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AN EFFICIENT SYNTHESIS OF A KEY INTERMEDIATE FOR VASOPRESSIN V_2 RECEPTOR AGONIST OPC-51803 BY LIPASE-CATALYZED ENANTIOSELECTIVE TRANSESTERIFICATION

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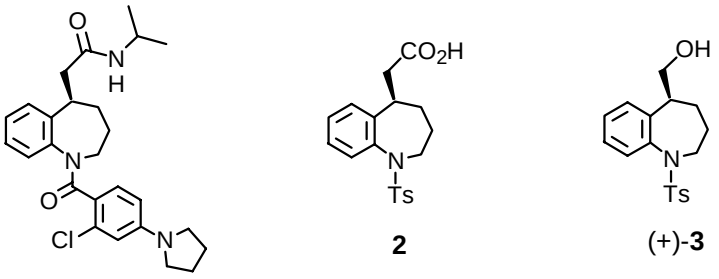
Abstract - An efficient and enantioselective synthesis of (*R*)-[1-(*p*-toluene-sulfonyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-5-yl]acetic acid (**2**), a key inter-mediate in the synthesis of (*R*)-2-{1-[2-chloro-4-(1-pyrrolidinyl)benzoyl]- 2,3,4,5-tetrahydro-1*H*-1-benzazepin-5-yl}-*N*-isopropylacetamide (OPC-51803, **1**), was accomplished. The chiral alcohol [(*S*)-**3**], the precursor of (*R*)-**2**, was separated from the racemic alcohol [(±)-**3**] using the lipase mediated transesterification in vinyl acetate. The obtained (*S*)-**3** was fractionated without using column chromatography and it was converted to **2** without a decrease in the enantiomeric excess.

INTRODUCTION

The benzazepine derivative, (*R*)-2-{1-[2-chloro-4-(1-pyrrolidinyl)benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepin-5-yl}-*N*-isopropylacetamide (OPC-51803, **1**),[1] is a new non-peptide vasopressin V_2 receptor agonist and is now undergoing clinical trials (Figure 1). Shinohara and co-workers have prepared **2** for the synthesis of **1** by the asymmetric hydrogenation of the corresponding 4,5-dehydro compound.[2] On the other hand, for the synthesis of optically active compounds, the separation of a racemate into two enantiomers is also a useful method and particularly, the lipase-catalyzed esterification and hydrolysis are widely utilized for this purpose. Generally, the enzymatic method is available for the optical resolution of secondary alcohols[3,4,5] and their esters[3]. However, for the kinetic resolution of primary alcohols, carboxylic acids and their esters, it is necessary to select an appropriate substrate for this method, because in some instances, the enantioselectivities decrease depends on the relationship between the reaction site and the stereogenic center. Regarding this point, we have recently reported the synthesis of a drug[6] and drug metabolites[7] by the lipase-catalyzed transesterification of a primary alcohol. During the course of the investigation, we have noted the substrate [(±)-**3**], which has a primary hydroxyl group in the immediate neighborhood of the chiral carbon atom, in the enzyme-catalyzed reaction. Herein we wish to describe the synthesis of the optical active compound [(+)-**3**] and the derivation of (+)-**3** to **2**.



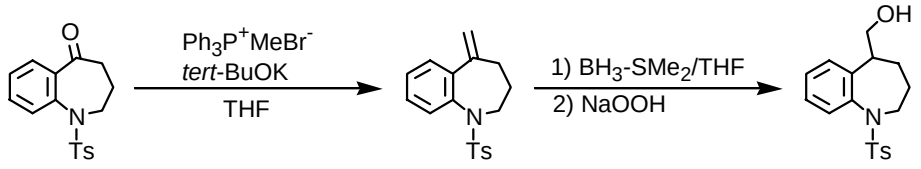
OPC-51803 (**1**) **2** (+)-**3**

Figure 1

RESULTS AND DISCUSSION

First, considerating the effective substrate for the enantioselective kinetic resolution of the primary alcohol, we planned to investigate the lipase-catalyzed transesterification of (±)-**3** having a primary hydroxyl group in the immediate neighborhood of the chiral carbon atom.

The preparation of the substrate [(±)-**3**] is shown in Scheme 1. The Wittig reaction of **4**[8] with methyltriphenylphosphonium bromide and potassium *tert*-butoxide gave the methylene compound (**5**). Hydroboration of **5** with the borane-methyl sulfide complex followed by treatment with alkaline hydrogen peroxide afforded the hydroxymethyl compound [(±)-**3**] in quantitative yield.

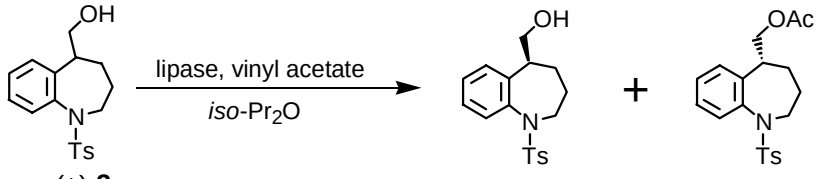


4 **5** (±)-**3**

Scheme 1

Various lipases were examined in the reaction with the primary alcohol [(±)-**3**] (Table 1). Based on the screening test, Lipase QL showed a good selectivity at 5 °C (Entry 1).

Table 1 Lipase-catalyzed transesterification[a]



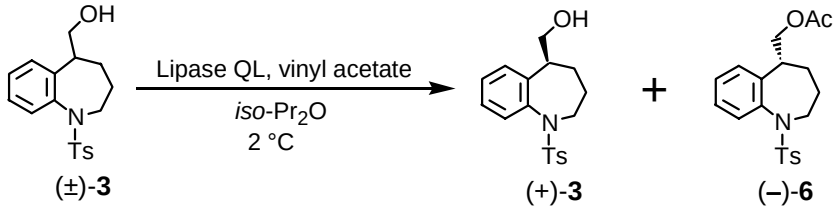
(±)-**3** (+)-**3** (–)-**6**

Entry	Lipase[b]	Temp. (°C)	Time	(+)-**3**		(–)-**6**		E value[e]
				Yield (%)[c]	% ee[d]	Yield (%)[c]	% ee[d]	
1	QL	5	50 min	63	56	37	95	62
2	PL	5	6 h	64	10[f]	36	17[g]	2
3	AY	r.t.	3 h	96	<1	4	16	1
4	Lipozyme IM	r.t.	72 h	77	13	23	44	3
5	Novozym 435	5	6 h	64	24[f]	36	43[g]	3

a. All reactions were carried out by stirring a mixture of substrate (10 mg), lipase (1 mg), and vinyl acetate (0.1 mL) in isopropyl ether (0.5 mL). b. QL, PL (Meito, *Alcaligenes* sp.), AY, Lipozyme IM (Novo Nordisk, *Mucor miehei*), Novozym 435 (Novo Nordisk, *Aspergillus oryzae*) c. Calculated from % ee of both products. d. Enantiomeric purities were determined by HPLC analysis using column packed with CHIRALCEL OJ (eluent: hexane/*iso*-PrOH/diethylamine =700/300/1). e. The E value is the ratio of the specificity constant of two enantiomers caluculated according to ref. 9. f. This compound was (–)-**3a**. g. This compound was (+)-**6**.

Table 2 summarizes the effect of the reaction time using Lipase QL and vinyl acetate in isopropyl ether at 2 °C. The unreacted alcohol [(+)-**3**] and acetate [(–)-**6**] were obtained in 47% yield, >99% ee and 53% yield, 90% ee, respectively, at 3 h (Entry 5).

Table 2 Lipase QL-catalyzed transesterification[a]

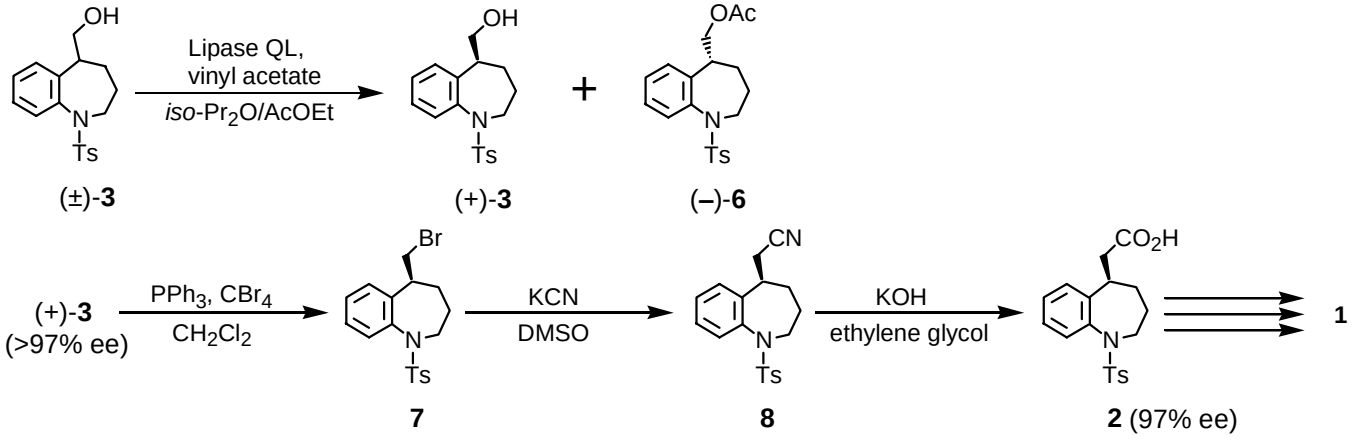


(±)-**3** (+)-**3** (–)-**6**

Entry	Time (h)	(+)-**3** (%)[b]	(% ee)[c]	(–)-**6** (%)[b]	(% ee)[c]
1	0.25	80	25	20	>99
2	0.5	79	42	31	97
3	1.0	57	71	43	95
4	2.0	48	98	52	92
5	3.0	47	>99	53	90
6	5.5	45	>99	55	83

a. All reactions were carried out by stirring a mixture of substrate (20 mg), Lipase QL (2 mg), and vinyl acetate (0.1 mL) in isopropyl ether (1 mL). b. Calculated from % ee of both products. c. Enantiomeric purities were determined by HPLC analysis using column packed with CHIRALCEL OJ (eluent: hexane/*iso*-PrOH/diethylamine = 700/300/1).

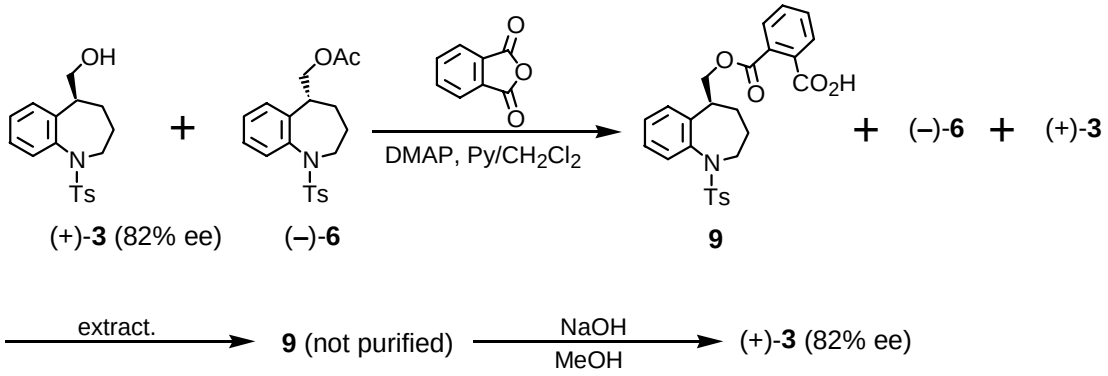
Next, the optimal condition was used for the preparative scale reaction followed by conversion to the carboxylic acid (**2**) (Scheme 2). A mixture of (±)-**3** (16.6 g), Lipase QL (1.3 g, 8 wt%) and vinyl acetate (13.8 mL, 3 eq.) in isopropyl ether was stirred at 0–5 °C for 4 h. The alcohol [(+)-**3**] with a high enantiomeric excess (>99% ee) was obtained in 47% yield. Treatment of (+)-**3** (97% ee) with triphenylphosphine and carbon tetrabromide gave the bromide (**7**) in 80% yield. The bromide (**7**) was reacted with potassium cyanide to give the cyanide compound (**8**) in 85% yield. Hydrolysis of **8** with potassium hydroxide afforded the carboxylic acid (**2**) (97% ee) in quantitative yield. The following derivation of **2** to **1** has already been established. [1]



Scheme 2

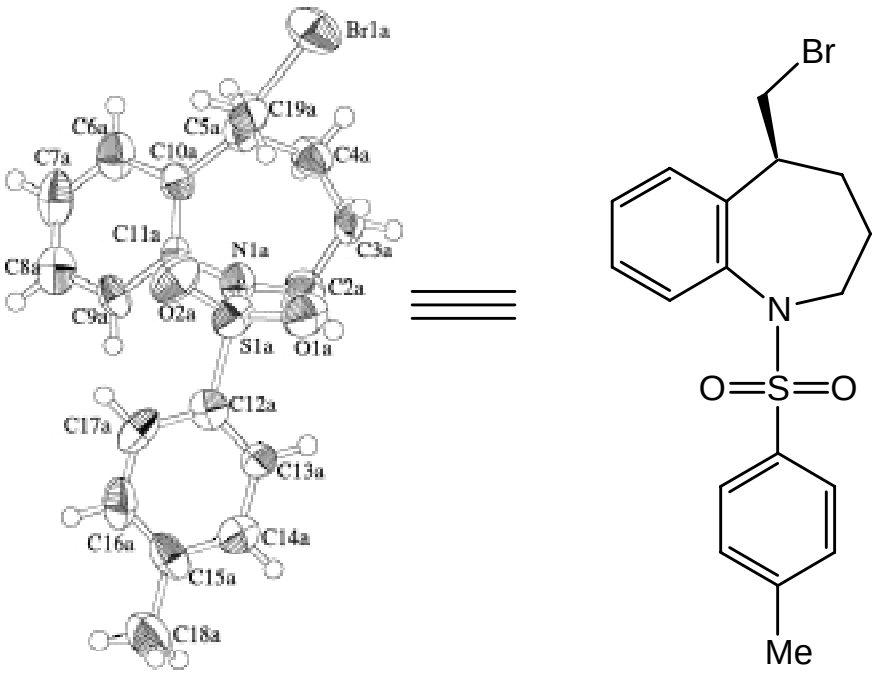
Furthermore, we attempted fractional purification without the use of column chromatography (Scheme 3). The mixture of (+)-**3** (82% ee) and (–)-**6** (70% ee) was treated with phthalic anhydride in the presence of 4-dimethylaminopyridine in pyridine to give the phthalic acid derivative (**9**), the unreacted acetate [(–)-**6**]

and the starting material [(+)-**3**]. The phthalic acid derivative (**9**) was separated from a solution of the reaction mixture in ethyl acetate by extraction with an aqueous potassium carbonate solution. Hydrolysis of the crude **9** with NaOH afforded the alcohol [(+)-**3**] (82% ee) without a decrease in the enantiomeric exess.



Scheme 3

The absolute configurations of these optically active compounds were determined as follows. The bromide (**7**) was subjected to X-Ray crystallographic analysis. A stereoscopic view of **7** is shown in Figure 2. The absolute configuration at C (5) was determined as *S*. Accordingly, the stereochemistry for (+)-**3** was also assigned as *S*. Thus the absolute configurations at C (5) for the isomer (**8**) are assigned as *R* and the isomer (**2**) was in agreement with the recent result.[2]



X-Ray crystal structure for **7**

Figure 2

In conclusion, we have established an efficient synthesis of (*S*)-(+)-5-hydroxymethyl-1-(*p*-toluene-sufonyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine [(*S*)-(+)-**3**] as the key intermediate of OPC-51803 (**1**) using lipase-catalyzed transesterification. The kinetic resolution of (±)-**3** having a chiral carbon atom near the primary hydroxyl group proceeded effectively and the desired isomer easily fractionated without the use

of column chromatography. The obtained (*S*)-(+)-**3** was converted to **2** without a decrease in the enantiomeric exess.

EXPERIMENTAL

Melting points were determined with a Yamato MP-21 apparatus and are uncorrected. The NMR spectra were recorded on Bruker AVANCE DPX 250 spectrometer at 250 MHz. The HRMS were obtained using JEOL JMS-SX 102A mass spectrometers. The IR spectra were recorded on a Perkin-Elmer FT-IR spectrophotometer Spectrum 1000. The optical rotations were measured on a JASCO DPI-370 digital polarimeter. Silica gel (Fuji Silysia Chemical, Ltd., BW-127ZH) was used for the column chromatography. Preparative thin layer chromatography (PLC) was carried out on plate (20 x 20 cm, 0.5 mm thickness) precoated with silica gel ($60F_{254}$, Merck Art 5744).

5-Methylene-1-(*p*-toluenesulfonyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine (5)

Potassium *tert*-butoxide (4.3 g, 38 mmol) was added to a suspension of methyltriphenyphosphonium bromide (14.3 g, 40 mmol) in THF (120 mL) under a nitrogen atmosphere at –5 °C and this mixture was then stirred for 50 mim at the same temperature. Compound (**4)** (6.3 g, 20 mmol) was added to this mixture at 0–5 °C and the reaction mixture was stirred at rt overnight. 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 purified by column chromatography (silica gel; eluent, CH_2Cl_2) to give **5** (6.3 g, quant.) as a colorless crystalline powder, mp 92.5–93.5 °C (hexane). ^{1}H NMR ($CDCl_3$) δ (ppm): 1.75–1.82 (2H, m), 2.20–2.25 (2H, m), 2.38 (3H, s), 3.77–3.82 (2H, m), 4.61 (1H, d, *J*=1.6 Hz), 4.74 (1H, d, *J*=1.6 Hz), 7.13–7.46 (6H, m), 7.47 (2H, d, *J*=8.5 Hz). IR (KBr): 3075, 1632, 1596, 1344, 1158 cm^{-1}. *Anal*. Calcd for $C_{18}H_{19}NO_2S$: C, 68.98; H, 6.11; N, 4.47. Found: C, 69.04; H, 6.01; N, 4.17.

5-Hydroxymethyl-1-(*p*-toluenesulfonyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine [(±)-3]

Borane-methyl sulfide complex (10 mol/L solution, 12.5 mL, 125 mmol) was added dropwise to an ice-cooled solution of **5** (26.0 g, 83 mmol) in THF (220 mL) under a nitrogen atmosphere and the mixture was stirred at rt for 7 h. Water (20 mL), 5N NaOH solution (33 mL) and 30% hydrogen peroxide (19 mL) were then added at 0–5 °C and the reaction mixture was stirred at rt overnight. 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 purified by column chromatography (silica gel; eluent, hexane/AcOEt=2/1) to give (±)-**3** (27.5 g, quant.) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.00–2.25 (4H, br), 2.44 (3H, s), 2.50–3.50 (2H, br), 3.70–4.00 (2H, br), 4.00–4.35 (2H, br), 6.90–7.40 (6H, m), 7.60–7.80 (2H, m). IR (neat): 3526, 1598, 1339, 1155 cm^{-1}. HR-FABMS: Calcd for $C_{18}H_{22}NO_3S$, $[M + H]^+$: 332.1322. Found: 332.1326.

General procedure of lipase-catalyzed transesterification

A mixture of (±)-**3** (10 mg), vinyl acetate (0.1 mL) and lipase (1 mg) in isopropyl ether (0.5 mL) was stirred at 5 °C. The ratio of the substrate and the acetylated product was monitored by HPLC (DAICEL

CHIRALCEL OJ was used for (*S*)-(+)-**3** and (*R*)-(–)-**6** with hexane/*iso*-PrOH/Et_2NH=700/300/1 as the eluent). When about half of the substrate was acetylated, the reaction mixture was filterd and the filtrate was evaporated. The residue was chromatographed on silica gel with a mixed solvent of hexane and AcOEt to afford both the optically active alcohol and the acetylated product.

Preparative scale lipase-catalyzed acetylation of (±)-3

A mixture of (±)-**3** (16.6 g, 50 mmol), Lipase QL (1.3 g) and vinyl acetate (12.9 g, 0.15 mol) in *iso*-Pr_2O (200 mL) and AcOEt (60 mL) was stirred at 0–5 °C for 4 h. The reaction mixture was filtered through a pad of Celite and the insoluble material was washed with CH_2Cl_2. The filtrate was then concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; hexane/AcOEt=3/2 to 1/4) to give (*R*)-**6** (9.9 g, 53%, 86% ee) and (*S*)-(+)-**3** (7.7 g, 47%, >99% ee) as a colorless crystalline powder. A part of (*R*)-**6** (86% ee) was recrystallized with AcOEt/hexane to give (*R*)-(–)-**6** (97.1% ee) as colorless plates. The spectroscopic data of (*S*)-**3** and (*R*)-**6** are as follows:

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

$[\alpha]_D^{25}$ +9.1° (c 1.0, $CHCl_3$), mp 88.5–90 °C. ^{1}H NMR (DMSO-d_6) δ (ppm): 1.20–1.50 (1H, m), 1.60–1.80 (3H, m), 2.41 (3H, s), 2.70–2.90 (1H, m), 3.20–3.40 (1H, m), 3.50–3.80 (3H, m), 4.71 (1H, t, *J*=4.9 Hz), 6.94 (1H, d, *J*=7.5 Hz), 7.00–7.30 (3H, m), 7.43 (2H, d, *J*=8.1 Hz), 7.73 (2H, d, *J*=8.1 Hz). IR (neat): 3518, 1598, 1338, 1155 cm^{-1}. *Anal*. Calcd for $C_{18}H_{21}NO_3S$: C, 65.23; H, 6.39; N, 4.23. Found: C, 65.18; H, 6.30; N, 4.14.

(*R*)-(–)- [1-(*p*-Toluenesulfonyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-5-yl]methyl acetate [(*R*)-6]

$[\alpha]_D^{25}$ –13.7° (c 1.0, $CHCl_3$), mp 97–99 °C. ^{1}H NMR ($CDCl_3$) δ (ppm): 0.80–2.14 (7H, br, including 2.04, s), 2.43 (3H, s), 2.61–3.61 (2H, br), 3.74–4.74 (3H, br, including 4.36, dd, *J*=7.0, 11.0 Hz), 6.98–7.44 (6H, m), 7.68 (2H, d, *J*=7.8 Hz). IR (KBr): 1731, 1597, 1350, 1157 cm^{-1}. *Anal*. Calcd for $C_{20}H_{23}NO_4S$: C, 64.32; H, 6,21; N, 3.75. Found: C, 64.43; H, 6.27; N, 3.77.

(*S*)-(+)-5-Bromomethyl-1-(*p*-toluenesulfonyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine (7)

A solution of (*S*)-**3** (1.3 g, 3.9 mmol), triphenyphosphine (2.1 g, 8.0 mmol) and carbon tetrabromide (2.7 g, 8.1 mmol) in CH_2Cl_2 (50 mL) was stirred at rt for 30 mim. The reaction mixture was poured into saturated $NaHCO_3$ solution and then extracted with CH_2Cl_2. 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/hexane=4/1) and recrystallization from Et_2O/hexane gave **7** (1.3 g, 80%) as colorless needles, which was 97% ee by an HPLC analysis using CHIRALPAK AD-H (eluent, hexane/EtOH=3/2). mp 110–111 °C. $[\alpha]_D^{25}$ +3.6° (c 0.1, MeOH). ^{1}H NMR ($CDCl_3$) δ (ppm):1.00–1.50 (2H, br), 1.50–2.00 (2H, br), 2.44 (3H, s), 2.50–4.50 (5H, br), 7.00–7.50 (6H, m), 7.50–7.80 (2H, m). IR (KBr): 1597, 1345, 1157 cm^{-1}. *Anal.* Calcd for $C_{18}H_{20}NO_2BrS$: C, 54.83; H, 5.11; N, 3.55. Found: C, 54.95; H, 5.09; N, 3.39.

(*R*)-(+)-5-Cyanomethyl-1-(*p*-toluenesulfonyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine (8)

A mixture of **7** (0.83 g, 2.1 mmol) and potassium cyanide (0.27g, 4.2 mmol) in DMSO (9 mL) was stirred at 45–50 °C for 3 h. The reaction mixture was poured into ice-water and then extracted with AcOEt/Et_2O.

The extract was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, hexane/AcOEt=6/1) and recrystallization from AcOEt/hexane gave **8** (0.60 g, 85%) as colorless needles, mp 106 °C. $[\alpha]_D^{25}$ +16.0° (c 0.1, MeOH). ^{1}H NMR ($CDCl_3$) δ (ppm): 1.00–2.00 (4H, br), 2.45 (3H, s), 2.50–4.50 (5H, br), 7.00–7.50 (6H, m), 7.50–8.00 (2H, m). IR (KBr): 2244, 1598, 1327, 1152 cm^{-1}. *Anal*. Calcd for $C_{19}H_{20}N_2O_2S$: C, 67.03; H, 5.92; N, 8.23. Found: C, 67.12; H, 6.00; N, 8.03.

(*R*)-(+)-[1-(*p*-Toluenesulfonyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-5-yl]acetic acid (2)

A mixture of **8** (0.10 g, 0.29 mmol) and potassium hydroxide (84 mg, 1.5 mmol) in ethylene glycol (2 mL) was stirred at 170–175 °C for 6 h. The reaction mixture was poured into water and acidified with 12N HCl. The entire solution was extracted with AcOEt and the extract was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by preparative thin layer chromatography (silica gel; solvent, CH_2Cl_2/MeOH = 9/1) to give **2** (0.11 g, quant.) as a colorless amorphous solid, which was 97% ee by HPLC analysis using CHIRALCEL OJ (eluent, hexane/EtOH/TFA=800/200/3). $[\alpha]_D^{25}$ +2.8° (c 0.5, MeOH). ^{1}H NMR (DMSO-d_6) δ (ppm): 0.71–2.01 (4H, br), 2.40 (3H, s), 2.53–2.74 (2H, m), 2.82–4.48 (3H, br), 6.81–7.08 (1H, m), 7.09–7.32 (3H, m), 7.33–7.52 (2H, m), 7.57–7.88 (2H, m), 12.14 (1H, br s). IR (KBr): 1705, 1599, 1346, 1161 cm^{-1}. HR-FABMS: Calcd for $C_{19}H_{22}NO_4S$, $[M+H]^+$: 360.1271. Found: 360.1292.

The method of fractional purification for lipase-catalyzed transesterification of (±)-3 without column chromatography

A mixture of (*S*)-**3** (99 mg, 0.30 mmol, 82% ee), (*R*)-**6** (112 mg, 0.30 mmol, 70% ee), phthalic anhydride (62 mg, 0.42 mmol), 4-dimethylaminopyridine (cat.) in pyridine (1 mL) and CH_2Cl_2 (2 mL) was stirred at rt overnight. The reaction mixture was poured into water, acidified with 12N HCl and then extracted with AcOEt. The AcOEt solution was extracted with 10% K_2CO_3 solution. The aqueous solution was acidified with 12N HCl and then extracted with CH_2Cl_2. The CH_2Cl_2 solution was dried over Na_2SO_4 and concentrated *in vacuo* to give the crude **9** (120 mg). A solution of the crude **9** (106 mg) and 5N NaOH (5 mL) in MeOH (4 mL) was refluxed for 1.5 h. The reaction mixture was poured into water and then extracted with CH_2Cl_2. The CH_2Cl_2 solution was dried over Na_2SO_4 and concentrated *in vacuo* to give (*S*)-**3** [80 mg, 91% (2 steps), 82% ee] as a colorless oil. The spectroscopic data of the crude **9** is as follows:

(*S*)-Mono-[1-(*p*-toluenesulfonyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-5-yl]methyl phthalate (9)

^{1}H NMR ($CDCl_3$) δ: 1.00–2.20 (4H, br), 2.39 (3H, s), 2.50–4.20 (3H, m), 4.50–4.80 (2H, m), 7.00–7.30 (6H, m), 7.50 –7.60 (2H, m), 7.60–7.80 (4H, m).

X-Ray analysis of 7

Suitable crystals of **7** for an X-Ray diffraction study were grown from a Et_2O/hexane solution. The crystal size 0.5 x 0.4 x 0.3 mm. All data were obtained using a Rigaku AFC-5S automated four circle diffractometer with graphite-monochromated Mo $K\alpha$ radiation. The final lattice parameters were obtained

from a least-squares refinement using 25 reflections. Crystal data: $C_{18}H_{20}NO_2BrS$, M=394.33, monoclinic, space group $P2_1$, a=9.892(2)Å, b=8.747(2)Å, c=20.987(2)Å, β=99.59(1) °, V=1790.4(4)Å^3, Z=4.0, Dx=1.463g/cm^3, F(000)=808, and μ(Mo$K\alpha$)= 24.276 cm^{-1}. The intensities were measured using $\omega/2\theta$ scan up to 50 °, 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. Of the 7009 independent reflections which were collected, all reflections were used for the structure determination and refinement. The structure was solved by the direct method using the TEXSAN crystallographic software package.[10] All non-H atoms were found in the Fourier map. All H atoms were geometrically located and not refined. The refinement of the atomic parameters was carried out by the full matrix least-squares refinement using anisotropic temperature factors for all the non-H atoms. The absorption (transmission factor=0.872–1.00) and decay (–1.93% decline) correlations were applied in the final refinement. The final refinement converged with $R1$=0.043 and Rw=0.152 for 414 parameters. Twenty of the Bijvoet pairs having a large intensity and high measurment accuracy were then selected. The absolute configuration of **7** was determined as *S* by the Bijvoet's anomalous-dispersion method.[11,12]

The Comparison of Observed and Calculated Friedel Pairs

			*F*o			*F*c		
h	*k*	*l*	(+)		(-)	(+)		(-)
1	2	0	147.30	<	480.43	170.57	<	485.63
3	2	0	252.02	<	520.48	304.29	<	564.89
2	1	8	352.77	<	626.16	356.35	<	628.94
1	1	0	286.35	<	394.93	327.48	<	462.91
3	2	-4	902.58	<	1248.22	886.16	<	1255.50
3	3	4	252.17	>	118.57	256.40	>	149.36
3	3	3	2057.20	>	1518.47	2047.50	>	1555.45
2	1	9	1087.85	>	818.49	1061.75	>	763.03
3	1	5	2947.09	>	2264.09	2913.44	>	2316.72
2	3	7	1079.11	>	860.25	1048.06	>	759.27
1	2	5	1528.43	>	1249.79	1553.39	>	1233.33
3	2	3	2256.42	<	2801.69	2281.06	<	2821.07
2	1	3	5742.96	>	4790.01	5674.38	>	4712.39
1	2	-14	209.83	<	255.61	162.88	<	268.57
3	1	7	2678.06	<	3275.18	2509.54	<	3064.18
4	1	-11	1119.23	<	1324.27	1084.01	<	1396.61
2	3	1	2897.32	>	2389.45	2816.79	>	2325.56
2	2	-9	114.30	<	216.13	120.44	<	192.37
6	1	1	3289.94	>	2678.70	3236.39	>	2658.22
5	5	-5	582.34	>	501.33	655.54	>	454.29

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