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The Synthesis of Azapeptidomimetic β-Lactam Molecules as Potential Protease Inhibitors

William P. Malachowski,* Chenyang Tie,† Katherine Wang,† and Robert L. Broadrup†

Department of Chemistry and Physics, The University of New England, Biddeford, Maine 04005, and Department of Chemistry, Bryn Mawr College, Bryn Mawr, Pennsylvania 19010-2899

wmalacho@brynmawr.edu

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Synthetic methods for the construction of a novel peptidomimetic structure are reported. The structure incorporates a β-lactam and an azapeptide in a peptide backbone with the intention of generating rationally designed substrate-based protease inhibitors. The β-lactam is formed by subjecting serine or threonine-azapeptides to Mitsunobu reaction conditions. Importantly, the azapeptidomimetic β-lactam structure permits extended binding inhibition and the synthetic methods to create tetrapeptidomimetic structures are described.

Introduction

Peptidomimetic molecules represent valuable structures because they mimic certain properties of proteins, such as three-dimensional structure, while conferring unique properties, such as enhanced stability to degradation or inhibition of normal peptide processing. In particular, peptidomimetic protease inhibitors, both natural and synthetic, have often initiated drug development programs to identify therapeutic agents.[1] Peptidomimetic inhibitors of serine and cysteine proteases typically place a reactive electrophilic functionality near the scissile bond of a normal protease substrate. The electrophilic group traps the nucleophilic serine hydroxyl group or cysteine thiol at the active site, thereby terminating the enzyme's catalytic activities.

Interactions on both the prime and nonprime side[2] of the scissile bond of protease ligands have been shown to enhance selectivity and catalytic activity with substrates,[3] and increase the strength of protease inhibitors.[4] Four commonly used electrophilic groups, aldehydes,[5] boronic acids,[6] chloromethyl ketones,[7] and trifluoromethyl ketones,[8] are structurally limited in their ability to generate so-called extended binding interactions (interactions between the inhibitor and the target enzyme on both sides of the scissile bond). Although there are a few structurally related inhibitors[4] that exploit interactions on either side of the scissile bond, the majority of protease inhibitors using these popular electrophilic groups do not exploit extended binding to maximize inhibitor strength. An inhibitor design that uses a reactive, electrophilic group, which is capable of forming extended binding interactions, is shown in Figure 1. Use of the reactive monocyclic β-lactam group as a serine[9] and cysteine[9f,g,10] protease inhibitor has been reported, although few of the reports are with peptidomimetic structures. Otto and co-workers have reported[9f,g] peptidomimetic β-lactam serine and cysteine protease inhibi-

* Address correspondence to this author at the Department of Chemistry, Bryn Mawr College, 101 N. Merion Ave., Bryn Mawr, PA 19010-2899.

† Bryn Mawr College.

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(2) Prime and nonprime refers to terminology originally proposed by I. Schechter and A. Berger (*Biochem. Biophys. Res. Commun.* **1967**, *27*, 157). The prime amino acids in a protease substrate extend in the carboxy terminal direction from the scissile bond starting with P_1'. The nonprime residues extend from the scissile bond in the amino terminal direction beginning with P_1. The subsites in the enzyme associated with each amino acid position are denoted with S, e.g. S_1' or S_1.

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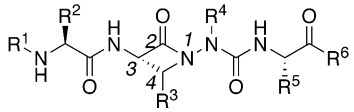

FIGURE 1. Azapeptidomimetic β-lactams.

tors; however, the inhibitors do not exploit extended binding interactions.

The inhibitor design shown in Figure 1 actually accomplishes extended binding by fusing azapeptides with the monocyclic β-lactam. Azapeptides have also demonstrated serine[11] and cysteine[12] protease inhibition. As the fusion of two documented protease inhibitor functionalities, the azapeptidomimetic β-lactam inhibitor design in Figure 1 represents a second generation of protease inhibitor design. It is anticipated that the use of an azapeptide in the P_1' position of the peptidomimetic structure will make the β-lactam carbonyl more reactive. The reactivity should be enhanced due to the polar effect of the α-nitrogen and the associated stabilization of the N-1 hydrazide leaving group on β-lactam cleavage.

In addition to affording enhanced reactivity of the β-lactam ring and the potential for extended binding interactions, it was anticipated that the use of an azapeptide in the P_1' position would allow efficient β-lactam synthesis. β-Lactam synthesis with acyl hydrazides has been reported,[13] although not with azapeptides. Efficient β-lactam synthesis can be accomplished under Mitsunobu conditions, due to the reduction in pK_a for the amide nitrogen in the acyl hydrazine.[14]

There are many synthetic methods for β-lactam synthesis, nevertheless the Mitsunobu cyclization reaction was considered especially attractive for C-3 amino, C-4 unsubstituted β-lactams (Figure 1, $R^3 = H$), which was one of the simplest inhibitors proposed and one of the initial targets. More popular methods of β−lactam synthesis, such as ester enolate−imine[15] and ketene−imine cycloadditions,[16] are not well-suited for the synthesis of C-3 amino, C-4 unsubstituted monocyclic β-lactams.[17]

Although recent structural studies[18] with peptidomimetic monocyclic β-lactam compounds have indicated β-turn character, the structures reported in the literature have notable differences with those proposed in this paper for the protease inhibitor design. For instance, one structure with well-characterized β-turn character[18a] has two quaternary α-carbons that further bias the peptidomimetic monocyclic β-lactam toward a folded secondary structure.[19] In addition, the prediction of inhibitor potential from static structural studies is untenable if enzymes bind substrates and inhibitors in a dynamic process by an induced fit[20] or by stabilization of conformational ensembles,[21] as is currently accepted.

Results and Discussion

A retrosynthetic analysis of the proposed azapeptidomimetic β-lactam inhibitors **1** (Scheme 1) focused our attention on a core monocyclic β-lactam structure **2** that could be extended in both the prime and nonprime directions by the appropriate reactions. Prime residues could be attached by reaction of a peptide isocyanate with the N-1 hydrazine group, while nonprime residues would be attached with standard peptide coupling reactions with the C-3 amino group. Subjecting an appropriately protected serine/threonine-azapeptide to Mitsunobu conditions could provide the important monocyclic β-lactam core **3**. Peptide coupling of a protected derivative of serine or threonine with an azapeptide would generate the starting material **4** for the Mitsunobu cyclization reaction.

Azapeptide Synthesis. The azapeptides were all synthesized from carbamoylation of various alkyl hydrazine compounds. Methyl hydrazine is commercially available and therefore was used first to develop most of the chemistry that follows. Reaction of methyl hydrazine with benzyl chloroformate (Cbz-Cl) under Schotten−Bauman conditions (Scheme 2) provided benzyl azaalanine **5**. Alternatively, reaction of methyl hydrazine with di-*tert*-butyl dicarbonate (Boc_2O) afforded the *tert*-butyl ester of azaalanine **6**.

It was considered important that the synthesis of the proposed inhibitors allow for a variety of azapeptides in the P_1' position. For this reason, the benzyl esters of azavaline (**7**), azaleucine (**8**), and azaphenylalanine (**9**) have been similarly generated from the reaction of benzyl

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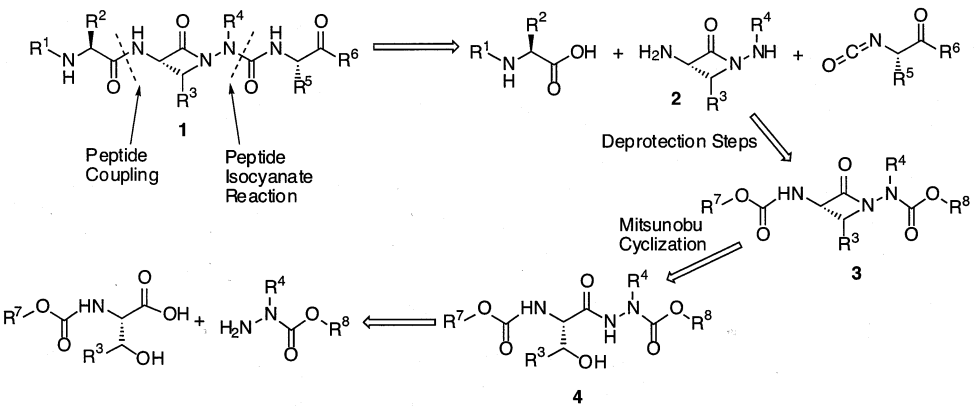
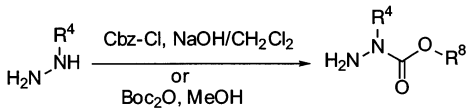
SCHEME 1

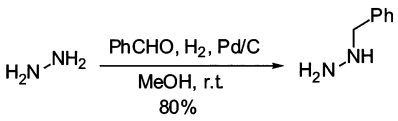


SCHEME 2



R^4	R^8	Product	Yield
CH_3	Bn	**5**	55%
CH_3	t-Bu	**6**	83%
i-Pr	Bn	**7**	64%
i-Bu	Bn	**8**	82%
Bn	Bn	**9**	38%

SCHEME 3



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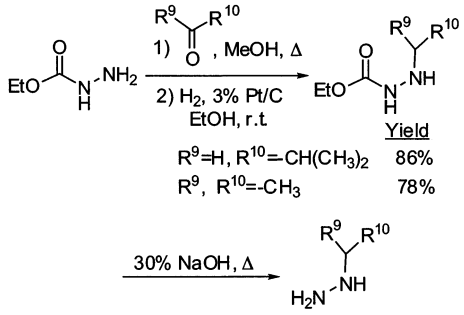

chloroformate with isopropyl hydrazine, isobutyl hydrazine, and benzyl hydrazine, respectively (Scheme 2). Since isopropyl, isobutyl, and benzyl hydrazine are not commercially available, literature methods were adapted to generate these alkyl and alkaryl hydrazine derivatives. Benzyl hydrazine was synthesized by direct reductive amination between hydrazine and benzaldehyde (Scheme 3). The analogous reductive aminations with acetone and isobutyraldehyde did not prove as effective, so a reductive amination with ethyl carbazate was performed (Scheme 4).[22] Hydrolysis of the ethyl carbamate afforded isopropyl and isobutyl hydrazine.

***β*-Lactam Core Synthesis.** Coupling of benzyl azaalanine (**5**) with *N*-*tert*-butoxycarbonyl-serine (*N*-Boc-serine) to yield **10** (Scheme 5) was most efficiently accomplished with 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ),[23] although a variety of agents (EDC,[24] BOP, and ethyl chloroformate) were tried. Subjecting pure serine-azaalanine to Mitsunobu conditions,[25] triphenylphosphine (Ph_3P) and diethyl azodicarboxylate (DEAD), afforded cyclized *β*-lactam product **11**, but the diethyl hydrazinodicarboxylate side product was difficult to separate. Use of di-*tert*-butyl azodicarboxylate (DBAD) afforded easier chromatographic separations of the *β*-lactam product and the di-*tert*-butyl hydrazinodicarboxylate side product. Coupling of *tert*-butyl azaalanine (**6**) with *N*-benzyloxycarbonyl-serine (*N*-Cbz-serine) also took place in good yield and subsequent cyclization under Mitsunobu conditions was similarly efficient providing an 89% yield of **13**. The use of the alternative protecting group combination was intended to provide flexibility in subsequent transformations that extended the *β*-lactam core. A two-step procedure involving mesylation (methanesulfonyl chloride, pyridine) of the serine alcohol of **10** followed by cyclization under mildly basic conditions (K_2CO_3, acetone, reflux) provided only 33% yield of the *β*-lactam product.[26]

Subsequent work has focused on applying the Mitsunobu conditions to a variety of analogues of serine-azaalanine (Scheme 5). Consequently, serine-azavaline (**14**), serine-azaleucine (**16**) and serine-azaphenylalanine (**18**) have all been synthesized in good yield with EEDQ coupling reactions. Subjecting each dipeptide to Mitsunobu conditions has been similarly efficient. In the Mitsunobu cyclization of **14**, **16**, and **18**, the choice of dialkyl azodicarboxylate was adjusted to provide the optimum conditions for chromatographic purification of the *β*-lactam product, i.e., maximum separation between the products (**15**, **17**, and **19**) and the dialkyl hydrazinodicarboxylate side product.

In addition to serine-azapeptides, threonine-azaalanine has also been successfully cyclized (Scheme 5). Coupling of *N*-Boc-threonine with benzyl azaalanine (**5**) was accomplished efficiently with EEDQ. Subjecting the dipep-

(22) Giegy, J. R. Monosubstituted Hydrazines. Swiss Patent 307,-629, Aug. 16, 1955; *Chem. Abstr.* **1957**, *51*, 3113f.

(23) (a) Belleau, B.; Malek, G. *J. Am. Chem. Soc.* **1968**, *90*, 1651. (b) Kiso, Y.; Yajima, H. *J. Chem. Soc., Chem. Commun.* **1972**, 942.

(24) Abbreviations: EDC, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride; BOP, benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate.

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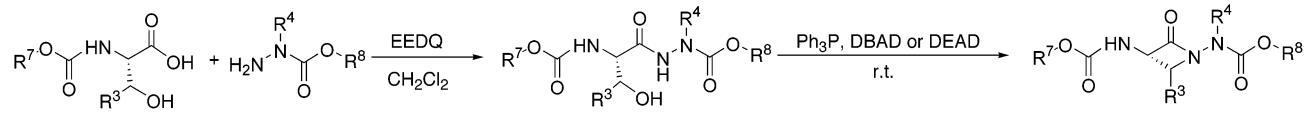
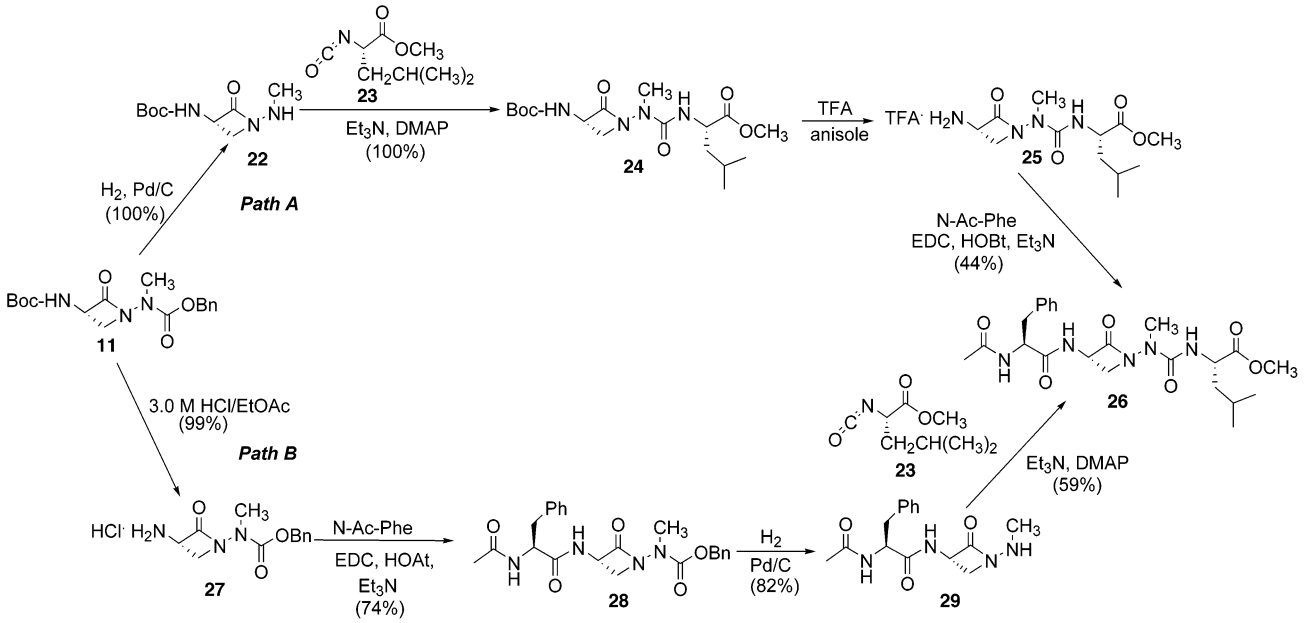
(26) The two-step procedure has been used as an alternative to Mitsunobu conditions for serine hydroxamate cyclization to a *β*-lactam. See: Floyd, D. M.; Fritz, A. W.; Cimarusti, C. M. *J. Org. Chem.* **1982**, *47*, 176.

SCHEME 5



	Azaamino acid	Product	Yield	Dialkyl azodicarboxylate	Product	Yield
Serine-Azapeptides, R^3=H						
Ser-Aala, R^4=CH_3						
R^7=t-Bu, R^8=Bn	**5**	**10**	67%	DBAD	**11**	88%
R^7=Bn, R^8=t-Bu	**6**	**12**	78	DBAD	**13**	89
Ser-Aval, R^4=i-Pr						
R^7=t-Bu, R^8=Bn	**7**	**14**	79	DEAD	**15**	71
Ser-Aleu, R^4=i-Bu						
R^7=t-Bu, R^8=Bn	**8**	**16**	75	DEAD	**17**	79
Ser-Aphe, R^4=Bn						
R^7=t-Bu, R^8=Bn	**9**	**18**	56	DBAD	**19**	48
Threonine-Azapeptides, R^3=CH_3						
Thr-Aala, R^4=CH_3						
R^7=t-Bu, R^8=Bn	**5**	**20**	89	DBAD	**21**	90

SCHEME 6



tide product **20** to Mitsunobu conditions (Ph_3P, DBAD) afforded a good yield of the β-lactam product.[27]

Extension of the Azapeptidomimetic β-Lactam Core. Important to the inhibitor design was the potential to test extended binding inhibitors. Consequently, the next stage of the synthesis required methods to elaborate the dipeptidomimetic β-lactam core, **3**, into the tetrapeptidomimetic structures **1**. Initially, the focus turned to what was regarded as the more difficult step in the process: carboxy terminal elaboration. Elaboration in the amino terminal direction would occur with standard peptide coupling procedures. To begin carboxy terminal elaboration, deprotection of the benzyloxycarbonyl (Cbz) group of **11** was accomplished uneventfully under hydrogenation conditions (Scheme 6, path A). The product **22** was fairly stable, but was usually reacted immediately with leucine methyl ester isocyanate **23**.[28] Four different conditions were explored for the isocyanate reaction with the hydrazino derivative **22**. Initially, when **22** and **23** were combined at room temperature, they failed to provide any product. Upon heating at 42 °C overnight, the reaction did occur to afford a 70% yield of **24**. The use of triethylamine (Et_3N), as a proton scavenger, allowed the reaction to occur at room temperature to afford 72% yield of the urea product **24**. Finally, use of the acylation catalyst 4,4′-(dimethylamino)pyridine (DMAP), in addition to Et_3N, provided **24** in 100% yield.

Deprotection of the amino-terminal Boc group with trifluoroacetic acid (TFA) went smoothly to afford **25**, the TFA salt of the amine. However, coupling with *N*-acetylalanine did not provide any product after column chromatography. There was some concern that the polarity

(27) Based on literature precedent with the Mitsunobu reaction of acyl hydroxamates (see: Miller, M. J.; Mattingly, P. G.; Morrison, M. A.; Kerwin, J. F., Jr. *J. Am. Chem. Soc.* **1980**, *102*, 7026), the β-carbon of L-threonine should undergo inversion of configuration. However, the stereochemistry at C-4 of the azetidinone in **21** could not be determined due to spectral broadening from rotamers.

(28) (a) Nowick, J. S.; Powell, N. A.; Nguyen, T. M.; Noronha, G. *J. Org. Chem.* **1992**, *57*, 7364. (b) Tsai, J. H.; Takaoka, L. R.; Powell, N. A.; Nowick, J. S. *Org. Synth.* **2000**, *78*, 220.

TABLE 1. Peptide Coupling Conditions to 28

27 → 28 (*N*-Ac-Phe) Conditions[30]	Yield
EDC, HOBt, Et_3N THF/DMF	61%
PyBOP, iPr_2NEt, DMF	43%
HATU, iPr_2NEt, DMF	60%
i-BCF, iPr_2NEt, DMF	20%
EDC, HOAt, Et_3N, DMF	74%

of the tetrapeptidomimetic and the absence of a chromophore in the product made purification by silica gel column chromatography difficult. Consequently, the next attempt coupled *N*-acetyl-phenylalanine (*N*-Ac-Phe) to the amine and afforded a 44% yield of **26** after column chromatographic purification. The product **26** represents a tetrapeptidomimetic β-lactam molecule capable of presenting P_2, P_1, P_1', and P_2' side chains to a protease enzyme.

The disappointingly low yield for the final step in path A was partially attributed to the presence of the TFA salt that can compete with the carboxylic acid component for carbodiimide in coupling reactions. Deprotection of the Boc group of **24** with BBr_3[29] afforded the HBr salt, but the subsequent coupling reaction with *N*-Ac-Phe did not proceed as desired. Bubbling HCl gas through an ethyl acetate solution of **24** at low temperature (−45 °C) led to decomposition of the β-lactam. It also appeared that the methyl ester of leucine was being cleaved under the strong acid reaction conditions.

Rather than consume more of precious compound **24** and to avoid potential cleavage problems with the methyl ester of leucine, deprotection of the Boc group was tested on compound **11**. Treatment of **11** with 3.0 M HCl in ethyl acetate (EtOAc) afforded the HCl salt of the amine **27** (Scheme 6, path B) in quantitative yield. Peptide coupling with *N*-Ac-Phe and EDC was accomplished in 61% yield. A study of this peptide coupling reaction was undertaken with a variety of peptide coupling reagents (Table 1). The optimum conditions used EDC with 1-hydroxy-7-azabenzotriazole (HOAt) to provide a 74% yield of **28**. Deprotection of **28** under hydrogenation conditions afforded **29**, which underwent reaction with leucine isocyanate (**23**) at room temperature in the presence of Et_3N (57% yield) or in the presence of Et_3N and DMAP (59% yield) to afford **26**.

Surprisingly, the intermediates in the second pathway were significantly less soluble in many organic solvents than the intermediates in the first pathway. This solubility problem contributed to lower yields in the hydrogenation reaction and the conversion of **29** to **26** in the second pathway. Although the deprotection procedure for the Boc group and the subsequent coupling with *N*-Ac-Phe was improved in path B, the hydrogenolytic deprotection of the Cbz group and the coupling reaction with **23** were not as efficient in path B as in path A. In the final analysis, both paths had a similar overall yield, 44% for path A and 35% for path B, for the four-step sequence to extend the dipeptidomimetic β-lactam core into a tetrapeptidomimetic β-lactam structure.

(29) Mattiingly, P. G.; Miller, M. J. *J. Org. Chem.* **1981**, *46*, 1557.

Conclusion

A flexible and efficient synthesis of azapeptidomimetic β-lactams has been accomplished. The current synthetic sequence provides ample opportunity to further modify side chain groups in positions on both sides of the scissile bond. As illustrated with threonine, the use of different β-substituted serine derivates will provide alternative P_1 side chains. The P_1' side chain can be modified by the use of different azapeptides in a manner analogous to the use of azavaline, azaleucine, and azaphenylalanine. Finally, the use of alternative amino acids or amino ester isocyanates will afford different groups in the P_2 and P_2' positions. In addition, the potential exists, in the current scheme, for even longer extension with the use of polypeptides in place of *N*-Ac-Phe or peptide isocyanates[31] for leucine methyl ester isocyanate. The flexibility of the synthesis and the efficiency of the β-lactam synthesis is currently being exploited to generate and test potential protease inhibitors. Inhibition studies will be forthcoming.

Experimental Section

General Methods. Unless otherwise stated, all air- or moisture-sensitive reactions were performed with magnetic stirring in oven-dried glassware under an argon or nitrogen atmosphere using dry, distilled solvents. Tetrahydrofuran (THF) was dried over microwave-activated 4-Å molecular sieves. Methylene chloride (CH_2Cl_2), ethyl acetate (EtOAc), and triethylamine (Et_3N) were distilled from calcium hydride. Methanol was dried over Mg and distilled. All other commercially obtained reagents were used as received. The 3.0 M HCl solution in EtOAc was generated by bubbling HCl gas into a cooled (−15 °C) solution of EtOAc. All reactions were monitored by thin-layer chromatography (TLC) using silica gel 60 Å K6F (0.25 mm) or silica gel 60 Å 5−17 mym particle size (0.25 mm) precoated glass-backed plates. TLC was visualized with UV light (254 nm), iodine, or ninhydrin. Flash chromatography was performed with the indicated solvent system using 0.040−0.060 mm silica gel (230−400 mesh) or silica gel 60 Å (200−400 mesh). Concentration refers to the removal of solvent with a rotary evaporator at normal aspirator pressure followed by further evacuation with a two-stage mechanical pump. Yields refer to chromatographically and spectroscopically pure compounds, except as otherwise indicated. All melting points were determined with an open capillary. ^1H and ^{13}C NMR spectra were recorded at 300 MHz. Chemical shifts were reported in δ values relative to tetramethylsilane in ^1H NMR and the solvent peak in ^{13}C NMR. Elemental analyses were conducted by Quantitative Technologies Inc., Whitehouse, NJ.

Comment on the Compiled Spectral Data. For several of the compounds reported (**10**−**21**), substantial peak broadening was seen presumably due to rotamers; however, high-temperature NMR studies did not improve peak resolution.

Benzyl Azaalanine (5). Methyl hydrazine (7.0 mL, 132 mmol) was dissolved in CH_2Cl_2 (140 mL) and cooled to 0 °C.

(30) Coupling reagent abbreviations: EEDQ, 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline; HOBt, 1-hydroxybenzotriazole hydrate; PyBOP, benzotriazol-1-yl-*N*-oxy-tris(dimethylamino)phosphonium hexafluorophosphate; HATU, *N*-[(dimethylamino)-1*H*-1,2,3-triazolo[4,5-*b*]-pyridino-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide; i-BCF, isobutylchloroformate.

(31) (a) Nowick, J. S.; Holmes, D. L.; Noronha, G.; Smith, E. M.; Nguyen, T. M.; Huang, S.-L. *J. Org. Chem.* **1996**, *61*, 3929. (b) Nowick, J. S.; Holmes, D. L.; Noronha, G.; Smith, E. M.; Nguyen, T. M.; Huang, S.-L.; Wang, E. H. *J. Org. Chem.* **1998**, *63*, 9144.

Sodium hydroxide (1.0 M, 106 mL) was added slowly and the biphasic mixture was stirred rapidly for 5 min. Benzyl chloroformate (14.4 mL, 101 mmol) was added dropwise and the reaction was slowly warmed to room temperature and stirred for 4 h. The reaction solution was separated and the organic layer was washed with H_2O and brine, dried with Na_2SO_4, filtered, and concentrated in vacuo. Purification of the crude oil by distillation (bp 104−134 °C, 0.2 mmHg) provided pure product as a yellow oil (10.01 g, 55% yield). ^{1}H NMR, ^{13}C NMR, and IR spectra matched a previous report of benzyl azaalanine (1-methyl-1-benzyloxycarbonylhydrazine).[32]

***tert*-Butyl Azaalanine (6).** Di-*tert*-butyl dicarbonate (1.55 g, 7.10 mmol) was dissolved in MeOH (10 mL) and treated with methyl hydrazine (0.50 mL, 9.4 mmol). The reaction was stirred for 40 min and then concentrated in vacuo to afford a yellow oil (0.868 g, 83% yield). ^{1}H NMR, ^{13}C NMR, and IR spectra matched a previous report of *tert*-butyl azaalanine (1-methyl-1-*tert*-butoxycarbonylhydrazine).[30]

Benzyl Azavaline (7). Ethyl carbazate (10.4 g, 0.100 mol) and acetone (5.8 g, 0.100 mol) were heated to reflux temperature for 12 h in CH_3OH (150 mL). Methanol was removed in vacuo to yield a solid hydrazone (14.2 g, 98% yield) that was used immediately in the next step. The hydrazone was dissolved in ethanol (150 mL) and reduced at atmospheric pressure under hydrogen in the presence of 3% Pt/C (500 mg). The catalyst was removed by filtration through Celite and the solvent was evaporated to give ethyl 2-isopropylcarbazate (11.5 g, 80% yield). The carbazate (11.5 g, 79 mmol) and 30% NaOH (53 mL) were heated to reflux for 12 h. The reaction was cooled to room temperature and CH_2Cl_2 (100 mL) was added. The biphasic mixture was cooled to 0 °C and benzyl chloroformate (8.7 mL, 61 mmol) was added dropwise. The mixture was stirred at 0 °C for 30 min, then warmed to room temperature and stirred overnight. The organic layer was washed with water and brine, dried with Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (eluted with 1:1 hexanes/EtOAc) to give **7**, 8.1 g (64% yield), as an opaque liquid. ^{1}H NMR ($CDCl_3$) δ 7.34 (s, 5 H), 5.15 (s, 2 H), 4.32 (m, 1 H), 3.67 (s, 2 H), 1.12 (d, 6 H, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$) δ 157.3, 136.8, 128.6, 128.2, 128.0, 67.5, 48.7, 19.6. IR ($CDCl_3$) 1689 cm^{-1}.

Benzyl Azaleucine (8). The reaction procedure was identical with that for benzyl azavaline (**7**), except isobutyraldehyde was used in place of acetone. The yield of the hydrazone was 94% and the hydrogenation product, ethyl 2-isobutylcarbazate, was obtained in 91% yield. The final step to afforded compound **8** (opaque liquid) in an 82% yield. ^{1}H NMR ($CDCl_3$) δ 7.33 (s, 5 H), 5.14 (s, 2 H), 4.07 (s, 2 H), 3.23 (d, 2 H, J = 7.2 Hz), 2.0 (m, 1 H), 0.87 (d, 6 H, J = 6.5 Hz). ^{13}C NMR ($CDCl_3$) δ 157.8, 136.6, 128.5, 128.0, 127.9, 67.5, 57.8, 26.8, 19.8. IR ($CDCl_3$) 1691 cm^{-1}.

Benzyl Azaphenylalanine (9). Benzaldehyde (11.7 mL, 115 mol) and hydrazine (3.6 mL,115 mmol) were dissolved in CH_3OH (150 mL). The mixture was reduced at atmospheric hydrogen pressure in the presence of 10% Pd/C (2 g). The catalyst was removed by filtration through Celite and the solvent was evaporated to give benzylhydrazine (11.1 g, 91 mmol) in 79% yield. Benzylhydrazine was dissolved in 100 mL of CH_2Cl_2, then cooled to 0 °C. Sodium hydroxide (1 M, 74 mL) was added and benzyl chloroformate (10 mL, 70 mmol) was added dropwise. The mixture was stirred at 0 °C for 30 min, then warmed to room temperature and stirred overnight. The organic layer was washed with water and brine, dried with Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (eluted with 1:1 hexanes/EtOAc) to give **9** (6.77 g, 38% yield) as an opaque liquid. ^{1}H NMR ($CDCl_3$) δ 7.34−7.22 (m, 10 H), 5.18 (s, 2 H), 4.60 (s, 2 H), 4.04 (br s, 2 H). ^{13}C NMR ($CDCl_3$) δ 157.6, 137.3, 136.4, 128.5, 128.3, 128.2, 128.1, 128.0, 127.5, 67.8, 54.5. IR ($CDCl_3$) 1689 cm^{-1}.

(32) Brosse, N.; Pinto, M.-F.; Jamart-Gregoire, B. *J. Org. Chem.* **2000**, *65*, 4370.

Benzyl *N*-(*tert*-Butoxycarbonyl)-L-serine-azaalanine (10). *N*-Boc-serine (1.10 g, 5.35 mmol) was suspended in CH_2Cl_2 (10 mL) and cooled to 0 °C. Benzyl azaalanine (917 mg, 5.09 mmol) was added as a CH_2Cl_2 solution (5 mL). The reaction was cooled to −12 °C and EEDQ (1.52 g, 6.11 mmol) was added as a CH_2Cl_2 solution (5 mL). The reaction was slowly warmed to room temperature and stirred overnight. The reaction was concentrated in vacuo and loaded on a silica gel column. The product was eluted with 1:1 hexanes/EtOAc to afford an opaque oil (1.26 g, 67% yield). ^{1}H NMR ($CDCl_3$) δ 9.32 (br s, 1 H), 7.31 (s, 5 H), 5.91 (br s, 1 H), 5.11 (s, 2 H), 4.33 (br s, 1 H), 3.91−3.67 (m, 2 H), 3.17 (s, 3 H), 1.41 (s, 9 H). ^{13}C NMR ($CDCl_3$) δ 170.8, 156.4, 155.6, 135.4, 128.3, 128.0, 127.6, 80.1, 68.1, 62.8, 54.4, 37.7, 28.0. IR (neat) 3428, 3305, 1722, 1676 cm^{-1}.

***tert*-Butyl *N*-(Benzyloxycarbonyl)-L-serine-azaalanine (12).** The reaction procedure was identical with that for benzyl *N*-(Boc)-L-serine-azaalanine (**10**) except *N*-Cbz-serine and **6** were used. The reaction afforded a 78% yield of **12**, a colorless oil. ^{1}H NMR ($CDCl_3$) δ 8.76 (br s, 1 H), 7.31 (s, 5 H), 5.92 (d, 1 H, J = 7.1 Hz), 5.10 (s, 2 H), 4.29 (br s, 1 H), 3.96 (d, 1 H, J = 6.7 Hz), 3.09 (s, 3 H), 1.43 (s, 9 H). ^{13}C NMR ($CDCl_3$) δ 170.4, 156.2, 155.6, 135.8, 128.3, 128.0, 127.8, 82.0, 66.9, 62.6, 54.9, 37.9, 27.9. IR (neat) 3436, 3283, 1729, 1691 cm^{-1}.

Benzyl *N*-(*tert*-Butoxycarbonyl)-L-serine-azavaline (14). The reaction procedure was identical with that for benzyl *N*-(Boc)-L-serine-azaalanine (**10**) except azavaline was used instead of azaalanine. The reaction afforded a white foam **14** in 79% yield. ^{1}H NMR ($CDCl_3$) δ 8.13 (br s, 1 H), 7.33 (s, 5 H), 5.50 (br s, 1 H), 5.15 (s, 2 H), 4.44 (br s, 1 H), 4.18 (br s, 1 H), 3.98 (br s, 1 H), 3.60 (br s, 1 H), 1.44 (s, 9 H), 1.14 (d, 6 H, J = 6.4 Hz). ^{13}C NMR ($CDCl_3$) δ 172.0, 155.8, 135.9, 128.7, 128.4, 128.1, 80.7, 68.4, 63.0, 54.6, 50.4, 28.4, 19.9. IR ($CDCl_3$) 3432, 2983, 1699 cm^{-1}.

Benzyl *N*-(*tert*-Butoxycarbonyl)-L-serine-azaleucine (16). The reaction procedure was identical with that for benzyl *N*-(Boc)-L-serine-azaalanine (**10**) except azaleucine was used in place of azaalanine. The reaction afforded a white foam **16** in 75% yield. ^{1}H NMR ($CDCl_3$) δ 8.79 (br s, 1 H), 7.33 (s, 5 H), 5.64 (br s, 1 H), 5.14 (s, 2 H), 4.24 (br s, 1 H), 4.10 (br s, 1 H), 3.96 (br s, 1 H), 3.64 (br s, 1 H), 3.36 (s, 2 H), 1.89 (s, 1 H), 1.43 (s, 9 H), 0.90 (s, 6 H). ^{13}C NMR ($CDCl_3$) δ 171.4, 156.8, 155.8, 135.7, 128.6, 128.3, 128.0, 80.6, 68.6, 63.2, 57.9, 54.7, 28.3, 26.9, 20.0. IR ($CDCl_3$) 3432, 2982,1698 cm^{-1}.

Benzyl *N*-(*tert*-Butoxycarbonyl)-L-serine-azaphenylalanine (18). The reaction procedure was identical with that for benzyl *N*-(Boc)-L-serine-azaalanine (**10**) except azaphenylalanine was used instead of azaalanine. The reaction afforded a white foam **18** in 56% yield. ^{1}H NMR ($CDCl_3$) δ 8.92 (br s, 1 H), 7.27−7.23 (m, 10 H), 5.68 (br s, 1 H), 5.10 (s, 2 H), 4.66 (s, 2 H), 4.15 (br s, 1 H), 3.98 (br s, 1 H), 3.76 (br s, 1 H), 3.51 (br s, 1 H), 1.33 (m, 9 H). ^{13}C NMR ($CDCl_3$) δ 169.7, 154.5, 134.7, 134.3, 128.3, 127.3, 127.1, 126.7, 126.6, 79.1, 67.3, 61.7, 53.5, 52.9, 27.7. IR ($CDCl_3$) 3431, 2983, 1699 cm^{-1}.

Benzyl *N*-(*tert*-Butoxycarbonyl)-L-threonine-azaalanine (20). The reaction procedure was identical with that for benzyl *N*-(Boc)-L-serine-azaalanine (**10**) except *N*-(Boc)-L-threonine was used instead of *N*-(Boc)-L-serine. The reaction afforded an opaque/cloudy yellow oil **20** in 93% yield. ^{1}H NMR ($CDCl_3$) δ 8.97 (s, 1 H), 7.33 (s, 5 H), 5.76 (br s, 1 H), 5.14 (s, 2 H), 4.27 (2 br s, 2 H), 3.60 (br s, 1 H), 3.24 (s, 3 H), 1.44 (s, 9 H), 1.26 (br s, 3 H). ^{13}C NMR ($CDCl_3$) δ 170.8, 156.4, 156.1, 135.6, 128.4, 128.1, 127,9, 80.3, 68.2, 67.6, 58.1, 38.3, 28.2, 19.5. IR ($CDCl_3$) 3428, 2983, 1720, 1699 cm^{-1}.

1-[(*N*-Methyl,*N*-benzyloxycarbonyl)-amino]-3-[(*tert*-butoxycarbonyl)amino]-2-azetidinone (11). Benzyl *N*-(Boc)-L-serine-azaalanine (7.15 g, 19.5 mmol) was combined with Ph_3P (5.62 g, 21.4 mmol) in THF (250 mL) and the homogeneous solution was treated with DBAD (4.93 g, 21.4 mmol). The DBAD was added in three portions allowing the yellow color of the reaction solution to fade with each addition. After being stirred overnight at room temperature, the reaction was

concentrated in vacuo and subjected to silica gel chromatography (eluted with 2:1 hexanes/EtOAc). A white crystalline solid, 6.00 g (88% yield), was obtained which was further purified by recrystallization (EtOAc/Hex) for analysis. Mp 99−101 °C. ^{1}H NMR ($CDCl_3$) δ 7.36 (s, 5 H), 5.35 (br s, 1 H), 5.16 (s, 2 H), 4.70 (br s, 1 H), 3.77 (br s, 1 H), 3.49 (br s, 1 H), 3.19 (s, 3 H), 1.44 (s, 9 H). ^{13}C NMR ($CDCl_3$) δ 166.3, 154.7, 135.4, 128.6, 128.4, 128.0, 80.5, 68.4, 55.2, 51.7, 36.1, 28.2. IR ($CDCl_3$) 3433, 1790, 1717 cm^{-1}. Anal. Calcd for $C_{17}H_{23}N_3O_5$: C, 58.44; H, 6.63; N, 12.03. Found: C, 58.49; H, 6.69; N, 11.99.

1-[(*N*-Methyl,*N*-*tert*-butoxycarbonyl)amino]-3-[(benzyloxycarbonyl)amino]-2-azetidinone (13). The reaction procedure was identical with that for **11** except **12** was used to afford an 89% yield of the product **13**. Mp 109.5−111 °C. ^{1}H NMR ($CDCl_3$) δ 7.34 (s, 5 H), 5.51 (br s, 1 H), 5.12 (s, 2 H), 4.72 (br s, 1 H), 3.79 (br s, 1 H), 3.53 (s, 1 H), 3.12 (s, 3 H), 1.46 (s, 9 H). ^{13}C NMR ($CDCl_3$) δ 165.6, 155.5, 153.7, 135.8, 128.5, 128.3, 128.1, 82.3, 67.3, 55.4, 51.4, 35.8, 28.1. IR ($CDCl_3$) 3437, 1792, 1717 cm^{-1}. Anal. Calcd for $C_{17}H_{23}N_3O_5$: C, 58.44; H, 6.63; N, 12.03. Found: C, 58.54; H, 6.70; N, 11.91.

1-[(*N*-Isopropyl,*N*-benzyloxycarbonyl)amino]-3-[(*tert*-butoxycarbonyl)amino]-2-azetidinone (15). The reaction procedure was identical with that for **11** except serine-azavaline **14** was used in place of **10** and DEAD was used instead of DBAD. The DEAD was added slowly dropwise to allow the yellow color of the reaction to fade. Column chromatography was performed with 3:1 hexanes/EtOAc. The β-lactam **15** was isolated as a white solid in 71% yield. Mp 95−96 °C. ^{1}H NMR ($CDCl_3$) δ 7.41−7.31 (m, 5 H), 5.15 (s, 2 H), 4.79 (br s, 1 H), 4.37 (br s, 1 H), 3.78 (br s, 1 H), 3.44 (br s, 1 H), 1.44 (s, 9 H), 1.20 (d, 6 H, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$) δ 168.6, 154.9, 154.1, 135.6, 128.8, 128.7, 128.2, 80.5, 68.5, 55.4, 55.6, 50.4, 28.3, 20.5. IR ($CDCl_3$) 3438, 2983, 1792, 1716 cm^{-1}. Anal. Calcd for $C_{19}H_{27}N_3O_5$: C, 60.46; H, 7.21; N, 11.13. Found: C, 60.05; H, 7.12; N, 10.91.

1-[(*N*-Isobutyl,*N*-benzyloxycarbonyl)amino]-3-[(*tert*-butoxycarbonyl)amino]-2-azetidinone (17). The reaction procedure was identical with that for **11** except serine-azaleucine **16** was used in place of **10** and DEAD was used instead of DBAD. Column chromatography was performed with 3:1 hexanes/EtOAc. The β-lactam **17** was isolated as a white solid in 75% yield. Mp 94−96 °C. ^{1}H NMR ($CDCl_3$) δ 7.40−7.33 (m, 5 H), 5.16 (s, 2 H), 4.74 (br s, 1 H), 3.78 (br s, 1 H), 3.37 (br s, 1 H), 3.31 (d, 2 H, J = 7.4 Hz), 1.95−1.84 (m, 1 H), 1.43 (s, 9 H), 0.93 (d, 6 H, J = 6.5 Hz). ^{13}C NMR ($CDCl_3$) δ 167.1, 154.9, 135.6, 128.7, 128.5, 128.0, 80.4, 68.5, 56.4, 55.1, 53.0, 28.3, 27.1, 19.8. IR ($CDCl_3$) 3439, 2966, 1792, 1717 cm^{-1}. Anal. Calcd for $C_{20}H_{29}N_3O_5$: C, 61.36; H, 7.47; N, 10.73. Found: C, 61.31; H, 7.60; N, 10.62.

1-[(*N*-Benzyl,*N*-benzyloxycarbonyl)amino]-3-[(*tert*-butoxycarbonyl)amino]-2-azetidinone (19). The reaction procedure was identical with that for **11** except serine-azaphenylalanine **18** was used and column chromatography was performed with 3:1 hexanes/EtOAc. The β-lactam **19** was isolated as a white solid in 48% yield. Mp 97−98 °C. ^{1}H NMR ($CDCl_3$) δ 7.34−7.31 (m, 10 H), 5.20 (s, 2 H), 4.95 (br s, 1 H), 4.71 (s, 2 H), 4.61 (br s, 1 H), 3.39 (br s, 1 H), 3.10 (br s, 1 H), 1.41 (s, 9 H). ^{13}C NMR ($CDCl_3$) δ 165.5, 153.6, 153.4, 134.5, 134.3, 127.6, 127.4, 127.1, 126.7, 79.4, 67.6, 54.1, 52.5, 51.9, 27.1. IR ($CDCl_3$) 3440, 2983, 1791, 1717 cm^{-1}. Anal. Calcd for $C_{23}H_{27}N_3O_5$: C, 64.93; H, 6.40; N, 9.88. Found: C, 64.70; H, 6.24; N, 9.93.

1-[(*N*-Methyl,*N*-benzyloxycarbonyl)amino]-3-[(*tert*-butoxycarbonyl)amino]-4-methyl-2-azetidinone (21). The reaction procedure was identical with that for **11** except threonine-azaphenylalanine **20** was used. The product was eluted with 1:1 hexanes/EtOAc to afford a yellow oil in 76% yield. ^{1}H NMR ($CDCl_3$) δ 7.40 (s, 5 H), 5.11 (s, 2 H), 4.27 (br s, 1 H), 4.21 (br s, 1 H), 3.80 (br s, 1 H), 3.24 (s, 3 H), 1.44 (s, 12 H). ^{13}C NMR ($CDCl_3$) δ 165.2, 154.9, 135.4, 129.4, 128.3, 127.9, 80.3, 68.4, 61.8, 61.5, 28.2, 27.7, 16.5. IR ($CDCl_3$) 3321, 2972, 1780, 1706 cm^{-1}.

1-[(*N*-Methyl)amino]-3-[(*tert*-butoxycarbonyl)amino]-2-azetidinone (22). 1-[(*N*-Methyl,*N*-benzyloxycarbonyl)amino]-3-[(*tert*-butoxycarbonyl)amino]-2-azetidinone (**11**, 200 mg, 0.573 mmol) was dissolved in methanol (8 mL) and Pd/C (20 mg) was added. The reaction atmosphere was purged with hydrogen (3×) and the reaction was left stirring under hydrogen for 2 h. The reaction mixture was filtered through Celite and concentrated to afford 129 mg (100% yield) of **22**. Mp 158−159.5 °C. ^{1}H NMR ($CDCl_3$) δ 5.43 (d, 1 H, J = 6.9 Hz), 4.62 (bs, 1 H), 4.10 (d, 1 H, J = 4.9 Hz), 3.70 (t, 1 H, J = 5.0 Hz), 3.37 (dd, 1 H, J = 5.0, 2.2 Hz), 2.70 (d, 3 H, J = 5.0 Hz), 1.44 (s, 9 H). ^{13}C NMR ($CDCl_3$) δ 166.2, 155.0, 80.3, 54.6, 51.4, 36.5, 28.2. IR ($CDCl_3$) 3442, 1769, 1717, 1508, 1370, 1249, 1164 cm^{-1}. Anal. Calcd for $C_9H_{17}N_3O_3$: C, 50.21; H, 7.96; N, 19.53. Found: C, 50.16; H, 7.95; N, 19.27.

1-[(*N*-Methyl)-*N*-(carbonyl-L-(methylleucyl))amino]-3-[(*tert*-butoxycarbonyl)amino]-2-azetidinone (24). Hydrazine derivative **22** (573 mg, 2.67 mmol) was dissolved in CH_2Cl_2 (40 mL), cooled to 0 °C, and treated with leucine isocyanate, methyl ester **23** (830 mg, 4.85 mmol) dissolved in CH_2Cl_2 (25 mL), Et_3N (0.950 mL, 6.82 mmol), and DMAP (69 mg, 0.565 mmol). The reaction was stirred for 22 h, then the reaction solution was concentrated and subjected to column chromatography (gradient: 1:1 hexane/EtOAc to EtOAc). The product **24** was obtained as a white crystalline solid (1.030 g, 100% yield), mp 136−8 °C. ^{1}H NMR ($CDCl_3$) δ 7.07 (d, 1 H, J = 8.2 Hz), 5.63 (d, 1 H, J = 7.1 Hz), 4.42 (q, 1 H, J = 7.8 Hz), 4.31 (m, 1 H), 3.80 (m, 2 H), 3.70 (s, 3 H), 3.12 (s, 3 H), 1.71 (m, 3 H), 1.44 (s, 9 H), 0.93 (t, 6 H, J = 6.0 Hz). ^{13}C NMR ($CDCl_3$) δ 173.7, 165.9, 156.8, 154.8, 81.3, 55.8, 52.4, 52.0, 48.3, 40.4, 34.4, 28.2, 24.9, 22.8, 21.7. IR ($CDCl_3$) 3460, 3354, 1793, 1736, 1706, 1671, 1508, 1471, 1370, 1254, 1165 cm^{-1}. Anal. Calcd for $C_{17}H_{30}N_4O_6$: C, 52.84; H, 7.83; N, 14.49. Found: C, 52.96; H, 7.85; N, 14.42.

1-[[*N*-Methyl,*N*-(carbonyl-L-(methylleucyl))]amino]-3-amino-2-azetidinone, Trifluoroacetate Salt (25). Trifluoroacetic acid (1.0 mL) was added to **24** (155 mg) dissolved in CH_2Cl_2 (5 mL) and anisole (0.5 mL) at 0 °C. The reaction was warmed to room temperature and stirred for 3.5 h. Concentration of the reaction solution afforded a viscous light-orange oil. The crude trifluoroacetate salt **25** was in excess of a quantitative yield (186 mg) and was used immediately in the next coupling reaction.

1-[(*N*-Methyl,*N*-benzyloxycarbonyl)amino]-3-amino-2-azetidinone, Hydrochloride Salt (27). 1-[(*N*-Methyl,*N*-*tert*-butoxycarbonyl)amino]-3-[benzyloxycarbonylamino]-2-azetidinone (**11**, 243 mg, 0.695 mmol) was treated with 3.0 M HCl in EtOAc (2.32 mL) at room temperature for 0.5 h. The reaction solution was concentrated in vacuo with a bath temperature maintained below 35 °C. Coevaporation with toluene and chloroform provided a white solid **7** (195 mg, 99% yield), mp 176−7 °C dec. ^{1}H NMR (CD_3OD) δ 7.40−7.33 (m, 5 H), 5.22 (s, 2 H), 4.92 (s, 3 H), 4.54 (dd, 1 H, J = 5.6, 2.4 Hz), 3.96 (t, 1 H, J = 5.8 Hz), 3.75 (dd, 1 H, J = 6.0, 2.4 Hz), 3.23 (s, 3 H). ^{13}C NMR (CD_3OD) δ 163.1, 156.5, 137.1, 129.6, 129.5, 129.2, 69.8, 53.7, 36.5. IR (KBr) 3700−2300, 1793, 1725 cm^{-1}.

1-[(*N*-Methyl,*N*-benzyloxycarbonyl)amino]-3-[(*N*-acetyl-L-phenylalanine)amino]-2-azetidinone (28). *N*-Acetyl-phenylalanine (265 mg, 1.28 mmol) was dissolved in DMF (3.5 mL) and the solution was cooled to 0 °C and treated with EDC (245 mg, 1.28 mmol) and 1-hydroxy-7-azabenzotriazole (HOAt, 140 mg, 1.02 mmol). Ten minutes later, a DMF solution (2.0 mL) of **27** (289 mg, 1.02 mmol) was added, followed shortly thereafter by Et_3N (0.440 mL, 3.16 mmol). After warming to room temperature and stirring overnight, the reaction solution was diluted with EtOAc, washed with 5% $KHSO_4$ (twice), 5% $NaHCO_3$ (twice), water, and brine, dried with $MgSO_4$, filtered, and concentrated. The oil was subjected to column chromatography (5% MeOH/CH_2Cl_2) to affford a white foam (332 mg, 74% yield). ^{1}H NMR (CD_3OD) δ 7.76 (br s, 1 H), 7.33 (s, 5 H), 7.28−7.15 (m, 5 H), 6.77 (d, 1 H, J = 8.0 Hz), 5.13 (s, 2 H), 4.77 (q, 1 H, J = 7.3 Hz), 4.62 (br s, 1 H), 3.69 (br s, 1 H), 3.54

(s, 1 H), 3.18 (s, 3 H), 3.09 (dd, 1 H, J = 13.9, 6.4 Hz), 2.95 (dd, 1 H, J = 13.9, 7.6 Hz), 1.89 (s, 3 H). ^{13}C NMR ($CDCl_3$) δ 172.1, 170.4, 165.7, 154.8, 136.3, 135.5, 129.2, 128.5, 128.4, 128.3, 127.9, 126.9, 68.3, 54.4, 54.0, 49.7, 38.6, 38.2, 22.9. IR ($CDCl_3$) 3425, 3304, 1787, 1721, 1671 cm^{-1}.

1-[(*N*-Methyl)amino]-3-[(*N*-acetyl-L-phenylalanine)amino]-2-azetidinone (29). Compound **28** (213 mg, 0.486 mmol) was combined with 10% palladium on carbon (20 mg) in CH_3OH (7 mL) and the reaction atmosphere was purged with H_2 (3×). The reaction was stirred at room temperature under a static H_2 atmosphere for 0.5 h. Filtration through Celite and concentration in vacuo provided a white solid (121 mg, 82% yield). ^{1}H NMR (CD_3OD) δ 7.30−7.17 (m, 5 H), 4.65 (dd, 1 H, J = 5.2, 2.3 Hz), 4.58 (dd, 1 H, J = 8.7, 5.9 Hz), 3.64 (t, 1 H, J = 5.1 Hz), 3.42 (dd, 1 H, J = 4.9, 2.3 Hz), 3.12 (dd, 1H, J = 13.8, 5.9 Hz), 2.88 (dd, 1 H, J = 13.8, 8.8), 2.61 (s, 3 H), 1.89 (s, 3 H). ^{13}C NMR (CD_3OD) δ 174.0, 173.1, 168.1, 138.3, 130.3, 129.5, 127.8, 56.0, 54.4, 39.0, 35.9, 22.4. IR ($CDCl_3$) 3285, 1765, 1643, 1542 cm^{-1}.

1-[[*N*-Methyl,*N*-(carbonyl-L-(methylleucyl))]amino]-3-[(*N*-acetyl-L-phenylalanyl)amino]-2-azetidinone(26).Method A (path A): The trifluoroacetate salt **25** (161 mg, 0.402 mmol) was dissolved in THF (5 mL) and CH_2Cl_2 (5 mL) and cooled to 0 °C. The amine was sequentially treated with Et_3N (0.290 mL, 2.08 mmol), HOBt (69 mg, 0.511 mmol), *N*-acetyl-phenylalanine (127 mg, 0.613 mmol), and EDC (127 mg, 0.662 mmol). The reaction solution was allowed to slowly warm to room temperature while stirring overnight. The reaction mixture was concentrated to remove THF, dissolved in EtOAc, and washed sequentially with 10% citric acid (twice), saturated $NaHCO_3$ (twice), water, and brine. The organic layer was dried with $MgSO_4$, filtered, and concentrated. The resulting residue was purified by column chromatography (EtOAc followed by 5% MeOH/CH_2Cl_2) to afford 84 mg (44% yield) of a white solid. **Method B (path B):** Hydrazine derivative **29** (105 mg, 0.345 mmol) was suspended in CH_2Cl_2 (5 mL) and cooled to 0 °C. Leucine isocyanate (138 mg, 0.807 mmol) was added as a CH_2Cl_2 solution (3 mL), followed shortly thereafter by the addition of Et_3N (0.120 mL, 0.861 mmol) and DMAP (9.0 mg, 0.074 mmol). The reaction was warmed to room temperature and stirred overnight. The reaction solution was concentrated and the crude product was purified by column chromatography (CH_2Cl_2, then 5% MeOH/CH_2Cl_2) to afford 96 mg (59% yield) of a white solid. ^{1}H NMR ($CDCl_3$) δ 7.94 (d, 1 H, J = 6.7 Hz), 7.29−7.13 (m, 6 H), 7.00 (d, 1 H, J = 7.9 Hz), 4.73 (dd, 1 H, J = 13.4, 8.1 Hz), 4.37−4.28 (m, 2 H), 3.77 (t, 1 H, J = 4.8 Hz), 3.71 (m, 1 H), 3.65 (s, 3 Hz), 3.19 (dd, 1 H, J = 14.1, 5.2 Hz), 3.09 (s, 3 H), 2.91 (dd, 1 H, J = 14.0, 8.5 Hz), 1.88 (s, 3 H), 1.77−1.58 (m, 3 H), 0.91 (dd, 6 H, J = 9.6, 5.8 Hz). ^{13}C NMR ($CDCl_3$) δ 174.3, 172.5, 170.9, 166.1, 157.1, 136.5, 129.0, 128.4, 126.8, 55.2, 53.8, 52.4, 52.0, 47.5, 40.0, 37.2, 34.3, 24.8, 23.0, 22.8, 21.3. IR ($CDCl_3$) 3434, 3345, 1787, 1736, 1671, 1536, 1253, 1202, 1046 cm^{-1}.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of **7**−**10**, **12**, **14**, **16**, **18**, **20**, **21**, and **26**−**29**. This material is available free of charge via the Internet at http://pubs.acs.org.

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