Formation of Dihydropyridone- and Pyridone-Based Peptide Analogs through Aza-Annulation of β-Enamino Ester and Amide Substrates with α-Amido Acrylate Derivatives

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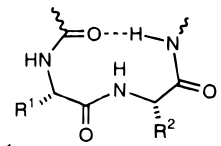
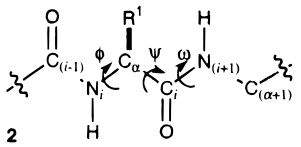
The aza-annulation of β-enamino ester and amide substrates with the mixed anhydride of 2-acetamidoacrylic acid was used for the efficient construction of highly substituted α-acetamido δ-lactam products. With the α-acetamido substituent, lactam functionality, and γ-carboxylate group, these δ-lactam products represent an interesting class of conformationally restricted dipeptide analogs. The framework of this lactam hub is structurally related to that of an α-amino acid coupled with a β-amino acid. When α-amino esters derived from naturally occurring amino acids were used in the enamine formation step, subsequent aza-annulation led to branched peptide surrogates with two C-termini that extended from a common N-terminus. Oxidation of the aza-annulation products resulted in the generation of a planar system with peptide functionality radiating from the 1, 3, and 5 positions of the pyridone hub. Alternatively, pyridone products could be formed directly from the enamino amides by reaction with 2-phenyl-4-(ethoxymethylene)oxazolone. Subsequent hydrolysis of the acetamido and ester substituents of the *N*-benzylpyridones was selectively performed to access unique β-amino acid products. Formation of the mixed anhydride of this acid, followed by amide bond formation with the ester of an α-amino acid, allowed extension of the peptide chain from the dihydropyridone structure.

Introduction

Inhibition of enzymatic pathways is one of the most efficient methods employed for the alteration of physiological processes with the use of minimal amounts of pharmacological agents. For many enzymatic processes, derivatives of amino acids are either the substrates or regulatory molecules for the catalytic action of the enzyme. Complexation of these amino acid-derived molecules with enzymes is governed by a specific combination of hydrogen bonds and hydrophobic interactions. As a result, molecular recognition is highly dependent on both the type of functional groups present and the topology of the peptide. An important class of secondary structures often involved in substrate recognition and binding are the reverse turn conformations (**1**), which include such varieties as the β- and γ-turns.[1]



1 Reverse turn



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The importance of secondary peptide structure in the process of molecular recognition has led to the strategic design and subsequent synthesis of β-turn mimics.[1] These synthetic analogs can be used to examine peptide folding processes and to probe peptide activity as a function of conformation. In some cases, these fragments can exhibit equivalent or even greater biological activity than the natural peptide substrate. An approach to the construction of peptide mimics has involved the preparation of α-amino-substituted γ-, δ-, and ϵ-lactams that restrict the conformation of the ψ dihedral angle (**2**, $N_i-C_\alpha-C_i-N_{(i+1)}$) and apply further constraints on the ω dihedral angle (**2**, $C_\alpha-C_i-N_{(i+1)}-C_{(\alpha+1)}$).[1,2] The cyclic structure provides a framework from which a variety of functional groups can radiate, and a peptide-like amide functionality is an integral part of the heterocycle that contains the peptide β-turn conformation mimic.

Further development in the use of δ-lactams as an approach to peptide mimics has led to the incorporation of conformationally restricted dipeptide δ-lactams into longer peptide sequences. Kemp *et al.*, were able to model the β-turn topology through the use of a tether between the C_α and $C_{(\alpha+1)}$ atoms and demonstrated the presence of further conformational control through intramolecular hydrogen bonding (**3**).[3] An alternative approach was developed by Freidinger *et al.*,[4] who tethered the C_α and $N_{(i+1)}$ atoms of dipeptide analogs to give **4**, and a number of conformationally restricted Freidinger-type α-amino lactams have been prepared. For example, **5** is an inhibitor of angiotensin converting enzyme (ACE).[5] This type of structure has also been

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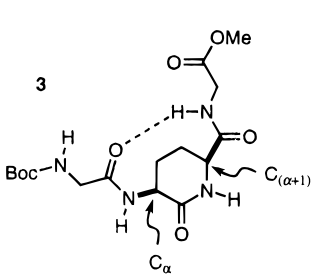
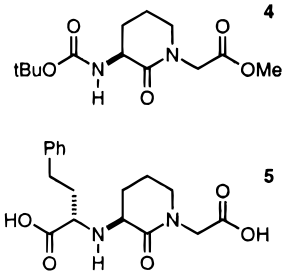
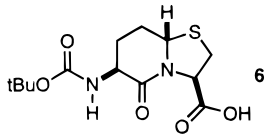
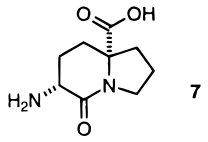




incorporated into the framework for an analog of Pro-Leu-Gly-NH_2, which serves to modulate the dopaminergic receptors in the central nervous system,[6] and as a dipeptide isostere for the Phe-His section of aspartic proteinase substrates.[7]

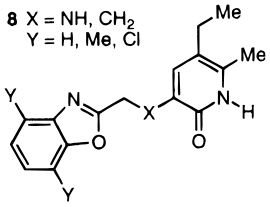
Bicyclic indolizidine structures have been used to construct conformationally restricted dipeptide models that contain Pro residues. This conceptual approach has been incorporated into the D-Phe-Pro mimic **6**, which has been used to examine the peptide folding of the type II′ β-turns present in luteinizing hormone-releasing factor, human growth hormone-releasing factor, gramicidin S, Leu-enkephalinamide, and a cyclic somatostatin analog.[8] The syntheses of potential Pro-Phe and Ala-Pro type II β-turn mimics,[9] as well as the type VI turn Gly[6]-Pro[7] analog **7**, which has been incorporated into bradykinin,[10] have also been reported.

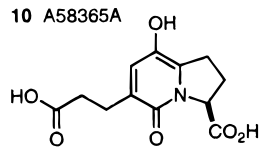


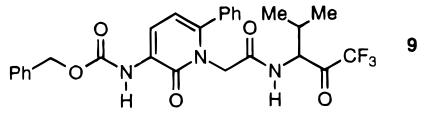


Similar heterocyclic strategies have been applied to the synthesis of mono- and bicyclic pyridone derivatives, which have played an important role in the development of bioactive compounds for the inhibition of enzymatic processes.[11] A number of representative pyridone derivatives, **8**, are effective inhibitors of HIV reverse transcriptase.[11a–c] Pyridone **9** is a potent (4.5 nM), reversible nonpeptidic inhibitor of human leukocyte elastase (HLE).[11d,e] When fused to a structure resembling proline, the pyridone unit is an important feature of A58365A (**10**), which is an ACE inhibitor for the treatment of hypertension.[12]

Our approach to the construction of conformationally restricted peptide analogs and homologs has utilized the







aza-annulation reaction of β-enamino carbonyl substrate **11** with acrylate derivative **12**, formed *in situ* by the treatment of sodium 2-acetamidoacrylate with EtO_2CCl (Scheme 1). This methodology has been an efficient tool for the formation of δ-lactams[13] and has been applied to the synthesis of naturally occurring alkaloids.[14] In addition, this approach has been used for the synthesis of conformationally restricted β-amino acids.[15] With the use of 2-acetamidoacrylic acid derivative **12**, α-acetamido substituents can be incorporated in the annulation process to form **13**, with structural features that resemble those of **4** and **5**.[15b,16] We have found that these systems offer a great deal of versatility with respect to the incorporation of α- or β-amino acids, and the directionality of the peptide constituents.[17] Oxidation of these species leads to the formation of highly substituted pyridone products such as **14**. An approach to direct

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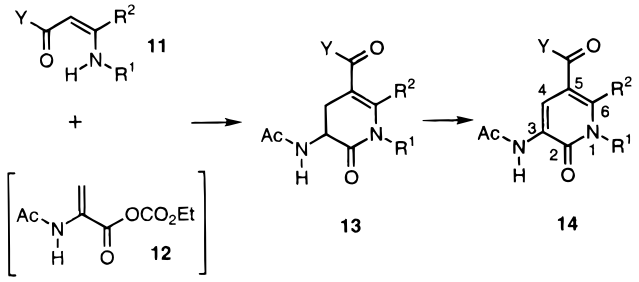
Scheme 1. General Strategy for the Construction of Conformationally Restricted Peptide Analogs through Aza-Annulation



pyridone formation, which involves the use of 2-phenyl-4-(ethoxymethylene)oxazolone, is also described.

Results and Discussion

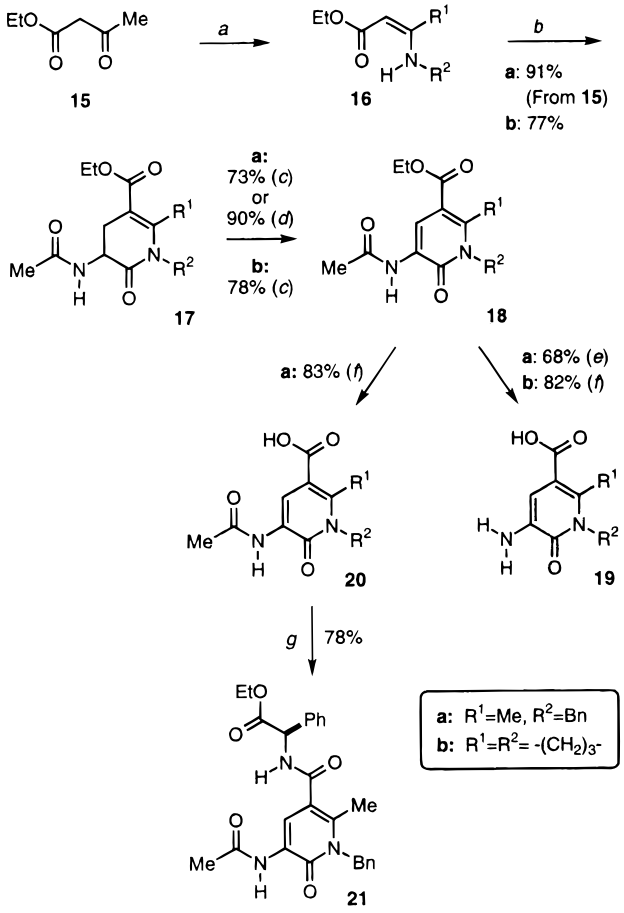
Aza-Annulation with β-Enamino Esters. The synthesis and oxidation of α-amido lactams was initially investigated for the β-amino acid homolog of alanine. Condensation of **15** with $BnNH_2$ (benzylamine) generated the intermediate β-enamino ester **16a**, which was taken on to the next step without isolation (Scheme 2). Treatment of **16a** with **12**, the mixed anhydride of 2-acetamidoacrylic acid, generated *in situ* by the reaction of $ClCO_2Et$ with sodium 2-acetamidoacrylate, resulted in the formation of **17a**. This aza-annulation procedure provided an efficient route for the rapid construction of conformationally restricted dipeptide **17a**, with structural features resembling those of α-Ala-β-Ala.

Dehydrogenation of **17a** was performed by two different methods (Scheme 2). Transformation of **17a** to **18a** was accomplished by heating the substrate with DDQ in toluene at reflux.[18] Alternatively, MnO_2 could be employed to affect the same transformation at reflux in xylenes.[19] In the latter case, a cleaner reaction was observed with significantly higher yield.

Further modification of the dipeptide analog was accomplished through standard procedures. Hydrolysis of both the ester and amide carboxylates provided the amino acid product **19a** (Scheme 2). Pyridone **19a** bears the features of both a γ-amino acid group (3,5 substituent pattern) and the conformationally restricted dipeptide α-Ala-β-Ala. Selective hydrolysis of **18a** was performed to give the N-protected dipeptide surrogate **20a**. Extension of the peptide chain with the ethyl ester of (*R*)-phenylglycine was accomplished through established peptide coupling protocol to give the tripeptide analog **21**.

The cyclic β-enamino ester **16b**,[20] related in structure to proline, was also an effective substrate for aza-annulation with the mixed anhydride of acrylic acid (Scheme 2).[21] Oxidation of the resulting β-enamido ester **17b** resulted in efficient aromatization to give **18b**. Hydrolytic removal of functional group protection gave the corresponding amino acid of the α-Ala-β-Pro dipeptide analog **19b** and could not be performed selectively to give the intermediate **20b**.

Scheme 2. Formation of Dipeptide Analogs through Aza-Annulation of β-Enamino Esters[a]



[a]Reaction conditions: (a) R^2NH_2, $BF_3{\bullet}OEt_2$, C_6H_6, reflux; (b) Sodium 2-acetamidoacrylate, $ClCO_2Et$, THF; (c) DDQ, toluene, reflux; (d) MnO_2, xylenes, reflux, (e) 30% H_2O_2, KOH; (f) KOH, H_2O; (g) i. NaH, EtO_2CCl, ii. (*R*)-phenylglycine ethyl ester.

Generation of the intermediate β-enamino ester through conjugate addition of $BnNH_2$ to alkynoate substrates provided an alternative method for aza-annulation (Scheme 3). Conjugate addition of $BnNH_2$ to **22a**, followed by aza-annulation with **12**, generated **24a**, a conformationally restricted dipeptide of α-Ala-α-Asp. Treatment with DDQ in toluene at reflux resulted in efficient oxidation of **24a** to **26**.

Conjugate addition of $BnNH_2$ to **22b** and **22c** provided a route to Phe and Ser analogs (Scheme 3). When initiated from **22b**, the two-step aza-annulation procedure resulted in the formation of **24b**, the protected derivative of the α-Ala-β-Ser dipeptide, in a fashion analogous to the formation of **17a** from **15**. However, similar reaction of **22c** with $BnNH_2$ resulted in divergent product formation. While the expected tetrasubstituted enamido ester **24c** comprised only 8% of the product mixture, kinetic deprotonation of the intermediate at the benzylic position generated the exocyclic enamide **25** as a 92:8 ratio of products.[22]

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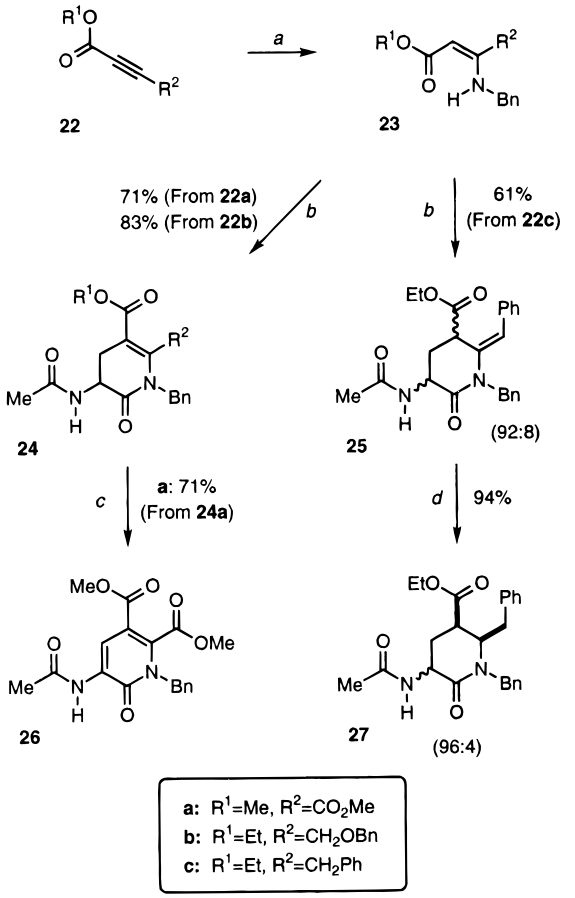
Scheme 3. Formation of α-Ala-*β*-Phe, α-Ala-A-Asp, and α-Ala-*β*-Ser Dipeptide Analogs from Acetylenic Esters[a]

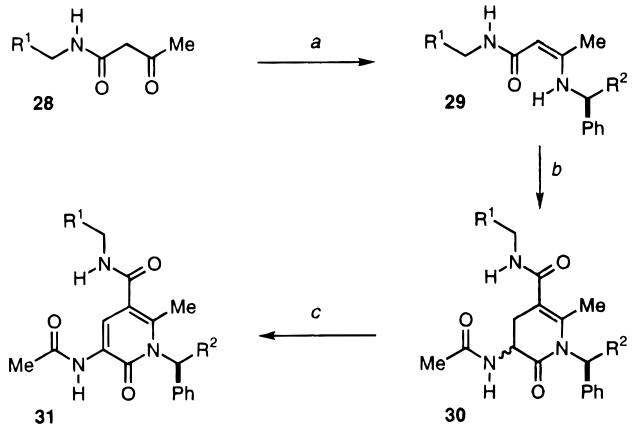


[a]Reaction conditions: (a) $BnNH_2$, BF_3•OEt_2, THF, 25 °C; (b) Sodium 2-acetamidoacrylate, $ClCO_2Et$, THF; (c) DDQ, toluene, reflux; (d) H_2 (15 psi), Pd/C, Na_2CO_3.

Opportunities for further modification of **24c** and **25** were somewhat limited (Scheme 3). Treatment of these products under the same conditions used to oxidize **17** to **18** did not result in oxidation of these substrates to the corresponding pyridone products. Instead, reaction of **24b** with DDQ under standard conditions, even for extended periods of time, resulted only in the recovery of unreacted **24b**. Similar reaction of **25** under the established DDQ oxidation conditions resulted only in alkene isomerization to produce an 80:20 mixture of **24c**:**25**, while only a trace of the corresponding pyridone product was observed.[23] Isolation and subsequent treatment of **24c** with DDQ under standard conditions still did not result in pyridone formation. An alternative means of product modification, hydrogenation of **25**, produced **27** as a 96:4 ratio of only two diastereomers, for which rigorous stereochemical assignment was not made. Presumably, hydrogen added to the double bond from the side opposite that of the ester functionality, which provided **27** with a cis relationship between the groups at C-5 and C-6. The 94:6 ratio reflects a mixture of isomers at C-3.

(22) Nuclear Overhauser enhancement (NOE) studies on **25** were used to confirm that the stereochemistry of the double bond for the major isomer was *E*. Irradiation of the vinyl proton resulted in the enhancement of the *N*-benzyl protons of 3.3% and 1.6%. The relationship of the minor and major isomers, whether isomeric in alkene geometry or cis/trans diasteromers, was not established.

Scheme 4[a] Formation of Peptide Analogs through Aza-Annulation and Pyridone Formation from *β*-Keto Amides[b]



[a]See Table 1 for substituents and reaction yields. [b]Reaction conditions: (a) $PhCH(R^2)NH_2$, BF_3•OEt_2, C_6H_6, reflux; (b) Sodium 2-acetamidoacrylate, $ClCO_2Et$, THF; (c) DDQ, toluene, reflux.

Table 1. Formation of Peptide Analogs through Aza-Annulation and Pyridone Formation from *β*-Keto Amides[a]

			isolated yield	
product	R^1	R^2	**28** to **30**	**30** to **31**
a	Ph	H	90	76
b	Ph	CO_2Et	87[b]	55
c	EtO_2C	H	95	78
d	EtO_2C	CO_2Et	86[b]	60

[a] Tabulated results for Scheme 4. [b] 51:49 ratio of diastereomers.

Aza-annulation with *β*-Enamino Amides. The aza-annulation reaction of **12** with intermediate *β*-enamino amide **29a**, generated from *β*-keto amide **28a** (R^1 = Ph), resulted in efficient formation of the heterocyclic product **30a** (Scheme 4). The corresponding oxidation of the enamido amide derivatives was substantially more sluggish than that of the related ester substrates.[18] In fact, dehydrogenation was typically incomplete and required a second treatment with DDQ to increase conversion to product. The use of xylenes as the solvent in place of toluene, or the use of increased equivalents of DDQ or MnO_2, did not provide an increased yield of product (Table 1). Despite the lower reactivity of **30a** toward oxidation, the dipeptide analog **31a** was still obtained in respectable yield.

A higher level of complexity in these systems was accessed through condensation of **28a** with the ethyl ester of (*R*)-phenylglycine (Scheme 4, Table 1). Aza-annulation of the intermediate *β*-enamino amide **29b** with **12** resulted in the formation of **30b** as an equal mixture of diastereomers (51:49). This two-step procedure served to rapidly construct a complex heterocyclic product in 87% yield from the three basic components **28b**, 2-acetamidoacrylic acid, and (*R*)-phenylglycine ethyl ester. As was observed for **30a**, DDQ oxidation of **30b** generated the amide-substituted pyridone system **31b**, but the reaction was not as facile as that of the related ester

(23) The 80:20 composition of the reaction mixture was determined by ^1H NMR. Characteristic peaks of **24c** were the following: 2.49 (td, J = 15.9, 3.0 Hz, 1 H), 3.55 (dd, J = 15.9, 6.3 Hz, 1 H), 4.63 (dt, J = 15.1, 6.3 Hz, 1 H).

substrates. Oxidation with MnO_2 resulted in only 50% conversion of **30b** to **31b** after 48 h at reflux in xylenes.[19]

Compounds **31a** and **31b** represent an interesting class of conformationally restricted peptide-like molecules. Peptide functional groups, both amino and carboxylate functionality, radiate from the 1, 3, and 5 positions of the pyridone hub. The amide functionality of the pyridone heterocycle displays structural features present in peptide derived molecules. Combination of the 1 and 5 substituents reflect the structural features of a linear dipeptide, while the 3 and 5 positions are similar to those found in conformationally bent peptide chains. Interestingly, the relationship between the 1 and 5 positions is one in which both an α and a *β* amino acid radiate from a common nitrogen atom.

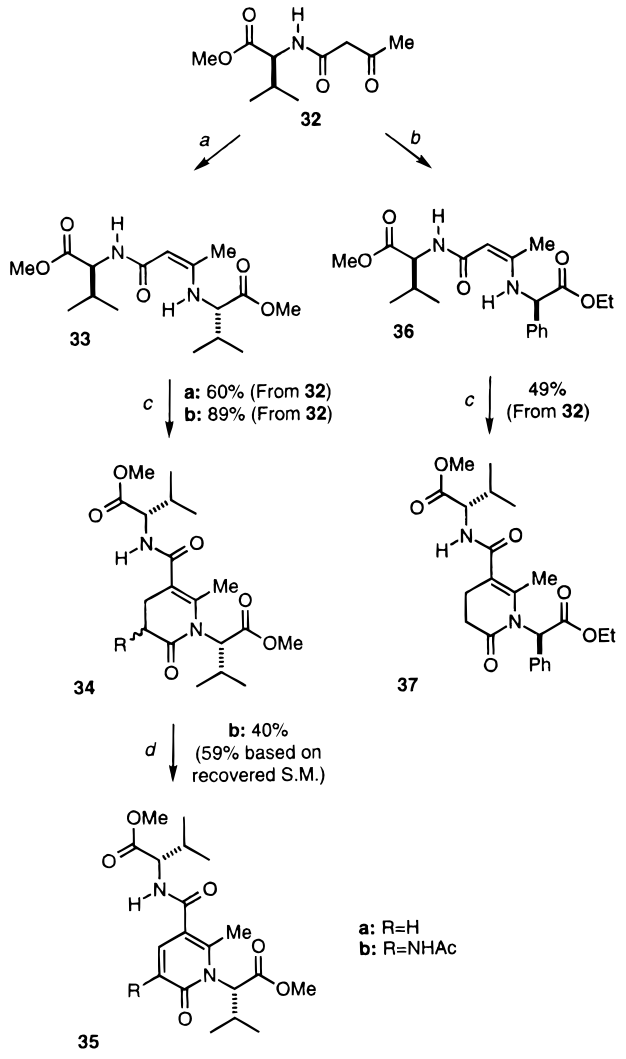
Efficient aza-annulation was observed with substrate **28c** ($R^1 = CO_2Et$), which was readily obtained by the reaction of diketene with glycine ethyl ester (Scheme 4, Table 1). Formation of *β*-enamino amide **29c**, followed by aza-annulation, gave the tripeptide analog **30c** in 95% yield for the two-step process from **28c**. Oxidation of **30c** proceeded in a fashion similar to that of **30b**, and two treatments with DDQ were required to accumulate a yield of 78%. Condensation of **28c** with (*R*)-phenylglycine ethyl ester generated **29d**, which gave **30d** as an equal mixture of diastereomers (51:49) upon aza-annulation with **12**. Oxidation of **30d** with DDQ in toluene at reflux generated the pyridone hub with amino acid functionality radiating from the 1, 3, and 5 positions.

In order to probe the compatibility of the aza-annulation reaction conditions with the stereochemical integrity of the amino acid components, lactam and pyridone products that contained two separate sites of asymmetry were formed. Condensation of **32** was performed separately with valine- and phenylglycine-derived esters to give **33** and **36**, respectively (Scheme 5). In each case, examination of the intermediate enamine showed the presence of a single diastereomer. Aza-annulation with sodium acrylate/$ClCO_2Et$ under standard reaction conditions led to the conversion of **33** to **34a** as a single diastereomer (>98:2 by NMR analysis of the crude reaction mixture). Similarly, treatment with sodium 2-acetamidoacrylate/$ClCO_2Et$ led to an 89% yield of **34b**, which was a 50:50 mixture of diastereomers at the 3 position of the lactam, but did not result in epimerization of the amino acid groups. Conversion of **36** to **37** also was accomplished as a single diastereomer. Based on these observations, epimerization of the amino acid stereocenters did not occur under the aza-annulation conditions.

Oxidation of **34** was dependent on the nature of the substituent at the 3 position of the lactam. When R = H, treatment of **34a** or **37** with DDQ led to a mixture of products which did not contain significant quantities of the desired pyridone products. However, when a 2-acetamido substituent was present (**34b**), oxidation resulted in the formation of **35b** as a single diastereomer. However, this reaction could not be driven to complete conversion without significant degradation of the desired product. After two sequential treatments with DDQ, the product was isolated in 40% yield, which represented a 59% yield based on recovered **34b**. The generation of a single stereoisomer demonstrated that the stereochemical integrity of the amino acid groups was maintained during the oxidation process.

Structural Analysis of 30c. During the course of these studies, α-amido lactam **30c** was obtained as a

Scheme 5. Determination of Epimerization during Aza-Annulation and Oxidation Reactions[a]



[a]Reaction conditions: (a) (*S*)-valine methyl ester•HCl, toluene, $NaHCO_3$, reflux; (b) (*R*)-phenyl glycine ethyl ester•HCl, toluene, $NaHCO_3$, reflux; (c) sodium acrylate or sodium 2-acetamidoacrylate, $ClCO_2Et$, THF, 25 °C; (d) DDQ, toluene, reflux, 40 h.

crystalline solid, which allowed for the single crystal X-ray analysis of this molecule.[27] The ORTEP representation of this molecule is shown in Figure 1. There are several features of this structure that are worth comment. In addition to structure confirmation, the orientation and interactions of the peptide-like chains at the 3 and 5 positions of the lactam ring, and the effects that the *N*-benzyl substitutent has on the packing of this molecule are interesting.

Although intramolecular hydrogen bonding in solution cannot be ruled out, the ORTEP representation of this molecule clearly illustrates an absence of intramolecular hydrogen bonding in the solid state. However, several intermolecular hydrogen bonding interactions were observed in this crystal lattice between the amide substituents at the 3 and 5 positions of the lactam heterocycle. As a result of these interactions, a "ladder" type structural feature was observed (Figure 2). The perspective in Figure 2 contains four molecules of **30c**, and the *N*-benzyl substituents have been omitted for clarity. From this representation, the alternating orientations of

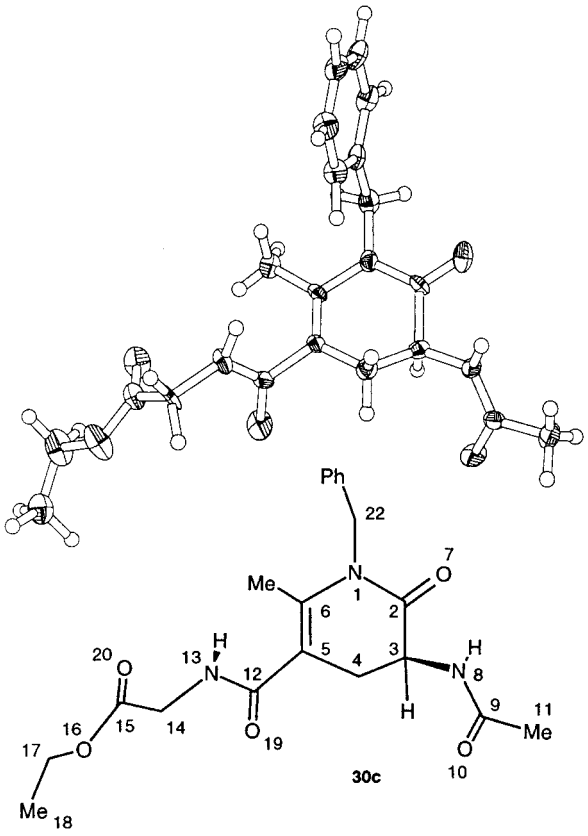


Figure 1. ORTEP, line representations, and numbering scheme of structural data obtained for **30c**.

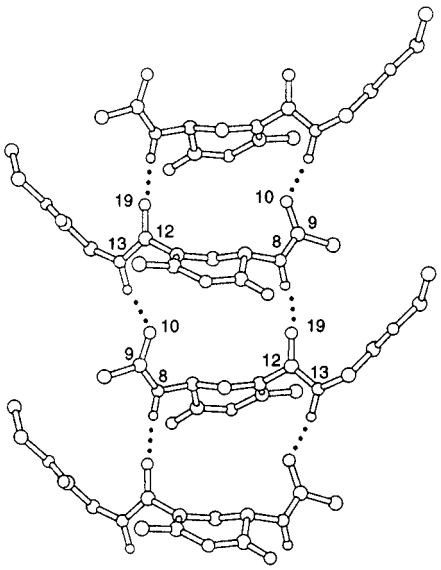
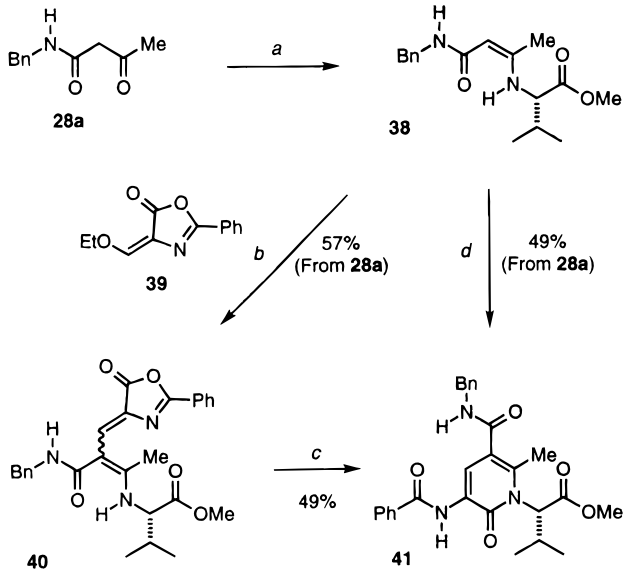


Figure 2. Intermolecular hydrogen bonding observed for **30c**. *N*-Benzyl groups have been omitted for clarity.

the ring system necessary to adopt this lattice is apparent, as is the directionality of the ladder.

These intermolecular hydrogen bond interactions were found between O(10) and H(13)−N(13), with distances of 1.794 and 1.045 Å for the O---H and H−N bonds, respectively. The O---H−N angle observed for this interaction was 158.5°, which is typical for hydrogen bonding geometry. Similarly, O(19) and H(8)−N(8) interactions were evident between two molecules of **30c**, with distances of 1.951 and 0.919 Å for the O---H and H−N bonds, respectively. A value of 161.6° was observed for the O---H−N angle of this hydrogen bond.

Scheme 6. Direct Pyridone Formation through Aza-Annulation[a]



[a]Reaction conditions: (a) (*S*)-valine methyl ester•HCl, $NaHCO_3$, toluene, reflux; (b) **39**, dioxane, reflux, 2 h; (c) DMF, reflux, 2 h; (d) **39**, DMF, reflux, 2 h.

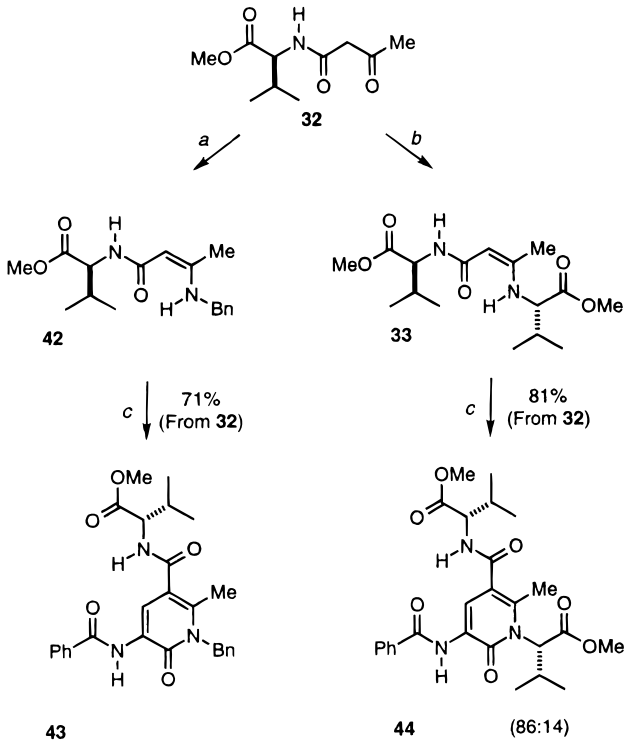
Direct Formation of Pyridones. The use of 2-phenyl-4-(ethoxymethylene)oxazolone (**39**), an alternative reagent for aza-annulation, was explored for the direct formation of pyridone products (Scheme 6). Reagent **39** was readily prepared from hippuric acid by reaction with ethyl orthoformate in acetic anhydride as previously reported.[24] Although aza-annulation of enamino esters and amides with this reagent had been reported to proceed in dioxane with added NEt_3 at 85 °C,[24] analogous reaction of enamino amide **38** with **39**, with or without NEt_3, resulted primarily in the formation of **40**. Cyclization of **40** to **41** was affected eventually by an increase in reaction temperature; when a solution of **40** was heated to reflux in DMF, complete conversion to **41** was achieved. This aza-annulation process was performed in a single procedure by treatment of **38** with **39** in DMF followed by reflux of the reaction mixture. The low isolated yields obtained for **41**, especially when compared to yields obtained for similar reaction of **39** with either **33** or **42**, were a consequence of the generation of reaction byproducts that were difficult to remove during isolation of **41**.

Aza-annulation of **42**, derived from **32**, resulted in more efficient ring formation to give **43** (Scheme 7). Isolation and analysis of **43** led to some interesting properties of these molecules in solution. Initial ^1H NMR analysis of **43** in $CDCl_3$ revealed a 70:30 ratio of two sets of resonances. However, systematic dilution of **43** resulted in conversion of this mixture into predominantly one set of peaks (90:10). This concentration dependent phenomena has been observed before with peptides, and has been attributed to intermolecular hydrogen bonding of these molecules, which becomes less prevalent upon increased dilution.[25]

Enamine **33**, formed as a single diastereomer as determined by ^1H NMR, was used to determine the extent to which epimerization occurred as a result of the

(24) Behringer, H.; Taul, H. *Chem. Ber.* **1957**, *90*, 1398.
(25) (a) Dobashi, A.; Saito, N.; Motoyama, Y.; Hara, S. *J. Am. Chem. Soc.* **1986**, *108*, 307. (b) Jursic, B. S.; Goldberg, S. I. *J. Org. Chem.* **1992**, *57*, 7172.

Scheme 7. Determination of Epimerization during Direct Pyridone Formation[a]



[a]Reaction conditions: (a) $BnNH_2$, toluene, reflux; (b) (*S*)-valine methyl ester•HCl, toluene, $NaHCO_3$, reflux; (c) **39**, DMF, reflux, 2 h.

aza-annulation process with **39** (Scheme 7). The reaction of **42** with **39**, generated by condensation of (*S*)-valine methyl ester with **32**, resulted in an 81% yield of **44** for the two-step condensation/aza-annulation process. Although this procedure provided an efficient route the rapid construction of a complex molecule from readily available starting materials, the diastereomer ratio that was produced in this reaction sequence was only 86:14. During this aza-annulation process, some epimerization had occurred at the sites of asymmetry due to the high temperature (154 °C) required for heterocycle formation.

Summary. The aza-annulation reaction provides an efficient route for the potential construction of the heterocyclic framework for complex bioactive compounds such as natural product targets or synthetic peptide mimetics. With this method, peptide analogs as complex as **31d** can be assembled in three steps in 52% overall yield, and the aza-annulation process with acrylate derivatives did not proceed with epimerization. The resulting compounds contain δ-lactam peptide-like bonds, which exhibit restricted rotation of both ψ and ω dihedral angles. These angles can be altered by oxidation of the dihydropyridone ($\psi = 166°$) to the pyridone ($\psi = 180°$). However, during the oxidation process, significant epimerization of the α-amino acid derivatives (20%) was observed. The pyridone substituents can be completely deprotected to give the corresponding amino acid, or can be selectively hydrolyzed to generate the α-amido carboxylic acid.

As potential bioprocess substrates, these conformationally restricted heterocyclic peptide analogs would be expected to show unique properties at the active site of enzymatic reactions. Hydrolysis of the enamides would lead to the generation of a nucleophilic enamine, but would not result in the fragmentation of the substrate chain. The enamine product could then either react in an intermolecular manner with an electrophile at the active site or intramolecularly revert to the lactam. Synthetic oxidation of the δ-lactams leads to pyridone peptide analogs, which would be inert to typical conditions for peptide hydrolysis. As possible peptide mimetics, these compounds have the potential to interfere with biochemical events that would lead to significant biological effects. The biological activity of these molecules is currently being examined and will be reported separately.

Experimental Section

General Methods. Unless otherwise noted, all reactions were carried out using standard inert atmosphere techniques to exclude moisture and oxygen, and reactions were performed under an atmosphere of nitrogen. Xylenes and decalin were heated over calcium hydride for a minimum of 12 h and then distilled prior to use. $LiAlH_4$ (1 M in THF) was obtained from Aldrich Chemical Co. MnO_2 was used without purification (Fisher Scientific).

Dehydration of condensation reactions was performed with the use of a modified Dean−Stark apparatus in which the cooled distillate was passed through 4-Å molecular sieves prior to return of the solvent to the reaction mixture.[26] The sieves were changed during reactions in which additional reagent was added after reaction had progressed.

General Method for the Formation of β-Keto Amides. Diketene (5.0−30.0 mmol, 1.0 equiv), $BnNH_2$ or $HCl•H_2NCH_2CO_2Et$ (1.0 equiv), and $NaHCO_3$ (2.0 equiv) were combined in benzene (0.5 M solution of amine) at 0 °C. The mixture was warmed to room temperature, stirred for 14 h, and then filtered. Removal of solvent under reduced pressure gave the product as a solid, and crystallization from $Et_2O/CHCl_3$ yielded the product as white leaflets.

28a: 3.59 g, 18.8 mmol, 81% yield; mp 100−102 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.24 (s, 3 H), 3.42 (s, 2 H), 4.44 (d, J = 6.0 Hz, 2 H), 7.25−7.40 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.90, 43.46, 49.56, 127.42, 127.62, 128.62, 137.88, 165.38, 204.35; IR (KBr) 3249, 3085, 1715, 1640, 1443, 1410, 1190, 1163 cm^{-1}; HRMS calcd for $C_{11}H_{13}NO_2$ m/z 191.0146, obsd m/z 191.0982.

28c: 1.74 g, 9.35 mmol, 99% yield; mp 52−53 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (t, J = 7.1 Hz, 3 H), 2.28 (s, 3 H), 3.50 (s, 2 H), 4.04 (d, J = 5.4 Hz, 2 H), 4.20 (q, J = 7.2 Hz, 2 H), 7.61 (bs, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.84, 30.36, 41.11, 49.63, 61.13, 166.16, 169.41, 203.54; IR (KBr) 3353, 2986, 1754, 1715, 1673, 1543, 1418, 1401, 1321, 1175 cm^{-1}; HRMS calcd for $C_8H_{13}NO_4$ m/z 187.0845, obsd m/z 187.0844.

32: Noncrystalline, purified by column chromatography, eluent: 50:50/diethyl ether:petroleum ether, 3.27 g, 15.2 mmol, 85% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (d, J = 7.2 Hz, 3 H), 0.89 (d, J = 7.2 Hz, 3 H), 2.12 (m, 1 H), 2.21 (s, 3 H), 3.43 (s, 2 H), 3.66 (s, 3 H), 4.46 (dd, J = 5.0, 8.6 Hz, 1 H), 7.48 (bd, J = 8.6 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.5, 18.8, 30.5, 30.8, 49.5, 51.9, 57.1, 165.8, 172.0, 203.9; IR (neat) 3320, 2967, 2878, 1746, 1653, 1541, 1437, 1360, 1267, 1156 cm^{-1}; HRMS calcd for $C_{10}H_{17}NO_4$ m/z 215.1158, obsd m/z 215.1149.

General Method for the Aza-Annulation of β-Keto Amides and β-Keto Esters. (*R*)-Phenylglycine ethyl ester hydrochloride salt was suspended in benzene (1.5 mL/mmol of substrate) and washed with saturated aqueous $NaHCO_3$. After the aqueous layer was washed with benzene (10 mL), the benzene layers were combined, washed with saturated aqueous NaCl, and dried ($MgSO_4$). The benzene solution was then used without further manipulation.

A mixture of the $BnNH_2$ or phenylglycine ethyl ester (0.5−5.0 mmol, 1.0 equiv) and the β-keto amide or β-keto ester (1.0 equiv) were taken up in benzene (0.5 *M* relative to the

(26) Barta, N. S.; Paulvannan, K.; Schwarz, J. B.; Stille, J. R. *Synth. Commun.* **1994**, *24*, 853.

(27) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

substrate), and $BF_3{\cdot}OEt_2$ (0.5 equiv) was added. The reaction vessel was fitted with a modified distillation apparatus for azeotropic removal of H_2O,[26] and the reaction was heated at reflux until complete as determined by NMR analysis (6−18 h). The solvent was then removed under reduced pressure, and the crude enamine was brought up in THF (0.1 M). The mixture was cooled to −78 °C, and the sodium salt of 2-acetamidoacrylic acid (1.3 equiv) was added. EtO_2CCl (1.3 equiv) was then added, and the reaction mixture was warmed to room temperature and stirred until complete (≈14 h). Saturated aqueous $NaHCO_3$ was then added, and the mixture was extracted with EtOAc. The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (Et_2O/EtOAc/MeOH).

17a: 0.56 g, 1.70 mmol, 74% yield; mp 132−135 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (t, J = 7.2 Hz, 3 H), 2.06 (s, 3 H), 2.27 (tq, J = 15.9, 2.6 Hz, 1 H), 2.37 (d, J = 2.1 Hz, 3 H), 3.40 (dd, J = 15.9, 6.3 Hz, 1 H), 4.17 (q, J = 7.2 Hz, 2 H), 4.55 (dt, J = 14.7, 6.0 Hz, 1 H), 4.78 (d, J = 16.1 Hz, 1 H), 5.22 (d, J = 16.1 Hz, 1 H), 6.61 (bd, J = 5.1 Hz, 1 H), 7.11 (d, J = 6.9 Hz, 2 H), 7.22−7.36 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.14, 16.11, 23.15, 27.69, 45.80, 48.96, 60.51, 109.12, 126.04, 127.41, 127.63, 128.83, 136.73, 147.35, 166.68, 170.12; IR (KBr) 3299, 2986, 1686, 1389, 1248, 1163 cm^{-1}; HRMS calcd for $C_{18}H_{22}N_2O_4$ m/z 330.1580, obsd m/z 330.1572.

17b: 1.27 g, 4.77 mmol, 74% yield; mp 150−151 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29 (t, J = 7.2 Hz, 3 H), 2.03 (quint, J = 7.3 Hz, 2 H), 2.07 (s, 3 H), 2.29 (tt, J = 15.6, 2.9 Hz, 1 H), 3.16 (td, J = 7.7, 2.1 Hz, 2 H), 3.40 (dd, J = 16.2, 7.5 Hz, 1 H), 3.68 (dt, J = 11.4, 7.3 Hz, 1 H), 3.79 (dt, J = 11.4, 7.2 Hz, 1 H), 4.19 (q, J = 7.2 Hz, 2 H), 4.54 (dt, J = 14.4, 7.2, 1 H), 6.39 (d, J = 5.7 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.33, 21.59, 23.17, 27.99, 31.20, 46.17, 49.60, 60.15, 100.82, 152.30, 166.41, 167.89, 170.23; IR (KBr) 3281, 2984, 2849, 1690, 1642, 1545, 1399, 1248, 1173, 1109 cm^{-1}; HRMS calcd for $C_{13}H_{18}N_2O_4$ m/z 266.1267, obsd m/z 266.1260.

30a: 0.78 g, 2.06 mmol, 90% yield; mp 82−85 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.92 (s, 3 H), 2.07 (d, J = 2.3 Hz, 3 H), 2.41 (btd, J = 15.3, 2.3 Hz, 1 H), 2.93 (dd, J = 15.5, 6.4 Hz, 1 H), 4.35 (dd, J = 14.7, 5.5 Hz, 1 H), 4.43 (dd, J = 14.7, 5.5 Hz, 1 H), 4.54 (dt, J = 15.0, 6.4 Hz, 1 H), 4.63 (d, J = 16.4 Hz, 1 H), 5.05 (d, J = 16.4 Hz, 1 H), 6.80 (bt, J = 5.7 Hz, 1 H), 6.98 (bd, J = 6.3 Hz, 1 H), 7.07 (d, J = 6.6 Hz, 2 H), 7.16−7.30 (m, 8 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.87, 22.79, 28.51, 43.44, 45.45, 48.78, 112.45, 125.86, 127.15, 127.57, 128.39, 128.61, 136.82, 138.02, 139.12, 167.80, 169.27, 170.21; IR (KBr) 3289, 3002, 1734, 1659, 1584, 1543, 1321, 1248 cm^{-1}; HRMS calcd for $C_{23}H_{25}N_3O_3$ m/z 391.1896, obsd m/z 391.1895.

30b: mixture of diastereomers, ratio 49:51; 0.36 g, 0.80 mmol, 87% yield; mp 83−85 °C (mixture); ^{1}H NMR (300 MHz, $CDCl_3$, characteristic peaks) δ (major isomer) 2.01 (s, 3 H), 2.22 (d, J = 1.2 Hz, 3 H), 2.30 (bdt, J = 9.2, 1.5 Hz, 1 H), 5.67 (s, 1 H), 5.92 (m, 1 H), (minor isomer) 2.02 (s, 3 H), 2.10 (d, J = 1.2 Hz, 3 H), 2.43 (btd, J = 9.2, 1.5 Hz, 1 H), 5.59 (s, 1 H), 5.95 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.87, 16.22, 16.50, 20.86, 22.78, 28.17, 28.33, 40.42, 43.46, 46.47, 48.94, 59.82, 61.67, 111.05, 113.61, 114.01, 117.30, 126.02, 127.06, 127.17, 127.50, 127.55, 127.71, 127.95, 128.21, 128.37, 128.41, 128.52, 134.26, 134.42, 137.88, 137.95, 138.52, 139.39, 167.46, 167.64, 168.02, 168.43, 169.22, 169.61, 170.13, 170.18; IR (KBr) 3297, 3007, 1742, 1651, 1532, 1217 cm^{-1}; HRMS calcd for $C_{26}H_{29}N_3O_5$ m/z 463.2107, obsd m/z 463.2150.

30c: 1.06 g, 2.74 mmol, 95% yield; mp 71−74 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (t, J = 7.1 Hz, 3 H), 2.00 (s, 3 H), 2.16 (d, J = 2.2 Hz, 3 H), 2.46 (btd, J = 15.3, 2.2 Hz, 1 H), 2.96 (dd, J = 15.3, 6.5 Hz, 1 H), 3.95 (dd, J = 18.1, 5.6 Hz, 1 H), 4.04 (dd, J = 18.1, 5.6 Hz, 1 H), 4.14 (q, J = 7.2 Hz, 2 H), 4.59 (dt, J = 15.3, 6.5 Hz, 1 H), 4.67 (d, J = 16.7 Hz, 1 H), 5.13 (d, J = 16.7 Hz, 1 H), 6.91 (t, J = 5.6 Hz, 1 H), 7.05−7.13 (m, 3 H), 7.19−7.34 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.84, 15.79, 22.78, 28.31, 41.18, 45.42, 48.74, 61.09, 111.95, 125.82, 127.12, 128.58, 136.78, 139.74, 168.09, 169.34, 169.69, 170.25; IR (KBr) 3285, 2984, 1744, 1657, 1584, 1543, 1319, 1190 cm^{-1}; HRMS calcd for $C_{20}H_{25}N_3O_5$ m/z 387.1794, obsd m/z 387.1789.

30d: mixture of diastereomers, ratio 49:51; 0.52 g, 1.13 mmol, 86% yield; mp 77−80 °C (mixture); ^{1}H NMR (300 MHz, $CDCl_3$, characteristic peaks) δ (major isomer) 2.03 (s, 3 H), 2.12 (d, J = 1.5 Hz, 3 H), 2.45 (btq, J = 9.0, 1.5 Hz, 1 H), 2.77 (ddd, J = 7.8, 3.3, 1.5 Hz, 1 H), 5.62 (s, 1 H), 6.17 (bt, J = 2.9 Hz, 1 H), (minor isomer) 2.02 (s, 3 H), 2.24 (d, J = 1.5 Hz, 3 H), 2.33 (btq, J = 9.0, 1.5 Hz, 1 H), 3.10 (ddd, J = 9.0, 3.3, 1.5 Hz, 1 H), 5.68 (s, 1 H), 6.13 (bt, J = 2.9 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.97, 16.29, 16.56, 22.75, 22.98, 28.16, 28.26, 41.35, 41.42, 46.44, 49.04, 59.71, 59.91, 60.78, 61.32, 61.80, 62.35, 100.38, 113.15, 113.52, 167.73, 127.71, 127.77, 127.99, 128.04, 128.09, 128.20, 128.34, 133.26, 134.22, 134.44, 139.46, 139.49, 140.42, 167.92, 168.04, 168.47, 169.04, 169.30, 169.35, 169.40, 169.74, 169.79, 170.22, 170.30, 171.05; IR (KBr) 3277, 2986, 1744, 1655, 1541, 1204 cm^{-1}; HRMS calcd for $C_{23}H_{29}N_3O_7$ m/z 459.2006, obsd m/z 459.2011.

34a: 48:48:4/diethyl ether:petroleum ether:methyl alcohol; 0.53 g, 1.39 mmol, 60% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.74 (d, J = 7.1 Hz, 3 H), 0.86 (d, J = 6.8 Hz, 3 H), 0.90 (d, J = 6.9 Hz, 3 H), 1.08 (d, J = 6.4 Hz, 3 H), 2.16 (m, 1 H), 2.14 (s, 3 H), 2.38−2.53 (m, 4 H), 2.61 (m, 1 H), 3.60 (s, 3 H), 3.69 (s, 3 H), 4.03 (bd, J = 8.5 Hz, 1 H), 4.55 (dd, J = 4.9, 8.5 Hz, 1 H), 5.93 (d, J = 8.5 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.5, 17.9, 18.9, 19.1, 22.0, 22.2, 28.0, 31.2, 52.0, 52.1, 57.0, 61.2, 113.2, 140.5, 168.8, 170.2, 170.6, 172.5; IR ($CHCl_3$) 3316, 2969, 2876, 1746, 1657, 1524, 1437, 1399, 1304, 1267 cm^{-1}; HRMS calcd for $C_{19}H_{30}N_2O_6$ m/z 382.2104, obsd m/z 382.2098.

34b: 90:5:5; Et_2O/petroleum ether/MeOH; 2.73 g, 6.21 mmol, 89% yield, 50:50 mixture of diastereomers; mp = 69−70 °C sealed, dec; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.74 (d, J = 7.2 Hz, 3 H), 0.75 (d, J = 7.2 Hz, 3 H), 0.85−0.94 (m, 12 H), 1.09 (d, J = 7.2 Hz, 3 H), 1.11 (d, J = 7.2 Hz, 3 H), 1.96 (s, 3 H), 1.97 (s, 3 H), 2.06 (d, J = 1.8 Hz, 3 H), 2.09−2.20 (m, 2 H), 2.20 (d, J = 1.8 Hz, 3 H), 2.24−2.42 (m, 2 H), 2.48−2.68 (m, 2 H), 2.91 (dd, J = 6.3, 15.3 Hz, 1 H), 2.99 (dd, J = 6.3, 15.3 Hz, 1 H), 3.61 (s, 3 H), 3.64 (s, 3 H), 3.69 (s, 6 H), 3.95 (d, J = 8.7 Hz, 1 H), 4.26 (bs, 1 H), 4.35−4.57 (m, 4 H), 6.19 (d, J = 8.7 Hz, 1 H), 6.42 (d, J = 8.4 Hz, 1 H), 6.56 (d, J = 5.7 Hz, 1 H), 6.61 (d, J = 5.7 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.5, 11.7, 13.16, 13.24, 14.2, 14.4, 17.0, 17.4, 18.2, 22.9, 23.5, 23.6, 23.8, 26.1, 26.4, 44.0, 44.3, 47.3, 47.4, 47.5, 52.5, 52.6, 56.9, 57.4, 107.9, 108.7, 134.0, 136.1, 162.8, 163.3, 164.4, 164.5, 164.8, 165.4, 165.5, 165.9, 167.5, 167.6; IR ($CHCl_3$) 3308, 3011, 2969, 1742, 1653, 1534, 1437, 1269, 1244 cm^{-1}; HRMS calcd for $C_{21}H_{33}N_3O_7$ m/z 439.2319, obsd m/z 439.2285.

37: 48:48:4/diethyl ether:petroleum ether:methyl alcohol, 0.29 g, 0.68 mmol, 49% yield; mp = 44−45 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (d, J = 6.9 Hz, 3 H), 0.90 (d, J = 6.8 Hz, 3 H), 1.21 (t, J = 7.1 Hz, 3 H), 2.06 (s, 3 H), 2.12 (m, 1 H), 2.40−2.55 (m, 2 H), 2.55−2.66 (m, 2 H), 3.69 (s, 3 H), 4.18 (q, J = 7.1 Hz, 2 H), 4.55 (dd, J = 4.8, 8.6 Hz, 1 H), 5.60 (s, 1 H), 5.84 (bd, J = 8.6 Hz, 1 H), 7.05−7.33 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 16.8, 17.9, 22.2, 31.2, 31.4, 52.2, 57.1, 59.8, 61.7, 114.1, 126.1, 128.0, 128.4, 128.7, 135.0, 140.1, 168.7, 168.8, 170.6, 172.5; IR ($CHCl_3$) 3324, 2967, 1744, 1659, 1522, 1395, 1374, 1302, 1262, 1156, 1028 cm^{-1}; HRMS calcd for $C_{23}H_{30}N_2O_6$ m/z 430.2104, obsd m/z 430.2105.

General Method for the Formation of Acetylenic Esters. To 3-(benzyloxy)propyne or 3-phenylpropyne (10−50 mmol, 1.0 equiv, 0.5 M in THF) at −78 °C was added *n*-BuLi (1.0 equiv, 2.5 M in hexane). After 10 min, EtO_2CCl (1.5 equiv) was added dropwise. The reaction mixture containing 3-phenylpropyne was slowly warmed to room temperature, and the mixture was stirred for 14 h. In the case of 3-(benzyloxy)-propyne, the reaction was promptly quenched as soon as a deep red color began to form in the solution. Each reaction was quenched by addition of H_2O, the organic layer was removed, and the solvent was removed under reduced pressure. The crude oils were purified by flash column chromatography (petroleum ether).

22b: 1.61 g, 7.45 mmol, 91% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29 (t, J = 7.2 Hz, 3 H), 4.22 (q, J = 7.2 Hz, 2 H), 4.25 (s, 2 H), 4.59 (s, 2 H), 7.22−7.40 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.78, 56.53, 61.90, 71.81, 78.07, 82.94, 127.87, 127.90, 128.29, 136.59, 152.87; IR (oil/NaCl) 3032, 2984, 2872, 2236, 1713, 1248 cm^{-1}.

22c: 3.06 g, 16.28 mmol, 94% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (t, J = 7.1 Hz, 3 H), 3.73 (s, 2 H), 4.23 (q, J = 7.1 Hz, 2 H), 7.25−7.40 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.00, 24.97, 61.87, 74.84, 86.20, 127.16, 127.99, 128.69, 134.07, 153.67; IR (oil/NaCl) 2984, 2238, 1709, 1255 cm^{-1}.

General Method for the Aza-Annulation of Acetylenic Esters. A mixture of $BnNH_2$ (0.5−5.0 mmol, 1.0 equiv) and acetylenic ester (1.0 equiv) was taken up in THF (0.5 M relative to the amine), and BF_3·OEt_2 (0.5 equiv) was added. The mixture was stirred at ambient temperature until the reaction had gone to completion, as indicated by ^{1}H NMR. The solvent was removed under reduced pressure, and the crude enamine was taken up in THF (0.1 M). The mixture was cooled to −78 °C, and the sodium salt of 2-acetamidoacrylic acid (1.3 equiv) was added to the enamine. EtO_2CCl (1.3 equiv) was then added, and the reaction mixture was warmed to room temperature and stirred until complete (≈14 h). Saturated aqueous $NaHCO_3$ was added, and the mixture was extracted with EtOAc. The combined organic fractions were dried over Na_2SO_4 and filtered, and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (Et_2O/EtOAc/MeOH).

24a: 3.60 g, 10.0 mmol, 71% yield; mp 151−154 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.05 (s, 3 H), 2.34 (dd, J = 16.3, 15.6 Hz, 1 H), 3.42 (dd, J = 16.3, 7.0 Hz, 1 H), 3.67 (s, 3 H), 3.73 (s, 3 H), 4.63 (ddd, J = 15.6, 7.0, 5.6 Hz, 1 H), 4.65 (d, J = 15.6 Hz, 1 H), 4.94 (d, J = 15.6 Hz, 1 H), 6.51 (bd, J = 5.6 Hz, 1 H), 7.16−7.22 (m, 2 H), 7.25−7.36 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.07, 26.41, 47.81, 48.43, 52.24, 52.90, 108.95, 127.13, 127.79, 128.56, 135.77, 141.88, 163.32, 165.05, 169.21, 170.14; IR (KBr) 3306, 2953, 1742, 1705, 1634, 1534, 1437, 1248 cm^{-1}; HRMS calcd for $C_{18}H_{20}N_2O_6$ m/z 360.1322, obsd m/z 360.1308.

24b: 3.32 g, 7.61 mmol, 83% yield; mp 97−99 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, J = 7.2 Hz, 3 H), 2.03 (s, 3 H), 2.29 (td, J = 16.0, 2.0 Hz, 1 H), 3.39 (dd, J = 16.0, 6.6 Hz, 1 H), 4.16 (q, J = 7.2 Hz, 2 H), 4.31 (dd, J = 12.9, 2.0 Hz, 1 H), 4.45 (dt, J = 15.0, 6.0 Hz, 1 H), 4.54 (d, J = 12.0 Hz, 1 H), 4.60 (d, J = 12.0 Hz, 1 H), 4.80 (d, J = 16.5 Hz, 1 H), 5.00 (d, J = 12.9 Hz, 1 H), 5.41 (d, J = 16.5 Hz, 1 H), 6.73 (bd, J = 5.7 Hz, 1 H), 6.98−7.02 (m, 2 H), 7.17−7.38 (m, 8 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.97, 22.99, 28.00, 45.62, 48.50, 60.90, 63.07, 72.50, 112.97, 125.91, 127.16, 127.87, 128.32, 128.64, 137.12, 137.39, 145.35, 165.91, 170.07; IR (KBr) 3310, 3011, 2936, 1673, 1632, 1497, 1392, 1372, 1217 cm^{-1}; HRMS calcd for $C_{25}H_{28}N_2O_5$ m/z 436.1998, obsd m/z 436.2064.

25: mixture of isomers, ratio 92:8; 2.64 g, 6.5 mmol, 61% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14 (t, J = 7.1 Hz, 3 H), 1.79 (ddd, J = 13.1, 11.1, 6.6 Hz, 1 H), 2.03 (s, 3 H), 2.80 (ddd, J = 13.1, 9.4, 7.0 Hz, 1 H), 3.85−4.87 (m, 3 H), 4.47 (dt, J = 11.1, 6.3 Hz, 1 H), 4.77 (d, J = 15.4 Hz, 1 H), 5.23 (d, J = 15.4 Hz, 1 H), 6.46 (s, 1 H), 6.84 (d, J = 5.8 Hz, 1 H), 7.13−7.38 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.84, 23.00, 29.05, 40.78, 48.71, 51.43, 61.38, 121.37, 127.32, 127.47, 128.40, 128.51, 128.90, 134.38, 135.82, 137.00, 169.53, 170.00, 171.91; IR (KBr) 3330, 2982, 1734, 1671, 1496, 1410, 1244, 1184 cm^{-1}; HRMS calcd for $C_{24}H_{26}N_2O_4$ m/z 406.1893, obsd m/z 406.1920.

General Method for the DDQ Oxidation of Aza-Annulation Products. A mixture of the aza-annulation product (0.5−50.0 mmol, 1.0 equiv) and DDQ (1.5 equiv) was taken up in toluene (0.1 M with respect to the aza-annulation product). After heating at reflux for 14 h, the solvent was removed under reduced pressure, and the crude product was purified by flash column chromatography (Et_2O/EtOAc) or crystallized ($CHCl_3$/EtOAc). For compounds derived from β-keto amides, the oxidation was repeated to acquire the indicated yields.

18a: 0.029 g, 0.088 mmol, 58% yield; mp 176−178 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37 (t, J = 7.1 Hz, 3 H), 2.19 (s, 3 H), 2.68 (s, 3 H), 4.30 (q, J = 7.1 Hz, 2 H), 5.47 (s, 2 H), 7.09 (d, J = 6.7 Hz, 2 H), 7.26−7.35 (m, 3 H), 8.30 (bs, 1 H), 8.91 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.19, 16.91, 24.63, 48.33, 61.15, 110.44, 122.64, 125.77, 126.05, 127.64, 128.94, 135.22, 145.30, 158.40, 165.88, 169.02; IR (KBr) 3308, 2982, 1713, 1638, 1516, 1192 cm^{-1}; HRMS calcd for $C_{18}H_{20}N_2O_4$ m/z 328.1423, obsd m/z 328.1411.

18b: 0.039 g, 0.150 mmol, 78% yield; mp 225−226 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (t, J = 7.1 Hz, 3 H), 2.18 (s, 3 H), 2.21 (quint, J = 7.7 Hz, 2 H), 3.50 (t, J = 7.7 Hz, 2 H), 4.16 (t, J = 7.7 Hz, 2 H), 4.28 (q, J = 7.1 Hz, 2 H), 8.14 (bs, 1 H), 8.85 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.31, 20.99, 24.63, 33.04, 49.43, 60.78, 106.11, 122.55, 126.13, 149.57 156.83, 164.86, 168.80; IR (KBr) 3297, 2982, 2936, 1715, 1684, 1636, 1532, 1196, 1100 cm^{-1}; HRMS calcd for $C_{13}H_{16}N_2O_4$ m/z 264.1110, obsd m/z 264.1108.

26: 0.21 g, 0.59 mmol, 71% yield; mp = 128−129 °C; ^{1}H NMR (300 Hz, $CDCl_3$) δ 2.19 (s, 3 H), 3.79 (s, 3 H), 3.85 (s, 3 H), 5.26 (s, 2 H), 7.19−7.32 (m, 5 H), 8.34 (bs, 1 H), 8.84 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.67, 50.44, 52.62, 53.41, 109.06, 120.06, 127.36, 128.04, 128.61, 128.83, 134.77, 138.14, 157.02, 163.12, 164.18, 169.23; IR (KBr) 3374, 3021, 2955, 1728, 1691, 1645, 1516, 1437, 1215 cm^{-1}; HRMS calcd for $C_{18}H_{18}N_2O_6$ m/z 358.1165, obsd m/z 358.1153.

31a: 0.21 g, 0.56 mmol, 76% yield; mp 180−181 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 2.10 (s, 3 H), 2.42 (s, 3 H), 4.55 (d, J = 6.0 Hz, 2 H), 5.51 (s, 2 H), 7.12−7.16 (m, 2 H), 7.19−7.56 (m, 8 H), 8.18 (t, J = 6.0 Hz, 1 H), 8.54 (s, 1 H), 8.96 (s, 1 H); ^{13}C NMR (75 MHz, acetone-d_6) δ 17.28, 24.36, 44.20, 48.79, 108.50, 122.42, 127.30, 127.83, 128.13, 128.45, 129.21, 129.51, 129.60, 136.99, 137.25, 145.43, 158.59, 168.47, 169.97; IR (KBr) 3299, 3067, 3034, 2880, 1705, 1634, 1507, 1476, 1248, 1003 cm^{-1}; HRMS calcd for $C_{23}H_{23}N_3O_3$ m/z 389.1739, obsd m/z 389.1762.

31b: 0.16 g, 0.35 mmol, 55% yield; mp = 155−156 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (t, J = 7.2 Hz, 3 H), 2.18 (s, 3 H), 2.50 (s, 3 H), 4.26 (q, J = 7.2 Hz, 2 H), 4.57 (dd, J = 5.6, 1.7 Hz, 2 H), 6.12 (s, 1 H), 6.19 (m, 1 H), 7.19−7.43 (m, 10 H), 8.27 (s, 1 H), 8.53 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.10, 17.52, 24.67, 44.28, 62.11, 62.69, 116.21, 120.69, 126.86, 127.73, 127.85, 128.15, 128.54, 128.62, 128.85, 133.01, 137.69, 139.77, 140.51, 167.20, 167.38, 169.27; IR (KBr) 3280, 2960, 2920, 1736, 1647, 1516, 1455, 1217 cm^{-1}; HRMS calcd for $C_{26}H_{27}N_3O_5$ m/z 461.1951, obsd m/z 461.1901.

31c: 0.31 g, 0.15 mmol, 80% yield; mp = 177−180 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 1.21 (t, J = 7.1 Hz, 3 H), 2.11 (s, 3 H), 2.48 (s, 3 H), 4.10 (d, J = 6.0 Hz, 2 H), 4.13 (q, J = 7.1 Hz, 2 H), 5.54 (s, 2 H), 7.14−7.17 (m, 2 H), 7.24−7.56 (m, 3 H), 8.01 (t, J = 6.0 Hz, 1 H), 8.54 (s, 1 H), 9.04 (s, 1 H); ^{13}C NMR (75 MHz, acetone-d_6) δ 14.42, 17.22, 24.38, 42.21, 48.85, 61.47, 108.55, 122.56, 127.30, 129.21, 129.52, 129.62, 137.19, 145.59, 158.65, 168.80, 170.10, 170.28; IR (KBr) 3277, 3032, 1748, 1671, 1644, 1512, 1210, 1003 cm^{-1}; HRMS calcd for $C_{20}H_{23}N_3O_5$ m/z 385.1638, obsd m/z 385.1623.

31d: 0.32 g, 0.70 mmol, 60% yield; mp = 204−205 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (t, J = 7.2 Hz, 3 H), 1.28 (t, J = 7.2 Hz, 3 H), 2.17 (s, 3 H), 2.49 (s, 3 H), 4.13−4.29 (m, 6 H), 6.14 (s, 1 H), 6.55 (bs, 1 H), 7.26−7.48 (m, 5 H), 8.32 (s, 1 H), 8.55 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.08, 17.53, 24.54, 41.88, 61.74, 62.17, 62.65, 112.68, 115.71, 121.15, 126.60, 128.08, 128.59, 128.92, 132.86, 134.72, 140.19, 157.78, 167.40, 167.67, 169.65; IR (KBr) 3314, 2986, 1744, 1645, 1524, 1217, 1082, 1003 cm^{-1}; HRMS calcd for $C_{23}H_{27}N_3O_7$ m/z 457.1849, obsd m/z 457.1853.

35b: 90:5:5; Et_2O/petroleum ether/MeOH; 0.20 g, 0.46 mmol, 40% yield; mp = 90−91 °C sealed, dec.; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.63 (d, J = 6.9 Hz, 3 H), 0.97 (d, J = 6.9 Hz, 3 H), 1.01 (d, J = 6.9 Hz, 3 H), 1.24 (d, J = 6.9 Hz, 3 H), 2.13 (s, 3 H), 2.19−2.32 (m, 2 H), 2.49 (bs, 3 H), 3.60 (s, 3 H), 3.76 (s, 3 H), 4.32 (bs, 1 H), 4.65 (dd, J = 4.5, 8.7 Hz, 1 H), 6.45 (d, J = 8.7 Hz, 1 H), 8.19 (bs, 1 H), 8.53 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.6, 17.8, 18.9, 19.1, 22.2, 24.4, 26.8, 31.2, 52.2, 52.3, 57.6, 64.9, 115.5, 120.8, 126.3, 139.6, 157.2, 167.5, 168.9, 169.1, 172.1; IR ($CHCl_3$) 3305, 3015, 2971, 2876, 1748, 1653, 1611, 1522, 1215 cm^{-1}; HRMS calcd for $C_{21}H_{31}N_3O_7$ m/z 437.2162, obsd m/z 437.2158.

Oxidation of 17a with MnO_2. Compound **17a** (0.28g, 0.89 mmol) and MnO_2 (0.46g, 5.3 mmol) were combined and suspended in xylenes (20 mL). The mixture was heated under an air atmosphere with azeotropic removal of H_2O for 16 h.[26] After the reaction mixture was cooled to room temperature, the solution was filtered through Celite and concentrated *in vacuo*. Purification was accomplished *via* flash column chro-

matography (80:20 EtOAc/petroleum ether) to give **18a** (0.25 g, 0.80 mmol) in 90% yield.

General Method for the Hydrolysis of Esters and Amides. A mixture of the pyridone (0.5−2.0 mmol, 1.0 equiv) and KOH (20.0 equiv) was taken up in H_2O (for hydrolysis of esters) or 30% H_2O_2 (for hydrolysis of amides) (0.1 M with respect to the pyridone). After 14 to 38 h, the reaction was extracted with $CHCl_3$, filtered, and neutralized with HCl. Compound **20a** was collected by filtration, and the unprotected amino acids (**19a** and **19b**) were collected by solvent removal under reduced pressure followed by extraction with MeOH or acetone. The products were then crystallized (MeOH/$CHCl_3$ or MeOH/Et_2O).

19a: 0.047 g, 0.183 mmol, 61% yield; mp 205−206 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.46 (s, 3 H), 5.46 (s, 2 H), 7.07−7.54 (m, 5 H), 8.02 (s, 1 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 16.83, 30.74, 115.41, 127.05, 128.34, 129.37, 129.86, 133.98, 135.86, 137.69, 160.60, 169.74; IR (KBr) 2928, 1709, 1640, 1549, 1455, 1256, 1024 cm^{-1}; HRMS calcd for $C_{14}H_{14}N_2O_3$ *m*/*z* 258.1004, obsd *m*/*z* 258.0987.

20a: 0.48 g, 2.03 mmol, 61% yield; mp >260 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 2.07 (s, 3 H), 2.70 (s, 3 H), 5.55 (s, 2 H), 7.17 (d, J = 6.9 Hz, 1 H), 7.26−7.35 (m, 4 H), 8.98 (s, 1 H); ^{13}C NMR (75 MHz, acetone-d_6) δ 17.09, 24.32, 48.52, 106.25, 123.00, 127.10, 128.14, 129.62, 130.55, 133.29, 137.24, 158.84, 167.42, 171.53; IR (KBr) 3277, 3031, 1692, 1622, 1603, 1553, 1387, 1190 cm^{-1}; HRMS calcd for $C_{16}H_{16}N_2O_4$ *m*/*z* 300.1110, obsd *m*/*z* 300.1096.

19b: 0.061 g, 0.314 mmol, 82% yield; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.03 (quint, J = 7.6 Hz, 2 H), 3.25 (t, J = 7.6 Hz, 2 H), 3.95 (t, J = 7.6 Hz, 2 H), 6.91 (s, 1 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 21.09, 32.45, 48.73, 111.03, 128.51, 129.14, 135.41, 143.12, 156.81; IR (KBr) 3364, 1698, 1615, 1536, 1117 cm^{-1}; HRMS calcd for $C_9H_{10}N_2O_3$ *m*/*z* 194.0692, obsd *m*/*z* 194.0681.

Formation of 21a. To a solution of **20a** (0.20 g, 0.85 mmol) in THF (8.5 mL) was added NaH (0.92 g, 0.85 mmol) at −78 °C. EtO_2CCl (0.081 mL, 0.85 mmol) was added to the reaction mixture followed by (*R*)-phenylglycine ethyl ester (0.183 g, 0.85 mmol). The reaction was warmed to room temperature and was stirred for 2 h. Saturated aqueous $NaHCO_3$ (excess) was added, and the mixture was extracted with EtOAc. The combined organic fractions were dried over Na_2SO_4 and filtered, and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (Et_2O/EtOAc/MeOH) to give **21a** (0.29 g, 0.66 mmol, 78% yield): mp 209−210 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 (t, J = 7.1 Hz, 3 H), 2.17 (s, 3 H), 2.42 (s, 3 H), 4.17 (dq, J = 10.7, 7.1 Hz, 1 H), 4.25 (dq, J = 10.7, 7.1 Hz, 1 H), 5.38 (s, 2 H), 5.63 (d, J = 7.1 Hz, 1 H), 6.98 (d, J = 7.1 Hz, 1 H), 7.09 (d, J = 6.5 Hz, 2 H), 7.25−7.44 (m, 8 H), 8.37 (s, 1 H), 8.55 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.90, 16.88, 24.43, 48.53, 57.22, 61.99, 126.20, 126.31, 127.33, 127.63, 128.49, 128.57, 128.84, 128.96, 135.02, 135.89, 140.32, 157.95, 166.84, 169.61, 170.58; IR (KBr) 3324, 3019, 1736, 1636, 1514, 1217 cm^{-1}; HRMS calcd for $C_{26}H_{27}N_3O_5$ *m*/*z* 461.1951, obsd *m*/*z* 461.1939.

Formation of 27. Enamine **25** (0.24 g, 1.05 mmol) was dissolved in EtOH (10.5 mL), and Na_2CO_3 (0.39 g, 3.67 mmol) and 10% Pd/C (0.10 g) were added. The reaction mixture was placed under an atmosphere of H_2. After stirring for 16 h, the reaction mixture was filtered, and the solvent was removed under reduced pressure. The resulting crude oil was purified by flash column chromatography (Et_2O). Removal of solvent gave a white solid, which was crystallized from EtOAc to give **27** as a mixture of diastereomers (96:4 product ratio, 0.23 g, 0.99 mmol, 94% yield): mp 202−205 °C; ^{1}H NMR (300 MHz, $CDCl_3$) (major diastereomer) δ 1.16 (t, J = 7.2 Hz, 3 H), 2.00 (s, 3 H), 2.32 (q, J = 13.7 Hz, 1 H), 2.55 (m, 1 H), 2.93 (dt, J = 13.7, 4.4 Hz, 1 H), 3.21 (dd, J = 13.7, 7.4 Hz, 1 H), 3.29 (d, J = 15.2 Hz, 1 H), 3.90 (dq, J = 10.8, 7.1 Hz, 1 H), 4.01 (dq, J = 10.8, 7.1 Hz, 1 H), 4.07 (m, 2 H), 5.24 (d, J = 15.2 Hz, 1 H), 7.00 (dd, J = 7.5, 1.9 Hz, 2 H), 7.12 (d, J = 6.4 Hz, 1 H), 7.21−7.34 (m, 8 H); ^{13}C NMR (75 MHz, $CDCl_3$) (major diastereomer) δ 13.92, 22.87, 25.69, 37.30, 42.80, 49.65, 50.81, 58.76, 60.95, 126.77, 127.37, 127.47, 128.51, 128.57, 129.34, 136.80, 138.09, 169.14, 170.45, 170.52; IR (solid/NaCl) 3297, 3067, 3009, 1732, 1642, 1541, 1455, 1217 cm^{-1}; HRMS calcd for $C_{24}H_{28}N_2O_4$ *m*/*z* 408.2049, obsd *m*/*z* 408.2075.

General Method for Aza-Annulation with 39. The corresponding enamine (0.78−2.6 mmol) was dissolved in anhydrous DMF (0.26 M) and **39** (1.0 equiv) was added. After the reaction mixture was heated to reflux for 2 h, the dark brown solution was concentrated to an oil (boiling water bath), and the crude product was purified by flash column chromatography (SiO_2, 230−400 mesh, Et_2O/petroleum ether/MeOH = 48:48:4).

41: 0.18 g, 0.38 mmol, 49% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.57 (d, J = 6.9 Hz, 3 H), 1.20 (d, J = 6.3 Hz, 3 H), 2.50 (s, 3 H), 2.93 (m, 1 H), 3.61 (s, 3 H), 4.32 (m, 1 H), 4.49 (dd, J = 14.7, 5.7 Hz, 1 H), 4.54 (dd, J = 15.6, 5.7 Hz, 1 H), 6.67 (bt, J = 5.1 Hz, 1 H), 7.16−7.32 (m, 5 H), 7.32−7.41 (m, 2 H), 7.46 (m, 1 H), 7.74−7.81 (m, 2 H), 8.59 (s, 1 H), 8.95 (bs, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.8, 18.9, 22.2, 26.8, 44.2, 52.4, 65.0, 115.9, 121.0, 126.2, 127.0, 127.6, 127.9, 128.7, 132.3, 133.6, 137.8, 140.0, 157.5, 165.8, 167.4, 169.0; IR ($CHCl_3$) 3372, 3015, 2971, 1750, 1638, 1611, 1582, 1520, 1491, 1389, 1275, 1215, 1024 cm^{-1}; HRMS calcd for $C_{27}H_{29}N_3O_5$ *m*/*z* 475.2107, obsd (M + 1) *m*/*z* 476.2174.

43: 0.62 g, 1.31 mmol, 71% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (d, J = 6.9 Hz, dimer), 0.89 (d, J = 6.9 Hz, dimer), 1.00 (d, J = 6.8 Hz, 3 H), 1.01 (d, J = 6.8 Hz, 3 H), 2.08 (m, dimer), 2.17 (s, dimer), 2.20 (s, 3 H), 2.24 (m, 1 H), 3.63 (s, dimer), 3.70 (s, 3 H), 4.44 (dd, J = 8.5, 5.1 Hz, dimer), 4.56 (dd, J = 8.5, 5.2 Hz, 1 H), 5.03 (bd, J = 15.7 Hz, 1 H), 5.31 (bd, J = 15.7 Hz, 1 H), 6.99 (d, J = 6.6 Hz, 2 H), 7.12−7.24 (m, 3 H), 7.34−7.52 (m, 3 H), 7.82 (d, J = 7.8 Hz, 2 H), 8.63 (s, 1 H), 9.09 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.6, 17.6, 18.1, 18.9, 19.1, 30.8, 48.3, 52.0, 52.1, 57.0, 57.9, 58.0, 115.65, 115.70, 121.0, 121.1, 125.8, 125.9, 126.2, 127.0, 127.2, 127.6, 128.6, 128.8, 132.1, 133.4, 133.5, 135.0, 140.0, 158.0, 158.1, 165.55, 165.63, 167.7, 167.8, 171.9, 172.1; IR (neat) 3306, 2967, 1744, 1646, 1522, 1210, 1154 cm^{-1}; HRMS calcd for $C_{27}H_{29}N_3O_5$ *m*/*z* 475.2107, obsd (M + 1) *m*/*z* 476.2172.

44: 0.75 g, 1.50 mmol, 81% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.50 (d, J = 6.6 Hz, 3 H), 0.80−0.90 (m, minor), 0.94 (d, J = 7.9 Hz, 3 H), 0.98 (d, J = 7.9 Hz, 3 H), 1.17 (d, J = 6.3 Hz, 3 H), 2.08 (m, minor), 2.21 (m, 1 H), 2.43 (s, 3 H), 2.88 (m, 1 H), 3.60 (s, 3 H), 3.62 (s, minor), 3.70 (s, 3 H), 4.29 (bd, J = 6.3 Hz, 1 H), 4.43 (dd, J = 8.3, 5.0 Hz, minor), 4.58 (dd, J = 8.3, 5.0 Hz, 1 H), 6.89 (bd, J = 6.6 Hz, 1 H), 7.30−7.50 (m, 3 H), 7.80 (d, J = 7.1 Hz, 2 H), 8.49 (s, minor), 8.66 (s, 1 H), 8.95 (bs, 1 H), 9.67 (bs, minor); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.6 (minor), 18.0, 18.8 (minor), 19.0, 22.0 (minor), 30.8 (minor), 31.0, 49.3 (minor), 51.9 (minor), 52.1, 52.3, 57.1 (minor), 57.8, 115.7, 121.0, 126.2, 127.0, 127.3 (minor), 128.4 (minor), 128.6, 128.8 (minor), 132.1, 133.6, 139.6, 165.6, 167.6, 172.1; IR (neat) 3366, 3305, 2969, 1742, 1640, 1613, 1516, 1389, 1380, 1271, 1210 cm^{-1}; HRMS calcd for $C_{26}H_{33}N_3O_7$ *m*/*z* 499.2319, obsd *m*/*z* 499.2323.

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Supporting Information Available: X-ray data for structure **30c**, and copies of NMR spectra of isolated products (39 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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