pharmacological profile of **1**, obtaining the optically active isomer was essential.



1 (OPC-41061)

Figure 1

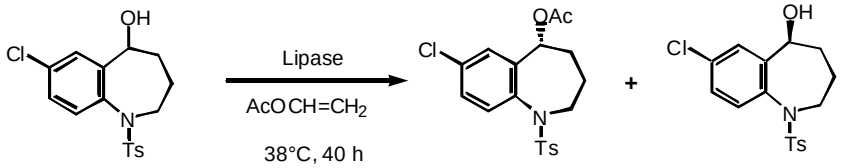
There are many useful methods of preparing optically active secondary alcohols. Lipase-catalyzed transesterification is one of the most useful technologies. We have already reported the asymmetric synthesis of the key intermediate and the metabolites of OPC-29030[2] *via* lipase-catalyzed

transesterification.[3] In this paper, we wish to report an efficient synthesis of optically active **1** using the lipase-catalyzed transesterification.

RESULTS AND DISCUSSION

First, to prepare both enantiomers of **1**, we examined the lipase-catalyzed transesterification of the key intermediate ((±)-**2**) with vinyl acetate. Based on the screening test (**Table 1**), most of the lipases except for lipase OF showed good selectivity. Especially, the selectivity of Lipozyme IM was excellent (Entry 6). When we prepare the compound on a practical scale, reactivity is also regarded as the important factor. Taking both the selectivity and the reactivity into consideration, using lipase QL (Entry 1) was the best condition for preparing (*R*)-(–)-**3** and (*S*)-(+)-**2**.

Table 1 Lipase-catalyzed transesterification[a]

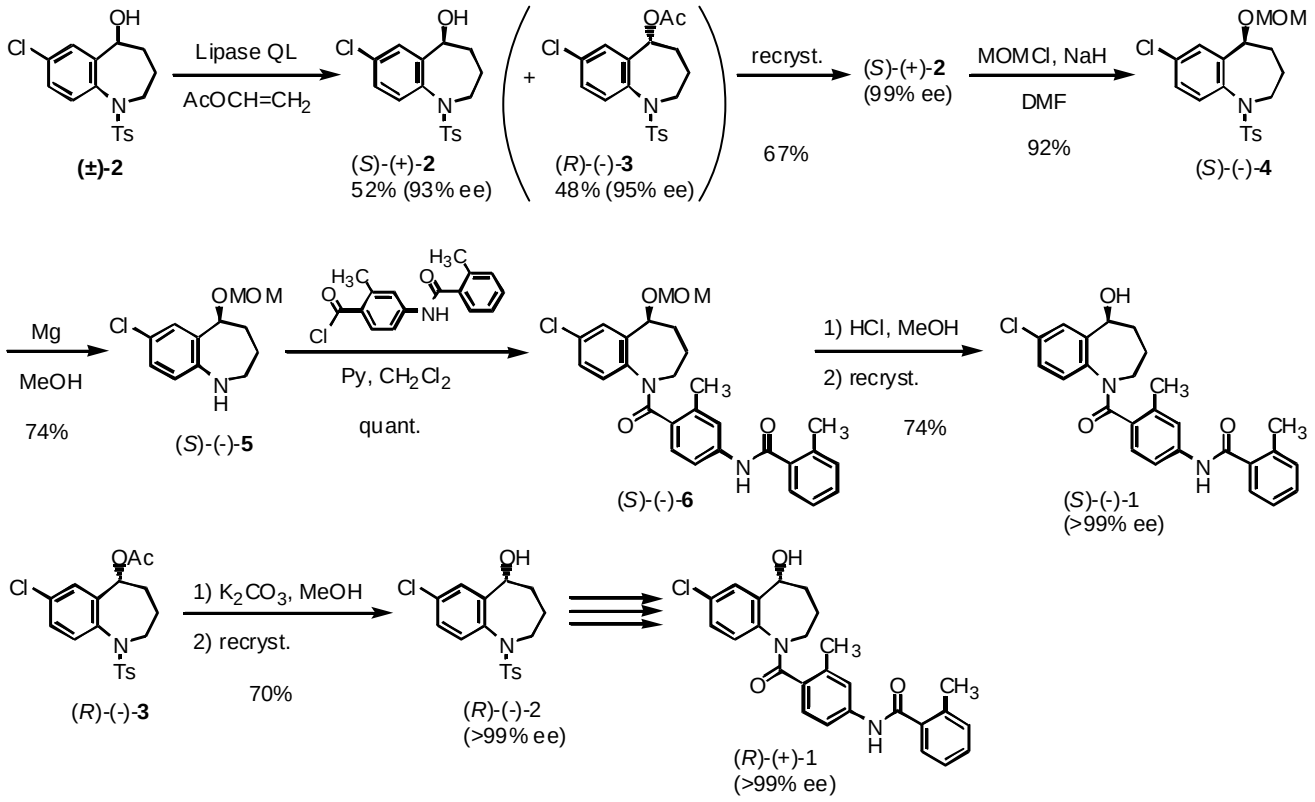


(±)-2 (*R*)-(-)-**3** (*S*)-(+)-**2**

Entry	Lipase[b]	(*R*)-(-)-**3**		(*S*)-(+)-**2**		E value[e]
		Yield (%)[c]	ee (%)[d]	Yield (%)[c]	ee (%)[d]	
1	QL	51	95	49	99	206
2[f]	QL	32	98	68	45	155
3	QLG	9	97	91	9	72
4	PL	19	97	81	23	82
5	OF	0	---	---	---	---
6	Lipozyme IM	11	> 99	89	13	453
7	Novozym 435	9	99	91	10	220
8	SP 524	4	98	96	4	103
9	Toyozyme LIP	10	99	90	10	220

a. All reactions were carried out by stirring a mixture of (±)-**2** (52 mg), lipase (52 mg), and vinyl acetate (2 mL) at 38°C for 40 h, except for Entry 2. b. PL, QL (Meito Sangyo, *Alcaligenes* sp.), QLG (Meito Sangyo, immobilized, *Alcaligenes* sp.), OF (Meito Sangyo, *Candida cylindracea*), Lipozyme IM (Novo Nordisk, *Mucor miehei*), Novozym 435, SP 524 (Novo Nordisk, *Aspergillus oryzae*), Toyozyme LIP (Toyo Boseki, *Pseudomonas* sp.). c. HPLC yield. d. Enantiomeric purities were determined by HPLC analysis using a column packed with CHIRALCEL OJ (Daicel Chemical). e. The E value is the ratio of the specificity constant of two enantiomers calculated according to ref. 4. f. Reaction at room temperature (24°C).

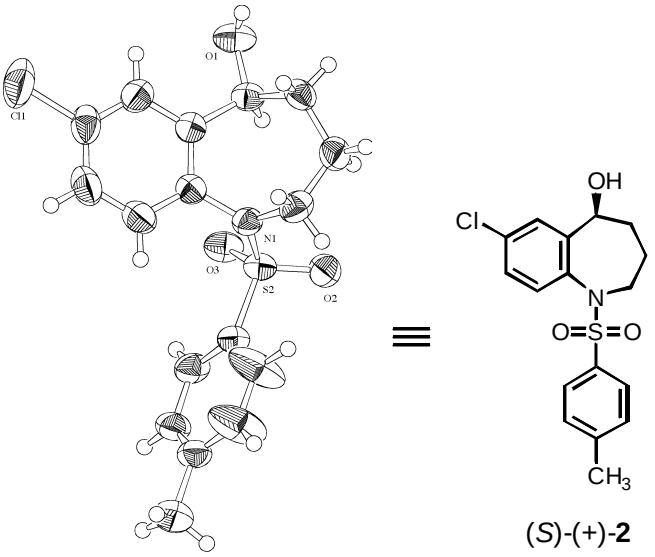
We applied the optimal conditions on a practical scale (35.0 g of the substrate) to convert the substrate into the target compound. Transesterification of (±)-**2** with vinyl acetate and lipase QL gave the acetate ((*R*)-(–)-**3**) (48% yield and 95% ee) and the unreacted alcohol ((*S*)-(+)-**2**) (52% yield and 93% ee). The crude (*S*)-(+)-**2** (93% ee) was recrystallized from EtOAc – hexane to give optically pure crystals (99% ee). Treatment of (*S*)-(+)-**2** with chloromethyl methyl ether in the presence of sodium hydride gave the methoxymethyl compound, which was reacted with magnesium in MeOH to give the benzazepine ((*S*)-(–)-**5**) in 68% yield (from (*S*)-(+)-**2**). Benzoylation of (*S*)-(–)-**5** with 2-methyl-4-[(2-methylbenzoyl)-amino]benzoyl chloride in the presence of pyridine afforded the benzoyl derivative ((*S*)-(–)-**6**) in quantitative yield. The target compound ((*S*)-(–)-**1**) was obtained by deprotection of (*S*)-(–)-**6** with hydrochloric acid in 74% yield, and the high enantiomeric excess was retained (>99% ee). On the other hand, the alcohol ((*R*)-(–)-**2**) was derived by hydrolysis of the acetate ((*R*)-(–)-**3**) with potassium carbonate, and recrystallized from EtOAc – hexane to give optically pure crystals (>99% ee). The antipodal enantiomer ((*R*)-(+)-**1**) (>99% ee) was synthesized similarly from (*R*)-(–)-**2**. (**Scheme 1**).



Scheme 1

Thus we accomplished the enantioselective synthesis of both enantiomers of **1**. This method was effective for preparing both enantiomers of the target compounds in good yield and high enantiomeric excess.

The absolute configurations of the above optically active compounds were determined as follows. The X-Ray crystal structure for (+)-**2** is shown in **Figure 2**. The absolute configuration of the 5-position was determined to be *S* by Bijvoet's anomalous-dispersion method.[5] Consequently, the compounds ((–)-**4**, (–)-**5**, (–)-**6**, and (–)-**1**) derived from (+)-**2** were of the *S* configuration.



(*S*)-(+)-**2**

X-Ray crystal structure for (+)-**2**

Figure 2

In conclusion, we have established the enantioselective synthesis of optically active OPC-41061 ((*S*)-(–)-**1** and (*R*)-(+)-**1**) from the key intermediates ((*S*)-(+)-**2** and (*R*)-(–)-**2**) obtained by means of lipase-catalyzed kinetic resolution.

EXPERIMENTAL

Melting points were determined with a Yamato MP-21 apparatus and are uncorrected. NMR spectra were recorded on a Bruker AVANCE DPX 250 spectrometer. MS spectra were obtained on Finnigan MAT GCQ instrument. IR spectra were recorded on a Perkin Elmer FT-IR spectrophotometer Spectrum 1000. Optical rotations were measured on a JASCO DIP-370 digital polarimeter. Silica gel (Fuji silysia chemical Ltd., BW-127ZH) was used for column chromatography.

General procedure of lipase catalyzed transesterification A mixture of (±)-**2** (52 mg), vinyl acetate (2 mL) and lipase QL (52 mg) was stirred at 38°C. The ratio of the substrate and the acetylated product was monitored by HPLC (DAICEL CHIRALCEL OJ was used for (*S*)-(+)-**2** and (*R*)-(–)-**3** with hexane : *iso*-PrOH : Et_2NH = 800 : 200 : 1 as the eluent) or the reaction was quenched after appropriate time. When about a half of the substrate was acetylated, the mixture was filtered and evaporated. The residue was chromatographed on silica gel with a mixed solvent (hexane : EtOAc = 4 : 1) to afford both the optically active alcohol and the acetylated product.

(*S*)-7-Chloro-5-hydroxy-1-(*p*-toluenesulfonyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine [(*S*)-(+)-2]

A mixture of (±)-**2** (35.0 g, 100 mmol) and lipase QL (22.0 g) in vinyl acetate (350 mL) was stirred at 38°C for 48 h. The mixture was filtrated by a pad of Celite and the insoluble material was washed with CH_2Cl_2. The filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, hexane : EtOAc = 4 : 1) to give (*S*)-(+)-**2** (18.1 g, 52%) and (*R*)-(–)-**3** (19.0 g, 48%), which were (*S*)-(+)-**2** (93% ee) and (*R*)-(–)-**3** (95% ee) by HPLC analysis using CHIRALCEL OJ

(hexane : *iso*-PrOH : Et_2NH = 800 : 200 : 1). The crude (*S*)-(+)-**2** was recrystallized from EtOAc – hexane to give (*S*)-(+)-**2** (12.2 g, 35%, 99% ee) as colorless prisms, mp 143 – 144°C. $[\alpha]_D^{27}$ +9.5° (c 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$) *d*: 1.50 – 2.20 (4 H, m), 2.44 (3 H, s), 3.00 – 3.30 (1 H, m), 3.90 – 4.20 (1 H, m), 4.50 – 4.65 (1 H, m), 7.05 (1 H, d, *J* = 8.4 Hz), 7.15 (1 H, dd, *J* = 8.4 Hz, 2.3 Hz), 7.29 (2 H, dd, *J* = 8.3 Hz, 2.1 Hz), 7.53 (1 H, d, *J* = 2.3 Hz), 7.65 (2 H, d, *J* = 8.3 Hz). IR (KBr): 3526, 1482, 1340, 1159 cm^{-1}. *Anal* Calcd for $C_{17}H_{18}NO_3ClS$: C, 58.03; H, 5.16; N, 3.98. Found: C, 57.88. H, 5.20; N, 4.08.

(*R*)-5-Acetoxy-7-chloro-1-(*p*-toluenesulfonyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine [(*R*)-(–)-3]
The crude (*R*)-(–)-**3** was recrystallized from MeOH to give (*R*)-(–)-**3** as colorless needles, mp 109 – 111°C. $[\alpha]_D^{28}$ –8.9° (c 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$) *d*: 1.50 – 2.00 (4 H, m), 2.13 (3 H, s), 2.43 (3 H, s), 3.00 – 3.30 (1 H, m), 3.90 – 4.20 (1 H, m), 5.42 (1 H, d, *J* = 9.0 Hz), 7.15 – 7.40 (5 H, m), 7.67 (2 H, d, *J* = 8.3 Hz). IR (KBr): 2932, 1745, 1341, 1243, 1225, 1164, 1038 cm^{-1}. *Anal* Calcd for $C_{19}H_{20}NO_4ClS$: C, 57.94; H, 5.12; N, 3.56. Found: C, 57.90; H, 5.05; N, 3.59.

(*R*)-7-Chloro-5-hydroxy-1-(*p*-toluenesulfonyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine [(*R*)-(–)-2]
A mixture of (*R*)-(–)-**3** (19.0 g, 48.2 mmol, 95% ee) and K_2CO_3 (6.66 g, 48.2 mmol) in MeOH (160 mL) was stirred at rt for 30 min. After removal of MeOH, the residue was poured into water and the solution was extracted with CH_2Cl_2. The extract was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was recrystallized from EtOAc – hexane to give (*R*)-(–)-**2** (11.8 g, 70%, >99% ee) as colorless prisms, mp 150°C. $[\alpha]_D^{27}$ –9.4° (c 1.0, $CHCl_3$). IR (KBr): 3520, 1482, 1341, 1159 cm^{-1}. *Anal* Calcd for $C_{17}H_{18}NO_3ClS$: C, 58.03; H, 5.16; N, 3.98. Found: C, 58.13. H, 5.20; N, 4.15.

(*S*)-7-Chloro-5-methoxymethyloxy-1-(*p*-toluenesulfonyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine [(*S*)-(–)-4] A 60% dispersion of NaH in oil (0.19 g, 4.8 mmol) was added to a ice-cooled solution of (*S*)-(+)-**2** (1.41 g, 4.0 mmol, 99% ee) in DMF (15 mL) and the mixture was stirred at the same temperature for 30 min. Chloromethyl methyl ether (0.46 mL, 6.0 mmol) was added to the mixture and stirred at rt for 18 h. The reaction mixture was poured into water and the solution was extracted with EtOAc – toluene. The extract was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, hexane : EtOAc = 3 : 1) to give (*S*)-(–)-**4** (1.45 g, 92%) as colorless oil. $[\alpha]_D^{27}$ –39.2° (c 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$) *d*: 1.40 – 2.10 (4 H, m), 2.41 (3 H, s), 3.00 – 3.25 (1 H, m), 3.28 (3 H, s), 4.00 – 4.20 (2 H, m), 4.30 (1 H, d, *J* = 6.7 Hz), 4.53 (1 H, d, *J* = 6.7 Hz), 7.15 – 7.35 (4 H, m), 7.41 (1 H, d, *J* = 2.4 Hz), 7.61 (2 H, d, *J* = 8.3 Hz). IR (neat) : 2936, 1600, 1480, 1349, 1161, 1093, 1034 cm^{-1}. *Anal* Calcd for $C_{19}H_{22}NO_4ClS$: C, 57.64; H, 5.60; N, 3.54. Found: C, 57.58. H, 5.70; N, 3.45.

(*R*)-7-Chloro-5-methoxymethyloxy-1-(*p*-toluenesulfonyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine [(*R*)-(+)-4] The title compound was prepared from (*R*)-(–)-**2**, NaH and chloromethyl methyl ether by the procedure described for the preparation of (*S*)-(–)-**4**. The product was purified by column chromatography to give (*R*)-(+)-**4** (quant.) as colorless oil. $[\alpha]_D^{27}$ +38.6° (c 1.0, $CHCl_3$). IR (neat): 2938, 1600, 1480, 1341, 1154, 1094, 1030 cm^{-1}. *Anal* Calcd for $C_{19}H_{22}NO_4ClS$: C, 57.64; H, 5.60; N, 3.54.

Found: C, 57.61. H, 5.67; N, 3.52.

(*S*)-7-Chloro-5-methoxymethyloxy-2,3,4,5-tetrahydro-1*H*-1-benzazepine [(*S*)-(–)-5] Magnesium (0.61 g, 25.1 mmol) was added to a solution of (*S*)-(–)-**4** (0.99 g, 2.5 mmol) in MeOH (18 mL) and the mixture was refluxed for 2 h. After removal of MeOH, the residue was diluted with CH_2Cl_2, and then Celite was added to the mixture. The insoluble material was filtrated and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, hexane : EtOAc = 3 : 1) to give (*S*)-(–)-**5** (0.45 g, 74%) as colorless oil. $[\alpha]_D^{27}$ –212° (c 1.0, MeOH). ^{1}H NMR ($CDCl_3$) *d*: 1.70 – 2.10 (4 H, m), 2.85 – 3.25 (2 H, m), 3.39 (3 H, s), 4.62 (1 H, d, *J* = 6.8 Hz), 4.66 (1H, br s), 4.71 (1 H, d, *J* = 6.8 Hz), 6.64 (1 H, d, *J* = 8.3 Hz), 7.03 (1 H, dd, *J* = 8.3 Hz, 2.4 Hz), 7.31 (1H, d, *J* = 2.4 Hz). IR (neat): 3372, 2938, 2818, 1493, 1150, 1033 cm^{-1}. HRMS Calcd for $C_{12}H_{16}NO_2{}^{35}Cl$: 241.0871, Found: 241.0889.

(*R*)-7-Chloro-5-methoxymethyloxy-2,3,4,5-tetrahydro-1*H*-1-benzazepine [(*R*)-(+)-5] The title compound was prepared from (*R*)-(+)-**4** and magnesium by the procedure described for the preparation of (*S*)-(–)-**5**. The product was purified by column chromatography to give (*R*)-(+)-**5** (88%) as colorless oil. $[\alpha]_D^{28}$ +202° (c 1.0, MeOH). IR (neat): 3372, 2936, 1494, 1150, 1035 cm^{-1}. HRMS Calcd for $C_{12}H_{16}NO_2{}^{35}Cl$: 241.0871, Found: 241.0860.

(*S*)-7-Chloro-5-methoxymethyloxy-1-[2-methyl-4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine [(*S*)-(–)-6] A solution of 2-methyl-4-(2-methylbenzoylamino)benzoyl chloride (0.17 g, 0.60 mmol) in CH_2Cl_2 (10 mL) was added dropwise to a ice-cooled solution of (*S*)-(–)-**5** (0.12 g, 0.50 mmol) and pyridine (0.22 mL, 2.73 mmol) in CH_2Cl_2 (5 mL) and the mixture was stirred at the same temperature for 0.5 h, and then at rt for 2 h. The reaction mixture was washed with 10% citric acid aqueous solution and saturated K_2CO_3 aqueous solution. The mixture was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, CH_2Cl_2 : MeOH = 30 : 1) to give (*S*)-(–)-**6** (0.28 g, quant.) as pale brown amorphous. $[\alpha]_D^{27}$ –126° (c 1.0, MeOH). ^{1}H NMR ($CDCl_3$) *d*: 1.50 – 2.35 (4 H, m), 2.40 (3 H, s), 2.46 (3 H, s), 2.75 – 3.00 (1 H, m), 3.42 (3H, s), 4.50 – 4.90 (3 H, m), 4.90 – 5.15 (1 H, m), 6.58 (1 H, d, *J* = 8.3 Hz), 6.77 (1 H, d, *J* = 8.2 Hz), 6.94 (1 H, dd, *J* = 8.3 Hz, 2.4 Hz), 7.00 – 7.70 (7 H, m). IR (KBr): 3300, 2925, 1636, 1524, 1400, 1314, 1030 cm^{-1}. HRMS Calcd for $C_{28}H_{30}N_2O_4{}^{35}Cl$ (MH^+): 493.1896, Found: 493.1895.

(*R*)-7-Chloro-5-methoxymethyloxy-1-[2-methyl-4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine [(*R*)-(+)-6] The title compound was prepared from (*R*)-(+)-**5**, 2-methyl-4-(2-methylbenzoylamino)benzoyl chloride and pyridine by the procedure described for the preparation of (*S*)-(–)-**6**. The product was purified by column chromatography to give (*R*)-(+)-**6** (74%) as yellow amorphous. $[\alpha]_D^{27}$ +122° (c 1.0, MeOH). IR (KBr): 3295, 2920, 1650, 1527, 1400, 1315, 1030 cm^{-1}. HRMS Calcd for $C_{28}H_{30}N_2O_4{}^{35}Cl$ (MH^+): 493.1896, Found: 493.1902.

(*S*)-7-Chloro-5-hydroxy-1-[2-methyl-4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1-

benzazepine [(*S*)-(–)-1] A conc. HCl (4.0 mL) was added to a solution of (*S*)-(–)-**6** (1.48 g, 3.0 mmol) in MeOH (20 mL) and the mixture was stirred at 55°C for 1.5 h. MeOH was evaporated and the residue was extracted with CH_2Cl_2. The extract was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, CH_2Cl_2 : MeOH = 50 : 1) and recrystallized from EtOH – H_2O to give (*S*)-(–)-**1** (1.00 g, 74%) as white powder, which was >99% ee by HPLC analysis using CHIRALCEL OD (hexane : *iso*-PrOH : Et_2NH = 600 : 400 : 1), mp 148 – 150°C. $[\alpha]_D^{26}$ –159° (c 0.1, MeOH). ^{1}H NMR ($CDCl_3$) *d*: 1.50 – 2.40 (4 H, m), 2.44 (3 H, s), 2.47 (3 H, s), 2.60 – 2.95 (1 H, m), 4.70 – 5.10 (2 H, m), 6.54 (1 H, d, *J* = 8.3 Hz), 6.64 (1 H, d, *J* = 8.4 Hz), 6.92 (1 H, d, *J* = 8.3 Hz), 7.00 – 7.70 (7 H, m). IR (KBr): 3425, 1627, 1522, 1400, 1315 cm^{-1}. *Anal* Calcd for $C_{26}H_{25}N_2O_3Cl{\cdot}1/4H_2O$: C, 68.87; H, 5.67; N, 6.18. Found: C, 68.84; H, 5.76, N, 5.81.

(*R*)-7-Chloro-5-hydroxy-1-[2-methyl-4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine [(*R*)-(+)-1] The title compound was prepared from (*R*)-(+)-**6**, and conc. HCl by the procedure described for the preparation of (*S*)-(–)-**1**. The product was recrystallized from EtOH – H_2O to give (*R*)-(+)-**1** (70%, >99% ee) as white powder, mp 149 – 152°C. $[\alpha]_D^{26}$ +165° (c 0.1, MeOH). IR (KBr): 3425, 1621, 1526, 1400, 1316 cm^{-1}. *Anal* Calcd for $C_{26}H_{25}N_2O_3Cl{\cdot}1/4H_2O$: C, 68.87; H, 5.67; N, 6.18. Found: C, 68.78; H, 5.72, N, 5.86.

X-Ray analysis of (+)-2: Suitable crystals of (+)-**2** for an X-Ray diffraction study were grown from a EtOAc – hexane solution. All data were obtained Rigaku AFC-5S automated four circle diffractometer with graphite-monochromated Cu *Ka* radiation. Crystal data : $C_{17}H_{18}NO_3ClS$, *M*r=351.85, orthorhombic, space group $P2_12_12_1$, *a*=12.917(6)Å, *b*=15.046(6)Å, *c*=8.723(4)Å, *V*=1695(2)Å^3, *Z*=4.0, *Dx*=1.378 g/cm^3, *Dm*=1.384(4) g/cm^3, F(000)=736, and *m*(Cu*Ka*)= 32.658 cm^{-1}. The intensities were measured using *w*/2*q* scan, and measurements were conducted on one component of Bijvoet pairs. Three standard reflections were monitored every 150 measurements. The data were corrected for Lorentz and polarization factors. Absorption and decay correlation was not applied. Of the 3320 independent reflections which collected, 3128 reflections with $I>3.0s(I)$ were used for structure determination and refinement. The structure was solved by direct method using TEXSAN crystallographic software package.[6] All non-H atoms were found in Fourier map. All H atoms were found in difference fourier map and refined isotropically. The refinement of atomic parameters were carried out by the full matrix least-squares refinement, using anisotropically temperature factors for all non-H atoms. The final refinement converged with *R*=0.048 and *Rw*=0.046 for 208 parameters. Then, 25 of Bijvoet pairs having large intensity and high measurement accuracy were selected. The absolute configuration of (+)-**2** was determined as *S* by the Bijvoet's anomalous-dispersion method.[5]

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7. The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Center. The coordinates can be obtained on request from The Director, Cambridge Crystallographic Data Center, University Chemical Laboratory, Lensfield Road, Cambridge CB12 1EW, UK.