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PRACTICAL SYNTHESIS OF BOTH ENANTIOMERS OF VASOPRESSIN V_2 RECEPTOR ANTAGONIST OPC-41061 USING THE CATALYTIC ASYMMETRIC HYDROGENATION

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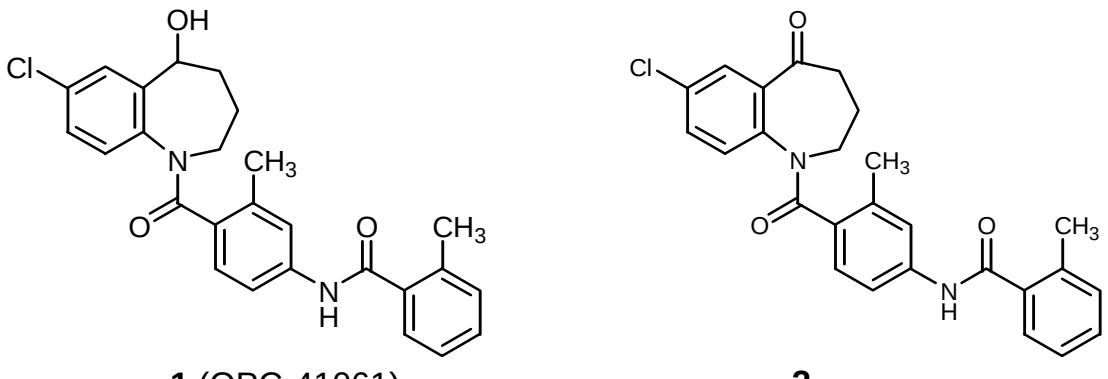
Abstract - The optically active enantiomers of 7-chloro-5-hydroxy-1-[2-methyl-4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine (OPC-41061, **1**) were enantioselectively synthesized. The asymmetric transfer hydrogenation of the ketone (**2**), which is the precursor of **1**, gave the corresponding secondary alcohols in good yield and excellent enantiomeric excess.

INTRODUCTION

The benzazepine derivative, 7-chloro-5-hydroxy-1-[2-methyl-4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine (OPC-41061, **1**), was previously synthesized by Ogawa *et al.*[1] It is a new vasopressin V_2 receptor antagonist and is now under clinical trial as a novel aquaretic agent. This compound (**1**) contains an asymetric center at position 5. In order to examine the pharmacokinetics and the toxicokinetics of the optically active isomers, the pure enantiomers of **1** were needed. In the metabolism studies of **1**, the oxidative metabolite (**2**)[1] was isolated from the urine of rat, dog and humans. Because the different bioavailabilities of the enantiomers are caused by the stereoselective metabolism, the ratio of enantiomers of **1** in the serum of animals and humans is an essential problem. Therefore, we initiated the synthesis of the optically active isomers of **1**.



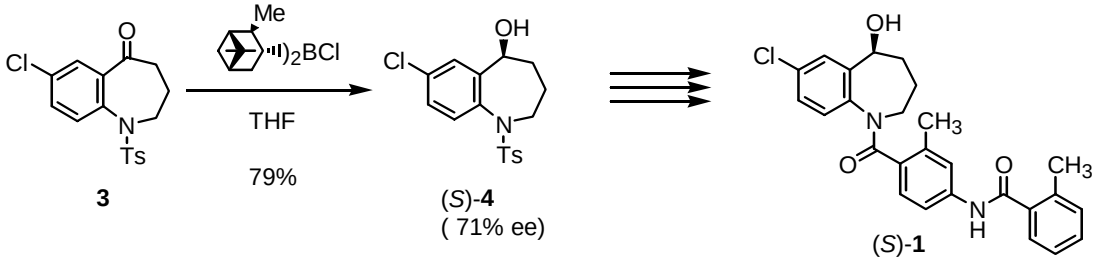
1 (OPC-41061) **2**

Figure 1

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[2] and α,β-acetylenic ketones[3] by the chiral ruthenium (II) complex. We have already reported the asymmetric synthesis of both enantiomers of **1** *via* the lipase-catalyzed transesterification.[4] 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**.

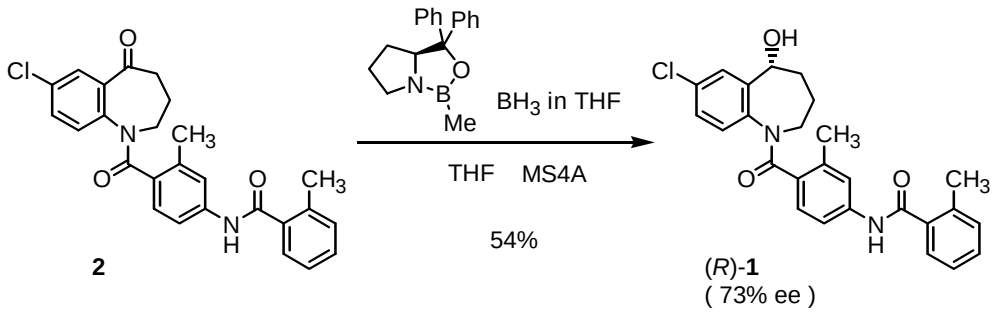
RESULTS AND DISCUSSION

In order to find the efficient synthesis of the key intermediate ((*S*)-**4**), we investigated the asymmetric reduction of the corresponding ketone (**3**)[4] utillizing the chiral reagents. The asymmetric reduction of **3** with (–)-diisopinocamphenylchloroborane,[5] (–)-Ipc$_2$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**.[4] (**Scheme 1**)



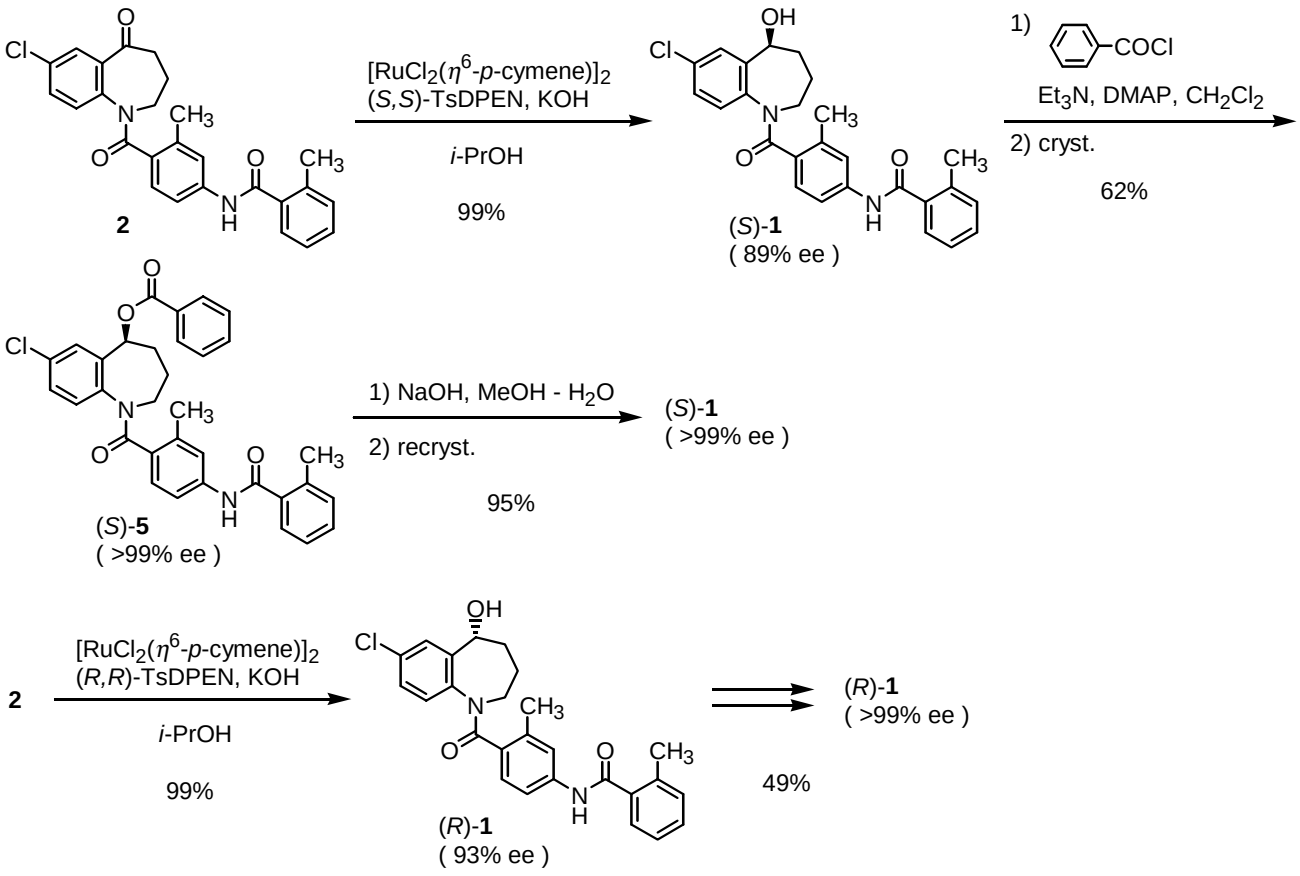
Scheme 1

Considering a more efficient synthesis of the optically active **1**, we explored the asymmetric reduction of the ketone (**2**). First, the asymmetic reduction of **2** with (–)-Ipc$_2$BCl did not give a good result. Next, the reduction of **2** using Corey's reagent[6] 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 $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$ 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$_2$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$_2$BCl (7.70 g, 24 mmol) in THF (20 mL) under N_2 atomosphere and the mixture was stirred at 4°C. After 18 h, 10% NaOH aqueous solution (30 mL) and 30% H_2O_2 aqueous solution (15 mL) were added to the mixture and stirred for 2.5 h at rt. The mixture was extracted with Et_2O. 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 **(*S*)-4** (5.58 g, 79%), which was 71% ee by HPLC analysis using CHIRALCEL OJ (hexane : *iso*-PrOH : Et_2NH = 800 : 200 : 1). The crude **(*S*)-4** was recrystallized from Et_2O – hexane to give **(*S*)-4** (3.8 g, 55%, 99% ee) as colorless prisms, mp 143 – 144°C. $[\alpha]_D^{27}$ +9.5° (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 1.50 – 2.20 (4 H, m), 2.44 (3 H, s), 3.00 – 3.30 (1 H, m), 3.90 – 4.20 (1 H, m), 4.50 – 4.65 (1 H, m), 7.05 (1 H, d, *J* = 8.4 Hz), 7.15 (1 H, dd, *J* = 8.4 Hz, 2.3 Hz), 7.29 (2 H, dd, *J* = 8.3 Hz, 2.1 Hz), 7.53 (1 H, d, *J* = 2.3 Hz), 7.65 (2 H, d, *J* = 8.3 Hz). IR (KBr): 3526, 1482, 1340, 1159 cm^{-1}. *Anal* Calcd for $C_{17}H_{18}NO_3ClS$: C, 58.03; H, 5.16; N, 3.98. Found: C, 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)-(–)-α, α-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_2 atomosphere. 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_2Cl_2. The extract was washed saturated $NaHCO_3$ aqueous solution, washed once with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, CH_2Cl_2 : 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_2NH = 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 [$RuCl_2$(η^6-*p*-cymene)]$_2$ (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_2 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_2SO_4 (4 drops) was added to the mixture, and 2-propanol was evaporated. The residue was extracted with CH_2Cl_2. The extract was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, 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-1*H*-1-benzazepine [(*R*)-1] Asymmetric Transfer Hydrogenation Method The title compound was prepared from **4**, $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$, (*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-1*H*-1-benzazepine [(*S*)-5] To a mixture of **(*S*)-1** (6.29 g, 14.0 mmol, 89% ee), Et_3N (2.4 mL, 16.8 mmol) and DMAP (0.17 g, 1.4 mmol) in CH_2Cl_2 (80 mL) was added benzoyl chloride (2.36 g, 16.8 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred at 40°C for 2 h, then Et_3N (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_2Cl_2 (10 mL) were added. The reaction mixture was stirred at 40°C for 2 h, and poured into ice-cooled 10% K_2CO_3 aqueous solution and the whole was extracted with CH_2Cl_2. The extract was washed with 10% citric acid aqueous solution, dried over Na_2SO_4 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_3CN), mp 228 – 230°C. $[\alpha]_D^{29}$ –97.2° (c 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 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^{-1}. *Anal* Calcd for $C_{33}H_{29}N_2O_4Cl$: 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-1*H*-1-benzazepine [(*R*)-5] The title compound was prepared from **(*R*)-1**, benzoyl chloride, DMAP and Et_3N 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. $[\alpha]_D^{27}$ +99.4° (c 1.0, $CHCl_3$). IR (KBr): 3310, 1724, 1680, 1633, 1530, 1270, 1097 cm^{-1}. *Anal* Calcd for $C_{33}H_{29}N_2O_4Cl$: 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-1*H*-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_2Cl_2. The extract was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was recrystallized from EtOH – H_2O to give **(*S*)-1** (3.40 g, 95%, >99% ee) as white powder, mp 148 – 150°C. $[\alpha]_D^{26}$ –159° (c 0.1, MeOH). ^{1}H NMR ($CDCl_3$) δ: 1.50 – 2.40 (4 H, m), 2.44 (3 H, s), 2.47 (3 H, s), 2.60 – 2.95 (1 H, m), 4.70 – 5.10 (2 H, m), 6.54 (1 H, d, *J* = 8.3 Hz), 6.64 (1 H, d, *J* = 8.4 Hz), 6.92 (1 H, d, *J* = 8.3 Hz), 7.00 – 7.70 (7 H, m). IR (KBr): 3425, 1627, 1522, 1400, 1315 cm^{-1}. *Anal* Calcd for $C_{26}H_{25}N_2O_3Cl \cdot 1/4H_2O$: C, 68.87; H, 5.67; N, 6.18. Found: C, 68.64; 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_2O to give **(*R*)-1** (99%, >99% ee) as white powder, mp 149 – 152°C. $[\alpha]_D^{26}$ +165° (c 0.1, MeOH). IR (KBr): 3425, 1621, 1526, 1400, 1316 cm^{-1}. *Anal* Calcd for $C_{26}H_{25}N_2O_3Cl \cdot 1/4H_2O$: C, 68.87; H, 5.67; N, 6.18. Found: C, 68.72; H, 5.71, N, 5.87.

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