Enantioselective Synthesis of α,α-Disubstituted Amino Acid Derivatives *via* Enzymatic Resolution: Preparation of a Thiazolyl-Substituted α-Methyl α-Benzyl Amine

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A new and efficient enantioselective synthesis of the (*S*)-α,α-disubstituted phenethylamine **1** *via* Lipase resolution of the esters **3** and **4** is described. The effect of pH, enzyme load, and solubilizing additives has been studied and optimized. Conversion of the carboxylic acid **10** to the desired thiazole **1** is accomplished in high overall yield *via* an intermediate oxazolinone **13**. This facile process requires only a single chromatographic step, and multigram quantities of **1** have been prepared.

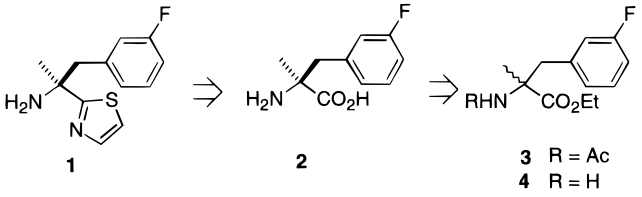
Introduction

The synthesis of α,α-disubstituted amino acids is of considerable importance since these compounds are useful intermediates for the construction of biologically active pharmaceuticals.[1] In recent years, a number of synthetic methods have been developed for this class of compounds utilizing approaches based on the self-reproduction of chirality,[2] the Strecker reaction,[3] and enzymatic resolutions.[4] We have been interested in developing an efficient, enantioselective synthesis of the (*S*)-α-methyl amine **1**. In a retrosynthetic analysis of the molecule, we envisioned that the thiazole could be derived from the α-methyl amino acid **2**. Herein, we report the synthesis of **2** in high enantiomeric excess *via* an enzymatic resolution of **3** or **4**, and we will detail a process for converting the resolved carboxylic acid **2** to the desired thiazole **1** in high yield (Scheme 1).

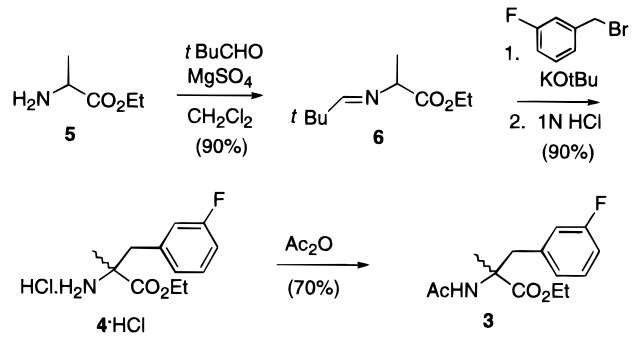
Results and Discussion

The use of enzymes to carry out asymmetric transformations in organic synthesis has many advantages. Enzymes are highly selective catalysts and provide products of high enantiomeric purity. The reaction conditions are mild (room temperature or gentle warming of the reaction mixture is typical), and the waste products of the reaction are environmentally acceptable. With these considerations in mind, our approach to the synthesis of the chiral thiazole precursor **2** is based on a lipase resolution of the racemic esters **3** and **4**.

Scheme 1



Scheme 2



The synthesis of the racemic esters **3** and **4** is outlined in Scheme 2. The ethyl ester of alanine was condensed with trimethylacetaldehyde to afford the Schiff base **6**. Alkylation with *m*-fluorobenzyl bromide and KO-*t*-Bu followed by hydrolysis of the imine with 1 N HCl afforded the amino ester **4**·HCl in high yield. Conversion to the amide **3** was accomplished with Ac_2O. This procedure is amenable to scale up, and we have prepared 100 g quantities of **3** using this sequence.

The lipase resolution of α-methyl α-benzyl amino esters has been reported by Walts and co-workers.[4a] In this work, 250% by weight of *Candida lipolytica* esterase is used in pH 7.5 phosphate buffer to resolve amino esters containing unsubstituted or hydroxy- or methoxy-substituted benzyl groups. No report was made of the enzyme accepting a halogenated benzyl group. Therefore, we began by subjecting our fluorobenzyl-substituted amino ester **4** to the enzymatic hydrolysis.

Our initial conditions for the resolution of the amino ester **4** were to use 200% by weight of Lipase L[5] in pH 7.4 phosphate buffer. The progress of the reaction was

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(1) For reviews see: (a) Jung, M. J. *Chemistry and Biochemistry of the Amino Acids*; Barrett, G. C., Ed.; Chapman and Hall: New York, 1985; p 227. (b) α-*Amino Acid Synthesis*; O'Donnell, M. J., Ed.; Tetrahedron Symposium-in-Print; Pergamon: London, 1988; Vol. 44, Issue 17. (c) Williams, R. W. *Synthesis of Optically Active* α-*Amino Acids*; Pergamon: Oxford, 1989.

(2) (a) Schollkopf, U.; Hausberg, H. H.; Hoppe, I.; Segal, M.; Reiter, U. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*(2), 117. (b) Seebach, D.; Fadel, A. *Helv. Chim. Acta* **1985**, *68*, 1243. (c) Fitzi, R.; Seebach, D. *Tetrahedron* **1988**, *44*(17), 5227. (d) Karady, S.; Amato, J. S.; Weinstock, L. M. *Tetrahedron Lett.* **1984**, *25*(39), 4337. (e) Zydowsky, T. M.; de Lara, E.; Spanton, S. G. *J. Org. Chem.* **1990**, *55*, 5437. (f) Cheng, H.; Keitz, P.; Jones, B. J. *J. Org. Chem.* **1994**, *59*, 7671. (g) Davies, S. G.; Alonso, F. *Tetrahedron Assymetry* **1995**, *6*(2), 353.

(3) Subramanian, P. K.; Woodard, R. W. *Synth. Commun.* **1986**, *16*(3), 337.

(4) (a) Yee, C.; Blythe, T. A.; McNabb, T. J.; Walts, A. E. *J. Org. Chem.* **1992**, *57*, 3525. (b) Liu, W.; Ray, P.; Benezra, S. A. *J. Chem. Soc., Perkin Trans. 1* **1995**, 553.

(5) Lipase L was purchased from Amano.

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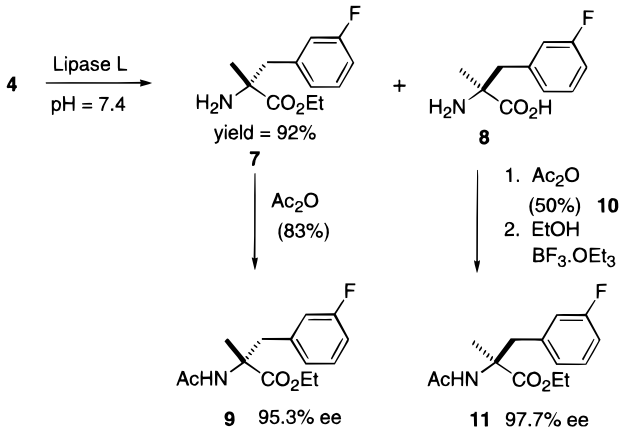
monitored by HPLC,[6] and 50% hydrolysis was achieved after 20 h. The *S* enantiomer was hydrolyzed to the acid, and the *R* enantiomer remained as the ester.[7] The amino ester **7** could easily be extracted out of the reaction mixture in 92% yield. However, the amino acid **8** was difficult to isolate and was acetylated first to aid its isolation. By this method, the best chemical yield of the acetylated amino acid **11** was 50%. To determine the ee of **7** and **8**, each enantiomer was converted to its corresponding acetylated amino ester, compounds **9** and **11**, respectively (Scheme 3). Enantiomeric excess determination was carried out by HPLC using a chiralpak AD column:[8] the ee of the *R* enantiomer **9** was determined to be 95.3%, the *S* enantiomer **11** 97.7% (Scheme 3).

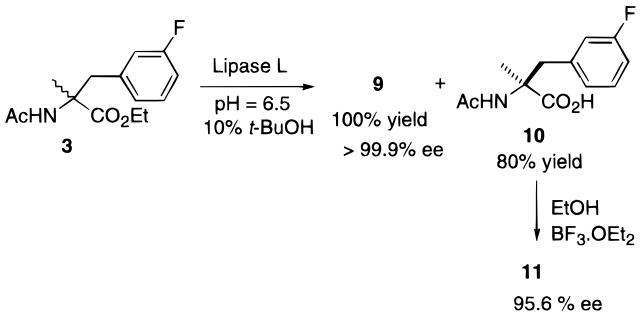
Scheme 3



To optimize the resolution shown in Scheme 3, the effect of the weight percent of enzyme and the effect of pH was studied. It was observed that the use of 50% by weight of the enzyme was sufficient to afford 50% hydrolysis of the amino ester **4** after 64 h. The use of less enzyme, 25% and 10%, afforded only 30% and 24% hydrolysis, respectively, after 64 h. Using 50% by weight of enzyme, we next determined the optimum pH for the reaction and varied the pH from 4 to 7. We observed that the reaction is fastest in the pH range of 5.5−6.5, which is lower than the one typically used in literature procedures for lipase hydrolysis.[9] Our optimum conditions for this hydrolysis were to carry out the reaction at pH = 6 using 50% by weight of Lipase L, and we observed 50% conversion in 24 h.

Due to the modest yield obtained in the isolation of the amino acid **8**, we have developed an alternative resolution of the *N*-acetylated amino ester **3**. This route directly provides an *N*-acetylated amino acid **10** that is easier to isolate from the reaction mixture. Again, we studied the effect of pH, enzyme concentration, and additives on the rate of hydrolysis. We found that the optimum pH for this hydroylysis is 6.5 and also observed that this reaction is quite slow (6 days) and requires 100% by weight of enzyme to obtain reasonable reaction rates. Also, the substrate **3** is not soluble in phosphate buffer, and a number of additives were investigated to increase the solublity and the rate of reaction. After the mixture was stirred for 6 days with no additive, there was essentially no hydrolysis. However, with the addition of Triton X-100, *t*-BuOH, or acetone, 50%, 45%, and 41% hydrolysis occurred, respectively. Although Triton X-100 gave good results, we were unable to extract the product out of the reaction mixture and therefore selected *t*-BuOH as the additive of choice (Scheme 4).

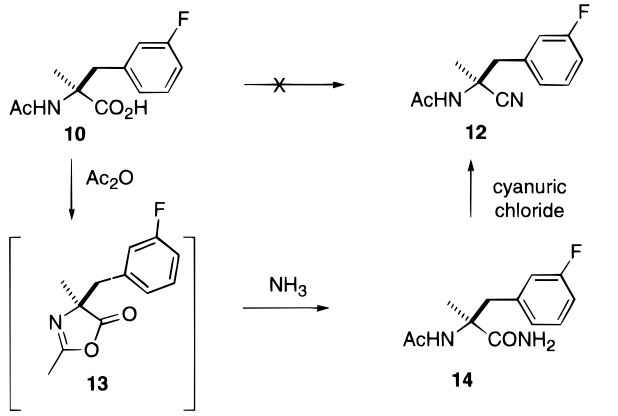
Scheme 4



The ee of the *R* ester **9** was determined to be 96.6%, and the ee of compound **11,** after conversion to its ethyl ester, was 96.8%. The advantage of carrying out the lipase resolution on the *N*-acetyl ester **3** is shown in the isolated yields, because the chemical yield of the acid **10** is 80% as opposed to 50% by the earlier procedure. We have used this procedure to resolve 40 g quantities of the racemic ester **3**.

With the desired *S* enantiomer **10** in hand, we next needed to convert the carboxylic acid to the corresponding thiazole. The initial approach was to convert the carboxylic acid first to a nitrile and then to a thioamide, followed by conversion to the thiazole. We had shown in related systems that sulfur nucleophiles could easily be added to the nitriles to form thioamides. Attempted conversion of the carboxylic acid **10** to the nitrile **12** using $SOCl_2$ and sulfamide failed; in addition, treatment with $ClSO_2NCO$ and triethylamine gave none of the desired product **12** but only the oxazolinone **13**. In fact, oxazolinone formation was quite facile under a variety of reaction conditions presumably due to a gem dimethyl effect.[10] Since the direct formation of the nitrile **12** from the carboxylic acid **10** was problematic, we added one step to the synthesis by going through the amide **14** (Scheme 5). Our initial attempts to form the amide **14** from the

Scheme 5



carboxylic acid **10** involved treatment of the acid with

(6) Nucleosil C18 reversed-phase column. Eluant = 1:1 acetonitrile/water with 1% TFA.

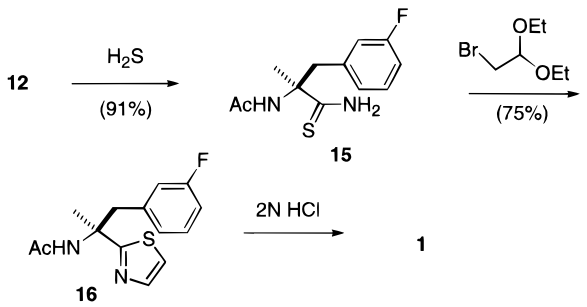
(7) Absolute configurations were determined by X-ray analysis of the final thiazolyl compounds.

(8) Chiralpak AD column: eluant = 95:5 hexane/EtOH and 0.5% Et_2NH.

(9) *Preparative Biotransformations*; Roberts, S. M., Wiggins, K., Casy, G., Eds.; Wiley: University of Exeter, Exeter, U.K., 1992; Chapter 1.

(10) Kirby, A. J. *Adv. Phys. Org. Chem.* **1980**, *17*, 183.

Scheme 6



$SOCl_2$ and NH_3 or ethyl chloroformate in the presence of TEA and NH_3, but only oxazolinone **13** was obtained. The oxazolinone **13** was turned into a useful intermediate by treating it directly with NH_3 to obtain the desired amide **14**. On the basis of this result, our final scheme was therefore to form the oxazolinone by treatment of the (*S*)-*N*-acetyl carboxylic acid **10** with acetic anhydride and then, without purification, to take the cyclized product directly on to the amide **14** by treatment with NH_3. Finally, again without purification, the amide **14** was treated with cyanuric chloride to afford the desired nitrile **12** in 83% yield for the three steps. The nitrile **12** was easily converted to the thioamide **15** in high yield with H_2S, and then thiazole formation was accomplished by reaction with bromoacetaldehyde diethyl acetal to afford **16**. The final step of the sequence, removal of the acetyl protecting group, was achieved by refluxing the substrate **16** with 2 N HCl to obtain the desired target compound **1** (Scheme 6). The conversion of the (*S*)-amino acid **10** derivative to the final product **1**[11] was accomplished in 46% overall yield, and only one chromatographic step[12] was required. In conclusion, we have demonstrated the ability of the Lipase-L to accept fluorinated substrates and provided optimized conditions of enzyme load and pH for this resolution. In addition, we have detailed a procedure that allows the isolation of the carboxylic acid product from the reaction mixture in a facile manner. We have also provided conditions for the efficient conversion of the carboxylic acid moiety to the corresponding thiazole in high overall yield.

Experimental Section

General Procedures. Proton and ^{13}C NMR spectra were measured at 270 MHz using TMS as the standard. The commercial chemicals were used as received without further purification, and all solvents were dried by standard methods prior to use. Column chromatography was carried out on silica gel 60 (E. Merck, 230−400 mesh). Melting points are uncorrected.

***N*-Neopentyliden-D,L-alanine Ethyl Ester (6).** A solution of D,L-alanine ethyl ester·HCl (101.6 g, 0.662 mol) in 400 mL of water was treated with triethylamine (97 mL, 0.69 mol) at room temperature. After being stirred for 0.5 h, the reaction mixture was extracted with CH_2Cl_2 (600 mL), dried over anhydrous Na_2SO_4, and concentrated to give the D,L-alanine ethyl ester (free base) as a colorless oil (70.35 g).

To a solution of D,L-alanine ethyl ester (from above) in 700 mL of CH_2Cl_2 at 0 °C was added anhydrous $MgSO_4$ (80 g) followed by trimethylacetaldehyde (66.25 mL, 0.61 mol). After the reaction mixture was stirred for 20 h at room temperature, $MgSO_4$ was filtered and the filtrate was washed with water, dried, and concentrated under reduced pressure to give the product **6** (100 g, 90%). ^1H NMR ($CDCl_3$) δ 1.07 (s, 9H), 1.24 (t, 3H, J = 7.0 Hz), 1.38 (d, 3H, J = 6.7 Hz), 3.83 (q, 1H, J = 6.7 Hz), 4.15 (q, 2H, J = 7.0 Hz), 7.55 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.9, 19.0, 26.5, 36.1, 60.6, 67.4, 172.5 and 173.9.

(±)-2-Amino-2-methyl-3-(3-fluorophenyl)propionic Acid Ethyl Ester Hydrochloride (4·HCl). A solution of imine **6** (100 g, 0.54 mol) and 3-fluorobenzyl bromide (72.40 mL, 0.59 mol) in toluene (750 mL) was cooled to −10 °C. To this stirring solution was added potassium *tert*-butoxide (1 M/THF, 650 mL, 0.65 mol) at such a rate that the internal temperature remained below −3 °C. After being stirred at this temperature for 2 h, the reaction mixture was diluted with ether, washed with water, dried, and concentrated to give a yellow oil. It was stirred with 1 N HCl (720 mL) at room temperature for 48 h. The reaction mixture was evaporated to dryness under reduced pressure to give the crude hydrochloride, which was purified by crystallization from reagent alcohol/ether to give a colorless crystalline solid **4**·HCl (131 g, 93%): mp 82−84 °C; ^1H NMR (DMSO) δ 1.22 (t, 3H, J = 7.0 Hz), 1.53 (s, 3H) 3.20 (s, 2H), 4.20 (q, 2H, J = 7.0 Hz), 7.03−7.20 (m, 3H), 7.40 (m, 1H) 8.72 (bs, 3H); ^{13}C NMR (DMSO) δ 18.85, 26.68, 46.58, 64.75, 67.12, 119.41 (J = 20.85 Hz), 122.22 (J = 21.9 Hz), 131.37, 135.44 (J = 8.4 Hz), 141.35 (J = 7.8 Hz), 167.22 (J = 250 Hz) and 175.31; HRMS calcd for $C_{12}H_{16}FNO_2$ 226.1243, found 226.1253.

Enzymatic Resolution of (4·HCl): (*R*)-2-Amino-2-methyl-3-(3-fluorophenyl)propionic Acid Ethyl Ester (7) and (*S*)-2-Amino-2-methyl-3-(3-fluorophenyl)propionic Acid (8). To a stirring suspension of racemic ester **4**·HCl (0.1 g, 0.38 mmol) in potassium phosphate buffer (50 mmol, pH 7.4, 10 mL) was added Lipase L-10 (0.2 g), and the mixture was stirred at room temperature for 4 h. HPLC showed 53% hydrolysis. After the pH was adjusted to 8.5 with a saturated solution of $NaHCO_3$, the reaction mixture was extracted with toluene, dried (Na_2SO_4), and concentrated. The residue was passed through a small silica gel column using 1:1 ethyl acetate/hexane to give **7** as an oil (0.038 g, 89%): ^1H NMR ($CDCl_3$) δ 1.26 (t, 3H, J = 7.1 Hz), 1.38 (s, 3H), 2.78 (d, 1H, J = 13.23 Hz), 3.11(d, 1H, J = 13.23 Hz), 4.14 (m, 2H), 6.87−6.96 (m, 3H), 7.19−7.27(m, 1H); ^{13}C NMR ($CDCl_3$) δ 14.33, 26.82, 46.59, 58.72, 61.33, 113.95 (J = 21.73 Hz), 117.01 (J = 20.38 Hz), 125.84, 129.81 (J = 8.83 Hz), 139.36, 162.75 (J = 250 Hz), and 176.99; MS data same as in **4**·HCl.

(*R*)-2-(Acetylamino)-2-methyl-3-(3-fluorophenyl)propionic Acid Ethyl Ester (9). Compound **7** (0.038 g, 0.17 mmol) was mixed with 1 mL of acetic anhydride and 0.5 mL of pyridine and was stirred for 20 h. The mixture was evaporated to dryness and passed through a plug of silica gel using ethyl acetate/hexane (1:1) to give **9** as a colorless oil (0.039 g, 92%) The NMR and MS data are the same as in **3**, and the ee was found to be 95.3%.

(*S*)-2-(Acetylamino)-2-methyl-3-(3-fluorophenyl)propionic Acid (10). The aqueous phase containing **8** from above was evaporated to dryness and was subjected to acetylation as described above. The compound **10** was purified on a silica gel column using ethyl acetate with 1% acetic acid (0.018 g, 50%). The NMR and MS data are shown below.

(*S*)-2-(Acetylamino)-2-methyl-3-(3-fluorophenyl)propionic Acid Ethyl Ester (11). Boron trifluoride etherate (3 drops) was added to a stirring solution of **10** (0.018 g, 0.075 mmol) in absolute ethyl alcohol (5 mL), and the reaction mixture was refluxed for 4 h. After the solvent was evaporated, the residue was dissolved in ethyl acetate, washed with water, dried (Na_2SO_4), and concentrated. The residue was purified on a silica gel column and eluted with 1:1 ethyl acetate/hexane to give **11** as colorless oil (0.018 g, 89%). The NMR and MS data are same as that of **3**, and the ee was found to be 97.7%.

(±)-2-(Acetylamino)-2-methyl-3-(3-fluorophenyl)propionic Acid Ethyl Ester (3). Pyridine (40.4 mL, 0.5 mol) was added to a stirring suspension of **4**·HCl (59.5g, 0.23 mol) in CH_2Cl_2 (600 mL) at 5−10 °C. After the mixture was stirred for 0.5 h, acetic anhydride (25.77 mL, 0.273 mol) was added. It was stirred for 20 h at room temperature. The reaction mixture was washed with water, followed by 1 N HCl and finally with water, and dried over anhydrous Na_2SO_4. Evapo-

(11) The ee of the final product was confirmed to be 99.6% after derivatization and recrystallization.

(12) Chromatographic conditions for each step are reported in the Experimental Section for characterization purposes only.

ration of solvent gave a colorless oil that solidified on standing. It was purified by crystallization from ethyl acetate/hexane to give **3** as colorless needles (43.8 g, 70%): mp 57−59 °C; ^{1}H NMR ($CDCl_3$) δ 1.33 (t, 3H, J = 7.3 Hz), 1.66 (s, 3H), 1.97 (s, 3H), 3.17 (d, 1H, J = 13.5 Hz), 3.60 (d, 1H, J = 13.5 Hz), 4.23 (m, 2H), 6.14 (bs, 1H), 6.73 - 6.91 (m, 3H), 7.19 (m, 1H); ^{13}C ($CDCl_3$) δ 14.29, 23.64, 24.23, 40.48, 61.24, 62.17, 113.93 (J = 21.06 Hz), 116.83 (J = 20.37 Hz), 125.69 (J = 4.07 Hz), 129.72 (J = 7.47 Hz), 139.36 (J = 6.79 Hz), 162.78 (J = 245.20 Hz), 169.82, and 173.93; MS (CI) 268 (MH^+). Anal. Calcd for $C_{14}H_{18}FNO_3$: C, 62.90; H, 6.78; N, 5.24. Found: C, 62.95; H, 6.66; N, 5.25.

Enzymatic Resolution of 3: (*R*)-2-(Acetylamino)-2-methyl-3-(3-fluorophenyl)propionic Acid Ethyl Ester (9) and (*S*)-2-(Acetylamino)-2-methyl-3-(3-fluorophenyl)propionic Acid (10). To a stirring suspension of racemic ester **3** (42.7 g, 0.16 mol) in potassium phosphate buffer (0.2M, pH 6.0, 850 mL) were added *t*-BuOH (85 mL) and lipase L-10 (42.7 g), and the mixture was stirred at room temperature for 5 d, keeping the pH of the reaction mixture constant by adding 2 N KOH solution as needed. Celite 545 (100 g) and reagent alcohol (500 mL) was added to the reaction mixture, which was then stirred for 1 h and filtered. The pH of the filtrate was adjusted to 8.8 with 2 N NaOH, and it was extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was passed through a small silica gel column using 1:1 ethyl acetate/hexane to give pure ester **9** as an oil (20.2 g, 47.3%): ^{1}H and ^{13}C are same as in **3**; HRMS calcd for $C_{14}H_{18}FNO_3$ 268.1349, found 268.1352. ee >99.9% as determined by chiral HPLC.

The pH of the aqueous layer was next adjusted to 7.0 with 2 N HCl and evaporated to dryness. The pure acid **10** was isolated from a silica gel column using 1% acetic acid/ethyl acetate as the eluant to afford a colorless solid (14 g, 36.7%): mp 210−211 °C; ^{1}H NMR (DMSO) δ 1.20 (s, 3H), 1.83 (s, 3H), 2.97 (d, 1H, J = 13.5 Hz), 3.33 (d, 1H, J = 13.5 Hz), 6.86−6.95 (m, 2H), 7.05 (t, 1H, J = 8.37 Hz), 7.33 (m, 1H), 7.85 (bs, 1H), and 12.46 (bs, 1H); ^{13}C NMR (DMSO) δ 22.40, 22.65, 40.00, 58.06, 113.21 (J = 20.68 Hz), 117.00 (J = 20.68 Hz), 126.69 (J = 2.38 Hz), 129.65 (J = 7.84 Hz), 140.95 (J = 7.84 Hz), 161.87 (J = 243.03 Hz), 169.06, and 174.98; MS (CI) 240 (MH^+). Anal. Calcd for $C_{12}H_{14}FNO_3$: C, 60.24; H, 5.89; N, 5.85. Found: C, 60.38; H, 5.99; N, 5.75. ee = 95.6%.

2-(Acetylamino)-2-methyl-3-(3-fluorophenyl)propionamide (14). Acetic anhydride (75 mL) was added to the acid **10** (8.00 g, 33.47 mmol), and the mixture was stirred at 140 °C for 0.25 h. After the reaction mixture was cooled to room temperature, acetic anhydride was evaporated under reduced pressure to give the oxazolinone **13** as light yellow oil (7.4 g, 99%): ^{1}H NMR ($CDCl_3$) δ 1.50 (s, 3H), 2.02 (s, 3H), 3.04 (s, 2H), 6.85−6.96 (m, 3H), 7.18−7.25 (m, 1H). It was used as such without further purification in the next step.

Ammonia was bubbled through a solution of **13** (0.3 g, 1.34 mmol) in dry $CHCl_3$ at −10 °C for 0.3 h. The tube was then sealed, and the reaction mixture was stirred at room temperature for 3 h. After the ammonia was evaporated, the reaction mixture was filtered and the solid washed with $CHCl_3$ and dried to give **14** as a colorless solid (0.27 g, 83%): mp 223−224 °C; ^{1}H NMR (DMSO) δ 1.25 (s, 3H), 1.84 (s, 3H), 3.13 (d, 1H, J = 13.23 Hz), 3.32 (d, 1H, J = 13.23 Hz), 6.83−7.33 (m, 6H), and 7.53 (bs, 1H); ^{13}C NMR (DMSO + $CDCl_3$) δ 22.21, 22.31, 37.80, 58.31, 111.58 (J = 20.85 Hz),115.31 (J = 20.85 Hz), 124.67 (J = 2.14 Hz), 127.77 (J = 8.18 Hz), 138.71 (J = 7.11 Hz), 160.67 (J = 243.97 Hz), 168.20, and 174.43; HRMS calcd for $C_{12}H_{15}FN_2O_3$ 239.1196, found 239.1198.

2-(Acetylamino)-2-methyl-3-(3-fluorophenyl)propionitrile (12). Cyanuric chloride (0.1 g, 0.55 mmol) was added in one portion to a stirring solution of amide **14** (0.2 g, 0.84 mmol) in DMF at 0 °C. After the reaction mixture was stirred for 8 h at room temperature, it was quenched with ice−water and extracted with CH_2Cl_2. The combined extracts were dried and concentrated. The pure product **12** was obtained by column chromatography, using 1:1 ethyl acetate/hexane, as a light yellow solid (0.14 g, 75%): mp 135−137 °C; ^{1}H NMR ($CDCl_3$) δ 1.64 (s, 3H), 2.01 (s, 3H), 3.26 (d, 1H, J = 13.64 Hz), 3.38 (d, 1H, J = 13.64 Hz), 5.48 (bs, 1H), 6.94−7.05 (m, 3H), and 7.28−7.36 (m, 1H); ^{13}C NMR (DMSO + $CDCl_3$) δ 21.96, 23.20, 41.49, 49.01, 113.23 (J = 20.88 Hz), 116.40 (J = 20.94 Hz), 119.45, 125.56 (J = 2.70 Hz), 128.77 (J = 8.49 Hz), 135.81 (J = 7.10 Hz), 161.32 (J = 245.23 Hz), and 169.16; HRMS calcd for $C_{12}H_{13}FN_2O$ 221.1090, found 221.1098.

2-(Acetylamino)-2-methyl-3-(3-fluorophenyl)thiopropionamide (15). H_2S gas was passed through a solution of nitrile **12** (0.061 g, 0.28 mmol) in ethyl alcohol (3 mL) and ammonium hydroxide (1 mL) at −10 °C until the reaction mixture was saturated. The flask was sealed, and the reaction mixture was stirred at room temperature for 20 h. After removal of excess H_2S, the reaction mixture was diluted with water and extracted with ethyl acetate. The combined extracts were dried (Na_2SO_4), evaporated, and subjected to column chromatography (elution with 1:1 ethyl acetate/hexane) to give **15** as a colorless viscous oil (0.064 g, 91%): ^{1}H NMR (DMSO) δ 1.32 (s, 3H), 1.84 (s, 3H), 3.47 (s, 2H), 6.85−6.94 (m, 2H), 7.02−7.09 (m, 1H), 7.28−7.36 (m, 1H), 7.77 (bs, 1H), 8.96 (bs, 1H), and 9.65 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 24.39, 25.87, 42.76, 64.84, 114.07 (J = 20.88 Hz), 117.08 (J = 21.07 Hz), 126.00 (J = 2.58 Hz), 129.63 (J = 8.30 Hz), 138.42 (J = 7.67 Hz), 162.58 (J = 245.67 Hz), 170.63, and 210.54; HRMS calcd for $C_{12}H_{15}FN_2OS$ 255.0967, found 255.0945.

***N*-Acetyl-1-(3-fluorophenyl)-2-methyl-2-(2-thiazolyl)-ethylamine (16).** To a solution of thioamide **15** (7.64 g, 27.33 mmol) in dry acetone (160 mL) was added bromoacetaldehyde diethyl acetal (20.6 mL, 136.65 mmol) and HCl/dioxane (4 N, 0.3 mL). After the mixture was refluxed for 24 h, acetone was evaporated and the residue was dissolved in CH_2Cl_2. It was washed with water, dried (Na_2SO_4), and concentrated. The pure product **16** was obtained by column chromatography on silica gel using 1:1 ethyl acetate/hexane as eluant to afford a light brown oil (5.70 g, 75%): ^{1}H NMR ($CDCl_3$) δ 1.90 (s, 3H), 2.01 (s, 3H), 3.35 (d, 1H, J = 13.36 Hz), 3.77 (d, 1H, J = 13.36 Hz), 6.50 (m, 1H), 6.61 (m, 1H), 6.71 (bs, 1H), 6.88 (m, 1H), 7.12 (m, 1H), 7.33 (d, 1H, J = 3.24 Hz), and 7.61 (d, 1H, J = 3.24 Hz); ^{13}C NMR ($CDCl_3$) δ 24.30, 27.89, 45.37, 60.12, 113.62 (J = 20.88 Hz), 116.94 (J = 21.07 Hz), 119.40, 125.71 (J = 2.01 Hz), 129.19 (J = 8.30 Hz), 138.73 (J = 7.48 Hz), 141.13, 162.37 (J = 245.17 Hz), 169.77, and 175.50; HRMS calcd for $C_{14}H_{15}FN_2OS$ 279.0967, found 279.0979.

1-(3-Fluorophenyl)-2-methyl-2-(2-thiazolyl)ethylamine (1). A mixture of **16** (4.70 g, 16.9 mmol) and 2 N HCl (40 mL) was refluxed for 6.5 h. After the reaction mixture was cooled, it was extracted with ethyl acetate. The organic layer was discarded, the aqueous phase was made basic with solid $NaHCO_3$, and the crude product was extracted with CH_2Cl_2. The combined extracts were dried over Na_2SO_4, the solvents were evaporated, and the amine **1** was obtained as a light brown oil from a silica gel column using 1:1 ethyl acetate/hexane as an eluant (3.23 g, 81%): ^{1}H NMR ($CDCl_3$) δ 1.59 (s, 3H), 1.78 (bs, 2H), 3.04 (d, 1H, J = 13.09 Hz), 3.32 (d, 1H, J = 13.09 Hz), 6.63−6.92 (m, 3H), 7.13−7.20 (m, 2H) and 7.76 (d, 1H, J = 3.24 Hz); ^{13}C NMR ($CDCl_3$) δ 30.30, 50.07, 57.46, 113.76 (J = 20.78 Hz), 117.26 (J = 20.58 Hz), 118.96, 126.17 (3.73 Hz), 129.55 (J = 8.62 Hz), 139.43 (J = 7.33 Hz), 142.85, 162.59 (J = 245.28 Hz), and 180.62; HRMS calcd for $C_{12}H_{13}FN_2S$ 237.0862, found 237.0867.

Supporting Information Available: Proton NMR spectra for compounds **1**, **4**·HCl, **9**, **12**, **14**, **15**, and **16** (7 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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