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EFFICIENT SYNTHESIS OF OPTICALLY ACTIVE 4,5-DIHYDROXY-2,3,4,5-TETRAHYDRO-1*H*-1-BENZAZEPINE DERIVATIVES UTILIZING LIPASE-CATALYZED TRANSESTERIFICATION

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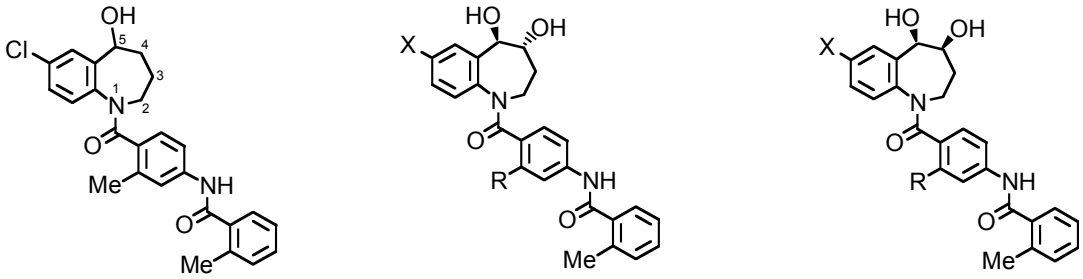
Abstract – As an efficient and enantioselective synthesis of the 4,5-dihydroxy-benzazepine compounds, the syntheses of optically active 5-*O*-protected *trans*-4,5-dihydroxybenzazepine derivatives were accomplished. The *trans*-7-chloro-4-hydroxy-5-methoxymethoxy-1-(*p*-toluenesulfonyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine [(±)-**4]** was kinetically resolved by lipase-catalyzed trans-esterification. The optically active **4*** was isomerized into the *cis* compound (**6***) utilizing the Mitsunobu esterification followed by hydrolysis. The chiral compounds (**4*** and **6***) were converted to the 4,5-bismethoxymethoxy compounds (**7***–**10***), which were the intermediates for the compounds (**2a, b** and **3a, b**).

INTRODUCTION

The benzazepene derivatives (tolvaptan, **1**[1]) have been applied as drug for vasopressin V_2 receptor antagonist.[1, 2] In its metabolic study, we found the 4,5-dihydroxybenzazepine compounds (**2a** and **3a**) as metabolites (Figure 1). In a previous paper, we reported the synthesis of optically active compounds by lipase-catalyzed enantioselective transesterification.[3] During the course of our investigation on the lipase-catalyzed asymmetric resolution, we have already reported the synthesis of the chiral diols (**2b** and **3b**) by utilizing the kinetic resolution of each of the *trans*- and *cis*-4,5-dihydroxy compounds.[3c] In this report, we focused our attention on the development of a more effective method for the synthesis of the compounds having a 4,5-dihydroxybenzazepine skelton, in optically active forms.



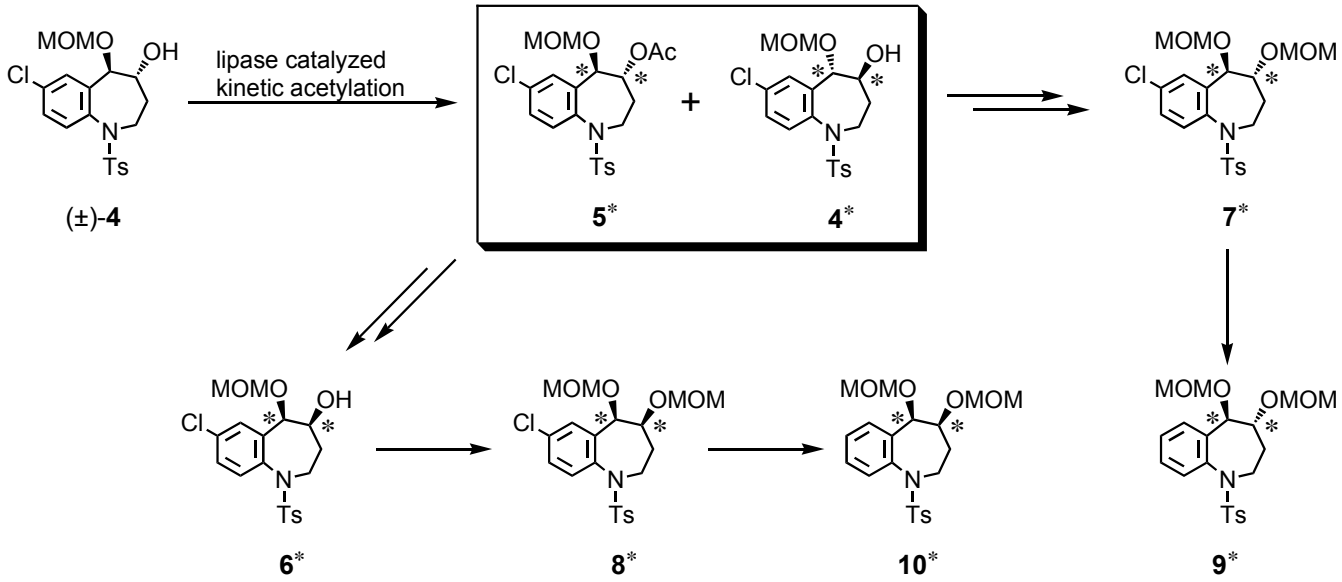
tolvaptan (**1**)

2a (X=Cl, R=Me)
2b (X=R=H)

3a (X=Cl, R=Me)
3b (X=R=H)

Figure 1

Our strategy is summarized in Scheme 1. In order to simplify the synthesis of the chiral 4,5-dihydroxy-benzazepine derivatives, we planed the optical resolution of an applicable intermediate for both of the *trans*- and *cis*-4,5-dihydroxy compounds. Here, we chose the 5-*O*-protected *trans*-4,5-dihydroxybenz-azepine compound [(±)-**4**], which has a 7-chloro moiety and is protected by a tosyl group on the nitrogen atom and by a methoxymethyl group on the 5-hydroxyl group, as the common starting material. If the optical resolution of the *trans*-monohydroxy compound [(±)-**4**] is achieved, it is also applicable to the synthesis of the chiral *cis*-monohydroxy compound (**6***) by utilizing isomerization of the chiral *trans*-monohydroxy compound (**4***). These compounds (**4*** and **6***) can be converted to the compounds (**7*** and **8***) as the intermediates of **2a** and **3a**, and the following dechlorinations of the compounds (**7*** and **8***) will afford the compounds (**9*** and **10***) as the intermediates of **2b** and **3b**, respectively.



(±)-**4**

5*

4*

7*

6*

8*

10*

9*

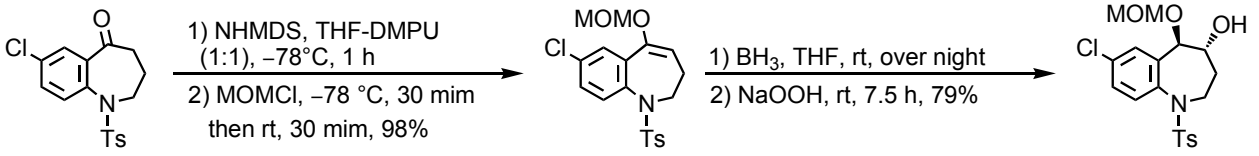
Scheme 1

RESULTS AND DISCUSSION

First, we studied the optical resolution of the *trans*-4-hydroxy-5-methoxymethoxybenzazepine derivative [(±)-**4**]. The regio- and diastereoselective synthesis of (±)-**4** is summarized in Scheme 2. The ketone (**11**)[1]

reacted with chloromethyl methyl ether (MOMCl) by treatment with sodium hexamethyldisilazide (NHMDS) in THF-DMPU (1:1) to give the enol ether (**12**) in 98% yield. The hydroboration of **12** followed by treatment with alkaline hydrogen peroxide afforded (±)-**4** in 79% yield.

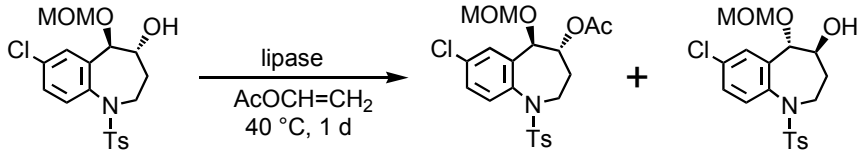
Scheme 2



11 **12** (±)-**4**

The screening tests of a variety of lipases on their catalyzed transesterification of (±)-**4** were carried out, and the results are listed in Table 1. Most of the lipases were inactive on this reaction (Entries 1–4 and 6), however, lipase QLM showed a good reactivity and selectivity (Entry 5).

Table 1 Screening tests of lipases on their catalyzed transesterification of (±)-**4**[a]



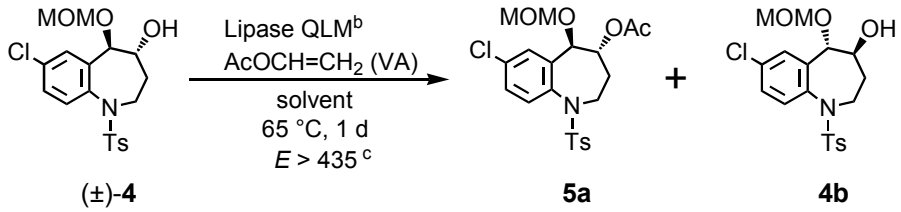
(±)-**4** **5a** **4b**

Entry	Lipase[b]	Acetate (**5a**)		Alcohol (**4b**)		*E* value[c]
		Yield (%)[d]	% ee	Yield (%)[d]	% ee	
1	AK Amano	2	95	98	2	40
2	AL	1	87	99	1	15
3	OF	<1	51	>99	0.1	3
4	PL	8	98	92	8	107
5	**QLM**	**43**	**>99**	**57**	**76**	**>459**
6	Novozym 435	1	93	99	1	28

a. All reactions were carried out by stirring a mixture of the substrate (20 mg) and lipase (20 mg) in vinyl acetate (2 mL) at 40 °C for 1 day.
b. AK Amano (Amano enzyme Inc., *Pseudomonas fluorescens*), AL (Meito sangyo, *Achromobacter sp.*), OF (Meito sangyo, *Candida cylindracea*), PL, QLM (Meito Sangyo, *Alcaligenes sp.*), Novozym 435 (Novo Nordisk, *Aspergillus orizae*).
c. The *E* value is the ratio of the specificity constant of two enantiomers calculated according to ref. 4.
d. Calculated yield.

As the next tests, we examined the solvent effect using lipase QLM as the catalyst at its enzymatic optimum temperature (65 °C). The results of these experiments under the various conditions of solvent type and the ratio of solvent and vinyl acetate are summarized in Table 2. Althrough the solvent effect was slight, to reduce the amount of vinyl acetate, we selected isopropyl ether as the solvent for preparation of the chiral alcohol (**4b**) (Entry 5) and acetonitrile as the solvent for preparation of the chiral acetate (**5a**) (Entry 13).

Table 2 Lipase-catalyzed transesterification of (±)-**4** in organic solvent [a]

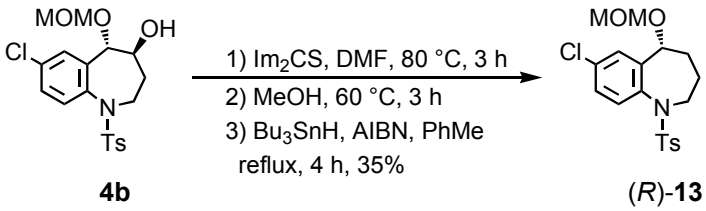


(±)-**4** **5a** **4b**

Entry	Solvent (Solvent / VA)	Acetate (**5a**) Yield (%)[d]	Acetate (**5a**) % ee	Alcohol (**4b**) Yield (%)[d]	Alcohol (**4b**) % ee
1	none	50	98.4	50	99.1
2	Hexane (1/1)	50	98.0	50	99.6
3	(3/1)	51	97.2	49	99.6
4	*iso*-Pr_2O (1/1)	51	97.8	49	99.6
5	(3/1)	51	96.7	**49**	**>99.9**
6	CCl_4 (1/1)	50	98.7	50	99.1
7	(3/1)	50	98.9	50	99.6
8	PhMe (1/1)	50	98.7	50	99.7
9	(3/1)	50	99.1	50	99.6
10	AcOEt (1/1)	50	98.6	50	99.6
11	(3/1)	50	97.8	50	99.2
12	CH_3CN (1/1)	50	99.3	50	98.6
13	(3/1)	**50**	**99.7**	50	99.4

a. All reactions were carried out by stirring a mixture of the substrate (20 mg) and Lipase QLM (20 mg) in a vinyl acetate-solvent (2 mL) at 65 °C for 1 day.
b. Meito Sangyo, *Alcaligenes sp.*.
c. The *E* value is the ratio of the specificity constant of two enantiomers calculated according to ref. 4.
d. Calculated yield.

The absolute configurations of the newly formed chiral carbon atoms in the above optically active compounds were determined as follows. The alcohol (**4b**), which was not an acetylated compound based on the above enzymatic reactions, was treated with 1,1'-thiocarbonyldiimidazole followed by the addition of MeOH, and then reduced by tributyltin hydride in the presence of AIBN to give the known (*R*)-**13**[3d] in 35% yield (Eq. 1). Therefore, **4b** and **5a** were assigned the (4*S*,5*S*) and the (4*R*,5*R*) configurations, respectively.

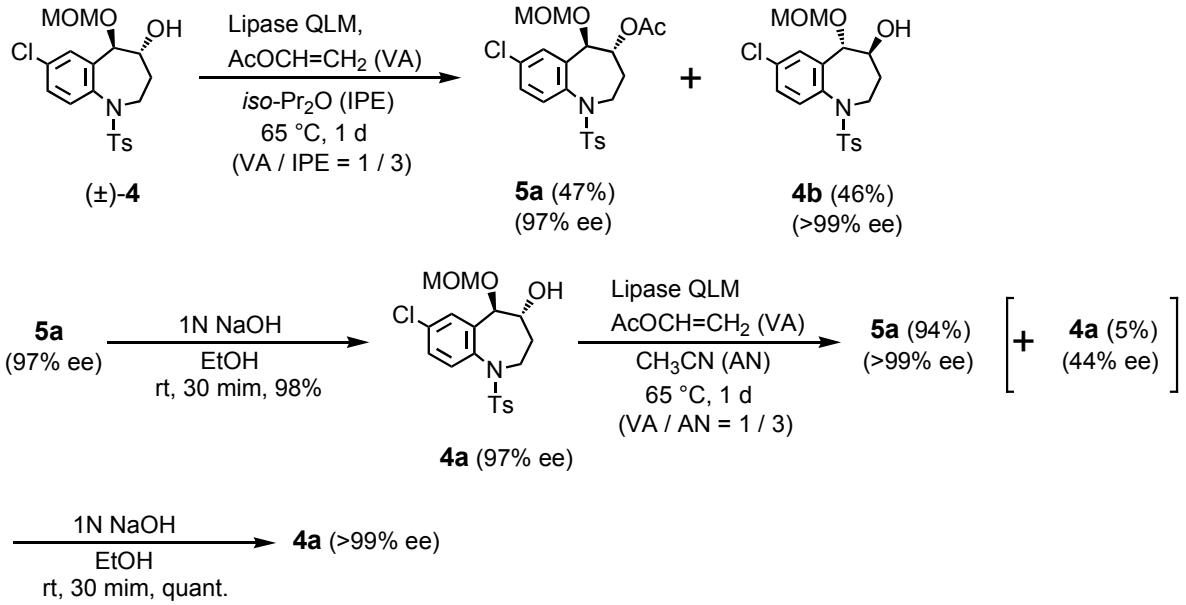


4b (*R*)-**13** (Eq. 1)

Next, the optimal conditions were applied to the preparative scale reaction (Scheme 3). The racemate [(±)-**4**] was kinetically acetylated in the presence of lipase QLM [10 weight % of (±)-**4**] in a mixture of

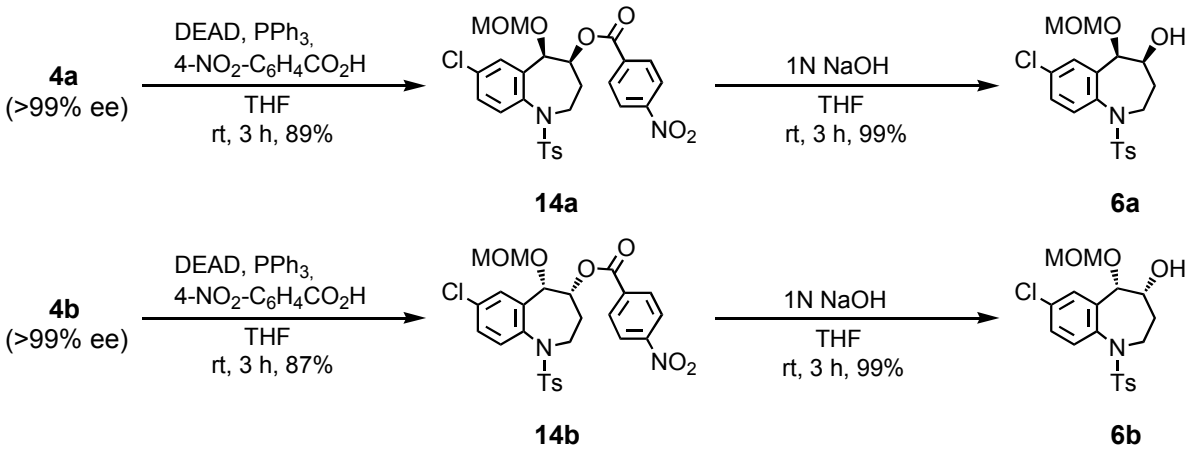
vinyl acetate and isopropyl ether (1:3, 10 times volume) at 65 °C for 1 day to give the acetylated product (**5a**, 97% ee) in 47% yield and the optically pure alcohol (**4b**, >99% ee) in 46% yield. The hydrolysis of **5a** gave **4a** (97%ee) in 98% yield. To increase the optical purity, **4a** was treated with lipase QLM (20 weight %) in a mixture of vinyl acetate and acetonitrile (1:3, 10 times volume) at 65 °C for 1 day to afford **5a** (>99% ee, 94% yield) and **4a** (44% ee, 5% yield). The optically pure alcohol (**4a**) (>99% ee) was obtained by the hydrolysis of **5a** (>99% ee).

Scheme 3



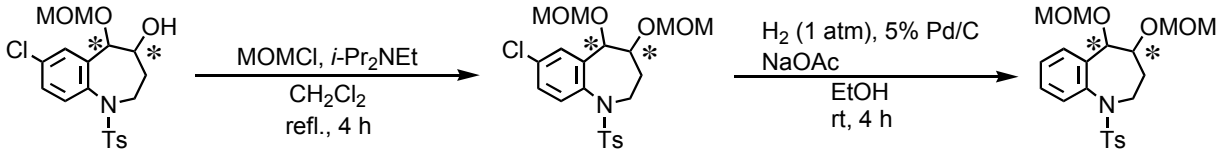
Secondly, in order to apply the above-mentioned resolution system to the synthesis of the *cis*-4,5-dihydroxybenzazepine derivatives, we investigated the isomerization of the *trans*-compounds (**4a**,**b**) utilizing the Mitsunobu reaction (Scheme 4). The chiral alcohols (**4a**,**b**) reacted with 4-nitrobenzoic acid in the presence of triphenylphosphine and diethyl azodicarboxylate (DEAD) to give the 4-nitrobenzoates (**14a**,**b**) in good yields. The chiral *cis*-compounds (**6a**,**b**) were quantitatively obtained by hydrolysis of the corresponding esters (**14a**,**b**).

Scheme 4



As the available intermediates for the compounds (**2a**,**b** and **3a**,**b**), we synthesized the corresponding 4,5-bismethoxymethoxy compounds (Scheme 5). The monomethoxymethoxy compounds (**4a**,**b** and **6a**,**b**) were treated with MOMCl in the presence of diisopropylethylamine to give the bismethoxymethoxy compounds (**7** and **8**) for the intermediates of **2a** and **3a**. The hydrogenation of **7** and **8** in the presence of 5% Pd/C and sodium acetate afforded the dechlorination compounds (**9** and **10**) for the intermediates of **2b** and **3b**.

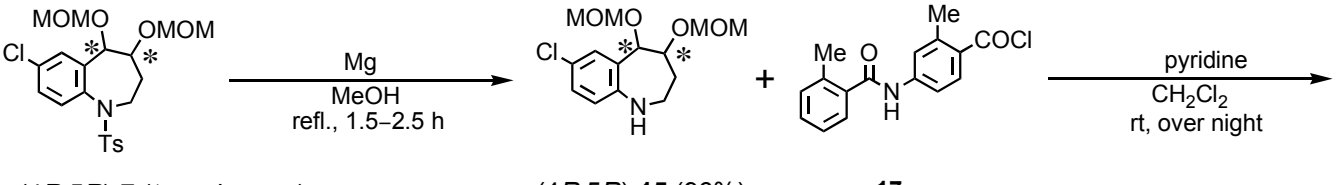
Scheme 5



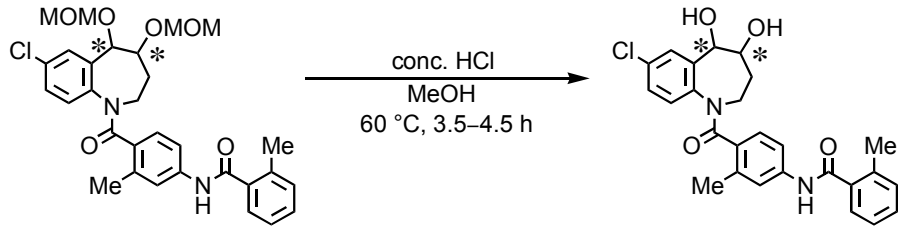
4a [*trans*-, (4*R*,5*R*)] (4*R*,5*R*)-**7** (97%) (4*R*,5*R*)-**9** (97%)
4b [*trans*-, (4*S*,5*S*)] (4*S*,5*S*)-**7** (93%) (4*S*,5*S*)-**9** (97%)
6a [*cis*-, (4*S*,5*R*)] (4*S*,5*R*)-**8** (98%) (4*S*,5*R*)-**10** (98%)
6b [*cis*-, (4*R*,5*S*)] (4*R*,5*S*)-**8** (97%) (4*R*,5*S*)-**10** (99%)

Finally, we accomplished the first synthesis of the optically active metabolites (**2a** and **3a**) of tolvaptan (**1**), as shown in Scheme 6. Detosylation of **7** and **8** using magnesium in MeOH quantitatively afforded **15** and **16**, respectively. Acylation of these compounds (**15** and **16**) with the acid chloride (**17**) followed by removal of the bismethoxymethyl ether moieties gave the target compounds [(4*R*,5*R*)-**2a**, (4*S*,5*S*)-**2a**, (4*S*,5*R*)-**3a** and (4*R*,5*S*)-**3a**]. Regarding the previously reported chiral compounds (**2b** and **3b**), we have also applied a similar procedure.

Scheme 6



(4*R*,5*R*)-**7** (*trans* isomer) (4*R*,5*R*)-**15** (96%) **17**
(4*S*,5*S*)-**7** (4*S*,5*S*)-**15** (93%)
(4*S*,5*R*)-**8** (*cis* isomer) (4*S*,5*R*)-**16** (99%)
(4*R*,5*S*)-**8** (4*R*,5*S*)-**16** (99%)



(4*R*,5*R*)-**18** (81%) (4*R*,5*R*)-**2a** (83% yield, >99% ee) (*trans* diol)
(4*S*,5*S*)-**18** (85%) (4*S*,5*S*)-**2a** (82% yield, >99% ee)
(4*S*,5*R*)-**19** (86%) (4*S*,5*R*)-**3a** (87% yield, >99% ee) (*cis* diol)
(4*R*,5*S*)-**19** (83%) (4*R*,5*S*)-**3a** (89% yield, >99% ee)

In conclusion, we have established the efficient synthesis of optically active 4,5-dihydroxybenzazepine compounds utilizing the lipase-catalyzed kinetic resolution of (±)-**4**. The enzymatic esterification of (±)-**4** proceeded with excellent enantioselectivities. The Mitsunobu reaction of the chiral *trans*-compounds (**4a**,**b**) was applicable for the synthesis of the corresponding *cis*-isomers (**6a**,**b**). In this manner, we succeeded in the syntheses of all four diastereomers of the 4,5-dihydroxybenzazepine derivatives by derivation from the racematic compound [(±)-**4**].

EXPERIMENTAL

All melting points were determined using a Yamato MP-21 apparatus and are uncorrected. The IR spectra were obtained using a Perkin-Elmer Spectrum 1000 FT-IR spectrophotometer. The ^{1}H NMR (250 MHz) and ^{13}C NMR (62.5 MHz) spectra were recorded by a Bruker AVANCE DPX 250 spectrometer. Chemical shifts are given in δ values (ppm) using tetramethylsilane (TMS) as the internal standard. The HRMS spectra were recorded by a JEOL JMS-SX 102A mass spectrometer. Optical rotations were measured using a JASCO DIP-370 digital polarimeter. Elemental analyses were performed using a Yamaco CHN CORDER MT-5. All reactions were monitored by TLC employing a 0.25 mm silica gel plate (Merck 5715; 60 F_{254}) and/or a 0.20 mm NH-silica gel plate (Fuji Silysia Chemical; NH). Column chromatography was carried out on silica gel [Kanto Chemical Silica Gel 60 (spherical); 63-210 μm and Biotage KP-Sil^{TM} Silica; 40-63 μm] and NH-silica gel (Fuji Silysia Chemical Chromatorex NH-DM1020; 100 μm). All reagents were used as purchased.

7-Chloro-5-methoxymethoxy-1-(*p*-toluenesulfonyl)-2,3-dihydro-1*H*-1-benzazepine (12)

A solution of sodium 1,1,1,3,3,3-hexamethyldisilazide (NHMDS) in THF (1.0 M, 6.9 mL, 6.9 mmol) was added to a stirring solution of 7-chloro-5-oxo-1-(*p*-toluenesulfonyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine (**11**) (2.0 g, 5.7 mmol) in THF (20 mL) and DMPU (20 mL) at –78°C under a nitrogen atmosphere, and the mixture was stirred at –78°C for 1 h. Chloromethyl methyl ether (MOMCl, 0.53 mL, 7.0 mmol) was added to the above mixture and the mixture was stirred at –78°C for 30 mim and then rt for 30mim. The reaction mixture was poured into a saturated $NaHCO_3$ solution and then extracted with AcOEt. The extract was washed with water (2 times) and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, hexane/AcOEt = 17/3 – 4/1) to give **12** (2.2 g, 98%) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ (ppm): 2.25 (2H, q, *J* = 6.3 Hz), 2.38 (3H, s), 3.36 (3H, s), 3.84-4.05 (2H, m), 4.60 (2H, s), 5.14 (1H, t, *J* = 6.3 Hz), 7.13-7.22 (2H, m), 7.31 (1H, dd, *J* = 2.5, 8.3 Hz), 7.40-7.55 (4H, m, including 7.48, d, *J* = 2.5 Hz and 7.51, d, *J* = 8.5 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 21.4, 25.4, 54.1, 56.0, 94.5, 105.1, 127.1, 127.6, 128.7, 129.2, 132.2, 133.8, 135.5, 136.2, 137.4,

142.9, 149.7. IR (neat): 2946, 2890, 1645, 1482, 1347, 1162, 1090, 1019, 814, 668 cm^{-1}. HRFAB-MS calcd for $C_{19}H_{21}NO_4ClS$ $(M+H)^+$: 394.0880, found: 394.0904.

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

A solution of borane-THF complex (0.92 mol/L, 12 mL, 11 mmol) was added to a stirring solution of **12** (2.2 g, 5.6 mmol) in THF (25 mL) at rt under a nitrogen atmosphere and the mixture was stirred overnight at rt. 1N NaOH solution (12 mL) and 30% H_2O_2 (12 mL) were added and the mixture was stirred at rt for 7.5 h. The reaction mixture was poured into water and extracted with AcOEt (2 times). The extract was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, hexane/AcOEt = 7/3 – 13/7) to give (±)-**4** (1.8 g, 79%) as a colorless viscous oil. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.51-1.72 (1H, m), 1.80-1.98 (1H, m), 2.41 (3H, s), 3.28-3.55 (6H, m, including 3.36, s), 3.57-3.69 (1H, m), 3.98-4.16 (2H, m, including 4.06, d, J = 6.5 Hz), 4.54 (1H, d, J = 6.5 Hz), 7.23-7.32 (3H, m), 7.33-7.38 (1H, m), 7.43 (1H, d, J = 8.5 Hz), 7.54-7.63 (2H, m). ^{13}C NMR ($CDCl_3$) δ (ppm): 21.4, 31.0, 44.2, 56.0, 70.2, 81.6, 96.8, 125.4, 126.9, 128.4, 129.8, 131.9, 133.5, 133.7, 137.0, 138.5, 143.8. IR (neat): 3530, 2947, 2890, 1483, 1348, 1162, 1104, 1040, 667 cm^{-1}. HRFAB-MS calcd for $C_{19}H_{22}NO_5ClS$ M^+: 411.0907, found: 411.0905.

General procedure of screening test on the reaction of lipase-catalyzed transesterification

A mixture of (±)-**4** (20 mg) and lipase (20 mg) in vinyl acetate (2 mL) or in a mixture of vinyl acetate and solvent (2 mL, the ratio of 1/1 or 1/3) was stirred at the appropriate temperature (40 or 65°C) for 1 day. The mixture was filtered and the insoluble material washed with AcOEt. The filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, hexane/AcOEt = 7/3 – 1/1) to give **5a** and **4b**. The obtained **5a** and **4b** were analyzed by HPLC using CHIRALCEL OJ-R (CH_3CN/H_2O = 9/11) and CHIRALCEL OD (hexane/*iso*-PrOH = 9/1).

(*R*)-7-Chloro-5-methoxymethoxy-1-(*p*-toluenesulfonyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine [(*R*)-13]

A solution of **4b** (92 mg, 0.22 mmol) and 1,1'-thiocarbonyldiimidazole (120 mg, 0.673 mmol) in DMF (2 mL) was stirred at 80°C for 3 h. After evaporation of DMF, MeOH (4 mL) was added to the mixture and the solution was stirred at 60°C for 3 h. After removal of MeOH, the residue was purified by column chromatography (silica gel; eluent, hexane/AcOEt = 9/1 – 3/1) to give the xanthate as a colorless oil. A solution of the above-mentioned product, tributyltin hydride (0.10 mL, 0.37 mmol) and AIBN (3.0 mg, 18 μmol) in PhMe (4 mL) was refluxed for 4 h under an argon atmosphere. After removal of PhMe, the

residue was purified by column chromatography (silica gel; eluent, hexane/CH_2Cl_2/AcOEt = 23/10/1 – 67/27/1 and then NH-silica gel; eluent, hexane/AcOEt = 9/1 – 4/1) to give (*R*)-**13** (30 mg, 35%) as a colorless oil. $[\alpha]_D^{26}$ = +42° (c 1.5, $CHCl_3$) [lit.,[3d] $[\alpha]_D^{27}$ = +38.6° (c 1.0, $CHCl_3$)]. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.37-1.79 (2H, m), 1.81-2.04 (2H, m), 2.41 (3H, s), 2.99-3.23 (1H, m), 3.28 (3H, s), 3.97-4.27 (2H, m), 4.31 (1H, d, *J* = 6.8 Hz), 4.53 (1H, d, *J* = 6.8 Hz), 7.20 (1H, dd, *J* = 2.5, 8.5 Hz), 7.23-7.34 (3H, m), 7.42 (1H, d, *J* = 2.5 Hz), 7.56-7.66 (2H, m). HRFAB-MS calcd for $C_{19}H_{22}NO_4ClS$ M^+: 395.0958, found: 395.0939.

Preparative scale resolution of (±)-4

A mixture of (±)-**4** (3.02 g, 7.33 mmol), lipase QLM (300 mg) in vinyl acetate–*iso*-Pr_2O (30 mL, the ratio of 1/3) was stirred at 65°C for 1day. The reaction mixture was filtered through a pad of Celite and the insoluble material was washed with AcOEt. The filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (NH-silicagel; eluent, CH_2Cl_2 and then silica gel; eluent, hexane/AcOEt = 4/1 – 1/1) to give **5a** (1.58 g, 47%) as a colorless viscous oil and **4b** (1.40 g, 46%) as a colorless viscous oil, which were **5a** (97%ee) and **4b** (>99%ee) by HPLC analysis using the above-mentioned conditions, respectively.

1N NaOH solution (5.2 mL) was added to a solution of **5a** (97%ee, 1.58 g, 3.48 mmol) in EtOH (16 mL) and the mixture was stirred at rt for 30 mim. The reaction mixture was poured into water and then extracted with AcOEt. The extract was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (NH-silica gel; eluent, CH_2Cl_2) to give **4a** (1.41 g, 98%, 97%ee) as a colorless viscous oil.

A mixture of **4a** (97%ee, 1.41 g, 3.42 mmol), lipase QLM (280 mg) in vinyl acetate–CH_3CN (14 mL, the ratio of 1/3) was stirred at 65°C for 1day. The reaction mixture was filtered through a pad of Celite and the insoluble material was washed with AcOEt. The filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (NH-silicagel; eluent, CH_2Cl_2 and then silica gel; eluent, hexane/AcOEt = 7/3 – 1/1) to give **5a** (1.46 g, 94%, >99%ee) as a colorless viscous oil and **4a** (73 mg, 5%, 44%ee) as a colorless viscous oil.

1N NaOH solution (4.4 mL) was added to a solution of **5a** (>99%ee, 1.34 g, 2.95 mmol) in EtOH (14 mL) and the mixture was stirred at rt for 30 mim. The reaction mixture was poured into water and then extracted with AcOEt. The extract was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (NH-silica gel; eluent, CH_2Cl_2) to give **4a** (1.21 g, quant., >99%ee) as a colorless viscous oil. The spectral data are listed below.

(4*R*,5*R*)-7-Chloro-4-hydroxy-5-methoxymethoxy-1-(*p*-toluenesulfonyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine (4a)

$[\alpha]_D^{28}$ = –75° (c 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$) δ (ppm): 1.51-1.73 (1H, m), 1.82-1.97 (1H, m), 2.41 (3H, s), 3.30-3.56 (6H, m, including 3.36, s), 3.56-3.69 (1H, m), 3.97-4.15 (2H, m, including 4.07, d, *J* = 6.5 Hz), 4.54 (1H, d, *J* = 6.5 Hz), 7.23-7.32 (3H, m), 7.33-7.38 (1H, m), 7.44 (1H, d, *J* = 8.5 Hz), 7.54-7.63 (2H, m). ^{13}C NMR ($CDCl_3$) δ (ppm): 21.5, 31.1, 44.2, 56.0, 70.3, 81.7, 96.9, 125.4, 126.9, 128.4, 129.8, 132.0, 133.5, 133.8, 137.1, 138.5, 143.8. IR (neat): 3522, 2948, 2890, 1484, 1348, 1163, 1104, 1041, 668 cm^{-1}. HRFAB-MS calcd for $C_{19}H_{22}NO_5ClS$ M^+: 411.0907, found: 411.0905.

(4*S*,5*S*)-7-Chloro-4-hydroxy-5-methoxymethoxy-1-(*p*-toluenesulfonyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine (4b)

$[\alpha]_D^{27}$ = +76° (c 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$) δ (ppm): 1.51-1.72 (1H, m), 1.81-1.97 (1H, m), 2.41 (3H, s), 3.29-3.55 (6H, m, including 3.36, s), 3.56-3.68 (1H, m), 3.99-4.15 (2H, m, including 4.07, d, *J* = 6.5 Hz), 4.54 (1H, d, *J* = 6.5 Hz), 7.22-7.32 (3H, m), 7.33-7.38 (1H, m), 7.43 (1H, d, *J* = 8.5 Hz), 7.53-7.64 (2H, m). IR (neat): 3524, 2947, 2890, 1484, 1348, 1163, 1104, 1040, 668 cm^{-1}. HRFAB-MS calcd for $C_{19}H_{22}NO_5ClS$ M^+: 411.0907, found: 411.0905.

(4*R*,5*R*)-4-Acetoxy-7-chloro-5-methoxymethoxy-1-(*p*-toluenesulfonyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine (5a)

$[\alpha]_D^{27}$ = –129° (c 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$) δ (ppm): 1.63-2.13 (5H, m, including 2.03, s), 2.42 (3H, s), 3.24 (3H, s), 3.46-3.95 (2H, m), 4.15-4.32 (2H, m, including 4.19, d, *J* = 6.8 Hz), 4.39 (1H, d, *J* = 6.8 Hz), 4.77-4.99 (1H, m), 7.23-7.37 (4H, m), 7.40 (1H, d, *J* = 8.5 Hz), 7.58-7.70 (2H, m). IR (neat): 2945, 2846, 1741, 1484, 1351, 1240, 1166, 1094, 1046, 667 cm^{-1}. HRFAB-MS calcd for $C_{21}H_{24}NO_6ClS$ M^+: 453.1013, found: 453.0980.

(4*S*,5*R*)-7-Chloro-5-methoxymethoxy-4-(*p*-nitrobenzoyloxy)-1-(*p*-toluenesulfonyl)-2,3,4,5-tetra-hydro-1*H*-1-benzazepine (14a)

Diethyl azodicarboxylate (40 wt% in PhMe, 1.8 mL, 4.0 mmol) was added to a solution of **4a** (844 mg, 2.05 mmol), 4-nitrobenzoic acid (682 mg, 4.08 mmol) and PPh_3 (1.07 g, 4.08 mmol) in THF (17 mL) and the mixture was stirred at rt for 3 h under an argon atmosphere. The reaction mixture was poured into a saturated $NaHCO_3$ solution and extracted with AcOEt. The extract was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, hexane/AcOEt = 4/1 – 7/3 and then NH-silica gel; eluent, CH_2Cl_2) to give **14a** (1.02 g, 89%) as a colorless amorphous solid. $[\alpha]_D^{27}$ = +46° (c 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$) δ (ppm): 1.96-2.57 (5H, m, including, 2.44, s), 3.03-3.58 (4H, m, including 3.31, s), 3.91-4.45 (2H, m, including 4.40, d, *J* = 6.8 Hz), 4.48-4.68 (2H, m, including 4.61, d, *J* = 6.8 Hz), 5.39-5.58 (1H, m), 7.23-7.37 (4H, m), 7.45-7.55 (1H, m),

7.62-7.72 (2H, m), 7.74-7.91 (2H, m), 8.14-8.24 (2H, m). IR (KBr): 3111, 2952, 1728, 1529, 1348, 1271, 1162, 1101, 1034, 720 cm^{-1}. Anal. Calcd for $C_{26}H_{25}N_2O_8ClS$: C, 55.66; H, 4.49; N, 4.99. Found: C, 55.46; H, 4.35; N, 4.97.

(4*R*,5*S*)-7-Chloro-5-methoxymethoxy-4-(*p*-nitrobenzoyloxy)-1-(*p*-toluenesulfonyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine (14b)

As a colorless amorphous solid, **14b** (913 mg, 87%) was obtained by the same treatment of **4b** (770 mg, 1.87 mmol) as in the case of **14a**. $[\alpha]_D^{27}$ = –47° (c 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$) δ (ppm): 1.96-2.56 (5H, m, including 2.44, s), 3.02-3.59 (4H, m, including 3.31, s), 3.90-4.44 (2H, m, including 4.40, d, *J* = 6.8 Hz), 4.50-4.67 (2H, m, including 4.61, d, *J* = 6.8 Hz), 5.39-5.60 (1H, m), 7.24-7.37 (4H, m), 7.44-7.55 (1H, m), 7.62-7.72 (2H, m), 7.74-7.91 (2H, m), 8.14-8.25 (2H, m). IR (KBr): 3111, 2952, 1728, 1531, 1348, 1271, 1162, 1101, 1034, 720 cm^{-1}. Anal. Calcd for $C_{26}H_{25}N_2O_8ClS$: C, 55.66; H, 4.49; N, 4.99. Found: C, 55.41; H, 4.34; N, 4.96.

(4*S*,5*R*)-7-Chloro-4-hydroxy-5-methoxymethoxy-1-(*p*-toluenesulfonyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine (6a)

1N NaOH solution (3.2 mL) was added to a solution of **14a** (887 mg, 1.58 mmol) in THF (18 mL) and the mixture was stirred at rt for 3 h. The reaction mixture was poured into a saturated $NaHCO_3$ solution and then extracted with AcOEt. The extract was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (NH-silica gel; eluent, CH_2Cl_2) to give **6a** (641 mg, 99%) as a colorless amorphous solid. $[\alpha]_D^{27}$ = –53° (c 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$) δ (ppm): 1.65-1.88 (1H, m), 1.89-2.03 (1H, m), 2.04-2.24 (1H, m), 2.42 (3H, s), 3.20-3.56 (4H, m, including 3.31, s), 3.82-4.12 (2H, m), 4.26 (1H, br s), 4.36 (1H, d, *J* = 6.8 Hz), 4.59 (1H, d, *J* = 6.8 Hz), 7.19-7.33 (4H, m, including 7.23, dd, *J* = 2.3, 8.5 Hz), 7.41 (1H, d, *J* = 2.3 Hz), 7.57-7.67 (2H, m). ^{13}C NMR ($CDCl_3$) δ (ppm): 21.5, 32.7, 44.4, 55.8, 69.1, 78.0, 95.5, 126.8, 127.8, 128.3, 129.8, 130.7, 133.9, 135.6, 137.9, 138.1, 143.8. IR (KBr): 3509, 2950, 2890, 1479, 1344, 1159, 1091, 1034, 918, 840, 722, 665 cm^{-1}. Anal. Calcd for $C_{19}H_{22}NO_5ClS$: C, 55.40; H, 5.38; N, 3.40. Found: C, 55.02; H, 5.21; N, 3.45.

(4*R*,5*S*)-7-Chloro-4-hydroxy-5-methoxymethoxy-1-(*p*-toluenesulfonyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine (6b)

As a colorless amorphous solid, **6b** (568 mg, 99%) was obtained by the same treatment of **14b** (782 mg, 1.39 mmol) as in the case of **6a**. $[\alpha]_D^{27}$ = +53° (c 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$) δ (ppm): 1.67-1.88 (1H, m), 1.89-2.03 (1H, m), 2.04-2.22 (1H, m), 2.42 (3H, s), 3.22-3.56 (4H, m, including 3.31, s), 3.83-4.12 (2H, m), 4.26 (1H, br s), 4.36 (1H, d, *J* = 6.8 Hz), 4.59 (1H, d, *J* = 6.8 Hz), 7.19-7.33 (4H, m, including

7.23, dd, *J* = 2.3, 8.5 Hz), 7.41 (1H, d, *J* = 2.3 Hz), 7.57-7.67 (2H, m). IR (KBr): 3502, 2951, 2890, 1479, 1344, 1160, 1091, 1034, 918, 840, 722, 665 cm^{-1}. Anal. Calcd for $C_{19}H_{22}NO_5ClS$: C, 55.40; H, 5.38; N, 3.40. Found: C, 55.04; H, 5.15; N, 3.39.

(4*R*,5*R*)-4,5-Bis(methoxymethoxy)-7-chloro-1-(*p*-toluenesulfonyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine [(4*R*,5*R*)-7]

A solution of **4a** (525 mg, 1.27 mmol), MOMCl (0.48 mL, 6.3 mmol) and *iso*-Pr_2NEt (1.3 mL, 7.5 mmol) in CH_2Cl_2 (5 mL) was refluxed for 4 h. The reaction mixture was poured into a 0.2 N HCl solution and then extracted with CH_2Cl_2. The extract was washed with a saturated $NaHCO_3$ solution, brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, hexane/AcOEt = 4/1 – 7/3) to give (4*R*,5*R*)-**7** (559 mg, 97%) as a colorless oil. $[\alpha]_D^{27}$ = –78° (c 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$) δ (ppm): 1.44-1.99 (2H, m), 2.41 (3H, s), 3.24 (3H, s), 3.33 (3H, s), 3.53-3.94 (3H, m), 4.01-4.30 (2H, m, including 4.24, d, *J* = 6.5 Hz), 4.36 (1H, d, *J* = 6.5 Hz), 4.62 (1H, d, *J* = 6.8 Hz), 4.67 (1H, d, *J* = 6.8 Hz), 7.18-7.35 (4H, m), 7.36-7.49 (1H, m), 7.56-7.69 (2H, m). IR (neat): 2947, 2890, 1484, 1351, 1165, 1104, 1089, 1033, 667 cm^{-1}. HRFAB-MS calcd for $C_{21}H_{26}NO_6ClS$ M^+: 455.1169, found: 455.1129.

(4*S*,5*S*)-4,5-Bis(methoxymethoxy)-7-chloro-1-(*p*-toluenesulfonyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine [(4*S*,5*S*)-7]

As a colorless oil, (4*S*,5*S*)-**7** (481 mg, 93%) was obtained by the same treatment of **4b** (464 mg, 1.13 mmol) as in the case of (4*R*,5*R*)-**7**. $[\alpha]_D^{27}$ = +76° (c 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$) δ (ppm): 1.43-1.98 (2H, m), 2.41 (3H, s), 3.24 (3H, s), 3.33 (3H, s), 3.52-3.93 (3H, m), 4.00-4.29 (2H, m, including 4.24, d, *J* = 6.5 Hz), 4.36 (1H, d, *J* = 6.5 Hz), 4.62 (1H, d, *J* = 6.8 Hz), 4.67 (1H, d, *J* = 6.8 Hz), 7.19-7.35 (4H, m), 7.37-7.48 (1H, m), 7.56-7.70 (2H, m). IR (neat): 2948, 2892, 1484, 1351, 1165, 1105, 1089, 1034, 667 cm^{-1}. HRFAB-MS calcd for $C_{21}H_{26}NO_6ClS$ M^+: 455.1169, found: 455.1129.

(4*S*,5*R*)-4,5-Bis(methoxymethoxy)-7-chloro-1-(*p*-toluenesulfonyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine [(4*S*,5*R*)-8]

As colorless needles, (4*S*,5*R*)-**8** (547 mg, 98%) was obtained by the same treatment of **6a** (506 mg, 1.23 mmol) as in the case of (4*R*,5*R*)-**7**. $[\alpha]_D^{27}$ = –60° (c 1.0, $CHCl_3$). mp 103-104°C (hexane-CH_2Cl_2). ^1H NMR ($CDCl_3$) δ (ppm): 1.78-1.98 (1H, m), 1.99-2.20 (1H, m), 2.41 (3H, s), 3.10-3.45 (7H, m, including 3.26, s, and 3.30, s), 3.96-4.07 (1H, m), 4.07-4.37 (3H, m, including 4.31, d, *J* = 6.8 Hz), 4.49 (1H, d, *J* = 6.8 Hz), 4.58 (1H, d, *J* = 6.8 Hz), 4.67 (1H, d, *J* = 6.8 Hz), 7.16-7.32 (4H, m, including 7.20, dd, *J* = 2.3, 8.5 Hz), 7.45 (1H, d, *J* = 2.3 Hz), 7.57-7.66 (2H, m). IR (KBr): 2952, 2928, 2896, 1479, 1349, 1161, 1049,

1022, 915, 845, 722, 664 cm^{-1}. Anal. Calcd for $C_{21}H_{26}NO_6ClS$: C, 55.32; H, 5.75; N, 3.07. Found: C, 55.07; H, 5.60; N, 3.06.

(4*R*,5*S*)-4,5-Bis(methoxymethoxy)-7-chloro-1-(*p*-toluenesulfonyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine [(4*R*,5*S*)-8]

As colorless needles, (4*R*,5*S*)-**8** (521 mg, 97%) was obtained by the same treatment of **6b** (487 mg, 1.18 mmol) as in the case of (4*R*,5*R*)-**7**. $[\alpha]_D^{27}$ = +57° (c 1.0, $CHCl_3$). mp 102-104°C (hexane-CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ (ppm): 1.78-1.98 (1H, m), 1.98-2.19 (1H, m), 2.41 (3H, s), 3.11-3.44 (7H, m, including 3.26, s, and 3.30, s), 3.95-4.07 (1H, m), 4.08-4.37 (3H, m, including 4.31, d, *J* = 6.8 Hz), 4.49 (1H, d, *J* = 6.8 Hz), 4.58 (1H, d, *J* = 6.8 Hz), 4.67 (1H, d, *J* = 6.8 Hz), 7.16-7.32 (4H, m, including 7.20, dd, *J* = 2.3, 8.5 Hz), 7.45 (1H, d, *J* = 2.3 Hz), 7.57-7.67 (2H, m). IR (KBr): 2952, 2928, 2896, 1479, 1349, 1160, 1049, 1022, 914, 847, 722, 664 cm^{-1}. Anal. Calcd for $C_{21}H_{26}NO_6ClS$: C, 55.32; H, 5.75; N, 3.07. Found: C, 55.08; H, 5.62; N, 3.07.

(4*R*,5*R*)-4,5-Bis(methoxymethoxy)-1-(*p*-toluenesulfonyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine [(4*R*,5*R*)-9]

A mixture of (4*R*,5*R*)-**7** (350 mg, 0.768 mmol), 5% Pd/C (35 mg) and NaOAc (189 mg, 2.30 mmol) in EtOH (7 mL) was stirred at rt for 4 h under a hydrogen atmosphere. The reaction mixture was filtered and the insoluble material was washed with EtOH. The filtrate was concentrated *in vacuo* and the residue was suspended in AcOEt. The AcOEt suspension was washed with a saturated $NaHCO_3$ solution, brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, hexane/AcOEt = 4/1 – 3/2) to give (4*R*,5*R*)-**9** (315 mg, 97%) as a colorless oil. $[\alpha]_D^{27}$ = –103° (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ (ppm): 1.53-2.04 (2H, m), 2.40 (3H, s), 3.25 (3H, s), 3.33 (3H, s), 3.55-3.92 (3H, m), 4.14-4.42 (3H, m, including 4.26, d, *J* = 6.5 Hz and 4.38, d, J = 6.5 Hz), 4.63 (1H, d, *J* = 6.8 Hz), 4.69 (1H, d, *J* = 6.8 Hz), 7.18-7.37 (5H, m), 7.38-7.52 (1H, m), 7.60-7.71 (2H, m). IR (neat): 2946, 2890, 1348, 1162, 1092, 1032, 920, 765, 716, 662 cm^{-1}. HRFAB-MS calcd for $C_{21}H_{27}NO_6S$ M^+: 421.1559, found: 421.1542.

(4*S*,5*S*)-4,5-Bis(methoxymethoxy)-1-(*p*-toluenesulfonyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine [(4*S*,5*S*)-9]

As a colorless oil, (4*S*,5*S*)-**9** (306 mg, 97%) was obtained by the same treatment of (4*S*,5*S*)-**7** (343 mg, 0.752 mmol) as in the case of (4*R*,5*R*)-**9**. $[\alpha]_D^{27}$ = +106° (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ (ppm): 1.52-2.02 (2H, m), 2.40 (3H, s), 3.25 (3H, s), 3.33 (3H, s), 3.55-3.93 (3H, m), 4.14-4.42 (3H, m,

including 4.26, d, J = 6.5 Hz and 4.38, d, J = 6.5 Hz), 4.63 (1H, d, J = 6.8 Hz), 4.69 (1H, d, J = 6.8 Hz), 7.19-7.37 (5H, m), 7.38-7.51 (1H, m), 7.60-7.71 (2H, m). IR (neat): 2946, 2890, 1349, 1163, 1092, 1033, 918, 766, 716, 662 cm^{-1}. HRFAB-MS calcd for $C_{21}H_{27}NO_6S$ M^+: 421.1559, found: 421.1577.

(4*S*,5*R*)-4,5-Bis(methoxymethoxy)-1-(*p*-toluenesulfonyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine [(4*S*,5*R*)-10]

A mixture of (4*S*,5*R*)-**8** (250 mg, 0.548 mmol), 5% Pd/C (25 mg) and NaOAc (135 mg, 1.65 mmol) in EtOH (5 mL) and THF (1 mL) was stirred at rt for 4 h under a hydrogen atmosphere. The following treatment was carried out the same as in the case of (4*R*,5*R*)-**9** to give (4*S*,5*R*)-**10** (226 mg, 98%) as a colorless oil. $[\alpha]_D^{27}$ = –86° (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ (ppm): 1.80-2.22 (2H, m), 2.41 (3H, s), 3.13-3.54 (7H, m, including 3.27, s, and 3.30, s), 3.88-4.24 (2H, m), 4.34 (1H, d, J = 6.8 Hz), 4.38-4.46 (1H, m), 4.50 (1H, d, J = 6.8 Hz), 4.57 (1H, d, J = 6.8 Hz), 4.70 (1H, d, J = 6.8 Hz), 7.16-7.37 (5H, m), 7.40-7.52 (1H, m), 7.59-7.71 (2H, m). IR (neat): 2948, 2890, 1345, 1161, 1091, 1029, 716 cm^{-1}. HRFAB-MS calcd for $C_{21}H_{27}NO_6S$ M^+: 421.1559, found: 421.1584.

(4*S*,5*S*)-4,5-Bis(methoxymethoxy)-1-(*p*-toluenesulfonyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine [(4*R*,5*S*)-10]

As a colorless oil, (4*R*,5*S*)-**10** (228 mg, 99%) was obtained by the same treatment of (4*R*,5*S*)-**8** (250 mg, 0.548 mmol) as in the case of (4*S*,5*R*)-**10**. $[\alpha]_D^{26}$ = +84° (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ (ppm): 1.80-2.23 (2H, m), 2.41 (3H, s), 3.10-3.55 (7H, m, including 3.27, s, and 3.30, s), 3.90-4.23 (2H, m), 4.34 (1H, d, J = 6.8 Hz), 4.38-4.47 (1H, m), 4.50 (1H, d, J = 6.8 Hz), 4.57 (1H, d, J = 6.8 Hz), 4.70 (1H, d, J = 6.8 Hz), 7.18-7.36 (5H, m), 7.40-7.50 (1H, m), 7.60-7.70 (2H, m). IR (neat): 2949, 2890, 1346, 1161, 1091, 1033, 716 cm^{-1}. HRFAB-MS calcd for $C_{21}H_{27}NO_6S$ M^+: 421.1559, found: 421.1584.

(4*R*,5*R*)-4,5-Bis(methoxymethoxy)-7-chloro-2,3,4,5-tetrahydro-1*H*-1-benzazepine [(4*R*,5*R*)-15]

A mixture of (4*R*,5*R*)-**7** (835 mg, 1.83 mmol) and magnesium (450 mg, 18.5 mg·atm) in MeOH (10 mL) was refluxed for 2.5 h. The reaction mixture was poured into a 10% citric acid solution and then extracted with CH_2Cl_2 (2 times). The extract was washed with a saturated $NaHCO_3$ solution, brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, hexane/AcOEt = 7/3 – 3/2) to give (4*R*,5*R*)-**15** (532 mg, 96%) as a yellow oil. $[\alpha]_D^{26}$ = –164° (c 1.0, MeOH). ^{1}H NMR ($CDCl_3$) δ (ppm): 1.84-2.01 (1H, m), 2.07-2.27 (1H, m), 3.07-3.23 (1H, m), 3.26-3.48 (7H, m, including 3.35, s, and 3.36, s), 3.75 (1H, br s), 3.93-4.04 (1H, m), 4.58 (1H, d, J = 6.8 Hz), 4.63 (1H, d, J = 6.8 Hz), 4.69-4.79 (3H, m, including 4.71, d, J = 6.8 Hz and 4.75, d, J = 6.8 Hz), 6.60 (1H, d, J = 8.3 Hz), 7.05 (1H, dd, J = 2.5, 8.3 Hz), 7.23 (1H, d, J = 2.5 Hz). ^{13}C NMR ($CDCl_3$) δ

(ppm): 30.6, 42.1, 55.56, 55.62, 75.3, 79.1, 94.8, 96.0, 120.4, 124.8, 128.3, 128.4, 130.5, 146.7. IR (neat): 3371, 2947, 2896, 1494, 1151, 1105, 1035, 918, 819 cm^{-1}. HRFAB-MS calcd for $C_{14}H_{20}NO_4Cl$ M^+: 301.1081, found: 301.1078.

(4*S*,5*S*)-4,5-Bis(methoxymethoxy)-7-chloro-2,3,4,5-tetrahydro-1*H*-1-benzazepine [(4*S*,5*S*)-15]

As a yellow oil, (4*S*,5*S*)-**15** (622 mg, 93%) was obtained by the same treatment of (4*S*,5*S*)-**7** (1.01 g, 2.22 mmol) as in the case of (4*R*,5*R*)-**15**. $[\alpha]_D^{26}$ = +163° (c 1.0, MeOH). ^{1}H NMR ($CDCl_3$) δ (ppm): 1.84-2.01 (1H, m), 2.09-2.26 (1H, m), 3.07-3.23 (1H, m), 3.27-3.47 (7H, m, including 3.35, s, and 3.36, s), 3.75 (1H, br s), 3.93-4.04 (1H, m), 4.58 (1H, d, *J* = 6.8 Hz), 4.63 (1H, d, *J* = 6.8 Hz), 4.69-4.82 (3H, m, including 4.71, d, *J* = 6.8 Hz and 4,75, d, *J* = 6.8 Hz), 6.60 (1H, d, *J* = 8.3 Hz), 7.05 (1H, dd, *J* = 2.5, 8.3 Hz), 7.23 (1H, d, *J* = 2.5 Hz). IR (neat): 3370, 2947, 2890, 1493, 1150, 1105, 1034, 918, 819 cm^{-1}. HRFAB-MS calcd for $C_{14}H_{20}NO_4Cl$ M^+: 301.1081, found: 301.1096.

(4*S*,5*R*)-4,5-Bis(methoxymethoxy)-7-chloro-2,3,4,5-tetrahydro-1*H*-1-benzazepine [(4*S*,5*R*)-16]

As a pale yellow oil, (4*S*,5*R*)-**16** (445 mg, 99%) was obtained by the same treatment of (4*S*,5*R*)-**8** (674 mg, 1.48 mmol) as in the case of (4*R*,5*R*)-**15**. $[\alpha]_D^{27}$ = –195° (c 1.0, MeOH). ^{1}H NMR ($CDCl_3$) δ (ppm): 1.92-2.22 (2H, m), 3.02-3.23 (2H, m), 3.37 (3H, s), 3.38 (3H, s), 3.79 (1H, br s), 4.01-4.15 (1H, m), 4.60-4.70 (2H, m), 4.73-4.83 (3H, m), 6.64 (1H, d, *J* = 8.3 Hz), 7.05 (1H, dd, *J* = 2.5, 8.3 Hz), 7.34 (1H, d, *J* = 2.5 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 32.9, 43.3, 55.3, 55.5, 75.4, 79.2, 95.0, 95.3, 120.6, 125.5, 127.8, 129.1, 129.9, 147.2. IR (neat): 3359, 2948, 2890, 1491, 1150, 1100, 1028, 917, 820 cm^{-1}. HRFAB-MS calcd for $C_{14}H_{20}NO_4Cl$ M^+: 301.1081, found: 301.1067.

(4*R*,5*S*)-4,5-Bis(methoxymethoxy)-7-chloro-2,3,4,5-tetrahydro-1*H*-1-benzazepine [(4*R*,5*S*)-16]

As a pale yellow oil, (4*R*,5*S*)-**16** (915 mg, 99%) was obtained by the same treatment of (4*R*,5*S*)-**8** (1.40 g, 3.07 mmol) as in the case of (4*R*,5*R*)-**15**. $[\alpha]_D^{27}$ = +198° (c 1.0, MeOH). ^{1}H NMR ($CDCl_3$) δ (ppm): 1.92-2.22 (2H, m), 3.03-3.23 (2H, m), 3.37 (3H, s), 3.38 (3H, s), 3.79 (1H, br s), 4.01-4.14 (1H, m), 4.61-4.69 (2H, m), 4.74-4.83 (3H, m), 6.63 (1H, d, *J* = 8.3 Hz), 7.05 (1H, dd, *J* = 2.5, 8.3 Hz), 7.34 (1H, d, *J* = 2.5 Hz). IR (neat): 3358, 2947, 2890, 1492, 1149, 1100, 1028, 917, 820 cm^{-1}. HRFAB-MS calcd for $C_{14}H_{20}NO_4Cl$ M^+: 301.1081, found: 301.1096.

(4*R*,5*R*)-4,5-Bis(methoxymethoxy)-7-chloro-1-[2-methyl-4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine [(4*R*,5*R*)-18]

A suspension of 2-methyl-4-(2-methylbenzoylamino)benzoic acid (650 mg, 2.41 mmol), $SOCl_2$ (0.23 mL, 2.7 mmol) and NMP (1 drop) in CH_2Cl_2 (7 mL) was refluxed for 30 mim to give the acid chloride (**17**).

The acid chloride (**17**) solution was added to a solution of (4*R*,5*R*)-**15** (483 mg, 1.60 mmol) and pyridine (2.2 mL, 27 mmol) in CH_2Cl_2 (5 mL) at 0°C and the mixture was stirred overnight at rt. The reaction mixture was poured into a 0.3N HCl solution and then extracted with CH_2Cl_2. The extract was washed with a saturated $NaHCO_3$ solution, brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (NH-silica gel; eluent, hexane/AcOEt = 7/3 – 13/7) to give (4*R*,5*R*)-**18** (717 mg, 81%) as a yellow amorphous solid. $[\alpha]_D^{27}$ = –98° (c 1.0, MeOH). ^{1}H NMR (DMSO-d_6, 100°C) δ (ppm): 1.60-2.12 (2H, m), 2.25-2.44 (6H, m), 3.07-4.31 (9H, m, including 3.29, s, and 3.32, s), 4.56-4.91 (5H, m), 6.68-7.66 (10H, m), 9.86 (1H, br s). IR (KBr): 3289, 1634, 1531, 1487, 1317, 1104, 1034, 918, 734 cm^{-1}. HRFAB-MS calcd for $C_{30}H_{34}N_2O_6Cl$ $(M+H)^+$: 553.2105, found: 553.2103.

(4*S*,5*S*)-4,5-Bis(methoxymethoxy)-7-chloro-1-[2-methyl-4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine [(4*S*,5*S*)-18]

As a yellow amorphous solid, (4*S*,5*S*)-**18** (907 mg, 85%) was obtained by the same treatment of (4*S*,5*S*)-**15** (578 mg, 1.92 mmol) as in the case of (4*R*,5*R*)-**18**. $[\alpha]_D^{27}$ = +98° (c 1.0, MeOH). ^{1}H NMR (DMSO-d_6, 100°C) δ (ppm): 1.60-2.12 (2H, m), 2.27-2.44 (6H, m), 3.09-4.34 (9H, m, including 3.29, s, and 3.32, s), 4.54-4.93 (5H, m), 6.67-7.68 (10H, m), 9.86 (1H, br s). IR (KBr): 3295, 1634, 1532, 1487, 1317, 1104, 1034, 918, 733 cm^{-1}. HRFAB-MS calcd for $C_{30}H_{34}N_2O_6Cl$ $(M+H)^+$: 553.2105, found: 553.2145.

(4*S*,5*R*)-4,5-Bis(methoxymethoxy)-7-chloro-1-[2-methyl-4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine [(4*S*,5*R*)-19]

As a pale yellow amorphous solid, (4*S*,5*R*)-**19** (703 mg, 86%) was obtained by the same treatment of (4*S*,5*R*)-**16** (445 mg, 1.47 mmol) as in the case of (4*R*,5*R*)-**18**. $[\alpha]_D^{27}$ = –156° (c 1.0, MeOH). ^{1}H NMR (DMSO-d_6, 100°C) δ (ppm): 1.83-2.22 (2H, m), 2.35 (3H, s), 2.36 (3H, s), 2.84-4.45 (9H, m, including 3.25, s, and 3.34, s), 4.59 (1H, d, J = 6.5 Hz), 4.67 (1H, d, J = 6.5 Hz), 4.70 (1H, d, J = 6.5 Hz), 4.79-5.07 (2H, m, including 4.85, d, J = 6.5 Hz), 6.70-7.72 (10H, m), 9.87 (1H, br s). IR (KBr): 3289, 1634, 1532, 1486, 1317, 1150, 1102, 1028, 918, 822, 733 cm^{-1}. HRFAB-MS calcd for $C_{30}H_{34}N_2O_6Cl$ $(M+H)^+$: 553.2105, found: 553.2103.

(4*R*,5*S*)-4,5-Bis(methoxymethoxy)-7-chloro-1-[2-methyl-4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine [(4*R*,5*S*)-19]

As a pale yellow amorphous solid, (4*R*,5*S*)-**19** (658 mg, 83%) was obtained by the same treatment of (4*R*,5*S*)-**16** (432 mg, 1.43 mmol) as in the case of (4*R*,5*R*)-**18**. $[\alpha]_D^{27}$ = +159° (c 1.0, MeOH). ^{1}H NMR

(DMSO-d_6, 100°C) δ (ppm): 1.86-2.20 (2H, m), 2.35 (3H, s), 2.36 (3H, s), 2.83-4.44 (9H, m, including 3.25, s, and 3.34, s), 4.59 (1H, d, J = 6.5 Hz), 4.67 (1H, d, J = 6.5 Hz), 4.69 (1H, d, J = 6.5 Hz), 4.78-5.06 (2H, m, including 4.85, d, J = 6.5 Hz), 6.67-7.71 (10H, m), 9.87 (1H, br s). IR (KBr): 3295, 1634, 1532, 1485, 1317, 1150, 1102, 1028, 918, 822, 733 cm^{-1}. HRFAB-MS calcd for $C_{30}H_{34}N_2O_6Cl$ $(M+H)^+$: 553.2105, found: 553.2108.

(4*R*,5*R*)-7-Chloro-4,5-dihydroxy-1-[2-methyl-4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine [(4*R*,5*R*)-2a]

A solution of (4*R*,5*R*)-**18** (679 mg, 1.23 mmol) and conc. HCl (2 mL) in MeOH (10 mL) was stirred at 60°C for 3.5 h. The reaction mixture was poured into water and then extracted with CH_2Cl_2 (2 times). The extract was washed with a saturated $NaHCO_3$ solution, brine, 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 – 20/1) to give (4*R*,5*R*)-**2a** (473 mg, 83%) as a colorless amorphous solid, which was >99% ee by HPLC analysis using CHIRALCEL OD-RH (CH_3CN/MeOH/H_2O = 8/5/7). $[\alpha]_D^{27}$ = –170° (c 1.0, MeOH). ^{1}H NMR (DMSO-d_6, 100°C) δ (ppm): 1.58-2.06 (2H, m), 2.34 (3H, s), 2.36 (3H, s), 2.79-4.39 (3H, m), 4.54-4.81 (2H, m), 5.23-5.47 (1H, m), 6.59-7.66 (10H, m), 9.86 (1H, br s). IR (KBr): 3296, 1634, 1486, 1404, 1318, 1180, 1099, 1055, 910, 821, 733 cm^{-1}. HRFAB-MS calcd for $C_{26}H_{26}N_2O_4Cl$ $(M+H)^+$: 465.1581, found: 465.1582.

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

As a colorless amorphous solid, (4*S*,5*S*)-**2a** (595 mg, 82%, >99% ee) was obtained by the same treatment of (4*S*,5*S*)-**18** (866 mg, 1.57 mmol) as in the case of (4*R*,5*R*)-**2a**. $[\alpha]_D^{27}$ = +167° (c 1.0, MeOH). ^{1}H NMR (DMSO-d_6, 100°C) δ (ppm): 1.60-2.05 (2H, m), 2.34 (3H, s), 2.36 (3H, s), 2.81-4.39 (3H, m), 4.54-4.80 (2H, m), 5.26-5.47 (1H, m), 6.62-7.64 (10H, m), 9.86 (1H, br s). IR (KBr): 3290, 1634, 1487, 1404, 1318, 1180, 1099, 1055, 911, 822, 733 cm^{-1}. HRFAB-MS calcd for $C_{26}H_{26}N_2O_4Cl$ $(M+H)^+$: 465.1581, found: 465.1584.

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

As a colorless amorphous solid, (4*S*,5*R*)-**3a** (436 mg, 87%), which was >99% ee by HPLC analysis using CHIRALCEL OD-RH (CH_3CN/MeOH/H_2O = 8/5/7), was obtained by the same treatment of (4*S*,5*R*)-**19** (596 mg, 1.08 mmol) as in the case of (4*R*,5*R*)-**2a**. $[\alpha]_D^{27}$ = –124° (c 1.0, MeOH). ^{1}H NMR (DMSO-d_6, 100°C) δ (ppm): 1.55-2.14 (2H, m), 2.34 (3H, s), 2.36 (3H, s), 2.71-4.46 (4H, m), 4.78-4.97 (1H, m),

5.21-5.34 (1H, m), 6.60-7.68 (10H, m), 9.86 (1H, br s). IR (KBr): 3298, 1634, 1404, 1317, 1058, 909, 822, 733 cm^{-1}. HRFAB-MS calcd for $C_{26}H_{26}N_2O_4Cl$ $(M+H)^+$: 465.1581, found: 465.1584.

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

As a colorless amorphous solid, (4*R*,5*S*)-**3a** (829 mg, 89%, >99% ee) was obtained by the same treatment of (4*R*,5*S*)-**19** (1.10 g, 1.99 mmol) as in the case of (4*R*,5*R*)-**2a**. $[\alpha]_D^{27}$ = +122° (c 1.0, MeOH). ^{1}H NMR (DMSO-d_6, 100°C) δ (ppm): 1.55-2.16 (2H, m), 2.34 (3H, s), 2.36 (3H, s), 2.69-4.45 (4H, m), 4.78-4.98 (1H, m), 5.20-5.33 (1H, m), 6.59-7.69 (10H, m), 9.86 (1H, br s). IR (KBr): 3290, 1634, 1403, 1317, 1058, 909, 822, 732 cm^{-1}. HRFAB-MS calcd for $C_{26}H_{26}N_2O_4Cl$ $(M+H)^+$: 465.1581, found: 465.1582.

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