The Synthesis of Optically-Active *erythro*-Methylphenidate by Diastereoselective Hydrogenation Using Ru-BINAP Complex Catalyst

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Abstract

Optically-active erythro-methylphenidate 1 has been synthesized from methyl 2-phenyl-2-(2'-piperidylidene)acetate 2 by diasteroselective hydrogenation using the Ru-BINAP complex catalyst as the key step. Piperidylidene acetate 2 was prepared by two routes either from 2,3,4,5-tetrahydro-6-methoxypyridine 4 or 5-N-carbobenzyloxyamino-pentanoic acid 5.

Keywords — *Diasteroselective hydrogenation; methylphenidate, methyl 2-phenyl-2-(2'-piperidyl)-acetate, methyl 2-phenyl-2-(2'-piperidylidene)acetate, Ru-BINAP complex catalyst.*

I. INTRODUCTION

The hydrochloride of methylphenidate **1** [Methyl 2-phenyl-2-(2'-piperidyl)acetate hydrochloride; Ritalin®] has already been commercially available as an antidepressant, and the structural analysis of the optically-active methylphenidate **1**, which exhibits a higher pharmacological activity as an antidepressant, has been made regarding the absolute configuration of this optically-active materials[1]. Furthermore, it has been reported that its d-*threo*-isomer **1a** (2R,2'R-isomer) exhibits a pharmacological activity about 5 times higher than the other stereoisomers[2,3].

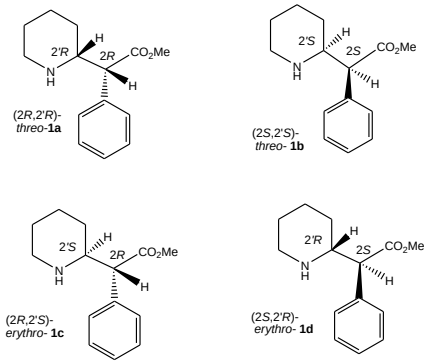


Fig. 1: The structures of the optically-active methyl 2-phenyl-2-(2'-piperidyl)acetate **1a-d**

Many syntheses of the optically-active **1** are known; for example,

(i) The initial synthesis from the condensation of phenylacetonitrile and 2-chloropyridine, followed by hydrolysis, reduction, then optically resolved using tartaric acid[4].

(ii) The synthesis by the Hoffmann decomposition reaction and oxidation of optically-active chloro-phenylamine[5].

(iii) The synthesis from optically-active pipecolinic acid as the starting compound with the use of (+)-$IPCBH_2$ at the key step of multistage reactions[6].

(iv) The enantioselective syntheses which are based on the Evans aldol reaction[7,8].

(v) The synthesis from *N*-methoxycarbonylpiperidine by utilizing electrochemical oxidation and the Evans aldol-type reaction[9,10].

(vi) Enantioselective synthesis of *erythro*-methyl-phenidate by utilizing Evans' 4-substitued- 2-oxazolidione chiral auxiliary[11].

More recently, there have been reported several new synthetic methods[12-14].

On the other hand, the enantioselective hydrogenation with the Ru-BINAP complex catalyst is one of the most powerful tools for the synthesis of optically-active compounds[15-21]. Moreover, new chiral phosphorous ligands for enantioselective hydrogenation are used, and their review has been reported[22].

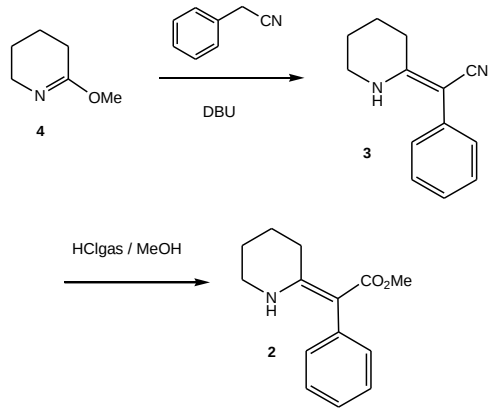
In particular, the enantioselective hydrogenations of the diketone, β-ketoesters, and enamide esters are well known. However, that of the cyclic β-enaminoesters, such as 2-phenyl-2-(2'-piperidylidene)acetate **2**, is little known. Also, the synthesis of optically-active methylphenidate **1** by an asymmetric reaction with metal chiral phoshorus ligands has not been reported. The author was interested in the diastereoselective synthesis of *erythro*-(2*S*, 2'*R*)-**1d** because it could be epimerized to *threo*-(2*R*, 2'*R*)-**1a**, as *l-erythro*-α-phenyl-α-(2-piperidyl)acetamide to the corresponding *threo*-isomer[1,11].

The authors have studied the asymmetric hydrogenation for developing the synthesis of optically-active methylphenidate **1** and now reports

the efficient synthesis of the optically-active *erythoro*-methylphenidate **1c** and **1d** from **2** *via* diastereo-selective hydrogenation using the Ru-BINAP complex catalyst[23].

II. RESULTS AND DISCUSSION

The preparation of 2-phenyl-2-(2'-piperidylidene)-acetate **2**, as a substrate for the diastereoselective hydrogenation is illustrated (Scheme 1). The synthesis of 2-(2'-piperidylidene)acetonitrile **3** is known as the method in which piperidone with P_2S_5 prepared the thiolactam, followed by MeI in the presence of KOH to synthesize a lactim thioether followed by the condensation with BnCN in the presence of DBN (1,5-diazabicyclo[4.3.0]-non-5-ene) to give **3**.[24] As a similar method, 2,3,4,5-tetrahydro-6-methoxypyridine **4**, which was obtained from piperidone with Me_2SO_4, was reacted with BnCN in the presence of DBN to give **3** by a known method[25,26].



Scheme 1: Synthesis of Methyl 2-phenyl-2-(2'-piperidylidene)acetate **2** from **4**

In this procedure, several bases, DBU (1,8-diaza-bicyclo[5,4,0]undec-7-ene), TMG (tetramethyl-guanidine) and DABCO (1,4-diazabicyclo[2,2,2]-octane), were investigated instead of DBN. The results are shown in Table 1.

Table 1: The yield of **3** in the case of the same bases

Run	Base	The yield of **3** (%)
1	DBN	62
2	DBU	71
3	TMG	48
4	DABCO	58

* The base used 0.1 mole equivalent for the substrate.
The reaction temperature is 150°C and the reaction time is 18h

The best yield of **3** is using DBU. The amount of DBU was improved. The results are shown in Table 2.

Table 2: The yield of **3** based on the variable amounts of DBU

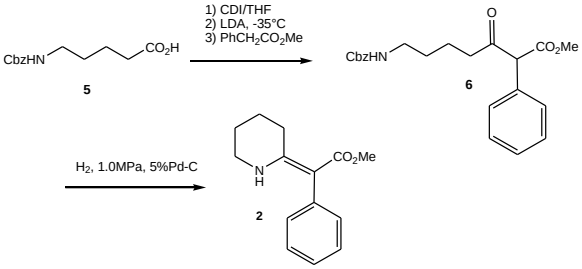
Run	Amount of DBU (Mol eq. for **4**)	Yield(%)
1	0.01	49
2	0.05	66
3	0.1	71
4	0.25	73

*Reaction temperature is 150°C and reaction time is 18h.

The only geometric-isomer of **3** was a single one from the spectral data, and it is predominately the *E*-isomer because the *E*-isomer is more stable than the *Z*-isomer from MM2 calculation by using Chem 3D Pro software (*E*-isomer; 2.0686kcal/mol, *Z*-isomer; 3.0948 kcal/mol).

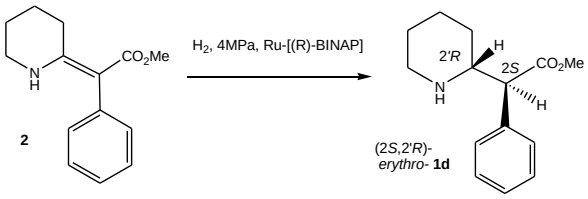
Subsequently, **3** was treated in the presence of HCl gas in MeOH at 45°C for 18h to obtain methyl 2-phenyl-2-(2'-piperidylidene)acetate **2** in 70% yield (Scheme 1).

Also, another route is described. Thus, 5-*N*-carbobenzyloxyaminopentanoic acid **5**, which is commercially available, was reacted with *N*,*N*'-carbonyldiimidazole (CDI) to prepare the imidazolide of **5** and it was condensed with the lithium enolate of methyl phenylacetate at -35°C to give methyl 7-*N*-benzyloxycarbonylamino-3-oxo-2-phenyl heptanoate **6**[27], which is shown to been keto-enol mixture by NMR, in 66% yield, then the de-benzyloxycarbonyl group of **6** and the cyclization were carried by hydrogenation (1.0Mpa press) in the presence of 5%Pd-carbon at room temperature to give **2** in 94% yield (Scheme 2).



Scheme 2: Synthesis of **2** from 7-N-carbobenzyloxyamino-heptanoic acid **5**

Next, the author examined the diastereoselective hydrogenation of methyl 2-phenyl-2-(2'-piperi-dylidene)acetate **2** in the presence of the Ru-(R)-BINAP complex[23] as a catalyst under several conditions. Therefore, the asymmetric hydrogenation of **2** produced the best result in the case of using $[NH_2Et_2][\{RuCl((R)\text{-}p\text{-toly-BINAP})\}_2(\mu\text{-}Cl)_3]$[28] as a catalyst (Scheme 3).



Scheme 3: Asymmetric hydrogenation of **2**

1d was obtained in 94% yield and the abosolute configuration was determined by the optical rotation data and spectral data of a previous report[6]. The %ee and %de were determined using a HPLC column. The optical yield and diasteremeric selectivety were 98%ee and 98%de. Based on this result, it was found that the *erythro*-rich product was obtained in the case of using the Ru-BINAP complex catalyst. Thus, it was found that the *erythro* (2*S*, 2'*R*)-**1d** obtained when using the (*R*)-BINAP catalyst. This procedure could also be used to synthesize the corresponding *erythro*-(2*R*, 2'*S*)-**1c** by using the Ru-(*S*)-BINAP complex catalyst.

III. MATERIALS AND METHOD

All reagents and solvents were obtained from commercial sources and used without further purification. Melting points were prepared using a Yanagimoto apparatus and are uncorrected. The NMR was a Bruker AM400 (400 MHz). The chemical shifts are given in ppm. HPLC was done using a Hitachi L-6200 with L-4000 UV as the detector. Column: ODS-2 (GL Sciences Inc.). Eluent: MeCN/ H_2O = 7/3, UV spectrometer (254 nm), flow rate: 0.4 ml/min. Analytical conditions for chirality: HPLC column: CHIRALPAK AD (Daicel Chemical Co., Ltd.), eluent: *n*-hexane/*i*-PrOH = 98/2, UV spectrometer (230 nm), flow rate: 0.4 ml/min. Mass spectra were obtained using a Hitachi M-80A spectrometer at 70eV.

Synthetic procedures

(*E*)-2-Phenyl-2-(2'-piperidylidene)acetonitrile (**3**): The mixture of 2,3,4,5-tetrahydro-6-methoxypyridine **4** (10.0 g, 88.4 mmol), benzyl cyanide (20.4 ml, 176.8 mmol) and DBU (1.34 g, 8.84 mmol) was heated at 150°C in N_2 for 20 h. The reaction mixture was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 6/1) to give **3** (12.4 g, 71%) as a white crystal: Mp. 112 - 114°C, ^{1}H-NMR ($CDCl_3$) 1.78 (m, 4H), 2.79 (m, 2H), 3.17 (m, 2H), 5.48 (br, 1H), 7.18 - 7.40 (m, 5H); ^{13}C-NMR ($CDCl_3$) 20.23 (CH_2), 22.70 (CH_2), 28.00 (CH_2), 42.40 (CH_2), 70.14 (C), 122.56 (CH), 126.80 (CH x 2), 128.84 (CH), 129.35 (CH x 2), 133.63 (C), 157.35 (CN). MS: 198 (M^+), 169, 155, 141, 115, 105, 82, 55, 43. Anal. Calcd. for $C_{13}H_{14}N_2$: C, 78.75; H, 7.12; N, 14.13; found: C, 78.65, H, 7.07, N, 14.03.

(*E*)-Methyl 2-phenyl-2-(2'-piperidylidene)acetate (**2**): **3** (10.0 g, 50.4 mmol) in MeOH (100 ml) was cooled, then HCl gas was babbled through the reaction mixture for 1 h and heated at 45°C for 18 h. MeOH was removed *in vacuo* and to the residue was added EtOAc (100 ml) and a 2N NaOH solution, then the organic layer was washed with 10% NaCl. The solvent was concentrated to give a crude product. The crude product was recrystallized from MeOH to give **2** (8.2 g, 70%) as a colorless crystal: Mp. 115 - 117°C, ^{1}H-NMR ($CDCl_3$) 1.56 (m, 2H), 1.73 (m, 2H), 2.11 (t, *J* = 6.5 Hz, 2H), 3.38 (m, 2H), 3.55 (s, 3H), 7.13 (m, 2H), 7.23 (m, 3H), 9.71 (br, 1H); ^{13}C-NMR ($CDCl_3$) 19.96 (CH_2), 22.32 (CH_2), 27.78 (CH_2), 41.41 (CH_2), 50.48 (OCH_3), 94.59 (C), 126.01 (CH x 2), 127.91 (CH), 132.38 (CH x 2), 138.24 (C), 161.40 (C), 170.39 (CO). MS: 231 (M^+), 198, 170, 143, 115, 84, 55. Anal. Calcd. for $C_{15}H_{21}NO_2$: C, 72.70; H 7.41; N 6.06; found: C 72.50, H 7.40, N 6.03.

Methyl 7-(*N*-carbobenzyloxyamino)-3-oxo-2-phenyl-heptanoate (**6**): To 5-*N*-carbobenzyloxyamino-pentanoic acid **5** (17.5 g, 69.8 mmol) in THF (350 ml), *N*,*N'*-carbonyldiimidazole (CDI) (12.4 g, 76.5 mmol) was added and reacted at rt for 18 h. *i*-Pr_2NH (27.4 ml, 209 mmol) and THF (350 ml) were placed in another flask and cooled to -35°C, then 1.63N *n*-BuLi in a hexane solution (128 ml, 209 mmol) was dropwise added to the mixture for 1h and continued at the same temperature for 1 h to prepare *i*-Pr_2NLi. Methyl phenylacetate (6.4 g, 209 mmol) in THF (100 ml) was then dropwise added to the *i*-Pr_2NLi for 45 min. After the addition, the resulting mixed solution was stirred at the same temperature for 1 h. The above-synthesized imidazolide was dropwise added to the enolate for 1 h, and the mixture was stirred for 3 h. After the presence of the product was confirmed, a saturated NH_4Cl solution (280 ml) was added to the mixture. 4N HCl (130 ml) was added to the reaction mixture to adjust the pH to 3, and extracted with EtOAc (350 m). The organic layer was washed with a saturated $NaCO_3$ solution (40 ml) and brine. The organic layer was dried using anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (Eluent: *n*-hexane/EtOAc = 4/1) to give **6** as a pale yellow oil (17.8 g, 66%). ^{1}H-NMR ($CDCl_3$) 1.40 (m, 2H), 1.53 (m, 2H), 2.13 (m, 0.35H, enol form CHOHC$\underline{H_2}$), 2.49 (m, 1.65H, keto type COC$\underline{H_2}$), 3.10 (m, 1.86H, ketro form NHC$\underline{H_2}$), 3.19 (m, 0.14H, enol type NHC$\underline{H_2}$), 3.67 (s, 0.68H, enol form OCH_3), 3.73 (s, 2.32H keto form OCH_3), 4.70 (s, 1.07H, keto type CH), 4.98 (brs, 1H, NH), 5.07 (s, 2H, $PhCH_2$), 7.1 - 7.4 (m, 5H, aromH), 13.1 (s, 0.14H, enol form OH); ^{13}C-NMR ($CDCl_3$): keto-enol form mixture; 20.50 (CH_2), 21.96 (CH_2), 23.67 (CH_2), 29.03 (CH_2), 29.33 (CH_2), 32.15 (CH_2), 33.52 (CH_2), 40.43 (CH_2), 40.61 (CH_2), 40.91 (CH_2), 51.56 (CH_2), 51.88 (CH_3), 52.58 (CH_3), 64.82 (CH_2), 66.59 (CH_2), 127.23 (CH_2), 128.08 (CH_2), 128.23 (CH_2), 128.34

(CH_2), 128.43 (CH_2), 128.54 (CH_2), 128.92 (CH_2), 129.04 (CH_2), 129.32, (CH_2) 129.40 (CH_2), 131.23 (CH_2), 132.46 (CH_2), 134.81 (C), 136.63 (C), 156.39 (CO), 168.98 (CO, enol form), 173.12 (CO, keto form), 176.36 (CO, enol form), 203.33 (CO, keto form). MS : 384 (M^++1), 322, 308, 276, 244, 222, 190, 158, 108, 91. HRMS calcd. for $C_{22}H_{25}NO_5$: 383.4376; found: 383.4374.

Methyl 2-phenyl-2-(2'-piperidylidene)acetate (**2**): **6** (16.0 g, 42 mmol) and MeOH (130 ml) were mixed in a 1-L autoclave. 5% Pd-C (2.6 g) and the mixture was reacted at rt. under H_2 (1.0 MPa) for 4 h. The reaction solution was analyzed by HPLC to confirm the complete consumption of the raw material. The Pd-C was then separated by filtration using Celite. The filtrate was concentrated under reduced pressure, and the residue was recrystallized from MeOH (40 ml) at -25°C to give **2** (9.0 g, 93%). The melting point and spectral data were identified based on the above data.

Hydrochloride of methyl (2S, 2'R)-2-phenyl-2-(2'-piperidyl)acetate (**1d**): Into a 500-ml autoclave were charged piperidylidene acetate **2** (10 g, 43.3 mmol), $[NH_2Et_2][\{RuCl((R)\text{-}p\text{-tolyl-BINAP})\}_2(\mu\text{-}Cl)_3]$[27] (37 mg, 0.0433 mmol), MeOH (80 ml) and an HCl solution (5 ml) containing 10% MeOH under an atmosphere of N_2. The atmosphere was then replaced with H_2 at 1.0 MPa and 50°C for 38 h. The resulting reaction mixture was concentrated and the solid residue was recrystallized from EtOH/Et_2O to give **1d** as a white solid (8.5 g, 74%). The optical yield and diastereomeric selectivity were 99%ee and 98%de, respectively. mp 217- 218 °C, (Lit. [1)], mp 233 -235 °C; Lit. [6)], mp 218 -219 °C), $[\alpha]^{20}_D$ -93.0° (c = 1.3, MeOH), (Lit. [1)], $[\alpha]^{26}_D$ -84.0°, c = 1.00, H_2O; Lit. [6)], $[\alpha]^{20}_D$ -94.5°, c = 1.59, MeOH). ^{1}H-NMR (D_2O) 1.40-1.60 (m, 3H), 1.90 (m, 2H), 2.13 (m, 1H), 2.99 (m, 1H), 3.31 (m, 1H), 3.73 (s, 3H), 3.83 (m, 1H), 3.98 (d, *J* = 9Hz, 1H), 7.45 (m, 5H); ^{13}C-NMR (D_2O) 24.03 (CH_2), 24.41 (CH_2), 30.16 (CH_2), 48.31 (CH_2), 55.81 (CH), 57.15 (CH_3), 60.69 (CH), 131.49 (CH), 132.18 (CH x 2), 132.52 (CH x 2), 134.72 (C), 175.44(CO). MS: 234 (MH^+), 151, 102, 85.

IV. CONCLUSIONS

The authors have described the synthesis of the optically-active methylphenidate **1,** which has already been known as an antidepressant. Thus, (2*S*, 2'*R*)-*erythro*-methylphenidate **1d** was synthesized from methyl 2-phenyl-2-(2'-piperidylidene)acetate **2** by diastereoselective hydrogenation using an optically-active Ru-BINAP complex catalyst. Piperidylidene acetate **2** was prepared by two different routes using, *O*-methoxyprolidone **4** or *N*-carbobenzyloxyamino-heptanoic acid **5** as the starting material.

ACKNOWLEDGMENT

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