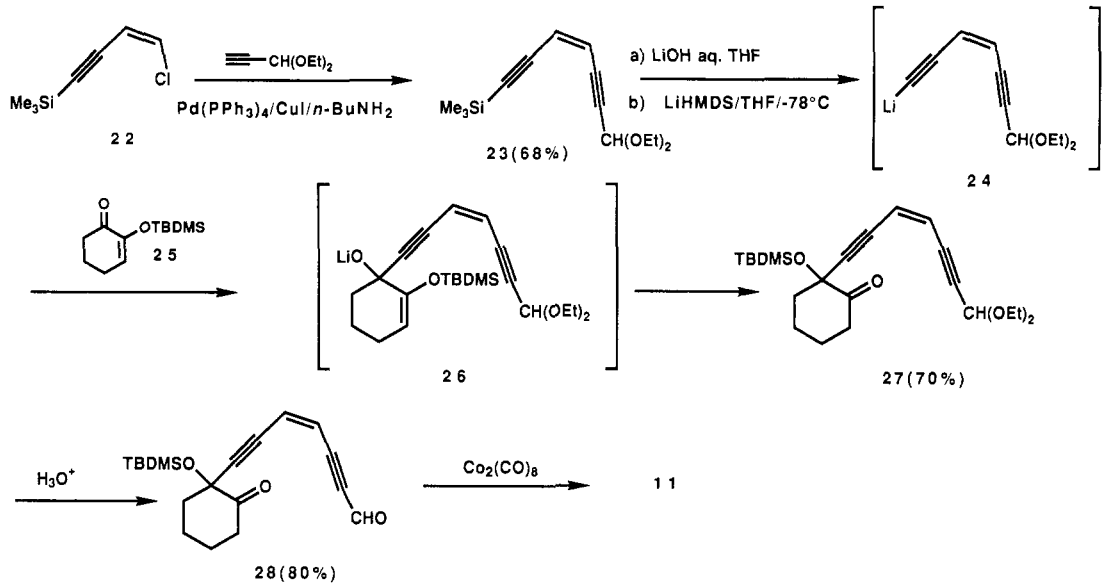
Scheme V



viding **27** (70%). Hydrolysis of **27** with trifluoroacetic acid/chloroform gave **28** (80%) which was converted directly into **11** (90%) by treatment with dicobalt octacarbonyl. This route allows access to 12β-hydroxybicyclo[7.3.1] diynene **17** in eight steps from *cis*-dichloroethylene and trimethylacetylene in an overall yield of 14% (unoptimized). The synclinal aldol mediated stereospecific synthesis of the 12β-hydroxybicyclo[7.3.1] diynene system **17** should allow the examination of bridgehead enol chemistry (C-1, C-13) in the presence of the 12β-substituent.

Acknowledgment. The National Institutes of Health are thanked for their financial support of this work.

Supplementary Material Available: Spectral data for compounds **11** and **13–18** (1 page). Ordering information is given on any current masthead page.

Articles

1-Hydroxy-3-amino-2-piperidone (δ-*N*-Hydroxycycloornithine) Derivatives: Key Intermediates for the Synthesis of Hydroxamate-Based Siderophores

Teodozyj Kolasa and Marvin J. Miller*

Department of Chemistry, University of Notre Dame, Notre Dame, Indiana 46556

Received September 19, 1989

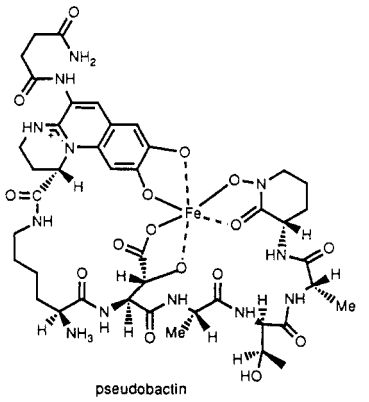
Several routes for the synthesis of δ-*N*-(benzyloxy)cycloornithine (**2**) from glutamic acid derived starting materials are described. Efficient methods were developed for the synthesis of glutamic acid γ-semialdehyde and δ-hydroxynorvaline derivatives as key substrates for preparation of δ-*N*-hydroxyornithine analogues. Thus, the best approaches to the synthesis of **2** were: (1) reductive cyclization of an *N*-hydroxysuccinimide ester of the *O*-benzyloxime **4** of α-amino-protected glutamic acid γ-semialdehyde **5** and (2) cyclization of the *N*-(benzyloxy)amide of δ-bromonorvaline (**7**).

Introduction

The pseudomonads represent a diversified group of Gram-negative bacteria widely distributed in the soil. The fluorescent pseudomonads which belong to group 1, according to their genetic homology, release yellow-green flourescent pigments when grown under iron-deficient conditions. These pigments are the siderophores of the fluorescent pseudomonads and are called pyoverdines[1-4] or pseudobactins[5-9] and serve as a biological source of iron for these bacteria.

(1) Wendenbaum, S.; Demange, P.; Dell, A.; Meyer, J. M.; Abdallah, M. A. *Tetrahedron Lett.* **1983**, *24*, 4877.
(2) Poppe, K.; Taraz, K.; Budzikievicz, H. *Tetrahedron* **1987**, *43*, 2261.
(3) Briskot, G.; Taraz, T.; Budzikievicz, H. *Z. Naturforsch.* **1986**, *41c*, 497.
(4) Cody, Y. S.; Gross, D. C. *J. Bacteriol.* **1987**, *169*, 2207.
(5) Van der Hofstad, G. A.; Marug, J. D.; Verjans, G. M.; Weisbeck, P. J. Iron, siderophores, and plant diseases, NATO ASI Series; Swinburne, T. R., Ed.; Plenum Press: New York, 1986; Vol. 117, pp 71–75.
(6) Yang, C. C.; Leong, J. *Biochemistry* **1984**, *23*, 3534.
(7) Buyer, J. S.; Wright, J. M.; Leong, H. *Biochemistry* **1986**, *25*, 5492.
(8) Teintze, M.; Hossain, M. B.; Barnes, C. L.; Leong, J.; Van der Helm, D. *Biochemistry* **1981**, *20*, 6446.

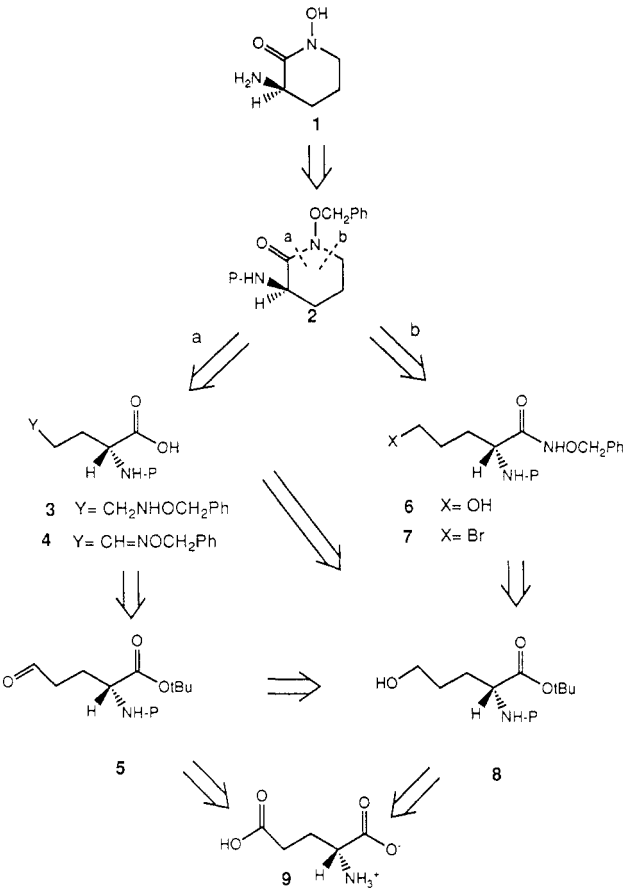
0022-3263/90/1955-1711$02.50/0



The fluorescent siderophore from *Pseudomonas putida B-10*, designated pseudobactin, consists of a linear hexapeptide in which the δ-nitrogen of the N^{δ}-hydroxyornithine is cyclized with the α-carboxyl, and the ε-amino group of the lysine is linked by an amide bond to a fluorescent quinoline derivative. δ-*N*-Hydroxy-L-ornithine is one of the most common constituents of the naturally occurring hydroxamic acid based siderophores,[10,11] whereas δ-*N*-hydroxy-D-ornithine has been found in only a few siderophores.[2,12-14] Both the L and D isomers of δ-*N*-hydroxycycloornithine (or 1-hydroxy-3-amino-2-piperidone) have been reported to be important structural elements of siderophores produced by *Pseudomonas*.[1,3,8,9] Akers and Neilands[15] reported that *Rhodotorula pilimanae* CBS 4479, when grown at pH 2.8 in iron-limited media, produced rhodotorulic acid and a second hydroxamic acid which was characterized as 1-hydroxy-3(*S*)-amino-2-piperidone. It was shown that the latter arose from cyclization of δ-*N*-hydroxyornithine. Syntheses of δ-*N*-hydroxycycloornithine were reported by Akers,[15] Emery,[16] Isowa,[17] and Olsen,[18] but these methods suffered from low overall yields.

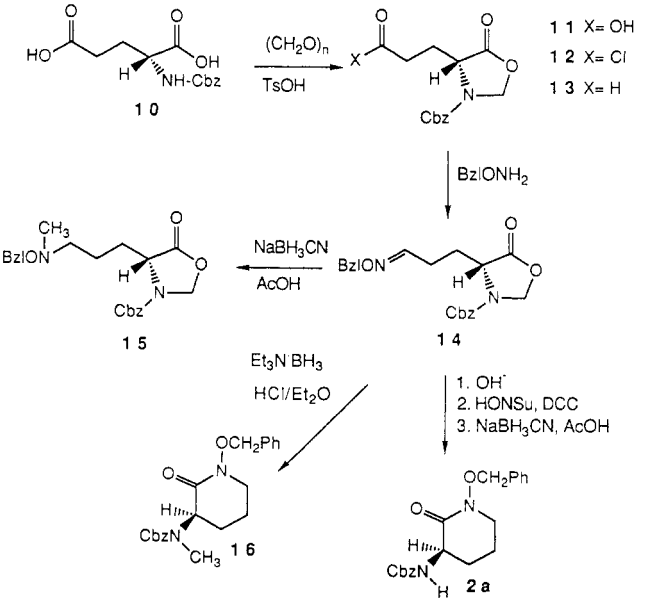
Here, we report alternate approaches to the synthesis of D- and L-δ-*N*-(benzyloxy)cycloornithine (**2**), a synthetically useful derivative of 1-hydroxy-3-amino-2-piperidone, **1**, as a part of our efforts related to the total synthesis of pseudobactin. A general method for the synthesis of chiral δ-*N*-hydroxyornithine derivatives preferably involves chiral amino acids as starting materials. Without homologation, only ornithine and glutamic acid are reasonable precursors of δ-*N*-hydroxyornithine. Two syntheses of δ-*N*-hydroxyornithine from ornithine have been reported.[19,20] Both methods involved epoxidation of a Schiff base derivative of the δ-amino group of ornithine followed by hydrolysis of the resulting oxaziridine. The transformation of glutamic acid into δ-*N*-hydroxyornithine derivatives also has been reported.[18,21] After comparison of aspects of both the ornithine and glutamic acid based approaches, the latter seemed to be a more convenient, versatile, and economical route to the δ-*N*-hydroxyornithine derivatives.

Scheme I[a]



[a] For clarity, only the isomer derived from the D-amino acid is shown in the Schemes even though representative samples of the D, L, and racemic forms were prepared for most compounds.

Scheme II



Results and Discussion

A retrosynthetic analysis of δ-*N*-(benzyloxy)cycloornithine (**2**) presented in Scheme I shows two strategies

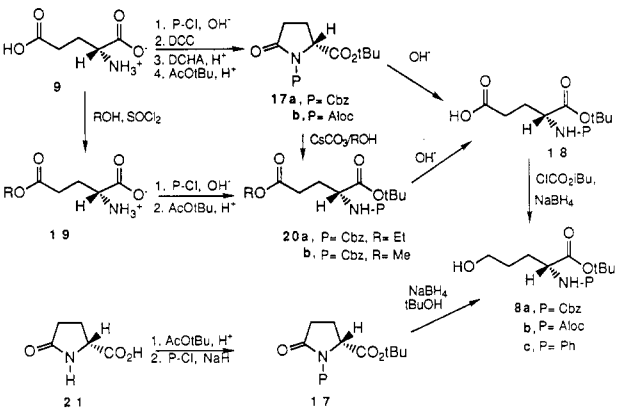
(9) Teintze, M.; Leong, J. *Biochemistry* **1981**, *20*, 6457.
(10) Maehr, H. *Pure Appl. Chem.* **1971**, *28*, 603.
(11) Miller, M. J. *Chem. Rev.* **1989**, *89*, 1563.
(12) Philson, S. B.; Llinas, M. *J. Biol. Chem.* **1982**, *257*, 8081.
(13) Eng-Wilmot, D. L.; Rahman, A.; Mendenhall, J. V.; Grayson, S. L.; Van der Helm, D. *J. Am. Chem. Soc.* **1984**, *106*, 1285.
(14) Demange, P.; Bateman, A.; Dell, A.; Abdallah, M. A. *Biochemistry* **1988**, *27*, 2745.
(15) Akers, H. A.; Neilands, J. B. *Biochemistry* **1973**, *12*, 1006.
(16) Emery, T. F. *Biochemistry* **1966**, *5*, 3694.
(17) Isowa, Y.; Takashima, T.; Ohmori, M.; Kurita, H.; Sato, M.; Mori, K. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 1464.
(18) Olsen, R. K.; Ramasamy, K.; Emery, T. *J. Org. Chem.* **1984**, *49*, 3527.
(19) Widmer, J.; Keller-Schierlein, W. *Helv. Chim. Acta* **1974**, *57*, 657.
(20) Gould, S. J.; Ju, S. *J. Am. Chem. Soc.* **1989**, *111*, 2329.
(21) Lee, B. H.; Miller, M. J. *Tetrahedron Lett.* **1984**, *25*, 927.

considered for construction of δ-*N*-hydroxycycloornithine derivatives. Cleavage of the lactam bond (path a) leads to δ-*N*-(benzyloxy)ornithine **3** or oxime **4**, which could be obtained from δ-glutamic semialdehyde **5**. This aldehyde was previously prepared in our group[21] by reduction of the γ-acid chloride of glutamic acid, or it could be obtained by oxidation of δ-hydroxynorvaline derivative **8**. The δ-hydroxynorvaline can be also a precursor for synthesis of δ-hydroxynorvaline hydroxamate **6** or its bromo derivative **7**. The hydroxamate approach is the basis of the second strategy (cleavage of the C^{δ}–N bond, path b) for synthesis of δ-*N*-(benzyloxy)cycloornithine **2**.

The aldehyde approach, which we previously used[21] to prepare δ-*N*-hydroxyornithine, initially appeared to be the most straightforward method for the preparation of δ-*N*-(benzyloxy)cycloornithine in large quantities. Unfortunately, we were unable to obtain a semialdehyde of glutamic acid **13** (Scheme II) in reasonable yield when the reaction sequence was performed on a 5-mmol or larger scale. The primary problem was the low yield (~30%) of the key aldehyde from reduction of acid chloride **12** due to competitive decomposition of the oxazolidinone ring. The small amount of crude aldehyde **13**, which was obtained, was directly transformed into oxime **14**. The resulting oxime was purified by column chromatography. Because oxazolidinones are used for activation of carboxyl groups in peptide chemistry, we expected the reduction of oxime **14** to the corresponding hydroxylamine with sodium cyanoborohydride in glacial acetic acid to provide the desired cycloornithine derivative **2a** directly. In fact, only a trace of 1-(benzyloxy)-3-(carbobenzoxyamino)-2-piperidone (**2a**) was detected. The major product of the reaction was identified as the δ-*N*-methylated derivative of δ-*N*-(benzyloxy)ornithine **15** (Scheme II). Reduction of oxime **14** with borane–triethylamine complex in hydrochloric acid saturated ethyl ether gave 1-(benzyloxy)-3-carbobenzoxy-3-(methylamino)-2-piperidone (**16**) as the major product in 50% yield. Previous reports also indicate that treatment of oxazolidinone derivatives of amino acids with reducing agents results in formation of the corresponding *N*-methyl amino acids.[22] Finally, tranformation of the oxazolidinone **14** into an active ester followed by reduction with sodium cyanoborohydride in acetic acid gave the desired δ-*N*-(benzyloxy)-α-*N*-carbobenzoxycycloornithine (**2a**) in more than 90% yield. Despite the high yields of the last steps, the overall yield was below 20% because of the low yield of preparation of aldehyde **13**. As described next, this problem was circumvented by an alternate synthesis of similar aldehydes from δ-hydroxynorvaline derivatives.

δ-Hydroxynorvaline or (*S*)-2-amino-5-hydroxypentanoic acid (**8**, P = R = H, Scheme I, but as the opposite optical isomer that is shown) is a competitive inhibitor of γ-cystathionase.[23] It also serves as the biological precursor of the polyoxins, in which its whole carbon skeleton is found intact.[24] The same amino acid is also incorporated into the oxazoline segment of clavulanic acid,[25] an important β-lactamase inhibitor. Forms of δ-hydroxynorvaline have been prepared previously from L-glutamic acid by several methods. Goodman and Felix[26] obtained δ-hydroxy-L-α-(tosylamino)valeric acid by reduction of the lithium salt of *N*-tosylpyroglutamic acid with lithium borohydride in

Scheme III



65% yield. A Japanese patent[27] described the reduction of γ-methyl (or γ-ethyl) esters of *N*-acyl-L-glutamic acid to δ-hydroxynorvaline derivatives with sodium borohydride in a average of 60% yield. A very simple and efficient method was provided by Barlos and co-workers.[28] Their approach involved a selective reduction of γ-methyl-L-*N*-trityl glutamate with lithium aluminum hydride.

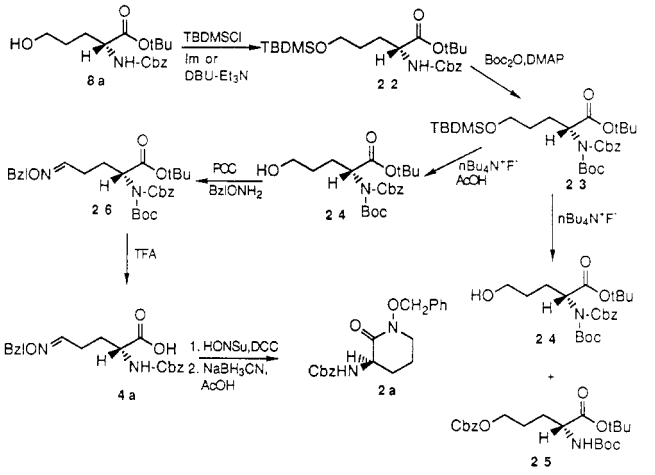
A key derivative of δ-hydroxynorvaline, required for our synthetic studies, was the *tert*-butyl ester of *N*-carbobenzoxy-δ-hydroxynorvaline (*tert*-butyl 2-(carbobenzoxyamino)-5-hydroxypentanoate, **8a**, Scheme III). Conceptually, this compound could be prepared from glutamic acid **9** or from pyroglutamic acid **21** as shown in Scheme III. Thus, three approaches to the construction of **8** were investigated. The first approach, based on the synthetic route devised by Gibian and Klieger,[29] involved the differentiation of the two carboxyl groups of glutamic acid (**9**) by its transformation into *N*-acylpyroglutamic acid derivatives which were then converted to the corresponding *tert*-butyl ester derivatives **17** with *tert*-butyl acetate and perchloric acid. Hydrolysis of **17a** or **17b** with 1 N sodium hydroxide gave the corresponding amino protected forms of the α-*tert*-butyl ester of glutamic acid, **18**. Reduction of the γ-carboxyl of **18** via the mixed carbonic anhydride and sodium borohydride[30] furnished the desired *tert*-butyl esters of N-protected norvalines, **8**.

The second approach (Scheme III) involved initial N-protection of readily available[31] γ-esters of glutamic acid (**19**) and formation of the α-*tert*-butyl esters by reaction with *tert*-butyl acetate and perchloric acid. Hydrolysis of the γ-ester of α-*tert*-butyl *N*-carbobenzoxyglutamate, **20**, followed by mixed anhydride formation and reduction with sodium borohydride, as described before, gave the *tert*-butyl ester of *N*-carbobenzoxy-δ-hydroxynorvaline, **8a**.

The last method considered for the synthesis of **8** from δ-*N*-hydroxynorvaline derivatives started with the preparation of the *tert*-butyl ester of *N*-acylpyroglutamic acids, **17a,b**. Esterification of the pyroglutamic acid with *tert*-butyl acetate in the presence of perchloric acid, followed by acylation of its sodium salt with alkyl chloroformates (P = Cbz and Aloc), gave the desired *tert*-butyl esters of *N*-acylpyroglutamic acids **17** in moderate yields. A direct reduction of **17** with sodium borohydride by slow addition

(22) Freidinger, R. M.; Hinkle, J. S.; Perlow, D. S.; Arison, B. H. *J. Org. Chem.* **1983**, *48*, 77.
(23) Washtien, W.; Cooper, A. J. L.; Abeles, R. H. *Biochemistry* **1977**, *16*, 460.
(24) Funayama, S.; Isono, K. *Biochemistry* **1977**, *16*, 3121.
(25) Townsend, C. A.; Ho, M. F. *J. Am. Chem. Soc.* **1985**, *107*, 1065.
(26) Goodman, M.; Felix, A. M. *Biochemistry* **1964**, *3*, 1529.
(27) Sato, T. Jpn. Patent, JP 62,242,653, Oct. 23, 1987; *Chem. Abstr.* **1988**, *109*, 93602e.
(28) Barlos, K.; Mamos, P.; Papaioannou, D.; Patriankou, S. *J. Chem. Soc., Chem. Commun.* **1987**, 1583.
(29) Gibian, H.; Klieger, E. *Justus Liebigs Ann. Chem.* **1961**, *640*, 145.
(30) Ishizumi, K.; Koga, K.; Yamada, S. *Chem. Pharm. Bull.* **1968**, *16*, 492.
(31) Hanby, W. E.; Waley, S. G.; Watson, J. *J. Chem. Soc.* **1950**, 3239.

Scheme IV

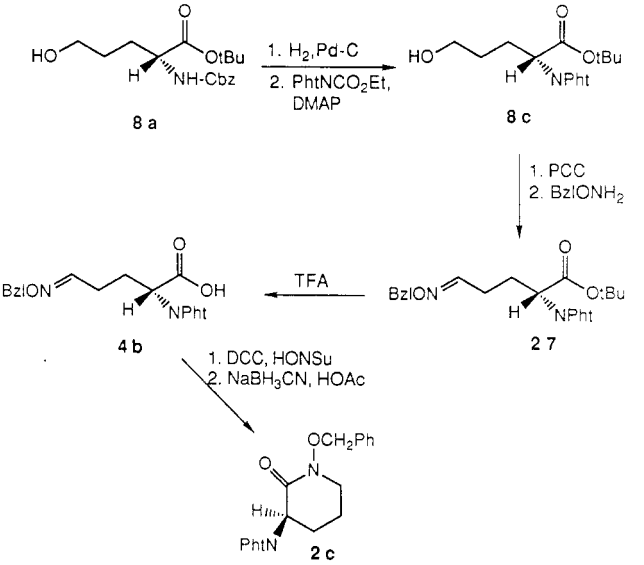


of *tert*-butyl alcohol[32] furnished the δ-hydroxynorvaline derivatives **8a,b** in good yields. When the reduction of **17a** was done in the presence of methanol, the desired δ-hydroxynorvaline derivative **8a** was formed in 37% yield, and the diester of *N*-carbobenzoxyglutamic acid **20b** was obtained in 43% yield.

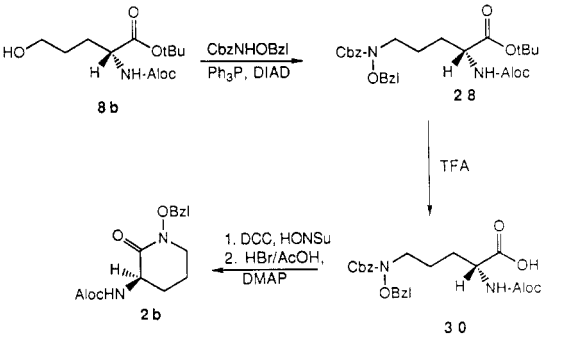
Comparison of the optical rotations of alcohols **8** obtained by all three methods showed some racemization. Using the Gibian and Klieger approach with slow addition of dicyclohexylcarbodiimide (DCC) at low temperature (0 °C or lower) and dicyclohexylamine (DCHA) at temperature below 5 °C reduced the level of racemization drastically. Up to 20% of racemization during the preparation of pyroglutamate derivatives has also been previously reported by others.[33]

Oxidation of hydroxynorvaline derivatives **8** to γ-glutamate semialdehyde **5** required full protection of the α-nitrogen to avoid the formation of a pyroglutamic acid derivative, as previously suggested by Olsen.[18] Thus, the hydroxyl group of **8a** was first protected by reaction with TBDMS chloride to provide **22**. The α-nitrogen was then protected with di-*tert*-butyl dicarbonate in the presence of (dimethylamino)pyridine[34] to give **23** quantitatively (Scheme IV). Initial deprotection of the δ-hydroxy group with tetrabutylammonium fluoride in THF induced a competitive migration of the Cbz group from the α-nitrogen to the δ-oxygen atom to form **25** in 26% yield. This problem was circumvented by addition of glacial acetic acid to the fluoride solution to maintain an apparent pH of 7. Although the removal of the TBDMS group then proceeded cleanly, it required a longer reaction time (about 20 h). Oxidation of alcohol **24** with pyridinium chlorochromate (PCC) followed by reaction of the crude aldehyde with *O*-benzylhydroxylamine provided oxime **26** in 80% yield from **24**, as a separable mixture of *Z* and *E* isomers. Simultaneous removal both the *tert*-butoxycarbonyl and *tert*-butyl ester groups by treatment with trifluoroacetic acid furnished the *E* and *Z* oximes **4a** in quantitative yield. Transformation of **4a** into the corresponding *N*-hydroxysuccinimide ester and reduction of the oxime double bond with sodium cyanoborohydride in glacial acetic acid resulted in direct cyclization to the desired δ-*N*-(benzyloxy)-α-*N*-carbobenzoxycycloornithine, **2a**, as planned, in 90% yield.

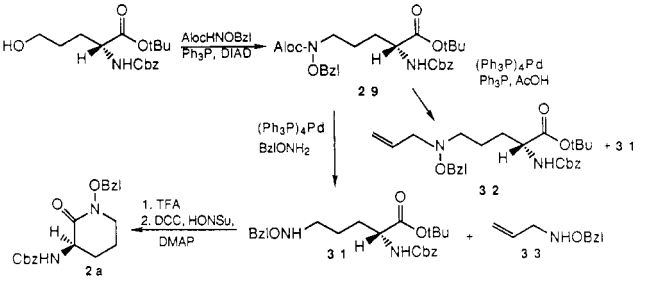
Scheme V



Scheme VI



Scheme VII

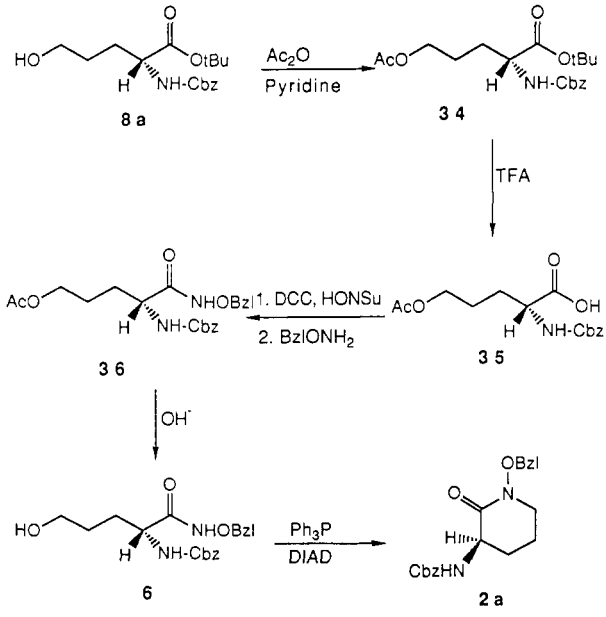


The required double protection of the α-nitrogen was also achieved by replacing the carbobenzoxy group with a phthaloyl group (Scheme V). Hydrogenation of the *tert*-butyl ester **8a** followed by acylation with *N*-carbethoxyphthalimide in the presence of DMAP gave alcohol **8c** in 90% yield. Upon treatment with PCC and then with *O*-benzylhydroxylamine, compound **8c** was converted into oxime **27** as a mixture of *E* and *Z* isomers. Removal of the *tert*-butyl group, followed by formation of the *N*-hydroxysuccinimide ester and oxime reduction with sodium cyanoborohydride in acetic acid again gave δ-*N*-(benzyloxy)-α-*N*-phthaloylcycloornithine, **2c**, in 91% yield.

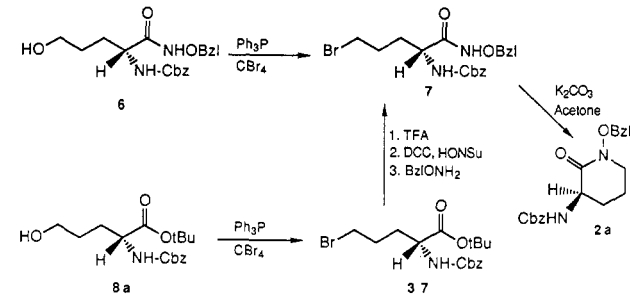
In order to avoid formation and reaction of sensitive glutamate semialdehyde derivatives, we next attempted incorporation of the δ-*N*-hydroxylamino group by direct reaction with suitable forms of δ-hydroxynorvaline (Schemes VI and VII). Accordingly, diisopropyl azodicarboxylate and triphenylphosphine[35] mediated alkylation

(32) Soai, K.; Oyamada, H.; Takase, M. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2327.
(33) Kemp, D. S.; Stites, W. E. *Tetrahedron Lett.* **1988**, *29*, 5057.
(34) Grehn, L.; Gunnarsson, K.; Ragnarsson, U. *Acta Chem. Scand.* **1986**, *B40*, 745.
(35) Maurer, P. J.; Miller, M. J. *J. Am. Chem. Soc.* **1982**, *104*, 3096.

Scheme VIII



Scheme IX



of *N*-carbobenzoxy-*O*-benzylhydroxylamine (CbzNHOBzl) and *N*-(allyloxycarbonyl)-*O*-benzylhydroxylamide (AlocNHOBzl) with alcohols **8b** and **8a**, respectively, gave the protected δ-*N*-(benzyloxy)ornithine derivatives **28** and **29** in 72% and 71% yields. Removal of the *tert*-butyl ester of α-*N*-(allyloxycarbonyl)-δ-*N*-carbobenzoxy-δ-*N*-(benzyloxy)ornithine (**28**) with trifluoroacetic acid gave acid **30**, which was transformed into the corresponding *N*-hydroxysuccinimide ester. Removal of the carbobenzoxy group with hydrobromide in acetic acid and subsequent treatment with pyridine induced cyclization to α-*N*-(allyloxycarbonyl)-δ-*N*-(benzyloxy)cycloornithine (**2b**) in 53% overall yield.

Alternate combinations of protecting groups were also found to be compatible with this general synthetic strategy. Removal of the allyloxycarbonyl group from δ-*N*-(allyloxycarbonyl)-δ-*N*-(benzyloxy)-α-*N*-carbobenzoxyornithine *tert*-butyl ester (**29**) by $(Ph_3P)_4Pd$ in the presence of acetic acid, as an allyl group scavenger, provided two products, δ-*N*-(benzyloxy)-α-*N*-carbobenzoxyornithine *tert*-butyl ester (**31**) and its δ-*N*-allyl derivative **32**, in 42% and 52% yields, respectively (Scheme VII). In contrast, use of *O*-benzylhydroxylamine as an allyl scavenger gave the desired hydroxylamine **31** and *N*-allyl-*O*-benzylhydroxylamine, **33**. It was interesting to note the exclusive formation of the mono-*N*-allyl derivative **33**. Not even a trace of diallylated hydroxylamine was observed, if at least 1 equiv of *O*-benzylhydroxylamine was used. After N–O bond reduction,[36] this process could provide a general approach to the preparation primary allylic amines, important constituents of a number of natural products.[37] Treatment of δ-*N*-(benzyloxy)-α-*N*-carbobenzoxyornithine (**31**) with TFA provided the corresponding free acid which was transformed into the *N*-hydroxysuccinimide ester and then cyclized in the presence of DMAP to give α-*N*-carbobenzoxy-δ-*N*-(benzyloxy)cycloornithine, **2a**, in 50% overall yield.

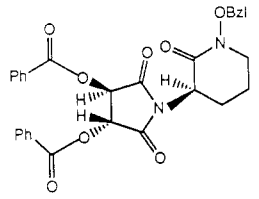
The second general approach for construction of δ-*N*-(benzyloxy)cycloornithine derivatives relied on N-alkylation of hydroxamates formed from δ-hydroxynorvaline (Scheme I, path b). Two specific routes were considered (Schemes VIII and IX). The first involved the cyclization of an *N*-benzyloxyamide derivative of δ-hydroxynorvaline **6** using the Mitsunobu reaction (Scheme VIII). The second process was to intramolecularly cyclize the *N*-benzyloxyamide of α-*N*-carbobenzoxy-δ-bromonorvaline **7** (Scheme IX). To avoid lactonization of intermediate hydroxy acids in the first route, the hydroxyl group of **8a** was acetylated with acetic anhydride in pyridine to produce acetate **34** quantitatively. Removal of the *tert*-butyl group with trifluoroacetic acid and subsequent conversion of the resulting acid **35** to the *N*-hydroxysuccinimide ester was followed by treatment with *O*-benzylhydroxylamine to give δ-acetoxy-α-*N*-carbobenzoxynorvaline hydroxamate **36** in 90% overall yield from **34**. Hydrolysis of **36** with sodium hydroxide produced **6** cleanly. Cyclization of alcohol **6** with triphenylphosphine–diisopropyl azodicarboxylate gave δ-*N*-(benzyloxy)-α-*N*-carbobenzoxycycloornithine, **2a**, in 81% yield. No carbonyl *O*-alkylated products (hydroximates) were observed. Olsen[18] observed the competitive formation of 15% cyclic hydroximates during cyclization of an α-*N*-carbo-*tert*-butoxy derivative of **2** with Ph_3P–DEAD.

In order to avoid troublesome column chromatographic separation of **2a** from reduced azodicarboxylate and triphenylphosphine oxide obtained from the Mitsunobu mediated cyclization, the δ-hydroxy group of hydroxamate **6** was transformed into the δ-bromo derivative with triphenylphosphine–carbon tetrabromide. Unfortunately, this reaction proceeded poorly, giving the δ-bromo compound **7** in only 50% yield along with several decomposition products. Because of this, the alcohol **8a** was first quantitatively transformed into the *tert*-butyl ester of δ-bromo-α-*N*-carbobenzoxynorvaline (**37**) and then in three steps, as shown in Scheme IX, it was converted to bromide **7** in more than 90% overall yield. Cyclization of bromohydroxamate **7** with potassium carbonate in acetone provided the desired cyclic compound **2a** in 98% yield.

The optical purity of δ-*N*-(benzyloxy)cycloornithine was determined by derivatization with dibenzoyltartaric acid (DBT), as we described previously for a number of amine and hydroxylamine derivatives.[38] Compound **2a** was first treated with HBr in acetic acid to remove the carbobenzoxy group, and the resulting free α-amino group was acylated with dibenzoyltartaric acid anhydride (DBTA). The proton NMR of DBT derivatives of δ-*N*-(benzyloxy)cycloornithine prepared from δ-hydroxynorvaline **8** showed that compound **2a** was essentially optically pure regardless of the method used for the preparation of α-*N*-carbobenzoxy-δ-hydroxynorvaline *tert*-butyl ester **8**. However, product **2a** obtained from δ-hydroxynorvaline, prepared by the method of Gibian and Klieger,[29] but without careful attention to detail, especially the reaction temperature, was contaminated with 10–15% of the op-

(36) Murahashi, S.-J.; Imada, Y.; Taniguchi, Y.; Kodera, Y. *Tetrahedron Lett.* **1988**, *29*, 2973.
(37) Connell, R. D.; Rein, T.; Åkermark, B.; Helquist, P. *J. Org. Chem.* **1988**, *53*, 3845.
(38) Kolasa, T.; Miller, M. J. *J. Org. Chem.* **1986**, *51*, 3055.

posite enantiomer. When prepared exactly as we describe in the Experimental Section, this same compound was enantiomerically pure. It is also noteworthy that, consistant with our previous general observations,[38] the chemical shift of the tartarimide protons of the L-amino acid isomer of the tartarimide derivative appeared downfield (δ = 6.060 ppm) relative to those of the D isomer (δ = 6.005 ppm).



38

In summary, we have presented general and very efficient methods that can be utilized for the preparation of δ-*N*-(benzyloxy)cycloornithine, a direct precursor of *N*-hydroxycycloornithine. The key reactions, reductive cyclization of the α-active ester of glutamic acid δ-semialdehyde *O*-benzyl oxime and cyclization the *N*-(benzyloxy)amide of α-*N*-carbobenzoxy-δ-bromonorvaline, provide chemically and optically pure forms of the desired cyclic product in high yields.

Experimental Section

General Comments. Melting products were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra (IR) were recorded on a Perkin-Elmer 1420 spectrophotometer. Proton NMR spectra were obtained on Varian EM-90, Nicolet NB-300, or GE-300 spectrophotometers. Chemical shifts are reported in ppm relative to tetramethylsilane (δ units). Mass spectra were recorded on DuPont DP102 and Finnigan MAT Model 8430 spectrometers. Optical rotations were determined with a Rudolph Autopol III instrument. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ. All solvents were distilled and dried by standard methods.

Conversion of Oxime 14 to N-Methylated Compounds 15 and 16 and to δ-*N*-(Benzyloxy)cycloornithine (2). Oxime **14** was prepared in 30% (for the D isomer) and 24% (for the L isomer) overall yields as previously described[21] starting from *N*-carbobenzoxyglutamic acid **10** as shown in Scheme II.

A. To a solution of 1.15 g (3 mmol) of D-oxime **14** in 10 mL of glacial acetic acid was added 200 mg (3 mmol) of sodium cyanoborohydride in one portion, and stirring was continued for 4 h at room temperature. Water (20 mL) was then added. The solution was concentrated under reduced pressure, and the residue was dissolved in ethyl acetate. The ethyl acetate solution was washed with 10% $NaHCO_3$, water, and brine, dried over anhydrous $MgSO_4$, and filtered. The solvent was removed under reduced pressure, and the residue was chromatographed on a silica gel column with hexanes–ethyl acetate (3:1) as the eluent to provide 220 mg (18%) of **15** as an oil, a trace of **2**, and a mixture of many unidentified compounds. **15**: $[\alpha]_D$ = −42.7° (*c* = 2.6, CH_2Cl_2); NMR (90 MHz, $CDCl_3$) δ 1.95 (m, 4 H), 2.66 (s, 3 H), 3.33 (m, 2 H), 4.23 (m, 1 H), 4.9 (d, 2 H, *J* = 1.5 Hz), 5.1 (s, 2 H), 5.43 (m, 1 H), 5.7 (m, 1 H), 7.33 (s, 10 H); IR (neat film) 1800, 1720, 1675 cm^{-1}; MS (CI, with isobutane) *m/e* 399 (M + 1), 398 (M), 367, 323.

B. To a solution of 764 mg (2mmol) of L-oxime **14** in 20 mL of anhydrous ethyl ether saturated with hydrochloric acid was added 460 mg (4mmol) of triethylamine–borane complex ($Et_3N{\cdot}BH_3$) and after 2 h reaction at room temperature this same amount of borane complex was added again and the reaction was continued for an additional 5 h. The solvent was then removed under reduced pressure, and the residue was purified on a silica gel column with hexanes–ethyl acetate (3:1) as the eluent to provide 350 mg (50%) of **16** as an oil: $[\alpha]_D$ = −16.4° (*c* = 4.5, CH_2Cl_2); NMR (90 MHz, $CDCl_3$) δ 1.65 (m, 4 H), 2.86 (s, 3 H), 3.66 (m, 2 H), 4.63 (s + m, 3 H), 5.1 (s, 2 H), 7.33 (m, 10 H); IR (neat) 1740, 1705 cm^{-1}; MS (EI) *m/e* 368 (M), 340, 323, 315.

C. To 10 mmol of oxime **14** in 20 mL of methanol was added at 0 °C 10 mmol of 1 N NaOH, and the reaction was continued for 30 min at room temperature. Then, the methanol was removed under reduced pressure. The aqueous solution was acidified with 10% citric acid to pH 3, and the product was extracted with ethyl acetate. The ethyl acetate layer was washed with water and brine, dried over anhydrous $MgSO_4$, and filtered. To the filtrate was added at 0 °C 10 mmol of *N*-hydroxysuccinimide followed by slow addition of 10 mmol of DCC in 15 mL of ethyl acetate, and the reaction mixture was stirred for 4 h at room temperature. The dicyclohexylurea was removed by filtration, and the filtrate was concentrated under reduced pressure. Glacial acetic acid (35 mL) and 10 mmol of $NaBH_3CN$ were added to the residue, and the reaction mixture was stirred at room temperature overnight. Water was added, and the solution was concentrated under reduced pressure. The residue was dissolved in ethyl acetate and washed with water, 10% sodium bicarbonate, water, and brine. The solution was dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified on a silica gel column with CH_2Cl_2–ethyl acetate (4:1) as the eluent to give **2** in 91% yield: mp 66–7 °C; $[\alpha]_D$ = −48.5° (*c* = 1, CH_2Cl_2); NMR (90 MHz, $CDCl_3$) δ 1.7 (m, 2 H), 2.3 (m, 2 H), 3.33 (m, 2 H), 4.12 (m, 1 H), 4.9 (d, 2 H, *J* = 2 Hz), 5.1 (s, 2 H), 5.97 (br d, 1 H, *J* = 8 Hz), 7.33 (s, 10 H); IR (Nujol) 3300, 1720, 1670 cm^{-1}; MS (El) *m/e* 354 (M^+), 322, 263.

***tert*-Butyl *N*-Acylpyroglutamates (17). General Procedures. Method A: 17a.** *N*-Carbalkoxyglutamic acid was converted to *N*-carbalkoxypyroglutamic acid as described by Gibian and Klieger[29] with the modifications described below. *N*-Cbz and *N*-Aloc (allyloxycarbonyl) pyroglutamic acids were converted into the corresponding *tert*-butyl esters with *tert*-butyl acetate–perchloric acid according to the literature procedure.[39]

To 0.1 mol of N-protected glutamic acid in 250 mL of anhydrous THF at 0 °C was added 0.1 mol of DCC in 50 mL of THF at such a rate to keep the internal temperature of the reaction mixture at 0 °C. The reaction mixture was then stirred for 5 h in an ice bath, allowed to warm to room temperature, and left overnight. The dicyclohexylurea was filtered off and washed with cold THF (50 mL), and 400 mL of anhydrous ethyl ether was added to the filtrate. The new solution was cooled to 0 °C, and 0.1 mol of dicyclohexylamine in 50 mL of ethyl ether was added dropwise at such a rate to keep the temperature below +5 °C. Next, the ice bath was removed and the reaction was stirred for 16 h at room temperature. The precipitated DCHA salt was filtered, washed with ethyl ether (50 mL), and dried under vacuum. The resulting salt was stirred with 200 mL of 1 N HCl and 300 mL of ethyl acetate until all of the solid had dissolved. The ethyl acetate layer was separated, washed with water and brine, and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure. To the residue was added 200 mL of *tert*-butyl acetate and 1 mL of 70% of perchloric acid. The tightly closed flask was left for 2 days at room temperature and then opened, and the contents were very slowly poured into a saturated solution of $NaHCO_3$. The organic layer was separated, dried over magnesium sulfate, filtered, and then concentrated under reduced pressure. Purification of the residue on a silica gel column with hexanes–ethyl acetate (3:1) as the eluent provided the *tert*-butyl esters.

L-**17a**: 77% yield; mp 48–52 °C; $[\alpha]_D$ = −36.9° (*c* = 4.5, CH_2Cl_2); NMR (300 MHz, $CDCl_3$) δ 1.4 (s, 9 H), 2.05 (m, 1 H, *J* = 3 and 4.5 Hz), 2.33 (m, 1 H), 2.57 (m, 2 H), 4.58 (dd, 1 H, *J* = 8 and 2 Hz), 5.3 (dd, 2 H, *J* = 12 Hz), 7.4 (m, 5 H); IR (Nujol) 1785, 1735 cm^{-1}; MS (CI with isobutane) *m/e* 320 (M + 1), 263 (M − 56), 219.

D-**17a**: 81% yield; mp 49–52 °C; $[\alpha]_D$ = +33.6° (*c* = 3, CH_2Cl_2); NMR (300 MHz, $CDCl_3$) δ 1.34 (s, 9 H), 1.7–2.63 (m, 4 H), 4.56 (dd, 1 H, *J* = 7 and 3 Hz), 5.23 (s, 2 H), 7.33 (m, 5 H); IR (film) 1800, 1760, 1730 cm^{-1}; MS (CI with isobutane) *m/e* 320 (M + 1), 263 (7 − 56); exact mass calcd for $C_{17}H_{21}NO_5$ 319.1420, found 319.1419.

D-**17b**: 78% yield; oil; $[\alpha]_D$ = +40.8° (*c* = 2, CH_2Cl_2); NMR (300 MHz, $CDCl_3$) δ 1.43 (s, 9 H), 2.05 (m, 1 H), 2.3 (m, 1 H), 2.57 (m, 2 H), 4.56 (dd, 1 H, *J* = 3 and 10 Hz), 4.73 (m, 2 H), 5.33 (4 d, 2 H, *J* = 1 Hz), 5.9 (m, 1 H); IR (neat) 1800, 1760, 1730 cm^{-1};

(39) Taschner, E.; Wasielewski, C.; Biernat, J. F. *Justus Liebigs Ann. Chem.* **1961**, *646*, 119.

MS (CI with isobutane) m/e 270 (M + 1), 214 (M − 56).

Method B. To 12.9 g (0.1 mol) of L-pyroglutamic acid **21** in 200 mL of *tert*-butyl acetate was added 3 mL (0.11 mol) of 70% $HClO_4$, and the reaction mixture was stirred overnight at room temperature in a tightly closed flask. Then, the reaction mixture was slowly poured into a saturated solution of $NaHCO_3$, and the product was extracted with ethyl ether. Drying ($MgSO_4$), filtration, and evaporation of the provided 11.3 g (60%) of *tert*-butyl L-pyroglutamate: mp 91–92 °C (lit.[40] mp 106–107 °C); MS (CI with isobutane) m/e 186 (M + 1). To 10 mmol of the *tert*-butyl ester in 50 mL of anhydrous THF was added 440 mg (11 mmol) of 60% NaH (in oil), and after 30 min, 11 mmol of alkyl (benzyl or allyl) chloroformate was added, and reaction mixture was stirred at room temperature for 48 h. Then, the solvent was removed under reduced pressure. The residue was treated with 10% citric acid, and the product was extracted with ethyl acetate. After drying ($MgSO_4$), filtration, and evaporation of the ethyl acetate under reduced pressure, the residue was chromatographed on a silica gel column with hexanes–ethyl acetate (3:1) as the eluent to provide the desired product **17**.

L-**17a**: 78% yield; mp 43–45 °C; $[\alpha]_D$ = −40.4° (c = 2.4, CH_2Cl_2). The spectral properties were identical with those given for the sample of **17a** prepared by the alternate procedure described above.

L-**17b**: 80% yield; oil; $[\alpha]_D$ = −43.0° (c = 0.9, CH_2Cl_2); NMR (300 MHz, $CDCl_3$) δ 1.48 (s, 9 H), 2.06 (m, 1 H, J = 3 Hz), 2.34 (m, 1 H, J = 10 Hz), 2.51 (m, 1 H, J = 3 Hz), 2.64 (m, 1 H, J = 10 Hz), 4.55 (dd, 1 H, J = 3 and 10 Hz), 4.73 (dd, 2 H, J = 1 and 5 Hz), 5.25, 5.30, 5.38, and 5.43 (4 d, 2 H, J = 1 Hz), 5.95 (octet, 1 H, J = 6 Hz); IR (neat) 1795, 1740, 1720, 1640 cm^{-1}; exact mass calcd for $C_{13}H_{19}NO_5$ 269.1263, found 269.1264.

γ-Alkyl-α-*tert*-butyl Esters of *N*-Carbobenzoxyglutamic Acid, 20. γ-Ethyl L-glutamate was purchased from Sigma. γ-Methyl D-glutamate was prepared as described[31] in 68% yield.

Method A. To a solution of 0.2 mol of **19** and 0.4 mol of $NaHCO_3$ in 250 mL of water was added with stirring 0.21 mol of carbobenzoxy chloride in 125 mL of ethyl acetate, and the solution was stirred at room temperature overnight. The water layer was acidified to pH 3, and the product was extracted with ethyl acetate. The ethyl acetate layer was washed with water and brine, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. To the residue was added 230 mL of *tert*-butyl acetate and 1.5 mL of 70% $HClO_4$, and the reaction mixture was left for 48 h in a tightly closed flask at room temperature. The flask was opened, and the reaction mixture was slowly poured into a saturated $NaHCO_3$ solution. The product was extracted with ethyl ether. After drying ($MgSO_4$), filtration, and removal of the solvent under reduced pressure, the residue was purified on a silica gel column with hexanes–ethyl acetate (4:1) as the eluent to provide pure **20**.

L-**20a**: 66% yield; oil; $[\alpha]_D$ = +5.9° (c = 1.1, CH_2Cl_2); NMR (300 MHz, $CDCl_3$) δ 1.24 (t, 3 H, J = 7 Hz), 1.46 (s, 9 H), 2.0 (septet, 1 H, J = 8 Hz), 2.2 (septet, 1 H, J = 8 Hz), 2.4 (m, 2 H), 4.13 (q, 2 H, J = 7 Hz), 4.3 (q, 1 H, J = 8 Hz), 5.1 (s, 2 H), 5.43 (d, 1 H, J = 9 Hz), 7.4 (s, 5 H); IR (film) 3340, 1740, 1700 cm^{-1}; MS (CI with isobutane) m/e 366 (M + 1), 310 (M − 56). Starting material was recovered in 22% yield.

D-**20b**: 52% yield; oil; $[\alpha]_D$ = −5.16° (c = 3.8, CH_2Cl_2); NMR (300 MHz, $CDCl_3$) δ 1.43 (s, 9 H), 1.95 (m, 1 H, J = 8 and 6 Hz), 2.16 (m, 1 H, J = 6 and 8 Hz), 2.38 (m, 2 H), 3.63 (s, 3 H), 4.27 (m, 1 H, J = 6 and 8 Hz), 5.1 (s, 2 H), 5.6 (d, 1 H, J = 8 Hz), 7.3 (s, 5 H); IR (film) 3320, 1740, 1705 cm^{-1}; MS (CI with isobutane) m/e 352 (M + 1), 296 (M − 56). Starting material was recovered in 20% yield.

Method B. To a solution of 1 mmol of **17a** in 15 mL of methanol was added 10 mg of Cs_2CO_3, and the reaction mixture was stirred for 30 min at room temperature. Then, the methanol was removed under reduced pressure, and the residue was dissolved in ethyl acetate, washed with water and brine, dried over $MgSO_4$, and filtered. Evaporation of the ethyl acetate under reduced pressure provided **20** quantitatively.

L-**20b**: $[\alpha]_D$ = +4.9° (c = 1.05, CH_2Cl_2).

D-**20b**: $[\alpha]_D$ = −4.6° (c = 4, CH_2Cl_2).

***tert*-Butyl Ester of *N*-Carbalkoxynorvaline, 8. General Procedures. Method A: From Pyroglutamate 17 through Ester 18.** To 10 mmol of **17** in 30 mL of methanol at 0 °C was added 10 mL of 1 N NaOH, dropwise. The ice bath was removed, and the saponification was continued at room temperature for 1 h. Then, the methanol was removed under reduced pressure. The aqueous solution was acidified with 10% citric acid, and the product was extracted with ethyl acetate. The ethyl acetate extracts were washed with water and brine, dried over $MgSO_4$, filtered, and evaporated. To the residue was added at −40 °C to −30 °C 12 mmol of Et_3N in 30 mL of THF followed by slow addition of 12 mmol of isobutyl chloroformate in 10 mL of THF. The reaction mixture was stirred below −20 °C for 45 min. Then, the triethylamine hydrochloride was filtered off and washed with cold THF (stored in dry ice), and the filtrate was added as quickly as possible to a suspension of 30 mmol of sodium borohydride in 20 mL of THF–water (8:1) at 0 °C with vigorous stirring. The stirring was continued at room temperature for 3 h, followed by acidification of the solution to pH 5. The THF was removed under reduced pressure, and the product was extracted with ethyl acetate. The ethyl acetate extracts were washed with water and brine and dried over anhydrous $MgSO_4$. Removal of the ethyl acetate under reduced pressure and purification of the residue on a silica gel column with CH_2Cl_2 (4:1) as the eluent gave **8** as an oily product.

D-**8a**: 87% yield; $[\alpha]_D$ = −5.56° (c = 3.5, CH_2Cl_2); NMR (90 MHz, $CDCl_3$) δ 1.4 (s, 9 H), 1.66 (m, 4 H), 2.56 (br s, 1 H), 3.6 (t, 2 H, J = 7 Hz), 4.22 (m, 1 H), 5.06 (s, 2 H), 5.6 (br d, 1 H, J = 8 Hz), 7.33 (s, 5 H); IR (neat) 3350 with a shoulder at 3450, 1740, 1720 cm^{-1}; MS (CI with isobutane) m/e 324 (M + 1), 268 (M − 56).

L-**8a**: 89% yield; $[\alpha]_D$ = +5.4° (c = 1.4, CH_2Cl_2); NMR (300 MHz, $CDCl_3$) δ 1.42 (s, 9 H), 1.6 (m, 2 H), 1.74 (m, 1 H, J = 8 Hz), 1.87 (m, 1 H), 2.3 (br s, 1 H), 3.63 (t, 2 H, J = 6 Hz), 4.27 (q, 1 H, J = 7 Hz), 5.1 (s, 2 H), 5.68 (d, 1 H, J = 9 Hz), 7.37 (s, 5 H); IR (neat) 3320, 1740, 1725, 1700 cm^{-1}; MS (CI with isobutane) m/e 324 (M + 1), 268 (M − 56).

D-**8b**: 80% yield; $[\alpha]_D$ = −6.3° (c = 3, CH_2Cl_2); NMR (300 MHz, $CDCl_3$) δ 1.48 (s, 9 H), 1.62 (m, 2 H), 1.75 (sextet, 1 H, J = 7 Hz), 1.9 (m, 1 H), 2.6 (br s, 1 H), 3.65 (t, 2 H, J = 7 Hz), 4.63 (q, 1 H, J = 7 Hz), 4.58 (d, 2 H, J = 9 Hz), 5.25 (d, 2 H, J = 2 Hz), 5.6 (d, 1 H, J = 10 Hz), 5.9 (octet, 1 H, J = 6 Hz); IR (film) 3320, 1740, 1720, 1700 cm^{-1}; MS (CI with isobutane) m/e 274 (M + 1), 218 (M − 56).

Method B. From γ-Ester 20. To 0.1 mol of **20** in 250 mL of methanol at 0 °C was added dropwise 0.1 mol of 1 N NaOH, and the resulting mixture was stirred at room temperature for 1 h. The methanol was then removed under reduced pressure. The resulting aqueous solution was acidified with 10% citric acid, and the product (**18**) was extracted with ethyl acetate. The ethyl acetate layer was washed with water and brine, dried over $MgSO_4$, and filtered. The ethyl acetate was removed under reduced pressure, and the residue was reduced to **8** as described in method A.

L-**8a**: 90% yield; $[\alpha]_D$ = +6.0° (c = 1.4, CH_2Cl_2). The spectral data was identical with that for L-**8a** obtained from method A.

D-**8a** obtained from method A.

Method C. To a solution of 1 mmol of **17** and 1 mmol of $NaBH_4$ in 25 mL of anhydrous THF was added at 50 °C to 60 °C dropwise, within 30 min, 5 mL of *tert*-butyl alcohol in 5 mL of THF. The reaction was continued 10 min longer, and then the solvents were removed under reduced pressure. To the residue was added 10% citric acid, and the product was extracted with ethyl acetate. The organic layers were washed with water and brine, dried over anhydrous $MgSO_4$, and filtered. The ethyl acetate was evaporated under reduced pressure, and the product was chromatographed on a silica gel column with CH_2Cl_2–ethyl acetate (4:1) as the eluant to provide **8**.

L-**8a**: 56% yield; $[\alpha]_D$ = +5.95° (c = 2, CH_2Cl_2). The spectral data was identical with that for L-**8a** obtained from method A.

L-**8b**: 59% yield; $[\alpha]_D$ = +6.95° (c = 2, CH_2Cl_2). The spectral data was identical with that for L-**8b** obtained from method A.

Conversion of δ-Hydroxynorvaline Derivative 8 into δ-*N*-Hydroxyornithine Derivatives 28 and 29. A. *tert*-Butyl Ester of α-*N*-(Allyloxycarbonyl)-δ-*N*-carbobenzoxy-δ-*N*-

(40) Johnson, A. L.; Price, W. A.; Wong, P. C.; Vavala, R. F.; Stump, J. M. *J. Med. Chem.* **1985**, *28*, 1596.

(benzyloxy)ornithine (28). To a solution of 792 mg (2.9 mmol) of **8b**, 917 mg (3.5 mmol) of triphenylphosphine, and 745 mg (2.9 mmol) of *N*-carbobenzoxy-*O*-benzylhydroxylamine in 25 mL of THF was added 0.7 mL (3.5 mmol) of DIAD in 5 mL of THF dropwise. The reaction mixture was stirred at room temperature overnight. The THF was removed under reduced pressure, and the residue was chromatographed on a silica gel column with benzene–ethyl acetate (19:1) as the eluent to provide 1.1 g (72%) of **28** as an oil: $[\alpha]_D = -7.3°$ (c = 0.9, $CHCl_3$); NMR (90 MHz, $CDCl_3$) δ 1.35 (s, 9 H), 1.67 (m, 4 H), 3.48 (m, 2 H), 4.21 (m, 1 H), 4.53 (d, 2 H, J = 6 Hz), 4.83 (s, 2 H), 5.2 (m, 5 H), 5.8 (m, 1 H), 7.33 (m, 10 H); IR (film) 3350, 1730 with a shoulder at 1745, 1710 cm^{-1}; MS (EI) m/e 512 (M), 456 (M – 56). Anal. Calcd from $C_{28}H_{36}N_2O_7$: C, 65.62; H, 7.03; N, 5.47. Found: C, 65.65; H, 7.07; N, 5.45.

B. *tert*-Butyl Ester of α-*N*-Carbobenzoxy-β-*N*-(allyloxycarbonyl)-δ-*N*-(benzyloxy)-D-ornithine (29). To a solution of 2.26 g (7 mmol) of **8a**, 2.62 g (10 mmol) of triphenylphosphine, and 1.45 g (7 mmol) of *N*-(allyloxycarbonyl)-*O*-benzylhydroxyalamine in 40 mL of THF was added 2 mL (10 mmol) of DIAD in 10 mL of THF, dropwise, and the reaction mixture was stirred overnight at room temperature. The THF was removed under reduced pressure, and the residue was chromatographed on a silica gel column with hexanes–ethyl acetate (4:1) as the eluent to provide 2.51 g (70%) of **29** as an oil: $[\alpha]_D = -5.0°$ (c = 3, CH_2Cl_2); NMR (90 MHz, $CDCl_3$) δ 1.4 (m, 9 H), 1.65 (m, 3 H), 1.9 (m, 1 H), 3.46 (t, 2 H, J = 6 Hz), 4.27 (m, 1 H), 4.65 (d, 2 H, J = 6 Hz), 4.84 (s, 2 H), 5.1 (s, 2 H), 5.3 (4 s + m, 3 H), 5.95 (octet, 1 H, J = 6 Hz), 7.38 (m, 10 H); IR (film) 3350, 1720 with a shoulder at 1740, 1690 cm^{-1}; MS (EI) m/e) 456 (M – 56), 411. Anal. Calcd for $C_{28}H_{36}N_2O_7$: C, 65.62; H, 7.03; N, 5.47. Found: C, 65.52; H, 6.95; N, 5.59.

α-*N*-(Allyloxycarbonyl)-δ-*N*-carbobenzoxy-δ-*N*-(benzyloxy)-D-cycloornithine (30). To a solution of 840 mg (1.7 mmol) of **28** in 3 mL of CH_2Cl_2 was added 3 mL of TFA, and the reaction mixture was left for 30 min at room temperature. The solution was concentrated under reduced pressure. The residue was dissolved in ethyl acetate, washed with water and brine, dried over anhydrous $MgSO_4$, and filtered. The ethyl acetate was removed under reduced pressure to provide 773 mg of product **30** as an oil in quantitive yield: $[\alpha]_D = -4.3°$ (c = 0.7, CH_2Cl_2); NMR (300 MHz, $CDCl_3$) δ 1.7 (m, 4 H), 3.48 (m, 2 H), 4.33 (m, 1 H), 4.56 (d, 2 H, J = 6 Hz), 4.82 (s, 2 H), 5.23 (s + m, 4 H), 5.73 (m, 1 H), 7.33 and 7.36 (2 s, 10 H), 11.3 (br s, 1 H); IR (film) 3330–2500, 1750, 1700 cm^{-1}; MS (EI) m/e 413 (M – 43), 304.

α-*N*-(Allyloxycarbonyl)-δ-*N*-(benzyloxy)-D-cycloornithine (2b). To a solution of 2.74 g (6 mmol) of **30** and 690 mg (6 mmol) of *N*-hydroxysuccinimide in 50 mL of ethyl acetate at 0 °C was added 1.24 g (6 mmol) of DCC in 10 mL of ethyl acetate, and the reaction mixture was stirred at room temperature for 4 h. The dicyclohexylurea was filtered off. The filtrate was concentrated under reduced pressure and redissolved in 10 mL of acetic acid. To this solution was added 10 mL of HBr in AcOH, and the reaction mixture was left at room temperature for 15 min. The solvent was then removed under reduced pressure. The residue was washed several times with cold ethyl ether to remove benzyl bromide and redissolved in 20 mL of pyridine. To the pyridine solution was added 200 mg of DMAP, and the reaction mixture was stirred overnight. The pyridine then was removed under reduced pressure. The residue was transfered to 50 mL of ethyl acetate, washed with water, 10% citric acid, water, and brine, dried over anhydrous $MgSO_4$, and filtered. The ethyl acetate was removed under reduced pressure, and the residue was chromatographed on a silica gel column with CH_2Cl_2–ethyl acetate (4:1) as the eluent to provide 960 mg (53%) of **2b** as an oil: $[\alpha]_D = -37.2°$ (c = 1, CH_2Cl_2); NMR (300 MHz, $CDCl_3$) δ 1.76 (m, 3 H), 2.3 (m, 1 H), 3.35 (m, 2 H), 4.2 (m, 1 H), 4.6 (d, 2 H, J = 6 Hz), 4.9 (s, 2 H), 5.3 (m, 2 H), 6.0 (m, 2 H), 7.4 (s, 5 H); IR (film) 3340, 1720, 1670 cm^{-1}; MS (CI with isobutane) m/e 305 (M + 1).

***tert*-Butyl Ester of α-*N*-Carbobenzoxy-δ-*N*-(benzyloxy)-D-ornithine (31). Method A (with Acetic Acid as the Allyl Scavenger).** To a solution of 563 mg (1.1 mmol) of **29** in 15 mL of CH_2Cl_2 were added 60 mg of $Pd(Ph_3P)_4$, 60 mg of Ph_3P, and 0.2 mL of acetic acid, and the reaction mixture was left overnight at room temperature. The reaction mixture was washed with 10% $NaHCO_3$, water, and brine, dried over anhydrous $MgSO_4$, and filtered. After evaporation of the solvent under reduced pressure, the residue was chromatographed on a silica gel column using hexanes–ethyl acetate (5:1) as the eluent to give 200 mg (42%) of **31** and 270 mg (52%) of **32** as oils.

31: NMR (90 MHz, $CDCl_3$) δ 1.3–1.9 (s + m, 13 H), 2.9 (t, 2 H, J = 7 Hz), 3.5 (br s, 1 H), 4.23 (m, 1 H), 4.66 (s, 2 H), 5.07 (s, 2 H), 5.35 (broad d, 1 H), 7.33 (s, 10 H); IR (film) 3300, 1720, 1700 cm^{-1}; MS (CI with isobutane) m/e 429 (M + 1), 373 (M – 56).

32: $[\alpha]_D = -5.5°$ (c = 0.4, CH_2Cl_2); NMR (90 MHz, $CDCl_3$) δ 1.4 (s, 9 H), 1.66 (m, 4 H), 2.66 (t, 2 H, J = 7 Hz), 3.34 (d, 2 H, J = 6 Hz), 4.2 (m, 1 H), 4.66 (s, 2 H), 5.07 (s, 2 H), 5.2 (d, 2 H, J = 7 Hz), 5.45 (br d, 1 H), 5.9 (m, 1 H), 7.36 (m, 10 H); IR (film) 3340, 1730, 1710 cm^{-1}; MS (CI with isobutane) m/e 469 (M + 1), 468 (M), 412.

Method B (with *O*-Benzylhydroxylamine as the Allyl Scavenger). To a solution of 770 mg (1.5 mmol) of **29** in 50 mL of CH_2Cl_2 were added 209 mg (1.7 mmol) of *O*-benzylhydroxylamine and 60 mg of $Pd(Ph_3P)_4$, and the reaction mixture was stirred for 12 h at room temperature. The reaction mixture was concentrated to about 10 mL and passed through a silica gel column using hexanes–ethyl acetate (5:1) as the eluent to provide 615 mg (95%) of **31** and 240 mg (99%) of **33**.

33: NMR (90 MHz, $CDCl_3$) δ 3.23 (d, 2 H, J = 6 Hz), 4.7 (s, 2 H), 5.23 (t, 2 H, J = 7 Hz), 5.52 (br s, 1 H), 5.9 (m, 1 H), 7.37 (s, 5 H); IR (neat) 3400, 1640 cm^{-1}; MS (CI with isobutane) m/e 164 (M + 1), 107, 91.

α-*N*-Carbobenzoxy-δ-*N*-(benzyloxy)-D-cycloornithine (2a). To a solution of 1.28 g (3 mmol) of **31** in 15 mL of CH_2Cl_2 was added 5 mL of TGA, and the reaction mixture was left at room temperature for 30 min. Then, the solution was concentrated under reduced pressure. The residue was dissolved in ethyl acetate, washed with water and brine, dried over anhydrous $MgSO_4$, and filtered. The ethyl acetate was removed under reduced pressure, and the residue was redissolved in 75 mL of CH_2Cl_2. To this solution were added 445 mg (3 mmol) of *N*-hydroxysuccinimide, 366 mg (3 mmol) of DMAP, and 618 mg (3 mmol) of DCC at 0 °C. The resulting mixture was stirred at room temperature for 72 h. The dicyclohexylurea was filtered off. The filtrate was washed with 1 N HCl, water, 10% $NaHCO_3$, water, and brine, dried over anhydrous $MgSO_4$, and filtered. The solvent was removed under reduced pressure, and the residue was purified on a silica gel column with CH_2Cl_2–ethyl acetate (9:1) as the eluent to provide 540 mg (51%) of **2a**: mp 59–61 °C; $[\alpha]_D = 46.1°$ (c = 1.1, CH_2Cl_2); NMR (90 MHz, $CDCl_3$) δ 1.77 (m, 3 H), 2.33 (m, 1 H), 3.4 (m, 2 H), 4.3 (m, 1 H), 5.05 (d, 2 H, J = 1.5 Hz), 5.27 (s, 2 H), 6.1 (d, 1 H, J = 6 Hz), 7.62 (s, 10 H); MS (CI with isobutane) m/e 355 (M + 1), 247 (M – 108). Anal. Calcd for $C_{20}H_{22}N_2O_4$: C, 67.78; H, 6.21; N, 7.91. Found: C, 67.83; H, 5.99; N, 7.99.

***tert*-Butyl Ester of α-*N*-Carbobenzoxy-δ-*O*-(*tert*-butyldimethylsilyl)-D-hydroxynorvaline (22). Method A.** A solution of 1.61 g (5 mmol) of **8a**, 769 mg (5.1 mmol) of TBDMSCl, and 340 mg (5.1 mmol) of imidazole in 10 mL of DMF was stirred overnight at room temperature. The reaction mixture was poured into 50 mL of water, and the product was extracted with ethyl acetate. The organic layer was washed with water, 10% citric acid, water, and brine, dried over anhydrous $MgSO_4$, and filtered. The ethyl acetate was removed under reduced pressure, and the residue was passed through a silica gel column with hexanes–ethyl acetate (4:1) as the eluent to give 2.15 g (98%) of oily product **22**: $[\alpha]_D = -4.0°$ (c = 1.08, CH_2Cl_2); NMR ($CDCl_3$) δ 0.82 (s, 9 H), 1.3–2.0 (s + m), 13 H), 3.6 (t, 2 H, J = 6 Hz), 4.3 (m, 1 H), 5.08 (s, 2 H), 5.4 (d, 1 H), 7.33 (s, 5 H); IR (film) 3320, 1730, 1720 cm^{-1}; MS (CI with isobutane) m/e 438 (M + 1), 383, 338.

Method B. A solution of 3.23 g (10 mmol) of **8a**, 0.3 mL (2 mmol) of DBU, and 1.4 mL (10 mmol) of Et_3N in 50 mL of CH_2Cl_2 was cooled to 0 °C, and then 1.58 g (10.5 mmol) of TBDMSCl was added and stirring was continued for 3 h at room temperature. After workup and purification as in method A, 4.1 g (94% yield) of the product, **22**, was obtained.

α-Carbo-*tert*-butoxy-α-carbobenzoxy-δ-*O*-(*tert*-butyldimethylsilyl)hydroxynorvaline *tert*-Butyl Ester (23). A mixture of 4.35 g (10 mmol) of **22**, 3.27 g (15 mmol) of di-*tert*-dicarbonate (Boc_2O), and 305 mg (2.5 mmol) of DMAP in 40 mL of dry acetonitrile was stirred at room temperature in a tightly closed flask for 24 h. The acetonitrile was then removed under

reduced pressure, and the residue was dissolved in ethyl acetate. The organic layer was washed with water, 10% citric acid, water, 10% $NaHCO_3$ solution, water, and brine, dried over anhydrous $MgSO_4$, and filtered. The solvent was then removed under reduced pressure, and the residue was chromatographed on a silica gel column with hexanes–ethyl acetate (19:1) as the eluent to provide 4.95 g (93%) of **23**: $[\alpha]_D = +8.2°$ ($c = 0.88$, CH_2Cl_2); NMR (90 MHz, $CDCl_3$) δ 0.82 (s, 9 H), 1.35 (s, 9 H), 1.4 (s, 9 H), 1.45 (m, 2 H), 2.0 (m, 2 H), 3.6 (t, 2 H, $J = 6$ Hz), 4.82 (m, 1 H, $J = 6$ Hz), 5.23 (s, 2 H), 7.36 (s, 5 H); IR (neat) 1790, 1740, 1700 cm^{-1}.

***α*-*N*-Carbo-*tert*-butoxy-*α*-*N*-carbobenzoxy-δ-hydroxy-D-norvaline *tert*-Butyl Ester (24). Method A.** To a solution of 670 mg (1.24 mmol) of **23** in 10 mL of THF was added 1.5 mL of 1 N tetrabutylammonium fluoride solution in THF, and the reaction mixtures was stirred at room temperature for 6 h. After removing the THF under reduced pressure, the residue was dissolved in ethyl acetate and was washed with water, 10% citric acid, water, 10% sodium bicarbonate solution, water, and brine. The solution was dried over anhydrous $MgSO_4$ and filtered. The ethyl acetate was removed under reduced pressure, and the crude material was passed through a silica gel column using hexanes–ethyl acetate (4:1) as the eluent to provide 350 mg (67%) of **24** and 120 mg (26%) of **25**.

24: NMR (90 MHz, $CDCl_3$) δ 1.36 (s, 9 H), 1.42 (s, 9 H), 1.55 (m, 2 H), 2.0 (m, 2 H), 2.33 (br s, 1 H), 3.6 (t, 2 H, $J = 6$ Hz), 4.85 (m, 1 H, $J = 6$ Hz), 5.23 (s, 2 H), 7.36 (s, 5 H); IR (film) 3500, 1790, 1740, 1700 cm^{-1}; MS (CI with isobutane) m/e 424 (M + 1), 312.

25: $[\alpha]_D = +3.6°$ ($c = 1$, CH_2Cl_2); NMR (90 MHz, $CDCl_3$) δ 1.38 (s, 18 H), 1.69 (m, 4 H), 4.15 (m, 3 H), 5.03 (br d, 1 H), 5.1 (s, 2 H), 7.33 (s, 5 H); IR (neat) 3350, 1750, 1720 cm^{-1}; MS (CI with isobutane) m/e 424 (M + 1), 369.

Method B. To a solution of 3.3 g (6.14 mmol) of **23** and 6 mL of acetic acid in 50 mL of THF was added 10 mL of a 1 N solution of n-$Bu_4N^+F^-$ in THF, and the reaction mixture was stirred for 20 h at room temperature. Then, 100 mL of water was added. The product was extracted with ethyl acetate, washed with water and brine, and dried over anhydrous $MgSO_4$. Filtration followed by removal of the solvent under reduced pressure provided **24** in quantitative yield.

***tert*-Butyl Ester of D-Glutamic Acid Semialdehyde Oxime 26.** A solution of 1.27 g (3 mmol) of **24** and 1.08 g (5 mmol) of PCC in 100 mL of CH_2Cl_2 was stirred for 1.5 h at room temperature. The CH_2Cl_2 solution was filtered through a short silica gel column, further eluting with CH_2Cl_2 and ethyl acetate until TLC analysis showed no more product in the eluent. The combined organic solvents were removed under reduced pressure. The residue was dissolved in ethyl acetate and was washed with 10% $NaHCO_3$, water, 10% citric acid, water, and brine. The organic layer was dried over $MgSO_4$ and filtered. After removal of the ethyl acetate under reduced pressure, the residue was dissolved in 25 mL of methanol and treated with a solution of 640 mg (4 mmol) of *O*-benzylhydroxylamine hydrochloride and 330 mg (4 mmol) of sodium acetate in 20 mL of water. The resulting reaction mixture was stirred overnight at room temperature. The methanol was then removed under reduced pressure. The residue was dissolved in ethyl acetate and washed with 10% citric acid, water, 10% $NaHCO_3$ solution, water, and brine. The organic layer was dried over anhydrous $MgSO_4$ and filtered. Removal of the ethyl acetate under reduced pressure and purification of the residue on a silica gel column, with hexanes–ethyl acetate (3:1) as the eluent, gave 1 g (80%) of **26** as a mixture of *Z* and *E* isomers.

***Z*-26**: $[\alpha]_D = +15.0°$ ($c = 0.9$, CH_2Cl_2); NMR (90 MHz, $CDCl_3$) δ 1.36 (s, 9 H), 1.42 (s, 9 H), 2.20 (m, 4 H), 4.83 (m, 1 H), 5.05 (s, 2 H), 5.20 (s, 2 H), 7.33 (m + s, 11 H); IR (neat) 1790, 1740, 1700 cm^{-1}; MS (CI with isobutane) m/e 527 (M + 1), 371, 304.

***E*-26**: $[\alpha]_D = +21.43°$ ($c = 0.77$, CH_2Cl_2); NMR (90 MHz, $CDCl_3$) δ 1.36 (s, 9 H), 1.4 (s, 9 H), 2.25 (m, 4 H), 4.84 (m, 1 H), 5.06 (s, 2 H), 6.66 (t, 1 H, $J = 6$ Hz), 7.30 and 7.33 (2 s, 10 H); IR (neat) 1790, 1740, 1700 cm^{-1}; MS (CI with isobutane) m/e 527 (M + 1). Anal. Calcd for $C_{29}H_{38}N_2O_7$: C, 66.16; H, 7.22; N, 5.32. Found: C, 66.32; H, 7.33; N, 5.45.

***O*-Benzyloxime of *α*-*N*-Carbobenzoxy γ-Aldehyde of D-Glutamic Acid, 4a.** A solution of 790 mg (1.5 mmol) of **26** as a mixture of the *Z* and *E* isomers and 5 mL of TFA in 15 mL of CH_2Cl_2 was left at room temperature for 30 min. The solvents were removed under reduced pressure, and the residue was twice evaporated with toluene to completely remove any residual trifluoroacetic acid, giving 560 mg (~100%) of oily **4a**: $[\alpha]_D = -3.43°$ ($c = 1.4$, CH_2Cl_2); NMR (90 MHz, $CDCl_3$) δ 1.7–2.5 (m, 4 H), 4.33 (m, 1 H), 5.05 (s, 2 H), 5.1 (s, 2 H), 5.66 (br s, 1 H), 6.7 (m, 0.5 H), 7.33 and 7.37 (2 s + m, 10.5 H), 11.0 (br s, 1 H); IR (film) 3600–2500 (with max 3400), 1780, 1715 (with a shoulder at 1680 cm^{-1}). MS (CI with isobutane) m/e 371 (M + 1), 294, 204. Anal. Calcd for $C_{20H22}N_2O_5$: C, 64.86; H, 5.95; N, 7.57. Found: C, 64.73; H, 5.83; N, 7.36.

***α*-*N*-Carbobenzoxy-δ-*N*-(benzyloxy)-D-cycloornithine (2a).** To a solution of 482 mg (1.3 mmol) of **4a** and 150 mg (1.3 mmol) of *N*-hydroxysuccinmide in 20 mL of ethyl acetate was added 268 mg (1.3 mmol) of DCC in 5 mL of ethyl acetate at 0 °C, and the reaction mixture was stirred at room temperature for 6 h. The dicyclohexylurea was then removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was dissolved in 8 mL of acetic acid and was treated with one 82-mg (1.3 mmol) portion of sodium cyanoborohydride, $NaBH_3CN$. The solution was stirred at room temperature for 15 h and was then concentrated under reduced pressure. Ethyl acetate was added to the residue, and the resulting solution was washed with 10% $NaHCO_3$, water, and brine. After drying over anhydrous $MgSO_4$ and filtration, the solvent was removed under reduced pressure. Recrystallization of the product from ethyl acetate–hexanes gave 320 mg (70%) of **2a**: mp 63–4 °C; $[\alpha]_D = -48.5°$ ($c = 0.92$, CH_2Cl_2). Spectral and analytical data were identical with the sample of **2a** prepared by the process described earlier in this Experimental Section.

***tert*-Butyl Ester of *α*-*N*-Phthaloyl-δ-hydroxy-D-norvaline (8c).** A mixture of 2.26 g (7 mmol) of **8a** in 25 mL of ethanol was hydrogenated over 10% Pd/C at room temperature at atmospheric pressure of hydrogen until all of the starting material disappeared (about 30 min). The catalyst was filtered off, and the filtrate was concentrated under reduced pressure. The oily residue was dissolved in 15 mL of anhydrous THF, and 1.56 g (7.1 mmol) of *N*-carbethoxyphthalimide in 10 mL of THF was added at 0 °C. The ice bath was then removed, and the reaction mixture was stirred at room temperature for 15 h. Because TLC analysis indicated the presence of unreacted material, 122 mg (1 mmol) of DMAP was added and the reaction mixture was stirred for an additional 15 h. Then, the THF was removed under reduced pressure, and the residue was chromatographed on a silica gel column with CH_2Cl_2–ethyl aceatate (4:1) as the eluent to provide 2 g (90%) of **8c**: $[\alpha]_D = +0.9°$ ($c = 2.1$, CH_2Cl_2); NMR (90 MHz, $CDCl_3$) δ 1.3–1.6 (m + s, 11 H), 1.87 (br s, 1 H), 2.3 (m, 2 H), 3.6 (t, 2 H, $J = 7$ Hz), 4.82 (t, 1 H, $J = 7$ Hz), 7.9 (m, 4 H); IR (film) 3520, 1780, 1735 cm^{-1}; MS (CI with isobutane) m/e 320 (M + 1), 2.64 (M − 56), 246.

***tert*-Butyl Ester of *α*-*N*-phthaloyl-γ-*O*-benzyl Oxime of D-Glutamic Acid Semialdehyde, 27.** To a solution of crude aldehyde, prepared in quantitative yield as described above from 160 mg (0.5 mmol) of **2c** and 216 mg (1 mmol) of PCC, in 25 mL of methanol, was added a solution of 160 mg (1 mmol) of *O*-benzylhydroxylamine hydrochloride and 82 mg (1 mmol) of sodium acetate in 20 mL of water. The reaction mixture was stirred overnight at room temperature. The MeOH was then removed under reduced pressure. The residue was dissolved in ethyl acetate and washed with 10% citric acid, water, 10% $NaHCO_3$, water, and brine, dried over anhydrous $MgSO_4$, and filtered. After removing the ethyl acetate under reduced pressure, the residue was separated on a silica gel column with CH_2Cl_2–ethyl acetate (4:1) as the eluent to provide 207 mg (96%) of **27** as an oily mixture of *Z* and *E* isomers (1:1): $[\alpha]_D = +8.5°$ ($c = 2.4$, CH_2Cl_2); NMR (90 MHz, $CDCl_3$) δ 1.47 (s, 9 H), 2.43 (m, 4 H), 4.95 (m, 1 H), 5.10 and 5.17 (2 s, 2 H), 6.92 (m, 0.5 H), 7.54 and 7.6 (2 s, 5 H), 7.68 (m, 0.5 H), 8.1 (m, 4 H); IR (film) 1775, 1740, 1720, 1610 cm^{-1}; MS (CI with isobutane) m/e 423 (M + 1), 422 (M^+), 367 (M − 56).

***N*-*α*-Phthaloyl-γ-*O*-benzyl Oxime of D-Glutamic Acid Semialdehyde, 4b.** A solution of 510 mg (1.2 mmol) of **27** and 3 mL of TFA in 10 mL of CH_2Cl_2 was stirred for 30 min at room temperature. Then, the solution was concentrated under reduced pressure. The residue was dissolved in a 10% $NaHCO_3$ solution, and the insoluble material was extracted with ethyl acetate. The aqueous solution was acidified with 1 N HCl, and the product

was extracted with ethyl acetate. Removal of the ethyl acetate under reduced pressure gave 400 mg (91%) of acid **4b** as an oil: $[\alpha]_D$ = +22.9° (*c* = 1, CH_2Cl_2); NMR (90 MHz, $CDCl_3$) δ 2.53 (m, 4 H), 5–5.25 (2 s + m, 3 H), 6.94 (m, 0.5 H), 7.56–7.84 (2 s + m, 5.5 H), 8.1 (m, 4 H), 9.54 (br s, 1 H); IR (Nujol) 3500–2500, 1770, 1720, 1695, 1610 cm^{-1}; MS (CI with isobutane) *m/e* 367 (M + 1), 366 (M).

α-*N*-Phthaloyl-δ-*N*-(benzyloxy)cyclo-D-ornithine (2c). The *N*-hydroxysuccinimide ester of **4b**, prepared from 183 mg (0.5 mmol) of **4b**, 58 mg (0.5 mmol) of *N*-hydroxysuccinimide, and 103 mg (0.5 mmol) of DCC, was dissolved in 5 mL of acetic acid and treated with 22 mg (0.5 mmol) of $NaBH_3CN$ for 16 h at room temperature. A 10% $NaHCO_3$ solution was added, and the product was extracted with ethyl acetate. The ethyl acetate layer was washed with water and brine, dried over anhydrous $MgSO_4$, and filtered. The ethyl acetate was removed under reduced pressure, and the residue was purified on a silica gel column with CH_2Cl_2–ethyl acetate (19:1) as the eluent to give 160 mg (91%) of **2c**: mp 89–91 °C; $[\alpha]_D$ = +18.0° (*c* = 0.5, CH_2Cl_2); NMR (90 MHz, $CDCl_3$) δ 2.07 (m, 4 H), 3.6 (m, 2 H), 4.98 (m, 1 H), 5.17 (s, 2 H), 7.66 (m, 5 H), 8.05 (m, 4 H); IR (Nujol) 1770, 1720, 1670 cm^{-1}. Anal. Calcd for $C_{20}H_{18}N_2O_4$: C, 68.57; H, 5.14; N, 8.00. Found: C, 68.62; H, 5.17; N, 8.10.

***tert*-Butyl Ester of α-*N*-Carbobenzoxy-δ-acetoxy-D-norvaline (34).** A mixture of 2.6 g (8 mmol) of **8a**, 3 mL (30 mmol) of acetic anhydride, and 2.43 mL (30 mmol) of pyridine in 50 mL of anhydrous CH_2Cl_2 was stirred at room temperature for 16 h and then concentrated under reduced pressure. The residue was dissolved in ethyl acetate, washed with water, 10% citric acid, water, 10% $NaHCO_3$, solution, water, and brine, dried over anhydrous $MgSO_4$, and filtered. Next, the ethyl acetate was removed under reduced pressure to give 2.9 g (100%) of **34** as an oil: $[\alpha]_D$ = −5.83° (*c* = 1.2, CH_2Cl_2); NMR (90 MHz, $CDCl_3$) δ 1.43 (s, 9 H), 1.7 (m, 4 H), 2.0 (s, 3 H), 4.1 (m, 3 H), 5.12 (s, 2 H), 5.5 (br s, 1 H), 7.36 (s, 5 H); IR (film) 3320, 1730, 1720 (with a shoulder at 1690) cm^{-1}; MS (CI with isobutane) *m/e* 310 (M − 56), 267.

α-*N*-Carbobenzoxy-δ-acetoxy-D-norvaline (35). A solution of 920 mg (2.5 mmol) of **34** and 5 mL of TFA in 10 mL of anhydrous CH_2Cl_2 was stirred for 30 min at room temperature and then concentrated under reduced pressure. The residue was evaporated twice with 10 mL of toluene to remove residual TFA and then dried under reduced pressure to provide 772 mg (100%) of **35** as an oil: $[\alpha]_D$ = −6.3° (*c* = 0.76, CH_2Cl_2); NMR (90 MHz, $CDCl_3$) δ 1.7 (m, 4 H), 2.0 (s, 2 H), 4.05 (m, 2 H), 4.36 (m, 1 H), 5.10 (s, 2 H), 5.50 (br d, 1 H, *J* = 8 Hz), 7.33 (s, 5 H); I r (Nujol) 3500–2500 (with a maximum at 3420), 1760, 1725, 1700 cm^{-1}; MS (CI with isobutane) *m/e* 310 (M + 1), 309 (M).

***N*-(Benzyloxy)amide of α-*N*-Carbobenzoxy-δ-acetoxy-D-norvaline (36).** To the *N*-hydroxysuccinimide ester, prepared quantitatively from 772 mg (2.5 mmol) of **35**, 288 mg (2.5 mmol) of *N*-hydroxysuccinimide and 515 mg (2.5 mmol) of DCC as described previously, in 30 mL of ethyl acetate was added a solution of 480 mg (3 mmol) of $BzlONH_2$·HCl and 420 mg (5 mmol) of $NaHCO_3$ in 20 mL of water. The reaction mixture was stirred at room temperature overnight. Then, the ethyl acetate layer was separated, washed with water, 1 N HCl, water, 10% $NaHCO_3$, water, and brine, dried over anhydrous $MgSO_4$, and filtered. The solvent was removed under reduced pressure to provide 920 mg (89%) of **36**: mp 105–107 °C (recrystallization from ethyl acetate–hexanes improved the mp (120–121 °C)); $[\alpha]_D$ = +14.6° (*c* = 0.52, CH_2Cl_2); NMR (90 MHz, $CDCl_3$) δ 1.66 (m, 4 H), 1.96 (s, 3 H), 4.03 (m, 3 H), 4.87 (s, 2 H), 5.03 (s, 2 H), 5.50 (br d, 1 H, *J* = 8 Hz), 7.31 and 7.33 (2 s, 10 H), 9.30 (br s, 1 H); IR (Nujol) 3280, 3230, 1743, 1680, 1650 cm^{-1}; MS (CI with isobutane) *m/e* 415 (M + 1), 372 (M − 43). Anal. Calcd for $C_{22}H_{26}N_2O_6$: C, 63.77; H, 6.28; N, 6.77. Found: C, 64.00; H, 6.36; N, 6.81.

***N*-(Benzyloxy)amide of α-*N*-Carbobenzoxy-δ-hydroxy-D-norvaline (6).** To a solution of 780 mg (1.8 mmol) of **36** in 10 mL of acetone and 7.5 mL of MeOH at 0 °C was added 3.6 mL (3.6 mmol) of 1 N NaOH. The mixture was stirred for 1 h at room temperature. The organic solvents were removed under reduced pressure. The unreacted material was extracted with ethyl acetate, and the aqueous layer was acidified with 2 N HCl. The product was extracted with ethyl acetate, washed with water and brine, dried over anhydrous $MgSO_4$, and filtered. Removal of the ethyl acetate under reduced pressure provided 670 mg (96%) of **6**: mp 85–86 °C crystallization from ethyl acetate–hexanes improved the mp to 95–7 °C); $[\alpha]_D$ = +9.33° (*c* = 0.45, CH_2Cl_2); NMR (90 MHz, $CDCl_3$) δ 1.63 (m, 4 H), 2.87 (br s, 1 H), 3.56 (m, 2 H), 4.16 (m, 1 H), 4.87 (s, 2 H), 5.03 (s, 2 H), 5.87 (br d, 1 H, *J* = 8 Hz), 7.33 (s, 10 H), 10.0 (br s, 1 H); IR (Nujol) 3380, 3180, 1695, 1660 cm^{-1}; MS (CI with isobutane) *m/e* 356 (M − 17). Anal. Calcd for $C_{20}H_{24}N_2O_5$: C, 64.52; H, 6.45; N, 7.53. Found: C, 64.42; H, 6.37; N, 7.70.

α-*N*-Carbobenzoxy-δ-*N*-(benzyloxy)-D-cycloornithine (2a). To a solution of 522 mg (1.4 mmol) of **6** and 524 mg (2 mmol) of Ph_3P in 100 mL of anhydrous THF was added 0.4 mL (2 mmol) of DIAD in 25 mL of THF at such a rate as to maintain the reaction at room temperature. After the addition, the mixture was stirred at room temperature under nitrogen overnight. The THF was removed under reduced pressure, and the residue was chromatographed on a silica gel column with CH_2Cl_2–ethyl acetate (25:1) to provide 400 mg (81%) of **2a**: mp 58–60 °C. $[\alpha]_D$ = −49.7° (*c* = 2, CH_2Cl_2). The spectral data was identical with that obtained from the alternate preparations of **2a** as previously described in this Experimental Section.

***N*-(Benzyloxy)amide of α-*N*-Carbobenzoxy-δ-bromo-D-norvaline (7).** A mixture of 372 mg (1 mmol) of **6**, 664 mg (2 mmol) of CBr_4, and 524 mg (2 mmol) of Ph_3P in 10 mL of THF was stirred at room temperature for 16 h. The THF was removed under reduced pressure, and the residue was purified on a silica gel column with CH_2Cl_2–ethyl acetate (9:1) as the eluent to provide 215 mg (50%) of **7**: mp 104–6 °C (crystallization from CH_2Cl_2–hexanes); $[\alpha]_D$ = +19.74° (*c* = 0.62, CH_2Cl_2); NMR (90 MHz, $CDCl_3$) δ 1.84 (m, 4 H), 3.4 (m, 2 H), 4.13 (m, 1 H), 4.95 (s, 2 H), 5.10 (s, 2 H), 5.76 (br d, 1 H, *J* = 8 Hz), 7.45 and 7.48 (2 s, 10 H), 9.82 (br s, 1 H); IR (Nujol) 3420, 3300, 1733, 1715 cm^{-1}; MS (CI with isobutane) *m/e* 437, 435 (M + 1), 355. Anal. Calcd for $C_{20}H_{23}N_2O_4Br$: C, 55.17; H, 5.29; N, 6.44. Found: C, 55.32; H, 5.44; N, 6.66.

***tert*-Butyl Ester of α-*N*-Carbobenzoxy-δ-bromonorvaline (37). General Procedure.** To a solution of 10 mmol of **8a** and 20 mmol of CBr_4 in 120 mL of THF was added, in one portion, 20 mmol of Ph_3P, and the reaction mixture was stirred overnight. The THF was removed under reduced pressure. The residue was passed through a silica gel column using hexanes–ethyl acetate (9:1) as the eluent to provide the desired product (**37**) in quantitative yield.

L-**37** (from **8a** obtained via pyroglutamate): $[\alpha]_D$ = +7.73° (*c* = 2.8, CH_2Cl_2); NMR (300 MHz, $CDCl_3$) δ 1.45 (s, 9 H), 1.83 (m, 2 H, *J* = 7 and 9 Hz), 1.95 (m, 2 H, *J* = 5 and 10 Hz), 3.4 (m, 2 H, *J* = 5 and 9 Hz), 4.29 (m, 1 H, *J* = 5 and 7 Hz), 5.10 (s, 2 H), 5.47 (d, 1 H, *J* = 8 Hz), 7.36 (s, 5 H); IR (film) 3340, 1735, 1720, 1700 cm^{-1}; MS (CI with isobutane) 388, 386 (M + 1), 332 (M − 45).

L-**37** (from **8a** via γ-ethyl ester): $[\alpha]_D$ = +8.30° (*c* = 3.8, CH_2Cl_2).

D-**37** (from **8a** obtained via pyroglutamate): $[\alpha]_D$ = −7.5° (*c* = 1.2, CH_2Cl_2); NMR (90 MHz, $CDCl_3$) δ 1.5 (s, 9 H), 1.84 (m, 2 H), 1.97 (m, 2 H), 3.41 (m, 2 H, *J* = 5 Hz), 4.28 (m, 1 H), 5.1 (s, 2 H), 5.41 (d, 1 H, *J* = 8 Hz), 7.4 (s, 5 H); MS (CI with isobutane) *m/e* 388, 386 (M + 1), 332, 330.

D-**37** (from **8a** via γ-methyl ester): $[\alpha]_D$ = −9.09° (*c* = 3.2, CH_2Cl_2); MS (CI with isobutane) *m/e* 386 (M + 1), 332 (M − 56).

***N*-(Benzyloxy)amide of α-*N*-Carbobenzoxy-δ-bromonorvaline (7). General Procedure.** A mixture of 10 mmol of **37** and 5 mL of TFA in 10 mL of CH_2Cl_2 was left at room temperature for 30 min and then was concentrated under reduced pressure. The residue was twice evaporated with 10 mL of toluene to completely remove the TFA. To the residue were added 40 mL of ethyl acetate, 10 mmol of *N*-hydroxysuccinimide, and 10 mmol of DCC in 10 mL of ethyl acetate at 0 °C. The reaction mixture was stirred at room temperature for 6 h. The precipitated dicyclohexylurea was filtered off and washed with 20 mL of ethyl acetate, and the filtrate was added to a solution of 12 mmol of *O*-benzylhydroxylamine and 10 mmol of $NaHCO_3$ in 30 mL of water. The resulting mixture was stirred at room temperature overnight. The ethyl acetate layer was separated, washed with water, 10% citric acid, water, and brine, dried over anhydrous $MgSO_4$, and filtered. The ethyl acetate was removed under reduced pressure, and the residue was recrystallized from

CH_2Cl_2–hexanes to provide pure **7**.

L-**7** (from **8a** obtained via pyroglutamate): 93% yield; mp 110–111 °C; $[\alpha]_D$ = −19.93° (*c* = 4, CH_2Cl_2); NMR (300 MHz, $CDCl_3$) δ 1.80 (m, 4 H), 3.35 (m, 2 H), 4.10 (m, 1 H, *J* = 6 Hz), 4.85 (s, 2 H), 4.97 (dd, 1 H, *J* = 12 Hz), 5.8 (d, 1 H, *J* = 8 Hz), 7.38 (m, 10 H), 9.8 (s, 1 H); IR (Nujol) 3320, 3190, 1675, 1660 cm^{-1}.

L-**7** (from **8a** obtained via γ-ethyl ester): 88% yield; mp 112–114 °C; $[\alpha]_D$ = −21.6° (*c* = 2, CH_2Cl_2). Anal. Calcd for $C_{20}H_{23}N_2O_4Br$: C, 55.17; H, 5.29; N, 6.44. Found: C, 55.30; H, 5.47; N, 6.51.

D-**7** (from **8a** obtained via pyroglutamate): 62% yield; $[\alpha]_D$ = +20.1° (*c* = 4.6, CH_2Cl_2); mp 109–111 °C. The spectral data were identical with that obtained for L-**7**.

D-**7** (from **8a** obtained via γ-methyl ester): 83% yield; mp 115–7 °C; $[\alpha]_D$ = +22.3° (*c* = 2.3, CH_2Cl_2); IR (Nujol) 3320, 3180, 1680, 1655 cm^{-1}; exact mass calcd for $C_{20}H_{23}N_2O_4Br$ 434.0841, found 434.0841.

α-*N*-Carbobenzoxy-δ-*N*-(benzyloxy)cycloornithine (2a). General Procedure. A solution of 10 mmol of **7** and 20 mmol of anhydrous K_2CO_3 in 300 mL of acetone was refluxed for 12 h at which time analysis by TLC revealed the absence of starting material. The acetone was removed under reduced pressure, and the residue was passed through a silica gel column with CH_2Cl_2–ethyl acetate (4:1) as the eluent to provide **2a**. The final product was obtained after recrystallization from ethyl acetate–hexanes.

D-**2a** (from **8a** obtained via pyroglutamate): 91% yield; mp 68–71 °C; $[\alpha]_D$ = −51.0° (*c* = 1.4, CH_2Cl_2).

D-**2a** (from **8a** obtained via γ-methyl ester): 98% yield; mp 75–76 °C; $[\alpha]_D$ = −51.7° (*c* = 1.8, CH_2Cl_2).

L-**2a** (from **8a** obtained via pyroglutamate): 82% yield; mp 71–73 °C; $[\alpha]_C$ = +52.0° (*c* = 1.45, CH_2Cl_2); MS (CI with isobutane) *m/e* 355 (M + 1), 247 (M − 108); NMR (300 MHz, $CDCl_3$) δ 1.57 (d, 1 H, *J* = 5 Hz), 1.85 (m, 2 H), 2.37 (m, 1 H), 3.32 (m, 1 H), 3.41 (sextet, 1 H, *J* = 6 Hz), 4.17 (quintet, 1 H, *J* = 6 Hz), 4.9 (dd, 2 H, *J* = 10.5 Hz), 5.16 (s, 2 H), 5.8 (br s, 1 H), 7.4 (m, 10 H).

L-**2a** (from **8a** obtained via γ-ethyl ester): 95% yield; mp 70–71 °C; $[\alpha]_D$ = +51.6° (*c* = 1.8, CH_2Cl_2). Anal. Calcd for $C_{20}H_{22}N_2O_4$: C, 67.78; H, 6.21; N, 7.91. Found: C, 67.59; H, 6.26; N, 7.93.

α-*N*-(Bis(benzoyloxy)succinyl)-δ-*N*-(benzyloxy)cycloornithine (38). The dibenzoyltartarimide (DBT) derivatives of *N*-(benzyloxy)cycloornithine **38** were made from **2a** as described in the literature.[38]

L-**38** (obtained via pyroglutamate): mp 94–97 °C; $[\alpha]_D$ = +93.0° (*c* = 0.3, CH_2Cl_2); NMR (300 MHz, $CDCl_3$) δ 1.85 (m, 1 H), 2.03 (m, 2 H), 2.32 (dq, 1 H, *J* = 3 and 12 Hz), 3.39 (dd, 1 H, *J* = 5 and 11 Hz), 3.55 (dt, 1 H, *J* = 4 and 11 Hz), 4.83 (dd, 1 H, *J* = 6 and 12 Hz), 5.0 (s, 2 H), 6.06 (s, 1 H), 7.4 (m, 11 H), 8.1 (d, 4 H, *J* = 7 Hz).

L-**38** (prepared via γ-ester route): mp 95–98 °C; $[\alpha]_D$ = +95.4° (*c* = 1.0, CH_2Cl_2); NMR spectrum (same as that reported above); IR (Nujol) 1795, 1730, 1710, 1670 cm^{-1}; MS (CI with isobutane) *m/e* 543 (M + 1), 314.

D-**38** (obtained via pyroglutamate): mp 154–157 °C; $[\alpha]_D$ = +116.3° (*c* = 0.8, CH_2Cl_2); NMR (300 MHz, $CDCl_3$) δ 2.0 (m, 3 H), 2.32 (dq, 1 H, *J* = 3 and 12 Hz), 3.42 (dd, 1 H, *J* = 5 and 12 Hz), 3.56 (dt, 1 H, *J* = 4 and 11 Hz), 4.86 (dd, 1 H, *J* = 6 and 12 Hz), 5.0 (s, 2 H), 6.01 (s, 1.7 H), 6.07 (s, 0.3 H), 7.4 (m, 11 H), 8.1 (d, 4 H, *J* = 7 Hz).

D-**38** (prepared via γ-ester): mp 170–172 °C; $[\alpha]_D$ = +119.1° (*c* = 0.7, CH_2Cl_2); NMR as above with the exception of only one 2 H singlet at 6.01 ppm; IR (Nujol) 1800, 1733, 1715, 1680 cm^{-1}; MS (CI with isobutane) *m/e* 543 (M + 1), 314.

Acknowledgment. We are pleased to acknowledge the NIH for support of this work.

Registry No. **2**, 125049-95-8; (*R*)-**2a**, 125049-95-8; (*S*)-**2a**, 125050-20-6; **2b**, 125049-92-5; **2c**, 125050-11-5; (*Z*)-**4a**, 125050-02-4; (*E*)-**4a**, 125050-03-5; (*Z*)-**4b**, 125050-07-9; (*E*)-**4b**, 125050-08-0; (*Z*)-**4b** (*N*-hydroxysuccinimide ester), 125050-09-1; (*E*)-**4b** (*N*-hydroxysuccinimide ester), 125050-10-4; **6**, 125050-15-9; D-**7**, 125050-16-0; L-**7**, 125050-19-3; D-**8a**, 125076-26-8; L-**8a**, 124620-51-5; D-**8b**, 125049-87-8; L-**8b**, 125137-57-7; **8c**, 125050-04-6; (*R*)-**14**, 125049-81-2; (*S*)-**14**, 89969-27-7; **15**, 125049-82-3; **16**, 125049-83-4; L-**17a**, 81470-51-1; D-**17a**, 125134-29-4; D-**17b**, 125049-85-6; L-**17b**, 125049-86-7; L-**19a**, 1119-33-1; D-**19a**, 45025-26-1; L-**20a**, 125076-24-6; D-**20a**, 125076-25-7; L-**20b**, 57732-63-5; D-**20b**, 23577-92-6; **22**, 125049-96-9; **23**, 125049-97-0; **24**, 125049-98-1; **25**, 125049-99-2; (*Z*)-**26**, 125050-00-2; (*E*)-**26**, 125050-01-3; (*Z*)-**27**, 125050-05-7; (*E*)-**27**, 125050-06-8; **28**, 125049-88-9; **29**, 125049-90-3; **30**, 125049-91-4; **31**, 125049-93-6; **32**, 125049-94-7; **34**, 125050-12-6; **35**, 125050-13-7; **35** (*N*-hydroxysuccinimide ester), 125076-27-9; **36**, 125050-14-8; L-**37**, 125050-17-1; D-**37**, 125050-18-2; (*S*)-**38**, 125076-07-5; (*R*)-**38**, 125050-21-7; L-CbzGluOH, 1155-62-0; D-GbzGluOH, 63648-73-7; $H_2C{=}CHCH_2OCOGluOH$, 125049-84-5; $CbzNHOCH_2Ph$, 15255-86-4; $H_2C{=}CHCH_2OCONHOCH_2Ph$, 125049-89-0.

2-Amino-5-imino-4,5-dihydrothiazoles: Synthesis by Reaction of Isocyanides with 2-Amino-3-aza-1-thiabutadienes and Base-Induced Rearrangement into Imidazolines or Diazolidines

Georges Morel, Evelyne Marchand, and Andrê Foucaud*

Groupe de Chimie structurale, associê au C.N.R.S., Universitê de Rennes I, 35042 Rennes, France

Loïc Toupet

Groupe de Physique cristalline, associê au C.N.R.S., Universitê de Rennes I, 35042 Rennes, France

Received June 20, 1989

The reaction of isocyanides R^3NC with 2-amino-3-aza-1-thiabutadienes **3** gives the 2-amino-5-imino-4,5-dihydrothiazoles **4**. The rearrangement of **4** (R^2 = H) was induced by 1,5-diazabicyclo[4.3.0]non-5-ene and leads to 4*H*-imidazoline-5-thiones **5** or 4-thioxo-1,3-diazolidines **6** according to the nature of the substituent R^1. The tautomeric form **5** is the only one obtained when R^1 is an alkyl group. Diazolidine **6** appears in the tautomeric mixture or is the single form observed when R^1 is the benzoyl or an aryl group. Structural assignments of **5** and **6** and the tautomeric equilibrium investigation are based on ^{13}C NMR spectral data. The same structures **5** and **6** (R^2 = H) are observed in the solid state by single-crystal X-ray analysis.

Isocyanides are stable nucleophilic carbenes that provide [1 + 4] cycloaddition reactions with conjugated electron-deficient heterodienes. It has been shown that these reactions are useful for the synthesis of functionalized

0022-3263/90/1955-1721$02.50/0