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Asymmetric Formation of Quaternary Centers through Aza-Annulation of Chiral β-Enamino Amides with Acrylate Derivatives

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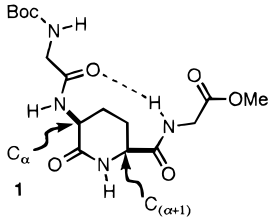
Abstract: The stereoselective formation of six-membered nitrogen heterocycles that contain an asymmetric quaternary carbon center was achieved through aza-annulation of β-enamino amide substrates with activated acrylate derivatives. Condensation of a racemic β-keto amide with an optically active primary amine, either (*R*)-α-methylbenzylamine or α-amino esters, generated the corresponding optically active tetrasubstituted secondary enamine, in which the enamine tautomer was stabilized through conjugation with an amide carbonyl. Treatment of the intermediate enamine with acryloyl chloride, acrylic anhydride, or sodium acrylate/ethyl chloroformate resulted in aza-annulation to give the corresponding δ-lactam with high diastereoselectivity (>96% de). For the variety of different β-enamino amide substrate classes examined in this reaction, the optimum method for activation of the acrylate derivative was the use of EtO_2CCl. When aza-annulation was performed with an α-acetamido-substituted acrylate derivative, the stereoselective formation of the quaternary carbon center was accompanied by poor selectivity for generation of the center α to the lactam carbonyl. Crystallographic analysis of one α-amido aza-annulation product was performed to identify the key structural features of these molecules.

Introduction

Conformationally constrained δ-lactam peptide analogues have been valuable tools for the exploration of active conformation and properties of several biologically active peptides.[1] Early work in this area established the potential use of six-membered nitrogen heterocycles for conformational control of peptide backbones,[2] and spectroscopic studies on **1** revealed the presence of intramolecular hydrogen bonding in solution.[3] More recently, the preparation of **2a** was reported, which is a *cis*-Gly-Pro dipeptide mimetic with the conformational features found in peptide type-VI turns, and this dipeptide-like fragment has been incorporated successfully into analogues of *cis*-Gly[6]-Pro[7]-bradykinin.[4] Intramolecular hydrogen bonding has also been observed spectroscopically for **2b**.[5]



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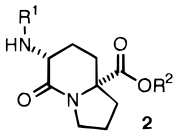

2

a: R^1=Fmoc, R^2=H
b: R^1=tBoc, R^2=Me

Our approach to the efficient construction of conformationally restricted molecules related in structure to dipeptides and homologated dipeptides has incorporated the aza-annulation

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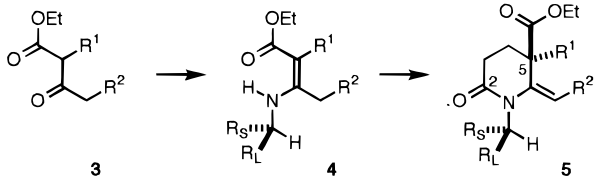
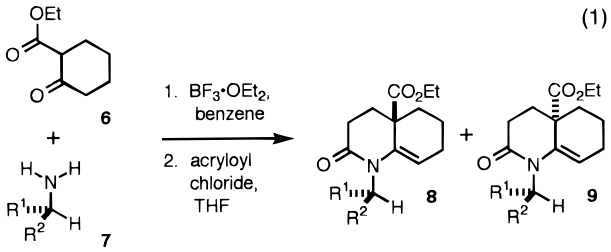
Scheme 1. General Strategy for Asymmetric Aza-Annulation Reactions



reaction as a route to δ-lactam products.[6] In previous studies, initial condensation of a racemic β-keto ester **3** with an optically active primary amine led to formation of a chiral β-enamino ester as a single geometric isomer **4** (Scheme 1).[7] Treatment of this optically active (*Z*)-enamine with an activated acrylic acid derivative then resulted in formation of the corresponding δ-lactam **5** through formal conjugate addition to form the carbon−carbon bond and *N*-acylation to generate the amide functionality. Heterocycle construction with this aza-annulation process resulted in the stereoselective generation of a quaternary center at C-5 with 1,4-asymmetric induction from the chiral amine.

Variation in the source of chirality, from α-methylbenzylamine to α-amino acid esters, gave poorer selectivity for the aza-annulation reaction with β-enamino ester substrate **6** (eq 1).[7] Although **7a** led to a >97:3 stereoselective formation of



(1)

8a with the quaternary center at C-5, use of the ethyl ester of phenylglycine (**7b**) resulted in a significantly lower (21:79) ratio of diastereomers **8** and **9** under the same reaction conditions (Table 1). Deviation from a phenyl substituent at R^1 or R^2, the use of the methyl ester of valine, led to poor diastereoselective δ-lactam formation (57:43). Although these substrates showed a great deal of promise for asymmetric construction of heterocycles, the scope of this method for the general synthesis of extended peptide structures with high enantiomeric purity was greatly limited.

Table 1. Effect of Chiral Amine and Temperature on Asymmetric Induction[a]

amine **7**	R^1	R^2	*T* (°C)	**8:9**[b]	yield (%)[c]
7a	Me	Ph	66	>97:3	85
7b	Ph	CO_2Et	66	21:79	63
7b	Ph	CO_2Et	0	7:93	68
7b	Ph	CO_2Et	−33	2:98	77
7c	CO_2Me	iPr	66	57:43	43

[a] See eq 1. [b] Determined by ^{1}H NMR of the crude reaction mixture. [c] Yield of the diastereomeric mixture after chromatography.

The utility of chiral α-amino ester derivatives in the asymmetric aza-annulation reaction has been greatly enhanced by the use of β-enamino amide derivatives. Herein, the reaction of activated acrylic acid derivatives with β-enamino amides for the general construction of six-membered nitrogen heterocycles is reported for the first time. Reaction with this class of substrates is dependent on the nature of the substrate, and has resulted in the rapid construction of conformationally restricted tri- and tetrapeptide analogues and a variety of other molecules with high asymmetric induction.

Results and Discussion

Modification of Ester Substrates. Our first approach to the construction of conformationally restricted peptide analogues incorporated the synthesis and extension of the bicyclic amino acid **12** derived from ester **11**. Synthesis of **11** was accomplished through the stepwise condensation of the β-keto ester **10** with **7a**, which gave the corresponding β-enamino ester, and subsequent aza-annulation with sodium acrylate/EtO_2CCl gave diastereomer **11** in 70% yield. Deprotection of the carboxylate gave the corresponding acid **12** without evidence for enamine reduction, even after extended exposure to the reaction conditions.

The utility of the aza-annulation reaction for the general synthesis of extended peptide structures with high enantiomeric purity was limited by the inability to efficiently modify fragment **12**. Initial attempts to extend the peptide sequence through the coupling of **12** with glycine ethyl ester proved somewhat problematic. A number of standard peptide coupling reagents were used for this purpose, but the steric hindrance around the activated carboxylic acid intermediate prevented efficient coupling at this site. The best yield for this reaction was achieved with the use of 1,3-dicyclohexylcarbodiimide (DCC), but gave only 15% of the desired product. Instead, formation of the stable *N*-acylurea adduct from the reaction of the acid with DCC was observed as the major product of the reaction.[8] Alternative methods used to prepare the amide, by reactions with either $(COCl)_2$/pyridine/glycine ethyl ester or ethyl chloroformate/glycine ethyl ester in THF, either were completely unsuccessful or gave only a trace of the product.

Interestingly, the use of DPPA as the reagent led to the formation of **13a** in 10% yield, but a significant amount of an alternative coupling product was formed. This unexpected product was isolated in 53% yield, and has been assigned the structure of the disubstituted urea **14** (Scheme 2). Generation of **14**, through Curtius rearrangement of the intermediate acyl azide, followed by reaction with glycine ethyl ester, has

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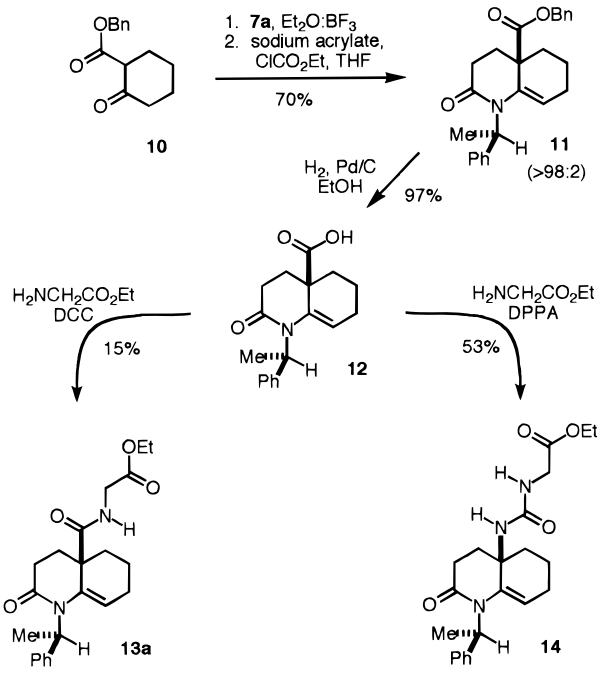
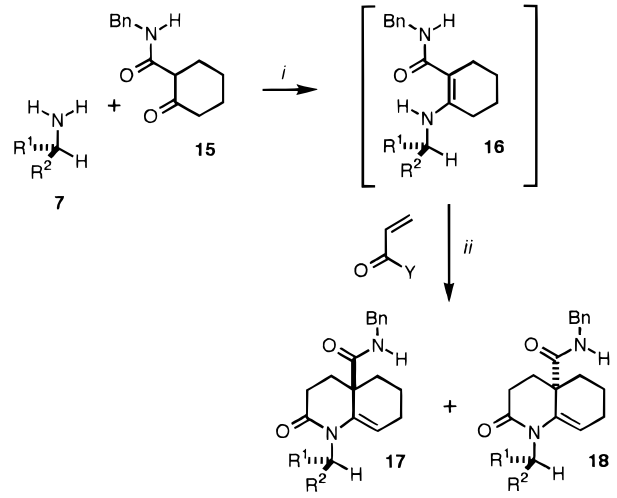
(8) Holmberg, K.; Hansen, B. *Acta Chem. Scand. B* **1979**, *33*, 410.

Scheme 2. Conversion of **10** to Amides with Extended Peptide Chains



Scheme 3. Asymmetric Aza-Annulation of β-Enamino Amide Intermediates with Acrylate Derivatives[a]



[a] Reaction conditions: (i) **7** or **7**·HCl/$NaHCO_3$, toluene, reflux; (ii) (method A) sodium acrylate, $ClCO_2Et$, THF, reflux; (method B) sodium acrylate/acryloyl chloride, THF, reflux; (method C) acryloyl chloride, THF, reflux.

precedent in related work.[9] The difficulties encountered in conversion of **12** to **13a** served to reinforce the need to examine methods for aza-annulation with β-keto amide substrates.

Cyclic Amide Substrates. Investigation of β-keto amide substrates in the asymmetric aza-annulation reaction was initiated with a study of aza-annulation reagents (Scheme 3). On the basis of our studies with achiral imine[10] and β-enamino carbonyl substrates,[6,7] as well as the use of this methodology in the synthesis of natural products,[11] three different classes of acrylate derivatives were examined. Acryloyl chloride, acrylic anhydride, and mixed anhydride reagents were employed for the aza-annulation with asymmetric β-enamino amides. To evaluate the effectiveness of each reagent, aza-annulation of the α-methylbenzylamine enamine **16a** was performed with these three different activated acrylate derivatives, and yields and diastereoselectivity ratios were obtained.

Table 2. Effect of Chiral Amine and Acrylate Derivative on the Asymmetric Aza-Annulation Reaction[a]

amine	R^1	R^2	method[b]	**17:18**[c]	yield (%)[d]
7a	Me	Ph	A	>98:2	99
			B	>98:2	86
			C	>98:2	67
7b	Ph	CO_2Et	A	2:>98	96
			B	2:>98	80
			C	2:>98	49
7c	CO_2Me	iPr	A	>98:2	90
7d	CO_2Et	Bn	A	95:5[e]	46

[a] See Scheme 3. [b] Reaction conditions: (i) **7** or **7**·HCl/$NaHCO_3$, toluene, reflux; (ii) (method A) sodium acrylate, $ClCO_2Et$, THF, reflux; (method B) sodium acrylate/acryloyl chloride, THF, reflux; (method C) acryloyl chloride, THF, reflux. [c] Determined by ^{1}H NMR of the crude reaction mixture. [d] Yield of the diastereomeric mixture after chromatography. [e] Assignment of the major diastereomer as **17** was made on the basis of ^{1}H NMR comparison to **17c**.

Efficient formation of δ-lactam products was obtained for aza-annulation of enamines derived from a variety of β-keto amides and (*R*)-methylbenzylamine **7a** (Table 2). A significant dependence of the aza-annulation reaction outcome on the type of reagent employed was observed. Although acryloyl chloride produced efficient heterocycle formation with β-enamino ester substrates,[7] similar reaction with the β-enamino amides gave significantly lower yields. The use of acrylic acid anhydride, generated in situ by the reaction of sodium acrylate with acryloyl chloride, resulted in somewhat improved yields. The mixed anhydride, formed by the combination of sodium acrylate with EtO_2CCl, proved to be the optimum reagent for aza-annulation with β-enamino amide substrates. The increased efficiency in product formation with anhydride reagents paralleled that found for the analogous ester substrates; however, the decreased diastereoselectivity observed for reaction of ester substrates with anhydride reagents was not observed for the corresponding amides.[7] In each case, the diastereoselective formation of the quaternary carbon from the β-enamino amide substrates was high (>98:2), and was independent of the acrylate derivative used for aza-annulation.[12]

A similar reactivity was observed for the β-enamino amide derived from condensation of phenylglycine ethyl ester (**7b**) with **15**. The aza-annulation of **16b** was significantly more efficient when acrylic acid anhydride was used instead of acryloyl chloride, and a further increase in yield was obtained through the use of the mixed anhydride. In each case, stereoselective formation of **18b** occurred to the extent of >98:2. Use of the valine-derived substrate **16c**, which resulted in poor diastereoselectivity in the case of the β-enamino ester substrate (57:43), gave excellent stereoselective formation of **17c** (>98:2) in high

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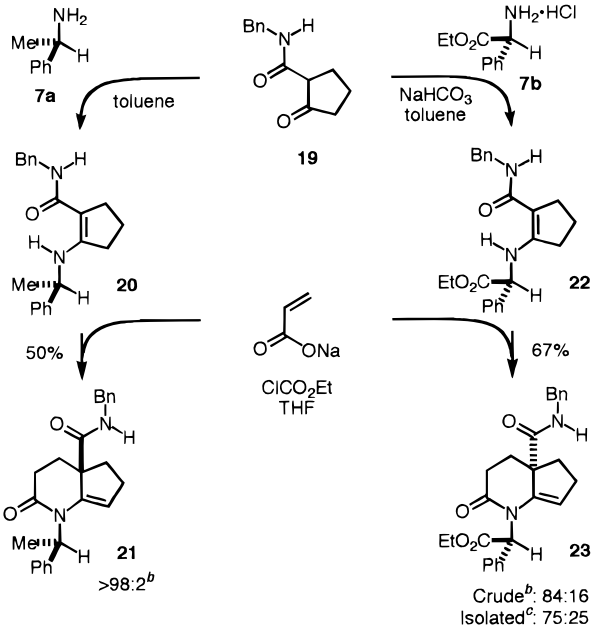
(12) Prior to purification, the crude ratio of diastereomers was determined by ^{1}H NMR. The major isomer was assigned by correlation to the previously reported analogous aza-annulation[7] and Michael addition reactions. For an excellent review on asymmetric Michael addition reactions, see: d'Angelo, J.; Desmaële, D.; Dumas, F.; Guingant, A. *Tetrahedron: Asymmetry* **1992**, *3*, 459.

Scheme 4. Asymmetric Aza-Annulation of Cyclopentanone-Derived β-Enamino Amide Intermediates with Acrylate Derivatives[a]



[a] Yields represent the two-step conversion of **19** to product. [b] Determined by ^{1}H NMR of the crude reaction mixture. [c] Ratio of the diastereomeric mixture after chromatography.

yield (90%) for the β-enamino amide. Interestingly, even the phenylalanine-derived **7d** was effective at asymmetric induction (95:5), but the yield of the aza-annulation reaction was low with this source of asymmetry.

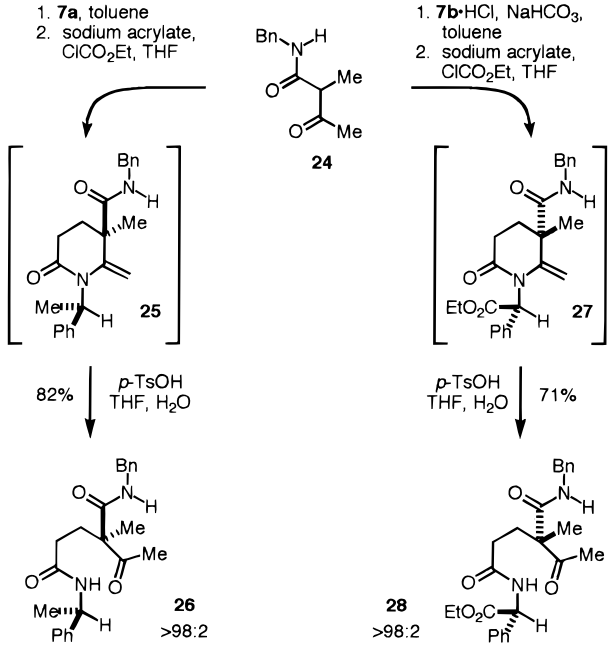
The five-membered ring substrate **19** showed different reactivity and stability patterns than the analogous six-membered ring substrate (Scheme 4). The β-keto amide **19** was generated from the corresponding β-keto ester species, and was used without extensive purification for subsequent formation of enamines **20** and **22**. Both **20** and **22** were more sluggish in their formation, and these enamines were isolated in low yield for use in the aza-annulation process. Aza-annulation of **20** led to generation of **21** in only moderate yield, but the product was obtained with high diastereoselectivity (>98:2). Treatment of **22** with the acrylate mixed anhydride led to a more efficient aza-annulation than that of **20**, but the amino acid source of asymmetry led to only an 84:16 crude ratio of diastereomers; after purification of **23**, a 75:25 ratio of diastereomers was obtained.

Acyclic Amide Substrates. The aza-annulation with acyclic β-keto amide substrates resulted in ring formation with a high degree of diastereoselectivity (Scheme 5). Condensation of **24** with **7a** efficiently generated the corresponding enamine as a single geometric isomer, as determined by ^{1}H NMR of the crude reaction mixture, and subsequent aza-annulation with the acrylate mixed anhydride generated **25** with high diastereoselectivity (>98:2). However, all attempts to isolate **25** resulted in partial hydrolysis of the mixture to **26**. To obtain an accurate yield for the carbon−carbon bond formation process, crude **25** was treated with *p*-TsOH in THF/H_2O to promote complete hydrolysis of the enamide functionality. For the three-step process of enamine formation, aza-annulation reaction, and hydrolysis, an 82% yield of **26** was achieved, and the product was obtained with a >98:2 diastereomer ratio.

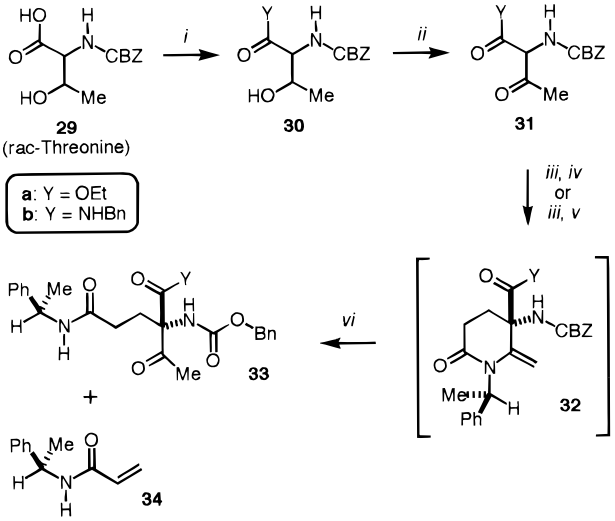
Reaction of **24** with **7b** followed by aza-annulation led to results similar to those obtained for **7a** (Scheme 5). Condensation of **24** with **7b** generated a single isomeric enamine intermediate, and aza-annulation gave δ-lactam **27** with >98:2 diastereoselectivity. Again, facile hydrolysis was observed for this disubstituted terminal enamide, which precluded efficient isolation of **27**. However, intentional hydrolysis and subsequent isolation gave a 71% yield of **28** for the three-step process without loss of stereochemical integrity.

Compounds **29a** and **29b**, protected derivatives of threonine, were the source of the next β-keto carboxylate species studied (Scheme 6). In this case, the β-keto ester was prepared in addition to the amide for comparative analysis. The corresponding amino-protected amino acid derivatives, **30a** and **30b**, were prepared through standard esterification and peptide coupling strategies, respectively. While oxidation of **30a**

Scheme 5. Asymmetric Aza-Annulation of Acyclic β-Enamino Amide Intermediates with Acrylate Derivatives



Scheme 6. Aza-Annulation with Threonine Derivatives[a]



[a] Reaction conditions: (i) (**a**) EtOH, HCl, reflux; (**b**) (1) 2,4,6-trichlorophenol, DCC (60%); (2) $BnNH_2$ (80%); (ii) PCC/Celite (1:1), CH_2Cl_2 (**a**) 91% (*i*−*ii*); (**b**) 56% based on recovered starting material); (iii) **7a**, toluene, reflux; (iv) sodium acrylate/EtO_2CCl, THF, 25 °C; (v) acryloyl chloride, THF reflux; (vi) hydrolysis (see the text). Overall aza-annulation yields; (*iii*, *iv*, *vi*) (**a**) 45%; (**b**) 75%; (*iii*, *v*, *vi*) **a**: 30%; **b**: 65%.

proceeded smoothly to give **31a** (91% yield for the two-step process from **29a**), oxidation of **30b** was more problematic. Oxidation of **30b** proceeded best with PCC/Celite (1:1), but the reaction was very sensitive and an unoptimized 56% yield of **31b**, based on recovered starting material, could be obtained.

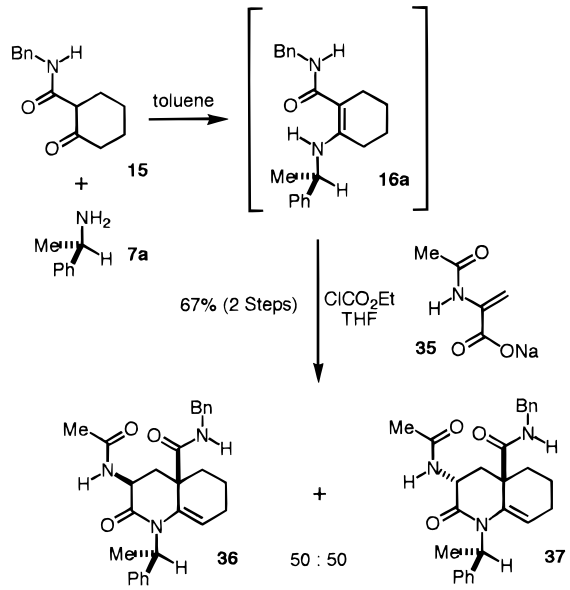
Condensation of the β-keto ester **31a** with **7a**, followed by treatment with the acrylate mixed anhydride, gave the aza-annulation reaction product **32a**. As observed for **25** and **27**, this terminal enamide was sensitive toward hydrolysis conditions, and even with aqueous $NaHCO_3$ workup, hydrolysis occurred completely to give the acyclic product. Overall, the threestep condensation/aza-annulation/hydrolysis procedure provided **33a** in 45% yield. Conversion of **31a** to **33a** was also performed with acryloyl chloride as the aza-annulation reagent; however, reaction under these conditions gave only a 30% overall yield of **33**. The major byproduct of the reaction was found to be the corresponding acrylamide **34**. Independent of the reagent used for this reaction, the chiral α-amino acid was formed with >98:2 stereoselectivity.

The three-step condensation/aza-annulation/hydrolysis procedure produced much better results for the analogous β-keto amide substrate. With the use of aza-annulation conditions that employed the generation of the mixed anhydride reagent (sodium acrylate/EtO_2CCl), a 75% yield of **33b** was obtained. In this case, complete hydrolysis of **32** to **33** was effected simply by attempted silica gel chromatographic purification of the product. Aza-annulation of **31** with acryloyl chloride as the reagent produced **33b** in 65% yield, which paralleled observations for the ester derivative.

Several important features of the aza-annulation reaction of acyclic β-keto carboxylate derivatives are of significance. The acyclic substrates were much more sensitive toward hydrolysis. However, after intentional hydrolysis of the reaction mixture, α-chiral β-keto amide products of carbon−carbon bond formation were obtained in good yield with high diastereoselective bond formation. The 1,4-asymmetric induction that occurred during the aza-annulation process appeared as a 1,6-relationship in the product of hydrolysis. In addition, the high diastereoselectivity obtained in these reactions resulted, in part, from the important formation of a single geometric isomer of the intermediate β-enamino carboxylate derivative.

α-Amino Lactam Products. The use of sodium 2-acetamidoacrylate (**35**) as the aza-annulation reagent led to the formation of 2-acetamido δ-lactam products **36** and **37** (Scheme 7).[7,13] Treatment of **16a** with the mixed anhydride of **35**, generated in situ by the reaction of **35** with $ClCO_2Et$, resulted in formation of equal amounts of two diastereomeric α-acetamido δ-lactam products in 67% yield. Separation of the diastereomers allowed for characterization of each product, and treatment of **37** with NaH led to epimerization α to the lactam carbonyl that resulted in a 45:55 ratio of stereoisomers **36** and **37**. On the basis of this information, >98:2 diastereoselective formation of the quaternary center occurred, with no bias for selective generation of the stereoisomers at the α position.

Scheme 7. Introduction of an α-Amido Substituent in the δ-Lactam Product



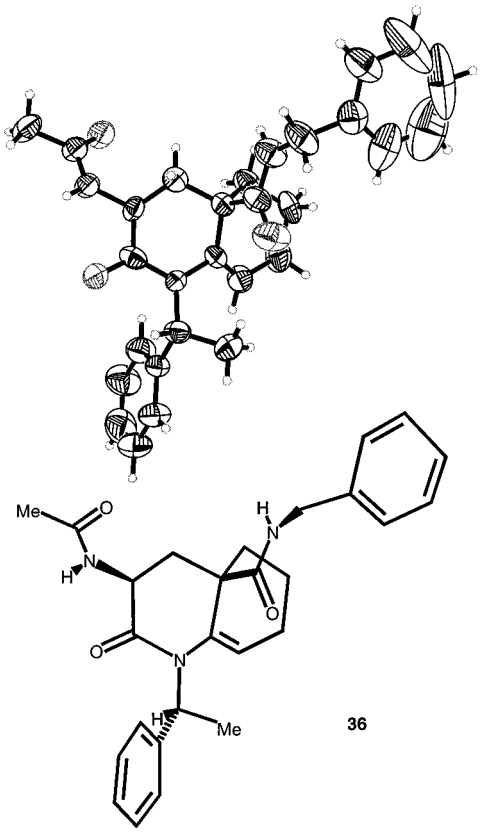
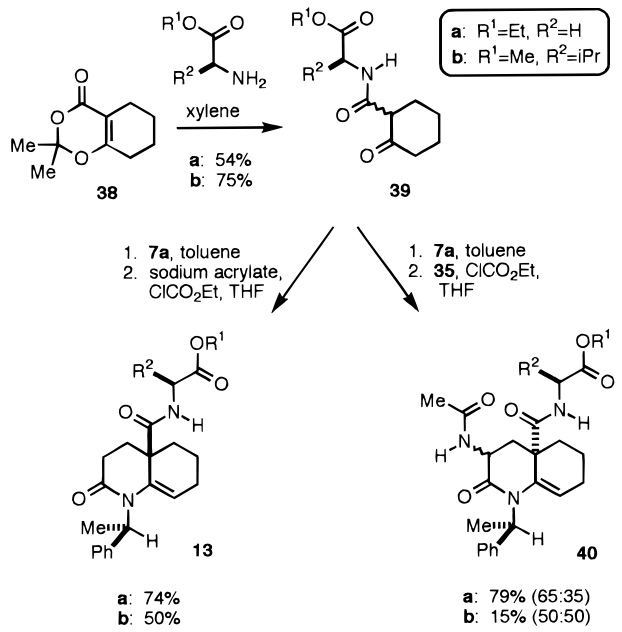


Figure 1. ORTEP representation of **36**.

Crystallization of diastereomer **36** allowed for the X-ray crystallographic characterization of the molecule, and the three-dimensional features of **36** are illustrated in Figure 1. With the stereochemical configuration of the chiral amine known, the generation of the quaternary carbon center resulted through carbon−carbon bond formation from the least hindered face of the enamino amide as shown by the favored orientation shown for **16** (Scheme 3, R^2 (Ph) > R^1 (Me)). Interestingly, although **36** had greater potential than **37** for intramolecular hydrogen bonding, with both the benzyl amide and the acetamido substituents cis relative to each other, intramolecular hydrogen bonding was not observed in the solid state. In the solid state,

(13) For previous reports of the use of 2-amidoacrylic acid derivatives in aza-annulation, see: (a) Thyagarajan, B. S.; Gopalakrishnan, P. V. *Tetrahedron* **1964**, *20*, 1051. (b) Meyer, H.; Bossert, F.; Horstmann, H. *Justus Liebigs Ann. Chem.* **1978**, 1483. (a) Danieli, B.; Lesma, G.; Palmisano, G. *J. Chem. Soc., Chem. Commun.* **1980**, 109. (c) Danieli, B.; Lesma, G.; Palmisano, G. *Gazz. Chim. Ital.* **1981**, *111*, 257. (c) McCabe, R. W.; Young, D. W.; Davies, G. M *J. Chem. Soc., Chem. Commun.* **1981**, 395. (d) Chiba, T.; Takahashi, T. *Chem. Pharm. Bull.* **1985**, *33*, 2731. (e) Chiba, T.; Takahashi, T.; Kaneko, C. *Chem. Pharm. Bull.* **1985**, *33*, 4002. (f) Capps, N. K.; Davies, G. M.; Loakes, D.; McCabe, R. W.; Young, D. W. *J. Chem. Soc., Perkin Trans. 1* **1991**, 3077. (g) Hua, D. H.; Park, J.-G.; Katsuhira, T.; Bharathi, S. N. *J. Org. Chem.* **1993**, *58*, 2144. (h) Kolar, P.; Tisler, M. *J. Heterocycl. Chem.* **1993**, *30*, 1253.

Scheme 8. Asymmetric Aza-Annulation of β-Enamino Amino Acid Intermediates with Acrylate Derivatives



the *cis*-acetamido substituent is oriented in a pseudoequatorial position directed away from the benzyl amide substituent. This could be the result of more favorable intramolecular interactions that are favored during lattice packing.

Although intramolecular hydrogen bonds were not present, several intermolecular hydrogen bonding interactions were observed. The lactam carbonyl [O(2)] and the α-NH [N(19)] of the acetamido substituent of one molecule form a complementary/reciprocal intermolecular hydrogen bonding relationship with the α-NH [N(19)] of the acetamido substituent and the lactam carbonyl [O(2)] of a second molecule, respectively (2.132 Å each). The NH [N(23)] of the benzyl amide was also found to interact (2.106 Å) with the carbonyl [O(20)] of the α-acetamido substituent of a third molecule. Although solid-state intramolecular hydrogen bonding was not observed in this case, this does not provide evidence against possible intramolecular hydrogen bonding in solution, which has been observed in similar molecules.[3]

***β*-Keto Amino Acid Substrates.** An important direction of this investigation, one which is key to the potential use of this methodology for the synthesis of conformationally restricted peptide derivatives, was the demonstrated ability to extend the amino acid sequence at the amide position of the substrate. The necessary substrates, **39a** and **39b**, were prepared by the reaction of the corresponding amino acid ester with **38** (Scheme 8). Subsequent condensation of **39** with **7a**, followed by aza-annulation with sodium acrylate/EtO_2CCl, gave **13a** as anticipated. Interestingly, the reaction of the glycine derivative **a** (74%) was significantly more efficient than that of the valine derivative **b** (50%). This difference in reaction efficiency became even more pronounced when aza-annulation was performed with **35**/EtO_2CCl. In this case, lactam formation resulted in a good yield of **40a** in the two step-process from **39a**, but produced only minor amounts of the desired aza-annulation products from **39b**. In the case of substrate **b**, epimerization of the amino acid residue was not observed under either of the aza-annulation reaction conditions.

Summary. The aza-annulation of chiral tetrasubstituted β-enamino amides with activated acrylate derivatives resulted in the efficient formation of quaternary asymmetric stereogenic centers. Condensation with chiral primary amines led to formation of β-keto carboxylic acid derivatives, to generate a single geometric isomer of the intermediate β-enamino amides. The β-enamino amides were formed from a variety of chiral primary amines, including α-methylbenzylamine and esters of α-amino acids, and gave high diastereoselective formation of quaternary carbon centers. Mixed anhydrides of acrylate derivatives were the most effective reagents for the aza-annulation reaction of β-enamino amides to form δ-lactams. Formation of extended peptide sequences was demonstrated at both the 2-position of the lactam and the carboxylate site of the β-keto amide substrate. Aza-annulation resulted in the rapid and efficient construction of δ-lactam products that can contain a high degree of complexity and have an asymmetrically substituted quaternary carbon.[14] Products derived from non-cyclohexanone substrates, the cyclopentanone and acyclic compounds, were sensitive toward hydrolysis, but the resultant products of "Michael addition" were formed in good yield with high asymmetric induction. In addition, the products of the aza-annulation reaction were β-amino acids, which are important species in the study of biologically active systems.[15]

Experimental Section

General Methods. All reactions were carried out by performing standard inert atmosphere techniques to exclude moisture and oxygen, and reactions were performed under an atmosphere of nitrogen or argon. Acryloyl chloride was purchased from Fluka and used without purification. Compounds **10**,[16] **15**,[17] and **19**[17] were prepared according to established procedures. Compound **24** was prepared by alkylation of benzylacetoacetamide with MeI in EtOH/EtONa. Azeotropic removal of H_2O was assisted by the use of 4-Å molecular sieves.[18] Isolated compounds were crystallized from a minimun amount of the eluent; those compounds for which melting points were not reported were oils.

General Procedure for the Preparation of *β*-Ketoamides: Method A (15). A mixture of the necessary β-keto ester (1 equiv), amine (2 equiv), and DMAP (0.3 equiv) in toluene was heated at reflux for 24 h. **Method B (15).** A mixture of the necessary β-keto ester (1 equiv) and amine (1.5 equiv) in xylene was heated at reflux for 24 h. **Method C (39a, 39b).** A mixture of **38** (10 mmol) and the appropriate amino acid (10 mmol) in xylene was heated at reflux for 2 h. Each reaction mixture was then cooled and concentrated to a residue, and the crude product was purified with flash column chromatography (eluent as indicated).

Data for 15:[17] 80:20; hexanes/EtOAc, 2.50 g, 10.8 mmol, 96% yield; mp 85−86 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.54−1.78 (m, 2 H), 1.80−2.00 (m, 2 H), 2.04 (m, 1 H), 2.20 (m, 1 H), 2.22−2.44 (m, 2 H), 3.14 (dd, J = 5.5, 10.5 Hz, 1 H), 4.36−4.46 (m, 2 H), 5.63 (br s, 1 H), 7.15−7.31 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) (mixture of tautomers) δ 21.8, 22.5, 22.6, 24.3, 27.3, 29.2, 31.7, 42.2, 43.1, 43.3, 55.7, 96.8, 127.3, 127.5, 127.6, 127.7, 128.6, 128.7, 138.1, 138.2, 168.9, 170.5, 172.3, 210.6; IR ($CHCl_3$) 1640, 1605, 1530 cm^{-1}; HRMS calcd for $C_{14}H_{17}NO_2$ m/z 231.1259, obsd m/z 231.1268.

(14) For reviews on methods for the formation of quaternary carbons, see: (a) Martin, S. F. *Tetrahedron* **1980**, *36*, 419. (b) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037.

(15) For the importance of β-amino acids, see: (a) Lubell, W. D.; Kitamura, M.; Noyori, R. *Tetrahedron: Asymmetry* **1991**, *2*, 543. (b) Juaristi, E.; Quintana, D.; Escalante, J. *Aldrichim. Acta* **1994**, *27*, 3.

(16) (a) Taber, J. F.; Amedio, J. C., Jr.; Patel, Y. K. *J. Org. Chem.* **1985**, *50*, 3618. (b) Hatakeyama, S.; Satoh, K.; Sakurai, K.; Takano, S. *Tetrahedron Lett.* **1987**, *28*, 2713.

(17) (a) Cossy, J., Thellend, A., *Synthesis* **1989**, 753. (b) Labelle, M.; Gravel, D. *J. Chem. Soc., Chem. Commun.* **1985**, 105.

(18) 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. Barta, N. S.; Paulvannan, K.; Schwarz, J. B.; Stille, J. R. *Synth. Commun.* **1994**, *24*, 583.

Data for 39b: 80:20; hexanes:EtOAc, 0.26 g, 1.02 mmol, 75% yield; ^{1}H NMR (300 MHz, $CDCl_3$) (mixture of tautomers) δ 0.84−0.92 (m, 12 H), 1.57−1.80 (m, 6 H), 1.82−2.02 (m, 3 H), 2.02−2.22 (m, 6 H), 2.22−2.48 (m, 3 H), 3.18 (dd, J = 5.4, 10.5 Hz, 1 H), 3.66 (s, 3 H), 3.69 (s, 3 H), 4.44−4.54 (m, 2 H), 5.82 (d, J = 8.1 Hz, 1 H), 7.34 (d, J = 8.1 Hz, 1 H), 7.50 (d, J = 8.1 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) (mixture of tautomers) δ 17.4, 17.6, 18.6, 18.8, 21.6, 22.20, 22.24, 23.8, 24.0, 27.0, 27.1, 29.0, 30.7, 30.9, 31.1, 31.4, 41.87, 41.94, 51.8, 51.9, 55.4, 55.6, 56.3, 56.8, 56.9, 77.2, 96.6, 125.7, 128.6, 168.8, 168.9, 170.5, 171.9, 171.9, 172.1, 172.3, 209.5, 209.9; IR (neat) 1744, 1642, 1526 cm^{-1}; HRMS calcd for $C_{13}H_{21}NO_4$ m/z 255.1471, obsd m/z 255.1472.

31a. The 2-(benzyloxycarbonyl)amino derivative **29** was prepared from *rac*-threonine.[19] A mixture of **29** (1.13 g, 4.46 mmol) and concentrated HCl (4 mL) was heated to reflux in EtOH (50 mL) for 5 h in a flask equipped for removal of H_2O.[18] After the reaction was complete, solvent was removed, and the crude viscous product was treated with a mixture of PCC (1.73 g, 8.03 mmol) and Celite (1:1 w/w) in CH_2Cl_2 (100 mL) at 0 °C. The mixture was stirred at 0 °C for 3 h, warmed gradually to room temperature, and stirred for an additional 10 h. The mixture was then filtered through a mixture of neutral alumina/silica gel/Celite, 4:4:1. The filtrate was concentrated, and the crude product (91% yield, two steps) was used in the aza-annulation step without further purification.

General Procedure For Aza-Annulation of *β*-Ketoamides and *β*-Ketoesters. The primary amine or primary amine salt (0.5−5 mmol, 1.1 equiv) was taken up in toluene (0.05 M relative to the amine), and the β-ketoamide or β-ketoester (1.0 equiv) was added at room temperature. In the case of amine hydrochloride salt, $NaHCO_3$ (1.5 equiv) was added, and for condensation that involved β-ketoesters, 0.02 mL of Et_2O/BF_3 (0.3 equiv) was added. The flask was fitted with a modified Dean−Stark trap filled with 4-Å molecular sieves,[18] and the mixture was heated at reflux until the reaction was complete as determined by NMR analysis (10−18 h). Solvent was removed under reduced pressure. A solution of acrylate derivative was then added to the intermediate enamine at room temperature, and the reaction mixture was stirred at room temperature for 12−18 h (method A, mixed anhydride of acrylic acid (freshly prepared from combination of sodium acrylate (1.3 equiv) and ethyl chloroformate (1.3 equiv) for 1 h in dry THF at −78 °C (0.05 M solution); method B, acrylic acid anhydride (freshly prepared from combination of sodium acrylate or the 2-acetamido acrylate derivative at −78 °C (1.3 equiv) and acryloyl chloride (1.3 equiv) for 1 h in dry THF (0.05 M solution); method C, acryloyl chloride (1.3 equiv) in dry THF (0.05 M solution)).[7] Reactions were quenched by the addition of H_2O (for mixed anhydrides or acrylic anhydride) or saturated aqueous $NaHCO_3$ (acryloyl chloride), and the mixture was extracted four times with either Et_2O or EtOAc. The combined organic fractions were dried (Na_2SO_4) and filtered, and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica, 230−400 mesh, eluent as indicated).

Data for 11: 80:20; hexanes/EtOAc, 1.98 g, 5.08 mmol, 70% yield; $[\alpha]^{20}_D$ = −93.5° (c = 1.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24−1.56 (m, 2 H), 1.51 (d, J = 7.1 Hz, 3 H), 1.69 (ddd, J = 6.4, 12.6, 12.8 Hz, 1 H), 1.76−1.92 (m, 2 H), 2.03 (m, 1 H), 2.16 (m, 1 H), 2.27 (ddd, J = 1.9, 6.4, 13.1 Hz, 1 H), 2.41 (m, 1 H), 2.58 (ddd, J = 2.0, 6.4, 18.0 Hz, 1 H), 4.91 (dd, J = 5.3, 3.0 Hz, 1 H), 5.02 (d, J = 13.0 Hz, 1 H), 5.09 (d, J = 13.0, 1 H), 6.20 (q, J = 7.2 Hz, 1 H), 7.04−7.30 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.6, 18.5, 24.4, 30.4, 31.0, 35.4, 46.7, 50.6, 67.1, 112.3, 125.6, 126.3, 128.3, 128.4, 128.5, 128.6, 133.6, 135.5, 142.4, 168.7, 174.2; IR ($CHCl_3$) 1728, 1669, 1638, 1497 cm^{-1}; HRMS calcd for $C_{25}H_{27}NO_3$ m/z 389.1991, obsd m/z 389.2190.

Data for 17a: 65:35; hexanes/EtOAc, 0.31 g, 0.80 mmol, 99% yield; mp 126−127 °C; $[\alpha]^{23}_D$ = −149.5° (c = 0.31, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28−1.44 (m, 2 H), 1.39 (d, J = 7.10 Hz, 3 H), 1.47−1.65 (m, 2 H), 1.85 (m, 1 H), 2.10 (m, 1 H), 2.38−2.64 (m, 3 H), 4.32 (dd, J = 5.4, 14.6 Hz, 1 H), 4.41 (dd, J = 6.0, 14.6 Hz, 1 H), 4.96 (dd, J = 3.5, 5.3 Hz, 1 H), 6.18 (br t, J = 5.2 Hz, 1 H), 6.33 (q, J = 7.1 Hz, 1 H), 7.06−7.29 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 18.0, 24.3, 30.2, 30.4, 35.3, 44.0, 46.7, 49.4, 112.8, 125.2, 126.4, 127.6, 128.5, 128.8, 133.7, 137.6, 141.2, 169.4, 173.0; IR ($CHCl_3$) 1665, 1634, 1512 cm^{-1}; HRMS calcd for $C_{25}H_{28}N_2O_2$ m/z 388.2151, obsd m/z 388.2147.

Data for 21: 65:35; hexanes/EtOAc, 0.045 g, 0.12 mmol, 50% yield; mp 57−58 °C; $[\alpha]^{25}_D$ = −38.2° (c = 0.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.51 (d, J = 7.2 Hz, 3 H), 1.60−1.94 (m, 2 H), 2.07−2.37 (m, 3 H), 2.57−2.78 (m, 3 H), 4.40 (dd, J = 5.5, 14.7 Hz, 1 H), 4.46 (dd, J = 5.7, 14.6 Hz, 1 H), 4.74 (t, 2.2 Hz, 1 H), 6.22 (q, J = 7.2 Hz, 1 H), 6.24 (br t, J = 5.5 Hz, 1 H), 7.10−7.30 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4, 29.2, 29.3, 30.8, 36.3, 43.9, 49.8, 55.9, 110.2, 126.0, 126.9, 127.5, 127.7, 128.5, 128.9, 137.9, 139.5, 140.2, 169.5, 172.4; IR ($CHCl_3$) 1669, 1628, 1509 cm^{-1}; HRMS calcd for $C_{24}H_{26}N_2O_2$ m/z 374.1994, obsd m/z 374.2000.

Data for 33b: $[\alpha]^{23}_D$ = +29.1° (c = 0.35, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (d, J = 6.9 Hz, 3 H), 1.84−2.14 (m, 2 H), 2.17 (s, 3 H), 2.47−2.66 (m, 2 H), 4.20−4.40 (m, 2 H), 4.96−5.16 (m, 3 H), 5.79 (d, J = 7.5 Hz, 1 H), 6.93 (br s, 1 H), 7.05 (bt, J = 5.4 Hz, 1 H), 7.13−7.40 (m, 15 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6, 25.1, 28.5, 30.6, 44.0, 48.8, 67.1, 71.5, 126.1, 127.3, 127.5, 127.5, 128.1, 128.2, 128.5, 128.6, 128.6, 136.1, 137.4, 143.0, 154.9, 166.5, 170.5, 205.4; IR ($CHCl_3$) 1715, 1669, 1534, 1497 cm^{-1}; HRMS calcd for $C_{30}H_{33}N_3O_5$ m/z 515.2420, obsd m/z 515.2402.

Data for 36: R_f = 0.27; 90:5:5; Et_2O/MeOH/petroleum ether, 0.15 g, 0.31 mmol, 67% yield; $[\alpha]^{24}_D$ = −322.8° (c = 0.36, $CHCl_3$); mp 119−120 °C (sealed); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45−1.72 (m, 3 H), 1.56 (d, J = 7.1 Hz, 3 H), 1.80−1.97 (m, 3 H), 1.93 (s, 3 H), 2.03−2.15 (m, 3 H), 2.41 (dd, J = 5.6, 13.2 Hz, 1 H), 4.10 (dd, J = 4.9, 14.5 Hz, 1 H), 4.28 (td, J = 12.0, 5.9 Hz, 1 H), 4.42 (dd, J = 6.2, 14.5 Hz, 1 H), 5.39 (t, J = 3.9 Hz, 1 H), 5.55 (q, J = 7.1 Hz, 1 H), 6.01 (br t, J = 5.1 Hz 1 H), 6.53 (d, J = 5.8 Hz, 1 H), 7.06−7.29 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.1, 18.0, 23.2, 24.0, 34.8, 36.5, 44.1, 47.8, 48.8, 55.4, 120.6, 126.3, 127.2, 127.7, 127.8, 128.6, 128.8, 135.7, 137.8, 141.3, 169.9, 170.4, 173.7; IR ($CHCl_3$) 1665, 1509 cm^{-1}; HRMS calcd for $C_{27}H_{31}N_3O_3$ m/z 445.2366, obsd m/z 445.2376.

Data for 37: R_f = 0.22; 90:5:5; Et_2O/MeOH/petroleum ether, 0.15 g, 0.31 mmol, 67% yield; $[\alpha]^{25}_D$ = −134.9° (c = 0.75, $CHCl_3$); mp 116−117 °C (sealed); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30−1.60 (m, 3 H), 1.48 (d, J = 6.8 Hz, 3 H), 1.80−2.15 (m, 4 H), 1.92 (s, 3 H), 2.75 (dd, J = 6.6, 13.2 Hz, 1 H), 3.97 (td, J = 6.6, 14.4 Hz, 1 H), 4.36 (dd, J = 4.2, 10.2 Hz, 1 H), 4.43 (dd, J = 5.7, 16.2 Hz, 1 H), 5.04 (dd, J = 4.4, 5.6 Hz, 1 H), 6.14 (q, J = 6.8 Hz, 1 H), 6.28 (t, J = 6.0, 1 H), 6.48 (d, J = 6.6 Hz, 1 H), 7.05−7.30 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.5, 17.7, 23.2, 24.3, 35.5, 35.9, 44.2, 46.3, 50.3, 51.4, 112.9, 125.5, 126.5, 127.8, 128.6, 128.9, 133.6, 137.8, 141.0, 168.4, 170.3, 172.9; IR ($CHCl_3$) 1669, 1640, 1511 cm^{-1}; HRMS calcd for $C_{27}H_{31}N_3O_3$ m/z 445.2366, obsd m/z 445.2327.

Data for 13a: 65:35; hexanes:EtOAc, 0.10 g, 0.26 mmol, 74% yield; 98:2 ratio of diastereomers; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27 (t, J = 7.2 Hz, 3 H), 1.36−1.54 (m, 2 H), 1.54−1.71 (m, 2 H), 1.76 (d, J = 6.9 Hz, 3 H), 1.92 (m, 1 H), 2.08−2.22 (m, 2 H)), 2.46 (m, 1 H), 2.52−2.70 (m, 2 H), 3.92 (dd, J = 4.5, 18.3 Hz, 1 H)), 4.10 (dd, J = 5.4, 18.3 Hz, 1 H)), 4.20 (q, J = 7.2 Hz, 2 H), 5.12 (dd, J = 3.0, 5.1 Hz, 1 H), 6.51 (dd, J = 12.3, 6.9 Hz, 1 H), 6.52 (br s, 1 H), 7.16−7.34 (m, 5 H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 14.5, 17.8, 24.3, 30.2, 30.3, 35.4, 41.7, 46.6, 49.4, 61.6, 113.1, 125.2, 126.4, 128.5, 133.3, 141.3, 169.36, 169.44, 173.6; IR (neat) 1748, 1660, 1632, 1507 cm^{-1}; HRMS calcd for $C_{22}H_{28}N_2O_4$ m/z 384.2049, obsd m/z 384.2049.

Hydrogenation of 11. To a solution of **11** (1.65 g, 1.27 mmol) in 40 mL of EtOH was added 10% Pd/C (0.15 g). The reaction vessel was flushed three times with H_2, and the reaction was placed under a balloon of H_2. The reaction mixture was stirred for 4 h, filtered through a pad of Celite, and concentrated under reduced pressure to give **12**: 0.37 g, 1.24 mmol, 97% yield; $[\alpha]^{24}_D$ = −116.1° (c = 1.73, THF); mp 133 °C dec; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.30−1.58 (m, 3 H), 1.50 (m, 1 H), 1.63 (d, J = 7.1 Hz, 3 H), 1.82 (m, 1 H), 2.01 (m, 1 H), 2.08−2.22 (m, 2 H), 2.38 (m, 1 H), 2.57 (m, 1 H), 4.90 (dd, J = 2.6, 4.7 Hz, 1 H), 6.12 (q, J = 7.1 Hz, 1 H), 7.12−7.32 (m, 5 H), 12.78 (br s, 1 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.8, 18.3, 24.0, 30.2, 34.7,

(19) Greenstein J. P., Winitz M. *Chemistry of the Amino Acids*; John Wiley & Sons: New York, 1961; Vol. 2, p 895.

45.9, 50.1, 55.0, 110.4, 125.4, 128.3, 129.4, 134.6, 142.5, 167.8, 175.6; IR (KBr) 1725, 1601 cm^{-1}; HRMS calcd for $C_{18}H_{21}NO_3$ *m*/*z* 299.1522, obsd *m*/*z* 299.1531.

Crystal Structure of 36. A single crystal of 0.1 × 0.2 × 0.2 mm dimensions was mounted on a glass capillary. Data were collected using copper radiation, at 293 K, on a conventional Siemens P3 X-ray diffractometer. Three standard reflections were measured every 97 reflections; no crystal decay was detected. Lorentz and polarization corrections were applied to the data; no corrections were made for absorption. The structures were solved by direct methods using the SHELX86,[20] and the remaining atoms were located in succeeding difference Fourier synthesis. The hydrogen atoms were generated at idealized positions and added to the structure factor calculations, but not refined. The structure was refined in full-matrix least-squares on F^2 using SHELXTL,[20] where the function minimized was $\sum w(||F_o^2| - |F_c^2||)^2$, and the weight *w* is defined per the Killean & Lawrence method[21] with terms of 0.020 and 1.0. Atomic scattering factors and the values for $\Delta f'$ and $\Delta f''$ were taken from the *International Tables for X-ray Crystallography*.[22] Anomalous dispersion effects were included in F_c.[23] The final difference Fourier map showed a maximum residual electron density of 0.78 e/Å^3. The residual electron density is attributed to a disordered diethyl ether molecule's presence in the lattice. The final indices were $R1 = 0.1002$, $wR2 = 0.2688$, where $I > 2\partial(I)$, and $R1 = 0.1144$, $wR2 = 0.2951$ for all data. The ratio of data to parameters is 2061:322, and the goodness-of-fit on F^2 is 1.129. The complete structural report is included in the Supporting Information and has been submitted to the Cambridge Structural Data Centre.

Peptide Coupling with DPPA. To the carboxylic acid **12** (0.40 g, 1.37 mmol) in dry THF (35 mL) were added DPPA and freshly prepared ethylglycine (0.16 g, 1.50 mmol) (generated by treatment of the corresponding hydrochloride salt with $Ba(OH)_2$ in $CHCl_3$) under Ar at 0 °C. The mixture was stirred for 30 min, Et_3N (0.22 g, 1.60 mmol) was added, and the solution was gradually warmed to room temperature. After the solution was stirred for an additional 12 h, the mixture was diluted with 30 mL of EtOAc and washed sequentially with 20 mL of 5% HCl, 2 × 30 mL of H_2O, 25 mL of saturated aqueous $NaHCO_3$, and 25 mL of brine. The organic layer was dried (Na_2SO_4), and then purified by flash column chromatography (hexanes:EtOAc gradient: 65:35 to 50:50 to 0:100) to give **13** (0.077 g, 0.20 mmol, 15% yield) and **14** (0.28 g, 0.70 mmol, 53% yield).

Data for 14: hexanes:EtOAc = 65:35 → 50:50 → EtOAc gradient, 0.28 g, 0.70 mmol, 53% yield; mp 85−86 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (t, J = 7.2 Hz, 3 H), 1.29 (m, 1 H), 1.42−1.52 (m, 2 H), 1.53 (d, J = 6.9 Hz, 3 H), 1.59−1.87 (m, 3 H), 1.97 (m, 1 H), 2.49−2.79 (m, 3 H), 3.72 (dd, J = 6.0, 18.0 Hz, 1 H), 3.80 (dd, J = 6.0, 18.0 Hz, 1 H), 4.09 (q, J = 7.2 Hz, 2 H), 4.87 (dd, J = 3.5, 4.7 Hz, 1 H), 5.00 (s, 1 H), 5.56 (t, J = 5.4 Hz, 1 H), 6.25 (q, J = 6.9 Hz, 1 H), 7.09−7.27 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 15.4, 17.8, 24.6, 29.3, 30.2, 33.8, 41.8, 50.0, 52.4, 61.2, 113.5, 125.4, 126.5, 128.5, 135.6, 141.7, 156.8, 170.2, 171.2; IR ($CHCl_3$) 1746, 1636, 1617, 1559 cm^{-1}; HRMS (FAB) M + 1 calcd for $C_{22}H_{29}N_3O_4$ *m*/*z* 299.1522, obsd *m*/*z* 299.1531.

General Procedure for Hydrolysis of Aza-Annulation Enamides. After workup of the aza-annulation reaction, the crude enamide product was taken up in a mixture of H_2O (5.0 mL) and THF (25 mL), and *p*-TsOH (0.03 g) was added. The mixture was stirred at room temperature for 24 h, washed with an excess of saturated aqueous $NaHCO_3$, and extracted with 15 mL of Et_2O three times, and the organic layers were combined and dried (Na_2SO_4). Products were crystallized from EtOAc/hexanes (1:1).

Data for 26: 0.30 g, 0.80 mmol, 82% yield; $[\alpha]^{20}_D = +58.81$ or (c = 0.7, $CHCl_3$); mp 159−160 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (s, 3 H), 1.38 (d, J = 6.9 Hz, 3 H), 1.88−2.22 (m, 4 H), 2.11 (s, 3 H), 4.28 (dd, J = 5.6, 14.8 Hz, 1 H), 4.34 (dd, J = 5.5, 14.8 Hz, 1 H), 4.98 (m, 1 H), 5.75 (br d, J = 7.5 Hz, 1 H), 6.69 (br t, J = 4.9 Hz, 1 H), 7.11−7.29 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.7, 21.8, 26.5, 31.4, 31.8, 43.7, 48.8, 59.0, 126.1, 127.3, 127.5, 127.6, 128.60, 128.61, 138.0, 143.0, 171.2, 208.8; IR ($CHCl_3$) 1717, 1628, 1541 cm^{-1}; HRMS calcd for $C_{23}H_{28}N_2O_3$ *m*/*z* 380.2100, obsd *m*/*z* 380.2107.

Data for 28: 0.30 g, 0.68 mmol, 71% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14 (t, J = 7.1 Hz, 3 H), 1.33 (s, 3 H), 2.02−2.22 (m, 4 H), 2.11 (s, 3 H), 4.01−4.22 (m, 2 H), 4.32 (d, J = 5.8 Hz, 2 H), 5.44 (d, J = 7.1 Hz, 1 H), 6.41 (br d, J = 7.1 Hz, 1 H), 6.52 (br t, J = 5.8 Hz, 1 H), 7.10−7.30 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 19.6, 26.6, 31.2, 31.5, 43.9, 56.5, 59.0, 61.9, 127.2, 127.6, 127.7, 128.5, 128.7, 128.9, 136.5, 137.9, 170.8, 170.8, 171.2, 208.9; IR ($CHCl_3$) 1746, 1709, 1646, 1532 cm^{-1}; HRMS calcd for $C_{25}H_{30}N_2O_5$ *m*/*z* 438.2155, obsd *m*/*z* 438.2157.

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Supporting Information Available: Physical data for selected compounds and copies of crystallographic data (11 pages). See any current masthead page for ordering information and Web access instructions.

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