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Original Article

The Asymmetric Synthesis of (2*S*,3*S*)-3-*N*-*tert*-Butoxycarbonylamino-2-Hydroxy-4-Phenylbutanoic Acid: A Core Component of Protease Inhibitors

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Abstract *— (2S,3S)-3-N-tert-Butoxycarbonylamino-2-hydroxy-4-phenylbutanoic acid 1, which can serve as a chiral building block of effective aspartic protease inhibitors, could be synthesized from methyl 4-phenyl-2-chloro-3-oxobutyrate 3 by the asymmetric hydrogenation using the Ru-BINAP complex catalyst as the key step in high optical purity and in good yield.*

Keywords — *Aspartic protease inhibitors, HIV-1 protease, α-hydroxy-β-amino acid, asymmetric hydrogenation, Ru-BINAP complex catalyst.*

I. INTRODUCTION

α-Hydroxy-β-amino acids are well known as inhibitors of the development of protease. To develop effective aspartic protease inhibitors, such as HIV-1 protease, malaria plasmepsin, and human β-secretase inhibitors, α-hydroxy-β-amino acids are also the critical core structure. Especially, an optically-active allophenylnorstatin derivative, (2*S*,3*S*)-3-*N*-*tert*-butoxy carbonyl amino-2-hydroxy-4-phenyl-butanoic acid **1**, is known as a useful and important material for synthesizing a peptide compound that exhibits HIV protease inhibitory activity (KNI-272 and KNI-764) [1]. (Fig. 1)

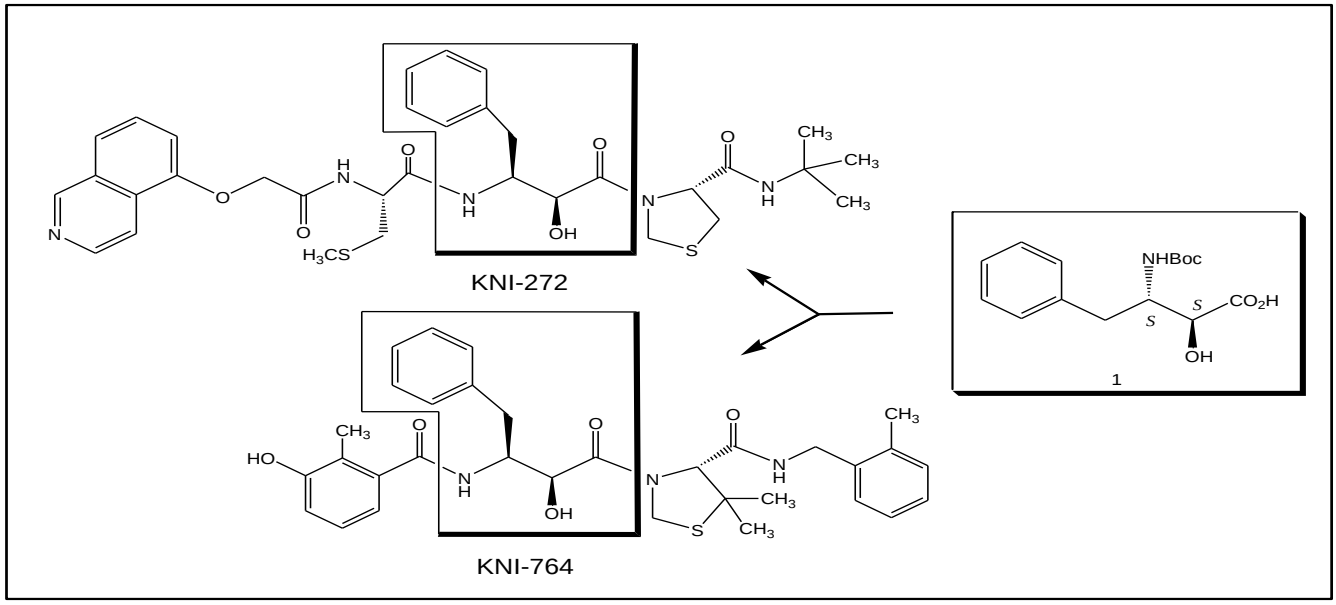


Fig. 1 Structures of KNI-272, KNI-764, and 1

It is known that **1** could be synthesized from phenylalaninal, which is prepared from phenylalanine in several steps. Phenylalaninal was added to hydrogen cyanide, followed by hydroxylating to give cyanohydrin, therefore, inverting the steric configuration of the hydroxyl groups to provide two optically active sites [2,3]. However, these processes have the same problems because of the involvement of an oxidation reaction, a step using harmful cyanide, and a step of steric inversion.

In addition, it has been difficult to obtain the desired compound with a high optical purity since the phenylalaninal intermediate is very labile and easily racemized. Therefore, it has been demanded to develop a process for preparing **1** with high optical purity, easily, safely, and in high yield.

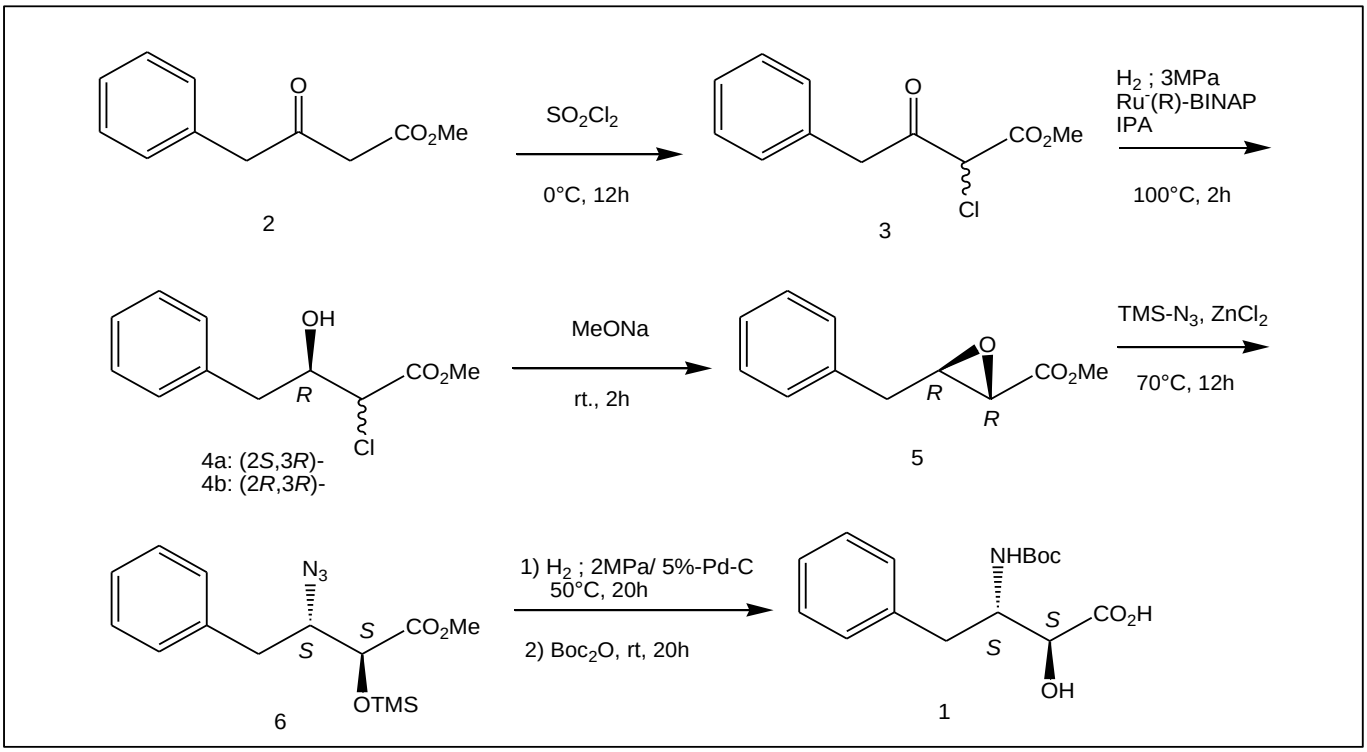
On the other hand, the enantioselective hydrogenation with the Ru-BINAP complex catalyst is one of the most powerful tools for the synthesis of optically active compounds [4]. Moreover, new chiral phosphorous ligands for enantioselective hydrogenation are used, and their review has been reported [5].

In particular, the asymmetric hydrogenations of diketones, β-ketoesters, and enamide esters are well known. Furthermore, it is known that the hydrogenation of the γ-chloro-β-ketoester or benzyloxy ketoester catalyzed by Ru-BINAP gives the intermediates of carnitine and compactin, respectively [4b, 6].

The author has studied asymmetric hydrogenation in order to develop the synthesis of the optically-active compounds as useful intermediates of drugs [7] and now reports the efficient synthesis of optically-active **1** from methyl 2-chloro-4-phenyl-3-oxobutyrate **3** by asymmetric hydrogenation using the Ru-BINAP complex catalyst [8] as a key step.

II. RESULTS AND DISCUSSION

First, the β-ketoester **2**, which was commercially available, was halogenated to give the α-chloro-β-ketoester **3** using SO_2Cl_2 in a conventional manner [9] with 88% yield. Next, **3** was reduced by asymmetric hydrogenation using a Ru-(*R*)-BINAP complex as a catalyst to predominately give methyl (2*S*)-chloro-(3*R*)-hydroxy-4-phenylbutyrate **4a** in 95% yield. The reaction was carried out at 50°C under the H_2 pressure of 3 MPa for 30 hours. In the case of using the Ru-(*R*)-BINAP complex, it was found that the 3-hydroxy group has the *R*-configuration [4b]. The stereoisomer ratio of **4a**/**4b** (*syn/anti*) was 87/13, and the optical purity was 81%ee (**4a**; *syn*) and 95%ee (**4b**; *anti*) by HPLC analysis.



Scheme The synthetic route of 1 from β-ketoester 2

The subsequent reaction, the epoxidation of **4** with a base, is known to proceed by 1,3-elimination via an S_{Ni} mechanism [10].

In the transition state of the elimination process, the reacting groups are in the antiperiplanar conformation. The epoxide formation is stereospecific. (Fig.2)

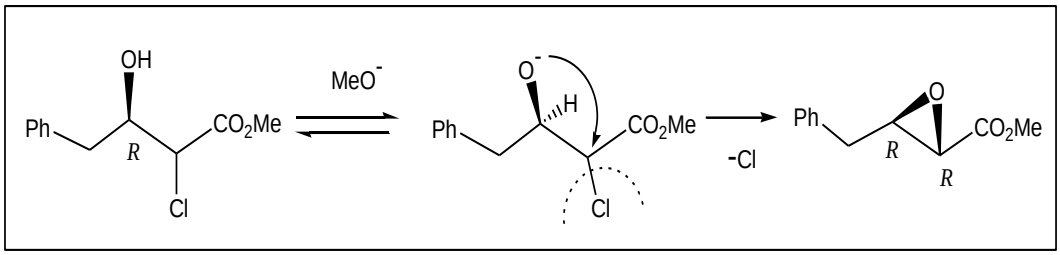


Fig. 2 Epoxide formation by 1,3-elimination via S_{Ni} mechanism

Thus, methyl (2*R*,3*R*)-2,3-epoxy-4-phenylbutyrate **5** was predominantly obtained by the epoxidizing of **4** with NaOMe as a base at room temperature for 3 hours. Furthermore, it is known that the epoxide is cleaved by trimethylsilylazide (TMS-N_3) and a catalytic amount of $ZnCl_2$ as a Lewis acid to give a hydroxyazide due to the regioselective cleavage of the epoxide by a nitrogen nucelophile [11]. (Fig. 3)

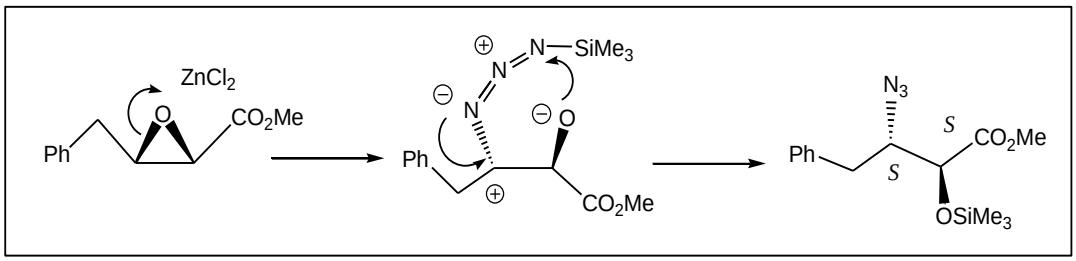


Fig. 3 The regioselective cleavage of the epoxide by a nitrogen nucleophile

The hydrogenolysis of **6** by using 5% Pd-on-carbon was carried out at 50°C under the H_2 pressure of 2 MPa for 10 hours. The trimethylsiloxy group at the 2-position was eliminated to form a hydroxyl group and followed by treating with *t*-butoxy carbonyl anhydride (Boc_2O) to afford to (2*S*,3*S*)-3-*N*-*tert*-butoxy carbonyl amino-2-hydroxy-4-phenylbutanoic acid **1**. The crude product was purified by recrystallization using EtOAc as a solvent to give the pure **1** in 50% yield. The configuration of **1** was determined by comparison of the optical rotation in the literature [3]. Therefore, the high optical purity of **1** was obtained from **3** in 4 steps by asymmetric hydrogenation using the Ru-(*R*)-BINAP catalyst as the key step.

III. MATERIALS AND METHODS

All reagents and solvents were obtained from commercial sources and used without further purification. The melting points were determined using a Yanagimoto micro melting apparatus and are uncorrected. The NMR spectra were recorded with TMS as the internal standard using a Bruker AM-400 (400MHz). The chemical shifts are given in ppm. Specific rotation: DIP-4 (JASCO). GC: HP 5890A (Hewlett Packard), HPLC: SPD10A, LC10AT (Shimadzu)

Synthetic procedures

Methyl 2-chloro-3-oxo-4-phenylbutyrate (3): Methyl 3-oxo-4-phenylbutyrate **2** (22 g, 0.115 mol) was cooled in an ice bath, SO_2Cl_2 (15.46 g, 0.115 mol) was then dropwise added, followed by overnight stirring. Excess SO_2Cl_2 was evaporated under reduced pressure, and the residue was dissolved in toluene and washed with an aqueous solution of $NaHCO_3$. The solvent was removed by evaporation, and the residue was purified by silica gel column chromatography using EtOAc/*n*-hexane (1/5) as the eluent to give **3** as an oily product (22.8 g, 88%).

Methyl (2*RS*,3*R*)-2-chloro-3-hydroxy-4-phenylbutyrate (4): Into a 500-ml autoclave were charged **3** (25 g, 0.11 mmol) in i-PrOH (50 ml) and $[NH_2Et_2][\{RuCl((R)\text{-p-tolyl-BINAP})\}_2\mu\text{-}Cl)_3]$ [8,12] (50 mg, 0.028 mmol) under an atmosphere of N_2. The atmosphere was then replaced with

H_2 at 3 MPa and 100°C for 2 h. The reaction mixture was then concentrated to give **4** as an oily product (25.15 g, 95%). The stereo isomer ratio of *syn*/*anti* = (2*S*,3*R*)/(2*R*,3*R*) was 87/13 by HPLC analysis (Column-1: Inertsil SIL; THF/*n*-hexane = 5/95, Solvent: CH_3CN/H_2O = 4/6 (pH = 2.3, H_3PO_4). Flow rate: 0.5 ml/min Detector: UV detector 230 nm. Column temp.: 35°C.). The optical purity was 81%ee (2*S*,3*R*) and 95%ee (2*R*,3*R*) by HPLC analysis. (Column-2: CHIRALCEL OD-H; Solvent; 2-propanol/*n*-hexane = 1/99, Flow rate: 1.0 ml/min. Detector: UV detector 254 nm, Column temp.: 35°C.). ^{1}H-NMR ($CDCl_3$): *Syn* (2*S*,3*R*): 2.47 (brs, 1H), 2.86 (dd, J = 14.0, 6.3Hz, 1H), 3.12 (dd, J = 13.9, 10.1 Hz, 1H), 3.80 (s, 3H), 4.18 (d, J = 7.3Hz, 1H), 4.27 (brs, 1H), 7.26 - 7.33 (m, 5H). *Anti* (2R,3R): 2.62 (brs, 1H), 2.90 (dd, J = 13.0, 3.9Hz, 1H), 2.99 (dd, J = 13.0, 9.8Hz, 1H), 3.78 (s, 3H), 4.27 (d, J = 3.1Hz, 1H), 4.21 - 4.30 (brs, 1H), 7.26 - 7.33 (m, 5H).

Methyl (2*R*,3*R*)-2,3-epoxy-4-phenylbutyrate (5): To the mixture of a 28% MeOH solution of NaOMe (20.9 g, 0.97 mol) and MeOH (25 ml), **4** (22.9 g, 0.09 mol) in MeOH (50 ml) was dropwise added with cooling in an ice bath and stirred at the same temperature for 2 h. To a 0.1 M phosphate buffer (pH=7, 120 ml) cooled in an ice bath, the reaction solution was slowly poured. MeOH was evaporated under reduced pressure, and the residue was extracted with EtOAc and washed with brine. The solvent next evaporated, then the residue was distilled to give **5** as an oil (11.1 g, 75%). bp. 105°C/0.3torr. The chemical purity was 93% by GC analysis (Column: Neutra bond 1, 30m x 0.25m Temp.: 100 - 250°C, 5°C/min.). ^{1}H-NMR ($CDCl_3$): 2.96 (d, J = 5.3Hz, 2H), 3.28 (d, J = 1.8Hz, 1H), 3.40-3.42 (m, 1 H), 3.76 (s, 3H), 7.23 - 7.32 (m, 5H).

Methyl (2*S*,3*S*)-3-azido-2-trimethylsiloxy-4-phenyl-butyrate (6): 5 (11.0 g, 0.057 mol), azidotrimethylsilane (TMS-N_3) (8.08 g, 0.16 mol), and $ZnCl_2$ (0.78 g, 5.6 mmol) were stirred at 70°C for 20 h. The reaction mixture was poured into toluene (100 ml) and silica gel (20 g), then stirred for 1 h, followed by filtration. The filtrate was washed with toluene and concentrated. The concentrate was purified by silica gel column chromatography (EtOAc/*n*-hexane = 5/95) to give **6** as an oily product (13.8 g, 79 %). The chemical purity was 77% by GC analysis (Column: Neutra bond 1, 30m x 0.25m Temp.: 100 - 220°C, 5°C/min.). ^{1}H-NMR ($CDCl_3$): 0.19 (s, 9H), 2.90-2.95 (m, 2H), 3.70 (s, 3H), 3.76 - 3.79 (m, 1H), 4.34 (d, J = 4.1Hz, 1H), 7.23 - 7.30 (m, 5H).

(2*S*,3*S*)-3-*tert*-Butoxycarbonylamino-2-hydroxy-4-phenyl butyric acid (1): In a 500-ml autoclave were charged **6** (13.3 g, 0.043 mol), 5%Pd-C (1 g) and THF (100 ml), and the mixture was stirred at 50°C under the H_2 pressure of 2MPa for 20 h. The catalyst was removed by filtration using Celite, and the solvent was evaporated. The residue (12.8 g) was cooled, and 1 N NaOH (100 ml) was added, followed by stirring overnight at room temperature. To the reaction mixture were dropwise added Boc_2O (10.3 g, 0.046 mol) in THF (60 ml) with cooling, then the mixture was stirred overnight at room temperature. The organic solvent was evaporated, and the residual aqueous layer was washed with toluene (100 ml). To the aqueous layer was added EtOAc (100 ml), and the mixture was neutralized to pH 4 - 5 with 20% H_3PO_4 while stirring with cooling. The solvent was evaporated to obtain **1** as a solid product (13.1 g, 85%). Recrystallization from EtOAc gave a pure **1** (5.4 g, 50%). mp. 147 - 148°C {lit.,[3] mp. 147 - 148°C}, $[\alpha]^{23}_D$ = +2.65° (c = 1.05, MeOH) {lit.,[3] $[\alpha]^{20}_D$ = +2.69° (c = 1.00, MeOH)}. ^{1}H-NMR (CD_3OD): 1.31 (brs, 9H), 2.69 - 2.81 (m, 2H), 4.11 - 4.16 (m, 1H), 4.18 - 4.20 (m, 1H), 7.12 - 7.25 (m, 5H).

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