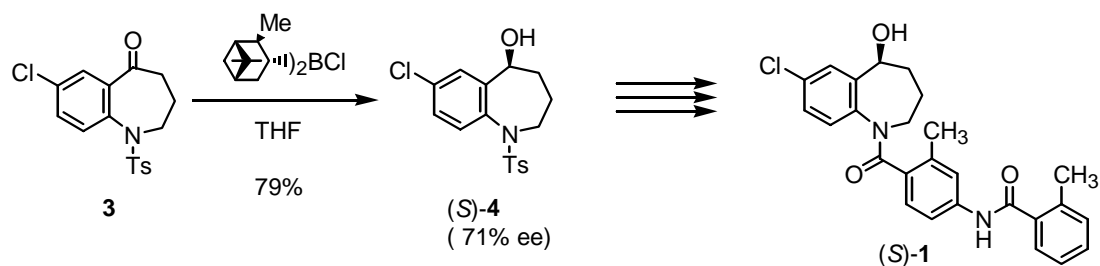




The synthetic method for the optically active compound using the catalytic asymmetric hydrogenation of the corresponding ketone has been generally adopted. Recently, Noyori *et al.* have reported the asymmetric transfer hydrogenation of the aromatic ketone<sup>2</sup> and  $\alpha,\beta$ -acetylenic ketones<sup>3</sup> by the chiral ruthenium (II) complex. We have already reported the asymmetric synthesis of both enantiomers of **1** via the lipase-catalyzed transesterification.<sup>4</sup> In this paper, we wish to report the practical synthesis of the optically active **1** (OPC-41061) by the catalytic asymmetric transfer hydrogenation of the ketone (**2**) which is the precursor of **1**.

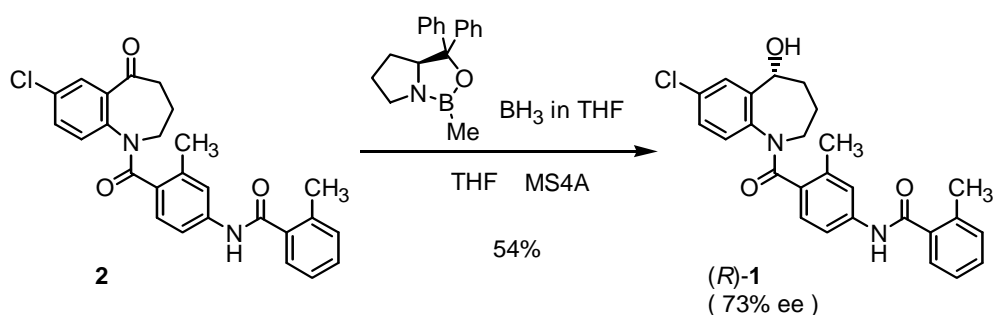
## RESULTS AND DISCUSSION

In order to find the efficient synthesis of the key intermediate ((*S*)-**4**), we investigated the asymmetric reduction of the corresponding ketone (**3**)<sup>4</sup> utilizing the chiral reagents. The asymmetric reduction of **3** with (–)-diisopinocampheylchloroborane,<sup>5</sup> (–)-Ipc<sub>2</sub>BCl, produced (*S*)-**4** in 79% yield and 71% ee. The recrystallization of (*S*)-**4** was then carried out in high enantiomer excess (99% ee). We synthesized the optically active (*S*)-**1** in four steps from (*S*)-**4**.<sup>4</sup> (**Scheme 1**)



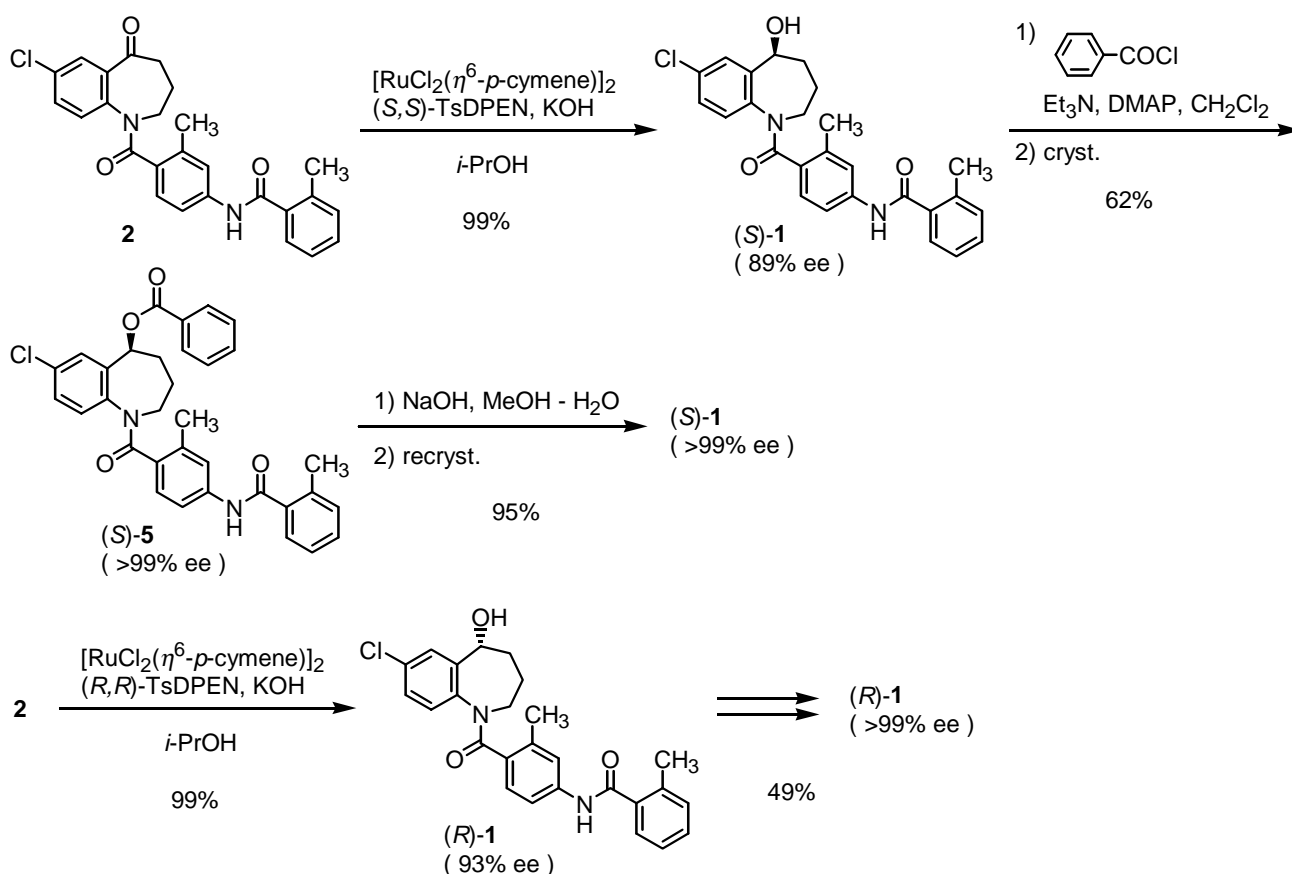
**Scheme 1**

Considering a more efficient synthesis of the optically active **1**, we explored the asymmetric reduction of the ketone (**2**). First, the asymmetric reduction of **2** with (–)-Ipc<sub>2</sub>BCl did not give a good result. Next, the reduction of **2** using Corey's reagent<sup>6</sup> in the presence of MS4A gave (*R*)-**1** in 54% yield and 73% enantiomeric excess. (**Scheme 2**)



**Scheme 2**

Furthermore, we attempted the catalytic asymmetric hydrogenation, which has been generally adopted. The reaction using a solution of **2** in 2-propanol in the presence of  $[\text{RuCl}_2(\eta^6\text{-}p\text{-cymene})]_2$  and (1*S*,2*S*)-*N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine [(*S,S*)-TsDPEN] gave (*S*)-**1** in 99% yield and 89% ee. Because the recrystallization of (*S*)-**1** did not improve the enantiomeric purity, we attempted to purify the benzoyl compound. The alcohol ((*S*)-**1**) (89% ee) prepared by Noyori's method was treated with benzoyl chloride in the presence of triethylamine and DMAP to give the benzoate ((*S*)-**5**). Crystallization from EtOAc gave the optically pure benzoate (>99% ee) in 62% yield. The target compound ((*S*)-**1**) was prepared by the hydrolysis of (*S*)-**5** with sodium hydroxide in 95% yield and >99% ee. On the other hand, the asymmetric reduction of **2** using the (*R,R*)-TsDPEN based Ru catalyst gave (*R*)-**1** in 99% yield and 93% ee. The antipodal enantiomer ((*R*)-**1**) (>99% ee) was obtained by the procedure described for the preparation of (*S*)-**1**.



**Scheme 3**

Thus we accomplished the enantioselective synthesis of the optical isomers of **1** by the catalytic asymmetric hydrogenation. This method was effective for preparing the target compounds with high enantiomeric excess. In conclusion, we have established the practical synthesis of the optically active OPC-41061 ((*S*)-**1**, (*R*)-**1**) by means of the catalytic asymmetric hydrogenation of the ketone (**2**), using chiral Ru (II) catalysts.

## EXPERIMENTAL

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

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

**Asymmetric reduction using (–)-Ipc<sub>2</sub>BCl** A solution of the ketone (**3**) (7.0 g, 20 mmol) in THF (40 mL) was added at –50°C to a solution of (–)-Ipc<sub>2</sub>BCl (7.70 g, 24 mmol) in THF (20 mL) under N<sub>2</sub> atmosphere and the mixture was stirred at 4°C. After 18 h, 10% NaOH aqueous solution (30 mL) and 30% H<sub>2</sub>O<sub>2</sub> aqueous solution (15 mL) were added to the mixture and stirred for 2.5 h at rt. The mixture was extracted with Et<sub>2</sub>O. The extract was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, CH<sub>2</sub>Cl<sub>2</sub>) to give **(S)-4** (5.58 g, 79%), which was 71% ee by HPLC analysis using CHIRALCEL OJ (hexane : *iso*-PrOH : Et<sub>2</sub>NH = 800 : 200 : 1). The crude **(S)-4** was recrystallized from Et<sub>2</sub>O – hexane to give **(S)-4** (3.8 g, 55%, 99% ee) as colorless prisms, mp 143 – 144°C. [ $\alpha$ ]<sub>D</sub><sup>27</sup> +9.5° (c 1.0, CHCl<sub>3</sub>). <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$ : 1.50 – 2.20 (4 H, m), 2.44 (3 H, s), 3.00 – 3.30 (1 H, m), 3.90 – 4.20 (1 H, m), 4.50 – 4.65 (1 H, m), 7.05 (1 H, d, *J* = 8.4 Hz), 7.15 (1 H, dd, *J* = 8.4 Hz, 2.3 Hz), 7.29 (2 H, dd, *J* = 8.3 Hz, 2.1 Hz), 7.53 (1 H, d, *J* = 2.3 Hz), 7.65 (2 H, d, *J* = 8.3 Hz). IR (KBr): 3526, 1482, 1340, 1159 cm<sup>-1</sup>. *Anal* Calcd for C<sub>17</sub>H<sub>18</sub>NO<sub>3</sub>ClS: C, 58.03; H, 5.16; N, 3.98. Found: C, 58.17; H, 5.21; N, 4.14.

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

**Asymmetric reduction using the chiral oxazaborolidine-catalyst** A solution of (S)-(–)- $\alpha$ ,  $\alpha$ -diphenyl-2-pyrrolidine methanol (0.12 g, 0.45 mmol) and methane boronic acid (0.028 g, 0.45 mmol) in dry benzene (5 mL) in the presence of MS 4A (1.0 g) was stirred for 4 h at rt under N<sub>2</sub> atmosphere. Benzene was removed and the residue was dissolved in dry THF (2 mL). The resulting solution was cooled at 0°C and treated dropwise with borane–THF complex (11.2 mmole). The mixture was stirred at 0°C and treated dropwise over 2 h with a solution of ketone **2** (2.0 g, 4.5 mmol) in THF (15 mL). The reaction mixture was stirred at 0°C for 1 h, quenched by adding 1N HCl aqueous solution and the whole was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The extract was washed saturated NaHCO<sub>3</sub> aqueous solution, washed once with brine, dried over MgSO<sub>4</sub>, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, CH<sub>2</sub>Cl<sub>2</sub> : MeOH = 20 : 1) to give **(R)-1** (1.1 g, 54%) as white powder, which was 73% ee by HPLC analysis using CHIRALCEL OD (hexane : *iso*-PrOH : Et<sub>2</sub>NH = 600 : 400 : 1).

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

**Asymmetric Transfer Hydrogenation Method** A mixture of [RuCl<sub>2</sub>( $\eta^6$ -*p*-cymene)]<sub>2</sub> (44 mg, 0.072 mmol) and (1*S*,2*S*)-*N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine [(*S,S*)-

TsDPEN, 102 mg, 0.29 mmol] in 2-propanol (20 mL) was heated at 80°C for 40 min under N<sub>2</sub> atmosphere. After cooling, 0.1 N KOH in 2-propanol (7.2 mL, 0.72 mmol) and **2** (6.44 g, 14.4 mmol) in 2-propanol (72 mL) were added dropwise. The mixture was stirred for 23 h at rt. A conc. H<sub>2</sub>SO<sub>4</sub> (4 drops) was added to the mixture, and 2-propanol was evaporated. The residue was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The extract was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, hexane : AcOEt = 2 : 1) to give (**S**)-**1** (6.37 g, 99%, 89% ee) as white powder.

**(R)-7-Chloro-5-hydroxy-1-[2-methyl-4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1H-1-benzazepine [(R)-1]** **Asymmetric Transfer Hydrogenation Method** The title compound was prepared from **4**, [RuCl<sub>2</sub>( $\eta^6$ -*p*-cymene)]<sub>2</sub>, (*R,R*)-TsDPEN and KOH by the procedure described for the preparation of (**S**)-**1**. The product was purified by column chromatography to give (**R**)-**1** (99%, 93% ee) as white powder.

**(S)-5-Benzoyloxy-7-chloro-1-[2-methyl-4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1H-1-benzazepine [(S)-5]** To a mixture of (**S**)-**1** (6.29 g, 14.0 mmol, 89% ee), Et<sub>3</sub>N (2.4 mL, 16.8 mmol) and DMAP (0.17 g, 1.4 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (80 mL) was added benzoyl chloride (2.36 g, 16.8 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL). The mixture was stirred at 40°C for 2 h, then Et<sub>3</sub>N (1.4 mL, 14.0 mmol), DMAP (0.17 g, 1.4 mmol) and the solution of benzoyl chloride (1.57 g, 11.2 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) were added. The reaction mixture was stirred at 40°C for 2 h, and poured into ice-cooled 10% K<sub>2</sub>CO<sub>3</sub> aqueous solution and the whole was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The extract was washed with 10% citric acid aqueous solution, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. The residue was crystallized from EtOAc to give (**S**)-**5** (4.82 g, 62%) as colorless needles, which was >99% ee by HPLC analysis using CHIRALCEL OD-RH (CH<sub>3</sub>CN), mp 228 – 230°C. [ $\alpha$ ]<sub>D</sub><sup>29</sup> –97.2° (c 1.0, CHCl<sub>3</sub>). <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$ : 1.80 – 2.00 (2 H, m), 2.15 – 2.40 (2 H, m), 2.46 (3 H, s), 2.48 (3 H, s), 2.85 – 2.95 (1 H, m), 4.84 (0.7 H, d, *J* = 13.7 Hz), 5.15 (0.3 H, d, *J* = 13.4 Hz), 6.25 – 6.45 (1 H, m), 6.63 (1 H, d, *J* = 8.4 Hz), 6.97 (1 H, dd, *J* = 8.4 Hz, 2.3 Hz), 7.05 (1H, s), 7.20 – 7.65 (10 H, m), 8.06 (0.6 H, d, *J* = 7.4 Hz), 8.19 (1.4 H, d, *J* = 7.2 Hz). IR (KBr): 3315, 1721, 1683, 1627, 1529, 1273, 1105 cm<sup>-1</sup>. *Anal* Calcd for C<sub>33</sub>H<sub>29</sub>N<sub>2</sub>O<sub>4</sub>Cl: C, 71.67; H, 5.29; N, 5.07. Found: C, 71.94; H, 5.28; N, 5.09.

**(R)-5-Benzoyloxy-7-chloro-1-[2-methyl-4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1H-1-benzazepine [(R)-5]** The title compound was prepared from (**R**)-**1**, benzoyl chloride, DMAP and Et<sub>3</sub>N by the procedure described for the preparation of (**S**)-**5**. The product was recrystallized from MeOH to give (**R**)-**5** (49%, >99% ee) as colorless needles, mp 230 – 233°C. [ $\alpha$ ]<sub>D</sub><sup>27</sup> +99.4° (c 1.0, CHCl<sub>3</sub>). IR (KBr): 3310, 1724, 1680, 1633, 1530, 1270, 1097 cm<sup>-1</sup>. *Anal* Calcd for C<sub>33</sub>H<sub>29</sub>N<sub>2</sub>O<sub>4</sub>Cl: C, 71.67; H, 5.29; N, 5.07. Found: C, 71.65; H, 5.35, N, 5.04.

**(S)-7-Chloro-5-hydroxy-1-[2-methyl-4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1H-1-benzazepine [(S)-1]** **From (S)-5** To a solution of (**S**)-**5** (4.42 g, 8.0 mmol) in MeOH (20 mL) and

dioxane (28 mL) was added 3N NaOH aqueous solution (8 mL, 24 mmol). The mixture was stirred at rt for 5 min. The reaction mixture was poured into water and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The extract was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. The residue was recrystallized from EtOH – H<sub>2</sub>O to give (*S*)-**1** (3.40 g, 95%, >99% ee) as white powder, mp 148 – 150°C. [ $\alpha$ ]<sub>D</sub><sup>26</sup> –159° (c 0.1, MeOH). <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$ : 1.50 – 2.40 (4 H, m), 2.44 (3 H, s), 2.47 (3 H, s), 2.60 – 2.95 (1 H, m), 4.70 – 5.10 (2 H, m), 6.54 (1 H, d, *J* = 8.3 Hz), 6.64 (1 H, d, *J* = 8.4 Hz), 6.92 (1 H, d, *J* = 8.3 Hz), 7.00 – 7.70 (7 H, m). IR (KBr): 3425, 1627, 1522, 1400, 1315 cm<sup>-1</sup>. *Anal* Calcd for C<sub>26</sub>H<sub>25</sub>N<sub>2</sub>O<sub>3</sub>Cl·1/4H<sub>2</sub>O: C, 68.87; H, 5.67; N, 6.18. Found: C, 68.64; H, 5.64, N, 5.80.

**(*R*)-7-Chloro-5-hydroxy-1-[2-methyl-4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine [(*R*)-**1**] From (*R*)-**5**** The title compound was prepared from (*R*)-**5** and NaOH by the procedure described for the preparation of (*S*)-**1**. The product was recrystallized from EtOH – H<sub>2</sub>O to give (*R*)-**1** (99%, >99% ee) as white powder, mp 149 – 152°C. [ $\alpha$ ]<sub>D</sub><sup>26</sup> +165° (c 0.1, MeOH). IR (KBr): 3425, 1621, 1526, 1400, 1316 cm<sup>-1</sup>. *Anal* Calcd for C<sub>26</sub>H<sub>25</sub>N<sub>2</sub>O<sub>3</sub>Cl·1/4H<sub>2</sub>O: C, 68.87; H, 5.67; N, 6.18. Found: C, 68.72; H, 5.71, N, 5.87.

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