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Note

Novel Synthesis of (−)-Bestatin from L-Aspartic Acid†

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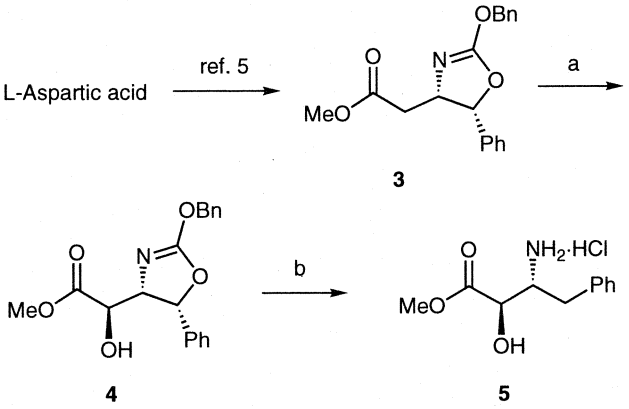
Oxazoline-4-acetate derivative 3 that could be readily obtained from L-aspartic acid was subjected to highly stereoselective hydroxylation, and subsequent Mitsunobu inversion of the hydroxyl group led to (2*S*,3*R*)-3-amino-3-benzyl-2-hydroxybutanoic acid derivative 8 in a good yield. Coupling of 8 with L-leucine benzyl ester and subsequent cleavage of the protective groups provided (−)-bestatin 1 in a high yield.

Key words: bestatin; α-hydroxy-β-amino acid; L-aspartic acid; diastereoselective hydroxylation

(−)-Bestatin **1** is a natural dipeptide that has been isolated from *Streptomyces olivoreticuli*[1] and clinically used as an immunological modifier and an antitumor agent.[2] Many synthetic methods for (−)-bestatin **1** have been developed by focusing on the stereoselective synthesis of the β-amino acid component, (2*S*,3*R*)-3-amino-4-phenyl-2-hydroxybutanoic acid **2**.[3] A more practical synthesis is, however, still needed in terms of the availability of the starting material and versatility which would enable access to a wide variety of bestatin derivatives. Described here is the synthesis of (−)-bestatin **1** from inexpensive L-aspartic acid[4] by applying our previously described synthetic method for chiral α-hydroxy-β-amino acids involving highly stereoselective hydroxylation of an oxazoline-4-acetate.[5]

Required oxazoline-4-acetate **3** was prepared from L-aspartic acid according to our previously reported procedure.[5] Hydroxylation of **3** with 3-phenyl-2-(phenylsulfonyl)oxaziridine proceeded with high stereoselectivity as we have reported[5] to give **4** as the sole product as crystals. Hydrogenation of **4** gave methyl (2*R*,3*R*)-3-amino-4-phenyl-2-hydroxybutanoate **5** in a good yield. The required (*S*)-configuration at the C-2 position was formed by protecting the amino group of **5** with a benzyloxycarbonyl group and subsequent Mitsunobu inversion of the hydroxyl group. Ammonolysis of the formyl group of **7** and subsequent hydrolysis gave (2*S*,3*R*)-3-benzyloxycarbonylamino-4-phenyl-2-hydroxybutanoic acid **8** in a high yield. Coupling **8** with L-leucine benzyl ester and then hydrogenolysis of the protective groups gave (−)-bestatin **1** in a high yield.

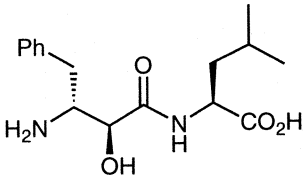


a: i) LiHMDS, -78°C, 1 h; ii) $PhSO_2N$(O)Ph, -78°C, 1h, 62%;
b: H_2/Pd-C, HCl, 86%

In conclusion, a facile synthesis of (−)-bestatin from L-aspartic acid was accomplished (13 steps, 5.4% overall yield). Although the Mitsunobu inversion of the hydroxyl group was necessary to construct the correct C-2 asymmetric center, this new process has such advantages as the ready accessibility of the starting material, the simple procedure and its applicability to the synthesis of a variety of (−)-bestatin derivatives.

Experimental

Infrared spectra were recorded by a Perkin-Elmer 1640 IR spectrophotometer and are reported as λ_{max} (cm^{-1}). ^{1}H-NMR spectra were measured with a Bruker AC-200 (200 MHz) spectrometer in $CDCl_3$, DMSO-d_6 or D_2O, with tetramethylsilane (for $CDCl_3$ and DMSO-d_6) and sodium β-(trimethylsilyl)propanoate (for D_2O) used as internal standards. Mass spectra were taken by a Hitachi M-2000A spectrometer at an ionizing potential of 70 eV. Optical rotation was measured with a Perkin-Elmer 241 polarimeter, and microanalyses were performed by a Perkin-Elmer 2400 Series II CHNS/O analyzer. Flash chromatography was accomplished by using Kieselgel 60 (230–400 mesh, E. Merck). Methyl (4*S*,5*R*)-5-phenyl-2-oxazolidinone-4-acetate was prepared from L-aspartic acid as previously described.[5]



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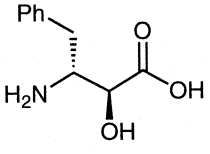

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† Synthesis of Amino Acids and Related Compounds, Part 48. For Part 47, see ref. 5

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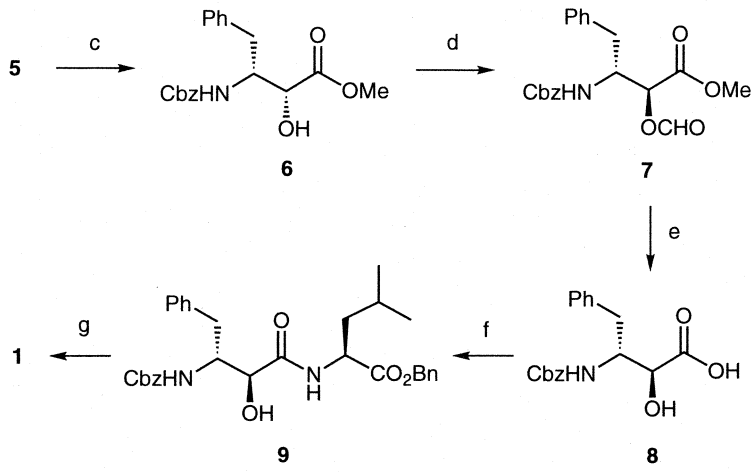

c: Cbz-Cl, $NaHCO_3$, 85%; d: DEAD, HCO_2H, 60%; e: i) NH_3, ii) NaOH, 70%; f: L-LeuOBn·TosOH, DCC, Hobt, Et_3N, quant.; g: H_2/Pd-black, 90%

Methyl (4S,5R)-2-Benzyloxy-5-phenyloxazoline-4-acetate (**3**). A mixture of methyl (4*S*,5*R*)-5-phenyl-2-oxazolidinone-4-acetate[5] (10 g, 43 mmol), benzyl bromide (17.6 g, 51 mmol) and silver carbonate (9.4 g, 34 mmol) in toluene (130 ml) was stirred at 60°C for 6 h. The mixture was filtered through Celite, and the filtrate was evaporated *in vacuo*. The residue was purified by silica-gel column chromatography (*n*-hexane:AcOEt=4:1) to give **3** (11.4 g, 83%) as a colorless oil, IR (nujol) ν_{max}: 1736, 1669 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.03 (dd, J=8.3, 16 Hz, 1H, CH_2), 2.34 (dd, J=6.8, 16 Hz, 1H, CH_2), 3.48 (s, 3H, CH_3), 4.77–4.89 (m, 1H, CH), 5.31 (s, 2H, CH_2 (benzyl)), 5.83 (d, J=9.1 Hz, 1H, CH (benzyl)), 7.17–7.46 (m, 10H, Ph×2). ^{13}C-NMR ($CDCl_3$) δ: 41.99 (t), 52.49 (q), 69.36 (d), 72.73 (t), 80.05 (d), 126.78 (d), 128.12 (d), 128.44 (d), 128.54 (d), 128.70 (d), 129.73 (d), 135.13 (s), 136.58 (s), 161.70 (s), 170.32 (s). SIMS *m/z*: 326 (M^++1). $[\alpha]_D^{25}$ −55° (*c*, 1.1, MeOH). *Anal.* Found: C, 69.89; H, 5.70; N, 4.11%. Calcd. for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31%.

Methyl (2R,4S,5R)-2-Benzyloxy-2-hydroxy-5-phenyloxazolin-4-acetate (**4**). Into a solution of **3** (3 g, 9 mmol) in tetrahydrofuran (11 ml) was added portionwise lithium bis(trimethylsilyl)amide (1.0 M in tetrahydrofuran, 11 ml, 11 mmol) at −78°C over 10 min, and the mixture was stirred at −78°C for 1 h. 3-Phenyl-2-(phenylsulfonyl)oxaziridine[5] (2.9 g, 11 mmol) in tetrahydrofuran (15 ml) was next added at −78°C, and the mixture was stirred again at −78°C for 1 h. To the mixture was finally added sat. aq. ammonium chloride (80 ml), and the tetrahydrofuran was evaporated *in vacuo*. The residue was extracted with dichloromethane (45 ml×3), and the combined extracts were washed with brine, dried over anhydrous magnesium sulfate and evaporated *in vacuo*. The residue was purified by silica-gel column chromatography (*n*-hexane:AcOEt=4:1 to 2:1 to 1:1) to give **4** (1.95 g, 62%) as colorless crystals, mp 92–93°C. IR (Nujol) ν_{max}: 3380, 1734 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.28 (d, J=5.2 Hz, 1H, OH), 3.52 (s, 3H, CH_3), 4.11–4.16 (m, 1H, CH), 4.70 (dd, J=4, 10 Hz, 1H, CH-N), 5.33 (d, J=12 Hz, 1H, CH), 5.40 (d, J=12 Hz, 1H, CH_2 (benzyl)), 5.82 (d, J=10 Hz, 1H, CH_2 (benzyl)), 7.26-7.48 (m, 10H, Ph×2). ^{13}C-NMR ($CDCl_3$) δ: 52.21 (q), 69.84 (d), 71.28 (d), 72.52 (t), 84.25 (d), 126.86 (d), 128.09 (d), 128.22 (d), 128.47 (d), 128.59 (d), 129.01 (d), 134.59 (s), 135.14 (s), 163.57 (s), 172.00 (s). SIMS *m/z*: 342 (M^++1). $[\alpha]_D^{25}$ −108° (*c*, 1.05, MeOH). *Anal.* Found: C, 66.70; H, 5.60; N, 4.12%. Calcd. for $C_{19}H_{19}NO_5$: C, 66.85; H, 5.61; N, 4.10%.

Methyl (2R,3R)-3-Amino-2-hydroxy-4-phenylbutanoate hydrochloride (**5**). A mixture of **4** (2 g, 6 mmol), 4-M hydrogen chloride in 1, 4-dioxane (2.2 ml, 8.8 mmol) and 10% palladium on carbon (50% wet, 580 mg) in methanol (150 ml) was hydrogenated at 25°C for 4 h in Parr apparatus (H_2 at 3.5 kg/cm^2). The mixture was filtered, and the filtrate was evaporated *in vacuo*. The crystals formed were collected and recrystallized from methanol-ether to afford **5** (1.24 g, 86%) as colorless crystals, mp 144–145°C. IR (KBr) ν_{max}: 3417, 1744, 1615 cm^{-1}. ^{1}H-NMR (D_2O) δ: 3.00 (dd, J=7.7, 15 Hz, 1H, CH_2 (benzyl)), 3.10 (dd, J=7.7, 15 Hz, 1H, CH_2 (benzyl)), 3.50 (s, 3H, CH_3), 4.15 (dt, J=2.9, 7.7 Hz, 1H, CH-N), 4.64 (d, J=2.9 Hz, 1H, CH-O), 7.30–7.47 (m, 5H, Ph). ^{13}C-NMR (D_2O) δ: 35.70 (t), 55.70 (q), 57.20 (d), 72.06 (d), 130.53 (d), 131.76 (d), 132.47 (d), 137.49 (s), 175.17 (s). SIMS *m/z*: 210 (M^+−HCl+1). $[\alpha]_D^{25}$ −14° (*c*, 1.1, MeOH). *Anal.* Found: C, 51.81; H, 6.46; N, 5.29%. Calcd. for $C_{11}H_{15}NO_3 \cdot HCl \cdot 1/2H_2O$: C, 51.86; H, 6.72; N, 5.50%.

Methyl (2R,3R)-3-(Benzyloxycarbonyl)amino-2-hydroxy-4-phenylbutanoate (**6**). Into a mixture of **5** (3.96 g, 16.1 mmol) and sodium hydrogen carbonate (5.41 g, 64.4 mmol) in water (100 ml) and ethyl acetate (100 ml) was added benzyl chloroformate (3.32 g, 19.4 mmol) at 5°C, and the mixture was stirred at 25°C for 17 h. The organic layer was separated and washed with

water, dried over anhydrous magnesium sulfate and evaporated. The crystals formed were collected by adding *n*-hexane to afford **6** (4.7 g, 85%) as colorless crystals, mp 120–121°C (lit.[3e] 121–122°C). IR (KBr) ν_{max}: 3337, 1742, 1693 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.79–2.83 (m, 2H, CH_2 (benzyl)), 3.20 (d, J=5 Hz, 1H, CH–O), 3.57 (s, 3H, CH_3), 4.33–4.50 (m, 2H, CH_2 (Cbz), 5.05–5.12 (m, 3H, CH–N+NH+OH), 7.18–7.37 (m, 10H, Ph×2). ^{13}C-NMR ($CDCl_3$) δ: 35.38 (t), 52.58 (q), 54.78 (d), 66.89 (t), 72.29 (d), 126.76 (d), 128.04 (d), 128.13 (d), 128.42 (d), 128.53 (d), 129.51 (d), 136.43 (s), 136.92 (s), 156.1 (s), 173.02 (s). SIMS m/z: 344 (M^++1). $[\alpha]_{578}^{25}$ +8.2° (*c*, 0.92, MeOH) (lit.[3e] $[\alpha]_{578}^{25}$ +6° (*c*, 0.98, MeOH)). *Anal.* Found: C, 66.16; H, 6.19; N, 4.04%. Calcd. for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.16; N, 4.08%.

Methyl (2S,3R)-3-(Benzyloxycarbonyl)amino-2-formyloxy-4-phenylbutanoate (**7**). Into a solution of **6** (340 mg, 1.0 mmol), triphenylphosphine (290 mg, 1.1 mmol) and formic acid (48.3 mg, 1.05 mmol) in tetrahydrofuran (3 ml) was added diethyl azodicarboxylate (190 mg, 1.1 mmol) at −20°C, and the mixture was gradually warmed to 25°C over 1 h. The mixture was evaporated, and the residue was purified by silica-gel column chromatography (*n*-hexane:AcOEt=4:1) to afford **7** (224.5 mg, 60%) as a colorless oil. IR (nujol) ν_{max}: 3344, 1780, 1731 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.73–3.01 (m, 2H, CH_2 (benzyl), 3.67 (s, 3H, CH_3), 4.51–4.63 (m, 1H, CH-N), 5.05 (s, 3H, CH_3), 5.16 (d, J=9.9 Hz, 1H, CH–O), 7.15–7.40 (m, 10H, Ph×2), 8.18 (s, 1H, CHO). ^{13}C-NMR ($CDCl_3$) δ: 38.26 (t), 52.74 (q), 53.09 (d), 66.96 (t), 71.50 (d), 127.16 (d), 127.98 (d), 128.18 (d), 128.52 (d), 128.88 (d), 129.07 (d), 129.25 (s), 136.21 (s), 155.54 (s), 159.34 (d), 167.94 (s). SIMS m/z: 372 (M^++1). $[\alpha]_D^{25}$ +55.9° (*c*, 1.29, MeOH). *Anal.* Found: C, 64.82; H, 5.98; N, 4.04%. Calcd. for $C_{20}H_{21}NO_6$: C, 64.68; H, 5.70; N, 3.77%.

(2S,3R)-3-(Benzyloxycarbonyl)amino-2-hydroxy-4-phenylbutanoic acid (**8**). Into a solution of **7** (300 mg, 0.81 mmol) in methanol (3 ml) was added conc. aq. ammonia (0.15 ml) at 25°C, and the mixture was stirred at 25°C for 1 h. The mixture was then evaporated, and the residue was dissolved in a mixture of 1,4-dioxane (12.5 ml) and water (12.5 ml). Sodium hydroxide (48 mg, 1.2 mmol) was added at 25°C, and the mixture was stirred again at 25°C for 1 h, before being evaporated to *ca.* 10 ml. The resulting aqueous solution was washed twice with dichloromethane and acidified to pH 1.0 by adding 2M-HCl. The mixture was extracted twice with ethyl acetate, and the combined extracts were washed with water, dried over anhydrous magnesium sulfate and evaporated. The crystals formed were collected by adding *n*-hexane to afford **8** (187 mg, 70%) as colorless crystals, mp 158–159°C (lit.[3e] 152–153°C). IR (nujol) ν_{max}: 3320, 1707, 1642 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.67–2.91 (m, 2H, CH_2 (benzyl), 3.92–4.00 (m, 1H, CH–O), 4.00–4.18 (m, 1H, CH-N), 4.88–5.02 (m, 2H, CH_2 (Cbz)), 7.05 (d, J=10 Hz, 1H, NH), 7.07–7.39 (m, 10H, Ph×2). ^{13}C-NMR (DMSO-d_6) δ: 37.21 (t), 55.23 (d), 64.94 (t), 70.51 (d), 126.07 (d), 127.24 (d), 127.52 (d), 128.13 (d), 128.19 (d), 129.08 (d), 137.06 (s), 138.49 (s), 155.44 (s), 173.86 (s). SIMS m/z: 330 (M^++1). $[\alpha]_{578}^{25}$ +84° (*c*, 0.71, AcOH) (lit.[3e] $[\alpha]_{578}^{25}$ +83° (*c*, 0.69, AcOH)). *Anal.* Found: C, 65.37; H, 6.00; N, 4.02%. Calcd. for $C_{18}H_{19}NO_5$: C, 65.64; H, 5.81; N, 4.25%.

(2S,3R)-3-(Benzyloxycarbonyl)amino-2-hydroxy-4-phenylbutanoyl-L-leucine benzyl ester (**9**). Into a mixture of **8** (100 mg, 0.304 mmol) and 1-hydroxybenzotriazole (61.6 mg, 0.456 mmol) in a mixture of dichloromethane (1 ml) and tetrahydrofuran (1 ml) was added dicyclohexylcarbodiimide (69 mg, 0.33 mmol) at 5°C, and the mixture was stirred at 5°C for 1 h. L-Leucine benzyl ester *p*-toluenesulfonate (131 mg, 0.334 mmol) and triethylamine (33.8 mg, 0.334 mmol) were then added, and the mixture was stirred at 25°C for 17 h. Water (5 ml) was next added, and the mixture was extracted with dichloromethane (5 ml×3). The combined extracts were collected and successively washed with water, sat. aq. sodium hydrogen carbonate and water, dried over anhydrous magnesium sulfate and evaporated. The residue was purified by silica-gel column chromatography (*n*-hexane:AcOEt=2:1) to afford **9** (161 mg, quant.) as colorless crystals, mp 129–130°C. IR (KBr) ν_{max}: 3397, 1735, 1718, 1655 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.85–0.88 (m, 6H, CH_3×2), 1.50–1.67 (m, 3H, CH+CH_2), 3.00 (d, J=7.4 Hz, 1H, CH-N), 4.00–4.20 (m, 2H, CH_2 (benzyl)), 4.60–4.71 (m, 1H, CO–CH–N), 4.97–5.07 (m, 2H, CH_2 (Cbz)), 5.13 (s, 2H, CH_2 (benzyl)), 5.40 (d, J=7.9 Hz, 1H, CH–O), 7.14–7.39 (m, 15H, Ph×3). ^{13}C-NMR ($CDCl_3$) δ: 21.54 (q), 22.89 (q), 24.82 (d), 36.36 (t), 41.11 (t), 50.54 (d), 55.75 (d), 67.12 (t), 73.44 (d), 126.67 (d), 127.93 (d), 128.21 (d), 128.42 (d), 128.51 (d), 128.60 (d), 129.25 (d), 135.33 (s), 136.04 (s), 137.72 (s), 157.45 (s), 172.26 (s), 172.54 (s). SIMS m/z: 533 (M^++1). $[\alpha]_D^{25}$ +11.0° (*c*, 0.35, MeOH). *Anal.* Found: C, 70.32; H, 7.18; N, 5.40%. Calcd. for $C_{31}H_{36}N_2O_6$: C, 69.90; H, 6.81; N, 5.26%.

[(2S,3R)-3-Amino-2-hydroxy-4-phenyl]butanoyl-L-leucine hydrochloride; (−)-Bestatin hydrochloride (**1**). Into a solution of **9** (60 mg, 0.11 mmol) in a mixture of methanol (10 ml) and water (4 ml) were added 2-M hydrochloric acid (0.1 ml) and palladium black (60 mg), and the mixture was hydrogenated in Parr apparatus at 25°C for 4 h (H_2 at 3.5 kg/cm^2). The mixture was filtered, and the filtrate was evaporated *in vacuo*. The crystals formed were collected by adding acetone to afford **1** as the hydrochloride (35 mg, 90.1%) as colorless crystals, mp 228–227°C (lit.[3g] 225–227°C). IR (KBr) ν_{max}: 1730, 1667 cm^{-1}. ^{1}H-NMR (D_2O+DCl) δ: 0.92 (d, J=6 Hz, 3H, CH_3), 0.95 (d, J=6 Hz, 3H, CH_3), 1.69–1.74 (m, 3H, CH+CH_2), 2.89–3.00 (m, 1H, CH_2 (benzyl)), 3.11–3.22 (m, 1H, CH_2 (benzyl)), 3.79–3.89 (m, 1H, CH-N), 4.31 (d, J=4 Hz, 1H, CH–O), 3.36–4.43 (m, 1H, CO–CH–N), 7.32–7.47 (m, 5H, Ph). ^{13}C-NMR (D_2O+DCl) δ: 23.68 (q), 25.00 (q), 27.41 (d), 37.71 (t), 41.96 (t), 54.41 (d), 57.87 (d), 72.52 (d), 130.72 (d), 132.17 (d), 132.34 (d), 137.82 (s), 175.72 (s), 178.92 (s). SIMS m/z: 309 (M^++1-HCl). $[\alpha]_D^{25}$ −12.6° (*c*, 0.5, 1M HCl) (lit.[3g] $[\alpha]_D^{25}$ −12.3° (*c*, 0.35, 1M HCl)). *Anal.*

Found: C, 54.99; H, 7.38; N, 7.82%. Calcd. for $C_{16}H_{24}N_2O_4 \cdot HCl$: C, 55.73; H, 7.31; N, 8.12%.

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