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Enantioselective Synthesis of the Metabolites of Vasopressin V_2 Receptor Antagonist OPC-31260 via Lipase-Catalyzed Transesterification

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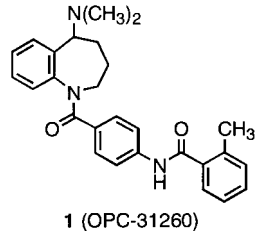
Abstract—The optical isomers of 5-dimethylamino-1-[4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine (OPC-31260, **1**) and its metabolites (**2**, **3**, **4**, **5** and **6**) were enantioselectively synthesized. The chiral acetate **8b** and alcohol **7a** were prepared via the resolution of the racemic alcohol (±)-**7** using the lipase-mediated transesterification in vinyl acetate. The compounds **8b** and **7a** were converted to the hydroxy metabolites (**2a** and **2b**), the methylamine metabolites (**3a** and **3b**), the dimethylamines (**1a** and **1b**), and the amine metabolites (**4a** and **4b**) in several steps while maintaining their absolute configurations. The 4,5-diol metabolites (**5a**, **5b**, **6a** and **6b**) were synthesized from the key intermediates obtained by the lipase-catalyzed transesterification.

Introduction

The benzazepine derivative, 5-dimethylamino-1-[4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine (OPC-31260, **1**),[1] is an orally effective, non-peptide vasopressin V_2 receptor antagonist and is now undergoing clinical trials as a promising aquaretic agent.

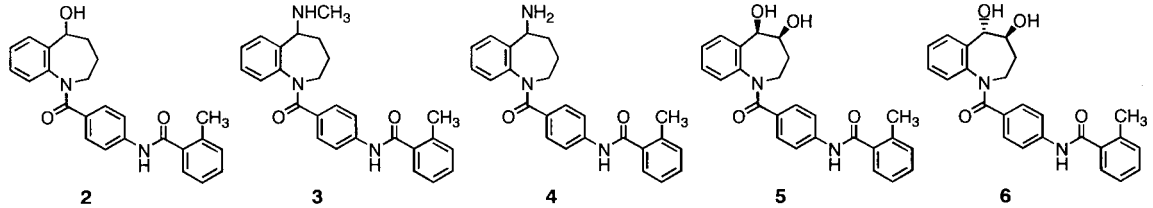


1 (OPC-31260)

Figure 1.

Metabolism studies are integral parts of all programs for new drug development and are essential for the assessment of the safety and efficacy of the medicines. In recent studies on the metabolism of **1**, several metabolites were isolated from the biological fluids of rats, dogs and humans. Some of them (**2**, **3**, **4**, **5** and **6**) have an asymmetric carbon at the 5-position of the benzazepine ring and showed potent activity (Figs. 1 and 2).[2] Biological activity of the optically active metabolites and stereoselectivity of the metabolites pose an interesting problem.

On the other hand, the general synthetic method of an optically active compound using lipase-catalysis has been recently accepted. This method is effective for simultaneously preparing both enantiomers of the compound. There are many investigations into the enzymatic resolution of secondary alcohols. However, there are only a few examples of the enzymatic resolution of 1,2-diols on the



2 3 4 5 6

Figure 2.

Keywords: kinetic resolution; vasopressin; benzazepine; enantioselective.

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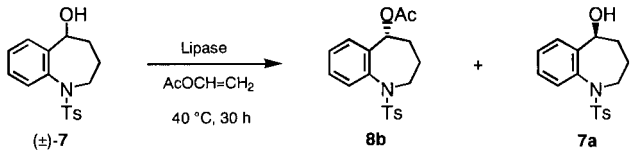
Table 1. Lipase-catalyzed transesterification



Entry	Lipase[a]	8b		7a		*E* value[b]
		Yield (%)[c]	% ee	Yield (%)[c]	% ee	
1	MY	Trace	–	–	–	–
2	AL	Trace	–	–	–	–
3	PL	17	95	83	19	47
4	QL	47	72	53	65	12
5[d]	QL	55	60	45	74	9
6	SP 524	Trace	–	–	–	–
7	SP 539	0	–	–	–	–
8	Subtilisin A	0	–	–	–	–
9	Lipozyme IM	4	95	96	4	41
10	Toyozyme LIP	10	94	90	10	36

[a] MY (Meito Sangyo, *Candida cylindracea nov.* sp.), AL (Meito Sangyo, *Achromobacter* sp.), PL, QL (Meito Sangyo, *Alcaligenes* sp.), SP 524 (Novo Nordisk, *Aspergillus oryzae*), Subtilisin A (Novo Nordisk, *Bacillus licheniformis*), Lipozyme IM (Novo Nordisk, *Mucor miehei*), Toyozyme LIP (Toyo boseki).
[b] The *E* value is the ratio of the specificity constant of two enantiomers calculated according to Ref. 5.
[c] Calculated yield.
[d] Reaction at 60°C for 9 h.

heterocyclic ring.[3] A common approach for improving the biocatalytic reaction rates of water-insoluble substrates is the use of cosolvents. In a previous paper, we reported the synthesis of optically active compounds by lipase-catalyzed enantioselective transesterification.[4] In the course of our investigation on the lipase-catalyzed asymmetric synthesis, we applied this to the synthesis of the optical isomers of **1** and its metabolites.

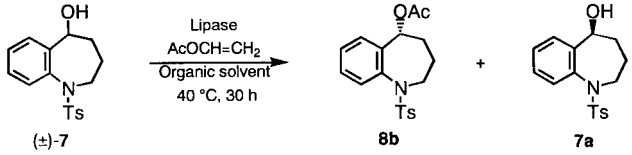
Results and Discussion

First, we planned the optical resolution of (±)-**2** using the lipase-catalyzed transesterification. However, most of the lipase showed a low reaction rate and did not catalyze the reaction. Therefore, we chose the compound (±)-**7** as the substrate for transesterification and several lipases were examined. As shown in Table 1, lipase PL showed good selectivity and the acetate **8b** was obtained with fairly high enantiomeric excess (entry 3). To obtain the alcohol **7a** with high enantioselectivity, increasing the conversion was necessary. We chose lipase QL showing good reactivity (entry 4). The effect of various organic cosolvents was then examined for lipase PL and lipase QL (Table 2). Based on the screening test, the use of hexane gave chiral compounds (**8b** and **7a**) with high degrees of enantioselectivity (entries 2 and 9).

The optimal conditions were applied to the preparative scale reactions. The optical pure alcohol **7a** (>99% ee) was obtained by the transesterification of (±)-**7** with vinyl acetate and lipase QL in hexane with a 28% yield. The antipode **7b** was synthesized as follows. Transesterification of (±)-**7** with vinyl acetate and lipase PL in hexane gave the acetate **8b** (94% ee) in 33% yield. The acetate **8b** (94% ee) was converted to the alcohol **7b** by hydrolysis with K_2CO_3. This **7b** (93% ee) was again subjected to the lipase-catalyzed acylation and the optically pure acetate **8b** (>99% ee) was obtained. Hydrolysis of the acetate afforded the alcohol **7b** (99% ee) in 89% yield (Scheme 1).

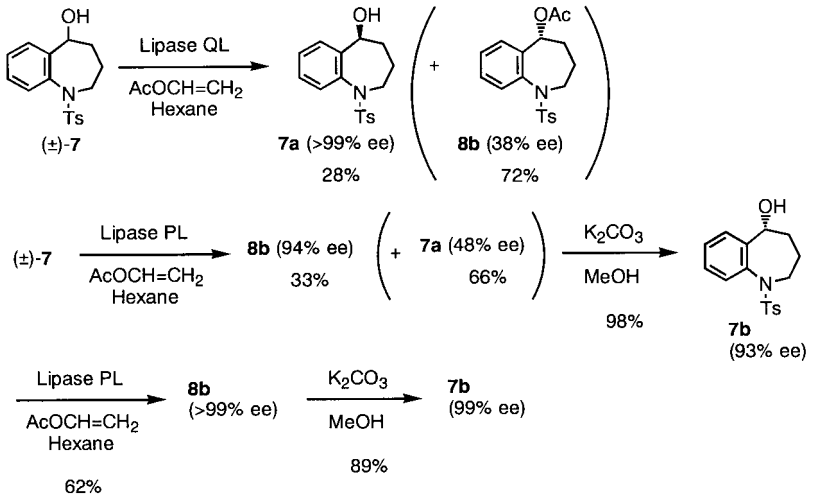
The benzazepine compound **9a** was prepared by deprotection of the alcohol **7a** (>99% ee) with magnesium turnings in 65% yield. The benzoylation of **9a** with 4-(2-methylbenzoylamino)benzoyl chloride in the presence of pyridine gave the hydroxy metabolite **2a** (>99% ee) in 92% yield.

Table 2. Lipase-catalyzed transesterification with organic cosolvents



Entry	Lipase[a]	Organic solvent	8b		7a		*E* value[b]
			Yield (%)[c]	% ee	Yield (%)[c]	% ee	
1	PL	None	17	95	83	19	47
2	**PL**	**Hexane**	**25**	**96**	75	32	**67**
3	PL	Cyclohexane	16	93	84	18	33
4	PL	CCl_4	9	90	91	9	21
5	PL	Toluene	18	96	82	21	60
6	PL	*i*-Pr_2O	20	96	80	24	62
7	PL	EtOAc	16	97	84	18	78
8	QL	None	47	72	53	65	12
9	**QL**	**Hexane**	71	38	**29**	**95**	7
10	QL	Cyclohexane	67	45	33	91	8
11	QL	CCl_4	64	48	36	85	7
12	QL	Toluene	61	54	39	84	8
13	QL	*i*-Pr_2O	63	54	37	92	10
14	QL	*MeCN*	23	59	77	18	5

[a] Lipase PL, QL (Meito Sangyo, *Alcaligenes* sp.).
[b] The *E* value is the ratio of the specificity constant of two enantiomers calculated according to Ref. 5.
[c] Calculated yield.



Scheme 1.

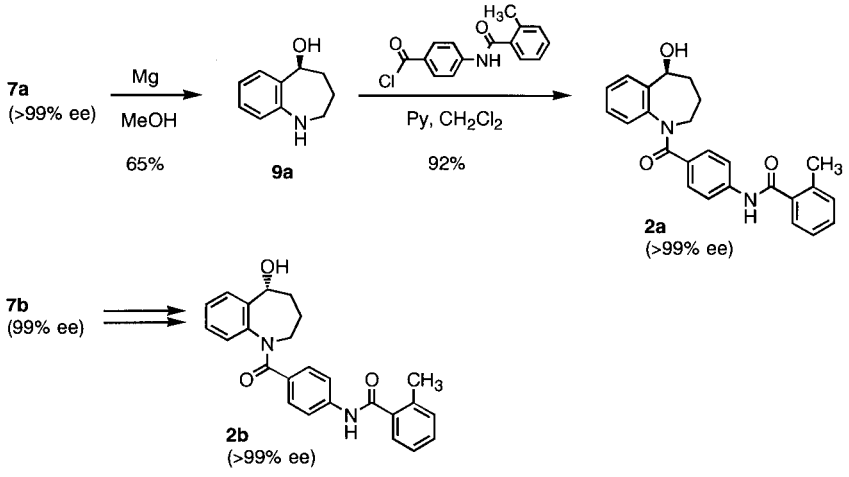
The antipode **2b** (>99% ee) was similarly synthesized from **7b** (Scheme 2).

Secondly, both enantiomers of the mother compound **1**, and the demethylated metabolites **3a**, **3b**, **4a** and **4b** were synthesized as shown in Schemes 3 and 4. The displacement of the hydroxy group of **7b** with a nitrogen was achieved under Mitsunobu reaction conditions and subsequent catalytic hydrogenation to give amine **10a** with high enantiomeric excess (>99% ee). The treatment of **10a** with di-*tert*-butyl dicarbonate in the presence of Et_3N afforded **11a** in 97% yield. The methylation of the Boc-protected amine **11a** with iodomethane gave the methylamine **12a** in 93% yield, followed by deprotection of the *p*-tosyl group with magnesium turnings to give **13a** in 78% yield. Benzoylation of **13a** with 4-(2-methylbenzoylamino)-benzoyl chloride gave **16a** in 66% yield. The methylamino metabolite **3a** (>99% ee) was obtained by deprotection of **16a** with trifluoroacetic acid (TFA) in 84% yield. The metabolite **3a** was converted to the dimethylamine **1a** (>99% ee) by reductive alkylation with formaldehyde and sodium cyanoborohydride in 87% yield.

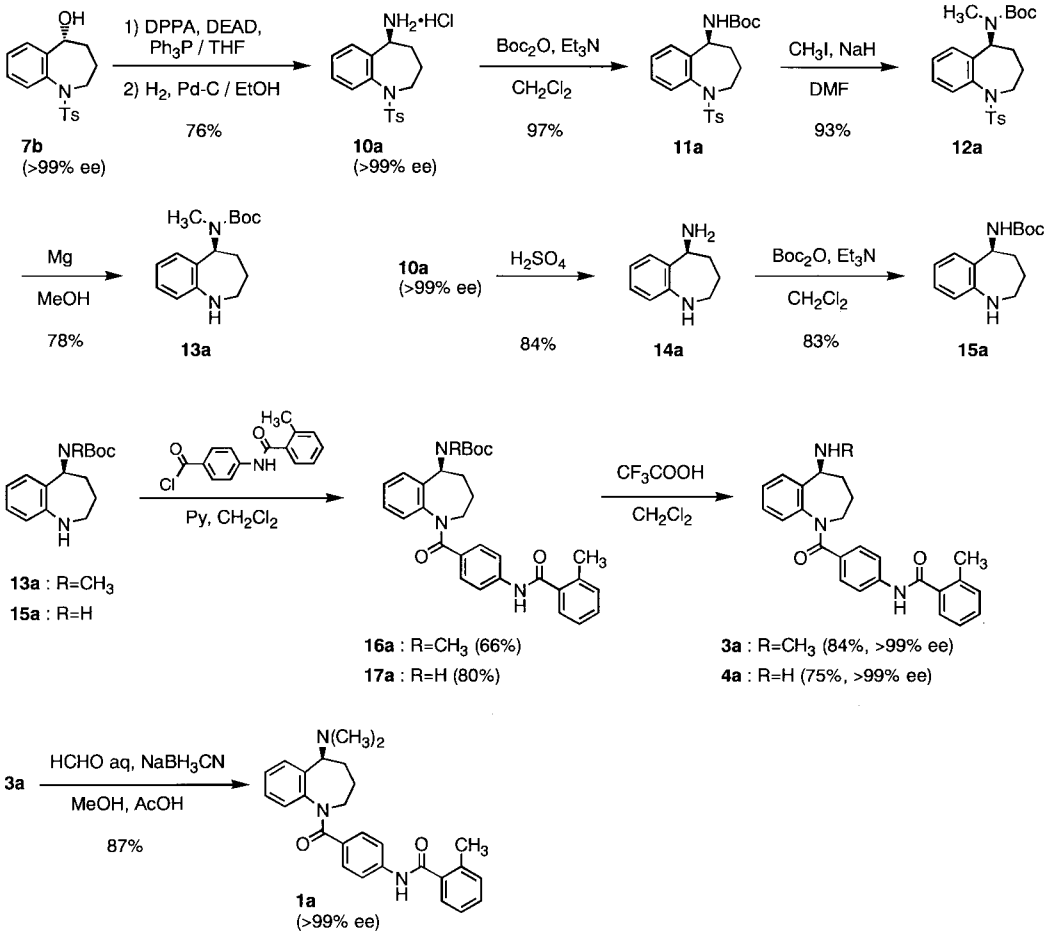
The amino metabolite **4a** was synthesized as follows. The amine **10a** was treated with H_2SO_4 to give **14a** in 84% yield. The amine **14a** was reacted with di-*tert*-butyl dicarbonate in the presence of Et_3N to give **15a** in 83% yield, followed by benzoylation with 4-(2-methyl-benzoylamino)benzoyl chloride to afford **17a** in 80% yield. The target metabolite **4a** (>99% ee) was obtained by deprotection of **17a** with TFA in 75% yield.

The antipodes **1b**, **3b** and **4b** were similarly synthesized from **7a**.

Third, the *cis*-4,5-diol metabolites **5a** and **5b** were prepared by the lipase-catalyzed transesterification of the key intermediate (±)-**19** as shown in Scheme 5. Oxidation of the 4,5-dehydro compound **18**, which was synthesized by the dehydration of (±)-**7** in the presence of *p*-TsOH in 93% yield, with osmium tetroxide and 4-methylmorpholine *N*-oxide gave the *cis*-diol compound (±)-**19** in 69% yield. Transesterification of (±)-**19** with lipase QL in vinyl acetate gave the unreacted alcohol **19a** and the 4-acetoxy compound **20b** in high optical purities (**19a**: 93% ee, **20b**: 99% ee). The unreacted alcohol **19a** (93% ee) was again subjected to the lipase-catalyzed acylation and the pure **19a** (>99% ee) was obtained in 90% yield. Protection of **19a**



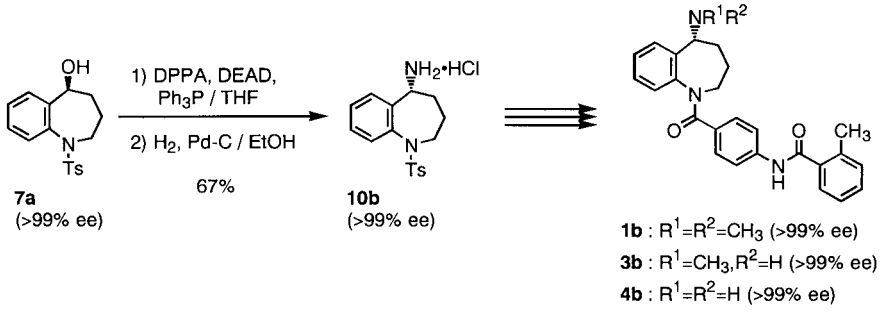
Scheme 2.



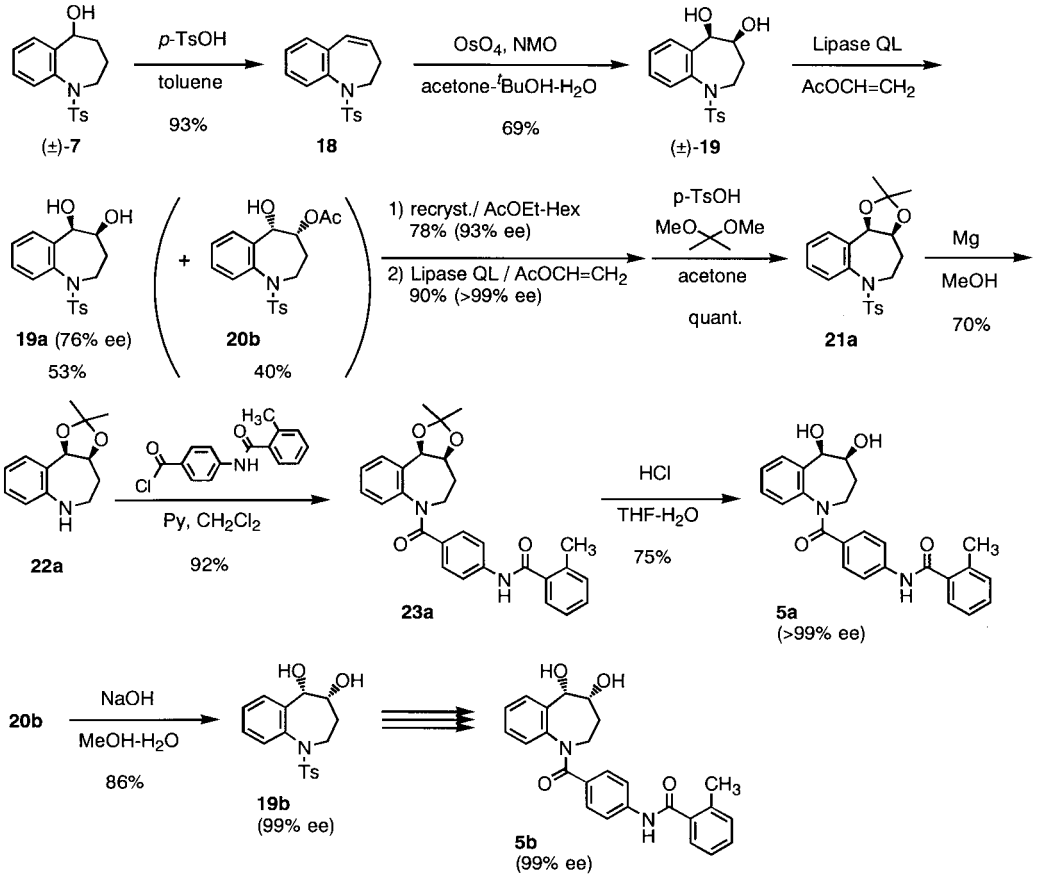
Scheme 3.

with 2,2-dimethoxypropane in the presence of *p*-TsOH, followed by treatment with magnesium turnings gave the benzazepine compound **22a** in 70% yield. Benzoylation of **22a** with 4-(2-methylbenzoylamino)benzoyl chloride gave **23a** in 92% yield. The target metabolite **5a** (>99% ee) was obtained by deprotection of the acetonide with HCl in 75% yield. The antipode **5b** (99% ee) was similarly synthesized from the diol **19b**, which was obtained by the hydrolysis of the 4-acetoxy compound **20b** with NaOH.

Lastly, the *trans*-4,5-diol metabolites **6a** and **6b** were synthesized by the optical resolution of (±)-**6** using the lipase-catalyzed transesterification as shown in Schemes 6 and 7. Although we had succeeded in the optical resolution of the *cis*-diol (±)-**19**, several steps were needed to convert it into the desired metabolites after resolution. Therefore, we attempted to resolve the final product (±)-**6** by the lipase-catalysis. The racemic compound (±)-**6** was synthesized as follows. The hydroxy group of (±)-**2**[2] was substituted for chloride with thionyl chloride to give **24** in 86% yield. Elimination of the hydrogen chloride from **24** with DBU and sodium iodide gave the 4,5-dehydro compound **25**, and **25** was oxidized with *m*-CPBA to give the epoxide **26** in 75% yield. The epoxide was opened with KOH to give the racemic *trans*-diol (±)-**6** in 72% yield (Scheme 6). Transesterification of (±)-**6** with Lipase QL in vinyl acetate scarcely proceeded. We assumed that the low reactivity was attributable to the low solubility of the substrate (±)-**6** in

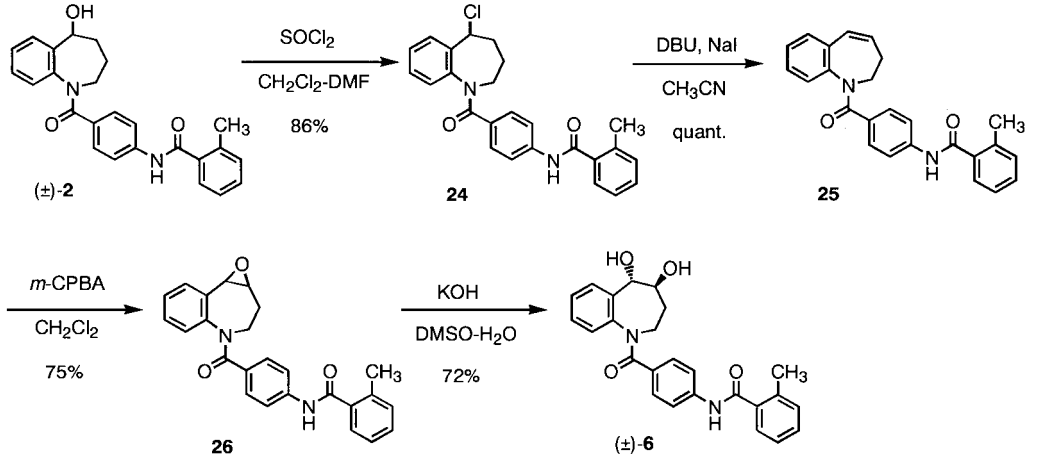


Scheme 4.

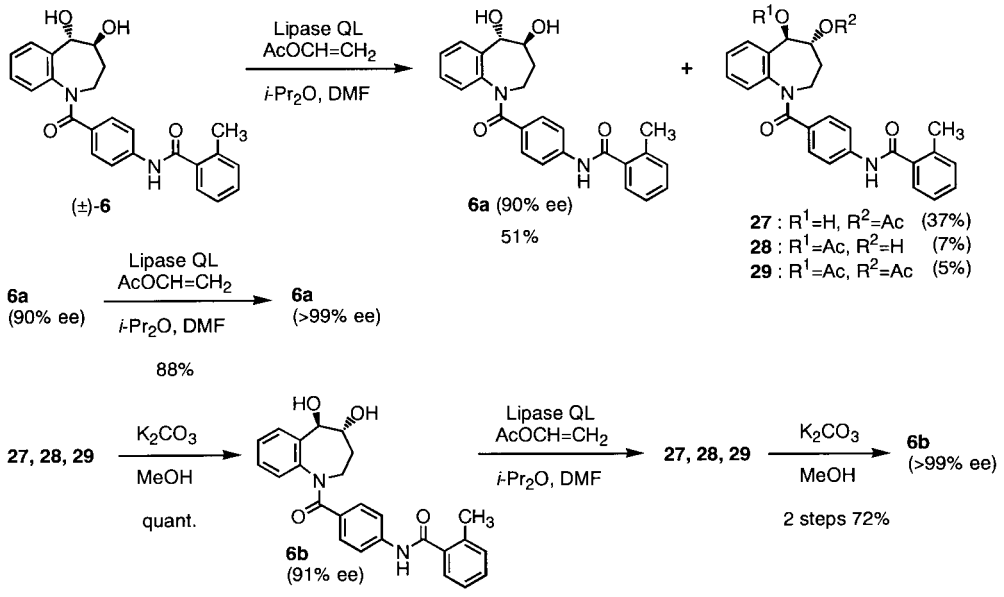


Scheme 5.

vinyl acetate. After several solvents were tested, the addition of the small amount of DMF was found to be effective. Table 3 summarizes the results of the experiments using lipase QL and vinyl acetate in various organic solvents with DMF as the cosolvent. The reaction was monitored by HPLC. Under these conditions, it was apparent that the suitable solvent was isopropyl ether and DMF (entry 4). Furthermore, we investigated the reaction conditions on a practical scale. The lipase-catalyzed acylation of (±)-**6** at 40°C for 22 h gave the unreacted alcohol **6a** (90% ee) in 51% yield, and the mixture of the acetates **27**, **28** and **29** in 37, 7 and 5% yield, respectively. The alcohol **6a** (90% ee) was again subjected to the lipase-catalyzed acylation, and the desired metabolite **6a** (>99% ee) was obtained in 88% yield. On the other hand, the mixture of the acetate **27**, **28** and **29** was converted to the diol **6b** by hydrolysis with K_2CO_3, and this **6b** (91% ee) was again subjected to the lipase-catalyzed transesterification to

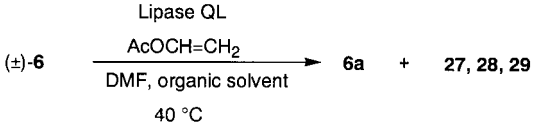


Scheme 6.



Scheme 7.

Table 3. Lipase-catalyzed transesterification with organic cosolvents (all reactions were carried out by stirring a mixture of substrate (50 mg), lipase (50 mg), vinyl acetate (2.5 mL), DMF (0.5 mL) and organic solvent (2.5 mL); Lipase QL (Meito Sangyo, *Alcaligenes* sp.))



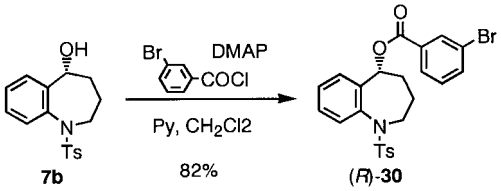
Entry	Organic solvent	Time (h)	**6a**		Acetate			*E* value[a]
			Yield (%)[b]	% ee[c]	Yield (%)[b]	(**27**:**28**:**29**)[b]	% ee[c,d]	
1	DMF	22	54	67	40	(29:9:2)	93	52
2	EtOAc+DMF	22	56	68	41	(32:7:2)	97	149
3	MeCN+DMF	30	56	70	41	(26:12:3)	89	37
4	***i*-Pr$_2$O+DMF**	**22**	50	**89**	47	(29:13:5)	**98**	**259**
5	Cyclohexane+DMF	22	51	85	45	(30:10:5)	95	216

[a] The *E* value is the ratio of the specificity constant of two enantiomers calculated according to Ref. 5.
[b] The yield and the rate of contents were determined by HPLC analysis using a column packed with TSK-80TM (Tosoh Company).
[c] Enantiomeric purities were determined by HPLC analysis using a column packed with CHIRALCEL OJ (Daicel Chemical).
[d] Ee for corresponding diol, prepared by hydrolysis of the mixture of the acetate **27**, **28**, **29** (K_2CO_3, MeOH, rt, 1 h).

give the mixture of acetates. The pure antipode **6b** (>99% ee) was prepared in two steps by hydrolysis of the acetates with K_2CO_3 in 72% yield.

The absolute configurations of the above optically active compounds were determined as follows. The 5-(3-bromobenzoyl) derivative **30**, which was synthesized by the benzoylation of **7b** with *m*-bromobenzoyl chloride in the presence of pyridine and DMAP, was subjected to X-ray crystallographic analysis (Scheme 8). As shown in Fig. 3, the absolute configuration at the 5-position of **30** was determined to be *R* using Bijvoet's anomalous-dispersion method.[6] Accordingly, the stereochemistries for **7b** and the derived compounds **9b** and **2b** were also determined to be *R* (Scheme 2). On the other hand, the hydroxy group of **7b** was displaced by the azide group with inversion, so the 5-position of **10a** was that of the *S* configuration. Consequently, all the compounds derived from **10a** were assigned to be the *S* configuration as depicted in Scheme 3. Each enantiomer of the above compounds were of the opposite configurations at the C (5) position (Scheme 4).

Next, the *cis*-4,5-diol compound **19a** was reacted with dibutyltin oxide to form the 5-membered cyclic dibutylstannoxane derivative, followed by methylation with iodomethane in the presence of tetrabutylammonium bromide to give the methoxy compound **31** in 78% yield. The compound **31** was treated with tetrabutylammonium



Scheme 8.

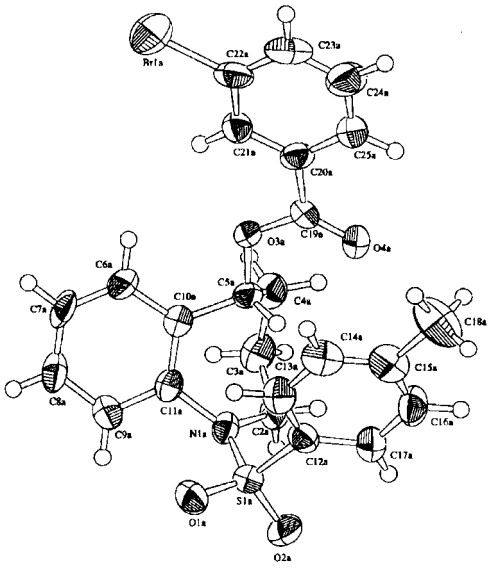
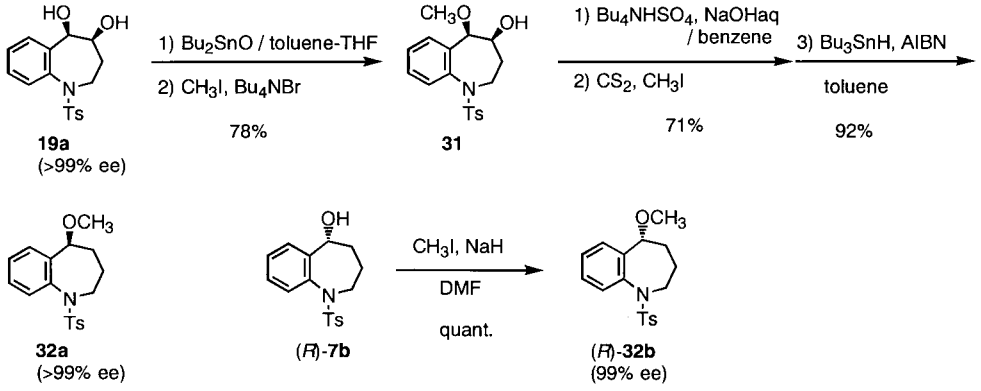


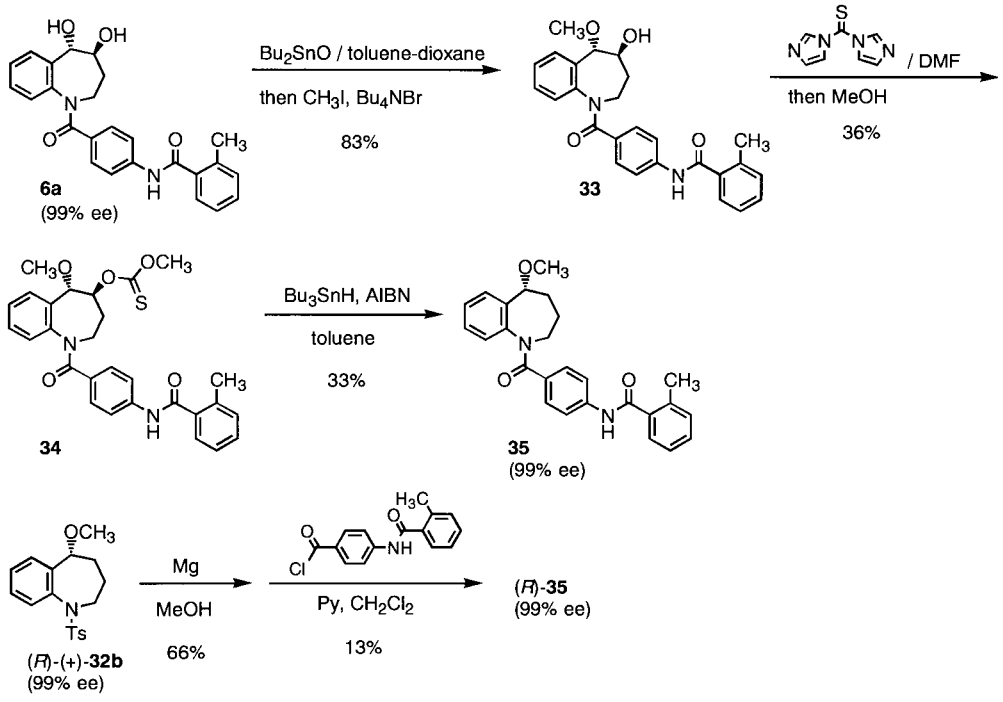
Figure 3. X-ray crystal structure for **30**.

hydrogen sulfate and NaOH, and then, with carbon disulfide and iodomethane to give the xanthate derivative in 71% yield. Reduction of the xanthate with tributyltin hydride and AIBN gave the methoxy compound **32a** (>99% ee) in 92% yield. The NMR spectrum of **32a** was identical to that of the 5-methoxy compound (*R*)-**32b** derived from (*R*)-**7b**. Therefore, the substituted methoxy group of **31** was assigned to be at the C (5) position. Moreover, the methoxy compound **32a** showed the opposite specific rotation and a different HPLC retention time compared with (*R*)-**32b** with the *R* configuration, that is the same as (*R*)-**7b**. The absolute configuration at the 5-position of **32a** was determined to be the *S* configuration. Accordingly the stereochemistries at C (5) of **19a** and **31** were the same configurations as **32a** (Scheme 9). Consequently, the *cis*-4,5-disubstituted compounds **5a** and **5b** were assigned as the (4*S*, 5*R*) and (4*R*, 5*S*) configurations, respectively (Scheme 5).

As concerns the *trans*-4,5-diol compound series, the 5-methoxy derivative **33** (83%) was synthesized by the same procedure used for **31**. Compound **33** was treated



Scheme 9.



Scheme 10.

with 1,1′-thiocarbonyldiimidazole followed by the addition of MeOH to give the thiocabonate **34** in 36% yield. Reduction of the thiocarbonate **34** with tributyltin hydride and AIBN gave the 5-methoxy compound **35** in 33% yield. This compound **35** showed the same specific rotation and was in good agreement with the HPLC retention time for (*R*)-**35** synthesized from (*R*)-**32b**. Accordingly, the absolute configuration at the 5-position of **33** and **34** was the same as **32b**. Also, the stereochemistry of the isomers of **6a** and **6b** were assigned to have the (4*S*, 5*S*) and (4*R*, 5*R*) configurations, respectively (Schemes 7 and 10).

In conclusion, we have established an enantioselective synthesis of the optical isomers of OPC-31260 and its metabolites from the key intermediates obtained using the lipase-catalyzed kinetic resolution. We also succeeded in the lipase-catalyzed transesterification of 1,2-diols on the heteroaromatic ring, and improved the enzymatic resolution of the water-insoluble substrates using the mixed cosolvents.

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 spectrometer 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. Preparative thin layer chromatography (PLC) was carried out on plates (20×20 cm, 0.5 mm, thickness) precoated with silica gel ($60F_{254}$, Merck Art 5744).

General procedure of lipase-catalyzed transesterification

A mixture of substrate (50 mg), vinyl acetate (1 mL) and lipase QL (50 mg) in the appropriate solvent (1 mL) was stirred at 40°C. A ratio of substrate and acetylated product was monitored by HPLC (CHIRALCEL OJ was used for **7a** and **8b** with hexane–*iso*-PrOH–Et_2NH=700:300:1 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 of hexane and AcOEt to afford both an optically active alcohol and an acetylated product.

(*S*)-5-Hydroxy-1-(*p*-toluenesulfonyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine (7a). A mixture of (±)-**7** (3.0 g, 9.45 mmol), vinyl acetate (60 mL) and lipase QL (3.0 g) in hexane (60 mL) was stirred at 40°C for 27 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–AcOEt=4:1) to give **7a** (0.83 g, 28%) as pale yellow amorphous [and **8b** (2.43 g, 72%)], which were **7a** (>99% ee) and **8b** (38% ee) by HPLC Analysis using CHIRALCEL OJ (hexane–*iso*-PrOH–Et_2NH=700:300:1), $[\alpha]_D^{28}=+7.2°$ (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 1.40–1.85 (2H, m), 1.85–2.10 (2H, m), 2.44 (3H, s), 3.20–3.40 (1H, m), 3.90–4.10 (1H, m), 4.69 (1H, d, *J*=9.0 Hz), 7.08 (1H, d, *J*=7.8 Hz), 7.18 (1H, dt, *J*=1.6, 7.3 Hz), 7.27–7.34 (3H, m), 7.51 (1H, d, *J*=7.3 Hz), 7.68 (2H, d, *J*=8.3 Hz). HRMS Calcd for $C_{17}H_{19}NO_3S$: 317.1087. Found: 317.1062.

(*R*)-5-Acetoxy-1-(*p*-toluenesulfonyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine (8b). A mixture of (±)-**7** (2.0 g, 6.3 mmol), vinyl acetate (40 mL) and lipase PL (2.0 g) in hexane (40 mL) was stirred at 40°C for 72 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–AcOEt=4:1) to give **8b** (0.75 g, 33%, 94% ee) and **7a** (1.31 g, 66%, 48% ee). The mixture of **8b** (0.74 g, 2.06 mmol, 94% ee) and K_2CO_3 (0.32 g, 2.32 mmol) in MeOH (15 mL) was stirred at room temperature for 30 min. The reaction mixture 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 purified by column chromatography (silica gel; eluent, hexane–AcOEt=2: 1) to give **7b** (0.63 g, 98%, 93% ee) as colorless amorphous. Next, the mixture of **7b** (0.63 g, 1.98 mmol, 93% ee), vinyl acetate (13 mL) and lipase PL (0.63 g) in hexane (13 mL) was stirred at 40°C for 72 h. The reaction mixture were filtered and evaporated. The residue was purified by column chromatography (silica gel; eluent, hexane–AcOEt=2:1) and recrystallized from AcOEt–hexane to give **8b** (0.44 g, 62%, >99% ee) as colorless prisms, mp 108–110°C. $[\alpha]_D^{28}=+8.8°$ (*c* 0.1, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 1.60–2.00 (4H, m), 2.13 (3H, s), 2.43 (3H, s), 3.25–3.45 (1H, m), 3.90–4.10 (1H, m), 5.56 (1H, d, *J*=8.6 Hz), 7.24–7.37 (6H, m), 7.71 (2H, d, *J*=8.2 Hz). Anal. Calcd for $C_{19}H_{21}NO_4S$: C, 63.49; H, 5.89; N,e 3.90. Found: C, 63.50; H, 5.75; N, 3.58.

(*R*)-5-Hydroxy-1-(*p*-toluenesulfonyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine (7b). A mixture of **8b** (140 mg, 0.39 mmol, >99% ee) and K_2CO_3 (60 mg, 0.43 mmol) in MeOH (10 mL) was stirred at room temperature for 30 min. The reaction mixture 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 purified by column chromatography (silica gel; eluent, hexane–AcOEt=2:1) to give **7b** (110 mg, 89%, 99% ee) as colorless amorphous. $[\alpha]_D^{27}=-8.2°$ (*c* 1.0, $CHCl_3$). HRMS Calcd for $C_{17}H_{19}NO_3S$: 317.1087. Found: 317.1085.

(*S*)-5-Hydroxy-2,3,4,5-tetrahydro-1*H*-1-benzazepine (9a). Magnesium (turnings, 0.78 g, 32.1 mmol) was added to a solution of **7a** (0.51 g, 1.61 mmol, >99% ee) in MeOH (30 mL) and the mixture was refluxed for 5 h. After cooling, conc. H_2SO_4 (1.8 mL, 33.8 mmol) was added dropwise to the ice-cooled mixture. The insoluble material was filtrated by a pad of Celite and the filtrate was adjusted to pH 8–9 with $NaHCO_3$ aqueous solution. The solution was extracted with CH_2Cl_2, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (silica gel; eluent, hexane–AcOEt=2:1) and recrystallized from AcOEt–hexane to give **9a** (0.17 g, 65%) as colorless prisms, mp 91–93°C, $[\alpha]_D^{27}=+19.3°$ (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 1.70–1.90 (2H, m), 1.90–2.20 (2H, m),

2.94–3.24 (3H, m), 4.79 (1H, d, J=6.8 Hz), 6.74 (1H, d, J=7.7 Hz), 6.92 (1H, t, J=7.4 Hz), 7.10 (1H, t, J=7.6 Hz), 7.27 (1H, d, J=5.4 Hz). Anal. Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.53. Found: C, 73.41; H, 8.12; N, 8.57.

(*R*)-5-Hydroxy-2,3,4,5-tetrahydro-1*H*-1-benzazepine (9b). The title compound was prepared from **7b** and magnesium by the procedure described for the preparation of **9a**. The product was recrystallized from AcOEt–hexane to give **9b** (59%) as colorless prisms, mp 90–92°C, $[\alpha]_D^{29}=-23.0°$ (c 1.0, $CHCl_3$). Anal. Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.42; H, 7.86; N, 8.64.

(*S*)-5-Hydroxy-1-[4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine (2a). A solution of thionyl chloride (1.0 mL, 13.9 mmol) in DMF (3 mL) was added to a suspension of 4-(2-methylbenzoylamino)benzoic acid (1.88 g, 7.36 mmol) in CH_2Cl_2 (70 mL) and the mixture was refluxed for 1 h to give the acid chloride. The acid chloride solution was added to a ice-cooled solution of **9a** (0.75 g, 4.60 mmol) and pyridine (3 mL, 37.2 mmol) in CH_2Cl_2 (50 mL) and the mixture was stirred for 1.5 h at room temperature. The reaction mixture was washed with water, dilute HCl and saturated $NaHCO_3$ solution. The CH_2Cl_2 solution was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (silica gel; eluent, CH_2Cl_2–MeOH=20:1) and the solid was recrystallized from MeOH to give **2a** (1.69 g, 92%) as colorless prisms, which was >99% ee by HPLC Analysis using CHIRALCEL OD (hexane–*iso*-PrOH–Et_2NH=700:300:1), mp 210–211°C. $[\alpha]_D^{25}=-159°$ (c 1.0, MeOH). ^1H NMR ($CDCl_3$) δ: 1.65–1.90 (2H, m), 1.90–2.30 (2H, m), 2.45 (3H, s), 2.74–2.84 (1H, m), 4.81–5.11 (2H, m), 6.64 (1H, d, J=7.4 Hz), 7.00 (1H, t, J=7.0 Hz), 7.16–7.40 (9H, m), 7.59 (1H, br s), 7.66 (1H, d, J=8.0 Hz). IR (KBr): 3350, 1695, 1549, 1428, 1346 cm^{-1}. Anal. Calcd for $C_{25}H_{24}N_2O_3$: C, 74.98; H, 6.04; N, 6.99. Found: C, 75.16; H, 6.00; N, 6.83.

(*S*)-5-Hydroxy-1-[4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine (2b). The title compound was prepared from **9b**, 4-(2-methylbenzoylamino)benzoic acid, thionyl chloride and pyridine by the procedure described for the preparation of **2a**. The product was recrystallized from MeOH to give **2b** (81%, >99% ee) as colorless prisms, mp 209–211°C. $[\alpha]_D^{25}=+161°$ (c 1.0, MeOH). IR (KBr): 3350, 1689, 1544, 1464, 1341 cm^{-1}. Anal. Calcd for $C_{25}H_{24}N_2O_3$: C, 74.98; H, 6.04; N, 6.99. Found: C, 74.78; H, 5.95; N, 6.83.

(*S*)-5-Amino-1-(*p*-toluenesulfonyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine hydrochloride (10a). A solution of diethyl azodicarboxylate (3.13 g, 18 mmol) in THF (5 mL), a solution of **7b** (3.81 g, 12 mmol, >99% ee) in THF (30 mL) and a solution of diphenylphosphoryl azide (3.30 g, 12 mmol) in THF (5 mL) were added in this order to an ice-cooled solution of triphenylphosphine (4.72 g, 18 mmol) in THF (40 mL) under nitrogen atmosphere. The mixture was stirred at the same temperature for 30 min. After removal of THF, the residue was purified by column chromatography (silica gel; eluent, hexane–AcOEt=9:1) to give the azide as white powder. A suspension of the azide and 10% Pd–C (0.38 g) in MeOH (60 mL) and HCl (7 mL) was stirred at 30°C under atomospheric pressure of hydrogen until theoretical amount of H_2 was absorbed. The catalyst was removed by filtration and the filtrate was concentrated. The residue was adjusted with 10% NaOH aqueous solution to alkaline and the solution 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=12:1). The main fraction were collected and concentrated in vacuo. Conc. HCl (6 mL) was added to the residue and the whole was distilled off. The residual material was recrystallized from EtOH–hexane to give **10a** (3.22 g, 76%) as colorless needles, which was >99% ee by HPLC Analysis using CHIRALCEL OJ-R (CH_3CN: 0.5 M $NaClO_4$ aq=1:3), mp 197–198°C. $[\alpha]_D^{26}=-38.8°$ (c 0.1, MeOH). ^1H NMR (DMSO-d_6) δ: 1.45–1.75 (2H, m), 1.75–2.20 (2H, m), 2.41 (3H, s), 2.94 (1H, t, J=12.3 Hz), 4.06 (1H, d, J=14.3 Hz), 4.23 (1H, d, J=10.3 Hz), 7.00 (1H, d, J=7.7 Hz), 7.27–7.41 (3H, m), 7.44 (2H, d, J=8.2 Hz), 7.74 (2H, d, J=8.0 Hz), 8.89 (3H, br s). Anal. Calcd for $C_{17}H_{21}ClN_2O_2S\cdot H_2O$: C, 55.05; H, 6.25; N, 7.55. Found: C, 55.01; H, 6.03; N, 7.48.

(*R*)-5-Amino-1-(*p*-toluenesulfonyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine hydrochloride (10b). The title compound was prepared from **7a**, diethyl azodicarboxylate, triphenylphosphine, diphenylphosphoryl azide and 10% Pd–C by the procedure described for the preparation of **10a**. The product was recrystallized from AcOEt to give **10b** (67%, >99% ee) as colorless needles, mp 198–199°C. $[\alpha]_D^{24}=+38.0°$ (c 0.1, MeOH). Anal. Calcd for $C_{17}H_{21}ClN_2O_2S\cdot H_2O$: C, 55.05; H, 6.25; N, 7.55. Found: C, 55.03; H, 6.14; N, 7.41.

(*S*)-5-*tert*-Butoxycarbonylamino-1-(*p*-toluenesulfonyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine hydrochloride (11a). Di-*tert*-butyl dicarbonate (1.48 g, 6.78 mmol) was added to a ice-cooled solution of **10a** (2.00 g, 5.67 mmol, >99% ee) and Et_3N (1.8 mL, 13.0 mmol) in CH_2Cl_2 (50 mL). The mixture was stirred at 0–10°C for 30 min, and then, at room temperature for 2 h. The reaction mixture was poured into 10% citric acid solution and 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, hexane–AcOEt=3:1) to give **11a** (2.28 g, 97%) as colorless amorphous. $[\alpha]_D^{24}=+1.2°$ (c 1.0, MeOH). ^1H NMR ($CDCl_3$) δ: 1.45 (9H, s), 1.60–1.90 (2H, m), 1.90–2.20 (2H, m), 2.45 (3H, s), 2.90–3.50 (1H, m), 3.75–4.25 (1H, m), 4.70–5.00 (1H, m), 5.35–6.20 (1H, m), 6.93 (1H, br s), 7.14 (1H, t, J=7.7 Hz), 7.23 (1H, t, J=7.6 Hz) 7.31 (1H, s), 7.33 (2H, d, J=8.1 Hz), 7.76 (2H, d, J=8.2 Hz). HRMS Calcd for $C_{22}H_{28}N_2O_4SLi$ $(M+Li)^+$: 423.1931. Found: 423.1914.

(*R*)-5-*tert*-Butoxycarbonylamino-1-(*p*-toluenesulfonyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine hydrochloride (11b). The title compound was prepared from **10b**, di-*tert*-butyl dicarbonate and Et_3N by the procedure described for the preparation of **11a**. The product was purified by column chromatography (silica gel; eluent, hexane–AcOEt=3:1) to give **11b** (97%) as colorless amorphous, $[\alpha]_D^{23}=-1.7°$ (c 0.1, MeOH). HRMS Calcd for $C_{22}H_{29}N_2O_4S$ $(MH)^+$: 417.1850. Found: 417.1830.

(*S*)-5-(*N*-Methyl-*tert*-butoxycarbonylamino)-1-(*p*-toluenesulfonyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine (12a). A 60% dispersion of NaH in oil (0.26 g, 6.50 mmol) was added to an ice cooled solution of **11a** (2.28 g, 5.47 mmol) in DMF (10 mL), and the mixture was stirred at the same temperature for 30 min. Iodomethane (0.55 mL, 8.83 mmol) was added to the mixture and stirred at room temperature for 1.5 h. The reaction mixture was poured into water and the solution was extracted with AcOEt and washed with water. The extract was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (silica gel; eluent, hexane–AcOEt=3:1) to give **12a** (2.20 g, 93%) as colorless amorphous. $[\alpha]_D^{22}=-18.2°$ (*c* 1.0, MeOH). ^{1}H NMR ($CDCl_3$) δ: 1.42 (9H, s), 1.70–1.90 (2H, m), 1.90–2.15 (2H, m), 2.44 (3H, s), 2.84 (3H, br s), 2.75–3.40 (1H, m), 4.10–4.30 (1H, m), 4.70–5.20 (1H, m), 7.04 (1H, d, *J*=7.6 Hz), 7.15 (1H, t, *J*=6.8 Hz), 7.22–7.26 (2H, m), 7.30 (2H, d, *J*=8.2 Hz), 7.73 (2H, d, *J*=8.1 Hz). HRMS Calcd for $C_{23}H_{31}N_2O_4S$ $(MH)^+$: 431.2006. Found: 431.2032.

(*R*)-5-(*N*-Methyl-*tert*-butoxycarbonylamino)-1-(*p*-toluenesulfonyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine (12b). The title compound was prepared from **11b**, NaH and iodomethane by the procedure described for the preparation of **12a**. The product was purified by column chromatography (silica gel; eluent, hexane–AcOEt=3:1) to give **12b** (94%) as colorless amorphous. $[\alpha]_D^{23}=+17.3°$ (*c* 1.0, MeOH). HRMS Calcd for $C_{23}H_{31}N_2O_4S$ $(MH)^+$: 431.2006. Found: 431.1996.

(*S*)-5-(*N*-Methyl-*tert*-butoxycarbonylamino)-2,3,4,5-tetrahydro-1*H*-1-benzazepine (13a). Magnesium (turnings, 3.50 g, 144 mmol) was added to a solution of **12a** (2.20 g, 5.11 mmol) in MeOH (70 mL) and the mixture was refluxed for 4 h. After cooling, 2 N-HCl (ca. 100 mL) was added dropwise to the ice-cooled mixture till the insoluble material was solved. The solution was extracted with AcOEt, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (silica gel; eluent, CH_2Cl_2–MeOH=19:1) to give **13a** (1.10 g, 78%) as pale yellow amorphous. $[\alpha]_D^{22}=-65.8°$ (*c* 1.0, MeOH). ^{1}H NMR ($CDCl_3$) δ: 1.43 (9H, s), 1.75–2.05 (4H, m), 2.87 (3H, br s), 3.27–3.36 (1H m), 3.50–4.00 (1H, m), 5.00–5.40 (1H, m), 6.70 (1H, d, *J*=7.6 Hz), 6.85 (1H, t, *J*=7.7 Hz), 6.95 (1H, d, *J*=7.2 Hz), 7.04 (1H, t, *J*=7.6 Hz). HRMS Calcd for $C_{16}H_{25}N_2O_2$ $(MH)^+$: 277.1916. Found: 277.1897.

(*R*)-5-(*N*-Methyl-*tert*-butoxycarbonylamino)-2,3,4,5-tetrahydro-1*H*-1-benzazepine (13b). The title compound was prepared from **12b** and magnesium by the procedure described for the preparation of **13a**. The product was purified by column chromatography (silica gel; eluent, CH_2Cl_2–MeOH=19:1) to give **13b** (83%) as pale yellow amorphous. $[\alpha]_D^{22}=+59.4°$ (*c* 1.0, MeOH). HRMS Calcd for $C_{16}H_{25}N_2O_2$ $(MH)^+$: 277.1916. Found: 277.1899.

(*S*)-1-[4-(2-Methylbenzoylamino)benzoyl]-5-(*N*-methyl-*tert*-butoxycarbonylamino)-2,3,4,5-tetrahydro-1*H*-1-benzazepine (16a). A solution of thionyl chloride (0.55 mL, 7.63 mmol) in DMF (3 mL) was added to a suspension of 4-(2-methylbenzoylamino)benzoic acid (2.00 g, 7.83 mmol) in CH_2Cl_2 (70 mL) and the mixture was refluxed for 1 h to give the acid chloride. The acid chloride solution was added to an ice-cooled solution of **13a** (1.10 g, 3.98 mmol) and pyridine (2 mL, 24.8 mmol) in CH_2Cl_2 (30 mL). The mixture was stirred at 0–10°C for 2 h. The reaction mixture was washed with $NaHCO_3$ aqueous solution and water, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified twice by column chromatography (silica gel; eluent, CH_2Cl_2–MeOH=50:1) and recrystallized from AcOEt to give **16a** (1.35 g, 66%) as colorless prisms, mp 223–225°C. $[\alpha]_D^{22}=-310°$ (*c* 1.0, MeOH). ^{1}H NMR ($CDCl_3$) δ: 1.47 (9H, s), 1.65–2.25 (4H, m), 2.47 (3H, s), 2.65–2.75 (1H, m), 3.06 (3H, s), 5.00–5.20 (1H, m), 5.25–5.60 (1H, m), 6.67 (1H, d, *J*=7.9 Hz), 6.97 (1H, t, *J*=8.2 Hz), 7.05–7.55 (10H, m). Anal. Calcd for $C_{31}H_{35}N_3O_4$: C, 72.49; H, 6.87; N, 8.18. Found: C, 72.51; H, 6.74; N, 8.16.

(*R*)-1-[4-(2-Methylbenzoylamino)benzoyl]-5-(*N*-methyl-*tert*-butoxycarbonylamino)-2,3,4,5-tetrahydro-1*H*-1-benzazepine (16b). The title compound was prepared from **13b**, 4-(2-methylbenzoylamino)benzoic acid, thionyl chloride and pyridine by the procedure described for the preparation of **16a**. The product was recrystallized from AcOEt to give **16b** (72%) as colorless prisms, mp 222–223°C. $[\alpha]_D^{22}=+300°$ (*c* 1.0, MeOH). Anal. Calcd for $C_{31}H_{35}N_3O_4$: C, 72.49; H, 6.87; N, 8.18. Found: C, 72.37; H, 6.91; N, 8.07.

(*S*)-5-Methylamino-1-[4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine (3a). Trifluoroacetic acid (4.0 mL, 51.9 mmol) was added to a ice-cooled solution of **16a** (0.89 g, 1.73 mmol) in CH_2Cl_2 (16 mL) and the mixture was stirred at room temperature for 1 h. After removal of solvent, the residue was dissolved in CH_2Cl_2. The CH_2Cl_2 solution was washed with saturated $NaHCO_3$ solution, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (silica gel; eluent, CH_2Cl_2–MeOH=19:1) and recrystallized from AcOEt to give **3a** (0.60 mg, 84%) as white powder, which was >99% ee by HPLC Analysis using ULTRON ES-CD (CH_3CN–20 mM KH_2PO_4 aq=15:85), mp 194–196°C. $[\alpha]_D^{23}=-236°$ (*c* 1.0, MeOH). ^{1}H NMR ($CDCl_3$) δ: 1.40–1.70 (2H, m), 1.70–2.30 (2H, m), 2.42 (0.9H, s), 2.46 (3H, s), 2.56 (2.1H, s), 2.60–2.80 (0.3H, m), 3.07–3.15 (0.7H, m), 3.74 (0.3H, br s), 4.04 (0.7H, dd, *J*=10.2, 3.8 Hz), 4.46–4.54 (0.7H, m), 5.12 (0.3H, br d, *J*=13.4 Hz), 6.65 (1H, d, *J*=7.5 Hz), 7.00 (1H, t, *J*=7.1 Hz), 7.11–7.51 (10H, m), 7.65 (1H, br s). IR (KBr): 3270, 1671, 1614, 1518, 1406, 1312 cm^{-1}. Anal. Calcd for $C_{26}H_{27}N_3O_2$: C, 75.52; H, 6.58; N, 10.16. Found: C, 75.53; H, 6.73; N, 10.05.

(*R*)-5-Methylamino-1-[4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine(3b). The title compound was prepared from **16b** and trifluoroacetic acid by the procedure described for the preparation of **3a**. The product was recrystallized from AcOEt to give **3b** (93%, >99% ee) as white powder, mp 194–195°C. $[\alpha]_D^{23}=+240°$ (*c* 1.0, MeOH). IR (KBr): 3269, 1672, 1614, 1518, 1406, 1313 cm^{-1}. Anal. Calcd for $C_{26}H_{27}N_3O_2$: C, 75.58; H, 6.58; N, 10.16. Found: C, 75.57; H, 6.59; N, 10.06.

(*S*)-5-Dimethylamino-1-[4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine (1a). Sodium

cyanoborohydride (60 mg, 0.95 mmol) was added to an ice-cooled solution of **3a** (200 mg, 0.48 mmol) and acetic acid (0.05 mL, 0.87 mmol) and 37% formaldehyde aqueous solution (0.10 mL, 1.23 mmol) in MeOH (5 mL), and the mixture was stirred at the same temperature for 30 min. A $NaHCO_3$ aqueous solution was added to the reaction mixture, and the whole solution was extracted with CH_2Cl_2, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (silica gel; eluent, CH_2Cl_2–MeOH=20:1) and recrystallized from EtOH to give **1a** (180 mg, 87%) as white powder, which was >99% ee by HPLC analysis using CHIRALCEL OD-RH (CH_3CN–0.5 M $NaClO_4$ aq=30:70), mp 222–223°C. $[\alpha]_D^{22}=-167°$ (*c* 0.2, MeOH). ^1H NMR ($CDCl_3$) δ: 1.20–1.85 (2H, m), 1.85–2.30 (2H, m), 2.18 (2.1H, s), 2.42 (3.9H, s), 2.47 (3H, s), 2.60–2.80 (0.3H, m), 3.06 (0.3H, br s), 3.40–3.55 (0.7H, m), 3.59 (0.7H, dd, *J*=10.6, 6.2 Hz), 4.08 (0.7H, t, *J*=11.2 Hz), 5.09 (0.3H, br d, *J*=12.4 Hz), 6.61 (0.7H, d, *J*=7.6 Hz), 6.70–6.80 (0.3H, m), 6.99 (1H, t, *J*=7.4 Hz), 7.14–7.60 (10H, m). IR (KBr): 3308, 1666, 1614, 1519, 1180 cm^{-1}. Anal. Calcd for $C_{27}H_{29}N_3O_2$: C, 75.85; H, 6.84; N, 9.83. Found: C, 75.96; H, 7.00; N, 9.71.

(*R*)-5-Dimethylamino-1-[4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine (1b). The title compound was prepared from **3b**, sodium cyanoborohydride, acetic acid and 37% formaldehyde aqueous solution by the procedure described for the preparation of **1a**. The product was recrystallized from EtOH to give **1b** (84%, >99% ee) as white powder, mp 221–222°C. $[\alpha]_D^{22}=+172°$ (*c* 0.2, MeOH). IR (KBr): 3306, 1667, 1614, 1504, 1180 cm^{-1}. Anal. Calcd for $C_{27}H_{29}N_3O_2$: C, 75.85; H, 6.84; N, 9.83. Found: C, 76.01; H, 6.78; N, 9.69.

(*S*)-5-Amino-2,3,4,5-tetrahydro-1*H*-1-benzazepine (14a). The amino compound **10a** (1.30 g, 3.68 mmol, >99% ee) was added to conc. H_2SO_4 (5 mL) and the mixture was stirred at 80°C for 1 h. The reaction mixture was poured into ice-water and the solution was alkalized with 10% NaOH aqueous solution. The whole solution was extracted with CH_2Cl_2, dried over Na_2SO_4 and concentrated in vacuo. The residue was recrystallized from AcOEt to give **14a** (0.50 g, 84%) as colorless prisms, mp 70–71°C. $[\alpha]_D^{25}$ +0.6° (*c* 1.0, MeOH). ^1H NMR ($CDCl_3$) δ: 1.70–2.20 (4H, m), 2.85–3.00 (1H m), 3.10–3.25 (1H, m), 3.60 (1H, br s), 4.04 (1H, dd, *J*=6.9, 2.2 Hz), 6.72 (1H, dd, *J*=7.7, 1.1 Hz), 6.89 (1H, dt, *J*=1.2, 7.4 Hz), 7.06 (1H, dt, *J*=1.6, 7.5 Hz), 7.21 (1H, dd, *J*=7.4, 1.5 Hz). Anal. Calcd for $C_{10}H_{14}N_2$: C, 74.03; H, 8.70; N, 17.27. Found: C, 74.06; H, 8.90; N, 17.14.

(*R*)-5-Amino-2,3,4,5-tetrahydro-1*H*-1-benzazepine (14b). The title compound was prepared from **10b** and conc. H_2SO_4 by the procedure described for the preparation of **14a**. The product was recrystallized from AcOEt to give **14b** (85%) as colorless prisms, mp 70–72°C. $[\alpha]_D^{25}=-0.6°$ (*c* 0.5, MeOH). Anal. Calcd for $C_{10}H_{14}N_2$: C, 74.03; H, 8.70; N, 17.27. Found: C, 73.98; H, 8.85; N, 17.36.

(*S*)-5-*tert*-Butoxycarbonylamino-2,3,4,5-tetrahydro-1*H*-1-benzazepine (15a). Di-*tert*-butyl dicarbonate (0.89 g, 4.1 mmol) was added to an ice-cooled solution of **14a** (0.55 g, 3.4 mmol) and Et_3N (0.57 mL, 4.1 mmol) in CH_2Cl_2 (22 mL). The mixture was stirred at 0–10°C for 1 h, and then at room temperature for 30 min. The reaction mixture was poured into 10% citric acid solution and extracted with CH_2Cl_2. The extract was dried over Na_2SO_4 and concentrated in vacuo. The residue was recrystallized from AcOEt–hexane to give **15a** (0.74 g, 83%) as colorless prisms, mp 153–154°C. $[\alpha]_D^{24}=-93.6°$ (*c* 0.1, MeOH). ^1H NMR (DMSO-d_6) δ: 1.50–1.80 (2H, m), 1.53 (9H, s), 1.90–2.20 (2H, m), 2.75–2.90 (1H, m), 3.20–3.40 (1H, m), 3.59 (1H, br s), 4.90 (1H, t, *J*=6.8 Hz), 5.71 (1H, d, *J*=7.0 Hz), 6.71 (1H, d, *J*=7.7 Hz), 6.75–6.95 (1H, m) 7.05–7.10 (1H, m), 7.22 (1H, d, *J*=7.2 Hz). Anal. Calcd for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45; N, 10.68. Found: C, 68.68; H, 8.46; N, 10.57.

(*R*)-5-*tert*-Butoxycarbonylamino-2,3,4,5-tetrahydro-1*H*-1-benzazepine (15b). The title compound was prepared from **14b**, di-*tert*-butyl dicarbonate and Et_3N by the procedure described for the preparation of **15a**. The product was recrystallized from AcOEt–hexane to give **15b** (89%) as white powder, mp 154–155°C. $[\alpha]_D^{24}=+93.6°$ (*c* 0.1, MeOH). Anal. Calcd for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45; N, 10.68. Found: C, 68.64; H, 8.44; N, 10.53.

(*S*)-5-*tert*-Butoxycarbonylamino-1-[4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine (17a). A solution of thionyl chloride (143 mg, 1.20 mmol) in DMF (0.05 mL) was added to a suspension of 4-(2-methylbenzoylamino)benzoic acid (153 mg, 0.60 mmol) in CH_2Cl_2 (10 mL) and the mixture was refluxed for 40 min to give the acid chloride. The acid chloride solution was added to a ice-cooled solution of **15a** (118 mg, 0.45 mmol) and pyridine (0.29 mL, 3.60 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred at 0–10°C for 40 min, and then, at room temperature for 1 h. The reaction mixture was poured into 10% citric acid aqueous solution and the whole was extracted with CH_2Cl_2. The extract was washed with 10% Na_2CO_3 aqueous solution and water, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (silica gel; eluent, hexane–AcOEt=1:1) and recrystallized from AcOEt–hexane to give **17a** (0.18 g, 80%) as colorless needles, mp 244–245°C. $[\alpha]_D^{23}=-266°$ (*c* 0.1, MeOH). ^1H NMR ($CDCl_3$) δ: 1.48 (9H, s), 1.50–2.30 (2H, m), 2.47 (3H, s), 2.70–3.20 (1H, m), 4.64 (0.7H, br s), 5.43 (0.3H, br s), 6.65 (1H, d, *J*=7.4 Hz), 7.00 (1H, t, *J*=7.3 Hz), 7.10–7.55 (10H, m). Anal. Calcd for $C_{30}H_{33}N_3O_4$: C, 72.12; H, 6.66; N, 8.41. Found: C, 71.79; H, 6.73; N, 8.31.

(*R*)-5-*tert*-Butoxycarbonylamino-1-[4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine (17b). The title compound was prepared from **15b**, 4-(2-methylbenzoylamino)benzoic acid, thionyl chloride and pyridine by the procedure described for the preparation of **17a**. The product was recrystallized from AcOEt–hexane to give **17b** (85%) as colorless needles, mp 242–244°C. $[\alpha]_D^{23}=+257°$ (*c* 0.1, MeOH). Anal. Calcd for $C_{30}H_{33}N_3O_4 \cdot 1/4H_2O$: C, 71.48; H, 6.70; N, 8.34. Found: C, 71.52; H, 6.65; N, 8.38.

(*S*)-5-Amino-1-[4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine (4a). Trifluoroacetic acid (0.7 mL, 9.09 mmol) was added to a solution of **17a** (0.3 g, 0.60 mmol) in CH_2Cl_2 (25 mL) and the mixture was

stirred at room temperature for overnight. The reaction mixture was poured into 10% Na_2CO_3 aqueous solution and extracted with CH_2Cl_2. The extract was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by preparative thin layer chromatography (silica gel; eluent, CH_2Cl_2–MeOH=8:1) and recrystallized from EtOH–H_2O to give **4a** (0.18 g, 75%) as white powder, which was >99% ee by HPLC analysis using ULTRON ES-CD (CH_3CN–20 mM KH_2PO_4 aq=15:85), mp 126–128°C. $[\alpha]_D^{26}=-280°$ (*c* 0.1, MeOH). ^1H NMR ($CDCl_3$) δ: 1.40–1.90 (2H, m), 1.90–2.25 (2H, m), 2.46 (3H, s), 2.80–3.00 (1H, m), 4.10–5.25 (2H, m), 6.67 (1H, d, *J*=8.2 Hz), 6.95–7.25 (9H, m), 7.69 (1H, d, *J*=7.7 Hz). IR (KBr): 3362, 1631, 1597, 1409, 1321 cm^{-1}. Anal. Calcd for $C_{25}H_{25}N_3O_2\cdot 1/2H_2O$: C, 73.51; H, 6.42; N, 10.29. Found: C, 73.09; H, 6.29; N, 10.65.

(*R*)-5-Amino-1-[4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine (4b). The title compound was prepared from **17b** and trifluoroacetic acid by the procedure described for the preparation of **4a**. The product was recrystallized from EtOH–H_2O to give **4b** (81%, >99% ee) as white powder, mp 125–126°C. $[\alpha]_D^{23}=+278°$ (*c* 0.1, MeOH). IR (KBr): 3362, 1629, 1598, 1409, 1321 cm^{-1}. Anal. Calcd for $C_{25}H_{25}N_3O_2\cdot 3/4H_2O$: C, 72.71; H, 6.47; N, 10.17. Found: C, 72.91; H, 6.19; N, 10.48.

1-(*p*-Toluenesulfonyl)-2,3-dihydro-1*H*-1-benzazepine (18). A solution of (±)-**7** (25.0 g, 78.8 mmol) and *p*-TsOH (3.15 g, 15.8 mmol) in toluene (800 mL) was refluxed under Dean–Stark apparatus for 6 h. The mixture was poured into water and the whole was extracted with AcOEt. The extract was dried over Na_2SO_4 and concentrated in vacuo. The residue was recrystallized from AcOEt–hexane to give **18** (22 g, 93%) as white powder, mp 106–108°C. ^1H NMR ($CDCl_3$) δ: 2.34 (3H, s), 2.60 (2H, d, *J*=5.6 Hz), 3.83 (2H, t, *J*=5.4 Hz), 5.63 (1H, dt, *J*=4.1, 12.3 Hz), 6.07 (1H, d, *J*=12.3 Hz), 7.09–7.23 (5H, m), 7.42 (2H, d, *J*=8.2 Hz), 7.56–7.60 (1H, m). Anal. Calcd for $C_{17}H_{17}NO_2S$: C, 68.20; H, 5.72; N, 4.68. Found: C, 68.15; H, 5.64; N, 4.64.

***cis*-4,5-Dihydroxy-1-(*p*-toluenesulfonyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine ((±)-19).** *N*-Methylmorpholine *N*-oxide (7.83 g, 66.8 mmol) and osmium tetroxide (4 wt% solution in water, 5.0 mL, 23.8 mmol) were added to a solution of **18** (10.0 g, 33.4 mmol) in acetone (200 mL), *t*-BuOH (50 mL) and water (50 mL) and the mixture was stirred at room temperature for 14 h. Osmium tetroxide (5 mL) was added to the reaction mixture and the mixture was stirred for 60 h. Saturated $NaHSO_3$ aqueous solution was added to the mixture and the solution was stirred for 5 min. The reaction mixture was extracted with AcOEt. The extract was washed with 1N HCl and water, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (silica gel; eluent, hexane–AcOEt=3:1) and recrystallized from AcOEt–hexane to give **19** (7.7 g, 69%), as white powder, mp 153–155°C. ^1H NMR (DMSO-d_6) δ: 1.60–1.80 (1H, m), 1.95–2.10 (1H, m), 2.39 (3H, s), 3.05–3.20 (1H, m), 3.85–4.00 (2H, m), 4.52 (1H, d, *J*=5.2 Hz), 4.57 (1H, d, *J*=3.9 Hz), 5.34 (1H, d, *J*=5.2 Hz), 6.96 (1H, d, *J*=7.7 Hz), 7.17 (1H, t, *J*=1.4 Hz), 7.27 (1H, t, *J*=6.5 Hz), 7.40 (2H, d, *J*=8.1 Hz), 7.52 (1H, d, *J*=7.4 Hz), 7.68 (1H, d, *J*=8.2 Hz). Anal. Calcd for $C_{17}H_{19}NO_4S$: C, 61.24; H, 5.74; N, 4.20. Found: C, 61.29; H, 5.69; N, 4.11.

(4*S*,5*R*)-4,5-Dihydroxy-1-(*p*-toluenesulfonyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine (19a). A mixture of (±)-**19** (5.52 g, 16.5 mmol), vinyl acetate (860 mL) and lipase QL (6.5 g) was stirred at room temperature for 6 h. The reaction mixture was filtered and lipase was washed with CH_2Cl_2. The filtrate was evaporated and the residue was purified by column chromatography (silica gel; eluent, hexane–AcOEt=4:1) to give the unreacted alcohol **19a** (2.90 g, 53%, 76% ee) and the acetate **20b** (2.48 g, 40%). The crude alcohol **19a** (76% ee) was recrystallized from hexane–AcOEt to give **19a** (2.27 g, 93% ee) from mother liquid. Next, a mixture of **19a** (2.27 g, 93% ee), vinyl acetate (350 mL) and lipase QL (2.0 g) was stirred at room temperature for 24 h. The reaction mixture was filtered and the filtrate was concentrated in vacuo. The residual oil was purified by column chromatography (silica gel; eluent, hexane–AcOEt=4:1) and the crystalline powder was washed with *iso*-PrOH to give pure **19a** (2.05 g, 90%) as white powder, which was >99% ee by HPLC analysis using CHIRALCEL OJ (hexane–EtOH–Et_2NH=700:300:1), mp 140–142°C. $[\alpha]_D^{25}=-24.5°$ (*c* 0.2, MeOH). Anal. Calcd for $C_{17}H_{19}NO_4S$: C, 61.24; H, 5.74; N, 4.20. Found: C, 61.35; H, 5.75; N, 4.07.

(4*R*,5*S*)-4,5-Dihydroxy-1-(*p*-toluenesulfonyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine (19b). A solution of **20b** (2.48 g, 6.61 mmol) and 1 N NaOH aqueous solution (72 mL) in MeOH (80 mL) was stirred at room temperature for 3 h. The reaction mixture was adjusted to pH 4–5 with 2 N HCl and the solution was extracted with CH_2Cl_2. The extract was dried over $MgSO_4$ and concentrated in vacuo. The crystalline residue was washed with *iso*-PrOH to give **19b** (1.89 g, 86%, 99% ee), mp 139–141°C. $[\alpha]_D^{24}=+23.8°$ (*c* 0.2, MeOH). Anal. Calcd for $C_{17}H_{19}NO_4S$: C, 61.24; H, 5.74; N, 4.20. Found: C, 61.19; H, 5.61; N, 4.24.

(4*S*,5*R*)-4,5-Dimethylmethylenedioxy-1-(*p*-toluenesulfonyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine (21a). A solution of **19a** (2.0 g, 6.0 mmol), 2,2-dimethoxypropane (1.1 mL, 8.94 mmol) and *p*-TsOH (48 mg, 0.25 mmol) in acetone (50 mL) was refluxed for 2 h, and the mixture was concentrated in vacuo. The residue was purified by column chromatography (silica gel; eluent, CH_2Cl_2–AcOEt=18:1) to give **21a** (2.5 g, quant.) as colorless oil. $[\alpha]_D^{24}=-58.8°$ (*c* 0.03, MeOH). ^1H NMR ($CDCl_3$) δ: 1.20–1.25 (1H, m), 1.39 (3H, s), 1.52 (3H, s), 2.10 (1H, t, *J*=3.3 Hz), 2.44 (3H, s), 3.29 (1H, d, *J*=4.1, 11.7 Hz), 4.05 (1H, dt, *J*=4.7, 16.8 Hz), 4.34–4.43 (1H, m), 5.08 (1H, d, *J*=7.5 Hz), 7.09 (1H, d, *J*=7.6 Hz), 7.22–7.38 (4H, m), 7.50 (1H, d, *J*=7.6 Hz), 7.71 (2H, d, *J*=8.2 Hz). Anal. Calcd for $C_{20}H_{23}NO_4S$: C, 64.32; H, 6.21; N, 3.75. Found: C, 64.07; H, 6.15; N, 3.70.

(4*R*,5*S*)-4,5-Dimethylmethylenedioxy-1-(*p*-toluenesulfonyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine (21b). The title compound was prepared from **19b**, 2,2-dimethoxypropane and *p*-TsOH by the procedure described for the preparation of **21a**. The product was purified by column chromatography to give **21b** (quant.) as colorless oil. $[\alpha]_D^{24}=+58.0°$ (*c* 0.1, MeOH). Anal. Calcd for $C_{20}H_{23}NO_4S$: C, 64.32; H, 6.21; N, 3.75. Found: C, 64.25; H, 6.06; N, 3.79.

(4*S*,5*R*)-4,5-Dimethylmethylenedioxy-2,3,4,5-tetrahydro-1*H*-1-benzazepine (22a). Magnesium (turnings, 1.43 g, 59 mmol) was added to a solution of **21a** (2.2 g, 5.89 mmol) in MeOH (60 mL) and the mixture was refluxed for 3 h. The reaction mixture was filtrated by a pad of Celite and the Celite was washed with CH_2Cl_2–MeOH. The filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel; eluent, CH_2C_{12}–AcOEt=50:1) to give **22a** (910 mg, 70%) as pale yellow oil. $[\alpha]_D^{25}=-146°$ (*c* 0.2, MeOH). ^{1}H NMR ($CDCl_3$) δ: 1.49 (3H, s), 1.60 (3H, s), 1.62–1.74 (1H, m), 1.93–2.02 (1H, m), 3.14–3.33 (2H, m), 4.45–4.53 (1H, m), 5.31 (1H, d, *J*=7.5 Hz), 6.68 (1H, d, *J*=7.7 Hz), 6.97 (1H, t, *J*=7.3 Hz), 7.15 (1H, t, *J*=7.3 Hz), 7.39 (1H, d, *J*=7.5 Hz). Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 70.95; H, 7.59; N, 6.52.

(4*R*,5*S*)-4,5-Dimethylmethylenedioxy-2,3,4,5-tetrahydro-1*H*-1-benzazepine (22b). The title compound was prepared from **21b** and magnesium by the procedure described for the preparation of **22a**. The product was purified by column chromatography to give **22b** (66%) as colorless oil. $[\alpha]_D^{24}=+149°$ (*c* 0.2, MeOH). Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 70.94; H, 7.47; N, 6.33.

(4*S*,5*R*)-4,5-Dimethylmethylenedioxy-1-[4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine (23a). A solution of thionyl chloride (430 μL, 5.85 mmol) in DMF (0.57 mL) was added to a suspension of 4-(2-methylbenzoylamino)benzoic acid (1.18 g, 4.64 mmol) in CH_2Cl_2 (60 mL) and the mixture was refluxed for 2 h to give a solution of the acid chloride. The acid chloride solution was added to an ice-cooled solution of **22a** (850 mg, 3.87 mmol) and pyridine (1.56 mL, 19.4 mmol) in CH_2Cl_2 (30 mL), and the mixture was stirred at room temperature for 24 h. A 2 N HCl solution (6 mL) was added to the reaction mixture and the whole was extracted with AcOEt. The extract was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (silica gel; eluent, CH_2Cl_2–MeOH=50:1) and recrystallized from Et_2O–hexane to give **23a** (1.62 g, 92%) as white powder, mp 134–135°C. $[\alpha]_D^{25}=+37.0°$ (*c* 0.2, MeOH). ^{1}H NMR ($CDCl_3$) δ: 1.45–1.64 (2H, m), 1.57 (6H, s), 2.21–2.25 (1H, m), 2.46 (3H, s), 3.20–3.48 (1H, m), 4.15–4.62 (1H, m), 5.20–5.53 (1H, m), 6.64 (1H, t, *J*=7.80 Hz), 7.08–7.62 (12H, m). Anal. Calcd for $C_{28}H_{28}N_2O_4$: C, 73.66; H, 6.18; N, 6.14. Found: C, 73. 27; H, 6.20; N, 6.12.

(4*R*,5*S*)-4,5-Dimethylmethylenedioxy-1-[4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine (23b). The title compound was prepared from **22b** and 4-(2-methylbenzoylamino)benzoic acid, thionyl chloride and pyridine by the procedure described for the preparation of **23a**. The product was recrystallized from Et_2O–hexane to give **23b** (82%) as white powder, mp 133–134°C. $[\alpha]_D^{25}=-36.3°$ (*c* 0.2, MeOH). Anal. Calcd for $C_{28}H_{28}N_2O_4$: C, 73.66; H, 6.18; N, 6.14. Found: C, 73.47; H, 6.32; N, 5.98.

(4*S*,5*R*)-4,5-Dihydroxy-1-[4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine (5a). 10% HCl (37 mL) was added to a solution of **23a** (1.4 g, 3.0 mmol) in THF (75 mL), and the mixture was stirred at room temperature for 20 h. The reaction mixture was adjusted with 5 N NaOH to pH 9–10 and the solution was extracted with CH_2Cl_2. The extract was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (silica gel; eluent, CH_2Cl_2–MeOH=50:1 to 18:1) and recrystallized from EtOH–Et_2O to give **5a** (990 mg, 75%) as white powder, which was >99% ee by HPLC analysis using CHIRALCEL OJ (hexane–EtOH–Et_2NH=700:300:1), mp 161–162°C. $[\alpha]_D^{23}=-36.8°$ (*c* 0.2, MeOH). ^{1}H NMR (DMSO-d_6) δ: 1.71–2.09 (1H, m), 2.32 (3H, s), 2.69–2.96 (1H, m), 3.69–4.09 (1H, m), 4.50–4.97 (3H, m), 5.51 (1H, t, *J*=5.6 Hz), 6.50–6.63 (1H, m), 6.96–7.59 (12H, m), 10.20–10.30 (1H, br s). IR (KBr): 3401, 1621, 1519, 1407, 1316, 1260 cm^{-1}. Anal. Calcd for $C_{25}H_{24}N_2O_4\cdot0.2H_2O$: C, 71.48; H, 5.85; N, 6.67. Found: C, 71.27; H, 5.93; N, 6.48.

(4*R*,5*S*)-4,5-Dihydroxy-1-[4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine (5b). The title compound was prepared from **23b** and HCl by the procedure described for the preparation of **5a**. The product was recrystallized from EtOH–Et_2O to give **5b** (90%, 99% ee) as white powder, mp 160–161°C. $[\alpha]_D^{23}=+35.3°$ (*c* 0.2, MeOH). IR (KBr): 3292, 1614, 1519, 1408, 1317, 1182 cm^{-1}. Anal. Calcd for $C_{25}H_{24}N_2O_4\cdot0.2H_2O$: C, 71.48; H, 5.85; N, 6.67. Found: C, 71.17; H, 6.04; N, 6.41.

5-Chloro-1-[4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine (24). DMF (10.0 mL) and thionyl chloride (9.2 mL, 0.13 mol) were added to a suspension of (±)-**2** (42.4 g, 0.106 mol) in CH_2Cl_2 (500 mL), and the mixture was stirred at room temperature for 2 h. After adding of $CHCl_3$, the solution was washed with water. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was recrystallized from EtOAc to give **24** (38.1 g, 86%) as white powder, mp 192–193 °C. ^{1}H NMR ($CDCl_3$) δ: 1.70–2.20 (2H, m), 2.30–3.20 (5H, m), 2.46 (3H, s), 4.50–5.60 (2H, m), 6.55–6.80 (1H, m), 6.90–7.85 (12H, m). Anal. Calcd for $C_{25}H_{23}N_2O_2Cl$: C, 71.68; H, 5.53; N, 6.69. Found: C, 71.73; H, 5.45; N, 6.66.

1-[4-(2-Methylbenzoylamino)benzoyl]-2,3-dihydro-1*H*-1-benzazepine (25). Sodium iodide (27.0 g, 0.18 mol) and DBU (21.0 mL, 0.14 mol) were added to an ice-cooled suspension of **24** (38.1 g, 90.9 mmol) in CH_3CN (800 mL), and the mixture was refluxed for 3.5 h. After removal of CH_3CN, water (1.0 L) was added to the residue. The precipitated solid was collected by filtration. The collected precipitate was dissolved in CH_2Cl_2, and washed with water. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was recrystallized from EtOAc to give **25** (38.0 g, quant.) as white powder, mp 212–213°C. ^{1}H NMR ($CDCl_3$) δ: 2.25–3.15 (3H, m), 2.46 (3H, s), 4.75–5.20 (1H, m), 6.00–6.20 (1H, m), 6.52 (1H, d, *J*=12.3 Hz), 6.65 (1H, d, *J*=7.8 Hz), 6.80–7.00 (1H, m), 7.00–7.45 (10H, m), 7.56 (1H, br s). Anal. Calcd for $C_{25}H_{22}N_2O_2$: C, 78.51: H, 5.80; N, 7.32. Found: C, 78.21; H, 5.67; N, 7.24.

4,5-Epoxy-1-[4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine (26). *m*-CPBA (80%, 2.0 g, 9.27 mmol) was added to a stirred and cooled (0°C) solution

of **25** (1.76 g, 4.60 mmol) in CH_2Cl_2 (60 mL) and the mixture was stirred at the same temperature for 20 h. The reaction mixture was washed with $Na_2S_2O_3$ solution and saturated $NaHCO_3$ solution. The CH_2Cl_2 layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (silica gel; eluent, CH_2Cl_2–AcOEt=18:1 to 10:1) and recrystallized from EtOH–H_2O to give **26** (1.37 g, 75%) as white powder, mp 176–177°C. ^{1}H NMR ($CDCl_3$) δ: 1.90–2.70 (2H, m), 2.45 (3H, s), 2.75–3.25 (1H, m), 3.40–3.75 (1H, m), 3.80–4.25 (1H, m), 4.35–5.00 (1H, m), 6.40–6.75 (1H, m), 6.85–7.90 (12H, m). Anal. Calcd for $C_{25}H_{22}N_2O_3$: C, 75.36; H, 5.57; N, 7.03. Found: C, 75.30; H, 5.57; N, 6.99.

***trans*-4,5-Dihydroxy-1-[4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine ((±)-6).** A solution of KOH (2.38 g, 34.5 mmol) in H_2O (550 mL) was added to a solution of **26** (27.7 g, 69.5 mmol) in DMSO (550 mL) and the mixture was stirred at 100°C for 7 h. After cooling, the insoluble material was collected by filtration and dissolved in AcOEt. The solution was washed with H_2O and saturated $NaHCO_3$ solution, 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) and recrystallized from EtOH–H_2O to give (±)-**6** (20.8 g, 72%) as white powder, mp 225–228°C. ^{1}H NMR (DMSO-d_6) δ: 1.45–2.65 (2H, m), 2.33 (3H, s), 2.85–3.25 (1H, m), 3.35–4.10 (1H, m), 4.15–5.25 (3H, m), 5.45–5.75 (1H, m), 6.35–6.75 (1H, m), 6.80–7.75 (11H, m), 10.15–10.45 (1H, m). IR (KBr): 3273, 1656, 1626, 1531, 1409, 1328, 1057 cm^{-1}. Anal. Calcd for $C_{25}H_{24}N_2O_4$: C, 72.10; H, 5.81; N, 6.73. Found: C, 72.09; H, 5.85; N, 6.83.

(4*S*,5*S*)-4,5-Dihydroxy-1-[4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine (6a). A mixture of (±)-**6** (2.02 g, 4.85 mmol), vinyl acetate (100 mL) and lipase QL (2.0 g) in isopropyl ether (100 mL) and DMF (20 mL) was stirred at 40°C for 22 h. The mixture was filtrated by a pad of Celite and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel; eluent, CH_2Cl_2–MeOH=20:1) to give **6a** (1.03 g, 51%, 90% ee) and the mixture of **27**, **28** and **29** (1.10 g in total, which yield were 37%, 7%, and 5% respectively by HPLC analysis using TSK-80T$_M$ (CH_3CN–H_2O=1:1)). Next, a mixture of **6a** (1.03 g, 2.47 mmol, 90% ee), vinyl acetate (50 mL) and lipase QL (1.0 g) in isopropyl ether (50 mL) and DMF (10 mL) was stirred at 40°C for 22 h. The mixture was filtrated by a pad of Celite and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel; eluent, CH_2Cl_2–MeOH=20:1) to give **6a** (0.91 g, 88%) as colorless amorphous, which was >99% ee by HPLC analysis using CHIRALCEL OJ (hexane–EtOH=4:1). $[\alpha]_D^{25}$= +166° (*c* 0.1, MeOH). ^{1}H NMR ($CDCl_3$) δ: 1.85–2.20 (2H, m), 2.38 (3H, s), 2.75–3.05 (1H, m), 3.35–3.80 (2H, m), 4.10–4.45 (1H, m), 4.65–5.00 (2H, m), 6.59 (1H, d, *J*=7.6 Hz), 6.85–7.55 (10H, m), 7.73 (1H, d, *J*=7.5 Hz), 8.00 (1H, br s). IR (KBr): 3418, 1614, 1519, 1408, 1318, 1183 cm^{-1}. Anal. Calcd for $C_{25}H_{24}N_2O_4$·1/4H_2O: C, 71.33; H, 5.87; N, 6.65. Found: C, 71.39; H, 6.03; N, 6.38.

(4*R*,5*R*)-4,5-Dihydroxy-1-[4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine (6b). A mixture of **27**, **28** and **29** (1.10 g in total) and K_2CO_3 (0.80 g, 5.80 mmol) in MeOH (20 mL) was stirred at room temperature for 30 min. After removal of MeOH, the residue was poured into water and the mixture was extracted with AcOEt. 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=20:1) to give **6b** (0.99 g, quant., 91% ee) as colorless amorphous. Next, a mixture of **6b** (0.99 g, 2.37 mmol, 91% ee), vinyl acetate (50 mL) and lipase QL (1.0 g) in isopropyl ether (50 mL) and DMF (10 mL) was stirred at 40°C for 10 h. The mixture was filtrated by Celite and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel; eluent, CH_2Cl_2–MeOH=30:1) to give **27**, **28** and **29** (0.95 g in total, 69, 11 and 7%, respectively). This mixture was dissolved in MeOH (20 mL), and K_2CO_3 (0.57 g, 4.12 mmol) was added. The mixture was stirred at room temperature for 1 h. After removal of MeOH, the residue was poured into water and the whole was extracted with AcOEt. The extract was washed with saturated NaCl solution, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (silica gel; eluent, CH_2Cl_2–MeOH=20:1) to give **6b** (0.71 g, 2 steps 72%, >99% ee) as colorless amorphous. $[\alpha]_D^{25}$=−162° (*c* 0.1, MeOH). IR (KBr): 3442, 1614, 1519, 1316, 1183 cm^{-1}. Anal. Calcd for $C_{25}H_{24}N_2O_4$·1/4H_2O: C, 71.33; H, 5.87; N, 6.65. Found: C, 71.39; H, 6.01; N, 6.46.

(*R*)-5-(3-Bromobenzoyloxy)-1-(*p*-toluenesulfonyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine (30). Thionyl chloride (0.17 mL, 2.33 mmol) was added to a solution of 3-bromobenzoic acid (380 mg, 1.89 mmol) and *N*-methylpyrrolidinone (3 drops) in CH_2Cl_2 (10 mL), and the mixture was refluxed for 2 h. After removing of the solvent, the residue was dissolved with toluene, and concentrated in vacuo to give the acid chloride. A solution of the acid chloride in CH_2Cl_2 (3 mL) was added dropwise to an ice-cooled solution of **7b** (300 mg, 0.95 mmol, 99% ee), pyridine (0.8 mL, 9.91 mmol) and *N*,*N*-dimethylaminopyridine (23 mg, 0.19 mmol) in CH_2Cl_2 (14 mL), and the mixture was stirred at room temperature for 14 h. 1 N HCl was added to the reaction mixture and the whole was extracted with CH_2Cl_2. The extract was washed with water, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (silica gel; eluent, hexane–AcOEt=5:1) and recrystallized from AcOEt–hexane to give **30** (390 mg, 82%) as colorless prisms, mp 105–106°C. $[\alpha]_D^{25}$=−56.4° (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 1.76–2.14 (4H, m), 2.43 (3H, s), 3.22–3.53 (2H, m), 3.84–4.21 (2H, m), 5.70–5.90 (1H, m), 7.17–7.34 (3H, m), 7.30 (2H, d, *J*=8.2 Hz), 7.36–7.44 (2H, m), 7.66–7.73 (1H, m), 7.73 (1H, d, *J*=8.2 Hz), 8.10 (1H, d, *J*=7.9 Hz), 8.28 (1H, t, *J*=1.6 Hz). Anal. Calcd for $C_{24}H_{22}BrNO_4S$: C, 57.61; H, 4.43; N, 2.80. Found: C, 57.62; H, 4.37; N, 2.69.

(4*S*,5*R*)-4-Hydroxy-5-methoxy-1-(*p*-toluenesulfonyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine (31). Dibutyltin oxide (550 mg, 2.11 mmol) was added to a solution of **19a** (590 mg, 1.77 mmol, >99% ee) in toluene (25 mL) and THF (25 mL) and the mixture was refluxed under Dean–Stark apparatus for 5 h. And then, tetrabutylammonium bromide (287 mg, 0.89 mmol) and methyl iodide (1.1 mL,

17.7 mmol) were added to the mixture and the reaction mixture was refluxed for 2 h. After removal of solvent, the residue was poured into water and the whole was extracted with CH_2Cl_2. The extract was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (silica gel; eluent, hexane–AcOEt=2:1 to 1:1) to give **31** (480 mg, 78%) as pale yellow oil. $[\alpha]_D^{23}=-26.2°$ (*c* 0.2, MeOH). ^{1}H NMR ($CDCl_3$) δ: 0.94–2.13 (2H, m), 2.42 (3H, s), 3.17 (3H, s), 3.48 (2H, d, *J*=5.5 Hz), 3.80–3.93 (2H, m), 4.00–4.07 (1H, m), 7.26–7.37 (6H, m), 7.65 (2H, d, *J*=8.3 Hz). HRMS Calcd for $C_{18}H_{22}NO_4S$ $(MH)^+$: 348.1270. Found: 348.1271.

(*S*)-5-Methoxy-1-(*p*-toluenesufonyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine (32a). Tetrabutylammonium hydrogen sulfate (520 mg, 1.52 mmol) and 5 N NaOH (8.96 mL) were added to a solution of **31** (480 mg, 1.38 mmol) in benzene (10 mL) with stirring at room temperature. And then, carbon disulfide (173 μL, 2.75 mmol) and methyl iodide (143 μL, 2.07 mmol) were added to the mixture, and the reaction mixture was stirred at room temperature for 30 min. The mixture was poured into water and the whole was extracted with Et_2O. The extract was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (silica gel; eluent, hexane–AcOEt=3:1) to give the xanthate (430 mg, 71%) as colorless oil. A solution of the xanthate (250 mg, 0.57 mmol), tributyltin hydride (333 mg, 1.14 mmol) and AIBN (6.3 mg, 0.04 mmol) in dry toluene (11 mL) was refluxed under nitrogen atmospheric pressure for 5 h. The reaction mixture was poured into water and the whole was extracted with AcOEt. The extract was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (silica gel; eluent, cyclohexane–AcOEt=4:1) and recrystallized from MeOH to give **32a** (175 mg, 92%) as colorless prisms, which was >99% ee by HPLC analysis using ULTRON ES-CD (CH_3CN–20 mM KH_2PO_4=45:55), mp 111–112°C. $[\alpha]_D^{25}=-33.5°$ (*c* 0.1, MeOH). ^{1}H NMR ($CDCl_3$) δ: 1.26–1.97 (4H, m), 2.41 (3H, s), 3.11 (3H, s), 3.16–3.20 (1H, m), 3.79 (1H, d, *J*=8.1 Hz), 4.06–4.10 (1H, m), 7.19–7.37 (6H, m), 7.64 (2H, d, *J*=8.3 Hz). Anal. Calcd for $C_{18}H_{21}NO_3S$: C, 65.23; H, 6.39; N, 4.23. Found: C, 65.32; H, 6.45; N, 4.06.

(*R*)-5-Methoxy-1-(*p*-toluenesufonyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine (32b). Sodium hydride (60%, 85.5 mg, 2.14 mmol) and iodomethane (179 μL, 2.83 mmol) were added to an ice-cooled solution of **7b** (450 mg, 1.42 mmol, >99% ee) in DMF (3.0 mL) and the mixture was stirred at room temperature for 17 h. The reaction mixture was poured into water and the whole was extracted with AcOEt. The extract was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (silica gel; eluent, hexane–AcOEt=9:1) and recrystallized from MeOH to give **32b** (470 mg, quant., 99% ee) as colorless prisms, mp 110–111°C. $[\alpha]_D^{26}=+33.0°$ (*c* 0.1, MeOH). Anal. Calcd for $C_{18}H_{21}NO_3S$: C, 65.23; H, 6.39; N, 4.23. Found: C, 65.13; H, 6.34; N, 4.08.

(4*S*,5*S*)-4-Hydroxy-5-methoxy-1-[4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine (33). Dibutyltin oxide (0.39 g, 1.6 mmol) was added to a suspension of **6a** (0.54 g, 1.3 mmol, 99% ee) in toluene (30 mL) and dioxane (30 mL), and the mixture was refluxed under Dean–Stark apparatus for 22 h. And then, iodomethane (3.0 mL, 48 mmol) and tetrabutylammonium bromide (0.22 g, 0.67 mmol) were added to an ice-cooled mixture, and the reaction mixture was stirred at 100–110°C for 9.5 h. After removal of the solvent, the residue was dissolved in CH_2Cl_2. The CH_2Cl_2 solution was washed with water, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (silica gel; eluent, AcOEt–hexane=2:1) to give **33** (0.46 g, 83%) as pale yellow amorphous. $[\alpha]_D^{25}=+116°$ (*c* 0.1, MeOH). ^{1}H NMR ($CDCl_3$) δ: 1.80–2.15 (2H, m), 2.46 (3H, s), 2.90–3.80 (3H, m), 3.61 (3H, s), 4.15–5.05 (2H, m), 6.50–6.80 (1H, m), 6.85–7.70 (12H, m). Anal. Calcd for $C_{26}H_{26}N_2O_4 \cdot 1/4H_2O$: C, 71.79; H, 6.14; N, 6.44. Found: C, 71.94; H, 6.05; N, 6.41.

***O*-Methyl *O*-(4*S*,5*S*)-5-Methoxy-1-[4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepin-4-yl thiocarbonate (34).** A solution of **33** (0.39 g, 0.9 mmol) and 1,1′-thiocarbonyldiimidazole (0.48 g, 2.7 mmol) in DMF (8 mL) was stirred at 80°C for 5 h. After evaporation of DMF, MeOH (10 mL) was added to the mixture, and the solution was stirred at room temperature for 16 h. After removal of the solvent, the residue was dissolved in CH_2Cl_2. The CH_2Cl_2 solution was washed with water, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (silica gel; eluent, hexane–AcOEt=2:1) to give **34** (0.16 g, 36%) as colorless amorphous. $[\alpha]_D^{27}=+115°$ (*c* 0.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 1.90–3.25 (2H, m), 2.46 (3H, s), 3.30–3.80 (4H, m), 3.80–5.10 (5H, m), 5.30–6.00 (1H, m), 6.50–6.85 (1H, m), 6.90–7.75 (12H, m). Anal. Calcd for $C_{28}H_{28}N_2O_5S$: C, 66.65; H, 5.59; N, 5.55. Found: C, 66.30; H, 5.62; N, 5.52.

(*R*)-5-Methoxy-1-[4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine (35). A solution of **34** (0.123 g, 0.244 mmol), tributyltin hydride (0.14 mL, 0.49 mmol) and AIBN (3.0 mg, 17 μmol) in toluene (5 mL) was refluxed for 1 h. The reaction mixture was poured into water and the whole was extracted with AcOEt. The extract was washed with water, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by preparative thin layer chromatography (silica gel; solvent, hexane–AcOEt=1:1) and the crystal was recrystallized from AcOEt–hexane to give **35** (33 mg, 33%) as colorless needles, which was 99% ee by HPLC analysis using ULTRON ES-OVM (CH_3CN–20 mM KH_2PO_4=15:85). mp 179–182°C. $[\alpha]_D^{26}=+22.8°$ (*c* 0.1, MeOH). ^{1}H NMR ($CDCl_3$) δ: 1.45–2.55 (4H, m), 2.44 (3H, s), 2.60–3.05 (1H, m), 3.20–3.70 (3H, m), 4.20–5.20 (2H, m), 6.65 (1H, d, *J*=7.5 Hz), 6.80–7.60 (11H, m), 7.65–8.10 (1H, m). Anal. Calcd for $C_{26}H_{26}N_2O_3$: C, 75.34; H, 6.32; N, 6.76. Found: C, 75.30; H, 6.45; N, 6.65.

(*R*)-5-Methoxy-1-[4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine (35) [from (*R*)-32b]. Magnesium (turnings, 0.32 g, 3.2 mmol) was added to a solution of (*R*)-(+)-**32b** (0.436 g, 1.32 mmol, 99% ee) in dry MeOH (10 mL) and the mixture was refluxed for 4 h. Conc. H_2SO_4 and water were added to the mixture and the solution was alkalized with saturated $NaHCO_3$ solution. The

whole was extracted with CH_2Cl_2, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (silica gel; eluent, CH_2Cl_2–MeOH=100:1) to give 5-methoxy-2,3,4,5-tetrahydro-1*H*-benzazepine (0.16 g, 66%) as yellow oil. The oil was dissolved in CH_2Cl_2 (20 mL), and to this ice-cooled solution, pyridine (0.35 mL, 4.4 mmol) and 4-(2-methylbenzoylamino)benzoyl chloride (0.335 g, 1.31 mmol) were added, and the mixture was stirred at room temperature for 16 h. The reaction mixture was washed with water and saturated $NaHCO_3$ solution, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by preparative thin layer chromatography (silica gel; solvent, hexane–AcOEt=1:1) and the crystal was recrystallized from AcOEt–hexane to give **35** (68 mg, 13%, 99% ee) as white powder, mp 177–179°C. $[\alpha]_D^{25}=+35.6°$ (*c* 0.1, MeOH). Anal. Calcd for $C_{26}H_{26}N_2O_3$: C, 75.34; H, 6.32; N, 6.76. Found: C, 75. 02; H, 6.27; N, 6.70.

X-Ray analysis of 30

Suitable crystals of **30** for an X-ray diffraction study were grown from a AcOEt–hexane solution. All data were obtained using a Rigaku AFC-5S four circle diffractometer with graphite-monochromated MoKα radiation. Crystal data: $C_{24}H_{22}BrNO_4S$, M_r=500.41, monoclinic, space group $P2_1$, a=9.908(2) Å, b=27.208(5) Å, c=8.357(2) Å, β=90.40(1)°, V=2252.7(7) Å^3, Z=4.0, D_x=1.475 g/cm^3, $F(000)$=1024, and μ (MoKα)=19.533 cm^{-1}. The intensities were measured using $\omega/2\theta$ 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 correlation (ψ-scan,[7] transmission factor=0.84–1.00) was applied. Of the 8788 reflections which collected, 5724 reflections with $I>2.0\sigma(I)$ were used for structure determination and refinement. The structure was solved by direct method using TEXSAN crystallographic software package.[8] All non-H atoms were found in Fourier map. All H atoms were calculated at geometrical positions and not refined. The refinement of atomic parameters were carried out by full matrix least-squares refinement, using anisotropically temperature factors for all non-H atoms. The final refinement converged with R=0.057 and Rw=0.046 for 558 parameters. Then, 25 of Bijvoet pairs having large intensity and high measurement accuracy were selected. The absolute configuration of **30** was determined as *R* by the Bijvoet's anomalous-dispersion method.[6,9]

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9. 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.