Asymmetric Synthesis of α-Alkyl-α-amino Acids from Chromium–Carbene-Complex-Derived β-Lactams

Pierre-Jean Colson and Louis S. Hegedus*

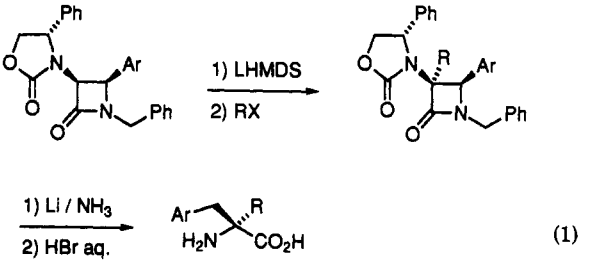
Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523

Received July 19, 1993•

Optically active bicyclic β-lactam **3** was synthesized by photolysis of optically active oxazolidine carbene chromium complex **1** with oxazine **2**. Conversion of the oxazolidine to the oxazolidinone gave a bicyclic β-lactam readily α-alkylated. Cleavage of the alkylated β-lactam gave optically active ester aldehyde **7**, which was converted to a number of optically active α-alkyl-α-amino acids. These include (*R*)-α-methylserine, (*S*)-α-methylglutamic acid, (*S*)-α-methylornithine, (*S*)-vinylalanine, (*S*)-ethynylalanine, and (*S*)-2-methyl-2,3-diaminopropionic acid.

Introduction

α-Alkyl-α-amino acids constitute an important class of nonproteinogenic amino acids which has received a great deal of recent attention.[1] Incorporation of these compounds into peptides results in conformational restrictions and increased rigidity, leading to enhanced resistance toward protease enzymes,[2] and to the favoring of particular secondary structures.[3] In addition, the compounds themselves may act as enzyme inhibitors.[4] Because of this range of biological activities, a wide variety of synthetic approaches to α-alkyl-α-amino acids have been developed.[5] Among the more general are the Schöllkopf's bis-lactim ether approach,[6] Seebach's imidazolidinone approach,[7] and William's oxazinone approach,[5a] although many others have been reported.[8] The most pertinent to this report is Ojima's β-lactam approach, in which optically active β-lactams (from the Staudinger reaction of imines with optically active oxazolidinone ketenes) are stereospecifically α-alkylated and then cleaved to produce α-alkyl-α-amino acids (eq 1).[9]



(1)

Research in our laboratories has recently centered on the synthesis of optically active α-amino acids and peptides utilizing photochemical reactions of chromium aminocarbene complexes.[10] Although this process is efficient and highly diastereoselective, α-alkyl-α-amino acids *cannot* be made by this procedure, since the α-center is set in an asymmetric protonation. Optically active β-lactams are also readily available by chromium aminocarbene complex photochemistry,[11] and, on the basis of the precedent in eq 1, one of them appeared to be an ideal precursor to an intermediate of general use in the synthesis of α-alkyl-α-amino acids (eq 2). Studies addressing this issue are presented.

Results and Discussion

Initial attempts to methylate β-lactam **3** under a wide variety of conditions failed, either resulting in recovered starting material or degradation. To determine if the problem lies with the deprotonation step or the alkylation step, compound **3** was treated with *tert*-butyllithium at −78 °C for 1 h and then quenched with D_2O. An 85% yield of >90% deuterated **3** was recovered indicating deprotonation had occurred efficiently and the problem lies with the alkylation step. The oxazolidine chiral

• Abstract published in *Advance ACS Abstracts,* September 15, 1993.

(1) (a) For an overview, see Williams, R. M. *Synthesis of Optically Active Amino Acids*; Pergamon Press: Oxford, 1989; Vol. 7. (b) For a recent review see: Heimgartner, H. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 238.

(2) Tomiolo, C.; Crisma, M.; Pegoraro, S.; Becker, E. L.; Polinelli, S.; Boesten, W. H. J.; Schoemaker, H. E.; Meijer, E. M.; Kamphuis, J.; Freer, R. *Peptide Res.* **1991**, *4*, 66.

(3) Paul, P. K. C.; Sukumar, M.; Bardi, R.; Piazzesi, A. M.; Valle, G.; Toniolo, C.; Balaram, P. *J. Am. Chem. Soc.* **1986**, *108*, 6363 and refs therein.

(4) For example: (a) Walsh, J. J.; Metzler, D. E.; Powell, D.; Jacobson, R. A. *J. Am. Chem. Soc.* **1980**, *102*, 7136. (b) Ramalingam, K.; Woodard, R. W. *Tetrahedron Lett.* **1985**, *26*, 1135.

(5) (a) Williams, R. M.; Im, M-N. *J. Am. Chem. Soc.* **1991**, *113*, 9276 and refs therein. (b) Obrecht, D.; Spiegler, C.; Schönholzer, P.; Müller, K.; Heimgartner, H.; Strerli, F. *Helv. Chim. Acta* **1992**, *75*, 1666 and refs therein.

(6) (a) Schöllkopf, U.; Schröder, J. *Liebigs Ann. Chem.* **1988**, 87. (b) Schöllkopf, U.; Westphalen, K.-O.; Schröder, J.; Horn, K. *Liebigs Ann. Chem.* **1988**, 781. (c) Schöllkopf, U.; Bardenhagen, J. *Liebigs Ann. Chem.* **1987**, 393. (d) Schöllkopf, U.; Hinrichs, R.; Lonsky, R. *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 143. (e) Schöllkopf, U.; Tolle, R.; Egert, E.; Nieger, M. *Liebigs, Ann. Chem.* **1987**, 399. (f) Schllkopf, U.; Scheuer, R. *Liebigs Ann. Chem.* **1984**, 939. (g) Groth, U.; Schöllkopf, U.; Chiang, Y-C. *Synthesis* **1982**, 864. (h) Groth, U.; Chiang, Y-C.; Schöllkopf, U. *Liebigs Ann. Chem.* **1982**, 175.

(7) (a) Seebach, D.; Imwinkelried, R.; Weber, T. *Modern Synthetic Methods*; Springer Verlag: Heidelberg, 1986; Vol. 4, p 128. (b) Seebach, D.; Burger, H. M.; Schickli, C. P. *Liebigs Ann. Chem.* **1991**, 669. (c) Seebach, D.; Vettiger, T.; Muller, H-M.; Plattner, D. A.; Petter, W. *Liebigs Ann. Chem.* **1990**, 687. (d) Gander-Coquoz, M.; Seebach, D. *Helv. Chim. Acta* **1988**, *71*, 224. (e) Fadel, A.; Salaun, J. *Tetrahedron Lett.* **1987**, *28*, 2243. (f) Seebach, D.; Juaristi, E.; Miller, D. D.; Schickli, C.; Weber, T. *Helv. Chim. Acta* **1987**, *70*, 237. (g) Weber, T.; Aeschimann, R.; Maetzke, T.; Seebach, D. *Helv. Chim. Acta* **1986**, *69*, 1365. (h) Aebi, J. D.; Seebach, D. *Helv. Chim. Acta* **1985**, *68*, 1507. (i) Calderari, G.; Seebach, D. *Helv. Chim. Acta* **1985**, *68*, 1592. (j) Seebach, D.; Aebi, J. D.; Naef, R.; Weber, T. *Helv. Chim. Acta* **1985**, *68*, 144. (k) Seebach, D.; Aebi, J. D.; Gander-Coquoz, M.; Naef, R. *Helv. Chim. Acta* **1987**, *70*, 1194.

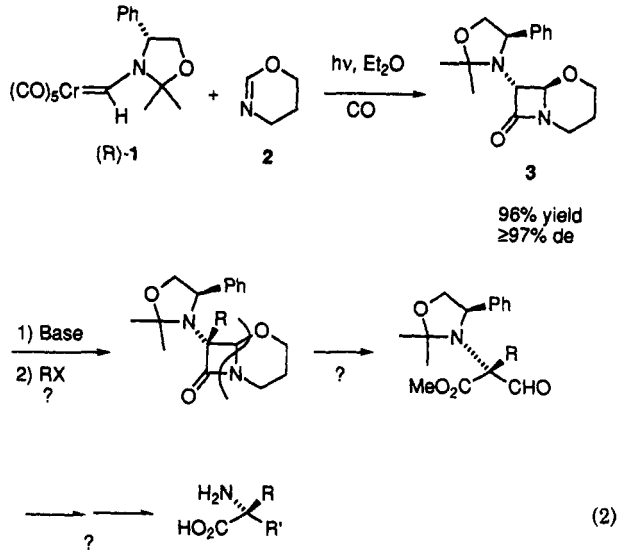
(8) For extensive bibliographies see refs 1a,b and 5a,b.

(9) (a) Ojima, I.; Komata, T.; Qiu, X. *J. Am. Chem. Soc.* **1990**, *112*, 770. (b) Ojima, I.; Pei, Y. *Tetrahedron Lett.* **1990**, *31*, 977. (c) Ojima, I.; Chen, H-J. C.; Nakahashi, K. *J. Am. Chem. Soc.* **1988**, *110*, 278. (d) Ojima, I; Chen, H-J. C.; Qiu, X. *Tetrahedron* **1988**, *44*, 5307.

(10) (a) Miller, J. R.; Pulley, S. R.; Hegedus, L. S. *J. Am. Chem. Soc.* **1992**, *114*, 5602. (b) Lastra, E.; Hegedus, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 87. (c) Vernier, J. M.; Hegedus, L. S.; Miller, J. B. *J. Org. Chem.* **1992**, *57*, 6914. (d) Hegedus, L. S.; Schwindt, M. A.; DeLombaert, S.; Imwinkelried, R. *J. Am. Chem. Soc.* **1990**, *112*, 2264. (e) Hegedus, L. S.; Lastra, E.; Narukawa, Y.; Snustad, D. C. *J. Am. Chem. Soc.* **1992**, *114*, 2991.

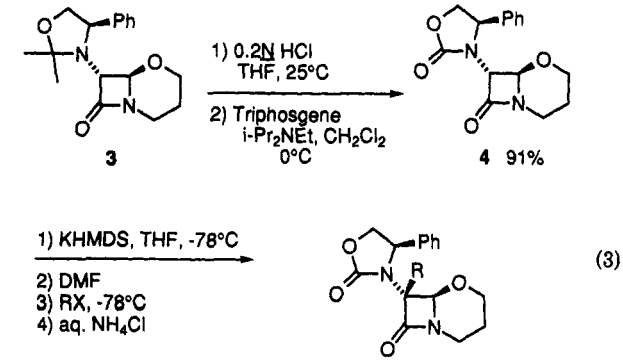
(11) Hegedus, L. S.; Imwinkelried, R.; Sargent, M-A.; Dvorak, D.; Satoh, Y. *J. Am. Chem. Soc.* **1990**, *112*, 1109.

0022-3263/93/1958-5918$04.00/0



(2)

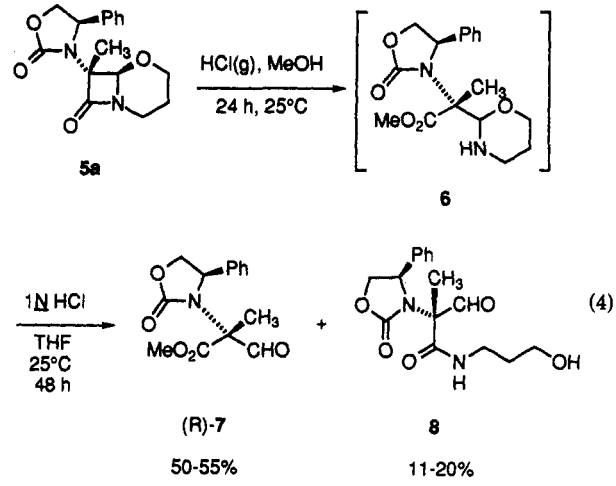
auxilliary in **3** is substantially more sterically hindered than the corresponding oxazolidinone in Ojima's system. Given the success of that system, the oxazolidine in **3** was converted to the oxazolidinone **4** by simple hydrolysis of the acetonide followed by recyclization with triphosgene. With lithium bases (*tert*-butyllithium, LDA) in the presence or absence of polar additives (HMPA, TMEDA), alkylation could be achieved, but yields were low and substantial losses through degradation occurred. In contrast, the use of potassium hexamethyldisilazide was considerably more efficient. Compound **4** was alkylated with retention of stereochemistry to give fair yields of product with very high diastereoselectivity (only a single diastereoisomer was detected by NMR spectra of the crude product) (eq 3). The reaction went with clean retention



(3)

5a R = Me 80%; ≥97% de
5b R = allyl 69%; ≥97% de
5c R = Bn 51%; ≥97% de

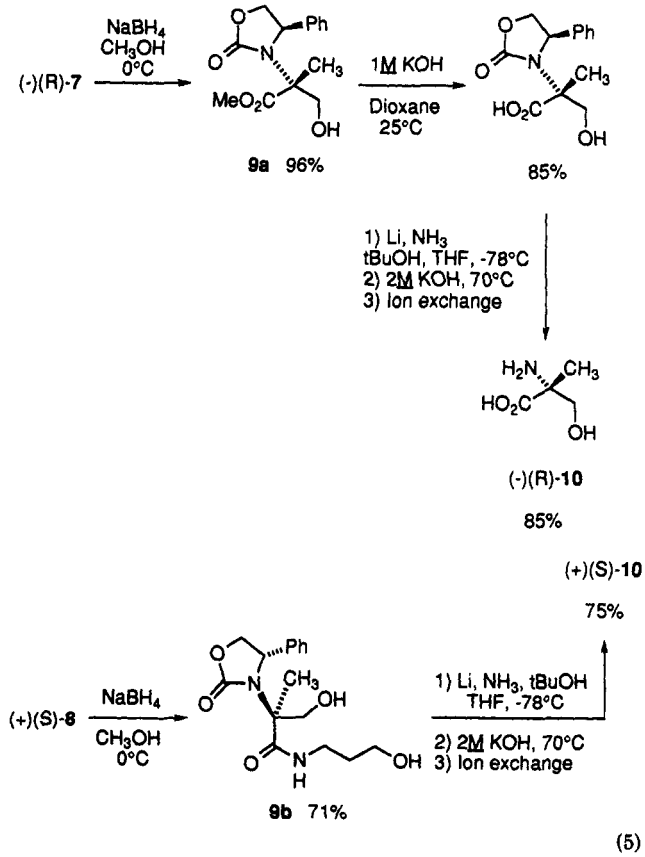
of stereochemistry (see discussion below for proof of absolute stereochemistry). The alkylation occurred from the *same* face as the substituent α to the lactam nitrogen in *trans*-β-lactam **4**, whereas it occurred *opposite* this same substituent in the *cis*-β-lactam in eq 1. The alkylation was limited to very reactive electrophiles. Ethyl iodide, methyl bromoacetate, and chloroiodomethane failed to undergo reaction. Because α-methyl-α-amino acids are of most interest, cleavage of **5a** was next addressed (eq 4). The β-lactam ring was readily cleaved under previously developed conditions[12] (gaseous HCl/methanol) and, without purification, the aminal was cleaved using 1 N HCl in THF. The desired product **7** was always accompanied by varying amounts of hydroxy amide **8**, from initial cleavage of the aminal rather than the β-lactam. However



(4)

these were easily separated, and manipulation of the aldehyde in **8** followed by ultimate hydrolysis of the amide converged with manipulation of the aldehyde in **7** to give the same product. By the same procedure, (*S*)-**7** was prepared by starting with (*S*)-**1** rather than (*R*)-**1**.

Compound **7** proved to be a stable and versatile intermediate for the synthesis of a variety of α-methyl-α-amino acids in reasonable yield. (−)-(2*R*)-α-Methylserine (**10**) was available in good yield and very high ee (the other enantiomer could not be detected by ^1H or ^{19}F NMR spectra of the Mosher's amide) from **7** and **8** by reduction of the aldehyde with sodium borohydride followed by hydrolysis/dissolving metal oxazolidinone cleavage[13] (eq 5). The overall yield of **10** from carbene

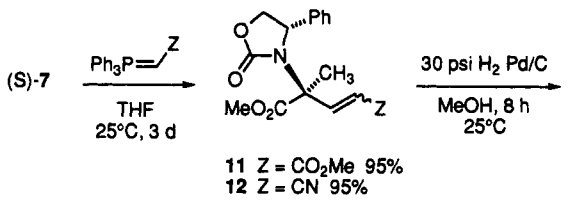


(5)

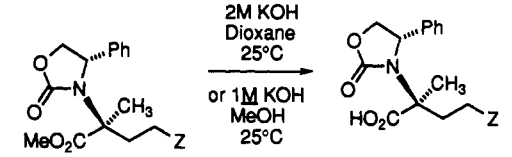
complex **1** was 26%, by converting only **7**, which could be increased to 36% by converting **8** as well.

(12) Thompson, D. K.; Suzuki, N.; Hegedus, L. S.; Satoh, Y. *J. Org. Chem.* **1992**, *57*, 1461.
(13) Evans, D. A.; Sjogren, B. E. *Tetrahedron Lett.* **1985**, *26*, 3783.

Aldehyde (*S*)-7 was quite reactive toward stabilized ylides giving unsaturated compounds 11 and 12 in excellent yield (eq 6). Ester 11 was converted to (+)-(*S*)-α-

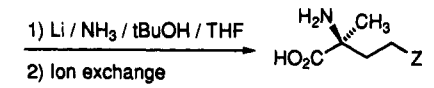


11 Z = CO_2Me 95%
12 Z = CN 95%



13 Z = CO_2Me 88%
14 Z = CN 80%

15 Z = CO_2H 93%
16 Z = CN 93%

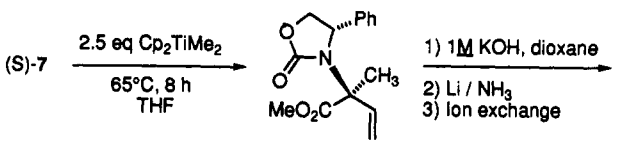


(6)

17 Z = CO_2H 86% (23%)
18 Z = CH_2NH_2 82% (20%)

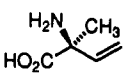
methylglutamic acid 17 by reduction of the double bond, followed by hydrolysis of the esters and reductive removal of the oxazolidinone. Nitrile 12 was converted to (+)-(*S*)-α-methylornithine 18 by a similar route. Note that the nitrile group reduces directly to the amine under the conditions for oxazolidinone cleavage. (The yields in parentheses are overall yields from carbene complex 1.)

Aldehyde (*S*)-7 was converted to (+)-(2*S*)-α-vinylalanine (20) by methylenation with Petasis' reagent[14] followed by the typical deprotection sequence (eq 7). The methyl-



19 52%

(+38% recovered 7)



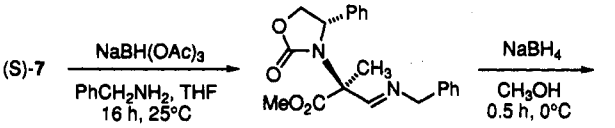
(7)

20 75% (14%)

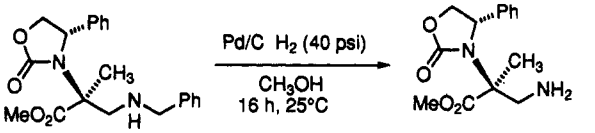
(22% from 1 based on consumed 7)

enation could never be carried to complete conversion. Use of excess reagent resulted in complete consumption of starting material, but still only a 52% yield of the desired product 19. Thus, the most efficient conditions, resulting in the highest yield of methylenation along with reasonable recovery of aldehyde 7, are reported.

Aldehyde (*S*)-7 was converted to (+)-(2*S*)-2-methyl-2,3-diaminopropionic acid (24) by a reductive amination[15] (eq 8). Strangely, acetoxyborohydride promoted the condensation of the aldehyde with benzylamine, but failed to

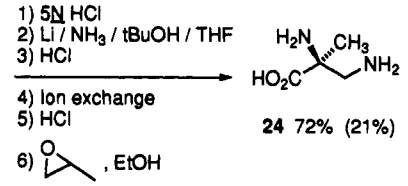


21



22 (86% from 7)

23 95%

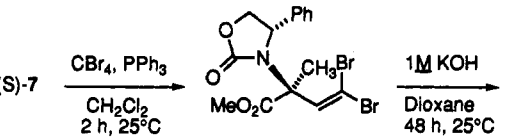


24 72% (21%)

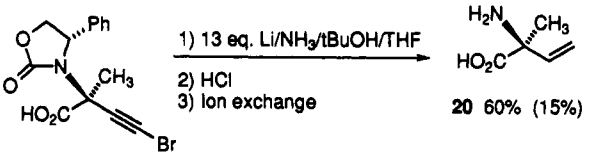
(8)

reduce the imine. Reduction with borohydride followed by debenzylation and the typical reductive removal of the oxazolidinone gave the desired product.

Finally, aldehyde (*S*)-7 was converted to (+)-(*S*)-α-ethynylalanine by treatment with carbon tetrabromide/triphenylphosphine, followed by elimination of HBr and very careful reductive cleavage of the oxazolidinone and the acetylenic halide (eq 9). If excess lithium was used in

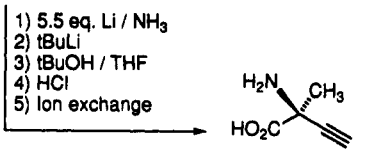


25 85%



20 60% (15%)

26 85%



(9)

27 75% (19%)

the first step, overreduction to 2-vinylalanine was observed.

In summary, by combining the efficient, highly stereoselective synthesis of β-lactam 3 with Ojima's β-lactam alkylation methodology, a versatile precursor to a number of optically active α-alkyl-α-amino acids was developed.

Experimental Section

General Procedure. Melting points were taken on a Mel-Temp apparatus and are uncorrected. 270-MHz ^1H NMR and 67-MHz ^{13}C NMR were obtained on a Bruker IBM-WP 270SY spectrometer. 300-MHz ^1H NMR and 75-MHz ^{13}C NMR spectra were obtained on a Bruker ACE-300 spectrometer. NMR spectra were recorded in $CDCl_3$, DMSO, D_2O, or D_2O/CD_3OD and chemical shifts are given in ppm relative to $(CH_3)_4Si$ (0 ppm, ^1H) or $CDCl_3$ (77.0 ppm, ^{13}C), DMSO (39.5 ppm, ^{13}C), CD_3OD (49.0

(14) Petasis, N.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392.
(15) Abdel-Magid, A. F.; Maryanoff, C. A.; Carson, K. G. *Tetrahedron Lett.* **1990**, *31*, 5595.

ppm, ^{13}C). IR spectra were recorded on a Perkin-Elmer 1600 series FTIR. Optical rotations were obtained on a Rudolph Research automatic polarimeter Autopol III. Specific rotations, $[\alpha]_D$ are reported in degrees per decimeter at 25 °C and the concentration (c) is given in grams per 100 mL in the specified solvent. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ. All the reactions were performed under an atmosphere of argon, except as specified.

The crude reaction mixtures were purified by column chromatography with silica gel (ICN Biomedicals Silitech 32–63 μm) or with acid cation-exchange resin [Sigma DOWEX-50W, hydrogen form, 200–400 mesh, previously washed with H_2O, 1 N, HCl, and H_2O (pH neutral)].

THF (Mallinckrodt) and Et_2O (Mallinckrodt) were distilled from sodium/benzophenone under an atmosphere of argon. DMF (Mallinckrodt) and tBuOH (E.M. Science) were distilled from CaH_2 under reduced pressure. CH_2Cl_2 (technical grade) was distilled from CaH_2. Liquid NH_3 was condensed at −78 °C and distilled from Li. Carbene complex 1 and β-lactams 3 were prepared by literature procedures.[11]

(6*R*,7*R*)/(6*S*,7*S*)-7-[(4*R*/4*S*)-2-oxo-4-phenyl-1,3-oxazolidin-3-yl]-1-aza-5-oxabicyclo[4.2.0]octan-8-one (4). A solution of β-lactam 3 (2.30 g, 7.6 mmol) in THF/0.2 N HCl (120 mL, 1 to 1) was stirred at 25 °C for 45 min. After removal of the THF under reduced pressure, the mixture was neutralized with a saturated solution of $NaHCO_3$, extracted with CH_2Cl_2 (4 × 100 mL), dried with $MgSO_4$, filtered, and concentrated to afford 2.07 g of crude product containing the free amino alcohol.

The crude product was dissolved in CH_2Cl_2 (150 mL) and cooled at 0 °C. Diisopropylethylamine (3.71 g, 28.7 mmol) was added and after 5 min at 0 °C, triphosgene (1.9 g, 6.4 mmol) was added by portion *via* a spatula. After 45 min of stirring at 0 °C, the mixture was filtered through a short pad of silica gel and concentrated. Chromatography (SiO_2, 150 g, eluent 3:1 CH_2Cl_2/EtOAc) afforded the compound 4[16] (2.00 g, 91%).

(−)-(6*R*,7*R*)/(+)-(6*S*,7*S*)-7-methyl-7-[(4*R*)/(4*S*)-2-oxo-4-phenyl-1,3-oxazolidin-3-yl]-1-aza-5-oxabicyclo[4.2.0]octan-8-one (5a). A solution of potassium bis(trimethylsilyl)amide (5.6 mmol, 11.25 mL, 0.5 M in toluene) was added to a solution of β-lactam 4 (0.440 g, 1.5 mmol) in THF (22 mL) at −78 °C. After 1 h at this temperature, DMF (7.5 mL) was added following after 5 min by methyl iodide (1.71 g, 12.0 mmol). After 15 min of stirring at −78 °C, a saturated solution of NH_4Cl (15 mL) was added. The mixture was extracted with EtOAc (2 × 30 mL), and the organic layers were combined, washed with brine (2 × 40 mL), dried with $MgSO_4$, filtered, and concentrated.

Chromatography (SiO_2, 150 g, elution 9:1 CH_2Cl_2/EtOAc) afforded the compound **5a** (0.330 g) and a mixture of the compounds **5a** and 4 (6/4, 0.040 g) (overall 80% of **5a** and 4% of 4).

Compound **5a**: mp 178–180 °C (recryst CH_2Cl_2/hexane); $[\alpha]^{25}_D$ = −85.0° (*c* = 2.6, CH_2Cl_2) for the *R* isomer and $[\alpha]^{25}_D$ = +86.7° (*c* = 2.2, CH_2Cl_2) for the *S* isomer; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.38 (m, 1H), 1.54 (s, 3H), 1.50–1.82 (m, 1H), 2.61 (td, 1H, *J* = 12.1, 4.6 Hz), 3.51–3.59 (m, 2H), 4.00 (m, 1H), 4.15 (dd, 1H, *J* = 3.7, 8.7 Hz), 4.62 (t, 1H, *J* = 8.7 Hz), 4.75 (s, 1H), 4.96 (dd, 1H, *J* = 3.5, 8.6 Hz), 7.24–7.37 (m, 5H); ^{13}C NMR ($CDCl_3$, 67 MHz) δ 13.36, 23.66, 37.02, 58.80, 64.74, 71.06, 71.64, 84.33, 126.49, 128.77, 128.86, 140.28, 156.81, 163.93; IR (KBr) ν 1744 cm^{-1}. Anal. Calcd for $C_{16}H_{18}O_4N_2$: C, 63.57; H, 6.00; N, 9.27. Found: C, 63.44; H, 6.11; N, 9.01.

(−)-(6*R*,7*R*)-7-allyl-7-[(4*R*)-2-oxo-4-pheny-1,3-oxazolidin-3-yl]-1-aza-5-oxabicyclo[4.2.0]octan-8-one (5b). A solution of potassium bis(trimethylsilyl)amide (0.7 mmol, 0.7 mL, 1 M in THF) was added to a solution of β-lactam 4 (0.100 g, 0.35 mmol) in THF (3 mL) at −78 °C. After 30 min at this temperature, DMF (1 mL) was added, followed after 5 min by allyl bromide (0.085 g, 0.7 mmol). After 2 h of stirring at −78 °C, a saturated solution of NH_4Cl (3 mL) was added. The mixture was extracted with EtOAc (3 × 5 mL). The organic layers were combined and washed with brine (2 × 15 mL), dried with $MgSO_4$, filtered, and concentrated. Chromatography (SiO_2, 30 g, elution 9:1 CH_2Cl_2/EtOAc) afforded the compound **5b** (0.079 g, 69%) as a white solid: mp 75–76 °C; $[\alpha]^{25}_D$ −95.0° (*c* = 2.9, CH_2Cl_2); ^1H NMR ($CDCl_3$, 270 MHz) δ 1.33–1.42 (m, 1H), 1.66–1.86 (m, 1H), 2.58 (dt, 1H, *J* = 13.3, 4.6 Hz), 2.67 (dd, 1H, *J* = 14.5, 6.0 Hz), 3.07 (dd, 1H, *J* = 14.6, 9.3 Hz), 3.59–3.64 (m, 2H), 4.02–4.11 (m, 1H), 4.14 (dd, 1H, *J* = 8.6, 2.9 Hz), 4.58 (t, 1H, *J* = 8.5 Hz), 4.82 (s, 1H), 4.92 (dd, 1H, *J* = 8.7, 2.9 Hz), 5.18–5.26 (m, 2H), 6.00–6.16 (m, 1H), 7.23–7.36 (m, 5H); ^{13}C NMR ($CDCl_3$, 67 MHz) δ 23.57, 32.46, 36.85, 59.29, 64.58, 70.97, 72.92, 83.77, 119.46, 126.29, 128.51, 128.67, 132.00, 140.22, 156.59, 162.59; IR (KBr) ν 1747 cm^{-1}. Anal. Calcd for $C_{18}H_{20}O_4N_2$: C, 65.84; H, 6.14; N, 8.53. Found: C, 66.00; H, 6.35; N, 8.42.

(−)-(6*R*,7*R*)-7-benzyl-7-[(4*R*)-2-oxo-4-phenyl-1,3-oxazolidin-3-yl]-1-aza-5-oxabicyclo[4.2.0]octan-8-one (5c). A solution of potassium bis(trimethylsilyl)amide (0.55 mmol, 0.55 mL, 1 M in THF) was added to a solution of β-lactam 4 (0.080 g, 0.28 mmol) in THF (2.4 mL) at −78 °C. After 30 min at this temperature, DMF (0.8 mL) was added, followed after 5 min by benzyl bromide (0.094 g, 0.55 mmol). After 2 h of stirring at −78 °C a saturated solution of NH_4Cl (2 mL) was added. The mixture was extracted with EtOAc (2 × 10 mL). The organic layers were combined, washed with brine (2 × 15 mL), dried with $MgSO_4$, filtered, and concentrated. Chromatography (SiO_2, 15 g, elution 9:1 CH_2Cl_2/EtOAc) afforded the compound **5c** (0.055 g, 52%) as a while solid: mp 48–49 °C; $[\alpha]^{25}_D$ = −106.6° (*c* = 1.4, CH_2Cl_2); ^1H NMR ($CDCl_3$, 270 MHz) δ 1.36–1.47 (m, 1H), 1.72–1.94 (m, 1H), 2.65 (td, 1H, *J* = 12.5, 4.7 Hz), 3.21 (d, 1H, *J* = 14.5 Hz), 3.61 (d, 1H, *J* = 14.4 Hz), 3.50–3.70 (m, 2 H), 3.86 (dd, 1H, *J* = 3.2, 8.3 Hz), 3.92 (t, 1H, *J* = 8.6 Hz), 4.03–4.19 (m, 2H), 4.96 (s, 1H), 7.09–7.20 (m, 2H), 7.22–7.40 (m, 6H), 7.44–7.47 (m, 2H); ^{13}C NMR ($CDCl_3$, 67 MHz) δ 23.89, 33.58, 36.99, 59.35, 64.74, 71.27, 73.12, 83.90, 126.26, 127.03, 128.25, 128.51, 128.70, 130.69, 135.25, 140.35, 157.06, 162.97; IR (KBr) ν 1751 (large) cm^{-1}. Anal. Calcd for $C_{22}H_{22}N_2O_4$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.57; H, 5.89; N, 7.34.

(−)-(2*R*)/(+)-(2*S*)-Methyl 2-Methyl-2-[(4*R*)/(4*S*)-2-oxo-4-phenyl-1,3-oxazolidin-3-yl]-3-oxopropanoate (7). HCl(g) was bubbled through a solution of β-lactam **5a** (0.800 g, 2.6 mmol) in MeOH (60 mL) for 15 min at −10 °C, 30 min at 0 °C, 5 min at 25 °C and then again for 15 min at 0 °C. The flask was then closed tightly and the mixture was warmed to 25 °C and stirred at this temperature for 24 h. The methanol was then removed under reduced pressure. The residue was dissolved in THF/1 N HCl (1:1, 60 mL) and this mixture was stirred at 25 °C for 48 h. The THF was removed under reduced pressure, and the mixture was neutralized to pH 7 with a saturated solution of $NaHCO_3$ and extracted with EtOAc (3 × 30 mL). Further $NaHCO_3$(s) was added to give a basic pH and the mixture extracted with EtOAc (1 × 30 mL). The organic layers were combined, dried with $MgSO_4$ (for 5 min), filtered, and concentrated. Chromatography (SiO_2, 30 g) afforded the compound 7 (0.365 g, 50%, elution 9:1 CH_2Cl_2/EtOAc) as a white solid and the compound 8 (0.169 g, 20% elution EtOAc) as an oil.

7: mp 119–120 °C (recryst. CH_2Cl_2/hexane); $[\alpha]^{25}_D$ = −62.2° (*c* = 1.06, CH_2Cl_2) for the (2*R*) isomer and $[\alpha]^{25}_D$ = +54.0° (*c* = 1.9, CH_2Cl_2) for the (2*S*) isomer; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.31 (s, 3H), 3.65 (s, 3H), 4.15 (dd, 1H, *J* = 8.7, 6.4 Hz), 4.75 (t, 1H, *J* = 8.8 Hz), 4.96 (dd, 1H, *J* = 6.4, 9.2 Hz), 7.25–7.43 (m, 5H), 9.77 (s, 1H); ^{13}C NMR ($CDCl_3$, 67 MHz) δ 17.83, 52.34, 59.38, 68.59, 71.74, 76.53, 126.81, 128.98, 129.18, 139.65, 194.65; IR (KBr) ν 1749 cm^{-1}. Anal. Calcd for $C_{14}H_{15}O_5N$: C, 60.64; H, 5.45; N, 5.05. Found: C, 60.76; H, 6.04; N, 5.12.

8: $[\alpha]^{25}_D$ = +24.0° (*c* = 1.4, CH_2Cl_2) for the (2*S*) isomer; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.33 (s, 3H), 1.55–1.75 (m, 2H), 2.61 (t, 1H, *J* = 5.9 Hz), 3.24 (dq, 1H, *J* = 5.6, 11.8 Hz), 3.43 (dq, 1H, *J* = 5.8, 12.5 Hz), 3.65–3.81 (m, 2H), 4.25 (dd, 1H, *J* = 5.7, 8.7 Hz), 4.79 (t, 1H, *J* = 8.8 Hz), 5.05 (dd, 1H, *J* = 6.2, 9.0 Hz), 7.01 (s, 1H, broad)), 7.31–7.50 (m, 5H), 9.80 (s, 1H); ^{13}C NMR ($CDCl_3$, 67 MHz) δ 19.45, 31.39, 37.30, 60.22, 60.28, 69.43, 71.65, 126.83, 129.25, 129.47, 139.13, 159.44, 169.29, 197.70; IR (KBr) ν 3375, 1746, 1666 cm^{-1}.

(−)-(2*R*)-Methyl 3-Hydroxy-2-methyl-2-[(4*R*)-2-oxo-4-phenyl-1,3-oxazolidin-3-yl]propanoate (9a). Sodium borohydride (0.016 g, 0.43 mmol) was added to a solution of the compound (*R*)-7 (0.100 g, 0.36 mmol) in MeOH (10 mL) at 0 °C. The mixture was stirred at 0 °C for 45 min and a saturated solution of NH_4Cl was added, the MeOH was removed under reduced pressure, and the mixture was extracted with CH_2Cl_2 (4 × 10 mL). The organic layers were combined, dried with $MgSO_4$, filtered, and concen-

(16) Hegedus, L. S.; Montgomery, J.; Narukawa, Y.; Snustad, D. C. *J. Am. Chem. Soc.* **1991**, *113*, 5784.

trated. Chromatography (SiO_2, 30 g elution 7:3 CH_2Cl_2/EtOAc) afforded the compound **9a** (0.095 g, 95%) as an oil: $[\alpha]^{25}_D$ −47.5° (c = 1.5, CH_2Cl_2); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.24 (s, 3H), 2.93 (t, 1H, J = 6.0 Hz), 3.71 (s, 3H), 3.75 (AB, 1H, J = 11.8, 6.8 Hz), 3.86 (AB, 1H, J = 6.1, 11.7 Hz), 4.10 (dd, 1H, J = 4.4, 8.6 Hz), 4.67 (t, 1H, J = 8.7 Hz), 5.10 (dd, 1H, J = 4.4, 9.0 Hz), 7.30–7.42 (m, 5H); ^{13}C NMR ($CDCl_3$, 67 MHz) δ 20.00, 52.51, 59.22, 63.49, 65.35, 71.38, 126.45, 128.64, 129.08, 141.34, 158.32, 172.60; IR (KBr) ν 3942, 1746 cm^{-1}. Anal. Calcd for $C_{14}H_{17}O_5N$: C, 60.21; H, 6.14; N, 5.01. Found: C, 60.39; H, 5.94; N. 5.03.

(+)-(2*S*)-*N*-(3′-Hydroxypropyl)-3-hydroxy-2-methyl-2-[(4*S*)-2-oxo-4-phenyl-1,3-oxazolidin-3-yl]propionamide (9b). Sodium borohydride (0.025 g, 0.66 mmol) was added to a solution of compound (*S*)-8 (0.160 g, 0.50 mmol) in MeOH (10 mL) at 0 °C. After 20 min of stirring at 0 °C, a saturated solution of NH_4Cl (5 mL) was added, the MeOH was removed under reduced pressure, and the mixture was extracted with CH_2Cl_2 (2 × 15 mL) and EtOAc (2 × 10 mL). The aqueous layer was kept to basic pH with a saturated solution of $NaHCO_3$ and extracted with EtOAc (3 × 10 mL). The organic layers were combined, dried with $MgSO_4$, filtered, and concentrated. Chromatography (SiO_2, 30 g, elution 9:1 EtOAc/MeOH) afforded the compound **9b** (0.115 g, 71%) as an oil: $[\alpha]^{25}_D$ +70.5° (c = 1.6, CH_2Cl_2); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.25 (s, 3H), 1.60–1.75 (m, 2H), 3.10–3.22 (m, 1H), 3.34–3.47 (m, 1H), 3.58–3.71 (m, 5H), 3.77 (d, 1H, J = 11.9 Hz), 4.12 (dd, 1H, J = 3.7, 8.6 Hz), 4.67 (t, 1H, J = 8.7 Hz), 5.22 (dd, 1H, J = 3.6, 8.7 Hz), 6.89 (s(broad), 1H), 7.31–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.49, 31.39, 37.29, 59.24, 60.23, 63.66, 64.77, 71.25, 126.43, 128.77, 129.21, 141.30, 158.25, 172.74; IR (KBr) ν 3376, 1732, 1651 cm^{-1}. Anal. Calcd for $C_{16}H_{22}O_5N_2$: C, 59.61; H, 6.98; N, 8.69. Found: C, 59.33; H, 7.00; N, 8.37.

General Procedure for the Reductive Removal of the Oxazolidinone. A solution of the carboxylic acid in THF/tBuOH was added to a blue-black solution of Li in NH_3 (1:2 THF/NH_3) at −78 °C. After 10 min at −78 °C, NH_4Cl was added, the mixture held at 25 °C, NH_3 distilled, and the THF removed under reduced pressure. The white residue was dissolved in H_2O (5–10 mL), kept at pH 1–2, washed with Et_2O (2 × 5 mL), and concentrated under reduced pressure. An ion-exchange chromatography purification (Dowex 50W, mesh 200–400, 5 g for 30 mg of amino acid, elution with H_2O to remove the salts (pH acid to neutral), then with a gradient of concentration in 0.1, 0.5, and 1 M NH_4OH) afforded a white powder which was rediluted in H_2O, filtered, concentrated, and dried under vacuum over P_2O_5 to afford the pure free amino acid.

General Procedure for the Preparation of the Mosher's Amide Derivatives. To a 0.2 M solution of the amino acid (1 equiv) in MeOH was added $SOCl_2$ (2 equiv) at 25 °C. The solution was heated at reflux until total conversion (5–6 h). After cooling to 25 °C, the mixture was concentrated under reduced pressure and dried under vacuum over P_2O_5. The residue was covered with THF and propylene oxide (10/1, 0.1 M) and the Mosher's acid chloride (1 equiv) was added. The mixture was then heated at reflux for 1.5 h, concentrated under reduced pressure, and quickly filtered through a short column of silica gel. The enantiomeric excess was measured by ^{19}F-NMR by comparison with racemic material. By this method α-methylserine and α-methylglutamic acid were "optically pure" within the limits of detection.

(−)-(2*R*)-α-Methylserine 10. A solution of compound **9a** (0.095 g, 0.36 mmol) in dioxane/1 M KOH (1/1, 8 mL) was stirred for 16 h at 25 °C. The dioxane was removed under reduced pressure and the solution washed with Et_2O (2 × 5 mL). The aqueous layer was kept to pH 1–2 and extracted with EtOAc (4 × 10 mL). The EtOAc layers were combined, dried with $MgSO_4$, filtered, and concentrated. The residue was washed with Et_2O to afford the acid (0.077 g, 85%) as a white solid: ^1H NMR (DMSO, 270 MHz) δ 1.49 (s, 3H), 3.65 (dd, 1H, J = 10.9, 5.6 Hz), 4.04 (AB, 1H, J = 8.8 Hz), 4.21 (t, 1H, J = 8.8 Hz), 4.38 (dd, 1H, J = 5.6, 8.8 Hz), 4.52 (AB, 1H, J = 8.8 Hz, 7.21–7.30 (m, 3H), 7.37–7.41 (m, 2H); ^{13}C NMR (DMSO, 67 MHz) δ 21.01, 59.04, 60.90, 63.54, 71.24, 127.01, 127.79, 127.91, 138.44, 156.25, 172.61; IR (KBr) ν 3505, 3440, 1724, 1677 cm^{-1}.

A solution of acid (0.077 g, 0.28 mmol) in THF (5 mL) and tBuOH (0.14 mL) was added to a blue-black solution of Li (0.014 g, 2.0 mmol) in NH_3 (10 mL) at −78 °C. After 10 min of stirring at −78 °C, solid NH_4Cl (0.060 g, 1.1 mmol) was added, the mixture held at 25 °C, and the NH_3 distilled. The THF was then removed under reduced pressure. The residue was diluted in 2 M KOH (4 mL) and warmed at 70 °C for 2 h. After cooling to 25 °C, the mixture was kept at pH 1–2, washed with Et_2O (2 × 5 mL), and concentrated under reduced pressure. The amino acid was purified as above in the general procedure to afford the α-methylserine **10** (0.028 g, 85%): mp 235–245 °C dec (lit.[6h] mp 242–245 °C dec); $[\alpha]^{25}_D$ = −6.1° (c = 0.9, H_2O) (lit.[6h] $[\alpha]^{20}_D$ = −6.2° (c = 1.0, H_2O)); ^1H NMR (D_2O, 300 MHz) δ 1.44 (s, 3H), 3.67 (1H, AB, J = 12.0 Hz), 3.93 (1H, AB, J = 12.0 Hz) (lit.[6h] ^1H NMR (DMSO, D_2O) δ 1.30 (s, CH_3), 3.47, 3.75 (AB, J_{AB} = 9 Hz, CH_2)); ^{13}C NMR (D_2O/CD_3OD, 75 MHz) δ 19.43, 62.71, 66.00, 176.57; IR (KBr) ν 3384, 2926, 2560, 1654, 1570, 1339, 1056 cm^{-1}.

(+)-(2*S*)-α-Methylserine 10. Following the same procedure as that for the (2*R*)-α-methylserine, a solution of compound **9b** (0.077 g, 0.24 mmol) in THF (5 mL) and tBuOH (0.14 mL) was added to a blue-black solution of Li (0.016 g, 2 mmol). The residue was diluted with 2 M KOH (5 mL) and warmed at 70 °C for 20 h. Usual purification afford the α-methylserine (0.021 g, 75%): mp 245–250 °C (lit. 250–260 °C,[7k] 235–240 °C,[17] 255–260 °C,[18] 264 °C[19]); $[\alpha]^{25}_D$ = +6.1° (c = 1.0, H_2O), lit. $[\alpha]^{rt}_D$ = +6.2° (c = 1.12, H_2O), and after recrystallization $[\alpha]^{rt}_D$ = +6.5° (c = 0.8, H_2O)[7k]; $[\alpha]^{20}_D$ = +6.3° (c = 1.0, H_2O);[17] $[\alpha]^{25}_D$ = +6.0° (2% in 0.1 M nitrilotris(ethanol) HCl buffer pH 7),[18] $[\alpha]^{10}_D$ = +4.7° (c = 0.89, H_2O);[19] NMR and IR data are in good agreement with the (2*R*) isomer and with the literature.[7k]

(+)-(2*S*)-Dimethyl 2-Methyl-2-[(4*S*)-2-oxo-4-phenyl-1,3-oxazolidin-3-yl]-(3*E*)-pentene-1,5-dioate (11). A solution of (carbomethoxymethylene)triphenylphosphorane (0.050 g, 0.18 mmol) and compound (*S*)-7 (0.056 g, 0.20 mmol) in THF (5 mL) was stirred at 25 °C for 3 days. The mixture was concentrated and chromatography (SiO_2, 15 g, elution 9:1 CH_2Cl_2/EtOAc) afforded the compound **11** (0.055 g, 92%) as an oil: $[\alpha]^{25}_D$ = +152.6° (c = 1.0, CH_2Cl_2); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.44 (s, 3H), 3.66 (s, 3H), 3.73 (s, 3H), 4.10 (dd, 1H, J = 8.7, 5.8 Hz), 4.66 (t, 1H, J = 8.9 Hz), 4.93 (dd, 1H, J = 5.9, 8.9 Hz), 5.72 (d, 1H, J = 16.0 Hz), 6.88 (d, 1H, J = 15.9 Hz), 7.28–7.34 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.78, 51.75, 53.08, 59.76, 63.35, 70.97, 122.26, 126.78, 128.90, 129.12, 140.02, 144.24, 157.71, 165.71, 170.72; IR (KBr) ν 1747, 1659 cm^{-1}. Anal. Calcd for $C_{17}H_{19}NO_6$: C, 61.26; H, 5.75; N, 4.20. Found: C, 61.40; H, 5.86; N, 4.23.

(2*S*)-Methyl 4-Cyano-2-methyl-2-[(4*S*)-2-oxo-4-phenyl-1,3-oxazolidin-3-yl]-3-butenoate (12). A solution of (cyanomethylene)triphenylphosphorane (0.165 g, 0.55 mmol) and compound (*S*)-7 (0.060 g, 0.22 mmol) in THF (3 mL) was stirred at 25 °C for 3 days. The mixture was concentrated and chromatography (SiO_2, 30 g, elution 9:1 CH_2Cl_2/EtOAc) afforded the compound **12** (0.063 g, 95%) as a mixture of *cis* and *trans* (33/67) isomers: ^1H NMR ($CDCl_3$, 300 MHz) δ (mixture of *cis* and *trans* isomer) *trans* 1.42 (s, 3H), 3.75 (s, 3H), 4.15 (dd, 1H, J = 5.7, 8.7 Hz), 4.69 (t, 1H, J = 8.8 Hz), 4.90 (dd, 1H, J = 5.8, 9.0 Hz), 5.34 (d, 1H, J = 16.7 Hz), 6.74 (d, 1H, J = 16.6 Hz); *cis* 1.43 (s, 3H), 3.67 (s, 3H), 4.25 (dd, 1H, J = 3.0. 8.5 Hz), 4.96 (t, 1H, J = 8.7 Hz), 5.22 (dd, 1H, J = 3.1, 8.9 Hz), 5.47 (d, 1H, J = 11.8 Hz); mixed signals 7.31–7.49 (5H (*trans*) + 6H (*cis*)); ^{13}C NMR ($CDCl_3$, 75 MHz) δ *trans* 21.52, 53.39, 59.61, 63.54, 71.14, 101.71, 139.65, 150.73, 155.79, 170.00; *cis* 22.74, 53.09, 59.99, 63.08, 72.00, 97.19, 140.61, 155.79, 157.21, 170.97; mixed signals 115.89, 126.74, 127.50, 128.80, 129.28, 129.39; IR (KBr) ν 2227, 1748 cm^{-1}. Anal. Calcd for $C_{16}H_{16}N_2O_4$: C, 63.99; H, 5.37; N, 9.33. Found: C, 64.20; H, 5.54; N, 9.27.

(+)-(2*S*)-Dimethyl 2-Methyl-2-[(4*S*)-2-oxo-4-phenyl-1,3-oxazolidin-3-yl]pentane-1,5-dioate (13). Pd/C (0.014 g, 10%) was added to a solution of compound **11** (0.050 g, 0.5 mmol) in MeOH (4 mL). After four purges of H_2 the mixture was stirred for 16 h in a pressure tube, fitted with a pressure head, under a pressure of 30 psi of H_2, filtered, and concentrated. Chromatography (SiO_2, 15 g, elution 9:1 CH_2Cl_2/EtOAc) afforded the compound **13** (0.044 g, 85%) as an oil: $[\alpha]^{25}_D$ +77.1° (c = 1.2, CH_2Cl_2); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.23 (s, 3H), 2.03–2.33 (m,

(17) Flynn, E. H.; Hinman, J. W.; Caron, E. L.; Woolf, D. O. *J. Am. Chem. Soc.* **1953**, *75*, 586.
(18) Wilson, E. M.; Snell, E. E. *J. Biol. Chem.* **1962**, *237*, 3180.
(19) Takamura, N.; Terashima, S.; Achiwa, K.; Yamada, S. *Chem. Pharm. Bull.* **1967**, *15*, 1776.

4H), 3.63 (s, 3H), 3.71 (s, 3H), 4.09 (dd, 1H, J = 3.9, 8.5 Hz), 4.65 (t, 1H, J = 8.6 Hz), 4.95 (dd, 1H, J = 3.9, 8.8 Hz), 7.31–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.88, 28.90, 31.31, 51.69, 52.48, 58.92, 62.25, 71.05, 126.40, 128.71, 129.12, 141.09, 157.39, 172.50, 172.90; IR (KBr) ν 1738 (broad) cm^{-1}. Anal. Calcd for $C_{17}H_{21}NO_6$: C, 60.89; H, 6.31; N, 4.18. Found: C, 61.04; H, 6.27; N, 4.18.

(+)-(2*S*)-Methyl 2-Methyl-4-cyano-2-[(4*S*)-2-oxo-4-phenyl-1,3-oxazolidin-3-yl]butanoate (14). Pd/C (10%, 0.018 g), was added to a solution of compound 12 (0.072 g, 0.24 mmol) in MeOH (4 mL). After four purges of H_2, the mixture was stirred at 25 °C for 7 h in a pressure tube (fitted with a pressure head) under a pressure of H_2 (30 psi), filtered, and concentrated. Chromatography (SiO_2, 15 g, elution 9:1 CH_2Cl_2/EtOAc) afforded the compound 14 (0.058, 80%) as a white solid: mp 79–80 °C; $[\alpha]^{25}_D$ +69.2° (c = 0.8, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.26 (s, 3H), 2.20 (td, 1H, J = 14.1, 7.6 Hz), 2.35 (td, 1H, J = 8.0, 14.7 Hz), 2.36–2.49 (m, 2H), 3.72 (s, 3H), 4.13 (dd, 1H, J = 3.7, 8.5 Hz), 4.75 (t, 1H, J = 8.7 Hz), 4.92 (dd, 1H, J = 3.8, 8.9 Hz), 7.25–7.41 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.50, 22.37, 31.95, 52.76, 59.13, 61.80, 71.22, 119.28, 126.44, 128.90, 129.19, 140.85, 157.55, 172.07; IR (KBr) ν 2247, 1744 cm^{-1}. Anal. Calcd for $C_{16}H_{18}N_2O$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.41; H, 6.12; N, 9.09.

(+)-(2*S*)-α-Methylglutamic Acid (17). A solution of compound 13 (0.048 g, 0.14 mmol) in dioxane/2 M KOH (1/1, 2 mL) was stirred at 25 °C for 48 h. The dioxane was removed under reduced pressure. The mixture was kept at pH 1–2, and extracted with EtOAc (3 × 5 mL), dried with $MgSO_4$, filtered, and concentrated. The crude product was washed with Et_2O to afford the diacid 15 (0.041 g, 93%) as a white solid: ^{1}H NMR (DMSO, 300 MHz) δ 1.11 (s, 3H), 2.00 (t, 2H, J = 8.4 Hz), 2.23 (m, 2H), 3.95 (dd, 1H, J = 3.3, 8.6 Hz), 4.65 (t, 1H, J = 8.6 Hz), 5.15 (dd, 1H, J = 3.2, 8.6 Hz), 7.29–7.43 (m, 5H), 12.45 (s (broad), 2H); ^{13}C NMR (DMSO, 75 MHz) δ 21.44, 28.77, 30.95, 57.83, 61.40, 70.93, 126.43, 128.18, 128.85, 142.24, 156.83, 173.57, 173.83; IR (KBr) ν 3040 (broad), 1720, 1702 cm^{-1}.

Following the general procedure, a solution of the diacid (0.041 g, 0.13 mmol) in THF (5 mL) and tBuOH (0.14 mL) was added to a solution of Li (0.010 g, 1.45 mmol) in NH_3 (10 mL). Usual purification afforded the α-methylglutamic acid 17 (0.02 g, 88%) which was converted to the hydrochloride salt for comparison with the literature. α-Methylglutamic acid: ^{1}H NMR (D_2O, 300 MHz) δ 1.50 (s, 3H), 1.97–2.15 (m, 2H), 2.22–2.40 (m, 2H); ^{13}C NMR (D_2O/CD_3OD) δ 23.46, 32.96, 34.19, 62.00, 177.30, 181.50.

α-Methylglutamic acid hydrochloride: mp 177–180 °C (lit.[7h] 179.5–181.0 °C); $[\alpha]^{25}_D$ +10.3° (c = 0.7, 5 N HCl) (lit. $[\alpha]^{rt}_D$ = −12.1° (c = 3.24, 5 N HCl),[7h] $[\alpha]^{rt}_D$ = −12.1° (c = 4, 6 N HCl) for the (*R*) isomer and $[\alpha]^{rt}_D$ = +12.1° (c = 4, 6 N HCl) for the (*S*) isomer[20]); ^{1}H NMR and IR data are in good agreement with the literature.[7h]

(+)-(2*S*)-α-Methylornithine (18). A solution of compound 14 (0.045 g, 0.15 mmol) in MeOH/1 M KOH (4 mL, 1/1) was stirred at 25 °C for 20 h. The methanol was removed under reduced pressure, and the mixture was kept at pH 1–2, extracted with EtOAc (3 × 5 mL), dried with $MgSO_4$, filtered, and concentrated. Filtration (SiO_2, 15 g, elution 1:1 CH_2Cl_2/EtOAc, 2% HCO_2H) afforded the acid 16 (0.040 g): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.30 (s, 3H), 2.10–2.30 (m, 1H), 2.30–2.57 (m, 3H), 4.15 (dd, 1H, J = 3.8, 8.6 Hz), 4.78 (t, 1H, J = 8.7 Hz), 4.98 (dd, 1H, J = 3.9, 8.9 Hz), 7.39–7.42 (m, 5H), 10.29 (s(broad), 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.52, 22.13, 31.66, 59.27, 61.86, 71.54, 119.27, 126.42, 129.00, 129.35, 140.60, 158.11, 175.58; IR (KBr) ν 3000–3620, 2550, 1738 cm^{-1}.

Following the general procedure, a solution of acid 16 (0.040 g, 0.14 mmol) in THF (5 mL) and tBuOH (0.14 mL) was added to a solution of Li (0.010 g, 1.45 mmol) in liquid NH_3 (10 mL). Usual purification afforded the α-methylornithine 18 (0.016 g, 80%) as a white solid: mp 178–180 °C dec (lit.[7d] mp = 197–199 °C dec) $[\alpha]_D$ = +10.9° (c = 0.4, 4 N HCl) (lit.[7d] $[\alpha]_D$ = −10.21°, (c = 0.7, 4 N HCl) for the (*R*) isomer); ^{1}H NMR and IR are in good agreement with the literature;[7d] ^{13}C NMR (75 MHz, D_2O/CD_3OD) δ 23.65, 25.13, 36.78, 40.44, 60.50, 181.17.

(20) Izumi, Y.; Tatsumi, S.; Imaida, M.; Fukuda, Y. *Bull. Chem. Soc. Jpn.* **1965**, *38*, 1338.

(+)-(2*S*)-Methyl 2-Methyl-2-[(4*S*)-2-oxo-4-phenyl-1,3-oxazolidin-3-yl]buten-3-oate (19). A solution of aldehyde (*S*)-7 (0.050 g, 0.18 mmol) and dimethyl titanocene (0.172 g, 0.72 mmol) in THF (1.5 mL) was heated at 65 °C for 20 h in a sealed pressure tube under argon. Hexane (1.5 mL) was then added and the mixture stirred for 1 h at 25 °C, filtered, and concentrated. The crude mixture was diluted with CH_2Cl_2 (2 mL) and H_2O (0.2 mL) and stirred for 20 h at 25 °C, filtered, and absorbed on silica gel. Separation by chromatography (SiO_2, 30 g, elution 3:1 hexane/EtOAc) afforded the compound 19 (0.026 g, 53%): $[\alpha]^{25}_D$ = +148.5° (c = 0.85, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.45 (s, 3H), 3.75 (s, 3H), 4.09 (dd, 1H, J = 5.3, 8.5 Hz), 4.66 (t, 1H, J = 8.7 Hz), 4.93 (dd, 1H, J = 5.4, 9.0 Hz), 5.07 (d, 1H, J = 17.4 Hz), 5.14 (d, 1H, J = 10.6 Hz), 5.81 (dd, 1H, J = 10.6, 17.4 Hz), 7.28–7.37 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.59, 52.79, 59.64, 64.36, 70.94, 117.66, 126.71, 128.65, 129.05, 135.70, 140.94, 157.84, 171.88; IR (KBr) ν 1748 cm^{-1}. Anal. Calcd for $C_{16}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.17; H, 6.44; N, 5.03.

(+)-(2*S*)-α-Methyl-α-vinylglycine (20). A solution of compound 19 (0.030 g, 0.11 mmol) in dioxane/1 M KOH (1:1, 2 mL) was stirred at 25 °C for 16 h. The dioxane was removed under reduced pressure. The mixture was washed with Et_2O (25 mL), kept at pH 1–2, and extracted with EtOAc (3 × 5 mL). The EtOAc layers were combined, dried with $MgSO_4$, filtered, and concentrated to afford the acid (0.025 g, 87%) as an oil.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.49 (s, 3H), 4.10 (dd, 1H, J = 5.4, 8.7 Hz), 4.67 (t, 1H, J = 8.8 Hz), 4.95 (dd, 1H, J = 5.4, 9.0 Hz), 5.18 (d, 1H, J = 17.4 Hz), 5.19 (d, 1H, J = 10.6 Hz), 5.82 (dd, 1H, J = 10.6, 17.4 Hz), 7.26–7.36 (m, 5H), 10.83 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.54, 59.69, 64.25, 71.13, 118.22, 126.64, 128.67, 129.10, 135.18, 140.78, 158.28, 176.11; IR (KBr) ν 2996, 1750 cm^{-1}.

Following the general procedure, a solution of acid (0.032 g, 0.12 mmol) in THF (4.5 mL) and tBuOH (0.14 mL) was added to a solution of Li (0.010 g, 1.45 mmol) in NH_3 (10 mL). Usual purification afforded the α-methyl-α-vinylglycine 20 (0.012 g, 87%) as a white solid: mp 214–215 °C (lit. 228–229 °C,[7g] 214 °C dec[19]); $[\alpha]^{25}_D$ = +36.1° (c = 0.5, H_2O) (lit. $[\alpha]^{rt}_D$ = −31.0° (c = 0.733, H_2O) for the (*R*) isomer[7g] and $[\alpha]^{rt}_D$ = +24° (c = 0.5, H_2O) for the (*S*) isomer;[7g] $[\alpha]^{27}_D$ = +33.0° (c = 0.612, H_2O));[19] ^{1}H NMR and IR data are in good agreement with the literature;[7g] ^{13}C NMR (D_2O/CD_3OD) δ 22.29, 62.85, 118.13, 138.61, 176.28.

(+)-(2*S*)-Methyl 3-(Benzylamino)-2-methyl-2-[(4*S*)-2-oxo-4-phenyl-1,3-oxazolidin-3-yl]propanoate (22). Benzylamine (0.013 g, 0.12 mmol) was added to a solution of compound (*S*)-7 (0.030 g, 0.11 mmol) in THF (2 mL) at 25 °C. After 5 min sodium triacetoxyborohydride (0.033 g, 0.15 mmol) was added *via* a spatula. After 16 h of stirring at 25 °C, the mixture was diluted with EtOAc (5 mL) and washed with brine (5 mL), dried with $MgSO_4$, filtered, and concentrated to afford a residue containing the imine 21: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.39 (s, 3H), 3.79 (s, 3H), 4.04 (dd, 1H, J = 6.4, 8.5 Hz), 4.54 (1H, AB, J = 14.4 Hz), 4.60 (1H, AB, J = 14.0 Hz), 4.65 (t, 1H, J = 8.6 Hz), 5.02 (dd, 1H, J = 6.4, 9.2 Hz), 7.21–7.37 (m, 10H), 7.88 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.44, 52.64, 59.40, 63.20, 65.23, 71.13, 126.33, 126.75, 127.32, 128.24, 128.38, 128.96, 138.45, 140.80, 158.57, 162.06, 171.24.

The crude product was diluted in MeOH (3 mL), cooled to 0 °C, and sodium borohydride (0.006 g, 0.14 mmol) was added. After 30 min of stirring at 0 °C, a saturated solution of NH_4Cl (3 mL) was added, the MeOH was removed under reduced pressure, and the mixture was extracted with EtOAc (2 × 5 mL). The organic layers were combined, dried with $MgSO_4$, filtered, and concentrated. Chromatography (SiO_2, 15 g, elution 6:5 CH_2Cl_2/EtOAc) afforded the compound 22 (0.035 g, 86%) as an oil: $[\alpha]^{25}_D$ = +16.6 (c = 1.4, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.21 (s, 3H), 1.59 (s, 1H), 2.78 (1H, AB, J = 12.7 Hz), 2.97 (1H, AB, J = 12.6 Hz), 3.66 (1H, AB, J = 13.4 Hz), 3.73 (s, 3H), 3.78 (1H, AB, J = 13.4 Hz), 4.04 (dd, 1H, J = 8.5, 4.4 Hz), 4.60 (t, 1H, J = 8.8 Hz), 5.11 (dd, 1H, J = 8.9, 4.4 Hz), 7.21–7.36 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.69, 52.53, 53.35, 54.03, 59.03, 62.96, 71.17, 126.40, 127.08, 128.15, 128.41, 128.53, 129.02, 140.08, 141.54, 158.00, 172.80; IR (KBr) ν 3350, 1746 cm^{-1}. Anal. Calcd for $C_{21}H_{24}N_2O_4$: C, 68.46; H, 6.57; N, 7.60. Found: C, 68.51; H, 6.61; N, 7.49.

(+)-(2*S*)-Methyl 3-Amino-2-methyl-2-[(4*S*)-2-oxo-4-phenyl-1,3-oxazolidin-3-yl]propanoate (23). Pd/C (10%, 0.035 g) was added to a solution of compound **22** (0.137 g, 0.37 mmol) in MeOH (10 mL). The mixture was purged four times with H_2 and stirred for 16 h under a pressure of H_2 (40 psi) in a pressure tube fitted with a pressure head. The mixture was filtered through a Celite pad and concentrated under reduced pressure. Chromatography (SiO_2, 30 g, elution 8:2 EtOAc/MeOH) afforded the compound **23** (0.098 g, 95%) as an oil: $[\alpha]^{25}_D$ +58.2° (*c* = 1.84, CH_2Cl_2); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.22 (s, broad, 2H), 1.28 (s, 3H), 2.96 (AB, 1H, *J* = 13.4 Hz), 3.12 (AB, 1H, *J* = 13.3 Hz), 3.72 (s, 3H), 4.07 (dd, 1H, *J* = 4.3, 8.5 Hz), 4.65 (t, 1H, *J* = 8.7 Hz), 5.13 (dd, 1H, *J* = 4.3, 9.0 Hz), 7.30–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.63, 46.83, 52.36, 59.17, 64.00, 71.13, 126.29, 128.55, 129.04, 141.41, 157.93, 172.80; IR (KBr) ν 3395, 3331, 1744 cm^{-1}. Anal. Calcd for $C_{14}H_{18}N_2O_4$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.36; N, 6.43; N, 9.95.

(+)-(2*S*)-2,3-Diamino-2-methylpropanoic Acid Hydrochloride (24). A solution of compound **23** (0.098 g, 0.35 mmol) in 5 N HCl (6 mL) was heated at reflux for 3 days, cooled to 25 °C, concentrated under reduced pressure, and dried under vacuum over P_2O_5 to afford the acid (0.103 g, 97%) as a white solid: ^1H NMR (D_2O, 300 MHz) δ 1.32 (s, 3H), 3.54 (s, 2H), 4.26 (dd, 1H, *J* = 3.2, 8.8 Hz), 4.86 (t, 1H, *J* = 8.9 Hz), 5.25 (dd, 1H, *J* = 8.9, 3.2 Hz), 7.43–7.54 (m, 5H); ^{13}C NMR (D_2O/CD_3OD, 75 MHz) δ 21.42, 45.09, 59.47, 61.29, 75.56, 127.76, 129.86, 130.05, 141.49, 160.78, 174.70; IR (KBr) ν 3422, 2921, 1933, 1734, 1618 cm^{-1}.

Following the general procedure, a solution of acid (0.070 g, 0.23 mmol) in THF (5 mL) and tBuOH (0.14 mL) was added to a solution of Li (0.020 g, 2.9 mmol) in NH_3 (10 mL). Usual purification afforded the free diamino acid **24** which was converted to the dihydrochloride salt by dilution in a minimum amount of 1 N HCl followed by concentration and drying under vacuum over P_2O_5. The monohydrochloride salt (0.025 g, 72%) was obtained by heating a solution of the dihydrochloride salt in ethanol (1.5 mL) and propylene oxide (0.3 mL) at 50 °C for 3 h followed by filtration and drying under vacuum over P_2O_5.

Dihydrochloride salt: ^1H NMR (D_2O, 300 MHz) δ 1.69 (s, 3H), 3.44 (AB, 1H, *J* = 13.0 Hz), 3.53 (AB, 1H, *J* = 13.5 Hz); ^{13}C NMR (D_2O/CD_3OD, 75 MHz) δ 20.84, 44.00, 57.90, 172.88.

Hydrochloride salt **24**: mp = 276–280 °C dec (lit.[21] 281–284 °C dec); $[\alpha]^{25}_D$ = +4.1° (*c* = 0.5, H_2O) (lit.[21] $[\alpha]^{20}_D$ = −3.5° (*c* = 0.7, H_2O) for the (*R*) isomer); ^1H NMR data are in good agreement with the literature:[21] ^{13}C NMR (D_2O/CD_3OD 75 MHz) δ 21.19, 44.36, 58.08, 174.79; IR (KBr) 3423, 2973, 2580, 2041, 1605, 1441, 1414, 1364 cm^{-1}. Anal. Calcd for $C_4H_{11}N_2O_2Cl$: C, 31.08; H, 7.17; N, 18.12. Found: C, 31.08; H, 7.29; N, 16.09.

(+)-(2*S*)-Methyl 4,4-Dibromo-2-methyl-2-[(4*S*)-2-oxo-4-phenyl-1,3-oxazolidin-3-yl]-3-butenoate (25). A solution of carbon tetrabromide (0.335 g, 1.01 mmol) in CH_2Cl_2 (2.2 mL) was added to a solution of triphenylphosphine (0.525 g, 2.02 mmol) in CH_2Cl_2 (4.5 mL) at 0 °C. After 30 min at 0 °C, a solution of aldehyde (*S*)-**7** (0.140 g, 0.5 mmol) in CH_2Cl_2 (2.2 mL) was added. The mixture was warmed to 25 °C and stirred for 20 h, added to hexane (15 mL), stirred for 1 h, filtered, and concentrated. Chromatography (SiO_2, 30 g, elution CH_2Cl_2, EtOAc, 20%) afforded the compound **25** (0.182 g, 84%) as a white solid: mp 128–129 °C; $[\alpha]_D$ = +88.7° (*c* = 1.1, CH_2Cl_2); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.55 (s, 3H), 3.67 (s, 3H), 4.20 (dd, 1H, *J* = 3.7, 8.6 Hz), 4.72 (t, 1H, *J* = 8.7 Hz), 5.08 (dd, 1H, *J* = 3.7, 8.9 Hz), 7.13 (s, 1H), 7.32–7.43 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.75, 53.09, 60.42, 64.16, 71.45, 89.54, 127.17, 128.81, 128.91, 137.89, 140.65, 157.10, 170.91; IR (KBr) ν 1741, 1725 cm^{-1}. Anal. Calcd for $C_{15}H_{15}Br_2NO_4$: C, 41.60; H, 3.49; N, 3.23. Found: C, 41.70; H, 3.61; N, 3.06.

(+)-(2*S*)-α-Ethinylalanine/(+)-(2*S*)-α-Methyl-α-vinylglycine. A solution of compound **25** (0.110 g, 0.25 mmol) in dioxane and 1 M KOH (6 mL, 1/1) was stirred at 25 °C for 48 h. The dioxane was removed under reduced pressure, and the mixture kept at pH 1–2, extracted with EtOAc (3 × 10 mL), dried with $MgSO_4$, filtered, and concentrated. Chromatography (SiO_2, 15 g, elution 49% CH_2Cl_2, 49% EtOAc, 2% HCO_2H) afforded the acid **26** (0.072 g, 85%) as an oil: ^1H NMR ($CDCl_3$, 300 MHz) δ 1.72 (s, 3H), 4.12 (dd, 1H, *J* = 6.2, 8.2 Hz), 4.72 (t, 1H, *J* = 8.8 Hz), 5.18 (dd, 1H, *J* = 6.7, 7.9 Hz), 7.33–7.43 (m, 5H), 10.46 (s (br)), 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.80, 49.68, 58.48, 61.17, 71.18, 126.29, 128.70, 129.12, 140.4, 157.94, 172.35; IR (KBr) ν 2223, 1756 cm^{-1}.

(+)-(2*S*)-α-Methyl-α-vinylglycine. A solution of acid **26** (0.050 g, 0.15 mmol) in THF (2.5 mL) was added to a blue-black solution of Li (0.012 g, 1.74 mmol) in liquid NH_3 (10 mL) at −78 °C. After 1 min a solution of tBuOH (0.100 mL) in THF (2.5 mL) was added followed by solid NH_4Cl (0.020 g). The mixture was warmed to 25 °C (distillation of liquid NH_3), the THF was removed under reduced pressure, and the residue was diluted in H_2O (5 mL). The mixture was kept at pH 1–2, washed with Et_2O (5 mL), and concentrated under reduced pressure. Ion-exchange chromatography (following the general procedure) afforded the α-methyl-α-vinylglycine (0.010 g, 60%).

(+)-(2*S*)-α-Ethinylalanine. A solution of acid **26** (0.060 g, 0.18 mmol) in THF (2.5 mL) was added to a solution of Li (0.007 g, 1 mmol) in liquid NH_3 (10 mL). After the addition, tBuLi (0.1 mL, 0.18 mmol, solution 1.7 M in pentane) was added, followed after 1 min by a solution of tBuOH (0.1 mL) in THF (2.5 mL) and solid NH_4Cl (10 mg). The mixture was warmed to 25 °C (distillation of liquid NH_3), the THF removed under reduced pressure, and the residue diluted in H_2O (5 mL). The mixture was kept at pH 1–2, washed with Et_2O (5 mL), and concentrated under reduced pressure. Ion-exchange chromatography (following the general procedure) afforded the α-ethynylalanine (0.015 g, 75%) as a white solid: mp 190–193 °C dec; $[\alpha]_D$ +43.9° (*c* = 0.9, H_2O); ^1H NMR (D_2O, 300 MHz) δ 1.74 (s, 3H), 3.03 (s, 1H); ^{13}C NMR (D_2O/CD_3OD, 75 MHz) δ 25.37, 55.39, 76.79, 80.74, 172.94; IR (KBr) ν 3307, 3244(s), 3060, 2567, 2273, 2124, 1974, 1618 (broad), 1450, 1391, 1357, 1336 cm^{-1}. Anal. Calcd for $C_5H_7NO_2$: C, 53.09; H, 6.24; N, 12.38. Found: C, 53.26; H, 6.10; N, 12.24.

Acknowledgment. Support of this research under Grant No. GM26178 from the National Institutes of General Medical Sciences (Public Health Service) is gratefully acknowledged.

(21) Hartwig, W.; Mittendorf, J. *Synthesis* **1991**, 939.