JOC*Note*

pubs.acs.org/joc

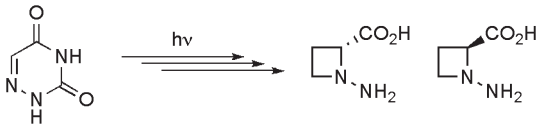
N-Aminoazetidinecarboxylic Acid: Direct Access to a Small-Ring Hydrazino Acid

Valérie Declerck and David J. Aitken*

Laboratoire de Synthèse Organique et Méthodologie, ICMMO (UMR 8182-CNRS), Université Paris−Sud 11, 15 rue Georges Clemenceau, 91405 Orsay cedex, France

david.aitken@u-psud.fr

Received October 25, 2010



A short and efficient synthesis of the previously unknown *N*-aminoazetidinecarboxylic acid has been established using a photochemical [2 + 2] cycloaddition strategy starting from 6-azauracil. Chiral derivatization with a nonracemic oxazolidinone provided access to both enantiomers of the title product.

There is a growing interest in cyclic β-amino acids as building blocks for the preparation of peptidomimetics which exhibit useful pharmacological activities and for the construction of molecular architectures displaying strong self-organization.[1] In particular, cyclopentane and cyclohexane β-amino acids have been widely studied, since these manifolds impart strong structuring propensities within their oligomers.[2] An "aza-replacement" in the peripheral part of the carbocycle was envisaged by Gellman, who studied peptides containing pyrrolidine and piperidine β-amino acids.[3] The specific "aza-substitution" of the β-carbon of a β-amino acid implies an α-hydrazino acid, and oligomers of these can be perceived as aza-β-peptides. Little work has been done on such materials, however,[4] and the first aza-β-peptide structures containing 5-membered cyclic α-hydrazino acids (aza-β-prolines) appeared only very recently.[5]

In keeping with the achievements and developments using larger rings, cyclobutane β-amino acids (ACBC) (Figure 1) have now emerged as useful building blocks.[6] Oligomers of *cis*-ACBC adopt strand-type conformations involving intraresidue hydrogen bonds.[7] Dipeptides incorporating *trans*-ACBC appear to adopt 8-membered hydrogen bond rings,[8] while longer oligomers adopt a 12-helix conformation both in solution and in the solid state.[9]

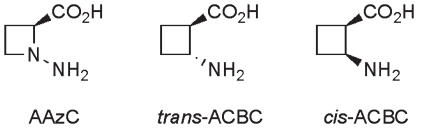


FIGURE 1. AAzC, an aza-analogue of ACBC.

The aza-analogue of ACBC, *N*-aminoazetidinecarboxylic acid (AAzC), would appear to be an interesting compound for continued studies (Figure 1). First, depending on the ring nitrogen atom's configuration, AAzC could be analogous to *trans*-ACBC, or to *cis*-ACBC, or perhaps be in a fluxional mode between these two limits. Furthermore, this additional backbone nitrogen might behave as a hydrogen bond acceptor, serving to stabilize secondary structure in oligomers.[4] However, the preparation of AAzC has never been previously described.

Since the first preparation of hydrazino acids in 1896 by Traube,[10] subsequently developed by Darapsky,[11] only a few methods have been established for their selective synthesis and the procedures are sometimes difficult to carry out and/or have a limited scope. A plausible synthetic precursor for a given hydrazino acid is the corresponding amino acid, although the transformation is not always straightforward.[4d,5,12] L-Azetidinecarboxylic acid is commercially available but prohibitively expensive, and the known synthetic routes to this compound involve several steps.[13] We

(1) (a) Fülöp, F. *Chem. Rev.* **2001**, *101*, 2181–2204. (b) Fülöp, F.; Martinek, T. A.; Tóth, G. K. *Chem. Soc. Rev.* **2006**, *35*, 323–334.

(2) (a) Appella, D. H.; Christianson, L. A.; Karle, I. L.; Powell, D. R.; Gellman, S. H. *J. Am. Chem. Soc.* **1996**, *118*, 13071–13072. (b) Appella, D. H.; Christianson, L. A.; Klein, D. A.; Richards, M. R.; Powell, D. R.; Gellman, S. H. *J. Am. Chem. Soc.* **1999**, *121*, 7574–7581. (c) Appella, D. H.; Christianson, L. A.; Karle, I. L.; Powell, D. R.; Gellman, S. H. *J. Am. Chem. Soc.* **1999**, *121*, 6206–6212. (d) Martinek, T. A.; Tóth, G. K.; Vass, E.; Hollósi, M.; Fülöp, F. *Angew. Chem., Int. Ed.* **2002**, *41*, 1718–1721. (e) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173–180.

(3) (a) Wang, X.; Espinosa, J. F.; Gellman, S. H. *J. Am. Chem. Soc.* **2000**, *122*, 4821–4822. (b) Porter, E. A.; Wang, X.; Schmitt, M. A.; Gellman, S. H. *Org. Lett.* **2002**, *4*, 3317–3319. (c) Schinnerl, M.; Murray, J. K.; Langenhan, J. M.; Gellman, S. H. *Eur. J. Org. Chem.* **2003**, 721–726.

(4) (a) Moquet, C.; Salaün, A.; Claudon, P; Le Grel, B.; Potel, M.; Guichard, G.; Jamart-Grégoire, B.; Le Grel, P. *J. Am. Chem. Soc.* **2009**, *131*, 14521–14525. (b) Salaün, A.; Potel, M.; Roisnel, T.; Gall, P.; Le Grel, P. *J. Org. Chem.* **2005**, *70*, 6499–6502. (c) Busnel, O.; Bi, L.; Dali, H.; Cheguillaume, A.; Chevance, S.; Bondon, A.; Muller, S.; Baudy-Floc'h, M. *J. Org. Chem.* **2005**, *70*, 10701–10708. (d) Lelais, G.; Seebach, D. *Helv. Chim. Acta* **2003**, *86*, 4152–4168. (e) Günther, R.; Hofmann, H.-J. *J. Am. Chem. Soc.* **2001**, *123*, 247–255. (f) Cheguillaume, A.; Salaün, A.; Sinbandhit, S.; Potel, M.; Gall, P.; Baudy-Floc'h, M.; Le Grel, P. *J. Org. Chem.* **2001**, *66*, 4923–4929.

(5) Hetényi, A.; Tóth, G.; Somlai, C.; Vass, E.; Martinek, T. A.; Fülöp, F. *Chem.—Eur. J.* **2009**, *15*, 10736–10741.

(6) Ortuño, R. M. In *Enantioselective Synthesis of β-Amino Acids*, 2nd ed.; Juaristi, J., Soloshonok, V. A., Eds.; Wiley: Hoboken, NJ, 2005; pp 117−137.

(7) (a) Rúa, F.; Boussert, S.; Parella, T.; Díez-Pérez, I.; Branchadell, V.; Giralt, E.; Ortuño, R. M. *Org. Lett.* **2007**, *9*, 3643–3645. (b) Torres, E.; Gorrea, E.; Burusco, K. K.; Da Silva, E.; Nolis, P.; Rúa, F.; Boussert, S.; Díez-Pérez, I.; Dannenberg, S.; Izquierdo, S.; Giralt, E.; Jaime, C.; Branchadell, V.; Ortuño, R. M. *Org. Biomol. Chem.* **2010**, *8*, 564–575.

(8) Torres, E.; Gorrea, E.; Da Silva, E.; Nolis, P.; Branchadell, V.; Ortuño, R. M. *Org. Lett.* **2009**, *11*, 2301–2304.

(9) Fernandes, C.; Faure, S.; Pereira, E.; Théry, V.; Declerck, V.; Guillot, R.; Aitken, D. J. *Org. Lett.* **2010**, *12*, 3606–3609.

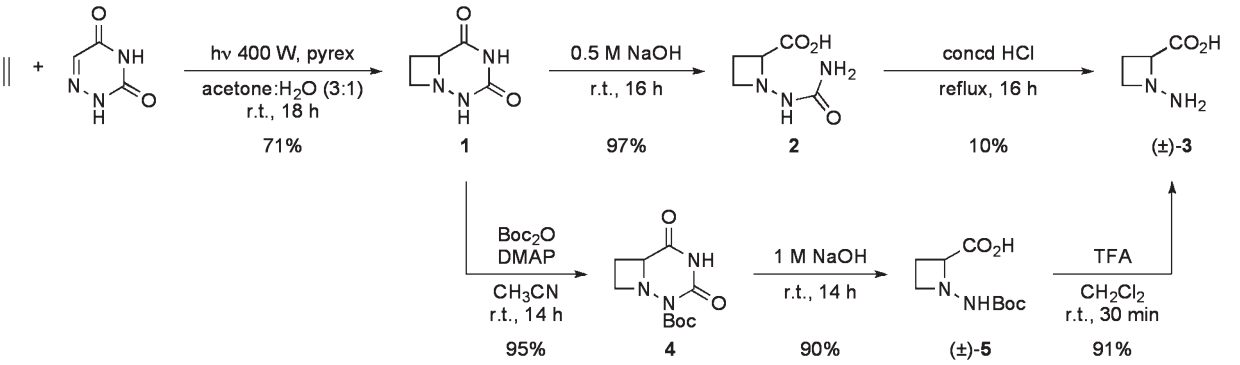
(10) Traube, W.; Longinescu, G. G. *Chem. Ber* **1896**, *29*, 670–675.

(11) Darapsky, A. *J. Prakt. Chem.* **1936**, *296*, 268–306.

(12) For examples of different strategies, see: (a) De Luca, L.; Falorni, M.; Giacomelli, G.; Porcheddu, A. *Tetrahedron Lett.* **1999**, *40*, 8701–8704. (b) Vidal, J.; Damestoy, S.; Guy, L.; Hannachi, J.-C.; Aubry, A.; Collet, A. *Chem.—Eur. J.* **1997**, *3*, 1691–1709. (c) Viret, J.; Gabard, J.; Collet, A. *Tetrahedron* **1987**, *43*, 891–894. (d) Achiwa, K.; Yamada, S. *Tetrahedron Lett.* **1975**, *16*, 2701–2704.

Published on Web 12/23/2010 DOI: 10.1021/jo102108t

SCHEME 1. Racemic Synthesis

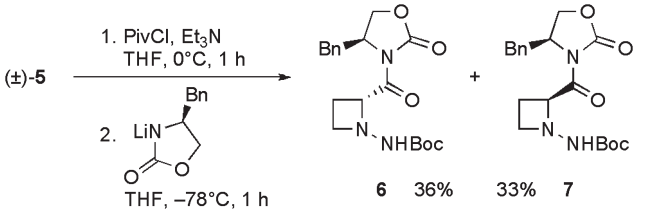


wished to investigate an intriguing alternative approach leading directly to AAzC, employing a photochemical [2 + 2] cycloaddition reaction to create the 4-membered ring. We have previously found this strategy fruitful for the elaboration of cyclobutane β-amino acids starting from uracil,[14] and although imines are not generally considered to be good partners in [2 + 2] photocycloadditions, there were sufficient precedents involving nitogen heterocycles[15] for us to investigate this approach.

A solution of commercially available 6-azauracil in an acetone/water mixture (3:1) was irradiated with a 400 W medium pressure Hg lamp fitted with a pyrex filter while ethylene was bubbled slowly through the mixture. After 18 h, the [2 + 2] cycloadduct **1** was isolated in 71% yield (Scheme 1). Straightforward treatment of **1** with 0.5 M aqueous NaOH provided the semicarbazide acid **2** in 97% yield. Hydrolysis of a semicarbazide moiety generally requires treatment with acidic or basic media in rather drastic conditions. Our attempts to perform this transformation on **2** in various conditions (1 M NaOH, 50 °C, 16 h; concd HCl, reflux, 16 h; 3 M H_2SO_4, reflux, 16 h) resulted in extensive degradation; at best the hydrazino acid (±)-**3** was isolated in only 10% yield. Attempts to perform the hydrolysis directly on the cycloadduct **1** gave similarly disappointing results. To circumvent this problem, we sought to improve the leaving group character of the semicarbazide moiety. Treatment of the cycloadduct **1** with 1 equiv of Boc_2O in the presence of DMAP allowed the selective introduction of a Boc group at the N1 position, furnishing derivative **4** in 95% yield. Gratifyingly, smooth cleavage of the heterocyclic ring ensued when compound **4** was treated with 1 M aqueous NaOH, giving 90% of the Boc-protected hydrazino acid (±)-**5**. The Boc group was removed with TFA to give the target *N*-aminoazetidine carboxylic acid (±)-**3** in 91% yield.

Having established this expedient synthesis of racemic *N*-aminoazetidine carboxylic acid (±)-**3**, we embarked on its chiral resolution. Esters of (±)-**5** were prepared by using a selection of chiral alcohols (menthol, borneol, *N*-methylephedrine) but the diastereomeric separation could not be achieved by either crystallization or chromatography. It was previously noted that the resolution of *cis*-ACBC could be achieved via amide formation with nonracemic α-phenylethylamine or α-(*p*-methoxyphenyl)ethylamine.[16] However, condensation of either of these reagents with (±)-**5** gave diastereomeric amide mixtures which were very difficult to separate. Noting a previous successful resolution by Evans,[17] we decided to use a chiral oxazolidinone for the resolution of (±)-**5**. Best results were obtained with pivaloyl chloride to activate the carboxylic acid of (±)-**5** as its *tert*-butyl anhydride, which reacted with the lithium salt of (*S*)-benzyloxazolidin-2-one to provide a mixture of the two diastereoisomers **6** and **7**. These derivatives were easily separated by chromatography and isolated in 36% and 33% yields, respectively (Scheme 2).

SCHEME 2. Chiral Resolution Using (*S*)-Benzyloxazolidin-2-one



One significant advantage of using an oxazolidine as a chiral derivatizing agent is its facile removal, and the treatment of each compound **6** and **7** with LiOOH in aqueous THF allowed smooth and efficient cleavage of the oxazolidinone auxiliary to furnish the two enantiomercially pure Boc-hydrazino acids (+)-**5** and (−)-**5** in quantitative yields. Furthermore, the oxazolidinone was recovered and could be reused in subsequent resolution operations (Scheme 3). TFA-mediated Boc group removal from (+)-**5** and (−)-**5** produced (+)-**3** and (−)-**3**, respectively, in high yields.

(13) For a recent review, see: Couty, F.; Evano, G. *Org. Prep. Proced. Int.* **2006**, *38*, 427–465. For a very recent synthesis, see: Bouazaoui, M.; Martinez, J.; Cavelier, F. *Eur. J. Org. Chem.* **2009**, 2729–2732.

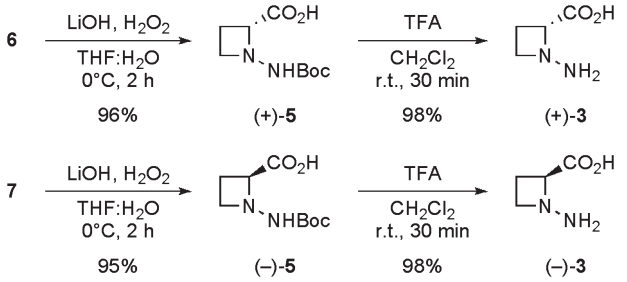
(14) (a) Mondière, A.; Peng, R.; Remuson, R.; Aitken, D. J. *Tetrahedron* **2008**, *64*, 1088–1093. (b) Fernandes, C.; Gauzy, C.; Yang, Y.; Roy, O.; Pereira, E.; Faure, S.; Aitken, D. J. *Synthesis* **2007**, 2222–2232. (c) Gauzy, C.; Saby, B.; Pereira, E.; Faure, S.; Aitken, D. J. *Synlett* **2006**, 1394–1398. (d) Roy, O.; Faure, S.; Aitken, D. J. *Tetrahedron Lett.* **2006**, *47*, 5981–5984. (e) Gauzy, C.; Pereira, E.; Faure, S.; Aitken, D. J. *Tetrahedron Lett.* **2004**, *45*, 7095–7097. (f) Aitken, D. J.; Gauzy, C.; Pereira, E. *Tetrahedron Lett.* **2002**, *43*, 6177–6179.

(15) For a comprehensive review of [2 + 2] cycloadditions which includes reactions leading to ring-fused azetidines, see: Crimmins, M. T.; Reinhold, T. L. In *Organic Reactions*; Paquette, L. A., Ed.; John Wiley & Sons, Inc.: New York, 1993; Vol. 44, pp 297−588.

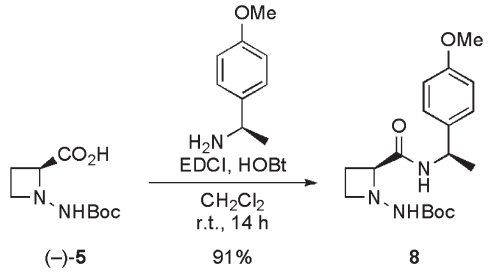
(16) Fernandes, C.; Pereira, E.; Faure, S.; Aitken, D. J. *J. Org. Chem.* **2009**, *74*, 3217–3220.

(17) Evans, D. A.; Britton, T. C.; Dorow, R. L.; Dellaria, J. F., Jr. *Tetrahedron* **1988**, *44*, 5525–5540.

SCHEME 3. Access to Single Enantiomers



SCHEME 4. Amide Formation



The absolute configuration of these new compounds was deduced by single crystal X-ray analysis of the amide **8**, which was obtained by condensation of (−)-**5** with (*R*)-α-(*p*-methoxyphenyl)ethylamine (Scheme 4). The X-ray structure (Figure 2) indicated an *S* configuration for compound (−)-**5**.

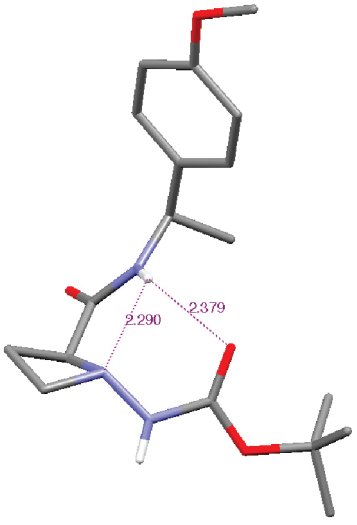


FIGURE 2. X-ray structure of compound **8**.

Further examination of the crystal structure revealed a configurational preference of the ring nitrogen which gives a trans-like relative configuration, and a dihedral angle ($N^{\beta}-N^{\alpha}$)−($C^{\alpha}-CO$) of 96.3° which is close to the value observed for (N−C^{β})−($C^{\alpha}-CO$) in the octamer of *trans*-ACBC.[9] The solid state structure also featured an 8-membered hydrogen-bonded ring, involving the amide NH and the carbamate CO (with a C═O···H—N distance of 2.38 Å) that was further stabilized by the hydrogen donor character of the ring nitrogen atom with a $N^{\alpha}\cdots$H—N distance of 2.29 Å; a "hydrazino turn" was thus clearly in evidence.[4a,b,f,18]

In summary, we have established a very short and efficient synthesis of the previously unknown *N*-aminoazetidinecarboxylic acid **3** using a [2 + 2] photocycloaddition strategy, which obviates the intermediacy of azetidinecarboxylic acid. Both enantiomers have been prepared by using a resolution procedure that employs a chiral oxazolidinone and combines easy separation with smooth cleavage and recycling of the resolving agent. A first indication of the noncovalent bond forming propensity of **3** is suggested by its adoption of a trans relative configuration, so that the ring nitrogen may contribute to the stabilization of a "hydrazino turn". The title compound should have some significant structuring potential in mixed peptides with β-amino acids or in other aza-β-peptides.

Experimental Section

1,2,4-Triazabicylo[4.2.0]octane-3,5-dione, 1. A solution of 6-azauracil (2.83 g, 25.0 mmol) in a 1:3 mixture of water and acetone (1 L) placed in a cylindrical reactor was degassed with an argon stream for 30 min, and then saturated with ethylene for 30 min. The solution was then irradiated for 18 h with a 400 W medium-pressure mercury lamp fitted with a Pyrex filter and a water-cooling jacket while ethylene was bubbled through. The solution was then evaporated under reduced pressure. Flash chromatography of the residue (CH_2Cl_2/MeOH = 98/2) gave a yellow solid that was washed with a minimum amount of cold MeOH to leave the cycloadduct **1** (2.49 g, 71%) as a white solid. Mp 183 °C dec; R_f 0.31 (AcOEt); IR (KBr) ν 3236, 3045, 1713, 1699; ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.90 (ddt, 1H, J_2 = 10.8 Hz, J_3 = 8.5 Hz, J_3 = 2.3 Hz), 2.39 (tt, 1H, J_2 = 10.5 Hz, J_3 = 8.2 Hz), 3.54 (tt, 1H, J_3 = 7.4 Hz, J_3 = 2.1 Hz), 3.58−3.67 (m, 1H), 4.12 (d, 1H, J_3 = 8.1 Hz), 9.02 (s, 1H), 10.58 (s, 1H); ^{13}C NMR (90 MHz, DMSO-d_6) δ 20.6, 58.8, 61.5, 152.4, 172.8; HRMS (ESI+) calcd for $C_5H_7N_3NaO_2$ $[M + Na]^+$ 164.0436, found 164.0429.

1-(*tert*-Butyloxycarbonyl)-1,2,4-triazabicylo[4.2.0]octane-3,5-dione, 4. To a suspension of cycloadduct **1** (2.15 g, 15.2 mmol, 1 equiv) in CH_3CN (90 mL) was added Boc_2O (3.32 g, 15.2 mmol, 1 equiv) and DMAP (18.6 mg, 0.15 mmol, 0.01 equiv). The mixture was stirred for 14 h at room temperature, then the solvent was evaporated under reduced pressure. Flash chromatography of the residue (AcOEt/*c*-C_6H_{12} = 30/70) gave the bicyclic compound **4** (3.49 g, 95%) as a white solid. Mp 152 °C dec; R_f 0.45 (AcOEt/*c*-C_6H_{12} = 50/50); IR (KBr) ν 3160, 3101, 3003, 1746, 1695; ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.54 (s, 9H), 2.11−2.20 (m, 1H), 2.64−2.76 (m, 1H), 3.81−3.96 (m, 2H), 4.41−4.46 (m, 1H), 8.14 (br s, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 21.7, 28.0, 58.7, 64.7, 84.9, 148.1, 150.3, 171.9; HRMS (ESI+) calcd for $C_{10}H_{15}N_3NaO_4$ $[M + Na]^+$ 264.0953, found 264.0955.

1-(*tert*-Butyloxycarbonylamino)azetidine-2-carboxylic Acid, (±)-5. Bicyclic compound **4** (2.47 g, 10.2 mmol) was treated with a 1 M aqueous NaOH solution (100 mL). The mixture was stirred for 14 h at room temperature, then was cooled to 0 °C and acidified with concentrated HCl to pH 2. The mixture was extracted with AcOEt (5 × 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and evaporated under reduced pressure to give the Boc-hydrazino acid (±)-**5** (2.00 g, 90%) as a white solid. Mp 135 °C dec; IR (KBr) ν 3231, 2982, 1733, 1647, 1533; ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.44 (s, 9H), 2.06−2.20 (m, 1H), 2.32−2.44 (m, 1H), 3.52−3.64 (m, 1H), 3.65−3.73 (m, 1H), 4.24 (t, 1H, J_3 = 8.9 Hz), 6.54 (br s, 1H),

(18) (a) Salaün, A.; Favre, A.; Le Grel, B.; Potel, M.; Le Grel, P. *J. Org. Chem.* **2006**, *71*, 150–158. (b) Zerkout, S.; Dupont, V.; Aubry, A.; Vidal, J.; Collet, A.; Vicherat, A.; Marraud, M. *Int. J. Pept. Protein Res.* **1994**, *44*, 378–387. (c) Aubry, A.; Mangeot, J.-P.; Vidal, J.; Collet, A.; Zerkout, S.; Maraud, M. *Int. J. Pept. Protein Res.* **1994**, *43*, 305–311. (d) Marraud, M.; Dupont, V.; Grand, V.; Zerkout, S.; Lelocq, A.; Boussard, G.; Vidal, J.; Collet, A.; Aubry, A. *Biopolymers* **1993**, *33*, 1135–1148. (e) Aubry, A.; Bayeul, D.; Mangeot, J.-P.; Vidal, J.; Sterin, S.; Collet, A.; Lecoq, A.; Marraud, M. *Biopolymers* **1991**, *31*, 793–801.

10.65 (br s, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 19.4, 28.3, 53.7, 69.7, 82.4, 156.6, 173.4; HRMS (ESI−) calcd for $C_9H_{15}N_2O_4$ $[M - H]^-$ 215.1037, found 215.1047. Anal. Calcd for $C_9H_{16}N_2O_4$: C, 49.99; H, 7.46; N, 12.96. Found: C, 49.88; H, 7.44; N, 12.75.

Chiral Derivatization with (*S*)-4-Benzyloxazolidin-2-one. To a cold (−78 °C) solution of Boc-hydrazino acid (±)-**5** (1.90 g, 8.8 mmol, 1 equiv) and Et_3N (1.47 mL, 10.5 mmol, 1.2 equiv) in dry THF (18 mL) was added dropwise pivaloyl chloride (1.13 mL, 9.2 mmol, 1.05 equiv). The mixture was stirred for 1 h at 0 °C to form the mixed anhydride, then cooled to −78 °C. In a separate flask, a cold (ca. −40 °C) solution of (*S*)-4-benzyl-1,3-oxazolidin-2-one (1.55 g, 8.8 mmol, 1 equiv) in THF (18 mL) was treated with *n*-BuLi (1.6 M solution in hexanes, 5.48 mL, 8.8 mmol, 1 equiv) and stirred for 5 min. The resulting solution was added by rapid cannulation to the cooled (−78 °C) solution of the mixed anhydride. Residual metalated oxazolidinone was taken up by rinsing with dry THF (2 × 9 mL), and added to the cooled reaction mixture; this latter was stirred for 1 h at −78 °C. After warming to 0 °C, the mixture was diluted with CH_2Cl_2 (40 mL) and saturated $NaHCO_3$ (20 mL). The organic phase was collected and the aqueous phase was extracted with CH_2Cl_2 (4 × 15 mL). The combined organic phases were washed successively with saturated $NaHCO_3$ (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Flash chromatography of the residue (Et_2O/petroleum ether = 75/25) gave the diastereoisomers **6** (1.18 g, 36%) and **7** (1.09 g, 33%) as white solids. **(*S*)-4-Benzyl-3-((*R*)-*N*-*tert*-butyloxycarbonylaminoazetidine-2-carboxyl)oxazolidin-2-one, 6:** mp 55 °C dec; R_f 0.75 (Et_2O); $[\alpha]^{25}_D$ +146 (*c* 0.50, $CHCl_3$); IR (film) ν 3385, 3316, 2979, 1785, 1705, 1518, 1386, 1368; ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.46 (s, 9H), 2.06−2.17 (m, 1H), 2.44−2.55 (m, 1H), 2.85 (dd, 1H, J_2 = 13.4 Hz, J_3 = 9.3 Hz), 3.30 (dd, 1H, J_2 = 13.4 Hz, J_3 = 2.6 Hz), 3.61−3.68 (m, 1H), 4.02 (dt, 1H, J_3 = 6.1 Hz, J_3 = 8.4 Hz), 4.17−4.23 (m, 1H), 4.23−4.31 (m, 1H), 4.65−4.74 (m, 1H), 5.56 (t, 1H, J_3 = 8.3 Hz), 6.59 (br s, 1H), 7.18−7.37 (m, 5H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 19.3, 28.4, 37.8, 53.8, 55.0, 67.0, 67.8, 80.5, 127.4, 129.0, 129.5, 135.1, 153.0, 154.9, 171.8; HRMS (ESI+) calcd for $C_{19}H_{25}N_3NaO_5$ $[M + Na]^+$ 398.1686, found 398.1666. **(*S*)-4-Benzyl-3-((*S*)-*N*-*tert*-butyloxycarbonylaminoazetidine-2-carboxyl)oxazolidin-2-one, 7:** mp 50 °C dec; R_f 0.33 (Et_2O); $[\alpha]^{25}_D$ −49 (*c* 0.50, $CHCl_3$); IR (neat) ν 3387, 3307, 2978, 1785, 1702, 1518, 1386, 1368; ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.49 (s, 9H), 2.03−2.15 (m, 1H), 2.39−2.51 (m, 1H), 2.82 (dd, 1H, J_2 = 13.5 Hz, J_3 = 9.6 Hz), 3.37 (dd, 1H, J_2 = 13.5 Hz, J_3 = 3.2 Hz), 3.59−3.67 (m, 1H), 4.02 (dt, 1H, J_3 = 6.3 Hz, J_3 = 8.3 Hz), 4.16−4.29 (m, 2H), 4.63−4.72 (m, 1H), 5.60 (t, 1H, J_3 = 8.2 Hz), 6.58 (br s, 1H), 7.18−7.37 (m, 5H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 19.2, 28.5, 37.7, 53.7, 55.1, 67.0, 67.7, 80.6, 127.4, 129.0, 129.5, 135.3, 152.9, 155.0, 171.9; HRMS (ESI+) calcd for $C_{19}H_{25}N_3NaO_5$ $[M + Na]^+$ 398.1686, found 398.1674.

(*R*)-(1-*tert*-Butyloxycarbonylamino)azetidine-2-carboxylic Acid, (+)-5. Caution: The use of hydrogen peroxide in THF presents a possible risk of peroxide formation; appropriate hazard precautions should be taken. To an ice-cold solution of compound **6** (1.17 g, 3.1 mmol, 1 equiv) in a 1:4 mixture of water and THF (78 mL) was added a 35% w/w solution of H_2O_2 (1.6 mL, 18.7 mmol, 6 equiv). The resulting mixture was stirred for 5 min at 0 °C then a solution of LiOH (149 mg, 6.2 mmol, 2 equiv) in water (18 mL) was added. The mixture was stirred for 2 h at 0 °C, then 1 M Na_2SO_3 (40 mL) and saturated $NaHCO_3$ (40 mL) were added successively. THF was removed under reduced pressure and the aqueous residue was washed with CH_2Cl_2 (3×40 mL) to remove the chiral auxiliary. The aqueous phase was acidified to pH 1 with concentrated HCl and extracted with CH_2Cl_2 (4 × 40 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and evaporated under reduced pressure to give the Boc-hydrazino acid (+)-**5** (647 mg, 96%) as a white solid. Mp 130 °C dec; $[\alpha]^{21}_D$ +22 (*c* 0.50, $CHCl_3$). Spectral data were as for (±)-**5**.

(*S*)-(1-*tert*-Butyloxycarbonylamino)azetidine-2-carboxylic Acid, (−)-5. The above procedure was repeated starting from compound **7** (1.06 g, 2.8 mmol) to give the Boc-hydrazino acid (−)-**5** (580 mg, 95%) as a white solid. Mp 130 °C dec; $[\alpha]^{21}_D$ −22 (*c* 0.51, $CHCl_3$). Spectral data were as for (±)-**5**.

(*R*)-1-Aminoazetidine-2-carboxylic Acid, (+)-3. TFA (1.15 mL) was added dropwise to a solution of Boc-hydrazino acid (+)-**5** (108 mg, 0.5 mmol) in CH_2Cl_2 (3.5 mL). The mixture was stirred for 30 min at room temperature then the solvent was evaporated under reduced pressure. The residue was taken up in water and the resulting solution was deposited on a cation-exchange column (Dowex 50X8W, H^+, 50−100 mesh). The column was washed with H_2O until the eluent was neutral, and the product was then eluted with 1 M NH_4OH. Evaporation (T < 25 °C) of appropriate fractions gave the hydrazino acid (+)-**3** (57 mg, 98%) as a white solid. Mp 74 °C dec; $[\alpha]^{23}_D$ +138 (*c* 0.50, H_2O); IR (KBr) ν 3429, 1622, 1416, 1312; ^{1}H NMR (360 MHz, D_2O) δ 2.22−2.36 (m, 1H), 2.53−2.65 (m, 1H), 3.70−3.81 (m, 1H), 3.93−4.04 (m, 1H), 4.40−4.50 (m, 1H); ^{13}C NMR (90 MHz, D_2O) δ 19.2, 54.8, 72.3, 175.1; HRMS (ESI−) calcd for $C_4H_7N_2O_2$ $[M - H]^-$ 115.0513, found 115.0511.

(*S*)-1-Aminoazetidine-2-carboxylic Acid, (−)-3. The above procedure was repeated starting from Boc-hydrazino acid (−)-**5** (108 mg, 0.5 mmol) to give the hydrazino acid (−)-**3** (57 mg, 98%) as a white solid. Mp 73 °C dec; $[\alpha]^{23}_D$ −138 (*c* 0.50, H_2O). Spectral data were as for (+)-**3**.

Acknowledgment. We are grateful to Dr. Régis Guillot (ICMMO) for the X-ray diffraction analysis of compound **8**.

Supporting Information Available: Experimental details, spectral data, copies of ^{1}H and ^{13}C NMR spectra for all new compounds, X-ray structure, and crystal data for compound **8** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.