Preparation of 4-Oxo-L-norvaline via Diazomethane Homologation of β-Aspartyl Semialdehyde

R. Marshall Werner, Ori Shokek, and Jeffery T. Davis*

Department of Chemistry and Biochemistry, University of Maryland at College Park, College Park, Maryland 20742

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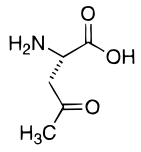
Introduction

Much effort has been devoted to the synthesis of peptidyl aldehydes and ketones as protease inhibitors.[1] In these inhibitors, the electrophilic carbonyl is located at the C-terminus of the peptide backbone. Recently, there has been increased interest in incorporating the oxo functionality into amino acid and peptide side chains.[2,3] In studying the mechanism of enzymatic asparagine glycosylation, we required a peptide that contained the rare amino acid 4-oxo-L-norvaline (**1**).[4] Oligosaccharyltransferase (OST) catalyzes the cotranslational N-glycosylation of the Asn-Xaa-Ser/Thr consensus sequence in eukaryotic proteins.[5] N-Benzoylated tripeptides, including Bz-Asn-Leu-Thr-NH_2 (**2**), are excellent in vitro glycosylation substrates for OST.[6] The related tripeptide **3**, designed as a potential OST substrate and/or inhibitor, contains 4-oxo-L-norvaline in place of the critical Asn residue. Before preparing peptide **3**, we required an efficient synthesis of 4-oxo-L-norvaline (**1**).



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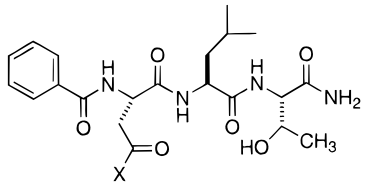

2 (X= NH_2)
3 (X= CH_3)

One route to 4-oxo-L-norvaline (**1**) is via reduction of 5-diazo-4-oxo-L-norvaline, which itself is derived from L-aspartic acid.[7] In addition, 4-oxo-L-norvaline (**1**) has been prepared from ozonolysis of 4,5-dehydroleucine, from L-serine, and by enzymatic resolution of racemic material.[3,8,9] In this paper, we report a new and efficient method for preparation of 4-oxo-L-norvaline (**1**). The synthetic methodology used to make **1**, insertion of a diazoalkyl into an aldehyde, promises to be general for the preparation of other oxo α-amino acids.

Results and Discussion

Diazomethane Homologation. Conversion of aldehydes to ketones via diazoalkyl insertion is a classic reaction.[10] A diazoalkyl insertion strategy, however, has not been previously reported for the synthesis of functionalized α-amino acids. Since aldehyde-containing α-amino acids are accessible from either alcohol- or carboxyl-containing side chains, we reasoned that diazoalkyl homologation would be a convenient method for preparation of keto α-amino acids. Our synthesis of 4-oxo-L-norvaline (**1**) is based on the homologation of an appropriately protected β-aspartyl semialdehyde, **5** (Scheme 1). As discussed below, use of *tert*-butyl protecting groups for the α-amino and carboxyl is important since these protecting groups can be easily removed without concomitant racemization of 4-oxo-L-norvaline (**1**).

Swern oxidation of the known L-homoserine derivative **4**[11] gave the key β-aspartyl semialdehyde **5** in excellent yield. Treatment of **5** with excess diazomethane in CH_2Cl_2 afforded methyl ketone **6** in 88% yield after purification. The ^{1}H NMR spectrum of the crude reaction mixture indicated that ketone **6** was the only major product formed in the homologation reaction. The high selectivity of diazomethane addition to β-aspartyl semialdehyde **5** is noteworthy since diazoalkyl insertion into aldehydes can be compromised by competing alkyl migration, double homologation, and epoxide formation.[10] The *tert*-butyl protecting groups of ketone **6** were removed under mild conditions, CF_3COOH in CH_2Cl_2 (1:2) at room temperature, to afford 4-oxo-L-norvaline (**1**) as the trifluoroacetate salt. Anion exchange with Dowex (Cl^-) resin provided the hydrochloride salt of 4-oxo-L-norvaline (**1**) in 96% yield from **6**. Importantly, no racemization could be detected in this 3-step transformation of homoserine **4** to 4-oxo-L-norvaline (**1**). Thus, comparison of the ^{1}H and ^{19}F NMR spectra of the Mosher's amides (*RS*)-**7** and (*RR*)-**7**, derived from both 4-oxo-DL-norvaline and 4-oxo-L-norvaline (**1**), indicated the presence of less than 1% of the (*RR*)-**7** diastereomer.[12,13]

The results outlined in Scheme 2 demonstrate that appropriate protecting groups are crucial in the synthesis of 4-oxo-L-norvaline (**1**) in enantiomerically pure form.

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(13) The accuracy of the ^{1}H NMR analysis of Mosher's amides was determined by addition of sequential amounts (0.5%, 1%, 2%, 4%, 8%, and 16%) of a purified 1:1 mixture of (*RS*)-**7**:(*RR*)-**7**, prepared from 4-oxo-DL-norvaline, to a $CDCl_3$ solution of (*RS*)-**7** derived from crude 4-oxo-L-norvaline (**1**). Integration of methyl ketone ^{1}H NMR signals for (*RS*)-**7** at 2.09 ppm and for (**RR**)-**7** at 2.19 ppm indicated that less than 1% racemization occurred during the synthesis of 4-oxo-L-norvaline (**1**) from homoserine **4**.

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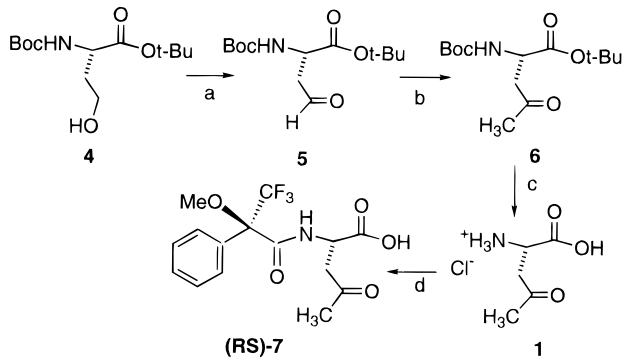
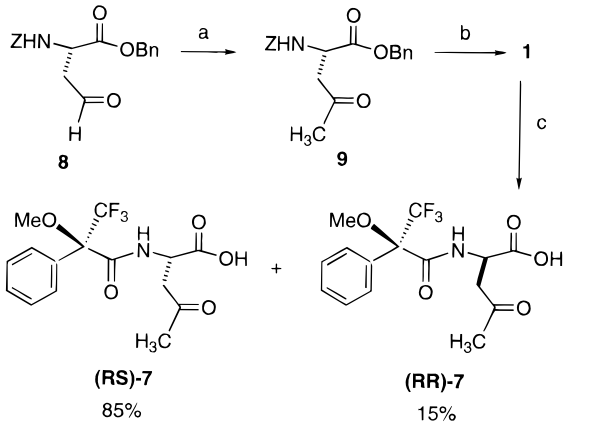
Scheme 1[a]



[a] (a) Oxalyl chloride, DMSO, NEt_3, −78 °C, 93%; (b) CH_2N_2, CH_2Cl_2, rt, 88%; (c) TFA−CH_2Cl_2 (1:2), rt, Dowex (Cl^-), 96%; (d) Hunig's base, *R* Mosher's acid chloride, DMF, rt.

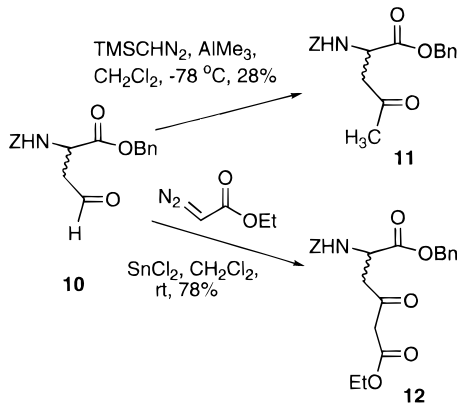
Scheme 2[a]



[a] (a) CH_2N_2, CH_2Cl_2, rt, 90%; (b) 3 N HCl, reflux 16 h, 100%; (c) Hunig's base, *R* Mosher's acid chloride, DMF.

Homologation of the known β-aspartyl semialdehyde **8**[14] with diazomethane smoothly afforded methyl ketone **9**. Attempts to deprotect **9** by hydrogenolysis, using either Pd/C or PtO_2, were unsatisfactory due to competitive reduction of the 4-oxo side chain. Instead, hydrolysis of the benzyl protecting groups in 3 N HCl at reflux gave the hydrochloride salt of 4-oxo-L-norvaline (**1**) in quantitative yield.[15] However, analysis of the amino acid's optical purity indicated that significant racemization of 4-oxonorvaline (**1**) had occurred during the acid-catalyzed hydrolysis. Comparison of the ^1H and ^{19}F NMR spectra of the Mosher's amides (*RS*)-**7** and (*RR*)-**7**, derived from racemic 4-oxo-DL-norvaline and the enriched 4-oxo-L-norvaline (**1**), revealed the presence of approximately 15% of the (*RR*)-**7** diastereomer. Racemization likely occurred during acid hydrolysis of **9**, especially since TFA deprotection of the *t*-Boc-4-oxo-L-norvaline *tert*-butyl ester (**6**) gave enantiomerically pure **1** (see Scheme 1).[16] In summary, the studies outlined in Schemes 1 and 2 indicate that preparation of optically pure 4-oxo-L-norvaline (**1**) depends on the proper protection of the α-amino and carboxylate groups.

Scheme 3



Generality of Diazo Additions to β-Aspartyl Semialdehyde. Diazo reagents other than diazomethane were also used to homologate β-aspartyl semialdehyde. For example, Yamamoto has described the use of (trimethylsilyl)diazomethane as a convenient and safe alternative to diazomethane in aldehyde homologations.[17] In our case, treatment of racemic β-aspartyl semialdehyde **10** with (trimethylsilyl)diazomethane and $AlMe_3$ at −78 °C in CH_2Cl_2 gave methyl ketone **11** in 28% yield after purification (Scheme 3). Although reaction of aldehyde **10** with (trimethylsilyl)diazomethane was not as clean as the diazomethane homologation, useful quantities of the 4-oxo-L-norvaline derivative **11** could be obtained using this reagent. In addition to 4-oxonorvaline, a novel α-amino acid with a keto ester side chain was prepared in good yield via diazoalkyl insertion using Roskamp's protocol.[18] Thus, treatment of racemic β-aspartyl semialdehyde **10** with ethyl diazoacetate and catalytic $SnCl_2$ gave the β-keto ester **12** in 78% yield after chromatography (Scheme 3).

In conclusion, we have prepared the rare amino acid 4-oxo-L-norvaline (**1**) via diazomethane homologation of β-aspartyl semialdehyde. Homologation of β-aspartyl semialdehyde was extended to two other diazoalkyl reagents, (trimethylsilyl)diazomethane and ethyl diazoacetate. These studies suggest that diazoalkyl insertion into β-aspartyl semialdehydes is a useful and general method for making 4-oxo α-amino acids. We have subsequently incorporated 4-oxo-L-norvaline (**1**) into keto tripeptide **3**. The synthesis and the OST substrate and inhibitor activity of tripeptide **3** will be the subject of a future report.

Experimental Section

General. All reactions were done under an inert atmosphere using distilled solvents. TLC was performed on Kieselgel 60 F_{254} silica-coated glass plates and visualized by ethanol/sulfuric acid or ninhydrin charring. Flash chromatography was performed using Kieselgel 60 brand silica gel (230−400 mesh). Solvents used for NMR spectroscopy were 99.0−99.9% deuterium-enriched. All ^{19}F NMR spectra were referenced relative to an external glass capillary containing neat TFA.

***tert*-Butyl (*S*)-2-[(*tert*-Butoxycarbonyl)amino]-4-oxobutanoate (5).** To a solution of 0.526 mL (6.03 mmol) of oxalyl

(14) Keith, D. D.; Tortora, J. A.; Ineichun, K.; Leimgruber, W. *Tetrahedron* **1975**, *31*, 2633.

(15) For a related acid hydrolysis to give 5-chloro-4-oxo-L-norvaline, see: Khedouri, E.; Anderson, P. M.; Meister, A. *Biochemistry* **1966**, *5*, 3552.

(16) We independently verified that the diazomethane homologation of β-aspartyl aldehyde does not give racemization. Thus the *R* Mosher's amides of both L-homoserine methyl ester and DL-homoserine methyl ester were transformed into the respective 4-oxonorvaline derivatives via our Swern oxidation−diazomethane homologation protocol. The ^1H, ^{19}F, and ^{13}C NMR analysis showed that a single 4-oxonorvaline enantiomer was produced from the *R* Mosher's amide of L-homoserine methyl ester, confirming that racemization does not occur during the oxidation−homologation steps.

(17) Maruoka, K.; Concepcion, A. B.; Yamamoto, H. *Synthesis* **1994**, 1283.

(18) Holmquist, C. R.; Roskamp, E. J. *J. Org. Chem.* **1989**, *54*, 3258.

chloride in 20 mL of CH_2Cl_2 at −78 °C was added 0.856 mL (12.06 mmol) of DMSO. To this mixture was added 1.51 g (5.48 mmol) of **4**[11] dissolved in 40 mL of CH_2Cl_2. After stirring for 30 min, 3.82 mL (27.4 mmol) of NEt_3 was added to the reaction mixture. The reaction mixture was stirred for 5 min at −78 °C and then warmed to rt. After 2 h, the reaction mixture was diluted with 100 mL of CH_2Cl_2 and washed with 100 mL of satd NaCl. The organic layer was dried over Na_2SO_4, concentrated in vacuo, and immediately subjected to silica gel flash chromatography (1:1 hexane−ethyl acetate) to afford 1.391 g (93%) of **5** as a white solid: mp 60−62 °C; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 9.69 (s, 1H), 5.33 (d, 1H, J = 7.3 Hz), 4.44 (m, 1H), 2.98 (dd, 1H, J = 5.0, 17.9 Hz), 2.90 (dd, 1H, J = 5.0, 17.8 Hz), 1.41 (s, 9H), 1.40 (s, 9H); ^{13}C NMR(100 MHz) ($CDCl_3$) δ 199.4, 169.9, 155.3, 82.6, 79.9, 49.3, 46.3, 28.2, 27.8; IR ($CDCl_3$) 3435, 1793, 1733, 1684; FAB MS m/z 274 (M^+ + 1, 5), 218 (8), 192 (12), 162 (30), 57 (100); HRMS (M^+ + 1) m/z calcd for $C_{13}H_{24}O_5N_1$ 274.165 44, found 274.164 11; $[\alpha]^{21}_D$ = +20.7 (c = 1.95 in CH_2Cl_2). Anal. Calcd for $C_{13}H_{24}O_5N_1$: C, 57.10; H, 8.50; N, 5.10. Found: C, 56.70; H, 8.49; N, 4.96.

***tert*-Butyl (*S*)-2-[(*tert*-Butoxycarbonyl)amino]-4-oxopentanoate (6).** To a solution of 1.26 g (4.61 mmol) of **5** in 100 mL of CH_2Cl_2 was added 9.34 mmol of ethereal diazomethane at rt. **Caution: Diazomethane should be generated from *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide using an Aldrich diazald glassware kit. Use appropriate precautions.**[19] The reaction mixture was stirred for 18 h, after which time diazomethane's characteristic yellow color had disappeared. The reaction was quenched with 10 mL of 0.1 N HCl and the mixture extracted with CH_2Cl_2. The organic layer was concentrated to afford 1.318 g (99.5%) of the methyl ketone **6** as a white solid. ^{1}H NMR of the crude reaction mixture indicated only minor impurities. Silica gel flash column chromatography (1.5:1 hexane−ethyl acetate) of the crude product afforded 1.17 g (88%) of **6** as a white solid: mp 64−65 °C; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 5.41 (d, 1H, J = 8.1 Hz), 4.34 (m, 1H), 3.08 (dd, 1H, J = 4.3, 17.9 Hz), 2.87 (dd, 1H, J = 4.3, 17.9 Hz), 2.13 (s, 3H), 1.43 (s, 9H), 1.41 (s, 9H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 206.0, 170.0, 155.3, 81.7, 79.4, 49.9, 45.3, 29.6, 28.1, 27.6; IR ($CDCl_3$) 3439, 1737, 1712, 1682; FAB MS m/z 288 (M^+ + 1, 13), 250 (18), 232 (25), 176 (87), 57 (100); HRMS (M^+ + 1) m/z calcd for $C_{14}H_{26}O_5N_1$ 288.181 09, found 288.182 39; $[\alpha]^{20}_D$ = +13.9 (c = 2.62 in CH_2Cl_2). Anal. Calcd for $C_{14}H_{26}O_5N_1$: C, 58.50; H, 8.78; N, 4.87. Found: C, 58.43; H, 8.74; N, 4.72.

4-Oxo-L-norvaline Hydrochloride (1). Method A: Via TFA Deprotection of 6. A solution of 1.268 g (4.40 mmol) of **6** in 30 mL of a 2:1 CH_2Cl_2−TFA solution was stirred for 16 h at room temperature. The reaction mixture was concentrated in vacuo to afford 1.165 g (99%) of the TFA salt of 4-oxo-L-norvaline as a yellow gum. Upon lyophilization from water, a light yellow solid was formed: mp 50−52 °C; $[\alpha]^{23}_D$ = +8.19 (c = 2.14 in H_2O). To a solution of 0.586 g (2.38 mmol) of this TFA salt in 15 mL of methanol was added 3.0 g (10.5 mequiv of Cl^-) of Dowex resin (Sigma). The suspension was gently shaken for 24 h, and the resin was filtered and washed with methanol (3 × 25 mL). The combined organic fractions were concentrated *in vacuo* to provide 0.381 g (96%) of the hydrochloride salt **1** as a light yellow solid. Recrystallization (3×) from methanol and ethyl acetate provided white solids: mp 148−149 °C dec (lit. mp 146 °C);[7a] ^{1}H NMR (400 MHz) (D_2O) δ 4.13 (t, 1H, J = 5.2 Hz), 3.18 (dd, 2H, J = 5.2, 16.5 Hz), 2.09 (s, 3H); ^{13}C NMR (100 MHz) (D_2O/DSS external reference) δ 212.9, 175.2, 52.0, 45.1, 31.8; IR (5% KBr) 3680−3297, 3297−2747, 1711, 1635; FAB MS m/z 132 (M^+, 100), 115 (37), 93 (25); HRMS (M^+) m/z calcd for $C_5H_{10}O_3N_1$ 132.066 07, found 132.065 35; $[\alpha]^{23}_D$ = +8.05 (c = 0.9 in H_2O). Anal. Calcd for $C_5H_{10}O_3NCl$: C, 35.83; H, 6.01; N, 8.36; Cl, 21.15. Found: C, 35.63; H, 5.85; N, 8.23; Cl, 21.07.

Method B: Via HCl-Catalyzed Hydrolysis of 9. A solution of 5.30 g of methyl ketone **9** in 50 mL of 3.0 N HCl was heated at reflux for 18 h. The solution was concentrated in vacuo to 10 mL and washed with 100 mL of ether, and the aqueous layer was lyophilized to afford 1.97 g (100%) of the hydrochloride salt of 4-oxo-L-norvaline (**1**) as a yellow oil. Analysis of the Mosher's amide derivatives (*RS*)-**7** and (*RR*)-**7** indicated that this sample of 4-oxonorvaline hydrochloride (**1**) contained 15% of the 4-oxo-D-norvaline enantiomer and 85% of 4-oxo-L-norvaline.

(19) Black, T. H. *Aldrichim. Acta* **1983**, *16*, 3.

Mosher's Amides (*RS*)-7 and (*RR*)-7 from 4-Oxo-DL-norvaline. To a solution of 0.054 g (0.323 mmol) of 4-oxo-DL-norvaline hydrochloride (**1**) in 0.25 mL of dry DMF were added 0.112 mL (0.646 mmol) of diisopropylethylamine and 0.067 mL (0.335 mmol) of (*R*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (Aldrich). After 2 h at rt the reaction was quenched with 1.0 mL of 0.1 N HCl, the mixture was extracted with 2.0 mL of ethyl acetate (3×), and the organic layers were concentrated in vacuo. The resulting yellow oil was purified by preparative HPLC using a C-18 column (0−100% CH_3CN over 90 min). A fraction with retention time of 50.0−50.8 min was collected and lyophylized to afford a 1:1 mixture of (*RS*)-**7**:(*RR*)-**7** as a white solid: ^{1}H NMR (400 MHz) ($CDCl_3$) δ 7.94 (d, 0.5H, J = 8.1 Hz), 7.63 (d, 0.5H, J = 7.9 Hz), 7.52−7.34 (m, 5H), 4.86−4.78 (m, 1H), 3.48 (q, 1.5H, $^4J_{H-F}$ = 1.5 Hz), 3.30 (q, 1.5H, $^4J_{H-F}$ = 1.5 Hz), 3.26−3.18 (m, 1H), 3.05−2.92 (m, 1H), 2.19 (s, 1.5H), 2.09 (s, 1.5H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 206.9, 206.6, 174.5, 174.4, 166.7, 131.5, 129.7, 129.6, 128.7, 128.6, 128.1, 127.3, 55.2, 54.5, 48.0, 47.9, 44.4, 44.0, 29.8, 29.8; ^{19}F NMR (400 MHz) ($CDCl_3$) δ 8.98 (s), 8.48 (s).

Mosher's Amide (*RS*)-7 from 4-Oxo-L-norvaline (1). To a solution of 0.0079 g (0.047 mmol) of 4-oxo-L-norvaline hydrochloride (**1**) (derived from method A) in 0.25 mL of dry DMF were added 0.017 mL (0.0946 mmol) of diisopropylethylamine and 0.010 mL (0.052 mmol) of (*R*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (Aldrich). After 2 h at rt the reaction was quenched with 1.0 mL of 0.1 N HCl, the mixture was extracted with 2.0 mL of ethyl acetate (3×), and the organic layers were concentrated in vacuo. The resulting crude mixture was dissolved in $CDCl_3$ and analyzed by ^{1}H and ^{19}F NMR spectroscopy. Integration of the (*RS*)-**7** methyl ketone resonance at 2.09 ppm indicated that the 4-oxo-L-norvaline (**1**) prepared using method A was >99% optically pure.[16] A small amount of (*RS*)-**7** was purified by silica gel flash column chromatography to aid in NMR peak assignment (see ^{1}H NMR spectrum in Supporting Information): ^{1}H NMR (400 MHz) ($CDCl_3$) δ 7.59 (d, 1H, J = 8.0 Hz), 7.47 (m, 2H), 7.36 (m, 3H), 4.81 (m, 1H), 3.49 (q, 3H, $^4J_{H-F}$ = 1.5 Hz), 3.21 (dd, 1H, J = 18.6, 4.3 Hz), 2.95 (dd, 1H, J = 18.6, 4.3 Hz), 2.09 (s, 3H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 206.5, 174.9, 166.6, 132.5, 129.6, 128.5, 127.3, 125.3, 122.1, 55.2, 47.9, 44.0, 29.7; IR (CH_2Cl_2) 3415, 1760, 1698; FAB MS m/z 348 (M^+ + 1, 25), 316 (19), 260 (24), 189 (100); HRMS (M^+ + 1) m/z calcd for $C_{15}H_{17}O_5N_1F_3$ 348.105 90, found 348.105 91; $[\alpha]^{23}_D$ = +7.42 (c = 0.74 in CH_2Cl_2); ^{19}F NMR (400 MHz) ($CDCl_3$) δ 8.98 (s).

Following the above procedure, 4-oxo-L-norvaline hydrochloride (**1**) derived from method B was converted to the Mosher's amides. The ^{1}H and ^{19}F NMR analysis indicated approximately 85% (*RS*)-**7** and 15% (*RR*)-**7**.

Benzyl (*S*)-2-(Carbobenzoxyamino)-4-oxopentanoate (9). To a solution of 5.08 g (14.9 mmol) of aldehyde **8**[14] in 50 mL of CH_2Cl_2 was added 23.3 mmol of ethereal diazomethane at rt. **Caution: Diazomethane was generated from *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide using an Aldrich diazald glassware kit. Use appropriate precautions.**[19] The reaction mixture was stirred open to the atmosphere for 15 h, after which time diazomethane's characteristic yellow color had disappeared. The reaction was quenched with 10 mL of 0.1 N HCl and the mixture extracted with CH_2Cl_2. Concentration of the reaction mixture afforded 5.30 g (99%) of the methyl ketone **6** as a yellow oil. Both TLC and ^{1}H NMR of the crude reaction mixture indicated that the ketone was the major product. The crude oil was dissolved in 100 mL of CH_2Cl_2, washed with 100 mL of 0.1 N HCl, 100 mL of satd $NaHCO_3$, and 100 mL of satd NaCl, dried over Na_2SO_4, concentrated in vacuo, and purified by silica gel flash column chromatography (2:1 hexane−ethyl acetate) to afford 4.77 g (90%) of ketone **9** as a yellow oil: ^{1}H NMR (400 MHz) ($CDCl_3$) δ 7.36−7.25 (m, 10H), 5.83 (d, 1H, J = 8.6 Hz), 5.13 (s, 2H), 5.09 (s, 2H), 4.59 (ddd, 1H, J = 4.2, 4.3, 8.6 Hz), 3.18 (dd, 1H, J = 4.3, 18.3 Hz), 2.95 (dd, 1H, J = 4.2, 18.3 Hz), 2.08 (s, 3H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 206.0, 170.7, 156.0, 136.1, 135.2, 128.5, 128.4, 128.3, 128.0, 127.9, 67.3, 66.9, 50.0, 45.1, 29.7; IR ($CDCl_3$) 1794, 1743, 1719; FAB MS m/z 356.3 (M^+ + 1, 6), 312.2 (3), 181.1 (6), 147.0 (6), 91.1 (100), 73.0 (16); HRMS (M^+) m/z calcd for $C_{20}H_{21}O_5N$ 355.1419, found 355.1436; $[\alpha]^{21}_D$ = +10.4 (c = 4.60 in $CHCl_3$).

Benzyl (*R/S*)-2-(Carbobenzoxyamino)-4-oxopentanoate (11) via (Trimethylsilyl)diazomethane. To a solution of

0.265 g (0.77 mmol) of DL-aldehyde **10** in 10 mL of CH_2Cl_2 was added 0.466 mL (0.93 mmol) of a 2.0 M solution of $AlMe_3$ in hexanes (Aldrich). The reaction mixture was cooled to −78 °C, and 1.4 mL of a 2.0 M solution of (trimethylsilyl)diazomethane in hexanes (Aldrich) was added. After stirring for 5 h at −78 °C the reaction mixture was diluted with 30 mL of 0.1 N HCl and an additional 10 mL of CH_2Cl_2. The organic fraction was separated and washed with 20 mL of satd NaCl, dried over Na_2SO_4, and concentrated in vacuo. The resulting yellow oil was immediately subjected to silica gel flash column chromatography (2:1 hexane−ethyl acetate) to afford 0.0745 g (28%) of the DL-methyl ketone **11** as a yellow oil. All NMR and MS spectral data for **11** were identical with that of the L-enantiomer **9**.

***N*-(Carbobenzyloxy)-4-oxo-5-(ethoxyacetyl)-DL-norvaline (12).** To a solution of 0.320 g (0.94 mmol) of DL-aldehyde **10** in 9 mL of CH_2Cl_2 at rt was added 0.0089 g (5 mol %) of tin(II) chloride and 0.103 mL (0.95 mmol) of ethyl diazoacetate (Aldrich). Immediate gas evolution was observed, and after 30 min, TLC indicated the reaction was complete. The reaction was quenched with 10 mL of 0.1 N HCl, and the reaction mixture was extracted with 20 mL of CH_2Cl_2. The combined organic layers were washed with 10 mL of satd NaCl, dried over Na_2SO_4, and concentrated in vacuo. Silica gel flash column chromatography (3:1 hexane−ethyl acetate) afforded 0.303 g (78%) of the β-keto ester **12** as a white solid: mp 112−113 °C; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 7.33−7.29 (m, 10H), 5.75 (d, 1H, J = 8.4 Hz), 5.14 (s, 2H), 5.08 (s, 2H), 4.62 (ddd, 1H, J = 4.3, 4.5, 8.5 Hz), 4.13 (q, 2H, J = 7.2, 14.3 Hz), 3.38 (s, 2H), 3.29 (dd, 2H, J = 4.5, 18.9 Hz), 3.12 (dd, 1H, J = 4.2, 18.5 Hz), 1.22 (t, 3H, J = 7.1, 14.2 Hz); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 200.7, 170.5, 166.9, 155.9, 136.1, 135.1, 128.5, 128.4, 128.2, 128.0, 67.5, 67.0, 61.5, 49.9, 49.1, 44.5, 14.0; IR ($CDCl_3$) 1792, 1733, 1718, 1684; FAB MS m/z 427.8 (M^+, 5), 153.9 (42), 135.9 (42), 90.9 (100); HRMS ($M^+ + 1$) m/z calcd for $C_{23}H_{25}O_7N$ 428.1666, found 428.1691.

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Supporting Information Available: ^{1}H NMR spectra for compounds **1**, **5**−**7**, **9**, and **12** and ^{13}C NMR spectra of **1**, **5**, and **6** (10 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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