# Syntheses of Optically Active, Protected and Unprotected Vinylglycines

Taisuke ITAYA,* Shigeyuki SHIMIZU, Satoshi NAKAGAWA, and Masatoshi MORISUE

*Faculty of Pharmaceutical Sciences, Kanazawa University, Takara-machi, Kanazawa 920, Japan.*
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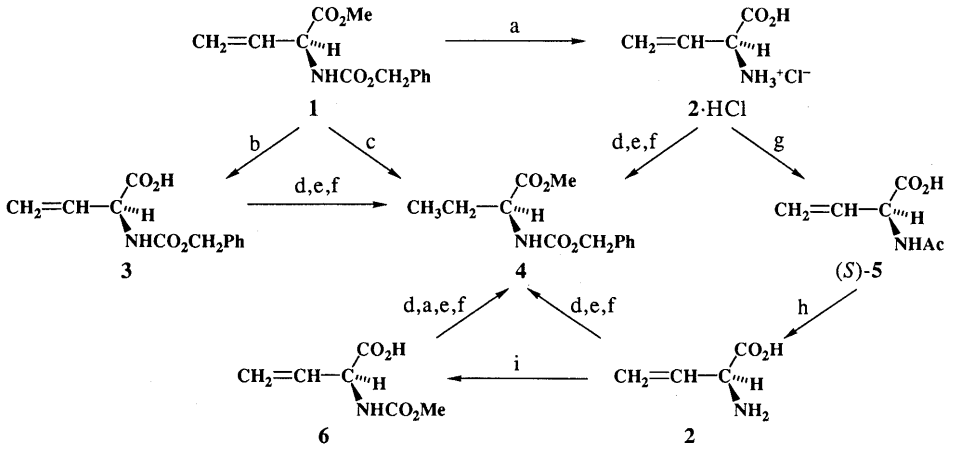
**Vinylglycine (2) has been shown to undergo racemization under acidic conditions. Optically pure 2 was obtained from 2·HCl by enzymatic hydrolysis through *N*-acetylvinylglycine (5), followed by recrystallization. (*S*)-*N*-(Methoxycarbonyl)vinylglycine (6) was configurationally so unstable under acidic conditions that 6 could not be obtained from 2 in an optically pure form. On the other hand, configurationally stable (*S*)-*N*-(9-phenylfluoren-9-yl)vinylglycine methyl ester (9) was synthesized from (*S*)-homoserine; 9 was hydrolyzed with sodium hydroxide to afford the carboxylic acid 10 of more than 99% ee.**

**Keywords** (*S*)-vinylglycine; optical purity; acid-catalyzed racemization; *N*-protected vinylglycine; chiral HPLC

(*S*)-Vinylglycine (**2**) has been synthesized as the hydrochloride by hydrolysis of (*S*)-*N*-(benzyloxycarbonyl)-vinylglycine methyl ester (**1**) with hydrochloric acid.[1] We have converted **2**·HCl[1b] into (*S*)-2-[(methoxycarbonyl)amino]-3-butenoic acid (**6**) and then utilized **6** in the Heck reaction for the synthesis of 3-β-D-ribofuranosylwybutine.[2] Because our sample of **6** was not optically pure, we attempted to identify where racemization had occurred.

As Rapoport's method seemed most convenient[3] among the reported syntheses of optically active vinylglycine,[1,4] we checked this procedure. Although modified procedures have been reported for the pyrolysis of (*S*)-*N*-(benzyloxycarbonyl)methionine methyl ester *S*-oxide,[5] we obtained **1** in 62% yield according to the original procedure,[1a] albeit at somewhat higher temperature.[6] The enantiomeric purity of **1** thus obtained was determined to be 98% ee by chiral HPLC analysis after conversion of **1** into **4**.[7] Recrystallization of crude **1** afforded a sample of greater than 99% ee. Hydrolysis of crude **1** by heating with 6 N hydrochloric acid afforded **2**·HCl. This was shown to be of 89% ee after its conversion to **4** by catalytic hydrogenation, followed successively by benzyloxycarbonylation and methylation. It thus became evident that acid hydrolysis of **1** had been accompanied with partial racemization. Purification of **2**·HCl was difficult.

We then converted **2**·HCl into the *N*-acetyl compound **5** in order to subject it to enzymatic resolution. Although (*S*)-**5** was efficiently purified by recrystallization, hydrolysis of (*S*)-**5** with 6 N hydrochloric acid caused partial racemization. Treatment of crude (*S*)-**5** with acylase I afforded **2** in 55% overall yield based on **1**. Compound **2** thus obtained was of 98% ee. Because (*R*)-**5** was resistant to digestion with the enzyme, we supposed that partial racemization of **2** and/or non-enzymatic hydrolysis of (*R*)-**5** had occurred on treatment with acidic resin during the isolation procedure. When (±)-**5** was subjected to the enzymatic resolution, **2** and (*R*)-**5** were obtained in 87% and 83% yields, respectively. Recrystallization of **2** from methanol provided an enantiomerically pure sample for the first time. Compound **6** prepared from crude **2** was of 95% ee and an enantiomerically pure sample of **6** could not be obtained by means of recrystallization. Partial racemization of **6** could have taken place on treatment with hydrochloric acid during the isolation procedure; indeed, **6** slowly underwent racemization in 0.1 N hydrochloric acid at 40 °C. Such easy acid-catalyzed




a, $HCl/H_2O$; b, $HCl/H_2O$/AcOH; c, $Pt/H_2$; d, Pd–C/$H_2$; e, $ClCO_2CH_2Ph/NaHCO_3$;

f, $Me_3SiCHN_2$/MeOH; g, $Ac_2O/NaHCO_3$; h, acylase I; i, $ClCO_2Me/NaHCO_3$

Chart 1

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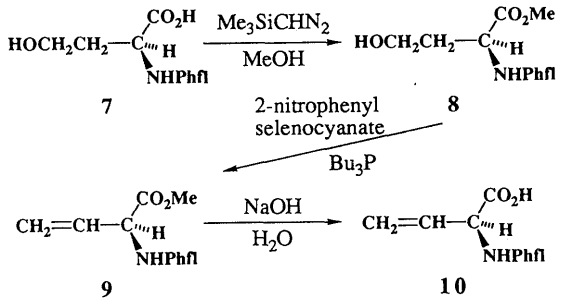


Phfl = 9-phenylfluoren-9-yl

Chart 2

racemization is explicable in terms of a mechanism analogous to that which we have already proposed for racemization of (2-arylvinyl)glycine derivatives.[8]

Crisp and Glink applied our method[2] to the synthesis of various $\beta,\gamma$-unsaturated amino acid derivatives by employing *N*-(benzyloxycarbonyl)vinylglycine (**3**).[9] The present results suggest that **3** prepared by acidic hydrolysis[6b,9] is not optically pure. However, **3** of more than 99% ee was obtained according to the literature procedure,[6b] followed by recrystallization.

In order to stabilize the configuration of **2**, we finally focused our attention on the 9-phenylfluoren-9-yl group which was developed for protecting the configuration of (*S*)-alaninal.[10] For the preparation of **9**, we synthesized **8** from (*S*)-homoserine through **7**. When we attempted to protect (*S*)-homoserine methyl ester, the product obtained in 40% yield was not **8**, but the $\gamma$-lactone. Compound **8** was then treated according to the literature procedure[4a] to afford **9**.[11] This compound was not sensitive to either racemization[8] or isomerization[1a] under basic conditions: on treatment with sodium hydroxide, it afforded the carboxylic acid **10** of greater than 99% ee.

Vinylglycine (**2**) and its derivatives are useful chiral synthons.[2,4g,5a,c,6a,b,9,12] Accordingly, the present syntheses of these compounds and determination of their optical purities should be of practical value for asymmetric syntheses.

## Experimental

All melting points were determined by using a Yamato MP-1 or Büchi 530 capillary melting point apparatus and are corrected. IR spectra were recorded on a JASCO A-202 or Shimadzu FTIR-8100 IR spectrophotometer. MS were recorded on a Hitachi M-80 mass spectrometer. NMR spectra were measured with a JEOL JNM-FX-100 or JEOL JNM-EX-270 NMR spectrometer. Unless otherwise stated, they were recorded at 270 MHz and 25 °C in $CDCl_3$ with tetramethylsilane as an internal standard. Optical rotations were measured with a JASCO DIP-181 polarimeter using a 1-dm sample tube. The HPLC system was a Waters model 204 ALC which included a 6000A pump, a U6K injector and a model 440 absorbance detector operating at 254 nm. Elemental analyses were performed by Mr. Itatani and his associates at Kanazawa University. Flash chromatography was performed according to the reported procedure.[13]

**Determination of the Enantiomeric Purity of 4** Compound (±)-**4** was cleanly resolved to the (*R*)-isomer (retention time, 19.2 min) and **4** (21.6 min) by HPLC on a Sumichiral OA-3200 column (4.6 × 250 mm) [hexane–ethanol (200 : 1, v/v); 1 ml/min] at room temperature. The peak areas of the components were determined by using a Takeda Riken TR-2217 automatic integrator, and the enantiomeric purities were estimated from a calibration curve which had been obtained with mixtures of known amounts of enantiomerically pure **4** and (±)-**4**.

**(±)-2-[(Benzyloxycarbonyl)amino]butanoic Acid Methyl Ester [(±)-4]** Compound (±)-**2**·HCl[14] (119 mg, 0.865 mmol) was hydrogenated over 10% palladium on carbon (106 mg) in water (5 ml) at room temperature for 4 h. The catalyst was filtered off and washed with methanol. The filtrate and the washings were combined, and concentrated *in vacuo* to leave (±)-2-aminobutanoic acid hydrochloride (100 mg, 83%) as a colorless solid, mp 223—225 °C (dec.) (lit.[15] mp 242 °C); $^1$H-NMR [$D_2O$; $Me_3Si(CH_2)_3SO_3Na$] $\delta$: 1.01 (3H, t, $J$=7.6 Hz, Me), 1.96 (2H, m, $CH_2$), 3.96 (1H, t, $J$=6 Hz, CH). A portion (97 mg, 0.69 mmol) of this sample was dissolved in water (5 ml). Sodium bicarbonate (292 mg) and benzyl chloroformate (138 mg) were added to the solution. The whole was stirred at room temperature for 20 h. The resulting mixture was washed with ethyl acetate (2 × 5 ml). The aqueous layer was brought to pH 1 with 10% hydrochloric acid and extracted with ethyl acetate (3 × 10 ml). The combined organic layers were dried over magnesium sulfate and concentrated *in vacuo* to leave (±)-2-[(benzyloxycarbonyl)amino]butanoic acid (86 mg, 52%) as a colorless oil (lit.[16] mp 77—79 °C) probably consisting of an interconverting mixture of carbamates,[17] $^1$H-NMR $\delta$: 0.98 (3H, dd, $J$=7.4 Hz each, Me), 1.77 (1H, m) and 1.95 (1H, m) [C($\beta$)$H_2$], 4.27 (1/6H, br) and 4.38 (5/6H, m) [C($\alpha$)H], 5.13 (2H, s, PhC$\underline{H}_2$), 5.26 (5/6H, d, $J$=7.9 Hz) and 5.85 (1/6H, br) (NH), 7.36 (5H, s, Ph). A portion (53 mg, 0.22 mmol) of this product was treated with trimethylsilyldiazomethane in the usual manner[18] and the resulting crude (±)-**4** was purified by layer chromatography on silica gel [benzene–ethyl acetate (15 : 1, v/v)] to afford (±)-**4** (51 mg, 91%) as a colorless oil, $^1$H-NMR $\delta$: 0.92 (3H, dd, $J$=7.4 Hz each, CMe), 1.72 (1H, m) and 1.88 (1H, m) [C($\beta$)$H_2$], 4.25 (1/5H, br) and 4.35 (4/5H, m) [C($\alpha$)H], 5.11 (2H, s, overlapping with a 1/5H signal due to NH, PhC$\underline{H}_2$), 5.29 (4/5H, d, $J$=7.6 Hz, NH), 7.36 (5H, s, Ph).

**(*S*)-2-[(Benzyloxycarbonyl)amino]butanoic Acid Methyl Ester (4)** This compound was prepared as a colorless oil from commercial (*S*)-2-aminobutanoic acid in a manner similar to that described above for the preparation of (±)-**4**. The IR and $^1$H-NMR spectra were identical with those of (±)-**4**.

**(*S*)-2-[(Benzyloxycarbonyl)amino]-3-butenoic Acid Methyl Ester (1)** (*S*)-2-[(Benzyloxycarbonyl)amino]-4-(methylsulfinyl)butanoic acid methyl ester[1a] (12.33 g, 39.3 mmol) was Kugelrohr distilled at 200 °C (2 mmHg) in three portions. The distillates (9.16 g) were combined and purified by flash chromatography [benzene–ethyl acetate (15 : 1, v/v)] to afford **1** (6.05 g, 62%) as an almost colorless solid, mp 34.5—35.5 °C; $[\alpha]_D^{22}$ −8.16° ($c$=1.79, MeOH) [lit.[1a] a colorless oil, $[\alpha]_D^{20}$ −11.8° ($c$=1.8, MeOH)]. Compound **1** (25 mg, 0.1 mmol) was hydrogenated over platinum dioxide (4 mg) in methanol (3 ml) at room temperature for 4 h. The catalyst was filtered off and washed with hot methanol. The filtrate and the washings were combined, and concentrated. The product was purified by layer chromatography on silica gel [hexane–ethyl acetate (3 : 1, v/v)] to afford **4** (23 mg, 91%) as a colorless oil of 98% ee.

Recrystallization of crude **1** from hexane afforded an analytical sample of **1** as colorless pillars, mp 35.5—36.5 °C; $[\alpha]_D^{22}$ −8.86° ($c$=1.84, MeOH); IR $\nu_{max}^{Nujol}$ cm$^{-1}$: 3289 (NH), 1748 (ester CO), 1690 (carbamate CO); $^1$H-NMR $\delta$: 3.77 (3H, s, Me), 4.86 (1/10H, br) and 4.94 (9/10H, br) [C($\alpha$)H], 5.13 (2H, s, PhC$\underline{H}_2$), 5.28 (1H, dd, $J$=1 and 10 Hz) and 5.37 (1H, dd, $J$=1 and 17 Hz) ($CH_2$=), 5.44 (br, NH), 5.91 (1H, ddd, $J$=6, 10, and 17 Hz, $CH_2$=C$\underline{H}$), 7.36 (5H, m, Ph). *Anal.* Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.61; H, 6.12; N, 5.55. This sample was shown to be of more than 99% ee after its conversion to **4**.

**(*S*)-2-Amino-3-butenoic Acid (2)** Compound **1** (12.4 g, 49.7 mmol) was heated in 6 N hydrochloric acid (200 ml) under reflux for 1 h. The resulting solution was washed with chloroform (2 × 50 ml) and then concentrated *in vacuo* to leave **2**·HCl (6.02 g, 88%), mp 151—154 °C (dec.); $[\alpha]_D^{30}$ +70.0° ($c$=2.00, $H_2O$) [lit.[1a] $[\alpha]_D^{20}$ +78.5° ($c$=1.9, $H_2O$)]. This compound (5.9 g) was acetylated in the manner described below to afford (*S*)-**5** (5.42 g, 78% overall yield), mp 140—142 °C; $[\alpha]_D^{25}$ +22.4° ($c$=0.508, MeOH). Crude (*S*)-**5** (2.00 g, 14 mmol) was dissolved in 0.1 M phosphate buffer (pH 7.5, 250 ml) and the pH was adjusted to 7.5 with 1 N aqueous sodium hydroxide. Acylase I[19] (14 mg) was added to the solution and the mixture was stirred at 38 °C for 2 h. The resulting solution was passed through a column packed with Dowex 50WX8 ($H^+$) (150 ml) and then the column was washed with water until the washings showed pH 7. The column was then eluted with 0.5 M aqueous pyridine[20] (3 l). The eluate was concentrated *in vacuo* to leave **2**·1/10$H_2O$ (1.01 g, 55% overall yield), mp 214—216 °C (dec.). A portion (94 mg, 0.93 mmol) of this sample was hydrogenated over 10% palladium on carbon (91 mg)

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in water (10 ml) at room temperature for 4 h to provide (*S*)-2-aminobutanoic acid (84 mg, 88%), mp 248—250 °C (dec.) [lit.[21] mp 270—280 °C (dec.)]; $^1$H-NMR ($D_2O$; $Me_3Si(CH_2)_3SO_3Na$) $\delta$: 0.97 (3H, t, $J$=7.6 Hz, Me), 1.89 (2H, m, $CH_2$), 3.70 (1H, dd, $J$=5.8 Hz each, CH). *N*-Benzyloxycarbonylation (82%) of this sample followed by methylation (85%) was conducted in the usual manner to afford **4** of 98% ee.

Recrystallization of crude **2**·1/10$H_2O$ from methanol followed by drying over phosphorus pentoxide at 2 mmHg and 50 °C for 10 h gave an analytical sample of **2**·1/10$H_2O$ as colorless minute crystals. Further drying at 2 mmHg and 75 °C for 10 h did not remove the water of crystallization of **2**·1/10$H_2O$, mp 216—218°C (dec.); $[\alpha]_D^{18}$ +125° ($c$=0.522, $H_2O$); $^1$H-NMR [$D_2O$; $Me_3Si(CH_2)_3SO_3Na$] $\delta$: 4.24—4.28 [1H, m, C(α)H], 5.45—5.51 (2H, m, $CH_2$), 5.90—6.03 (1H, m, $CH_2$=C<u>H</u>). *Anal.* Calcd for $C_4H_7NO_2$·1/10$H_2O$: C, 46.69; H, 7.05; N, 13.61. Found: C, 46.66; H, 6.83; N, 13.52. HPLC of **4** prepared from this sample of **2** no longer showed the peak due to the (*R*)-isomer.

After heating in 6 N hydrochloric acid under reflux for 1 h,[22] **2** was transformed into **4** in a manner similar to that described above. Compound **4** thus obtained was of 83% ee.

**(±)-2-(Acetylamino)-3-butenoic Acid [(±)-5]** Compound (±)-**2**·HCl[14] (275 mg, 2 mmol) was acetylated in a manner similar to that described below for the preparation of (*S*)-**5** to afford (±)-**5** (258 mg, 90%), mp 123.5—126 °C. Recrystallization of crude (±)-**5** from ethyl acetate–hexane (4:1, v/v) afforded an analytical sample as colorless prisms, mp 126.5—128 °C; $\nu_{max}^{Nujol}$ cm$^{-1}$: 3240 (NH), 1709 (COOH). *Anal.* Calcd for $C_6H_9NO_3$: C, 50.35; H, 6.34; N, 9.79. Found: 50.22; H, 6.30; N, 9.77.

**(*S*)-2-(Acetylamino)-3-butenoic Acid [(*S*)-5]** Acetic anhydride (613 mg, 6 mmol) was added dropwise into a solution of **2**·HCl (678 mg, 4.93 mmol) and sodium bicarbonate (2.10 g, 25 mmol) in water (25 ml) over 10 min under cooling with ice water. The mixture was stirred at 0 °C for another 40 min, brought to pH 1 with 10% hydrochloric acid, and concentrated *in vacuo* to *ca.* 10 ml. The solution was then extracted with dichloromethane using a continuous extractor. The extracts were dried over magnesium sulfate and concentrated *in vacuo* to afford (*S*)-**5** (610 mg, 87%), mp 139—142°C. Recrystallization of this product from ethyl acetate (40 ml) gave colorless prisms (461 mg), mp 143.5—145 °C; $[\alpha]_D^{22}$ +24.3° ($c$=0.512, MeOH). Further recrystallization of (*S*)-**5** afforded an analytical sample as colorless prisms, mp 150—151.5 °C (lit.[12e] mp 155—157°C); $[\alpha]_D^{26}$ +23.3° ($c$=0.497, MeOH); $\nu_{max}^{Nujol}$ cm$^{-1}$ 3260 (NH), 1707 (COOH); 100 MHz $^1$H-NMR [$(CD_3)_2SO$] $\delta$: 1.88 (3H, s, Me), 4.82 [1H, dddd, $J$=8, 6, 1.6, and 1.6 Hz, C(α)H], 5.21 (1H, ddd, $J$=10, 1.6, and 1.6 Hz) and 5.30 (1H, ddd, $J$=17, 1.6, and 1.6 Hz) ($CH_2$=), 5.92 (1H, ddd, $J$=17, 10, and 6 Hz, $CH_2$=C<u>H</u>), 8.32 (1H, d, $J$=8 Hz, NH), 12.75 (1H, br, $CO_2H$). *Anal.* Calcd for $C_6H_9NO_3$: C, 50.35; H, 6.34; N, 9.79. Found: C, 50.53; H, 6.48; N, 9.67.

When (*S*)-**5** was heated under reflux in 6 N hydrochloric acid for 2 h, **2**·HCl, mp 153—154.5 °C, of low optical purity $[\alpha]_D^{22}$ +42.2° ($c$=0.440, $H_2O$)] was obtained in 96% yield.

**(*R*)-2-(Acetylamino)-3-butenoic Acid [(*R*)-5]** Compound (±)-**5** (264 mg, 1.84 mmol) was treated with acylase I and then with Dowex 50WX8 ($H^+$) in the same manner as described for the preparation of **2**. The aqueous washings of the column were concentrated *in vacuo* to *ca.* 30 ml, brought to pH 1 with 10% hydrochloric acid, and then extracted with dichloromethane using a continuous extractor. The organic layer was dried over magnesium sulfate and concentrated *in vacuo* to afford (*R*)-**5** (109 mg, 83%), mp 134—136 °C; $[\alpha]_D^{27}$ −15° ($c$=0.50, MeOH). The column was eluted with 0.5 M aqueous pyridine (300 ml) and the eluate was concentrated *in vacuo* to afford **2**·1/10$H_2O$ (83 mg, 87%), mp 206—209 °C (dec.); $[\alpha]_D^{29}$ +97.7° ($c$=0.470, $H_2O$).

Recrystallization of crude (*R*)-**5** from ethyl acetate afforded an analytical sample, whose IR spectrum was identical with that of (*S*)-**5**, as colorless prisms, mp 148—151 °C; $[\alpha]_D^{22}$ −23.0° ($c$=0.200, MeOH). *Anal.* Calcd for $C_6H_9NO_3$: C, 50.35; H, 6.34; N, 9.79. Found: C, 50.15; H, 6.31; N, 9.77. (*R*)-Vinylglycine was not formed after treatment of this sample with acylase I under conditions similar to those described for the preparation of **2**.

**(*S*)-2-[(Methoxycarbonyl)amino]-3-butenoic Acid (6)** A mixture of **2** (0.61 g, 6 mmol), sodium bicarbonate (2.62 g, 31 mmol), methyl chloroformate (0.63 g, 6.7 mmol), and water (40 ml) was stirred at room temperature for 1 h. The resulting solution was concentrated *in vacuo* to *ca.* 20 ml, brought to pH 1 with 10% hydrochloric acid, and then extracted with dichloromethane using a continuous extractor for 17 h. The extracts were dried over magnesium sulfate and concentrated *in vacuo* to leave **6** as a colorless solid (0.79 g, 82%), mp 84—86 °C. Recrystallization of crude **6** several times from benzene afforded an analytical sample of **6** as colorless scales, mp 89—90 °C; $[\alpha]_{365}^{21}$ +61.2° ($c$=0.503, MeOH); $^1$H-NMR $\delta$: 3.72 (3H, s, Me), 4.81 (3/10H, br) and 4.97 (7/10H, br) [C(α)H], 5.33 (1H, d, $J$=10.6 Hz) and 5.41 (1H, d, $J$=16.8 Hz) (overlapping with a 7/10H signal due to NH, $CH_2$=), 5.96 (1H, m, $CH_2$=C<u>H</u>), 6.94 (3/10H, br, NH). *Anal.* Calcd for $C_6H_9NO_4$: C, 45.28; H, 5.70; N, 8.80. Found: C, 45.20; H, 5.63; N, 8.84. A small amount of this sample was hydrogenated over 10% palladium on carbon in methanol at room temperature for 6 h. The product was then heated under reflux in 6 N hydrochloric acid for 2.5 h and the resulting amino acid was treated with benzyl chloroformate, followed by methylation with trimethylsilyldiazomethane to give **4** of 95% ee. The enantiomeric purity of **6** decreased to 93% ee after it was kept in 0.1 N hydrochloric acid at 40 °C for 24 h.

**(*S*)-2-[(Benzyloxycarbonyl)amino]-3-butenoic Acid (3)** This compound (1.43 g), mp 119—122 °C, which was obtained from crude **1** (1.86 g, 7.46 mmol) according to the literature procedure,[6b] was recrystallized from a mixture of hexane (4 ml) and ethyl acetate (3.5 ml) to afford **3** (1.03 g, 59%) as colorless scales, mp 126—128.5 °C. A small portion of this sample was hydrogenated in methanol over 10% palladium on carbon at room temperature for 2 h and the resulting amino acid was treated with benzyl chloroformate, followed by methylation to afford **4** of 99% ee. Two more recrystallizations of **3** afforded a sample of greater than 99% ee, mp 129—129.5 °C (lit.[6b] mp 130—131 °C); $^1$H-NMR $\delta$: 4.87 (1/5H, br) and 4.99 (4/5H, br) [C(α)H], 5.14 (2H, s, $PhCH_2$), 5.33 (1H, d, $J$=10.2 Hz) and 5.42 (1H, d, $J$=16.8 Hz) (overlapping with a 4/5H signal due to NH, $CH_2$=), 5.96 (1H, m, $CH_2$=C<u>H</u>), 6.50 (1/5H, br, NH), 7.36 (5H, m, Ph).

**(*S*)-Dihydro-3-[(9-phenylfluoren-9-yl)amino]-2(3*H*)-furanone** Thionyl chloride (0.42 ml, 5.8 mmol) was added dropwise into dry methanol (3 ml) at −5—0 °C. (*S*)-Homoserine (0.52 g, 4.4 mmol) was then added and the mixture was stirred at room temperature for 1 h and then at 40 °C for a further 2 h. The resulting solution was concentrated *in vacuo* and the residue was washed with ether (5 ml) to afford a colorless solid (0.62 g), mp *ca.* 180 °C (dec.). This was dissolved in a mixture of chloroform (12.5 ml) and acetonitrile (2.5 ml), followed by addition of chlorotrimethylsilane (0.64 ml, 5 mmol) and triethylamine (0.70 ml, 5 mmol). The mixture was refluxed for 2 h under nitrogen and cooled with ice water, whereupon lead(II) nitrate (1.00 g, 3 mmol), 9-bromo-9-phenylfluorene[23] (1.60 g, 4.98 mmol), and triethylamine (1.40 ml, 10 mmol) were added. The whole was stirred at room temperature under nitrogen for 41 h. The solids were filtered off and washed with chloroform (3 × 5 ml). The filtrate and the washings were combined, washed with 5% aqueous citric acid (3 × 10 ml), dried over magnesium sulfate, and concentrated *in vacuo* to leave a brown oil (1.64 g). This was mixed with a solution of citric acid (0.16 g) in dry methanol (5 ml) and allowed to stand at room temperature for 2 h. The resulting precipitate was collected by filtration, washed with methanol (10 ml), and dried to afford the title compound as a colorless solid (0.59 g, 40%), mp 187—197 °C. Recrystallization from hexane–benzene (5:1, v/v) gave an analytical sample as colorless prisms, mp 201.5—202.5 °C; $[\alpha]_D^{25}$ −333° ($c$=0.641, $CHCl_3$); MS $m/z$: 341 ($M^+$); IR $\nu_{max}^{Nujol}$ cm$^{-1}$: 3310 (NH), 1770 (CO); 100 MHz $^1$H-NMR $\delta$: 1.30 [1H, ddd, $J$=12, 8, and 6 Hz, C(4α)H], 1.78 [1H, dddd, $J$=12, 11, 11, and 8 Hz, C(4β)H], 2.94 [1H, dd, $J$=11 and 8 Hz, C(3)H], 3.15 (1H, br s, NH), 3.72 [1H, ddd, $J$=11, 9, and 6 Hz, C(5α)H], 4.11 [1H, dd, $J$=9 and 8 Hz, C(5β)H], 7.05—7.48 (11H, m) and 7.55—7.76 (2H, m) (aromatic protons).[24] *Anal.* Calcd for $C_{23}H_{19}NO_2$: C, 80.92; H, 5.61; N, 4.10. Found: C, 80.95; H, 5.58; N, 4.40.

**(*S*)-4-Hydroxy-2-[(9-phenylfluoren-9-yl)amino]butanoic Acid (7)** A mixture of (*S*)-homoserine (2.98 g, 25 mmol), chlorotrimethylsilane (6.5 ml, 51 mmol), triethylamine (3.5 ml, 25 mmol), acetonitrile (12.5 ml), and chloroform (63 ml) was refluxed under nitrogen for 2 h and cooled to room temperature. Lead(II) nitrate (5.00 g, 15.1 mmol), a solution of 9-bromo-9-phenylfluorene[23] (8.03 g, 25 mmol) in chloroform (21 ml), and triethylamine (7.0 ml, 50 mmol) were then added to the mixture, and the whole was stirred at room temperature under nitrogen for 24 h. Dry methanol (1 ml) was added to the resulting mixture and the precipitate was filtered off. The filtrate was concentrated *in vacuo* and a solution of citric acid (2.22 g) in methanol (20 ml) was added to the residue. The mixture was then washed with water (3 × 50 ml). The residue was mixed with hot benzene (35 ml), cooled to room temperature, collected by filtration, washed with benzene (50 ml), and dried to afford **7** (4.81 g).

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The aqueous washings were allowed to stand at room temperature and the resulting precipitate was filtered off, washed with water (30 ml), and dried to give a second crop of **7** (0.85 g; the total yield was 63%). Recrystallization of **7** from water–ethanol (2 : 1, v/v) gave an analytical sample as colorless needles, mp 158—159 °C; $[\alpha]_D^{20}$ −135° ($c$=0.203, MeOH); 100 MHz $^1$H-NMR $\delta$: 1.70 [2H, m, C($\beta$)H$_2$], 2.82 [1H, dd, $J$=5 Hz each, C($\alpha$)H], 3.64 [2H, m, C($\gamma$)H$_2$], 4.54 (3H, br, NH, OH, and $CO_2$H), 7.16—7.60 (11H, m) and 7.60—7.82 (2H, m) (aromatic protons). *Anal.* Calcd for $C_{23}H_{21}NO_3$: C, 76.86; H, 5.89; N, 3.90. Found: C, 77.06; H, 5.91; N, 3.79.

**(*S*)-4-Hydroxy-2-[(9-phenylfluoren-9-yl)amino]butanoic Acid Methyl Ester (8)** A 1.5 M solution of trimethylsilyldiazomethane in ether (1.7 ml, 26 mmol) was added to a solution of **7** (3.73 g, 10.4 mmol) in a mixture of methanol (25 ml) and benzene (25 ml). The resulting solution was concentrated *in vacuo*. The residual solid was triturated with hexane (5 ml), collected by filtration, washed with hexane (3 × 5 ml), and dried to give **8** (3.44 g), mp 87—90 °C; $[\alpha]_D^{20}$ −237° ($c$=0.201, MeOH). The filtrate and the washings were combined and purified by flash chromatography [hexane–ethyl acetate (4 : 3, v/v)] to afford a second crop (0.22 g; the total yield was 94%) of **8**, mp 93—95 °C. Recrystallization of crude **8** from hexane–benzene (20 : 1, v/v) afforded an analytical sample as colorless prisms, mp 96—97 °C; $[\alpha]_D^{21}$ −244° ($c$=0.204, MeOH); $\nu_{max}^{Nujol}$ cm$^{-1}$: 1727 (CO); 100 MHz $^1$H-NMR $\delta$: 1.60 [2H, m, overlapping with a 1H broad signal due to OH, C($\beta$)H$_2$], 2.78 [1H, dd, $J$=9.4 and 4.5 Hz, C($\alpha$)H], 3.28 (3H, s, Me), 3.44—3.85 [2H, m, overlapping with a 1H broad signal due to NH, C($\gamma$)H$_2$], 7.07—7.52 (11H, m) and 7.63—7.78 (2H, m) (aromatic protons). *Anal.* Calcd for $C_{24}H_{23}NO_3$: C, 77.19; H, 6.21; N, 3.75. Found: C, 77.34; H, 6.28; N, 3.99.

**(*S*)-2-[(9-Phenylfluoren-9-yl)amino]-3-butenoic Acid Methyl Ester (9)** This compound was prepared from **8** (560 mg, 1.5 mmol) according to the procedure reported for the preparation of (*S*)-*N*-[(benzyloxy)-carbonyl]vinylglycine isopropyl ester.[4a] Purification of the crude product by flash chromatography [hexane–ethyl acetate (10 : 1, v/v)] afforded **9** (470 mg, 88%) as a yellow oil, $[\alpha]_D^{20}$ −141° ($c$=0.214, MeOH); $^1$H-NMR $\delta$: 3.05 (1H, br, NH), 3.30 [1H, d, $J$=5.6 Hz, C($\alpha$)H], 3.36 (3H, s, Me), 5.03 (1H, ddd, $J$=10, 1.3, and 1.3 Hz) and 5.23 (1H, ddd, $J$=17, 1.3, and 1.3 Hz) ($CH_2$=), 5.68 (1H, ddd, $J$=17, 10, and 5.6 Hz, $CH_2$=C<u>H</u>), 7.15—7.46 (11H, m) and 7.65—7.70 (2H, m) (aromatic protons).

**(*S*)-2-[(9-Phenylfluoren-9-yl)amino]-3-butenoic Acid (10)** Compound **9** (371 mg, 1.04 mmol) was dissolved in a mixture of methanol (65 ml) and water (5 ml), and 1 M aqueous sodium hydroxide (5.2 ml) was added. The whole was stirred at room temperature for 48 h. The resulting mixture was diluted with water (200 ml) and washed with ether (2 × 100 ml). The aqueous phase was brought to pH 3 and extracted with ether (2 × 100 ml). The ethereal extracts were dried over magnesium sulfate and concentrated *in vacuo* to leave **10** as a colorless foam (274 mg, 77%), $[\alpha]_D^{19}$ −17.7 ($c$=0.198, MeOH); 100 MHz $^1$H-NMR $\delta$: 3.22 [1H, ddd, $J$=6, 1.2, and 1.2 Hz, C($\alpha$)H], 5.03 (1H, ddd, $J$=17, 1.2, and 1.2 Hz) and 5.05 (1H, ddd, $J$=10, 1.2, and 1.2 Hz) ($CH_2$=), 5.28 (2H, br, NH and $CO_2$H), 5.65 (1H, ddd, $J$=17, 10, and 6 Hz, $CH_2$=C<u>H</u>), 7.00—7.48 (10H, m) and 7.56—7.76 (3H, m) (aromatic protons). A small amount of **10** was hydrogenated in methanol over 10% palladium on carbon at room temperature for 2 h. The catalyst was filtered off and washed with hot methanol. The filtrate and the washings were combined and concentrated. The residue was partitioned between water and dichloromethane. The aqueous layer was treated with benzyl chloroformate in the presence of sodium bicarbonate, followed by methylation with trimethylsilyldiazomethane to afford **4** of greater than 99% ee.

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