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Practical Asymmetric Preparation of Azetidine-2-carboxylic Acid

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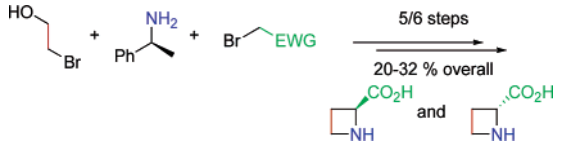
Received July 29, 2005



Facile and straightforward syntheses of both enantiomers of azetidine-2-carboxylic acid are described. The syntheses depart from inexpensive chemicals and allow for the production, in five to six steps, of practical quantities of each enantiomer. Synthetic highlights include the construction of the azetidine ring using an intramolecular alkylation and the use of optically active α-methylbenzylamine as chiral auxiliary.

L-Azetidine-2-carboxylic acid (**1**), also commonly named L-Aze (Figure 1), was first isolated in 1955 by Fowden from *Convallaria majalis* and was the first known example of naturally occurring azetidine.[1] Following this first discovery, many natural products such as mugineic acid (**2**)[2] or nicotianamine (**3**)[3] have been reported to incorporate this amino acid in their structure. Recently, pharmacologically important molecules such as thrombin inhibitors Melagatran or Exenta (**4**)[4] have been derived from this unique compound. As a constrained amino acid, L-Aze has found many applications in the modification of peptides conformations[5] and in the area of asymmetric synthesis, which include its use in the asymmetric reduction of ketones,[6] Michael additions,[7] cyclopropanations,[8] and Diels−Alder reactions.[9]

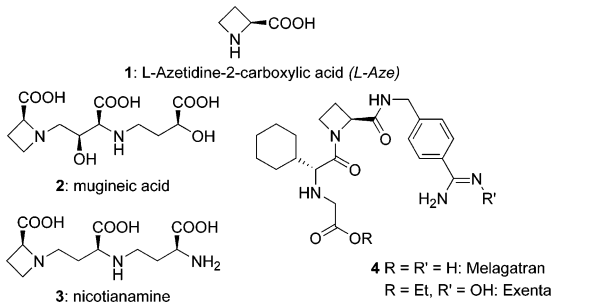


FIGURE 1. L-Azetidine carboxylic acid and derived compounds.

Many racemic synthesis of azetidine carboxylic acid have been reported[1,10] since its isolation, but although the (*S*)-enantiomer is commercially available in milligram quantities only, a satisfactory route to both enantiomers in practical quantities is not yet accessible. Most asymmetric syntheses usually either rely on chemical[10a,11] or enzymatic resolution[12] or require the use of sophisticated chiral auxiliaries[13] and/or elaborated starting materials.[1,14] None of these syntheses are ideal for large-scale preparation of both enantiomers in terms of cost, safety issues, or number of steps involved.

As part of our ongoing interest in the chemistry of azetidines[15] and for our specific research interests, we required a cost-effective, safe synthesis of both enantiomers of azetidine-2-carboxylic acid that was amenable to large-scale preparation. We therefore designed a practical synthesis for this cyclic amino acid, and described herein is our straightforward approach to both enantiomers of **1**. This synthesis features an intramolecular 4-*exo-tet* alkylation for the key cyclization step and relies on the use of α-methylbenzylamine, inexpensive and available in both enantiomeric forms, as the source of chirality. In comparison to literature synthesis,[10−14] this route requires the purification of only one intermediate, employs inexpensive and commercially available starting materials, and avoids using expensive chiral auxiliaries or resolving agents such as tyrosine hydrazide, enzymes, or homochiral sultams.

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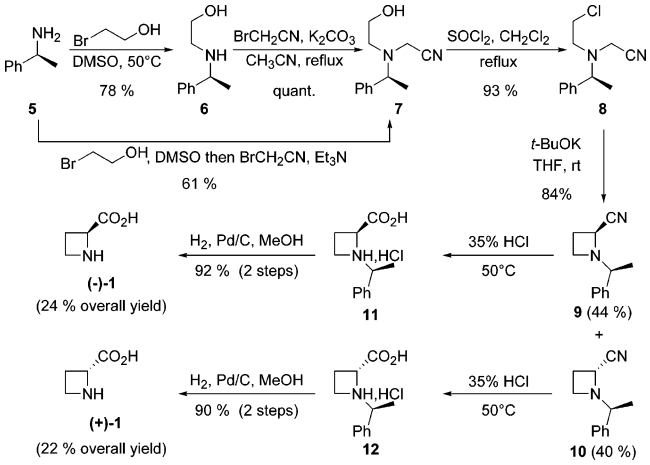
10.1021/jo0515881 CCC: $30.25
Published on Web 10/05/2005

A very short method to form the four-membered ring could make use of an intramolecular 4-*exo-tet* alkylation[15a] starting from compound **8** (Scheme 1) possessing both leaving and electron-withdrawing groups. We therefore synthesized this chloride **8** in a three-step sequence starting from commercially available α-methylbenzylamine **5** as the source of chirality. Thus, this amine was subjected to two consecutive alkylation reactions with bromoethanol and bromoacetonitrile to afford the tertiary amine **7** in excellent overall yield. Optimization of the first alkylation step clearly demonstrated that best results were obtained when a stoichiometric ratio of amine and bromoethanol were used in the absence of base. Using these conditions, only minor amounts of bis-alkylated amine were detected in the crude reaction mixtures and amino alcohol **6** could therefore be easily purified by distillation. Furthermore, to overcome the workup issues associated with the highly polar and volatile intermediate **6**, an efficient one-pot double alkylation was achieved by successively treating **5** with bromoethanol, triethylamine, and finally bromoacetonitrile. Alcohol **7** could be obtained in a 61% yield (Scheme 1). Chloride **8** was then efficiently prepared by reaction with thionyl chloride in dichloromethane.

SCHEME 1. Synthesis of (+)- and (−)-Azetidine-2-carboxylic Acid

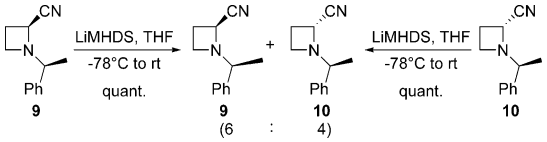


Without further purification chloride **8** was subjected to the key cyclization step to form the four-membered ring. After screening various conditions, the intramolecular alkylation was found to be best achieved by simply reacting **8** with potassium *tert*-butoxide in THF for 10 min at room temperature. Using these conditions, a crude 6:4 mixture of diastereoisomers **9** and **10** was obtained in excellent yield.[16] Attempts to improve the selectivity by variation in the reaction parameters (i.e., solvent, base, additive, or temperature) showed virtually no improvement and resulted in the use of less practical reaction conditions. Diastereoisomers **9** and **10** displaying highly different polarities were easily separated by flash column chromatography. Further functional group transformations from either **9** or **10** would then provide access to both enantiomers of the desired cyclic amino acid and would therefore render the synthesis enantiodivergent.

(16) Relative configurations of **9** and **10** were assigned on the basis of optical rotations and chiral HPLC analysis of the derived amino acids.

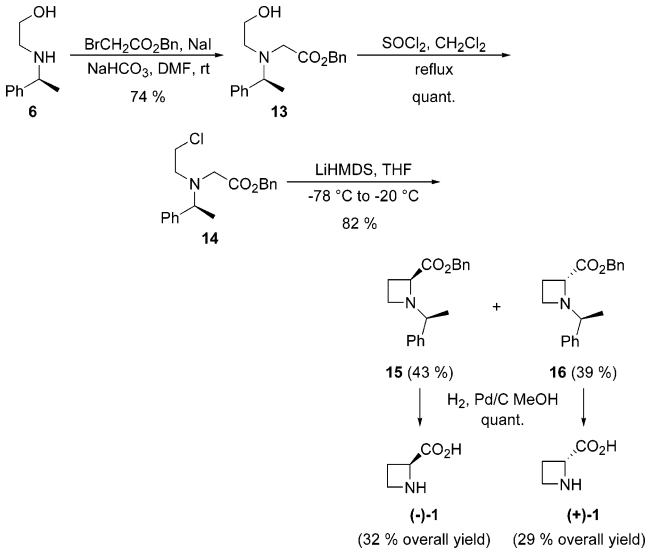
Moreover, we were pleased to find that both of those diastereoisomers could be equilibrated: by reacting **9** or **10** with LiHMDS in THF from −78 °C to room temperature, a 6:4 thermodynamic ratio of diastereoisomers was obtained, therefore allowing for recycling either diastereosiomer (Scheme 2).

SCHEME 2. Equilibration of Cyano-azetidines 9 and 10



Hydrolysis of cyclic aminonitrile **9** with concentrated hydrochloric acid proceeded very smoothly and cleanly to give the benzyl-protected amino acid **11** as its hydrochloride by simple evaporation (Scheme 1). Finally, hydrogenolysis of this HCl salt **11** with 10% Pd/C in methanol gave the desired azetidine-2-carboxylic acid (−)-**1** as its white crystalline hydrochloride (92%, 2 steps). Zwitterionic amino acid (−)-**1** could be obtained by ion-exchange chromatography (Dowex 50x8-200), and spectroscopic data were in complete agreement with those reported.[13,17] Optical purity was found to be 95% by chiral HPLC analysis of the *N*-CBz derivative.[18] The exact same hydrolysis/debenzylation sequence starting from **10** yielded the enantiomer (+)-**1** in excellent yield.

SCHEME 3. Five-Step Synthesis of (+)- and (−)-Azetidine-2-carboxylic Acid



Further investigations to improve and shorten our synthesis revealed that a slight modification would allow for a five-step synthesis. By replacing the nitrile group by a benzyl ester in the previous synthetic scheme, both carboxylic acid and amine groups of the target could be simultaneously deprotected at the end of the synthesis (Scheme 3). Starting from **6**, the first step consisted of the introduction of the electron-withdrawing group by

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(18) Chiral HPLC analysis of *N*-CBz derivative: (*R*,*R*) Whelk-01 Regis column, heptane/isopropyl alcohol/acetic acid 73:27:0.5. Retention time (*S*)-enantiomer: 8.39 min. Retention time (*R*)-enantiomer: 9.50 min.

alkylation with benzyl bromoacetate. After optimization of this alkylation, we eventually found that subjection of **6** to benzyl bromoacetate in the presence of sodium iodide and sodium hydrogencarbonate in DMF minimized the proportion of morpholinone formation and resulted in the isolation of **13** in 74% yield. Chlorination and cyclization went smoothly, and results obtained with this route compare well with the those obtained with the initial one. Finally, double debenzylation by hydrogenolysis provided both enantiomers (−)-**1** or (+)-**1** starting either from ester **15** or **16** in excellent yield (Scheme 3). This modified route therefore allowed for a five-step access to both enantiomers of azetidine-2-carboxylic acid with a good overall yield. One extra purification step by column chromatography is however required in this case to obtain a clean alkylated product **13**.

In summary, practical syntheses of both enantiomers of azetidine-2-carboxylic acid were developed. Overall yields over this enantiodivergent five- or six-step synthesis range from 20% to 32% for each enantiomer. The route starts from commercially available α-methylbenzylamine, and a single purification by column chromatography is required when a nitrile group is used for the cyclization step. Reagents, reaction concentrations, and conditions are easily amenable for large-scale synthesis.

Experimental Section

(*S*)-2-(1-Phenylethylamino)-ethanol (6). To a solution of L-(−)-α-methylbenzylamine (10.0 g, 82 mmol) in DMSO (50 mL) was added bromoethanol (5.9 mL, 82 mmol). The resulting solution was then stirred at 50 °C for 72 h, concentrated under vacuum, treated with a saturated aqueous solution of $NaHCO_3$, and extracted with ether. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated. The residue was purified by distillation under high vacuum (Vigreux column, 4 mmHg, 134−135 °C) to give the desired amino alcohol (10.6 g, 78%) as a colorless oil that crystallized upon storage in a freezer. Mp 49 °C; $[\alpha]^{20}_D$ −57 (*c* 0.9, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18−7.30 (m, 5H), 3.74 (q, *J* = 6.6 Hz, 1H), 3.44 (q, *J* = 6.2 Hz, 2H), 2.92 (ddd app oct., *J* = 7.0 Hz, 2H), 1.36 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.9, 128.8, 127.8, 127.3, 61.8, 52.7, 40.0, 20.4. MS (electrospray): 166.1, 104.7. Anal. Calcd for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.67; H, 9.16; N, 8.50.

(*S*)-[(2-Hydroxy-ethyl)-(1-phenyl-ethyl)-amino]-acetonitrile (7). To a solution of **6** (12.1 g, 73 mmol) in acetonitrile (500 mL) were added bromoacetonitrile (6.1 mL, 86 mmol) and potassium carbonate (14.2 g, 103 mmol). The resulting mixture was then refluxed for 5 h, concentrated under vacuum, diluted with water, and extracted with ether. Combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated to afford the desired compound (14.8 g, quantitative yield) as a yellow oil. $[\alpha]^{20}_D$ −93 (*c* 1.2, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.23−7.39 (m, 5H), 3.82 (q, *J* = 6.5 Hz, 1H), 3.52−3.72 (m, 4H), 2.75−2.92 (m, 2H), 2.14 (broad s, 1H), 1.46 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.1, 129.0, 128.0, 127.4, 115.0, 62.0, 59.5, 52.4, 39.4, 20.4. MS (electrospray): 215.1, 178.4, 176.1, 132.8, 118.7, 104.7, 100.5. Anal. Calcd for $C_{12}H_{16}N_2O$: C, 70.56; H, 7.90; N, 13.71. Found: C, 70.37; H, 7.97; N, 13.69.

(*S*)-[(2-Hydroxy-ethyl)-(1-phenyl-ethyl)-amino]-acetonitrile (7). One-Pot Procedure from α-Methylbenzylamine. To a solution of L-(−)-α-methylbenzylamine (1.0 g, 8.2 mmol) in DMSO (5 mL) was added bromoethanol (1.07 g, 8.61 mmol). The resulting solution was then stirred at 50 °C for 72 h, cooled to room temperature, and successively treated with triethylamine (3.4 mL, 24.6 mmol) and bromoacetonitrile (680 μL, 9.8 mmol). The resulting mixture was next stirred at room temperature for 5 h, diluted with water, and extracted with ether. Combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated. The brownish residue was purified by flash column chromatography over silica gel (AcOEt/EP: 8/2) to afford the desired compound (1.1 g, 61%).

(*S*)-[(2-Chloro-ethyl)-(1-phenyl-ethyl)-amino]-acetonitrile (8). To a solution of **7** (13.8 g, 67 mmol) in dichloromethane (350 mL) was added dropwise thionyl chloride (9.9 mL, 135 mmol) at 0 °C. The resulting mixture was heated under gentle reflux for 2 h, cooled to room temperature, and carefully hydrolyzed with a saturated aqueous solution of $NaHCO_3$. The aqueous layer was then extracted with dichloromethane, and the combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated to give the desired chloride (13.9 g, 93%) as a yellow solid. Mp 49 °C; $[\alpha]^{20}_D$ −52 (*c* 0.9, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36−7.38 (m, 5H), 3.85 (q, *J* = 6.6 Hz, 1H), 3.50−3.57 (m, 4H), 2.99 (ddd app oct., *J* = 7.0 Hz, 2H), 1.44 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.0, 128.8, 127.9, 127.4, 115.0, 61.8, 52.8, 42.0, 40.1, 20.5. MS (electrospray): 104.6. Anal. Calcd for $C_{12}H_{15}ClN_2$: C, 64.71; H, 6.79; N, 12.58. Found: C, 64.95; H, 6.88; N, 12.49.

[1(1*S*),2*S*]-1-(1-Phenyl-ethyl)-azetidine-2-carbonitrile (9) and [1(1*S*),2*R*]-1-(1-Phenyl-ethyl)-azetidine-2-carbonitrile (10). A solution of **8** (3.0 g, 13.4 mmol) in THF (255 mL) was treated with potassium *tert*-butoxide (1.8 g, 16.2 mmol). The resulting mixture was stirred at room temperature for 10 min, quenched by addition of a saturated aqueous solution of NH_4Cl, concentrated under vaccuum, and extracted with ethyl acetate. Combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated. The brownish residue was purified by flash column chromatography over silica gel (AcOEt/PE: 2/8) to afford **9** (first eluting diastereoisomer, colorless crystals, 1.1 g, 44%) and **10** (second eluting diastereoisomer, colorless crystals, 1.0 g, 40%). **9**: mp 44 °C; $[\alpha]^{20}_D$ −134 (*c* 0.9, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25−7.36 (m, 5H), 3.86 (t, *J* = 7.1 Hz, 1H), 3.55 (q, *J* = 6.5 Hz, 1H), 3.21 (qd, *J* = 6.4 and 0.7 Hz, 1H), 3.05 (q, *J* = 7.3 Hz, 1H), 2.38 (qd, *J* = 6.9 and 1.4 Hz, 2H), 1.35 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.8, 128.5, 127.6, 127.3, 119.6, 66.2, 51.5, 50.7, 21.9, 20.8. MS (electrospray): 209.2, 160.0, 104.6. Anal. Calcd for $C_{12}H_{14}N_2$: C, 77.38; H, 7.58; N, 15.04. Found: C, 77.25; H, 7.77; N, 14.94. **10**: mp 41 °C; $[\alpha]^{20}_D$ −18 (*c* 1.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27−7.37 (m, 5H), 3.87 (t, 1H, *J* = 7.3 Hz), 3.40−3.83 (m, 2H), 3.05 (q, *J* = 7.3 Hz, 1H), 2.37 (qd, *J* = 7.6 and 1.9 Hz, 2H), 1.35 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.9, 128.6, 127.7, 127.3, 118.8, 66.5, 51.5, 50.7, 21.9, 20.4. MS (electrospray): 209.2, 160.0, 104.6. Anal. Calcd for $C_{12}H_{14}N_2$: C, 77.38; H, 7.58; N, 15.04. Found: C, 77.22; H, 7.79; N, 14.93.

(*S*)-Azetidine-2-carboxylic Acid [(−)-1]. A 50 mL flask was charged with **9** (351 mg, 1.88 mmol) and 35% hydrochloric acid (30 mL). After complete dissolution, the resulting mixture was heated to 50 °C for 3 days, cooled to room temperature, concentrated, and dried under high vacuum to yield the desired amino acid as its hydrochloride salt. Mp 115 °C. ^{1}H NMR (300 MHz, D_2O): δ 7.36−7.40 (m, 5H), 5.04 (t, *J* = 9.8 Hz, 1H), 4.43 (q, *J* = 6.9 Hz, 1H), 3.86 (q, *J* = 9.8 Hz, 1H), 3.45 (td, *J* = 9.9 and 4.1 Hz, 1H), 2.38−2.62 (m, 2H), 1.51 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, D_2O): δ 170.8, 133.6, 130.0, 129.2, 128.1, 65.2, 64.6, 49.0, 20.0, 15.9. MS (electrospray): 206.2, 104.6. HRMS (CI, NH_3) *m/z* calcd for $C_{12}H_{16}ClNO_2$ $[M]^+$ 241.087, found 241.089. The residue was dissolved in methanol (45 mL), and Pd/C (10wt % Pd, 450 mg) was added. The resulting mixture was then stirred under an atmosphere of hydrogen for 4 days, filtered over a short plug of Celite, rinsed with methanol, and concentrated to yield azetidine-2-carboxylic acid hydrochloride as a white crystalline solid. This residue was dissolved in distilled water and purified by ion exchange chromatography (Dowex 50x8-200, 10 g, washed with water before use until pH 7 and first eluted with water until pH 7 and then with a 1% aqueous ammonia solution) to give the desired zwitterionic amino acid after lyophilization (175 mg, 92% over two steps). Mp 212 °C (dec); $[\alpha]^{20}_D$ −118 (*c* 3.6, H_2O). ^{1}H NMR (300 MHz, D_2O): δ 4.51−4.74 (m, 1H), 3.86 (q, *J* = 9.2 Hz, 1H), 3.45 (q, *J*

= 8.5 Hz, 1H), 2.66 (quint, J = 8.1 Hz, 1H), 2.43 (quint, J = 8.2 Hz, 1H). ^{13}C NMR (75 MHz, D_2O): δ 174.1, 59.0, 42.8, 23.3. MS (electrospray): 326.3, 304.3, 225.2, 212.2, 203.1, 123.8, 101.6. HRMS (CI, NH_3) m/z calcd for $C_4H_8NO_2$ $[M + H]^+$ 102.055, found 102.056.

(*R*)-Azetidine-2-carboxylic Acid [(+)-1]. A 50 mL flask was charged with **9** (320 mg, 1.72 mmol) and 35% hydrochloric acid (30 mL). After complete dissolution, the resulting mixture was heated to 50 °C for 3 days, cooled to room temperature, concentrated, and dried under high vacuum to yield the desired amino acid as its hydrochloride salt. Mp: 215 °C. ^{1}H NMR (300 MHz, D_2O): δ 7.33−7.43 (m, 5H), 4.63−4.79 (t, J = 9.5 Hz, 1H), 4.40 (q, J = 6.8 Hz, 1H), 4.09 (dd, J = 8.7 and 8.1 Hz, 2H), 2.56−2.61 (m, 1H), 2.38−2.45 (quint, J = 9.6 Hz, 1H), 1.51(d, J = 6.9 Hz, 3H), ^{13}C NMR (75 MHz, D_2O): δ 170.3, 133.3, 130.1, 129.2, 128.3, 65.5, 63.9, 50.4, 19.8, 15.1. MS (electrospray): 206.2, 104.6. HRMS (CI, NH_3) m/z calcd for $C_{12}H_{16}ClNO_2$ $[M]^+$ 241.087, found 241.088. The residue was dissolved in methanol (40 mL), and Pd/C (10 wt % Pd, 400 mg) was added. The resulting mixture was then stirred under an atmosphere of hydrogen for 4 days, filtered over a short plug of Celite, rinsed with methanol, and concentrated to yield azetidine-2-carboxylic acid hydrochloride as a white crystalline solid. This residue was dissolved in distilled water and purified by ion exchange chromatography (Dowex 50x8-200, 10 g, washed with water before use until pH 7 and first eluted with water until pH 7 and then with a 1% aqueous ammonia solution) to give the desired zwitterionic amino acid after lyophilization (156 mg, 90% over two steps). Mp 212 °C (dec); $[\alpha]^{20}_D$ +118 (c 3.6, H_2O). ^{1}H NMR (300 MHz, D_2O): δ 4.51−4.74 (m, 1H), 3.86 (q, J = 9.2 Hz, 1H), 3.45 (q, J = 8.5 Hz, 1H), 2.66 (quint, J = 8.1 Hz, 1H), 2.43 (quint, J = 8.2 Hz, 1H). ^{13}C NMR (75 MHz, D_2O): δ 174.1, 59.0, 42.8, 23.3. MS (electrospray): 326.3, 304.3, 225.2, 212.2, 203.1, 123.8, 101.6. HRMS (CI, NH_3) m/z calcd for $C_4H_8NO_2$ $[M + H]^+$ 102.055, found 102.055.

(*S*)-Benzyl [(2-hydroxy-ethyl)-(1-phenyl-ethyl)-amino]-ethanoate (13). To a solution of **6** (1.6 g, 9.7 mmol) in anhydrous DMF (30 mL) were added sodium hydrogencarbonate (1.6 g, 19.5 mmol), sodium iodide (2.9 g, 19.5 mmol), and benzyl bromoacetate (3.1 mL, 19.5 mmol). The resulting mixture was stirred at room temperature for 7 h and poured into a mixture of ether and saturated aqueous solution of NH_4Cl. The aqueous layer was extracted with ether, and the combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated. The brownish residue was purified by flash column chromatography over silica gel (AcOEt/PE 4:6) to afford the desired compound (2.25 g, 74%) as a pale yellow oil. To avoid the formation of morpholinone by lactonization, this compound was immediately engaged in the next step. $[\alpha]^{20}_D$ +2 (c 1.9, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.23−7.44 (m, 10H), 5.15 (s, 2H), 4.07 (q, J = 6.7 Hz, 1H), 3.47−3.59 (m, 2H), 3.45 (A of AB syst, J = 18.2 Hz, 1H), 3.28 (B of AB syst, J = 18.2 Hz, 1H), 2.78−2.85 (m, 2H), 1.42 (d, J = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.9, 142.9, 135.5, 128.7, 128.6, 128.5, 128.4, 127.6, 127.4, 66.6, 60.5, 59.4, 53.9, 51.9, 17.0. MS (electrospray): 279.1, 206.5, 190.2, 147.6. Anal. Calcd for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40; N, 4.47. Found: C, 72.59; H, 7.19; N, 4.52.

(*S*)-Benzyl [(2-chloro-ethyl)-(1-phenyl-ethyl)-amino]-ethanoate (14). To a solution of **13** (1.2 g, 3.8 mmol) in dichloromethane (30 mL) was added dropwise thionyl chloride (560 μL, 7.7 mmol) at 0 °C. The resulting mixture was heated under gentle reflux for 2 h, cooled to room temperature, and carefully hydrolyzed with a saturated aqueous solution of $NaHCO_3$. The aqueous layer was then extracted with dichloromethane, and the combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated to give the desired chloride (1.3 g, 93%) as a pale oil. $[\alpha]^{20}_D$ −22 (c 1.3, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27−7.45 (m, 10H), 5.19 (s, 2H), 4.17 (q, J = 6.7 Hz, 1H), 3.64 (A of AB syst, J = 17.7 Hz, 1H), 3.49 (dd, J = 14.6 and 7.1 Hz, 1H), 3.48 (B of AB syst, J = 17.7 Hz, 1H), 3.00−3.16 (m, 2H), 1.41 (d, J = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.3, 141.9, 135.7, 128.4, 128.3, 128.1, 128.0, 127.5, 127.0, 68.1, 66.2, 64.4, 50.9, 20.9, 20.0. MS (electrospray): 331.2, 241.7, 104.6. Anal. Calcd for $C_{19}H_{22}ClNO_2$: C, 68.77; H, 6.68; N, 4.22. Found: C, 68.92; H, 6.46; N, 4.05.

[1(1*S*),2*S*]-Benzyl 1-(1-Phenyl-ethyl)-azetidine-2-carboxylate (15) and [1(1*S*),2*R*]-benzyl 1-(1-phenyl-ethyl)-azetidine-2-carboxylate (16). To a solution of **14** (1.0 g, 3.0 mmol) in THF (70 mL) was added LiHMDS (1.05 M solution in THF, 3.5 mL, 3.7 mmol) dropwise at −78 °C. The resulting mixture was slowly warmed to −20 °C over 2 h and quenched with a saturated aqueous solution of NH_4Cl. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated. The residue was purified by flash column chromatography over silica gel (AcOEt/PE: 1/9) to afford **15** (first eluting diastereoisomer, colorless oil, 380 mg, 43%) and **16** (second eluting diastereoisomer, colorless oil, 345 mg, 39%). **15**: $[\alpha]^{20}_D$ −81 (c 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.11−7.27 (m, 10H), 5.13 (A of AB syst, J = 12.3 Hz, 1H), 5.06 (B of AB syst, J = 12.3 Hz, 1H), 3.71 (t, J = 8.3 Hz, 1H), 3.36 (q, J = 6.6 Hz, 1H), 3.03 (qd, J = 7.5 and 2.8 Hz, 1H), 2.70 (q, J = 8.4 Hz, 1H), 2.03−2.25 (m, 2H), 1.11 (d, J = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.0, 142.6, 135.6, 128.5, 128.3, 128.1, 127.8, 127.5, 127.2, 67.2, 66.4, 64.0, 50.0, 21.1, 20.9. MS (electrospray): 296.1. Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.57; H, 7.34; N, 4.59. **16**: $[\alpha]^{20}_D$ +26 (c 0.8, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.97−7.30 (m, 10H), 4.74 (A of AB syst, J = 12.3 Hz, 1H), 4.62 (B of AB syst, J = 12.3 Hz, 1H), 3.48−3.59 (m, 2H), 3.30 (q, J = 6.5 Hz, 1H), 2.93 (qd, J = 6.8 and 1.3 Hz, 1H), 2.17−2.29 (m, 1H), 2.00−2.10 (m, 1H), 1.19 (d, J = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.3, 141.9, 135.7, 128.5, 128.4, 128.2, 127.5, 127.3, 127.0, 68.1, 66.2, 64.4, 50.9, 20.9, 20.0. MS (electrospray): 296.1. Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.01; H, 7.28; N, 4.84.

(*S*)-Azetidine-2-carboxylic Acid [(−)-1]. To a solution of **15** (205 mg, 0.7 mmol) in methanol (20 mL) was added Pd/C (10wt % Pd, 200 mg). The resulting mixture was then stirred under an atmosphere of hydrogen for 4 days, filtered over a short plug of Celite, rinsed with methanol and concentrated to yield azetidine-2-carboxylic acid as a white crystalline solid (71 mg, quantitative yield).

(*R*)-Azetidine-2-carboxylic Acid [(+)-1]. To a solution of **16** (180 mg, 0.6 mmol) in methanol (18 mL) was added Pd/C (10 wt % Pd, 180 mg). The resulting mixture was then stirred under an atmosphere of hydrogen for 4 days, filtered over a short plug of Celite, rinsed with methanol, and concentrated to yield azetidine-2-carboxylic acid as a white crystalline solid (61 mg, quantitative yield).

Acknowledgment. We thank Dr. Laurence Menguy for HPLC analysis and CNRS for financial support ("ATIP jeune équipe").

Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra for all intermediates and azetidine-2-carboxylic acid. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0515881