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HIGHLY STEREOSELECTIVE SYNYHESIS OF (2*R*,3*R*)-2-AMINO-3-CYCLOHEXYL-3-HYDROXYPROPIONIC ACID USING ASYMMETRIC HYDROGENATION†

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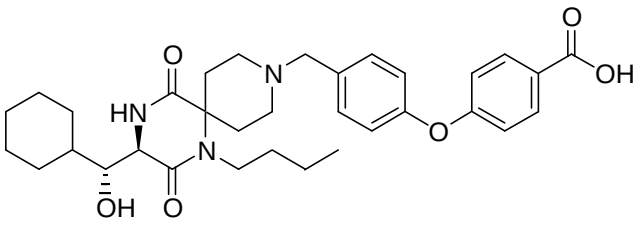
Abstract (2*R*,3*R*)-2-Amino-3-cyclohexyl-3-hydroxypropionic acid, a β-hydroxy-α-amino acid in a new CCR5 antagonist, was efficiently synthesized by the Noyori asymmetric hydrogenation of α-benzoylamino-β-keto ester (**6**) and intramolecular S_N2-type inversion as the key steps.

INTRODUCTION

(2*R*,3*R*)-2-Amino-3-cyclohexyl-3-hydroxypropionic acid is a chiral core of a new CCR5 antagonist (ONO-4128/GW873140) as shown in Figure 1. The CCR5 antagonist has attracted attention as a new agent for the anti-HIV chemotherapy.[1] In the course of our studies on the synthesis of natural cyclodepsipeptides, we have demonstrated the development of enantio- and diastereoselective synthesis of β-hydroxy-α-amino acids.[2,3] Using this methodology, we succeeded in stereoselective and concise synthesis of the (2*R*,3*R*)-2-amino-3-cyclohexyl-3-hydroxypropionic acid.[2a] We report here an alternative approach for the synthesis of (2*R*,3*R*)-2-amino-3-cyclohexyl-3-hydroxypropionic acid using the Noyori's asymmetric hydrogenation through dynamic kinetic resolution.[4,5]



ONO-4128/GW873140

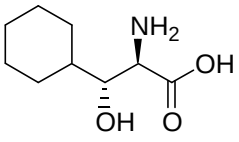


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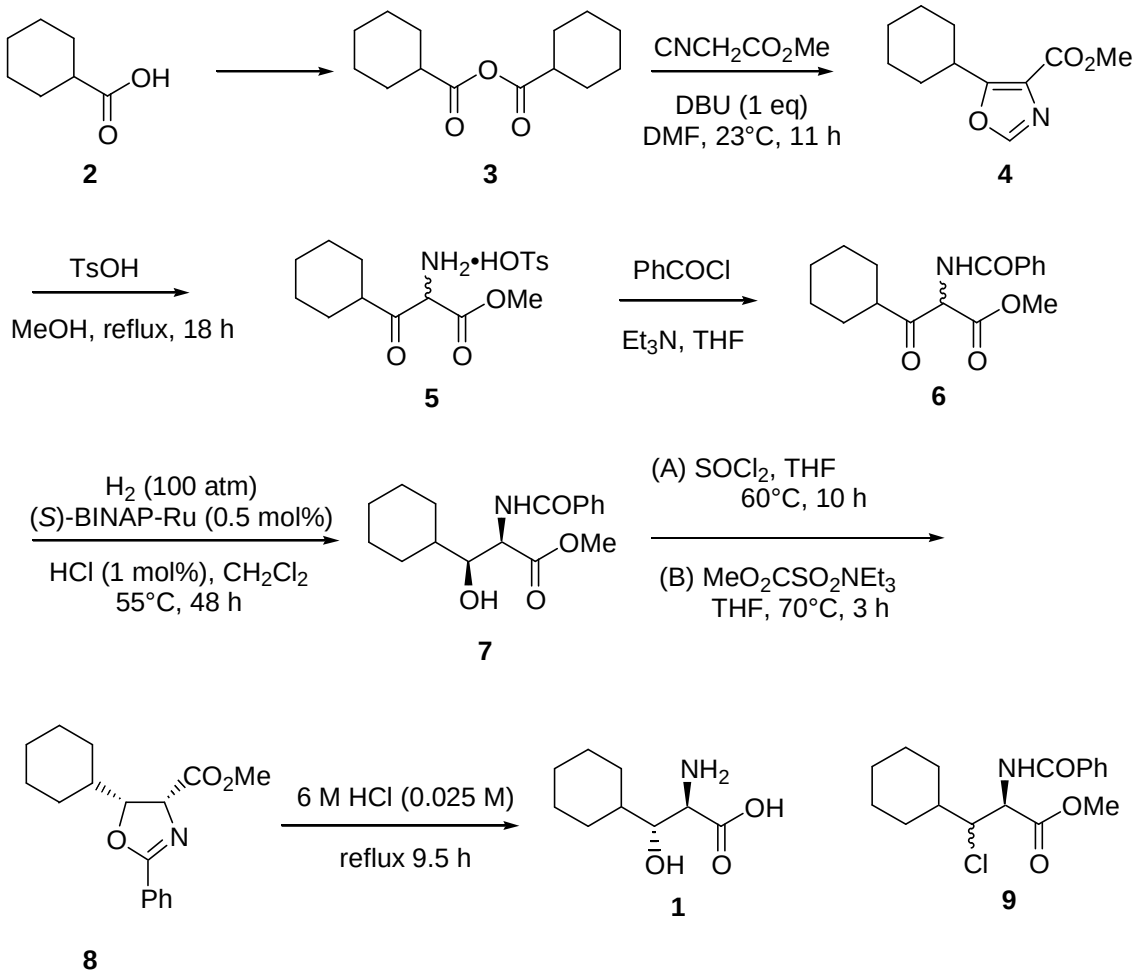
Figure 1. (2*R*,3*R*)-2-Amino-3-cyclohexyl-3-hydroxypropionic acid

† This paper is dedicated to Professor Emeritus Keiichiro Fukumoto on the occasion of his 75th birthday.

RESULTS AND DISCUSSION



Scheme 1. Synthesis of (2*R*,3*R*)-2-Amino-3-cyclohexyl-3-hydroxypropionic acid

Synthesis of the required substrate, an α-amino-β-keto ester, commenced with preparation of cyclohexanecarboxylic anhydride. Treatment of the obtained anhydride with methyl isocyanoacetate in the presence of diazabicyclo[4.3.0]undecene (DBU) afforded oxazole (**4**) in 80% yield. Acid-catalyzed cleavage of **4** with *p*-toluenesulfonic acid (TsOH) proceeded cleanly under reflux in methanol to give α-amino-β-keto ester (**5**) in quantitative yield.[6] Protection of **5** using benzoyl chloride and triethylamine in tetrahydrofuran (THF) at the nitrogen function provided methyl 2-benzoylamino-3-cyclohexyl-3-oxopropionate (**6**) in 86% yield in two steps. The key hydrogenation of **6** using $RuCl_2$((*S*)-binap)[7] (0.5 mol%) in the presence of hydrogen chloride (1 mol%) in methylene chloride was found to be sluggish and required higher temperature. Finally, the reaction at 55 °C for 48 h gave the (2*R,* 3*S*)-2-*N*-benzoylamino-3-cyclohexyl-3-hydroxypropionic acid methyl ester ((-)-**7**) in 95% yield. The

enantiomeric excess (ee) of **7** was shown to be 98% ee by HPLC analysis using a chiral column. The absolute stereostructure of **7** was unambiguously determined by comparison with authentic sample.[2a] The product **7** has 2,3-*syn* stereochemistry and can be convert to the desired 2,3-*anti*-β-hydroxy-α-amino acid using an intramolecular S_N2-type inversion. Thus, the S_N2-type inversion of the C(3) stereochemistry of (-)-**7** was carried out but, compared with that of the isopropyl counterpart,[6a] was unexpectedly sluggish and difficult due to generating the side product **9**.[8] Finally, the reaction by treatment with thionyl chloride in THF at 0 °C and then heating to 60 °C for 10 h furnished the *cis*-oxazoline ((-)-**8**) with (2*R*,3*R*)-stereochemistry in 60% yield. In order to prevent the formation of the byproduct, we examined several alternative approachs for this cyclization. Among them, only the Burgess reagent[9] in THF at 70°C for 3 h afforded a comparable result. The thus obtained (-)-**8** was hydrolyzed with 6 M hydrochloric acid under reflux to afford (2*R*,3*R*)-2-amino-3-cyclohexyl-3-hydroxypropionic acid ((-)-**1**) in 85% yield. The overall yield of (-)-**1** are 38% yield from **3**.

The above reaction sequences comprise a facile synthesis of (2*R*,3*R*)-2-amino-3-cyclohexyl-3-hydroxypropionic acid in seven steps with a good overall yield, which is comparable with that of the reported method.[2a]

EXPERIMENTAL

Melting points are uncorrected. IR spectra were recorded on a JASCO FT/IR-230 spectrometer. NMR spectra were recorded on JEOL JNM GSX400A, JNM GSX500A, and JNM ECP400 spectrometers. FAB mass spectra were obtained with a JEOL JMS-HX-110A spectrometer. Optical rotations were determined on a JASCO DIP-140 polarimeter. Column Chromatography was carried out with silica gel BW-820MH (Fuji silysia).

Cyclohexanecarboxylic anhydride

To a stirred solution of cyclohexanecarboxylic acid (53.6 g, 0.418 mol) and triethylamine (58.3 mL, 0.418 mol) in THF (418 mL) at 0 °C was added dropwise cyclohexanecarboxylic acid chloride (56 mL, 0.419 mol) and the reaction mixture was stirred at 23 °C for 24 h. After removal of the precipitates by filtration using Celite, the filtrate was diluted with Et_2O (1 L), washed with 5 % aqueous sodium hydrogen carbonate and saturated brine, dried over sodium sulfate, and filtered. The filtrate was concentrated in vacuo to give the anhydride (**3**, 102g, quant) as a colorless oil: IR (neat) 2933, 2669, 1811, 1740, 1450 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.19-1.36 (4H, m), 1.43-1.67 (4H, m), 1.72-1.81 (6H, m), 1.93-1.98 (4H, m), 2.37-2.45 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.07, 28.31, 43.86, 67.83, 171.76.

5-Cyclohexyloxazole-4-carboxylic acid methyl ester (**4**)

To a stirred solution of **3** (8.20 g, 34.4 mmol) and methyl isocyanoacetate (3.11 g, 31.3 mmol) in DMF (10 mL) at 0 °C was added dropwise DBU (4.68 mL, 31.3 mmol) and the reaction mixture was stirred at

23 °C for 11 h. The mixture was diluted with EtOAc/*n*-hexane (5/1, 48 mL), washed with saturated brine, 1M hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and saturated brine, and dried over sodium sulfate. After filtration, the filtrate was condensed in vacuo to give the crude oxazole (**4**, 7.22 g), which was recrystallized from *n*-hexane/EtOAc to give pure **4** (5.0 g, 75 %): mp 97.5-101 °C; IR (KBr) 2931, 2852, 1719, 1599, 1199 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.26-1.89 (10H, M), 3.45-3.48 (1H, m), 3.91 (3H, s), 7.74 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.65, 25.93, 30.64, 35.42, 51.91, 125.23, 148.56, 162.64, 164.07; EI-LRMS 209 (M^+). Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 62.92; H, 7.11; N, 6.52.

2-Benzoylamino-3-cyclohexyl-3-oxopropionic acid methyl ester (**6**)

To a stirred solution of **4** (3.94 g, 18.8 mmol) in MeOH (94 mL) at 23 °C was added in one portion *p*-toluenesulfonic acid hydrate (8.95 g, 47 mmol) and the reaction mixture was heated at reflux for 18 h. After cooling the mixture to rt, the mixture was concentrated in vacuo to give the white solids which were triturated with Et_2O and filtered. The obtained solids (8.64 g) were used as such for next reaction.

The above solids were suspended in THF (37.6 mL) and cooled to 0 °C. Benzoyl chloride (2.18 mL, 18.8 mmol) followed by triethylamine (7.86 mL, 56.4 mmol) were added dropwise. After stirring the mixture at 23 °C for 12 h, the reaction mixture was diluted with water and a mixture of EtOAc and *n*-hexane (5/1) and the mixture was separated. The organic layer was washed with 1M hydrochloric acid, water, saturated aqueous sodium hydrogen carbonate, and saturated brine, dried over sodium sulfate, and filtered. The filtrate was concentrated in vacuo to give the residue (5.47 g) as a yellow oil, which was chromatographed on silica gel (*n*-hexane/EtOAc = 3/1) to afford the benzamide (**6**, 4.90 g, 86 %) as colorless solids: IR (KBr) 3319, 1757, 1707, 1639 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.21-2.09 (10 H, m), 2.87-2.88 (1H, m), 3.84 (3H, s), 5.59 (1H, d, J = 6.6 Hz), 7.32 (1H, d, J = 5.6 Hz), 7.84-7.86 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.09, 25.59, 25.70, 27.80, 29.18, 48.56, 61.14, 127.25, 128.64, 132.08, 133.07, 166.70, 166.97, 204.09; EI-LRMS 303 (M^+). Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.12; H, 6.71; N, 4.53.

(2*R*, 3*S*)-2-Benzoylamino-3-cyclohexyl-3-hydroxypropionic acid methyl ester (**7**)

The (*S*)-BINAP-Ru catalyst was prepared from $[RuCl_2(C_6H_6)]_2$ (10.3 mg, 0.0206 mmol) and (*S*)-BINAP (28.3 mg, 0.0453 mmol) according to the Noyori's procedure.[7] A degassed solution of *N*-benzoyl α-amino-β-keto ester (**6**, 2.52 g, 8.31 mmol) in CH_2Cl_2 (5.1 mL) followed by 4 M HCl-dioxane (21.0 μL, 0.0840 mmol) was added via cannula to the obtained catalyst under an argon atmosphere. The reaction mixture was hydrogenated under 100 atm of hydrogen at 55°C for 48 h in an autoclave. After releasing the pressure and removal of volatiles, the residue was chromatographed on silica gel (*n*-hexane/EtOAc = 2/1) to give the amino acid (**7**, 2.41 g, 95 %) as a colorless oil, which was judged to be 98 % ee by HPLC analysis (CHIRALCEL OD-H, *n*-hexane/*i*-PrOH = 85/15, flow rate = 0.5 mL/min, retention time: 10.5

min for 2*R*,3*S*-isomer, 17.6 min for 2*S*,3*R*-isomer). **7**: $[\alpha]_D^{24}$ -16.2 (*c* 1.18, $CHCl_3$); IR (neat) 3446, 1735, 1654 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.00-2.00 (1H, m), 2.12-2.13 (1H, m), 3.78 (3H, s), 3.79-3.93 (1H, m), 5.03 (1H, d, *J* = 9.3 Hz), 6.83 (1H, d, *J* = 9.3 Hz), 6.86-7.86 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.66, 25.73, 26.13, 28.75, 29.19, 40.15, 52.65, 54.00, 127.20, 128.62, 131.84, 133.88, 167.53, 172.40. HRMS (FAB) calcd for $C_{17}H_{23}NO_4$: 306.1706(M^++1). Found: 306.1718.

(4*R*,5*R*)-5-Cyclohexyl-2-phenyl-4,5-dihydrooxazole-4-carboxylic acid methyl ester (**9**)

Mehod (A): To a cooled stirred solution of **7** (300 mg, 0.982 mmol) in THF (10 mL) at 0 °C was added dropwise thionyl chloride (79μL, 1.08 mmol) and the mixture was heated to 60 °C for 10 h. After cooling the mixture to 0 °C, the mixture was carefully quenched with saturated aqueous sodium hydrogen carbonate. The whole was extracted with EtOAc and the organic layer was washed with water and saturated brine. After filtration, the filtrate was concentrated in vacuo to give the residue, which was chromatographed on silica gel (*n*-hexane/EtOAc = 4/1) to afford the *cis*-oxazoline (**8**, 169 mg, 60 %) as a colorless oil along with the byproduct **9**. **8**: $[\alpha]_D^{20}$ -75.4 (*c* 1, $CHCl_3$); IR (neat) 2928, 1746, 1644 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.09-2.00 (1H, m), 3.79 (1H, m), 4.55 (1H, dd, *J* = 7.7, 9.7 Hz), 4.94 (1H, d, *J* = 9.7 Hz), 7.40-7.53 (3H, m), 7.98-8.00 (2H, m); EI-LRMS 287 (M^+); ^{13}C NMR ($CDCl_3$) δ 170.6, 166.6, 131.7, 128.4, 128.2, 127.2, 86.5, 70.4, 52.0, 38.8, 29.8, 28.9, 26.0, 25.7, 25.4. HRMS (FAB) calcd for $C_{17}H_{21}NO_3$: 288.1593(M^++1). Found: 288.1605. The crude **9** was a ca.3:1 mixture of diastereomers and was chromatographed on silica gel (*n*-hexane/EtOAc = 2/1) to give the major isomer as a colorless oil. **9** (major): $[\alpha]_D^{25}$ -55.5 (*c* 1.1, $CHCl_3$); IR (neat) 2926, 2853, 1603, 1580 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.03-2.16 (11H, m), 3.80 (3H, s), 4.33 (1H, dd, *J* = 2.0 Hz, 9.6 Hz), 5.43 (1H, dd, *J* = 2.0 Hz, 9.8 Hz), 6.76 (1H, d, *J* = 10 Hz), 7.47-7.58 (3H, m), 7.82-7.86 (2H, m); ^{13}C NMR ($CDCl_3$) δ 170.6, 166.6, 131.7, 128.4, 128.2, 127.2, 86.5, 70.4, 52.0, 38.8, 29.8, 28.9, 26.0, 25.7, 25.4; HRMS (FAB) calcd for $C_{17}H_{23}ClNO_3$: 324.1366(M^++1). Found: 324.1379.

Method (B): A mixture of **7** (59 mg, 0.193 mmol) and the Burgess reagent (110 mg, 0.46 mmol) in THF (2.5 mL) was heated to 70 °C for 3 h. After cooling the mixture to rt, the residue was chromatographed on silica gel (*n*-hexane/EtOAc = 4/1) to give the *cis*-oxazoline (**9**, 34 mg, 62 %) as a colorless oil.

(2*R*,3*R*)-2-Amino-3-cyclohexyl-3-hydroxypropionic acid (**1**)

6 M Aqueous hydrochloric acid (15 mL) was added to **9** (101.5 mg, 0.353 mmol) and the mixture was heated at reflux for 9.5 h. After cooling the mixture to rt, the mixture was extracted with Et_2O. The aqueous layer was concentrated in vacuo to give the amino acid hydrochloride (**1**, 105 mg). This crude hydrochloride was charged on Dowex 50W-X4 ion-exchange resin (20 mL, H^+ form). The resin was eluted with water and then 2 M pyridine aqueous solution. The combined aqueous pyridine fractions were condensed in vacuo to give the pure amino acid (**1**, 68 mg, quant) as white powder. The analytical sample was obtained by precipitation from aqueous MeOH.

mp 179-183 ℃ (decomp.); $[\alpha]_D^{25}$ -38.1 (*c* 0.78, 1M HCl); IR (neat) 3342, 3316, 2919, 2849, 1601 cm^{-1}; ^1H NMR (D_2O, 55 ℃) δ 1.03-2.16 (11H, m), 3.50 (1H, dd, *J* =3.2 Hz, 9.2 Hz), 3.81 (1H, d, *J*=3.2 Hz); ^{13}C NMR (D_2O, 55 ℃) δ 172.5, 75.8, 58.0, 40.4, 29.9, 29.7, 26.7, 26.2, 26.1. HRMS (FAB) calcd for $C_9H_{18}NO_3$: 188.1287 (M^++1). Found: 188.1281.

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