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Original Article

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

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Abstract - *Optically-active methyl 2-phenyl-2-(2'-pyperidyl)acetate (Methylphenidate)* ***1*** *could be produced from methyl 7-N-(benzyloxycarbonylamino)-3-oxo-2-phenylheptanoate* ***2*** *by diastereoselective hydrogenation using the Ru-BINAP complex catalyst as the key step of 3 steps.*

Keywords - *(2S, 2R')-2-phenyl-2-(2'-pyperidyl)acetate, methyl (2S, 3R)-7-N-(benzyloxy- carbonylamino)-3-hyroxy-2-phenylheptanoate, diastereoselective hydrogenation, Ru-BINAP complex catalyst.*

1. Introduction

The antidepressant, methyl 2-phenyl-2-(2'-piperidyl)-acetate hydrochloride (Methylphenidate, Ritalin®), is commercially available in the form of racemic compounds [1]. Furthermore, the *d-threo*-form of methylphenidate **1a** is known for this antidepressant as a specific stereoisomer that has a pharmacological activity five times higher than that of other stereoisomers [2,3] (Fig. 1).

Many syntheses of optically active **1** are known [4-10]. More recently, there have been several new reported synthetic methods [11-13]. 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 [14-20].

In particular, the enantioselective hydrogenations of diketone, β-ketoesters and enamide esters are well known. Moreover, new chiral phosphorous ligands for enantioselective hydrogenation are used, and their review has been reported [21].

The authors have studied the asymmetric hydrogenation in order to develop the synthesis of optically active methylphenidate 1 and reported that (2*S*, 2'*R*)-*erythro*-methylphenidate 1d cloud be synthesized from methyl 2-phenyl-2-(2'-piperidylidene)acetate by diastereoselective hydrogenation using an optically-active Ru-BINAP complex catalyst [22]*.

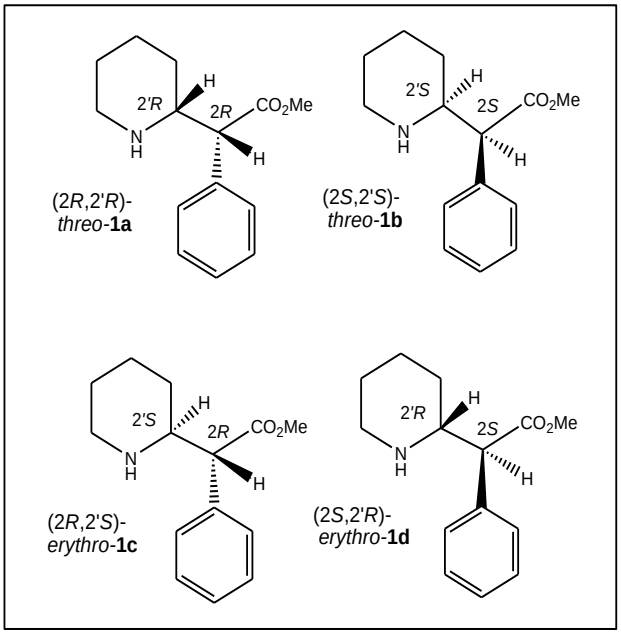
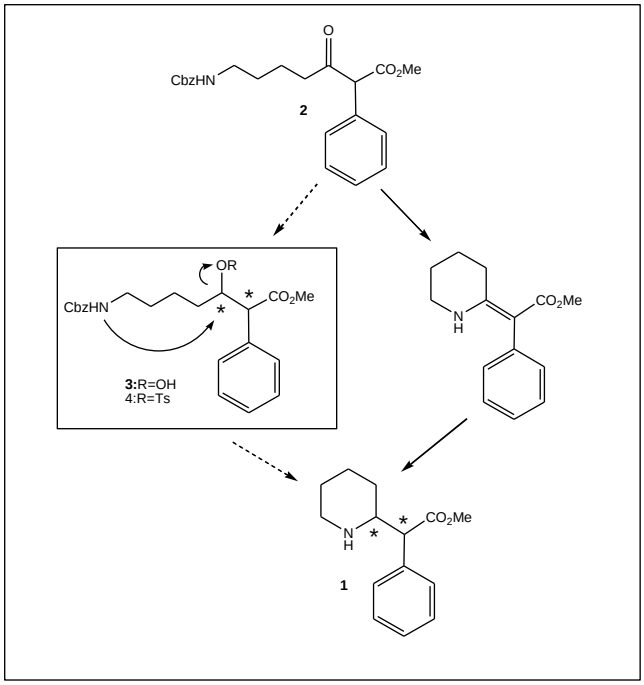


Fig. 1 The structure of the optically-active methyl phenidate 1a-d

The authors now report the new route of (2*S*, 2'*R*)-*erythro*-methylphenidate 1d from the optically-active methyl 7-(*N*-benzyloxycarbonylamino)-3-hydroxy-2-phenylheptanoate 3 which is obtained from 7-*N*-(benzyloxycarbonylamino)-3-oxo-2-phenylheptanoate 2 by asymmetric hydrogenation by using the Ru-(*R*)-BINAP complex catalyst (Scheme 1 and Figure 2).



Scheme 1. Summary of the synthetic route from methyl 7-*N*-(benzyloxycarbonylamino)-3-oxo-2-phenylheptanoate 2 to the optically-active methylphenidate 1

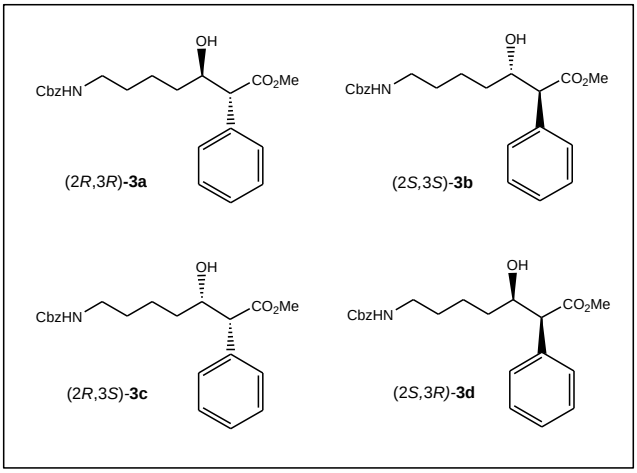


Fig. 2 The structure of the optically-active methyl 7-*N*-(benzyloxy-carbonylamino)-3-hydroxy- 2-phenylheptanoate 3a-d

2. Materials and Methods

All the reagents and solvents were obtained from commercial sources and used without further purification. The melting points were prepared using a Yanagimoto apparatus and were uncorrected. The optical rotations were obtained using a JASCO DIP-4 digital polarimeter. The NMR was a Bruker AM400 (400 MHz). The chemical shifts are given in ppm. HPLC was done using a Hitachi L-6200 with an L-4000 UV as the detector. Column: ODS-2 (GL Sciences, Inc.), Eluent: MeCN/ H_2O = 7/3, UV spectrometer (254 nm), Flow rate: 0.5 ml/min. Analytical conditions for chirality: HPLC column: CHIRALPAK AD (Daicel Chemical Co., Ltd.), Eluent: *n*-hexane/*i*-PrOH = 98/2, Flow rate: 0.4 ml/min, Detector: UV spectrometer (230 nm), Flow rate: 0.4 ml/min. The mass spectra were obtained using a Hitachi M-80A spectrometer at 70eV.

2.1. Synthetic Procedures

Methyl (2*S*, 3*R*)-7-*N*-(benzyloxycarbonylamino)-3-hydroxy-2-phenyl heptanoate (3d): Methyl 7-(*N*-benzyloxycarbonylamino)-3-oxo-2-phenylheptanoate 2 (22.6g, 59 mmol), which was prepared according to the literature [22]*, $[NH_2Et_2][\{RuCl((R)\text{-}p\text{-}tolyl\text{-}BINAP)\}_2(\mu\text{-}Cl)_3]$ [24] (370 mg, 0.433 mmol) was in CH_2Cl_2 (80 ml) under an atmosphere of N_2. The atmosphere was then replaced with H_2 of 8 MPa at 80°C for 40 h. After the completion of the reaction was confirmed by HPLC, the reaction solution was concentrated under reduced pressure. The residue was then purified by silica gel column chromatography (eluent: hexane/EtOAc = 2/1) to give the crude 3d as a colorless oil (19.7 g, 87%). Based on the HPCL analysis, the ratio of the *erythro*-form to the *threo*-form was 8:2, and the optical purity of each of the forms was 98% ee and 96% ee, respectively. The crude product 3d was again purified by silica gel column chromatography (eluent: hexane/EtOAc/MeOH = 2/2/1) to give the *erythro*-form 3d (3.6g). *Erythro*-form 3d: mp. 62-64° C. $[\alpha]^{20}_D$ = -20.5° (c = 1.1, MeOH), ^{1}H-NMR ($CDCl_3$) 1.3 - 1.85 (m, 6H, CH_2), 2.44 (br, 1H, OH), 3.17 (m, 2H, CH), 3.56 (d, J = 6.5 Hz, 1H, CH), 3.66 (s, 3H, OCH_3), 4.17 (m, 1H, CH), 4.80 (m, 1H, CH), 5.08 (br, 2H, $PhCH_2O$), 7.19-7.35 (m, 10H, aromH). ^{13}C-NMR ($CDCl_3$) 22.88 (CH_2), 29.73 (CH_2), 33.99 (CH_2), 40.88 (CH_2), 52.12 (CH_3), 57.27 (CH_2), 66.58 (CH), 71.99 (CH), 127.85 (CH), 128.06 (CH x 2), 128.10 (CH x 2), 128.50 (CH), 128.73 (CH x 2), 129.19 (CH x 2), 135.01 (C), 136.67 (C), 156.67 (CO), 173.66 (CO). MS: 386(M^++1), 342, 324, 278, 234, 218, 192, 174, 151, 108, 91, 79.

Methyl (2*S* 3*R*)-7-N-(benzyloxycarbonylamino)-3-p-toluenesulfonyloxy-2-phenylheptanoate (4): 3d (3.5 g, 9.1mmol) in pyridine (40 ml), DMAP (0.2 g, 1.6 mmol) was added, and *p*-toluenesulfonyl chloride (2.6 g, 13.6 mmol) was dropwise added over 1h at 0 ° C, then further stirred at room temperature for 20h. EtOAc (150 ml) and 2N HCl were added to the mixture to adjust the pH to 4 for extraction. A saturated $NaHCO_3$ solution was added to the organic layer to neutralized and, washed with a saturated NaCl solution and dried with anhydrous $MgSO_4$. After the organic solution was concentrated under reduced pressure, the residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 3/1) to give 4 as a pale yellow oil (2.3 g, 48%). ^{1}H-NMR ($CDCl_3$) 1.45 (m, 4H), 1.81 (m, 2H), 2.37 (s, 3H, CH_3), 3.14 (m, 2H), 3.63 (s, 3H, OCH_3), 3.85 (d, J = 8.5 Hz, 1H), 4.82 (br, 1H, OH), 5.10 (s, 2H, CH_2Ph), 5.14 (m, 1H), 7.0 - 7.4 (m, 14H). ^{13}C-NMR ($CDC1_3$) 21.36 (CH_3), 21.55 (CH_2), 29.38 (CH_2), 32.32 (CH_2), 40.62 (CH_2), 52.35 (CH_3), 55.17 (CH_2),

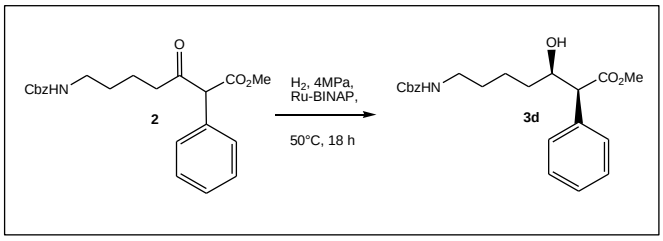
60.38 (CH_2), 66.57 (CH_2), 82.96 (CH), 127.52 (CH), 127.86 (CH), 128.05 (CH x 2), 128.51 (CH x 2), 128.59 (CH x 2), 128.96 (CH x 2), 129.51 (CH x 2), 133.79 (CH), 134.25 (CH), 136.70 (C), 144.24 (C), 156.38 (C), 171.02 (CO), 171.12 (CO). MS: 539 (M^+), 496, 368, 324, 260, 234, 200, 173, 108, 91.

Methyl (2*S*, 2'*R*)-2-phenyl-2-(2'-pyperidyl)acetate (1d): Methyl (2*S*, 3*R*)-7-*N*-(benzyloxycarbonylamino)-*p*-toluene-sulfonyloxy-2-phenylheptanoate 4 (2.2 g, 3.9 mmol) and 5%Pd-C (0.8 g) were placed in an autoclave. To the mixture were added AcOH (2 ml) and MeOH (60 ml). The mixed solution was reacted at room temperature under the H_2 pressure of 1 MPa for 3h. After the completion of the reaction was confirmed by HPLC, the Pd-C was separated by filtration using a Celite pad. The filtrate was concentrated under reduced pressure. The product was dissolved in MeOH (100 ml) and K_2CO_3 (3 g, 49 mmol) was added to the mixed solution, then the mixture was reacted while reflux heating for 18 h. The reaction solution was concentrated under reduced pressure. The residue was extracted by EtOAc (100 ml) and washed with water. The organic layer was dried using anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: *n*-hexane/EtOAc/MeOH = 2/2/1) to give 1d as a pale yellow. oil (1.9 g, 77%). ^{1}H-NMR ($CDCl_3$) 1.1- 1.9 (m, 6H), 2.49 - 3.10 (m, 4H), 3.64 (s, 3H), 7.20 - 7.38 (m, 5H). ^{13}C-NMR ($CDC1_3$) 14.07 (CH_2), 24.34 (CH_2), 25.78 (CH_2), 29.85 (CH_2), 46.89 (CH), 58.44 (CH), 58.69 (CH_3), 127.80 (CH), 128.59 (CH), 128.61 (CH), 128.71 (CH), 128.83 (CH), 136.23 (C), 172.59 (CO). MS: 233(M^+), 150, 118, 84, 55.

Hydrochloride of methyl (2*S*, 2'*R*)-2-phenyl-2-(2'-piperidyl)acetate (1d): 1d (1.8 g, 8 mmol) was dissolved in MeOH (30 ml) and an HCl solution (5 ml) containing 10% MeOH was added under an atmosphere of N_2 at room temperature for 3 h. The resulting reaction mixture was concentrated and the solid residue was recrystallized from EtOH/Et_2O to give the hydrochloride of 1d as a white solid (0.66 g, 32%). The optical yield and diastereomeric selectivity were 99%ee and 98%de, respectively. mp 216 - 218 °C, (Lit. [1], mp 233 -235 °C; Lit. [6], mp 218 -219 °C, Lit. [22], mp 217 -218 °C), $[\alpha]^{20}_D$ -91.0° (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; Lit. [22]*, $[\alpha]^{20}_D$ -93.0°, c =1.3, MeOH).

3. Results and Discussion

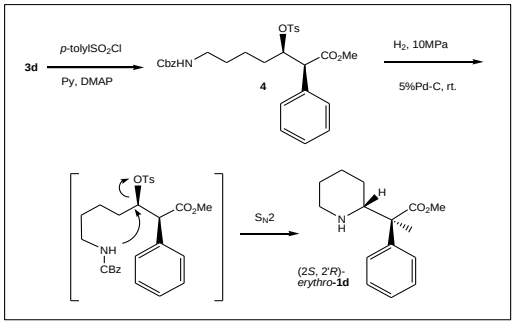
First, the β-ketoester 2, which has already been prepared according to our previous report [22]*, was evaluated for the diastereoselective hydrogenation in the presence of some Ru-(*R*)-BINAP complexes [23] as a catalyst under several conditions. Therefore, the asymmetric hydrogenation of 2 produced the best result in the case of using $[NH_2Et_2][\{RuCl((R)\text{-}p\text{-}tolyl\text{-}BINAP)\}_2(\mu\text{-}Cl)_3]$ [24] as the catalyst and the best solvent was CH_2Cl_2 (Scheme 2).



Scheme 2. Asymmetric hydrogenation of methyl 7-*N*-(benzyloxycarbonylamino)-3-oxo-2-phenylheptanoate 2

The absolute configuration of 3d was determined by comparing the optical rotation data and spectral data from a previous report [14] after conversion to 1d. The stereo-isomer ratio of *erythro*/*threo* (3d/3a) was 8:2, and the optical purity of each of the forms was 98% ee and 96% ee, respectively. The stereoisomer ratio of *erythro*/*threo* (3d/3a) and the optical purity of 3d were determined by HPLC analysis. The conditions of the analysis are shown in the Material and Method section.

The crude 3d was purified by silica gel chromatography, then treated with *p*-toluenesulfonyl chloride in pyridine and dimethylaminopyridine (DMAP) to give the *p*-tosylate 4 in 77.5% yield. The *erythro/threo* ratio of 4 was determined by HPLC to be 8:2. Next, the crude 4 was dissolved in MeOH, including AcOH and treated under the H_2 pressure of 1 MPa in the presence of 5%Pd-carbon to give 1d. This closing reaction occurred by a S_N2 reaction (Scheme 3).



Scheme 3. The synthesis of (2*S*, 2'*R*)-*erythro*-methylphenidate 1d from methyl (2S, 3*R*)-7-*N*-(benzyloxycarbonylamino)-3-hydroxy-2-phenyl heptanoate 3d

The crude 1d was converted to the hydrochloride salt by HCl solution in MeOH, and the recrystallization was repeated several times for purification. The optical rotation and spectral data of 1d agreed with the reported data [22]*.

4. Conclusion

The authors have described the synthesis of (2*S*, 2'*R*)-*erythro*-methylphenidate 1d which is known as an antidepressant. Thus, 1d was synthesized by tosylation and

cyclization of methyl (2*S*, 3*R*)-7-*N*-(benzyloxycarbonyl-amino)-3-hydroxy-2-phenylheptanoate 3d from methyl *N*-(benzyloxycarbonylamino)-3-oxo-2-phenylhepta-noate 2 by diastereoselective hydrogenation using the Ru-(*R*)-BINAP complex catalyst.

Acknowledgments

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