A General Method for the Synthesis of Enantiomerically Pure β-Substituted, β-Amino Acids through α-Substituted Succinic Acid Derivatives

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Received May 6, 1999

A general procedure for the synthesis of enantiopure β-substituted, β-amino acids is presented. Alkylation of the sodium enolates derived from chiral *N*-acyloxazolidinone imides **2** (R = Me, *i*-Pr, *t*-Bu, Ph, Bn) with *tert*-butyl bromoacetate afforded the 2-substituted succinate derivatives **3** in good yields (82−89%) and with high selectivity (≥93:7). Following hydrolysis, Curtius rearrangement of the resulting carboxylic acid provided the enantiopure benzyloxycarbonyl (Cbz)-protected β-amino esters **6** in good yields (74−79%).

Introduction

β-Amino acids are useful compounds, whether as analogues for α-amino acids to increase the resistance of peptides to enzymatic degradation[1] or as precursors to β-lactams and that family of antibiotics.[2] In addition, these building blocks and their derivatives are present in a number of potentially biologically useful natural products.[3] Although numerous methods for synthesizing enantiomerically pure β-amino acids have been reported, considerable effort continues to be devoted toward the development of more reliable and enantioselective strategies to conveniently access these molecules.[4] One strategy has been the directed conjugate addition of amines or amides to α,β-unsaturated esters. On the basis of the precedent established by Hawkins and Fu,[5] Davies and Ichihara demonstrated that 1,4-addition of chiral lithium amides to α,β-unsaturated esters stereoselectively afforded β-amino esters.[6] A similar approach has been successfully employed by others.[7,8] Another strategy has focused on stereoselective alkylations en route to enantiopure β-amino acids. Juaristi and Seebach showed that alkylation of enantiomerically pure pyrimidinones proceeded with high stereoselectivities, and subsequent hydrolysis of the heterocycle afforded substituted β-amino acids.[9] In addition, previous reports from this laboratory have demonstrated that amidoalkylation of the *N*-propionyloxazolidinone-derived titanium enolate with *N*-(chloromethyl)benzamide proceeds with excellent diastereoselectivity, suggesting a possible route to α-substituted, β-amino acids.[10] Recently, Sibi and co-workers presented a new route to 3-amino sugars via *N*-BOC amino lactones, which were synthesized by asymmetric aldol reactions and Curtius rearrangement of the lactone acids.[11] The use of the *n*-BuLi/(−)-sparteine for the deprotonation of carbamates has been exploited by Beak for the asymmetric synthesis of β-aryl amino acids.[12] Examples of recent advances in catalytic methods include asymmetric Mannich reactions[13] and conjugate additions of amines to acylpyrazoles.[14]

The purpose of this paper is to present a general strategy for the synthesis of differentially protected, enantiopure β-substituted, β-amino acids using the chiral auxiliary (4*S*)-4-benzyl-1,3-oxazolidin-2-one (**1**)[15] as the source of asymmetry (Scheme 1). The approach reported herein relies on observations made previously in these laboratories: (1) Chiral sodium and lithium imide enolates undergo highly diastereoselective alkylation reactions.[16] (2) Hydrolysis of the chiral auxiliary is possible using lithium hydroxide/hydrogen peroxide.[17] Thus, alkylation of **2** with *tert*-butyl bromoacetate, followed by removal of the chiral auxiliary with lithium hydroxide/hydrogen peroxide, afforded carboxylic acids **5**, which were then converted via a two-step, one-pot Curtius rearrangement to the differentially protected β-amino esters **6**. The synthetic utility of this procedure derives from its general applicability to a variety of acyl imides and the consistently high diastereoselectivities observed for the alkylation reaction.

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10.1021/jo990756k CCC: $18.00
Published on Web 08/04/1999

Scheme 1

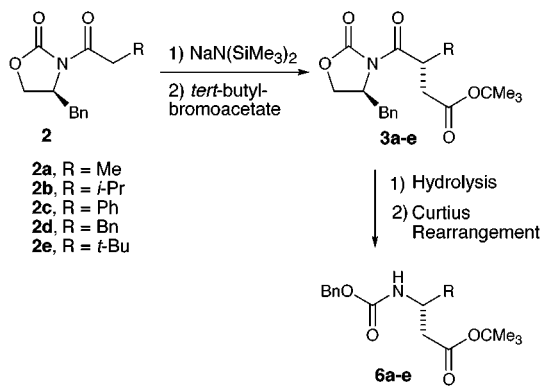
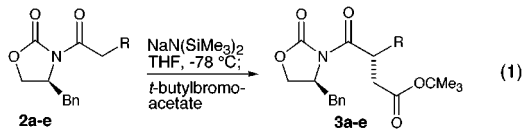


Table 1. Diastereoselective Alkylations of Imide 2 (eq 1)[a]



(1)

entry	imide (R)	yield, %[b] (time, h)	d.r.[c]	product, mp (°C)	$[\alpha]_D$[d]
1	**2a** (Me)	84 (3)	96:4	**3a**, 113.5-114.8	+49.6°
2	**2b** (*i*-Pr)	85 (6)	99:1	**3b**, 135.6-136.7	+69.6°
3	**2c** (Ph)	89 (2)	93:7	**3c**, 130.4-131.8	+144.1°
4	**2d** (Bn)	82 (2.5)	97:3	**3d**, 111.2-113.4	+106.4°
5	**2e** (*t*-Bu)	84 (15)	128:1	**3e**, 117.5-118.6	+51.4°

[a]Reactions run in THF with 1.1 equiv of sodium base and 3 equiv of *tert*-butylbromoacetate at -78 °C unless otherwise noted. [b]Isolated yield of the major diastereomer. [c]Diastereomer ratios determined by HPLC. See Experimental Section for details. [d]CH_2Cl_2, c 1.0. [e]Using *tert*-butyl iodoacetate as alkylating agent provided **3e** in comparable yield with a d.r. of 98:2 (2.5 h). See Discussion for details.

Results and Discussion

As reported previously, the crystalline imides **2** (**2a**, R = Me; **2b**, R = *i*-Pr; **2c**, R = Ph; **2d**, R = Bn; **2e**, R = *t*-Bu) derived from oxazolidinone (**1**) and the appropriate acid chloride were prepared in good yield.[18,19] Optimal conditions for the alkylation of **2a**−**e** with *tert*-butyl bromoacetate were obtained via enolization of **2** with sodium hexamethyldisilazide (THF, 0.5 M, −78 °C), followed by addition of the electrophile (Table 1).[20] Diastereoselectivities for the alkylations of imides **2a**−**e** ranged from 32:1 to 128:1, as determined by HPLC (see Experimental Section for details). In all cases, recrystallization of the unpurified reaction mixture afforded the diastereomerically pure major product, confirmed by HPLC. The mother liquors of the recrystallization were chromatographed on silica gel to yield an enriched diastereomeric mixture of **3** which, after recrystallization, afforded another crop of the major diastereomer resulting in combined isolated yields from 82% to 89%.

In the case of imide **2e** (R = *t*-Bu), alkylation with *tert*-butyl bromoacetate proceeded slowly but afforded **3e** in 84% yield after 15 h with excellent diastereoselectivity (128:1). Due to the insolubility of **2e** at higher concentrations (0.5 M) at −78 °C, it was necessary to reduce the reaction concentration of **2e** to 0.2 M. In an attempt to shorten the reaction time, alkylation was carried out with *tert*-butyl iodoacetate, prepared from sodium iodide and *tert*-butyl bromoacetate (acetone, 25 °C).[21] This reaction was complete in 2−2.5 h and afforded **3e** (R = *t*-Bu) in comparable yield, although the diastereoselectivity dropped to 49:1 due to the higher reactivity of the iodide.

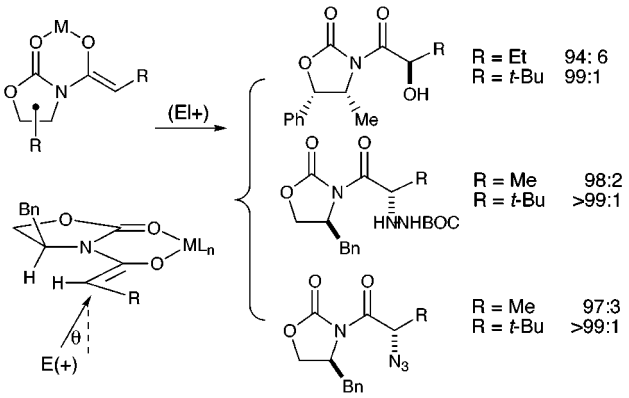


Figure 1. Diastereoselectivity trends in reactions of chiral imide enolates and proposed altered electrophile trajectory (θ).

The imide alkylation diastereoselectivities exhibit a modest increase with the increasing size of the alkyl groups pendant to the enolate carbon (Table 1, entries 1, 2, and 5). This is a trend that has been noted consistently by us in other enolate−electrophile reactions (Figure 1).[22] A possible explanation for this trend is that the electrophile, E(+), approaching the enolate must alter its trajectory due to steric interactions with the increasingly large R group, thus amplifying the influence of the (*S*)-benzyl substituent on the chiral auxiliary and increasing the $\Delta\Delta G^{\ddagger}$ for the process. Related trends have been previously noted in diastereoselective carbonyl addition reactions.[23]

After isolation of alkylated imides **3**, the oxazolidinone auxiliary was removed using lithium hydroperoxide.[17] In the case of imides **3a**−**d**, this reagent was effective in cleaving selectively at the exocyclic carbonyl, giving the carboxylic acids **5a**−**d** in high yields (>84%) with reaction times between 1 and 7 h at 0 °C (Table 2).

Oxazolidinone **3e** (R = *t*-Bu) could not be cleaved efficiently to the carboxylic acid using lithium hydroperoxide due to excessive steric hindrance at its exocyclic imide carbonyl. As a result, a two-step hydrolysis procedure was implemented (eq 3). Following the precedented use of lithiomercaptides to remove hindered oxazolidinones with excellent exocyclic selectivities,[24] imide **3e** was transformed to its derived thioester **4** in 85% yield. Quantitative conversion of **4** to the acid **5e** was achieved using a slightly modified version of the general hydrolysis procedure (see Experimental Section).

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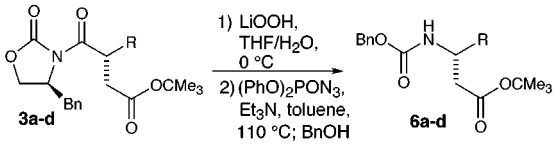
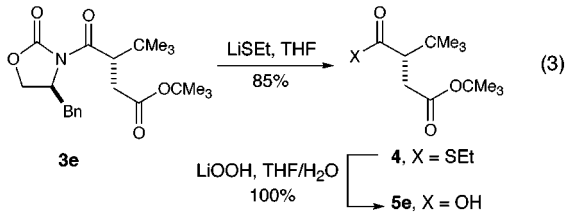
Table 2. Hydrolysis[a] and Curtius Rearrangement[b] of Imide 3 (eq 2)



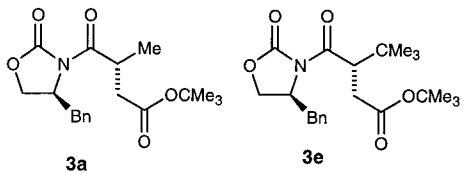
		Hydrolysis		Rearrangement	
entry	imide (R)	yield, % (time, h)	product	yield, % (time, h)	product
1	**3a** (Me)	95 (2)	**5a**	76 (22)	**6a**
2	**3b** (*i*-Pr)	84 (7)	**5b**	76 (24)	**6b**
3	**3c** (Ph)	89 (1.5)	**5c**	74 (6.5)	**6c**
4	**3d** (Bn)	91 (1)	**5d**	79 (5)	**6d**

[a]Reactions run in 3:1 THF/H_2O with 4 equiv of hydrogen peroxide and 2 equiv of lithium hydroxide at 0 °C. [b]Reactions run in refluxing toluene with 1.2 equiv of triethylamine and 1.0 equiv of DPPA to form the isocyanate, followed by the addition of 3 equiv of BnOH.



Two different Curtius rearrangement procedures for the conversion of **5** to the differentially protected β-amino esters **6** were investigated. The use of diphenyl phosphorazidate (DPPA) in such a reaction has been reported: refluxing 1 equiv of a carboxylic acid, DPPA, and triethylamine gave an intermediate isocyanate that was trapped by the alcoholic solvent to afford the corresponding carbamate.[25] These one-stage procedures typically required reaction times of greater than 14 h with yields ranging from 44% to 90%. Application of this procedure to **5b** (R = *i*-Pr) afforded the corresponding *N*-protected amino ester **6b** in 46% yield after 19.5 h. In an effort to improve the yield of the process, a related protocol reported by Jacobi was employed for subsequent reactions.[26] In a typical experiment, triethylamine (1.1 equiv) and DPPA (1.0 equiv) were added to carboxylic acids **5a**−**d** (1.0 equiv) in toluene at room temperature. The resulting solution was heated at reflux for 1.5−3.5 h to form the corresponding isocyanates,[27] which were then treated with benzyl alcohol (3.0 equiv). Yields for **6a**−**d** ranged from 74 to 79% (Table 2).

Our attempts to apply this procedure to **5e** (R = *t*-Bu) failed, with no discernible formation of the isocyanate after 7 h at 110 °C. As a result, we sought a different route to effect the transformation, using a two-stage procedure reported by Yakushijin et al.[28] Formation of the acyl azide via the intermediate mixed anhydride was achieved by treatment of **5e** with ethyl chloroformate and triethylamine (THF, 0 °C), followed by sodium azide (H_2O, 25 °C). The resulting acyl azide was heated in toluene with benzyl alcohol (3 equiv, 110 °C, 12 h) to effect rearrangement and carbamate formation, affording **6e** in 74% yield from **5e** (eq 4).



Selected dihedral angles (deg) for **3a** and **3e**

measurement	3a	3e
O2-C3-N-C1	-7.0	-14.7
C3-N-C1-O1	-179.3	+178.0
H-C2-C1-O1	-146.8	-158.6

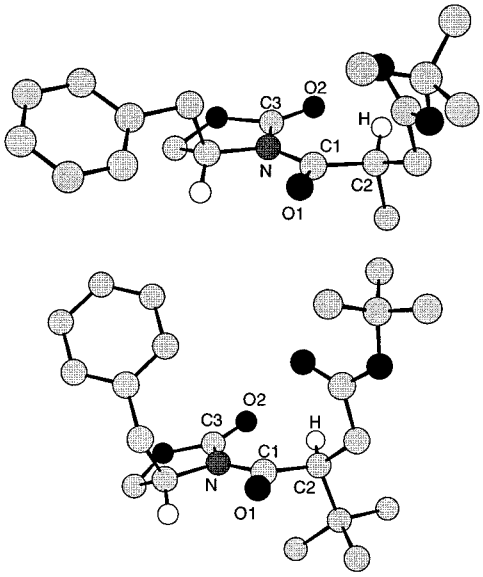
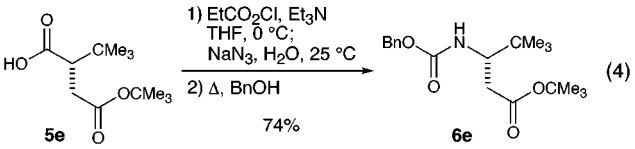


Figure 2. X-ray crystal structures of alkylated imides **3a**,**e**.



X-ray crystal structures of **3a** (R = Me) and **3e** (R = *t*-Bu) confirmed the absolute stereochemistry of amino esters **6a** and **6e** (Figure 2). The imide carbonyls of **3a**,**e** exhibited the expected dipole-minimized anti conformation. The absolute stereochemistry of **6b**−**d** was confirmed by conversion to the corresponding carboxylic acids **7b**−**d** and β-amino acid **8** (Scheme 2) and comparison of their specific rotations with those reported in the literature [**7c**, synthetic, $[\alpha]_D$ −23.2° (*c* 1.0, EtOH), lit.[29] $[\alpha]_D$ −24.4° (*c* 1.0, EtOH); **7d**, synthetic, $[\alpha]_D$ +26.7° (*c* 1.0, AcOH), lit.[30] $[\alpha]_D$ −28.5° (*c* 1.0, AcOH) for the enantiomer; **8**, synthetic, $[\alpha]_D$ +51.5° (*c* 0.6, H_2O), lit.[31] $[\alpha]_D$ +52.3° (*c* 0.6, H_2O)]. In all cases, the sense of induction for the alkylation step was consistent with attack of a chelated (*Z*) enolate on the diastereoface opposite the benzyl group of the auxiliary.[16] In addition

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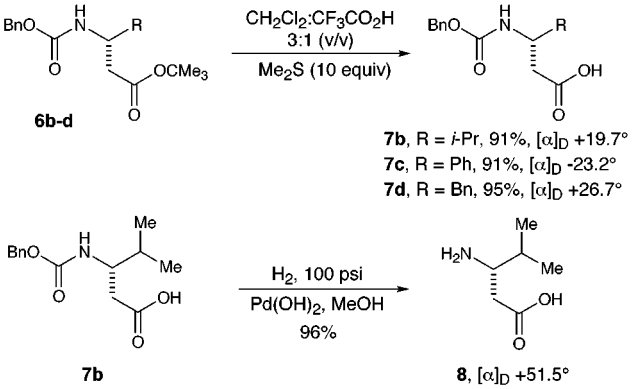
Scheme 2



to establishing the configuration of the products, these experiments illustrate an attractive feature of the method: the orthogonality of the protecting groups on the acid and amine allows the desired functional group to be selectively revealed in high yield.

Conclusion

The ability to access enantiomerically pure β-amino acids is of great utility not only in organic synthesis but also in medicinal and biological chemistry. Although slight modifications are necessary in synthesizing β-amino acids with sterically demanding groups at the β position, this procedure provides an attractive option for the synthesis of enantiopure β-substituted, β-amino acids due to the generality of the alkylation, hydrolysis, and Curtius rearrangement steps. It also allows access to compounds that may be difficult to synthesize by current methods.

Experimental Section

General Methods. Melting points are uncorrected. Combustion analyses were performed by Atlantic Microlab, Inc. (Norcross, GA). Analytical chromatography was performed on EM reagents 0.25-mm silica gel 60-F plates. Flash chromatography was performed on EM reagents silica gel 60 (230−400 mesh). Tetrahydrofuran (THF) was distilled from sodium metal/benzophenone ketyl. Toluene was distilled from potassium. Triethylamine was distilled from calcium hydride. Benzyl alcohol was distilled under reduced pressure. All other commercially obtained reagents were used as received. Unless otherwise noted, all nonaqueous reactions were carried out under a dry nitrogen atmosphere with flame-dried glassware.

General Procedure for the Alkylation of Oxazolidinone-Derived Sodium Enolates. To a solution of **2** (10.1 mmol, 1.0 equiv) in 20 mL of THF at −78 °C was added sodium hexamethyldisilazide (1.1 equiv, 1.0 M in THF) via syringe. The solution was then stirred at −78 °C for 1.5−2 h. To the reaction was added 3 equiv of *tert*-butyl bromoacetate via syringe. Alkylation was allowed to proceed at −78 °C until TLC analysis indicated complete consumption of the starting material (3−6 h). The reaction flask was allowed to warm to 0 °C before the contents were partitioned between 60 mL of saturated aqueous NH_4Cl and 50 mL of EtOAc. The layers were separated, and the aqueous layer was extracted with three 50 mL portions of EtOAc. The combined organic extracts were dried ($MgSO_4$), filtered through cotton, and concentrated in vacuo to yield a solid. The unpurified product was analyzed by HPLC (Zorbax SIL 4.6 mm i.d. × 25 cm (5 μm), 4% isopropyl alcohol/hexane, 1.00 mL/min, 254 nm, unless otherwise noted). Recrystallization of the solid residue from hexanes/ether afforded exclusively the major diastereomer, confirmed by HPLC. The mother liquors were concentrated and chromatographed on silica gel using an appropriate solvent mixture to purify the remainder of the major diastereomer.

(4*S*)-3-((2*R*)-4-(*tert*-Butoxy)-2-methyl-4-oxobutanoyl)-4-(phenylmethyl)-1,3-oxazolidin-2-one (3a). According to the general procedure, 1.5 mL of sodium hexamethyldisilazide (0.84 M in THF, 1.18 mmol) was added dropwise to a stirring solution of 0.25 g of **2a** (1.07 mmol) in 2.2 mL of THF at −78 °C. After 1 h, 0.475 mL of *tert*-butyl bromoacetate (0.628 g, 3.22 mmol) was added. The solution was stirred at −78 °C for an additional 2.5 h. Extraction and concentration yielded a solid residue. The solid (96:4 diastereomeric ratio by HPLC, using conditions according to the general procedure; t_r(major) = 9.034, t_r(minor) = 8.271) was recrystallized from a minimal volume of hexanes/ether to yield white crystals in 84% yield (0.32 g, 0.92 mmol): $[\alpha]^{25}_D$ +49.6° (*c* 1.00, CH_2Cl_2); mp 113.5−114.8 °C; IR (neat) 1782, 1727, 1699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36−7.27 (m, 5H), 4.69−4.63 (m, 1H), 4.21−4.12 (m, 3H), 3.34 (dd, J = 13.5, 3.2 Hz, 1H), 2.85 (dd, J = 16.7, 10.1 Hz, 1H), 2.75 (dd, J = 13.4, 9.9 Hz, 1H), 2.39 (dd, J = 16.8, 4.7 Hz, 1H), 1.43 (s, 9H), 1.20 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 171.0, 152.8, 135.4, 129.3, 128.7, 127.0, 80.4, 65.7, 55.2, 38.8, 37.4, 34.3, 27.8, 16.8; TLC R_f = 0.43 (30% EtOAc/hexane). Anal. Calcd for $C_{19}H_{25}NO_5$: C, 65.69; H, 7.25; N, 4.03. Found: C, 65.74; H, 7.29; N, 4.04. Exact mass: calcd for $C_{19}H_{29}N_2O_5$ (M + NH_4), 365.2076; found, 365.2082 (CI, NH_3).

(4*S*)-3-((2*S*)-4-(*tert*-Butoxy)-2-(1-methylethyl)-4-oxobutanoyl)-4-(phenylmethyl)-1,3-oxazolidin-2-one (3b). According to the general procedure, 14.0 mL of sodium hexamethyldisilazide (0.91 M in THF, 12.7 mmol) was added dropwise to a stirring solution of 3.01 g of **2b** (11.5 mmol) in 9.1 mL of THF at −78 °C. After 1 h, 5.2 mL of *tert*-butyl bromoacetate (6.75 g, 34.6 mmol) was added. The solution was stirred at −78 °C for an additional 6 h. Extraction and concentration yielded a solid residue. The solid (99:1 diastereomeric ratio by HPLC, using conditions according to the general procedure; t_r(major) = 6.230, t_r(minor) = 4.903) was recrystallized from a minimal volume of methanol to yield white crystals in 85% yield (3 crops, 3.67 g, 9.79 mmol): $[\alpha]^{25}_D$ +69.6° (*c* 1.00, CH_2Cl_2); mp 135.6−136.7 °C; IR (neat) 1780, 1724, 1697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36−7.25 (m, 5H), 4.69−4.63 (m, 1H), 4.18−4.12 (m, 3H), 3.35 (dd, J = 13.5, 3.2 Hz, 1H), 2.83 (dd, J = 16.9, 11.7 Hz, 1H), 2.74 (dd, J = 13.5, 10.1 Hz, 1H), 2.45 (dd, J = 16.9, 3.5 Hz, 1H), 2.01−1.97 (m, 1H), 1.42 (s, 9H), 1.01 (d, 3H, J = 6.9 Hz), 0.91 (d, 3H, J = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 171.8, 153.1, 135.9, 129.5, 128.9, 127.2, 80.6, 65.7, 55.7, 44.4, 37.4, 33.6, 29.8, 28.1, 20.7, 18.3; TLC R_f = 0.48 (30% EtOAc/hexane). Anal. Calcd for $C_{21}H_{29}NO_5$: C, 67.18; H, 7.79; N, 3.73. Found: C, 67.24; H, 7.85; N, 3.69. Exact mass: calcd for $C_{19}H_{33}N_2O_5$ (M + NH_4), 393.2389; found, 393.2388 (CI, NH_3).

(4*S*)-3-((2*S*)-4-(*tert*-Butoxy)-4-oxo-2-phenylbutanoyl)-4-(phenylmethyl)-1,3-oxazolidin-2-one (3c). According to the general procedure, 11.1 mL sodium hexamethyldisilazide (1.0 M in THF, 11.1 mmol) was added dropwise to a stirring solution of 3.00 g of **2c** (10.1 mmol) in 20.2 mL of THF at −78 °C. After 1.5 h, 4.5 mL of *tert*-butyl bromoacetate (5.93 g, 30.4 mmol) was added. The solution was stirred at −78 °C for an additional 2 h. Extraction and concentration yielded a solid residue. The yellow residue (93:7 diastereomeric ratio by HPLC, using conditions according to the general procedure; t_r(major) = 5.039, t_r(minor) = 7.287) was recrystallized from a minimal volume of hexane/ether to afford white crystals. Flash chromatography (30% *tert*-butyl methyl ether/pentane) yielded additional product for a total yield of 89% (3.65 g, 8.9 mmol): $[\alpha]^{25}_D$ +144.1° (*c* 0.99, CH_2Cl_2); mp 130.4−131.8 °C; IR ($CHCl_3$) 1782, 1724, 1696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41−7.24 (m, 10H), 5.49 (dd, J = 11.4, 4.3 Hz, 1H), 4.62−4.56 (m, 1H), 4.11−4.00 (m, 2H), 3.38 (dd, J = 13.4, 3.2 Hz, 1H), 3.30 (dd, J = 17.0, 11.4 Hz, 1H), 2.80 (dd, J = 13.4, 9.9 Hz, 1H), 2.62 (dd, J = 16.7, 4.4 Hz, 1H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 171.6, 153.2, 137.6, 136.1, 129.9, 129.3, 129.1, 128.9, 128.0, 127.6, 81.0, 65.7, 55.8, 40.0, 37.4, 27.8; TLC R_f = 0.43 (30% *tert*-butyl methyl ether/pentane).

Anal. Calcd for $C_{24}H_{27}NO_5$: C, 70.42; H, 6.60; N, 3.42. Found: C, 70.27; H, 6.70; N, 3.36.

(4*S*)-3-((2*R*)-4-(*tert*-Butoxy)-4-oxo-2-(phenylmethyl)butanoyl)-4-(phenylmethyl)-1,3-oxazolidin-2-one (3d). According to the general procedure, 18.1 mL of sodium hexamethyldisilazide (0.91 M in THF, 16.4 mmol) was added dropwise to a stirring solution of 4.65 g of **2e** (15.0 mmol) in 40 mL of THF at −78 °C. After 1.5 h, 6.65 mL of *tert*-butyl bromoacetate (8.78 g, 45.0 mmol) was added. The solution was stirred at −78 °C for an additional 2.5 h. Extraction and concentration yielded a yellow oil that solidified at −20 °C. The solid (97:3 diastereomeric ratio by HPLC, using conditions according to the general procedure; t_r(major) = 5.281, t_r(minor) = 4.470) was recrystallized from a minimal volume of hexane/ether to yield white needles. The mother liquors were concentrated and chromatographed on silica gel (2:1 hexane/EtOAc) to yield additional product for a combined yield of 82% (5.20 g, 12.3 mmol): $[\alpha]^{25}_D$ +106.4° (*c* 0.96, CH_2Cl_2); mp 111.2−113.4 °C; IR ($CHCl_3$) 1779, 1724, 1698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36−7.20 (m, 10 H), 4.55−4.45 (m, 2H), 4.08 (dd, *J* = 8.9, 2.4 Hz, 1H), 3.96−3.92 (m, 1H), 3.31 (dd, *J* = 13.3, 3.3 Hz, 1H), 3.01 (dd, *J* = 13.1, 6.2 Hz, 1H), 2.85 (dd, *J* = 16.9, 10.9 Hz, 1H), 2.73 (dd, *J* = 13.5, 10.0 Hz, 1H), 2.64 (dd, *J* = 13.1, 9.1 Hz, 1H), 2.38 (dd, *J* = 16.9, 4.1 Hz, 1H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 171.2, 153.0, 138.1, 135.8, 129.6, 129.3, 129.0, 128.5, 127.3, 126.8, 80.9, 65.9, 55.7, 41.3, 38.4, 37.7, 36.9, 28.1; TLC R_f = 0.57 (2:1 hexane/EtOAc). Anal. Calcd for $C_{25}H_{29}NO_5$: C, 70.92; H, 6.86; N, 3.31. Found: C, 70.81; H, 6.93; N, 3.26.

(4*S*)-3-((2*S*)-4-(*tert*-Butoxy)-2-(1,1-dimethylethyl)-4-oxobutanoyl)-4-(phenylmethyl)-1,3-oxazolidin-2-one (3e). According to the general procedure, 2.40 mL of sodium hexamethyldisilazide (0.84 M in THF, 2.0 mmol) was added dropwise to a stirring solution of 0.50 g of **2e** (1.82 mmol) in 9 mL of THF at −78 °C. After 2.5 h, 0.81 mL of *tert*-butyl bromoacetate (1.06 g, 5.45 mmol) was added. The solution was stirred at −78 °C for an additional 15 h. Extraction and concentration yielded a solid residue (128:1 diastereomeric ratio by HPLC, 1.3% isopropyl alcohol/hexanes; t_r(major) = 5.290, t_r(minor) = 6.413). Flash chromatography (20% EtOAc/hexane) afforded a white solid, which was recrystallized from a minimal amount of hexane to provide the major isomer as white needles in 84% yield (0.59 g, 1.52 mmol): $[\alpha]^{25}_D$ +51.4° (*c* 1.00, CH_2Cl_2); mp 117.5−118.6 °C; IR (neat) 1782, 1729, 1693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36−7.24 (m, 5H), 4.69−4.63 (m, 1H), 4.36 (dd, *J* = 12.2, 3.2 Hz, 1H), 4.15−4.07 (m, 2H), 3.38 (dd, *J* = 13.4, 3.1 Hz, 1H), 2.90 (dd, *J* = 16.9, 12.2 Hz, 1H), 2.68 (dd, *J* = 13.4, 10.6 Hz, 1H), 2.51 (dd, *J* = 16.9, 3.2 Hz, 1H), 1.41 (s, 9H), 1.00 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 171.9, 153.4, 136.3, 129.6, 128.9, 127.1, 80.7, 65.5, 56.2, 46.0, 37.1, 35.0, 33.3, 28.1, 27.5; TLC R_f = 0.58 (30% EtOAc/hexane); exact mass calcd for $C_{22}H_{35}N_2O_5$ (M + NH_4) 407.2546, found 407.2541 (CI, NH_3).

General Procedure for Lithium Hydroxide/Hydrogen Peroxide Hydrolysis. To a solution of **3** (6.4 mmol) in 96 mL of THF at 0 °C was added 4 equiv of H_2O_2 (35 wt %) dropwise via syringe, followed by the addition of a solution of 2 equiv of anhydrous LiOH in 32 mL of H_2O. The solution was stirred at 0 °C for 1−2 h. After TLC indicated completion of the hydrolysis, 20 mL of saturated Na_2SO_3 and 20 mL of saturated $NaHCO_3$ were added at 0 °C. The contents were partially concentrated in vacuo and diluted with 50 mL of H_2O. The aqueous solution was extracted with four 50 mL portions of dichloromethane. The dichloromethane extracts were combined, dried ($MgSO_4$), filtered through cotton, and concentrated in vacuo to yield free oxazolidinone **1** as a white solid, which was recrystallized from hexane/ethyl acetate. At 0 °C, the aqueous layer was acidified to pH ∼1.5 with 6 M HCl and extracted with four 50 mL portions of ethyl acetate. The combined organic extracts were dried ($MgSO_4$), filtered through cotton, and concentrated in vacuo to yield an oil, which solidified at −20 °C. The residue was recrystallized or chromatographed on silica gel, using an appropriate solvent mixture, to yield the carboxylic acid.

(*R*)-4-(*tert*-Butoxy)-2-methyl-4-oxobutanoic acid (5a). Following the general procedure, a solution of 4.86 g of **3a** (8.3 mmol) in 210 mL of THF was treated with 5.7 mL of hydrogen peroxide (30 wt %, 1.90 g, 56.0 mmol) and a solution of 0.67 g of LiOH (28.0 mmol) in 70 mL of water at 0 °C. Hydrolysis proceeded for 2 h. Acidification of the aqueous layer, extraction, and concentration yielded the carboxylic acid, which was recrystallized from hexane to afford the product as large white crystals in 95% yield (2.51 g, 13.4 mmol): $[\alpha]^{25}_D$ +3.9° (*c* 1.00, CH_2Cl_2); mp 59.3−59.9 °C; IR (neat) 2979, 1721, 1705 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.92−2.87 (m, 1H), 2.64 (dd, *J* = 16.5, 8.2 Hz, 1H), 2.36 (dd, *J* = 16.5, 5.8 Hz, 1H), 1.44 (s, 9H), 1.24 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.9, 171.0, 81.0, 38.7, 35.9, 28.0, 16.7. Anal. Calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.37; H, 8.66. Exact mass: calcd for $C_9H_{20}NO_4$ (M + NH_4), 206.1392; found, 206.1384 (CI, NH_3).

(*S*)-4-(*tert*-Butoxy)-2-(1-methylethyl)-4-oxobutanoic acid (5b). Following the general procedure, a solution of 3.41 g of **3b** (9.1 mmol) in 135 mL of THF was treated with 3.7 mL of hydrogen peroxide (30 wt %, 1.23 g, 36.3 mmol) and a solution of 0.44 g of LiOH (18.2 mmol) in 45 mL of water at 0 °C. Hydrolysis proceeded for 7 h. Acidification of the aqueous layer, extraction, and concentration afforded the product as an oil in 84% yield (1.65 g, 7.66 mmol): $[\alpha]^{25}_D$ +7.86° (*c* 1.00, CH_2Cl_2); IR (neat) 2966, 1734, 1708 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.72−2.57 (m, 2H), 2.35 (dd, *J* = 16.3, 3.6 Hz, 1H), 2.06−1.97 (m, 1H), 1.42 (s, 9H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.6, 171.5, 80.8, 47.4, 34.0, 29.8, 27.9, 20.0, 19.4; TLC R_f = 0.37 (50% EtOAc/hexanes); exact mass calcd for $C_{11}H_{24}NO_4$ (M + NH_4) 234.1705, found 234.1700 (CI, NH_3).

(*S*)-4-(*tert*-Butoxy)-4-oxo-2-phenylbutanoic acid (5c). Following the general procedure, a solution of 2.64 g of **3c** (6.4 mmol) in 96 mL of THF was treated with 2.28 mL of hydrogen peroxide (35 wt %, 1.13 g, 33.2 mmol) and a solution of 0.31 g of LiOH (12.8 mmol) in 32 mL of water at 0 °C. Hydrolysis proceeded for 1.5 h. Acidification of the aqueous layer, extraction, and concentration yielded the carboxylic acid, which was recrystallized from hexane to afford the product as white needles in 89% yield (1.44 g, 5.7 mmol): $[\alpha]^{25}_D$ +106° (*c* 0.95, CH_2Cl_2); mp 76.0−78.5 °C; IR ($CHCl_3$) 2980, 1729, 1710 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34−7.25 (m, 5H), 4.03 (dd, *J* = 10.1, 5.5 Hz, 1H), 3.08 (dd, *J* = 16.7, 10.1 Hz, 1H), 2.61 (dd, *J* = 16.7, 5.6 Hz, 1H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.9, 170.5, 137.2, 128.9, 127.9, 127.9, 81.3, 47.4, 38.7, 27.9; TLC R_f = 0.32 (2:1 hexane/EtOAc). Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.20; H, 7.20. Found: C, 67.09; H, 7.21.

(*R*)-4-(*tert*-Butoxy)-4-oxo-2-(1-phenylmethyl)butanoic acid (5d). Following the general procedure, a solution of 3.50 g of **3d** (8.3 mmol) in 125 mL of THF was treated with 3.0 mL of hydrogen peroxide (35 wt %, 25.6 mmol) and a solution of 0.40 g of LiOH (16.6 mmol) in 42 mL of water at 0 °C. Hydrolysis proceeded for 1 h. Acidification of the aqueous layer, extraction, and concentration yielded the carboxylic acid, which was recrystallized from hexane to afford the product as large white crystals in 91% yield (1.99 g, 7.5 mmol): $[\alpha]^{25}_D$ +7.1° (*c* 1.00, CH_2Cl_2); mp 57.0−59.8 °C; IR ($CHCl_3$) 2979, 1730, 1709 cm^{-1};^1H NMR (400 MHz, $CDCl_3$) δ 7.32−7.18 (m, 5H), 3.13−3.06 (m, 2H), 2.76 (dd, *J* = 15.4, 10.3 Hz, 1H), 2.56 (dd, *J* = 16.7, 8.9 Hz, 1H), 2.34 (dd, *J* = 16.9, 4.8 Hz, 1H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.5, 170.9, 138.1, 129.1, 128.6, 126.8, 81.1, 43.2, 37.4, 36.1, 28.0; TLC R_f = 0.17 (2:1 hexanes/EtOAc). Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.18; H, 7.58. Found: C, 68.24; H, 7.63.

***S*-Ethyl (*S*)-4-(*tert*-Butoxy)-2-(1,1-dimethylethyl)-4-oxobutanthioate (4)**. To a solution of 0.45 mL of ethanethiol (0.36 g, 5.8 mmol, 3.4 equiv) in 10 mL of THF at −78 °C was added 1.7 mL of *n*-butyllithium (2.5 M in hexanes, 0.27 g, 4.2 mmol, 2.5 equiv) via syringe. The solution was allowed to warm to 0 °C. The cloudy solution was stirred for 15 min before a precooled (−78 °C) solution of 0.66 g of **3e** (1.7 mmol, 1.0 equiv) in 10 mL of THF was added via cannula. The reaction was stirred at 0 °C for 9 h before being partitioned between 40 mL of 1 M aqueous NaOH and 30 mL of ethyl ether. The layers

were separated, and the aqueous layer was extracted with two 30 mL portions of ethyl ether. The combined organic extracts were washed with 50 mL of brine, dried (Na_2SO_4), filtered through cotton, and concentrated in vacuo to afford a chunky white residue (0.713 g). Purification by flash chromatography (15% EtOAc/hexanes) provided the thioester as a colorless oil in 85% yield (0.395 g, 1.4 mmol): $[\alpha]^{25}_D$ +25.3° (*c* 0.57, CH_2Cl_2); IR (neat) 1734, 1684 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.94−2.81 (m, 3H), 2.68 (dd, *J* = 15.8, 10.8 Hz, 1H), 2.41 (dd, *J* = 15.8, 3.2 Hz, 1H), 1.43 (s, 9H), 0.99 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.6, 171.4, 80.9, 59.3, 34.8, 33.2, 28.1, 28.0, 27.3, 23.7; TLC R_f = 0.53 (15% EtOAc/hexanes); exact mass calcd for $C_{14}H_{30}O_3NS$ (M + NH_4) 292.1946, found 292.1943 (CI, NH_3).

(*S*)-4-(*tert*-Butoxy)-2-(1,1-dimethylethyl)-4-oxobutanoic acid (5e). Following a modified version of the lithium hydroperoxide hydrolysis general procedure, a solution of 0.838 g of **4** (3.05 mmol, 1.0 equiv) in 60 mL of a 3:1 THF/H_2O (v/v) solution was treated with 2.16 mL of H_2O_2 (35 wt %, 0.83 g, 24.5 mmol, 8.0 equiv) and 0.52 g of LiOH·H_2O (12.3 mmol, 4.0 equiv) at room temperature. After being stirred at room temperature for 3 days, the mixture was worked up according to the general procedure to give the crude product as an oil. Purification by flash chromatography (50% EtOAc/hexanes) afforded the carboxylic acid as a clear oil in 100% yield (0.700 g, 3.04 mmol): $[\alpha]^{25}_D$ +27.8° (*c* 1.00, CH_2Cl_2); IR (neat) 2969, 1732, 1706 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.68 (dd, *J* = 15.8, 11.9 Hz, 1H), 2.59 (dd, *J* = 11.8, 2.5 Hz, 1H), 2.42 (dd, *J* = 15.8, 2.6 Hz, 1H), 1.43 (s, 9H), 1.00 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.1, 171.7, 81.1, 51.5, 34.1, 32.5, 28.0, 27.9; TLC R_f = 0.46 (50% EtOAc/hexanes); exact mass calcd for $C_{12}H_{26}O_4N$ (M + NH_4) 248.1862, found 248.1875 (CI, NH_3).

General Procedure for the Modified Curtius Rearrangement of Carboxylic Acids. To a solution of the carboxylic acid **5** (3.98 mmol) in 22.5 mL of toluene was added via syringe 1.1 equiv of triethylamine, followed by 1.0 equiv of DPPA. The solution was stirred at room temperature and for 30 min before being heated slowly to reflux. Nitrogen evolution was observed at 70−75 °C. Isocyanate formation was monitored by IR for the appearance of a strong signal in the 2300−2200 cm^{-1} range and disappearance of the carboxylic acid carbonyl peak. After IR indicated complete consumption of **5**, the reaction was cooled to 50 °C and 3 equiv of benzyl alcohol was added via syringe. Following the addition, the reaction flask was heated to reflux until TLC analysis indicated complete consumption of the isocyanate. The reaction was cooled to room temperature and quenched with saturated aqueous $NaHCO_3$ (40 mL), and the mixture was extracted with three 40 mL portions of ethyl ether. The combined ether extracts were dried (Na_2SO_4), filtered through cotton, and concentrated in vacuo to yield the carbamate **6** as an oil, which was chromatographed on silica gel, using an appropriate solvent mixture, to afford the pure product.

***tert*-Butyl (3*R*)-*N*-(Benzyloxycarbonyl)-3-aminobutanoate (6a)**. Following the general procedure, a solution of 0.100 g of **5a** (0.54 mmol) in 10 mL of toluene was treated with 0.090 mL of triethylamine (0.066 g, 0.65 mmol) and 0.120 mL of DPPA (0.015 g, 0.54 mmol). After 30 min, the reaction was heated to reflux for 3.5 h. After cooling to 50 °C, 0.170 mL of benzyl alcohol (0.174 g, 1.61 mmol) was added to the reaction flask and the solution was heated to reflux for an additional 18 h. Following extraction and concentration, the residue was purified by flash chromatography (15% EtOAc/hexanes) to give the product as an oil in 76% yield (0.12 g, 0.43 mmol): $[\alpha]^{25}_D$ +9.8° (*c* 1.00, CH_2Cl_2); IR (neat) 3334, 1727 cm^{-1}; ^1H NMR (400 MHz, CD_3OD, 57 °C) δ 7.34−7.25 (m, 5H), 5.06−5.02 (m, 2H), 4.35 (s, 1H), 4.00 (q, *J* = 6.7 Hz, 1H), 2.42 (dd, *J* = 14.9, 7.0 Hz, 1H), 2.33 (dd, *J* = 14.9, 6.6 Hz, 1H), 1.41 (s, 9H), 1.17 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 155.5, 136.6, 128.4, 128.0, 80.9, 66.4, 44.2, 41.7, 28.0, 20.3; TLC R_f = 0.43 (30% EtOAc/hexane). Anal. Calcd for $C_{16}H_{23}NO_4$: C, 65.51; H, 7.90; N, 4.77. Found: C, 65.25; H, 8.00; N, 4.65. Exact mass: calcd for $C_{16}H_{24}NO_4$ (M + NH_4) 294.1705; found, 294.1700 (CI, NH_3).

***tert*-Butyl (3*S*)-*N*-(Benzyloxycarbonyl)-3-amino-4-methylpentanoate (6b).** Following the general procedure, a solution of 0.94 g of **5b** (4.37 mmol) in 25 mL of toluene was treated with 0.8 mL of triethylamine (0.574 g, 5.68 mmol) and 0.94 mL of DPPA (1.21 g, 4.37 mmol). After 30 min, the reaction was heated to reflux for 2.5 h. After cooling to 50 °C, 2.2 mL of benzyl alcohol (2.37 g, 21.9 mmol) was added to the reaction flask and the solution was heated to reflux for an additional 21 h. Following extraction and concentration, the residue was purified by flash chromatography (15% EtOAc/hexanes) to give the product as a creamy, pale-yellow solid in 76% yield (1.06 g, 3.32 mmol): $[\alpha]^{25}_D$ +16.8° (*c* 1.00, CH_2Cl_2); mp 38.1−38.5 °C; IR (neat) 3335, 1727 cm^{-1}; ^1H NMR (400 MHz, CD_3OD, 57 °C) δ 7.34−7.24 (m, 5H), 5.09−5.02 (m, 2H), 4.37 (s, 1H), 3.81−3.78 (m, 1H), 2.43 (dd, *J* = 14.8, 4.8 Hz, 1H), 2.29 (dd, *J* = 14.8, 9.3 Hz, 1H), 1.77−1.70 (m, 1H), 1.39 (s, 9H), 0.90 (d, *J* = 5.3, 3H), 0.88 (d, *J* = 5.3, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 155.9, 136.7, 128.3, 127.9, 80.7, 66.4, 53.7, 38.3, 31.9, 27.9, 19.1, 18.4; TLC R_f = 0.43 (30% EtOAc/hexane); exact mass calcd for $C_{18}H_{28}NO_4$ (M + NH_4) 322.2018, found 322.2003 (CI, NH_3).

***tert*-Butyl (3*S*)-*N*-(Benzyloxycarbonyl)-3-amino-3-phenylpropanoate (6c).** Following the general procedure, a solution of 1.00 g of **5c** (3.9 mmol) in 23 mL of toluene was treated with 0.61 mL of triethylamine (0.44 g, 4.4 mmol) and 0.86 mL of DPPA (1.10 g, 3.9 mmol). After 30 min, the reaction was heated to reflux for 3 h. After cooling to 50 °C, 1.25 mL of benzyl alcohol (1.29 g, 12 mmol) was added to the reaction flask and the solution was heated to reflux for an additional 3 h. Following extraction and concentration, the residue was purified by flash chromatography (25% *tert*-butyl methyl ether/pentane) to afford the product as a white solid in 74% yield (1.03 g, 2.9 mmol): $[\alpha]^{25}_D$ −158° (*c* 1.04, CH_2Cl_2); mp 75.3−76.5 °C; IR ($CHCl_3$) 3330, 1727 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35−7.26 (m, 10H), 5.80 (broad s, 1H), 5.10 (broad m, 3H), 2.76 (m, 2H), 1.32 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 155.6, 153.8, 140.9, 136.5, 128.6, 128.5, 127.6, 126.3, 81.3, 66.8, 51.9, 41.9, 27.9; TLC R_f = 0.58 (2:1 hexanes/EtOAc). Anal. Calcd for $C_{21}H_{25}NO_4$: C, 70.98; H, 7.04; N, 3.94. Found: C, 71.11; H, 7.11; N, 4.00.

***tert*-Butyl (3*R*)-*N*-(Benzyloxycarbonyl)-3-amino-4-phenylbutanoate (6d).** Following the general procedure, a solution of 1.00 g of **5d** (3.8 mmol) in 20 mL of toluene was treated with 0.59 mL of triethylamine (0.43 g, 4.2 mmol) and 0.82 mL of DPPA (1.05 g, 3.8 mmol). After 30 min, the reaction was heated to reflux for 1.5 h. After cooling to 50 °C, 0.59 mL of benzyl alcohol (0.62 g, 5.7 mmol) was added to the reaction flask and the solution was heated to reflux for an additional 2 h. Following extraction and concentration, the residue was purified by flash chromatography (30% *tert*-butyl methyl ether/pentane) to give the product as a clear oil in 79% yield (1.1 g, 3.0 mmol): $[\alpha]^{25}_D$ +13.7° (*c* 0.98, CH_2Cl_2); IR (neat) 3335, 1724 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36−7.16 (m, 10H), 5.38 (broad d, *J* = 7.9 Hz, 1H), 5.07 (s, 2H), 4.21−4.17 (m, 1H), 2.96−2.80 (m, 2H), 2.42 (dd, *J* = 15.7, 5.4 Hz, 1H), 2.34 (dd, *J* = 15.7, 5.7 Hz, 1H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 155.6, 137.7, 136.7, 129.4, 128.5, 128.4, 128.0, 126.6, 81.1, 66.5, 49.6, 40.3, 38.7, 28.1; TLC R_f = 0.61 (2:1 hexanes/EtOAc); exact mass calcd for $C_{22}H_{31}N_2O_4$ 387.2284 (M + NH_4), found 387.2271 (CI, NH_3).

***tert*-Butyl (3*S*)-*N*-(Benzyloxycarbonyl)-3-amino-4,4-dimethylpentanoate (6e).** To a solution of 0.144 g of **5e** (0.63 mmol, 1.0 equiv) in 5 mL of THF at 0 °C was added 0.100 mL of triethylamine (0.072 g, 0.71 mmol, 1.1 equiv) via syringe and a precooled (0 °C) solution of 0.070 mL of ethyl chloroformate (0.077 g, 0.71 mmol, 1.1 equiv) in 2.5 mL of THF via cannula. The solution was stirred for 4 h at 0 °C before a solution of 0.122 g of NaN_3 (1.88 mmol, 3.0 equiv) in 1.25 mL of H_2O was added via cannula. After being stirred for 5 h at room temperature, the reaction contents were poured into ice water and extracted with three 20 mL portions of ethyl ether. The combined organic extracts were dried ($MgSO_4$), filtered through cotton, and concentrated in vacuo to afford a milky oil. A solution of the oil in 15 mL of toluene and 0.200 mL of BnOH (0.203 g, 1.88 mmol, 3.0 equiv) was then heated to reflux

for 12 h. Concentration of the solution gave a yellow oil, which was chromatographed on silica gel (20% EtOAc/hexanes) to afford the product as a pale yellow oil in 74% yield (0.155 g, 0.46 mmol): $[\alpha]^{25}_D$ +17.1° (*c* 2.00, CH_2Cl_2); IR (neat) 3329, 1732, 1716 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35−7.27 (m, 5H), 5.08 (s, 2H), 4.92 (d, 1H, J = 10.2 Hz), 3.96−3.90 (m, 1H), 2.54 (dd, J = 14.5, 3.9 Hz), 2.14 (dd, J = 14.4, 10.4 Hz, 1H), 1.39 (s, 9H), 0.91 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 156.1, 136.7, 128.5, 128.2, 128.0, 80.9, 66.6, 56.8, 37.5, 36.9, 27.9, 26.3; TLC R_f = 0.51 (30% EtOAc/hexanes); exact mass calcd for $C_{19}H_{33}N_2O_4$ (M + NH_4) 353.2440, found 353.2425 (CI, NH_3).

General Procedure for the Acid Deprotection of β-Amino Esters. To a 0 °C solution of the β-amino ester **6** (0.312 mmol) in 3 mL of a 70:30 (v/v) CH_2Cl_2/trifluoroacetic acid solution was added 10 equiv of Me_2S. The solution was stirred at room temperature for 3.5 h, and the contents were concentrated in vacuo and under high vacuum to yield a residue. The residue was dissolved in 10 mL of CH_2Cl_2 and extracted with 15 mL of 1 M NaOH. After washing with two 15 mL portions of CH_2Cl_2, the aqueous layer was acidified to a pH < 2 with 1 M HCl. The aqueous solution was extracted with three 10 mL portions of CH_2Cl_2. The combined CH_2Cl_2 extracts were dried ($MgSO_4$), filtered through cotton, and concentrated in vacuo to yield the acid **7** as a white solid.

(3*S*)-*N*-(Benzyloxycarbonyl)-3-amino-4-methylpentanoic acid (7b). A solution of 0.100 g of **6b** (0.312 mmol) in 3 mL of a 70:30 (v/v) solution of CH_2Cl_2/trifluoroacetic acid was treated with 0.230 mL of Me_2S (0.193 g, 3.12 mmol) at 0 °C. After the mixture was stirred for 3.5 h at room temperature, the product was isolated according to the general procedure to afford a white solid in 91% yield (0.075 g, 0.283 mmol): $[\alpha]^{25}_D$ +19.7° (*c* 1.38, CH_2Cl_2).

(3*S*)-*N*-(Benzyloxycarbonyl)-3-amino-3-phenylpropanoic acid (7c). A solution of 0.150 g of **6c** (0.422 mmol) in 4.2 mL of a 70:30 (v/v) solution of CH_2Cl_2/trifluoroacetic acid was treated with 0.310 mL of Me_2S (0.262 g, 4.22 mmol) at 0 °C. After the mixture was stirred for 3 h at room temperature, the product was isolated according to the general procedure to afford a white solid in 91% yield (0.115 g, 0.385 mmol): $[\alpha]^{25}_D$ −23.2° (*c* 1.0, EtOH).

(3*R*)-*N*-(Benzyloxycarbonyl)-3-amino-4-phenylbutanoic acid (7d). A solution of 0.104 g of **6d** (0.282 mmol) in 3 mL of a 70:30 (v/v) solution of CH_2Cl_2/trifluoroacetic acid was treated with 0.200 mL of Me_2S (0.175 g, 2.82 mmol) at 0 °C. After the mixture was stirred for 3 h at room temperature, the product was isolated according to the general procedure to afford a white solid in 95% yield (0.084 g, 0.268 mmol): $[\alpha]^{25}_D$ +26.7° (*c* 1.0, AcOH).

(3*S*)-3-Amino-4-methylpentanoic Acid (8). A solution of 0.043 g of **7b** (0.162 mmol) in 2 mL of MeOH was treated with a catalytic amount of $Pd(OH)_2$. The mixture was stirred at room temperature under 100 psi of H_2 for 4.5 h. The catalyst was removed by filtering the mixture through a bed of Celite. The filtrate was evaporated in vacuo to afford a white solid in 96% yield (0.020 g, 0.156 mmol): $[\alpha]^{25}_D$ +51.5° (*c* 0.6, H_2O).

Acknowledgment. This research was supported by the NIH (Grant GM-33328). We acknowledge the NIH BRS Shared Instrumentation Grant Program 1-S10-RR04870 and the NSF (Grant CHE 88-14019) for providing NMR facilities. Enantiopure (4*S*)-4-(phenylmethyl)-1,3-oxazolidin-2-one was generously provided by NSC Technologies.

Supporting Information Available: Tables of X-ray data and ^1H NMR spectra for compounds **2e**, **4**, **5b**,**e**, and **6b**,**d**, and **6e**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO990756K