20% yield. In any case, it is possible to differentiate the olefins which will facilitate further synthetic manipulations.

In summary, fragmentation studies have been carried out on various derivatives of 9-bromocamphor using aromatic radical anions as the electron transfer agent. The studies indicate that an endo orientation of a mesylate leaving group is crucial for fragmentation to occur. This has led to the development of C4-C7 fragmentation of readily available 3,9-dibromocamphor derivatives providing access to a class of six-membered ring chiral pool elements possessing a useful stereogenic quaternary carbon center.

Acknowledgment. U.N.S. wishes to thank Wayne State University for an Undergraduate Merit Scholarship and the Johnson and Johnson Corporation for a travel grant.

Supplementary Material Available: ^1H NMR and ^{13}C spectra of compounds 9-18 (22 pages). Ordering information is given on any current masthead page.

Articles

Synthesis of Proline-Valine Pseudodipeptide Enol Lactones, Serine Protease Inhibitors

Peter E. Reed and John A. Katzenellenbogen*

Department of Chemistry, University of Illinois, Urbana, Illinois 61801

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Pseudodipeptides of proline-valine that incorporate protio or halo enol lactone moieties have been synthesized from common acetylenic acid precursors; in each case, two diasteromers were prepared in enantiomerically pure form. The preparation began with isomeric propargylic alcohols derived from L-prolinal, which are further elaborated into the methyleneoxy valine pseudodipeptide analogues via an oxalactam intermediate. Stereochemical assignments were made by comparisons of nuclear Overhauser enhancement factors. The pseudodipeptide acetylenic acids could by cyclized to the protio enol lactones by mercuric salts and could be elaborated to tetrapeptide analogues either before or after cyclization. The relative stability of the two diastereomeric enol lactone systems toward intramolecular acyl transfer could be rationalized by molecular mechanics energy calculations on ground-state and tetrahedral intermediates believed to be involved in the reaction. While the halo enol lactones derived from the pseudotetrapeptides proved to be very unstable, they could be prepared from the *n*-butyl carbamate derivatives of the dipeptide. An evaluation of these protio and halo enol lactone systems as inhibitors of serine proteases will be discussed elsewhere.

The involvement of serine proteases in a variety of biological processes has stimulated the development of mechanism-based inhibitors for this class of enzymes.[1] Particular attention has been focused on the development of inhibitors of the serine protease human leukocyte elastase (HLE),[2a-c] because of its reputed involvement in serious degenerative diseases, such as emphysema.[3]

We have prepared various substituted 5- and 6-membered protio and halo enol lactones as serine protease inhibitors.[4a-e] We have found that some of the halo enol lactones are very potent inactivators ("suicide substrates") of α-chymotrypsin;[5a-c] these lactones react with the enzyme to give an acyl enzyme species possessing a reactive halomethyl ketone moiety which inactivates the enzyme by alkylating an active site nucleophile. Certain of the protio enol lactones, as well, act as alternate substrate inhibitors of α-chymotrypsin by forming extremely stable acyl enzyme intermediates.[4e,6]

In order to increase the specificity of these lactones toward their targeted serine proteases, we have prepared amino acid analogues which incorporate an enol lactone.[4c,d] We now report the synthesis of the enantiomerically pure enol lactone pseudodipeptides **1a,b** and **2a,b**. These compounds were prepared as potential inhibitors of human leukocyte elastase and were intended to mimic the dipeptide Pro-Val that terminates many oligopeptide substrates of HLE such as methoxysuccinyl-L-Ala-L-Ala-L-Pro-L-Val *p*-nitroanilide.[7]

(1) Silverman, R. B. *Mechanism-Based Enzyme Inactivation: Chemistry and Enzymology*; CRC Press: Boca Raton, FL, 1988; Vols. 1 and 2.

(2) (a) Bode, W.; Meyer, E.; Powers, J. C. *Biochemistry* **1989**, *28*(5), 1951-1963. (b) Mehdi, S.; Agelastro, M. R.; Burkhart, J. P.; Koehl, J. R.; Peet, N. P.; Bey, P. *Biochem. Biophys. Res. Commun.* **1990**, *166*(2), 595-600. (c) Powers, J. C.; Oleksyszyn, J.; Narasimhan, S. L.; Kam, C.-M.; Radhakrishnan, R.; Meyer, E. F. *Biochemistry* **1990**, *29*, 3108-3118.

(3) Groutas, W. C. *Med. Res. Rev.* **1987**, *7*(2), 227-241.

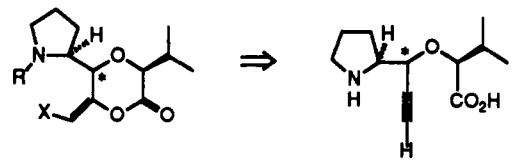
(4) (a) Sofia, M. J.; Katzenellenbogen, J. A. *J. Med. Chem.* **1986**, *29*, 230-238. (b) Krafft, G. A.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1981**, *103*, 5459-5466. (c) Sofia, M. J.; Chakravarty, P. K.; Katzenellenbogen, J. A. *J. Org. Chem.* **1983**, *48*, 3318-3325. (d) Sofia, M. J.; Katzenellenbogen, J. A. *J. Org. Chem.* **1985**, *50*, 2331-2336. (e) Baek, D.-J.; Daniels, S. B.; Reed, P. E.; Katzenellenbogen, J. A. *J. Org. Chem.* **1989**, *54*, 3963-3972.

(5) (a) Chakravarty, P. K.; Krafft, G. A.; Katzenellenbogen, J. A. *J. Biol. Chem.* **1982**, *257*, 610-612 (b) Daniels, S. B.; Katzenellenbogen, J. A. *Biochemistry* **1986**, *25*, 1436-1444. (c) Daniels, S. B.; Cooney, E.; Sofia, M. J.; Chakravarty, P. K.; Katzenellenbogen, J. A. *J. Biol. Chem.* **1983**, *258*, 15046-15053.

(6) Baek, D.-J.; Reed, P. E.; Daniels, S. B.; Katzenellenbogen, J. A. *Biochemistry* **1990**, *29*, 4305-4311.

(7) Nakajima, K.; Powers, J. C.; Ashe, B. M.; Zimmerman, M. *J. Biol. Chem.* **1979**, *254*, 4027-4032.

0022-3263/91/1956-2624$02.50/0



	X	B	:		:
1a	H	MeOSuc-Ala-Ala	S	3a	R
1b	H	MeoSuc-Ala-Ala	R	3b	S
1c	H	nBuOCO	S		
2a	Br	nBuOCO	S		
2b	Br	nBuOCO	R		

Results and Discussion

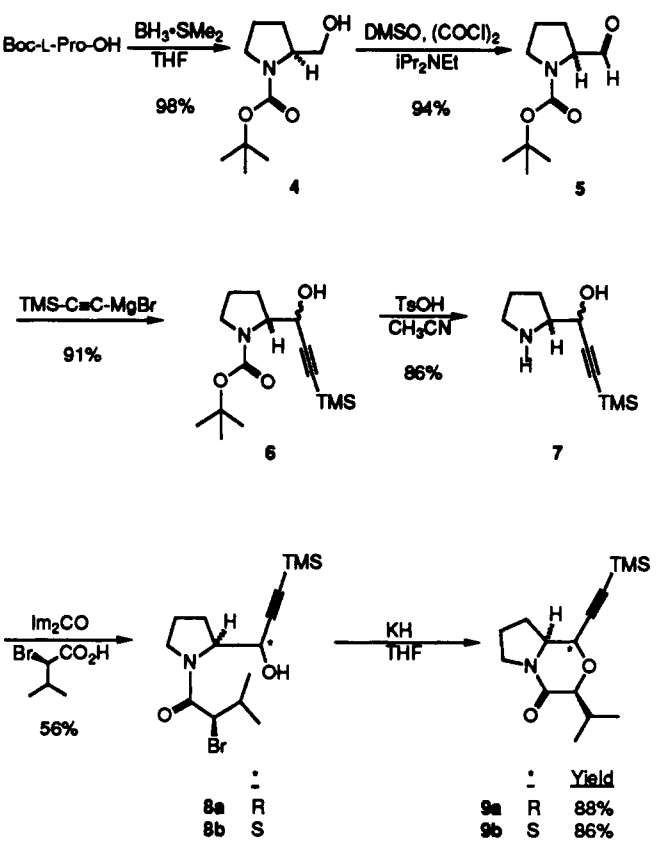
Preparation of the Acetylenic Amino Acid 3. The key intermediate in the synthesis of the lactone targets is the acetylenic amino acid **3**, which was prepared as described in Scheme I. Reduction of Boc-L-proline to Boc-L-prolinol (**4**) with borane methyl sulfide complex was followed by oxidation under Swern conditions[8] to give Boc-L-prolinal (**5**). Due to the reported configurational lability of N-protected α-amino aldehydes,[9a,b] we took precautions to minimize epimerization of the aldehyde **5**, including the use of hindered diisopropylethylamine instead of triethylamine as base in the Swern oxidation, the avoidance of silica gel chromatography during isolation, and the storage of the product below 0 °C. The stereochemical purity of **5** was ascertained by $NaBH_4$ reduction of the aldehyde **5** back to the alcohol **4**, followed by quantitative conversion of **4** to its (*R*)-Mosher ester derivative[10] **10** (Scheme II). The NMR of the Mosher ester was identical with the Mosher ester derived from Boc-L-proline and showed single peaks for both the methoxy (^1H NMR) and trifluoromethyl (^{19}F NMR) groups. By this approach we can estimate an enantiomeric excess of >95% for the aldehyde **5**.

Ethynylation of Boc-L-prolinal with the Grignard reagent prepared from trimethylsilyl acetylene gave the Boc-protected amino alcohol diastereomers **6** in a 2:1 ratio favoring the anti Felkin–Ahn product. Initial attempts to effect this transformation with the corresponding lithium acetylide led to only partial (20%) conversion of the aldehyde to products, presumably because of competing enolization that led to the regeneration of aldehyde upon workup. The configurational integrity of the α-carbon of **5** during the ethynylation reaction was checked by quantitative conversion of the crude diastereomers comprising **6** to their Mosher ester derivatives[10] **11** (Scheme II). The ^1H NMR of the Mosher ester diastereomers showed only the two expected methoxy singlets (present in the same ratio as the diastereomeric precursors **6**, as was determined by GC). By this method, we can estimate that there was less than 10% epimerization during the ethynylation of the aldehyde **5** with the Grignard reagent.

An attempt was made to convert the alcohol **6** to the acetylenic amino acid **3** by carbenoid insertion into the OH bond of the alcohol (Scheme II). Intermolecular insertions of this type have been carried out on propargylic alcohols using alkyl diazoacetates as carbene precursors and rhodium tetraacetate as Lewis acid. This method gives a high ratio of OH insertion to alkyne cycloaddition.[11a,b] Attempts to carry out OH insertion on the propargylic alcohol **6** using the carbene precursor ethyl α-diazoisovalerate[12] and three different Lewis acid catalysts (rhodium tetraacetate, copper(I) triflate, and boron trifluoride etherate) failed, giving only starting material, which slowly decomposed in the prescence of the Lewis acid. A model reaction run under the same conditions but using the less hindered Boc-prolinol **4** and ethyl diazoacetate gave moderate yields of the desired OH insertion product **12** (Scheme II).

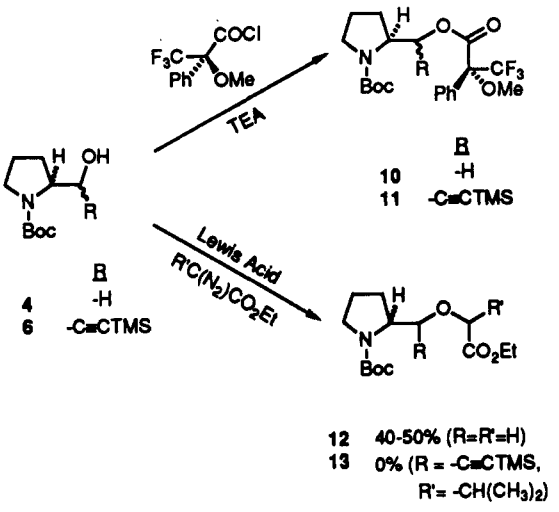
The amino acid **3** was successfully prepared by amide bond hydrolysis of the bicyclic oxa lactams **9a,b**, which in

Scheme I



	:	Yield		:	Yield
8a	R		9a	R	88%
8b	S		9b	S	86%

Scheme II



	R
10	-H
11	-C≡CTMS

	R
4	-H
6	-C≡CTMS

12 40-50% (R=R'=H)
13 0% (R = -C≡CTMS, R'= -CH(CH$_3$)$_2$)

(8) Mancuso, A. J.; Huang, S.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480–2482.
(9) (a) Lubell, W. D.; Rappoport, H. *J. Am. Chem. Soc.* **1987**, *109*, 136–139. (b) Rittle, K. E.; Homnick, C. F.; Poticello, G. S. Evans, B. E. *J. Org. Chem.* **1982**, *47*, 3016–3018.
(10) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.
(11) (a) Noels, A. F.; Demonceau, A.; Petiniot, N.; Hubert, A. J.; Teyssié, Ph. *Tetrahedron* **1982**, *38*(17), 2733–2739. (b) Petiniot, N.; Anciaux, A. J. Noels, A. F.; Hubert, A. J.; Teyssié, Ph. *Tetrahedron Lett.* **1978**, 1239–1242.
(12) Takamura, N.; Mizoguchi, T.; Koga, K.; Yamada, S. *Tetrahedron* **1975**, *31*, 227–230.

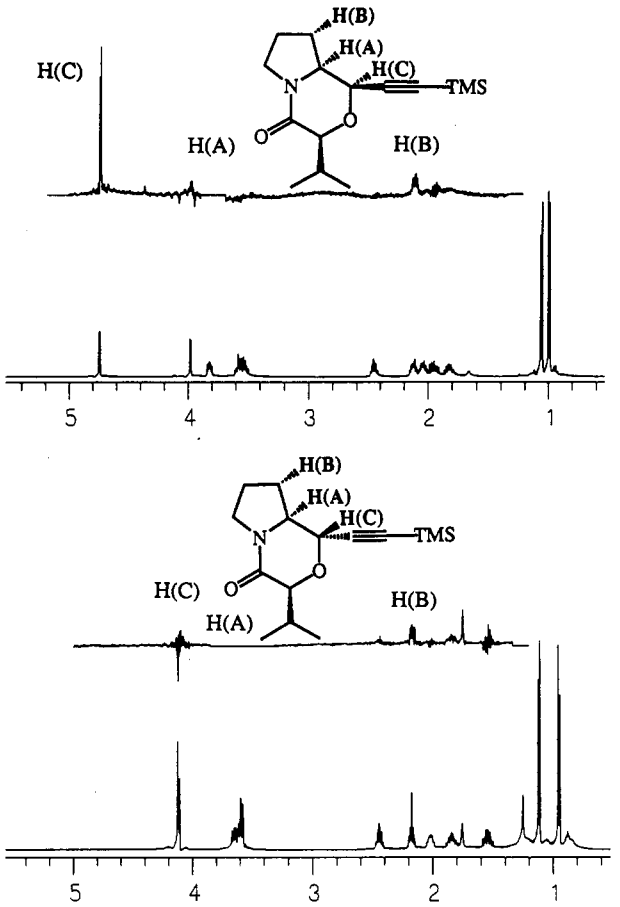
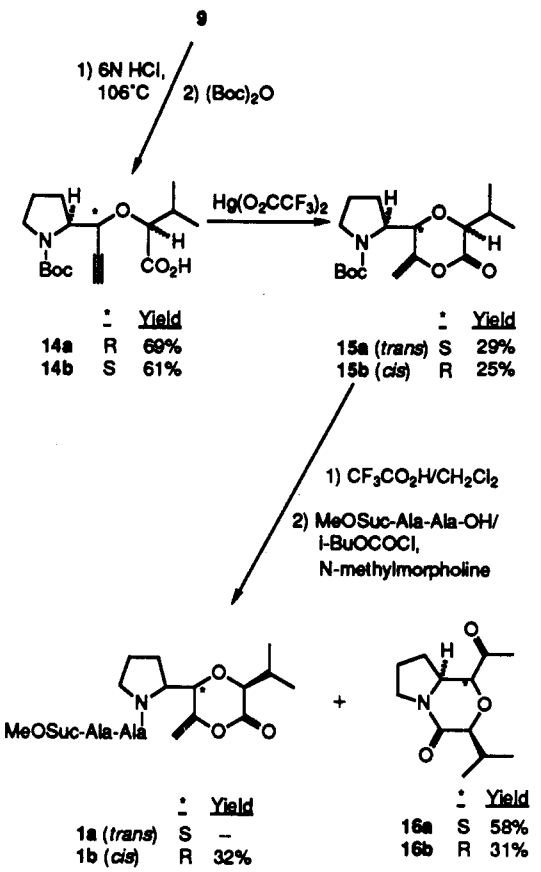


Figure 1. Assignment of configuration of the stereogenic center bearing the ethynyl group by an NOE study. Shown are the ^1H NMR spectra of both lactam epimers **9a** (top) and **9b** (bottom), along with an inset spectrum produced after irradiation of H(A). A significant NOE enhancement of H(C) is seen only for **9a**, so this epimer was assigned to have an *R* configuration at the carbon bearing H(C).

turn were prepared by an intramolecular cyclization of the hydroxy bromoamides **8a,b** (Scheme I). This strategy has been used previously to prepare methyleneoxy peptide isosteres by both Nicolaides[13] and Tenbrink.[14] Deprotection of the Boc-protected alcohol **6** was effected with toluenesulfonic acid in acetonitrile.[15] Alternate deprotection methods using trifluoroacetic acid or trimethylsilyl iodide led to decomposition of the starting material. The amino alcohol **7** was then coupled to (*R*)-2-bromoisovaleric acid[16] using carbonyldiimidazole to give bromoamide epimers **8a,b** that were conveniently separated at this point by flash chromatography ($\Delta R_f = 0.10$). The yield of this reaction was limited in part by the formation of O,N-diacylated byproducts, but the overall yield was not improved by use of the hydroxyl-protected trimethylsilyl ether of **7**.

Intramolecular cyclization of the separated bromo amide epimers **8a,b** was achieved via the potassium alkoxide, generated with KH, and furnished the oxa lactams **9a,b**. Configurational assignment of the carbon bearing the ethynyl group was made at this point based on an NOE

Scheme III



experiment (Figure 1). Irradiation of the methine proton on the pyrrolidine ring (H_A) resulted in an NOE enhancement of the proton on the adjacent methylene carbon (H_B) that was comparable in size for both isomers. In contrast, the proton on the adjacent methine carbon (H_C) showed a significant NOE enhancement for only one of the isomers. Having established a syn relationship between the adjacent methines H_A and H_C for this isomer, the carbon bearing the ethynyl group was designated as having an *R* configuration based on the known L-proline-derived *S* configuration of the adjacent stereogenic center.

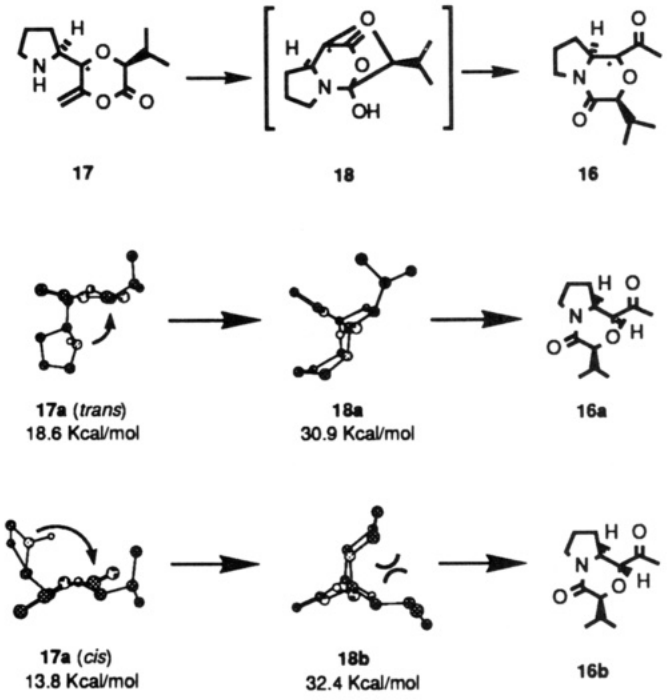
The lactams **9a,b** furnish the acetylenic amino acids **3a,b** upon hydrolysis in 6 N HCl at 106 °C for 28 h. While these amino acids can be isolated by silica gel chromatography using an aqueous eluent, their isolation is more efficient after conversion of the crude amino acids to N-protected or C-protected derivatives.

Preparation of the Protio Enol Lactones. The lactams **9a,b** were converted to the N-protected enol lactones **15a,b** (Scheme III), which we hoped would allow for straightforward incorporation of the lactone into the C-terminus of a peptide. Amide bond hydrolysis in 6 N HCl followed by N-protection with Boc anhydride gave the Boc-protected amino acids **14a,b**. Cyclization to the lactones **15a,b** proceeded with catalytic mercuric trifluoroacetate. Low yields in this reaction were consistently encountered in spite of the fact that molecular mechanics calculations indicated that the acetylenic acids **14a,b** could adopt low-energy conformations favorable for cyclization.

The lactones **15a,b** displayed, after deprotection, an unfortunate propensity to decompose by a pathway involving intramolecular attack on the lactone carbonyl by the pyrrolidine nitrogen to give the acetyl oxalactams **16a,b**. For example, when the trans isomer of the enol lactone **15a** was deprotected with trifluoroacetic acid, and the resulting amino lactone trifluoroacetate salts were

(13) Nicolaides, E. D.; Tinney, F. J.; Kaltenbronn, J. S.; Repine, J. T.; DeJohn, D. A.; Lunney, E. A.; Roark, W. H.; Marriott, J. G.; Davis, R. E.; Voigtman, R. E. *J. Med. Chem.* **1986**, *29*, 959–971.
(14) TenBrink, R. E. *J. Org. Chem.* **1987**, *52*, 418–422.
(15) Chauvette, R. R.; Pinnington, P. A.; Ryan, C. W.; Cooper, R. D. G.; José, F. L.; Wright, I. G.; Van Heyningen, E. M.; Huffman, G. W. *J. Org. Chem.* **1971**, *36*(9), 1259–1267.
(16) Chang, S.; Gil-AV, E.; Charles, R. *J. Chromatogr.* **1984**, *289*, 53–61.

Scheme IV

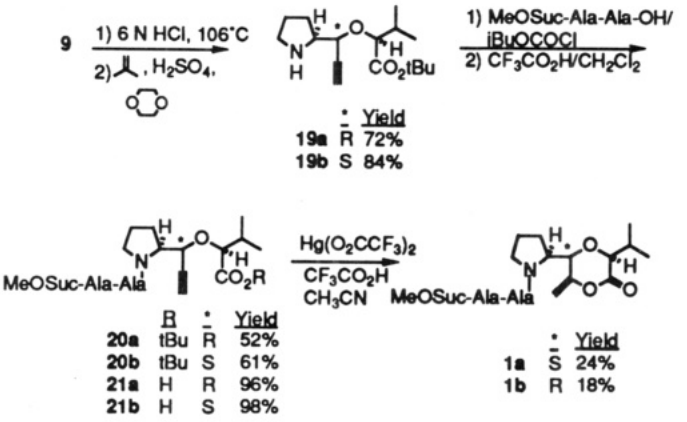


neutralized and treated with the mixed anhydride prepared from methoxysuccinyl-L-alanyl-L-alanine[17] and isobutyl chloroformate, only the acetyl oxalactam **16a** was isolated. From the cis isomer of the enol lactone **15b** a 1:2 lactone/lactam mixture was obtained from which the desired pseudotetrapeptide protio enol lactone **1b** was isolated in 32% yield. Surprisingly, the lactam byproduct **16a,b** was noted upon TLC analysis of aliquots from the deprotection reaction mixture, in spite of the fact that the Boc protecting group was removed under acidic conditions sufficient to render the piperidine nitrogen relatively nonnucleophilic. Proton NMR analysis of the crude deprotected lactones showed a 5:1 ratio of the desired lactone to the undesired lactam byproduct for the cis isomer, but only a 3:5 ratio of lactone to lactam for the less stable trans isomer.

The relative instability of the deprotected trans lactone isomer compared to the cis lactone isomer prompted us to examine the decomposition reaction more closely (Scheme IV). Molecular mechanics calculations using the MM2 force field were used to obtain the low energy conformations of the trans and cis amino lactones **17a** and **17b**, along with the protonated [2.2.2] tricyclic compounds **18a** and **18b** which served as crude models for the transition state structures for lactone decomposition. The trans amino lactone **17a** was found to adopt a conformation resembling a half-chair which places the pyrrolidine ring in a pseudoaxial orientation, presumably to avoid A-strain with the exocyclic methylene. The cis amino lactone adopts a twist boatlike conformation that is 4.8 kcal/mol more stable than the trans isomer. The relative stability of the tricyclic compounds **18a,b** used to model the transition structure is reversed: The cis isomer, suffering from steric interactions resulting from the close proximity of the isopropyl group to the pyrrolidine ring, is 1.5 kcal/mol less stable than the trans isomer. Crude estimates of the activation energy for this reaction can be made from the differences in energy between the transition-state model **18** and the ground-state structure **17**. The results show

(17) Digenis, G. A.; Agha, B. J.; Tsuji, K.; Kato, M.; Shinogi, M. *J. Med. Chem.* **1986**, *29*, 1468–1476.

Scheme V



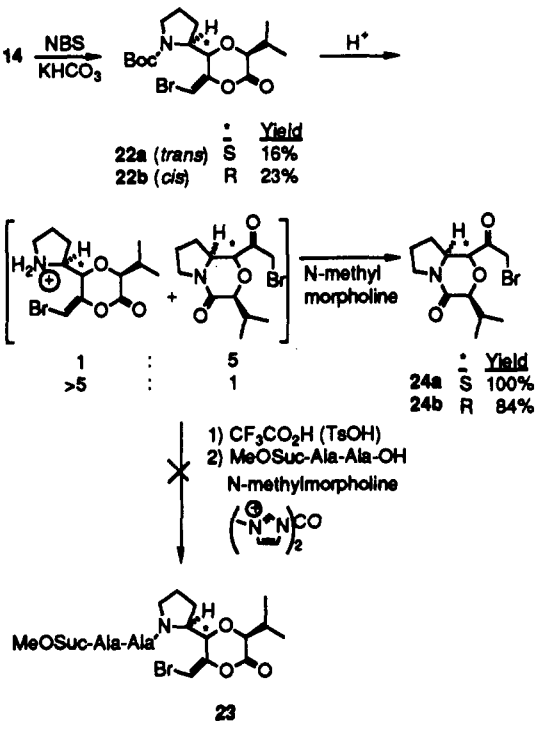
that the activation energy for decomposition of the trans isomer is about 6 kcal/mol lower than the activation energy for the cis isomer, and therefore the trans isomer would be expected to decompose more readily. These results are corroborated by the experimental data and suggest that this decomposition pathway could be restricted if the pyrrolidine ring were geometrically restrained from approaching the lactone carbonyl. One way of accomplishing this would be to replace the sp^3-hybridized methyleneoxy isostere with an sp^2-hybridized trans alkene isostere.

The difficulties encountered in preparing the peptide protio enol lactone **1a** from the Boc-protected lactone **15a** could be circumvented by coupling the amino acid **3** to the N-protected dipeptide methoxysuccinyl-L-alanyl-L-alanine prior to cyclization to the lactone (Scheme V). The unprotected amino acids could only be coupled to the pseudodipeptide in low yields, so the amino acids were coupled in their C-protected form. Acid labile *tert*-butyl esters were used for C-protection, since they could be removed with preservation of the terminal acetylene and the stereogenic center bearing the isopropyl substituent. The *tert*-butyl esters **19a,b** were prepared from the oxa lactams **9a,b** by amide bond hydrolysis followed by treatment with isobutylene in the presence of sulfuric acid. Coupling to the N-protected dipeptide was effected by the mixed anhydride method to give the esters **20a,b**, which were deprotected with trifluoroacetic acid to furnish the pseudotetrapeptide acetylenic acids **21a,b**.

Previously, mercuric trifluoroacetate in only catalytic quantity was used to effect transformation of substituted hexynoic acids to protio enol lactones.[4a,b,d,e] In the case of the peptide acetylenic acid **21a,b**, however, stoichiometric quantities of mercuric trifluoroacetate were required. The initial product appeared as a high R_f spot on TLC that stained negatively with I_2 and positively with H_2S. These data are consistent with the presence of a vinyl organomercuric trifluoroacetate intermediate. This intermediate normally becomes protonated by displaced trifluoroacetic acid to form the protio enol lactone product and regenerate mercuric trifluoroacetate.[4b] Because of the stability of the peptide intermediate derived from **21**, however, it was necessary to add additional trifluoroacetic acid in order to effect protonation and produce the desired lactones **1a,b**.

Preparation of the Bromo Enol Lactones. The Boc-protected bromo enol lactones **22a,b** could be formed from the acetylenic acid precursors **14a,b** using *N*-bromosuccinimide (NBS) as an electrophilic halogen source and $KHCO_3$ as a base (Scheme VI). These bromo enol lactones were even more susceptible to decomposition after deprotection than the corresponding protio enol lactones **15a,b**. This might be expected since a bromo enol lactone

Scheme VI

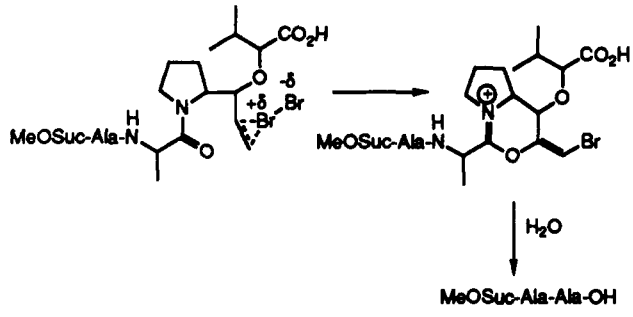


possesses a more electrophilic carbonyl group than a protio enol lactone. The trans isomer **22a** was once again the less stable, giving after deprotection a 1:5 ratio of desired amino lactone trifluoroacetate salt to undesired bromoacetyl lactam byproduct **24b**. The deprotected cis amino lactone isomer was stable as the *p*-toluenesulfonic acid salt, but rapidly decomposed upon neutralization. Thus, even with use of the coupling reagent, 1,1′-carbonylbis(3-methylimidazolium) triflate (CBMIT), a methylated form of carbonyldiimidazole reported to be very effective in causing acylation of hindered amines,[18] only the lactam **24** was isolated from attempts to prepare the pseudotetrapeptide bromo enol lactone **23**.

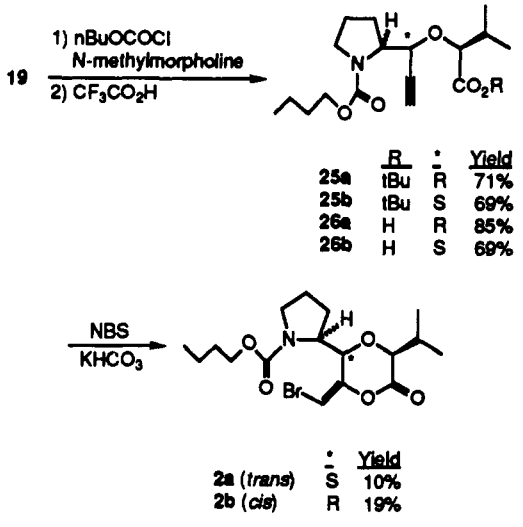
The alternate route to the pseudotetrrapeptide bromo enol lactones, via halolactonization of the peptide acetylenic acids, **21a,b**, was also unsuccessful because the dipeptide fragment hindered the halolactonization reaction. Trace amounts of the desired bromoenol lactone product, identified by ^{1}H NMR and FAB MS, could be obtained by reacting **21** with KI–I_2 in CH_2Cl_2/pH 6.5 phosphate buffer,[19] but other conventional methods failed completely. These included NBS/$KHCO_3$-nBu_4NOH in CH_2Cl_2/H_2O,[4b] NBS, NIS, or I_2 with $KHCO_3$ in CH_2Cl_2,[5c] NBS/$KHCO_3$ in CH_3CN or THF, or $Br_2/KHCO_3$ in CH_3CN. The peptide acetylenic acid decomposed when the reaction was heated or when an excess of halogen source was used; (methoxysuccinyl)alanylalanine was a major byproduct resulting from cleavage of the amide bond to the pyrrolidine nitrogen. The susceptibility of this bond to cleavage may be due to its proximity to the terminal acetylene, where it could attack the complex formed between the acetylene and the halogen (Scheme VII). Attempts to prepare the peptide bromo enol lactone from the *tert*-butyl ester **20** were also unsuccessful.

Since vinyl organomercury compounds are known to undergo halogenation to yield vinyl halides,[20] we attempted

Scheme VII



Scheme VIII



to halogenate the vinyl organomercury compound formed from the peptide acetylenic acid **22** and mercuric trifluoroacetate under conditions sufficiently mild to preserve the lactone ring. Treatment of this intermediate, prepared from **21** and 1 equiv of mercuric trifluoracetate, with 1–2 equiv of I_2 or Br_2 at various temperatures gave a complex mixture of products that contained the desired lactones in only trace amounts. When the more electrophilic Br_2 was used, only the bromoacetyl lactam **24**, arising from halolactonization and cleavage of the pyrrolidine nitrogen amide, could be isolated from the reaction mixture.

Preparation of *n*-Butyloxycarbonyl Lactones. Because the pseudotetrapeptide bromo enol lactone **23** proved difficult to prepare from either the Boc-protected lactone **23** or the peptide acetylenic acid **21**, we decided to replace the dipeptide fragment of the acetylenic acid **21** with a nonpeptide fragment that might allow for a more facile halolactonization and yield a lactone that would still have the potential to show good binding and selectivity toward the target enzyme human leukocyte elastase. An *n*-butyl carbamate was chosen to substitute for the dipeptide because it would replace the pyrrolidine amide group that is labile in the halolactonization reaction, with the less nucleophilic carbamate. Also, the *n*-butyl group has the potential to bind to the hydrophobic cleft of the enzyme where the dipeptide would normally reside. The synthesis of the *n*-butyl carbmate bromo enol lactones **2a,b** is shown in Scheme VIII. Acylation of the *tert*-butyl amino ester **19** with *n*-butyl chloroformate followed by deprotection in trifluoroacetic acid/methylene chloride gave the acetylenic acid **26**, which underwent halolactonization with NBS to give the bromo enol lactones

(18) Saha, A. K.; Schultz, P.; Rappoport, H. *J. Am. Chem. Soc.* **1989**, *111*, 4856–4859.

(19) Doi, J. T.; Luehr, G. W.; del Carmen, D.; Lippsmeyer, B. C. *J. Org. Chem.* **1989**, *54*, 2764–2767.

(20) Larock, R. C. *Organomercury Compounds in Organic Synthesis*; Springer-Verlag: Berlin, 1985; pp 155–175 and 423-431.

2a,b in low yields. The trans protio lactone analogue **1c** was prepared by lactonization of **26a** with mercuric trifluoroacetate in the presence of trifluoroacetic acid.

Conclusion

The Pro-Val pseudodipeptide acetylenic amino acids **3a,b** have been prepared in enantiomerically pure form from Boc-L-proline. Both epimers underwent protection and segment condensation with methoxysuccinyl-L-alanyl-L-alanine followed by lactonization to give the pseudotetrapeptide protio enol lactones **1a,b**, potential alternate substrate inhibitors of human leukocyte elastase. The corresponding bromo enol lactone analogs **23a,b** failed to form by lactonization of the peptide acetylenic acid precursors or by condensation of the preformed lactones with methoxysuccinyl-L-alanyl-L-alanine. Replacement of the N-protected dipeptide with an *n*-butyl carbamate, however, allowed for the preparation of the bromoenol lactones **2a,b**, potential inactivators of human leukocyte elastase. As is reported elsewhere, the protio enol and bromo enol lactones prepared in this study were tested for inhibitory activity against human leukocyte elastase, and the bromo enol lactone **2a** was found to be a very potent inactivator.[21]

Experimental Section

General. Reaction progress was monitored by analytical thin-layer chromatography, using a Hewlett-Packard Ultra 1 fused silica capillary column. Visualization of TLC was done by UV light, iodine vapor, phosphomolybdic acid stain, or a vanillin spray reagent containing 0.5% $H_2SO_{4(conc)}$. Flash chromatography[22] was performed using 15 cm of Woelm 32–63 μm silica gel packing. Column diameter and eluent are indicated parenthetically. All reactions using nonaqueous reagents were run under a dry nitrogen atmosphere with magnetic stirring. Product isolation involved extraction of the quenched reaction mixture and washing and drying and concentration of the extract; the solvent and other agents used are indicated in parenthesis.

Solvents were purified by distillation from the indicated drying agent: dichloromethane, CH_2Cl_2 (P_2O_5), dimethyl sulfoxide, DMSO (CaH_2), chloroform, $CHCl_3$ (P_2O_5), triethylamine, Et_3N (CaH_2), acetonitrile, CH_3CN (CaH_2), and tetrahydrofuran, THF (sodium benzophenone ketyl). L-Alanyl-L-alanine and Boc-L-proline were purchased from Sigma Chemical Co.

(*S*)-*N*-(*tert*-Butoxycarbonyl)-2-(hydroxymethyl)-pyrrolidine (4). Method A. To a solution of Boc-L-proline (10.1 g, 47.1 mmol) dissolved in THF (250 mL) was added, dropwise over the course of 45 min with stirring, BH_3·SMe_2 (26 mL of a 2 M THF solution, 52 mmol). The reaction mixture was then heated to gentle reflux for 45 min, cooled to room temperature, concentrated, and dissolved in a mixture of CH_2Cl_2 (300 mL) and water (100 mL). The organic layer was isolated, washed (saturated $NaHCO_3$, saturated NaCl), dried ($MgSO_4$), and concentrated to a white solid (9.28 g, 98%): mp 56–58 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.95 (m, 1, NC*H*$(CH_2)_2$), 3.60 (m, 2, CH_2OH), 3.46 (m, 1, NC*H*HCH$_2$), 3.34 (m, 1, NCH*H*CH$_2$), 2.02 (m, 1), 1.82 (m, 2), 1.58 (m, 1), 1.47 (s, 9, C(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.6 (C=O), 80.0 (C$(CH_3)_3$), 67.1 (CH_2OH), 60.0 (NCHRR′), 47.4 (NCH$_2$), 28.5 (NCH$_2$CH_2), 28.4 (C(CH_3)$_3$), 23.9 (NCH$_2$CH$_2$CH_2); mass spectrum, *m/z* 201 (M^+, 0.4), 170 (M – CH_2OH, 21), 128 (12), 114 (170 – C_4H_8, 66), 70 (114 – CO_2, 100), 61 (14), 57 ($C_4H_9^+$, 67); IR ($CHCl_3$) 3373, 2979, 1667, 1369, 1206, 1167, 1045 cm^{-1}. Anal. Calcd for $C_{10}H_{19}NO_3$: C, 59.68; H, 9.52; N, 6.96. Found: C, 59.48; H, 9.34; N, 6.95.

Method B. A solution of Boc-L-prolinal **5** (485 mg, 2.43 mmol, dissolved in 5 mL of absolute ethanol) was added dropwise to a stirring solution of $NaBH_4$ (100 mg, 2.92 mmol, dissolved in 15 mL of absolute ethanol). After 45 min, the reaction solution was diluted into ether, washed (saturated NH_4Cl, brine, saturated $NaHCO_3$, and brine), dried ($MgSO_4$), concentrated, and distilled (175 °C (0.3 Torr)) to give the solid product, mp 57–58 °C (421 mg, 86%). The product coeluted on GC with a product sample prepared by method A. Anal. Calcd for $C_{10}H_{19}NO_3$: C, 59.68; H, 9.52; N, 6.96. Found: C, 59.58; H, 9.33; N, 6.98.

(2*S*,2′*R*)-*N*-(*tert*-Butoxycarbonyl)-2-(((2′-methoxy-2′-(trifluoromethyl)-2′-phenylacetyl)oxy)methyl)pyrrolidine (10). (*S*)-2-Methoxy-2-(trifluoromethyl)-2-phenylacetyl chloride was prepared by addition of PCl_5 (1.1 equiv) to an ether solution (2 mL/mmol) of (*R*)-2-methoxy-2-(trifluoromethyl)-2-phenylacetic acid (1 equiv). The solution was then stirred for 15 min and concentrated. The acid chloride thus prepared (106 mg, 0.421 mmol) was dissolved in 1.1 mL of ether and added to a stirred solution of Boc-L-prolinol (**4**) (68 mg, 0.337 mmol), Et_3N (60 μL, 0.421 mmol), and *N*,*N*-dimethyl-4-aminopyridine (1 mg) dissolved in THF (2 mL). After 2 h, GC analysis showed complete consumption of Boc-prolinol, so the reaction mixture was diluted into EtOAc, washed (saturated NH_4Cl, water, saturated $NaHCO_3$, and brine), dried ($MgSO_4$), and concentrated to an oil that contained small amounts of impurities. Analysis of these byproducts by GCMS showed peaks derived from the acid chloride (*m/e* 189), but none of the byproducts showed MS peaks characteristic of *N*-Boc-protected 2-substituted pyrrolidines (*m/e* 170, 114, 70, 57), so these impurities were separated from the product by flash chromatography (20 mm, 20% EtOAc/hexane). Each fraction was analyzed by GC, and all fractions containing the product were combined and concentrated to give the clear colorless oil product (127 mg, 90%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (br s, 2), 7.41 (br s, 3), 4.36–4.68 (m, 2, OCH_2R), 3.95–4.07 (m, 1, NCHRR′), 3.54 (s, 3, OCH_3), 3.2–3.4 (br m, 2, NCH_2), 1.91–1.97 (m, 1), 1.73–1.84 (m, 3), 1.47 (s, 9, C$(CH_3)_3$); ^{19}F NMR (90 MHz, toluene-d_8, 100 °C) δ −71.91 (s); mass spectrum, *m/z* 189 (21), 170 (18), 114 (60), 70 (91), 57 (100); mass spectrum (FAB), *m/z* 418 (M + H, 21), 362 (100), 318 (65), 279 (33), 189 (33); IR (neat) 2977, 1754 (ester C=O), 1696 (carbamate C=O), 1395, 1173, 1123, 1024 cm^{-1}; exact mass calcd for $C_{20}H_{27}FN_3O_5$ *m/e* 418.1841, obsd *m/e* 418.1829.

Ethyl (2′*S*)-4-(*N*-(*tert*-Butoxycarbonyl)pyrrolidin-2′-yl)-3-oxabutanoate (12). Boc-prolinol (**4**) (158 mg, 0.790 mmol) was combined with a mixture of ethyl diazoacetate (99 mg of an 87% $CHCl_3$ solution, 0.790 mmol) and $CHCl_3$ (0.050 mL) and stirred vigorously under nitrogen. Boron trifluoride etherate complex (0.010 mL, 0.080 mmol) was then added, and the solution was allowed to stir until gas evolution subsided and the yellow color of ethyl diazoacetate disappeared (3 h). The reaction solution was then poured into 5% HCl and extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were washed (brine), dried ($MgSO_4$), and concentrated to 193 mg oil. Purification by flash chromatography (20 mm, 40% EtOAc/hexane) provided the pure ester **12** as a clear colorless oil (115 mg, 51%): ^{1}H NMR (200 MHz, $CDCl_3$, all signals were broadened due to the presence of slowly interconverting rotamers) δ 4.19–4.28 (m, 2, OCH_2CH_3), 3.9–4.15 (m, 2, NCH_2), 3.6–3.7 (m, 1, NCHRR′), 3.28–3.60 (m, 4, CH_2OCH_2), 1.83–2.12 (m, 4, NCH$_2$CH_2CH_2), 1.46–1.50 (m, 9, C$(CH_3)_3$), 1.26–1.32 (m, 3, OCH_2CH_3); mass spectrum (FAB), *m/z* 288 (M + H, 23), 232 (M – C_4H_7, 23), 188 (51), 119 (100); IR (neat) 2917, 2849, 1754 (ester C=O), 1694 (carbamate C=O), 1457, 1391, 1138 cm^{-1}; exact mass calcd for $C_{14}H_{26}NO_5$ *m/e* 288.1811, obsd *m/e* 288.1812.

(2*S*)-*N*-(*tert*-Butoxycarbonyl)pyrrolidine-2-carboxaldehyde (5). A solution of DMSO (7.9 mL, 111 mmol) dissolved in 25 mL CH_2Cl_2 was added dropwise over a 10-min period to a stirred, cooled (−63 °C) solution of oxalyl chloride (5.3 mL, 61 mmol) dissolved in 125 mL of CH_2Cl_2. After 10 min, a solution of the alcohol **4** (10.16 g, 50.5 mmol) dissolved in 50 mL of CH_2Cl_2 was added dropwise over a 15-min period, and the reaction mixture was stirred for 30 min. Diisopropylethylamine (35 mL, 202 mmol) was then added over a 4-min period, and the mixture was allowed to warm to room temperature over a 30-min period. The reaction mixture was then washed (three times 5% HCl, three times water, saturated NaCl), dried ($MgSO_4$), and concentrated to an oil (9.45 g, 94%) that was stored in a freezer and used without further purification. Distillation (165 °C (0.6 Torr)) of a small portion provided analytically pure product. VT NMR (−50 to 50 °C) showed that the product exists as a 3:2 mixture of isomers due to restricted rotation about the carbamate C–N bond (T_c = 50

(21) Reed, P. E.; Katzenellenbogen, J. A. *J. Biol. Chem.*, in press.
(22) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

°C/200 MHz): ^{1}H NMR (200 MHz, $CDCl_3$, 24 °C) δ 9.54 and 9.45 (d, 1, J = 1.2 and 8 Hz, RCHO), 4.20 and 4.04 (m, 1, NCHRR'), 3.50 (m, 2, NCH_2), 2.11 and 1.97 (m, 2, $NCH_2CH_2CH_2$), 1.83 (m, 2, NCH_2CH_2), 1.46 and 1.42 (s, 9, $OC(CH_3)_3$); mass spectrum, m/z 170 (M^+ – CHO, 11), 114 (41), 70 (100), 57 (81); IR ($CHCl_3$) 2982, 2870, 2805, 2710, 1734, 1686, 1402, 1369, 1165 cm^{-1}. Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.27; H, 8.69; N, 6.90.

(3*R*/*S*,2′*S*)-3-(*N*-(*tert*-Butoxycarbonyl)pyrrolidin-2′-yl)-1-(trimethylsilyl)prop-1-yn-3-ol (6). (Trimethylsiilyl)-acetylene (7.67 mL, 54.3 mmol) was added to a cold (0 °C) solution of ethylmagnesium bromide (27.1 mL of a 2 M THF solution, 54.3 mmol) dissolved in 150 mL of THF. This solution was stirred for 1 h at 5–15 °C and for 15 min at room temperature. A solution of the aldehyde **5** (9.0 g, 45.2 mmol dissolved in 90 mL THF) was then added dropwise over a 30-min period. The reaction solution was allowed to stir for an additional 30 min before being quenched with $NH_4Cl_{(satd)}$ and concentrated. The resulting mixture was dissolved in ether, washed ($NH_4Cl_{(satd)}$, brine), dried ($MgSO_4$), and concentrated to give an oil which contained a 2:1 ratio of the 3*S*:3*R* epimers (R_f = 0.53 (3*S*) and 0.48 (3*R*) in 50% ethyl acetate/hexane). Both isomers were isolated together by flash chromatography (80 mm, 33% ethyl acetate/hexane) and used subsequently without separation (13.46 g of amber oil, 91%): ^{1}H NMR (300 MHz, $CDCl_3$, structural assignments are based on a COSY experiment) (**3*R*,2′*S***) δ 4.37 (m, 1, RR′C*H*OH), 4.03 (m, 1, NCHRR′), 3.53 (m, 1, NC*H*HCH$_2$), 3.32 (m, 1, NCH*H*CH$_2$) 2.13 (m, 1, NCH_2CH_2CHH), 1.99 (m, 1, NCH_2CH_2CHH), 1.75 (m, 2, $NCH_2CH_2CH_2$), 1.49 (s, 9, $C(CH_3)_3$), 0.16 (s, 9, $Si(CH_3)_3$); (**3*S*,2′*S***) δ 4.36 (m, 1), 4.00 (m, 1), 3.35 (m, 2), 2.01 (m, 2), 1.84 (m, 2), 1.44 (s, 9), 0.17 (s, 9); ^{13}C NMR (75 MHz, $CDCl_3$) (**3*R*,2′*S***) δ 157.1 (CO), 104.3 (*C*CTMS), 89.6 (C*C*TMS), 80.4 ($C(CH_3)_3$), 67.7 (CHOH), 63.4 (NCHRR′), 48.3 (NCH_2CH_2), 29.4 ($NCH_2CH_2CH_2$), 28.5 ($C(CH_3)_3$), 23.9 ($NCH_2CH_2CH_2$), –0.2 ($Si(CH_3)_3$); (**3*S*,2′*S***) δ 157.5, 105.1, 89.9, 80.7, 67.5, 62.7, 47.7, 28.7, 28.4, 23.8, –0.1; mass spectrum, m/z 170 (M – CH(OH)C≡CTMS, 33), 114 (170 –C_4H_8, 100), 84 (36), 70 (87), 57 (37); IR ($CHCl_3$) 3332, 3028, 2980, 2172, 2164, 1667, 1658, 1416, 1406, 1167, 1160 cm^{-1}. Anal. Calcd for $C_{15}H_{27}NO_3Si$: C, 60.57; H, 9.15; N, 4.71. Found: C, 60.70; H, 9.19; N, 4.47.

(3*R*/*S*,2′*S*,2″*R*)-3-(*N*-(*tert*-Butoxycarbonyl)pyrrolidin-2′-yl)-3-((2″-methoxy-2″-(trifluoromethyl)-2″-phenylacetyl)oxy)-1-(trimethylsilyl)prop-1-yne (11). (*S*)-2-Methoxy-2-(trifluoromethyl)-2-phenylacetyl chloride (106 mg, 0.421 mmol), prepared as described in the procedure for compound **10**, was dissolved in 1.1 mL of ether and added to a stirring solution of the alcohol **6** (100 mg, 0.337 mmol), Et_3N (60 μL, 0.438 mmol), and *N*,*N*-dimethyl-4-aminopyridine (1 mg) dissolved in THF (2 mL). After 12 h, GC analysis showed complete consumption of starting material so the reaction mixture was diluted into EtOAc and washed (saturated NH_4Cl, water, saturated $NaHCO_3$, and brine), dried ($MgSO_4$), and concentrated to an oil that contained small amounts of impurities. Analysis of these byproducts by GCMS showed peaks derived from the acid chloride (m/e 189), but none of the byproducts showed peaks characteristic of N-Boc protected 2-substituted pyrrolidines (m/e 170, 114, 70, 56), so these impurities were separated from the product by flash chromatography (20 mm, 15% EtOAc/hexane). Each fraction was analyzed by GC, and all fractions containing the product were combined and concentrated to give the clear colorless oil product (153 mg, 89%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (m, 2), 7.40 (m, 3), 6.11 and 6.16 (d, 1, J = 4.5 Hz and 4.8 Hz, TMSCCCHRR′), 3.86 and 3.99 (m, 1, NCHRR′), 3.50 and 3.57 (s, 3, OCH_3), 3.08 and 3.38 (m, 2, NCH_2CH_2), 2.09 (m, 2, $NCH_2CH_2CH_2$), 1.62–1.95 (m, 2, $NCH_2CH_2CH_2$), 1.45 and 1.51 (s, 9, $OC(CH_3)_3$), 0.17 (s, 9, $Si(CH_3)_3$); mass spectrum, m/z 189 (28), 170 (31), 114 (100), 70 (75), 57 (62); mass spectrum (FAB), m/z 514 (M + H, 11), 458 (71), 414 (29), 224 (100), 189 (53), 180 (57), 170 (19), 114 (67); IR (neat) 2975, 2182 (acetylene), 1759 (ester C=O), 1699 (carbamate C=O), 1395, 1252, 1169, 1122, 1019 cm^{-1}; exact mass calcd for $C_{23}H_{35}FN_3O_5Si$ m/e 514.2237, obsd m/e 514.2249. Anal. Calcd for $C_{23}H_{34}FN_3O_5Si$: C, 58.46; H, 6.67; N, 2.73. Found C, 58.15; H, 6.77; N, 2.68.

(3*R*/*S*,2′*S*)-3-(Pyrrolidin-2′-yl)-1-(trimethylsilyl)prop-1-yn-3-ol (7). Toluenesulfonic acid monohydrate (15.3 g, 80 mmol) was added to a solution of the Boc-protected amine **6** (11.9 g, 40 mmol) dissolved in 500 mL of CH_3CN, and the resulting solution was allowed to stir for 3 h. After concentration, 60 mL $NaHCO_{3(satd)}$ was added with stirring, followed by enough solid $NaHCO_3$ to saturate the solution. Product isolation (ether, $NaHCO_{3(satd)}$, Na_2SO_4) gave an oil that was purified by bulb-to-bulb distillation (150–200 °C (0.1 Torr)), affording the product, a water soluble, pale yellow semisolid (6.77 g, 86%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.29 (m, 1, C*H*OH), 3.85 (br s, 1, CHO*H*), 3.22 (m, 1, NC*H*RCH$_2$), 2.96, (m, 1, NC*H*HCH$_2$), 2.84 (m, 1, NCH*H*CH$_2$), 1.6–1.9 (m, 4, $NCH_2CH_2CH_2$) 0.1 (s, 9, $Si(CH_3)_3$); mass spectrum, m/z 198 (M + 1, 2), 182 (M – CH_3, 2), 164 (3), 83 (7), 75 (10), 71 (50), 70 (M – CH(OH)CCTMS, 100), 68 (23); IR (neat) 3295 (br, OH), 2961, 2874, 2107 (–CC–), 1655, 1051 cm^{-1}. Anal. Calcd for $C_{10}H_{19}NOSi$: C, 60.86; H, 9.70; N, 7.10. Found: C, 60.48; H, 9.79; N, 7.27.

(3*R*,2′*S*,2″*R*)- and (3*S*,2′*S*,2″*R*)-3-(*N*-(2″-Bromo-3″-methylbutanoyl)pyrrolidin-2′-yl)-1-(trimethylsilyl)prop-1-yn-3-ol (8a and 8b). Carbonyldiimidazole (3.94 g, 24.3 mmol) was added, in four portions under a nitrogen atmosphere, to a stirring solution of (*R*)-2-bromo-3-methylbutanoic acid[16] (4.40 g, 24.3 mmol) dissolved in 50 mL of THF. The resulting solution was stirred for 1 h and then transferred to an addition funnel and added dropwise over a 30-min period to a cooled (0 °C) solution of the amino alcohol **7** (4.79 g, 24.3 mmol) dissolved in 60 mL of THF. After stirring for 2.5 h at 0 °C, the reaction was quenched at 0 °C with 100 mL of water. Product isolation (EtOAc, $NH_4Cl_{(satd)}$, brine, $MgSO_4$) gave a pale amber oil. The product epimers were separated by flash chromatography in four portions (80 mm, 40% EtOAc/hexane) to give, in 56% total yield, the white solids **8a** (R_f = 0.35, 1.69 g, mp 129–130 °C) and **8b** (R_f = 0.25, 3.19 g, mp 114–115 °C).

8a: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.97 (d, 1, J = 9.0 Hz, CHO*H*), 4.80 (m, 1, C*H*OH), 4.28 (m, 1, NC*H*RR′), 4.10 (d, 1, J = 9.4 Hz, C*H*Br), 3.65 (m, 2, NCH_2CH_2), 2.34 (m, 1, $CH(CH_3)_2$), 2.16 (m, 2, $NCH_2CH_2CH_2$), 1.88 (m, 2, $NCH_2CH_2CH_2$), 1.61 (d, 3, J = 6.6 Hz, $CH(CH_3)CH_3$), 1.00 (d, 3, J = 6.6 Hz, $CH(CH_3)CH_3$), 0.14 (s, 9, $Si(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1 (*C*=O), 103.5 (*C*CTMS), 90.3 (C*C*TMS), 67.0 (*C*HOH), 64.7 (*N*CHRR′), 53.9 (*C*HBr), 49.2 (NCH_2CH_2), 31.7 ($CH(CH_3)_2$), 28.7 ($NCH_2CH_2CH_2$), 24.2 ($NCH_2CH_2CH_2$), 20.9 ($CH(CH_3)CH_3$), 20.1 ($CH(CH_3)CH_3$), –0.1 ($Si(CH_3)_3$); mass spectrum, m/z 359/361 (M^+, 0.3), 232/234 (M – CH(OH)CCTMS, 14), 70 (100), 58 (20); IR ($CHCl_3$), 3250 (br, OH), 2921, 2138 (CC), 1634 (C=O), 1377, 1239, 1024 cm^{-1}. Anal. Calcd for $C_{15}H_{26}BrNO_2Si$: C, 49.99; H, 7.27; N, 3.89; Br, 22.17. Found: C, 50.26; H, 7.36; N, 3.85; Br, 21.88.

8b: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.77 (d, 1, J = 6.1 Hz, C*H*OH), 4.71 (br s, 1, CHO*H*), 4.19 (m, 1, NC*H*RR′), 3.98 (d, 1, J = 9.5 Hz, C*H*Br), 3.51 (m, 2, NCH_2CH_2), 2.07–2.09 (m, 3, C*H*-$(CH_3)_2$ and $NCH_2CH_2CH_2$), 1.82–2.01 (m, 2, $NCH_2CH_2CH_2$), 1.07 (d, 3, J = 6.6 Hz, $CH(CH_3)CH_3$), 0.90 (d, 3, J = 6.7 Hz, $CH(CH_3)CH_3$), 0.07 (s, 9, $Si(CH_3)_3$); mass spectrum, m/z 359/361 (M^+, 0.3), 232/234 (M – CH(OH)CCTMS, 16), 70 (100); IR (melt), 3390 (br, OH), 2963, 2172 (CC), 1630 (C=O), 1443, 1055 cm^{-1}. Anal. Calcd for $C_{15}H_{26}BrNO_2Si$: C, 49.99; H, 7.27; N, 3.89; Br, 22.17. Found: C, 50.34; H, 7.41; N, 3.85; Br, 21.77.

(3*S*,5*R*,6*S*)-2-Oxo-3-isopropyl-5-((trimethylsilyl)-ethynyl)-1-aza-4-oxabicyclo[4.3.0]nonane (9a). To a cooled (0 °C) mixture of potassium hydride (0.538 g of a 35 wt % dispersion in mineral oil, 4.71 mmol) and 80 mL of THF was added a solution of the bromoamide **8a** (1.54 g, 4.28 mmol dissolved in 15 mL THF) dropwise over a 10-min period. The reaction miture was stirred at 0 °C, and reaction progress was followed closely by GC or TLC. After 1.5 h the reaction was quenched by addition of 1 mL of $NH_4Cl_{(satd)}$ to the cold reaction mixture, followed by 250 mL of ether. Product isolation (ether, water, brine, $MgSO_4$) gave a mixture that was purified by flash chromatography (40 mm, 20–50% EtOAc/hexane) to give a white solid (1.05 g, 88%): mp 46–47 °C; ^{1}H NMR (300 MHz, $CDCl_3$, structural assignments are based on a HETCOR experiment) δ 4.70 (d, 1, J = 3.7 Hz, C*H*C≡CTMS), 3.94 (d, 1, J = 3.2 Hz, C*H*CH$(CH_3)_3$), 3.78 (m, 1, NC*H*RR′), 3.47–3.57 (m, 2, NCH_2CH_2), 2.41 (m, 1, CHC*H*-$(CH_3)_3$), 1.74–2.13 (m, 4, $NCH_2CH_2CH_2$), 1.02 (d, 3, J = 7.1 Hz, $CH(CH_3)CH_3$), 0.95 (d, 3, J = 6.7 Hz, $CH(CH_3)CH_3$), 0.08 (s, 9, $Si(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6 (*C*=O), 101.8 (*C*≡CTMS), 92.6 (C≡*C*TMS), 78.6 (*C*HCH$(CH_3)_2$), 66.7 (CHC≡CTMS), 58.5 (*N*CHRR′), 45.5 (NCH_2CH_2), 29.1 ($CH(CH_3)_2$), 28.6 ($NCH_2CH_2CH_2$), 22.6 ($NCH_2CH_2CH_2$), 19.7 (CH(C-

H_3)CH_3), 17.2 (CH(CH_3)CH_3), –0.5 (Si(CH_3)$_3$); mass spectrum, m/z 279 (M^+, 1), 264 (M – CH_3, 2), 237 (6), 153 (40), 125 (39), 73 (15), 70 (100); IR ($CHCl_3$) 3017, 2969, 2170 (CC), 1651 (C=O), 1448, 1206 cm^{-1}. Anal. Calcd for $C_{15}H_{25}NO_2Si$: C, 64.47; H, 9.02; N, 5.01. Found: C, 64.40; H, 8.95; N, 5.06.

(3*S*,5*S*,6*S*)-2-Oxo-3-isopropyl-5-((trimethylsilyl)ethynyl)-1-aza-4-oxabicyclo[4.3.0]nonane (9b). This compound was prepared from **8b** (3.05 g, 8.47 mmol) using the same procedure described above for **9a** at twice the scale. Chromatographic purification afforded a white solid (2.05 g, 86%): mp 86 °C; ^1H NMR (300 MHz, $CDCl_3$, structural assignments are based on a HETCOR experiment) δ 4.07 (d, 1, J = 8.6 Hz, C*H*CCTMS), 4.06 (d, 1, J = 4.7 Hz, C*H*CH(CH_3)$_2$), 3.61 (m, 1, NC*H*RR'), 3.55 (m, 2, NC*H*$_2$CH$_2$), 2.39 (m, 1, CHC*H*(CH_3)$_2$), 2.14 (m, 1, NCH$_2$CH$_2$C*H*H), 1.96 (m, 1, NCH$_2$C*H*HCH$_2$), 1.78 (m, 1, NCH$_2$CH*H*CH$_2$), 1.50 (m, 1, NCH$_2$CH$_2$CH*H*), 1.06 (d, 3, J = 7.0 Hz, CH(C*H*$_3$)CH$_3$), 0.90 (d, 3, J = 6.9 Hz, CH(CH$_3$)C*H*$_3$), 0.17 (s, 9, Si(C*H*$_3$)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.4 (*C*=O), 100.1 (*C*CTMS), 91.8 (C*C*TMS), 79.7 (CHCH(CH_3)$_2$), 68.4 (CHC*C*TMS), 61.6 (NC*H*RR'), 45.5 (NCH$_2$CH$_2$), 31.0 (C*H*(CH_3)$_2$), 29.9 (NCH$_2$CH$_2$*C*H$_2$), 21.9 (NCH$_2$*C*H$_2$CH$_2$), 19.7 (CH(*C*H$_3$)CH$_3$), 17.7 (CH(CH$_3$)*C*H$_3$), –0.4 (Si(*C*H$_3$)$_3$); mass spectrum, m/z 279 (M^+, 1), 237 (6), 153 (39), 125 (38), 70 (100); IR($CHCl_3$) 3017, 1641, 1522, 1452, 1226 cm^{-1}. Anal. Calcd for $C_{15}H_{25}NO_2Si$: C, 64.47; H, 9.02; N, 5.01. Found: C, 64.45; H, 9.06; N, 4.91.

(2*S*,4*R*,2'*S*)-2-Isopropyl-4-(*N*-(*tert*-butoxycarbonyl)pyrrolidin-2'-yl)-3-oxahex-5-enoic Acid (14a). The oxa lactam **9a** (145 mg, 0.522 mmol) was combined with 4 mL of 6 N HCl and heated to reflux for 28 h (106 °C bath temperature). The resulting homogeneous solution was concentrated to a brown foam and dissolved in 5 mL of CH_3CN. Di-*tert*-butyl dicarbonate (160 mg, 0.734 mmol) and Et_3N (0.204 mL, 1.468 mmol) were then added, and the reaction solution was stirred for 17 h and concentrated. Purification by flash chromatography (20 mm, gradient elution with 30% EtOAc/hexane (200 mL), EtOAc (130 mL), and methanol (130 mL)) provided the product as a light brown foam (117 mg, 69%): mp 69–71 °C; ^1H NMR (due to the presence of slowly interconverting rotamers (see Boc-prolinal **5**), broadened peaks were observed for all signals; 300 MHz, $CDCl_3$) δ 4.61 (m, 1), 4.05 (m, 1), 3.72 (m, 1, NC*H*RCH$_2$), 3.43 (m, 2, NCH$_2$), 2.47 (d, 1, J = 2.0 Hz, acetylenic H), 1.96–2.25 (m, 4, CHC*H*(CH_3)$_2$ and NCH$_2$CH*H*CH$_2$), 1.83 (m, 1, NCH$_2$C*H*HCH$_2$), 1.47 (s, 9, OC(CH_3)$_3$), 1.05 (d, 3, J = 7.8 Hz, CH(C*H*$_3$)CH$_3$), 0.92 (d, 3, J = 7.6 Hz, CH(CH$_3$)C*H*$_3$); mass spectrum (FAB), m/z 326 (M + H, 46), 306 (57), 270 (100), 262 (48), 226 (96), 188 (32); exact mass calcd for $C_{17}H_{28}NO_5$ m/e 326.1967, obsd m/e 326.1959.

(2*S*,4*S*,2'*S*)-2-Isopropyl-4-(*N*-(*tert*-butoxycarbonyl)pyrrolidin-2'-yl)-3-oxahex-5-enoic Acid (14b). The oxa lactam **9b** (191 mg, 0.682 mmol) was combined with 5 mL of 6 N HCl and heated to reflux for 28 h (106 °C bath temperature). The resulting homogeneous solution was concentrated to a brown foam and dissolved in 6 mL of CH_3CN. Di-*tert*-butyl dicarbonate (223 mg, 1.02 mmol) and Et_3N (0.284 mL, 2.05 mmol) were then added, and the reaction solution was stirred for 30 h and concentrated. Purification by flash chromatography (33 mm, gradient elution with EtOAc (130 mL), then methanol (130 mL)) provided the product as a light brown foam (136 mg, 61%): mp 151–154 °C; ^1H NMR (due to the presence of slowly interconverting rotamers (see Boc-prolinal **5**), broadened peaks were observed for all signals; 300 MHz, $CDCl_3$) δ 4.38 (m, 1), 4.23 (m, 1), 4.01 (m, 1, NC*H*RCH$_2$), 3.42 (m, 2, NCH$_2$), 2.59 (S, 1, acetylenic H), 2.19 (m, 1, C*H*(CH_3)$_2$), 1.82–2.09 (m, 4, NCH$_2$C*H*$_2$CH$_2$), 1.48 (S, 9, OC(CH_3)$_3$), 1.06 (d, 3, J = 6.4 Hz, CH(C*H*$_3$CH$_3$), 1.08 (d, 3, J = 6.8 Hz, CH(CH$_3$)C*H*$_3$); mass spectrum (FAB), m/z 326 (M + H, 52), 306 (100), 270 (43), 262 (27), 226 (57), 188 (22); IR ($CHCl_3$) 3262 (br), 2963, 2112, 1765, 1684, 1250, 1172, 1073 cm^{-1}; exact mass calcd for $C_{17}H_{28}NO_5$ m/e 326.1967, obsd m/e 326.1972.

(3*S*,5*S*,2'*S*)-5-(*N*-(*tert*-Butoxycarbonyl)pyrrolidin-2'-yl)-3-isopropyl-6-methylene-4-oxatetrahydro-2-pyranone (15a). To a solution of the acetylenic acid **14a** (80 mg, 0.246 mmol) dissolved in 10 mL of dry CH_3CN was added mercuric trifluoroacetate (19 mg 0.049 mmol). The reaction solution was stirred for 14 h, concentrated, and subjected to flash chromatography (25 mm, 25% ethyl acetate/hexane) to isolate the product as a clear colorless oil (23 mg, 29%), homogeneous by TLC (R_f = 0.42 in 30% EtOAc/hexane): ^1H NMR (due to the presence of slowly interconverting rotamers (see Boc-prolinal **5**), broadened peaks were observed for all signals; 300 MHz, $CDCl_3$) δ 4.92 (br s, 1, NCHRC*H*R'R''), 4.81 (br s, 1, C=C*H*H), 4.39 (br s, 1, C=CH*H*), 4.0–4.2 (m, 2, NCHRR' and C*H*(CH_3)$_2$), 3.30–3.50 (m, 2, NCH$_2$), 2.13–2.31 (m, 1, C*H*(CH_3)$_2$), 1.79–2.05 (m, 4, NCH$_2$C*H*$_2$), 1.45 (br s, 9, OC(CH_3)$_3$), 1.02 (d, 3, J = 6.0 Hz, CH(C*H*$_3$)CH$_3$), 0.99 (d, 3, J = 6.3 Hz, CH(CH$_3$)C*H*$_3$).

(3*S*,5*R*,2'*S*)-5-(*N*-(*tert*-Butoxycarbonyl)pyrrolidin-2'-yl)-3-isopropyl-6-methylene-4-oxatetrahydro-2-pyranone (15b). To a solution of the acetylenic acid **14b** (60 mg, 0.185 mmol) dissolved in 9 mL of dry CH_3CN was added mercuric trifluoroacetate (30 mg 0.076 mmol). The reaction solution was stirred for 10 h, concentrated, and subjected to flash chromatography (12 mm, 20% ethyl acetate/hexane) to isolate the product as a clear colorless oil (16 mg, 25%), homogeneous by TLC (R_f = 0.43 in 30% EtOAc/hexane): ^1H NMR (Due to the presence of slowly interconverting rotamers (see Boc-prolinal **5**), broadened peaks were observed for all signals; 200 MHz, $CDCl_3$) δ 5.05 (m, 1), 4.91 (br s, 1, C=C*H*H), 4.43 (br s, 1, C=CH*H*), 4.14 (m, 1), 3.83 (m, 1), 3.46 (m, 1, NC*H*HCH$_2$), 3.30 (m, 1, NCH*H*CH$_2$), 2.28 (m, 1, C*H*(CH_3)$_2$), 1.67–2.01 (m, 4, NCH$_2$C*H*$_2$CH$_2$), 1.48 (br s, 9, OC(CH_3)$_3$), 1.08 (d, 3, J = 7.4 Hz, CH(C*H*$_3$)CH$_3$), 1.02 (d, 3, J = 7.3 Hz, CH(CH$_3$)C*H*$_3$); mass spectrum, m/z 325 (M^+, 1), 269 (M – C_4H_8, 1), 224 (M – Boc, 3), 170 (27), 114 (100), 70 (99), 57 (94).

(3*S*,5*R*,6*S*)-2-Oxo-5-acetyl-3-isopropyl-1-aza-4-oxabicyclo[4.3.0]nonane (16a). The Boc-protected lactone **15a** (23 mg, 0.071 mmol) was dissolved in a cold (0 °C) mixture of CH_2Cl_2 (1.5 mL) and trifluoroacetic acid (1.5 mL), and stirred until the starting material disappeared by TLC (80 min). The reaction solution was then concentrated at 0 °C to give a hygroscopic white solid. NMR analysis showed that this crude product contained a 1.5:1.0 mixture of the lactam **16a** and the deprotected amino lactone trifluoroacetate salt **17a**. Neutralization in EtOAc/saturated $NaHCO_3$ provided the amber oil **16a** (15 mg, 94%): ^1H NMR (300 MHz, $CDCl_3$) δ 4.25 (d, 1, J = 5.8 Hz, C*H*COCH$_3$), 3.77 (d, 1, J = 2.6 Hz, C*H*HCH$_2$), 3.73 (m, 1, NCHRR'), 3.50 (m, 1, NC*H*HCH$_2$), 3.05 (m, 1, NCH*H*CH$_2$), 2.33 (m, 1, C*H*(CH_3)$_2$), 2.09 (s, 3, COCH$_3$), 1.59–1.83 (m, 4, NCH$_2$C*H*$_2$CH$_2$), 0.94 (d, 3, J = 7.1 Hz, CH(C*H*$_3$)CH$_3$), 0.76 (d, 3, J = 6.9 Hz, CH(CH$_3$)C*H*$_3$); mass spectrum, m/z 225 (M^+, 1), 183 (5), 182 (M – COCH$_3$, 9), 154 (27), 83 (26), 70 (100), 43 (27); IR (neat) 2965, 1723 (ketone C=O), 1655 (amide C=O), 1449, 1105, 1012 cm^{-1}; exact mass calcd for $C_{12}H_{19}NO_3$ m/e 225.1365, obsd m/e 225.1365.

***tert*-Butyl (2*S*,4*R*,2'*S*)-2-Isopropyl-4-(pyrrolidin-2'-yl)-3-oxahex-5-ynoate (19a).** The oxa lactam **9a** (1.08 g, 3.85 mmol) was combined with 20 mL of 6 N HCl, and the mixture was heated to reflux for 28 h (106 °C bath temperature). The resulting homogeneous solution was concentrated to a brown foam, dissolved in a solution prepared from 6.75 mL of *p*-dioxane and 0.675 mL of $H_2SO_{4(conc)}$, and transferred in equal portions to three 10-mL reacti-vials. Each vial was cooled to –78 °C, 3 mL of isobutylene was added, and the vial was sealed and allowed to warm to room temperature behind a blast shield. After 10 h of vigorous stirring, the isobutylene was removed by evaporation in a fume hood at –78 °C to room temperature, and the contents of each vial were added to an ice-cold mixture of 250 mL of 1 N NaOH and 300 mL of ether. Product isolation (ether, Na_2SO_4) gave an amber oil product (0.783 g, 72%): ^1H NMR (300 MHz, $CDCl_3$) δ 4.00 (m, 1, C*H*CCH), 3.74 (d, 1, J = 4.5 Hz, C*H*CH(CH_3)$_2$), 3.26 (m, 1, NC*H*RR'), 2.99 (m, 1, NC*H*HCH$_2$), 2.78 (m, 1, NCH*H*CH$_2$), 2.34 (d, 1, J = 1.8 Hz, CHCC*H*), 1.99 (m, 1, C*H*(CH_3)$_2$), 1.79 (m, 2, NCH$_2$CH$_2$C*H*$_2$), 1.68 (m, 2, NCH$_2$C*H*$_2$CH$_2$), 1.41 (s, 9, C(C*H*$_3$)$_3$), 0.92 (d, 3, J = 6.9 Hz, CH(C*H*$_3$)CH$_3$), 0.85 (d, 3, J = 6.9 Hz, CH(CH$_3$)C*H*$_3$); mass spectrum (FAB), m/z 282 (M + H, 100), 262 (25), 226 (56); IR (neat) 3308 (NH), 2967, 2874, 2107 (C≡C), 1736 (C=O), 1367, 1167, 1140, 1086 cm^{-1}; exact mass calcd for $C_{16}H_{28}NO_3$ m/e 282.2069, obsd m/e 282.2059.

***tert*-Butyl (2*S*,4*S*,2'*S*)-2-Isopropyl-4-(pyrrolidin-2'-yl)-3-oxahex-5-ynoate (19b).** This compound was prepared from **19b** (2.05 g, 7.32 mmol) using the same procedure as described above for **19a** at twice the scale. The product was obtained as an amber oil (1.73 g, 84%): ^1H NMR (300 MHz, $CDCl_3$) δ 3.98 (dd, 1, J_1 = 7.4 Hz, J_2 = 1.9 Hz, C*H*CCH), 3.65 (d, 1, J = 5.9 Hz, C*H*CH(CH_3)$_2$), 3.18 (m, 1, NC*H*RR'), 3.00 (m, 1, NC*H*HCH$_2$), 2.85 (m, 1, NCH*H*CH$_2$), 2.37 (d, 1, J = 1.9 Hz, CHCC*H*), 2.17 (br s, 1, NH), 2.00 (m, 1, C*H*(CH_3)$_2$), 1.57–1.88 (br m, 4, NCH$_2$C*H*$_2$CH$_2$),

1.47 (s, 9, C(CH_3)$_3$), 0.95 (d, 3, J = 6.8 Hz, CH(CH_3)CH_3), 0.94 (d, 3, J = 6.9 Hz, CH(CH_3)CH_3); mass spectrum (FAB), m/z 282 (M + H, 100), 262 (31), 226 (66); IR (neat) 3258 (NH), 2969, 2874, 2109 (CC), 1741 (C=O), 1367, 1163, 1138, 1086 cm^{-1}; exact mass calcd for $C_{16}H_{28}NO_3$ m/e 282.2069, obsd m/e 282.2073.

***tert*-Butyl (2*S*,4*R*,2′*S*)-2-Isopropyl-4-[*N*-(methoxysuccinyl-L-alanyl-L-alanyl)pyrrolidin-2′-yl]-3-oxahex-5-ynoate (20a).** To a cooled (−10 °C) solution of methoxysuccinyl-L-alanyl-L-alanine[17] (234 mg, 0.854 mmol) and *N*-methylmorpholine (0.094 mL, 0.854 mmol) dissolved in THF (7.5 mL) was added, dropwise over a 1-min period, isobutyl chloroformate (0.109 mL, 0.854 mmol). After the mixture was stirred for a 10-min period, a solution of the amine **19a** (218 mg, 0.776 mmol, dissolved in 2.5 mL of THF) was added dropwise over a 10-min period, and the resulting solution was stirred for 1 h at −10 °C and 4 h at room temperature. The reaction mixture was then concentrated and subjected to flash chromatography (40 mm, 25% acetone/EtOAc) to yield the white solid (229 mg, 55%). The product was homogeneous by TLC (R_f = 0.48 in 25% acetone/EtOAc): mp 40–42 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.83 (br d, J = 7 Hz, amide NH), 6.32 (br d, J = 7 Hz, amide NH), 4.67 (m, 1, NHC*H*(CH_3)CONH), 4.64 (m, 1, HCCC*H*RR′), 4.46 (m, 1, NHC*H*(CH_3)CON), 4.32 (m, 1, $NCH_2CH_2CH_2CHRR'$), 3.84 (d, 1, J = 6.2 Hz, C*H*CH(CH_3)$_2$), 3.68 (s, 3, CO_2CH_3), 3.60 (m, 1, NCH_2CH_2), 2.67 (m, 2, $CH_2CH_2CO_2CH_3$), 2.51 (m, 2, $CH_2CH_2CO_2CH_3$), 2.39 (s, 1, HCCR), 2.30 (m, 1, C*H*(CH_3)$_2$), 2.20 ((m, 1, NCH_2CHHCH_2), 1.9–2.1 (m, 3, NCH_2CHHCH_2), 1.67 (s, 9, C(CH_3)$_3$), 1.66 (d, 3, J = 7.2 Hz, NHCH(CH_3)CO), 1.38 (d, 3, J = 7.0 Hz, NHCH(CH_3)CO), 0.99 (d, 3, J = 7.2 Hz, CH(CH_3)CH_3), 0.89 (d, 3, J = 7.1 Hz, CH(CH_3)CH_3); mass spectrum (FAB), m/z 538 (M + 1, 31), 518 (15), 482 (111), 282 (17), 262 (37), 226 (100), 186 (61), 119 (75); exact mass calcd for $C_{27}H_{44}N_{O8}$ m/e 538.3128, obsd m/e 538.3115.

***tert*-Butyl (2*S*,4*S*,2′*S*)-2-Isopropyl-4-[*N*-(methoxysuccinyl-L-alanyl-L-alanyl)pyrrolidin-2′-yl]-3-oxahex-5-ynoate (20b).** To a cooled (−10 °C) solution of methoxysuccinyl-L-alanyl-L-alanine[17] (420 mg, 1.53 mmol) and *N*-methylmorpholine (0.168 mL, 1.53 mmol) dissolved in THF (15 mL) was added, dropwise over a 1-min period, isobutyl chloroformate (0.196 mL, 1.53 mmol). After the miture was stirred for a 10-min period, a solution of the amine **19a** (391 mg, 1.39 mmol, dissolved in 2.5 mL of THF) was added dropwise over a 10-min period, and the resulting solution was stirred for 1 h at −10 °C and for 4 h at room temperature. The reaction miture was then concentrated and subjected to flash chromatography (40 mm, 30% acetone/EtOAc) to yield the white solid (494 mg, 66%). The product was homogeneous by TLC (R_f = 0.40 in 30% acetone/ethyl acetate): mp 40–42 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (br d, J = 7.2 Hz, amide NH), 6.59 (br d, J = 6.0 Hz, amide NH), 4.81 (dd, 1, J_1 = 4.5 Hz, J_2 = 2.1 Hz, HCCC*H*RR′), 4.63 (m, 1, NHC*H*(CH_3)CONH), 4.47 (m, 1, NHC*H*(CH_3)CON), 4.24 (m, 1, $NCH_2CH_2CH_2CHRR'$), 3.64 (s, 3, CO_2CH_3), 3.58 (d, 1, J = 5.4 Hz, OC*H*CH(CH_3)$_2$) 3.56–3.62 (m, 1, NC*H*HCH$_2$), 3.40–3.48 (m, 1, NCH*H*CH$_2$), 2.63 (t, 2, J = 6.5 Hz, $CH_2CH_2CO_2CH_3$), 2.48 (t, 2, J = 6.5 Hz, $CH_2CH_2CO_2CH_3$), 2.28 (d, 1, J = 2.0 Hz, HCCR), 2.22–2.29 (m, 1, C*H*(CH_3)$_2$), 1.80–2.18 (m, 4, $NCH_2CH_2CH_2$), 1.43 (s, 9, C(CH_3)$_3$), 1.31 (d, 3, J = 7.4 Hz, NHCH(CH_3)CO), 1.23 (d, 3, J = 7.4 Hz, NHCH(CH_3)CO), 0.90 (d, 3, J = 6.6 Hz, CH(CH_3)CH_3), 0.89 (d, 3, J = 6.6 Hz, CH(CH_3)CH_3); mass spectrum (FAB), m/z 538 (M + 1, 67), 518 (23), 482 (15), 282 (40), 262 (88), 226 (100), 186 (89); IR (melt) 3289 (br), 2974, 2876, 2110, 1740, 1638, 1541, 1458, 1368, 1167, 1089 cm^{-1}; exact mass calcd for $C_{27}H_{44}N_3O_8$ m/e 538.3128, obsd m/e 538.3136.

(2*S*,4*R*,2′*S*)-2-Isopropyl-4-[*N*-(methoxysuccinyl-L-alanyl-L-alanyl)pyrrolidin-2′-yl]-3-oxahex-5-ynoic Acid (21a). Trifluoroacetic acid (4 mL) was slowly added to a precooled (0 °C) solution of the ester **20a** (225 mg, 0.419 mmol) dissolved in CH_2Cl_2 (4 mL). After stirring for 3 h at 0 °C, the reaction solution was concentrated and subjected to flash chromatography (33 mm, gradient elution with 60% acetone/EtOAc to methanol) to give a crude product that was further purified by dissolution in water and passage through Amberlite IR-12 (plus) resin. The white foam product thus obtained (193 mg, 96%) was homogeneous by TLC (9:0.9:0.1 CH_2Cl_2/methanol/acetic acid, R_f = 0.33): mp 145–146 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 4.73 (m, 1, HCCC*H*RR′), 4.63 (m, 1, NC*H*(CH_3)CONHR), 4.39 (m, 1, NC*H*(CH_3)CONRR′), 4.31 (d, 1, J = 5.7 Hz, OC*H*(R)CO_2H), 4.27 (m, 1, NC*H*RCH$_2$), 3.70 (s, 3, CO_2CH_3), 3.32 (m, 2, NCH_2CH_2), 2.99 (s, 1, HCCR), 2.65 (m, 2, $CH_2CH_2CO_2R$), 2.55 (m, 2, $CH_2CH_2CO_2R$), 2.23–2.36 (m, 2, C*H*(CH_3)$_2$ and $NCH_2CHHCHH$), 2.14 (m, 1, $NCH_2CHHCHH$), 1.99 (m, 2, $NCH_2CHHCHH$), 1.43 (d, 3, J = 7.5 Hz, NCH(CH_3)CO), 1.37 (d, 3, J = 7.4 Hz, NCH(CH_3)CO), 1.07 (d, 3, J = 6.9 Hz, CHCH(CH_3)CH_3), 0.97 (d, 3, J = 7.0 Hz, CHCH(CH_3)CH_3); mass spectrum (FAB), m/z 482 (M + H, 98), 279 (30), 226 (100), 186 (19), 119 (37); exact mass calcd for $C_{23}H_{36}N_3O_8$ m/e 482.2502, obsd m/e 482.2497.

(2*S*,4*S*,2′*S*)-2-Isopropyl-4-[*N*-(methoxysuccinyl-L-alanyl-L-alanyl)pyrrolidin-2′-yl]-3-oxahex-5-ynoic Acid (21b). Trifluoroacetic acid (10 mL) was slowly added to a precooled solution of the ester **20b** (800 mg, 1.49 mmol) dissolved in CH_2Cl_2 (10 mL). After stirring for 3 h, the reaction solution was concentrated and subjected to flash chromatography (43 mm, gradient elution with 60% acetone/EtOAc to methanol) to give a crude product that was further purified by dissolution in water and passage through Amberlite IR-12 (plus) resin. The white foam product thus obtained (702 mg, 98%) was homogeneous by TLC (9:0.9:0.1 CH_2Cl_2/methanol/acetic acid, R_f = 0.37): mp 70–73 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (br d, 1, J = 6.8 Hz, amide NH), 6.74 (br d, 1, J = 7.1 Hz, amide NH), 4.77 (m, 1, HCCC*H*RR′), 4.69 (m, 1, NC*H*(CH_3)CONHR), 4.52 (m, 1, NC*H*(CH_3)CONRR′), 4.34 (m, 1, NC*H*RCH$_2$), 3.92 (d, 1, J = 4.9 Hz, OC*H*(R)CO_2H), 3.75 (m, 1, NCH*H*CH$_2$), 3.65 (s, 3, CO_2CH_3), 3.49 (m, 1, NCH*H*CH$_2$), 2.64 (m, 2, $CH_2CH_2CO_2R$), 2.49 (m, 2, $CH_2CH_2CO_2R$), 2.47 (d, 1, J = 2.0 Hz, HCCR), 2.17 (m, 1, C*H*(CH_3)$_2$), 2.08 (m, 2, $NCH_2CH_2CH_2$), 1.93 (m, 2, $NCH_2CH_2CH_2$), 1.32 (d, 3, J = 7.3 Hz, NCH(CH_3)CO), 1.30 (d, 3, J = 7.3 Hz, NCH(CH_3)CO), 0.97 (d, 3, J = 6.9 Hz, CHCH(CH_3)CH_3), 0.93 (d, 3, J = 7.0 Hz, CHCH(CH_3)CH_3); mass spectrum (FAB), m/z 482 (M + H, 47), 262 (27), 226 (100), 186 (72), 119 (99); IR (melt) 33450, 2961, 2831, 2120, 1750, 1637, 1466, 1172 cm^{-1}; exact mass calcd for $C_{23}H_{36}N_3O_8$ m/e 482.2502 obsd m/e 482.2501.

(3*S*,5*S*,2′*S*)-5-(*N*-(*tert*-Butoxycarbonyl)pyrrolidin-2′-yl)-6(*E*)-(bromomethylene)-3-isopropyl-4-oxatetrahydro-2-pyranone (22a). To a solution of the acetylenic acid **14a** (86 mg, 0.263 mmol) dissolved in 30 mL of dry CH_3CN was added *N*-bromosuccinimide (47 mg, 0.263 mmol) and $KHCO_3$ (26 mg, 0.263 mmol). The reaction mixture was stirred with protection from light for 36 h, concentrated, dissolved in 150 mL of CH_2Cl_2, washed (5% $Na_2S_2O_3$, brine) dried ($MgSO_4$), an concentrated to an oil. Purification by flash chromatography (22 mm, 30% EtOAc/hexane) yielded the white solid **22a** (17 mg, 16%, R_f = 0.33 in 30% EtOAc/hexane): mp 110 °C; ^{1}H NMR (due to the presence of slowly interconverting rotamers (see Boc-prolinal **5**), broadened peaks were observed for most signals; 300 MHz, $CDCl_3$) δ 6.11 (s, 1, C=C*H*Br), 5.50 (m, 1), 4.21 (m, 1), 4.06 (m, 1), 3.43 (m, 2, NCH_2), 2.27 (m, 1, C*H*CCH$_3$)$_3$), 1.79–2.05 (m, 4, $NCH_2CH_2CH_2$), 1.43 (br s, 9, OC(CH_3)$_3$), 0.90 (m, 6, CH(C*H*$_3$)$_2$); mass spectrum (FAB), m/z 404/406 (M + H, 12) 348/350 (M − C_4H_8, 60), 304 (29), 240 (32), 170 (38), 114 (100); exact mass calcd for $C_{17}H_{27}NO_5{}^{79}Br$ m/e 404.1073, obsd m/e 404.1078.

(3*S*,5*R*,2′*S*)-5-(*N*-(*tert*-Butoxycarbonyl)pyrrolidin-2′-yl)-6(*E*)-(bromomethylene)-3-isopropyl-4-oxatetrahydro-2-pyranone (22b). To a solution of the acetylenic acid **14b** (125 mg, 0.385 mmol) dissolved in 12 mL of dry CH_3CN was added *N*-bromosuccinimide (72 mg, 0.404 mmol) and $KHCO_3$ (38 mg, 0.385 mmol). The reaction mixture was stirred under protection from light for 23 h, concentrated, dissolved in 150 mL of CH_2Cl_2, washed (5% $Na_2S_2O_3$, brine), dried ($MgSO_4$), and concentrated to an oil. Product isolation by flash chromatography (22 mm, 30% EtOAc/hexane) yielded the clear colorless oil **22b** (36 mg, 23%, R_f = 0.35 in 20% EtOAc/hexane): ^{1}H NMR (due to the presence of slowly interconverting rotamers (see Boc-prolinal **5**), two peaks in a 3:1 ratio were observed for many signals; 300 MHz, $CDCl_3$) δ 5.50 and 5.36 (br s, 1, C=C*H*Br), 5.04 and 4.74 (br s, 1, NCHRC*H*R′R″), 4.12 and 4.28 (m, 1, NC*H*RR′), 3.81 and 3.72 (m, 1, C*H*CH(CH_3)$_2$), 3.45 (m, 1, NC*H*HCH$_2$), 3.32 (m, 1, NCH*H*CH$_2$), 2.30 (m, 1, C*H*(CH_3)$_2$), 1.76–1.98 (m, 4, $NCH_2CH_2CH_2$), 1.49 and 1.56 (s, 9, OC(CH_3)$_3$), 1.07 (m, 3, CH(CH_3)CH_3), 1.01 (m, 3, CH(CH_3)CH_3); mass spectrum (FAB), m/z 404/406 (M + H, 6), 348/350 (M − C_4H_8, 37), 304 (9), 170 (27), 114 (100); IR (neat) 2972, 1794 (lactone C=O), 1692 (carbamate C=O), 1646, 1392, 1366, 1167, 1119 cm^{-1}; exact mass calcd for

$C_{17}H_{27}NO_5{}^{79}Br$ *m/e* 404.1073, obsd *m/e* 404.1075.

(3*S*,5*R*,6*S*)-2-Oxo-5-(bromoacetyl)-3-isopropyl-1-aza-4-oxabicyclo[4.3.0]nonane (24a). The Boc-protected lactone **22a** (16 mg, 0.040 mmol) was dissolved in a cold (0 °C) mixture of trifluoroacetic acid (0.25 mL) and CH_2Cl_2 (1.5 mL) and stirred until the absence of starting material was indicated by TLC (2 h). The reaction solution was then concentrated at 0 °C to give a white solid. NMR analysis indicated the presence of a 5:1 mixture of the lactam **24a** and the deprotected amino lactone trifluoroacetate salt of the starting material. Neutralization in EtOAc/saturated $NaHCO_3$ provided a quantitative yield of the amber oil **24a** (12 mg, R_f = 0.53 in 20% EtOAc/hexane): ^1H NMR (300 MHz, $CDCl_3$) δ 4.66 (d, 1, J = 3.8 Hz, C*H*COCH$_2$Br), 4.20 (AB qt, J = 9.3 Hz, $\Delta\delta$ = 0.19, COCH$_2$Br), 3.98 (d, 1, J = 2.4 Hz, C*H*CH(CH$_3$)$_2$), 3.89 ((m, 1, NC*H*RR'), 3.74 (m, 1, NC*H*HCH$_2$), 3.24 (m, 1, NCH*H*CH$_2$), 2.53 (m, 1, C*H*(CH$_3$)$_2$), 1.78–2.36 (m, 4, NCH$_2$C*H*$_2$C*H*$_2$), 1.08 (d, 3, J = 5.6 Hz, CH(C*H*$_3$)CH$_3$), 0.90 (d, 3, J = 5.4 Hz, CH(CH$_3$)C*H*$_3$); mass spectrum (FAB), 304/306 (M + H, 31), 281 (86), 262 (57), 226 (100), 119 (100); exact mass calcd for $C_{12}H_{19}NO_3{}^{79}Br$ *m/e* 304.0548, obsd *m/e* 304.0561.

(3*S*,5*S*,6*S*)-2-Oxo-5-(bromoacetyl)-3-isopropyl-1-aza-4-oxabicyclo[4.3.0]nonane (24b). The Boc-protected lactone **22b** (16 mg, 0.040 mmol) and toluenesulfonic acid monohydrate (8 mg, 0.042 mmol) were dissolved dry CH_3CN (1.5 mL) and stirred for 30 h. NMR analysis of the concentrated reaction mixture showed a less than 1:5 ratio of the lactam **24b** to the deprotected amino lactone toluenesulfonic acid salt of the starting material. The small amount of lactone present was converted to the lactam **24b** by exposure to an excess of *N*-methylmorpholine in EtOAc. The product was isolated by flash chromatography (22 mm, 20% EtOAc/hexane) to give the amber oil **24b** (9.8 mg, 84%, R_f = 0.53 in 20% ethyl acetone/hexane): ^1H NMR (300 MHz, $CDCl_3$) δ 4.26 (AB qt, J = 13 Hz, $\Delta\delta$ = 0.15, COC*H*$_2$Br), 3.83 (m, 2, C*H*C-OCH$_2$Br and C*H*CH(CH$_3$)$_2$), 3.65 (m, 1, NC*H*RR'), 3.57 (m, 2, NCH$_2$CH$_2$), 2.52 (m, 1, CH(CH$_3$)$_2$), 2.34 (m, 1, NCH$_2$CHHC*H*H), 2.04 (m, 1, NCH$_2$C*H*HCHH), 1.84 (m, 1, NCH$_2$CH*H*CHH), 1.59 (m, 1, NCH$_2$CHHCH*H*), 1.13 (d, 3, J = 7.3 Hz, CH(C*H*$_3$)CH$_3$), 0.98 (d, 3, J = 7.2 Hz, CH(CH$_3$)C*H*$_3$); ^{13}C NMR (300 MHz, $CDCl_3$) δ 198.9 (*C*OCH$_2$Br), 167.1 (*N*COR), 80.3 (*C*HCOCH$_2$Br), 79.9 (*C*HCH(CH$_3$)$_2$), 58.4 (NCHRR'), 44.9 (NCH$_2$), 31.9 (CO*C*H$_2$Br), 30.9 (CH(CH$_3$)$_2$), 30.5 (NCH$_2$*C*H$_2$), 22.5 (NCH$_2$*C*H$_2$), 19.8 (CH$_3$), 17.7 (CH$_3$); mass spectrum (FAB), 304/306 (M + H, 53) 226 (43), 135 (74), 119 (100); IR (neat) 2963, 1740 (ketone C=O), 1650 (amide C=O), 1451, 1074, 1011 cm^{-1}; exact mass calcd for $C_{12}H_{19}NO_3{}^{79}Br$ *m/e* 304.0548, obsd *m/e* 304.0551.

(3*S*,5*S*,2'*S*)-3-Isopropyl-5-[*N*-(methoxysuccinyl-L-alanyl-L-alanyl)pyrrolidin-2'-yl]-6-methylene-4-oxatetrahydro-2-pyranone (1a). Trifluoroacetic acid (5 μL) was added to a solution of the acid **21a** (70 mg, 0.146 mmol) and mercuric trifluoroacetate (11 mg, 0.029 mmol) dissolved in acetonitrile (5 mL). After being stirred for 12 h, the reaction solution was concentrated, and the product was purified by flash chromatography (22 mm, 35% acetone/EtOAc) to give a clear colorless oil (17 mg, 24%) that was homogeneous by TLC (R_f = 0.37 in 40% acetone/EtOAc): ^1H NMR (500 MHz, $CDCl_3$, structural assignments are based on a COSY experiment) δ 7.04 (br d, 1, J = 6.7 Hz, amide NH), 6.39 (br s, 1, J = 6.7 Hz, amide NH), 4.87 (d, 1, J = 2.6 Hz, CdbdC*H*H), 4.86 (m, 1, OC*H*RC(R')=CH$_2$), 4.68 (m, 1, NC*H*(CH$_3$)CONH), 4.48 (m, 1, NC*H*(CH$_3$)CONRR'), 4.54 (s, 1, C=CH*H*), 4.40 (m, 1, NCH$_2$CH$_2$CH$_2$C*H*R), 3.98 (d, 1, J = 8.7 Hz, C*H*CH(CH$_3$)$_2$), 3.70 (m, 1, NC*H*HCH$_2$), 3.67 (s, 3, CO$_2$CH$_3$), 3.48 (m, 1, NCH*H*CH$_2$), 2.66 (m, 2, CH$_2$C*H*$_2$CO$_2$CH$_3$), 2.50 (m, 2, C*H*$_2$CH$_2$CO$_2$CH$_3$), 2.18 (m, 1, CHC*H*(CH$_3$)$_2$), 1.88–2.16 (m, 4, NCH$_2$C*H*$_2$C*H*$_2$), 1.34 (d, 3, J = 7.0 Hz, NCH(C*H*$_3$)CO), 1.32 (d, 3, J = 6.9 Hz, NCH(C*H*$_3$)CO), 0.97 (d, 3, J = 6.6 Hz, CH-(C*H*$_3$)CH$_3$), 0.93 (d, 3, J = 6.5 Hz, CH(CH$_3$)C*H*$_3$); mass spectrum (FAB), *m/z* 482 (M + H, 100), 380 (15), 309 (23), 279 (25), 186 (43); IR (neat) 3403 (br), 3009, 1653 (br), 1406, 1315, 1019 cm^{-1}; exact mass calcd for $C_{23}H_{36}N_3O_8$ *m/e* 482.2502, obsd *m/e* 482.2503.

(3*S*,5*R*,2'*S*)-3-Isopropyl-5-[*N*-(methoxysuccinyl-L-alanyl-L-alanyl)pyrrolidin-2'-yl]-6-methylene-4-oxatetrahydro-2-pyranone (1b). Method A. Trifluoroacetic acid (3 μL) was added to a solution of the acid **21b** (50 mg, 0.104 mmol) and mercuric trifluoroacetate (12 mg, 0.031 mmol) dissolved in CH_3CN (5 mL). After being stirred for 12 h, the reaction solution was concentrated, and the product was purified by flash chromatography (22 mm, 45% acetone/EtOAc) to give a clear colorless oil (9 mg, 18%) that was homogeneous by TLC (R_f = 0.35 in 40% acetone/EtOAc): ^1H NMR (500 MHz, $CDCl_3$, structural assignments are based on a COSY experiment) δ 6.93 (br d, 1, J = 6.7 Hz, amide NH), 6.30 (br d, 1, J = 6.9 Hz, amide NH), 4.96 (m, 1, OC*H*RC(R')=CH$_2$), 4.93 (m,, 1, C=C*H*H), 4.68 (m, 1, NC*H*(CH$_3$)CONH), 4.43–4.50 (m, 2, NC*H*(CH$_3$)CONRR' and NCH$_2$CH$_2$CH$_2$C*H*R), 4.39 (s, 1, C=CH*H*), 3.82 (d, 1, J = 3.9 Hz, C*H*CH(CH$_3$)$_2$), 3.69 (s, 3, CO$_2$CH$_3$), 3.44 (m, 2, NC*H*$_2$CH$_2$), 2.66 (m, 2, CH$_2$C*H*$_2$CO$_2$CH$_3$), 2.51 (m, 2, C*H*$_2$CH$_2$CO$_2$CH$_3$), 2.26 (m, 1, CHC*H*(CH$_3$)$_2$), 1.91–2.03 (m, 4, NCH$_2$C*H*$_2$C*H*$_2$), 1.37 (d, 3, J = 7.3 Hz, NCH(C*H*$_3$)CO), 1.36 (d, 3, J = 7.2 Hz, NCH(C*H*$_3$)CO), 1.07 (d, 3, J = 6.8 Hz, CH(C*H*$_3$)CH$_3$), 1.02 (d, 3, J = 6.7 Hz, CH(CH$_3$)C*H*$_3$); mass spectrum (FAB), *m/z* 482 (M + H, 42), 380 (25), 309 (100), 279 (43), 226 (40), 186 (74); IR (neat) 3416 (br), 3005, 1653 (br), 1437, 1406, 1316, 1021 cm^{-1}; exact mass calcd for $C_{23}H_{36}N_3O_8$ *m/e* 482.2502, obsd *m/e* 482.2497.

Method B. The Boc-protected lactone **15b** (15 mg, 0.046 mmol) was deprotected by dissolution into a cold (−10 °C) mixture of trifluoroacetic acid (0.5 mL) and CH_2Cl_2 (1.5 mL). After 1.5 h, the reaction mixture was concentrated, and the crude amino lactone trifluoroacetate salt was dissolved in 0.25 mL of THF.

To a cold (−10 °C) solution of methoxysuccinyl-L-alanyl-L-alanine[17] dissolved in 0.75 mL of THF were added Et_3N (6.4 μL, 0.046 mmol) and isobutyl chloroformate (5.9 μL, 0.046 mmol). After 6 min, Et_3N (6.4 μL, 0.046 mmol) was added, followed by the amino lactone solution, prepared as described above, over a 1-min period. After 15 min, the reaction solution was diluted into EtOAc, washed (saturated $NaHCO_3$), dried ($MgSO_4$), and concentrated to a red-orange oil that was purified by flash chromatography (10 mm, gradient eluted with 18–100% acetone/EtOAc) to give the lactone **1b** as a clear colorless oil (3.5 mg, 32%, R_f = 0.22 in 30% acetone/EtOAc), that was shown by ^1H NMR and MS to be identical with the product prepared by method A: exact mass calcd for $C_{23}H_{36}N_3O_8$ *m/e* 482.2502, obsd *m/e* 482.2496.

***tert*-Butyl (2*S*,4*R*,2'*S*)-4-(*N*-(*n*-Butyloxycarbonyl)-pyrrolidin-2'-yl)-2-isopropyl-3-oxahex-5-ynoate (25a).** To a cold (0 °C) solution of the amine **19a** (0.783 mL, 2.79 mmol) and *N*-methylmorpholine (0.321 mL, 2.93 mmol) dissolved in 30 mL of THF was slowly added, over a 5-min period, *n*-butyl chloroformate (0.372 mL, 2.93 mmol). The resulting solution was allowed to stir 5 min at 0 °C and then 1.5 h at room temperature. The reaction mixture was then diluted into EtOAc and product isolation (saturated NH_4Cl, brine, $MgSO_4$) gave an amber oil that was purified by flash chromatography (43 mm, 18% EtOAc/hexane) to give the clear colorless oil **25a** (0.754 g, 71%, R_f = 0.34 in 18% EtOAc/hexane): ^1H NMR (due to the presence of slowly interconverting rotamers (see Boc-prolinal **5**), two peaks in a 2:1 ratio were observed for many signals, and other peaks were broadened; 300 MHz, $CDCl_3$) δ 4.59 and 4.44 (m, 1, NCHRC*H*R''), 4.0–4.12 (m, 2, C*H*CH(CH$_3$)$_2$ and OC*H*$_2$CH$_2$) 3.84 (m, 1, NCHRR'), 3.40–3.51 (m, 2, NCH$_2$), 2.39 (m, 1, HCCR), 2.51 (m, 1, CH(CH$_3$)$_2$), 1.80–2.13 (m, 4, NCH$_2$C*H*$_2$C*H*$_2$), 1.61 (m, 2, OCH$_2$C*H*$_2$), 1.44 (s, 9, OC(CH$_3$)$_3$), 1.41 (m, 2, OCH$_2$CH$_2$C*H*$_2$), 0.93 (m, 9, CH(C*H*$_3$)$_2$ and OCH$_2$CH$_2$CH$_2$C*H*$_3$); mass spectrum, *m/z* 381 (M$^+$, 1), 325 (1), 280 (3), 224 (10), 170 (100), 114 (11), 70 (15), 57 (10); IR (neat) 2965, 2876, 2120, 1741 (ester C=O), 1698 (carbamate C=O), 1417, 1369, 1138, 1109 cm^{-1}; exact mass calcd for $C_{21}H_{35}NO_5$ *m/e* 381.2515, obsd *m/e* 381.2515.

***tert*-Butyl (2*S*,4*S*,2'*S*)-4-(*N*-(*n*-Butyloxycarbonyl)-pyrrolidin-2'-yl)-2-isopropyl-3-oxahex-5-ynoate (25b).** To a cold (0 °C) solution of the amine **19b** (1.50 g, 5.34 mmol) and N-methylmorpholine (0.645 mL, 5.87 mmol) dissolved in 50 mL of THF was slowly added, over a 5-min period, *n*-butyl chloroformate (0.747 mL, 5.87 mmol). The resulting solution was allowed to stir 5 min at 0 °C and then 1.0 h at room temperature. The reaction mixture was then diluted into EtOAc, and product isolation (saturated NH_4Cl, brine, $MgSO_4$) gave an amber oil that was purified by flash chromatography (60 mm, 24% EtOAc/hexane) to give the clear colorless oil **25b** (0.754 g, 71%, R_f = 0.38 in 24% EtOAc/hexane): ^1H NMR (due to the presence of slowly interconverting rotamers (see Boc-prolinal **5**), two peaks in a 1:1 ratio were observed for many signals, and other peaks were broadened; 300 MHz, $CDCl_3$) δ 4.76 and 4.54 (m, 1, NCHRC*H*R''), 4.03–4.12 (m, 3, OCH$_2$ and NCHRR'), 3.59 and 3.64 (d, 1, J = 5.6 Hz, C*H*CH(CH$_3$)$_2$), 3.43 (m, 2, NCH$_2$), 2.33 (m,

1, HCCR), 2.02–2.14 (m, 2, $CH(CH_3)_2$ and $NCH_2CH_2CH_2$), 1.80 (m, 2, NCH_2CH_2), 1.62 (m, 2, OCH_2CH_2), 1.49 (br s, 9, $OC(CH_3)_3$), 1.43 (m, 2, $OCH_2CH_2CH_2$), 0.95 (m, 9, $CH(CH_3)_2$ and $OCH_2CH_2CH_2CH_3$); mass spectrum (FAB), m/z 382 (M+H, 53), 326 (100), 225 (27), 170 (100); IR (neat) 2963, 2876, 2110 (acetylene), 1744 (ester C=O), 1701 (carbamate C=O), 1367, 1165, 1088 cm^{-1}; exact mass calcd for $C_{21}H_{36}NO_5$ m/e 382.2593, obsd m/e 382.2609.

(2*S*,4*R*,2′*S*)-4-(*N*-(*n*-Butyloxycarbonyl)pyrrolidin-2′-yl)-2-isopropyl-3-oxahex-5-ynoic Acid (26a). Trifluoroacetic acid (7 mL) was slowly added, over a 1-min period, to a cold (0 °C) solution of the ester **25a** (0.705 g, 1.85 mmol) dissolved in 21 mL of CH_2Cl_2. After being stirred for 8 h at room temperature, the reaction mixture was concentrated and subjected to flash chromatography (43 mm, 9:0.9:0.1 CH_2CH_2/methanol/acetic acid) to yield a viscous oil. Bulb-to-bulb distillation (240 °C (0.05 Torr)) provided a white solid (0.511 g, 85%, R_f = 0.5 in 9:0.9:0.1 CH_2Cl_2/methanol/acetic acid): mp 60–62 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 4.59 (m, 1, NCHRC*H*R′R″), 4.12 (m, 1, NC*H*RR′), 4.10 (t, 2, J = 6.6 Hz, OCH_2CH_2), 4.03 (d, 2, J = 3.7 Hz, $CHCH(CH_3)_2$), 3.49 (m, 2, NCH_2), 2.46 (d, 1, J = 1.9 Hz, HCCR), 2.15–2.18 (m, 4, $NCH_2CH_2CH_2$), 1.83 (m, 1, $CH(CH_3)_2$), 1.61 (m, 2, OCH_2CH_2), 1.38 (m, 2, $OCH_2CH_2CH_2$), 1.04 (d, 3, J = 6.8 Hz, $CH(CH_3)CH_3$), 0.94 (m, 6, $CH(CH_3)CH_3$ and $OCH_2CH_2CH_2CH_3$); mass spectrum (FAB), m/z 326 (M + H, 100), 244 (23), 170 (95), 114 (47); IR (melt) 3292 (br), 2965, 2112, 1717, 1657, 1439, 1207, 1062 cm^{-1}; exact mass calcd for $C_{17}H_{28}NO_5$ m/e 326.1967, obsd m/e 326.1962.

(2*S*,4*S*,2′*S*)-4-(*N*-(*n*-Butyloxycarbonyl)pyrrolidin-2′-yl)-2-isopropyl-3-oxahex-5-ynoic Acid (26b). Trifluoroacetic acid (12 mL) was slowly added, over a 1-min period, to a cold (0 °C) solution of the ester **25a** (1.20 g, 3.15 mmol) dissolved in 30 mL of CH_2Cl_2. After being stirred for 8 h at room temperature, the reaction mixture was concentrated and subjected to flash chromatography (43 mm, 9:0.9:0.1 CH_2Cl_2/methanol/acetic acid), followed by bulb-to-bulb distillation (240 °C (0.05 Torr)) to yield a viscous oil (0.704 g, 69%, R_f = 0.5 in 9:0.9:0.1 CH_2Cl_2/methanol/acetic acid): ^1H NMR (300 MHz, $CDCl_3$) δ 4.49 (d, 1, J = 7.9 Hz, NCHRC*H*R′R″), 4.22 (d, 2, J = 4.8 Hz, $CHCH(CH_3)_2$), 3.89 (m, 3, NC*H*RR′ and OCH_2CH_2), 3.47 (m, 2, NCH_2), 2.58 (s, 1, HCCR), 1.84–2.27 (m, 5, $NCH_2CH_2CH_2$ and $CH(CH_3)_2$), 1.62 (m, 2, OCH_2CH_2), 1.41 (m, 2, $OCH_2CH_2CH_2$), 0.98 (m, 9, $CH(CH_3)_2$ and $OCH_2CH_2CH_2CH_3$); mass spectrum (FAB), m/z 326 (M + H, 100), 309 (10), 279 (30), 170 (68); IR (melt) 3240 (br), 2965, 2876, 2112, 1740, 1697, 1419, 1201, 1078 cm^{-1}; exact mass calcd for $C_{17}H_{28}NO_5$ m/e 326.1967, obsd m/e 326.1959.

(3*S*,5*S*,2′*S*)-5-(*N*-(*n*-Butyloxycarbonyl)pyrrolidin-2′-yl)-6(*E*)-(bromomethylene)-3-isopropyl-4-oxatetrahydro-2-pyranone (2a). A mixture of the acetylenic acid **26a** (100 mg, 0.308 mmol) and powdered $KHCO_3$ (31 mg, 0.308 mmol) dissolved in 30 mL of dry CH_2CN was warmed to 50 °C, allowed to stir for 30 min, and cooled to room temperature. *N*-Bromosuccinimide (58 mg, 0.323 mmol) was added, and the reaction mixture was stirred under protection from light for 45 h and quenched with 5% $Na_2S_2O_3$. Product isolation (CH_2Cl_2, Na_2SO_4) gave an oil that was purified by flash chromatography (30 mm, 30% EtOAc/hexane) to give a white solid (11.4 mg, 9%) that was shown to be pure by TLC and GC analysis (TLC R_f = 0.40 in 30% ethyl acetate/hexane): mp 71–72 °C; ^1H NMR (due to the presence of slowly interconverting rotamers (see Boc-prolinal **5**), two peaks in a 1:1 ratio were observed for most signals, and other peaks were broadened; 300 MHz, $CDCl_3$) δ 6.11 and 6.14 (s, 1, C=CHBr), 4.83 and 5.11 (d, 1, J = 7.4 Hz and 5.6 Hz, NCHRC*H*R′R″), 4.32 and 4.42 (m, 1, NCHRR′), 4.11 and 4.14 (d, 1, J = 6.3 and 6.4 Hz, $CHCH(CH_3)_2$), 4.07 (m, 2, OCH_2), 3.47 (br m, 2, NCH_2), 2.18 (m, 1, $CH(CH_3)_2$), 1.93–2.03 (m, 4, $NCH_2CH_2CH_2$), 1.61 (m, 2, OCH_2CH_2), 1.38 (m, 2, $OCH_2CH_2CH_2$), 0.99 (m, 3, $OCH_2CH_2CH_2CH_3$), 0.94 (d, 3, J = 7.4 Hz, $CH(CH_3)CH_3$), 0.92 (d, 3, J = 7.3 Hz, $CH(CH_3)CH_3$); mass spectrum (FAB), m/z 404/406 (M + H, 24), 362 (12), 296 (23), 170 (100); IR ($CHCl_3$) 2963, 1762 (lactone C=O), 1682 (carbamate C=O), 1423, 1223, 1130, 891 cm^{-1}; exact mass calcd for $C_{17}H_{27}NO_5{}^{79}Br$ m/e 404.1073 obsd m/e 404.1082.

(3*S*,5*R*,2′*S*)-5-(*N*-(*n*-Butyloxycarbonyl)pyrrolidin-2′-yl)-6(*E*)-(bromomethylene)-3-isopropyl-4-oxatetrahydro-2-pyranone (2b). This compound was prepared using the acetylenic acid **26b** by the same method described above for lactone **2a**. The product (24.2 mg, 19%), a light amber oil, was homogeneous by TLC (R_f = 0.42 in 25% EtOAc hexane): ^1H NMR (due to the presence of slowly interconverting rotamers (see Boc-prolinal **5**), two peaks in a 1.2:1 ratio were observed for most signals, and other peaks were broadened; 300 MHz, $CDCl_3$) δ 6.27 and 6.30 (s, 1, C=CHBr), 5.09 and 5.26 (d, 1, J = 7.4 Hz and 5.6 Hz, NCHRC*H*R′R″), 4.29 and 4.35 (m, 1, NC*H*RR′), 4.09 (m, 2, OCH_2), 3.74 (br s, 1, $CHCH(CH_3)_2$), 3.32–3.54 (br m, 2, NCH_2), 2.27 (m, 1, $CH(CH_3)_2$), 1.78–2.06 (m, 4, $NCH_2CH_2CH_2$), 1.63 (m, 2, OCH_2CH_2), 1.41 (m, 2, $OCH_2CH_2CH_2$), 1.10 (d, 3, J = 7.4 Hz, $CH(CH_3)CH_3$), 1.04 (d, 3, J = 7.3 Hz, $CH(CH_3)CH_3$), 0.96 (m, 3, $OCH_2CH_2CH_2CH_3$); mass spectrum (FAB), m/z 404/406 (M + H, 38), 382 (39), 362 (57), 296 (26), 171 (70), 170 (100); IR (neat) 2961, 1792 (lactone CO), 1700 (carbamate CO), 1645, 1369, 1117, 972 cm^{-1}; exact mass calcd for $C_{17}H_{27}NO_5{}^{79}Br$ m/e 404.1073, obsd m/e 404.1074.

(3*S*,5*S*,2′*S*)-5-(*N*-(*n*-Butyloxycarbonyl)pyrrolidin-2′-yl)-6-methylene-3-isopropyl-4-oxatetrahydro-2-pyranone (1c). To a solution of the acetylenic acid **36a** (25 mg, 0.077 mmol) dissolved in 4 mL of CH_3CN was added mercuric trifluoroacetate (12 mg, 0.031 mmol) and trifluoroacetic acid (1 μL). After 15 h, the solution was concentrated and subjected to flash chromatography (12 mm, 25% EtOAc/hexane) to provide the clear colorless oil **1c** (7.1 mg, 28%, R_f = 0.39 in 33% ethyl acetate/hexane): ^1H NMR (due to the presence of slowly interconverting rotamers (see Boc-prolinal **5**), two peas in a 1:1 ratio were observed for most signals, and other peaks were broadened; 300 MHz, $CDCl_3$) δ 4.86 (s, 1, C=C*H*H), 4.80 and 4.89 (s, 1, NCHRC*H*R′R″), 4.45 (s, 1, C=CH*H*), 4.31 and 4.37 (m, 1, NCHRR′), 4.00–4.16 (m, 3, OCH_2 and $CHCH(CH_3)_2$), 1.81–2.07 (m, 4, $NCH_2CH_2CH_2$), 1.61 (m, 2, OCH_2CH_2), 1.39 (m, 2, $OCH_2CH_2CH_2$), 0.92–1.03 (m, 9, $OCH_2CH_2CH_2CH_3$ and $CH(CH_3)_2$); mass spectrum (FAB), m/z 326 (M + H, 96), 289 (23), 226 (30), 171 (56), 170 (100), 114 (48); IR (neat) 2963, 2876, 1769 (lactone C=O), 1696 (carbamate C=O), 1418, 1213, 1107 cm^{-1}; exact mass calcd for $C_{17}H_{28}NO_5$ m/e 326.1967, obsd m/e 326.1959.

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Registry No. **1a**, 132127-35-6; **1b**, 132201-34-4; **1c**, 132127-36-7; **2a**, 132127-37-8; **2b**, 132127-38-9; **4**, 69610-40-8; **5**, 69610-41-9; (3*R*)-**6**, 132127-39-0; (2*S*)-**6**, 132127-40-3; (3*R*)-**7**, 132127-41-4; (3*S*)-**7**, 132127-42-5; **8a**, 132127-43-6; **8b**, 132201-35-5; **9a**, 132127-44-7; **9b**, 132201-36-6; **10**, 132127-45-8; (3*R*)-**11**, 132127-46-9; (3*S*)-**11**, 132201-37-7; **12**, 132127-47-0; **14a**, 132127-48-1; **14b**, 132201-38-8; **15a**, 132127-49-2; **15b**, 132201-39-9; **16a**, 132127-50-5; **19a**, 132127-51-6; **19b**, 132201-40-2; **20a**, 132127-52-7; **20b**, 132201-41-3; **21a**, 132127-53-8; **21b**, 132201-42-4; **22a**, 132127-54-9; **22b**, 132127-55-0; **24a**, 132127-56-1; **24b**, 132201-43-5; **25a**, 132127-57-2; **25b**, 132201-44-6; **26a**, 132127-58-3; **26b**, 132201-45-7; (*S*)-MTPA-Cl, 20445-33-4; Boc-Pro-OH, 15761-39-4; MeOSuc-Ala-Ala-OH, 102284-27-5; N_2=CHCOOEt, 623-73-4; $Me_3SiC{\equiv}CH$, 1066-54-2; (*R*)-$Me_2CHCHBrCOOH$, 76792-22-8; $Me_2C{=}CH_2$, 115-11-7; serine protease, 37259-58-8.

Supplementary Material Available: ^1H NMR spectra for **1a–b**, **2a–b**, **14a–b**, **15a–b**, **21a–b**, **22b**, and **26a–b** (13 pages). Ordering information is given on any current masthead page.