Preparation of (*S*)-3-Carbethoxy-3-benzylpiperidine and the Growth Hormone Secretagogue L-163,540

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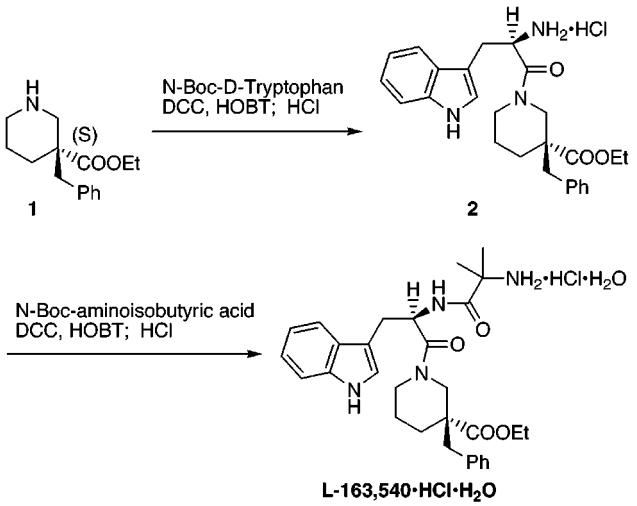
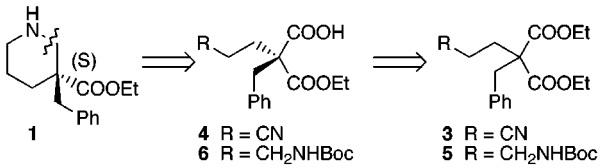
Human growth hormone (GH) is valuable for the treatment of GH-deficient children and has potential uses in burn victims, hip fracture cases, and the improvement of the quality of life in the frail elderly. The relatively high expense of natural GH has spurred the search for less complex molecules which could act as orally efficacious peptidomimetic GH secretagogues.[1] These agents act by inducing the endogenous release of GH and include MK-677.[2] Recently, L-163,540 has been introduced as a potential new GH secretagogue candidate.[3]

The preparation of L-163,540 requires the optically active piperidine **1** (Scheme 1). Initially, **1** was prepared by selective C-benzylation of ethyl nipecotate with benzyl chloride[4] followed by resolution of the racemate.[5] However, an asymmetric synthesis of **1** was desired. It was envisaged (Scheme 2) that a precursor to **1** could be chiral disubstituted malonic acid monoester **4** or **6** potentially available from enzymatic hydrolysis of the desired enantiotopic ester of the corresponding prochiral diesters **3** or **5**. Diester **5** was prepared (Scheme 3) from diethyl benzylmalonate by Michael reaction with acrylonitrile in the presence of catalytic NaOEt in *tert*-butyl methyl ether (MTBE) to give nitrile **3** in nearly quantitative yield. Enzymatic hydrolysis of **3** gave only low yields of **4** with

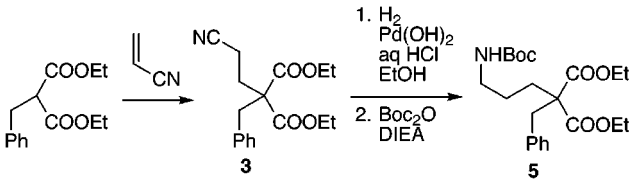
Scheme 1



Scheme 2



Scheme 3



low enantioselectivity. Catalytic hydrogenation of **3** with Pearlman's catalyst in the presence of HCl followed by protection of the resulting amine with Boc_2O and DIEA gave the Boc derivative **5** in 62% yield after crystallization. Enzymatic hydrolysis of **5** (Scheme 4) with porcine liver esterase (PLE) gave the optically active mono acid **6** in 99% ee and 86% yield. Boc removal with TFA followed by cyclization with DCC and HOBT gave the piperidone **7** in 70% yield.

Chemoselective reduction of the lactam **7** was necessary to provide **1**. Attempts to selectively reduce the lactam in the presence of the ester with $LiBH_4$ or DIBAL gave no reaction, while BH_3•Me_2S gave overreduction. Thionation of **7** (Scheme 5) with Lawesson's reagent followed by treatment of the thiolactam **8** with Raney nickel gave mixtures of **1** and imine **9**. Further reduction of the crude mixture with $NaBH_4$ gave **1** in 30% yield and 99% ee. In an improved protocol, **7** was activated as its Boc derivative **10** in 90% yield and reduced with lithium triethylborohydride to a diastereomeric mixture of the *N*-Boc aminals **11**. Further reduction with triethylsilane and BF_3•OEt_2 followed by acidic workup gave **1** in 85% overall yield from **10** and 99% ee.

Installation of the dipeptide side chain on **1** provided L-163,540 (Scheme 1). Both peptide couplings were readily effected with DCC and HOBT and were followed by deprotection with HCl to provide **2** and L-163,540 as

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(4) Unpublished results, Brands, J.; Maligres, P. E.; Upadhyay, V., Department of Process Research, Merck Research Laboratories, Merck & Co. Inc., P.O. Box 2000, Rahway, NJ 07065. Ethyl nipecotate **1** can be directly alkylated with BnCl in the presence of KHMDS in THF without nitrogen protection/deprotection. Thus, direct benzylation of **1** in toluene at ≤ −25 °C (1.3 equiv of KHMDS in THF, 1.05 equiv of BnCl) gave racemic **2** in 81% HPLC assay yield as a solution in toluene after extractive workup.

(5) Racemic **1** could be resolved as its tartaric acid salt by crystallization from 3:1 acetone/water (37% yield, 99% ee).

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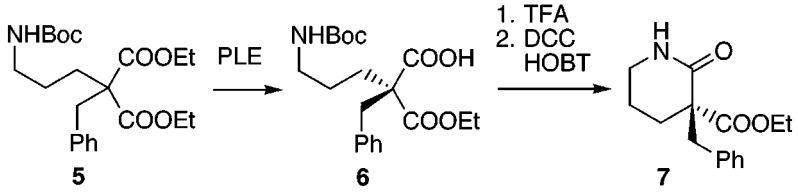
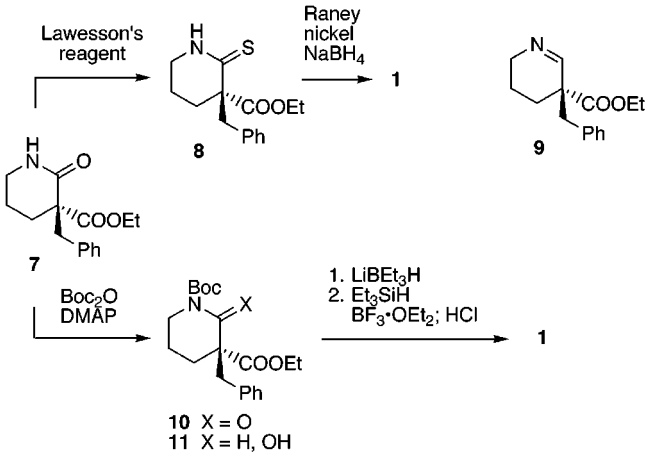
Scheme 4



Scheme 5



crystalline HCl salts. The well-known problem of the slow separation of the DCU byproduct from the reaction mixture was remedied by an oxalic acid quench which rapidly and quantitatively converts all remaining DCC to DCU with the formation of CO_2 and CO under mild conditions.[6] L-163,540 was isolated in 23% overall yield from benzyl diethylmalonate as a crystalline HCl salt monohydrate with >99.4% purity by HPLC analysis. In summary, we have demonstrated the synthesis of chiral quaternary piperidine **1** via enantioselective hydrolysis of a prochiral diester derived from malonate.

Experimental Section

General. Reagents were used as received unless otherwise stated; 3 Å molecular sieves were used to dry solvents for anhydrous reactions. Unless otherwise noted, all manipulations were carried out under an inert atmosphere of nitrogen gas. High-pressure liquid chromatography (HPLC) was performed using a B-03-5 YMC Basic (S-5 micron) 250 × 4.6 mm column with isocratic elution over 10 min (42/58 MeCN/0.025% H_3PO_4), then gradient elution over 5 min (42/58 → 62/38 MeCN/0.025% H_3PO_4), and then isocratic elution over 15 min (62/38 MeCN/0.025% H_3PO_4, 1.0 mL/min flow at 25 °C with detection at 220 nm). Analytical TLC and flash column chromatography was performed using silica gel (Merck). Elemental analyses were obtained from Quantitative Technologies Inc, Whitehouse, NJ.

Diethyl Benzyl(2-cyanoethyl)malonate (3). A solution of 21% NaOEt in EtOH (3 mL) was added to a solution of diethyl benzylmalonate (250.3 g, 1.00 mol), acrylonitrile (72.4 mL, 58.4 g, 1.10 mol), and methyl *tert*-butyl ether (MTBE) (100 mL) in a 500 mL flask equipped with a coldfinger condenser filled with dry ice/acetone. Within 5−10 min an exotherm set in and the mixture began to reflux (10−15 min). The mixture was aged at 40 °C for 1 h, diluted 9:1 v/v MTBE−hexane (100 mL), and filtered through a pad of silica (15 g), washing the pad with 9:1 v/v MTBE−hexane (100 mL). The filtrate was evaporated to give malonate **3** (300.3 g, 99%) as a colorless oil. **3**: HPLC retention time = 19.7 min; R_f = 0.55 (1:1 hexane−MTBE); ^{1}H NMR (250.1 MHz, $CDCl_3$) δ 7.26 (m, 3 H), 7.07 (m, 2 H), 4.23 (q, J = 7.1, 4 H), 3.26 (s, 2 H), 2.44 (t, J = 8.3, 2 H), 2.10 (t, J = 8.3, 2 H), 1.27 (t, J = 7.1, 6 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 170.5, 135.4, 130.3, 129.0, 127.9, 119.6, 62.3, 58.1, 40.0, 29.2, 14.4, 13.6; FTIR (thin film) ν_{max} 2983, 1730, 1200, 1185 cm^{-1}; HRMS (EI) m/z calcd for $C_{17}H_{21}NO_4$ (M^+) 303.1471, found 303.1492.

Diethyl Benzyl(3-*N*-Boc-aminopropyl)malonate (5). The crude malonate **3** from above (300.3 g, 0.99 mol) was dissolved in a mixture of EtOH (1750 mL) and 5 M aqueous HCl (250 mL, 1.25 mol). Pearlman's catalyst containing 20% palladium hydroxide (40 g) was added, and the mixture was hydrogenated in a 1 gallon Hastalloy vessel on a Parr shaker at 50 °C under 40 psi H_2 for 22 h. The slurry was filtered through a pad of solkafloc (100 g), and the pad was washed with EtOH (2.0 L). The filtrates were evaporated (25 in. Hg, bath at 100 °C), and the oily residue was dissolved in water (3.5 L). The aqueous solution was washed with 2:1 v/v hexane−MTBE (1.0 L), and the organic phase was extracted with water (500 mL). The combined aqueous phases were extracted with CH_2Cl_2 (3 × 500 mL). The organic extracts were dried over Na_2SO_4 and evaporated (100 °C at 10 Torr) to an oily residue which crystallized upon cooling to afford crude diethyl benzyl(3-aminopropyl)-malonate HCl salt (240.0 g, 70%): HPLC retention time = 5.2 min; FTIR (thin film) ν_{max} 2980, 2930, 1729, 1221, 1137 cm^{-1}; HRMS (EI) m/z calcd for $C_{17}H_{25}NO_4$ (M^+) 307.1784, found 307.1775. To a solution of the crude HCl salt (100.0 g, 0.291 mol) in CH_2Cl_2 (600 mL) cooled to 10 °C was added Et_3N (6.6 mL, 4.8 g, 0.047 mol) followed by a solution of Boc_2O (65.5 g, 0.30 mol) and Et_3N (38 mL, 27.6 g, 0.27 mol) in CH_2Cl_2 (20 mL) added over 15 min. The temperature rose to 30 °C and was accompanied by gas evolution (CO_2). The mixture was aged for 2 h at 25 °C and was evaporated to a semisolid/oil. The residue was diluted with MTBE (600 mL) and hexane (200 mL) and washed with saturated aqueous NaH_2PO_4 (200 mL), 20% aqueous NaH_2PO_4 (300 mL), water (500 mL), and saturated aqueous NaCl (200 mL). The organic phase was dried over $MgSO_4$ and filtered through a pad of silica (40 g), washing with 2:1 MTBE−hexane (200 mL). The filtrates were concentrated to an oil and redissolved in hexane (200 mL). Once crystallization had begun, hexane (600 mL) was added over 1 h. The mixture was gradually cooled to −20 °C over 26 h and filtered cold (−20 °C) to give Boc carbamate **5** (105.0 g, 89%) as a white crystalline solid. **5**: HPLC retention time = 23.0 min; R_f = 0.20 (4:1 hexane−MTBE); mp = 53−55 °C; ^{1}H NMR (250.1 MHz, $CDCl_3$) δ 7.23 (m, 3 H), 7.05 (m, 2 H), 4.57 (br t, J = 6, 1 H), 4.17 (q, J = 7.0, 4 H), 3.22 (s, 2 H), 3.09 (q, J = 6.1, 2 H), 1.76 (m, 2 H), 1.50 (overlapped m, 2 H), 1.43 (s, 9 H), 1.23 (t, J = 7.0, 6 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 171.1, 155.8, 136.0, 129.8, 128.3, 127.0, 79.1, 61.3, 58.5, 40.5, 38.1, 29.1, 28.4, 24.8, 14.0; FTIR (thin film) ν_{max} 3401, 2983, 1712, 1502 cm^{-1}. Anal. Calcd for $C_{22}H_{33}NO_6$: C, 64.84; H, 8.16; N, 3.44; O, 23.56. Found: C, 65.17; H, 8.18; N, 3.37; O, 23.44.

(*S*)-2-Carbethoxy-2-benzyl-2-(*N*-Boc-amino)pentanoic Acid (6). A 14 L bioreactor (New Brunswick Scientific, Edison, NJ) was charged with 10 mM phosphate buffer (pH 7.0, 10 L), diester **5** (10.0 g, 24.5 mmol), and porcine liver esterase (20 000

(6) Despite the insolubility of DCU in common reaction solvents, small quantities of this urea tend to come out of solution even after repeated filtrations. This problem is presumably due to the slow hydrolysis of the remaining DCC in the reaction product solution. Since carbodiimides are far more easily hydrolyzed in acidic media, addition of an acid to the reaction mixture prior to filtration would eliminate any remaining DCC. In the case of acid-stable peptides, the addition of aqueous HCl at the end of the reaction rapidly hydrolyzed the DCC, but a milder quench would be required for more sensitive peptides. A simple carboxylic acid could rapidly react with DCC but can introduce new byproducts. Oxalic acid was found to circumvent this problem by rapidly reacting with DCC to give DCU and the gaseous byproducts CO_2 and CO. Furthermore, oxalic acid reacts with DCC under a wide range of pH values.

units, Sigma, St. Louis, MO). The mixture was agitated (220 rpm) at 37 °C. After 7 h a second portion of porcine liver esterase (20 000 units) was added, and after 27 h HPLC analysis indicated completion of reaction. Quantitative HPLC analysis indicated 8.30 g of monoacid **6** present in the mixture, and HPLC analysis of the (*R*)-(+)-1-(naphthyl)ethylamide derivative (vide infra) of **6** indicated >99.5% ee. The mixture was extracted with EtOAc (2 × 5 L), and the organic extracts were concentrated to on oil. The crude residue was dissolved in EtOAc (10 mL) and treated with $MgSO_4$ (0.4 g) and Darco G60 carbon (0.1 g) for 15 min at 25 °C. The mixture was filtered through a pad of silica (3 g), washing with EtOAc (40 mL). The filtrates were evaporated to give **6** (9.6 g) as a pale yellow gum. Quantitative HPLC analysis indicated that this matarial contained 8.00 g (86%) of **6**. A 2.00 g portion of the crude gum was dissolved in toluene (4 mL) at 60 °C. Crystallization was completed by the slow addition of hexane (20 mL) over 2 h at 20 °C. The slurry was filtered to provide **6**·0.5 toluene (1.27 g, 58%) as a white crystalline solid. Prolonged drying under vacuum removed the remaining toluene from a 100 mg sample. HPLC analysis of the (*R*)-(+)-1-(naphthyl)ethylamide derivative of **6** indicated >99.5% ee. Sample preparation for (*R*)-(+)-1-(naphthyl)ethylamide derivatization: a mixture of 0.5 mg of monoacid **6**, 0.5 mg of (*R*)-(+)-1-(naphthyl)ethylamine, 0.5 mg of EDC·HCl, 0.5 mg of HOBT, and 0.1 mL of MeCN was heated at 55 °C (4−5 min) and made up to 1 mL with 1:1 MeCN and H_2O. HPLC retention times: (*R*)-(+)-1-(naphthyl)ethylamide derivative of **(*S*)-6** = 25.6 min, (*R*)-(+)-1-(naphthyl)ethylamide derivative of **(*R*)-6** = 26.2 min. **6**: HPLC retention time = 16.7 min; R_f = 0.30 (1:1 hexane−MTBE); mp = 110−112 °C. ^{13}C NMR indicated **6** to be a ca. 3:2 mixture of carbamate rotamers, major rotamer: ^1H NMR (250.1 MHz, $CDCl_3$) δ 7.26 (m, 3 H), 7.10 (m, 2 H), 4.62 (br t, 1H), 4.23 (m, 2 H), 3.34 (d, J = 13.9, 1 H), 3.16 (d, J = 13.9, 1 H), 3.10 (m, 2 H), 2.90 (m, 2 H), 1.50 (overlapped m, 2 H), 1.44 (s, 9 H), 1.24 (br t, J = 7.4, 3 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 174.6, 172.4, 156.1, 135.8, 129.7, 128.4, 127.1, 79.4, 61.9, 58.6, 41.5, 40.4, 30.5, 28.4, 25.1, 14.0; FTIR (thin film) ν_{max} 2979, 1706, 1510, 1250 cm^{-1}. Anal. Calcd for $C_{20}H_{29}NO_6$: C, 63.31; H, 7.70; N, 3.69; O, 25.30. Found: C, 63.53; H, 7.77; N, 3.58; O, 24.94.

(*S*)-3-Carbethoxy-3-benzyl-2-piperidone (7). Method A. A solution of Boc carbamate **6** (759 mg, 2.0 mmol) and TFA (764 mg, 6.70 mmol) in CH_2Cl_2 (3 g) was aged at 40 °C for 1.5 h. The mixture was evaporated, and the residue containing the crude amine (HPLC retention time = 3.5 min) was dissolved in CH_2Cl_2 (3 g). DIEA (491 mg, 3.80 mmol), HOBT (41 mg, 0.30 mmol), DCC (516 mg, 2.5 mmol), and DMAP (12 mg, 0.10 mmol) were added sequentially, and the mixture was aged for 20 h at 25 °C. Oxalic acid dihydrate (250 mg) and MTBE (5 mL) were added, and the mixture was aged for 1 h. The mixture was filtered from the DCU, and the filter cake was washed with a mixture of CH_2Cl_2 (2 mL) and MTBE (15 mL). The filtrate was washed with saturated aqueous NaH_2PO_4 (2 × 10 mL), water (10 mL), saturated aqueous $NaHCO_3$ (10 mL), water (10 mL), and saturated aqueous NaCl (10 mL). The organic phase was dried over $MgSO_4$ and evaporated. The residue was purified by chromatography (silica, gradient elution, 10% MTBE in hexane then MTBE) to provide piperidone **7** (366 mg, 70%) as a white crystalline solid. Chiral supercritical phase chromatography (SFC) indicated **7** to be in >99.5% ee. SFC conditions: Sumichiral AG OA3200 250 × 4.6 mm column, isocratic elution, 16% MeOH in supercritical CO_2 at 300 bar, 2.0 mL/min flow at 35 °C with detection at 210 nm. SFC retention times: **(*R*)-7** = 2.35 min, **(*S*)-7** = 2.87 min. **7**: HPLC retention time = 7.35 min; R_f = 0.38 (MTBE); ^1H NMR (250.1 MHz, $CDCl_3$) δ 7.24 (br s, 5 H), 6.10 (br s, 1 H), 4.24 (m, 2 H), 3.60 (d, J = 13.5, 1 H), 3.22 (m, 1 H), 3.06 (d, J = 13.5, 1 H), 2.98 (m, 1 H), 2.10 (m, 1 H), 1.79 (m, 2 H), 1.55 (m, 1 H), 1.29 (t, J = 7.2, 3 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 172.8, 170.5, 136.6, 130.6, 128.1, 126.6, 61.5, 54.8, 42.0, 40.5, 28.9, 19.5, 14.0; FTIR (thin film) ν_{max} 2939, 1732, 1668, 1515, 1236, 1155 cm^{-1}. Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36; O, 18.37. Found: C, 69.15; H, 7.39; N, 5.28; O, 18.67.

(*S*)-3-Carbethoxy-3-benzyl-2-piperidone (7). Method B. HCl gas was passed into a solution of carboxylic acid monoester **6** (5.0 g, 13.2 mmol) in CH_2Cl_2 (50 mL) in a 250 mL flask was cooled to 0 °C until 50 mmol was absorbed. The reaction mixture was stirred for 2 h and was found to be complete by HPLC analysis. The volatiles were evaporated, and the crude HCl salt was redissolved in 50 mL of CH_2Cl_2. DIEA (5.05 mL, 28.99 mmol) and 2-chloro-1-methylpyridinium iodide (5.05 g, 19.77 mmol) were added, and the mixture was aged for 30 min. EtOAc (150 mL) and water (50 mL) were added to the mixture. The aqueous phase was separated, and the organic phase was washed with 0.4 N HCl (75 mL), saturated $NaHCO_3$ (50 mL), and 10% brine (50 mL) and dried over Na_2SO_4. The mixture was concentrated, and the residue was purified by chromatography (silica, gradient elution, 10% MTBE in hexane then MTBE) to give lactam **7** (2.76 g, 80%). Chiral SFC indicated **7** to be in >99.5% ee.

(*S*)-3-Carbethoxy-3-benzyl-piperidine (1) via Thiolactam 8. A mixture of piperidone **7** (349 mg, 1.34 mmol), Lawesson's reagent (594 mg, 1.47 mmol), and toluene (1.5 mL) was heated to 110 °C for 2 h. The mixture was cooled to 25 °C, aged for 15 min, and filtered through a cotton plug, washing with toluene (3.5 mL). The filtrate was evaporated, and the residue containing thiolactam **8** was dissolved in THF (2 mL) and EtOH (2 mL). A 50% aqueous slurry of Raney nickel (1 mL) was added.[7] After a 5 min age, another portion of the Raney nickel (1 mL) was added followed by $NaBH_4$ (25 mg). After 15 min the mixture was filtered through a pad of solkafloc, washing the pad with THF (5 mL) and EtOH (5 mL). The filtrates were evaporated to 4 mL and diluted with MTBE (20 mL). The mixture was extracted with 0.5 M aqueous HCl (2 × 3 mL), and the aqueous extract was basified with 5 M aqueous NaOH (0.7 mL). The aqueous mixture was extracted with CH_2Cl_2 (2 × 3 mL). The organic extracts were dried over Na_2SO_4 and evaporated to give piperidine **1** (100 mg, 30%) as a colorless oil. HPLC analysis of the Marfey's derivative of **1** indicated >99.5% ee. Sample preparation for Marfey's derivatization: a mixture of 0.5 mg of piperidine **1**, 0.5 mg of Marfey's reagent {*N*-(2,4-dinitro-5-fluorophenyl)-L-alaninamide}, 50 μL of 6 M $NaHCO_3$, and 0.5 mL of acetone was heated at 55 °C (4−5 min) and made up to 1 mL with 1:1 MeCN−H_2O. HPLC retention times: Marfey's derivatized **(*S*)-1** = 19.5 min, Marfey's derivatized **(*R*)-1** = 19.9 min. **1**: HPLC retention time = 4.0 min; R_f = 0.20 (9:1 MTBE−MeOH); ^1H NMR (250.1 MHz, $CDCl_3$) δ 7.23 (m, 3 H), 7.05 (m, 2 H), 4.11 (m, 2 H), 3.36 (dd, J = 13.0, 2.3, 1 H), 2.95 (m, 1 H), 2.80 (d, J = 13.4, 1 H), 2.75 (d, J = 13.4, 1 H), 2.58 (m, 1 H), 2.54 (d, J = 13.0, 1 H), 2.19 (m, 1 H), 2.10 (br s, 1 H), 1.59 (m, 1 H), 1.51−1.35 (overlapping m, 2 H), 1.19 (t, J = 6.9, 3 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 175.1, 136.5, 129.6, 127.8, 126.4, 60.2, 53.1, 47.8, 46.1, 44.3, 32.8, 24.3, 13.9; FTIR (thin film) ν_{max} 2938, 1723, 1454, 1222 cm^{-1}; HRMS (EI) m/z calcd for $C_{15}H_{21}NO_2$ (M^+) 247.1572, found 247.1582.

(*S*)-3-Carbethoxy-3-benzyl-*N*-Boc-2-piperidone (10). To a solution of lactam **7** (2.30 g, 8.80 mmol) in toluene (25 mL) was added DMAP (1.61 g, 13.2 mmol) followed by Boc_2O (2.31 g, 10.56 mmol). The resulting mixture was heated to 60 °C for 1 h, diluted with toluene (50 mL), and washed with saturated NaH_2PO_4 (2 × 50 mL) and brine (50 mL). The mixture was dried over Na_2SO_4 and concentrated; the residue was purified by flash chromatography (silica, 3:1 hexane−MTBE), affording **10** (2.96 g, 93%, >95 A% purity by HPLC analysis). **3**: HPLC retention time = 21.5 min; R_f = 0.23 (4:1 hexane−MTBE); ^1H NMR (250.1 MHz, $CDCl_3$) δ 7.3−7.1 (overlapping m, 5 H), 4.21 (m, 2 H), 3.55, (m, 1 H), 3.48 (d, J = 13.6, 1 H), 3.30 (m, 1 H), 3.16 (d, J = 13.6, 1 H), 2.16 (m, 1 H), 1.9−1.6 (overlapping m, 3 H), 1.54 (s, 9 H), 1.27 (t, J = 7.1, 3 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 172.0, 170.3, 152.8, 136.1, 130.7, 128.1, 126.9, 82.9, 61.7, 57.7, 45.6, 41.6, 29.0, 28.0, 20.0, 14.0; FTIR (thin film) ν_{max} 3030, 2987, 1740, 1453, 1385 cm^{-1}. Anal. Calcd for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.53; N, 3.88. Found: C, 66.81; H, 7.61; N, 3.60.

(*S*)-3-Carbethoxy-3-benzyl-2-hydroxy-*N*-Boc-piperidine (11). A solution 1.0 M Superhydride (4.1 mL, 4.05 mmol)

(7) In a similar experiment the mixture was filtered at this stage. Evaporation followed by extractive workup provided a ca. 1:1 mixture of piperidine **1** and cyclic imine **9**. The mixture was subjected to preparative TLC (silica, EtOAc) to provide **1** and **9**. **9**: ^1H NMR (250.1 MHz, $CDCl_3$) δ 7.89 (s, 1 H), 7.27 (m, 3 H), 7.13 (m, 2 H), 4.15 (q, J = 7.1, 2 H), 3.65 (m, 1 H), 3.40 (m, 1 H), 3.02 (q, J = 13.4, 2 H), 2.13 (m, 1 H), 1.55 (m, 3 H), 1.23 (t, J = 7.1, 3 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 172.6, 162.2, 135.8, 129.9, 128.3, 127.0, 61.2, 49.7, 49.4, 43.4, 27.2, 19.6, 14.1.

was added over 30 min to a solution of **10** (1.22 g, 3.37 mmol) in THF (5 mL) cooled to −10.0 °C. After 2 h at 0 °C the reaction mixture was quenched with water (15 mL) and extracted with EtOAc (40 mL). The organic phase was evaporated, and the residue was purified by flash chromatography (silica, 1:1 MTBE−hexane) to afford **11** (1.10 g, 90%). **11**: HPLC retention time = 20.0 min. ^{13}C NMR indicated **11** to be a ca. 3:2 mixture of isomers: ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 173.1, 171.4, 154.9, 136.8, 136.7, 129.9, 129.8, 128.3, 128.1, 126.8, 126.7, 80.8, 80.2, 60.7, 60.4, 52.8, 51.8, 43.2, 38.0, 28.5, 28.4, 26.8, 22.3, 21.2, 20.1, 14.3, 14.1, 14.0; FTIR (thin film) ν_{max} 3360, 2976, 1700, 1158 cm^{-1}.

(*S*)-3-Carbethoxy-3-benzylpiperidine (1). A solution of *N*-Boc-aminal **11** (580 mg, 1.59 mmol) and triethylsilane (255 μL, 1.59 mmol) in CH_2Cl_2 (8 mL) was cooled to −78 °C, and BF_3·OEt_2 (197 μL, 1.59 mmol) was then added dropwise under a nitrogen atmosphere. After 30 min, more triethylsilane (255 μL, 1.59 mmol) and BF_3·OEt_2 (197 μL, 1.59 mmol) were added. The resulting mixture was stirred for 2 h at −78 °C, and reaction was found to be complete by HPLC analysis (retention time of *N*-Boc derivative of **1** = 25.4 min). The *N*-Boc piperidine was deprotected by passing HCl gas through the reaction mixture until 87 mg had been absorbed. The amine HCl salt was extracted into water (50 mL), and the aqueous phase was washed with MTBE (50 mL) and basified with 5 N NaOH (7 mL) (pH = 11.5). The mixture was extracted with EtOAc (2 × 40 mL). The organic extracts were dried over Na_2SO_4 and evaporated to afford **1** as a colorless oil (363 mg, 85%). HPLC analysis of the Marfey's derivative of **1** indicated >99.5% ee (vide supra).

Monopeptide 2. A solution of DCC (1.79 kg, 8.68 mol) in EtOAc (1.79 Kg) was added to a mixture of (*S*)-**1** (1.95 kg, 8.09 mol), *N*-Boc-D-tryptophan (2.46 kg, 8.09 mol), HOBt (1.07 kg, 7.89 mol), and EtOAc (10.8 kg) over 30 min, and the mixture was aged for 16 h at 22 °C. Oxalic acid (314 g, 2.49 mol) was added to quench any remaining DCC. The mixture was heated to 55 °C and aged for 1 h and then cooled over 3 h to −8 °C and stirred for 45 min. The slurry was filtered, and the DCU cake was washed with EtOAc (4 × 4 L). The combined filtrates were washed with 2 M HCl (8 L), 10% brine (8 L), 7% aqueous $NaHCO_3$ (16 L), and 20% brine (8 L). **2** *N*-Boc derivative: R_f = 0.15 (1:1 hexane−MTBE); HRMS (EI) *m*/*z* calcd for $C_{31}H_{39}N_3O_5$ (M^+) 533.2890, found 533.2905. The organic phase containing the *N*-Boc-protected monopeptide (HPLC retention time = 21.6 min; FTIR (thin film) ν_{max} 3316, 2978, 2932, 1713, 1634, 1456 cm^{-1}) was concentrated, and the residue was dissolved in EtOH (8 L). A solution of HCl (604 g, 16.5 mol) in EtOH (4 L) was added, and the mixture was aged at 60 °C for 1 h. EtOAc (41 L) was added to the mixture over 20 min, and the slurry was aged for 16 h at 20 °C. The slurry was filtered, and the filter cake was washed with EtOAc (2 × 8 L) to provide 3.41 kg of HCl salt **2** (3.41 kg, 92%, >98 A% purity by HPLC). **2**: HPLC retention time = 6.3 min; R_f = 0.10 (9:1 MTBE−MeOH); mp = 229−231 °C dec; major rotamer ^{13}C NMR (62.9 MHz, CD_3OD) δ 175.3, 169.1, 138.2, 137.5, 131.1, 129.2, 128.4, 127.9, 125.7, 123.0, 120.5, 119.0, 112.8, 108.0, 61.8, 51.6, 49.4, 49.3, 47.0, 42.8, 32.2, 29.0, 22.9, 14.3; FTIR (thin film) ν_{max} 3400, 3227, 2932, 1715, 1644, 1458 cm^{-1}; HRMS (EI) *m*/*z* calcd for $C_{26}H_{31}N_3O_3$ (M^+) 433.2365, found 433.2341.

L-163,540·HCl·H_2O. A solution of DCC (1.61 kg, 7.80 mol) in EtOAc (1.61 kg) was added to a mixture of **2** (3.33 kg, 7.09 mol), HOBt (1.11 kg, 7.26 mol), and *N*-Boc-Me alanine (1.48 kg, 7.26 mol), DIEA (962 g, 7.442 mol) was added to a mixture of HCl salt (3.33 kg, 7.088 mol) and EtOAc (21.3 kg) over 30 min, and the mixture was aged for 1 h at 26 °C. Oxalic acid (134 g, 1.06 mol) was added to quench any remaining DCC. The mixture was heated to 50 °C for 1 h and then cooled over 1 h to −5 °C and stirred for 20 min. The slurry was filtered, and the DCU cake was washed with EtOAc (4 × 4 L). The combined filtrates were washed with 7% $NaHSO_4$ (14 L), 10% brine (10 L), 6% aqueous $NaHCO_3$ (2 × 14 L), and 20% brine (14 L). L-163,540 *N*-Boc derivative: HRMS (EI) *m*/*z* 618.3417, found 618.3429. The organic phase containing *N*-Boc-protected L-163,540 (HPLC retention time = 20.4 min; R_f = 0.50 (MTBE); FTIR (thin film) ν_{max} 3318, 2980, 2934, 1716, 1632, 1496, 1456 cm^{-1}) was concentrated to ca. 9 L. A solution of HCl (2.44 kg, 66.9 mol) in EtOH (7.3 kg) was added, and the mixture was aged at 25 °C for 2 h. The mixture was concentrated, and the residue was dissolved in EtOAc (20 L). The mixture was extracted with water (2 × 14 L). The combined aqueous extracts were basified (pH = 10.5) with 5 M NaOH (2.2 L) and extracted with EtOAc (2 × 14 L). The organic extracts were concentrated to ca. 9 L and diluted with EtOH (3.6 L). The solution containing L-163,540 free base (3.30, 6.34 mol by quantitative HPLC assay) was cooled to 5 °C, and 6.0 M HCl (1.04 L, 6.34 mol) was added over 5 h. The mixture was aged at 20 °C for 16 h. The slurry was filtered, and the filter cake washed with EtOAc containing 15% EtOH and 1% H_2O by wt (2 × 8 kg) to provide L-163,540·HCl·H_2O (3.01 kg, 83%, >99.4 A% purity by HPLC).

L-163,540·HCl·H_2O: HPLC retention time = 6.9 min; $[\alpha]^{25}_{365}$ = −200° (*c* 2%, CH_3OH/H_2O, 50/50); R_f = 0.20 (9:1 MTBE−MeOH); mp = 165−185 °C dec; major rotamer ^{13}C NMR (100.5 MHz, CD_3OH) δ 175.3, 172.6, 172.1, 138.1, 137.6, 130.9, 129.0, 128.5, 127.6, 125.0, 122.5, 120.0, 119.0, 112.5, 110.3, 61.6, 58.2, 51.3, 49.1, 48.7, 47.1, 42.4, 32.2, 29.3, 24.2, 24.1, 22.9, 14.2; FTIR (thin film) ν_{max} 3307, 2963, 2929, 1723, 1634, 1456 cm^{-1}.

Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra for compound **1** in $CDCl_3$ and CD_3OD and ^{1}H NMR and ^{13}C NMR spectra for L-163,540 in CD_3OH. Mass spectra for compound **1** and L163,540 (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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