23068-95-3; 4-methoxybenzyl alcohol, 105-13-5; 2-chloroethanol, 107-07-3; 4-lithio-4-(phenylsulfonyl)pent-1-ene, 82599-01-7; lithium methyl(diethoxyphosphinyl)acetate, 67393-41-3; sodium methyldiethylphosphonoacetate, 61961-70-4.

Supplementary Material Available: ^{1}H NMR spectra of **16** (400 MHz), **20** (200 MHz), (*Z*)-**20** (200 MHz), **22**, **23**, the acetate of **24**, **26**, **27**, (*Z*)-**27** (400 MHz), **28**, (*Z*)-**28**, **29**, **4b** (400 MHz), **35**, **36**, **37**, **38**, **38** Me ester, **39**, **40**, **41**, and (±)-**3**; ir spectra of **16**, **20**, (*Z*)-**20**, **22**, **23**, **24**, **27**, **28**, (*Z*)-**28**, **29**, **4b**, **35**, **36**, **38**, **38** Me ester, **39**, **40**, **41**, and (±)-**3** (44 pages). Ordering information is given on any current masthead page.

Synthesis of N^{α},N^{δ}-Protected N^{δ}-Hydroxy-L-ornithine from L-Glutamic Acid

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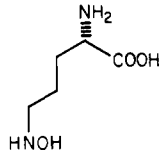
The synthesis of N^{α}-(*tert*-butyloxycarbonyl)-N^{δ}-acetyl-N^{δ}-(benzyloxy)-L-ornithine (**3**) has been accomplished by alkylation of the anion of *O*-benzyl acetohydroxamate with the chiral 2-amino-5-bromopentanoic acid **4**, the latter substance being derived from L-glutamic acid. In a similar manner, N^{δ}-(benzyloxy)-N^{δ}-tosyl-L-ornithine (**16**) was prepared and was shown to be optically pure. Two other approaches to the ornithine **3** were investigated; however, these approaches were not successful due to (1) the propensity of the urethane nitrogen to undergo intramolecular cyclization with a δ-aldehyde function present in glutamic semialdehyde derivatives generated in situ and (2) the occurrence of transamidation rearrangement processes upon attempted reduction of the δ-carboxyl group in certain glutamic acid α-hydroxamate derivatives.

Methods for the synthesis of optically active amino acids are of continuing interest.[1] Preparation and resolution of DL-α-amino acids commonly afford the desired optically active amino acids. Transformation of one chiral amino acid into another chiral amino acid also has received considerable attention.[2] By application of the latter approach, we report a convenient synthesis from L-glutamic acid of N^{δ}-hydroxy-L-ornithine, a component of several peptidyl hydroxamate antibiotics such as ferrichrome (**2**),[3]



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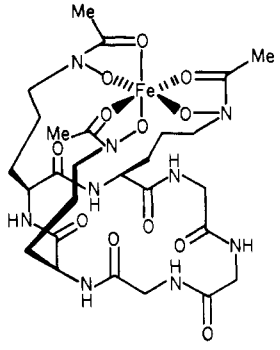
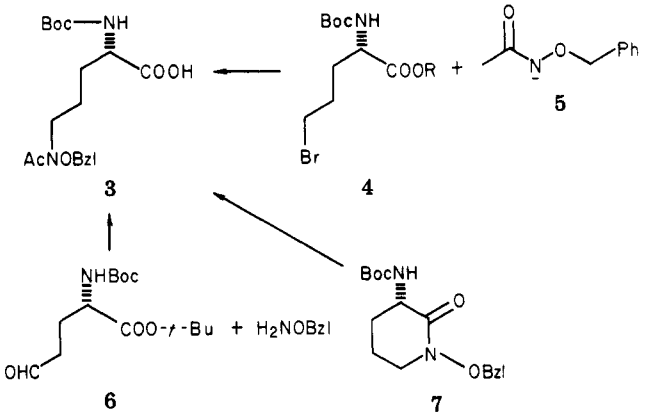


ferrichrome (**2**)

fusarinine,[4] dimeric acid,[5] rhodotorulic acid,[6] and related antibiotics.[7] The problems associated with the preparation and utilization of N^{δ}-hydroxy-L-ornithine in the total synthesis of ferrichrome,[8] dimeric acid,[9] and rhodotorulic acid[10] have prompted interest in a practical synthesis of the above amino acid.

Scheme I



Syntheses of N^{δ}-hydroxyornithine (**1**) have been reported. A racemic synthesis of **1** by Rogers and Neilands[11] involved reduction of an ω-nitro derivative to the hydroxyamino group with zinc dust, a reaction that pro-

(1) For some recent examples, see: Schollkopf, U.; Neubauer, H-J. *Synthesis* **1982**, 861. Bajgrowicz, J. A.; Cossec, B.; Pigiere, Ch.; Jacquier, R.; Viallfont, Ph. *Tetrahedron Lett.* **1983**, *24*, 3721. MacNeil, P. A.; Roberts, N. K.; Bosnich, B. *J. Am. Chem. Soc.* **1981**, *103*, 2273. Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. *Ibid.* **1980**, *102*, 7932. Vineyard, B. D.; Knowles, W. S.; Sabacky, M. J.; Bachman, G. L.; Weinkauff, D. J. *Ibid.* **1977**, *99*, 5946. Nakajima, K.; Oda, H.; Okawa, K. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 520.

(2) For some recent examples, see: Seebach, D.; Aebi, J. B. *Tetrahedron Lett.* **1983**, *24*, 3311. Seebach, D.; Weber, T. *Ibid.* **1983**, *24*, 3315. Bernardini, A.; Hallaoui, A. E.; Jacquier, R.; Pigiere, Ch.; Viallefont, Ph.; Bajgrowicz, J. *Ibid.* **1983**, *24*, 3717. Seebach, D.; Boes, M.; Naef, R.; Schweizer, W. B. *J. Am. Chem. Soc.* **1983**, *105*, 5390. Noguchi, N.; Kurada, T.; Hatanaka, M; Ishimaru, T. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 633. Schollkopf, U.; Nozulak, J.; Groth, U. *Synthesis* **1982**, 868. Rich, D. H.; Sun, E. T.; Boparai, A. S. *J. Org. Chem.* **1978**, *43*, 3624. Ramasamy, K.; Olsen, R. K.; Emery, T. *Synthesis* **1982**, 42. Scott, A. I; Wilkinson, T. J. *Synth.* Commun. **1980**, *10*, 127.

(3) Neilands, J. B.; *J. Am. Chem. Soc.* **1952**, *74*, 4846. Rogers, S.; Neilands, J. B. *Biochemistry* **1965**, *4*, 1410.

(4) Emery, T. *Biochemistry* **1965**, *4*, 1410.

(5) Diekmann, H. *Arch. Mikrobiol.* **1970**, *73*, 65.

(6) Atkin, C. L.; Neilands, J. B. *Biochemistry* **1968**, *7*, 3734.

(7) Giaribaldi, J. A.; Neilands, J. B. *J. Am. Chem. Soc.* **1955**, 77, 2429. Emery, T.; Neilands, J. B. *J. Am. Chem. Soc.* **1961**, *83*, 1626. Atkin, C. L.; Neilands, J. B.; Phaff, H. J. *J. Bacteriol.* **1970**, *103*, 722. Keller-Schierlein, W.; Deer, A. *Helv. Chim. Acta* **1963**, *46*, 1907. Tadenuma, M.; Sato, S. *Agric. Biol. Chem.* **1967**, *31*, 1482. Keller-Schierlein, W.; Deer, A. *Helv. Chim. Acta* **1963**, *46*, 1920. Sayer, J. M.; Emery, T. *Biochemistry* **1968**, *7*, 184. Moore, R. E.; Emery, T. *Ibid.* **1976**, *15*, 2719. Diekmann, H. *Agnew. Chem.* **1968**, *7*, 551. Pidacks, C.; Whitehill, A. R.; Pruess, L. M.; Hesseltine, C. W.; Hutchings, B. L.; Bohonos, N.; Williams, J. H. *J. Am. Chem. Soc.* **1953**, *75*, 6064. Keller-Schierlein, W.; Diekmann, H. *Helv. Chim. Acta* **1970**, *53*, 2035. Maurer, B.; Muller, A.; Keller-Schierlein, W..; Zahner, H. *Arch. Microbiol.* **1968**, *60*, 326. Maehr, H. *Pure Appl. Chem.* **1971**, *28*, 603. Poddubnaya, N. A.; Krysin, E. P. *J. Gen. Chem. USSR* (Engl. Transl.) **1962**, *32*, 990.

(8) (a) Keller-Schierlein, W. *Helv. Chim. Acta* **1969**, *52*, 603. (b) Isowa, Y.; Takashima, T.; Ohmori, M.; Kurita, H.; Sato, M.; Mori, K. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 215.

(9) Widmer, J.; Keller-Schierlein, W. *Helv. Chim. Acta* **1974**, *57*, 1904.

(10) Isowa, Y.; Takashima, T.; Ohmori, M.; Kurita, H.; Sato, M.; Mori, K. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 1467.

(11) Rogers, S.; Neilands, J. B. *Biochemistry* **1963**, *2*, 6.

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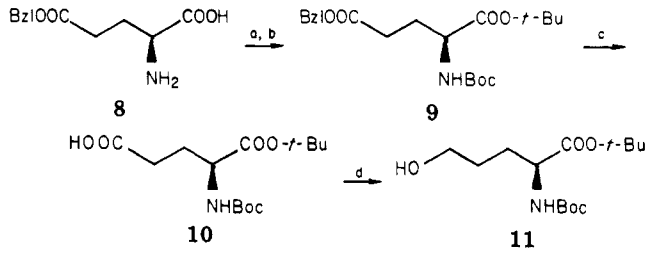
Scheme II[a]



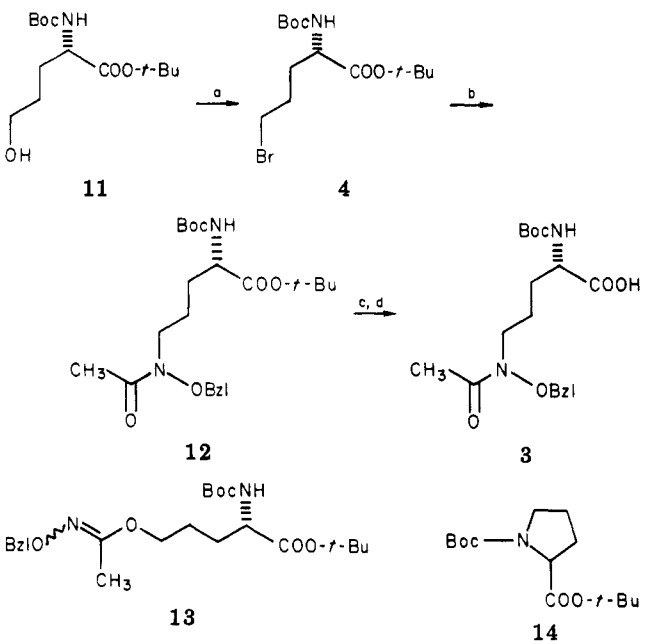
[a] (a) Isobutylene, H_2SO_4, dioxane; (b) di-*tert*-butyl dicarbonate, DMF/H_2O, 82% overall; (c) H_2, Pd/C, EtOH, 78%; (d) ethyl chloroformate, Et_3N, THF, then $NaBH_4$, H_2O, 61%.

ceeded in only 16% yield. Isowa et al.[12] have provided a practical synthesis of **1** involving alkylation of an achiral halide with the anion of *N*-tosyl-*O*-benzylhydroxylamine, followed by resolution. Widmer and Keller-Schierlein[13] have prepared **1** on a milligram scale and of unspecified optical purity from N^{α}-*t*-Boc-L-ornithine *tert*-butyl ester via epoxidation and hydrolysis of the corresponding Schiff base. After the work reported in this paper was completed, Lee and Miller described[14] a synthesis of **1** from L-glutamic acid via reduction of an oxime derived from a δ-glutamic semialdehyde derivative.

In devising a synthesis of N^{α}-Boc-N^{δ}-acetyl-N^{δ}-(benzyloxy)-L-ornithine (**3**) from L-glutamic acid, three strategies for construction of the *N*-hydroxyamino acid were investigated (Scheme I). The approach that proved to be applicable involved displacement of an δ-bromo group in **4** by the anion of *N*-acetyl-*O*-benzylhydroxylamine. This approach has been used by Maurer and Miller[15] in the synthesis of N^{ϵ}-hydroxy-L-lysine and is similar also to the above cited alkylation step employed by Isowa et al.[12] A second method envisioned condensation of δ-glutamic semialdehyde **6** with hydroxylamine to form the oxime, which could then undergo reduction and acylation to the *N*-hydroxyamino acid. This approach recently was reduced to practice in the synthesis of **1** by Miller and Lee.[14] A third strategy was to form the lactam **7** by intramolecular alkylation of the *O*-benzyl hydroxamate derivative of the δ-bromo derivative **4** or an equivalent substrate, followed by opening of the lactam ring. Although this approach has been used for the synthesis of cobactin T,[16] it has not been employed for the synthesis of N^{δ}-hydroxyornithine. The preparation of **7** is of interest due to the presence of this moiety in the siderophores pseudobactin[17] and pyoverdine.[18]

A key compound required for our synthetic studies was *tert*-butyl (*S*)-2-[(*tert*-butyloxycarbonyl)amino]-5-hydroxypentanoate (**11**). This substance was readily prepared (Scheme II) from δ-benzyl L-glutamate (**8**) by acid-catalyzed esterification with isobutylene to furnish the α-*tert*-butyl ester,[19] followed by introduction of the Boc (*tert*-butyloxycarbonyl) group to give **9**. Hydrogenolysis of the δ-benzyl ester gave monoacid **10**,[20] which was reduced, via the mixed carbonic anhydride and sodium borohydride,[21] to the desired alcohol **11**.

Scheme III[a]



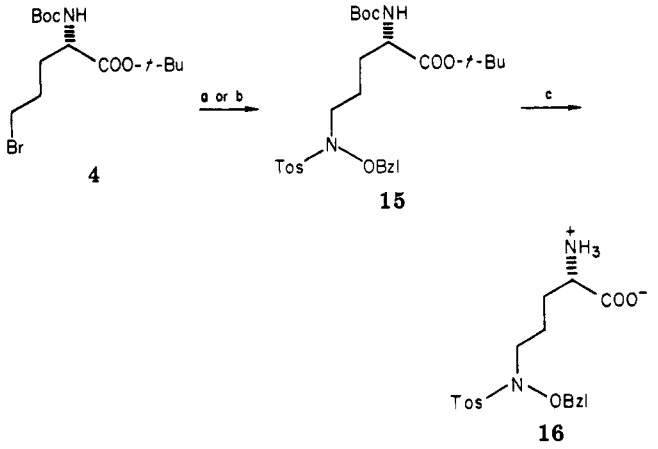
[a] (a) CBr_4, Ph_3P, THF, 77%; (b) AcNHOBzl, K_2CO_3, acetone, 60%; (c) TFA; (d) di-*tert*-butyl dicarbonate, Et_3N, DMF/H_2O, 79%.

tert-Butyl (*S*)-2-[(*tert*-butyloxycarbonyl)amino]-5-bromopentanoate (**4**) was prepared in 77% yield from alcohol **11** by reaction with triphenylphosphine and carbon tetrabromide[22] (Scheme III). Treatment of bromide **4** with *N*-acetyl-*O*-benzylhydroxylamine[15] and anhydrous potassium carbonate in dry acetone for three days at reflux temperatures produced the desired N-alkylated hydroxamate **12** in 60% yield. Addition of a catalytic amount of potassium iodide to the reaction mixture, as per the procedure of Miller,[15] allowed reduction of the reaction time to 24 h. However, the yield of hydroxamate **12** was only 54% with an apparent increase of the number of side products formed in the reaction. We have characterized these side products, which include the *O*-alkylated *E*- and *Z*-hydroximates **13** (18–25%) and *N*-Boc-L-proline *tert*-butyl ester **14**, (20%). The formation of the latter product is to be expected as the transformation of glutamic acid into proline has been observed.[23] These results indicate an increased amount of intramolecular *N*-alkylation as also *O*-alkylation may be occurring from the iodide as compared with bromide **4**, while the intermolecular *N*-alkylation of bromide **4**, though slower, is a cleaner reaction than that of the corresponding iodide.

Conversion of the hydroxamate **12** into the natural product synthon **3** was achieved by removal of both the N^{α}-Boc and *tert*-butyl ester groups by treatment with trifluoroacetic acid to give the trifluoroacetate salt, which without characterization, was caused to react with di-*tert*-butyl dicarbonate[24] in dimethylformamide–water–triethylamine to furnish **3** in 79% yield from **12**. The preparation of **3** in a protected form suitable for use in

(12) Isowa, Y.; Takashima, T.; Ohmori, M.; Kurita, H.; Sato, M.; Mori, K. *Bull. Chem. Soc. Jpn.* **1974**, *45*, 1461.
(13) Widmer, J.; Keller-Schierlein, W. *Helv. Chim. Acta* **1974**, *57*, 657.
(14) Lee, B. H.; Miller, M. J. *Tetrahedron Lett.* **1984**, *25*, 927.
(15) Maurer, P. J.; Miller, M. J. *J. Am. Chem. Soc.* **1982**, *104*, 3096.
(16) Maurer, P. J.; Miller, M. J. *J. Org. Chem.* **1981**, *46*, 2835.
(17) Teintze, M.; Hossain, M. B.; Barnes, C. L.; Leong, J.; vanderHelm, D. *Biochemistry* **1981**, *20*, 6446. Teintze, M.; Leong, J. *Ibid.* **1981**, *20*, 6457.
(18) Wendenbaum, S.; Demange, P.; Dell, A.; Meyers, J. M.; Abdallah, M. A. *Tetrahedron Lett.* **1983**, *24*, 4877.
(19) Roeske, R. *J. Org. Chem.* **1963**, *28*, 1251.
(20) For a previous synthesis of **10**, see: Tomasz, J. *Acta Chim. Acad. Sci. Hung.* **1971**, *70*, 255.
(21) Ishizumi, K.; Koga, K.; Yamada, S. *Chem. Pharm. Bull.* **1968**, *16*, 492.
(22) Ayelrod, E. H.; Milne, G. M.; Tamelen, E. E. *J. Am. Chem. Soc.* **1970**, *92*, 2139.
(23) Pravda, Z.; Rudinger, J. *Collect. Czech. Chem. Commun.* **1955**, *20*, 1.
(24) Maroder, L.; Hallet, A.; Wunsch, E.; Keller, D.; Wersin G. *Hoppe-Seyler's Z. Physiol. Chem.* **1976**, 357, 1651.

Scheme IV[a]



[a] (a) TosNHOBzl, K_2CO_3, acetone, 57%; (b) TosNHOBzl, K_2CO_3, KI, acetone, 80%; (c) 6 N HCl, EtOAc, then pyridine, 76%.

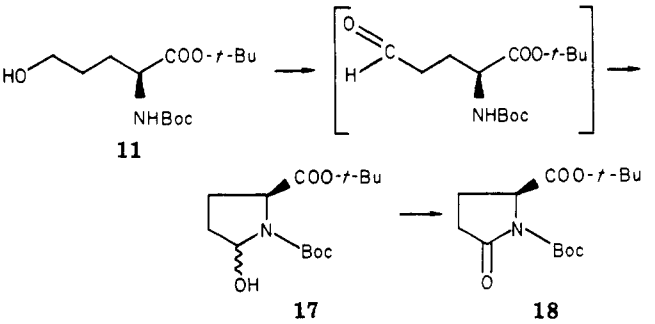
peptide synthesis provides a potential building stone for the total syntheses of many natural hydroxamate peptidyl siderophores.

We planned to prepare the known[12] N^{δ}-(benzyloxy)-N^{δ}-tosyl-L-ornithine (**16**) to determine the optical purity of our reaction products. Accordingly, alkylation of *O*-benzyl-*N*-tosylhydroxamate[12] with bromide **4**, as described previously, gave the N^{δ}-(benzyloxy)-N^{δ}-tosyl-L-ornithine **15** in 57% yield. In contrast to the above described alkylation of *O*-benzyl acetohydroxamate, addition of freshly dried potassium iodide caused the yield of **15** to increase to 80%. Deprotection of the N^{α}-Boc and *tert*-butyl ester groups from **15** with 6 N hydrochloric acid in ethyl acetate furnished N^{δ}-(benzyloxy)-N^{δ}-tosyl-L-ornithine (**16**) in optically pure form,[12] thus establishing the chiral integrity of the reaction sequence leading to **3**.

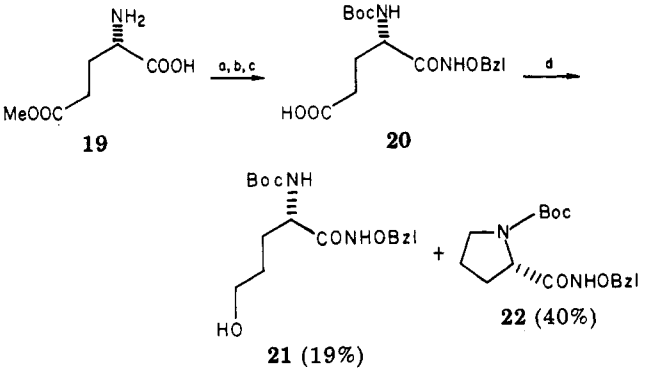
Direct alkylation of *N*-acetyl-*O*-benzylhydroxylamine or *N*-(benzyloxycarbonyl)-*O*-benzylhydroxylamine with the alcohol **11**, as mediated by diethyl azodicarboxylate and triphenylphosphine,[25] gave a mixture of products in each case, which mixture could not be separated even on repeated chromatography over silica with medium-pressure liquid chromatography.

We have attempted to prepare a δ-glutamate semialdehyde derivative in order to study the preparation of N^{δ}-hydroxy-L-ornithine via reduction of an oxime intermediate (Scheme I). Oxidation of alcohol **11** with chromium(VI) oxide–pyridine[26] in dichloromethane gave two products, **17** and **18**, isolated in 30% and 40% yields, respectively. Neither of these products showed an aldehyde proton in their respective ^1H NMR spectra. Oxidation of alcohol **11** with pyridinium chlorochromate (PCC)[27] gave **18** in 81% yield. Compound **17**, upon treatment with PCC, was transformed into **18**. These results are consistent for formation of the aldehyde, which rapidly undergoes cyclization to the carbinolamide **17**, followed by oxidation to the second product, *N*-Boc-L-pyroglutamic acid *tert*-butyl ester (**18**) (Scheme V). The facile cyclization of the urethane nitrogen onto the aldehyde function during the oxidation reaction precludes preparation of this aldehyde as derived from glutamic acid via alcohol **11**. Lee and Miller[14] in their synthesis of **1** via a δ-glutamate semialdehyde, used oxazolidinone protection that precluded

Scheme V



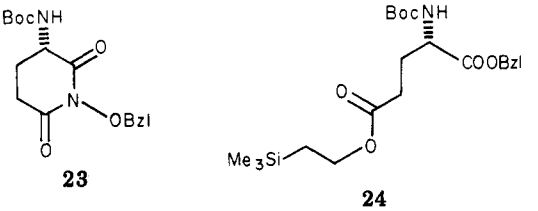
Scheme VI[a]



[a] (a) $(Boc)_2O$, DMF, H_2O, TEA, 100%; (b) $BzlONH_2$, DCC, CH_2Cl_2, 85%; (c) NaOH, acetone, 83%; (d) B_2H_6, THF.

interaction of the aldehyde with the α-amino function.

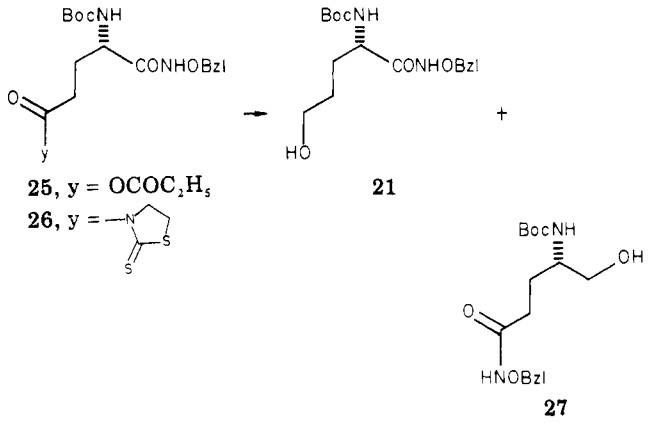
A third approach investigated involved preparation of the cyclic hydroxamate **7** by intramolecular alkylation of the δ-hydroxy hydroxamate derivative **21**, with the intent to effect subsequent ring opening of **7** to furnish a δ-hydroxyornithine derivative. Preparation of **21** proceeded from L-glutamic acid δ-methyl ester **19** by sequential introduction of the N^{α}-Boc group and condensation with *O*-benzylhydroxylamine (Scheme VI). Saponification of the methyl ester gave the acid **20**. That no transmidation[28] had occurred, via **23**, in the hydrolysis reaction to give acid



20 was established by preparation of acid **20** from the δ-[2-(trimethylsilyl)ethyl] ester **24** by a sequence of reactions involving hydrogenolysis of the α-benzyl ester, condensation with *O*-benzylhydroxylamine, and removal of the (trimethylsilyl)ethyl group with fluoride ion.[29] The product acids prepared by these two routes were shown to be identical.

Reduction of acid **20** to the alcohol **21** proved to be the problem. Reduction of **20** with diborane gave two products, the desired alcohol **21** (19%) and the hydroxamate derivative **22** (40%) of *N*-Boc-L-proline. Likewise, conversion of acid **20** to the mixed anhydride **25** and reduction with sodium borohydride[21] furnished **21** (15%) and an

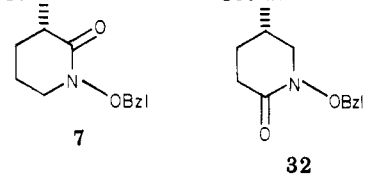
(25) Wada, M.; Mitsunobu, O. *Tetrahedron Lett.* **1972**, 1279.
(26) Collins, J. C.; Hess, W. W.; Frank, F. J. *Tetrahedron Lett.* **1968**, 3363.
(27) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.
(28) Transamidation is known to occur during peptide synthesis involving glutamic acid; see: Schroder, E.; Lubke, K. "The Peptides"; Academic Press: New York, 1965; Vol. I, pp 188–190.
(29) Sieber, P. *Helv. Chim. Acta* **1977**, *60*, 2711.



isomeric alcohol assigned structure **27** (26%). Similar results were obtained upon reduction with sodium borohydride of the 1,3-thiazolidine-2-thione ester **26**,[30] which provided a mixture of **21** (17%) and **27** (40%). Formation of **27** presumably arises by reduction of the α-carbonyl of the cyclic imide **23** formed by amidation of the activated δ-carboxyl groups present in **25** and **26**.

Corroboration of the structural assignment for **21** was obtained by synthesis of **21** by a second route utilizing reactions that preclude rearrangement (Scheme VII). Reduction of glutamic acid derivative **28**[31] with diborane gave the alcohol **29** (30%) and the proline derivative **30** (37%). Acetylation and hydrogenolysis of **29** furnished acetate **31**, which was converted to **21** by standard procedures.

Cyclization of alcohol **21** to the cyclic hydroxamate **7** was effected in a yield of 64% by reaction with diethyl azodicarboxylate and triphenylphosphine.[25] A mixture of *E* and *Z* isomers of the corresponding cyclic hydroximate, formed by *O*-alkylation, also was formed in 15% yield. In a similar manner, isomeric alcohol **27** was transformed to **32**. Assignment of structure to the isomeric cyclic hy-

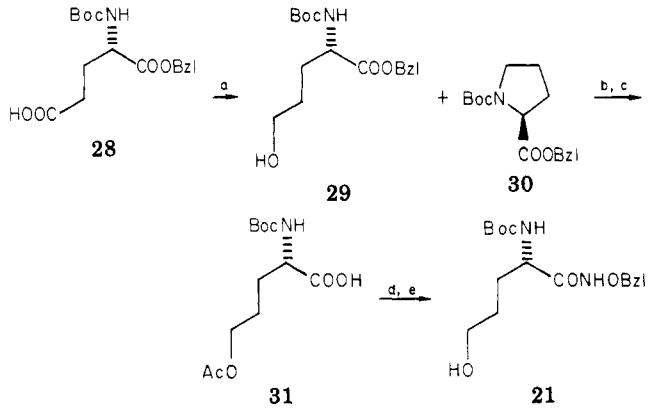


droxamates **7** and **32** was readily made from data obtained by 360-MHz homonuclear decoupling experiments. For **32**, irradiation of the α-hydrogen at δ 3.96 resulted in decoupling of the methylene protons α to the hydroxamate nitrogen to furnish a pair of AB doublets centered at 3.13 and 3.66 ppm. In contrast, irradiation of the α-hydrogen in **7** (δ 4.10) had no effect on the multiplet at 3.28 ppm assigned to the methylene protons next to the hydroxamate nitrogen.

The low yields (15–19%) of alcohol **21** obtained in the above studies made the above approach to the title compound, via cyclic hydroxamate **7**, rather unpromising. Because of this, further studies to effect conversion of **7** to ornithine **3** were not pursued.

In summary, an efficient synthesis of N^{α}-Boc-N^{δ}-acetyl-N^{δ}-(benzyloxy)-L-ornithine (**3**) from L-glutamic acid has been developed. A key reaction in the synthesis invokes Miller's procedure[15] involving N-alkylation of a hydroxamate anion by a δ-bromo derivative derived from L-glutamic acid. Two other approaches that were investigated proved not to be amendable for the synthesis of **3** due to (1) the propensity of the Boc urethane nitrogen to undergo cyclization onto an aldehyde function generated at the terminus of the glutamate side chain and (2) the occurrence of transamidation rearrangement processes upon attempted reduction of the δ-carboxyl function in hydroxamates **25** and **26**.

Scheme VII[a]



[a] (a) BH_3/THF; (b) Ac_2O, pyridine; (c) H_2, Pd/C; (d) H_2NOBzl, EDC; (e) NaOH, acetone.

Experimental Section

The L-amino acids and coupling reagents used in this study were commercially available. Tetrahydrofuran was distilled prior to use from sodium benzophenone ketyl. Methylene chloride was distilled from phosphorous pentoxide and stored over Linde 3A molecular sieves. Dimethylformamide was distilled from calcium hydride. Dry acetone was distilled from potassium permanganate and then from anhydrous potassium carbonate.

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on Varian EM-360, JEOL FT-90Q, and Nicolet NT-360 spectrometers. Optical rotations were recorded on a Perkin-Elmer 241 automatic polarimeter. Thin-layer chromatography was performed on commercial silica gel on glass plates (1 × 3 in.). Medium-pressure liquid chromatography (MPLC) was performed at 60–100 psi in glass columns packed with silica gel 60 (0.040–0.063 mm).

***α-tert*-Butyl γ-Benzyl N^{α}-(*tert*-Butyloxycarbonyl)-L-glutamate (9).** This compound was prepared by a modification of the procedure of Roeske.[19] γ-Benzyl L-glutamic acid (10 g, 42 mmol) was dissolved in a mixture of dioxane (100 mL) and 10 mL of concentrated sulfuric acid in a 500 mL pressure bottle and cooled to 10–15 °C. Isobutylene (70 mL) was added and the mixture was shaken mechanically at room temperature for 4 h. The mixture was poured carefully during a 10-min period into a cold, stirred mixture of triethylamine/water (60:100 mL). To this dilute, cold mixture, di-*tert*-butyl dicarbonate (8.7 g, 40 mmol) was added and the mixture was stirred at room temperature for 4 h. The dioxane/water was removed in vacuo to give an oily residue, which was suspended in ethyl acetate and made acidic (pH 2) with aqueous $KHSO_4$ solution. The EtOAc (2 × 100 mL) extract was washed with H_2O (50 mL) and brine (25 mL) and dried over Na_2SO_4, and the solvent evaporated to give **9** as an oil. This oil was purified by MPLC upon elution with hexane/acetone; yield 13.6 g (82%).

***α-tert*-Butyl N^{α}-(*tert*-Butyloxycarbonyl)-L-glutamate (10).** α-*tert*-Butyl γ-benzyl N^{α}-(*tert*-butyloxycarbonyl)-L-glutamate (10 g, 25 mmol) and 700 mg of 5% palladium–carbon in 100 mL of 95% ethanol were shaken under hydrogen for 12 h. The catalyst was filtered and the filtrate evaporated to give an oil, which was crystallized from ether/petroleum ether (30–60 °C) to provide a white crystalline compound: yield, 6 g (78%); mp 102–105 °C; $[\alpha]^{25}_D$ −26.5° (*c* 1, MeOH) [lit.[20] mp 110–114 °C; $[\alpha]^{25}_D$ −30.2° (c 1, MeOH)].

***tert*-Butyl (*S*)-2-[(*tert*-Butyloxycarbonyl)amino]-5-hydroxypentanoate (11).** Ethyl chloroformate (2.16 g, 20 mmol)

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(31) Schroder, V. E.; Klieger, E. *Liebigs Ann. Chem.* **1964**, *673*, 196.

was added at −10 °C to a stirred solution of α-*tert*-butyl N^{α}-(*tert*-butyloxycarbonyl)-L-glutamic acid monoester (5.9 g, 19.5 mmol) and triethylamine (2.02 g, 20 mmol) in tetrahydrofuran 80 mL) and the mixture was stirred at −10 °C for 30 min. The precipitated mass was filtered and the filtrate was added over a period of 0.5 h to a solution of sodium borohydride (2.3 g, 60 mmol) in a mixture of water/THF (5:20 mL) at 10–15 °C. The reaction mixture was stirred at room temperature for 4 h, acidified with HCl, and the THF was removed under reduced pressure. The aqueous solution was extracted with EtOAc (2 × 75 mL), washed with 10% NaOH (25 mL), H_2O (25 mL), and brine (25 mL), dried over anhydrous Na_2SO_4, and concentrated to give an oil. This crude oil was purified by using MPLC with elution by chloroform/acetone: yield, 3.4 g (61%); $[\alpha]^{25}_D$ +8.1° (*c* 2, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.45 (s, 9 H, Boc), 1.6–1.8 (m, 4 H, CH_2), 3.5–3.75 (m, 2 H), 4.05–4.3 (m, 1 H), 5.25 (d, 1 H, NH).

Anal. Calcd for $C_{14}H_{27}NO_5$: C, 58.1; H, 9.40; N, 4.84. Found: C, 57.96; H, 9.40; N, 4.84.

***tert*-Butyl (*S*)-2-[(*tert*-Butyloxycarbonyl)amino]-5-bromopentanoate (4).** *tert*-Butyl 2-[(*tert*-butyloxycarbonyl)-amino]-5-hydroxypentanoate (1.5 g, 5.2 mmol) and carbon tetrabromide (2.3 g, 6.9 mmol) were dissolved in dry THF (50 mL) and cooled to ~15 °C. To this cooled solution was added Ph_3P (1.8 g, 6.9 mmol), and the mixture was stirred at ~15 °C for 10 min and at room temperature overnight. The THF was removed under reduced pressure and the crude residue was chromatographed over silica with chloroform as eluant: yield, 1.4 g (77%); $[\alpha]^{25}_D$ −12° (*c* 2, acetone); ^1H NMR ($CDCl_3$) δ 1.45 (d, 18 H, Boc and *tert*-butyl), 1.7–2.5 (m, 4 H), 3.4 (t, 2 H), 4.15 (m, 1 H, α-H), 5.12 (d, 1 H, NH).

Anal. Calcd for $C_{14}H_{26}NO_4Br$: C, 47.7; H, 7.44; N, 3.97. Found: C, 47.62; H, 7.31; N, 3.98.

α-*tert*-Butyl N^{α}-(*tert*-Butyloxycarbonyl)-N^{δ}-acetyl-N^{δ}-(benzyloxy)-L-ornithine (12). A mixture of *tert*-butyl 2-[(*tert*-butyloxycarbonyl)amino]-5-bromo-L-pentanoate (3.23 g, 9.3 mmol), *O*-benzyl acetohydroxamate[15] (1.53 g, 9.3 mmol), KI (0.6 g, 3.6 mmol), and anhydrous K_2CO_3 (3.03 g, 22 mmol) in 60 mL of dry acetone was refluxed for 24 h. The reaction mixture was made acidic with dilute HCl and extracted with ethyl acetate (2 × 75 mL). The EtOAc extract was washed with 0.5 N NaOH (25 mL), H_2O (25 mL), and brine (25 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by using MPLC with elution by hexane/acetone to give the following.

(i) N-Alkylated product **12** was obtained as an oil in 54% yield: $[\alpha]^{25}_D$ +9.4° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.44 (s, 18 H, Boc and *tert*-butyl), 1.68 (bt, 4 H, CH_2), 2.08 (s, 3 H, CH_3), 3.64 (bt, 2 H, CH_2), 4.12 (m, 1 H, α-H), 4.8 (s, 2 H, CH_2), 5.02 (d, 1 H, NH), 7.37 (s, 5 H, Ph).

Anal. Calcd for $C_{23}H_{36}N_2O_6$: C, 63.3; H, 8.3; N, 6.4. Found: C, 63.13; H, 8.16; N, 6.22.

(ii) The O-alkylated, more polar *E* isomer (**13**) was obtained as oil in 3.2% yield: $[\alpha]^{25}_D$ +9.3° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.5 (s, 18 H, Boc and *tert*-butyl), 1.66–1.97 (m, 4 H, CH_2), 2.0 (s, 3 H, CH_3), 3.9–4.37 (m, 3 H, CH_2 and α-H), 5.0 (s, 2 H, CH_2Ph), 5.13 (d, 1 H, NH), 7.43 (s, 5 H, Ph).

Anal. Calcd for $C_{23}H_{36}N_2O_6$: C, 63.3; H, 8.3; N, 6.4. Found: C, 62.96; H, 8.17; N, 6.23.

(iii) A third fraction was a mixture of products, which was chromatographed again on MPLC by eluting with ethyl acetate/hexane to obtain the *Z* isomer (**13**) as an oil in 11% yield: $[\alpha]^{25}_D$ +10.6° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.47 (s, 18 H, Boc and *tert*-butyl), 1.7–2.1 (m, 4 H, CH_2), 1.96 (s, 3 H, CH_3), 4.0–4.43 (m, 3 H, CH_2 and α-H), 5.03 (s, 2 H, CH_2Ph), 5.27 (d, 1 H, NH), 7.43 (s, 5 H, Ph).

Anal. Calcd for $C_{23}H_{36}N_2O_6$: C, 63.3; H, 8.3; N, 6.4. Found: C, 63.28; H, 8.47; N, 6.33.

The proline derivative **14** also was obtained as a colorless oil in 14% yield: $[\alpha]^{25}_D$ −48.9° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.48 (s, 18 H, Boc and *tert*-butyl), 1.76–2.53 (m, 4 H, CH_2), 3.3–3.73 (bt, 2 H, CH_2), 4.03–4.37 (m, 1 H, α-H).

N^{α}-(*tert*-Butyloxycarbonyl)-N^{δ}-acetyl-N^{δ}-(benzyloxy)-L-ornithine (3). α-*tert*-Butyl N^{α}-[(*tert*-butyloxy)carbonyl]-N^{δ}-acetyl-N^{δ}-(benzyloxy)-L-ornithine (340 mg, 0.8 mmol) was dissolved in 5 mL of anhydrous trifluoroacetic acid and stirred at room temperature for 5 h. The reaction mixture was concentrated and the residue was dissolved in dry CH_3OH (10 mL) and evaporated under reduced pressure at 50 °C. This procedure was repeated three times and the resulting residue was treated with dry ether to give a solid, which was filtered and dried in a vacuum desicator over KOH pellets.

The above dried trifluoroacetate salt (250 mg, 0.66 mmol) was dissolved in a mixture of DMF/H_2O (1:1, 15 mL). To the above solution was added triethylamine (0.14 g, 1.4 mmol) and di-*tert*-butyl dicarbonate (218 mg, 1 mmol) and the mixture was stirred at room temperature for 2 h. The DMF/H_2O was removed in vacuo and the residue was suspended in ethyl acetate and made acidic (pH 2) with an aqueous solution of $KHSO_4$. The EtOAc extract was washed with H_2O (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated to give an oil. The oil was purified on a gravity column of silica gel with $CHCl_3$/MeOH as eluant. An analytical sample was prepared by using preparative thin-layer chromatography: yield, 200 mg (79%); $[\alpha]^{25}_D$ +6.2° (*c* 1, EtOH); ^1H NMR ($CDCl_3$) δ 1.41 (s, 9 H, Boc), 1.72 (bt, 4 H, CH_2), 2.09 (s, 3 H, CH_3), 3.66 (bt, 2 H, CH_2), 4.2 (m, 1 H, α-H), 4.81 (s, 2 H, CH_2Ph), 5.5 (d, 1 H, NH), 7.36 (s, 5 H, Ph).

Anal. Calcd for $C_{19}H_{28}N_2O_6$: C, 59.98; H, 7.42; N, 7.36. Found: C, 60.03; H, 7.10; N, 7.17.

α-*tert*-Butyl N^{α}-(*tert*-Butyloxycarbonyl)-N^{δ}-tosyl-N^{δ}-(benzyloxy)-L-ornithine (15). A mixture of *tert*-butyl 2-[(*tert*-butyloxycarbonyl)amino]-5-bromo-L-pentanoate (450 mg, 1.3 mmol), *O*-benzyl-*N*-tosylhydroxylamine[12] (360 mg, 1.3 mmol), KI (100 mg, 0.6 mmol), and anhydrous K_2CO_3 (800 mL, 5.8 mmol) in 30 mL of dry acetone was refluxed for 36 h. The reaction mixture was made acidic with dilute HCl and the acetone was removed. The aqueous solution was extracted with EtOAc (2 × 50 mL), washed with water (10 mL) and brine (10 mL), and dried over anhydrous Na_2SO_4, and the solvent removed to give the crude product. The crude product was purified by using MPLC with elution by hexane/acetone (8:2): yield, 560 mg (80%); $[\alpha]^{25}_D$ +14.2° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.44 (d, 18 H, Boc and *tert*-butyl), 1.5–1.75 (m, 4 H), 2.4 (s, 3 H, CH_3), 2.7–3.00 (bt, 2 H, CH_2), 4.1 (m, 1 H, α-H), 4.97 (d, 1 H, NH), 5.08 (s, 2 H, CH_2Ph), 7.28 (d, 2 H, Ph), 7.38 (s, 5 H, Ph), 7.72 (d, 2 H, Ph).

Anal. Calcd for $C_{28}H_{40}N_2SO_7 \cdot {}^1/_2H_2O$: C, 60.31; H, 7.41; N, 5.02. Found: C, 60.16; H, 7.47; N, 5.00.

N^{δ}-Tosyl-N^{δ}-(benzyloxy)-L-ornithine (16). α-*tert*-Butyl N^{α}-(*tert*-butyloxycarbonyl)-N^{δ}-tosyl-N^{δ}-(benzyloxy)-L-ornithine (100 mg) was stirred at room temperature in a two-phase mixture of 6 N HCl (10 mL) and EtOAc (10 mL) for 4 h. The reaction mixture was concentrated in vacuo to dryness and the residue was dissolved in 0.1 N HCl (0.5 mL) and the solution was adjusted to pH 5 with pyridine and diluted with absolute ethanol (3 mL). This solution, on cooling in a refrigerator for a few days, gave a white crystalline product, which was filtered and dried: yield, 50 mg (76%); mp 220–222 °C; $[\alpha]^{25}_D$ +19.8° (*c* 0.5, CH_3COOH) [lit[12] mp 222.5–224.8 °C; $[\alpha]_D$ +20.7° (*c* 3, CH_3COOH).

α-*tert*-Butyl N^{α}-(*tert*-Butyloxycarbonyl)-L-pyroglutamate (18). A mixture of alcohol **11** (200 mg, 0.7 mmol) and pyridinium chlorochromate (PCC) (602 mg, 1.8 mmol) in 50 mL of dry methylene chloride was stirred at room temperature for 12 h. The solution was filtered and the residue was washed with additional CH_2Cl_2. The combined organic phase was washed with 5% sodium hydroxide (25 mL), 5% hydrochloric acid (25 mL), 5% sodium bicarbonate (25 mL), water (25 mL), and brine (25 mL) and dried over anhydrous Na_2SO_4. The crude product was chromatographed over silica gel with hexane/acetone as eluant to give **18**: 160 mg (81%); $[\alpha]^{25}_D$ −35.3° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.43 (d, 18 H, Boc and *tert*-butyl), 2.0 (m, 1 H), 2.3 (m, 1 H), 2.48 (m, 1 H), 2.62 (m, 1 H), 4.5 (dd, 1 H, α-H).

Anal. Calcd for $C_{14}H_{23}NO_5$: C, 58.93; H, 8.13; N, 4.91. Found: C, 58.73; H, 8.05; N, 4.87.

N^{α}-(*tert*-Butyloxycarbonyl)-γ-methyl-L-glutamic Acid. γ-Methyl-L-glutamic acid (3.2 g, 20 mmol) was suspended in a mixture of DMF/H_2O (25:25 mL). A clear solution was obtained when triethylamine (2.02 g, 20 mmol) was added. Di-*tert*-butyl dicarbonate (4.4 g, 20 mmol) was added and the reaction mixture was stirred at room temperature for 1 h. The solvent was removed in vacuo, and the residue was suspended in EtOAc, made acidic with aqueous $KHSO_4$ solution, and extracted with EtOAc (2 × 75 mL). The EtOAc extract was washed with 1 N HCl (40 mL), H_2O (25 mL), and brine (25 mL), dried over anhydrous Na_2SO_4,

and concentrated to give an oil. The product was used as such for the next step without characterization: yield, 5.15 g (100%).

O^{α}-Benzyl N^{α}-(*tert*-Butyloxycarbonyl)-γ-methyl-L-glutamic Acid α-Hydroxamate. A mixture of γ-methyl N^{α}-(*tert*-butyloxycarbonyl)-L-glutamic acid (5.2 g, 20 mmol), *O*-benzylhydroxylamine hydrochloride (3.2 g, 20 mmol), triethylamine (2.02 g, 20 mmol), and dicyclohexylcarbodiimide (DCC) (4.4 g, 20 mmol) in 150 mL of dry CH_2Cl_2 was stirred at room temperature for 12 h. The precipitated solid was filtered and the solvent removed. The residue was partitioned between EtOAc/H_2O and extracted with EtOAc (2 × 75 mL). The EtOAc extract was washed with 1 N HCl (50 mL), 0.5 N $NaHCO_3$ (25 mL), H_2O (25 mL), and brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated. The crude product was chromatographed over silica with chloroform/acetone as eluant: yield, 6.2 g (85%); mp 90–92 °C (hexane/acetone); $[\alpha]^{25}_D$ −26.7° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.43 (s, 9 H, Boc), 1.67–2.6 (m, 4 H, CH_2), 3.7 (s, 3 H, CH_3), 4.15 (m, 1 H, α-H), 4.93 (s, 2 H, CH_2Ph), 5.6 (d, 1 H, NH), 7.43 (s, 5 H, Ph), 9.97 (bs, 1 H, NH).

Anal. Calcd for $C_{18}H_{26}N_2O_6$: C, 59.00; H, 7.15; N, 7.65. Found: C, 58.88; H, 7.18; N, 7.71.

O^{α}-Benzyl N^{α}-(*tert*-Butyloxycarbonyl)-L-glutamic Acid α-Hydroxamate (20). O^{α}-Benzyl N^{α}-(*tert*-butyloxycarbonyl)-γ-methyl-L-glutamic acid α-hydroxamate (6.7 g, 18 mmol) was dissolved in 25 mL of acetone. To this was added 35 mL (35 mmol) of 1 N sodium hydroxide and the mixture was stirred at room temperature for 1 h. The acetone was removed under reduced pressure and the aqueous alkaline solution was washed with 50 mL of EtOAc. The aqueous solution was made acidic with 1 N HCl and extracted with EtOAc. The EtOAc extract was washed with H_2O (50 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated to give an oily product. The oil was crystallized from acetone/hexane as a white crystalline compound: yield, 5.3 g (83%); mp 131–134 °C; $[\alpha]^{25}_D$ −34° (*c* 1, CH_3OH); ^1H NMR ($CDCl_3$) δ 1.38 (s, 9 H, Boc), 1.65–1.9 (m, 2 H, CH_2), 2.0–2.3 (m, 2 H, CH_2), 3.7–3.98 (m, 1 H, α-H), 4.79 (s, 2 H, CH_2Ph), 6.75 (bd, 1 H, NH), 7.35 (s, 5 H, Ph), 11.15 (s, 1 H, NH).

Anal. Calcd for $C_{17}H_{24}N_2O_6$: C, 57.9; H, 6.86; N, 7.90. Found: C, 57.79; H, 6.79; N, 7.97.

α-Benzyl N^{α}-(*tert*-Butyloxycarbonyl)-γ-[2-(trimethylsily)ethyl]-L-glutamate (24). α-Benzyl N^{α}-(*tert*-butyloxycarbonyl)-L-glutamate (**28**)[31] (2.1 g, 6.3 mmol) was dissolved in 50 mL of dry methylene chloride and cooled at 0 °C. To this cooled solution were added dry pyridine (1.2 mL, 14.9 mmol) and 2-(trimethylsilyl)ethanol (0.83 g, 7 mmol) and the mixture was stirred for 10 min. *N,N'*-Dicyclohexylcarbodiimide was added and stirring was continued at 0 °C for 6 h and at room temperature overnight. The reaction mixture was cooled to 0 °C and the precipitated solid was filtered and washed with dry CH_2Cl_2. The filtrate was evaporated to give an oil, which was extracted with aqueous ethyl acetate (2 × 50 mL). The EtOAc extract was washed with 10% citric acid (25 mL), 0.3 N $NaHCO_3$ (25 mL), H_2O (25 mL), and brine (20 mL), dried over Na_2SO_4, and concentrated. The crude product was chromatographed on silica gel, eluting with hexane/acetone (95:5) to obtain **24** as a colorless oil: 1.8 g (66%); $[\alpha]^{25}_D$ +1.1° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.0 (s, 9 H, $SiCH_3$), 0.94 (t, 2 H, CH_2), 1.39 (s, 9 H, Boc), 1.6–2.33 (m, 4 H, CH_2), 4.13 (t, 2 H, CH_2), 4.3 (m, 1 H, α-H), 5.13 (s, 2 H, CH_2Ph), 5.2 (d, 1 H, NH), 7.3 (s, 5 H, Ph).

N^{α}-(*tert*-Butyloxycarbonyl)-γ-[2-(trimethylsilyl)-ethyl]-L-glutamic Acid. α-Benzyl N^{α}-(*tert*-butyloxycarbonyl)-γ-[2-(trimethylsilyl)ethyl]-L-glutamate (**24**) (1.8 g, 4.12 mmol) and 200 mg of 5% palladium–carbon in 50 mL of 95% ethanol were shaken under hydrogen for 12 h. The catalyst was filtered and the filtrate evaporated to give an oil. The oil was used for the next reaction without characterization: yield, 1.4 g (98%).

O^{α}-Benzyl N^{α}-(*tert*-Butyloxycarbonyl)-γ-[2-(trimethylsilyl)ethyl]-L-glutamic Acid α-Hydroxamate. A mixture of N^{α}-(*tert*-butyloxycarbonyl)-γ-[2-(trimethylsilyl)ethyl]-L-glutamic acid (1.4 g, 4 mmol), *O*-benzylhydroxylamine hydrochloride (0.78 g, 5 mmol), triethylamine (0.51 g, 5 mmol), and 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (0.96 g, 5 mmol) in 50 mL of dry methylene chloride was stirred at 0 °C for 3 h and at room temperature overnight. The reaction mixture was concentrated and extracted with aqueous ethyl acetate (2 × 40 mL). The EtOAc extract was washed with 10% citric acid (20 mL), H_2O (20 mL), and brine (20 mL), dried (anhydrous Na_2SO_4), and concentrated. The crude product was purified by using MPLC eluting with hexane/acetone: yield, 1.5 g (82%); $[\alpha]^{25}_D$ −18.4° (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.0 (s, 9 H, $SiCH_3$), 0.93 (t, 2 H, CH_2), 1.38 (s, 9 H, Boc), 2.09 (bt, 2 H, CH_2), 2.32 (bt, 2 H, CH_2), 4.11 (t, 3 H, CH_2 and α-H), 4.85 (s, 2 H, CH_2Ph), 5.70 (bd, 1 H, NH), 7.3 (s, 5 H, Ph), 10.33 (bs, 1 H, NH).

Anal. Calcd for $C_{22}H_{36}N_2SiO_6$: C, 58.4; H, 8.02; N, 6.19. Found: C, 58.24; H, 8.23; N, 6.11.

O^{α}-Benzyl N^{α}-(*tert*-Butyloxycarbonyl)-L-glutamic Acid α-Hydroxamate (20). O^{α}-Benzyl N^{α}-(*tert*-butyloxycarbonyl)-γ-[2-(trimethylsilyl)ethyl]-L-glutamic acid α-hydroxamate (200 mg, 0.44 mmol) was dissolved in dry THF and treated with tetrabutylammonium fluoride trihydrate (200 mg) (dried under vacuum at 80 °C overnight before use). The reaction mixture was stirred at room temperature for 4 h and the solvent was removed. The residue obtained was made acidic with 1 N HCl and extracted with ethyl acetate. The EtOAc extract was washed with H_2O (10 mL), and brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated to give an oil. The oil was purified on a gravity column of silica gel using chloroform/acetone (7:3) as eluant. The pure compound was crystallized from ether/petroleum ether (bp 30–60 °C): yield, 140 mg (90%); $[\alpha]^{25}_D$ −34.8° (*c* 0.5, MeOH); mp 132–134 °C. This material was shown to be identical to compound **20** prepared above.

(*S*)-*O*-Benzyl 2-[(*tert*-Butyloxycarbonyl)amino]-5-hydroxypentanohydroxamate (21). Method A. O^{α}-Benzyl N^{α}-(*tert*-butyloxycarbonyl)-L-glutamic acid α-hydroxamate (1.1 g, 3 mmol) was dissolved in 20 mL of dry THF and added dropwise to a solution of 6 mL of 1 M BH_3·THF stirred at 0 °C. The addition occurred over 20 min, and the reaction mixture was allowed to stir at 0 °C for 3 h and at room temperature 1 h. The reaction was quenched with 10% acetic acid in methanol and was concentrated to an oily residue. The crude product was dissolved in ethyl acetate (75 mL) and washed with 1 N HCl (25 mL), H_2O (25 mL), and 1 N NH_4HCO_3 (20 mL). The organic extract was dried over anhydrous Na_2SO_4 and the solvent removed to give a white solid. Compounds **21** and **22** were separated on MPLC by elution with $CHCl_3$/acetone.

Compound **21** was obtained (200 mg, 19%) as an oil: $[\alpha]^{25}_D$ −17.6° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.40 (s, 9 H, Boc), 1.5–2.2 (m, 4 H, CH_2), 3.2–3.9 (m, 3 H, CH_2, α-H), 4.85 (s, 2 H, CH_2Ph), 5.33 (d, 1 H, NH), 7.35 (s, 5 H, Ph), 10.27 (s, 1 H, NH).

Anal. Calcd for $C_{17}H_{26}N_2O_5$: C, 60.3; H, 7.7; N, 8.30. Found: C, 60.29; H, 7.72; N, 8.24.

Compound **22** was obtained (400 mg, 40%) as a white crystalline compound: mp 182–185 °C (CH_2Cl_2); $[\alpha]^{25}_D$ −82.2° (*c* 0.5, MeOH); ^1H NMR ($CDCl_3$/Me_2SO) δ 1.4 (s, 9 H, Boc), 1.6–2.1 (m, 4 H, CH_2), 3.2–3.5 (m, 2 H, CH_2), 3.82–4.1 (m, 1 H, α-H), 4.81 (s, 2 H, CH_2Ph), 7.34 (s, 5 H, Ph), 11.0 (bd, 1 H, NH).

Method B. O^{α}-Benzyl N^{α}-(*tert*-butyloxycarbonyl)-L-glutamic acid α-hydroxamate (1.05 g, 3 mmol) was dissolved in 20 mL of dry THF and cooled to −15 °C. To this cold stirred solution triethylamine (354 mg, 3.5 mmol) and ethyl chloroformate were added and the mixture was stirred at −15 °C for 0.5 h. The precipitated solid was filtered and the filtrate was added to an aqueous $NaBH_4$ solution, with vigorous stirring, at 5 °C. After the addition, the reaction mixture was stirred at room temperature for 4 h. The reaction mixture was made acidic with 1 N HCl and the THF was removed under reduced pressure. The aqueous acidic solution was extracted with ethyl acetate (2 × 30 mL). The EtOAc extract was washed with H_2O (20 mL) and brine (15 mL), dried over Na_2SO_4, and concentrated. The crude product was purified by using MPLC with elution by $CHCl_3$/acetone (7:3) to yield **21** and **27**.

Compound **21** was obtained in (150 mg) a 15% yield: $[\alpha]^{25}_D$ −19.1° (*c* 0.5, $CHCl_3$).

Compound **27** was obtained in (250 mg) a 26% yield as an oil: $[\alpha]^{25}_D$ −24.8° (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.4 (s, 9 H, Boc), 1.78 (bt, 2 H, CH_2), 2.13 (bt, 2 H, CH_2), 3.49 (bt, 2 H, CH_2), 4.12 (m, 1 H, α-H), 4.85 (s, 2 H, CH_2Ph), 5.42 (d, 1 H, NH), 7.33 (s, 4 H, Ph), 10.3 (bs, 1 H, NH).

Method C. A solution of O^{α}-benzyl N^{α}-(*tert*-butyloxycarbonyl)-γ-(2-thioxo-1,3-thiazolidin-3-yl)-L-glutamic acid α-hydroxamate (**26**) (2.07 g, 4.6 mmol) in 30 mL of THF was added

to a stirred solution of $NaBH_4$ (1.1 g, 30 mmol) in THF (20 mL)/H_2O (7 mL) during a 0.5-h period. After the addition, the reaction mixture was stirred at room temperature for 4 h. The reaction mixture was made acidic with 1 N HCl and the THF was removed under reduced pressure. The aqueous acidic solution was extracted with ethyl acetate (2 × 75 mL). The EtOAc extract was washed with H_2O (50 mL) and brine (25 mL) and dried over anhydrous Na_2SO_4, and the solvent removed. The crude product was purified by using MPLC with elution by $CHCl_3$/acetone. Two products, **21** and **27**, were obtained in a yield of 17% and 40%, respectively.

Method D. A solution of *O*-benzyl N^{α}-[(*tert*-butyloxycarbonyl)amino]-5-acetoxypentanohydroxamate (0.9 g, 2.4 mmol) in 15 mL of acetone was treated with 1 N NaOH (5 mL, 5 mmol) and the reaction mixture was stirred at room temparture for 1 h. Acetone was removed and the aqueous alkaline solution was made acidic with 1 N HCl. The aqueous solution was extracted with ethyl acetyl (2 × 50 mL). The EtOAc extract was washed with 0.5 N $NaHCO_3$ (25 mL), H_2O (25 mL), and brine (20 mL) and dried over anhydrous Na_2SO_4 and the solvent removed to give an oil. The oil was passed through a gravity column of silica by elution with $CHCl_3$, then $CHCl_3$/acetone to give **21** (0.8 g, 99%): $[\alpha]^{25}_D$ −19.6° (*c* 0.5, $CHCl_3$).

***O*-Benzyl N^{α}-(*tert*-Butyloxycarbonyl)-L-proline Hydroxamate (22).** A mixture of N^{α}-(*tert*-butyloxycarbonyl)-L-proline (0.22 g, 1 mmol), *O*-benzylhydroxylamine hydrochloride (0.16 g, 1 mmol), triethylamine (0.10 g, 1 mmol), and 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (EDCI) (190 mg, 1 mmol) in 30 mL of dry CH_2Cl_2 was stirred at room temperature for 12 h. Dichloromethane was removed in vacuo and the residue was partitioned between EtOAc/H_2O. The EtOAc (2 × 20 mL) extract was washed with 1 N HCl (15 mL), 0.5 N $NaHCO_3$ (15 mL), H_2O (10 mL), and brine (10 mL), dried over Na_2SO_4, and concentrated. The solid obtained was purified on chromatography over silica with CH_2Cl_2 and was crystallized from the same solvent: yield, 250 mg (76%); mp 182–185 °C; $[\alpha]^{25}_D$ −83° (*c* 0.5, MeOH); ^1H NMR ($CDCl_3$ + Me_2SO) δ 1.4 (s, 9 H, Boc), 1.6–2.1 (m, 4 H, CH_2), 3.2–3.5 (m, 2 H, CH_2), 3.85–4.1 (m, 1 H, α-H), 4.81 (s, 2 H, CH_2Ph), 7.34 (s, 5 H, Ph), 11.00 (bd, 1 H, NH).

***O*$^{\alpha}$-Benzyl N^{α}-(*tert*-Butyloxycarbonyl)-γ-(2-thioxo-1,3-thiazolidin-3-yl)-L-glutamic Acid α-Hydroxamate (26).** A mixture of *O*-benzyl N^{α}-(*tert*-butyloxycarbonyl)-L-glutamic acid α-hydroxamate (1.75 g, 5 mmol), thiazolidine-2-thione (0.6 g, 5 mmol), and dicyclohexylcarbodiimide (1.1 g, 5 mmol) in 50 mL of ethyl acetate was stirred at room temperature for 12 h. The precipitated solid was filtered and the filtrate was evaporated to dryness. The oily residue obtained was chromatographed over silica with $CHCl_3$ as eluant: yield, 1.6 g (71%); mp 153–155 °C (acetone/hexane). The compound was used as such without characterization.

Benzyl (*S*)-2-[(*tert*-Butyloxycarbonyl)amino]-5-hydroxypentanoate (29). 1-Benzyl N^{α}-(*tert*-butyloxycarbonyl)-L-glutamate (9.2 g, 27.3 mmol) in 60 mL of dry THF was cooled to 0 °C in an ice–salt bath. Diborane (1 M in THF, 60 mL) was added dropwise during a 0.5-h period. After the addition, the reaction mixture was stirred at 0 °C for 4 h. The reaction mixture was quenched with a 10% solution of acetic acid in methanol and concentrated to a residue. The residue was dissolved in ethyl acetate (2 × 100 mL), washed with 1 N HCl (30 mL), H_2O, 1 N NH_4HCO_3 (30 mL), and brine (25 mL), dried over anhydrous Na_2SO_4, and concentrate to give an oil. The oil was purified on MPLC with hexane/acetone as eluant and two products, **29** and **30**, were separated.

Compound **29** was obtained as an oil (2.6 g, 30%): $[\alpha]^{25}_D$ −2.9° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.42 (s, 9 H, Boc), 1.6–2.37 (m, 4 H, CH_2), 3.40 (t, 2 H, CH_2) 4.33 (m, 1 H, α-H), 5.16 (s, 2 H, CH_2Ph), 5.3 (d, 1 H, NH), 7.34 (s, 5 H, Ph).

Anal. Calcd for $C_{17}H_{25}NO_5$: C, 63.13; H, 7.79; N, 4.33. Found: C, 62.98; H, 7.89; N, 4.39.

Compound **30** was obtained as an oil in (3.0 g) 37% yield: $[\alpha]^{25}_D$ −53° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.43 (d, 9 H, Boc), 1.83 (m, 4 H, CH_2), 3.41 (bt, 2 H, CH_2), 4.28 (m, 1 H, α-H), 5.1 (s, 2 H, CH_2Ph), 7.29 (s, 5 H, Ph).

Benzyl (*S*)-2-[(*tert*-Butyloxycarbonyl)amino]-5-acetoxypentanoate. Benzyl (*S*)-2-[(*tert*-butyloxycarbonyl)-amino]-5-hydroxypentanoate (1.6 g, 4.95 mmol) was dissolved in 30 mL of dry methylene chloride. Acetic anhydride (0.51 g, 5 mmol) and pyridine (0.395 g, 5 mmol) were added and the reaction mixture was stirred at room temperature for 4 h. The solvent was removed to give an oil and the oil was passed through a gravity column of silica gel and eluted with hexane/acetone (95:5) to obtain pure product (1.55 g, 86%) as an oil: $[\alpha]^{25}_D$ −15.6° (*c* 0.5, acetone); ^1H NMR ($CDCl_3$) δ 1.43 (s, 9 H, Boc), 1.73 (bt, 4 H, CH_2), 1.99 (s, 3 H, $COCH_3$), 4.02 (bt, 2 H, CH_2), 4.34 (m, 1 H, α-H), 5.1 (s, 2 H, CH_2Ph), 5.3 (d, 1 H, NH), 7.33 (s, 5 H, Ph).

(*S*)-2-[(*tert*-Butyloxycarbonyl)amino]-5-acetoxypentanoic Acid (31). Benzyl (*S*)-2-[(*tert*-butyloxycarbonyl)amino]-5-acetoxypentanoate (1.3 g, 3.6 mmol) was dissolved in 90% ethyl alcohol and treated with 5% palladium on carbon (200 mg) at room temperature for 12 h. The catalyst was filtered and the filtrate was evaporated to give an oil. The oil was dissolved in methanol, passed through a bed of silica, and eluted with the same solvent. The eluant, upon evaporation, gave pure product, which was used as such for the next reaction, yield, 0.9 g (92%).

***O*-Benzyl (*S*)-2-[(*tert*-Butyloxycarbonyl)amino]-5-acetoxypentanohydroxamate.** A mixture of 2-[(*tert*-butyloxycarbonyl)amino]-5-acetoxypentanoic acid (0.9 g, 3.3 mmol), *O*-benzylhydroxylamine hydrochloride (0.78 g, 5 mmol), and triethylamine (0.51 g, 5 mmol) in 50 mL of dry methylene chloride was stirred for 15 min. To this stirred solution, 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (0.95 g, 5 mmol) was added and the reaction mixture was stirred for 12 h at room temperature. The solvent was removed and the residue was extracted with aqueous ethyl acetate (2 × 75 mL). The EtOAc extracts were washed with 1 N HCl (25 mL), 0.5 N $NaHCO_3$ (25 mL), H_2O (25 mL) and brine (25 mL), dried over Na_2SO_4, and concentrated. The crude product was purified on MPLC with elution by hexane/acetone. The pure compound was crystallized from ether/petroleum ether (30–60 °C) (1.1 g, 88%): mp 92–95 °C; $[\alpha]^{25}_D$ −37° (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.43 (s, 9 H, Boc), 1.67 (m, 4 H, CH_2), 2.03 (s, 3 H, $COCH_3$), 4.1 (m, 3 H, α-H and CH_2), 4.97 (s, 2 H, CH_2Ph), 5.6 (d, 1 H, NH), 7.46 (s, 5 H, Ph), 10.05 (bs, 1 H, NH).

1-Benzyl N^{α}-(*tert*-Butyloxycarbonyl)-L-proline (30). A solution of N^{α}-(*tert*-butyloxycarbonyl)-L-proline (215 mg, 1 mmol) and benzyl alcohol (108 mg, 1 mmol) in 20 mL of dry methylene chloride was cooled to 0 °C. To this cold stirred solution were added 4-(dimethylamino)pyridine (DMAP) (12 mg, 0.1 mmol) and 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (239 mg, 1.25 mmol) and the reaction mixture was stirred at 0 °C for 3 h and at room temperature overnight. The solvent was removed and the residue was taken up in H_2O (20 mL) and extracted with ethyl acetate (2 × 25 mL). The EtOAc extract was washed with 1 N HCl (2 × 25 mL), saturated $NaHCO_3$ (2 × 25 mL), H_2O (20 mL), and brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated to give **30** (225 mg, 90%) as an oil: $[\alpha]^{25}_D$ −51.5° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.43 (d, 9 H, Boc), 1.83 (m, 4 H, CH_2), 3.41 (bt, 2 H, CH_2), 4.28 (m, 1 H, α-H), 5.1 (s, 2 H, CH_2Ph), 7.29 (s, 5 H, Ph).

1-(Benzyloxy)-3-[(*tert*-butyloxycarbonyl)amino]-2-piperidone (7). A mixture of *O*-benzyl 2-[(*tert*-butyloxycarbonyl)amino]-5-hydroxy-L-pentanohydroxamate (580 mg, 1.7 mmol), triphenylphosphine (524 mg, 2 mmol), and diethyl azodicarboxylate (DEAD) (348 mg, 2 mmol) in 40 mL of dry THF was stirred at room temperature for 24 h. The THF was removed under reduced pressure and the residue was chromatographed by using MPLC with hexane/acetone (9:1) as eluant. Three products were separated in impure form. Again all three products were rechromatographed, separately, with hexane/acetone as eluant to give the following.

(i) N-Alkylated product **7** (350 mg, 64%) as a crystalline white compound which was recrystallized from ether/petroleum ether (bp 30–60 °C): $[\alpha]^{25}_D$ +28.2° (*c* 0.5, acetone); mp 76–79 °C; ^1H NMR ($CDCl_3$) δ 1.45 (s, 9 H, Boc), 1.77 (m, 2 H, CH_2), 2.30 (m, 2 H, CH_2), 3.35 (m, 2 H, CH_2), 4.11 (m, 1 H, α-H), 4.9 (dd, 2 H, CH_2Ph), 5.52 (d, 1 H, NH), 7.36 (s, 5 H, Ph).

Anal. Calcd for $C_{17}H_{24}N_2O_4$: C, 63.7; H, 7.6; N, 8.7. Found: C, 63.82; H, 7.67; N, 8.67.

(ii) O-Alkylated product (80 mg, 15%, a mixture of *E* and *Z* isomers) as an oil: ^1H NMR ($CDCl_3$) δ 1.45 (s, 9 H, Boc), 1.88 (m, 2 H, CH_2), 2.4 (m, 2 H, CH_2), 4.17 (m, 3 H, CH_2 and α-H), 5.06 (s, 2 H, CH_2Ph), 5.16 (d, 1 H, NH), 7.33 (s, 5 H, Ph).

1-(Benzyloxy)-5-[(*tert*-butyloxycarbonyl)amino]-piperidone (32). A mixture of *O*-benzyl 4-[(*tert*-butyloxycarbonyl)amino]-5-hydroxy-L-pentanohydroxamate (680 mg, 2 mmol), triphenylphosphine (629 mg, 2.4 mmol), and diethyl azodicarboxylate (418 mg, 2.4 mmol) in 50 mL of dry THF was stirred at room temperature for 24 h. The THF was removed under reduced pressure and the residue was purified by using MPLC with elution by EtOAc/hexane. Triphenylphosphine oxide and the reduced form of DEAD were coeluted with the main product, which was separated on repeated chromatography.

Product **32** was obtained in 62% yield: $[\alpha]^{25}_D$ −21.4° (*c* 0.5, acetone); ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 9 H, Boc), 1.7-1.93 (m, 2 H, CH_2), 2.4-2.6 (m, 2 H, CH_2), 3.1-3.15 (m, 1 H), 3.65 (dd, 1 H), 3.95 (m, 1 H, α-H), 4.5 (d, 1 H, NH), 5.0 (dd, 2 H, CH_2Ph), 7.4 (s, 5 H, Ph).

Anal. Calcd for $C_{17}H_{24}N_2O_4$: C, 63.7; H, 7.6; N, 8.7. Found: C, 63.89; H, 7.44; N, 8.49.

A mixture of what appeared to be the *E* and *Z* isomers of O-alkylated products were obtained in 10% yield.

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Registry No. **3**, 52816-29-2; **4**, 91229-86-6; **7**, 91279-50-4; **8**, 1676-73-9; **9**, 28812-54-6; **10**, 24277-39-2; **11**, 90194-99-3; **12**, 90195-02-1; **12**·trifluoroacetate salt, 91229-87-7; (*E*)-**13**, 91229-88-8; (*Z*)-**13**, 91229-89-9; **14**, 91237-84-2; **15**, 91229-90-2; **16**, 37513-14-7; **18**, 91229-91-3; **19**, 1499-55-4; **20**, 91229-93-5; **21**, 91229-94-6; **22**, 26048-86-2; **24**, 91229-92-4; **26**, 91229-95-7; **27**, 91229-96-8; **28**, 30924-93-7; **29**, 91229-97-9; **30**, 37787-77-2; **31**, 89545-84-6; **32**, 91229-98-0; di-*tert*-butyl dicarbonate, 24424-99-5; *O*-benzyl acetohydroxamate, 4797-81-3; *O*-benzyl-*N*-tosylhydroxylamine, 1576-39-2; N^{α}-(*tert*-butyloxycarbonyl)-γ-methyl-L-glutamic acid, 45214-91-3; O^{α}-benzyl N^2-(*tert*-butyloxycarbonyl)-γ-methyl-L-glutamic acid α-hydroxamate, 91229-99-1; N^{α}-(*tert*-butyloxycarbonyl)-γ-[-(trimethylsilyl)ethyl]-L-glutamic acid, 91230-00-1; O^{α}-benzyl N^{α}-(*tert*-butoxycarbonyl)-γ-[2-(trimethylsilyl)ethyl]-L-glutamic acid α-hydroxamate, 91230-01-2; N^{α}-(*tert*-butyloxycarbonyl)-L-proline, 15761-39-4; thiazolidine-2-thione, 96-53-7; *O*-benzylhydroxylamine hydrochloride, 2687-43-6; 1-benzyl (*S*)-2-[(*tert*-butyloxycarbonyl)amino]-5-acetoxypentanoate, 91230-02-3; *O*-benzyl (*S*)-2-[(*tert*-butyloxycarbonyl)amino]-5-acetoxypentanoate hydroxamate, 91230-03-4; 2-[(*tert*-butyloxycarbonyl)amino]-5-acetoxypentanoic acid, 109-52-4; L-glutamic acid, 56-86-0.

Synthesis and Structural Studies of Certain Novel Imidazo[1,2-*b*]pyrazole Nucleosides[1,2]

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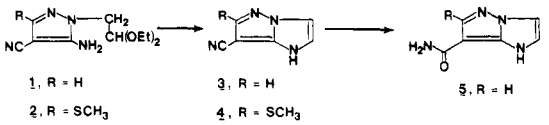
The first chemical syntheses of imidazo[1,2-*b*]pyrazole-7-carbonitrile (**3**), the corresponding ribonucleosides (**10** and **16**), and certain related derivatives of a new class of purine analogues containing a bridgehead nitrogen atom are described. Condensation of 2-hydrazinoacetaldehyde diethyl acetal with (ethoxymethylene)malononitrile and subsequent ring closure gave **3**. Direct glycosylation of the Me_3Si derivative of **3** with blocked ribofuranose (**8**) in the presence of trimethylsilyl triflate gave the blocked nucleosides **9** and **15**, which on further ammonolysis gave 1-β-D-ribofuranosylimidazo[1,2-*b*]pyrazole-7-carbonitrile (**10**) and the corresponding N-5 glycosyl isomer (**16**), the first known example of a nucleoside in which the glycon moiety is attached to a nitrogen adjacent to a bridgehead nitrogen atom. The isomeric ratio of **9** and **15** was found to be time dependent. Similarly, reaction of 2,2-bis(methylthio)-1-cyanoacrylonitrile with 2-hydrazinoacetaldehyde diethyl acetal gave 6-(methylthio)-imidazo[1,2-*b*]pyrazole-7-carbonitrile (**4**). Glycosylation of the Me_3Si derivative of **4** with **8** and subsequent debenzoylation gave 6-(methylthio)-1-β-D-ribofuranosylimidazo[1,2-*b*]pyrazole-7-carbonitrile (**12**). The absolute structures of **10** and **16** were determined by single-crystal X-ray diffraction techniques employing Mo Kα radiation. The glycosidic bond in the kinetically less stable isomer **16** is considerably longer (1.505 Å) than the corresponding bond in the more stable isomer **10** (1.451 Å). The two five-membered azole rings in both **10** and **16** are planar and the dihedral angle between the planes in each compound is less than 1°.

As part of an ongoing synthetic program directed toward the preparation of novel azole nucleosides, we became interested in aromatic azapentalene nucleosides. Until the present work, nucleosides of this type have not been described, and we wish to report the first chemical synthesis and structural elucidation of certain imidazo[1,2-*b*]pyrazole nucleosides. Azapentalene ring systems, which contain two heteroaromatic five-membered rings fused together, can be construed to mimic purine analogues in which the six-membered pyrimidine ring has been contracted in size by one member. Nucleoside derivatives of these ring systems thus result in a class of compounds that may possibly exhibit interesting biological activity.

Scheme I



Replacement of the heterocyclic moiety in naturally occurring purine nucleosides with an appropriately substituted azapentalene ring will result in purine nucleoside

(1) A portion of this work was presented at the 184th American Chemical Society Meeting, Kansas City, MO, September, 1982. Wood, S. G.; Revankar, G. R.; Robins, R. K. "Abstracts of Papers", MEDI 34. This work is taken, in part from the Ph.D. Dissertation of S.G.W., Brigham Young University, 1983.

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