Synthesis of *N,N′*-Orthogonally Protected (*S*)-Piperazine-2-carboxylic Acid

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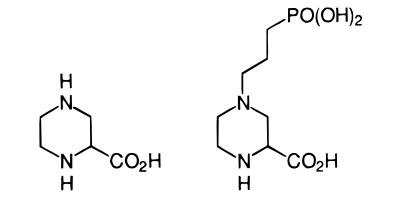
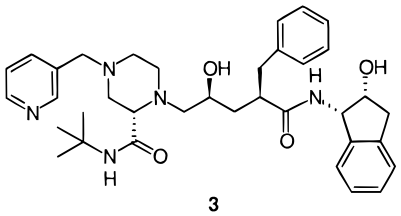
Piperazine-2-carboxylic acid (**1**) is a conformationally restricted nonproteinogenic amino acid which has been incorporated into a number of medicinally useful compounds. *N*-methyl-D-aspartate (NMDA) antagonist **2**[1] and HIV protease inhibitor **3**[2] provide examples. Piperazine-2-carboxylic acid is commercially available only in racemic form. Homochiral material has been obtained from racemic preparations by separating enantiomers through the corresponding chiral amine salts[3] or menthol esters.[4] An enzymatic resolution of the N^{β}-*tert*-Boc carboxamide derivative has also provided optically enriched material.[5] Aebischer et al.[4] reported a synthesis of (*R*)-piperazine-2-carboxylic acid from D-asparagine to correlate the absolute configurations of compounds derived from a separation of enantiomers; however, this sequence proceeded in less than 5% overall yield. Herein we describe an efficient asymmetric synthesis of *N,N′*-diprotected (*S*)-piperazine-2-carboxylic acid utilizing an extension of Vederas' serine lactone ring opening methodology and a chemoselective reduction of an aminal intermediate.[6]



1 **2**



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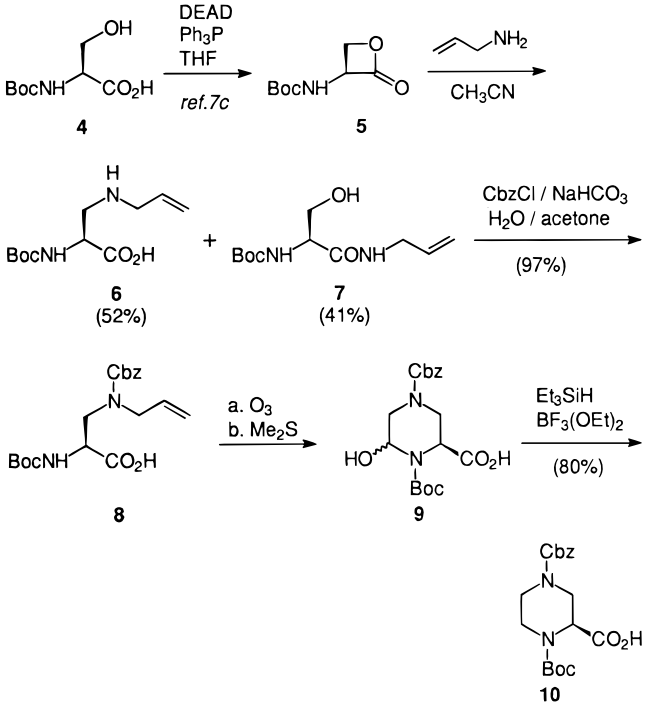
Scheme 1



4 **5** **6** **7** **8** **9** **10**

In 1985, Vederas described the conversion of *N*-*tert*-Boc- and *N*-Cbz-L-serine to the corresponding β-lactones and subsequent nucleophilic ring opening reactions.[7] Depending upon the choice of nucleophile and reaction conditions, selective ring opening at either the lactone methylene or carbonyl carbon could be achieved.[7,8] For the synthesis of *N,N′*-diprotected (*S*)-piperazine-2-carboxylic acid, allylamine was chosen as the nucleophile, being an inexpensive and volatile α-amino aldehyde surrogate.

Our synthesis began with the conversion of commercially available *N*-*tert*-Boc-L-serine (**4**) to lactone **5** by the literature protocol[7c] (Scheme 1). We found that the addition of allylamine to a solution of lactone **5** in CH_3CN or THF yielded serine amide **7** predominantly. However, inverse addition of lactone **5** to allylamine in CH_3CN afforded the desired amino acid **6** in 52% yield along with amide **7** in 41% yield. The reaction workup was quite simple. The solution was concentrated, and the residue was slurried with acetonitrile to give essentially pure amino acid **6** by filtration and amide **7** by concentration of the filtrate.

Amino acid **6** was protected as Cbz derivative **8** using standard Schotten−Baumann conditions in 97% yield. Cleavage of the olefin by ozonolysis gave the 6-membered ring aminal **9**.[9] This assignment was consistent with the following spectral data. The mass spectrum (CI/CH_4) showed the molecular ion of *m/z* 363 corresponding to $[M + H - H_2O]^+$, and no aldehyde resonance was

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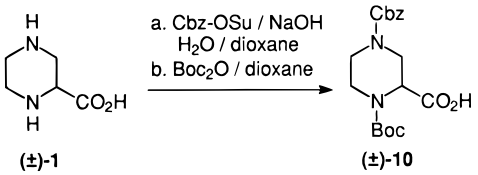
Scheme 2



(±)-1 (±)-10

detected in the ^{1}H NMR spectrum using $CDCl_3$ as solvent. The crude ozonolysis reaction product was carried on without purification. Chemoselective reduction of the aminal was effected using triethylsilane and boron trifluoride diethyl etherate in CH_2Cl_2.[10] Final product **10** was obtained in 80% yield over the last two steps after the only chromatographic purification of the synthesis.

The optical purity of **10** was determined using chiral HPLC.[11] For this analysis, a sample of racemic compound was prepared according to the literature method.[12] Racemic piperazine-2-carboxylic acid was treated sequentially with *N*-[(benzyloxycarbonyl)oxy]succinimide and di-*tert*-butyl dicarbonate (Scheme 2). The optical purity of our final product was found to be >99.8%, exceeding the detection limits of the chromatographic method used. Thus, the optical purity of our starting material (**4**), derived from naturally occuring L-serine, was retained through the reaction sequence.

In summary, an asymmetric synthesis of *N*,*N*′-orthogonally protected (*S*)-piperazine-2-carboxylic acid has been achieved in four steps and in 40% overall yield from *N*-*tert*-Boc-L-serine *β*-lactone. The reaction sequence required only a single chromatographic purification and yielded optically pure material.

Experimental Section

General. Reagents and anhydrous solvents were obtained from commercial sources and used without further purification. Melting points are uncorrected.

(*S*)-*N*^{2}-(*tert*-Butoxycarbonyl)-*N*^{3}-(2-propenyl)-2,3-diaminopropanoic Acid (6). A solution of *N*-(*tert*-butoxycarbonyl)-L-serine *β*-lactone (**5**)[7c] (1.50 g, 8.01 mmol) in dry CH_3CN (150 mL) was added dropwise at ambient temperature over 2 h to a stirred solution of allylamine (12.0 mL, 200 mmol) in dry CH_3CN (300 mL). After 2 h, the solution was concentrated using a rotary evaporator. The solid residue was slurried with CH_3CN and filtered to afford **6** as a white solid (1.01 g, 52%). The filtrate was concentrated to yield *N*-(*tert*-butoxycarbonyl)-L-serine allyl amide (**7**) as a tan solid (0.803 g, 41%). Amino acid **6**: mp 172−173 °C (dec); $[\alpha]^{20}_D$ −3.6 (*c* 1.00, 0.01 M aqueous NaOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.36 (s, 9H), 3.49−3.52 (m, 2H), 3.59−3.75 (m, 2H), 3.90−3.97 (m, 1H), 4.80 (brs, 1H), 5.00 (dd, 1H, *J* = 1.5, 10 Hz), 5.18 (dd, 1H, *J* = 1.8, 17 Hz), 5.78 (ddt, 1H, *J* = 5.1, 10, 16 Hz), 6.58 (d, 1H, *J* = 8.1 Hz), 7.92 (brt, 1H, *J* = 4.5 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 28.1, 47.7, 49.0, 50.4, 78.1, 120.0, 131.9, 155.2, 171.7; HRMS calcd for ($C_{11}H_{20}N_2O_4$ + H) 245.150132, found 245.149973.

Amino amide **7**: mp 125−126 °C; $[\alpha]^{20}_D$ −57.3 (*c* 0.99, $CHCl_3$); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.45 (s, 9H), 3.26 (brs, 1H), 3.62−3.71 (m, 1H), 3.80−3.98 (m, 2H), 4.06−4.20 (m, 2H), 5.14 (dd, 1H, *J* = 1.4, 10 Hz), 5.19 (dd, 1H, *J* = 1.4, 17 Hz), 5.62 (brd, 1H, *J* = 7.0 Hz), 5.82 (ddt, 1H, *J* = 5.4, 10, 17 Hz), 6.84 (brs, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 28.3, 41.7, 54.7, 62.8, 80.6, 116.3, 133.6, 156.3, 171.3. Anal. Calcd for $C_{11}H_{20}N_2O_4$: C, 54.08; H, 8.25; N, 11.47. Found: C, 53.95, H, 8.44, N, 11.31.

(*S*)-*N*^{2}-(*tert*-Butoxycarbonyl)-*N*^{3}-(benzyloxycarbonyl)-*N*^{3}-(2-propenyl)-2,3-diaminopropanoic Acid (8). A solution of amino acid **6** (1.08 g, 4.43 mmol) in saturated aqueous $NaHCO_3$ (14 mL) and water (2 mL) was treated dropwise at ambient temperature with a solution of benzyl chloroformate (0.71 mL, 5.0 mmol) in acetone (1 mL) over 10 min. The cloudy reaction mixture was stirred for 2 h. The resulting solution was partitioned between methyl *tert*-butyl ether (50 mL) and water (25 mL). The aqueous layer was cooled in an ice bath, brought to pH ∼2 using 5% aqueous HCl, saturated with NaCl, and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to give **8** as a viscous colorless oil (1.62 g, 97%). This material was used in the next step without further purification: $[\alpha]^{20}_D$ + 5.4 (*c* 0.98, $CHCl_3$); NMR data for major conformers, ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.37 (s, 9H), 3.23−3.33 (m, 1H), 3.65−3.72 (m, 1H), 3.75−3.85 (m, 1H), 3.92−4.00 (m, 1H), 4.25 (dt, 1H, *J* = 5.3, 8.4 Hz), 5.04−5.16 (m, 4H), 5.69−5.82 (m, 1H), 7.06 (d, 0.5H, *J* = 8.3 Hz), 7.13 (d, 0.5H, *J* = 8.3 Hz), 7.28−7.40 (m, 5H), 12.75 (brs, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 27.8, 28.1, 46.8, 47.8, 49.9, 52.2, 52.4, 66.2, 66.3, 78.2, 116.1, 116.6, 127.2, 127.7, 128.3, 133.6, 133.9, 136.8, 155.1, 155.4, 155.5, 172.2; HRMS calcd for ($C_{19}H_{26}N_2O_6$ + H) 379.186912, found 379.186794.

(*S*)-1,2,4-Piperazinetricarboxylic Acid, 1-*tert*-Butyl-4-benzyl Ester (10). A solution of **8** (697 mg, 1.84 mmol) in CH_2Cl_2 (25 mL) and MeOH (2.5 mL) was cooled in a dry ice/acetone bath under argon. Ozone was passed through the solution until a pale blue color persisted (6 psi O_2, 1.5 SLPM, 75 V, 3 min). The excess ozone was purged by bubbling argon through the solution for 15 min. Dimethyl sulfide (2.5 mL) was added, and the solution was allowed to warm gradually to ambient temperature overnight. After 20 h, the reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed with brine (20 mL). The organic layer was dried (Na_2SO_4) and concentrated to a pale yellow foam (745 mg, 106%). The ^{1}H NMR spectrum (300 MHz, $CDCl_3$) showed no aldehyde proton resonance; mass spectral data gave the following molecular ions: (CI/CH_4) *m*/*z* 363 [M + H − H_2O] and (CI/NH_3) *m*/*z* 380 [M + NH_4 − H_2O].

The crude material and triethylsilane (0.31 mL, 1.9 mmol) in dry CH_2Cl_2 (45 mL) under argon were cooled in a dry ice/acetone bath and treated dropwise with boron trifluoride diethyl etherate (0.24 mL, 1.9 mmol). After 30 min, more triethylsilane (0.31 mL, 1.9 mmol) and boron trifluoride diethyl etherate (0.24 mL, 1.9 mmol) were added in similar fashion. The reaction mixture was stirred for 2 h at −78 °C, brine (40 mL) was added, and the cold mixture was extracted with CH_2Cl_2 (2 × 75 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by flash chromatography (3 × 20 cm silica column) using CH_2Cl_2:ethyl acetate:acetic acid (2:1:0.03) to give **10** as an off-white solid (540 mg, 80%): mp 50−53 °C; $[\alpha]^{20}_D$ −17.5 (*c* 1.02, $CHCl_3$); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.35 + 1.39 (2s, 9H), 2.77−3.27 (m, 3H), 3.70 (brd, 1H, *J* = 12 Hz), 3.87 (brd, 1H, *J* = 12 Hz), 4.30−4.57 (m, 2H), 5.05 (brs, 2H), 7.28−7.38 (m, 5H), 12.95 (brs, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 27.9, 28.1, 28.2, 41.2, 42.8, 43.98, 44.01, 44.4, 53.3, 54.6, 66.6, 79.8, 80.0, 127.6, 128.0, 128.2, 128.6, 136.9, 154.6, 154.8, 155.0, 171.6, 171.8; HRMS calcd for ($C_{18}H_{25}N_2O_6$ + H) 365.170331, found 365.171262.

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Supporting Information Available: ^{1}H NMR spectra for compounds **6**, **7**, **8**, and **10**; chiral HPLC traces for (±)-**10** and (−)-**10** (5 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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