An Efficient Asymmetric Route to 2,3-Diaminobutanoic Acids

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Nonproteingenic amino acids have been uncovered in a growing number of naturally occurring compounds.[1] Consequently, interest in their application as building blocks for peptidomimetics in medicinal chemistry efforts has also increased due to their protease resistance and potential conformational constraints.[2] The α,*β*-diamino acid family constitutes a key structural element found in a variety of antibiotics,[3] antifungal dipeptides,[4] and other biologically active compounds.[5] In particular, α,*β*-diaminobutanoic acids such as **1** (Figure 1) have attracted numerous synthetic efforts, since they are the simplest member of the α,*β*-diamino acid family yet form key elements in both peptide antibiotics and toxins.[6]

Several methods for the synthesis of α,*β*-diaminobutanoic acids have been reported. Noteworthy was a method reported by Schmidt and co-workers[7] in which threonine or *allo*-threonine was exploited as starting materials and Mitsunobu reaction conditions were used for the installation of the second amino group. While this tact is reliable, only the anti isomers **1b** and **1d** are accessible from threonine, whereas the syn isomers **1a** and **1c** must be obtained from *allo*-threonine. In related studies, Shin[6a,b] described syntheses leading to all four isomers of **1** using L- or D-threonine as starting materials and double inversion chemistry to obtain the syn diastereomers **1a** and **1c**. Utilizing a completely different strategy, Davies and co-workers[6c] reported the synthesis of epimers **1a** and **1d** based on the asymmetric addition of a chiral lithium amide to *tert*-butyl crotonate, followed by the introduction of the second amino group using trisyl azide. Very recently, all four isomers of **1** were synthesized on the basis of the nucleophilic addition of methylmagnesium bromide to differentially protected nitrones that were derived from either L- or D-serine.[8] Critical in this approach was the protecting group strategy used on the starting nitrone, as this dictated the stereochemical outcome of the reaction.

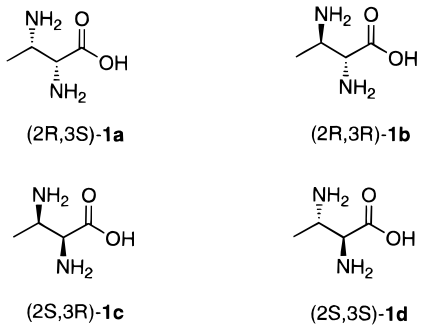

Figure 1. The four enantiomers of 2,3-diaminobutanoic acid.

Except for the approach outlined by Davies (vide supra), all syntheses of the α,*β*-diaminobutanoic acids have required the use of optically active α-amino acids as starting material. Furthermore, while Davies's methodology is apt to apply toward the synthesis of other α,*β*-diamino acids, it requires stoichiometric quantities of chiral reagents for two key steps, a Michael and an electrophilic addition. Herein, we report an efficient stereoselective synthesis of α,*β*-diaminobutanoic acids that eliminates the drawbacks found in the previous syntheses. Our route utilizes the highly enantioselective Sharpless asymmetric aminohydroxylation (AA) reaction and regioselective ring opening of an aziridine functionality.

Commercially available *tert*-butyl crotonate (**2**) was the starting point of our synthesis (Scheme 1). Crotonate **2** was functionalized using $(DHQD)_2PHAL$ and the benzylcarbamate-based Sharpless AA[9] reaction gave **3** in high regioselectivity and enantioselectivity. The ratio of the regioisomer was about 9:1 based on ^1H NMR spectrum of the crude product, and the initial ee of 90% could be easily raised to >99% by a single recrystallization from hexane/ethyl acetate. Ester **3** was converted to its methanesulfonate **4**, which was successfully transformed to the *anti*-α-azido species with inversion of configuration at C-2.[6c] Catalytic hydrogenation and subsequent acidic hydrolysis of azide **5** gave enantiomerically pure diaminobutanoic acid **1b** as its HCl salt {$[\alpha]^{20}_D$ −8.9 (*c* 1.0, 6 N HCl), lit.[10] $[\alpha]^{20}_D$ −11.0 (*c* 1.0, 6 N HCl)}. For the synthesis of the syn isomer **1a**, compound **4** was converted to aziridine species **6** in 80% yield with potassium *tert*-butoxide. For the ring opening of **6**, solvent turned out to be a critical factor. Initial attempts with TMS−N_3 and MeOH in DMF[11] gave no product, even after a prolonged reaction time (48 h), and reactions conducted in either THF or benzene showed no measurable change. However, use of MeOH as a solvent granted azide **7** as a single diastereomer (NMR), this by regiospecific C-3 ring

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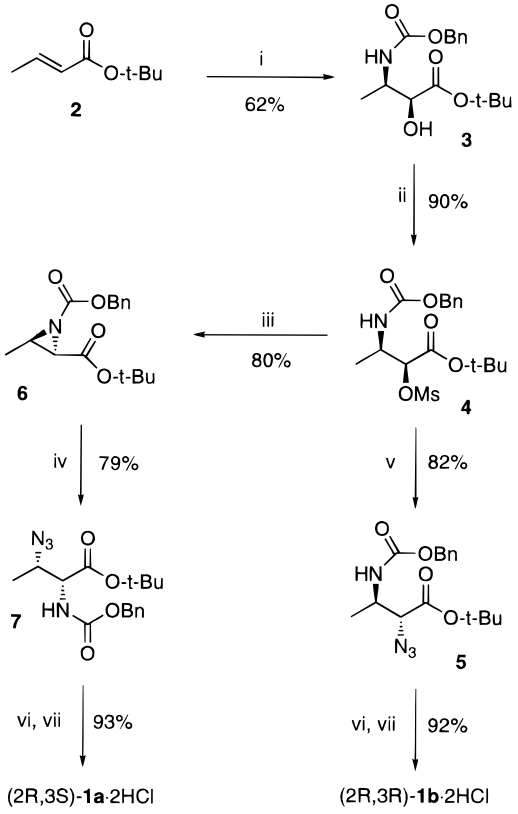
Scheme 1[a]



[a] (i) $(DHQD)_2PHAL$, 5%; $K_2OsO_2(OH)_4$, 4%; Cbz-NHCl, 3 equiv; CH_3CN/H_2O, 0 °C. (ii) $MsCl/(Et)_3N$, CH_2Cl_2. (iii) *t*-BuO^-K^+, THF. (iv) $(Me)_3SiN_3$, MeOH. (v) NaN_3, DMF. (vi) H_2, 10% Pd/C, MeOH. (vii) CF_3COOH/CH_2Cl_2 and then 1 N HCl.

opening of aziridine **6**. Catalytic hydrogenation and subsequent acidic hydrolysis of azide **7** generated syn isomer **1a** in an overall yield of 33% {$[\alpha]^{20}_D$ −34.3 (*c* 1.0, 6 N HCl), lit.[10] $[\alpha]^{20}_D$ −38.1 (*c* 1.0, 6 N HCl)}.

The NMR spectra of the syn isomer **1a** and the anti isomer **1b** showed a distinct difference in coupling constants and splitting patterns (Figure 2). The coupling constant between H-2 and H-3 for the syn isomer **1a** was 3.5 Hz and that for the anti isomer **1b** was 7.0 Hz. The H-3 proton of the syn isomer **1a** shows a simple multiplet pattern, whereas the H-3 proton of the anti isomer **1b** shows a quartet−doublet pattern (J = 6.8 and 3.5 Hz). The coupling constants and splitting patterns observed are consistent with those reported by Davies et al.[6c]

The chemistry described (vide supra) can be extended in a succinct manner to the remaining two enantiomers, **1c** and **1d** (Figure 1). Thus use of $(DHQ)_2PHAL$ for the aminohydroxylation reaction of *tert*-butyl crotonate gave the 2*S*,3*R* enantiomer of amino alcohol **3** (89% ee, 63% yield). Subsequent application of the strategy described in Scheme 1 to this isomer produced enantiomers **1c** in 32% yield {$[\alpha]^{20}_D$ +9.1 (*c* 1.0, 6 N HCl), lit.[10] $[\alpha]^{20}_D$ +10.3 (*c* 1.0, 6 N HCl)} and **1d** in 40% yield {$[\alpha]^{20}_D$ +33.4 (*c* 1.0, 6 N HCl), lit.[10] $[\alpha]^{20}_D$ +39.3 (*c* 1.0, 6 N HCl)}.

In conclusion, we have shown an efficient stereoselective synthesis of the four isomers of 2,3-diaminobutanoic acid from a readily available starting material, *tert*-butyl crotonate. Our strategy eliminates the drawbacks found in previous syntheses, which included a need for optically active α-amino acids as starting materials or stoichiometric amounts of chiral reagents. Furthermore, our synthetic strategy can be applied to the synthesis of other α,β-diamino acids by simply varying the starting olefin. Extension of this technology to the preparation of other molecules of interest is currently under investigation.

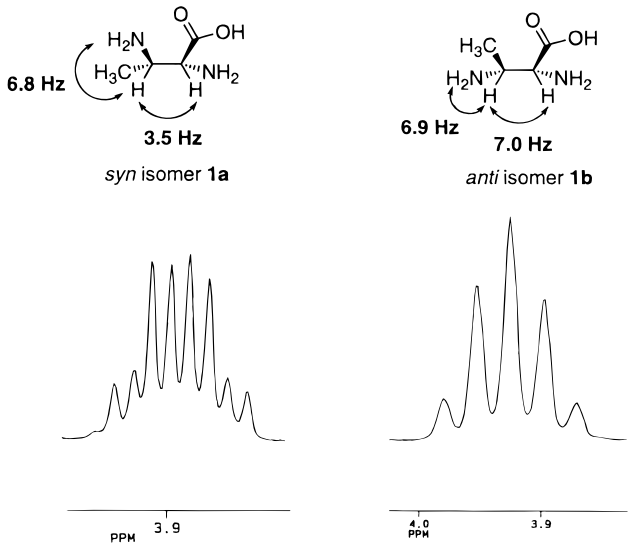


Figure 2. ^1H NMR (250 MHz) in D_2O of the 3-H syn isomer **1a** and the anti isomer **1b**.

Experimental Section

General Methods. NMR spectra were recorded in $CDCl_3$ or D_2O at either 250 or 400 MHz. Flash chromatography were carried out with Mallinckrodt silica gel 60 (230−400 mesh). Analytical TLC was performed on Merck glass plates coated with 0.25 mm silica. Chloroform and methylene chloride were distilled from calcium hydride, and THF was distilled from sodium. Methanol was distilled from magnesium before its use.

(2*S*,3*R*)-*tert*-Butyl 2-Hydroxy-3-(*N*-benzyloxycarbonyl)-aminobutanoate (3). A solution of sodium hydroxide (2.44 g, 61 mmol) in water (150 mL) was prepared in a single-necked round-bottom flask (500 mL) equipped with a magnetic stir bar. Approximately 10 mL of this solution was transferred into a flask (25 mL) with a Pasteur pipet, and potassium osmate dihydrate (294 mg, 0.8 mmol) was solubilized by gentle swirling. Benzyl carbamate (9.38 g, 62 mmol) was added in 80 mL of acetonitrile and was stirred vigorously until 90% of the carbamate was in solution (20 min). The reaction flask was immersed in a room-temperature water bath and *tert*-butyl hypochlorite (6.92 mL, 61 mmol) was added dropwise with stirring over a period of 20 min. In a single-necked, round-bottom flask (250 mL), hydroquinidine 1,4-phthalazinediyl diether $(DHQD)_2PHAL$ (780 mg, 1 mmol) and *tert*-butyl crotonate (3.20 mL, 20 mmol) were added to acetonitrile (70 mL) with stirring. This solution was transferred to the reaction mixture with a Pasteur pipet. The pink $K_2[OsO_2(OH)_4]$ solution was added to the reaction flask and stirred at room temperature. After 1 h, to the reaction mixture was added sodium sulfite (20 g, 160 mmol) and this reaction mixture was stirred for 45 min. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (4 × 100 mL). The combined organic layers were extracted with water and brine, dried over $MgSO_4$, and concentrated to dryness to afford the crude product contaminated by some excess benzyl carbamate. The ratio of the regioisomer was about 9:1 based on the ^1H NMR spectrum of the crude product. Purification by flash chromatography (hexane/ethyl acetate 2/1, v/v) provided 3.85 g of desired product (62% yield, 90% ee). The enatiomeric excess was also determined to be 90% as judged by ^1H NMR using Mosher's ester. The initial 90% ee was raised to >99% after single crystallization from hexane/ethyl acetate: mp 82−85 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.24 (d, J = 6.9 Hz, 3H), 1.43 (s, 9H), 3.09 (d, J = 3.9 Hz, 1H), 3.97 (m, 1H), 4.23

(m, 1H), 4.93 (d, J = 9.9 Hz, 1H), 5.03 (d, J = 4.2 Hz, 2H), 7.33 (m, 5H); HRMS [FAB, $(M + 1)^+$] calcd for 310.1654, found 310.1664.

(1*S*,2*R*)-2-(*N*-Benzyloxycarbonyl)amino-1-(*tert*-butoxycarbonyl)propyl-1-methanesulfonate (4). To a stirred solution of methanesulfonyl chloride (471 μL, 6.7 mmol) in methylene chloride (25 mL) at 0 °C was added **3** (2.0 g, 6.4 mmol) and triethylamine (849 μL, 6.7 mmol) in methylene chloride (25 mL) dropwise. After the addition was complete, the ice bath was removed and the reaction mixture was warmed to room temperature. Upon stirring for 1 h at room temperature the solution was concentrated under reduced pressure and purified by flash chromatography (hexane/ethyl acetate 3/1, v/v) to give a sticky oil. Recrystallization from hexane/ethyl acetate gave methanesulfonate **4** (2.24 g, 90% yield) as a white solid: mp 95−98 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.28 (d, J = 6.9 Hz, 3H), 1.43 (s, 9H), 3.16 (s, 3H), 4.51 (m, 1H), 4.88 (d, J = 2.4 Hz, 1H), 5.02 (d, J = 9.9 Hz, 1H), 5.12 (d, J = 4.2 Hz 2H), 7.34 (m, 5H); HRMS [FAB, $(M + 1)^+$] calcd for 388.1430, found 388.1444.

(2*R*,3*R*)-*tert*-Butyl 2-Azido-3-(*N*-benzyloxycarbonyl)aminobutanoate (5). To a stirred solution of **4** (1.5 g, 3.9 mmol) in DMF (25 mL) was added sodium azide (275 mg, 4.2 mmol). The mixture was heated to 70 °C for 12 h until **4** was consumed. The reaction mixture was poured into 50 mL of water and extracted with ethyl acetate (4 × 50 mL). The combined organic layers were extracted with brine, dried over $MgSO_4$, and concentrated to dryness to afford the crude product. Purification by flash chromatography (hexane/ethyl acetate 3/1, v/v) provided 1.07 g of (2*S*,3*R*)-**5** (82% yield) as colorless oil: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.10 (d, J = 6.7 Hz, 3H), 1.48 (s, 9H), 4.17 (d, J = 3.5 Hz, 1H), 4.25 (m, 1H), 5.00 (d, J = 8.3 Hz, 1H), 5.09 (s, 2H), 7.33 (m, 5H); HRMS [FAB, $(M + 1)^+$] calcd for 335.1719, found 335.1725.

(2*R*,3*R*)-*N*-Benzyloxycarbonyl-2-(*tert*-butoxycarbonyl)-3-methylaziridine (6). To a stirred solution of **4** (2.0 g, 5.2 mmol) in dry THF (30 mL) was added potassium *tert*-butoxide (602 mg, 5.4 mmol) also in THF (30 mL) dropwise under argon. After the mixture stirred for 1 h at room temperature, 50 mL of water was added to the reaction mixture, followed by 100 mL of ethyl acetate, and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (2 × 50 mL), and the combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Pure aziridine **6** (1.22 g, 80% yield) as a white solid was isolated by flash chromotography (hexane/ethyl acetate 3/1, v/v): mp 110−113; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.32 (d, J = 5.6 Hz, 3H), 1.46 (s, 9H), 2.74 (m, 1H), 3.06 (d, J = 6.7 Hz, 1H), 5.09 (d, J = 12.2 Hz, 1H), 5.14 (d, J = 12.2 Hz, 1H), 7.33 (m, 5H); HRMS [FAB, $(M + 1)^+$] calcd for 292.1549, found 292.1555.

(2*R*,3*S*)-*tert*-Butyl 2-(*N*-Benzyloxycarbonyl)amino-3-azidobutanoate (7). Trimethylsilyl azide (1.2 mL) was added quickly to a stirred solution of **6** (1.0 g, 3.4 mmol) in dry methanol (1.2 mL) in a 4 mL vial at 0 °C. The vial was closed tightly with a Teflon disk lid and the reaction mixture was heated at 70 °C for 5 h. After removal of solvent under reduced pressure, the pure product (0.9 g, 79% yield) was obtained as a colorless oil by flash chromotography (hexane/ethyl acetate 3/1, v/v): ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.33 (d, J = 6.7 Hz, 3H), 1.46 (s, 9H), 4.10 (qd, J^2 = 6.6 Hz, J = 2.6 Hz, 1H), 4.29 (dd, J^2 = 9.2 Hz, J = 2.7 Hz, 1H), 5.11 (s, 2H), 5.35 (d, J = 9.1 Hz, 1H), 7.33 (m, 5H); HRMS [FAB, $(M + 1)^+$] calcd for 335.1719, found 335.1731.

(2*R*,3*S*)-1a·2HCl. To a stirred solution of **7** (0.9 g, 2.7 mmol) in 30 mL of methanol in a 100 mL round-bottom flask charged with an atmospheric H_2 balloon was added 10 mol % Pd−carbon. The Pd−carbon was removed by filtration and the product was concentrated under reduced pressure. The product was dissolved in a 25 mL of trifluoroacetic acid/methylene chloride mixture (1/1). The reaction mixture was stirred at room temperature for 1 h and the product was concentrated under reduced pressure. Approximately 10 mL of 1 N HCl was added to the isolated material and the solvent was removed under reduced pressure after stirring for 1 h. Pure **(2*R*,3*S*)-1a**·2HCl (93% yield, 0.3 g) was obtained. The optical rotation observed and the ^{1}H NMR data obtained were consistent with the literature values:[6c] $[\alpha]^{20}_D$ −34.3 (*c* 1.0, 6 N HCl), lit.[10] $[\alpha]^{20}_D$ −38.1 (*c* 1.0, 6 N HCl); ^{1}H NMR (D_2O, 250 MHz) δ 1.35 (d, J = 6.8 Hz, 1H), 3.89 (qd, J^2 = 6.8 Hz, J = 3.5 Hz, 1H), 4.28 (d, J = 3.5 Hz, 1H).

(2*R*,3*R*)-1b·2HCl. To a stirred solution of **5** (1.0 g, 3.0 mmol) in 30 mL of methanol in a 100 mL round-bottom flask charged with an atmospheric H_2 balloon was added 10 mol % Pd−carbon. The Pd−carbon was removed by filtration and the product was concentrated under reduced pressure. The product was dissolved in a 25 mL of trifluoroacetic acid/methylene chloride mixture (1/1). The reaction mixture was stirred at room temperature for 1 h and the product was concentrated under reduced pressure. Approximately 10 mL of 1 N HCl was added to the isolated material and the solvent was removed under reduced pressure after stirring for 1 h. Pure **(2*R*,3*R*)-1b**·2HCl (92% yield, 329 mg) was obtained. The optical rotation observed and the ^{1}H NMR data obtained were consistent with the literature values:[6c] $[\alpha]^{20}_D$ −8.9 (*c* 1.0, 6 N HCl), lit.[10] $[\alpha]^{20}_D$ −11.0 (*c* 1.0, 6 N HCl); ^{1}H NMR (D_2O, 250 MHz) δ 1.43 (d, J = 6.9 Hz, 1H), 3.93 (m, 1H) 4.16 (d, J = 7.0 Hz, 1H); HRMS [FAB, $(M + 1)^+$] calcd for 119.0821, found 119.0824.

(2*R*,3*S*)-*tert*-Butyl 2-Hydroxy-3-(*N*-benzyloxycarbonyl)-aminobutanoate. Benzyl carbamate (9.38 g, 62 mmol) was dissolved in 80 mL of *n*-propyl alcohol in a single-necked round-bottomed flask (500 mL) equipped with a magnetic stir bar. To this stirred solution was added a freshly prepared solution of NaOH [NaOH (2.44 g, 61 mmol) in 150 mL of water], followed by *tert*-butyl hypochlorite (6.92 mL, 61 mmol). Next, a solution of the ligand $(DHQ)_2PHAL$ (780 mg, 1 mmol) in 70 mL of *n*-propyl alcohol was added. The reaction mixture was homogeneous at this point. The vial was then immersed in a room-temperature water bath and stirred for 3 min, and the olefin (*tert*-butyl crotonate, 3.20 mL, 20 mmol) was added, followed by the osmium catalyst ($K_2OsO_2(OH)_4$, 294 mg, 0.8 mmol). The reaction mixture was stirred for 40 min, and the light green color gave way to light yellow. After TLC analysis confirmed the absence of starting material, 140 mL of ethyl acetate was added, and the phases were separated. The lower, aqueous phase was extracted with water and brine, dried over $MgSO_4$, and concentrated to dryness to afford the crude product contaminated by some excess benzyl carbamate. The ratio of the regioisomer was about 8:1 based on the ^{1}H NMR spectrum of the crude product. Purification by flash chromatography (hexane/ethyl acetate 2/1, v/v) provided 3.91 g of desired product (63% yield, 89% ee). The enatiomeric excess was also determined to be 89% as judged by ^{1}H NMR using Mosher's ester. The initial 89% ee was raised to >99% after single crystallization from hexane/ethyl acetate: mp 83−86 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.23 (d, J = 6.9 Hz, 3H), 1.42 (s, 9H), 3.19 (d, J = 3.9 Hz, 1H), 3.98 (m, 1H), 4.25 (m, 1H), 5.04 (s, 2H), 7.33 (m, 5H); HRMS [FAB, $(M + 1)^+$] calcd for 310.1654, found 310.1663.

(1*R*,2*S*)-2-(*N*-Benzyloxycarbonyl)amino-1-(*tert*-butoxycarbonyl)propyl-1-methanesulfonate. To a stirred solution of methanesulfonyl chloride (471 μL, 6.7 mmol) in methylene chloride (25 mL) at 0 °C were added (2*R*,3*S*)-*tert*-butyl 2-hydroxy-3-(*N*-benzyloxycarbonyl)aminobutanoate (2.0 g, 6.4 mmol) and triethylamine (849 μL, 6.7 mmol) in methylene chloride (25 mL) dropwise. After the addition was complete, the ice bath was removed and the reaction mixture was warmed to room temperature. Upon stirring for 1 h at room temperature, the solution was concentrated under reduced pressure and purified by flash chromatography (hexane/ethyl acetate 3/1, v/v) to give a sticky oil. Recrystallization from hexane/ethyl acetate gave the desired product (2.18 g, 88% yield) as a white solid: mp 93−96 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.30 (d, J = 6.9 Hz, 3H), 1.44 (s, 9H), 3.18 (s, 3H), 4.52 (m, 1H), 4.90 (d, J = 2.4 Hz, 1H), 4.97 (d, J = 9.9 Hz, 1H), 5.08 (s, 2H), 7.34 (m, 5H); HRMS [FAB, $(M + 1)^+$] calcd for 388.1430, found 388.1440.

(2*S*,3*S*)-*tert*-Butyl 2-Azido-3-(*N*-benzyloxycarbonyl)aminobutanoate. To a stirred solution of (2*R*,3*S*)-*N*-benzyloxycarbonyl-2-carbo-*tert*-butoxy-3-methanesulfonate (1.5 g, 3.9 mmol) in DMF (25 mL) was added sodium azide (275 mg, 4.2 mmol). The mixture was heated to 70 °C for 12 h until the starting material was consumed. The reaction mixture was poured into 50 mL of water and extracted with ethyl acetate (4 × 50 mL). The combined organic layers were extracted with brine, dried over $MgSO_4$, and concentrated to dryness to afford the crude product. Purification by flash chromatography (hexane/ethyl

acetate 3/1, v/v) provided 1.06 g of desired product (81% yield) as colorless oil: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.10 (d, J = 6.7 Hz, 3H), 1.48 (s, 9H), 4.17 (d, J = 3.5 Hz, 1H), 4.25 (m, 1H), 5.00 (d, J = 8.3 Hz, 1H), 5.09 (s, 2H), 7.33 (m, 5H); HRMS [FAB, $(M + 1)^+$] calcd for 335.1719, found 335.1727.

(2*S*,3*S*)-*N*-Benzyloxycarbonyl-2-(*tert*-butoxycarbonyl)-3-methylaziridine. To a stirred solution of (2*R*,3*S*)-*N*-benzyloxycarbonyl-2-carbo-*tert*-butoxy-3-methanesulfonate (2.0 g, 5.2 mmol) in dry THF (30 mL) was added potassium *tert*-butoxide (602 mg, 5.4 mmol) in dry THF (30 mL) dropwise under argon. After stirring for 1 h at room temperature, 50 mL of water was added to the reaction mixture followed by 100 mL of ethyl acetate. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 × 50 mL). The combined organic materials were extracted with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The product (1.25 g, 82% yield) was obtained as a white solid by flash chromotography (hexane/ethyl acetate 3/1, v/v): mp 109−112; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.31 (d, J = 5.6 Hz, 3H), 1.43 (s, 9H), 2.75 (m, 1H), 3.06 (d, J = 6.7 Hz, 1H), 5.09 (d, J = 12.2 Hz, 1H), 5.14 (d, J = 12.2 Hz, 1H), 7.33 (m, 5H).

(2*S*,3*R*)-*tert*-Butyl 2-(*N*-Benzyloxycarbonyl)amino-3-azidobutanoate. Trimethylsilyl azide (1.2 mL) was added quickly to a stirred solution of (2*S*,3*S*)-*N*-benzyloxycarbonyl-2-carbo-*tert*-butoxy-3-methylaziridine (1.0 g, 3.4 mmol) in dry methanol (1.2 mL) in a 4 mL vial at 0 °C. The vial was closed tightly with a Teflon disk lid and the reaction mixture was heated at 70 °C for 5 h. After removal of solvent under reduced pressure, the pure product (877 mg, 77% yield) was isolated as a colorless oil by flash chromotography (hexane/ethyl acetate 3/1, v/v); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.32 (d, J = 6.7 Hz, 3H), 1.43 (s, 9H), 4.10 (qd, J^2 = 6.6 Hz, J = 2.6 Hz, 1H), 4.29 (dd, J^2 = 9.2 Hz, J = 2.7 Hz, 1H), 5.11 (s, 2H), 5.35 (d, J = 9.1 Hz, 1H), 7.33 (m, 5H); HRMS [FAB, $(M + 1)^+$] calcd for 335.1719, found 335.1727.

(2*S*,3*R*)-1c·2HCl. To a stirred solution of (2*S*,3*R*)-*tert*-butyl-2-(*N*-benzyloxycarbonyl)amino-3-azido-butanoate (800 mg, 2.4 mmol) in 30 mL of methanol in a 100 mL round-bottom flask charged with an atmospheric H_2 balloon was added 10 mol % Pd−carbon. The Pd−carbon was removed by filtration and the product was concentrated under reduced pressure. The product was dissolved in a 20 mL of trifluoroacetic acid/methylene chloride mixture (1/1). The reaction mixture was stirred at room temperature for 1 h and the product was concentrated under reduced pressure. Approximately 8 mL of 1 N HCl was added to the isolated material and the solvent was removed under reduced pressure after stirring for 1 h. Pure **(2*S*,3*R*)-1c**·2HCl (92% yield, 263 mg) was obtained. The optical rotation observed and the ^{1}H NMR data obtained were consistent with the literature values:[6c] $[\alpha]^{20}_D$ +33.4 (*c* 1.0, 6 N HCl), lit.[10] $[\alpha]^{20}_D$ +39.3 (*c* 1.0, 6 N HCl); ^{1}H NMR (D_2O, 250 MHz) δ 1.36 (d, J = 6.8 Hz, 1H), 3.90 (qd, J^2 = 6.8 Hz, J = 3.5 Hz, 1H), 4.27 (d, J = 3.5 Hz, 1H); HRMS [FAB, $(M + 1)^+$] calcd for 119.0821, found 119.0827.

(2*S*,3*S*)-1d·2HCl. To a stirred solution of (2*S*,3*S*)-*tert*-butyl 2-azido-3-(*N*-benzyloxycarbonyl)aminobutanoate (1 g, 3.0 mmol) in 30 mL of methanol in a 100 mL round-bottom flask charged with an atmospheric H_2 balloon was added 10 mol % Pd−carbon. The Pd−carbon was removed by filtration and the product was concentrated under reduced pressure. The product was dissolved in a 25 mL of trifluoroacetic acid/methylene chloride mixture (1/1). The reaction mixture was stirred at room temperature for 1 h and the product was concentrated under reduced pressure. Approximately 10 mL of 1 N HCl was added to the isolated material and the solvent was removed under reduced pressure after stirring for 1 h. Pure **(2*S*,3*S*)-1d**·2HCl (90% yield, 321 mg) was obtained. The optical rotation observed and the ^{1}H NMR data obtained were consistent with the literature values:[6c] $[\alpha]^{20}_D$ +9.1 (*c* 1.0, 6 N HCl), lit.[10] $[\alpha]^{20}_D$ +10.3 (*c* 1.0, 6 N HCl); ^{1}H NMR (D_2O, 250 MHz) δ 1.43 (d, J = 6.9 Hz, 1H), 3.92 (m, 1H) 4.02 (d, J = 7.0 Hz, 1H); HRMS [FAB, $(M + 1)^+$] calcd for 119.0821, found 119.0831.

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Supporting Information Available: Methods for the syntheses of the compounds discussed here and their ^{1}H NMR spectra (23 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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