An Efficient Asymmetric Route to 2,3-Diaminobutanoic Acids

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Nonproteogenic 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-workers7 in which threonine or allo-threonine was exploited as starting materials and Mitsunobu reaction conditions were used for the installation of the second aminogroup. While this tactic 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, Shin6a,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-workers8c 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 methylvanadium 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.

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 enantiopure 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 AA9 reaction gave 3 in high regioselectivity and enantioselectivity. The ratio of the regioisomers 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-amino species with inversion of configuration at C-2.6c Catalytic hydrogenation and subsequent acidic hydrolysis of azide 5 gave enantiomerically pure diamino acid 1b as its HCl salt [α]20D = −8.9 (c 1.0, 6 N HCl), lit.10 [α]20D = −11.0 (c 1.0, 6 N HCl) for 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-N3 and MeOH in DMF11 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

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

metric amounts of chiral reagents. Furthermore, our synthetic strategy can be applied to the synthesis of other \( \alpha,\beta \)-diamino acids by simply varying the starting olefin. Extension of this technology to the preparation of other molecules of interest is currently under investigation.

**Experimental Section**

**General Methods.** NMR spectra were recorded in CDCl\(_3\) or D$_2$O 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.

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**Notes**

1. (i) (DHQD)$_2$PHAL, 5%; K$_2$OsO$_2$(OH)$_4$, 4%; Cbz-NHCl, 3 equiv; CH$_3$CN/H$_2$O, 0°C. (ii) MsCl/(Et)$_3$N, CH$_2$Cl$_2$. (iii) t-BuO$^+$K$^-$, THF. (iv) (Me)$_3$SiN$_3$, MeOH. (v) NaN$_3$, DMF. (vi) H$_2$, 10% Pd/C, MeOH. (vii) CF$_3$COOH/CH$_2$Cl$_2$ 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% ([\( \alpha \)]$^D_{20}$ = -34.3 (c 1.0, 6 N HCl), lit.\(^{10} \) [\( \alpha \)]$^D_{20}$ = -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)$_2$PHAL for the aminohydroxylation reaction of tert-buty1 crotonate gave the 2S,3R 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 ([\( \alpha \)]$^D_{20}$ = 9.1 (c 1.0, 6 N HCl), lit.\(^{10} \) [\( \alpha \)]$^D_{20}$ = 10.3 (c 1.0, 6 N HCl)) and 1d in 40% yield ([\( \alpha \)]$^D_{20}$ = 33.4 (c 1.0, 6 N HCl), lit.\(^{10} \) [\( \alpha \)]$^D_{20}$ = 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-buty1 crotonate. Our strategy eliminates the drawbacks found in previous syntheses, which included a need for optically active \( \alpha \)-amino acids as starting materials or stoicho-
(15S)-2-(N-Benzoxycarbonyl)amino-1-(tert-butoxycarbonyl)propyl-1-methanesulfonate (4). To a stirred solution of methanesulfonyl chloride (471 \mu L, 6.7 mmol) in methylene chloride (25 mL) at 0 °C was added 3 (2.0 g, 6.4 mmol) and triethylamine (849 \mu L, 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 a white solid: mp 95–98 °C; \( \text{H} \) NMR (CDCl₃, 400 MHz) \( \delta \) 1.28 (d, \( J = 6.9 \) Hz, 3H), 1.43 (s, 9H), 2.45 (m, 1H), 4.86 (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 335.1719, found 335.1725.

(2R,3R)-t-Butyl 2-Azido-3-(N-benzoxycarbonyl)amino-3-butanone (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 at 70 °C for 12 h until 4 was consumed. The reaction mixture was poured into 50 mL of water, and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (4 × 50 mL). The combined organic layers were washed with brine, dried over MgSO₄, and concentrated to a sticky oil. Purification by flash chromatography (hexane/ethyl acetate 3/1, v/v) provided 3.91 g of desired product (63% yield, 89% ee). The \( \text{H} \) NMR data obtained were consistent with the literature values: [FAB, (M + 1)⁺] calcd for 335.1719, found 335.1725.

(2R,3R)-t-Butyl 2-Hydroxy-3-(N-benzoxycarbonyl)amino-3-butanone. To a stirred solution of 5 (3.0 g, 6.4 mmol) in 30 mL of methanol in a 100 mL round-bottom flask charged with an atmospheric H₂ 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 heating for 1 h. Pure (2R,3S)-1a-2HCl (93% yield, 0.3 g) was obtained. The optical rotation observed and the \( \text{H} \) NMR data obtained were consistent with the literature values: [FAB, (M + 1)⁺] calcd for 310.1654, found 310.1654.

(2R,3S)-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 H₂ 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 heating for 1 h. Pure (2R,3S)-1b-2HCl (93% yield, 0.3 g) was obtained. The optical rotation observed and the \( \text{H} \) NMR data obtained were consistent with the literature values: [FAB, (M + 1)⁺] calcd for 310.1654, found 310.1654.

Notes

acetate 3/1, v/v) provided 1.06 g of desired product (81% yield) as colorless oil: {1}H NMR (CDCl₃, 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.

(25,3S)-N-Benzoylcarbonyl-2-(tert-butoxycarbonyl)-3-methylaziridine. Dried filtered concentrate of the organic material was extracted with brine, dried over MgSO₄, and concentrated under reduced pressure. The product (1.25 g, 82% yield) was obtained as a white solid by flash chromatography (hexane/ethyl acetate 3/1, v/v); 1H NMR (CDCl₃, 250 MHz) δ 1.43 (d, J = 6.9 Hz, 3H), 1.51 (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).

(25,3R)-tert-Butyl-2-(N-Benzoylcarbonyl)amino-3-azido-butanate. Trimethylsilyl azide (1.2 mL) was added quickly to a stirred solution of (25,3S)-N-benzyloxy carbonyl-2-carboxytert-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 disc lid and the reaction mixture was heated at 70 °C for 5 h. After removal of solvent under reduced pressure, a pure product (0.877 g, 77% yield) was isolated as a colorless oil: 1H NMR (CDCl₃, 250 MHz) δ 1.06 g of desired product (81% yield) was obtained. The optical rotation observed and the 1H NMR data obtained were consistent with the literature values: 25 (α)D + 33.4 (c 1.0, 6 N HCl), lit. 26 (α)D + 39.3 (c 1.0, 6 N HCl); 1H NMR (D₂O, 250 MHz) δ 1.36 (d, J = 6.8 Hz, 1H), 3.90 (q, J = 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.

(25,3S)-1d·2HCl. To a stirred solution of (25,3S)-tert-butyl-2-azido-3-(N-benzyloxy carboxyl)amino butanate (1 g, 3.0 mmol) in 30 mL of methanol in a 100 mL round-bottom flask charged with an atmospheric H₂ balloon was added 10 mol % Pd–carbon. The Pd–carbon was removed by filtration 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 (25,3S)-1d·2HCl (90% yield, 321 mg) was obtained. The optical rotation observed and the 1H NMR data obtained were consistent with the literature values: 25 (α)D + 9.1 (c 1.0, 6 N HCl), lit. 26 (α)D + 10.3 (c 1.0, 6 N HCl); 1H NMR (D₂O, 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 119.0831, found 119.0831.

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Supporting Information Available: Methods for the synthesis of the compounds discussed here and other 1H 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.