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dissertation entitled

The Aza-Annulation Reaction as a Synthetic Tool for Asymmetric Synthesis and the Construction of Potentially Biologically Active Compounds

presented by

Petr Benovsky

has been accepted towards fulfillment
of the requirements for

Ph.D. degree in Organic Chemistry

William Reusch
Major professor

Date July 21, 1997

THE AZA-ANNULATION REACTION AS A SYNTHETIC TOOL FOR ASYMMETRIC SYNTHESIS AND THE CONSTRUCTION OF POTENTIALLY BIOLOGICALLY ACTIVE COMPOUNDS

By

Petr Beňovský

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ABSTRACT

THE AZA-ANNULATION REACTION AS A SYNTHETIC TOOL FOR ASYMMETRIC SYNTHESIS AND THE CONSTRUCTION OF POTENTIALLY BIOLOGICALLY ACTIVE COMPOUNDS

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The stereoselective formation of six-membered nitrogen heterocycles with an asymmetric quaternary carbon center could be achieved through aza-annulation of β-enamino amide substrates, prepared by a condensation of a racemic β-keto amide with an optically active primary amine, and activated acrylate derivatives. A variety of different β-enamino amide substrate classes were examined in this reaction. When aza-annulation reaction was performed with an α-acetamido substituted acrylate derivative, the quaternary carbon center was formed stereoselectively, but poor selectivity was observed for generation of the stereogenic center α to lactam carbonyl.

The aza-annulation reaction provides an efficient route for the potential construction of the heterocyclic 2-pyridone framework for complex bioactive compounds, such as natural product targets or synthetic peptide mimetics. Peptide analogs could be assembled in three steps and in good overall yield.

The aza-annulation was then shown to constitute a quick and efficient method of building up isoquinoline derivatives, which might serve as non-benzodiazepine sleep inducing drugs.

To my family and my parents

ACKNOWLEDGMENTS

I would like to express my great appreciation to Dr.Stille for his dedication to the field of chemistry and for all he has taught me throughout my graduate career. Without your "pushing" it would be much more difficult. I would also like to thank Dr.Reusch as a "foster" advisor, your lectures, Tuesday night meeting problems, and explanations were perfect. I have to thank Dr.Maleczka for letting me to join his group meetings, and numerous consultations. Thanks to Drs.Nocera, Rathke, and McCracken for their enthusiasm.

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Without a support of American friends, particularly the Wheelers, the Selle family, Pastor Dave, the Huffords, the life, especially in the beginning, would be much more difficult. You all are a part of my success.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF SCHEMES

LIST OF ABBREVIATIONS

Ac	Acetyl
AIBN	2,2'-Azobisisobutyronitrile
Arg	Arginine
Asp	Asparagine
$(Boc)_2O$	Di-*tert*-butyldicarbonate
n-Bu	Normal Butyl
m-CPBA	*m*-Chloroperbenzoic Acid
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-Dicyclohexylcarbodiimide
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DMAP	4-Dimethylaminopyridine
DMF	N,N-Dimethylformamide
DMSO	Dimethylsulfoxide
DPPA	Diphenylphosphoryl azide
dppp	1,3-Bis(diphenylphosphino)propane
Et	Ethyl
EWG	Electron Withdrawing Group
FAB	Fast Atom Bombardment
Gly	Glycine

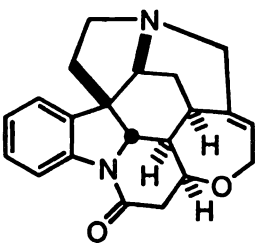
His	Histidine
HRMS	High Resolution Mass Spectroscopy
Ile	Isoleucine
Leu	Leucine
LDA	Lithium Diisopropyl Amide
Me	Methyl
NBS	N-Bromosuccinimide
NMO	4-Methylmorpholine N-oxide
NMR	Nuclear Magnetic Resonance
Ph	Phenyl
Phe	Phenylalanine
i-Pr	Isopropyl
PCC	Pyridinium Chloro Chromate
Ser	Serine
THF	Tetrahydrofurane
TLC	Thin Layer Chromatography
TMEDA	N,N,N',N'-Tetramethylethylenediamine
TMS	Tetramethylsilane
p-TsOH	*p*-Toluenesulfonic Acid
Tyr	Tyrosine
Val	Valine

CHAPTER I

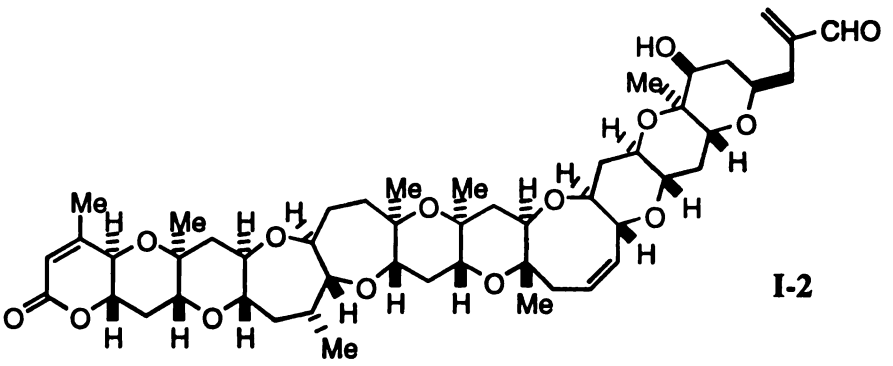
ASYMMETRIC SYNTHESIS OF NATURAL PRODUCTS

Asymmetry itself brings to any system an element of disorder and, consequently new and unusual properties and behavior. In chemistry as a discipline, the presence of an asymmetric center in a compound makes synthesis of the molecule even more difficult. Construction of a chiral molecule has been always a challenging problem and has required a lot of effort to build up more complex structures.

Recently, the importance of efficient asymmetric synthesis has soared, and methods for preparing useful and active chemical substances are in great demand (either for suitable model compounds in biochemical processes or for new drug substances). Chemists commonly strive to develop new methods and technologies for the selective formation of stereogenic centers. Numerous efforts to synthesize compounds that occur naturally in plants and other organisms, or to make potentially more active analogs, have been made. A few ingenious syntheses include those of strychnine (**I-1**), vitamin B12 and brevetoxine B (**I-2**) by Woodward[1] and Nicolaou[2], respectively.



I-1



I-2

Compounds of biological interest such as natural products, synthetic enzyme inhibitors, or models of naturally occurring scaffolds may be elaborated by several different techniques:[3,4,5]

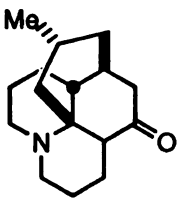
- The reagent or reactant may contain a chiral auxiliary, a group in the vicinity of the reaction site that controls the stereochemistry of the center(s) to be built, and can be easily removed afterwards;
- A homochiral catalyst (enzyme or synthetic product) may be employed;
- A "chiral pool approach", in which readily available homochiral molecules, often from a natural source, are used as building blocks. Alkaloids, amino acids and carbohydrates are probably the most important chiral building blocks and tools for the construction of complicated structures.

In the past, easily available, naturally occurring asymmetric compounds have been used as chiral auxiliaries for specific or more selective preparation of desired molecules.

Among many examples of chiral compounds, there is a large group of molecules having a quaternary carbon stereogenic center. Some representatives are presented in

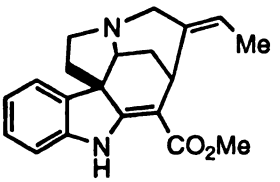
Figure I-1, and include lycopodine (**I-3**)[6], akvammicine (**I-4**)[7], cephalotaxine (**I-5**)[8], eburnamonine (**I-6**)[9], morphine (**I-7**)[10], aspidospermidine (**I-8**)[11] and α-obscurine (**I-9**).[12]

Figure I-1. Examples of Compounds with a Quaternary Stereogenic Center.



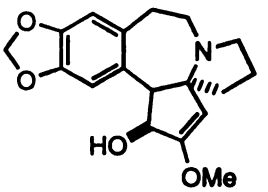
LYCOPODINE

I-3



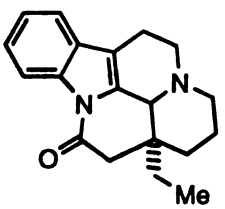
AKVAMMICINE

I-4



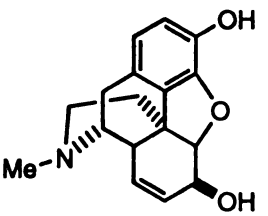
CEPHALOTAXINE

I-5



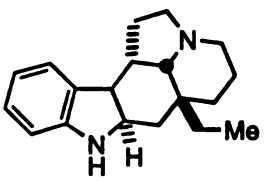
EBURNAMONINE

I-6



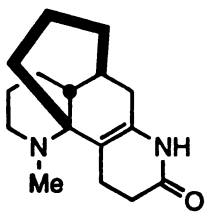
MORPHINE

I-7



(+)-ASPIDOSPERMIDINE

I-8



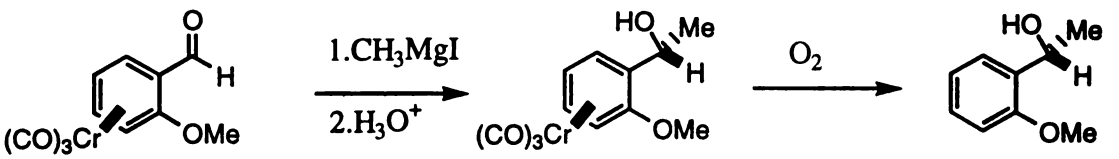
α-OBSCURINE

I-9

Due to the relative difficulty of the construction of quaternary carbon stereogenic centers, new, highly efficient methods are needed. One of the new interesting solutions is illustrated in **Scheme I-1**. Here, the complex of a suitably substituted benzene ring with chromium carbonyl undergoes nucleophilic addition to an aldehyde functionality only

from one side. Moreover, the rotation of the aldehyde group is restricted by the presence of an *ortho* substituent. The result is a significant asymmetric induction.[3]

Scheme I-1. Asymmetric Synthesis Using Chromium Carbonyl Derivative.



A few methods provide a relatively convenient approach to the construction of a stereogenic quaternary carbon center. The aza-annulation methodology, closely related to Michael reaction, is one of them.

Aza-annulation methodology meets these two important requirements:

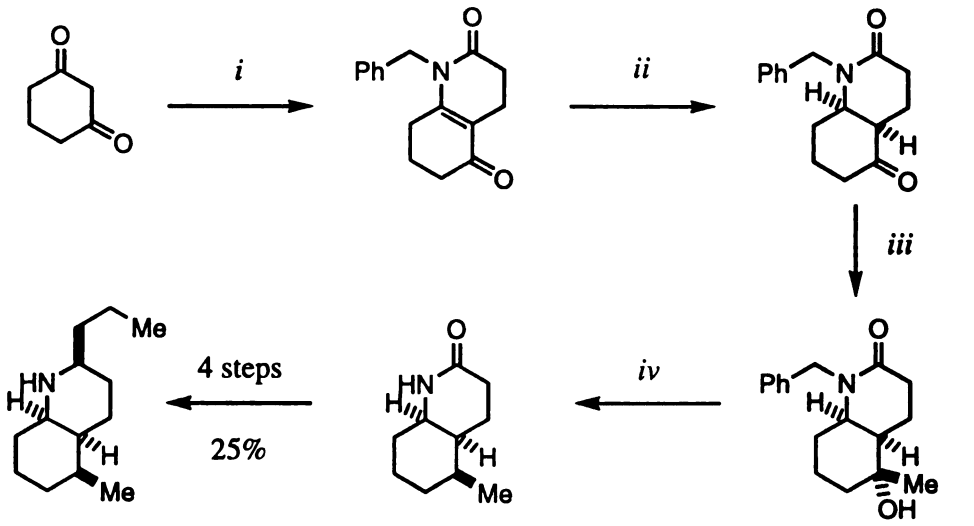
- Formation of a new carbon-carbon bond.
- Tandem cyclization with formation of a new heterocyclic ring.

Aza-annulation reactions have been used for the construction of a variety of structures. The synthesis of (±)-lupinine[13] and (±)-5-epipumiliotoxin C[14] (**Scheme I-2**), (±)-8-oxocephalotaxine[15] (**Scheme I-3**), (±)-costaclavine[16] (**Scheme I-4**) and 21-epiaspidospermine[17] (**Scheme I-5**) serve as illustrative examples.

Aza-annulation reactions have been studied by our group, and several naturally occurring compounds have been synthesized with this methodology. For example, syntheses of (±)-mannonolactam (**I-11**), (±)-deoxymannojirimycin (**I-10**) and (±)-prosopinine (**I-12**) have been prepared recently in our group[18] (**Scheme I-6, Scheme I-7**). Aza-annulation reactions have been exhaustively reviewed[19] and the background details will not be discussed in this work.

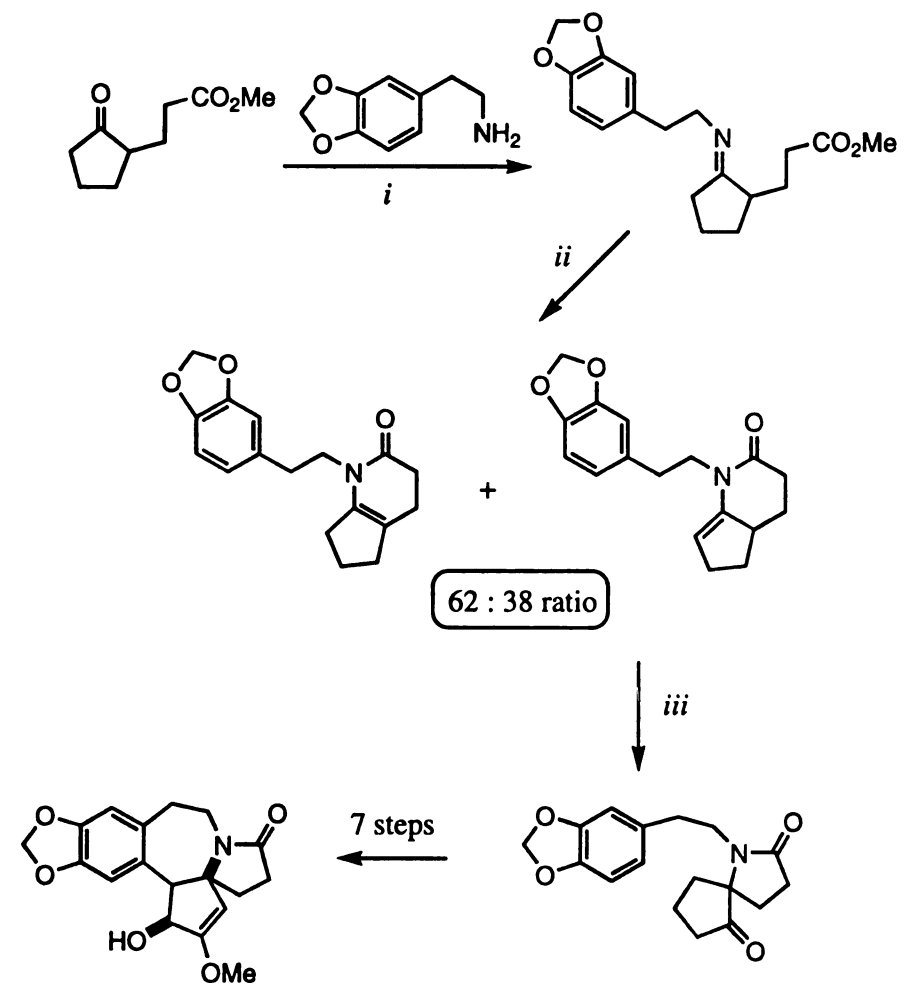
Now aza-annulation is used even as a powerful and efficient tool for an asymmetric formation of a quaternary carbon stereogenic center.

Scheme I-2. Construction of 5-Epipumiliotoxin.



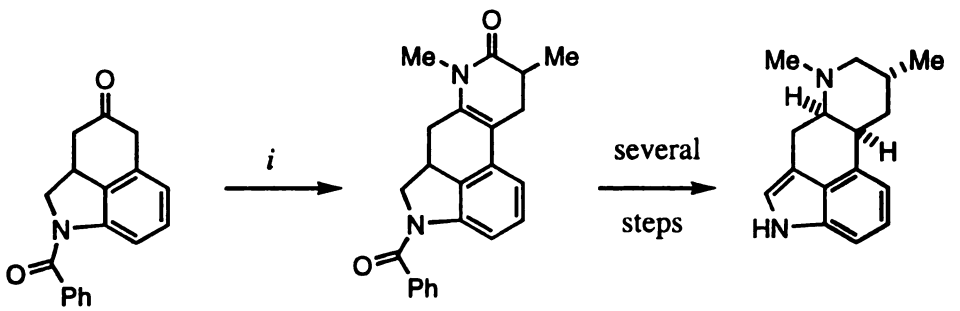
Reaction Conditions. *i*) benzylamine, benzene, reflux, then acryloyl chloride, THF, 75% yield; *ii*) 1 atm of H_2, Pd/C(10%), Na_2CO_3 then $(COCl)_2$, DMSO, Et_3N, 85% yield; *iii*) MeMgBr 68% yield; *iv*) NaH, CS_2 then MeI then Bu_3SnH, AIBN, 52% yield.

Scheme I-3. Synthesis of 8-Oxocephalotaxine.



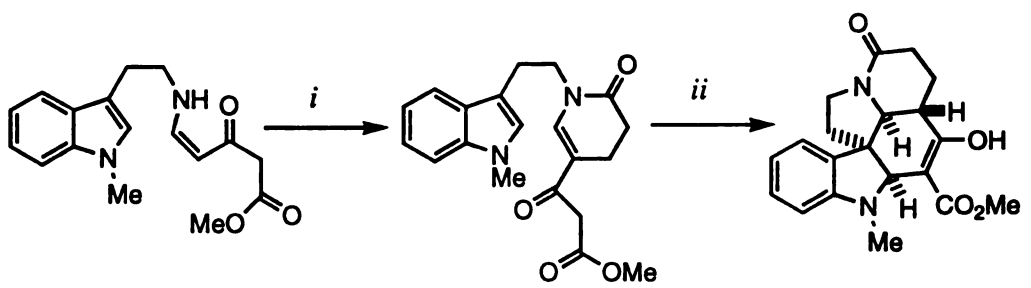
Reaction Conditions. *i*) benzene, *p*-TsOH, reflux, 2 h; *ii*) 210° C, 96% (2 steps); *iii*) $Pb(OAc)_4$, benzene, reflux then MeOH, MeONa, 94%.

Scheme I-4. Preparation of (±)-Costaclavine.



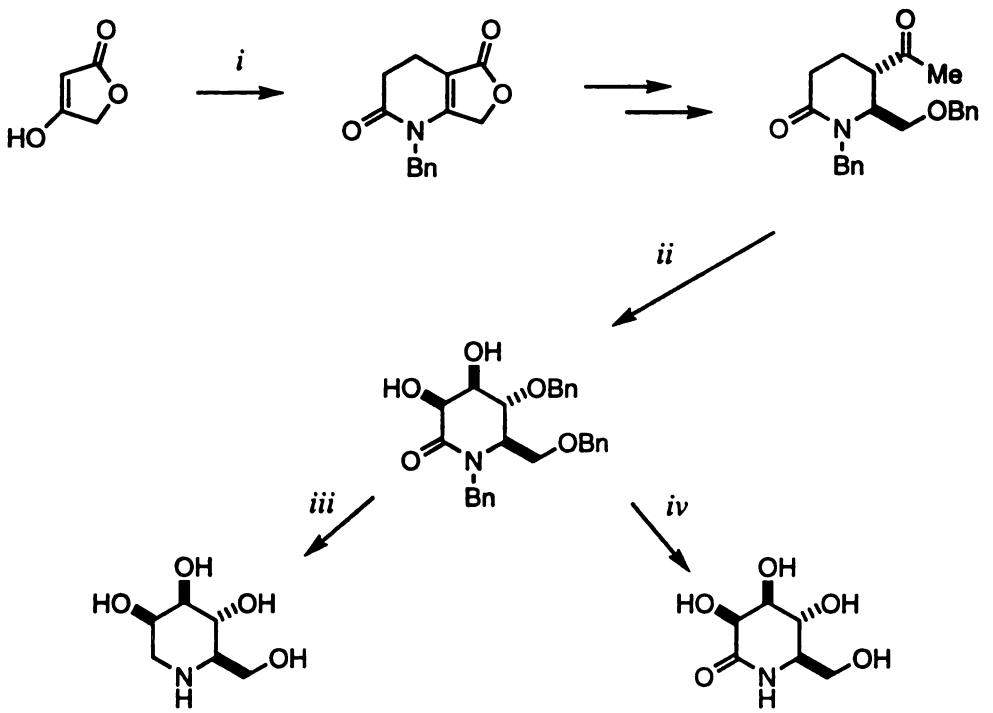
Reaction Conditions. *i*) methylamine then methacryloyl chloride, 66%.

Scheme I-5. Synthesis of (±)-21-Epiaspidospermin.



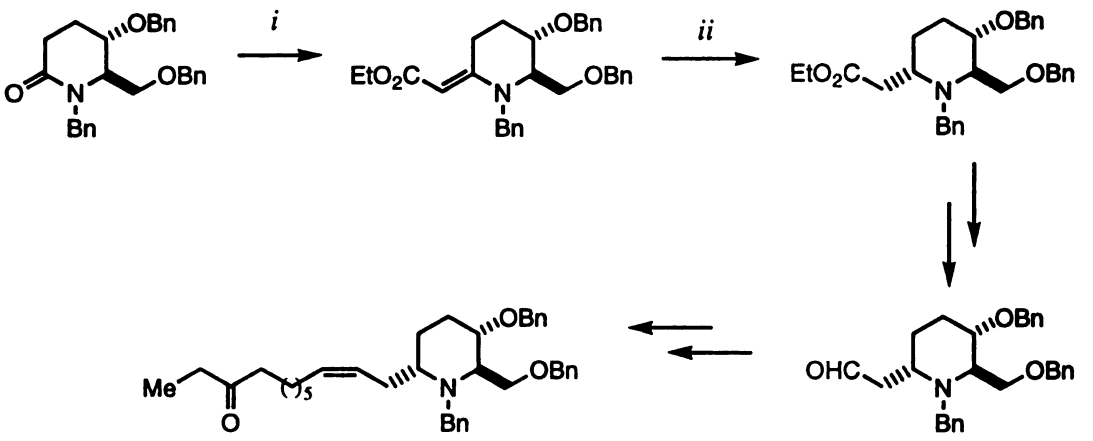
Reaction Conditions. *i*) acryloyl chloride, pyridine, DMAP, MeCN; *ii*) $TiCl_4$, $ClCH_2CH_2Cl$, 80° C, 63% (2 steps).

Scheme I-6. Construction of (±)-Mannonolactam (I-11) and (±)-Deoxymannojirimycin (I-10).



Reaction Conditions. *i*) benzylamine, benzene, reflux then acrylic anhydride, THF, 66° C, 71%; *ii*) a) CF_3CO_2H, *m*-CPBA, 55%; b) KOH, H_2O, 85%; c) KOH, benzyl bromide, 84%; d) LDA, PhSeCl, $NaIO_4$, 78% then OsO_4, NMO, 65%; *iii*) $LiAlH_4$, NaOH, H_2O, 98% then 1 atm of H_2, Pd/C, MeOH, 52%; *iv*) Li/NH_3, 44%.

Scheme I-7. Preparation of (±)-Prosopinine (I-12).



Reaction Conditions. *i*) a) Lawesson's reagent, 94%; b) EtO_2CCH_2Br, NEt_3, 81%, *ii*) $NaBH_3CN$, pH 4.0, 88% (>90:10 ratio of diastereomers).

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CHAPTER II

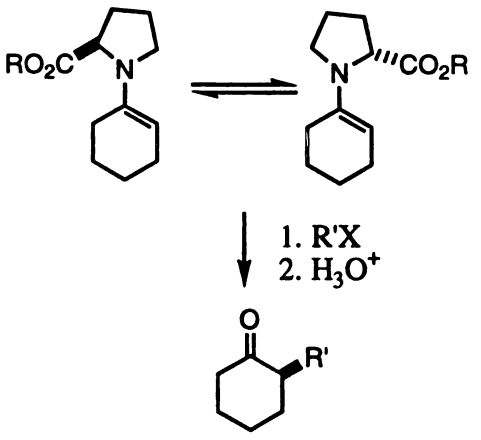
ASYMMETRIC FORMATION OF QUATERNARY CENTERS THROUGH AZA-ANNULATION OF CHIRAL β-ENAMINO AMIDES WITH ACRYLATE DERIVATIVES

Introduction.

Methods of forming new carbon-carbon bonds in a stereospecific or stereoselective fashion are copious, e.g. Claisen, Cope rearrangements and their hetero modifications. Asymmetric variations of classical organic reactions such as the Diels-Alder, Mannich, aldol and Michael reactions are cited in the literature to an increasing degree.

One of the first experiments in which enantioselective Michael addition was examined was carried out by Horeau[1] and Yamada.[2] In the latter paper, the authors reported the first in a series of investigations of the alkylation of chiral enamines formed from various proline esters (**Scheme II-1**).

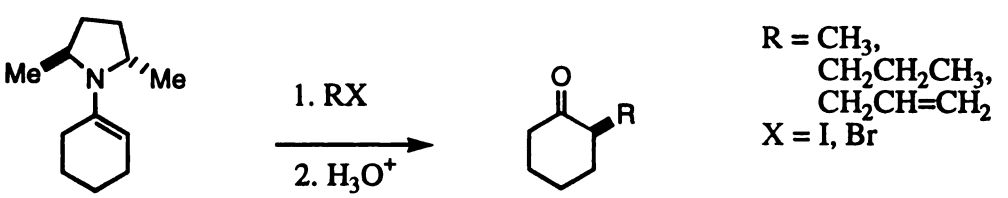
Scheme II-1. Use of Proline Esters as Chiral Auxiliaries.



Of the four possible transition states resulting from the distinct pathways of approach of the alkylating agent, the ester moiety would be expected to exert a significant steric interaction in only one of them. Due to rotation around the carbon-nitrogen single enamine bond, the asymmetric induction in this system is limited to 10-35% ee.

Whitesell[3] improved this idea by using a chiral auxiliary having a C_2 axis of symmetry (**Scheme II-2**). This alkylation method was much more selective (82-93% ee).

Scheme II-2. Use of a Chiral Auxiliary with a C_2 Axis in the Michael Reaction.



Whitesell proposed that both diastereomeric immonium ions are formed in a relatively *nonselective* alkylation, with a subsequent, selective hydrolysis providing enantioselectivity by kinetic resolution. Attempts to construct a quaternary carbon center by regioselective alkylation of more substituted enamines failed, and the major alkylation product was the less substituted isomer.

Aza-annulation has been fully developed and studied in our group, and has been successfully applied to the syntheses of naturally occurring compounds (see selected examples in Chapter 1). This transformation is one of the simplest ways to construct six

membered nitrogen heterocycles from ketones, amines and activated derivatives of α,β-unsaturated acids.

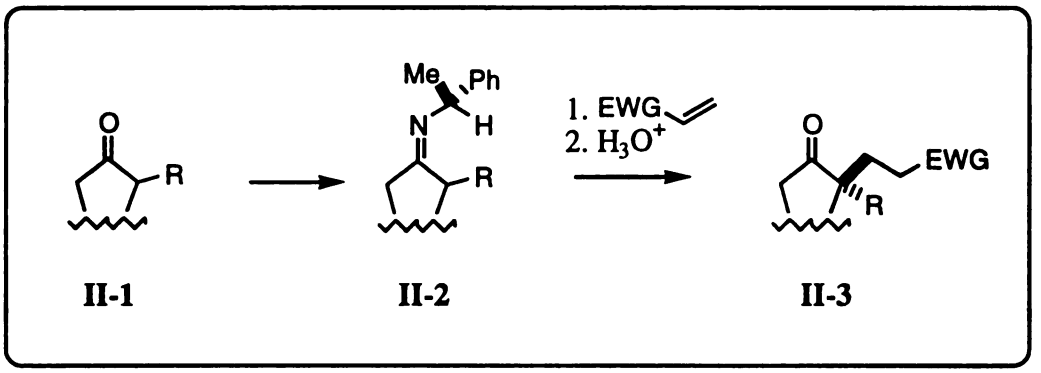
Asymmetric Induction in the Aza-Annulation Reactions. Aza-annulation reactions with chiral enamines (enamines with a chiral auxiliary attached) provide an efficient method of stereoselective construction of quaternary carbon centers. In 1988, d'Angelo used chiral enamines for deracemizing alkylation of α-substituted cyclanones[4] under neutral conditions (**Scheme II-3**). In the following series of papers, d'Angelo and coworkers introduced a particularly efficient method for regioselective and stereoselective alkylation of ketones.

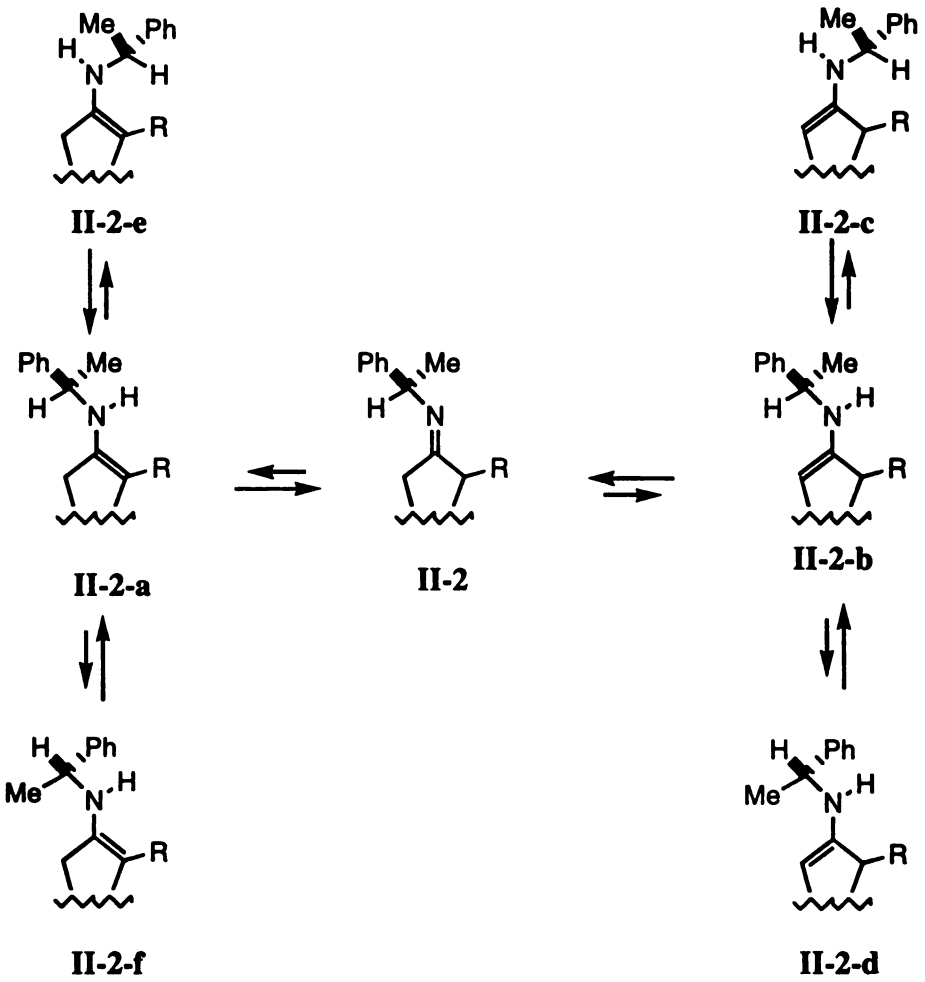
Considering the tautomeric equilibrium of chiral imine **II-2** with two corresponding regioisomeric secondary enamines, it is clear that the energetically preferred conformations of these enamines are those depicted in formulas **II-2-a** and **II-2-b**, in which the main steric interactions are minimized. Indeed, these structures exhibit two main degrees of freedom. By rotation of 180° around the carbon-nitrogen bond, **II-2-a** leads to **II-2-e** and **II-2-b** to **II-2-c**. By rotation of 120° around the carbon-nitrogen bond, **II-2-a** and **II-2-b** give **II-2-f** and **II-2-d**, respectively. All the conformers **II-2-c**, **II-2-d**, **II-2-e** and **II-2-f** suffer from a strong destabilizing steric interactions which is not encountered in the structures **II-2-a** and **II-2-b**.

High regioselectivity is explained by an easy proton transfer in tautomeric enamine **II-2-a** and by the additional hyperconjugative interaction of the alkyl group. Due to restricted rotation around the single carbon-nitrogen bond of an enamine, the

bulky substituent efficiently blocks one π-face of the enamine species allowing approach of the electrophilic alkene only from one side.[5]

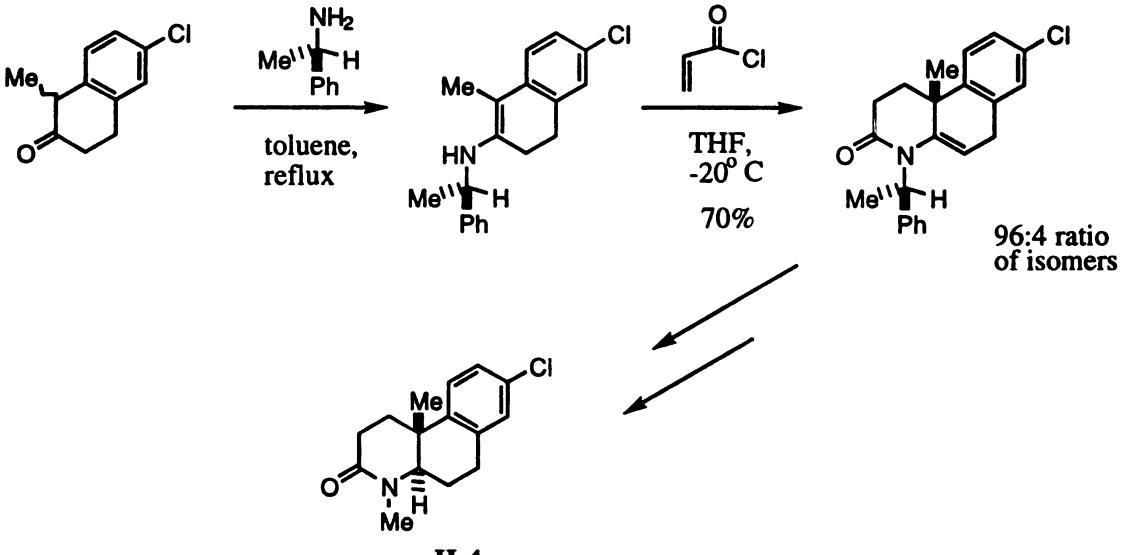
Scheme II-3. Deracemizing Alkylation of α-Substituted Cyclanones.





Audia used aza-annulation for the preparation of heterocyclic analogs to steroidal enzyme substrates as **II-4** (a selective inhibitor of human Type I steroid 5-α-reductase)[6] **(Scheme II-4)**.

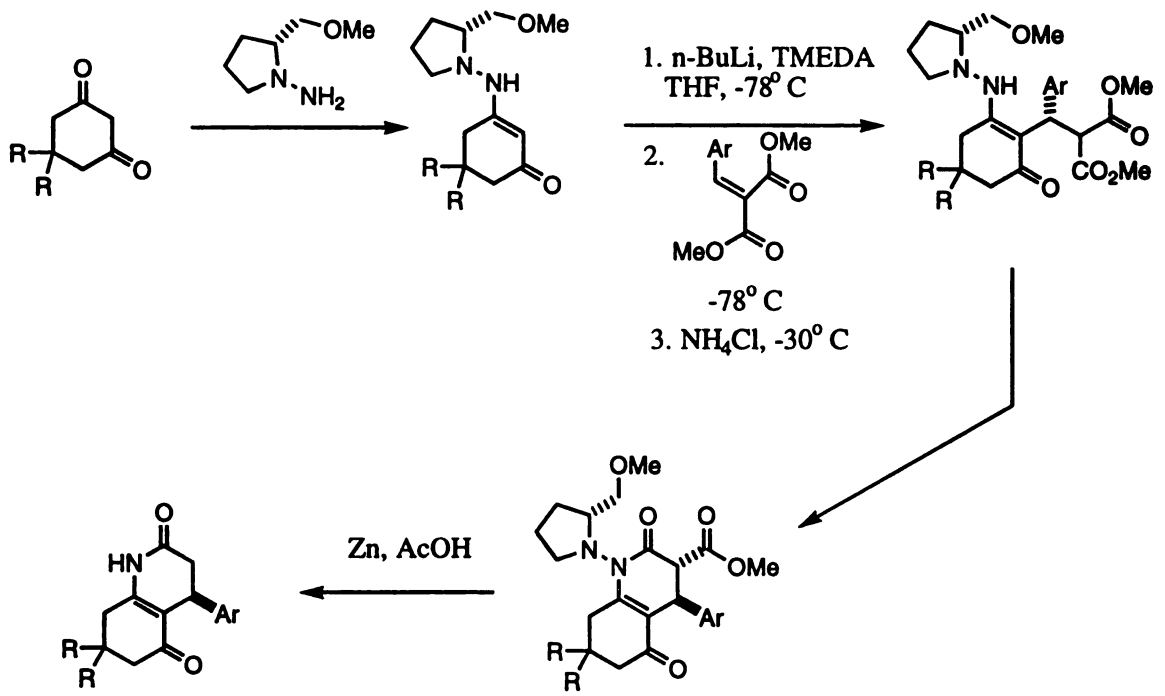
Scheme II-4. Aza-Annulation as a Synthetic Tool for Preparation of a Selective Inhibitor of Human Type I Steroid 5-α-Reductase.



II-4

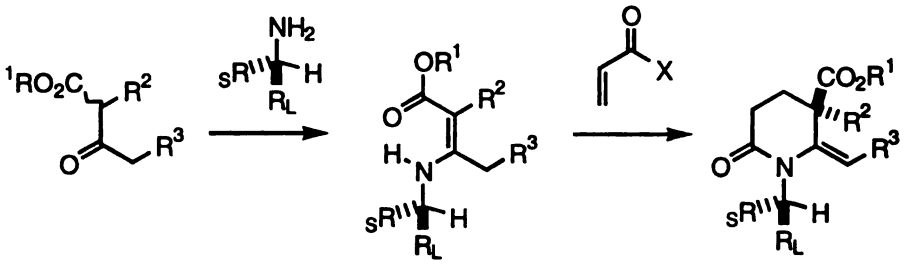
The same idea was used by Enders and coworkers with a different chiral auxiliary - (*S*)-(-)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP) and (*R*)-(+)-1-amino-2-(methoxymethyl)pyrrolidine (RAMP)[7] (**Scheme II-5**).

Scheme II-5. Asymmetric Aza-Annulation with RAMP as a Chiral Auxiliary.



Stille demonstrated the power of asymmetric aza-annulation in a study of reactions of chiral β-enamino esters with acrylate derivatives yielding δ-lactam derivatives[8] (**Scheme II-6**).

Scheme II-6. General Strategy for Asymmetric Aza-Annulation Reactions.

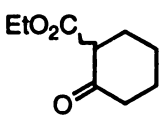
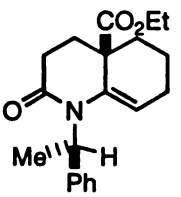
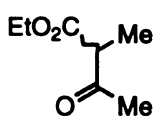
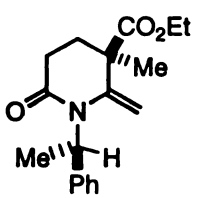
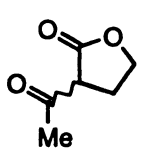
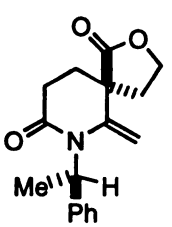
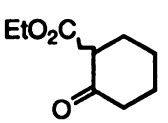
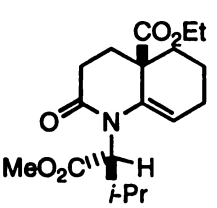


II-5 **II-6** **II-7**

The reaction of various β-keto esters, (*R*)-phenethylamine, and an acrylate derivative provided δ-lactam products with excellent stereoselectivity in very good yield (**Table II-1**). When the size of the chiral auxiliary substituents at different faces of diastereotopic system **II-6** was comparable, as in entry 4, diastereoselectivity dropped.

Unlike asymmetric Michael reactions,[9] these reactions were affected by reaction temperature. For example, for reaction in THF the product ratio was 79:21 at 66° C, 93:7 at 0° C and 98:2 at –33° C (**Scheme II-7, Table II-2**). In each case, a decrease in reaction temperature also resulted in increased product yield. In dioxane, the differences were even more dramatic.

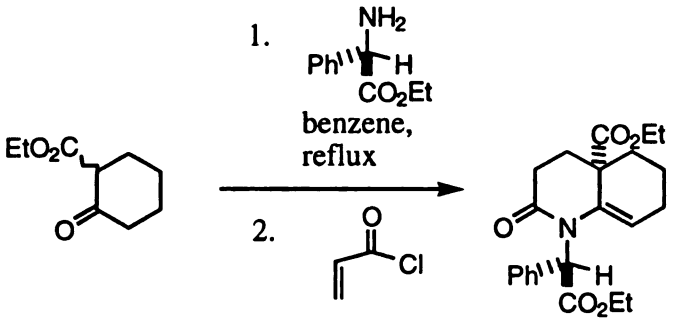
Table II-1. Effects of Substrate Variations on Asymmetric Induction.

entry	substrate	product	diastereomer ratio[a]	yield[b]
1			>97:3	85%
2			97:3	92%
3			94:6	80%
4			57:43	43%

[a]Determined by ^{1}H NMR analysis of the crude reaction mixture.

[b]Yield of the diastereomeric mixture after chromatography.

Scheme II-7. Asymmetric Aza-Annulation with Ester Derivatives.

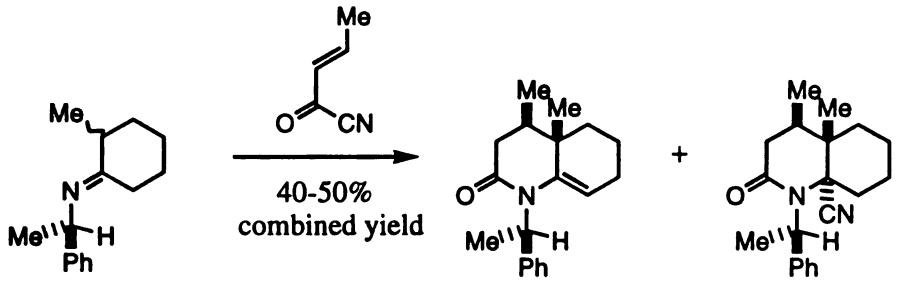


II-8 **II-9**

Table II-2. Temperature Effects on Asymmetric Induction and Reaction Yield

solvent	temp [° C]	diastereomer[a] ratio	yield[b] [%]
THF	-33	98:2	77
THF	0	93:7	68
dioxane	0	92:8	24
THF	66	79:21	63
dioxane	66	82:18	43
dioxane	101	36:64	28

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



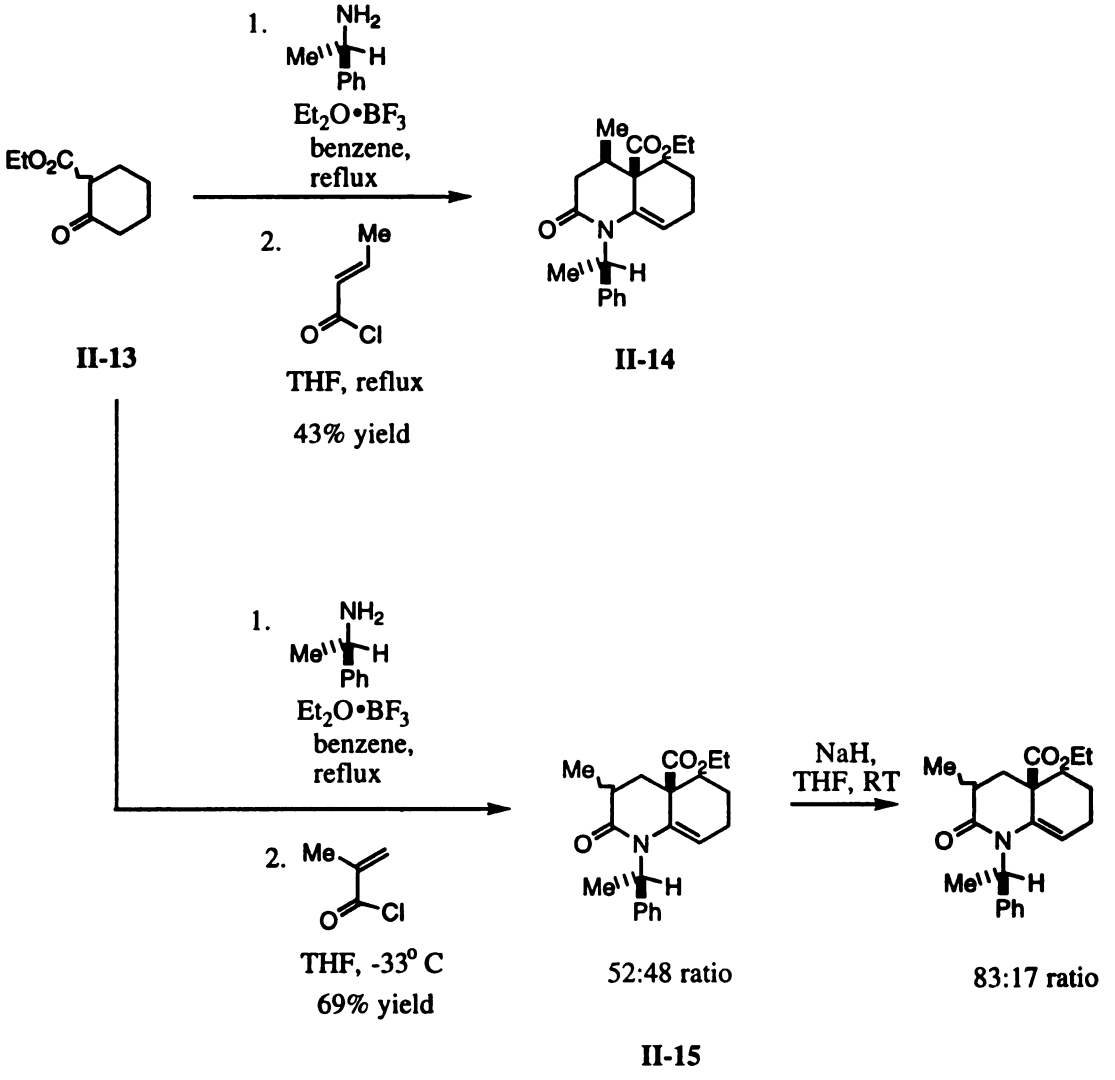
(reaction II-1)

II-10 **II-11** **II-12**

Stille utilized d'Angelo's pioneering studies[4] (reaction **II-1**) for examination of the concomitant formation of two new stereogenic centers at α- or β-positions of carbonyl group of lactam functionality.[8] Due to steric hindrance, reaction with crotonyl chloride proceeded in much lower yield, and the reaction needed longer reaction time and higher temperature. With a methyl substituent at the α-position, the reaction was more rapid, but complete lack of stereoselectivity at the α-carbon of the lactam moiety was observed.

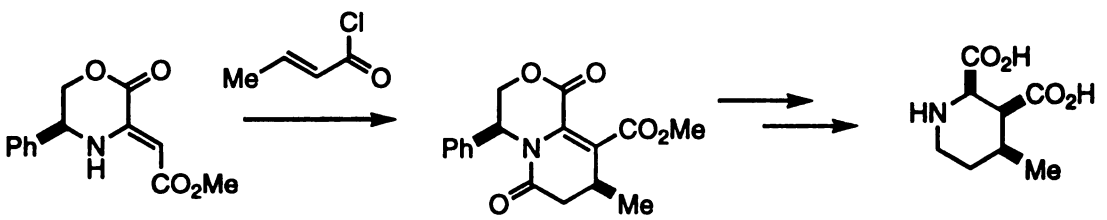
Reaction of **II-15** with NaH at ambient temperature in THF increased diastereomeric ratio to 83:17 (**Scheme II-8**). With the use of the mixed anhydride of 2-acetamidoacrylic acid, a mixture of diastereomers was formed in ratio 64:23:9:4 (i.e. 73:27 at the α-carbon and incomplete asymmetric induction at the quaternary center (87:13)).

Scheme II-8. Concomitant Formation of Two Stereogenic Centers.

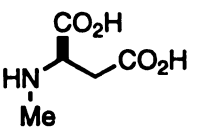


Agami recently demonstrated the enantioselective synthesis of restricted analogs of N-methyl-D-aspartic acid (NMDA, receptor involved in neuroexcitatory transmission effects) based on the same methodology (**Scheme II-9**).[10]

Scheme II-9. Preparation of Restricted NMDA Analogs.



II-16 **II-17** **II-18**

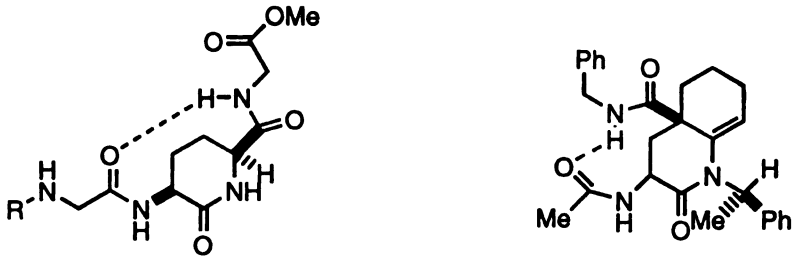


NMDA

RESULTS AND DISCUSSION

The stereoselective aza-annulation reaction provides a very good method for the synthesis of oligopeptide analogs having restricted conformations.

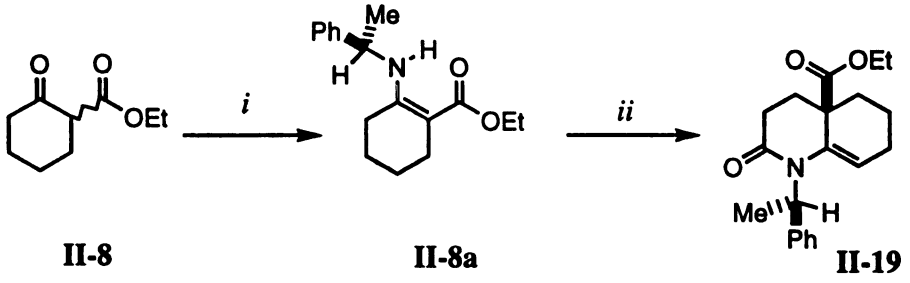
Figure II-1. Oligopeptide Analogs with Restricted Conformations.



Key structure could be prepared by the stereoselective aza-annulation reaction of suitable starting material, followed by subsequent transformations into corresponding amide derivatives (peptide analogs), or by the aza-annulation reaction of amide precursors.

The first approach to the preparation of the starting material for this study seemed to be straightforward. Ester compound **II-19** was readily prepared in 85% yield from ethyl 2-oxocyclohexane carboxylate, (*R*)-phenethylamine and acrylic acid mixed anhydride[8] **(Scheme II-10)**.

Scheme II-10. Asymmetric Aza-Annulation of Ester Derivatives.

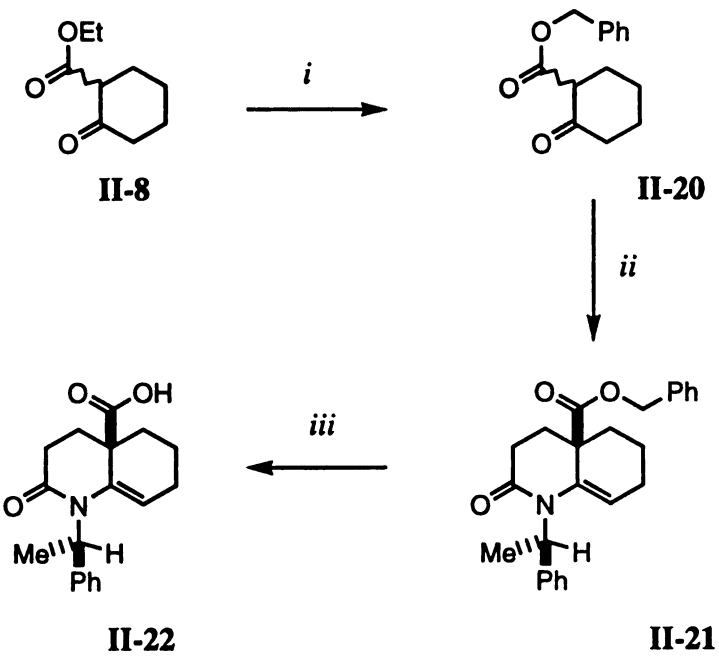


II-8 **II-8a** **II-19**

Reaction Conditions. *i*) (*R*)-phenethylamine, $Et_2O{:}BF_3$, benzene *ii*) sodium acrylate, $ClCO_2Et$, THF, 85% yield.

All attempts to hydrolyze ethyl ester **II-19** failed. The starting material either decomposed, or proved resistant to reaction conditions. Steric congestion around the carboxylate was probably responsible for the lack of reactivity. Carboxylic acid derivative **II-22** was finally prepared from benzyl ester **II-21** by catalytic hydrogenation over palladium to deprotect the acid (**Scheme II-11**). All attempts to prepare an amide **II-23** were unsuccessful or gave the desired product in very low yield. **Scheme II-12** and **Table II-3** summarize the results obtained.

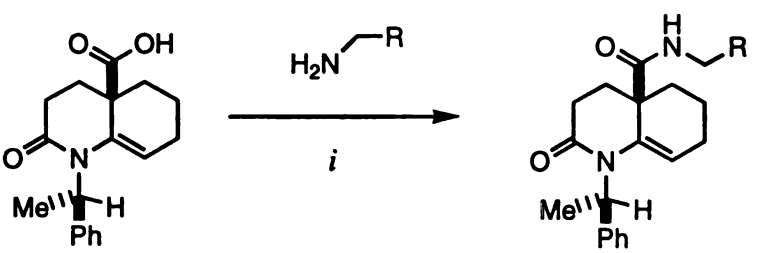
Scheme II-11. Formation of Amides from Ester Analogs.



Reaction Conditions. *i*) benzyl alcohol, DMAP, xylene, 68% yield; *ii*) (*R*)-phenethylamine, $Et_2O{:}BF_3$, benzene, reflux then sodium acrylate, $ClCO_2Et$, THF, 70% yield; *iii*) Pd/C(10%), 1 atm of H_2, EtOH, 100% yield.

Interestingly, reaction of carboxylic acid derivative and DPPA, followed by an addition of benzyl amine or ethyl glycine, gave Curtius rearrangement product **II-24** rather than desired amide (**Scheme II-13**).The difficulties encountered in conversion of **II-22** into **II-23** served to reinforce the need to examine methods for aza-annulation with β-keto amide substrates rather than modification of their ester analogs.

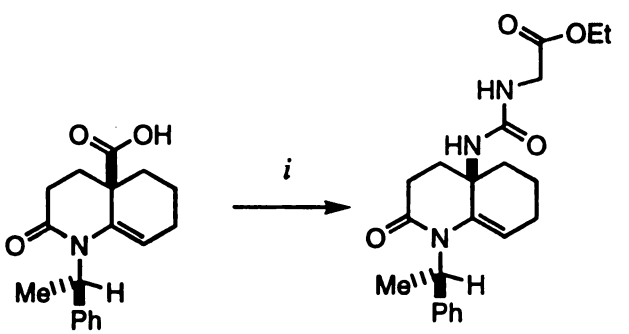
Scheme II-12. Unsuccessful Attempts to Prepare an Amide II-23.



II-22 **II-23**

Reaction Conditions. see **Table II-3**.

Scheme II-13. Curtius Rearrangement.



II-22 **II-24**

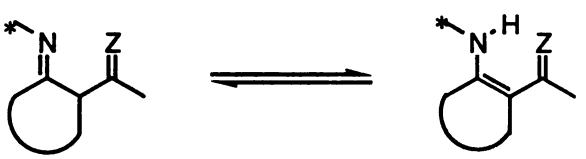
Reaction Conditions. *i*) glycine ethyl ester, DPPA, CH_2Cl_2, 53% yield.

Table II-3. Unsuccessful Attempts to Prepare Amide II-23.

i	R	Yields, results
NaH, $ClCO_2Et$	$-CO_2Et$	0%
DCC	$-CO_2Et$	0-15%, 10:1 ratio of diastereomers stable DCC derivative
$(ClCO)_2$, THF, pyridine	$-CO_2Et$	0%
$(ClCO)_2$, $(imid)_2CO$, THF, RT	$-CO_2Et$	Starting material recovered
DPPA, THF, Et_3N, 0° C	-Ph	6-10% major product – urea derivative
TsCl, pyridine	-Ph	0-10% + recovered starting material

Aza-annulation reactions with cyclic β-ketoamides. One advantage of cyclic imines derived from cyclic ketones is that the corresponding enamine has defined *Z*-geometry (dictated by the presence of the ring). Moreover, in the presence of β-carbonyl functionality, the rotation around carbon-nitrogen single bond of enamine is restricted due to a formation of an intramolecular hydrogen bond (see **Scheme II-14**) forming thus a more stable, conjugated tautomeric form of an imine.

Scheme II-14. Imine-Enamine Tautomerism.



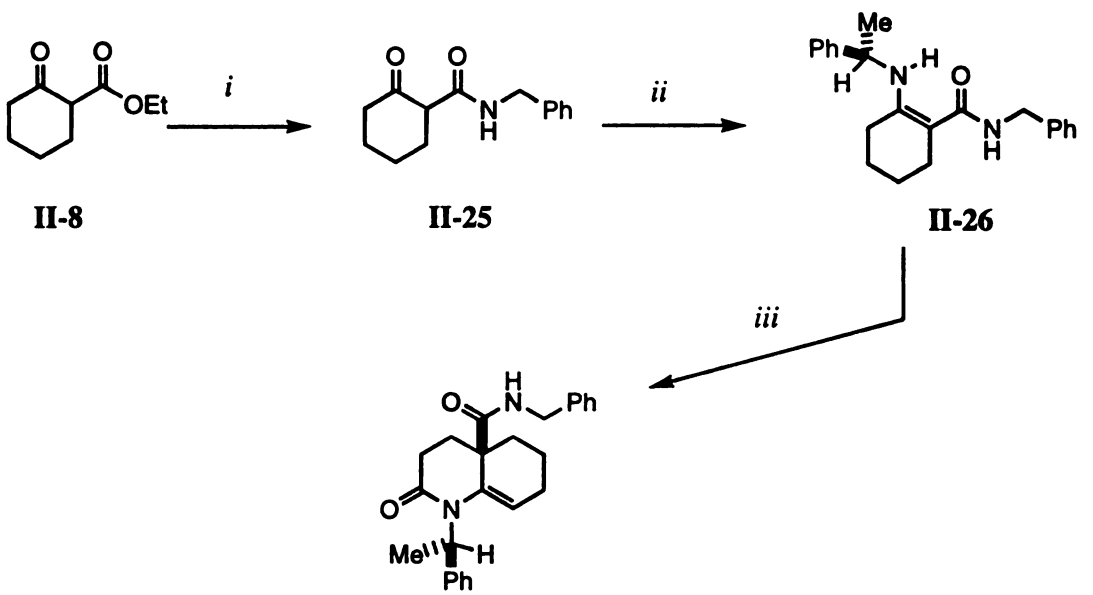
a star represents a chiral auxiliary

Based on previous studies with achiral imines and β-enamino esters and ketones,[11] as well as the use of this methodology in the synthesis of natural products,[12] three different classes of acrylate derivatives have been studied. β-Keto amide **II-25**, prepared from commercially available β-keto ester by several methods,[13] was used as a starting material for the enamine aza-annulation sequence as illustrated in **Scheme II-15**.

A significant dependence of the aza-annulation reaction outcome on the type of acrylic derivative employed was observed (**Table II-4**). Unlike the aza-annulation reactions of β-enamino ester substrates, reactions with acryloyl chloride gave lower

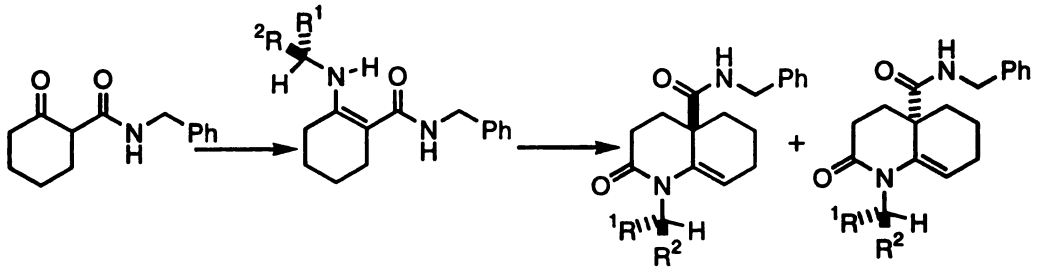
yields; the use of acrylic acid anhydride, generated *in situ* by the reaction of sodium acrylate with acryloyl chloride, resulted in somewhat improved yields. However, use of the mixed anhydride, formed by the combination of sodium acrylate with ethyl chloroformate just before reaction, proved to be the optimum reagent for aza-annulation with β-enamino amide substrates. In each case, the diastereoselectivity of the quaternary carbon formation from the β-enamino amide substrate was high, and was independent of the acrylate derivative used for the aza-annulation reaction.

Scheme II-15. Asymmetric Aza-Annulation with Amide Derivatives.



Reaction Conditions. *i*) benzylamine, DMAP, xylene, reflux, 91% yield; *ii*) (*R*)-phenethylamine, toluene, reflux; *iii*) sodium acrylate, $ClCO_2Et$, THF, 99% yield.

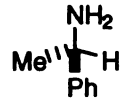
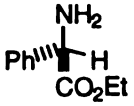
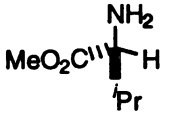
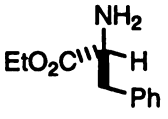
Scheme II-16. Asymmetric Aza-Annulation of β-Enamino Amide Intermediates with Acrylate Derivatives



II-25 **II-28** **II-29-32a** **II-29-32b**

A similar reactivity was observed for the β-enamino amide derived from condensation of phenyl glycine ethyl ester (**II-30**) with **II-25**. The aza-annulation of **II-25** was significantly more efficient when acrylic acid anhydride was used instead of acryloyl chloride, and further increase in yield was obtained through the use of the mixed anhydride. In each case, stereoselective formation of **II-30b** occurred to the extent of >98:2. Use of the valine derived substrate **II-31**, which resulted in poor diastereoselectivity in the case of the β-enamino ester substrate (57:43), gave excellent stereoselective formation of **II-31b** (>98:2) in high yield (90%) for the β-enamino amide. Interestingly, even the phenylalanine derived compound **II-28d** was effective at asymmetric induction (95:5), but the yield of the aza-annulation reaction was low with this auxiliary. For each example, enamine **II-28** was readily generated, and the reaction products **II-29-32a-b** were stable to moderate hydrolysis conditions.

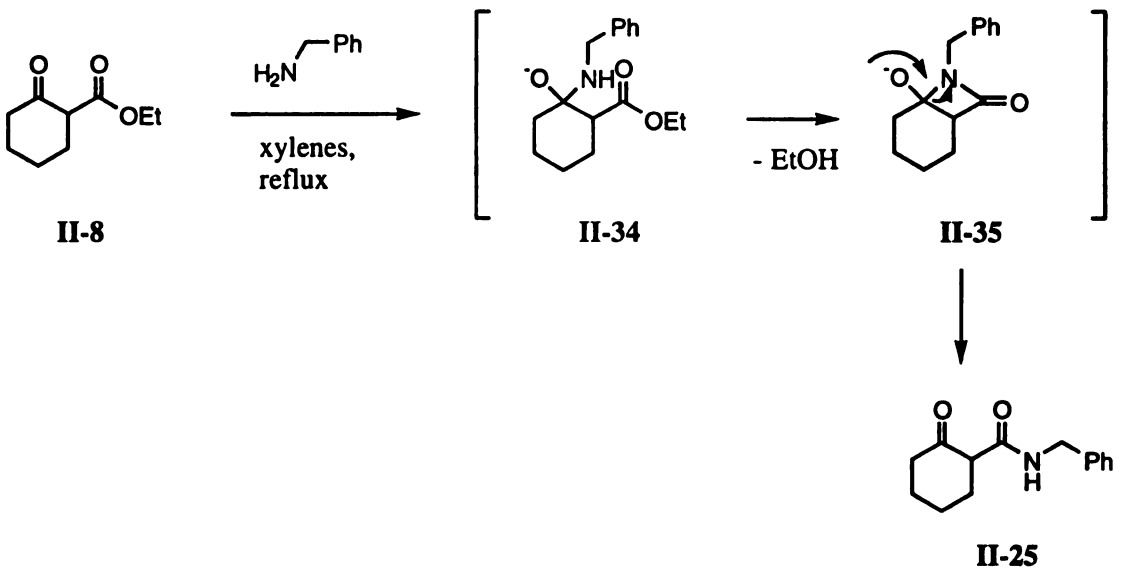
Table II-4. Effect of Chiral Amine and Acrylate Derivative on the Asymmetric Aza-Annulation Reaction.[a]

Comp. #	Amine	R^1	R^2	Method	II-29a-32a : II-29b-32b[b]	Yield [%][c]
II-29	II-33a	Me	Ph	A	>98:2	99
				B	>98:2	86
				C	>98:2	67
II-30	II-33b	Ph	CO_2Et	A	>2:98	98
				B	>2:98	80
				C	>2:98	49
	II-33c					
II-31		CO_2Me	^{i}Pr	A	>98:2	90
	II-33d					
II-32		CO_2Et	Bn	A	95:5	46

See **Scheme II-16.** [a]**Reaction conditions:** (I) **II-33a** or **II-33b-d**•HCl/$NaHCO_3$, toluene, reflux; (ii) method A: sodium acrylate, $ClCO_2Et$, THF, -78° C; method B: sodium acrylate/acryloyl chloride, THF, -78° C; method C: acryloyl chloride, THF, RT. [b]Determined by ^{1}H NMR of the crude reaction mixture. [c]Yield of the diastereomeric mixture after flash column chromatography.

The use of α-amino acid derivatives instead of benzyl amine in preparation of β-ketoamides proved to be much more complicated; direct synthesis using DMAP and corresponding amine, as in the case of the benzylamides, did not give the desired product. At this stage of the research, it was decided to explore the interesting formation of β-keto amides from β-keto esters by reaction with primary or secondary amines.[13b] This reaction is believed to occur via a 4-membered cyclic transition state from the initially formed intermediate **II-34** to a β-ketoamide (**Scheme II-17**). This type of mechanism may also be involved in the reaction of β-ketoesters with amines in the presence of DMAP. Reaction of ethyl 2-cyclohexanone carboxylate with benzylamine and DMAP provided the expected product in 91% yield, but reaction with ethyl glycine or N-methyl glycine (sarcosine) did not give the desired products under the same reaction conditions. Moreover, in the case of sarcosine, only N,N-dimethyl amide was isolated, the product of decarboxylation of the desired product.

Scheme II-17. Possible Transition State of β-Keto Amide Formation

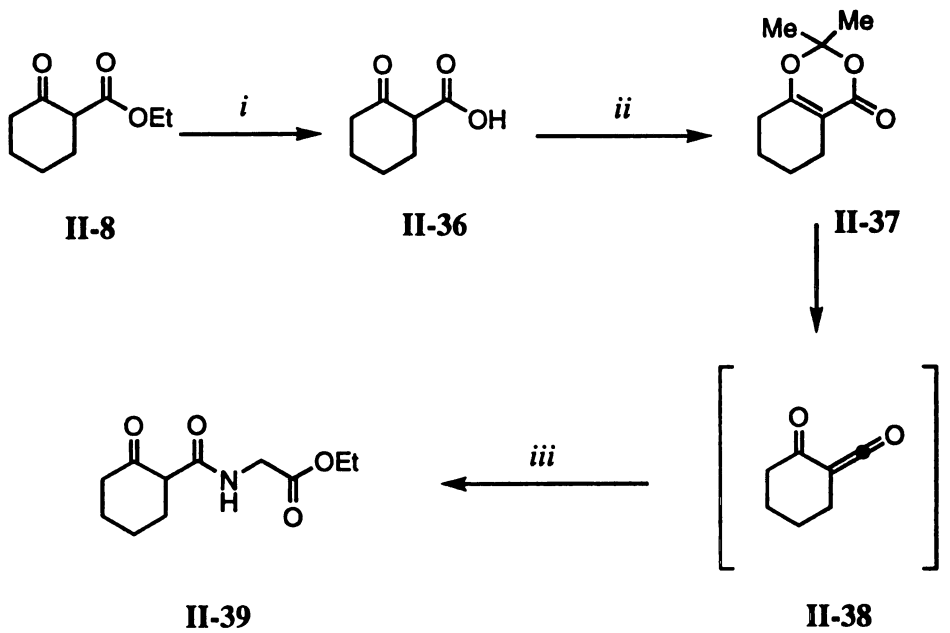


II-8 **II-34** **II-35** **II-25**

A different method for the preparation of β-keto amides is based on the thermal instability of 2,2-dimethyl-2H,4H-1,3-dioxin-4-one derivatives.[13c] Thermolysis in refluxing xylenes in the presence of an amine resulted in formation of the corresponding β-ketoamide, via ketene intermediate **II-38** (**Scheme II-18**).

This method was successfully used for the preparation of various β-keto amides derived from α-amino acids (**Table II-5**). Aza-annulation products were readily obtained from chiral amines, and the enamine intermediates were immediately used in the next step to complete the synthesis (**Scheme II-19, Table II-6**). Products of this type may serve as models of restricted α-amino acid-β-amino acid sequences.

Scheme II-18. Using of 2,2-Dimethyl-1,3-Dioxin-4-One Derivatives for Preparation of β-Keto Amides.

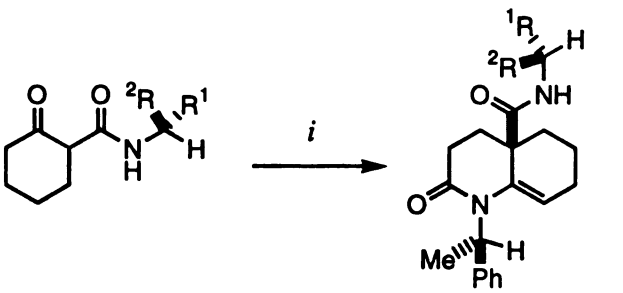


II-8 **II-36** **II-37**

II-39 **II-38**

Reaction Conditions. *i*) NaOH, H_2O; *ii*) acetone, acetic anhydride, H_2SO_4, 54% (2 steps); *iii*) ethyl glycine, xylene, reflux, 1 h, 54%.

Scheme II-19. Asymmetric Aza-Annulation with Amide Derivatives.



Reaction Conditions. *i*) (*R*)-phenethylamine, toluene, reflux, then sodium acrylate, $ClCO_2Et$, THF

Table II-5. Formation of β-Keto Amides.

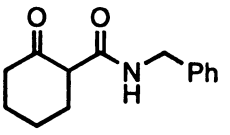
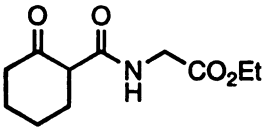
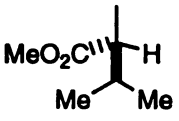
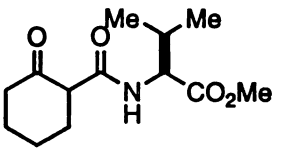
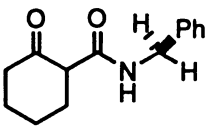
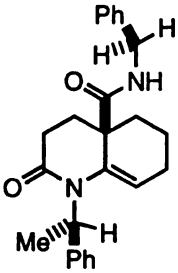
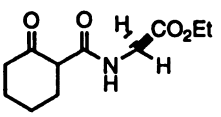
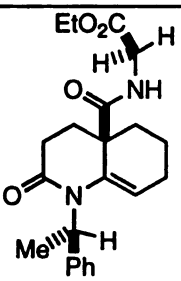
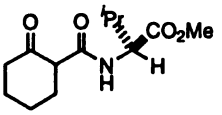
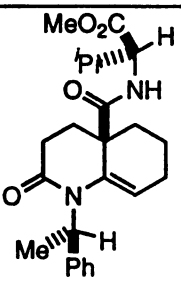
R	Product	Yield
-CH_2Ph	 **II-25**	61%
-CH_2CO_2Et	 **II-39**	54%
	 **II-40**	75%

Table II-6. Asymmetric Aza-Annulation with β-Keto Amides.

R^1	R^2	Amide	Product	Yield [%]	de[a] [%]
Ph	H	 **II-25**	 **II-29a**	99%	>98:2
CO_2Et	H	 **II-39**	 **II-41**	74%	>98:2
CO_2Me	^{i}Pr	 **II-40**	 **II-42**	50%	>98:2

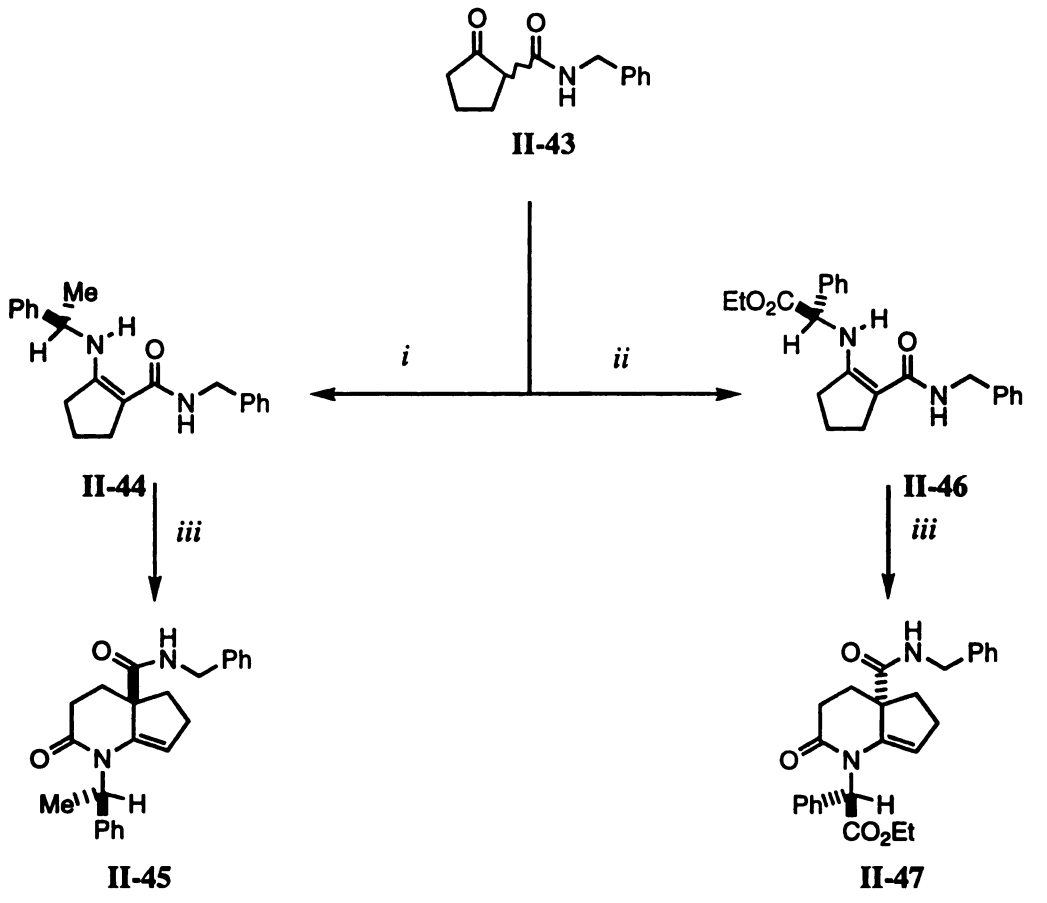
[a]Ratio at the quaternary carbon stereogenic center.

The five-membered substrate **II-43**, prepared from ethyl cyclopentanone-2-carboxylate according to the same reaction scheme as **II-25**, showed different reactivity and stability patterns than the analogous six-membered ring substrates (**Scheme II-20**). Due to its thermal instability, compound **II-43** was used without extensive purification for subsequent formation of enamines **II-44** and **II-46**. These reactions were slower than their six-membered ring analogs. Before the aza-annulation step, it was necessary to purify these enamines by flash column chromatography, thus, the isolated yield dramatically dropped. Aza-annulation of **II-42** led to generation of **II-45** in only moderate yield, but the product was obtained with high diastereoselectivity (>98:2). Treatment of **II-46** with the acrylate mixed anhydride led to a more efficient aza-annulation than that of **II-42**, but the crude ratio of diastereomers was only 84:16 (based on ^{1}H NMR measurement), and after purification of **II-47**, a 75:25 ratio of diastereomers was obtained. The products **II-45** and **II-47** were resistant to catalytic hydrogenolysis under an atmospheric pressure of hydrogen.

In an attempt to broaden the spectrum of potential synthetic applications, with the intention to prepare a spiro compound similar to products prepared by Stille and coworkers,[8] 1-*tert*-Boc-5-acetyl-3-methyl-4-oxoimidazolidin **II-50** was synthesized[14] (**Scheme II-21**).

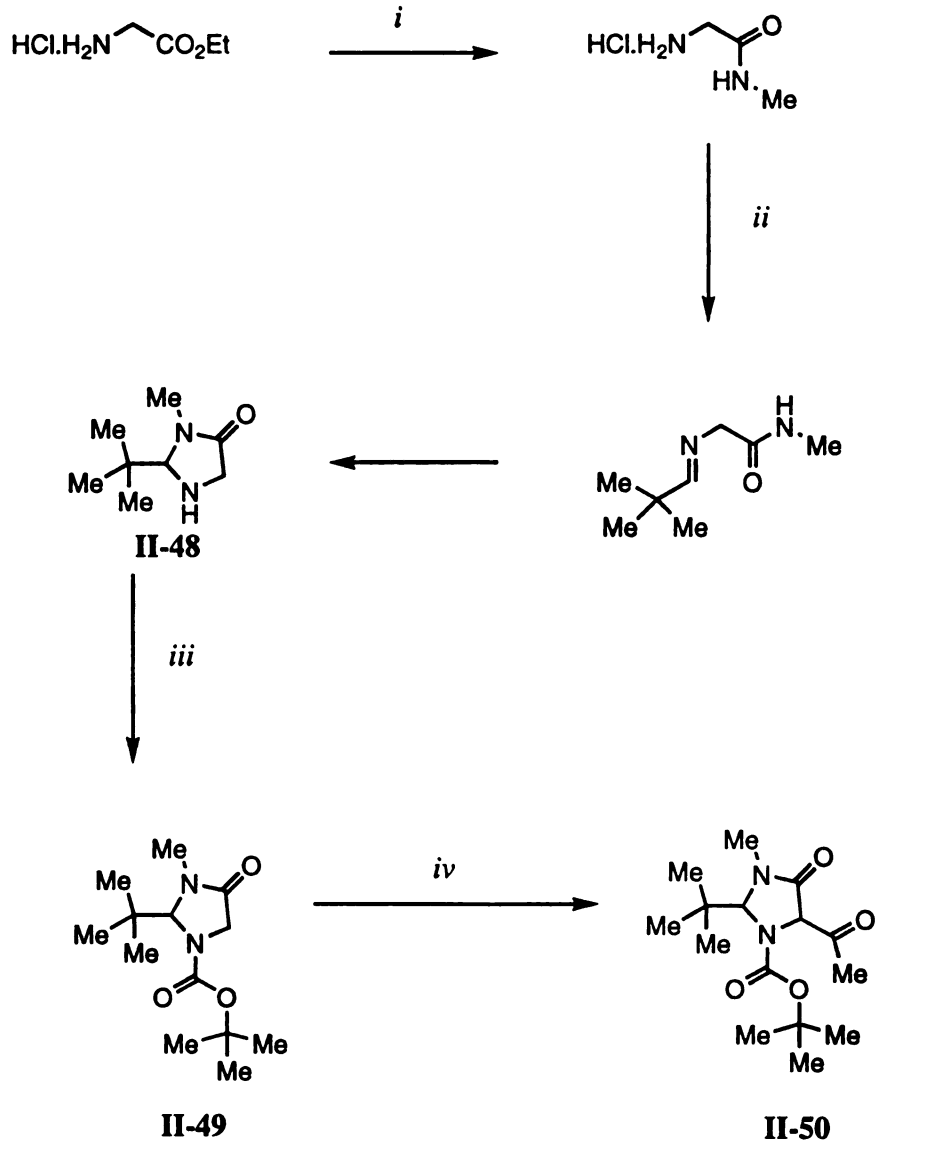
Unfortunately, reaction of compound **II-50** with (*R*)-phenethylamine gave no enamine product. Prolonged heating of a toluene solution of these reactants, with or without the presence of an acid catalyst (*p*-toluenesulfonic acid or Lewis acids), gave only starting material or products of decomposition.

Scheme II-20. Asymmetric Aza-Annulation of Cyclopentanone Derived β-Enamino Amide Intermediates with Acrylate Derivatives.



Reaction Conditions. *i*) (*R*)-phenethylamine, toluene, reflux; *ii*) (*R*)-ethyl phenylglycine hydrochloride, toluene, $NaHCO_3$, reflux; *iii*) sodium acrylate, $ClCO_2Et$, THF, 50% for **II-45**, 67% for **II-47** (75:25 ratio of diastereomers).

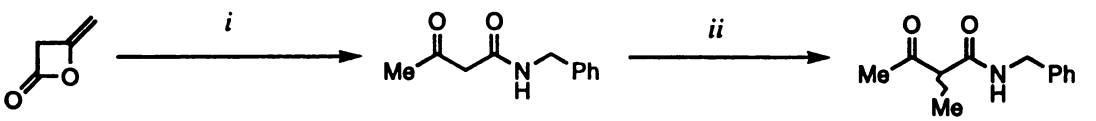
Scheme II-21. Preparation of an 4-Oxoimidazolidin Derivative.



Reaction Conditions. *i*) methylamine, MeOH; *ii*) pivaloyl aldehyde, Et_3N, CH_2Cl_2; *iii*) $(Boc)_2O$, DMAP, acetone, 80% yield; *iv*) LDA, THF, -78° C then acetyl chloride, -78° C, 95% yield.

Aza-annulation reactions with acyclic substrates. The aza-annulation with acyclic β-keto amide substrates also resulted in initial ring formation with a high degree of diastereoselectivity (**Scheme II-23**). Condensation of (*R*)-phenethylamine and **II-53**, prepared by reaction of diketene with benzyl amine in benzene solution, followed by routine alkylation of the β-keto amide product **II-52** with sodium ethoxide and methyl iodide in ethyl alcohol (**Scheme II-22**), efficiently generated the corresponding enamine as a single geometric isomer. This species had a relatively rigid structure due to an intramolecular hydrogen bond, confirmed by ^{1}H NMR spectroscopy of the crude reaction mixture. Subsequent aza-annulation with the mixed anhydride of acrylic acid, made *in situ*, generated **II-54** with high diastereoselectivity (>98:2). All attempts to isolate and purify compound **II-54** either by flash column chromatography or by crystallization led to hydrolysis of the product to **II-55**, the open chain keto diamide.

Scheme II-22. Preparation of Acyclic β-Keto Amides.



II-51 **II-52** **II-53**

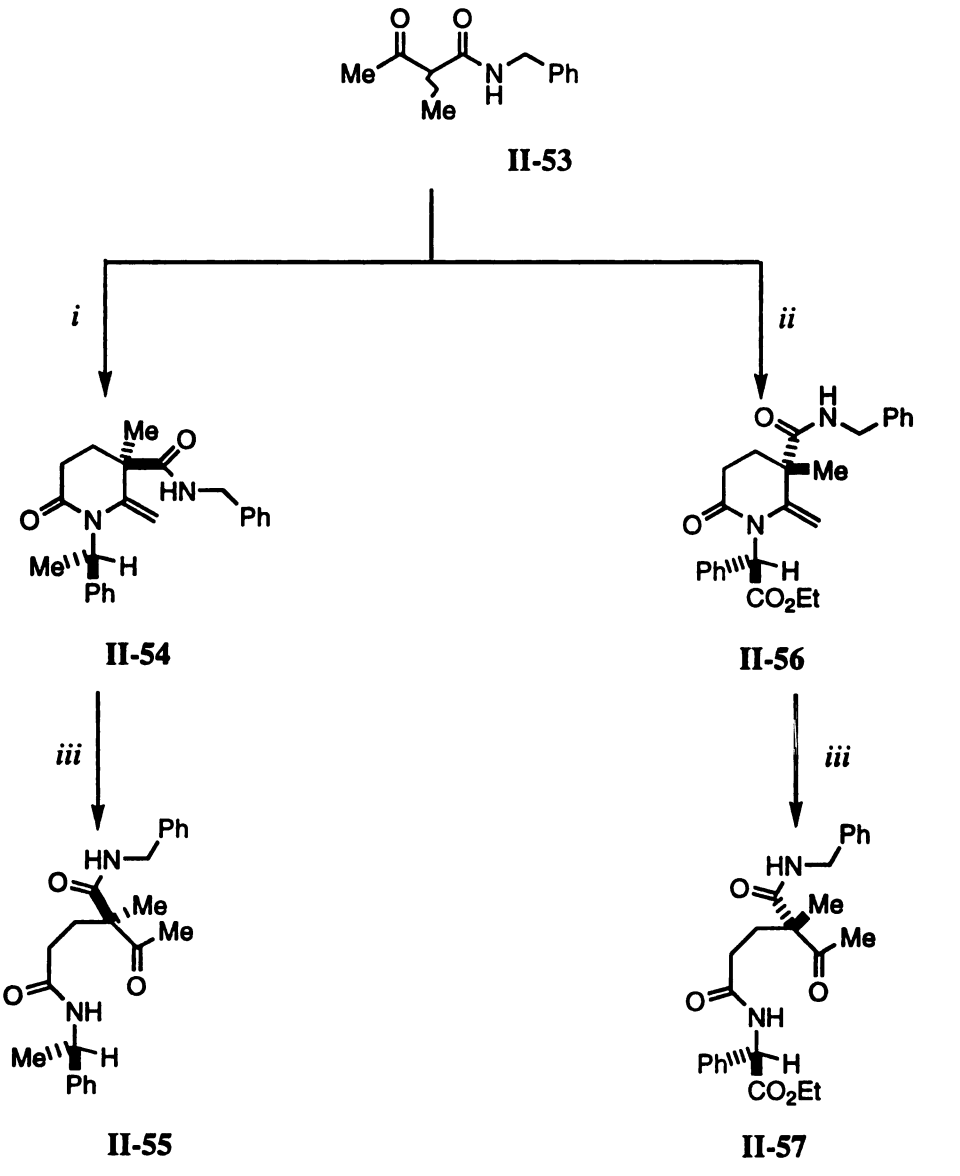
Reaction Conditions. *i*) benzylamine, benzene, 0° C, 81%; *ii*) NaOEt, EtOH, MeI, 100%.

In order to obtain an accurate yield for the carbon-carbon bond formation process, crude **II-54** was treated with *p*-toluenesulfonic acid in wet tetrahydrofuran to promote complete hydrolysis of the enamide functionality. The product **II-55** was obtained in an overall 82% yield in the three-step process of enamine formation, aza-annulation reaction, and hydrolysis, with a >98:2 diastereomer ratio.

Reaction of **II-53** with a different chiral amine followed by aza-annulation led to similar results as those obtained for **II-55** (**Scheme II-23**). Thus, condensation of **II-53** with (*R*)-ethyl 2-phenylglycine hydrochloride generated an enamine intermediate as a single geometric isomer, and the annulation reaction gave δ-lactam **II-56** with >98:2 diastereoselectivity. Facile hydrolysis of the disubstituted terminal enamide **II-56** was observed during the purification process. As a result, compound **II-56** was subjected to hydrolysis and the acyclic product **II-57** was isolated in 71% overall yield without loss of stereochemical integrity.

Compound **II-59**, a benzyloxycarbonyl protected derivative of D,L-threonine **II-58**,[15] was the source of the next β-keto carboxylate species studied (**Scheme II-24**). In this case, however, instead of the corresponding amide, the β-keto ester **II-61** was prepared first, oxidation of ester **II-60** by PCC giving the desired β-keto ester **II-61** in 91% yield for the two-step process. Condensation with (*R*)-phenethylamine, followed by treatment with the acrylate mixed anhydride gave the aza-annulation reaction product **II-62**. As observed for **II-54** and **II-56**, this terminal enamide was sensitive toward hydrolysis conditions, and even with aqueous $NaHCO_3$ work up, hydrolysis occurred completely to give **II-63** in 45% overall yield.

Scheme II-23. Asymmetric Aza-Annulation with Acyclic β-Keto Amides.

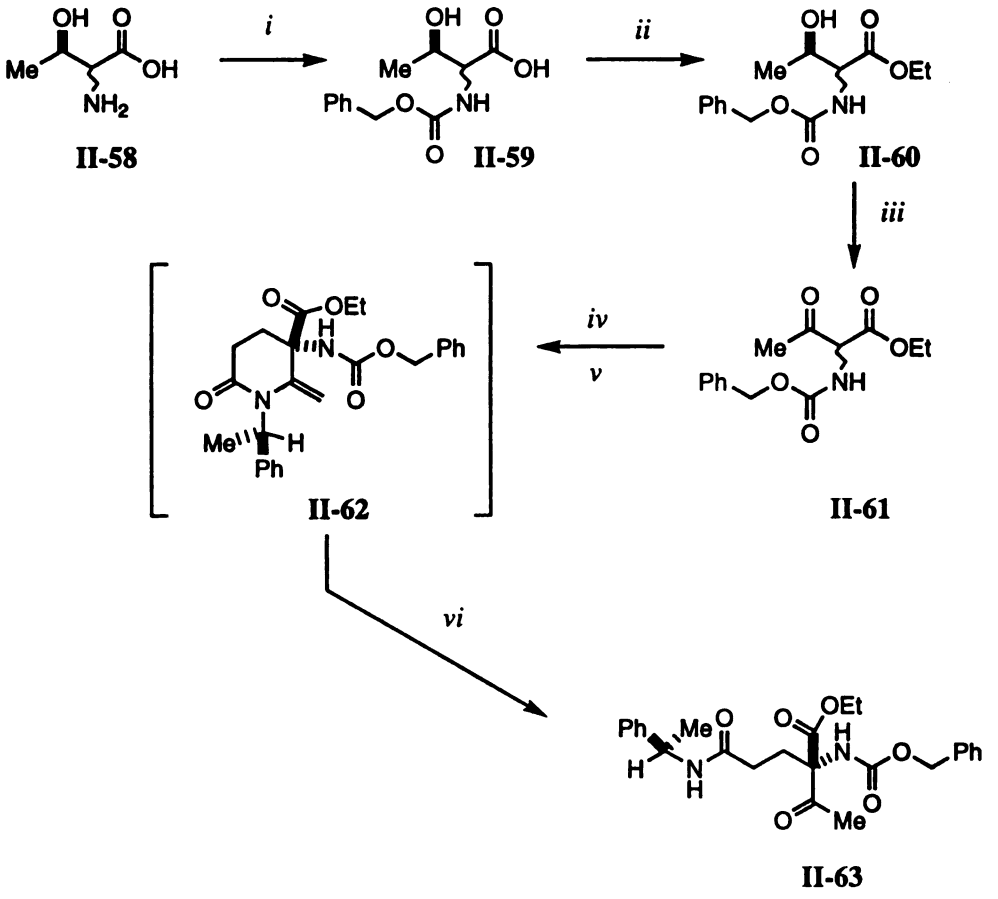


Reaction Conditions. *i)* (*R*)-phenethylamine, toluene, reflux then sodium acrylate, $ClCO_2Et$, THF; *ii*) (*R*)-ethyl 2-phenylglycine:HCl, $NaHCO_3$, toluene, reflux; then sodium acrylate, $ClCO_2Et$, THF; *iii*) *p*-TsOH, H_2O, THF.

An analogous amide derivative was prepared by a similar reaction scheme (**Scheme II-25**). Enamine formation with (*R*)-phenethylamine, followed by the aza-annulation reaction with a mixed anhydride made *in situ* from sodium acrylate and ethyl chloroformate at low temperature gave a product **II-67** having an exo-double bond. The open chain structure **II-68** was again obtained during the purification of the crude product on the SiO_2 column. The yield after column purification was 85%, i.e. higher than for the ester analog. Aza-annulation with acryloyl chloride yielded the same product **II-68** in 73% yield.

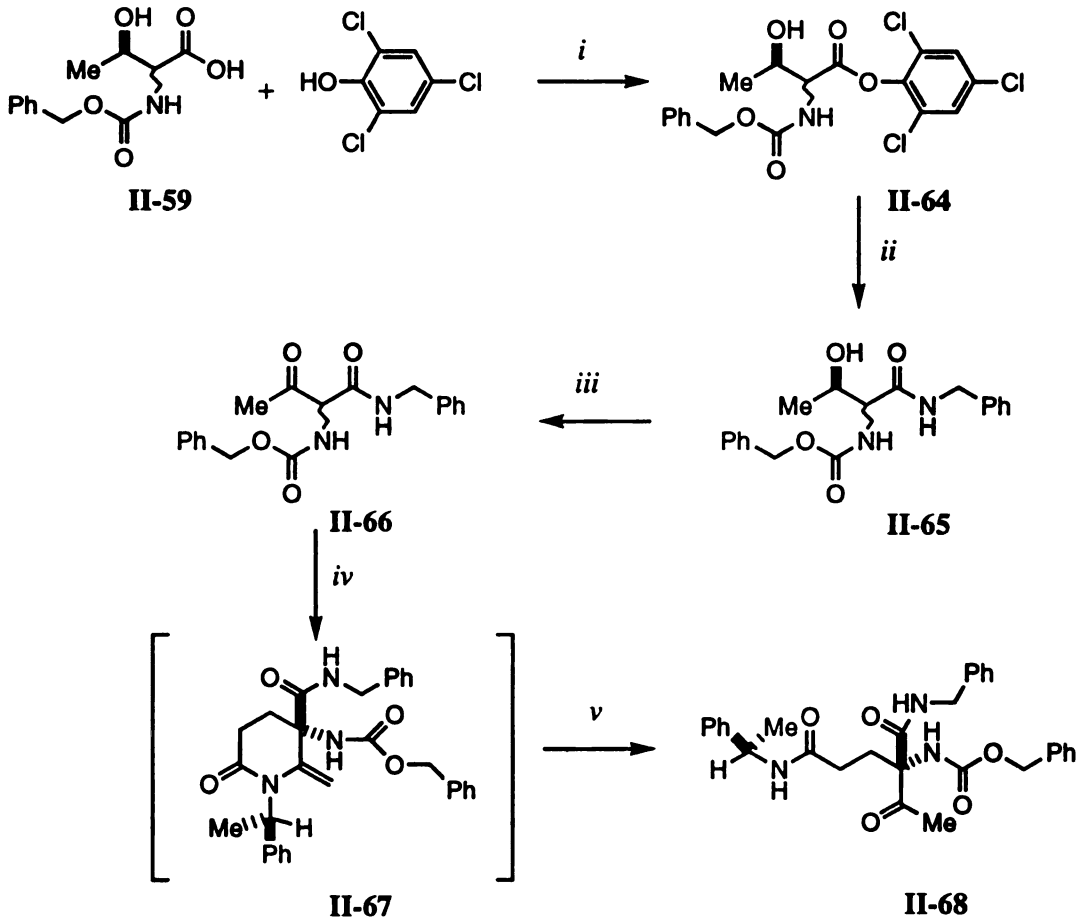
In general, a comparison of the reactions of ester derivatives and amide derivatives, indicate that the latter compounds undergo slower aza-annulation reaction but in higher yields. The major by-product of the reaction was found to be the corresponding acrylamide. Independent of the reagent used for this reaction, the chiral α-amino acid was formed with >98:2 stereoselectivity.

Scheme II-24. Asymmetric Aza-Annulation with Acyclic β-Keto Amides Derived from D,L-Threonine - Ester Route.



Reaction Conditions. *i*) $PhCH_2OCOCl$, $NaHCO_3$, H_2O, 95% yield; *ii*) EtOH, HCl, reflux; *iii*) PCC, Celite (1:1 ratio), CH_2Cl_2, 91% yield (2 steps); *iv*) (*R*)-phenethylamine, toluene, reflux; *v*) sodium acrylate, EtO_2CCl, THF; *vi*) aq.$NaHCO_3$, 45% yield.

Scheme II-25. Asymmetric Aza-Annulation with Acyclic β-Keto Amides Derived from D,L-Threonine - Amide Route.



Reaction Conditions. *i*) DCC, EtOAc, 60%; *ii*) benzylamine, Et_3N, dioxane, H_2O, 80%; *iii*) PCC, Celite (1:1 ratio), CH_2Cl_2, 56%; *iv*) (*R*)-phenethylamine, toluene, reflux then sodium acrylate, $ClCO_2Et$, THF; *v*) SiO_2, H_2O, 75%.

The instability of enamide products having an exo double carbon-carbon bond such as **II-62** and **II-67** is noteworthy. Comparing these compounds with relatively stable structures made by Stille and Barta,[8] suggests the possibility of nitrogen participation in nucleophilic attack of a water molecule to the enamine carbon-carbon double bond.

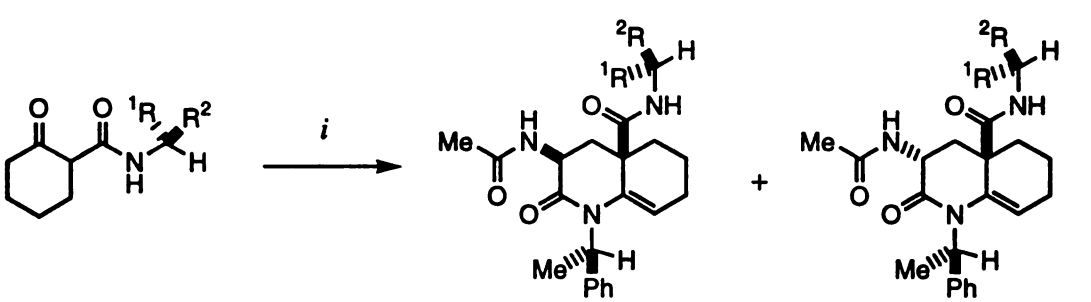
Several important features of the aza-annulation reaction of acyclic β-keto carboxylate derivatives are of significance. The unexpected hydrolysis process yielded acyclic substrates in good yields and high diastereoselectivity. As a result, the 1,4-asymmetric induction that occurred during the reaction appeared as a 1,6-relationship in the hydrolysis product. This suggests a relatively rigid transition state with strictly defined geometry, where the carbamate nitrogen is a much weaker base for participation in hydrogen bonding and consequently in the nucleophilic displacement.

Selectivity of formation of substituted α-amino lactams. Reaction of different β-keto amides **II-25**, **II-39** and **II-40** with (*R*)-phenethylamine, followed by the aza-annulation with a mixed anhydride, prepared by treatment of 2-acetamido acrylic acid with ethyl chloroformate at -78° C, resulted in formation of roughly equal amounts of two diastereomeric α-acetamido δ-lactam products **II-69a-c** and **II-70a-c** (**Scheme II-26**). Results are summarized in **Table II-7**, with yields and diastereomeric ratios indicated. The selectivity in forming a quaternary carbon stereogenic center was still excellent (>98:2), with no bias for selective generation of the stereoisomers at the α position.

Separation of the diastereomers by column chromatography allowed characterization of each product, with the exception of diastereomers **II-69c** and **II-70c**. Mutual relationship of two stereocenters (a quaternary carbon center and the α-carbon center of lactam functionality) in compound **II-69a** was confirmed by X-ray crystallography (**Appendix 1**).

Reaction of **II-69a** with NaH led to epimerization α to the lactam carbonyl that resulted in a 45:55 ratio of **II-69a** and **II-70a**, favoring the more thermodynamically stable diastereomer. No epimerization was observed with DBU as a base. These results were in an agreement with the behavior of similar substrates, prepared in different research projects by our group.[16]

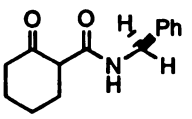
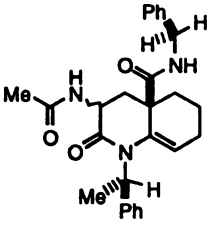
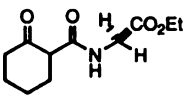
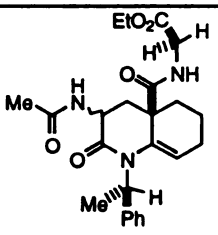
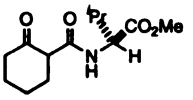
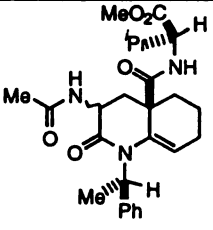
Scheme II-26. Asymmetric Aza-Annulation Providing α-Substituted Lactam Derivative.



II-69a-c **II-70a-c**

Reaction Conditions. *i*) (*R*)-phenethylamine, toluene, reflux, then sodium 2-acetamidoacrylate, $ClCO_2Et$, THF.

Table II-7. α-Substituted Lactam Products of Asymmetric Aza-Annulation.

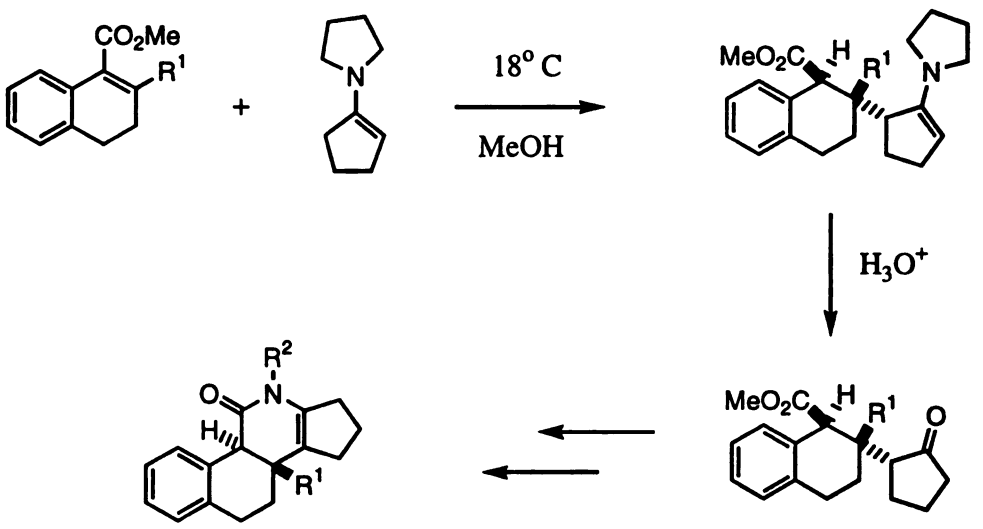
R^1	R^2	Amide	Product	Yield	Ratio[a]
H	Ph	 **II-25**	 **II-69a, II-70a**	67%	50:50
H	CO_2Et	 **II-39**	 **II-69b, II-70b**	79%	65:35
*i*Pr	CO_2Me	 **II-40**	 **II-69c, II-70c**	15%	50:50

[a] diastereomeric ratio at α-carbon of the lactam ring.

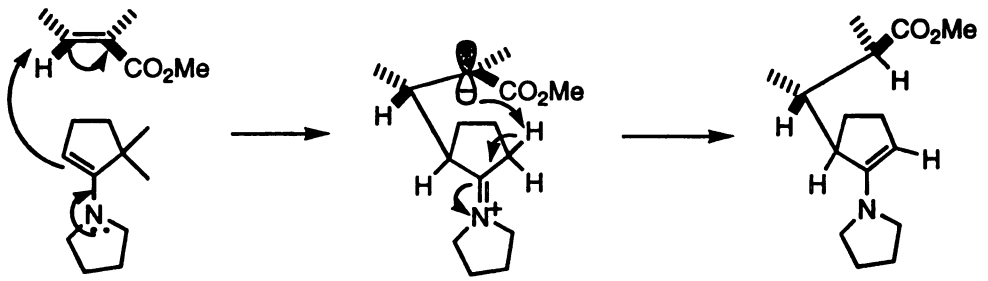
Mechanistic Discussion. A detailed mechanism of the aza-annulation reaction is still not known, and several hypotheses have been suggested. Aza-annulation is closely related to the Michael addition reaction, in which a carbon-carbon bond formation occurs between an enamine nucleophile and α,β-unsaturated carbonyl system, followed by acylation at nitrogen atom of an enamine species. In 1967, Pandit[17] described reactions of cyclic tertiary enamines with α,β-unsaturated esters (**Scheme II-27**). To explain stereoselectivity of the course of the reaction, authors suggested a formation of a dipolar intermediate **II-71** with subsequent intramolecular hydrogen transfer (**Scheme II-28**).

In 1981, Seebach formulated the general, topological rule[18] based on his experimental results with open-chain nitroolefins and open-chain enamines,[19] and previous experiments done by Risaliti with enamines prepared from cyclic ketones and nitroolefins.[20]

Scheme II-27. The Preparation of a 12-Azasteroid Systems.



Scheme II-28. Pandit's Explanation for Stereoselectivity of the Michael Reaction.



II-71

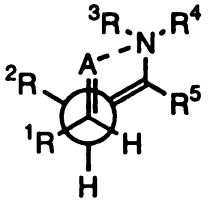
Seebach postulated that the approach of the two reactants is in a synclinal fashion, where :

- All bonds in the transition state are staggered;
- The donor (C-N bond) and the acceptor C=A and C-H bonds are in a synclinal conformation;

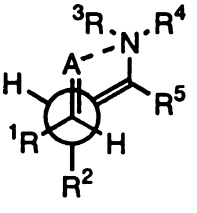
- A hydrogen atom (the smaller substituent on the donor component) is in an antiperiplanar position with respect to the C=A bond (*Re-Si* approach in **Scheme II-29**);
- The components, if they can exist in *E/Z* isomeric forms, orient the actual donor and acceptor atoms close to each other.

In the cases where very bulky groups R^1, R^2, R^3 and R^4 were present and/or the solvent was protic, antiperiplanar rather than synclinal approach, allowing for better solvation of the donor and acceptor heteroatoms, is kinetically preferred.

Scheme II-29. Seebach's Topological Rule. Two Possible Approaches.



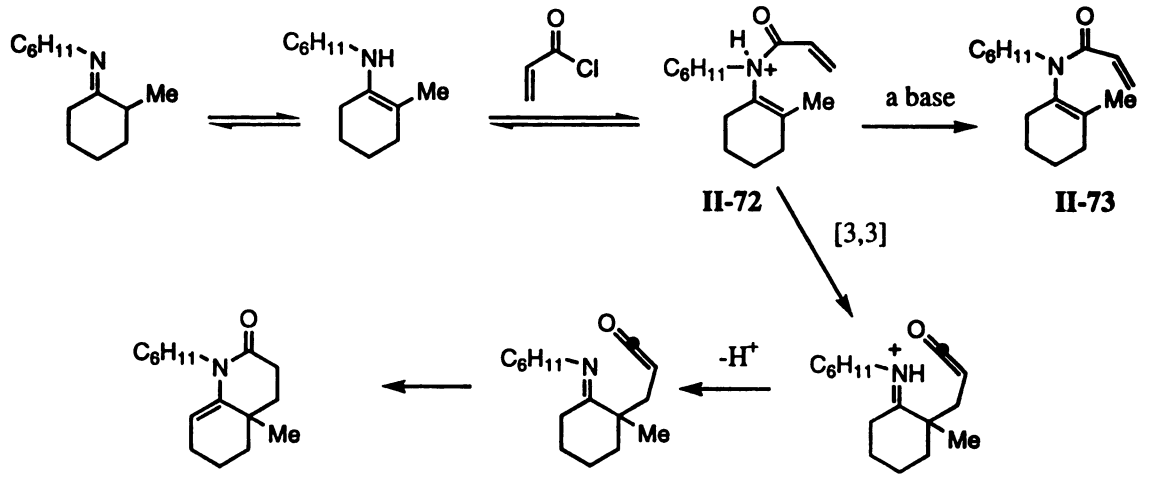
Re-Si approach



Re-Re approach

Hickmott proposed a reaction mechanism that involved formation of an amide, followed by [3,3] sigmatropic rearrangement to a ketene intermediate.[21] In the presence of a base (triethylamine), the positively charged ammonium species **II-72** loses a proton providing only the amide **II-73**. In the absence of a base, intermediate **II-72** undergoes sigmatropic rearrangements to give the ketene species, which consequently cyclizes to a lactam compound (**Scheme II-30**).

Scheme II-30. Hickmott's Mechanism of Aza-Annulation.



Matsuyama and coworkers[22] used an asymmetric Michael reaction for the preparation of α-disubstituted unsaturated cyclanones, and suggested a hetero-Diels-Alder transition state (**Scheme II-31, Figure II-2**). In support of this hypothesis, they cited analogous results from acyliminoacetates and chiral enamines, and the isolation and spectral characterization of a cyclic intermediate.[23]

Scheme II-31. Stereoselective Preparation of 2,2-Disubstituted 3-Cyclopentenone Derivatives by Asymmetric Michael Reaction.

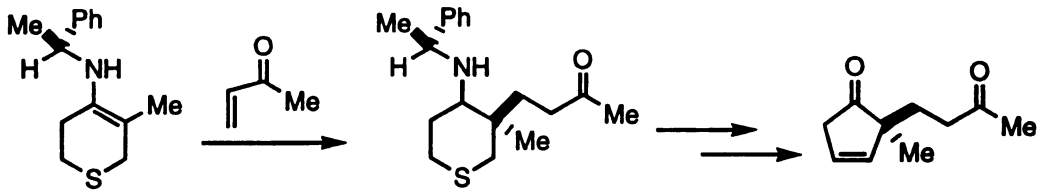
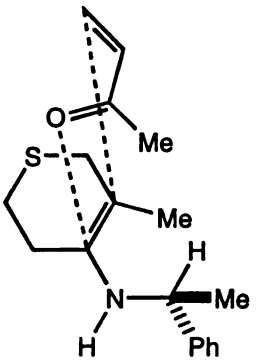
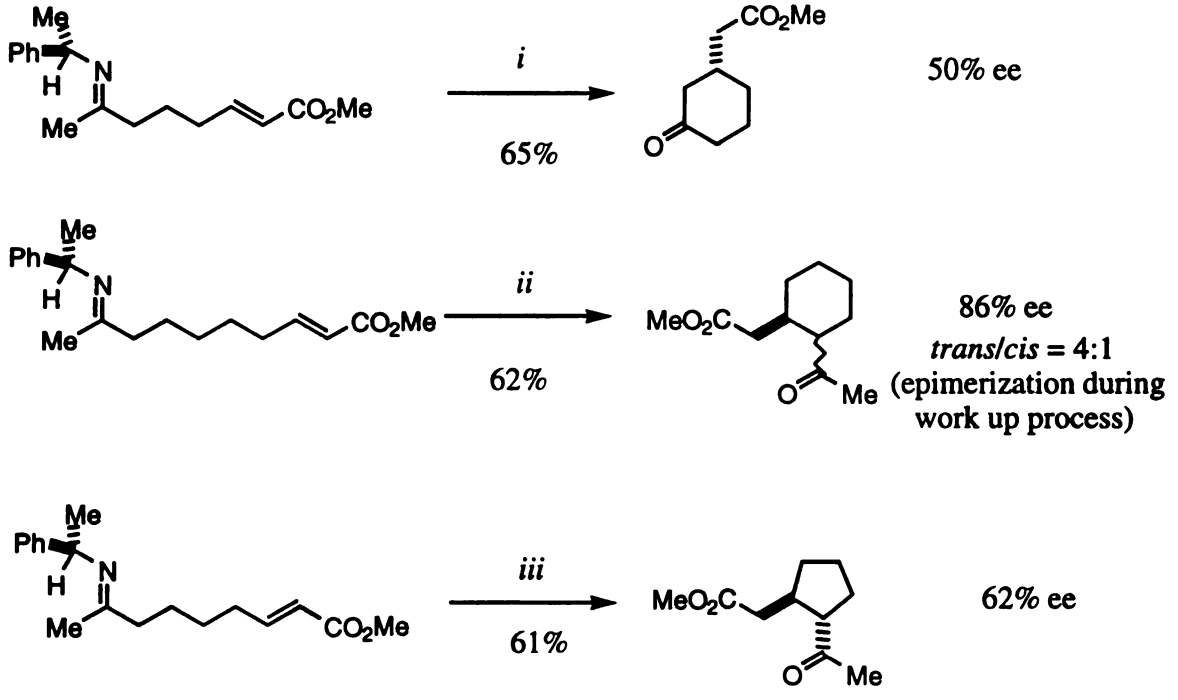


Figure II-2. Matsuyama's Hetero-Diels-Alder Transition State for the Aza-Annulation Reaction



d'Angelo studied the influence of a chiral enamine intermediate in intramolecular asymmetric Michael additions (**Scheme II-32**).[24] Based on the experimental results from their laboratory, they suggested an intramolecular mechanism proceeding via a cyclic chair-like compact transition state with almost concerted hydrogen transfer from a nitrogen atom. (**Scheme II-33**).

Scheme II-32. d'Angelo's Asymmetric Michael Addition Reactions.



Reaction Conditions. *i*) $MgBr_2$ (2 equiv.), Et_2O, 0° C, 5 min.; *ii*) benzene, 80° C, 6 h; *iii*) 12 kbar, THF, 20° C, 60 h.

Scheme II-33. Transition State Suggested by d'Angelo.

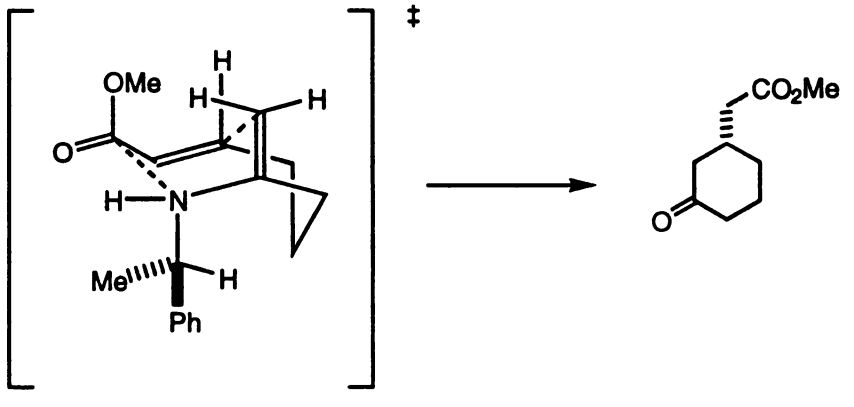
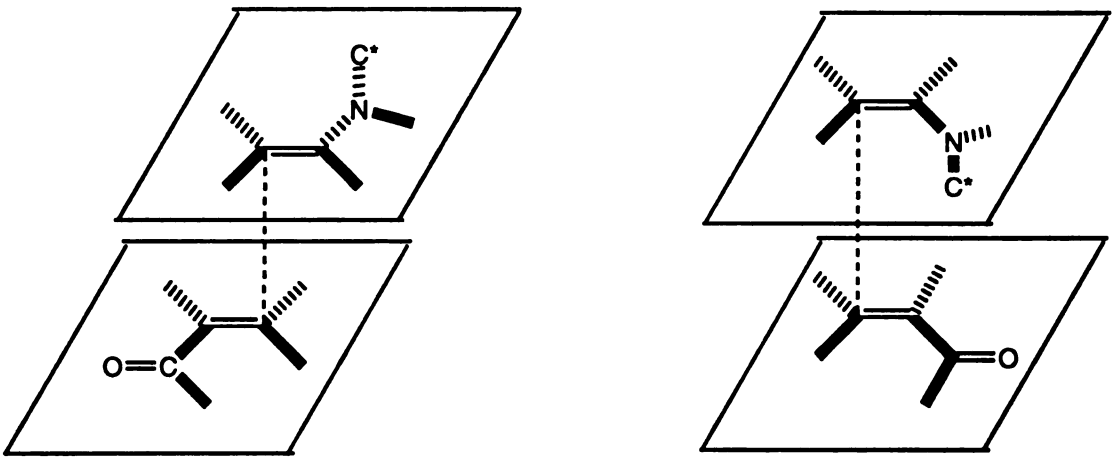


Figure II-3. "Loose" and "Compact" Complex Approaches.

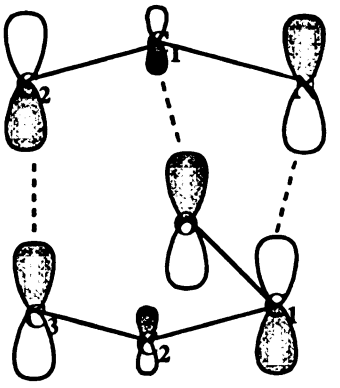


"loose" complex

"compact" complex

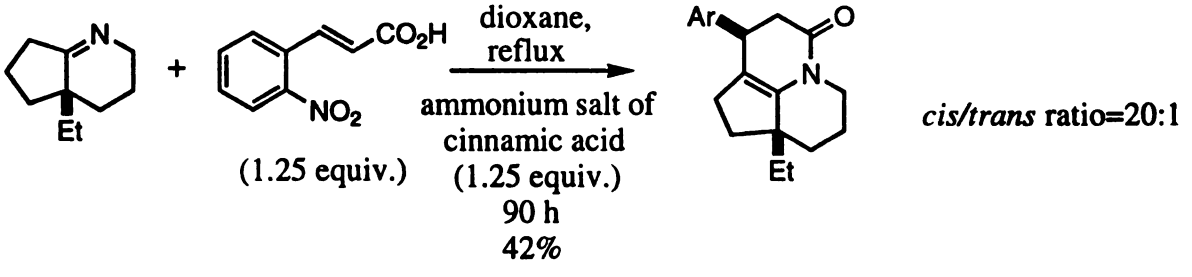
Pfau and Sevin[25] supported the idea of a cyclic transition state by 3-21G, MNDO and *ab initio* calculations for simpler reactants, and confirmed that the energy of a "loose" transition state is only slightly lower than that of a "compact" transition state (**Figure II-3**). However, in aprotic solvents, the formation of a zwitterionic species would be very unlikely and energetically demanding. Extra attractive interactions resulting from HOMO-LUMO interactions between an enamine and an acrylic acceptor (**Figure II-4**) shifts the "compact" transition state to almost the same energy level.

Figure II-4. Frontier Orbital Interaction.

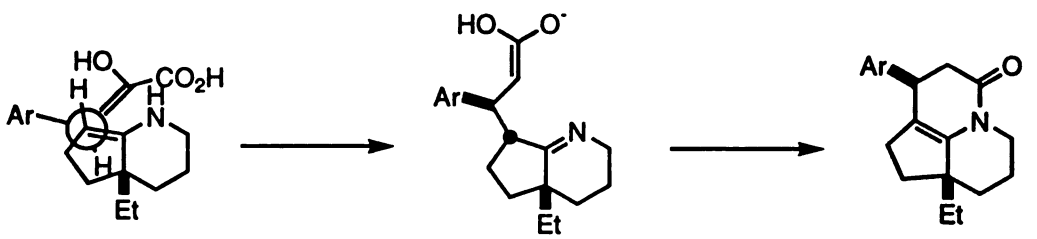


Heathcock utilized an aza-annulation reaction as a key step in the total synthesis of (±)-vallesamidine[26] (**Scheme II-34**). Even in dioxane at reflux, the less hindered synclinal complex was favored, giving 20:1 mixture of *cis/trans* isomers (**Scheme II-35**).

Scheme II-34. A Key Step in the Total Synthesis of (±)-Vallesamidine.



Scheme II-35. Favored Synclinal Approach in the Total Synthesis of (±)-Vallesamidine

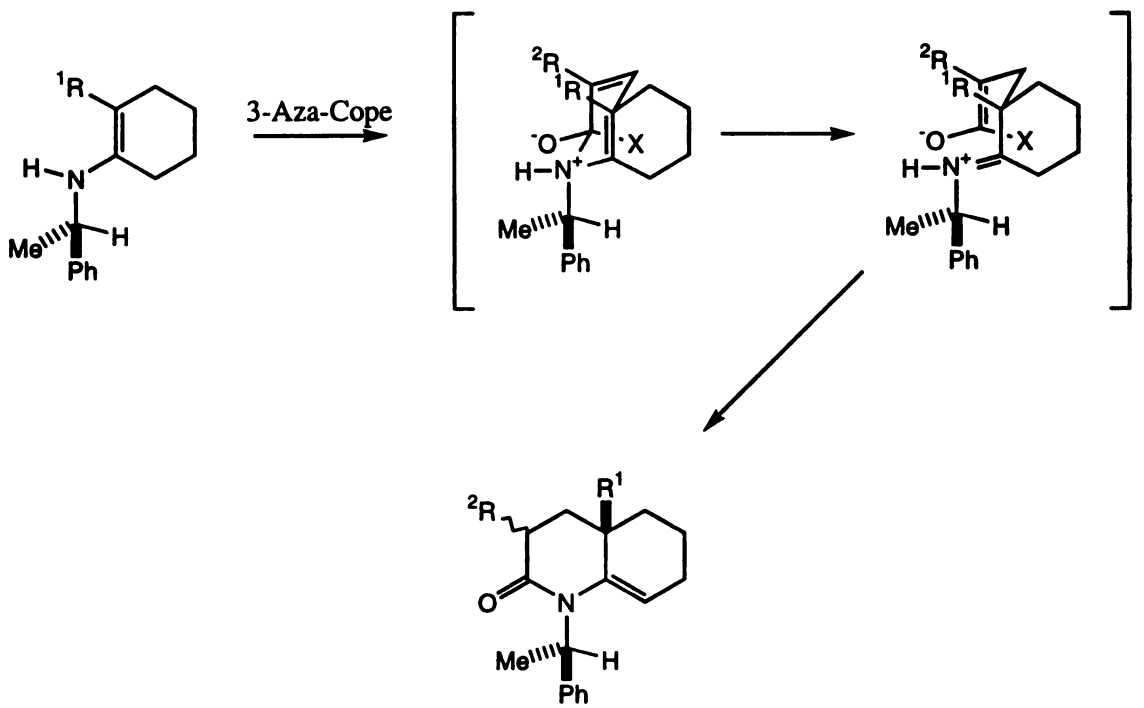


Stille assumes similar factors in the Michael addition reaction and the aza-annulation reaction, but points out some differences,[8] too :

- The lower reactivity of β-enamine esters toward unsaturated esters, sulfonyl and nitrile derivatives in the Michael reaction is well documented[27]. Aza-annulation reactions with the same substrates are fast;
- Lack of stereoselectivity at a stereogenic center α to the acrylate derivative was observed for the aza-annulation reactions;
- Stereoselectivity in carbon-carbon bond formation in aza-annulation depends on both temperature and the acrylate like reagent (sulfone, methyl, *t*-butyl esters), but not for the Michael reaction.

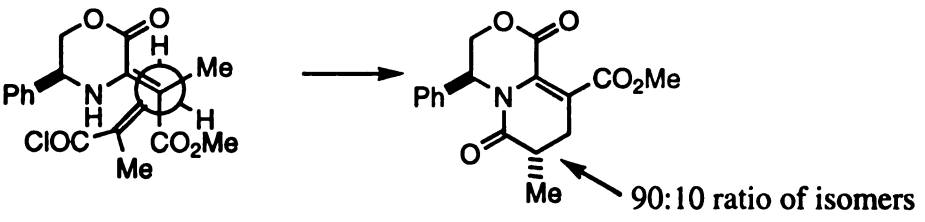
Stille proposed three different pathways likely to be responsible for the stereochemical course of reaction, with the aza-Cope-like transition state as the most likely one (**Scheme II-36**). He assumed that pathways in which equilibration occurs α to the lactam carbonyl can be used to explain the generation of epimeric products during the course of a cyclization.

Scheme II-36. 3-Aza-Cope Transition State for Asymmetric Induction in the Aza-Annulation Reaction.



Agami and coworkers[28] suggested frontier orbitals participation (AM1 calculations), but as an explanation of a possible mechanism considered only Michael addition of the enamine moiety onto crotonyl chloride in accordance with Seebach's topological rule (synclinal approach), followed by the formation of the lactam group **(Scheme II-37)**.

Scheme II-37. Synclinal Approach in Aza-Annulation Reaction.

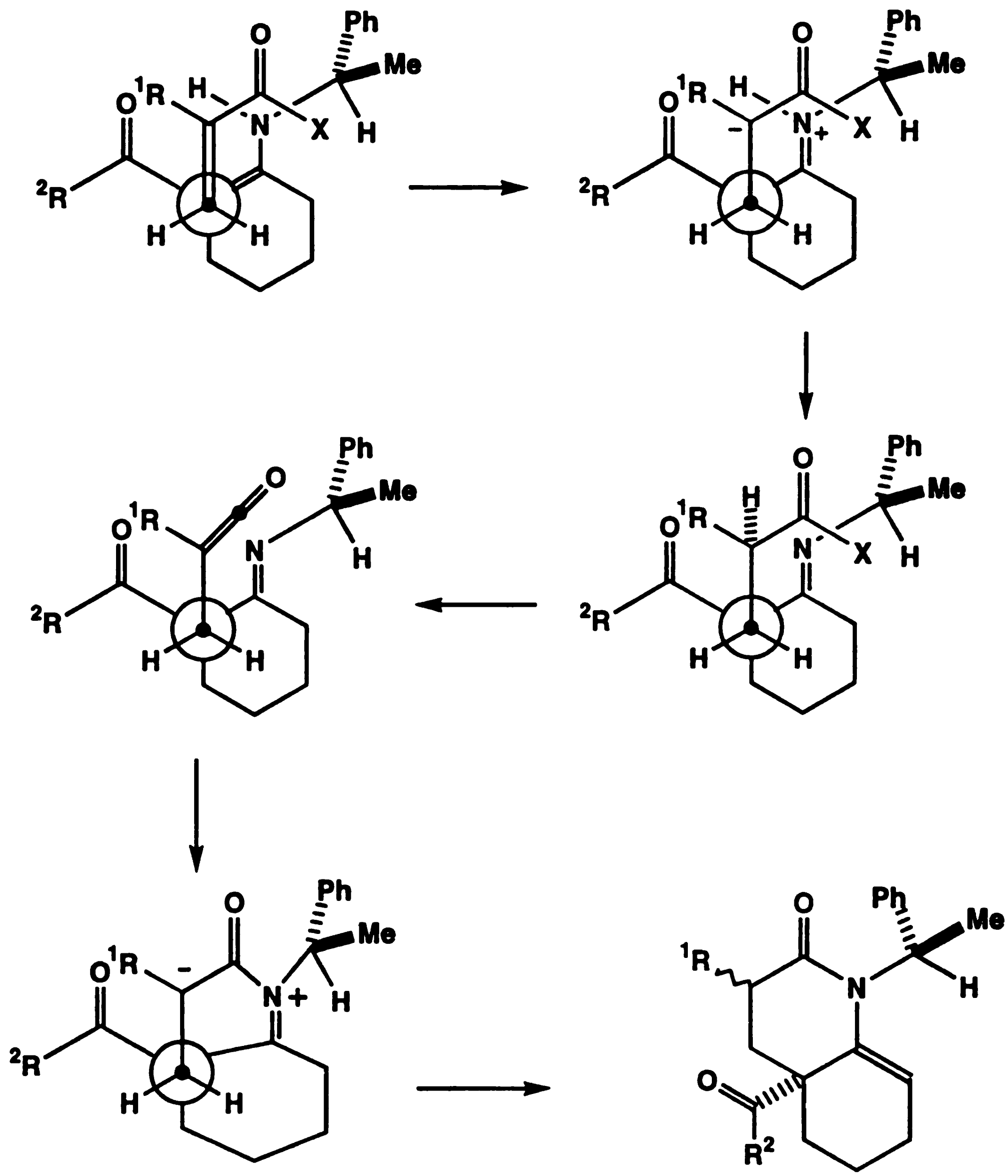


All the facts and experimental results cited above form a relative complex picture of a possible mechanism for the aza-annulation reactions. Although a detailed mechanism cannot be written, this information allows speculation about the most likely pathway. Different reaction conditions make a comparison even more difficult due to strong dependence of reaction pathway on temperature, type of a solvent and the presence of bulky groups.

The character of a chiral auxiliary, particularly the orientation of the most bulky group of this auxiliary, influences the interaction of two reagents favoring the less sterically hindered side. This defines the stereochemistry at the β center in the lactam functionality. Two reactants encounter each other in a chair-like compact cyclic transition state structure of the 3-aza-Cope type. There is a strong attractive interaction of the HOMO-LUMO frontier orbitals of the enamine and acrylate species.

After Michael addition step and a selective hydrogen transfer, the better leaving group X might leave the product, generating a ketene intermediate, which undergoes an acylation reaction with an imine. Then, the logical result is the epimerization at the α center of lactam moiety (**Scheme II-38**).

Scheme II-38. Suggested Mechanism of Aza-Annulation.



Conclusions. The stereoselective formation of six-membered nitrogen heterocycles having an asymmetric quaternary carbon center can be 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 derived from amino acids, can generate the corresponding optically active tetrasubstituted secondary enamine, in which the enamine tautomer is stabilized through conjugation with an amide carbonyl, and by the presence of a hydrogen bond between the enamine N-H bond and the amide functionality. Treatment of the intermediate enamine with either acryloyl chloride, acrylic anhydride, or sodium acrylate/ethyl chloroformate derivatives results in aza-annulation to give the corresponding δ-lactam with high diastereoselectivity. A variety of different β-enamino amide substrate classes were examined in this reaction. When the aza-annulation reaction was performed with an α-acetamido substituted acrylate derivative, the quaternary carbon center was formed stereoselectively, but poor selectivity was observed the stereogenic center α to the lactam carbonyl.

EXPERIMENTAL RESULTS.

General Methods. All reactions were carried out performing standard inert atmosphere techniques to exclude moisture and oxygen, and reactions were performed under an atmosphere of nitrogen or argon. Acryloyl chloride and 2-acetamidoacrylic acid were purchased from Fluka or Aldrich, respectively, and used without purification. Sodium acrylate was either freshly made before reaction by reaction of acrylic acid and NaH in dry THF at -78° C or purchased directly from Aldrich. Compound **II-53** was prepared by alkylation of benzylacetoacetamide with MeI in EtOH/EtONa.[33] Azeotropic removal of water was assisted by the use of 4-Å molecular sieves in the modified Dean-Stark adapter[29]. Concentration of solutions after work up was performed by rotary evaporator Buchi. Flash column chromatography was performed using SiO_2 of 230-400 mesh. Reactions were monitored by TLC using Whatman K6F Silica Gel 60Å 250 μm thickness plates. Acetyl chloride was distilled from PCl_5 in the presence of quinoline.

IR spectra were recorded using a Nicolet 42 FT-IR instrument, ^1H NMR spectra are reported as follows : chemical shift relative to residual $CHCl_3$ (7.24 ppm) or TMS (0.0 ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling, and integration. ^{13}C NMR data are reported as chemical shifts relative to $CDCl_3$ (77.00 ppm). High resolution mass spectra were carried out on a JEOL AX-505 double-focusing mass spectrometer (EI) or a JEOL HX-110 double-focusing mass spectrometer with helium as the collision gas (FAB). Optical rotation measurement was performed on the Perkin-Elmer 141 instrument.

Preparation of Benzyl 2-Oxocyclohexane Carboxylate II-20.

To a solution of ethyl 2-oxocyclohexyl carboxylate in toluene was added freshly distilled benzyl alcohol and the mixture was refluxed under nitrogen for 42 hours. The solution was concentrated under reduced pressure and the residue of the starting material was removed by the bulb-to-bulb distillation (oven 105° C/1 mm). The residual product was pure enough for using in the next step without further purification. Yield : 68%.

Hydrogenation of II-21.

To a solution of **II-21** (1.65 g, 1.27 mmol) in 40 mL of EtOH, 10% Pd/C (0.15 g) was added, the reaction vessel was flushed 3 times with H_2, and the reaction was placed under a balloon of H_2. The reaction mixture was stirred 4 hours at RT, filtered through a pad of Celite, and concentrated under reduced pressure to give **II-22** (0.38 g, 1.27 mmol, 100% yield).

II-22 : (0.37 g, 1.27 mmol, 100% yield); $[\alpha]_D^{24}$=-116.1 (c=1.73, THF); m.p.=133° C (decomp.); ^{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 (bs, 1 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.8, 18.3, 24.0, 30.2, 34.7, 45.9, 50.1, 55.0, 110.4, 125.4, 128.3, 129.4, 134.6, 142.5, 167.8, 175.6; IR (KBr) 3410, 2920, 1725, 1601, 1449, 1188, 749, 704 cm^{-1}; HRMS calcd for $C_{18}H_{21}NO_3$ *m/z* 299.1522, obsd *m/z* 299.1531.

Peptide Coupling with DPPA.

To the carboxylic acid **II-22** (0.4 g, 1.37 mmol, 1 equiv.) in dry THF (35 mL) was added DPPA (0.32 mL, 1.50 mmol, 1.12 equiv.) and freshly prepared ethyl glycine (0.16 g, 1.50 mmol, 1.12 equiv.) (from its hydrochloride with $Ba(OH)_2$ in $CHCl_3$ (dried over activated 4-Å molecular sieves) under Ar at 0° C. The mixture was stirred for 30 min, Et_3N (0.22 mL, 1.60 mmol, 1.20 equiv.) was added, and the solution was gradually warmed to room temperature. After the mixture was stirred for an additional 12 hours, the mixture was diluted with 30 mL of EtOAc, washed sequentially with 20 mL of 5% HCl, 2 x 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 (hexane:EtOAc gradient: 65:35 to 50:50 to 0:100) to give **II-27** (as a 91:9 mixture of both diastereomers) (0.05 g, 0.13 mmol, 10% yield) and **II-24** (0.28 g, 0.70 mmol, 53% yield).

II-24: (hexane:ethyl acetate=65:35-50:50-ethyl acetate gradient, 0.281 g, 0.70 mmol, 53% yield), m.p.=(85-86)° C; ^1H 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, 18.3 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 (dd, *J*=5.4, 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 ($CHCl_3$) 3372, 2986, 2938, 1746, 1636, 1617,

1559, 1397 cm^{-1}; HRMS (FAB) M+1 calcd for $C_{22}H_{29}N_3O_4$ *m/z* 400.2236, obsd *m/z* 400.2242.

II-27: (65:35/hexane:ethyl acetate, 0.05g, 0.13 mmol, 9.4% yield, 91:9 ratio of diastereomers); ^1H NMR (300 MHz, $CDCl_3$) (significant peaks) δ 1.22 (t, *J*=7.2 Hz, 3 H), 1.31-1.66 (m, 4 H), 1.72 (d, *J*=6.9 Hz, 3 H), 1.82-2.00 (m, 2 H), 2.03-2.17 (m, 2 H), 2.41 (m, 1 H), 2.56 (m, 1 H), 3.87(dd, *J*=4.8, 18.6 Hz, 1 H), 4.05 (dd, *J*=5.4, 18.3 Hz, 1 H), 4.15 (q, *J*=7.2 Hz, 2 H), 5.07 (dd, *J*=3.0, 4.8 Hz, 1 H), 5.30 (dd, minor), 5.95 (bt, minor), 6.30 (q, minor), 6.40-6.52 (m. 2 H), 7.11-7.29 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) (major isomer) δ 14.1, 14.5, 17.8, 24.3, 30.2, 30.4, 35.5, 41.7, 46.6, 49.4, 61.6, 113.2, 125.3, 126.4, 128.6, 133.3, 141.4, 169.4, 169.5, 173.6; IR ($CHCl_3$) 3357, 2940, 1748, 1665, 1636, 1512, 1449, 1397, 1198, 1030, 913, 731 cm^{-1}.

Preparation of β-Keto Amides.

Method A : The mixture of β-keto ester (1 equiv.) and an amine (2 equiv.) and DMAP (0.3 equiv.) in toluene was heated to reflux for 24 hours. Then the solution was concentrated under reduced pressure and the residue purified by a flash column chromatography (eluent as indicated).

Method B : The mixture of β-keto ester (1.0 equiv.) and an amine (1.5 equiv.) in xylene was brought to reflux and kept at this temperature for 24 hours. The solution was concentrated under reduced pressure and the crude product purified by flash column chromatography (eluent as indicated).

Method C : A solution of **II-37** (1.0 equiv.) and a corresponding amine (1.1 equiv.)was brought to reflux in xylene and kept at this temperature for 2 hours. The solvent was evaporated under reduced pressure and the crude product purified by flash column chromatography (eluent as indicated).

II-25 : (80:20/hexane:ethyl acetate, 2.5 g, 10.8 mmol, 96% yield); m.p.=(85-86)^{o} 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 (bs, 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 ($CHCl_3$) 3389, 3019, 2938, 1640, 1605, 1530 cm^{-1}; HRMS calcd for $C_{14}H_{17}NO_2$ *m/z* 231.1259, obsd *m/z* 231.1268.

II-39: (hexane:ethyl acetate/8:2, 0.16 g, 0.70 mmol, 54% yield based on a recovery of the starting material); ^{1}H NMR (300 MHz, $CDCl_3$) (mixture of tautomers) δ 1.22 (t, *J*=7.2 Hz, 3H), 1.24 (t, *J*=7.2 Hz, 3H), 1.58-1.82 (m, 6H), 1.85-2.10 (m, 3H), 2.10-2.23 (m, 4H), 2.24-2.49 (m, 3H), 3.21 (dd, *J*=5.7, 9.9 Hz, 1H), 3.21 (dd, *J*=5.7, 9.9 Hz, 1H), 3.90-4.07 (m, 4H), 4.15 (q, *J*=7.2 Hz, 2H), 4.17 (q, *J*=7.2 Hz, 2H), 6.01 (bs, 1H), 7.45 (bs, 1H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 21.7, 22.3, 23.9, 27.1, 29.1, 31.1, 40.9, 41.2, 41.9, 55.6, 61.2, 61.4, 96.7, 169.2, 169.5, 169.9, 170.6, 172.3, 209.7; IR ($CHCl_3$) 3378, 2942, 1750, 1717, 1640, 1538, 1377, 1202, 1026 cm^{-1}; HRMS calc. for $C_{11}H_{17}NO_4$ *m/z* 227.1158, obsd *m/z* 227.1160.

II-40: (hexane:ethyl acetate/8:2, 0.26 g, 1.02 mmol, 75% yield) ^{1}H NMR (300 MHz, $CDCl_3$) (mixture of tautomers) δ 0.84-0.92 (m, 12H), 1.57-1.80 (m, 6H), 1.82-2.02 (m, 3H), 2.02-2.22 (m, 6H), 2.22-2.48 (m, 3H), 3.18 (dd, *J*=5.4, 10.5 Hz, 1H), 3.66 (s, 3H), 3.69 (s, 3H), 4.44-4.54 (m, 2H), 5.82 (d, *J*=8.1 Hz, 1H), 7.34 (d, *J*=8.1 Hz, 1H), 7.50 (d, *J*=8.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) (mixture of tautomers) δ 17.5, 17.6, 18.6, 18.8, 21.6, 22.2, 22.2, 23.8, 24.0, 27.0, 27.1, 29.0, 30.7, 30.9, 31.1, 31.4, 41.9, 41.09, 51.8, 51.9, 55.4, 55.6, 56.3, 56.8, 56.9, 77.2, 96.6, 125.7, 128.6, 168.6, 168.9, 170.6, 171.9, 171.9, 172.1, 172.3, 209.5, 209.9; IR (neat) 3366, 2961, 2874, 1744, 1642, 1526, 1437, 1314, 1212, 1154, 756 cm^{-1}; HRMS calc. for $C_{13}H_{21}NO_4$ *m/z* 255.1471, obsd. *m/z* 255.1472.

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 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 activated 4-Å molecular sieves, and the mixture was heated at reflux until the reaction was complete as determined by NMR analysis (10-18 hours). 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 allowed to stir at room temperature for 12-18 hours. [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 hour in dry THF (0.05 M solution); Method B: acrylic acid anhydride: (freshly prepared from combination of sodium acrylate or the acetamido derivative (1.3 equiv.) and acryloyl chloride (1.3 equiv.) for 1 hour in dry THF (0.05 M solution); Method C: acryloyl chloride (1.3 equiv.) in dry THF (0.05 M solution). 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 4 times with 20 mL of either Et_2O or EtOAc. The combined organic fractions were dried (Na_2SO_4), filtered, and the solvent evaporated under reduced pressure. The crude product was purified by flash column chromatography (eluent as indicated).

II-21 : (8:2/hexane:ethyl acetate, 1.98 g, 5.08 mmol, 70% yield); $[\alpha]_D^{20}$=-93.5 (c=1.7, $CHCl_3$); ^1H 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 ($CHCl_3$) 3420, 3060, 3033, 2940, 2869, 1728, 1669, 1638, 1497, 1453, 1393, 1341, 1281, 1237, 1161 cm^{-1}; HRMS calcd for $C_{25}H_{27}NO_3$ *m/z* 389.1991, obsd *m/z* 389.2190.

II-29a : (65:35/hexane:ethyl acetate, 0.31 g, 0.80 mmol, 99% yield); m.p.=(126-127)° C; $[\alpha]_D^{25}$= -149.5(c=0.31,CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ (m, 2 H), 1.39 (d, *J*

=7.1 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 (bt, *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 ($CHCl_3$) 3420, 2944, 1665, 1634, 1512, 1451, 1393, 1302 cm^{-1}; HRMS calcd for $C_{25}H_{28}N_2O_2$ *m/z* 388.2151, obsd *m/z* 388.2147.

II-30b : (65:35/hexane:ethyl acetate, 0.36 g, 0.81 mmol, 95% yield); $[\alpha]_D^{23}$=+83.3 (c=1.59, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$) d 1.18 (t, *J*=7.1 Hz, 3 H), 1.30-1.48 (m, 2 H), 1.56-1.76 (m, 2 H), 2.01-2.10 (m, 2 H), 2.38-2.54 (m, 3 H), 2.60 (dd, *J*=5.0, 16.6 Hz, 1 H), 4.06-4.26 (m, 2 H), 4.41 (dd, *J*=5.8, 14.8 Hz, 1 H), 4.49 (dd, *J*=5.8, 14.8 Hz, 1 H), 5.04 (t, *J*=3.8 Hz, 1 H), 7.07 (s, 1 H), 7.17-7.35 (m, 10 H), 8.04 (t, *J*=5.8 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 18.1, 24.2, 29.9, 30.6, 34.9, 43.8, 46.9, 58.2, 62.2, 111.3, 127.0, 127.4, 127.4, 127.6, 128.0, 128.3, 134.0, 135.0, 138.5, 168.8, 169.9, 173.2, IR ($CHCl_3$) 3343, 2984, 2934, 1721, 1665, 1644, 1534, 1497, 1451, 1393, 1384, 1339, 1217, 1200, 1026, 752, 700 cm^{-1}; HRMS calcd for $C_{27}H_{30}N_2O_4$ *m/z* 446.2206, obsd *m/z* 446.2190.

II-31a : (65:35/hexane:ethyl acetate, 0.30 g, 0.75 mmol, 90% yield); $[\alpha]_D^{23}$=+121.4 (c=1.34, $CHCl_3$); m.p.=(128-129)° C; ^1H NMR (300 MHz, $CDCl_3$) δ 0.72 (d, *J*=7.1 Hz, 3 H), 1.10 (d, *J*=6.4 Hz, 3 H), 1.16-1.38 (m, 2 H), 1.42-1.68 (m, 2 H), 2.05-2.33 (m, 2 H), 2.36-2.52 (m, 2 H), 2.69 (m, 1 H), 3.49 (s, 3 H), 3.83 (d, *J*=9.3 Hz, 1 H), 4.19 (dd, *J*=5.2, 14.8 H, 1 H), 4.57 (dd, *J*=6.9, 14.8 Hz, 1 H), 5.22 (t, 3.8 Hz, 1 H), 7.10-7.25 (m, 5

H), 7.41 (bt, *J*=5.8 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.3, 18.6, 21.8, 24.8, 26.5, 29.5, 30.8, 35.0, 43.8, 47.1, 52.1, 63.6, 108.2, 127.0, 127.4, 128.3, 138.5, 138.5, 168.4, 170.9, 172.9; IR ($CHCl_3$) 3413, 2960, 2930, 1717, 1653, 1638, 1522, 1456, 1399 cm^{-1}; HRMS calcd for $C_{23}H_{30}N_2O_4$ *m/z* 398.2206, obsd *m/z* 398.2204.

II-32a: (65:35/hexane:ethyl acetate; 0.36g, 0.78 mmol, 46% yield; 95:5 ratio of diastereomers); m.p.=(144-145)° C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.04-1.46 (m, 3 H), 1.24 (t, *J*=7.0 Hz, 3 H), 1.55 (m, 1 H), 1.83 (m, 1 H), 2.06 (dt, *J*=17.9, 4.8 Hz, 1 H), 2.18-2.38 (m, 2 H), 2.39-2.58 (m, 2 H), 3.33 (dd, *J*=9.1, 14.0 Hz, 1 H), 3.52 (dd, *J*=5.5, 14.0 Hz, 1 H), 4.17 (q, *J*=7.0 Hz, 2 H), 4.21 (dd, *J*=5.2, 7.0 Hz, 1 H), 4.41 (bt, *J*=3.6 Hz, minor), 4.52 (dd, *J*=5.7, 9.0 Hz, 1 H), 4.61 (dd, *J*=7.0, 14.7 Hz, 1 H), 4.83 (t, *J*=3.6 Hz, 1 H), 5.11 (bt, *J*=5.4 Hz, minor), 7.12-7.31 (m, 10 H), 7.44 (bt, *J*=5.4 Hz, 1 H), 7.8 (bt, *J*=5.4 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 18.4, 24.8, 29.9, 30.9, 34.4, 35.0, 43.9, 47.0, 59.4, 61.7, 108.0, 108.6 (minor), 126.7, 127.0, 127.6, 128.3, 128.4, 129.4, 135.1 (minor), 137.4, 137.9, 138.7, 168.8, 170.4, 171.1 (minor), 173.0; IR ($CHCl_3$) 3359, 3021, 2944, 1740, 1642, 1514, 1455, 1399 cm^{-1}; HRMS calcd for $C_{28}H_{32}N_2O_4$ *m/z* 460.2362, obsd *m/z* 460.2360.

II-41: (hexane:ethyl acetate/65:35, 0.10 g, 0.26 mmol, 74% yield); (98:2 ratio of diastereomers); ^1H NMR (300 MHz, $CDCl_3$) δ 1.27 (t, *J*=7.2 Hz, 3H), 1.36-1.54 (m, 2H), 1.54-1.71 (m, 2H), 1.76 (d, *J*=6.9 Hz, 3H), 2.02 (m, 1H), 2.08-2.22 (m, 2H), 2.46 (m, 1H), 2.52-2.70 (m, 2H), 3.92 (dd, *J*=4.5, 18.3 Hz, 1H)), 4.10 (dd, *J*=5.4, 18.3 Hz, 1H)), 4.20 (q, *J*=7.2 Hz, 2H), 5.12 (dd, *J*=3.0, 5.1 Hz, 1H), 6.51 (q, *J*=6.9 Hz, 1H), 6.51 (bs, 1H), 7.16-7.34 (m, 5H), ^{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, 169.4, 169.4, 173.6; IR (neat) 3359, 2940, 1748, 1660, 1632, 1507, 1397, 1194, 1030, 752 cm^{-1}; HRMS calc for $C_{22}H_{28}N_2O_4$ *m/z* 384.2049, obsd *m/z* 384.2049.

II-42: (hexane:ethyl acetate/2:1, 0.10 g, 0.24 mmol, 50% yield); >98:2 ratio of diastereomers; ^1H NMR (300 MHz, $CDCl_3$) δ 0.81 (d, *J*=6.9 Hz, 3H), 0.85 (d, *J*=6.9 Hz, 3H), 1.27-1.68 (m, 4H), 1.73 (d, *J*=7.2 Hz, 3H), 1.86 (m, 1H), 2.00-2.20 (m, 3H), 2.33-2.54 (m, 2H), 2.64 (m, 1H), 3.67 (s, 3H), 4.51 (dd, *J*=5.1, 8.4 Hz, 1H), 5.04 (dd, *J*=3.3, 5.1 Hz, 1H), 6.53-6.64 (m, 2H), 7.10-7.30 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4, 17.7, 18.1, 18.9, 24.2, 30.0, 30.5, 31.2, 25.5, 47.0, 48.8, 52.1, 57.5, 113.2, 125.1, 126.4, 128.5, 132.8, 141.2, 169.3, 172.3, 173.5; IR ($CHCl_3$) 3407, 3007, 2963, 1740, 1669, 1636, 1497, 1449, 1393, 1341, 1300, 1273, 1154 cm^{-1}; HRMS calc for $C_{24}H_{32}N_2O_4$ *m/z* 412.2362, obsd *m/z* 412.2382.

II-45: (65:35/hexane:ethyl acetate, 0.045 g, 0.12 mmol, 50% yield); m.p.=(57-58)° C; $[\alpha]_D^{25}$=-38.2 (c=0.4, $CHCl_3$); ^1H 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 (bt, *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 ($CHCl_3$) 3400, 1669, 1628, 1509, 1266, 706, 670 cm^{-1}; HRMS calcd for $C_{24}H_{26}N_2O_2$ *m/z* 374.1994, obsd *m/z* 374.2000.

II-47: (65:35/hexane:ethyl acetate, 0.20 g, 0.47 mmol, 67% yield, 75:25 ratio of diastereomers); ^1H NMR (300 MHz, $CDCl_3$) characteristic peaks (both isomers) δ 1.16

(t, *J*=7.1 Hz, minor), 1.17 (t, *J*=7.1 Hz, 3 H), 1.60 (m, 1 H), 1.71 (m, 1 H), 2.05-2.31 (m, 3 H), 2.45 (m, 1 H), 2.53-2.67 (m, 2 H), 4.12 (q, *J*=7.1 Hz, 2 H), 4.28 (dd, *J*=5.8, 14.8 Hz, 1 H), 4.42 (dd, *J*=6.1, 14.8 Hz, 1 H), 4.75 (bt, *J*=2.6 Hz, 1 H), 4.99 (bt, *J*=2.2 Hz, minor), 6.08 (s, minor), 6.18 (bt, *J*=5.4 Hz, minor), 6.78 (s, 1 H), 7.05-7.30 (m, 10 H), 7.83 (bt, *J*=5.4 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) (both isomers) δ 14.0, 28.8 (minor), 29.0, 29.6, 30.4, 36.8, 37.2 (minor), 43.6 (minor), 43.7, 55.8 (minor), 56.4, 58.2, 60.3 (minor), 61.8 (minor), 62.2, 62.3 (minor), 109.6 (minor), 110.4, 127.0, 127.2 (minor), 127.4, 127.9 (minor), 127.9, 128.2 (minor), 128.4, 128.5 (minor), 133.8 (minor), 134.1, 138.2 (minor), 138.6, 139.4, 140.7 (minor), 169.1 (minor), 169.4, 169.5, 172.5 (minor), 173.1; IR (CH_2Cl_2) 3345, 2934, 1732, 1667, 1638, 1497, 1266, 739, 704 cm^{-1}; HRMS calcd for $C_{26}H_{28}N_2O_4$ *m/z* 432.2049, obsd *m/z* 432.2025.

II-54 : ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (s, 1 H), 1.42 (d, *J*=7.1 Hz, 3 H), 1.62 (m, 1 H), 2.15 (s, 3 H), 2.41 (ddd, *J*=2.2, 6.8, 13.1 Hz, 1 H), 2.57 (ddd, *J*=2.2, 6.2, 18.5 Hz, 1 H), 2.76 (ddd, *J*=6.7, 12.2, 18.5 Hz, 1 H), 4.29-4.36 (m, 3 H), 4.45 (d, *J*=1.9 Hz, 1 H), 6.21 (bt, *J*=5.3 Hz, 1 H), 6.27 (q, *J*=7.1 Hz, 1 H), 7.10-7.25 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 25.6, 29.5, 30.2, 43.8, 47.4, 50.2, 98.4, 125.4, 126.6, 127.6, 127.7, 128.5, 128.8, 137.8, 141.1, 145.0, 169.9, 172.5.

II-56 : ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (t, *J*=7.1 Hz, 3 H), 1.40 (s, minor), 1.50 (s, 3 H), 1.75 (ddd, *J*=7.5, 11.6, 12.7 Hz, 1 H), 2.48 (m, 1 H), 2.58-2.70 (m, 2 H), 4.18 (q, *J*=7.1 Hz, 2 H), 4.31 (dd, *J*=5.9, 14.9 Hz, 1 H), 4.45 (dd, *J*=5.9, 14.9 Hz, 1 H), 4.45 (d, *J*=3.0 Hz, 1 H), 4.62 (d, *J*=3.0 Hz, 1 H), 6.86 (s, 1 H), 7.20-7.40 (m, 10 H), 7.69 (bt, *J*=5.9 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 25.5, 30.2, 30.7, 43.8, 47.6, 59.3,

62.3, 97.7, 127.2, 127.5, 127.7, 127.9, 128.3, 128.5, 134.1, 138.5, 145.8, 169.5, 169.6, 173.0; IR($CHCl_3$) 3345, 3021, 1727, 1667, 1626, 1516, 669 cm^{-1}.

II-69a: (90:5:5/diethyl ether:methyl alcohol:petroleum ether, 0.15 g, 0.31 mmol, 34% yield); $[\alpha]_D^{24}$=-322.8 (c=0.36, $CHCl_3$); m.p.=(119-120)° C (sealed); ^1H 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 (bt, *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 ($CHCl_3$) 3400, 3021, 2963, 1665, 1509, 1262, 1098, 1015 cm^{-1}; HRMS calcd for $C_{27}H_{31}N_3O_3$ *m/z* 445.2366, obsd *m/z* 445.2376.

II-70a: (90:5:5/diethyl ether:methyl alcohol:petroleum ether, 0.15 g, 0.31 mmol, 34% yield); $[\alpha]_D^{25}$= -134.9 (c=0.75, $CHCl_3$); m.p.=(116-117)° C (sealed); ^1H 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 (ddd, *J*=6.6, 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

($CHCl_3$) 3420, 3330, 3021, 2963, 1669, 1640, 1511, 1261, 1096, 1019 cm^{-1}; HRMS calcd for $C_{27}H_{31}N_3O_3$ *m/z* 445.2366, obsd *m/z* 445.2327.

II-69b: diethyl ether:petroleum ether:methyl alcohol/90:5:5, 0.083 g, 0.144 mmol, 51% yield); ^1H NMR (300 MHz, $CDCl_3$) δ 1.21 (t, *J*=7.2 Hz, 3H), 1.56-1.68 (m, 2H), 1.70 (d, *J*=7.2 Hz, 3H), 1.81-1.98 (m, 2H), 1.94 (s, 3H), 2.02-2.22 (m, 3H), 2.38 (dd. *J*=5.4, 13.2 Hz, 1H), 3.68 (dd, *J*=4.5, 18.3 Hz, 1H), 3.98 (dd, *J*=6.0, 18.6 Hz, 1H), 4.12 (q, *J*=7.2 Hz, 2H), 4.31 (ddd, *J*=6.0, 6.0, 12.3 Hz, 1H), 5.49 (dd, *J*=3.8, 3.8 Hz, 1H), 5.59 (q, *J*=7.2 Hz, 1H), 6.33 (bt, *J*=5.0 Hz, 1H), 6.60 (d, *J*=6.0 Hz, 1H), 7.13-7.29 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 17.3, 17.8, 23.1, 23.9, 34.7, 36.3, 41.5, 47.6, 48.6, 55.5, 61.6, 120.8, 126.2, 127.1, 128.5, 135.5, 141.3, 169.6, 169.9, 170.3, 174.0; IR ($CHCl_3$) 3335, 3009, 2942, 1744, 1651, 1512, 1449, 1406, 1375, 1240, 1022 cm^{-1}; HRMS calc for $C_{24}H_{31}N_3O_5$ *m/z* 441.2264, obsd *m/z* 441.2278.

II-70b: (diethyl ether:petroleum ether:methyl alcohol/90:5:5, 0.045 g, 0.10 mmol, 28% yield); ^1H NMR (300 MHz, $CDCl_3$) δ 1.28 (t, *J*=7.2 Hz, 3H), 1.46-1.64 (m, 3H), 1.79 (d, *J*=7.2 Hz, 3H), 1.90-2.24 (m, 4H), 2.00 (s, 3H), 2.84 (dd, *J*=6.0, 12.6 Hz, 1H), 4.00 (dd, *J*=5.4, 18.6 Hz, 1H), 4.06 (m, 1H), 4.11 (dd, *J*=5.4, 18.3 Hz, 1H)), 4.21 (q, *J*=7.2 Hz, 2H), 5.19 (dd, *J*=3.0, 5.3 Hz, 1H), 6.32 (q, *J*=7.2 Hz, 1H), 6.39 (d, *J*=5.7 Hz, 1H), 6.58 (t, *J*=5.3 Hz, 1H), 7.17-7.38 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 14.8, 17.5, 23.2, 24.2, 35.5, 35.9, 41.8, 46.2, 50.2, 51.4, 61.6, 113.2, 125.5, 126.5, 128.6, 133.2, 141.0, 168.4, 169.5, 170.3, 173.3; IR ($CHCl_3$) 3328, 3007, 2942, 1744, 1640, 1518, 1449, 1377, 1267, 1032 cm^{-1}; HRMS calc for $C_{24}H_{31}N_3O_5$ *m/z* 441.2264, obsd *m/z* 441.2253.

II-69c/II-70c (diethyl ether:petroleum ether:methyl alcohol/90:5:5, 0.035 g, 0.075 mmol, 15.2% yield), (50:50 ratio of diastereomers); ^{1}H NMR (300 MHz, $CDCl_3$) (both diastereomers) δ 0.79 (d, *J*=4.2 Hz, 3H), 0.82 (d, *J*=4.2 Hz, 3H), 0.84 (d, *J*=6.9 Hz, 3H), 0.87 (d, *J*=6.9 Hz, 3H), 1.36-1.66 (m, 8H), 1.72 (d, *J*=7.2 Hz, 3H), 1.74 (d, *J*=7.2 Hz, 3H), 1.78-2.29 (m, 8H), 1.95 (s, 6H), 2.48 (dd, *J*=5.4, 12.9 Hz, 1H), 2.75 (dd, *J*=5.6, 12.5 Hz, 1H), 3.68 (s, 6H), 3.96 (ddd, *J*=6.0, 6.0, 12.6 Hz, 1H), 4.29 (ddd, *J*=5.7, 5.7, 12.3 Hz, 1H), 4.43 (dd, *J*=4.8, 8.1 Hz, 1H), 4.50 (dd, *J*=5.1, 8.4 Hz, 1H), 5.11 (dd, *J*=3.0, 5.1 Hz, 1H), 5.45 (dd, *J*=3.8 3.8 Hz, 1H), 5.65 (q, *J*=7.2 Hz, 1H), 6.24 (bd, *J*=7.8 Hz, 2H), 6.39 (q, *J*=7.2 Hz, 1H), 6.56 (d, *J*=6.0, 1H), 6.59 (d, *J*=8.7 Hz, 1H), 7.12-7.30 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) (both diastereomers) δ 14.1, 14.8, 17.1, 17.4, 17.7, 18.2, 18.7, 19.0, 23.2, 23.8, 24.2, 29.6, 31.2, 31.3, 35.2, 35.6, 35.7, 36.3, 46.4, 47.8, 48.7, 50.2, 50.7, 52.2, 54.7, 57.5, 57.7, 113.6, 120.7, 125.4, 126.1, 126.5, 126.9, 128.5, 128.6, 132.6, 134.9, 140.9, 141.4, 168.5, 170.0., 170.2, 170.4, 172.3, 172.4, 173.2, 174.2; IR ($CHCl_3$) 3337, 3011, 2959, 2938, 1738, 1661, 1499, 1373, 1267 cm^{-1}; HRMS calc for $C_{26}H_{35}N_3O_5$ *m/z* 469.2577, obsd *m/z* 469.2566.

General Procedure for Hydrolysis of Aza-Annulation Enamides.

After aza-annulation, the crude enamide product **II-54** or **II-56** was mixed with 5.0 mL of H_2O (280 equiv.) in THF and *p*-TsOH (0.03 g) was added. The mixture was stirred at room temperature for 24 hours, washed with an excess of saturated aqueous $NaHCO_3$, extracted with 15 mL of Et_2O 3 times, and the combined organic layers were dried over Na_2SO_4. Products were crystallized from EtOAc/hexanes=1:1.

II-55 : (0.30 g, 0.80 mmol, 82% yield (crystallization from ethyl acetate:hexane=1:1)); $[\alpha]_D^{20}$=+58.81 (c=0.7, $CHCl_3$); m.p.=(159-160)° C; ^1H 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 (d, *J*=7.5 Hz, 1 H), 6.69 (bt, *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, 128.6, 128.6, 138.0, 143.0, 171.2, 208.8; IR ($CHCl_3$) 3295, 3029, 1717, 1628, 1541, 1456, 1356 cm^{-1}; HRMS calcd for $C_{23}H_{28}N_2O_3$ m/z 380.2100, obsd m/z 380.2107.

II-57: (0.30 g, 0.68 mmol, 71% yield); ^1H 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 (bd, *J*=7.1 Hz, 1 H), 6.52 (bt, *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 ($CHCl_3$) 3324, 3289, 3021, 1746, 1709, 1646, 1532, 1181, 1026, 700, 669 cm^{-1}; HRMS calcd for $C_{25}H_{30}N_2O_5$ *m/z* 438.2155, obsd *m/z* 438.2157.

II-63: (50:50/diethyl ether:petroleum ether, 0.44 g, 0.92 mmol, 60% yield); $[\alpha]_D^{26}$=+27.0 (c=3.6, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.09 (t, *J*=6.8 Hz, 3 H), 1.33 (d, *J*=6.9 Hz, 3 H), 1.83-2.26 (m, 2 H), 2.11 (s, 3 H), 2.45-2.68 (m, 2 H), 4.01-4.17 (m, 2 H), 4.88-5.03 (m, 3 H), 5.92 (bd, *J*=7.6 Hz, 1 H), 6.37 (bs, 1 H), 7.11-7.28 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7, 21.5, 24.4, 27.7, 30.4, 48.7, 62.6, 66.8, 71.3, 126.0, 127.1, 127.9, 128.1, 128.3, 128.5, 135.9, 142.9, 154.4, 168.1, 170.2, 199.6; IR

(neat) 3391, 3305, 3033, 2980, 2934, 1709, 1644, 1489, 1455, 1370, 1250, 1055, 756, 698 cm^{-1}; HRMS calcd for $C_{25}H_{30}N_2O_6$ *m/z* 454.2104, obsd *m/z* 454.2131.

II-68: (gradient diethyl ether:petroleum ether/2:1-diethyl ether-ethyl acetate, 0.22 g, 0.427 mmol, 75% yield, >98:2 ratio of diastereomers); m.p. = (49-50)° C; $[\alpha]_D^{23}$ = 29.1 (c=0.35, EtOH); ^1H NMR (300 MHz, $CDCl_3$) δ 1.42 (d, *J*=6.9 Hz, 3H), 1.84-2.14 (m, 2H), 2.17 (s, 3H), 2.47-2.66 (m, 2H), 4.20-4.40 (m, 2H), 4.96-5.16 (m, 3H), 5.79 (d, *J*=7.5 Hz, 1H), 6.93 (bs, 1H), 7.05 (bt, *J*=5.4 Hz, 1H), 7.13-7.40 (m, 15H); ^{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 ($CHCl_3$) 3332, 3033, 2930, 1715, 1669, 1534, 1497, 1455, 1242, 1067, 754 cm^{-1}; HRMS calcd for $C_{30}H_{33}N_3O_5$ *m/z* 515.2420, obsd *m/z* 515.2402.

Preparation of 2,2-Dimethyl-1,3-Dioxin-4-One Derivatives.[30]

Concentrated sulfuric acid (0.01 mmol) was added dropwise to a mixture of β-keto acid (0.05 mmol), acetone (0.1 mmol), and acetic anhydride (0.1 mmol) with stirring at 0° C. The mixture was stirred under ice-cooling for 3 hours and then was kept in a refrigerator for 12 hours. Then it was poured into 10% sodium carbonate solution (120 mL) under ice-cooling. The mixture was stirred at room temperature for 30 minutes to give the corresponding product.

Preparation of 2,4,6-Trichlorophenyl Ester of Carbobenzoxy D,L-Threonine II-64.[31]

To a solution of the carbobenzoxy-D,L-threonine (3.0 g, 11.85 mmol, 1.0 equiv.) in ethyl acetate (35 mL) was added 2,4,6-trichlorophenol (2,81 g, 14.21 mmol, 1.2 equiv.). N,N'-Dicyclohexylcarbodiimide (2.44 g, 11.85 mmol, 1.0 equiv.) was added to the solution at 0° C. After 0.5 hour the mixture was allowed to warm up to room temperature and was kept at ambient temperature for 1 hour. The N,N'-dicyclohexylurea was filtered off and washed with ethyl acetate. The combined filtrate and washings were evaporated to dryness under reduced pressure and the solid residue was recrystallized from ethyl acetate and petroleum ether. Yield : 3.0 g (60%).

Preparation of Carbobenzoxy D,L-Threonine Benzylamide II-65.[32]

2,4,6-Trichlorophenyl ester of carbobenzoxy D,L-threonine (1.50 g, 3.47 mmol, 1.0 equiv.) in a mixture of THF (7.5 mL) and dioxane (4.0 mL) was added to a solution of benzylamine (0.67 g, 6.24 mmol, 1.8 equiv.) and triethylamine (0.87 mL) in H_2O (7.5 mL) and the solution was stirred at room temperature for 28 hours. The solvent was evaporated under reduced pressure and the residue was dissolved in H_2O (40 mL), which was acidified with 5 M HCl (litmus). The crude product was extracted with ethyl acetate, organic layers washed with H_2O and brine, and dried over Na_2SO_4, then concentrated and crystallized from EtOAc and petroleum ether (low boiling) . Yield : 0.95 g (80%).

General Oxidation with PCC.

To the stirred suspension of PCC (1.8 equiv.) and Celite (1:1/w:w) in CH_2Cl_2 was added β-hydroxy ester or β-hydroxy amide in CH_2Cl_2 dropwise at 0° C and the mixture was stirred at 0° C for 3 hours. Then it was gradually warmed up and stirred for 10-15 additional hours. Filtered through a pad of neutral alumina:SiO_2:Celite=4:4:1 and the filtrate concentrated. The crude product is pure enough to use without further purification.

Synthesis of *t*-Butyl Ester of 3-Methyl-4-oxoimidazolidin-1-carboxylic Acid.[14a]

A) Glycine ethyl ester hydrochloride (7.0 g, 50 mmol) was added to a solution of methylamine in methyl alcohol (75 mL of 2.0M solution, 3.0 equiv.) at 0° C (ice-bath) with stirring. Then reaction mixture was stirred at room temperature for 18 hours, the suspension was concentrated under reduced pressure and a slurry was dissolved in CH_2Cl_2 (15 mL) and concentrated under reduced pressure three times (overall with 45 mL of CH_2Cl_2). The crude product was immediatelly used for the next step without isolation or purification.

B) The crude product from part A, pivaloyl aldehyde (6.46 g, 8.15 mL, 75 mmol, 1.5 equiv.) and triethylamine (10.45 mL, 1.5 equiv.) in dry CH2Cl2 (50 mL) was refluxed with a modified Dean-Stark trap (4Å activated molecular sieves) for 15 hours. After cooling the mixture was filtered through a coarse sintered glass filter and the solid was washed with 25 mL of diethyl ether. The combined filtrates were concentrated under reduced pressure and dissolved in 15 mL of methyl alcohol. 30

mL of 2.0 M solution of HCl in diethyl ether was added to the solution at 0° C, the mixture stirred for 30 minutes at 0° C and then 6 hours at room temperature. Then solution was concentrated under reduced pressure, the residue dissolved in 40 mL of CH_2Cl_2 and washed with 40 mL of 3M NaOH. Organic layers were evaporated to give the crude product, which crystallized upon cooling. Yield : 3.75 g (48%).

C) The mixture of di-*t*-butyl-dicarbonate (0.89 g, 4.1 mmol), DMAP (0.04 g, 0.31 mmol) in 30 mL of acetone was added to the crude product (0.5 g, 3.2 mmol) from part B by a cannula at 0° C. After stirring at ambient temperature for 8 hours, 0.5 mL (3.1 mmol) of triethylamine was added, the mixture stirred for 1 hour, 5.0 mL of H_2O added and the solution stirred for 1 additional hour. Then it was concentrated at reduced pressure and the residue extracted with diethyl ether. Combined organic layers were washed with 15 mL of 1M HCl and with 15 mL of saturated $NaHCO_3$, and dried over $MgSO_4$. The solution was filtered and concentrated under reduced pressure to give yellowish oil. Yield :0.66 g (80%).

Preparation of *t*-Butyl Ester of 5-Acetyl-3-Methyl-4-Oxoimidazolidin-1-Carboxylic Acid.[14c]

Hexane solution of *n*-butyllithium (0.30 mL of 2.5 M solution in hexane, 2.15 mmol, 1.1 equiv.) was added dropwise to freshly distilled diisopropylamine (0.86 mL, 1.1 equiv.) in the flame dried flask at 0° C. The mixture was stirred for 30 minutes, cooled to -78° C and **II-49** (0.5 g, 1.95 mmol) in dry THF (20 mL) was added dropwise by a cannula. The mixture was stirred for 30 minutes at -78° C and then freshly distilled acetyl chloride was added dropwise at -78° C and the mixture was stirred for 1 hour. Then it was slowly

quenched at -78° C with 7.0 mL of phosphate buffer (pH=7.0; 50 mL of 0.1 M NaH_2PO_4:H_2O, 29.1 mL of 0.1 M solution of NaOH), 15 mL of the mixture H_2O/Et_2O=1:1 was added, water layer was extracted 3 times with 30 mL of diethyl ether, combined organic layers washed with 30 mL of brine and dried over $MgSO_4$. The crude product crystallized from hexane. Yield : 0.55 g (95%).

Preparation of β-Keto Amides from 2,2-Dimethyl-1,3-Dioxin-4-One Derivatives and α-Amino Acids. [13c]

A solution of 2,2-dimethyl-1,3-dioxin-4-one derivative (10 mmol) and an α-amino acid (10 mmol) in xylene (20 mL) was heated to reflux for 1-2 hours. The solvent was evaporated *in vacuo* and the residue was either crystallized or purified as indicated.

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CHAPTER III

FORMATION OF DIHYDROPYRIDONE- AND PYRIDONE-BASED PEPTIDE ANALOGS THROUGH AZA-ANNULATION OF β-ENAMINO AMIDE SUBSTRATES WITH α-AMIDO ACRYLATE DERIVATIVES

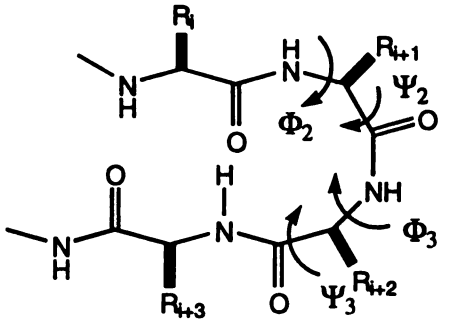
Introduction.

Biological processes are extremally important and scientists have made an effort to understand these systems in details. Recently, the secondary structure of biologically active peptides, i.e. the conformation of succesive adjacent amino acid residues in peptide chains, was shown to be crucial to the efficiency and selectivity of recognition processes. The secondary structure of peptides, one of the most important groups of biological active compounds, can be determined and potentially modified by an interaction of different parts of a molecule, by steric repulsions, hydrogen bonding, and electrostatic attractions, just to name a few. The most common secondary peptide and protein structure types are α-helix, β-sheet and reverse turn conformations, which include such varieties as the β- and γ-turns (**Figure III-1**).

A mimic of a β-turn should meet the following criteria.[1] It should :

- Reproduce the spatial area of a β-turn;
- Contain the side chains of the amino acid residues *i+1* and *i+2* in the correct stereochemistry;
- Minimize steric interactions beyond the peptide backbone;
- Contain the N- and C-terminal ends.

Figure III-1. Typical β-Turn Arrangement.



Thirteen types of β-turns that vary in their dihedral angles Φ_2, Ψ_2, Φ_3 and Ψ_3 [1] can be distinguished (**Table III-1**).

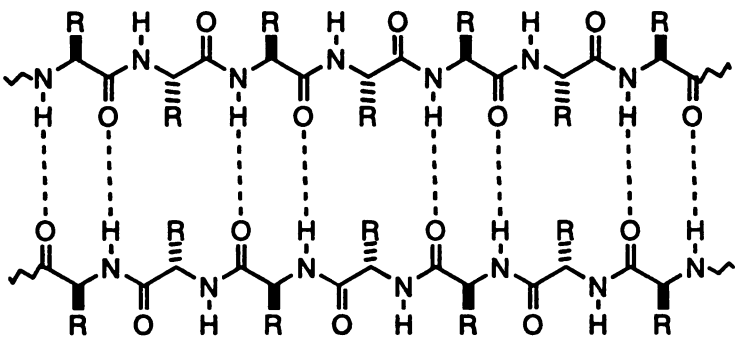
Table III-1. Different β-Turn Types.

Helix and sheet structures	Φ	Ψ		
α-Helix	-57	-47		
Parallel chain	-119	+113		
Antiparallel chain	-139	+135		
Reverse (β) turns	Φ_{i+1}	Ψ_{i+1}	Φ_{i+2}	Ψ_{i+2}
Type I	-60	-30	-90	0
Type I'	+60	+30	+90	0
Type II	-60	+120	+80	0
Type II'	+60	-120	-80	0
γ-Turn	Ψ_i	Φ_{i+1}	Ψ_{i+1}	Ψ_{i+2}
	+120	-65	+80	-120

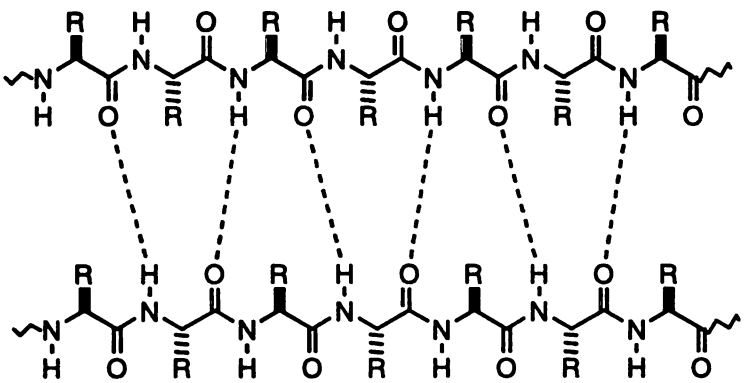
Potential drug candidates often do not meet demanding requirements due to unfavorable solubility, biodegradation, bioavalibility and bioselectivity properties.

Conformationally restricted amino acids and oligopeptides, as well as peptide mimetics, can be employed to address these disadvantages and to improve the biological activity.

Figure III-2. β-Sheet Arrangements.



anti-parallel β-sheet



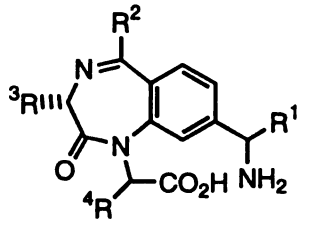
parallel β-sheet

β-Sheets are a dominant structural motif characterizing the V_H and V_L domains in antibodies (**Figure III-2**).[2] β- And γ-turns are often involved in diverse biochemical recognition mechanisms. In many cases, recognition is the first step in a cascade of events leading to the biological effect. Turns are important in the recognition necessary for post-translation modification of proteins by phosphorylation and glycosylation. Interestingly, it has been noted that β-turns play an important role even in the construction of spider webs.[3]

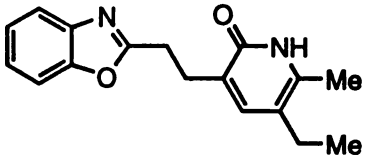
Because of the flexibility of peptide molecules, the desired biologically active conformations are hidden in a population of many other conformers. To attain the best conformation leading to an optimal biological effect, it would be desirable to rule out unfavorable conformations by fixing the molecule structure, and decreasing the flexibility of the backbone.

To illustrate these features, several examples of the structures known as enzyme inhibitors have been chosen. Ripka described benzodiazepine derivatives **III-1** able to mimic cyclic peptides having a β-turn.[4] Houpis and coworkers constructed a similar 2-pyridone skeleton **III-2**, which showed activity against HIV-reverse transcriptase.[5]

Figure III-3. β-Turn Mimics.



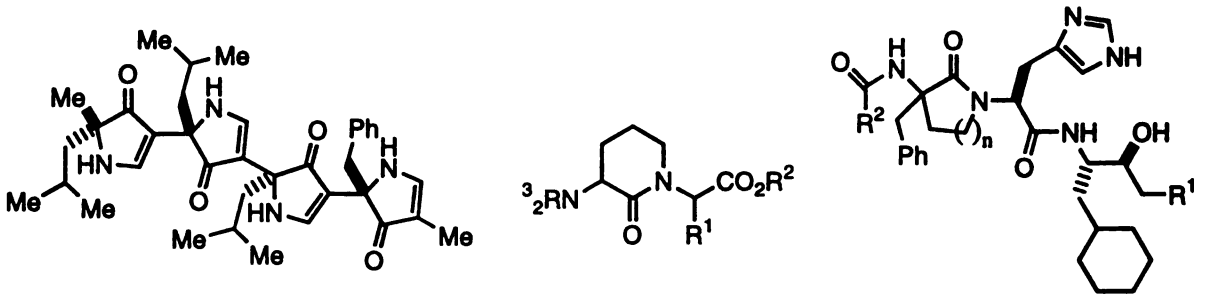
III-1



III-2

Smith introduced the idea that hydrogen bonding involving the amide backbone plays a critical role in the binding of peptide inhibitors to proteolytic enzymes. With help of interactive computer modeling, he suggested that the series of 3,5-linked pyrroline-4-ones would adopt a backbone conformation mimicking a β-strand **III-3**.[6] Structure **III-3** mimics a Leu-Leu-Val-Phe fragment in a peptide backbone. Freidinger proposed that lactam-constrained dipeptide analogs **III-4** could behave as enzyme inhibitors.[7] Zydowsky constructed chymotrypsin inhibitors, designed as dipeptide isosters for the Phe-His portion **III-5**.[8]

Figure III-4. β-Turn Mimics.

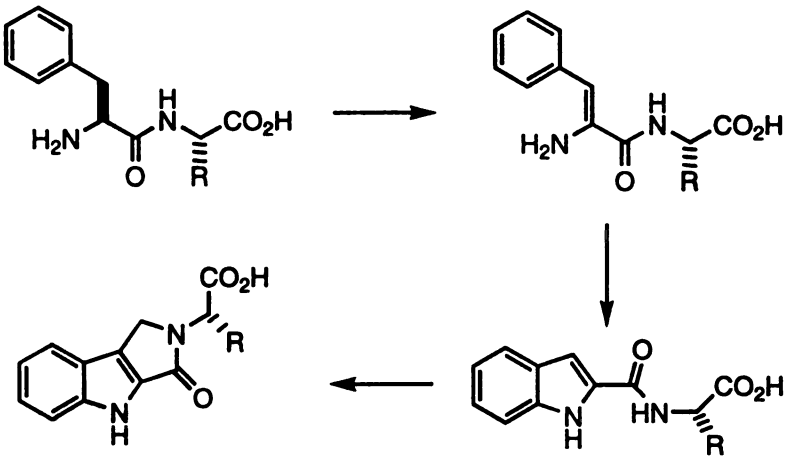


III-3 **III-4** **III-5**

Kempf and Condon, from the Abbott Laboratories, prepared human renin inhibitors having the rigid α-amino lactam feature **III-6**.[9] Genin developed spirolactams **III-7** and **III-8** as β-turn mimics (**Figure III-5**).[10] The cyclopentapeptide *cyclo*(Arg-Gly-Asp-*D*-Phe-Val) **III-9** was tested as a selective endothelial cell integrin $\alpha_v\beta_3$ antagonist (**Figure III-6**).[11]

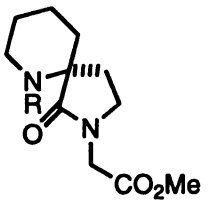
These examples of active structures were carefully chosen to show a common structural feature - amine functionality at the α-position to a lactam group. This skeletal feature may also be prepared through aza-annulation methodology.

Scheme III-1. Construction of Human Renin Inhibitors.

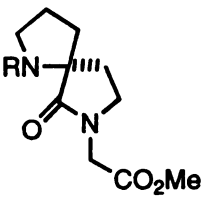


III-6

Figure III-5. β-Turn Mimics.

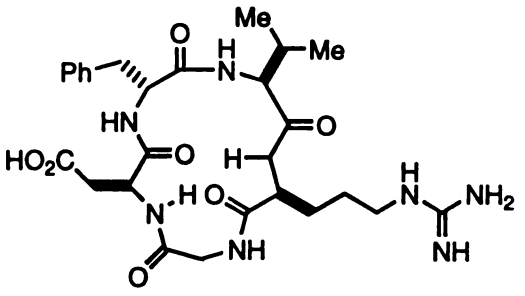


III-7



III-8

Figure III-6. The Endothelial Cell Integrin $\alpha_v\beta_3$ Antagonist.



III-9

Initially, this work focused on the preparation of potential angiotensin converting enzyme (ACE) inhibitors through the aza-annulation reaction. ACE facilitates the removal of dipeptide or in some cases tripeptide fragments from the C-terminus of the angiotensin I molecule. The enzyme is a glycoprotein, with a molecular weight between 130 and 160 kDa. The whole cascade degradation of angiotensinogen into angiotensin II is illustrated in **Scheme III-2.**[12]

The enzyme has low requirements for substrate specificity :

- A free carboxylic acid group at the C-terminus
- Absence of a proline unit in the penultimate position of the peptide chain.

ACE appears to have a high affinity for peptide substrates having an aromatic amino acid in the antepenultimate position. Although the mechanism of its action is still not fully understood, efforts to prepare inhibitors of ACE have culminated in the development of captopril **III-10** and enalapril **III-11** (**Figure II-7**).

Scheme III-2. Angiotensinogen Degradation.

Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu-Leu-Val-Tyr-Ser — Angiotensinogen

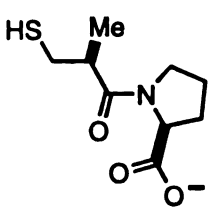
↓ Renin

Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu — Angiotensin I

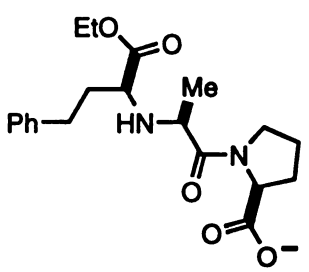
↓ ACE

Asp-Arg-Val-Tyr-Ile-His-Pro-Phe — Angiotensin II

Figure III-7. Captopril (III-10) and Enalapril (III-11).



III-10

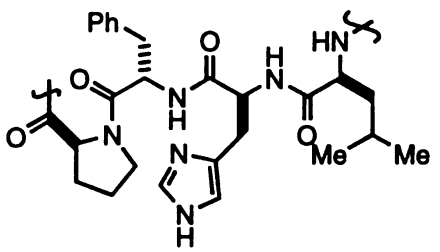


III-11

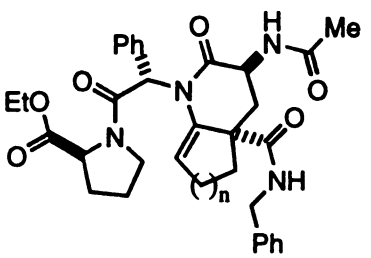
In order to mimic the cleavage site of the natural substrate, it was suggested that bicyclic system **III-12** could successfully play the role of a phenylalanine-histidine

fragment mimic, thus providing an inhibitor of angiotensin I - angiotensin II conversion (**Figure III-8**).

Figure III-8. Potential Inhibitor of Angiotensin I - Angiotensin II Conversion.



-Pro-Phe-His-Leu

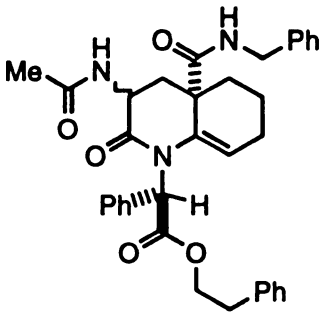


n = 0, 1

III-12

RESULTS AND DISCUSSION

The initial formation of the aza-annulation benzyl ester amide product **III-16** proceeded smoothly in 69% yield. Hydrogenolysis of **III-16** on Pd under atmospheric pressure of hydrogen gave a near quantitative yield of the corresponding acid **III-17**, but many attempts to extend the side chain by peptide coupling gave the product **III-18** in very low yield (**Scheme III-3**). For the construction of even more complex systems with an amino substituent at carbon α of lactam system **III-19**, problems with inseparable mixtures of diastereomeric products added to the above-mentioned complications.

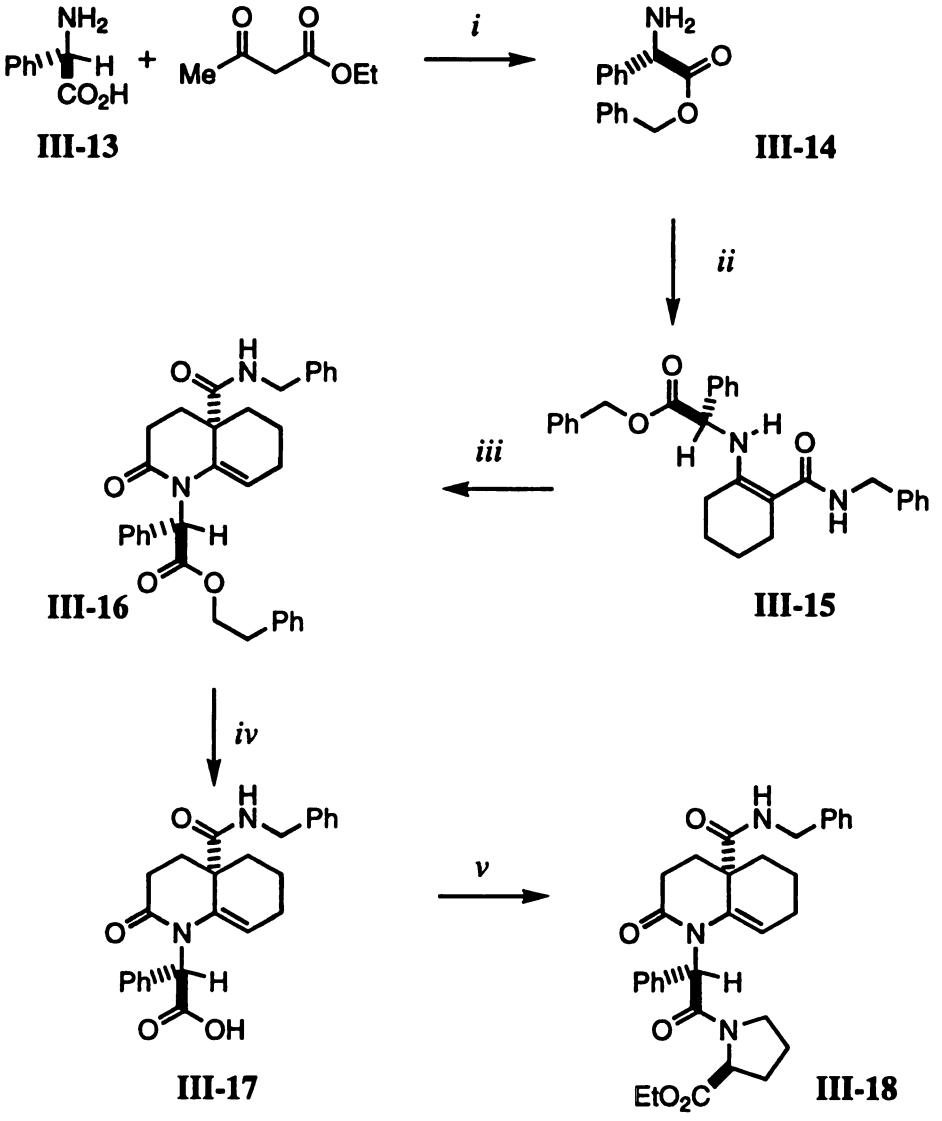


III-19

After a series of unsuccessful reactions with disappointing yields and poor stereoselectivity, it was decided to change direction in the research. The new approach to the construction of peptide mimetics has involved the preparation of α- and/or β-amino acid-substituted δ-lactams that restrict the conformation of the Ψ dihedral angle. Typical approaches, and examples of products of this type, have been mentioned in the introduction part of this chapter.

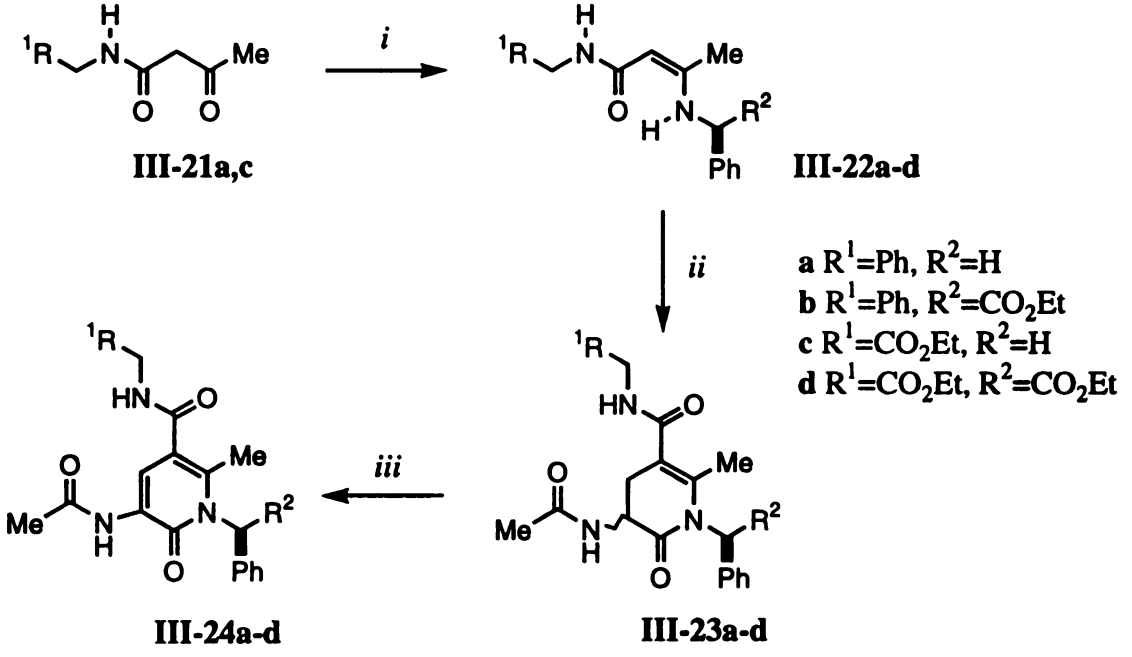
A synthetic strategy using suitably substituted amides instead of β-enamino esters introduces another amino acid unit into a peptide mimetic, thus building the complex synthetic target in several steps.

Scheme III-3. Attempts to Prepare a Tripeptide Analog Fragment.



Reaction Conditions. *i*) KOH, benzyl chloride, MeOH, DMF, 69%; *ii*) 2-oxo-cyclohexane carboxylate benzylamide, toluene, reflux; *iii*) sodium acrylate, $ClCO_2Et$, THF, 69%; *iv*) Pd/C, 1 atm of H_2, EtOH, 99%; *v*) L-ethyl proline, DCC, CH_2Cl_2, 1%.

Scheme III-4. Formation of Peptide Analogs through Aza-Annulation and Pyridone Formation from β-Keto Amides.



Reaction Conditions. *i*) $PhCH(R_2)NH_2$, BF_3:OEt_2, benzene, reflux; *ii*) sodium 2-acetamidoacrylate, $ClCO_2Et$, THF; *iii*) DDQ, toluene, reflux

The aza-annulation reaction of the mixed anhydride, made from α-acetamidoacrylic acid and ethyl chloroformate in THF *in situ*, with intermediate β-enamino amide **III-22a**, generated from β-keto amide **III-21a**, resulted in efficient formation of the dihydropyridone product **III-23** (Scheme **III-4**). Even more complex systems were accessed through condensation of **III-21** with ethyl (*R*)-phenylglycine (Scheme **III-4, Table III-2**). Aza-annulation of the intermediate β-enamino amide

Table III-2. Formation of Peptide Analogs through Aza-Annulation and Pyridone Formation from β-Keto Amides.

Product	R_1	R_2	Isolated yield **III-22** to **III-23**	Isolated yield **III-23** to **III-24**
a	Ph	H	90	76
b	Ph	CO_2Et	87[x]	55
c	CO_2Et	H	95	78
d	CO_2Et	CO_2Et	86[x]	60

[x]51:49 ratio of diastereomers.

III-22b with the corresponding mixed anhydride, resulted in the formation of **III-23b** as an equal mixture of diastereomers. This two-step procedure provides a rapid and efficient way of preparing complex heterocyclic products from simple components.

DDQ oxidation of **III-23b** generated the amide-substituted 2-pyridone derivative **III-24b** in 55% yield. Attempts to oxidize **III-23b** with MnO_2 in xylene at reflux resulted in even lower yield (50%).[13]

For preparation of the pyridone system **III-24c**, compound **III-21c**, readily obtained by the reaction of diketene with ethyl glycine, was used in a condensation with benzylamine, followed by aza-annulation, giving the tripeptide analog **III-23c** in 95% yield for the two-step process. Oxidation of **III-23c** proceeded in a fashion similar to that of **III-23b**, additional treatment with DDQ was necessary to achieve a yield of 78%. Condensation of the amide **III-21c** with (*R*)-phenyl glycine ethyl ester provided **III-22d**, which gave **III-23d** as an equal mixture of diastereomers (**Table III-2**) upon aza-annulation with the mixed anhydride. Oxidation of the product **III-23d** with DDQ in

refluxing toluene generated the pyridone derivative **III-24d** with amino acid functionality radiating from the 1,3, and 5 positions.

The substituted 2-pyridone products **III-24a** and **III-24b** represent an interesting class of conformationally restricted peptide-like molecules. Peptide functional groups, both amino and carboxylate functionalities, radiate from the 1,3, and 5 positions of the pyridone hub. The lactam functionality of the pyridone heterocycle mimics a peptide amide bond. Combination of the 1 and 5 substituents reflects the structural features of a linear dipeptide, while the 3 and 5 positions are similar to those found in conformationally restricted peptide chains. For compounds **III-24b** the relationship between the 1 and 5 positions is one in which both an α and β-amino acid radiate from a common nitrogen atom.

The drawback of the use of amide substrates is the substantially more sluggish DDQ oxidation than that of the related ester substrates[13b]. The dehydrogenation reaction of **III-23b** and **III-23d** with approximately one equivalent of DDQ was incomplete and required prolonged reaction times with additional DDQ to increase yields of the desired products. The use of a higher boiling solvent (xylene) in place of benzene or toluene, or the initial use of an increased amount of oxidation agent, did not improve yields of the products. Application of a recently published catalytic DDQ oxidation procedure failed to improve the yield.[14]

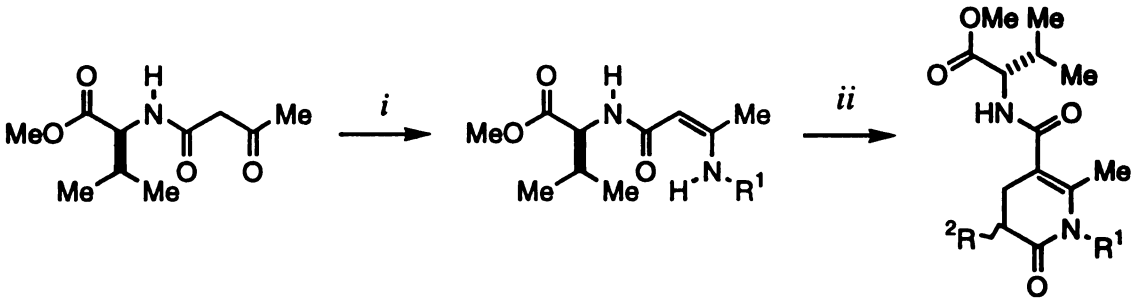
Structural Analysis of III-23c. α-Amido lactam **III-23c** was obtained as a crystalline solid, which permitted a the single crystal X-ray analysis of this molecule. **Appendix 2** shows the ORTEP representation of this molecule. In addition to structure confirmation, the orientation and interactions of the peptide-like chains at the 3 and 5 positions of the 2-pyridone derivative 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 substituent at the 3 and 5 positions of the lactam heterocycle. As a result of these interactions, a "ladder" type structural arrangement was observed.

In order to test compatibility of the aza-annulation reaction conditions with the stereochemical integrity of the amino acid components, lactam and pyridone products that contain two separate sites of asymmetry were constructed. Condensation of **III-25** with either valine- or (*R*)-phenylglycine-derived esters was performed in toluene to give **III-27** and **III-30**, respectively (**Scheme III-6**). In each case, examination of the intermediate enamine **III-26** or **III-29** by ^{1}H NMR analysis revealed the presence of a single diastereomer. Aza-annulation with sodium acrylate and ethyl chloroformate under established standard reaction conditions led to the conversion of **III-27** to **III-28a** as a single diastereomer (>98:2 by NMR analysis of the crude reaction mixture).

Similarly, treatment with sodium 2-acetamidoacrylate and ethyl chloroformate led to an 89% yield of **III-27b**, which was a 50:50 mixture of diastereomers at C-3 of the lactam, but did not result in epimerization of the amino acid side chains.

Scheme III-5. Determination of Epimerization during the Aza-Annulation.



Reaction Conditions. *i*) H_2NR^1, toluene, reflux; *ii*) $CH_2=CH(R^2)CO_2Na$, $ClCO_2Et$, THF.

Conversion of **III-29** to **III-30** also proceeded to a single stereoisomer. Based on these observations, epimerization of the stereocenters in amino acid side chains did not occur under the aza-annulation conditions. A summary of results and reaction conditions is shown in **Scheme III-5** and **Table III-3**.

The yields and general efficiency of the oxidation of lactam compounds **III-27a-b** and **III-30** was dependent on the nature of the susbtituent at C-3 of the lactam ring. When R^2=H (**Scheme III-5**), treatment of **III-27a** or **III-30** with DDQ led to a mixture of side-products containing no significant quantity of the desired pyridone products. However, when R^2=2-acetamido substituent (**III-27b**), oxidation gave **III-28** as a single diastereomer. 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 only 40% yield, which represented a 59% yield based on recovered **III-27b**.

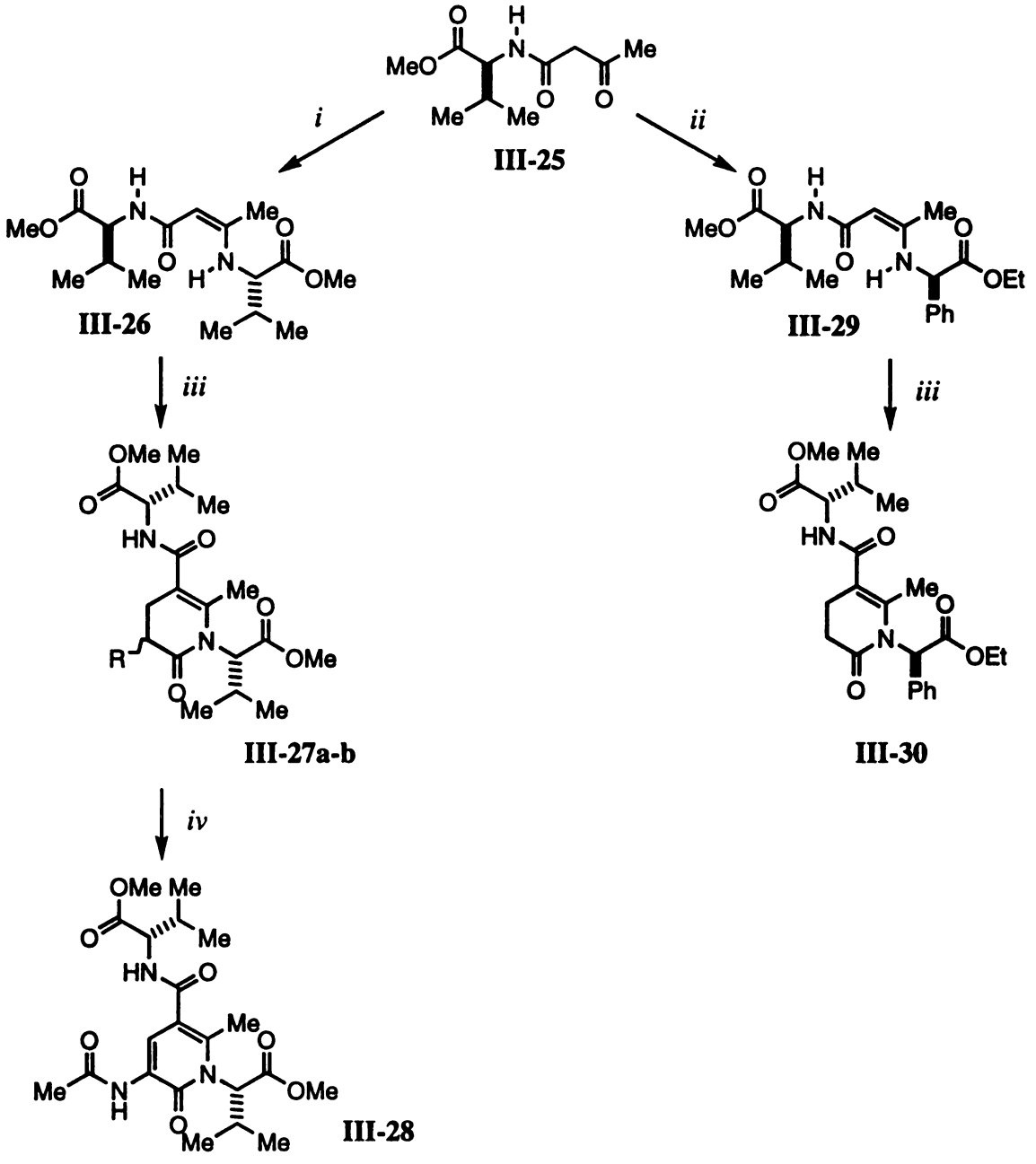
The generation of a single stereoisomer demonstrated that the stereochemical integrity of the amino acid groups was maintained even during the oxidation process.

Direct Formation of Pyridones. 2-Phenyl-4-(ethoxymethylene)oxazolone **III-33** was explored as an alternative reagent for the direct formation of pyridone products in the aza-annulation reaction (**Scheme III-7**). Reagent **III-33** was readily prepared from hippuric acid with ethyl orthoformate in acetic anhydride, as previously reported.[15]

Although aza-annulation of enamino esters and amides with this reagent had been reported to proceed in dioxane with triethylamine as a base at 85° C,[15] analogous reaction of enamino amide **III-32** with **III-33**, with or without triethylamine, resulted primarily in the formation of **III-34**. Cyclization of **III-34** to **III-35** was effected eventually by heating a solution of **III-34** in refluxing DMF. This aza-annulation process was accomplished in a one-pot procedure by treatment of **III-32** with **III-33** in DMF followed by reflux of the reaction mixture. The low isolated yields obtained for **III-35**, especially when compared to yields obtained for other similar reaction of **III-33** (**Scheme III-8**), were a consequence of the generation of reaction byproducts and their difficult separation.

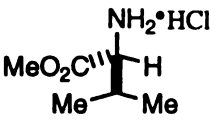
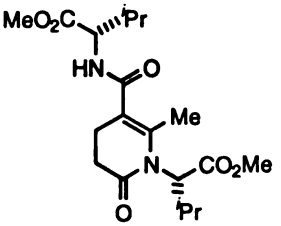
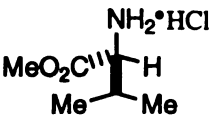
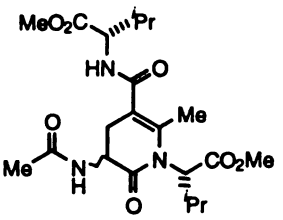
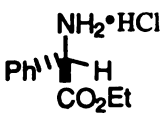
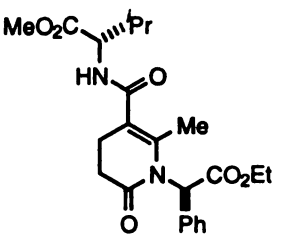
Aza-annulation of **III-36**, derived from **III-25**, resulted in more efficient ring formation to give **III-37** (**Scheme III-8**). Isolation and analysis of **III-37** led to some interesting properties of these molecules in solution. Initial ^{1}H NMR analysis of **III-37** in $CDCl_3$ revealed a 70:30 ratio of two sets of resonances. However, systematic dilution of **III-37** 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.[16]

Scheme III-6. Determination of Epimerization during the Aza-Annulation and Oxidation Reactions.



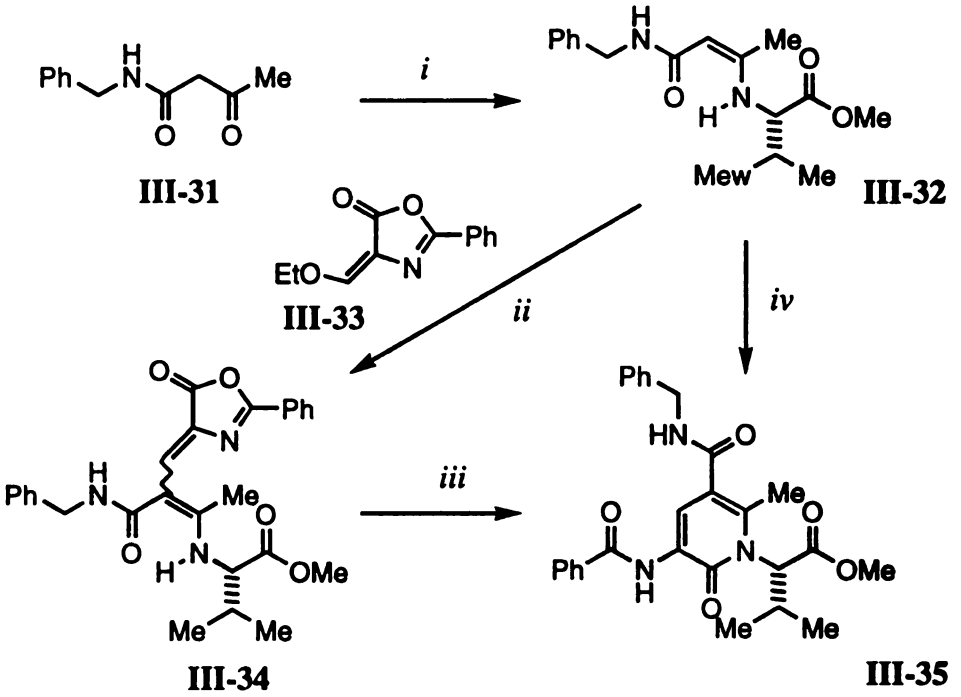
Reaction Conditions. *i*) (*S*)-methyl valine:HCl, toluene, $NaHCO_3$, reflux; *ii*) (*R*)-ethyl phenylglycine:HCl, toluene, $NaHCO_3$, reflux; *iii*) sodium acrylate or sodium 2-acetamidoacrylate, $ClCO_2Et$, THF; *iv*) DDQ, toluene, reflux, 40 h.

Table III-3. Aza-Annulations with Different α-Amino Acids.

Amine	Product	Yield	de[a]
	 **III-27a**	60%	>98:2
	 **III-27b**	89%	>98:2 in amino acid side chains; 50:50 mixture of diastereomers at C-3
	 **III-30**	49%	>98:2

[a]The ratio was determined by ^{1}H NMR analysis of the crude reaction mixture.

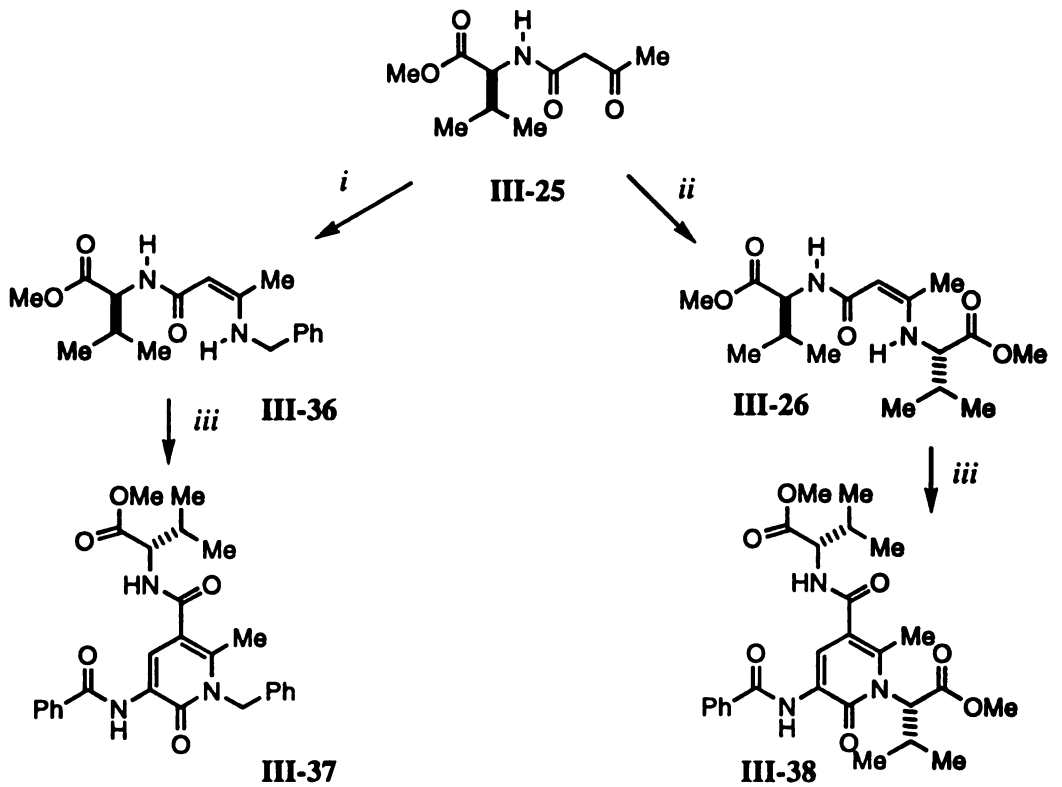
Scheme III-7. Direct Pyridone Formation through Aza-Annulation.



Reaction Conditions. *i*) (*S*)-Valine methyl ester:HCl, $NaHCO_3$, toluene, reflux; *ii*) **III-33**, dioxane, reflux; *iii*) DMF, reflux; *iv*) **III-33**, DMF, reflux.

Enamine **III-26**, formed as a single diastereomer as determined by ^1H NMR, was used to determine the extent to which epimerization occurred in the aza-annulation of **III-33** (**Scheme III-8**). The reaction of **III-33** with **III-26**, generated by condensation of (*S*)-valine methyl ester with **III-25**, resulted in an 81% yield of **III-38** for the two-step condensation/aza-annulation process. Although this procedure provided an efficient route for the rapid construction of a complex molecules from readily available starting materials, the diastereomer ratio from this reaction sequence was only 86:14. During this aza-annulation process, some epimerization had occurred at the site of asymmetry due to the high temperature required for heterocycle formation.

Scheme III-8. Determination of Epimerization during Direct Pyridone Formation.



Reaction Conditions. *i*) benzylamine, toluene, reflux; *ii*) (*S*)-valine methyl ester :HCl, toluene, $NaHCO_3$, reflux; *iii*) **III-33**, DMF, reflux.

Conclusions. Attempts to prepare the inhibitors of the ACE cascade, mimicking the Phe-His fragment were not successful due to low yields and inseparable mixtures of diastereomers. The aza-annulation reaction provides an efficient route for the potential

construction of the heterocyclic 2-pyridone framework for complex bioactive compounds such as natural product targets or synthetic peptide mimetics. With this method, peptide analogs as **III-24b** and **III-24d** can be assembled in three steps and in good overall yield. 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 ($\Psi=166^{o}$) to the 2-pyridone ($\Psi=180^{o}$). However, the oxidation process using DDQ gave lower yields due to a loss of the product during the course of the reaction. 2-Pyridone peptide analogs are inert to typical conditions for peptide hydrolysis. As possible peptide mimics, these compounds have the potential to interfere with biochemical events, and may exhibit significant biological effects.

EXPERIMENTAL RESULTS.

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 either nitrogen or argon. Benzene, toluene, tetrahydrofuran (THF), dichloromethane and diethyl ether were distilled from sodium/benzophenone immediately prior to use. Unless specified, concentration of solutions after workup was performed on a Buchi rotary evaporator. Oven temperature ranges are reported for bulb to bulb (Kugelrohr) distillations.

NMR spectra were obtained on Varian Gemini 300 or VXR-300 spectrometers with $CDCl_3$, and acetone-d_6 as solvents. ^1H NMR spectra are reported as follows : chemical shift relative to residual $CHCl_3$ (7.24 ppm) or TMS (0.0 ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling, and integration. ^{13}C NMR data are reported as chemical shifts relative to $CDCl_3$ (77.00 ppm). Flash column chromatography was performed using SiO_2 of 230-400 mesh. Reactions were monitored by TLC using Whatman K6F Silica Gel 60Å 250 μm thickness plates. High resolution mass spectra were carried out on a JEOL AX-505 double-focusing mass spectrometer (EI) or a JEOL HX-110 double-focusing mass spectrometer with helium as the collision gas (FAB). Optical rotation measurement was performed on the Perkin-Elmer 141 instrument, the instrument Siemens (Nicolet) PRV has been used for X-ray measurement. 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.[17] The sieves were changed during reactions in which additional reagent was added after reaction had progressed.

Preparation of Benzyl (*R*)-Phenyl Glycine III-13.[18]

KOH (1.85 g, 33 mmol, 1.0 equiv.) was dissolved in methyl alcohol (66 mL), phenyl glycine (5.00 g, 33.1 mmol, 1.0 equiv.) was added and dissolved by gentle heating. Ethyl acetoacetate (4.73 g, 36.4 mmol, 1.1 equiv.) was added and the mixture was brought to reflux for 10 minutes, then the solvent was removed under reduced pressure to yield a solid cake. The cake was dissolved in DMF (33 mL) and benzyl chloride (4.19 g, 33.1 mmol, 1.0 equiv.) was added. The mixture was stirred at room temperature for 20 hours. The resulting suspension was diluted with 1M $NaHCO_3$ (150 mL) and ethyl acetate (150 mL), washed with water. Combined organic layers were dried over Na_2SO_4. After concentration, to the crude oil 1M Et_2O solution of HCl was added and after 10 minutes, the solution was concentrated under reduced pressure. The oil solidified after addition of Et_2O. The product was pure enough to be used in the next step without further purification. Yield : 6.34 g (69%).

Hydrogenolysis of III-16.

To a solution of **III-16** (0.25 g, 0.49 mmol) in 15 mL of EtOH, 10% Pd/C (0.06 g) was added, the reaction vessel was flushed 3 times with H_2, and the reaction was placed under a balloon of H_2. The reaction mixture was stirred 4 hours at RT, filtered through a pad of Celite, and concentrated under reduced pressure to give **III-17** (0.20 g, 0.48 mmol, 99% yield).

III-17: (0.20 g, 0.48 mmol, 99% yield); m.p. = (114-115)° C (sealed); $[\alpha]_D^{22}$ = +22.9; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10-1.36 (m, 2H), 1.40-1.63 (m, 2H), 1.80-1.98 (m, 2H), 2.18-2.38 (m, 3H), 2.51 (m, 1H), 4.24 (d, *J*=5.1 Hz, 2H), 5.04 (m, 1H), 6.99 (s, 1H), 7.03-7.14 (m, 5H), 7.14-7.28 (m, 5H), 8.41 (bt, *J*=5.1 Hz, 1H), 1020 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.0, 24.3, 29.7, 30.3, 34.7, 43.8, 46.9, 58.1, 112.6, 127.3, 127.5, 127.6, 128.1, 128.4, 133.8, 134.4, 138.2, 169.5, 171.5, 174.2; IR ($CHCl_3$) 3306, 3015, 2934, 1715, 1671, 1644, 1619, 1541, 1453, 1364, 1283 cm^{-1}; HRMS ***m/z*** calcd for $C_{25}H_{26}N_2O_4$ 418.1893, obsd 418.1887.

Peptide Coupling Reaction of III-17 with Ethyl Proline.

To **III-17** (0.20 g, 0.48 mmol, 1.0 equiv.) in 10 mL of dichloromethane was added triethylamine (0.07 mL, 0.48 mmol, 1.0 equiv.) and L-ethyl proline hydrochloride (0.085 g, 0.48 mmol, 1.0 equiv.), the mixture cooled to 0° C and DCC (0.1 g, 0,48 mmol, 1.0 equiv.) was added at once. The mixture was stirred for 1 hour at 0° C and then 18 hours at room temperature. N,N'-dicyclohexylurea was filtered off on the pad of Celite, washed with dichloromethane, extracted with 0.1 M HCl, saturated $NaHCO_3$, brine and water. Organic layers were dried over Na_2SO_4. The crude product purified by flash column chromatography (diethyl ether:petroleum ether:methyl alcohol/48:48:4). Yield of **III-18** : 0.003 g (1%).

General Method for the Formation of β-Keto Amides.

Diketene (5.0-30.0 mmol, 1.0 equiv), benzylamine, HCl•(*R*)-ethyl phenylglycine or HCl•(*S*)-methyl valine (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 slowly warmed to room temperature, stirred for 10-15 hours, and then filtered. Removal of solvent under reduced pressure gave the product pure enough to use it for the next step without further purification.

III-21a: (3.60 g, 18.8 mmol, 81% yield; m.p.=(100-101)° C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.24 (s, 3H), 3.42 (s, 2H), 4.44 (d, *J*=6.0 Hz, 2H), 7.25-7.400 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.9, 43.5, 49.6, 127.4, 127.6, 128.6, 137.9, 165.4, 204.4; 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.

III-21c: (1.74 g, 9.35 mmol, 99% yield); m.p. = (52-53)° C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (t, *J*=7.1 Hz, 3H), 2.28 (s, 3H), 3.50 (s, 2H), 4.04 (d, *J*=5.4 Hz, 2H), 4.20 (q, *J*=7.2 Hz, 2H), 7.61 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 30.4, 41.1, 49.6, 61.1, 166.2, 169.4, 203.5; 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.

III-25: 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, 3H), 0.89 (d, *J*=7.2 Hz, 3H), 2.12 (m, 1H), 2.21 (s, 3H)), 3.43 (s, 2H), 3.66 (s, 3H), 4.46 (dd, *J*=5.0, 8.6 Hz, 1H), 7.48 (bd, *J*=8.6 Hz, 1H); ^{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.

A mixture of the benzylamine, (*R*)-phenylglycine ethyl ester hydrochloride or (*S*)-valine methyl ester hydrochloride (0.5-5.0 mmol, 1.0 equiv) and the β-keto amide (1.0 equiv) and in the case of hydrochloride salts sodium bicarbonate (1.5 equiv) were taken up in toluene (0.5 M relative to the substrate). The reaction vessel vas fitted with a modified distillation apparatus for azeotropic removal of H_2O,[17] and the reaction was heated at reflux until complete as determined by NMR analysis (10-18 hours). The solvent was then removed under reduced pressure, and the crude enamine product was brought up in THF (0.1 M). To the mixture mixed anhydride made freshly before reaction by reaction of NaH, appropriate acid (acrylic acid derivatives) and ethyl chloroformate in THF at -78° C. The reaction mixture was stirred at room temperature for 10-20 hours. The mixture was then washed with water and extracted with ethyl acetate or dichloromethane. The combined organic fractions were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (eluent as indicated).

III-16: (diethyl ether:petroleum ether/1:1, 0.63 g, 1.24 mmol, 69%); m.p. = (46-47)° C (sealed); $[\alpha]_D^{22}$ = + 28 (c=2.7, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.08-1.37 (m, 2H), 1.40-1.64 (m, 3H), 1.84 (m, 1H), 2.27-2.60 (m, 4H), 4.29 (dd, *J*=5.8, 14.8 Hz, 1H), 4.37 (dd, *J*=6.1, 14.6 Hz, 1H), 4.82 (dd, *J*=2.8, 4.9 Hz, 1H), 5.01 (d, *J*=12.2 Hz, 1H), 5.02 (d,

J=13.8, 1H), 7.00 (s, 1H), 7.10-7.27 (m, 15H), 7.82 (t, *J*=5.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.0, 24.0, 30.0, 30.6, 34.9, 43.8, 46.9, 58.4, 67.9, 111.6, 127.1, 127.5, 127.6, 127.7, 128.1, 128.4, 128.5, 128.6, 128.7, 133.8, 134.6, 134.9, 138.5, 168.9, 170.0, 173.2; IR ($CHCl_3$) 3345, 3033, 3011, 2932, 1721, 1661, 1644, 1532, 1497, 1451, 1341, 1277, 1286, 698 cm^{-1};

III-23a: 0.78 g, 2.06 mmol, 90% yield; m.p. = (82-85)° C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.92 (s, 3H), 2.07 (d, *J*=2.3 Hz, 3H), 2.41 (btd, *J*=15.3, 2.3 Hz, 1H), 2.93 (dd, *J*=15.5, 6.4 Hz, 1H), 4.35 (dd, *J*=14.7, 5.5 Hz, 1H), 4.43 (dd, *J*=14.7, 5.5 Hz, 1H), 4.54 (dt, *J*=15.0, 6.4 Hz, 1H), 4.63 (d, *J*=16.4 Hz, 1H), 5.05 (d, *J*=16.4 Hz, 1H), 6.80 (bt, *J*=5.7 Hz, 1H), 6.98 (bd, *J*=6.3 Hz, 1H), 7.07 (d, *J*=6.6 Hz, 2H), 7.16-7.30 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.9, 22.8, 28.5, 43.4, 45.5, 48.8, 112.5, 125.9, 127.2, 127.6, 128.4, 128.6, 136.8, 138.0, 139.1, 167.8, 169.3, 170.2; IR (KBr) 3289, 3002, 1734, 1659, 1584, 1543, 1321, 1248 cm^{-1}; HRMS calcd for C23H25N3O3 *m/z* 391.1896, obsd *m/z* 391.1895.

III-23b: (diethyl ether:petroleum ether:methyl alcohol/90:5:5, mixture of diastereomers, ratio 49:51; 0.36 g, 0.80 mmol, 87% yield); m.p. = (83-85)° C (mixture); ^{1}H NMR (300 MHz, $CDCl_3$) (characteristic peaks) δ (major isomer) 2.01 (s, 3H), 2.22 (d, *J*=1.2 Hz, 3H), 2.30 (bdt, *J*=9.2, 1.5 Hz, 1H), 5.67 (s, 1H), 5.92 (m, 1H), (minor isomer) 2.02 (s, 3H), 2.10 (d, *J*=1.2 Hz, 3H), 2.43 (btd, *J*=9.2, 1.5 Hz, 1H), 5.59 (s, 1H), 5.95 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 16.2, 16.5, 20.9, 22.8, 28.2, 28.3, 40.4, 43.5, 46.5, 48.9, 59.8, 61.7, 111.1, 113.6, 114.0, 117.3, 126.0, 127.1, 127.2, 127.5, 127.6, 127.7, 128.0, 128.2, 128.4, 128.4, 128.5, 134.3, 134.4, 137.9, 138.0, 138.5, 139.4, 167.5, 167.6,

168.0, 168.4, 169.2, 169.6, 170.1, 170.2; 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.

III-23c: (diethyl ether:petroleum ether:methyl alcohol/90:5:5, 1.06 g, 2.74 mmol, 95% yield); m.p. = (71-74)° C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (t, *J*=7.1 Hz, 3H), 2.00 (s, 3H), 2.16 (d, *J*=2.2 Hz, 3H), 2.46 (btd (*J*=15.3, 2.2 Hz, 1H), 2.96 (dd, *J*=15.3, 6.5 Hz, 1H), 3.95 (dd, *J*=18.1, 5.6 Hz, 1H), 4.04 (dd, *J*=18.1, 5.6 Hz, 1H), 4.14 (q, *J*=7.2 Hz, 2H), 4.59 (dt, *J*=15.3, 6.5 Hz, 1H), 4.67 (d, *J*=16.7, 1H), 5.13 (d, *J*=16.7 Hz, 1H), 6.91 (t, *J*=5.6 Hz, 1H), 7.05-7.13 (m, 3H), 7.19-7.34 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 15.8, 22.8, 28.3, 41.2, 45.4, 48.7, 61.1, 112.0, 125.8, 127.1, 128.6, 136.8, 139.7, 168.1, 169.3, 169.7, 170.3; 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.

III-23d: (diethyl ether:petroleum ether:methyl alcohol/90:5:5, mixture of diastereomers, ratio 49:51; 0.52 g, 1.13 mmol, 86% yield); m.p. = (77-80)° C (mixture); ^1H NMR (300 MHz, $CDCl_3$), characteristic peaks) δ (major isomer) 2.03 (s, 3H), 2.12 (d, *J*=1.5 Hz, 3H), 2.45 (btq, *J*=9.0, 1.5 Hz, 1H), 2.77 (ddd, *J*=7.8, 3.3, 1.5 Hz, 1H), 5.62 (s, 1H), 6.17 (bt, *J*=2.9 Hz, 1H), (minor isomer) 2.02 (s, 3H), 2.24 (d, *J*=1.5 Hz, 3H), 2.33 (btq, *J*=9.0, 1.5 Hz, 1H), 3.10 (ddd, *J*=9.0, 3.3, 1.5 Hz, 1H), 5.68 (s, 1H), 6.13 (bt, *J*=2.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 16.3, 16.6, 22.8, 23.0, 28.2, 28.3, 41.4, 41.4, 46.4, 49.0. 59.7, 59.9, 60.8, 61.3, 61.8, 62.4, 100.4, 113.2, 113.5, 113.5, 167.7, 127.7, 127.8, 128.0, 128.0, 128.1, 128.2, 128.3, 133.3, 134.2, 134.4, 139.5, 139.5, 140.4, 167.2, 168.0, 168.5, 169.0, 169.3, 169.4, 169.4, 169.7, 169.8, 170.2, 170.3, 171.1; 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.

III-27a: (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, 3H), 0.86 (d, *J*=6.8 Hz, 3H)), 0.90 (d, *J*=6.9 Hz, 3H), 1.08 (d, *J*=6.4 Hz, 3H), 2.14 (s, 3H), 2.16 (m, 1H), 2.38-2.53 (m, 4H), 2.61 (m, 1H), 3.60 (s, 3H), 3.69 (s, 3H), 4.03 (bd, *J*=8.5 Hz, 1H); ^{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.

III-27b: (90:5:5/diethyl ether:petroleum ether:methyl alcohol; 2.73 g, 6.21 mmol, 89% yield); (50:50 mixture of diastereomers; m.p. = (69-70)° C sealed, dec); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.74 (d, *J*=7.2 Hz, 3H), 0.75 (d, *J*=7.2 Hz, 3H), 0.85-0.94 (m, 12H), 1.09 (d, *J*=7.2 Hz, 3H), 1.11 (d, *J*=7.2 Hz, 3H), 1.96 (s, 3H), 1.97 (s, 3H), 2.06 (d, *J*=1.8 Hz, 3H), 2.09-2.20 (m, 2H), 2.20 (d, *J*=1.8 Hz, 3H), 2.24-2.42 (m, 2H), 2.48-2.68 (m, 2H), 2.91 (dd, *J*=6.3, 15.3 Hz, 1H), 2.99 (dd, *J*=6.3, 15.3 Hz, 1H), 3.61 (s, 3H), 3.64 (s, 3H), 3.69 (s, 6H), 3.95 (d, *J*=8.7 Hz, 1H), 4.26 (bs, 1H), 4.35-4.57 (m, 4H), 6.19 (d, *J*=8.7 Hz, 1H), 6.42 (d, *J*=8.4 Hz, 1H), 6.56 (d, *J*=5.7 Hz, 1H), 6.61 (D, *J*=5.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) d 11.5, 11.7, 13.2, 13.2, 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, 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.

III-30: (48:48:4/diethyl ether:petroleum ether:methyl alcohol, 0.29 g, 0.68 mmol, 49% yield); m.p. = (44-45)° C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (d, *J*=6.9 Hz, 3H), 0.90 (d, *J*=6.8 Hz, 3H), 1.21 (t, *J*=7.1 Hz, 3H), 2.06 (s, 3H), 2.12 (m, 1H), 2.40-2.55 (m, 2H), 2.55-2.66 (m, 2H), 3.69 (s, 3H), 4.18 (q, *J*=7.1 Hz, 2H), 4.55 (dd, *J*=4.8, 8.6 Hz, 1H), 5.60 (s, 1H), 5.84 (bd, *J*=8.6 Hz, 1H), 7.05-7.33 (m, 5H); ^{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.

Direct Method for the DDQ Oxidation of Aza-Annulation Products.

A mixture of the aza-annulation product (0.5-20.0 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 10-18 hours, the solvent was removed under reduced pressure, the residue dissolved in dichloromethane, filtered through a pad of Celite and the crude product was purified by flash column chromatography (eluent as indicated). The oxidation was repeated to acquire the indicated yields.

III-24a: (diethyl ether:ethyl acetate/2:1, 0.21 g, 0.59 mmol, 71% yield); m.p. = (180-181)° C; ^{1}H NMR (300 MHz, acetone-d_6) δ 2.10 (s, 3H), 2.42 (s, 3H), 4.55 (d, *J*=6.0 Hz, 2H), 5.51 (s, 2H), 7.12-7.16 (m, 2H), 7.19-7.56 (m, 8H), 8.18 (t, *J*=6.0 Hz, 1H), 8.54 (s, 1H), 8.96 (s, 1H); ^{13}C NMR (75 MHz, acetone-d_6) d 12.3, 24.4, 44.2, 48.8, 108.5, 122.4, 127.3, 127.8, 128.1, 128.5, 129.2, 129.5, 129.6, 137.0, 137.3, 145.4, 158.6, 168.5, 170.0;

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.

III-24b: (diethyl ether:ethyl acetate/2:1, 0.16 g, 0.35 mmol, 55% yield); m.p. = (155-156)° C; 1H NMR (300 MHz, $CDCl_3$) δ 1.24 (t, *J*=7.2 Hz, 3H), 2.18 (s, 3H), 2.50 (s, 3H), 4.26 (q, *J*=7.2 Hz, 2H), 4.57 (dd, *J*=5.6, 1.7 Hz, 2H), 6.12 (s, 1H), 6.19 (m, 1H), 7.19-7.43 (m, 10H), 8.27 (s, 1H), 8.53 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 17.5, 24.7, 44.3, 62.1, 62.7, 116.2, 120.7, 126.9, 127.7, 127.9, 128.2, 128.5, 128.6, 128.9, 133.0, 137.7, 139.8, 140.5, 167.2, 167.4, 169.3; 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.

III-28: (90:5:5/diethyl ether:petroleum ether:methyl alcohol, 0.20 g, 0.46 mmol, 40% yield); m.p. = (90-91)° C (sealed), dec.; ^1H NMR (300 MHz, $CDCl_3$) δ 0.63 (d, *J*=6.9 Hz, 3H), 0.97 (d, *J*=6.9 Hz, 3H), 1.01 (d, *J*=6.9 Hz, 3H), 1.24 (d, *J*=6.9 Hz, 3H), 2.13 (s, 3H), 2.19-2.32 (m, 2H), 2.49 (bs, 3H), 3.60 (s, 3H), 3.76 (s, 3H), 4.32 (bs, 1H), 4.65 (dd, *J*=4.5, 8.7 Hz, 1H), 6.45 (d, *J*=8.7 Hz, 1H), 8.19 (bs, 1H), 8.53 (s, 1H); ^{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.

General Method for Aza-Annulation with III-33 (2-Phenyl-4-(ethoxymethylene)oxazolone).

The corresponding enamine (0.78-2.6 mmol) was dissolved in anhydrous DMF (0.26 M) and **III-33** (1.0 equiv) was added. After the reaction mixture was heated to reflux for 2 hours, the dark brown solution was concentrated to an oil (boiling water bath), dissolved in dichloromethane, filtered through a pad of Celite/SiO2=1:1 (w/w) and purified by flash column chromatography (eluent as indicated).

III-35: (90:5:5/diethyl ether:petroleum ether:methyl alcohol, 0.18 g, 0.38 mmol, 49%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.57 (d, *J*=6.9 Hz, 3H), 1.20 (d, *J*=6.3 Hz, 3H), 2.50 (s, 3H), 2.93 (m, 1H), 3.61 (s, 3H), 4.32 (m, 1H), 4.49 (dd, *J*=14.7, 5.7 Hz, 1H), 4.54 (dd, *J*=15.6, 5.7 Hz, 1H), 6.67 (bt, *J*=5.1 Hz, 1H), 7.16-7.32 (m, 5H), 7.32-7.41 (m, 2H)), 7.46 (m, 1H), 7.74-7.81 (m, 2H)), 8.59 (s, 1H), 8.95 (bs, 1H); ^{13}C NR (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.

III-37: (90:5:5/diethyl ether:petroleum ether:methyl alcohol, 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, 3H), 1.01 (d, *J*=6.8 Hz, 3 H), 2.08 (m, dimer), 2.17 (s, dimer), 2.20 (s, 3H), 2.24 (m, 1H), 3.63 (s, dimer), 3.70 (s, 3H), 4.44 (dd, *J*=8.5, 5.1 Hz, dimer), 4.56 (dd, *J*=8.5, 5.2 Hz, 1H), 5.03 (bd, *J*=15.7 Hz, 1H), 5.31 (bd, *J*=15.7 Hz, 1H), 6.99 (d, *J*=6.6 Hz, 2H), 7.12-7.24 (m, 3H), 7.34-7.52 (m, 3H), 7.82 (d, *J*=7.8 Hz, 2H), 8.63 (s,

1H), 9.09 (s, 1H); ^{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, 57.00, 57.9, 58.0, 115.7, 115.7, 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, 165.6, 165.6, 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.

III-38: (90:5:5/diethyl ether:petroleum ether:methyl alcohol, 0.75 g, 1.50 mmol, 81% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.50 (d, *J*=6.6 Hz, 3H), 0.80-0.90 (m, minor), 0.94 (d, *J*=7.9 Hz, 3H), 0.98 (d, *J*=7.9 Hz, 3H), 1.17 (d, *J*=6.3 Hz, 3H), 2.008 (m, minor), 2.21 (m, 1H), 2.43 (s, 3H), 4.29 (bd, *J*=6.3 Hz, 1H), 4.43 (dd, *J*=8.3, 5.0 Hz, minor), 4.58 (dd, *J*=8.3, 5.0 Hz, 1H), 6.89 (bd, *J*=6.6 Hz, 1H), 7.30-7.50 (m, 3H)), 7.80 (d, *J*=7.1 Hz, 2H), 8.49 (s, minor). 8.66 (s, 1H), 8.95 (bs, 1H), 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), 300.8 (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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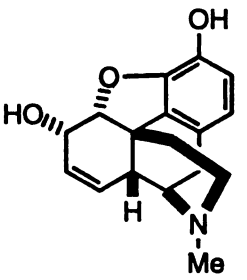
CHAPTER IV

PREPARATION OF ISOQUINOLINE ALKALOID ANALOGS THROUGH THE AZA-ANNULATION METHODOLOGY

Introduction

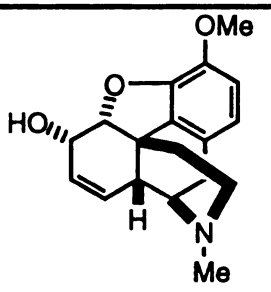
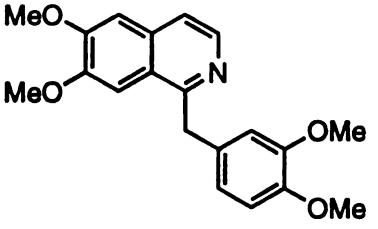
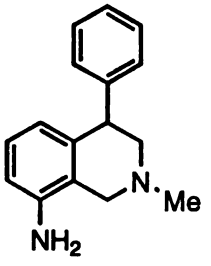
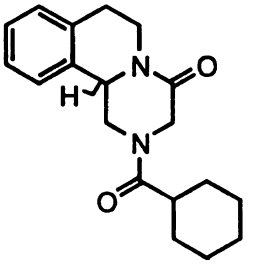
The broad variety of potential applications of isoquinoline alkaloids, or their analogs, emphasizes the importance of this class of compounds. The isoquinoline moiety represents a valuable template which has led to the discovery of many quite different drugs.

On the one side of the spectrum is morphine (**IV-1**), one of the major opium alkaloids, still indispensable in modern medical practice on account of its analgesic, hypnotic, and sedative activity. On the other side, there is a class of new isoquinoline derivatives having very different properties. Some examples are shown in **Table IV-1**.[1]

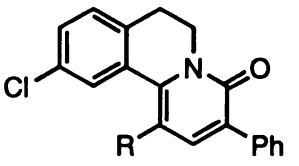


IV-1

Table IV-1.Examples of Isoquinoline Drugs.

Name	Structure	Activity
Codeine		antitussive
Papaverine		spasmolytic
Nomifensin		antidepressant
Praziquantel		anthelmintic

Because of their broad physiological applications, new isoquinoline derivatives are prepared as potential drugs. Recently, the novel tricyclic isoquinoline drug **IV-2** was prepared and evaluated for its activity as a central benzodiazepine receptor agent, acting thus as a potential sleep inducer.[2,3]

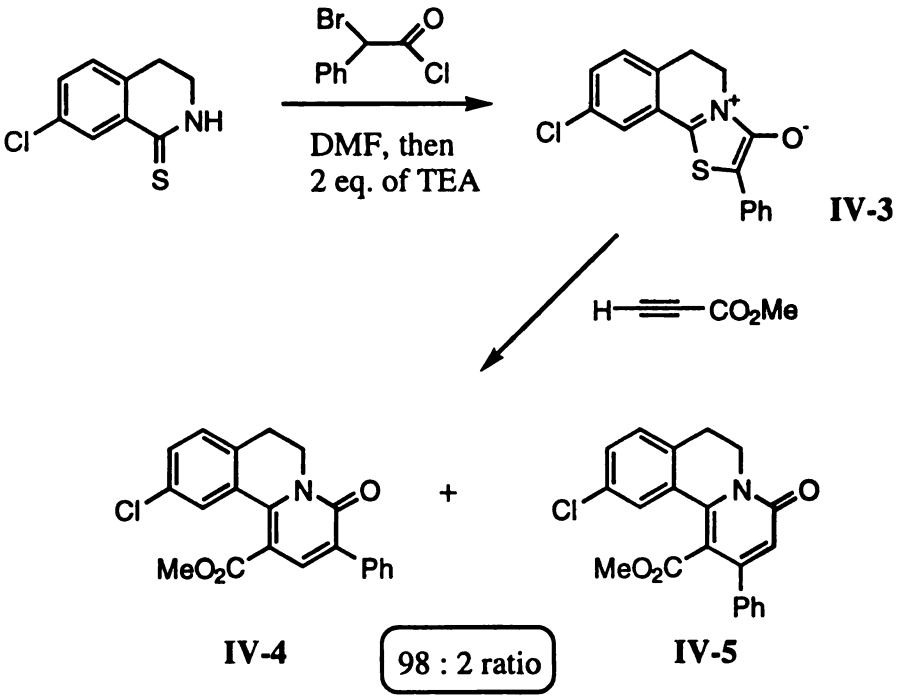


IV-2

Interestingly, this compound does not have typical hydroxy or alkoxy substituents in the positions 6 and 7 of isoquinoline system. The chlorine atom at carbon 7 is crucial for the induction and maintenance of the effective non-sedative hypnotic activity.

There are two reported syntheses of compound **IV-2**. One, developed by Widmer[2] (R=CO_2Me), proceeds by 1,3-dipolar cycloaddition reaction of compound **IV-3** with methyl prop-2-ynoate to give, after extrusion of sulfur from the primary adduct under the reaction conditions, a mixture of regioisomeric pyridones **IV-4** and **IV-5**, where the former one is the major product (**Scheme IV-1**).

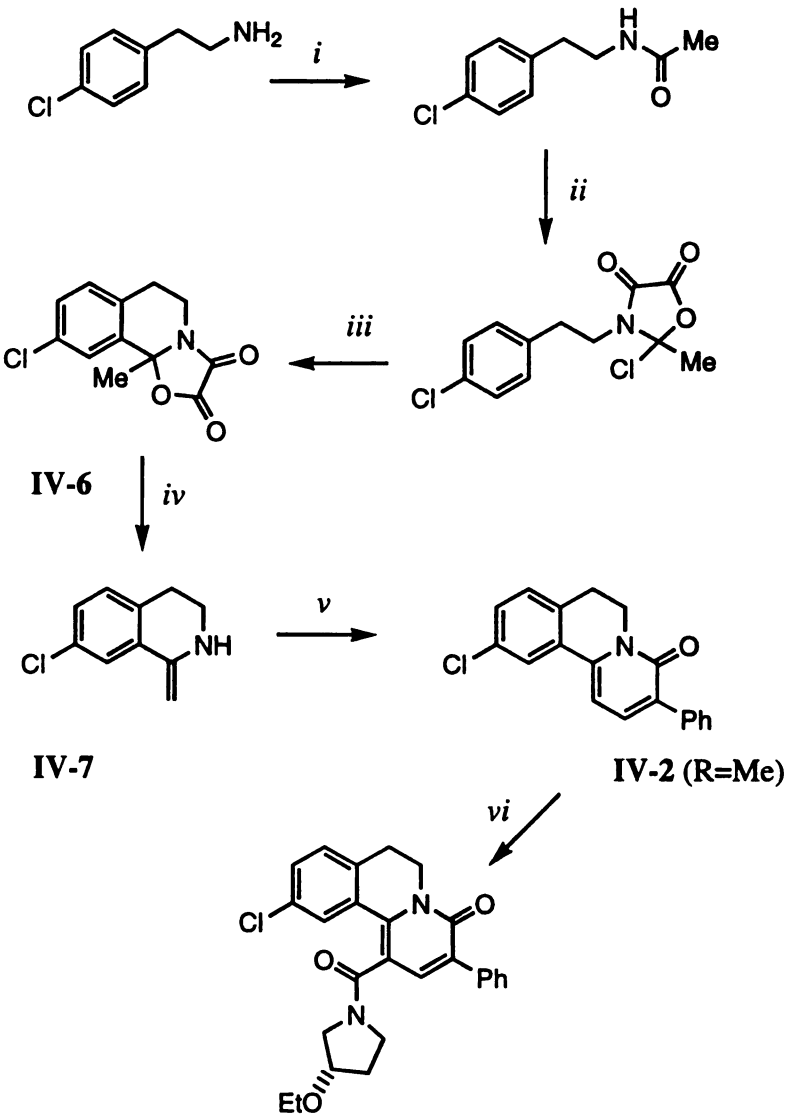
Scheme IV-1. 1,3-Dipolar Cycloaddition Approach.



A more recent synthesis has been developed by Spurr,[3] from the Hoffmann La-Roche company. The compound **IV-2** (R=Me) was prepared by annulation of a suitable enamine substrate with ethyl 3-dimethylamino-2-phenylacrylate (**Scheme IV-2**).

The enamine compound was constructed by a novel variation on the Bischler-Napieralski procedure,[4] using the chlorooxazolidinedione intermediate, which behaved in the presence of $FeCl_3$ as a superior acylating agent to produce the oxalyl-adduct **IV-6** in good yield. Methanolysis of the crude product in $MeOH/H_2SO_4$ solution released the cyclic oxalyl-protecting group and provided the corresponding enamino compound **IV-7**. Compound **IV-7** on annulation with ethyl 3-dimethylamino-2-phenylacrylate gave the product **IV-2** (R=Me) in 70-75% yield.

Scheme IV-2. Annulation Approach.



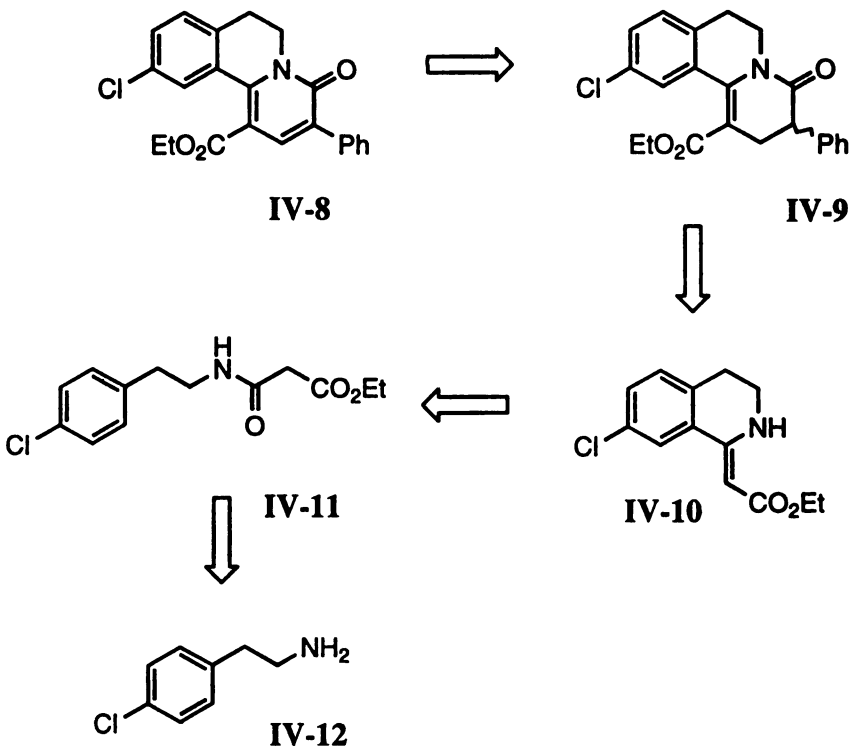
Ro 41-3696

Reaction Conditions. *i*) Ac_2O, toluene, 100%; *ii*) $(COCl)_2$, CH_2Cl_2; *iii*) $FeCl_3$, 85% (2 steps); *iv*) H_2SO_4, MeOH, 80%; *v*) ethyl 3-dimethylamino-2-phenyl acrylate, AcOH, 70%; *vi*) NBS, AcOH, 75% then (*S*)-3-ethoxy pyrrolidine, $Pd(OAc)_2$, dppp, $KHCO_3$, MeCN, 20 bar CO, 85%.

RESULTS AND DISCUSSION

Compound **IV-8** ($R=CO_2Et$) was chosen as a synthetic target. Retrosynthetic analysis shows that ring C can be made by the aza-annulation reaction (**Scheme IV-3**). In order to demonstrate the utility of the aza-annulation reaction in this class of molecules, transformations suggested by this scheme were explored.

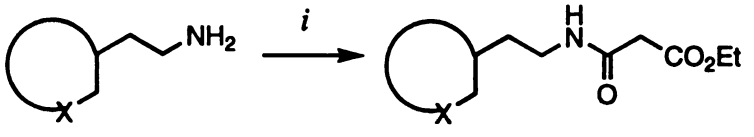
Scheme IV-3. Retrosynthetic Analysis.



Preparation of the amide **IV-11** proceeded smoothly, using commercially available 4-chlorophenethylamine **IV-12** and ethyl malonyl chloride. However, attempts to successfully cyclize the amide substrate into an enamine derivative **IV-10** left either uncyclized starting material or gave undesired side-products. Many experimental

procedures mentioned in the literature were tried for Bischler cyclization, for example cyclization in polyphosphoric acid (PPA)[5] or polyphosphate ester (PPE),[6] activation with triflic anhydride,[7] or classical cyclization in the presence of $POCl_3$ or PCl_5,[8] but none of them gave the desired product. In this case, the presence of the halogen atom caused deactivation of aromatic ring toward electrophilic attack. The attempts to cyclize the appropriate amide under Bischler conditions failed even for other substrates, including heterocycle **IV-18** (**Table IV-2**). Cyclization of an unsubstituted amide **IV-15** gave the enamino product only in very low yield, and the same type of cyclization either with an amino group (**IV-17**), or protected amino group as a substituent generated insoluble polymeric products. Even Bischler cyclization of the 4-methoxy substituted amide did not generate the desired product (**Scheme IV-4** and **Table IV-2**).

Scheme IV-4. Preparation of Amide Derivatives.



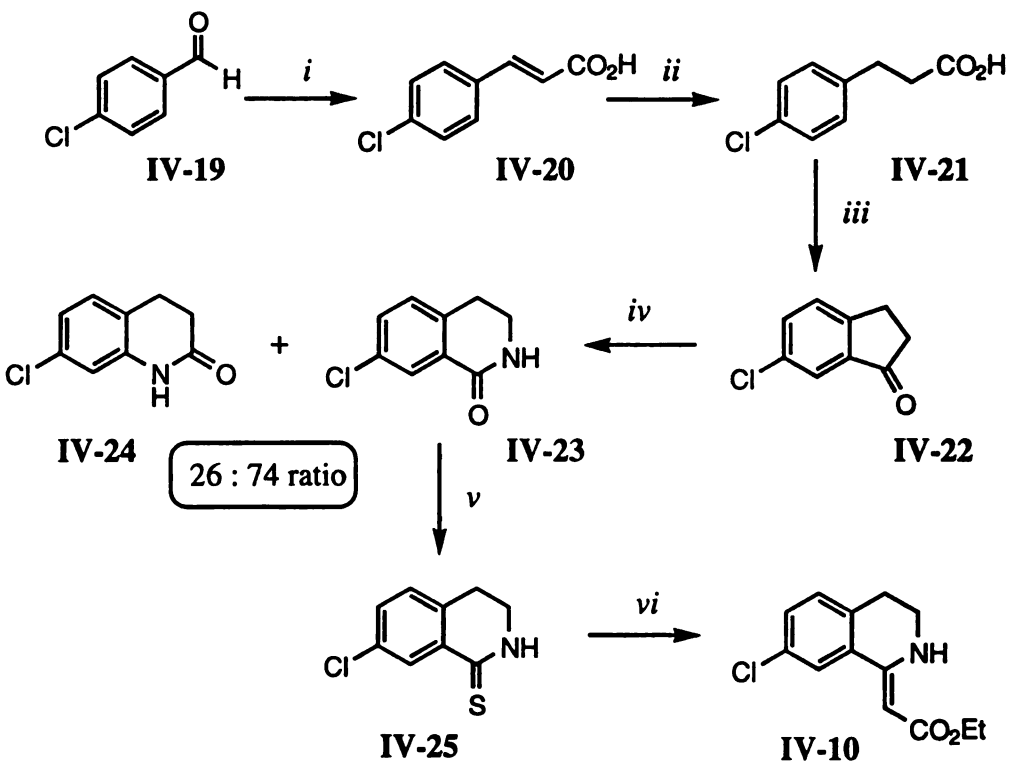
Reaction Conditions. *i*) $ClCOCH_2CO_2Et$, CH_2Cl_2 or Et_2O, K_2CO_3 or Et_3N.

This complication initiated an effort to construct the enamine molecule in another way, shown in **Scheme IV-5**. 4-Chloro substituted benzaldehyde **IV-19** served as a starting material, and gave 6-chloro-1-indanone **IV-22** as the desired product via Perkin reaction,[9] catalytic hydrogenation and cyclization in hot concentrated sulfuric acid.[10] This

product was then transformed then into lactam **IV-23** by Schmidt rearrangement with sodium azide in trichloroacetic acid.[11] This procedure also provided the undesired regioisomer **IV-24** in significant amount (15% yield), and generation of this byproduct was a major drawback of this approach (74:26 crude ratio). Interestingly, the intramolecular Friedel-Crafts cyclization of a chloride of the corresponding acid, mentioned in the literature, did not give the desired indanone derivative.[15] Lactam product **IV-23** was transformed with Lawesson's reagent into thiolactam **IV-25**[12] and this product was used for the construction of an enamine product **IV-10** using Eschenmoser sulfide extrusion.[13]

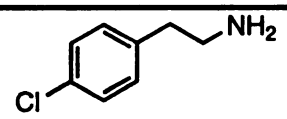
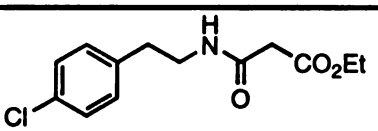
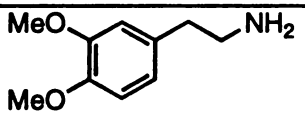
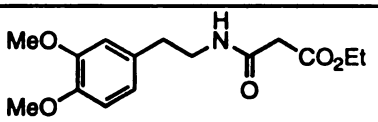
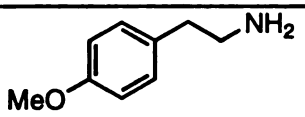
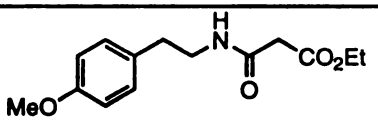
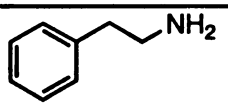
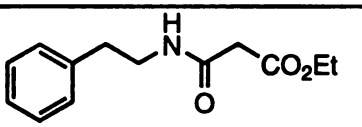
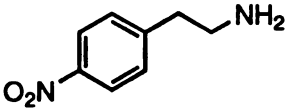
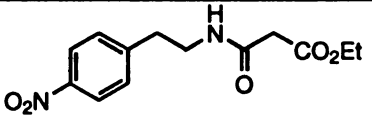
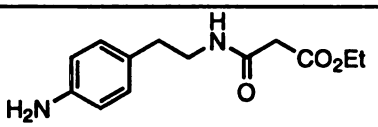
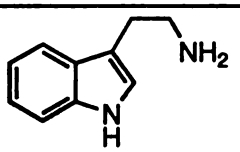
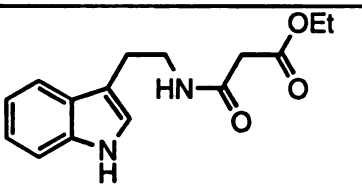
To avoid the time consuming separation of two lactam regioisomers, it was decided to look for a different and better way for enamine **IV-10** preparation. Finally, a relatively simple and efficient procedure was found, using the corresponding isothiocyanate made from an amine, carbon disulfide and ethyl chloroformate in the presence of triethylamine. Cyclization of the crude product was achieved, using either polyphosphoric acid, or $AlCl_3$ in 1,1,2,2-tetrachloroethane.[14] This approach has been chosen as the best way of making different thiolactams. The products were usually pure enough to use in the next step without further purification (**Scheme IV-6**). They have been subsequently used for the preparation of all enamino derivatives by Eschenmoser sulfide extrusion without difficulty.

Scheme IV-5. 6-Chloro-indan-1-one Approach.



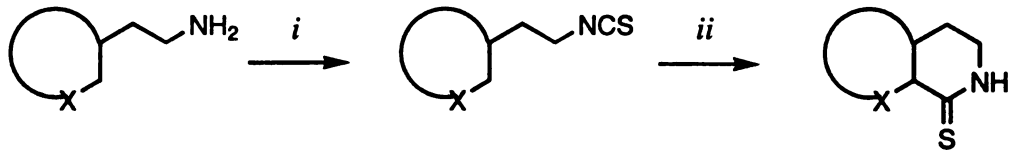
Reaction Conditions. *i*) $CH_2(CO_2H)_2$, DMSO, piperidine, 90° C, 10 h, 87%; *ii*) Pd/C, 2 atm of H_2, dioxan, 14 h, 98%; *iii*) conc.H_2SO_4, 175° C, 30 s, 64%; *iv*) NaN_3, Cl_3CCO_2H, 65° C, 4 h, 85% overall yield; *v*) Lawesson's reagent, toluene, reflux, 45 min., 98%; *vi*) $BrCH_2CO_2Et$, PPh_3, Et_3N, MeCN, 68 h, 78%.

Table IV-2. Preparation of Amide Derivatives.

Amine	Product	Product #	Yield [%]
		**IV-11**	66
		**IV-13**	49
		**IV-14**	58
		**IV-15**	36
		**IV-16**	43
-		**IV-17**	100[a]
		**IV-18**	29

[a]Prepared by reduction of the corresponding nitro derivative.

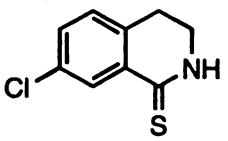
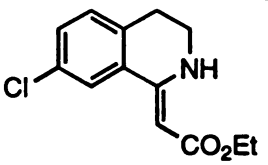
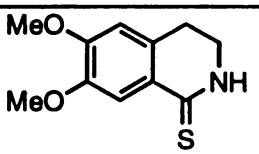
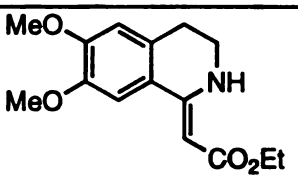
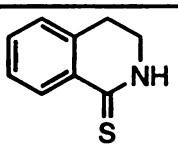
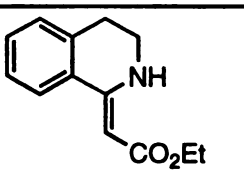
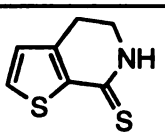
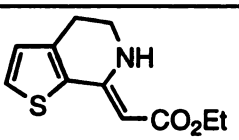
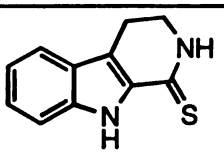
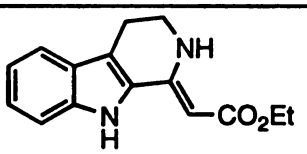
Scheme IV-6. Formation of Thiolactams through Isothiocyanates.



Reaction Conditions. *i*) CS_2, CH_2Cl_2, Et_3N, $ClCO_2Et$; *ii*) PPA or $Cl_2CHCHCl_2$, $AlCl_3$.

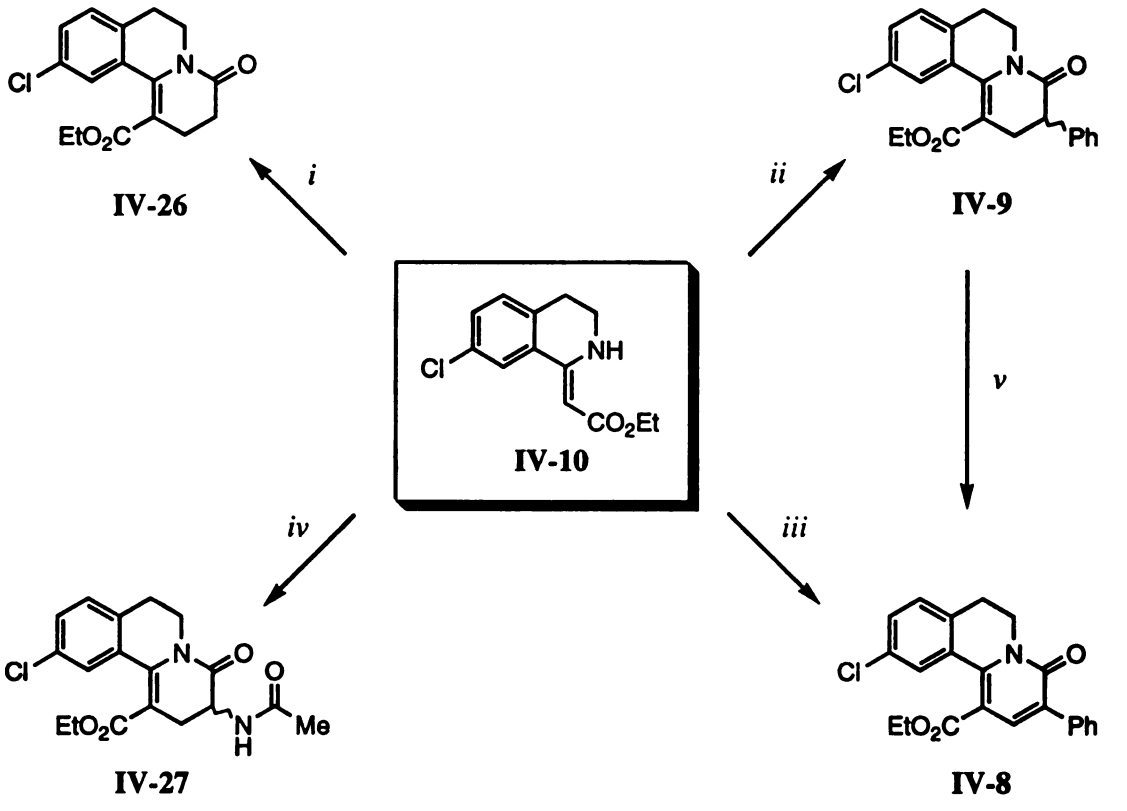
With the successful synthesis of enamino substrates in hand, the aza-annulation with different derivatives of acrylic acid was explored. Chloro substituted enamine **IV-10** was treated with either the unsubstituted mixed anhydride of acrylic acid in THF, generating thus **IV-26** in 68% yield, or with mixed anhydrides of 2-substituted derivatives of acrylic acid. 2-Phenyl acrylic acid, made from α-bromo styrene with n-BuLi and carbon dioxide,[16] generated mixed anhydride *in situ* with NaH and ethyl chloroformate, and the reaction of this compound and **IV-10** provided the desired synthetic target **IV-9** in 81% yield (**Scheme IV-7**). Analogous reactions with 2-acetamido substituted acrylic mixed anhydride with **IV-10** gave the product **IV-27** in 84% yield. The oxidation of **IV-9** with DDQ in toluene at reflux provided the 2-pyridone derivative **IV-8** in 81% yield. The alternative direct preparation of **IV-8** from **IV-10** and ethyl 3-dimethylamino-2-phenyl acrylate **IV-28** in hot glacial acetic acid, generated the product **IV-8** in only 17% yield (**Scheme IV-7**).

Table IV-3. Formation of Enamino Esters.

Thiolactam	Enamino Ester	Product #	Yield [%]
		**IV-10**	78
		**IV-29**	77[a]
		**IV-35**	10[a]
		**IV-38**	91
		**IV-41**	77

[a]Prepared directly from the corresponding amide by Bischler cyclization.

Scheme IV-7. Preparation of Chloro Substituted Tricyclic Isoquinoline Derivatives.



Reaction Conditions. *i*) sodium acrylate, $ClCO_2Et$, THF, 68%; *ii*) sodium 2-phenyl acrylate, $ClCO_2Et$, THF, 81%; *iii*) **IV-28**, glacial HOAc, 95° C, 17%; *iv*) sodium 2-acetamidoacrylate, $ClCO_2Et$, THF, 84%; *v*) DDQ, toluene, reflux, 81%.

Preparation of dimethoxy enamino substrate **IV-29** by Bischler reaction proceeded smoothly due to the presence of two activating substituents on the aromatic ring, and the product **IV-29** was made from **IV-13** in 77% yield. The same derivatives of acrylic acid as for chloro substituted analogs have been used for aza-annulation reactions

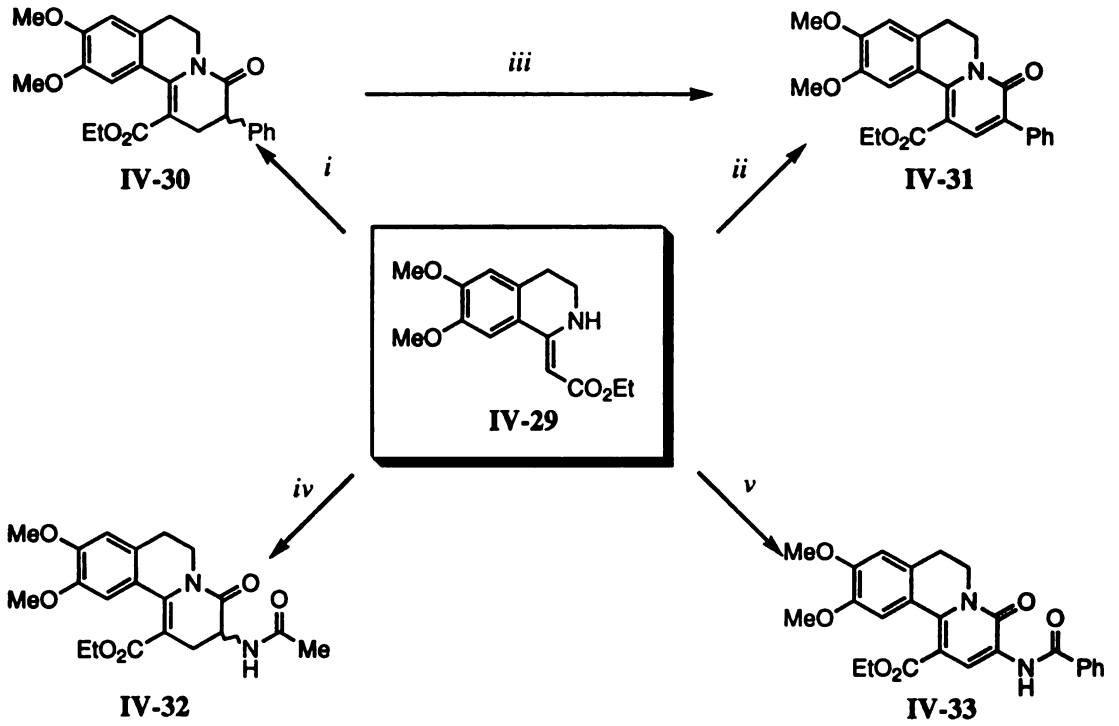
of **IV-29** and the products and yields are shown in **Scheme IV-8**. The compound **IV-31** was prepared either by DDQ dehydrogenation of **IV-30** in 81% yield, or directly by reaction of **IV-29** with **IV-28**. Preparation of **IV-32** using 2-acetamidoacrylic mixed anhydride as an active aza-annulation component was not complete and gave the product in only 29% yield. The compound **IV-33** was made by direct cyclization with 2-phenyl-4-(ethoxymethylene)oxazolone **IV-34** in DMF in 25% yield.

The unsubstituted derivative **IV-35** was prepared in much lower yield through the amide derivative via Bischler reaction. The product with an unsubstituted aromatic ring **IV-36** was prepared in 69% yield by reaction of enamine **IV-35** in 69% yield with 2-phenyl acrylic mixed anhydride, and subsequently oxidized with DDQ according to the common protocol into **IV-37** in 79% yield (**Scheme IV-9**).

At this stage of research it was decided to prepare heterocyclic analogs as promising biologically active compounds.[17] As starting materials, tryptamine and 2-thiophen-3-yl-ethylamine (prepared by hydrogenolysis of 3-thiopheneacetonitrile in the presence of Raney-nickel) were chosen. The corresponding thiolactams were generated via the corresponding isothiocyanates without problems.

Eschenmoser sulfide extrusion gave enamine **IV-38** which was used in aza-annulation reactions with either 2-phenylacrylic acid or 2-acetamidoacrylic acid mixed anhydrides. The results and yields are shown in **Scheme IV-10**. This type of product is a thiophene isostere of the isoquinoline alkaloids, and might have potentially new and important properties.

Scheme IV-8. 6,7-Dimethoxy Substituted Tricyclic Isoquinoline Derivatives.

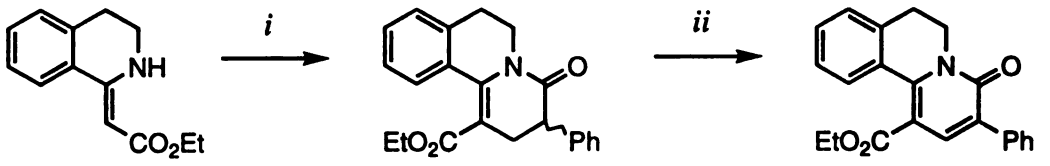


Reaction Conditions. *i*) sodium 2-phenylacrylate, $ClCO_2Et$, THF, 76%; *ii*) **IV-28**, glacial HOAc, 95° C, 55%; *iii*) DDQ, toluene, reflux, 81%; *iv*) sodium acetamido acrylate, $ClCO_2Et$, THF, 29%; *v*) **IV-34**, DMF, reflux, 25%.

The analogous aza-annulation reaction of enamino compound **IV-41,** derived from tryptamine, with the same reagents used in previous schemes, provided interesting products **IV-42**, **IV-43**, and **IV-44** in 89%, 58%, and 48% yields, respectively (**Scheme IV-11**).

All attempts to prepare the yohimbine-like compound **IV-45** either via the mixed anhydride of 1-cyclohexene-1-carboxylic acid **IV-46** or directly with DPPA[17b] and **IV-46** have been unsuccessful (**Scheme IV-12**). An important factor in this failure is probably the steric congestion at the β-carbon of the acrylic species.

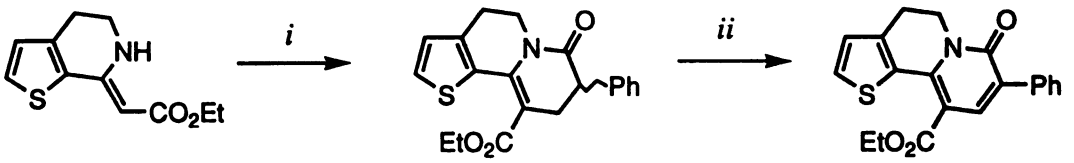
Scheme IV-9. Unsubstituted Tricyclic Isoquinoline Derivatives.



IV-35 **IV-36** **IV-37**

Reaction Conditions. *i*) sodium 2-phenylacrylate, $ClCO_2Et$, THF, 69%, *ii*) DDQ, toluene, reflux, 79%.

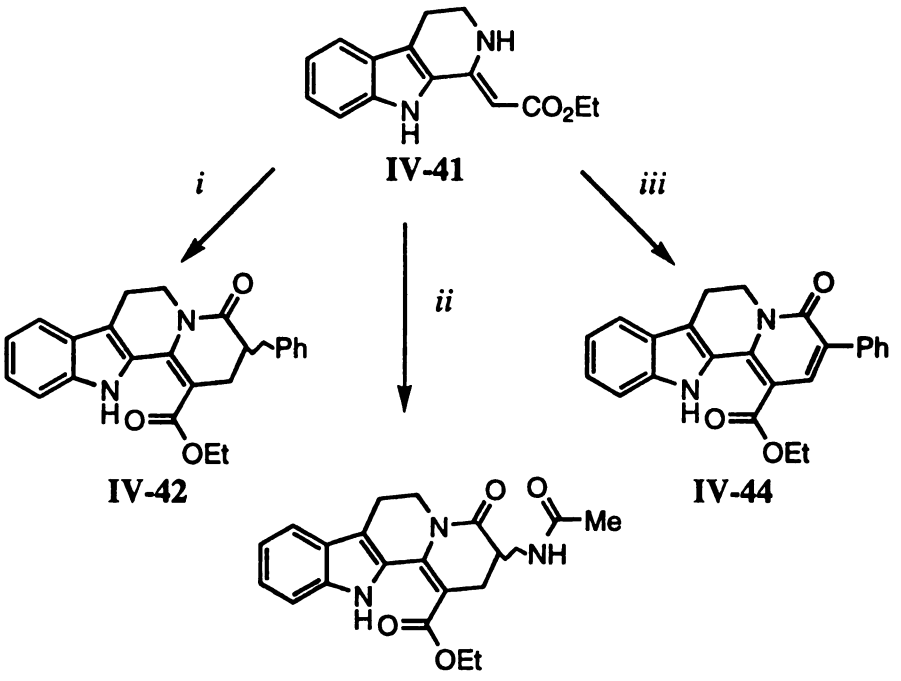
Scheme IV-10. Preparation of Thiophene Analogs of Isoquinoline Derivatives.



IV-38 **IV-39** **IV-40**

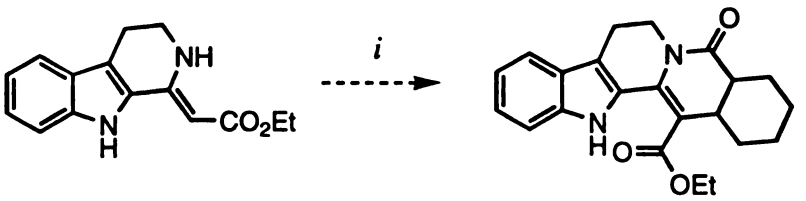
Reaction Conditions. *i*) Sodium 2-phenylacrylate, $ClCO_2Et$, THF, 64%; *ii*) DDQ, toluene, reflux, 97%.

Scheme IV-11. Preparation of Indole Substituted Derivatives.



Reaction Conditions. *i*) Sodium 2-phenylacrylate, $ClCO_2Et$, THF, 89%; *ii*) sodium 2-acetamidoacrylate, $ClCO_2Et$, THF, 58% , *iii*) **IV-28**, glacial HOAc, 95° C, 48%.

Scheme IV-12. Unsuccessful Preparation of a Yohimbine Analog.



IV-41 **IV-45**

Reaction Conditions. *i*) 1-cyclohexen-1-carboxylic acid, DPPA, MeCN, 24 h or sodium 1-cyclohexen-1-carboxylate, $ClCO_2Et$, THF, 24 h.

Conclusions.

Comparing with previously reported methods, [2,3] a broad variety of substrates has been constructed using the aza-annulation methodology. Enamino esters have been prepared as the starting materials for the aza-annulation reaction. Bischler cyclization proceeded well only with sufficiently activating substituents on the aromatic ring. Unsubstituted aromatic β-ester amides generated enamino ester products only in low yields. The presence of a halogen substituent on the aromatic ring caused deactivation of the system to the electrophilic aromatic substitution, and alternative methods for the preparation of the desired substrates had to be sought. A chloro substituted ester enamine was prepared from 6-chloro-1-indanone derivative, and was then transformed into the desired product by Schmidt rearrangement, formation of a thiolactam, and Eschenmoser sulfide extrusion. The best method for the synthesis of enamino esters

has been found to be via preparation of a thiolactam intermediate directly from the corresponding amine compound and its isothiocyanate derivative.

The enamino esters have been used in aza-annulation reactions, generating a wide variety of the products, and thus providing more evidence for the versatility of this methodology.

EXPERIMENTAL RESULTS.

General Methods. All reactions were carried out performing standard inert atmosphere techniques to exclude moisture and oxygen, and reactions were performed under an atmosphere of nitrogen or argon. 2-acetamidoacrylic acid was purchased from Aldrich, and used without purification. Sodium acrylate was either freshly made before reaction by reaction of acrylic acid and NaH in dry THF at -78° C or purchased directly from Aldrich. Azeotropic removal of water was assisted by the use of 4-Å molecular sieves in the modified Dean-Stark adapter.[18] Concentration of solutions after work up was performed by rotary evaporator Buchi. Flash column chromatography was performed using SiO_2 of 230-400 mesh. Reactions were monitored by TLC using Whatman K6F Silica Gel 60Å 250 μm thickness plates.

IR spectra were recorded using a Nicolet 42 FT-IR instrument, ^1H NMR spectra are reported as follows : chemical shift relative to residual $CHCl_3$ (7.24 ppm) or TMS (0.0 ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling, and integration. ^{13}C NMR data are reported as chemical shifts relative to $CDCl_3$ (77.00 ppm). High resolution mass spectra were carried out on a JEOL AX-505 double-focusing mass spectrometer (EI).

Preparation of 4-Chlorocinnamic Acid IV-20 :

To a mixture of 20.0 g (142.3 mmol) of 4-chlorobenzaldehyde and 16.4 g (157.9 mmol) of malonic acid dissolved in 50 mL of DMSO was added 2.0 mL of piperidine. After an initial exothermic reaction subsided, the mixture was heated at (85-90)° C for 10 hours. The mixture was then poured on 500 g of ice and the resulting slurry was acidified with 5

M HCl (indicated by a litmus paper). After the ice melted, the mixture was filtered and the solid was washed repeatedly with water. The product was recrystallized from ethyl alcohol. Yield : 22.8 g (87%).

Preparation of 6-Chloroindan-1-one IV-22:

a) 4-Chlorocinnamic acid (25.0 g, 136.9 mmol) was shaken under 75-80 psi of hydrogen over 10% Pd/C (1.95 g) in 150 mL of dioxan for 14 hours. The filtered solution was evaporated and the residue was crystallized from ethyl alcohol to yield β-4-chloropropionic acid. Yield : 24.8 g (98.1%).

b) β-4-Chloropropionic acid (20.0 g, 108.3 mmol) was rapidly added to well stirred sulfuric acid (375 g, 200 mL) at (175-180)° C, after 30 seconds the solution was poured onto ice (150 g). The precipitated product was crystallized from ethyl alcohol. Yield : 11.5 g (64%).

IV-22: (2.89 g, 17.32 mmol, 64% yield) ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.68-2.74 (m, 2H), 3.07-3.13 (m, 2H), 7.41 (d, *J*=8.2 Hz, 1H), 7.52 (dd, *J*=2.0, 8.2 Hz, 1H), 7.68 (d, *J*=2.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.4, 36.6, 123.4, 127.8, 133.6, 134.5, 138.5, 153.1, 205.4; IR ($CHCl_3$) 3393, 3052, 3021, 2965, 2936, 1709, 1597, 1466, 1443, 1258, 1194, 1115, 1038 cm^{-1}.

Preparation of 7-Chloro-3,4-Dihydro-2H-Isoquinolin-1-one IV-23 - Schmidt rearrangement :

Sodium azide (1.28 g, 19.7 mmol, 1.1 equiv.) was added to a mixture of 6-chloroindan-1-one (2.98 g, 17.9 mmol) and molten trichloroacetic acid (29.2 g, 178.9 mmol, 10 equiv.)

at 65° C and stirring was continued for 4 hours. The solution was then cooled, diluted with ice water, neutralized with sodium bicarbonate, and extracted with chloroform. Organic layers dried over sodium sulfate, filtered, concentrated and purified by flash column chromatography (gradient diethyl ether:petroleum ether/1:1-diethyl ether-diethyl ether:petroleum ether:methyl alcohol/90:5:5). Yield : 1.38 g (43%) (70% based on the recovery of the starting material). Yield of lactam regioisomer : 15%.

IV-23: (gradient diethyl ether:petroleum ether/1:1-diethyl ether:petroleum ether:methyl alcohol/90:5:5, 0.54 g, 2.97 mmol, 62% yield based on recovery of 1.46 g of the starting material); m.p. = (151-152)° C; ^{1}H NMR (300 MHz, $CDCl_3$) d 2.96 (t, *J*=6.6 Hz, 2H), 3.56 (dd, *J*=1.8, 6.6 Hz, 1H), 3.58 (dd, *J*=1.8, 6.6 Hz, 1H), 7.15 (bs, 1H), 7.40 (dd, *J*=2.4, 8.1 Hz, 1H), 8.03 (d, *J*=2.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.3, 36.5, 123.4, 127.8, 133.6, 134.5, 138.4, 153.1, 205.4.

General Procedure for Preparation of Thiolactams with Lawesson's Reagent :

The mixture of 1.5 equiv. of a lactam and 1.0 equiv. of 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (Lawesson's reagent) in toluene (0.1 M) was heated to reflux for 1 hour, concentrated under reduced pressure and purified by flash column chromatography if necessary.

General Method for Eschenmoser Sulfide Contraction:

The thiolactam (1.0 equiv.) and ethylbromoacetate (1.2 equiv.) were stirred in diethyl ether (0.3 M) for 24-36 hours. The solvent was evaporated and the thionium salt was

dissolved in acetonitrile (0.3 M). Triethylamine (1.5 equiv.) was added and the mixture was stirred at room temperature for 15 minutes. Triphenylphosphine (1.2 equiv.) was added and the mixture was allowed to stir for 15 minutes. Triethylamine (1.5 equiv.) was added again and the solution was heated to reflux for 40-70 hours. Dark brown mixture was concentrated and the crude product was purified by flash column chromatography (eluent as indicated).

IV-10: (0.80 g, 3.18 mmol, 78% yield) ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 (t, *J*=7.2 Hz, 3H), 2.78 (t, *J*=6.3 Hz, 2H), 3.32 (dd, *J*=3.3, 6.3 Hz, 1H), 3.34 (dd, *J*=3.00, 6.0 Hz, 1H), 4.08 (q, *J*=7.2 Hz, 2H), 5.04 (s, 1H), 7.05 (d, *J*=8.4 Hz, 1H), 7.22 (m, 1H), 7.56 (d, *J*=2.4 Hz, 1H), 8.91 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.5, 28.5, 38.6, 58.7, 78.9, 125.2, 154.6, 171.0; IR ($CHCl_3$) 3299, 2979, 1649, 1609, 1560, 1480, 1300, 1266, 1177, 1038 cm^{-1}. HRMS calcd for $C_{13}H_{14}NO_2Cl$ *m/z* 251.0713, obsd *m/z* 251.0709 .

IV-29: (ethyl acetate:hexane/2:1, 0.29 g, 1.05 mmol, 77% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, *J*=7.2 Hz, 3H), 2.78 (t, *J*=6.5 Hz, 2H), 3.38 (dt, *J*=3.0, 6.00 Hz, 2H), 3.84 (s, 3H), 3.86 (s, 3H), 4.12 (q, *J*=7.2 Hz, 2H), 5.01 (s, 1H), 6.61 (s, 1H), 7.08 (s, 1H), 9.00 (bs, 1H)); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.6, 28.4, 38.8, 55.8, 58.4, 76.8, 107.9, 110.5, 121.4, 129.8, 147.6, 150.9, 156.2, 171.0; IR ($CHCl_3$) 3299, 3019, 2977, 2940, 2838, 1647, 1601, 1572, 1499, 1464, 1341, 1281, 1262, 1177, 1121, 1057 cm^{-1}; HRMS calcd for $C_{15}H_{19}NO_4$ *m/z* 277.1314, obsd *m/z* 277.1317.

IV-35: (diethyl ether:petroleum ether/1:2, 0.10 g, 0.46 mmol, 10% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (t, *J*=7.2 Hz, 3H), 2.90 (t, *J*=6.3 Hz, 2H), 3.42 (dd, *J*=3.5, 6.5 Hz, 1H), 3.44 (dd, *J*=3.5, 6.2 Hz, 1H), 4.16 (q, *J*=7.2 Hz, 2H), 5.16 (s, 1H), 7.15-7.39 (m, 3H), 7.66 (d, *J*=8.1 Hz, 1H), 9.05 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.6, 29.0,

38.7, 58.6, 78.1, 125.2, 126.9, 128.2, 129.5, 130.3, 136.4, 156.1, 171.2; IR 3299, 2979, 2953, 1710, 1648, 1602, 1484, 1305, 1266, 1178, 1034 cm^{-1}; HRMS calcd for $C_{13}H_{15}NO_2$ *m/z* 217.1103, obsd (M+1) *m/z* 218.1182.

IV-41: (diethyl ether:petroleum ether/1:2, 1.70 g, 6.63 mmol, 77% yield); ^1H NMR (300 MHz, $CDCl_3$) δ 1.22 (t, *J*=7.2 Hz, 3H), 2.87-2.96 (m, 2H), 3.44-3.53 (m, 2H), 4.11 (q, *J*=7.2 Hz, 2H), 4.84 (s, 1H), 7.03-7.11 (m, 1H), 7.17-7.24 (m, 1H), 7.27-7.33 (m, 1H), 7.47-7.53 (m, 1H), 8.13 (bs, 1H), 8.22 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.6, 20.7, 40.5, 58.8, 77.6, 111.6, 116.1, 119.5, 120.3, 124.6, 126.2, 127.7, 137.1, 150.5, 170.6; IR ($CHCl_3$) 3328, 2930, 1640, 1605, 1538, 1273, 1175, 1132, 1038 cm^{-1}; HRMS calcd for $C_{15}H_{16}N_2O_2$ *m/z* 256.1212, obsd *m/z* 256.1220.

IV-38: (diethyl ether:petroleum ether/1:2, 0.12 g, 0.54 mmol, 91% yield); ^1H NMR (300 MHz, $CDCl_3$) δ 1.22 (t, *J*=7.2 Hz, 3H), 2.76-2.83 (m, 2H), 3.38-3.45 (m, 2H), 4.08 (q, *J*=7.2 Hz, 2H), 4.89 (s, 1H), 6.82 (d, *J*=5.1 Hz, 1H), 7.23 (d, *J*=5.1 Hz, 1H), 8.39 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.6, 25.0, 39.9, 58.7, 79.3, 127.4, 127.5, 130.9, 140.2, 152.6, 170.7; IR ($CHCl_3$) 3314, 2979, 2938, 2901, 2857, 1734, 1649, 1603, 1530, 1495, 1439, 1368, 1285, 1167, 1129, 1051 cm^{-1}; HRMS calcd for $C_{11}H_{13}NO_2S$ *m/z* 223.0667, obsd *m/z* 223.0658.

Hydrogenolysis of 3-Thiopheneacetonitrile:

The slurry of 3-thiopheneacetonitrile (3.0 g, 24.35 mmol), 2.2 g of 50% suspension of Ra-Ni in water in methyl alcohol with 10 drops of saturated solution of ammonium hydroxide was kept in atmospheric pressure of hydrogen for 24-30 hours at room temperature. Then the mixture was carefully filtered and concentrated under reduced

pressure. The crude product was purified by flash column chromatography (diethyl ether:petroleum ether/2:1). Yield : 2.0 g (65%). The crude product was pure enough to be used for the next step without further purification.

Preparation of 2-Phenylacrylic acid:

α-Bromostyrene (1.0 g, 5.46 mmol) was added dropwise to the mixture of n-BuLi in diethyl ether at -(35-40)° C. After 10 minutes a solution was poured onto an excess of dry ice and warmed to room temperature. 100 mL of water was added and an emulsion was acidified by diluted HCl to pH 2-3 (indicated by a litmus paper). Recrystallized from 80% ethyl alcohol or purified by flash column chromatography (diethyl ether:petroleum ether/1:1). Yield : 0.65 g (80%).

General Procedure for Aza-Annulation Reactions of Enamino Esters :

A solution of mixed anhydride of a corresponding derivative of acrylic acid (freshly prepared from a corresponding acrylic acid, NaH and ethyl chloroformate in THF at -78° C) was added to the enamine solution in THF at room temperature and the reaction mixture was allowed to stir at room temperature for 12-18 hours. Reactions were quenched by the addition of H_2O, and the mixture was extracted 4 times with 20 mL of either Et_2O or EtOAc. The combined organic fractions were dried (Na_2SO_4), filtered, and the solvent evaporated under reduced pressure. The crude product was purified by flash column chromatography (eluent as indicated). (The concentrated crude product may be purified directly by flash column chromatography).

IV-26: (diethyl ether:petroleum ether/1:1, 0.045 g, 0.15 mmol, 68% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (t, *J*=7.2 Hz, 3H), 2.52-2.60 (m, 2H), 2.65-2.74 (m, 2H), 2.78 (t, *J*=6.2 Hz, 2H), 3.67 (t, *J*=5.9 Hz, 2H), 7.09 (d, *J*=8.1 Hz, 1H), 7.23 (m, 1H), 7.29 (d, *J*=1.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7, 21.7, 28.3, 30.7, 40.0, 61.0, 110.5, 128.1, 129.5, 129.5, 131.4, 131.9, 135.4, 140.8, 168.1, 169.8; IR 3416, 2980, 2882, 1671 (broad), 1613, 1372, 1300, 1188 cm^{-1}; HRMS calcd for $C_{16}H_{16}NO_3Cl$ *m/z* 305.0819, obsd *m/z* 305.0776 .

IV-9: (diethyl ether:petroleum ether/1:1, 0.12 g, 0.32 mmol, 81% yield) m.p. = (189-190)° C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 (t, *J*=7.2 Hz, 3H), 2.78-2.85 (m, 2H), 2.98 (dd, *J*=8.9, 17.7 Hz, 1H), 3.06 (dd, *J*=7.1, 17.7 Hz, 1H), 3.63-3.80 (m, 3H), 4.06 (q, *J*=7.2 Hz, 2H), 7.06-7.32 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7, 28.4, 28.9, 40.2, 45.6, 61.1, 109.9, 127.3, 127.9, 128.0, 128.6, 129.5, 129.6, 131.4, 131.8, 135.4, 137.4, 140.7, 167.8, 170.3; IR ($CHCl_3$) 3019, 1690, 1671, 1377 cm^{-1}; HRMS calcd for $C_{22}H_{20}NO_3$ *m/z* 381.1132, obsd *m/z* 381.1111.

IV-8: (0.08 g, 0.20 mmol, 81% yield) ^{1}H NMR (300 MHz, $CDCl_3$) d 1.16 (t, *J*=7.2 Hz, 3H), 2.89-2.97 (m, 2H), 4.21 (q, *J*=7.2 Hz, 2H), 4.15-4.24 (m, 2H), 7.18-7.40 (m, 6H), 7.64-7.70 (m, 2H), 7.85 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) d 13.8, 28.0, 40.8, 61.7, 110.8, 128.2, 128.5, 128.6, 129.2, 129.7, 130.1, 130.7, 131.9, 135.8, 135.9, 137.6, 143.8, 160.7, 167.6; IR ($CHCl_3$) 2928, 1711, 1647, 1534, 1250, 1109 cm^{-1}; HRMS calcd for $C_{22}H_{18}NO_3$ *m/z* 379.0975, obsd *m/z* 379.0978.

IV-27: (0.09 g, 0.25 mmol, 84% yield based on recovery of the 0.126 g of the starting ester enamine) ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 (t, *J*=7.2 Hz, 3H), 2.02 (s, 3H, 2.28 (dd, *J*=15.3, 16.5 Hz, 1H), 2.75-2.85 (m, 2H), 3.08 (m, 1H), 3.48 (dd, *J*=6.9, 17.1 Hz,

1H), 3.97-4.16 (m, 2H), 4.32 (ddd, *J*=3.8, 3.8, 12.6 Hz, 1H), 4.50 (ddd, *J*=6.6, 6.6, 14.7 Hz, 1H), 6.49 (d, *J*=5.4 Hz, 1H), 7.08 (d, *J*=8.1 Hz, 1H), 7.24 (dd, *J*=1.8, 8.1 Hz, 1H), 7.37 (d, *J*=1.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7, 23.2, 28.1, 28.1, 40.3, 48.5, 61.2, 110.2, 128.0, 129.9, 129.9, 131.3, 131.5, 135.1, 140.4, 166.6, 168.3, 170.3; IR ($CHCl_3$) 3341, 3017, 1686 (broad), 1543, 1387, 1312, 1258 cm^{-1}; HRMS calcd for $C_{18}H_{19}ClN_2O_4$ *m/z* 362.1033, obsd *m/z* 362.1033 .

IV-30: (diethyl ether:petroleum ether/1:1, 0.25 g, 0.61 mmol, 76% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.12 (t, *J*=7.2 Hz, 3H), 2.83 (m, 2H), 2.99 (dd, *J*=10.2, 17.1 Hz, 1H), 3.10 (dd, *J*=6.6, 17.4 Hz, 1H), 3.66 (m, 1H), 3.76-3.93 (m, 2H), 3.80 (s, 3H), 3.90 (s, 3H), 4.10 (q, *J*=7.2 Hz, 2H), 6.69 (s, 1H), 6.88 (s, 1H), 7.21-7.38 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 28.3, 29.3, 40.0, 45.8, 55.8, 56.0, 60.6, 107.2, 109.4, 113.0, 122.2, 127.1, 128.0, 128.4, 130.4, 137.9, 142.0, 146.6, 150.4, 168.3, 170.5; IR ($CHCl_3$) 3031, 3006, 2977, 2940, 1690, 1661, 1605, 1512, 1486, 1377, 1347, 1279, 1242, 1134, 1044 cm^{-1}; HRMS calcd for $C_{24}H_{25}NO_5$ *m/z* 407.1733, obsd *m/z* 407.1727.

IV-31: (diethyl ether:petroleum ether/4:1, 0.08 g, 0.20 mmol, 81% yield) ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23 (t, *J*=7.2 Hz, 3H), 2.85-3.00 (m, 2H), 3.84 (s, 3H), 3.96 (s, 3H), 4.18-4.30 (m, 2H), 4.25 (q, *J*=7.2 Hz, 2H), 6.79 (s, 1H), 6.94 (s, 1H), 7.30-7.46 (m, 3H), 7.69-7.75 (m, 2H), 7.89 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 28.0, 40.6, 56.0, 56.1, 61.3, 109.3, 109.7, 112.9, 120.6, 127.4, 127.8, 128.1, 128.6, 131.3, 136.3, 127.7, 145.4, 147.2, 151.6, 160.8, 168.1; IR ($CHCl_3$) 3019, 1703, 1640, 1507 cm^{-1}; HRMS calcd for $C_{24}H_{23}NO_5$ *m/z* 405.1577, obsd *m/z* 405.1584.

IV-33: (diethyl ether:petroleum ether/4:1, 0.04 g, 0.09 mmol, 25% yield); m.p. = (195-196)° C (sealed), (decomp.); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 (t, *J*=7.2 Hz, 3H), 2.85-

2.92 (m, 2H), 3.77 (s, 3H), 3.88 (s, 3H), 4.15-4.24 (m, 2H), 4.22 (q, *J*=7.2 Hz, 2H), 6.70 (s, 1H), 6.87 (s, 1H), 7.38-7.44 (m, 3H), 7.84-7.92 (m, 2H), 8.83 (s, 1H), 9.11 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 27.9, 41.2, 56.1, 61.6, 109.9, 110.4, 112.3, 120.4, 122.4, 126.1, 127.2, 128.8, 130.2, 132.1, 134.1, 138.5, 147.4, 151.1, 157.1, 165.7, 168.1; IR ($CHCl_3$) 3376, 3019, 2957, 1722, 1707, 1646, 1609, 1505, 1489, 1300, 1279, 1239 cm^{-1}; HRMS calcd for $C_{25}H_{24}N_2O_6$ *m/z* 448.1634, obsd *m/z* 448.1628.

IV-32: (diethyl ether:petroleum ether:methyl alcohol/90:5:5, 0.09 g, 0.23 mmol, 29% yield); m.p. = (189-190)° C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15 (t, *J*=7.2 Hz, 3H), 2.06 (s, 3H), 2.30 (dd, *J*=15.0, 16.5 Hz, 1H), 2.71-2.93 (m, 2H), 3.16 (ddd, *J*=4.8, 11.6, 11.9 Hz, 1H), 3.49 (dd, *J*=6.9, 16.8 Hz, 1H), 3.81 (s, 3H), 3.88 (s, 3H), 4.00-4.16 (m, 2H), 4.30 (ddd, *J*=4.2, 4.2, 12.6 Hz, 1H), 4.54 (ddd, *J*=6.3, 6.3, 15.3 Hz, 1H), 6.58 (d, *J*=5.4 Hz, 1H), 6.66 (s, 1H), 6.96 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 23.1, 28.0, 28.1, 40.1, 48.6, 55.8, 55.9, 60.7, 107.5, 109.2, 113.2, 121.7, 129.9, 141.9, 146.6, 150.5, 167.0, 168.6, 170.3; IR 3320, 3017, 2940, 1676 (broad), 1512, 1385, 1277, 1258, 1115 cm^{-1}; HRMS calcd for $C_{20}H_{24}N_2O_6$ *m/z* 388.1635, obsd (M+1) *m/z* 389.1713.

IV-36: (diethyl ether:petroleum ether/1:1, 0.06 g, 0.18 mmol, 69% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.01 (t, *J*=7.2 Hz, 3H), 2.80-2.87 (m, 2H), 2.98 (dd, *J*=9.3, 17.4 Hz, 1H), 3.05 (dd, *J*=6.9, 17.4 Hz, 1H), 3.62-3.82 (m, 3H), 4.01 (q, *J*=7.2 Hz, 2H), 7.08-7.31 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7, 28.8, 28.9, 40.2, 45.7, 60.8, 108.9, 125.8, 126.7, 127.2, 128.0, 128.5, 129.6, 129.8, 130.3, 137.0, 137.7, 142.1, 168.2, 170.5; IR ($CHCl_3$) 3017, 1674 (broad), 1381, 1306, 1237, 1169 cm^{-1}; HRMS calcd for $C_{22}H_{21}NO_3$ *m/z* 347.1522, obsd *m/z* 347.1525.

IV-37: (diethyl ether:petroleum ether/1:1, 0.04 g, 0.13 mmol, 79% yield); m.p. = (145-146)° C, (sealed); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (t, *J*=7.2 Hz, 3H), 2.99 (m, 2H), 4.23 (q, *J*=7.2 Hz, 2H), 4.21-4.30 (m, 2H), 7.24-7.48 (m, 7H), 7.72-7.77 (m, 2H), 7.92 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 28.4, 40.7, 61.4, 110.3, 126.2, 127.2, 127.9, 128.2, 128.3, 128.5, 128.6, 129.8, 131.0, 136.2, 137.4, 137.7, 145.4, 160.8, 168.0; IR ($CHCl_3$) 3007, 1709, 1647, 1534, 1298, 1252, 1107 cm^{-1}; HRMS calcd for $C_{22}H_{19}NO_3$ *m/z* 345.1365, obsd *m/z* 345.1359.

IV-42: (diethyl ether:petroleum ether/1:2, 0.4 g, 1.04 mmol, 89%); m.p. = (145-146)° C (sealed) (decomp.); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, *J*=7.2 Hz, 3H), 2.89-2.96 (m, 2H), 3.02-3.09 (m, 2H), 3.67 (m, 1H), 4.00 (m, 1H), 4.22 (q, *J*=7.2 Hz, 2H), 4.53 (m, 1H), 7.04 (m, 1H), 7.13-7.29 (m, 7H), 7.36 (d, *J*=8.1 Hz, 1H), 7.49 (d, *J*=8.1 Hz, 1H), 12.16 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 21.1, 29.5, 41.7, 46.4, 61.4, 105.8, 112.2, 119.4, 120.0, 124.9, 125.1, 126.1, 127.3, 128.0, 128.6, 136.7, 137.5, 141.0, 168.6, 171.4; IR ($CHCl_3$) 3247, 3015, 2932, 1671, 1576, 1368, 1283, 1167, 1130, 1034 cm^{-1}; HRMS calcd for $C_{24}H_{22}N_2O_3$ *m/z* 386.1631, obsd *m/z* 386.1636 .

IV-43: (gradient diethyl ether:petroleum ether/1:2-diethyl ether-ethyl acetate; 0.25 g, 0.68 mmol, 58% yield), ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37 (t, *J*=7.2 Hz, 3H), 2.08 (s, 3H), 2.38 (dd, *J*=15.6 Hz, 1H), 2.90-3.03 (m, 2H), 3.30 (m, 1H), 3.60 (dd, *J*=5.7, 16.2 Hz, 1H), 4.23-4.38 (m, 2H), 4.45 (ddd, *J*=5.7, 5.7, 14.7 Hz, 1H), 5.23 (ddd, *J*=3.3, 3.3, 11.7 Hz, 1H), 6.67 (d, *J*=5.4 Hz, 1H), 7.12 (m, 1H), 7.29 (m, 1H), 7.43 (d, *J*=8.1 Hz, 1H), 7.54 (d, *J*=7.8 Hz, 1H), 12.20 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 21.0, 23.2, 28.6, 42.1, 48.8, 61.6, 105.4, 112.2, 117.9, 119.4, 120.0, 124.7, 125.2, 125.6, 136.7,

139.9, 168.3, 169.5, 170.2; IR ($CHCl_3$) 3283, 3011, 1667, 1574, 1516, 1391, 1256, 1169, 1109, 1034 cm^{-1}; HRMS calcd for $C_{20}H_{21}N_3O_4$ *m/z* 367.1532, obsd *m/z* 367.1590 .

IV-44: (diethyl ether:petroleum ether/1:2, 0.29 g, 0.75 mmol, 48% yield); m.p. = (165-166)° C (sealed) (decomp.); ^1H NMR (300 MHz, $CDCl_3$) δ 1.44 (t, *J*=7.2 Hz, 3H), 3.07 (m, 2H), 4.45 (q, *J*=7.2 Hz, 2H), 4.60-4.67 (m, 2H), 7.18 (m, 1H), 7.30-7.51 (m, 5H), 7.63 (d, *J*=7.8 Hz, 1H), 7.73-7.79 (m, 2H), 8.13 (s, 1H), 11.75 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 19.4, 42.5, 62.1, 106.0, 112.3, 118.9, 119.6, 120.3, 124.3, 125.5, 126.2, 127.2, 127.8, 128.1, 128.5, 136.4, 137.3, 138.3, 142.0, 161.2, 168.1; IR ($CHCl_3$) 3297, 3011, 1696, 1644, 1541, 1495, 1447, 1372, 1339, 1264, 1233, 1188, 1164, 1119 cm^{-1}; HRMS calcd for $C_{24}H_{20}N_2O_3$ *m/z* 384.1474, obsd *m/z* 384.1485.

IV-39: (diethyl ether:petroleum ether/1:2, 0.03 g, 0.09 mmol, 64%); ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (t, *J*=7.2 Hz, 3H), 2.75-2.82 (m, 2H), 2.94 (d, *J*=8.4 Hz, 2H), 3.70 (dd, *J*=8.7, 8.7 Hz, 1H), 3.79 (m, 1H), 4.21 (q, *J*=7.2 Hz, 2H), 4.26 (m, 1H), 6.78 (d, *J*=5.4 Hz, 1H), 7.16-7.31 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 25.7, 29.9, 40.1, 46.3, 61.2, 107.0, 126.2, 127.3, 127.7, 128.1, 128.6, 129.0, 1137.4, 137.7, 141.5, 167.9, 170.9; IR ($CHCl_3$) 3013, 2932, 1706, 1680, 1377, 1239, 1153, 1129 cm^{-1}; HRMS calcd for $C_{20}H_{19}NO_3S$ *m/z* 353.1086, obsd 353.1096.

IV-40: (gradient diethyl ether:petroleum ether/1:1-2:1-diethyl ether-ethyl acetate, 0.026 g, 0.074 mmol, 97% yield) ^1H NMR (300 MHz, $CDCl_3$) δ 1.30 (t, *J*=7.2 Hz, 3H), 2.90-2.97 (m, 2H), 4.32 (q, *J*=7.2 Hz, 2H), 4.32-4.40 (m, 2H), 6.90 (d, *J*=5.4 Hz, 1H), 7.24-7.39 (m, 3H), 7.43 (d, *J*=5.4 Hz, 1H), 7.61-7.70 (m, 2H), 7.72 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 24.0, 41.2, 61.8, 77.2, 108.6, 125.9, 127.9, 128.0, 128.2, 128.6,

130.7, 136.2, 137.1, 140.5, 142.6, 160.9, 167.1; IR ($CHCl_3$) 3013, 2930, 1713, 1644, 1538, 1240, 1132 cm^{-1}; HRMS calcd for $C_{20}H_{17}NO_3S$ *m/z* 351.0929, obsd *m/z* 353.0925.

Preparation of Ethyl 3-(N,N-Dimethylamino)-2-phenylpropenoate :[19]

A mixture of 1.04 g (6.3 mmol) of ethyl phenyl acetate and 1.29 g (9.75 mmol, 1.6 equiv.) of bis(methoxy)dimethylaminomethane was stirred at 60° C for 48 hours. The reaction mixture was concentrated under reduced pressure and then bulb-to-bulb distilled (oven: (80-85)° C, pressure: 1mm of Hg) to afford 0.71 g of the product as a residue (51%).

Preparation of Ethyl Potassium Malonate :[20]

KOH (5.6 g, 100 mmol) was dissolved in 100 mL of absolute ethyl alcohol and the solution was added dropwise to a stirred solution of diethylmalonate (20.23 g, 100 mmol) in 100 mL of absolute ethyl alcohol, at 0° C during 1 hour. The reaction mixture was then allowed to warm up to room temperature and the stirring was continued for an additional 1 hour. The white crystals of the salt were separated by filtration and dried under vacuum. Yield : 11.4 g (67%).

Preparation of Ethyl Malonyl Chloride :[20]

Oxaloyl chloride (3.2 g, 25 mmol) in 10 mL of dry benzene was added dropwise to a stirred suspension of ethyl potassium malonate (2.42 g, 20 mmol) in 50 mL of dried benzene at 0° C during 1 hour. After the solution had been stirred at room temperature for 1 hour, the solid residue was removed by filtration and the filtrate was concentrated under

reduced pressure, diluted with dry dichloromethane and concentrated again. The product used immediately for the next step without further purification.

General Procedure for the Preparation of Ester Amides.

To suspension of ethyl potassium malonate (1.65 equiv.) in dry benzene was added oxalyl chloride (2.1 equiv.) in benzene dropwise at 0° C during a period 50 minutes and the mixture was stirred for 1 hour at 0° C. Then the mixture was gradually warmed to the room temperature mand stirring was continued for 1 additional hour. The solution was filtered and concentrated under reduced pressure, diluted with CH_2Cl_2 and concentrated again. The residue was dissolved in CH_2Cl_2 and added by a cannula to a solution of a primary amine (1.0 equiv.) and triethylamine (1 equiv., in the case of hydrochloride 2 equiv.) in CH_2Cl_2 at 0° C. The mixture was stirred for 12-20 hours at the room temperature, then neutralized with 3M HCl, extracted with CH_2Cl_2, organic layers dried over Na_2SO_4. Concentrated and the crude product crystallized or purified by the flash column chromatography.

IV-11: (6.2 g, 28.8 mmol, 66% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13 (t, *J*=7.2 Hz, 3H), 2.67 (t, *J*=7.1 Hz, 2H), 3.12 (s, 2H), 3.32 (d, *J*=7.2 Hz, 1H), 3.37 (d, *J*=7.2 Hz, 1H), 4.03 (q, *J*=7.2 Hz, 2H), 6.98-7.04 (m, 2H), 7.09-7.15 (m, 2H), 7.33 (bt, *J*=7.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7, 34.4, 40.3, 41.3, 61.0, 128.2, 129.8, 131.7, 137.1, 165.1, 168.5; IR ($CHCl_3$) 3291, 2984, 2940, 1740, 1651, 1555, 1493, 1370, 1339, 1196, 1157, 1092, 1032, 1017 cm^{-1}.

IV-13: (ethyl acetate:hexane/4:1, 2.40 g, 8.13 mmol, 49% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (t, *J*=7.2 Hz, 3H), 2.71 (m, 2H), 3.19 (s, 2H), 3.39-3.44 (m, 2H), 3.77 (s,

3H), 3.79 (s, 3H), 4.08 (q, *J*=7.2 Hz, 2H), 6.63-6.76 (m, 3H), 7.15 (bt, *J*=7.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7, 34.8, 40.7, 41.1, 55.5, 55.6, 61.2, 111.1, 111.7, 120.3, 131.1, 147.3, 148.7, 164.8, 169.0; IR ($CHCl_3$) 3312, 2938, 1740, 1655, 1516, 1264, 1239, 1157, 1144, 1028 cm^{-1}.

IV-15: (3.5 g, 14.9 mmol, 36% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.17 (t, *J*=7.2 Hz, 3H), 2.75 (m, 2H), 3.17 (s, 2H), 3.42 (m, 2H), 4.06 (q, *J*=7.2 Hz, 2H), 7.08-7.24 (m, 5H), 7.41 (bt, *J*-5.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.5, 35.0, 40.5, 41.3, 60.8, 125.9, 128.0, 128.2, 138.4, 165.1, 168.3; IR ($CHCl_3$) 3299, 2982, 2938, 1740, 1653, 1555, 1370, 1337, 1192, 1157 cm^{-1}; HRMS calcd for $C_{13}H_{17}NO_3$ *m/z* 235.1209, obsd *m/z* 235.1214.

IV-16: (ethyl acetate:petroleum ether/6:1, 2.52 g, 9.0 mmol, 43% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (t, *J*=7.2 Hz, 3H), 2.86-2.93 (m, 2H), 3.22 (s, 2H), 3.51 (dd, *J*=7.1, 13.1, 2H), 4.10 (q, *J*=7.2 Hz, 2H), 7.32 (d, *J*=8.7 Hz, 2H), 7.32 (bs, 1H), 8.06 (d, *J*=8.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 35.2, 40.0, 40.9, 61.4, 123.5, 129.5, 146.4, 146.6, 165.4, 169.0; IR ($CHCl_3$) 3264, 2986, 1744, 1638, 1559, 1520, 1372, 1347, 1194 cm^{-1}; HRMS calcd for $C_{13}H_{16}N_2O_5$ *m/z* 280.1059, obsd *m/z* 280.1053.

IV-17: (1.72 g, 6.87 mmol, 100% yield) ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (t, *J*=7.2 Hz, 3H), 2.70 (t, *J*=7.1 Hz, 2H), 3.24 (s, 2H), 3.44 (d, *J*=7.2 Hz, 1H), 3.48 (d, *J*=7.2 Hz, 1H), 3.55 (bs, 2H), 4.15 (q, *J*=7.2 Hz, 2H), 6.61 (d, *J*=8.4 Hz, 2H), 6.97 (d, *J*=8.4 Hz, 2H), 7.03 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 34.5, 41.0, 41.3, 61.4, 115.2, 128.4, 129.4, 144.8, 164.8, 169.2.

IV-14: (ethyl acetate:hexane/2:1, 2.23 g, 8.39 mmol, 58% yield); m.p. = (53-54)° C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13 (t, *J*=7.2 Hz, 3H), 2.61-2.70 (m, 2H), 3.13 (s, 2H), 3.30-3.40 (m, 2H), 3.63 (s, 3H), 4.03 (q, *J*=7.2 Hz, 2H), 6.70 (d, *J*=8.4 Hz, 2H), 7.00 (d, *J*=8.4

Hz, 2H), 7.27 (bt, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.6, 34.1, 40.7, 41.3, 54.7, 60.9, 113.4, 129.2, 130.4, 157.7, 165.0, 168.5; IR ($CHCl_3$) 3316, 3009, 2938, 1738, 1659, 1514, 1248, 1179, 1034 cm^{-1}; HRMS calcd for $C_{14}H_{19}NO_4$ *m/z* 265.1314, obsd *m/z* 265.1315.

IV-18: (diethyl ether:petroleum ether/3:1, 1.0 g, 3.65 mmol, 29% yield) ^1H NMR (300 MHz, $CDCl_3$) δ 1.23 (t, *J*=7.2 Hz, 3H), 2.98 (t, *J*=7.1 Hz, 2H), 3.23 (s, 2H), 3.58 (d, *J*=6.6 Hz, 1H), 3.62 (d, *J*=6.6 Hz, 1H), 4.13 (q, *J*=7.2 Hz, 2H), 6.98 (s, 1H), 7.08-7.27 (m, 3H), 7.35 (d, *J*=8.1 Hz, 1H), 7.60 (d, *J*=8.1 Hz, 1H), 8.94 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7, 24.8, 39.8, 41.4, 61.2, 111.2, 111.9, 118.2, 118.8, 121.5, 122.2, 126.9, 136.2, 165.3, 168.7; IR 3397, 3316, 3007, 1732, 1659, 1545, 1458, 1389, 1194, 1159, 1030 cm^{-1}.

Preparation of the Corresponding (3,4-Dihydro-2H-isoquinolin-1-ylidene) Acetic Acid Ethyl Ester Derivatives (Bischler-Napieralski Reaction) :

The mixture of the corresponding N-phenethyl-malonamic acid ethyl ester derivative (1.0 equiv.) in acetonitrile (0.14 M) was taken up to reflux and $POCl_3$ (6.5 equiv.) was added at once. The mixture was then heated to reflux for 1-2 hours and then concentrated, diluted with ethyl acetate and concentrated again. Then diluted with ethyl acetate, washed with saturated $NaHCO_3$, water layer extracted with ethyl acetate and combined organic layers were washed with water and dried over Na_2SO_4. The crude product was purified by flash column chromatography (an eluent as indicated).

Direct Method for the DDQ Oxidation of Aza-Annulation Products.

A mixture of the aza-annulation product (0.5-20.0 mmol, 1.0 equiv) was taken up in toluene (0.1 M with respect to the aza-annulation product). After heating at reflux for 10-18 hours, the solvent was removed under reduced pressure, the residue dissolved in dichloromethane, filtered through a pad of Celite and the crude product was purified by flash column chromatography (an eluent as indicated).

General Procedure of Preparation of Isothiocyanates :

A solution of carbon disulfide (1.0 equiv.) in dichloromethane was added dropwise during 15 minutes to a stirred mixture of an appropriate amine (1.0 equiv.), triethylamine (1.0 equiv.) and dichloromethane (2.76 M) at 0° C, and the resulting mixture was allowed to warm slowly to room temperature. The mixture was then cooled to 0° C again, and ethyl chloroformate (1.0 equiv.) was added dropwise during 15 minutes at this temperature and the mixture was allowed to warm up slowly to ambient temperature. Triethylamine (1.0 equiv.) was added and the mixture was stirred for a further 1.5 hour at room temperature, and finally heated under reflux for 15 minutes. An excess of water was added and the mixture was made alkaline with 2M NaOH. Extraction with diethyl ether and concentration under reduced pressure gave the product pure enough to use it without further purification for the next step.

Cyclization of Isothiocyanates with Polyphosphoric Acid :

The isothiocyanate was stirred with polyphosphoric acid (10 times excess) at 150° C for 1-4 hours and the resultant blood-red mixture was poured into an excess of water. The

solution was neutralized with saturated $NaHCO_3$ and extraction with dichloromethane gave the corresponding product. It was purified by flash column chromatography (an eluent as indicated).

Cyclization of 2-(4-Chlorophenyl)ethyl Isothiocyanate with Aluminium Chloride :

The 2-(4-chlorophenyl)ethyl isothiocyanate (0.99 g, 5.0 mmol, 1 equiv.) was added dropwise to a stirred suspension of powdered $AlCl_3$ (1.5 g, 11.2 mmol, 2.24 equiv.) in tetrachloroethane (7.0 mL) at (10-20)° C. The mixture was heated at 110° C for 15-20 minutes and then poured onto a mixture of ice and 5M HCl (5.0 mL). The residue was filtered off and washed with tetrachloroethane, the combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure, and the product purified by flash column chromatography (diethyl ether:petroleum ether/2:1). Yield : 2.29 g (58% in 2 steps). (m.p. = (189-190)° C).

General Method for Aza-Annulation with 2-Phenyl-4-(ethoxymethylene)oxazolone.

The corresponding enamine (0.78-2.6 mmol) was dissolved in anhydrous DMF (0.26 M) and 2-phenyl-4-(ethoxymethylene)oxazolone (1.0 equiv) was added. After the reaction mixture was heated to reflux for 2 hours, the dark brown solution was concentrated to an oil (boiling water bath), dissolved in dichloromethane, filtered through a pad of Celite/SiO2=1:1 (w/w) and purified by flash column chromatography (eluent as indicated).

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LIST OF REFERENCES

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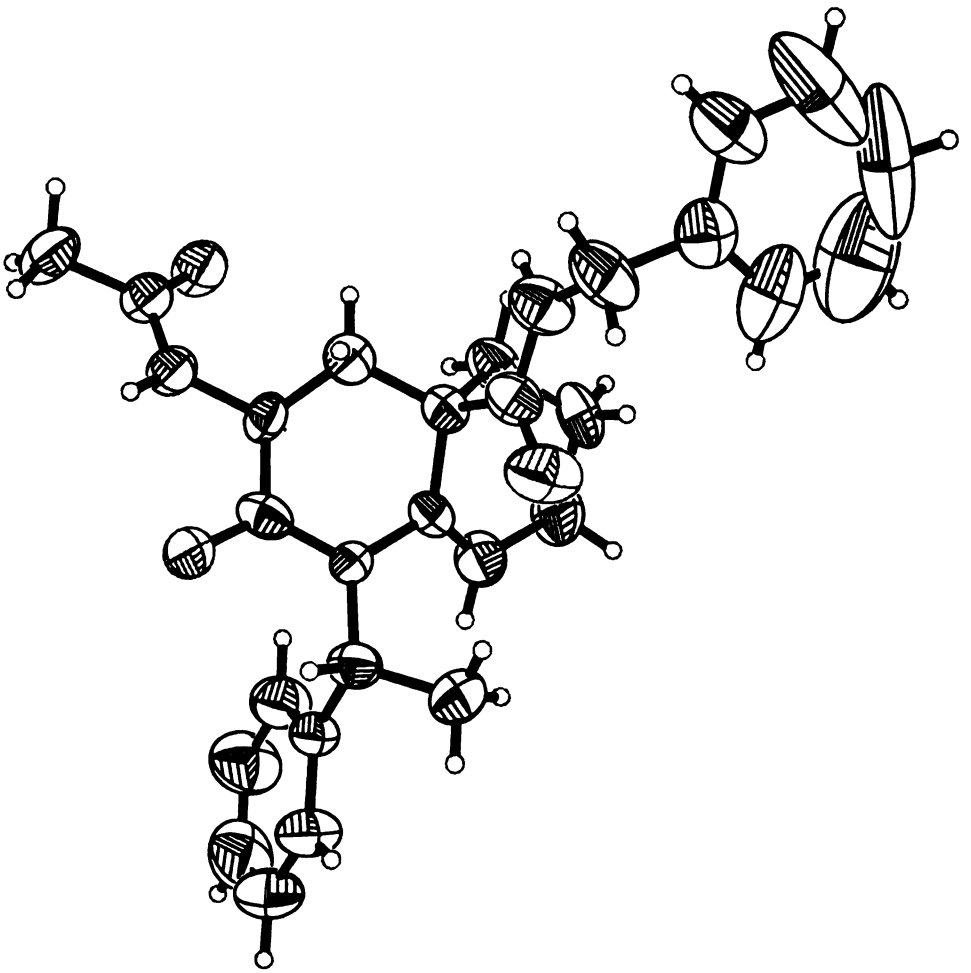
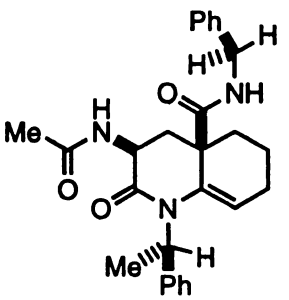
APPENDICES

APPENDIX 1

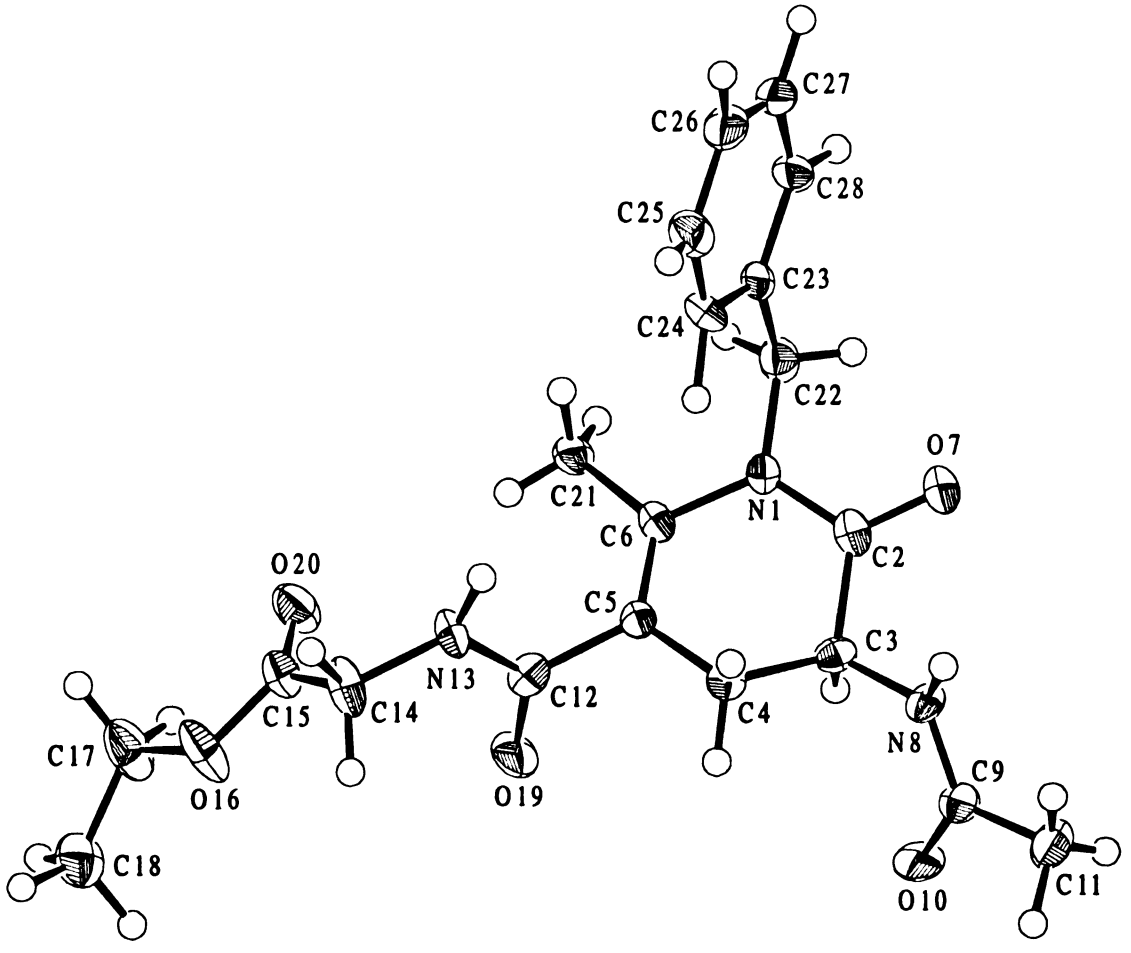
Appendix 1. ORTEP Representation of II-69a.

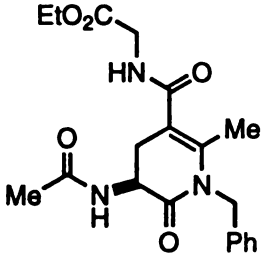




APPENDIX 2

Appendix 2. ORTEP Representation of III-23c.





III-23c

APPENDIX 3

J. Org. Chem. 1997, *62*, 1033–1042

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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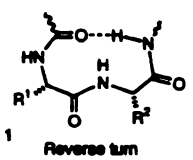
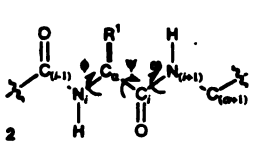
The aza-annulation of β-enamino ester and amide substrates with the mixed anhydride of 2-acetamidoacrylic acid was used for the efficient construction of highly substituted α-acetamido δ-lactam products. With the α-acetamido substituent, lactam functionality, and γ-carboxylate group, these δ-lactam products 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



2

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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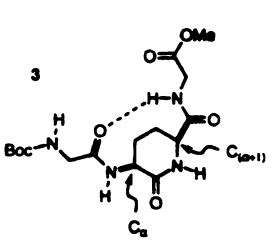
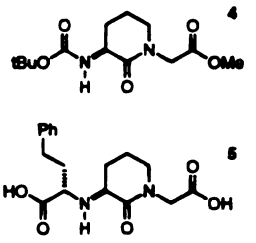
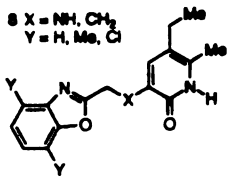
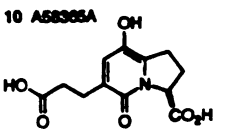
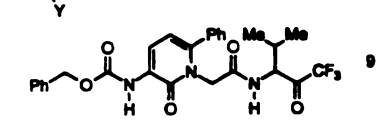




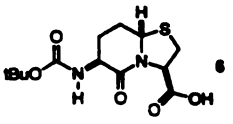


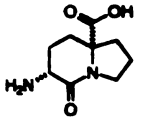




incorporated into the framework for an analog of Pro-Leu-Gly-NH_2, which serves to modulate the dopaminergic receptors in the central nervous system,[6] and as a dipeptide isostere for the Phe-His section of aspartic proteinase substrates.[7]

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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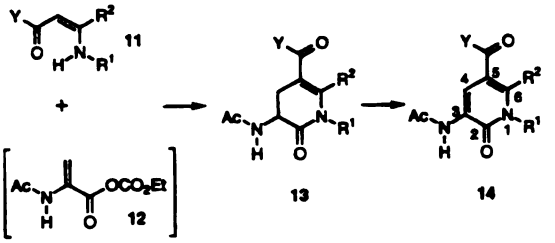
(16) For previous reports of the use of 2-amidoacrylic acid derivatives in aza-annulation, see: (a) Thyagarajan, B. S.; Gopalakrishnan, P. V. *Tetrahedron* **1964**, *20*, 1051. (b) Meyer, H.; Bossert, F.; Horstmann, H. *Justus Liebigs Ann. Chem.* **1978**, 1483. (a) Danieli, B.; Lesma, G.; Palmisano, 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 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

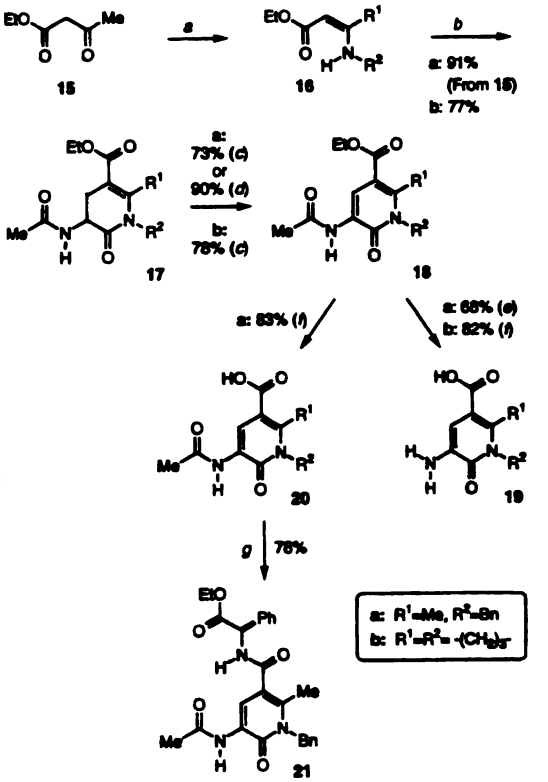
Aza-Annulation with β-Enamino Esters. The synthesis and oxidation of α-amido lactams was initially investigated for the β-amino acid homolog of alanine. Condensation of **15** with $BnNH_2$ (benzylamine) generated the intermediate β-enamino ester **16a**, which was taken on to the next step without isolation (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.[16] 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, $BF_3{\cdot}OEt_2$, 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]

(17) 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.

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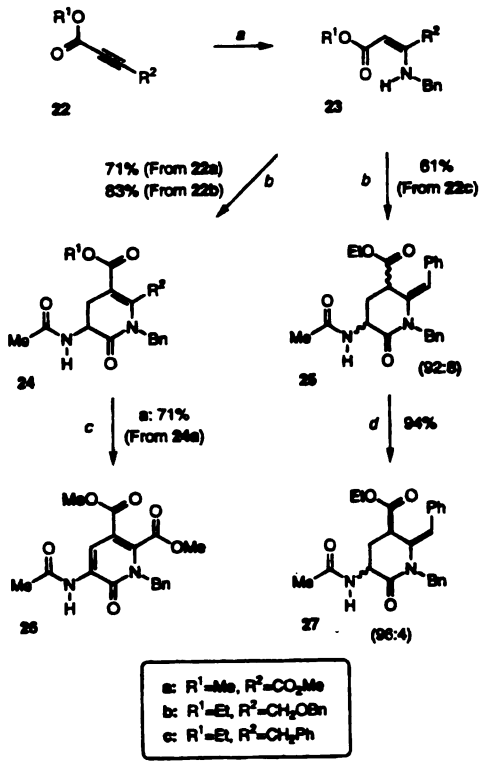
(20) The synthesis of **16b** was accomplished through methods described in: Celerier, J. P.; Deloisy-Marchalant, E.; Lhommet, G.; Maitte, P. *Org. Synth.* **1988**, *67*, 170.

(21) For other applications of **16b** and related compounds for aza-annulation reactions, see: (a) Danishefsky, S.; Etheredge, S. J. *J. Org. Chem.* **1974**, *39*, 3430. (b) Nagasaka, T.; Inoue, H.; Ichimura, M.; Hamaguchi, F. *Synthesis* **1982**, 848. (c) Nagasaka, T.; Inoue, H.; Hamaguchi, F. *Heterocycles* **1983**, *20*, 1099. (d) Brunerie, P.; Célérier, J.-P.; Huché, M.; Lhommet, G. *Synthesis* **1985**, 735. (e) ref 12c. (f) Shen, W.; Coburn, C. A.; Bornmann, W. G.; Danishefsky, S. J. *J. Org. Chem.* **1993**, *58*, 611. (g) Reference 14c. (h) Reference 15a.

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

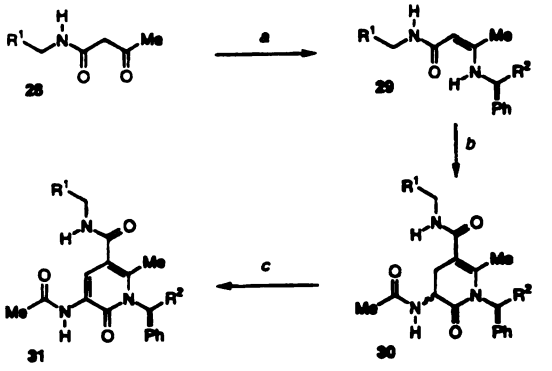


[a]Reaction conditions: (a) $BnNH_2$, BF_3-OEt_2, THF, 25 °C; (b) Sodium 2-acetamidoacrylate, $ClCO_2Et$, THF; (c) DDQ, toluene, reflux; (d) H_2 (15 psi), Pd/C, Na_2CO_3.

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 diastereomers, 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.

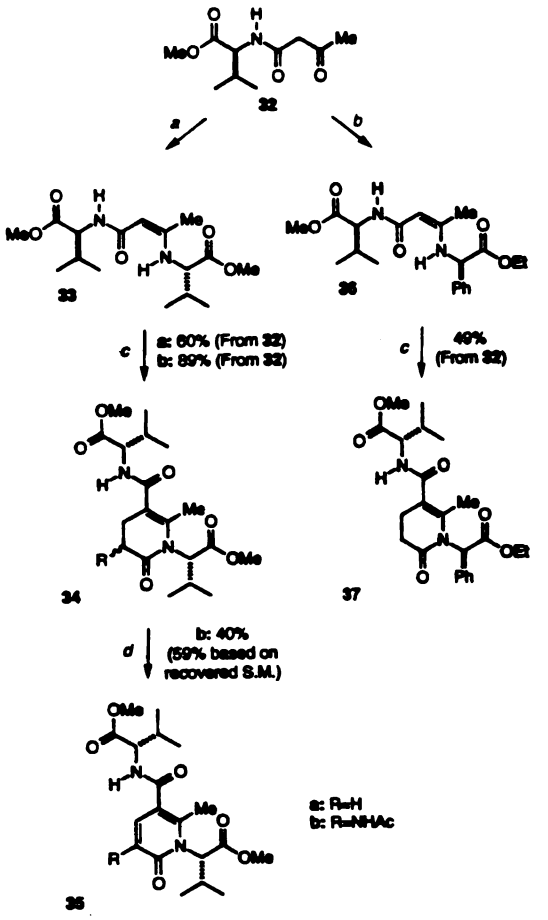
In order to probe the compatibility of the aza-annulation reaction conditions with the stereochemical integrity of the amino acid components, lactam and pyridone products that contained two separate sites of asymmetry were formed. Condensation of **32** was performed separately with valine- and phenylglycine-derived 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 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

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.

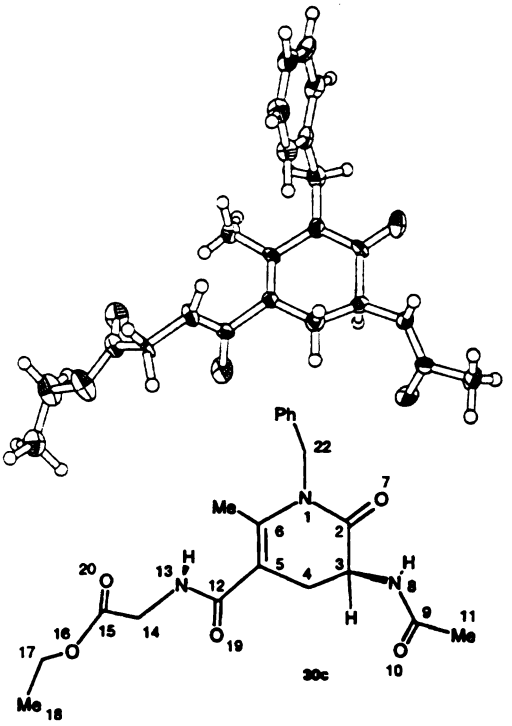


Figure 1. ORTEP, line representations, and numbering scheme of structural data obtained for **30c**.

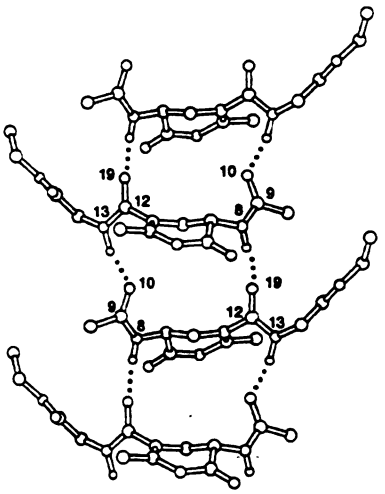
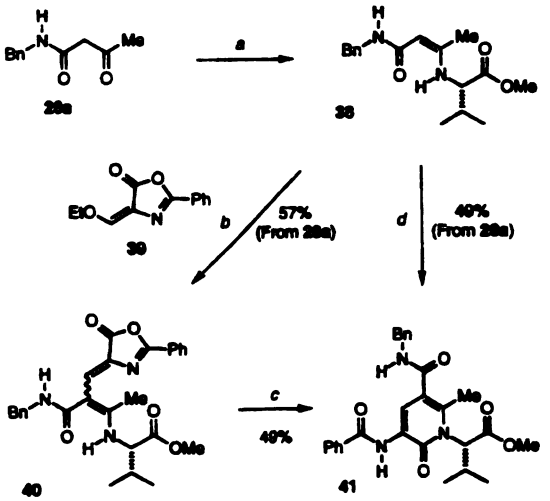


Figure 2. Intermolecular hydrogen bonding observed for **30c**. *N*-Benzyl groups have been omitted for clarity.

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.

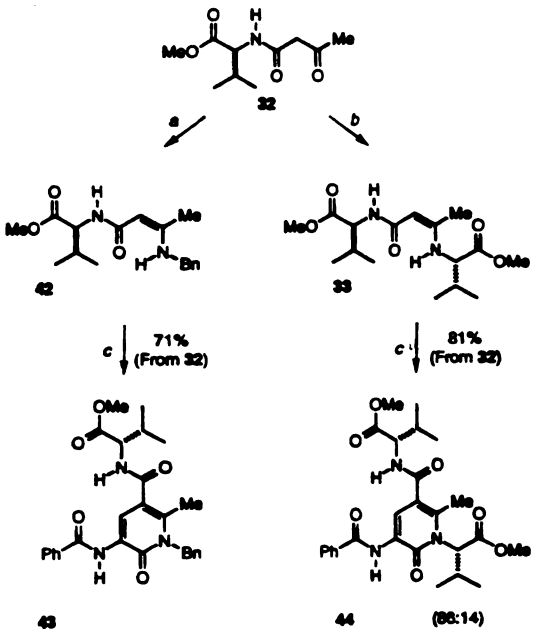
Direct Formation of Pyridones. The use of 2-phenyl-4-(ethoxymethylene)oxazolone (**39**), an alternative reagent for aza-annulation, was explored for the direct formation of pyridone products (Scheme 6). Reagent **39** was readily prepared from hippuric acid by reaction with ethyl orthoformate in acetic 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 (ψ = 166°) to the pyridone (ψ = 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; ^1H 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; ^1H 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; ^1H 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, 165.6, 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·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 $C_{15}H_{22}N_2O_4$ 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 $C_{12}H_{18}N_2O_4$ 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 $C_{22}H_{25}N_3O_3$ 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 $C_{28}H_{29}N_3O_5$ 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 $C_{28}H_{29}N_3O_7$ 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 $C_{22}H_{30}N_2O_6$ 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, 2962, 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, 2962, 2936, 1715, 1684, 1636, 1532, 1196, 1100 cm^{-1}; HRMS calcd for $C_{12}H_{16}N_2O_4$ 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, 106.50, 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 $C_{23}H_{23}N_3O_5$ 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 $C_{28}H_{27}N_3O_5$ 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 $C_{29}H_{33}N_3O_5$ 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.[36] 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, 1696, 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 $C_{28}H_{27}N_3O_5$ 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.

42: 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 $C_{28}H_{33}N_3O_7$ 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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