

Synthetic Study of Optically Active 3-Azabicyclo[3.3.0]octane-2,6,8-tricarboxylic Acid

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Synthesis of (1*R*,2*S*,5*S*,6*R*,8*S*)-3-azabicyclo[3.3.0]octane-2,6,8-tricarboxylic acid (2**) from *trans*-4-hydroxy-L-proline (**5**) was attempted. A Diels–Alder reaction of 3,4-dehydroproline derivative **9** and cyclopentadiene afforded a single stereoisomer **11**. The Diels–Alder adduct was smoothly converted to the hydrochloride of **2** (**24**) via RuO₄ oxidation. Although some racemization of the material or product was observed during the synthetic processes, the amino acid **24** proved to be optically pure.**

Key words *trans*-4-hydroxy-L-proline; Diels–Alder reaction; ruthenium tetroxide; 3,4-dehydroproline; dicyclopentadiene; (1*R*,2*S*,5*S*,6*R*,8*S*)-3-azabicyclo[3.3.0]octane-2,6,8-tricarboxylic acid

During our study on the synthesis of amino acids using Diels–Alder adducts,^{1–3} we synthesized racemic 3-azabicyclo[3.3.0]octane-2,6,8-tricarboxylic acid (**1**)¹ as an analog of kainic acid. However, considering its potential biological uses, the optically active compound has more advantages, so we wanted to synthesize optically active 3-azabicyclo[3.3.0]octane-2,6,8-tricarboxylic acid (**2**). In this paper, we report a synthetic approach to **2** and the related chemistry.

Retro-synthesis of **2** (Chart 1) gave the Diels–Alder adduct **3** and then the derivative of 3,4-dehydroproline **4**, which should be derived from readily available *trans*-4-hydroxy-L-proline (**5**). To obtain the derivative of 3,4-dehydroproline **4**, selective 3,4-elimination of **5** is needed,^{4–7} so the hydroxyl group of **5** must be converted to a phenylseleno group, which would cause elimination similar to the Cope elimination reaction after H₂O₂ oxidation.⁴

The starting **5** was converted to the *N*,*C*-protected form **6** by usual method⁸) in 94% yield. Treatment of **6** with *p*-toluenesulfonyl chloride (TsCl) and 4-dimethylaminopyridine (DMAP) in pyridine afforded **7**⁹) in 91% yield. Compound **7** was allowed to react with sodium phenylselenide,^{4–7}) which was generated from diphenyldiselenide and sodium borohydride *in situ*, to afford compound **8** in 97% yield. Oxidation of **8** with 30% H₂O₂ in CH₂Cl₂ in the presence of pyridine afforded dienophile **9** in 70% yield. Estimation of the optical purity of **9** was difficult on HPLC analysis using a chiral col-

umn (DAICEL CHIRALCEL OD), so **9** was hydrogenated to form **10a** (Chart 3). Its specific rotation ($[\alpha]_D^{18} -96.7^\circ$) was compared with that of **10b**, which was prepared from L-proline ($[\alpha]_D^{18} -101.7^\circ$),¹⁰) and the optical purity of **10a** proved to be 95.1% ee.

Next, a Diels–Alder reaction of the dienophile **9** and cyclopentadiene was attempted. When compound **9** was heated with cyclopentadiene in a bomb tube at 90 °C, almost no reaction was observed. Additions of a Lewis acid such as (C₂H₅)₂O·BF₃, SnCl₄ or ZnI₂ at –70–0 °C into the mixture of **9** and the cyclopentadiene were investigated, but they resulted in the formation of polymers (when used (C₂H₅)₂O·BF₃ or SnCl₄) or the decomposition of **9** (when used ZnI₂). We then tried to employ dicyclopentadiene (cyclopentadiene dimer) as both reagent and solvent at a higher temperature (Chart 4). A solution of **9** in dicyclopentadiene was heated in a bomb tube at 150 °C (oil bath temp., inner temp.: 135 °C), and **9** had completely disappeared after 48 h, giving the desired **11a** in 52% yield (after recrystallization). At 170 °C (oil bath temp., inner temp.: 153 °C), **9** had disappeared after 36 h and **11b** was obtained in 52% yield. Both products **11a**, **b** had the same specific rotation, $[\alpha]_D^{20} -73.2^\circ$. Although four stereoisomers were expected to form in this reaction, only one isomer **11** was isolated; on analysis of mass spectra (MS) for the other constituents of the reaction mixture, there was no peak of 297 (M⁺), which would have been indicative of the diastereomers. The stereochemistry of **11** was confirmed by differential nuclear Overhauser effect (NOE) experiments of ¹H-NMR; +NOEs were observed between a signal at δ 4.58 assigned to the 3-proton and signals at δ 6.05, 6.07, 6.27, and 6.36 assigned to olefinic protons (signals split due to the rotamers).

As we feared that racemization would occur under the reaction conditions employed, the following experiments were

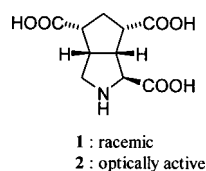


Fig. 1

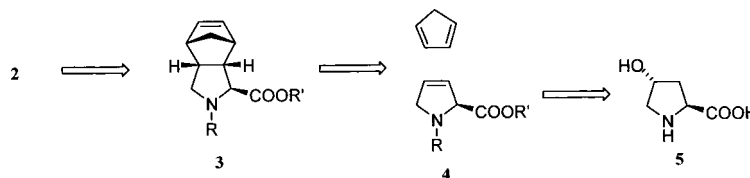


Chart 1

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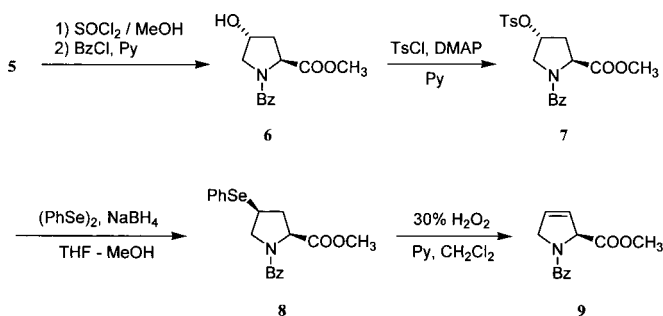


Chart 2

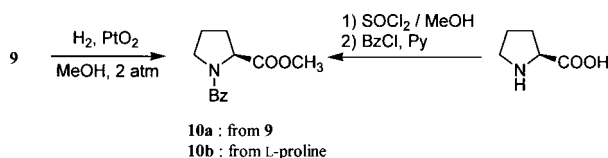


Chart 3

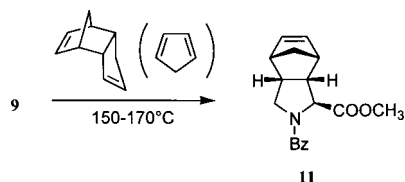


Chart 4

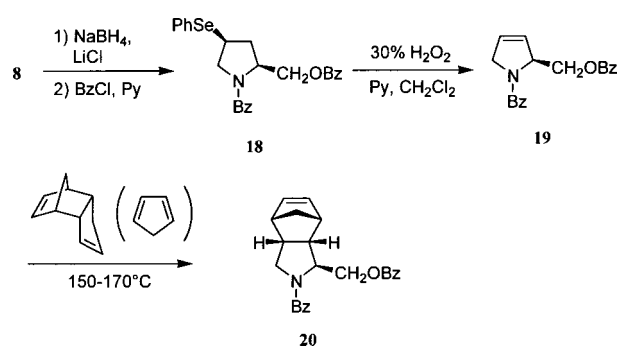


Chart 5

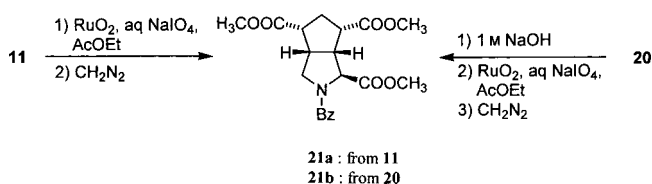


Chart 6

attempted. A solution of **9** ($[\alpha]_D^{18} -357.8^\circ$) in xylene was heated in a bomb tube at 150°C (oil bath temp.) for 48 h, and the recovered **9** had $[\alpha]_D^{20} -292.3^\circ$. When heated at 170°C (oil bath temp.) for 36 h, the recovered **9** had $[\alpha]_D^{20} -231.5^\circ$. When heated at 170°C (oil bath temp.) for 48 h, the recovered **9** had $[\alpha]_D^{20} -202.4^\circ$. Despite exchanging xylene for dicyclopentadiene as a solvent, Diels–Alder adduct **11** obtained from the reaction at 150°C (oil bath temp.) for 48 h had the same specific rotation $[\alpha]_D^{20} -73.2^\circ$ (after one recrystallization) as that obtained from the reaction at 170°C (oil bath temp.) for 36 h or 48 h. Furthermore, when the obtained **11** was heated in dicyclopentadiene at these temperatures, no formation of **9** was observed; the retro-Diels–Alder reaction could not occur under these conditions. These results suggest that the rate of the Diels–Alder reaction is much faster than that of racemization of **9**.

To estimate the exact optical purity of the obtained **11** and ratio of the racemization under the reaction conditions, we prepared the enantiomer **17** from *cis*-4-hydroxy-D-proline (**12**) and compared the enantiomers on HPLC using a chiral column (DAICEL CHIRALCEL OD, 0.46 cm i.d. $\times$ 25 cm). Compound **12** was converted to the *N,C*-protected form **13** by the usual method in 85% yield. Treatment of **13** with *p*-TsCl in pyridine afforded **14** in 90% yield. When DMAP was added to the reaction mixture as a catalyst similar to the conversion of **6** to **7**, the yield of the product decreased by *ca.* 20% with increasing by-products. Compound **14** was treated with sodium phenylselenide to afford **15** in 97% yield. Oxidation of **15** with 30% H_2O_2 in CH_2Cl_2 in the presence of

pyridine afforded **16** in 74% yield. Dienophile **16** was subjected to a Diels–Alder reaction similarly to **9**, giving **17** in 51% yield. A mixture of enantiomers **11** and **17** were separable under the following condition: solvent, hexane–2-propanol (9:1); flow rate, 1 ml/min; column temperature, 30°C . The retention time for **17** was 9.2 min and that for **11** was 11.9 min. A solid of **11** obtained by separation using silica gel column chromatography from the Diels–Alder reaction mixture was analyzed and proved to be 91.1% ee. After one recrystallization of the solid from diisopropyl ether, the optical purity increased to 99.8% ee. After two recrystallizations, **11** did not contain the enantiomer (100% ee). As such, the once-recrystallized **11** was used as the starting material for the following stage because of the balance between quality and quantity.

However, to avoid racemization under the Diels–Alder reaction conditions, we next chose compound **19** as another dienophile (Chart 5). Reduction of ester **8** by NaBH_4 –LiCl in THF–EtOH^{11,12} followed by treatment with benzoyl chloride (BzCl) afforded benzoate **18** in 91% yield. Oxidation of **18** in a similar manner to that employed for the oxidation of **8** afforded the desired dienophile **19** in 64% yield. Compound **19** was heated with dicyclopentadiene in a bomb tube at 170°C for 48 h, and the Diels–Alder adduct **20** was obtained in 51% yield. The stereochemistry of **20** was confirmed by identification of the product **21b** at the next step with **21a**. Diastereomers of **20** were not detected by MS analysis in the other constituents of the reaction mixture, which had *Rf* values on TLC similar to that of **19**.

Ruthenium tetroxide (RuO_4) oxidation^{1–3} of **11** followed by treatment with diazomethane afforded triester **21a** in 83% yield, the specific rotation of which was $[\alpha]_D^{20} -35.0^\circ$. In contrast, benzoate **20** was first hydrolyzed by 1 M NaOH, oxidized by ruthenium tetroxide, then treated with diazomethane to afford **21b** in 71% yield, for which the specific rotation was $[\alpha]_D^{20} -33.5^\circ$.

We attempted to elucidate the reason for the lower optical purity of **21b** than **21a** as follows. Compound **19** was hydro-

generated in the presence of 10% Pd/C and converted to compound **23a**, for which the specific rotation was $[\alpha]_D^{18} -157.2^\circ$. This product was then compared with the authentic **23b** derived from L-prolinol (**22**),¹³ for which the specific rotation was $[\alpha]_D^{18} -168.0^\circ$, and the optical purity of **23a** proved to be 93.6%ee. The proportion of partial racemization of **23a** was slightly more than that of **10a**. Therefore, the lower optical purity of **21b** appeared to be due to the purification of **20** by recrystallization not being possible because **20** was obtained as an oil.

Compounds **21a** and **21b** were heated with 6 M HCl–AcOH at 100 °C for 24 h, respectively, and the salts of the target amino acid **2** (**24**) were quantitatively obtained by concentration of the aqueous solution washed with benzene. The structure of **24** was confirmed by identification of ¹H- and ¹³C-NMR data with those of **1**. In the case of racemic **1**, the hydrochloride salt was desalted simply by being dissolved in water, giving the free amino acid as a crystal. In particular, when the pH of the aqueous solution was adjusted to 4 with NaOH, the crystallization was quantitative. A crude hydrochloride of **2** (from **21a**) was treated similarly, but no solid was deposited. When a crude hydrochloride of **2** (from **21b**) was treated similarly, a small amount of free amino acid was deposited, but the yield was only 6%; moreover, the crystal did not exhibit optical rotation, consisting only of **1**. As it turned out that the deposited crystal of the amino acid was a racemate, crude **2** (from **21a**) was purified as a hydrochloride; reprecipitation of the hydrochloride from water–acetone gave **24** as a white powder in 83% yield.

To evaluate the optical purity of the target amino acid, racemic **1** was esterified with SOCl₂–MeOH, followed by treatment with (*S*)-(+)- α -methoxy- α -trifluoromethylphenyl-acetyl chloride [(*S*)-(+)-MTPA-Cl, 98%ee],^{14,15} and converted into a comparable mixture of both epimers **25** and **26** in 62% yield. Optically active **24** was treated similarly to **1**,

giving a mixture of MTPA amides in 61% yield. Mixtures of both epimers were separable on HPLC using a silica gel column [JASCO Finepak SIL, hexane–AcOEt (1 : 1), retention time; **25**: 8.70 min, **26**: 9.99 min] and the diastereo mixture from **21a** proved to consist of 99% **25** and 1% **26** (or enantiomer **27**). ¹H-NMR analysis also supported this result, indicating that the signal of a proton at the 2-position of **25** exists at δ 4.41 and that of **26** exists at δ 4.68; the component ratio of **25**:**26** (or enantiomer **27**) was 99 : 1. The diastereomeric purity of the MTPA amide derived from **24** reflected the optical purity of (*S*)-(+)-MTPA-Cl (98%ee). Consequently, the target amino acid **2** proved to be optically pure.

In conclusion, while the free target **2** has not been isolated, we synthesized an optically active (1*R*,2*S*,5*S*,6*R*,8*S*)-3-azabicyclo[3.3.0]octane-2,6,8-tricarboxylic acid as hydrochloride **24**.

Experimental

Melting points were measured with a Yanagimoto micromelting point apparatus and are uncorrected. Specific rotations were determined with a JASCO DIP-370 polarimeter. NMR spectra, except for the amino acids, were recorded in chloroform-*d* (CDCl₃) on a GSX-400 spectrometer using tetramethylsilane as an internal standard. For the amino acids, analysis was performed in 2 M deuterium chloride (DCl) using 1,4-dioxane as an internal standard (δ : 3.7 for ¹H-NMR and δ : 67.4 for ¹³C-NMR). Infrared (IR) spectra were recorded on a Hitachi 270-30 spectrophotometer. Mass spectra (MS) were obtained with a JEOL JMS-DX300 instrument. TLC was performed on Silica gel 60 F₂₅₄ plates (0.25 mm, Merck). Column chromatography was performed on silica gel (Kieselgel 60, 70–230 mesh, Merck) or alumina (Aluminium oxide 90, 70–230 mesh, Merck). Flash chromatography was performed on silica gel (Silica Gel 60, 230–400 mesh, Nacalai Tesque).

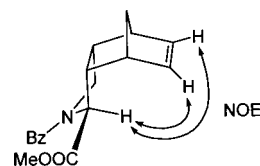


Fig. 2. NOE Relationships of Diels–Alder Adduct **11**

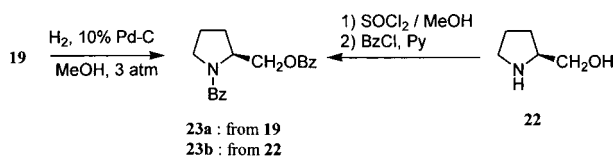


Chart 7

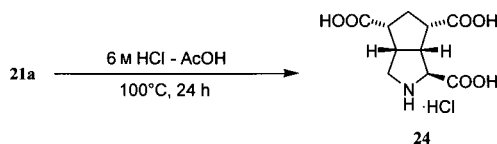


Chart 8

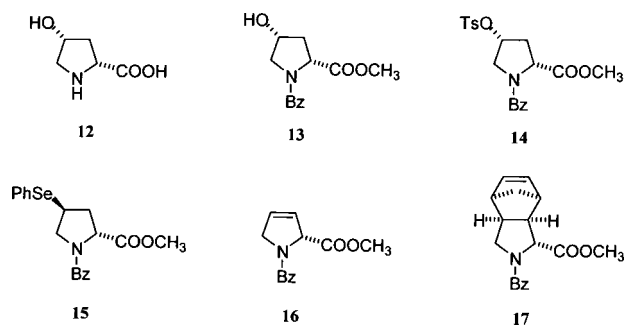


Fig. 3

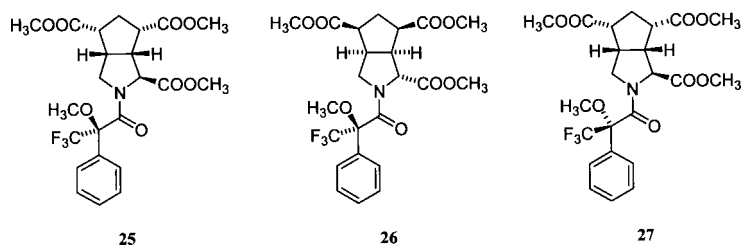


Fig. 4

Methyl (2S,4R)-1-Benzoyl-4-hydroxypyrrolidine-2-carboxylate (6) Thionyl chloride (21.8 ml) was added dropwise to MeOH (500 ml) at -10°C . After 30 min, *trans*-4-hydroxy-L-proline (**5**, 26.2 g, 0.20 mol) was added to the solution, and the whole was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure, and MeOH (300 ml) was added to the residue, after which the solution was concentrated under reduced pressure to give a white solid. The solid was dissolved in 1,4-dioxane (400 ml), and the solution was cooled in an ice bath. After aqueous NaHCO_3 (50.4 g/450 ml) was added in several portions, benzoyl chloride (25.8 ml, 0.22 mol) was added dropwise with vigorous stirring at 0°C and the stirring was continued for 4 h at room temperature. The reaction mixture was concentrated to a half volume under reduced pressure. The white precipitate was filtered off and washed with water (200 ml). The filtrate was saturated with NaCl, and the whole was extracted with CHCl_3 (400 ml $\times$ 2). The organic layer was washed with brine (120 ml), dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure to give a white solid. A mixture of the white precipitate and the white solid was recrystallized from benzene to give compound **6** (47.0 g, 94%) as colorless prisms, mp $143\text{--}145^{\circ}\text{C}$, (lit.⁸) mp 141°C , $[\alpha]_{\text{D}}^{25} -144.1^{\circ}$ ($c=1.0$, CHCl_3), [lit.⁸] $[\alpha]_{\text{D}}^{25} -142.4^{\circ}$ ($c=1.6$, CHCl_3).

Methyl (2S,4R)-1-Benzoyl-4-(*p*-toluenesulfonyloxy)pyrrolidine-2-carboxylate (7) A solution of *p*-toluenesulfonyl chloride (23.0 g, 0.12 mol) in pyridine (120 ml) was added dropwise to a solution of **6** (25.0 g, 0.10 mol) and DMAP (20 mg) in pyridine (80 ml) at 0°C , and the mixture was stirred at room temperature for 6 d. The mixture was then concentrated under reduced pressure, and water was added to the residue at 0°C . The whole was extracted with AcOEt (400 ml). The organic layer was washed with 5% HCl (30 ml $\times$ 3) and water (40 ml $\times$ 3), dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure to give a white solid. Recrystallization from AcOEt-hexane gave compound **7** (36.8 g, 91%) as colorless needles, mp $113\text{--}115^{\circ}\text{C}$, (lit.⁹) mp $113\text{--}114.5^{\circ}\text{C}$, $[\alpha]_{\text{D}}^{20} -76.7^{\circ}$ ($c=1.0$, CHCl_3), [lit.⁹] $[\alpha]_{\text{D}}^{26} -61.8^{\circ}$ ($c=1.14$, EtOH). $^1\text{H-NMR}^{16}$ (CDCl_3) δ : 2.14–2.68 (5H, m), 3.33–3.89 (5H, m), 4.57 (0.2H, brt), 4.80 (0.8H, t, $J=8.2$ Hz), 5.10 (1H, br), 7.30–7.70 (9H, m). $^{13}\text{C-NMR}^{16}$ (CDCl_3) δ : 21.68 (q), 35.43 (t), 52.57 (q), 55.05 (t), 57.41 (d), 79.14 (d), 127.44 (d), 127.61 (d), 128.37 (d), 130.07 (d), 130.69 (d), 133.38 (s), 135.00 (s), 145.35 (s), 169.70 (s), 171.98 (s). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1742 (C=O), 1628 (C=O). MS m/z : 403 (M^+).

Methyl (2S,4S)-1-Benzoyl-4-phenylselenopyrrolidine-2-carboxylate (8) Under argon atmosphere, NaBH_4 (2.04 g, 54 mmol) was slowly added to a solution of diphenyl diselenide (8.43 g, 27 mmol) in THF–MeOH (50 ml–50 ml), and the mixture was stirred until NaBH_4 was completely dissolved. A solution of **7** (17.2 g, 43 mmol) in THF (50 ml) was added to the pale yellow solution, and the whole was refluxed for 2 h. The mixture was then concentrated under reduced pressure, and the residue was dissolved in AcOEt (300 ml). The solution was washed with water (200 ml $\times$ 3), dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure. The resulting yellow oil was subjected to column chromatography on silica gel (benzene, then AcOEt), and the fractions eluted with AcOEt were collected. After evaporation of the solvent, the residue was recrystallized from AcOEt–*i*-Pr $_2$ O, giving compound **8** (16.0 g, 97%) as colorless needles, mp $77.5\text{--}78.5^{\circ}\text{C}$, $[\alpha]_{\text{D}}^{19} -85.7^{\circ}$ ($c=1.0$, CHCl_3). $^1\text{H-NMR}^{16}$ (CDCl_3) δ : 1.93–2.43 (1H, m), 2.55–3.06 (1H, m), 3.48–4.36 (6H, m), 4.41 (0.2H, br), 4.69 (0.8H, t, $J=8.4$ Hz), 7.20–8.10 (10H, m). $^{13}\text{C-NMR}^{16}$ (CDCl_3) δ : 36.75 (t), 37.48 (d), 52.41 (q), 56.22 (t), 58.97 (d), 126.73 (d), 127.37 (s), 127.57 (d), 128.32 (d), 129.34 (d), 130.65 (d), 134.94 (d), 135.38 (s), 169.17 (s), 171.75 (s). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1750 (C=O), 1640 (C=O). MS m/z : 389 (M^+). Anal. Calcd for $\text{C}_{19}\text{H}_{19}\text{NO}_3\text{Se}$: C, 58.77; H, 4.93; N, 3.61. Found: C, 58.81; H, 4.97; N, 3.60.

Methyl (2S)-1-Benzoylpyrrolidin-3-ene-2-carboxylate (9) Thirty-percent aqueous H_2O_2 solution (28 ml, 0.25 mol) was added dropwise to a solution of **8** (19.4 g, 0.05 mol) and pyridine (8.0 ml, 0.10 mol) in CH_2Cl_2 (100 ml) at 0°C , and the whole was then vigorously stirred at room temperature for 2 h. CH_2Cl_2 (100 ml) was added to the reaction mixture, washed with 5% HCl (100 ml $\times$ 2), sat. NaHCO_3 (100 ml), and water (100 ml $\times$ 3). The organic layer was dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure. The residual orange oil was subjected to column chromatography on silica gel [hexane–AcOEt (4 : 1)] to give **9** (8.10 g, 70%) as a pale yellow oil, $[\alpha]_{\text{D}}^{18} -357.8^{\circ}$ ($c=1.1$, CHCl_3). $^1\text{H-NMR}^{16}$ (CDCl_3) δ : 3.49 (0.2H, s), 3.79 (0.8H, s), 4.16–4.54 (2H, m), 5.11 (0.2H, brs), 5.47 (0.8H, m), 5.73 (0.2H, br), 5.88 (0.8H, ddd, $J=6.2$, 1.8, 1.8 Hz), 5.94 (0.8H, dd, $J=2.2$, 1.8 Hz), 6.10 (0.2H, br), 7.39–7.59 (5H, m). $^{13}\text{C-NMR}^{16}$ (CDCl_3) δ : 52.37 (q), 52.44 (q), 53.86 (t), 55.90 (t), 66.42 (d), 68.12 (d), 124.61 (d), 124.86 (d), 126.52 (d), 127.02 (d), 128.40 (d), 128.67 (d), 129.31 (d), 129.93 (d), 130.24 (d), 135.93 (s), 136.38 (s), 169.63 (s), 170.14 (s). IR $\nu_{\text{max}}^{\text{neat}}$ cm^{-1} :

1754 (C=O), 1646 (C=O). MS m/z : 231 (M^+).

Estimation of the Optical Purity of 9 by Converting to 10a Compound **9** (302 mg) was dissolved in MeOH (20 ml) and hydrogenated in the presence of PtO_2 (40 mg) under a pressure of 2 atm for 12 h. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure to give **10a** (294 mg, 97%) as a white solid, mp $87.5\text{--}89^{\circ}\text{C}$, $[\alpha]_{\text{D}}^{18} -96.7^{\circ}$ ($c=1.0$, CHCl_3). Authentic **10b** was prepared from L-proline by the reported procedure,¹⁰ mp $89\text{--}89.5^{\circ}\text{C}$, (lit. mp $89\text{--}89.5^{\circ}\text{C}$), $[\alpha]_{\text{D}}^{18} -101.7^{\circ}$ ($c=1.0$, CHCl_3). Comparison of the specific rotations indicated the optical purity of **9** was 95.1%ee.

Partial Racemization of 9 at Higher Temperature A solution of **9** (200 mg) in xylene (5 ml) was heated in a bomb tube at 150°C or 170°C for 36–48 h. The mixture was concentrated under reduced pressure, and the residue was subjected to column chromatography on silica gel [hexane–AcOEt (4 : 1)] to recover partially racemized **9**, which was then analyzed by optical rotation.

Methyl (1R,2S,3S,6R,7S)-4-Benzoyl-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3-carboxylate (11) A mixture of compound **9** (3.35 g, 14.5 mmol) and dicyclopentadiene (20 ml) was heated in a bomb tube at 150°C (oil bath temp., inner temp.: 135°C) for 48 h or at 170°C (oil bath temp., inner temp.: 153°C) for 36 h. The reaction mixture was subjected to column chromatography on silica gel (benzene, then AcOEt), and the fractions eluted with AcOEt were collected. The residue after concentration was subjected to flash chromatography [hexane–AcOEt (5 : 1)], and the resultant white solid was recrystallized from *i*-Pr $_2$ O, giving **11** (2.24 g, 52%) as colorless prisms, mp $118\text{--}120^{\circ}\text{C}$, $[\alpha]_{\text{D}}^{20} -73.2^{\circ}$ ($c=1.0$, CHCl_3). $^1\text{H-NMR}^{16}$ (CDCl_3) δ : 1.35–1.63 (3H, m), 2.82–3.15 (4H, m), 3.64–3.85 (4H, m), 4.58 (1H, d, $J=2.6$ Hz), 6.00–6.10 (1H, m), 6.27 and 6.36 (1H, dd, $J=5.5$, 2.9 Hz), 7.22–7.45 (5H, m). $^{13}\text{C-NMR}^{16}$ (CDCl_3) δ : 42.75 (d), 45.10 (d), 46.89 (d), 47.13 (d), 47.28 (d), 47.89 (d), 48.66 (d), 51.24 (t), 51.47 (t), 51.53 (t), 51.81 (t), 52.32 (q), 60.91 (d), 64.62 (d), 126.02 (d), 126.84 (d), 128.26 (d), 128.49 (d), 129.60 (d), 129.81 (d), 133.85 (d), 134.70 (d), 134.81 (d), 135.78 (d), 136.85 (s), 137.31 (s), 169.22 (s), 169.88 (s), 172.94 (s), 173.06 (s). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1748 (C=O), 1634 (C=O). MS m/z : 297 (M^+). Anal. Calcd for $\text{C}_{18}\text{H}_{19}\text{NO}_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.72; H, 6.40; N, 4.75. HPLC analysis using a chiral column [DAICEL CHIRALCEL OD, 0.46 cm I.D. $\times$ 25 cm, solvent: hexane–2-propanol (9 : 1), sample injection: 1 μl (1.00 g/l CHCl_3 solution), flow rate 1 ml/min, column temp.: 30°C] showed the ratio of the enantiomers was 99.9 : 0.01. The crystals were used in the next step, but could be further purified by one more recrystallization to give optically pure **11**, mp $119\text{--}121^{\circ}\text{C}$, $[\alpha]_{\text{D}}^{20} -73.3^{\circ}$ ($c=1.0$, CHCl_3).

Methyl (2R,4R)-1-Benzoyl-4-hydroxypyrrolidine-2-carboxylate (13) Thionyl chloride (1.70 ml) was added dropwise to MeOH (38.5 ml) at -10°C . After 30 min, *cis*-4-hydroxy-D-proline (**12**, 1.96 g, 14.9 mmol) was added to the solution and the whole was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure, and MeOH (23.0 ml) was added to the residue, after which the solution was concentrated under reduced pressure to give a white solid. The solid was dissolved in 1,4-dioxane (31.0 ml), and the solution was cooled in an ice bath. After aqueous NaHCO_3 (3.86 g/35.0 ml) was added in several portions, benzoyl chloride (1.97 ml, 16.8 mmol) was added dropwise with vigorous stirring at 0°C and vigorous stirring was continued for 4 h at room temperature. The reaction mixture was concentrated to a half volume under reduced pressure. The white precipitate was filtered off and washed with water (40 ml). The filtrate was saturated with NaCl, and the whole was extracted with CHCl_3 (40 ml $\times$ 2). The organic layer was washed with brine (40 ml), dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure to give a white solid. A mixture of the white precipitate and the white solid (3.69 g) was recrystallized from benzene to give compound **13** (3.17 g, 85%) as colorless prisms, mp $100.5\text{--}101.5^{\circ}\text{C}$, $[\alpha]_{\text{D}}^{21} -25.4^{\circ}$ ($c=1.0$, CHCl_3). $^1\text{H-NMR}^{16}$ (CDCl_3) δ : 1.98–2.44 (2H, m), 3.57–3.92 (6H, m), 4.33–4.68 (2H, m), 7.28–7.53 (5H, m). $^{13}\text{C-NMR}^{16}$ (CDCl_3) δ : 36.89 (t), 39.63 (t), 52.57 (q), 52.84 (q), 58.15 (t), 58.20 (d), 69.26 (d), 70.99 (d), 127.29 (d), 128.38 (d), 130.48 (d), 135.52 (s), 170.07 (s), 174.62 (s). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3324 (OH), 1766 (C=O), 1610 (C=O). MS m/z : 249 (M^+). Anal. Calcd for $\text{C}_{13}\text{H}_{15}\text{NO}_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.93; H, 6.10; N, 5.57.

Methyl (2R,4R)-1-Benzoyl-4-(*p*-toluenesulfonyloxy)pyrrolidine-2-carboxylate (14) A solution of *p*-toluenesulfonyl chloride (2.07 g, 10.9 mmol) in pyridine (14 ml) was added dropwise to a solution of **13** (2.25 g, 9.03 mmol) in pyridine (9 ml) at 0°C , and the mixture was stirred at room temperature for 4 d. The mixture was then concentrated under reduced pressure, water (20 ml) was added to the residue at 0°C , and the whole was stirred at room temperature for 0.5 h, then extracted with AcOEt (40 ml). The organic layer was washed with 5% HCl (20 ml $\times$ 3) and water

(20 ml×5), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel [hexane–AcOEt (2 : 1)] to give **14** (3.27 g, 90%) as a white powder. Recrystallization from benzene–hexane gave colorless needles, mp 100–101.5 °C, [α]_D²⁵ +59.3° (*c*=1.0, CHCl₃). ¹H-NMR¹⁶ (CDCl₃) δ : 2.33–2.49 (5H, m), 3.63–5.00 (7H, m), 7.27–7.76 (9H, m). ¹³C-NMR¹⁶ (CDCl₃) δ : 21.69 (q), 34.90 (t), 52.61 (q), 54.10 (t), 56.85 (d), 126.78 (d), 127.17 (d), 127.76 (d), 128.48 (d), 130.02 (d), 130.56 (d), 133.38 (s), 135.34 (s), 145.34 (s), 169.70 (s), 170.98 (s). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1748 (C=O), 1622 (C=O). MS *m/z*: 403 (M⁺). *Anal.* Calcd for C₂₀H₂₁NO₆S: C, 59.54; H, 5.25; N, 3.47. Found: C, 59.43; H, 5.25; N, 3.64.

Methyl (2R,4S)-1-Benzoyl-4-phenylselenopyrrolidine-2-carboxylate (15) Under argon atmosphere, NaBH₄ (0.38 g, 10 mmol) was slowly added to a solution of diphenyl diselenide (1.52 g, 4.87 mmol) in THF–MeOH (9.0 ml–9.0 ml), and the mixture was stirred until NaBH₄ was completely dissolved. A solution of **14** (3.13 g, 7.76 mmol) in THF (9.0 ml) was added to the pale yellow solution, and the whole was refluxed for 2 h. The solution was concentrated under reduced pressure, and the residue was dissolved in AcOEt (100 ml). The solution was then washed with water (40 ml×3), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The resulting yellow oil was subjected to column chromatography on silica gel (benzene, then AcOEt) to give compound **15** (2.92 g, 97%) as a colorless oil, [α]_D²⁵ +37.9° (*c*=1.0, CHCl₃). ¹H-NMR¹⁶ (CDCl₃) δ : 2.36–2.42 (2H, m), 3.50–3.57 (2H, m), 3.77–4.01 (4H, m), 4.79–4.82 (1H, m), 7.22–7.59 (10H, m). ¹³C-NMR¹⁶ (CDCl₃) δ : 36.13 (t), 36.76 (t), 38.31 (d), 52.41 (q), 55.80 (t), 58.62 (d), 58.99 (d), 126.59 (s), 127.31 (d), 127.55 (d), 128.31 (d), 128.38 (d), 129.31 (d), 130.34 (d), 134.96 (d), 135.22 (d), 135.69 (s), 169.64 (s), 172.37 (s). IR $\nu_{\text{max}}^{\text{neat}}$ cm⁻¹: 1750 (C=O), 1642 (C=O). MS *m/z*: 389 (M⁺).

Methyl (2R)-1-Benzoylpyrrolidin-3-ene-2-carboxylate (16) Thirty-percent aqueous H₂O₂ solution (4.0 ml) was added dropwise to a solution of **15** (2.73 g, 7.03 mmol) and pyridine (1.12 ml) in CH₂Cl₂ (15 ml) at 0 °C, and the whole was then vigorously stirred at room temperature for 2 h. CH₂Cl₂ (15 ml) was added to the reaction mixture, then washed with 5% HCl (15 ml×2), sat. NaHCO₃ (15 ml), and water (15 ml×3). The organic layer was dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residual orange oil was subjected to column chromatography on silica gel [hexane–AcOEt (4 : 1)] to give **16** (1.21 g, 74%) as a pale yellow oil, [α]_D²⁵ +338.0° (*c*=1.0, CHCl₃). ¹H-NMR, ¹³C-NMR, IR, and MS data completely coincided with those of the enantiomer **9**.

Methyl (1S,2R,3R,6S,7R)-4-Benzoyl-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3-carboxylate (17) A mixture of compound **16** (1.16 g, 5.02 mmol) and dicyclopentadiene (7 ml) was heated in a bomb tube at 150–170 °C for 48 h. The reaction mixture was subjected to column chromatography on silica gel (benzene, then AcOEt), and the AcOEt eluate was concentrated under reduced pressure. The residue was subjected to flash chromatography [hexane–AcOEt (5 : 1)], and the resultant white solid was recrystallized from i-Pr₂O, giving **17** (0.76 g, 51%) as colorless prisms, mp 118–120 °C, [α]_D²⁵ +73.1° (*c*=1.0, CHCl₃). ¹H-NMR, ¹³C-NMR, IR, and MS data completely coincided with those of the enantiomer **11**.

(2S,4S)-(1-Benzoyl-4-phenylselenopyrrolidin-2-yl)methyl Benzoate (18) Under argon atmosphere, LiCl (4.66 g, 110 mmol) and NaBH₄ (4.16 g, 110 mmol) were added to a solution of compound **8** (21.3 g, 54.9 mmol) in THF (90 ml), and EtOH (160 ml) was dropwise added to the mixture with stirring at room temperature. The stirring was continued overnight. Water (180 ml) was added, and the whole was extracted with CH₂Cl₂ (100 ml×3). The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residual yellow oil was dissolved in anhydrous pyridine (110 ml) and cooled in an ice bath. Benzoyl chloride (8.6 g, 61 mmol) was added dropwise, and the mixture was stirred overnight. The mixture was then concentrated under reduced pressure, and the residue was dissolved in CH₂Cl₂ (400 ml). The solution was washed with 2% HCl (100 ml×2), sat. NaHCO₃ (10 ml), and water (100 ml×3), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was subjected to column chromatography on alumina (AcOEt), and the resulting solid was recrystallized from AcOEt–hexane to give **18** (23.2 g, 91%) as colorless prisms, mp 107–108 °C, [α]_D²¹ –74.3° (*c*=1.0, CHCl₃). ¹H-NMR¹⁶ (CDCl₃) δ : 2.03–2.11 (1H, m), 2.59–2.64 (1H, m), 3.38–3.58 (2H, m), 3.78–3.93 (1H, m), 4.46–4.78 (3H, m), 7.19–8.06 (15H, m). ¹³C-NMR (CDCl₃) δ : 35.19 (t), 36.93 (d), 56.15 (d), 57.13 (t), 64.44 (t), 127.09 (d), 127.61 (s), 128.25 (d), 128.37 (d), 128.48 (d), 129.22 (d), 129.61 (d), 129.92 (s), 130.57 (d), 133.06 (d), 135.11 (d), 136.05 (s), 166.23 (s), 169.85 (s). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1726 (C=O), 1636 (C=O). MS *m/z*: 465 (M⁺). *Anal.* Calcd for C₂₅H₂₃NO₃Se: C, 64.65; H, 4.99; N, 3.02. Found: C, 64.69;

H, 4.96; N, 3.00.

(2S)-(1-Benzoyl-3-pyrrolin-2-yl)methyl Benzoate (19) Thirty-percent aqueous H₂O₂ solution (12 ml) was added dropwise to a solution of **18** (9.29 g, 20 mmol) and pyridine (2.0 ml) in CH₂Cl₂ (100 ml) at 0 °C, and the whole was then vigorously stirred at room temperature for 5 h. The reaction mixture was washed with 5% HCl (50 ml×2), sat. NaHCO₃ (50 ml), and water (50 ml×3). The organic layer was dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residual orange oil was subjected to column chromatography on silica gel [hexane–AcOEt (5 : 1)] to give **19** (3.92 g, 64%) as a pale yellow oil, [α]_D¹⁸ –393.0° (*c*=1.0, CHCl₃). ¹H-NMR (CDCl₃) δ : 4.03–4.13 (1H, m), 4.29–4.45 (2H, m), 4.69 (1H, dd, *J*=11.2, 4.0 Hz), 4.75 (1H, dd, *J*=11.2, 2.4 Hz), 5.42 (1H, br), 5.77–5.96 (2H, m), 7.30–8.09 (10H, m). ¹³C-NMR (CDCl₃) δ : 56.59 (t), 63.62 (d), 64.10 (t), 126.78 (d), 127.11 (d), 127.40 (d), 128.43 (d), 128.63 (d), 129.57 (d), 130.19 (s), 130.19 (d), 133.13 (d), 136.55 (s), 166.30 (s), 170.34 (s). IR $\nu_{\text{max}}^{\text{neat}}$ cm⁻¹: 1724 (C=O), 1644 (C=O), 1624 (C=C). MS *m/z*: 307 (M⁺).

(1R,2S,3S,6R,7S)-(4-Benzoyl-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-3-yl)methyl Benzoate (20) A mixture of compound **19** (2.50 g, 8.13 mmol) and dicyclopentadiene (15 ml) was heated in a bomb tube at 170 °C for 48 h. The reaction mixture was subjected to column chromatography on silica gel (benzene, then AcOEt), and the fractions eluted with AcOEt were collected. The residue after concentration was subjected to flash chromatography [hexane–Et₂O (3 : 1)] to give **20** (1.55 g, 51%) as a pale yellow oil, [α]_D²⁰ –84.3° (*c*=1.0, CHCl₃). ¹H-NMR¹⁶ (CDCl₃) δ : 1.35 (1H, d, *J*=8.4 Hz), 1.48 (1H, d, *J*=8.4 Hz), 3.60–3.83 (1H, m), 4.15 (0.3H, m), 4.48 (2H, d, *J*=4.4 Hz), 4.55 (0.7H, m), 5.95 (1H, dd, *J*=5.7, 2.9 Hz), 6.31 (1H, dd, *J*=5.5, 2.9 Hz), 7.27–8.07 (10H, m). ¹³C-NMR¹⁶ (CDCl₃) δ : 45.43 (d), 46.81 (d), 46.93 (d), 47.01 (d), 51.38 (t), 52.31 (t), 57.73 (d), 66.29 (t), 126.81 (d), 128.23 (d), 128.52 (d), 129.60 (d), 129.69 (d), 130.04 (s), 133.08 (d), 134.35 (d), 134.91 (d), 137.37 (s), 166.56 (s), 169.25 (s). IR $\nu_{\text{max}}^{\text{neat}}$ cm⁻¹: 1724 (C=O), 1634 (C=O). MS *m/z*: 373 (M⁺).

Trimethyl (1R,2S,5S,6R,8S)-3-Benzoyl-3-azabicyclo[3.3.0]octane-2,6,8-tricarboxylate (21a) Derived from Compound 11 A solution of **11** (1.19 g, 4.00 mmol) in AcOEt (30 ml), RuO₂·xH₂O (10 mg), and a 10% NaIO₄ aqueous solution (34 ml) were mixed and then vigorously stirred at 0 °C for 12 h. The AcOEt layer was separated, and the aqueous layer was extracted with AcOEt (50 ml×6). Isopropyl alcohol (10 ml) was added to the combined AcOEt layers and the solution was left to stand for 1 h. The precipitated RuO₂ was filtered off and the solution was dried over anhydrous Na₂SO₄, then concentrated under reduced pressure. The residue was dissolved in MeOH (10 ml) and treated with diazomethane. The solution was concentrated, and the residual white solid was recrystallized from AcOEt–hexane to give **21a** (1.29 g, 83%) as colorless needles, mp 81.5–82.5 °C, [α]_D²⁰ –35.0° (*c*=1.0, CHCl₃). ¹H-NMR¹⁶ (CDCl₃) δ : 2.14 (1H, ddd, *J*=12.7, 6.3, 6.3 Hz), 2.46 (1H, ddd, *J*=12.7, 12.7, 12.7 Hz), 2.94–3.13 (4H, m), 3.41–3.82 (11H, m), 4.25 and 4.71 (1H, each brs), 7.29–7.50 (5H, m). ¹³C-NMR¹⁶ (CDCl₃) δ : 29.24 (t), 45.20 (d), 45.95 (d), 46.42 (d), 49.10 (d), 51.34 (t), 51.82 (q), 52.14 (q), 52.50 (q), 60.90 (d), 127.16 (d), 128.26 (d), 130.10 (d), 135.99 (s), 169.46 (s), 172.13 (s), 172.30 (s), 172.43 (s). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1744 (C=O), 1630 (C=O). MS *m/z*: 389 (M⁺). *Anal.* Calcd for C₂₀H₂₃NO₇: C, 61.69; H, 5.95; N, 3.60. Found: C, 61.74; H, 5.93; N, 3.54.

Trimethyl (1R,2S,5S,6R,8S)-3-Benzoyl-3-azabicyclo[3.3.0]octane-2,6,8-tricarboxylate (21b) Derived from Compound 20 1 M NaOH (5.0 ml) was added dropwise to a solution of **20** (1.87 g, 5.01 mmol) in MeOH (30 ml), and the mixture was stirred at 0 °C for 4 h. Water (100 ml) was added, and the whole was extracted with AcOEt (200 ml×3). The organic layer was washed with water (100 ml), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residual pale yellow oil was dissolved in AcOEt (50 ml). The solution, RuO₂·xH₂O (30 mg), and a 10% NaIO₄ solution (112 ml) were mixed and then vigorously stirred at 0 °C for 8 h. The AcOEt layer was separated and the aqueous layer was extracted with AcOEt (200 ml×5). Isopropyl alcohol (15 ml) was added to the combined AcOEt layers, and the solution was left to stand for 1 h. The precipitated RuO₂ was filtered off, and the solution was dried over anhydrous Na₂SO₄, then concentrated under reduced pressure. The residue was dissolved in MeOH (15 ml) and treated with diazomethane. The solution was concentrated, and the residual colorless oil was subjected to flash chromatography [hexane–AcOEt (2 : 1)] to give a white solid. Recrystallization from AcOEt–hexane gave **21b** (1.38 g, 71%) as colorless needles, mp 81–82.5 °C, [α]_D²⁰ –33.5° (*c*=1.0, CHCl₃). ¹H-NMR, ¹³C-NMR, IR, and MS data completely coincided with those of **21a**.

Estimation of the Optical Purity of 19 by Converting to 23a Compound **19** (300 mg) was dissolved in MeOH (20 ml) and hydrogenated in the

presence of 10% Pd/C (50 mg) under a pressure of 3 atm for 6 h. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure to give **23a** (295 mg, 98%) as a colorless oil, $[\alpha]_D^{18} -157.2^\circ$ ($c=1.0$, CHCl_3). Authentic **23b** was prepared from **22** by the reported procedure,¹³ $[\alpha]_D^{18} -168.0^\circ$ ($c=1.0$, CHCl_3), [lit. $[\alpha]_D^{21} -154.0^\circ$ (CHCl_3)]. Comparison of the specific rotations indicated that the optical purity of **19** was 93.6%ee.

(1R,2S,5S,6R,8S)-3-Azabicyclo[3.3.0]octane-2,6,8-tricarboxylic Acid Hydrochloride (24) Compound **21a** (778 mg, 2.00 mmol) was heated in AcOH (40 ml) and 6 M HCl (40 ml) at 100 °C for 24 h. The reaction mixture was concentrated under reduced pressure, and water (50 ml) was added to the residue. The whole was washed with benzene (50 ml×3) to remove benzoic acid, and the aqueous layer was filtered. The filtrate was concentrated under reduced pressure to give **24** (553 mg, 99%) as a white solid, which was reprecipitated from water–acetone to give a white powder (465 mg, 83%), mp 213 °C (dec.), $[\alpha]_D^{20} +38.3^\circ$ ($c=1.0$, 2 M HCl). ¹H- and ¹³C-NMR data completely coincided with those of racemic **1**.¹⁾ IR $\nu_{\text{max}}^{\text{KBr}} \text{cm}^{-1}$: 3168, 1740. MS (FAB) m/z : 244 ($\text{M}^+ - \text{Cl}$). Anal. Calcd for $\text{C}_{10}\text{H}_{14}\text{ClNO}_6$: C, 42.95; H, 5.05; N, 5.01. Found: C, 42.84; H, 4.99; N, 4.97.

Compound **21b** was treated similarly to **21a** and afforded similar results before recrystallization. However, when a white solid obtained from **21b** before recrystallization was dissolved in a minimum amount of water and the solution was adjusted to pH 4 with NaOH, a 6% yield of free **1** was crystallized as colorless prisms, mp 284 °C (dec.), $[\alpha]_D^{20} 0^\circ$ ($c=1.0$, 2 M HCl). In the case of **21a**, no solid precipitated from the pH 4 solution.

Estimation of the Optical Purity of 24 First, for an authentic sample, racemic **1** was converted to MTPA amide. Thionyl chloride (33 μl) was added to MeOH (5.0 ml) at -10°C . After 30 min, compound **1** (24.3 mg, 0.10 mmol) was added to the solution, and the whole was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure, and MeOH (5.0 ml) was added to the residue, after which the solution was concentrated under reduced pressure to give a white solid (33.0 mg). This product was dissolved in anhydrous pyridine (5.0 ml), and the solution was cooled in an ice bath. (S)-(+)-MTPA-Cl (Aldrich, 98%ee, 27.8 mg, 0.11 mmol) and DMAP (1.2 mg) were added with vigorous stirring at 0 °C, and the stirring was continued for 24 h at room temperature. The reaction mixture was concentrated under reduced pressure. Water (10 ml) was added, and the whole was extracted with benzene (20 ml). The benzene layer was washed with cold 5% HCl (10 ml×2), sat. NaHCO_3 (10 ml), and water (10 ml×3). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel (AcOEt) to give a mixture of **25** and **26** (31.0 mg,

62%). The mixture was used in ¹H-NMR and HPLC analyses. Second, compound **24** (27.9 mg, 0.10 mmol) was similarly treated to give a mixture of **25** and **26** (or its enantiomer **27**) in 61% yield. Analyses on HPLC were done under the condition [JASCO Finepak SIL, 0.46 cm i.d.×25 cm, solvent: hexane–AcOEt (1:1), sample injection: 20 μl (1.00 g/l CHCl_3 solution), flow rate 1 ml/min, column temp.: 40 °C] and showed that the ratio of the enantiomers derived from **24** was 99:1. (retention time; **25**: 8.70 min, **26**: 9.99 min). ¹H-NMR analyses were carried out in CDCl_3 solutions by the comparison of integrated intensities of δ 4.41 (**25**) and δ 4.68 (**26**), and these results supported the HPLC results.

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