*Tetrahedron: Asymmetry* Vol. 4, No. 10, pp. 2179-2182, 1993
Printed in Great Britain

0957-4166/93 $6.00+.00
Pergamon Press Ltd

# Enantioselective Synthesis of L- and D-Isoserine via Asymmetric Hydrogenation of Methyl *N*-Phthaloyl-3-amino-2-oxopropanoate

**Kyoko Nozaki, Naomasa Sato, and Hidemasa Takaya***

Division of Material Chemistry, Faculty of Engineering,
Kyoto University, Sakyo-ku, Kyoto 606-01, Japan

(*Received in Japan* 12 *July* 1993)

**Abstract:** L- and D-isoserine were synthesized enantioselectively via asymmetric hydrogenation of 3-amino-2-oxoester **5** catalyzed by [RuCl(binap)(benzene)]Cl. Recrystallization and deprotection of (*S*)-**6** (81% *ee*) afforded enantiomerically pure L-isoserine. The enantioface selection by the catalyst was opposite to that observed in asymmetric hydrogenation of other 2-oxoesters, such as methyl phenylglyoxylate and methyl 2-oxocyclohexylacetate.

L-Isoserine ((*S*)-3-amino-2-hydroxypropanoic acid) is a biologically active β-amino acid[1] and a constituent of antibiotic peptides such as edeine[2] and tatumine.[3] Several asymmetric synthesis of L- or D-isoserine have been reported.[4] In view of the physiological significance of these aminoacids as therapeutic agents, the opening of a new efficient synthetic route of L- and D-isoserine is still earnestly desired.

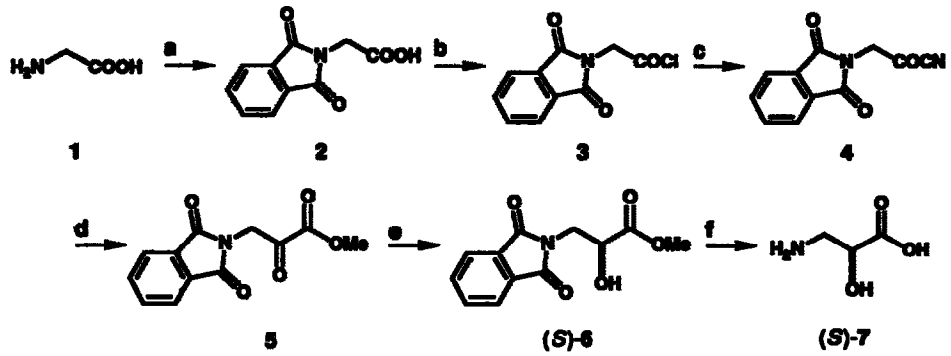
In our recent studies on the asymmetric hydrogenation of various carbonyl compounds, we have found that hydrogenation of 2-oxoesters catalyzed by cationic Ru(II) complex [RuCl(binap)(benzene)]Cl affords the corresponding 2-hydroxyesters in good to excellent enantiomeric excesseses.[5] In this paper, we describe our new synthesis of L- and D-isoserine using the asymmetric hydrogenation of methyl *N*-phthaloyl-3-amino-2-oxopropanoate (**5**) as a key step.[6]

The synthetic route is shown in Scheme 1. Glycine was converted into the corresponding 3-amino-2-oxoester **5** via 3-amino-2-oxonitrile **4**. Replacement of the chloride in **3** with iodide by treatment of **3** with sodium iodide was essential to obtain **4** in good yield.[7] Asymmetric hydrogenation of **5** catalyzed by [RuCl((*R*)-binap)(benzene)]Cl in methanol afforded protected L-isoserine, *N*-phthaloyl-L-isoserine methyl ester ((*S*)-**6**) in 99% yield, and in 74% *ee*. The enantioface selection by the catalyst in this reaction was opposite to that chosen in the asymmetric hydrogenation of other 2-oxoesters, such as methyl phenylglyoxylate and methyl 2-oxocyclohexylacetate.[5] The difference could be explained by a significant chelation effect of the carbonyl moiety of the phthaloyl group in **5** on the metal center.

In further studies, it was found that addition of $HBF_4$ (10 equiv. to catalyst) improved the enantioselectivity to give (*S*)-**6** in up to 81% *ee*. Similar phenomena have been observed in the asymmetric hydrogenation of other 2-oxoesters which have either an aryl or an alkyl substituent at the C2-position.[5] The use of [RuCl((*S*)-binap)(benzene)]Cl as the catalyst under the same acidic conditions afforded (*R*)-**6** in 80% *ee* (88% yield). Enantiomerically pure (*S*)-**6** was obtained by recrystallization of (*S*)-**6** (81% *ee*) from chloroform—hexane (5 : 3) in 64% yield. Deprotection of (*S*)-**6** gave L-isoserine ((*S*)-**7**) whose spectral data

were identical with those of the authentic sample.[4a] The present method could be extended for the synthesis of other 3-amino-2-hydroxy-propanoic acid derivatives.

**Scheme 1**




1 2 3 4

5 (*S*)-6 (*S*)-7

a: Phthalic anhydride b: $PCl_5$ c: NaI, and then CuCN d: MeOH (1.0 equiv. to 4)—dry HCl, and then cold water e: $H_2$, catalyst: [RuCl((*R*)-binap)(benzene)]Cl with or without $HBF_4$ (10 equiv. to the catalyst) f: HCl aq, and then $NH_2NH_2{\cdot}H_2O$

## Experimental Section

**General.** All manipulations of oxygen- and moisture sensitive materials were conducted under purified argon atmosphere (BASF-Catalyst R3-11) by the use of the standard Schlenk techniques. Silica-gel chromatography was performed using Wakogel C-200. Nuclear magnetic resonance spectra were taken with JEOL EX-270 ($^1H$ 270 MHz and $^{13}C$ 67.8 MHz) spectrometer using tetramethylsilane ($^1H$, $^{13}C$) as internal standard, and coupling constants were given in hertz. All melting points measured with Yanagimoto-Seisakusho Micro Melting Point Apparatus were not corrected. Optical rotation values were given with JASCO DIP-360 spectrometer. IR spectra were obtained on a JASCO IR-810 grating spectrometer. Most reagents were available from Wako Pure Chemical Industries LTD or Nacalai Tesque. All the anhydrous solvents were purified by distillation under argon after drying. Dichloromethane, methanol, and acetonitrile were dried over calcium hydride, magnesium methoxide, and phosphorus pentoxide, respectively. Diethyl ether was dried over sodium benzophenone ketyl. Complex [RuCl(binap)(benzene)]Cl was prepared according to the literature procedure.[8]

**Preparation of *N*-Phthaloylglycyl Cyanide (4).**[7] *N*-Phthaloylglycyl chloride[9] (3) (4.73 g, 21.1 mmol) was added to a solution of NaI (6.35 g, 42.4 mmol) in $CH_3CN$ (40 mL). The solution instantaneously became pale yellow suspension which was stirred for 1 h at 0 °C. After being concentrated, $CH_2Cl_2$ (60 mL) was added to the residue. The suspension was filtered and the filtrate was concentrated. To the residue were added CuCN (2.44 g, 27.2 mmol) and $CH_3CN$ (200 mL). The resulting mixture was stirred for 2 h at 45 °C, and then the suspension was concentrated. To the residue was added $CH_2Cl_2$ (100 mL) to extract organic compounds. The organic phase was concentrated to afford *N*-phthaloylglycyl cyanide (4) (3.07 g, 68% yield): mp 132.7—133.3 °C (benzene); $^1H$ NMR ($CDCl_3$) $\delta$ 4.70 (s, $CH_2$), 7.74—7.78 (m, 2H, aromatic protons),

7.85—7.89 (m, 2H, aromatic protons); $^{13}$C NMR ($CDCl_3$) δ 47.6, 111.8, 124.1, 131.6, 134.8, 166.7, 170.5; IR (nujol) 2226 (CN), 1774, 1721 (CO) $cm^{-1}$. Anal. Calcd for $C_{11}H_6N_2O_3$: C, 61.69; H, 2.82; N, 13.08. Found: C, 61.81; H, 3.02; N, 12.93.

**Preparation of Methyl *N*-Phthaloyl-3-amino-2-oxopropanoate (5).**[10] A solution of *N*-phthaloylglycyl cyanide (4) (5.15 g, 24.0 mmol) and anhydrous methanol (0.77 g, 24.0 mmol) in dry $CH_2Cl_2$ (190 mL) was cooled to 0 °C. At this temperature, anhydrous hydrogen chloride was passed through the solution for 1 h. To the reaction mixture was added cold absolute diethyl ether (0 °C, 200 mL) to afford white precipitate. The precipitate was collected by filtration, washed with cold ether (0 °C, 25 mL x 2), and stirred in cold water. The resulting mixture was extracted with $CH_2Cl_2$ (50 mL x 5). The combined organic layers were dried over $Na_2SO_4$ and concentrated to give 2.61 g of methyl *N*-phthaloyl-3-amino-2-oxopropanoate (5) in 44% yield as colorless solid: mp 145.8—146.3 °C (methanol); $^1$H NMR ($CDCl_3$) δ 3.88 (s, OMe), 4.97 (s, $CH_2$) 7.64—7.96 (m, 4H, aromatic protons); $^{13}$C NMR ($CDCl_3$) δ 44.8, 53.4, 123.7, 131.9, 134.3, 159.5, 167.2, 185.4; IR (nujol) 1773, 1714 (CO) $cm^{-1}$. Anal. Calcd for $C_{12}H_9NO_5$: C, 58.30; H, 3.68; N, 5.67. Found: C, 58.28; H, 3.85; N, 5.59.

**Preparation of Racemic *N*-Phthaloylisoserine Methyl Ester ((±)-6).** A mixture of phthalic anhydride and racemic isoserine[11] ((±)-7) was heated at 145 °C for 30 min. The crude mixture was cooled to ambient temperature. To this was added a solution of methanol (10 mL) and thionyl chloride (2.5 mL) keeping the temperature at - 5 °C. The solution was stirred at room temperature for 17 h. After concentration, the crude mixture was purified by preparative TLC to give (±)-*N*-phthaloylisoserine methyl ester ((±)-6)) as white solid (35.2 mg, 48% yield): mp 110.0—110.5 °C ($CHCl_3$—hexane).

**Catalytic Hydrogenation of Methyl *N*-Phthaloyl-3-amino-2-oxopropanoate (5).** Methyl *N*-phthaloyl-3-amino-2-oxopropanoate (5) (60.9 mg, 0.25 mmol) was added to a solution of [RuCl((*R*)-binap)(benzene)]Cl (4.3 mg, 4.9 μmol) in methanol (3.0 mL). The mixture was treated with 100 atm of hydrogen at 30 °C for 70 h. *N*-phthaloyl-L-isoserine methyl ester ((*S*)-6) was obtained (60.1 mg, 99% yield). Enantiomeric excess was determined by $^1$H NMR analysis of (*R*)-(+)-MTPA ester of the product (74% *ee*).

**Catalytic Hydrogenation of Methyl *N*-Phthaloyl-3-amino-2-oxopropanoate (5) in the Presence of $HBF_4$.** Methyl *N*-phthaloyl-3-amino-2-oxopropanoate (5) (198 mg, 0.80 mmol) was added to a solution of [RuCl((*R*)-binap)(benzene)]Cl (12.7 mg, 14.6 μmol) in methanol (11.0 mL) which contained $HBF_4$ (12.9 mM). The mixture was treated with 100 atm of hydrogen at 30 °C for 70 h. *N*-phthaloyl-L-isoserine methyl ester ((*S*)-6) was obtained (168 mg, 85% yield, 81% *ee*). Hydrogenation of 5 under the same condition using [RuCl((*S*)-binap)(benzene)]Cl as catalyst gave *N*-phthaloyl-D-isoserine methyl ester ((*R*)-6) in 88% yield and in 80% *ee*.

**Recrystallization of *N*-Phthaloyl-L-isoserine Methyl Ester ((*S*)-6).** To a solution of *N*-phthaloyl-L-isoserine methyl ester ((*S*)-6) (151 mg, 81% *ee*) in $CHCl_3$ (2.5 mL) was added hexane (1.5 mL). The two layered solution was allowed to stand for 24 h at 25 °C to give homogeneous mother liquid and enantiomerically pure (*S*)-6 as colorless needles (97.4 mg, 64% yield): mp 124.3—124.5 °C; $^1$H NMR ($CDCl_3$) δ 3.11 (d, $J$ = 6.60, OH), 3.82 (s, OMe), 4.01 (dd, $J$ = 14.02, 6.26, C*H*H), 4.08 (dd, $J$ = 14.02, 5.28, CH*H*), 4.51 (ddd, $J$ = 6.60, 6.26, 5.28, C*H*OH), 7.72—7.75 (m, 2H, aromatic protons), 7.85—7.88 (m, 2H, aromatic protons); $^{13}$C NMR ($CDCl_3$) δ 41.1, 53.0, 68.5, 123.5, 131.9, 134.2, 168.2, 173.0; IR (nujol) 3440 (OH), 1772, 1746, 1695 (CO) $cm^{-1}$; $[\alpha]_D^{20}$ -5.90 (*c* 1.02, $CHCl_3$). Anal. Calcd for $C_{12}H_{11}NO_5$: C, 57.82; H, 4.45; N, 5.62. Found: C, 57.60; H, 4.50; N, 5.65.

**Deprotection of *N*-Phthaloyl-L-isoserine Methyl Ester ((*S*)-6).** A suspension of *N*-phthaloyl-L-isoserine methyl ester ((*S*)-6) (101 mg, 0.41 mmol, 100% *ee*) in 1*N* HClaq (10 mL) was heated at 60 °C. After 30 min, the suspension became a clear solution which was further heated at 60 °C for 2 h. After the solution was cooled to room temperature, ethyl acetate (50 mL) was added to the solution. The combined organic layer was separated, and the aqueous layer was extracted with ethyl acetate (50 mL) four times. The organic layers were dried over $Na_2SO_4$ and concentrated *in vacuo* to give *N*-phthaloyl-L-isoserine. To a suspension of the crude *N*-phthaloyl-L-isoserine in methanol (10 mL) was added 1.0 *M* $NH_2NH_2 \cdot H_2O$ in methanol (20 mL). The suspension was heated at reflux for 9 h and then cooled to room temperature. To the crude mixture obtained by evaporation of solvents was added ethanol (50 ml) to give enantiomerically pure L-isoserine ((*S*)-7) as precipitate (33.1 mg, 78% yield): $^1H$ NMR ($D_2O$) δ 3.06 (dd, $J$ = 8.25, 13.20, 1H, C*H*H), 3.29 (dd, $J$ = 3.96, 13.20, 1H, CH*H*), 4.17 (dd, $J$ = 3.96, 8.25, 1H, C*H*OH); $[\alpha]_D^{25}$ -31.7 (*c* 0.98, $H_2O$). (lit.,[4a] $[\alpha]_D^{20}$ -31.7 (*c* 1.0, $H_2O$)).

**Acknowledgment.** One of the author (K.N.) is grateful to Inoue Foundation for Science and Hayashi Memorial Foundation for Female Natural Scientists for partial financial support. This work has been supported by the Grant-in-Aid for Developmental Scientific Research No. 05236106 from the Ministry of Education, Science and Culture, Japan.

## References and Notes

(1) Leibman, K. C.; Fellner, S. K. *J. Org. Chem.* **1962**, *27*, 438.

(2) (a) Roncari, G.; Kurylo-Borowska, Z.; Craig, L. C. *Biochemistry* **1966**, *5*, 2153. (b) Hettinger, T. P.; Craig, L. C. *ibid.* **1970**, *9*, 1224.

(3) Heaney-Kieras, J.; Kurylo-Borowska, Z. *J. Antibiot.* **1980**, *33*, 359.

(4) (a) Miyazawa, T.; Akita, E.; Ito, T. *Agric. Biol. Chem.* **1976**, *40*, 1651. (b) Dureault, A.; Tranchepain, I.; Depezay, J. C. *Synthesis* **1987**, 491. (c) Andruszkiewicz, R.; Czerwinski, A.; Grzybowska, J. *Synthesis* **1983**, 31. (d) Williams, T. M.; Crumbie, R.; Mosher, H. S. *J. Org. Chem.* **1985**, *50*, 91. (e) Solladie-Cavallo, A.; Khiar, N. *Tetrahedron Lett.* **1988**, *29*, 2189. (f) Lu, Y.; Miet, C.; Kunesch, N.; Poisson, J. E. *Tetrahedron: Asymmetry* **1991**, *2*, 871, and other references cited therein.

(5) Mashima, K.; Kusano, K.; Sato, N.; Matsumura, Y.; Nozaki, K.; Kumobayashi, H.; Sayo, N.; Hori, Y.; Ishizaki, T.; Akutagawa, S.; and Takaya, H. submitted for publication.

(6) Enantioselective synthesis of γ-amino-β-hydroxyesters via asymmetric hydrogenation catalyzed by $RuBr_2$(binap) was reported. Nishi, T.; Kitamura, M.; Ohkuma, T.; Noyori, R. *Tetrahedron Lett.* **1988**, *29*, 6327.

(7) (a) Haase, K.; Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 83. (b) Oku, A.; Urano, S.-I.; Nakaji, T.; Qing, G.; Abe, M. *J. Org. Chem.* **1992**, *57*, 2263.

(8) Mashima, K.; Kusano, K.; Ohta, T.; Noyori, R.; Takaya, H. *J. Chem. Soc., Chem. Commun.* **1989**, 1208.

(9) Sheehan, J. C.; Frank, V. S. *J. Am. Chem. Soc.* **1949**, *71*, 1856.

(10) Eastham, J. F.; Selman, S. *J. Org. Chem.* **1961**, *26*, 293.

(11) Comercially available from Tokyo Kasei Kogyo Co. LTD.