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AZA-ANNULATION:
METHODOLOGY DEVELOPMENT
AND
APPLICATIONS IN ALKALOID SYNTHESIS

presented by

Kumarapandian Paulvannan

has been accepted towards fulfillment
of the requirements for

Ph.D. degree in Chemistry

John R. Stille
Major professor

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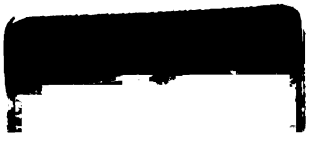

AZA-ANNULATION:

METHODOLOGY DEVELOPMENT AND APPLICATIONS IN ALKALOID SYNTHESIS

By

Kumarapandian Paulvannan

A DISSERTATION

Submitted to
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Department of Chemistry

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ABSTRACT

AZA-ANNULATION:

METHODOLOGY DEVELOPMENT AND APPLICATIONS IN ALKALOID SYNTHESIS

By

Kumarapandian Paulvannan

Aza-annulation is an elegant method for the preparation of six-membered lactams from the reaction of imine-enamine tautomers with α,β-unsaturated acid derivatives. The aza-annulation process was systematically studied to define its mechanism and limitations as well as to apply this methodology in alkaloid synthesis.

Reaction of imines with α,β-unsaturated acid chlorides gave a mixture of acyclic enamides and six-membered lactams. With triethylamine in the mixture, the reaction of imines and α,β-unsaturated acid chlorides gave acyclic enamides as the major product. Changing from acid chlorides to other acid derivatives, such as α,β-unsaturated acid anhydrides, α,β-unsaturated acids in the presence of diphenylphosphoryl azide or ethyl chloroformate, predominantly gave lactams as the major product. The presence of a substituent in the α position of the α,β-unsaturated acid derivatives exhibited a steric effect during the carbon-carbon bond formation, and gave 36-63% of acyclic enamides along with lactams. The reaction of α,β-unsaturated acid chlorides and anhydrides with bulky *N*-substituted imines predominantly gave six-membered lactams. Acyclic imines were sensitive to acids and gave a considerable amount of side products during the aza-annulation. Mechanistic studies of the aza-annulation showed that this annulation took

place *via* initial Michael addition of the enamine tautomer onto the α,β-unsaturated acid derivative followed by intramolecular *N*-acylation.

The aza-annulation was also carried out on enamines conjugated with electron withdrawing groups. In contrast to the reaction of imines with α,β-unsaturated acid chlorides, these reactions gave only six-membered lactams and in high yield. Catalytic hydrogenation of the annulated products obtained from enamino ester and enamino amide gave excellent cis selectivity (>95:5). Other electron withdrawing groups, such as phosphate and ketones, gave poor selectivity.

The cis decahydroquinoline alkaloid, (±)-5-epipumiliotoxin C, was synthesized from readily available 1,3-cyclohexanedione. The quinolizidine alkaloid (±)-lupinine and indolizidine alkaloids (±)-tashiromine and (±)-5-epitashiromine were synthesized starting from a common acyclic starting material, ethyl acetoacetate. Aza-annulation was used as the key reaction for the construction of the octahydroquinolone ring skeleton. Catalytic hydrogenation was used to establish the cis stereochemistry of (±)-5-epipumiliotoxin C, (±)-lupinine and (±)-5-epitashiromine.

To my wife Susila

and

daughters Devi and Kiruthika

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Foremost, I would like to thank my advisor professor John Stille for his guidance, patience, and understanding during my studies at Michigan State University. Joining his research group was one of the best decisions I ever made. He allowed me to pursue my research interests and spent a great deal of time listening to my suggestions and criticisms and for that I will be forever grateful. I would also like to thank my graduate committee members, Dr. Eugene Le Goff, Dr. George Leroi, and Dr. John Allison for their help and understanding.

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Finally, I take this opportunity to thank my wife and my daughters for their love, understanding, caring and support.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF SCHEMES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AIBN	Azobisisobutyronitrile
Bn	Benzyl
Bu	Butyl
n-Bu_3SnH	Tributyltin Hydride
n-BuLi	*n*-Butyllithium
CH_2Cl_2	Methylene Chloride
C_6H_6	Benzene
CS_2	Carbon disulfide
DCC	Dicyclohexylcarbodiimide
DIBALH	Diisobutylaluminum Hydride
DMAP	4-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
DMSO	Methyl Sulfoxide
DPPA	Diphenylphosphoryl Azide
Et	Ethyl
EtOH	Ethyl Alcohol
Et_2O	Diethyl Ether
$LiAlH_4$	Lithium Aluminum Hydride
LDA	Lithium Diisopropylamide
MCPI	Methyl-2-Chloropyridinium Iodide
Me	Methyl
MeOH	Methyl Alcohol

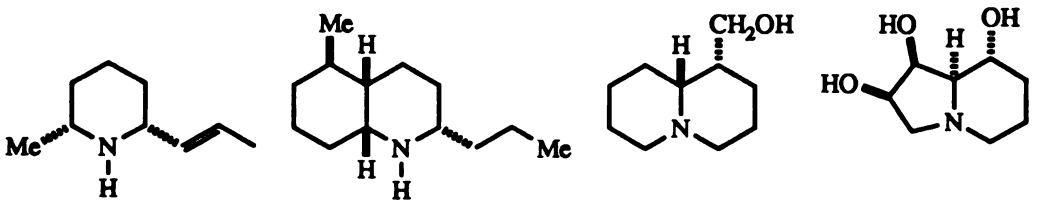
MeI	Methyl Iodide
Ms	Methanesulfonyl
$NaBH_4$	Sodium Borohydride
$Ni(acac)_2$	Nickel acetylacetonate
Ph	Phenyl
Pr	Propyl
iPr	Isopropyl
TBAF	Tetrabutylammonium Fluoride
TBDMS	*tert*-Butyldimethylsilyl
TEA	Triethylamine
THF	Tetrahydrofuran
p-TsOH	*p*-Toluenesulfonic Acid

CHAPTER I

AZA-ANNULATION OF IMINES

INTRODUCTION

Saturated six-membered nitrogen heterocycles, such as piperidines, decahydroquinolines, quinolizidines and indolizidines, occupy a pivotal position in organic chemistry. A wide range of biologically important alkaloids (e.g. pinidine (**1**), pumiliotoxin (**2**), lupinine (**3**), swainsonine (**4**)) possessing these skeletons have been isolated and have been synthetic targets of organic chemists of several generations.[1]



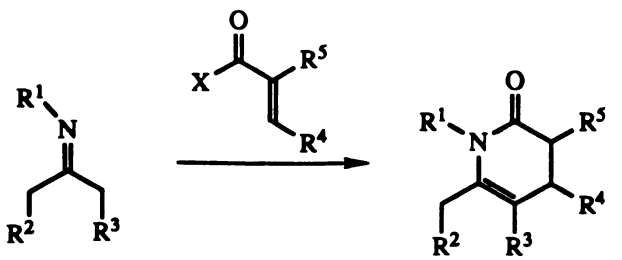
1 Pinidine (Piperidine)

2 Pumiliotoxin C (Hydroquinoline)

3 Lupinine (Quinolizidine)

4 Swainsonine (Indolizidine)

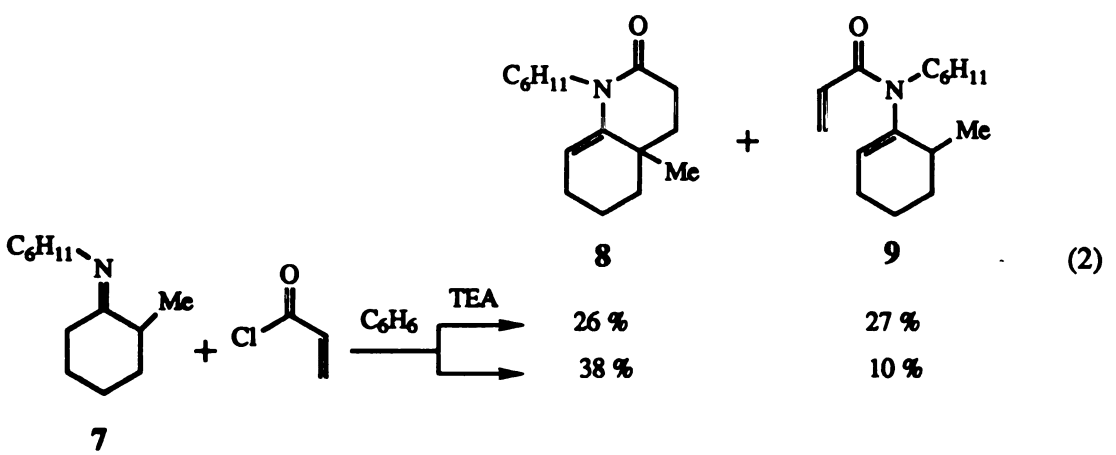
Due to our interest in alkaloid synthesis, we wanted to develop a general methodology that could be used to prepare a variety of six-membered nitrogen heterocycles. Numerous methodologies have been reported for the construction of six-membered nitrogen heterocycles, and these heterocycles have been utilized in natural product synthesis.[2] Among all the reported methodologies, the aza-annulation reaction[3] attracted our attention because of its simplicity to make six-membered lactams. Aza-annulation has been used to prepare six-membered lactams, 1,2,3,4-tetrahydro-2-pyridones (**6**), from the reaction of imines **5** with α,β-unsaturated acids (X = OH),[4] and acid derivatives such as acid chlorides (X = Cl),[3] esters (X = OR),[5] and amides (X = NH_2)[6] (eq 1).



5 6 (1)

a) Reactions of Imines with α,β-Unsaturated Acid Chlorides

In 1971, Hickmott reported that reaction of imine **7** with acryloyl chloride gave a 1:1 mixture of lactam **8** and enamide **9** in the presence of triethylamine (TEA, eq 2).[3a] In this case, TEA was added followed by the addition of acryloyl chloride to imine **7**. Without the addition of TEA to this reaction mixture, a 4:1 mixture of **8** and **9** was obtained. These conditions produce a very inefficient reaction and caused the very low yield of lactam **8**.



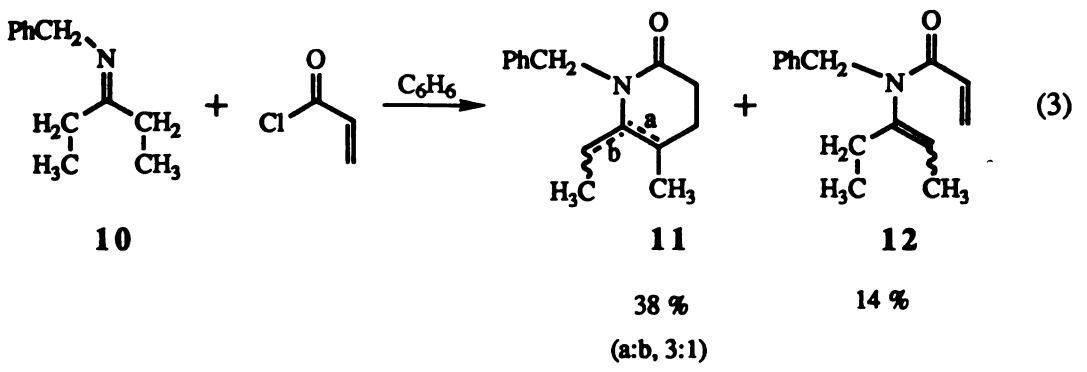
8 **9** (2)

26 % 27 %

38 % 10 %

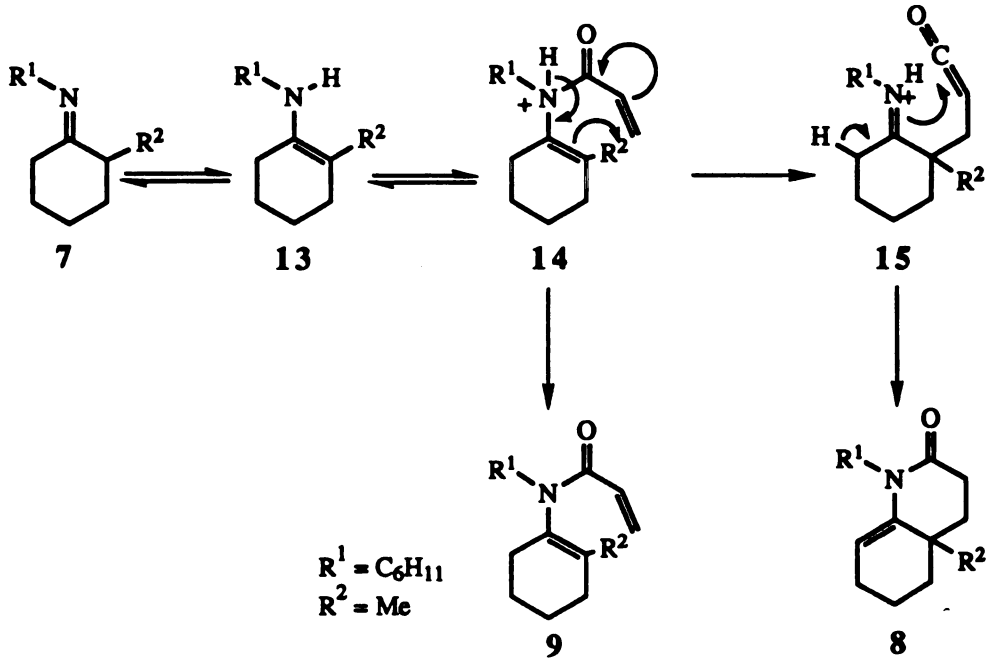
7

Hickmott also studied the reaction of acryloyl chloride with the acyclic ketimine **10**. Formation of a 3:1 mixture of cyclic lactam **11** and enamide **12** was observed upon reaction of imine **10** with acryloyl chloride (eq 3). Lactam **11** was obtained in low yields as an inseparable 1:3 mixture of exo:endo double bond isomers.[3a]

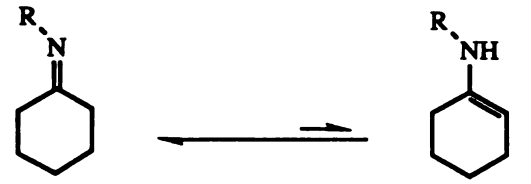


Hickmott suggested a mechanism for the formation of lactam **8** and enamide **9** from the reaction of imine **7** with acryloyl chloride (Scheme I).[3a] He proposed that *N*-acylation of the enamine tautomer **13** gave **14**, which after [3,3] sigmatropic rearrangement, gave ketene **15**. The loss of a proton from **14** gives neutral enamide **9**, while attack of nitrogen on the ketene carbon of **15** gives lactam **8**. In the presence of TEA, enamide **9** would be the major product because of the removal of proton from **14**.

Scheme I. Proposed Mechanism for Aza-Annulation.



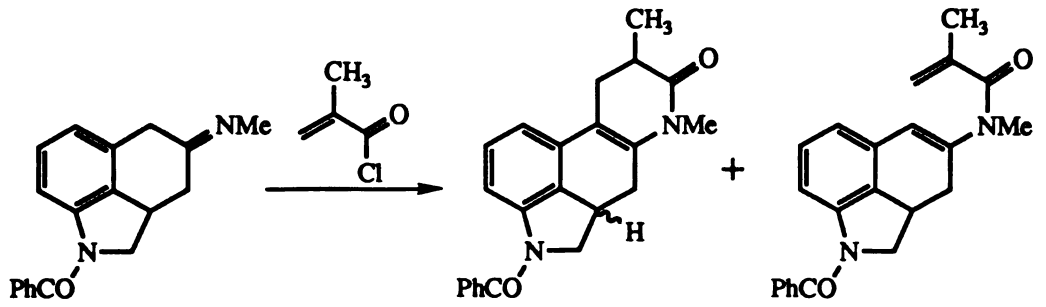
Imine **16** is in equilibrium with its enamine tautomer **17** (eq 4). In this case, the enamine form is not stabilized by further conjugation. As a result, the equilibrium is predominantly in favor of the imine **16**. On the other hand, imine **18** is stabilized by further conjugation, and the equilibrium lies in favor of the enamine form **19** (eq 5). The imine-enamine tautomer equilibrium has been confirmed by spectral studies.[7]



16 favored **17** (4)

18 **19** favored (5)

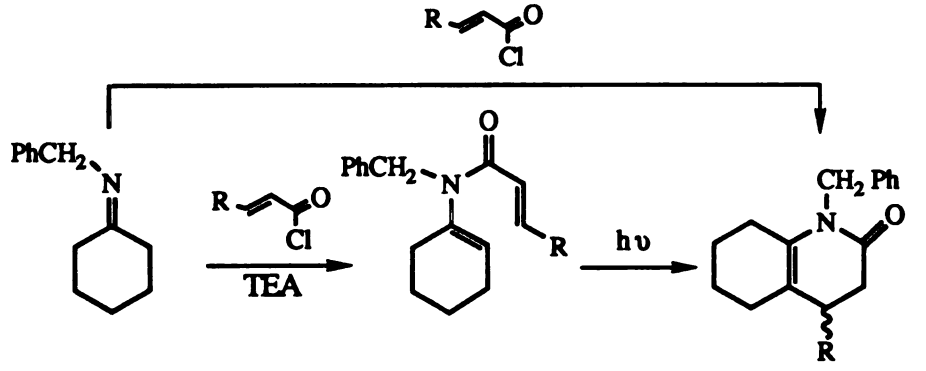
Using Hickmott's conditions, Ninomiya prepared a 4:1 mixture of lactam **21** and enamide **22** in 66% yield from the reaction of imine **20** and methacryloyl chloride (eq 6). Even though considerable amount of enamide **22** was isolated along with lactam **21**, this annulation regioselectively gave the six-membered lactam in one step. The lactam **21** was an important intermediate in the synthesis of the alkaloid costaclavine, and this annulation was used as the key step for construction of the six-membered lactam.[8]



(6)

20 **21** **22**

Ninomiya prepared lactams **26** and **27** from the reaction of imine **23** with acryloyl chloride and cinnamoyl chloride, respectively (eq 7).[9] On the other hand, enamides **24** and **25** were prepared from the reaction of imine with the corresponding acid chlorides and TEA. Lactams **26** and **27** were prepared by irradiation of enamides **24** and **25** under conditions of high dilution (0.02 M). Since photocyclization of enamides into lactams requires very dilute conditions, this route cannot be used to prepare lactams efficiently in bulk amounts.

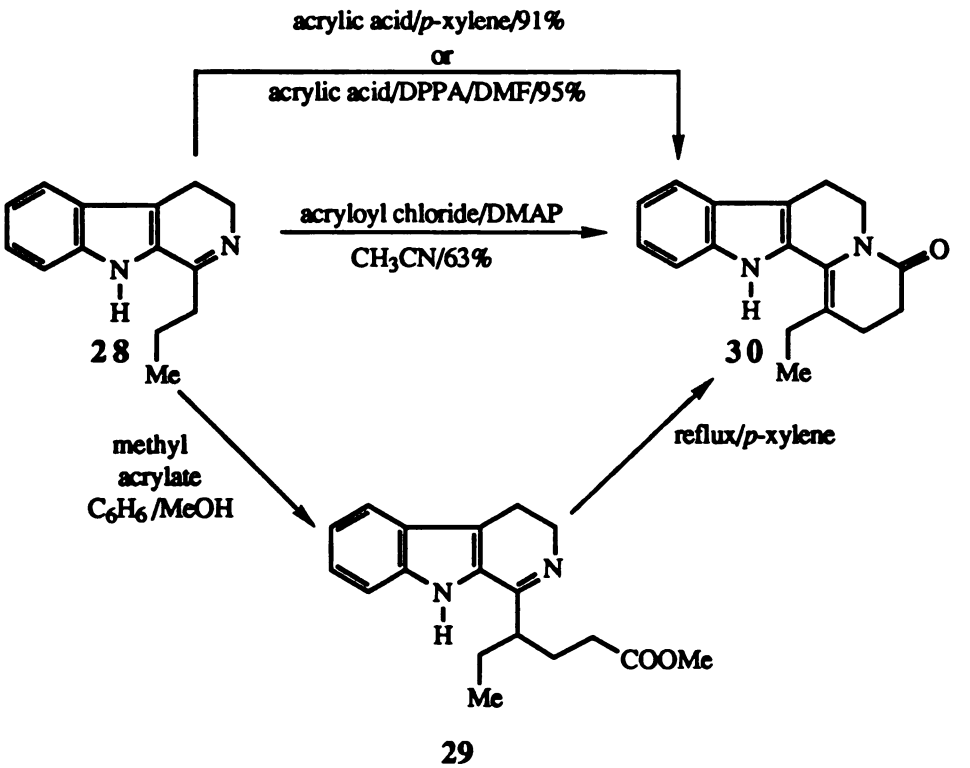


(7)

23 58% R=H **24** R=Ph **25** 61% R=H **26** R=Ph **27**

Danieli developed several pathways to prepare lactam **30** from imine **28**.[4a] In one approach, lactam **30** was prepared in 63% yield by heating imine **28** and acryloyl chloride in refluxing acetonitrile with a catalytic amount of 4-dimethylaminopyridine (DMAP), which is known to increase the reactivity of acyl groups (eq 8).[10] Danieli demonstrated

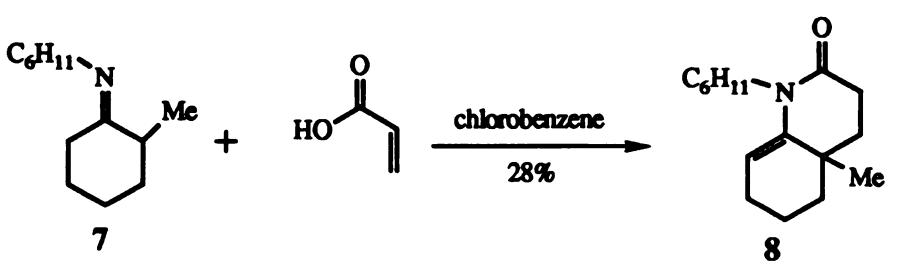
the use of DMAP in avoiding the formation of enamide during the reaction of imine **28** with acryloyl chloride. Further chemical transformations were carried out to convert the lactam **30** to the eburnane alkaloid apovincamine.



(8)

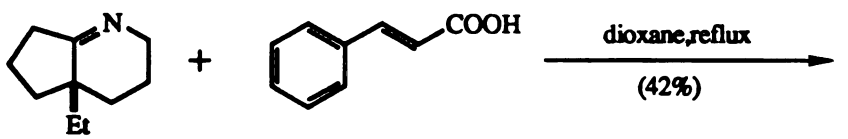
b) Reactions of Imines with α,β-Unsaturated Acids

In refluxing chlorobenzene, the reaction of acrylic acid with imine **7** produced lactam **8** in 28% yield (eq 9).[3a] The reaction of imine **7** with acrylic acid required higher temperatures than with acryloyl chloride, and the lactam **8** was isolated in low yield.



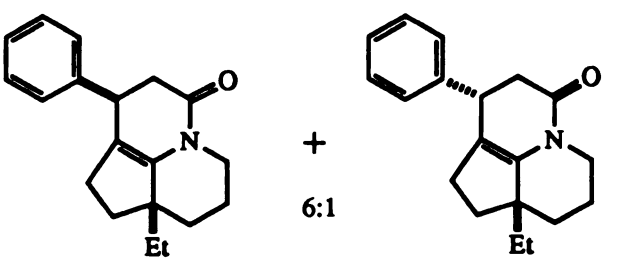
(9)

Heathcock used this methodology to prepare a key intermediate in the synthesis of the alkaloid vallesamidine. A 6:1 stereoisomeric mixture of cyclic lactams **33** and **34** was obtained in 42% yield from imine **31** and cinnamic acid (**32**, eq 10).[4b] Acyclic enamide was not observed as a product of this reaction. The low yield of the lactams could have been due to the steric effect of the β-phenyl group during C-C bond formation. Attempts to cyclize the enamide, prepared from the imine and cinnamoyl chloride in the presence of TEA, under thermal and acid catalyzed conditions gave only a trace of lactams **33** and **34**.



31 **32**

(10)

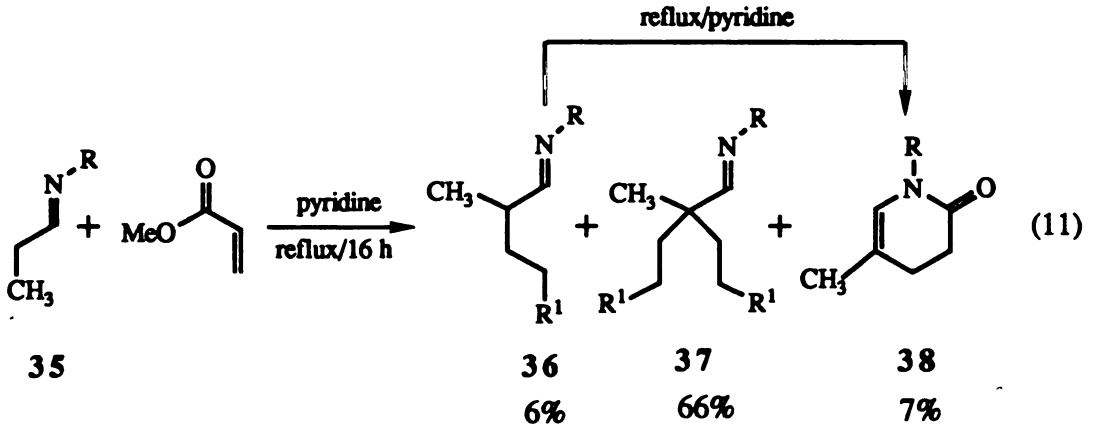


33 **34**

In Danieli's second approach to apovincamine, lactam **30** was prepared in 91% yield by heating acrylic acid and imine **28** to reflux in anhydrous *p*-xylene (eq 8).[4a] Danieli also used acrylic acid in the presence of the acid activating reagent diphenylphosphoryl azide (DPPA) which resulted in a 95% yield of the lactam **30**. He increased the scope of this annulation reaction by replacing the α,β-unsaturated acid chloride with an α,β-unsaturated acid and DPPA to prepare lactams in high yields.

c) Reactions of Imines with α,β-Unsaturated Esters

Takahashi obtained lactam **38** in 7% yield along with mono and bis-*C*-alkylated products **36** and **37** from the reaction of aldimine **35** and methyl acrylate (eq 11).[11] Products **36** and **37** result from Michael addition reaction. The lactam **38** was also prepared separately by heating **36** in pyridine. Danieli reacted methyl acrylate with the imine **28** in refluxing 1:1 benzene-methanol solution to give the *C*-alkylation product **29** (eq 8).[4a] The ester **29** was converted into lactam **30** in 52% yield by heating in *p*-xylene for 96 h. The reaction of an α,β-unsaturated ester with an imine appears to be a two-step process requiring longer reaction times and more severe reaction conditions.

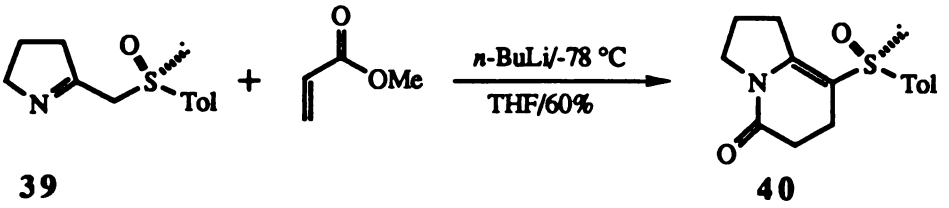


(11)

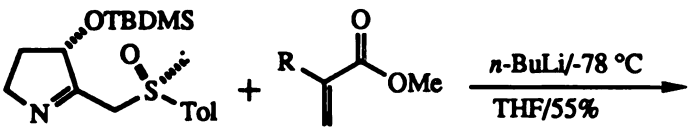
R=CH(CH$_3$)$_2$ R^1=COOMe

Aza-annulation has also been used to prepare indolizidine skeletons. Hua prepared indolizidinone **40** in 60% yield from the reaction of methyl acrylate and α-sulfinyl ketimine **39** (eq 12).[5a] The 1,4-addition reaction of the chiral α-sulfinyl ketimine anion, derived from **39** and *n*-BuLi, with methylacrylate followed by intramolecular *N*-acylation gave indolizidinone **40**. Since esters are not good acylating agents, *n*-BuLi was used in this reaction to initiate the intramolecular *N*-acylation after the C-C bond formation. Hua also reacted the anion of the α-sulfinyl ketimine **41** with the α-amidoacrylate **42** to give a 55% yield of indolizidinones **43** and **44** in a ratio of 3:2

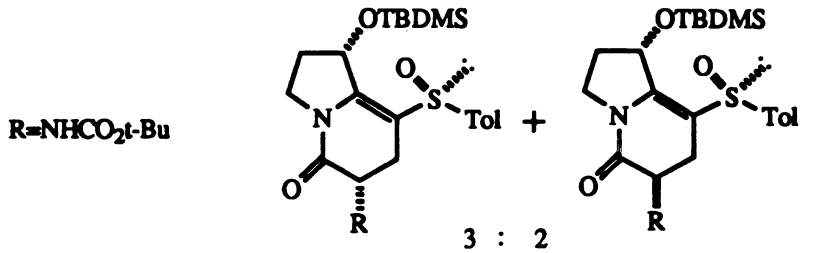
(eq 13).[5b] After several reaction sequences, indolizidinone **43** was converted into (-)-slaframine. Hua also studied this reaction with a variety of substituted acrylate derivatives[5c] and applied this methodology in the asymmetric synthesis of various indolizidine alkaloids such as alloyohimban,[5a] elaeokanines A&B[5d] and lupinine.[5e]



39 **40** (12)



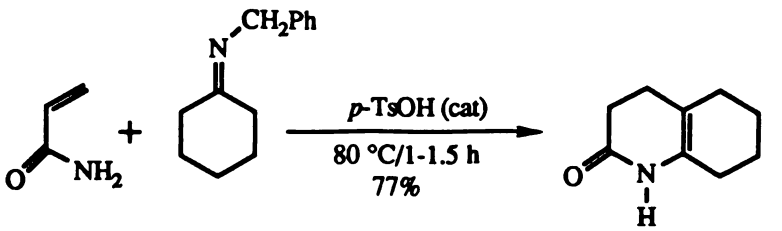
41 **42** (13)



43 **44**

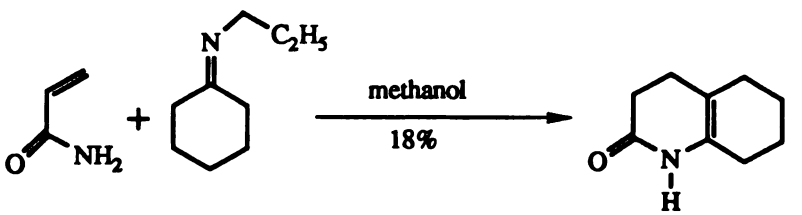
d) Reactions of Imines with α,β-Unsaturated Amides

Ninomiya prepared lactam **45** in 77% yield from the reaction of imine **23** with acrylamide in the presence of a catalytic amount of *p*-toluenesulfonic acid (*p*-TsOH, eq 14).[6a] Lactam **45** was formed *via* initial conjugate addition of the enamine tautomer to acrylamide followed by intramolecular C-N bond formation with elimination of benzylamine. By refluxing acrylamide and imine **46** in methanol, Hickmott isolated lactam **45** in 18% yield along with Michael addition products (eq 15).[6b]



(14)

23 45

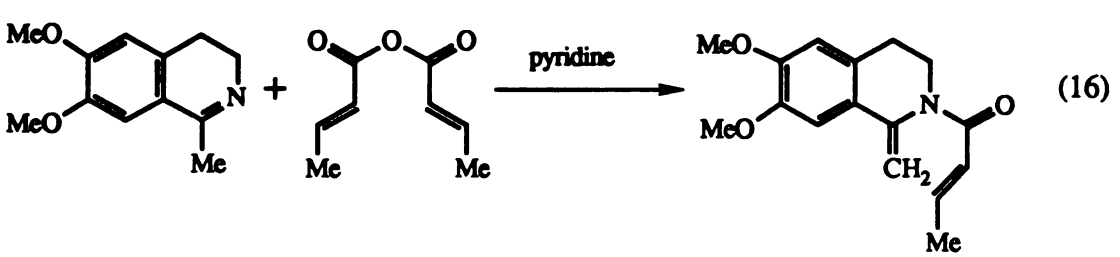


(15)

46 45

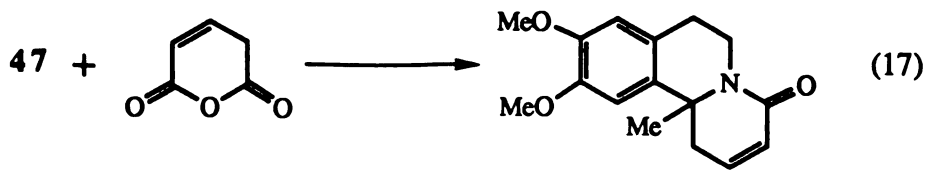
e) Reactions of Imines with α,β-Unsaturated Anhydrides

Kametani attempted to synthesize benzoquinolizines from the reaction of crotonic anhydride (**48**) and imine **47** in the presence of pyridine (eq 16).[12] Only enamide **49** was obtained as the major product. The formation of enamide **49** could be due to the steric effect exhibited by β-methyl group of the crotonic anhydride. Attempts to cyclize the enamide **49** using irradiation or treatment with acids, including various Lewis acids, resulted in failure. He prepared benzoquinolizinone **51** in 56% yield by reacting imine **47** with glutaconic anhydride (**50** eq 17). Glutaconic anhydride did not behave as previous α,β-unsaturated acid derivatives. He proposed that compound **51** could have formed by nucleophilic attack of the methylene carbon of the anhydride at imine carbon followed by *N*-acylation and subsequent decarboxylation.



(16)

47 48 49



(17)

50 51

From the literature survey on aza-annulation, we have found that the aza-annulation has not been extensively studied and efficiently utilized in organic synthesis. In order to make this reaction valuable for organic synthesis, especially in alkaloid synthesis, we decided to re investigate this reaction with the following goals:

1) Selectivity:

To selectively prepare lactams in high yield from the reaction of imines with α,β-unsaturated acid derivatives.

2) α,β-Unsaturated acid derivatives:

To study the reaction of imines with a variety of α,β-unsaturated acid derivatives, such as anhydrides and carboxylic acids activated by various acid activating reagents.

3) Substituent effect:

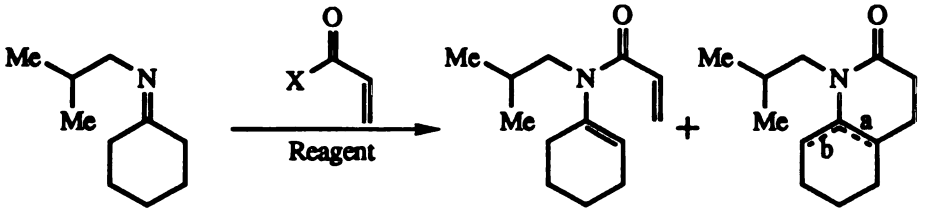
a) To study the effect of α-substituted or β-substituted acid derivatives on the product distribution and yield of the reaction.

b) To carry out this annulation with different *N*-substituted imines to gain an insight on the mechanism of this annulation reaction.

RESULTS AND DISCUSSION

a) Acrylic Acid Derivatives

Initial optimization studies were conducted with the reaction of imine **52** and acrylic acid derivatives (eq 18). Imine **52** was prepared from isobutyl amine and cyclohexanone in 87% yield by azeotropic removal of H_2O *via* modified Dean-Stark trap designed in our laboratories. In order to find a suitable solvent to carry out this annulation, the reaction of imine **52** and acryloyl chloride was performed in a variety of solvents including benzene, toluene, THF, DMF and CH_3CN. The ratio of enamide **53** and lactam **54** was obtained by gas chromatographic analysis and was found to vary according to solvent. Both THF and DMF gave predominantly lactam **54**. THF's low boiling point and ease of handling made it a suitable solvent for this reaction.



52 **53** **54** (18)

The optimized results of the reaction of imine **52** with various acrylic acid derivatives are given in Table I. In the presence of TEA, reaction of imine **52** with acryloyl chloride gave enamide **53** as the major product (entry 1). In the absence of TEA, lactam **54** was obtained as the major product (entries 2 and 3). Attempts to cyclize the enamide **53** into lactam **54** using acids, including various Lewis acids and thermal conditions, were unsuccessful. Similar observations were reported previously by Heathcock,[4b] Hickmott,[3a] and Kametani.[12] These observations provided evidence that enamide **53** was

not an intermediate in the formation of lactam **54**. Only upon irradiation using very dilute conditions, enamide **53** was converted into lactam **54**.

Table I. The Reaction of Imine **52** with Acrylic Acid Derivatives.

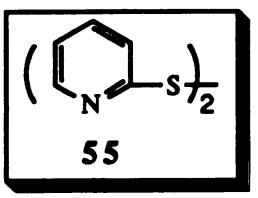
Entry	X	Reagent	(Temp/Time)	Yields[a]	53 : 54	(a : b)
1	Cl	TEA	66 °C / 7 h	68%	96 : 4	-
2	Cl	-	25 °C / 31 h	16%	23 : 77	(86 : 14)
3	Cl	-	66 °C / 17 h	32%	13 : 87	(83 : 17)
4	Cl	H_2CCHCO_2Na	- 45 °C / 3 h	59%	0 : 100	(26 : 74)
5	Cl	H_2CCHCO_2Na	25 °C / 1 h	67%	0 : 100	(45 : 55)
6	Cl	H_2CCHCO_2Na	66 °C / 1.5 h	70%	0 : 100	(81 : 19)
7	Cl	Imidazole	66 °C / 33 h	81%	0 : 100	(74 : 26)
8	OH	EtO_2CCl	25 °C / 3.5 h	77%	4 : 96	(34 : 66)
9	OH	$(PhO)_2P(O)N_3$	0 °C / 2 h	69%	5 : 95	(76 : 24)
10	OH	MCPI/NEt_3	66 °C / 2 h	58%	21 : 79	(38 : 62)

[a]Values represent isolated yields of the major product.

In order to study the effect of the reaction of imines with various α,β-unsaturated acid derivatives on product distribution (enamide vs lactam), a variety of acid derivatives were considered. The order of increasing reactivity of the acylating agents are RCO-NR_2 < R-COOH < R-COOR < RCO-O-COR < R-COCl < R-CH=C=O.[13] Initially, acrylic anhydride, a relatively poor acylating agent compared to acryloyl chloride, was chosen. Acrylic anhydride was prepared from the reaction of sodium acrylate with acryloyl chloride. The reaction of anhydride with imine **52** gave lactam **54** as the major product (entries 4 to 6, Table I). Lactam **54** was obtained as an inseparable mixture of double bond isomers **54a** and **54b**. At low reaction temperatures, the double bond isomer **54b** was the major product, and at 66 °C, isomer **54a** was the major product. Attempts to isomerize the mixture into a single isomer produced the 81:19 thermodynamic mixture. In the next series of experiments, acyl imidazole, another relatively poor acylating agent, was chosen.[14] The

use of acyl imidazole resulted in the formation of only lactams **54a** and **54b** (entry 7). The above results proved that the less reactive acylating agent was more efficient for lactam formation.

A more efficient approach to activate carboxylic acids would eliminate the need for acid derivatives such as chlorides and anhydrides. Acid activating agents that meet this requirement are Mukaiyama's reagent, Ph_3P/Py_2S_2 (**55**),[15] dicyclohexylcarbodiimide (DCC, **56**),[16] ethyl chloroformate (**57**),[17] diphenylphosphoryl azide (DPPA, **58**),[18] and methyl-2-chloropyridinium iodide (MCPI **59**).[19] The aforementioned activating reagents have been used by others to activate carboxylic acids to prepare amides, esters, β-lactams and macrolides under mild conditions.



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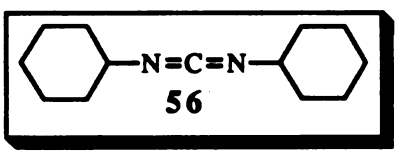

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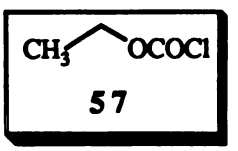

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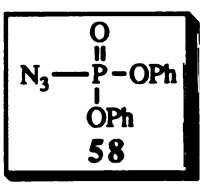

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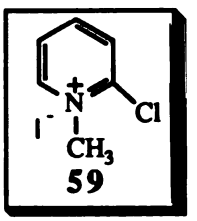
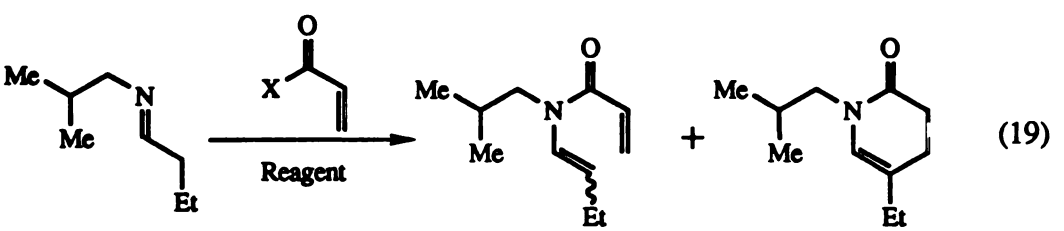


59

Imine **52** was reacted with acrylic acid in the presence of various activating agents **55** to **59**. Mukaiyama's reagent, **55** and DCC (**56**) gave lactam **54** in low yields, and isolation of product was more difficult. Under mild conditions, acrylic acid, activated by ethyl chloroformate (**57**), and DPPA (**58**) gave lactam **54** as the major product with a trace of enamide. MCPI (**59**) gave more enamide **53** compared with activating agents **55** to **58**. The formation of more enamide **53** might be due to the better leaving ability of *N*-methylpyridininone or due to the presence of two equivalents of TEA.

Annulation of acyclic imine **60** with various acrylic acid derivatives was investigated. Imine **60** was made from the condensation of butyraldehyde and isobutylamine in 76% yield. Imine **60** was treated with various acrylic acid derivatives (eq 19) and the results are given in Table II. The reaction of imine **60** with acryloyl chloride gave enamide **61** as the major product both in the presence or absence of TEA (entries 1 and 2). Lactam **62** was obtained as the major product up on reaction with acrylic anhydride (entry 3). For ease in the isolation of the lactam, the small amount of enamide **61** produced as a side product was selectively hydrolyzed by stirring with *p*-TsOH in methanol at room temperature. Reaction of imine **60** with acrylic acid and ethyl chloroformate gave enamide **61** as the major product (entry 4) and treatment of imine **60** with acrylic acid in the presence of DPPA provided lactam **62** as the major product in low yield (entry 5).



(19)

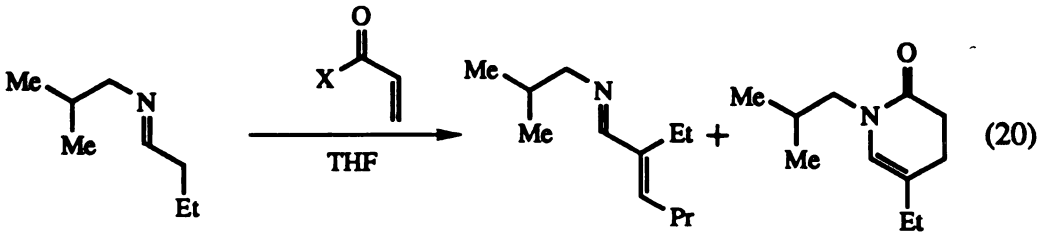
60 **61** **62**

Table II. The Reaction of Imine **60** with Acrylic Acid Derivatives.

Entry	X	Reagent	(Temp/Time)	Yields[a]	61 : 62
1	Cl	TEA	66 °C / 5 5 h	84%	100 : 0
2	Cl	-	25 °C / 11 h	14%[b]	96 : 4
3	Cl	H_2CCHCO_2Na	66 °C / 12 h	47%	15 : 85
4	OH	EtO_2CCl	25 °C / 7 h	15%[c]	78 : 22
5	OH	$(PhO)_2P(O)N_3$	0 °C / 2 h	39%[c]	3 : 97

[a]Values represent isolated yields of the major product. [b]Mixture of **61** and **62**.
[c]Gas chromatography yields of the major product.

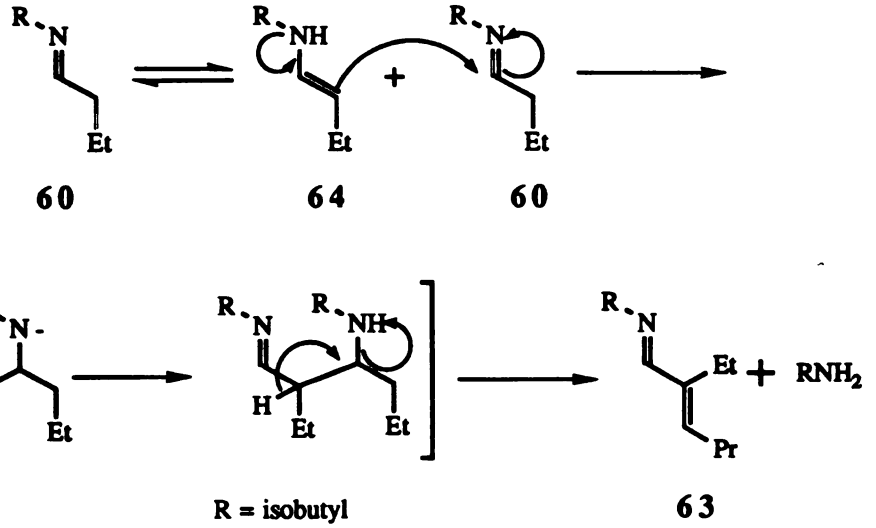
The consequence of reacting imine **60** with acyl imidazole provided the unexpected 1-aza-1,3-butadiene (**63**, eq 20). Compound **63** might have arisen from the attack of enamine tautomer **64** on imine **60** (Scheme 2). A similar result has been reported by Pfau.[20] Compound **63** was also prepared from the imine **60** by stirring with a catalytic amount of camphorsulfonic acid (CSA) and this clearly shows that the acyclic imine **60** is more acid sensitive and in the presence of acid source acyclic imine can easily undergo aldol type condensation.



60 **63** **62**

X = imidazole

Scheme II. Formation of 1-Aza-1,3-Butadiene From Imine **60**.

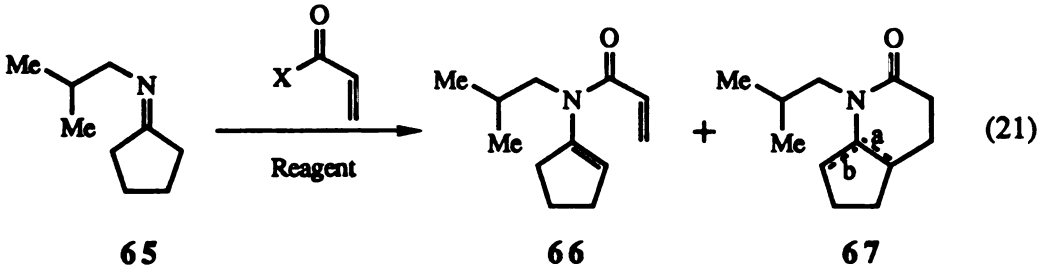


60 **64** **60**

R = isobutyl **63**

The annulation methodology was extended to imine **65**, which was synthesized from cyclopentanone and isobutylamine in 53% yield. Imine **65** was treated with various

acrylic acid derivatives (eq 21) and the results are shown in Table III. In the presence of TEA, the reaction of acryloyl chloride with imine **65** gave enamide **66** as the major product (entry 1, Table III). Lactam **67** was obtained as the major product from the reaction of **65** with other acrylic acid derivatives (entries 2 to 5). Lactam **67** was isolated as an inseparable mixture of double bond isomers **67a** and **67b**. Unfortunately, the two isomers **67a** and **67b** could not be isomerized to a single compound. The ratio of the two isomers was determined from GC analysis and ^{1}H NMR spectroscopy. From the results of the reactions of various acrylic acid derivatives with imines **52** and **65**, it was obvious that acrylic anhydride and acrylic acid, activated by either ethyl chloroformate **57** or DPPA **58**, were the better reagents to selectively prepare lactams in high yield.



65 **66** **67**

Table III. The Reaction of Imine **65** with Acrylic Acid Derivatives.

Entry	X	Reagent	(Temp/Time)	Yields[a]	66 : 67	(a : b)
1	Cl	TEA	66 °C / 7 h	87%	100 : 0	-
2	Cl	-	66 °C / 30 h	29%[b]	15 : 85	(46 : 54)
3	Cl	H_2CCHCO_2Na	66 °C / 1 h	53%	2 : 98	(43 : 57)
4	OH	EtO_2CCl	66 °C / 4 h	63%	5 : 95	(46 : 54)
5	OH	$(PhO)_2P(O)N_3$	25 °C / 2.5 h	51%	0 : 100	(54 : 46)

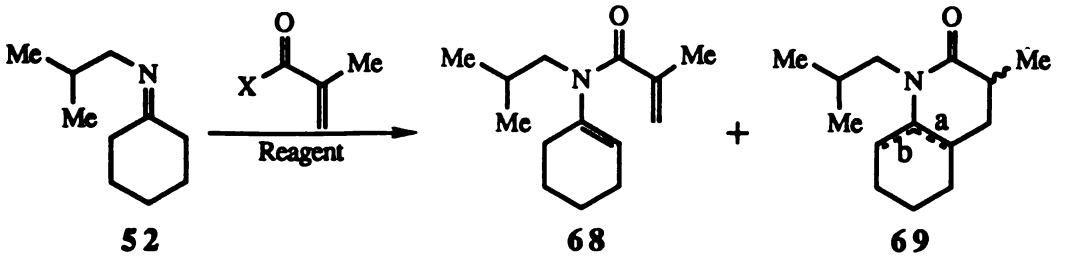
[a]Values represent isolated yields of the major product. [b]Mixture of **66** and **67**.

b) α- or β-Substituent Effect

The effect of α- or β-substituted acrylic acid derivatives on this annulation was studied with methacrylic acid and crotonic acid derivatives. Since the α-substituent on the methacrylic acid does not provide any significant steric hindrance during the carbon-carbon bond formation or carbon-nitrogen bond formation, the methacrylic acid derivatives were expected to show reactivity similar to acrylic acid derivatives. In the case of crotonic acid derivatives, the presence of a β-methyl group was expected to inhibit carbon-carbon bond formation, and hence, more uncyclized enamide formation was expected in comparison to methacrylic and acrylic acid derivatives.

c) Methacrylic Acid Derivatives

In order to study the effect of the α-substituted acrylic acid derivatives on the annulation product distribution, methacrylic acid derivatives were reacted with imine **52** (eq 22). The results are shown in Table IV. With added TEA, methacryloyl chloride reacted with imine **52** and gave enamide **68** as the major product (entry 1), and in the absence of TEA, a 39:61 mixture of enamide **68** and lactam **69** was obtained (entry 2). Lactam **69** was obtained as the major product with other methacrylic acid derivatives (entries 3-6). The minor product, enamide **68**, was selectively hydrolyzed by heating with 0.2 eq of *p*-TsOH in methanol. The lactam **69** was obtained as inseparable double bond isomers **69a** and **69b**. The isomer **69b** was obtained as two diastereomers. Under the isomerization conditions, *p*-TsOH and methanol, the mixture of isomers **69a** and **69b** was isomerized mostly to **69a**. The ratio of isomer **69a** to diastereomers **69b** and **69c** was determined by ^{1}H NMR spectroscopy.



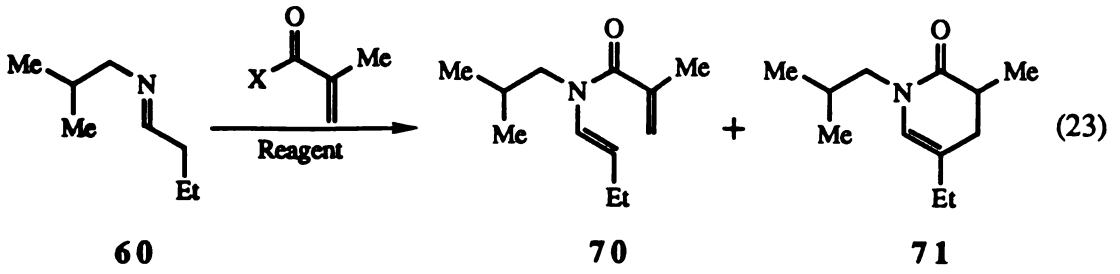
52 68 69 (22)

Table IV. The Reaction of Imine **52** with Methacrylic Acid Derivatives.

Entry	X	Reagent	(Temp/Time)	Yields[a]	68 : 69	(a : b : c)
1	Cl	TEA	66 °C / 8 h	67%	96 : 4	-
2	Cl	-	66 °C / 24 h	54%[b]	39 : 61	-
3	Cl	$H_2CCCH_3CO_2Na$	66 °C / 1 h	69%	2 : 98	(40 : 53 : 7)
4	OH	EtO_2CCl	66 °C / 1 h	87%	1 : 99	(92 : 6 : 2)
5	OH	$(PhO)_2P(O)N_3$	25 °C / 40 min	64%	0 : 100	(95 : 4 : 1)
6	OH	MCPI/NEt_3	66 °C / 2.5 h	82%[b]	24 : 76	-

[a]Values represent isolated yields of the major product. [b]Mixture of **68** and **69**.

The acyclic imine **60** was also treated with methacrylic acid derivatives (eq 23), and the results are shown in Table V. Comparable to our earlier results, enamide **70** was obtained as the major product from the reaction of imine **60** with methacryloyl chloride in the presence of TEA (entry 1). Lactam **71** was produced as the major product from the reaction of methacrylic anhydride and imine **60** (entry 2). The lactam **71** was separated from the mixture by selectively hydrolyzing the enamide using *p*-TsOH in methanol. The reaction of imine **60** with methacrylic acid in the presence of acid activating reagents **57** - **59** gave compound **63**. In order to avoid the formation of compound **63** in the presence of free acid, sodium salt of the methacrylic acid was reacted with imine **60** in the presence of activating reagent **57** or **58**. Only a trace of the lactam **71** was observed even after longer reaction times, however, the aldol-type reaction was prevented.



60 70 71 (23)

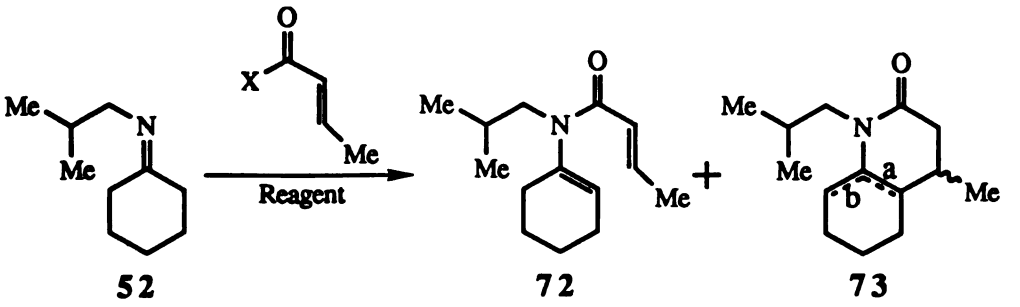
Table V. The Reaction of Imine **60** with Methacrylic Acid Derivatives.

Entry	X	Reagent	(Temp/Time)	Yields[a]	70 : 71
1	Cl	TEA	66 °C / 8 h	62%	100 : 0
2	Cl	$H_2CCCH_3CO_2Na$	66 °C / 16 h	25%	11 : 89

[a]Values represent isolated yields of the major product.

d) Crotonoic Acid Derivatives

Imine **52** was reacted with various crotonic acid derivatives and the results are given in Table VI (eq 24). As expected, the methyl group in the β position had an influence on this reaction. The reaction of imine **52** with crotonic acid derivatives required more vigorous conditions and longer reaction times than the reaction of imine **52** with acrylic or methacrylic acid derivatives. Both in the presence and absence of TEA in the reaction mixture, the reaction of crotonoyl chloride with imine **52** gave enamide **72** as the major product (entries 1 and 2). The reaction of **52** with crotonic anhydride and crotonic acid in the presence of ethyl chloroformate gave lactam **73** as the major product with 30-40% of enamide **72** (entries 3 and 4). Imine **52** reacted with crotonic acid, activated by MCPI, and gave enamide **72** as the major product (entry 5). Isolation of lactam **73** was made easier by selectively hydrolyzing enamide **72**. Lactam **73** was obtained as a mixture of double bond isomers **73a** and **73b**. The isomer **73b** was obtained as two diastereomers. Under isomerization conditions, compound **73a** was isolated as the major product. The ratio of isomer **73a** to diastereomers **73b** and **73c** was determined by ^1H NMR spectroscopy.



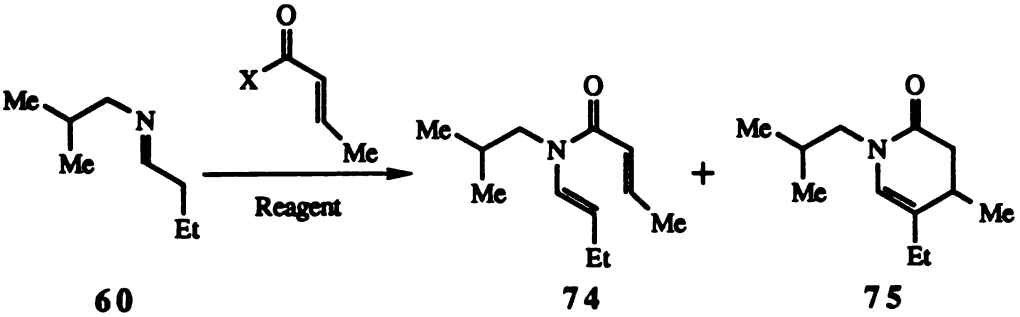
(24)

Table VI. The Reaction of Imine **52** with Crotonic Acid Derivatives.

Entry	X	Reagent	(Temp/Time)	Yields[a]	72 : 73	(a:b:c)
1	Cl	TEA	66 °C / 4 h	76%	100 : 4	-
2	Cl	-	66 °C / 20 h	34%[b]	82 : 18	-
3	Cl	$H_3CCHCHCO_2Na$	66 °C / 5 h	33%	36 : 64	(81:15:4)
4	OH	EtO_2CCl	66 °C / 15 h	79%[b]	45 : 55	(79:14:7)
5	OH	MCPI/NEt_3	66 °C / 3 h	50%[b]	62 : 38	-

[a]Values represent isolated yields of the major product. [b]Mixture of **72** and **73**.

The reaction of imine **60** with crotonic acid derivatives showed the influence β-methyl group during the carbon-carbon bond formation, and the results are given in Table VII (eq 25). Only enamide **74** was obtained as the major product from the reaction of imine **60** with either crotonoyl chloride or crotonic anhydride (entries 1 and 2). Treatment of imine **60** with crotonic acid, in the presence of acid activating reagents such as DPPA and ethyl chloroformate, provided only a trace of lactam **75**.



(25)

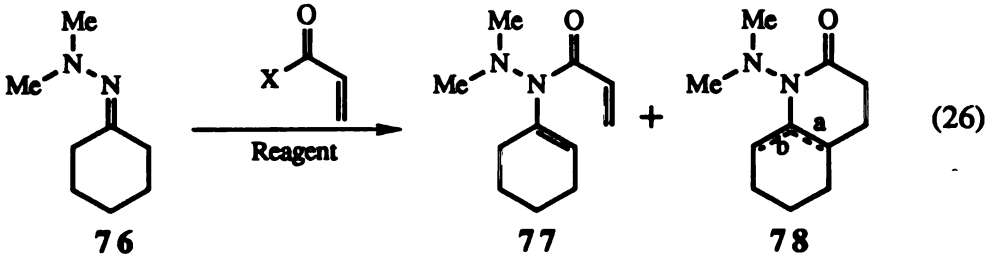
Table VII. The Reaction of Imine **60** with Crotonic Acid Derivatives.

Entry	X	Reagent	(Temp/Time)	Yields[a]	74 : 75
1	Cl	TEA	66 °C / 8 h	62%	96 : 4
2	Cl	$H_3CCHCHCO_2Na$	66 °C / 16 h	18%	63 : 37

[a]Values represent isolated yields of the major product.

e) Nitrogen Substituents

In order to expand the scope of this annulation and to study the product distribution with other substituents on the nitrogen, both -CH_2Ph and -NMe_2 were chosen as *N*-substituents. Since both -CH_2Ph and -NMe_2 can be readily removed after annulation, the annulated product can be modified for use in organic synthesis.



76 **77** **78** (26)

Table VIII. The Reaction of Hydrazone **76** with Acrylic Acid Derivatives.

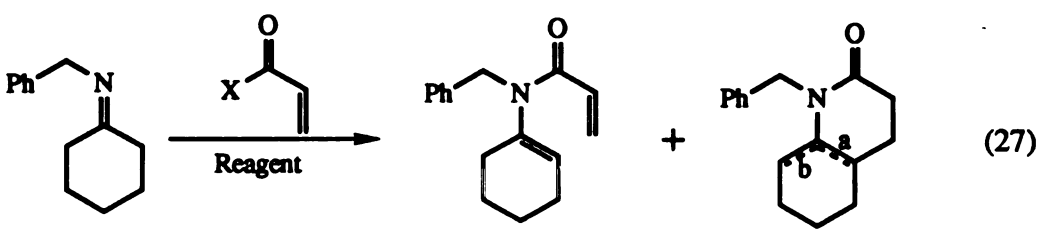
Entry	X	Reagent	(Temp/Time)	Yields[a]	77 : 78	(a:b)
1	Cl	TEA	66 °C / 21 h	77%	96 : 1	-
2	Cl	-	66 °C / 22 h	-	64 : 36	-
3	Cl	H_2CCHCO_2Na	66 °C / 18 h	70%	1 : 99	(83:17)

[a]Values represent isolated yields of the major product.

Hydrazone **76**, prepared from cyclohexanone and 1,1-dimethylhydrazine in 72% yield, was treated with acrylic acid derivatives (eq 26), and the results are given in Table VIII. In the presence or absence of TEA in the reaction mixture, acryloyl chloride reacted with hydrazone **76** to give enamide **77** as the major product (entries 1 and 2). However,

lactam **78** was obtained as the major product upon treatment of hydrazone **76** with acrylic anhydride (entry 3). Reaction of hydrazone **76** with acrylic anhydride required longer reaction times as compared with the reaction of acrylic anhydride with imine **52**. The slow reactivity of hydrazone **76** could be due to the inductive effect from -NMe_2 substituent. The reaction of hydrazone **76** with both methacrylic anhydride and crotonic anhydride did not provide any product. Hence, further studies were not pursued with this hydrazone.

Further investigation into this methodology, annulation of imine **23** was investigated. Imine **23** was made from cyclohexanone and benzylamine in 85% yield. Benzylamine derivatives have been widely used in organic synthesis because of the ease with which benzyl group can be removed from nitrogen. Imine **23** was expected to behave similarly to isobutyl imine **52**. The imine **23** was reacted with acrylic acid derivatives, methacrylic acid derivatives and crotonic acid derivatives (eq 27, 28 and 29), and the results are given in Tables IX-XI, respectively.



(27)

23 **24** **26**

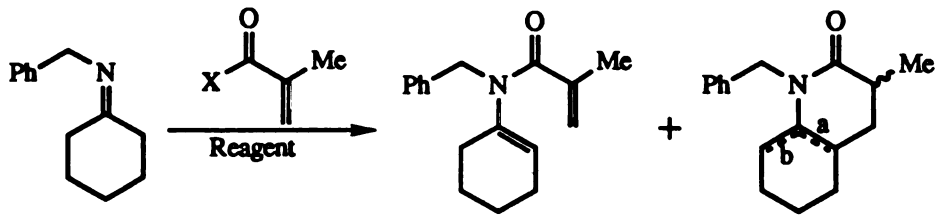
Table IX. The Reaction of Imine **23** with Acrylic Acid Derivatives.

Entry	X	Reagent	(Temp/Time)	Yields[a]	24 : 26	(a : b)
1	Cl	TEA	66 °C / 3 h	70%	99 : 1	-
2	Cl	-	66 °C / 12 h	60%[b]	15 : 85	-
3	Cl	$CH_2CHCOONa$	66 °C / 2 h	70%	0 : 100	(33 : 67)
4	OH	EtO_2CCl	66 °C / 2 h	77%	0 : 100	(76 : 24)
5	OH	$(PhO)_2P(O)N_3$	0 °C / 2 h	71%	3 : 97	(77 : 23)

[a]Values represent isolated yields of the major product. [b]Mixture of **24** and **26**.

With added TEA, reaction of imine **23** with acryloyl chloride gave enamide **24** as the major product (entry 1, Table IX). Lactam **26** was isolated as the major product from the reaction of imine **23** with other acrylic acid derivatives (entries 2-5). As before, the lactam was obtained as a mixture of two double bond isomers **26a** and **26b**, and the ratio of isomers **26a** and **26b** was determined by ^{1}H NMR spectroscopy.

Treatment of methacryloyl chloride with imine **23** provided enamide **79** as the major product (entries 1 and 2, Table X). Reaction of other methacrylic acid derivatives with imine **23** gave lactam **80** as the major product (entries 3-5). Again, lactam **80** was obtained as a mixture of isomers **80a** and **80b**. Under isomerization condition, **80a** was obtained as the major isomer.



23 **79** **80** (28)

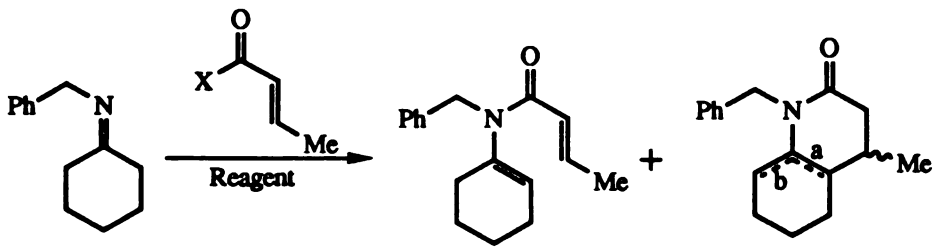
Table X. The Reaction of Imine **23** with Methacrylic Acid Derivatives.

Entry	X	Reagent	(Temp/Time)	Yields[a]	79 : 80	(a:[b+c])
1	Cl	TEA	66 °C / 4 h	80%	98 : 2	-
2	Cl	-	66 °C / 22 h	39%[b]	52 : 48	-
3	Cl	$H_2CCCH_3CO_2Na$	66 °C / 2.5 h	81%	0 : 100	(>95:<5)
4	OH	EtO_2CCl	66 °C / 2 h	81%	1 : 99	(>95:<5)
5	OH	$(PhO)_2P(O)N_3$	25 °C / 2 h	63%	0 : 100	(>95:<5)

[a]Values represent isolated yields of the major product. [b]Mixture of **79** and **80**.

In the presence or absence of TEA, reaction of imine **23** with crotonyl chloride gave enamide **81** as the major product (entries 1 and 2). Reaction of other crotonic acid derivatives with imine **23** gave lactam **82** as the major product (entries 3 and 4, Table XI). In order to

isolate lactam **82** from the mixture of enamide and lactam, enamide **81** was selectively hydrolyzed using *p*-TsOH and methanol. As before, the lactam **82** was obtained as a mixture of isomers **82a** and **82b**, and the mixture was isomerized to **82a**. The ratio of isomer **82a** and the diastereomers **82b** and **82c** could not be determined by ^{1}H NMR spectroscopy.



23 **81** **82** (29)

Table XI. The Reaction of Imine **23** with Crotonic Acid Derivatives.

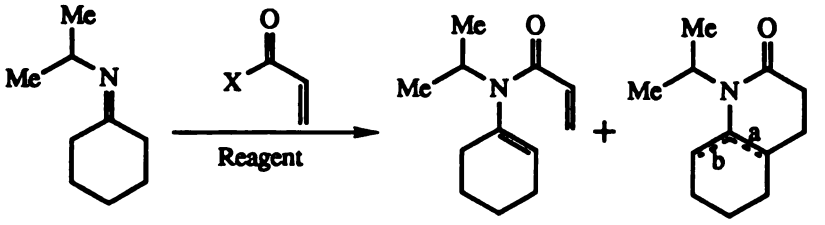
Entry	X	Reagent	(Temp/Time)	Yields[a]	81 : 82	(a:[b+c])[b]
1	Cl	TEA	66 °C / 4 h	55%	100 : 0	-
2	Cl	-	66 °C / 20 h	73%[c]	91 : 9	-
3	Cl	$H_3CCHCHCO_2Na$	66 °C / 12 h	62%[c]	36 : 64	-
4	OH	EtO_2CCl	66 °C / 24 h	65%[c]	44 : 56	-

[a]Values represent isolated yields of the major product. [b]Isomer ratio could not be determined. [c]Mixture of **81** and **82**.

In order to study the effect of bulky groups on the nitrogen, as well as to gain more insight into the mechanism of this reaction, imine **83** was treated with acrylic, methacrylic and crotonic acid derivatives. In the annulation reactions, the presence of a bulky isopropyl group on the nitrogen was expected to show a steric effect during the C-N bond formation compared to imines **23** or **52**, and this effect was expected to change the product distribution.

Imine **83**, prepared from the condensation of isopropyl amine and cyclohexanone in 79% yield, was reacted with acrylic acid derivatives and the results are given in Table XII (eq 30). Enamide **84** was obtained as the major product from the reaction of imine **83**

with acryloyl chloride and TEA (entry 1). Lactam **85** was obtained as a single product with other acrylic acid derivatives (entries 2 to 5). The reaction of imine **83** with acryloyl chloride gave more lactam **85** (**84**:**85**, 5:95, entry 2, Table XII) than the reaction of imine **52** with acryloyl chloride (**53**:**54**, 13:87, entry 2, Table I). The slight enhancement of lactam **85** formation shows the influence isopropyl group on this annulation. Lactam **85** was obtained as double bond isomers **85a** and **85b**. The ratio of isomers **85a** and **85b** was determined by ^{1}H NMR spectroscopy.



83 **84** **85** (30)

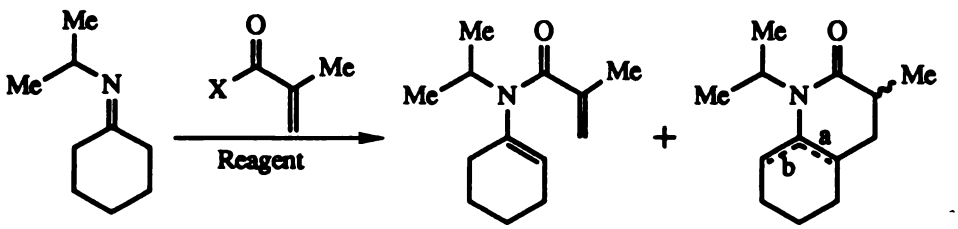
Table XII. The Reaction of Imine **83** with Acrylic Acid Derivatives.

Entry	X	Reagent	(Temp/Time)	Yields[a]	84 : 85	(a : b)
1	Cl	TEA	66 °C / 2 h	87%	100 : 0	-
2	Cl	-	66 °C / 10 h	32%	5 : 95	(81:19)
3	Cl	H_2CCHCO_2Na	66 °C / 2 h	67%	0 : 100	(81:19)
4	OH	EtO_2CCl	66 °C / 2 h	77%[c]	0 : 100	(84:19)
5	OH	$(PhO)_2P(O)N_3$	25 °C / 4 h	53%	0 : 100	(91:9)

[a]Values represent isolated yields of the major product.

The result of the reaction of imine **83** with methacrylic acid derivatives are shown in Table XIII (eq 31). In the presence of TEA, enamide **86** was produced as the major product with methacryloyl chloride (entry 1). Without the addition of TEA, the reaction of imine **83** with methacryloyl chloride gave lactam **87** as the major product (**86**:**87**, 3:97, entry 2). In contrast to this result, the reaction of imine **52** with methacryloyl chloride gave enamide **68** as the major product (**68**:**69**, 61: 39, entry 2, Table IV). The increase in considerable amount of lactam **87** formation showed that the bulky *N*-isopropyl group

substituent favored the lactam formation. Only lactam **87** was isolated in moderate to high yields from the reaction of imine **83** with other methacrylic acid derivatives (entries 3 to 5). The isomer **87a** was obtained as the major product with a small trace of isomer **87b**. The ratio of the isomer **87a** and the diastereomers **87b** and **87c** was determined by ^{1}H NMR spectroscopy.



83 **86** **87** (31)

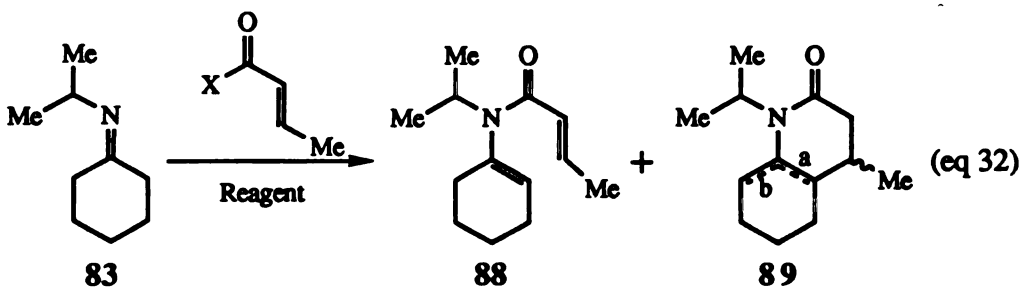
Table XIII. The Reaction of Imine **83** with Methacrylic Acid Derivatives.

Entry	X	Reagent	(Temp/Time)	Yields[a]	86 : 87	(a:b:c)
1	Cl	TEA	66 °C / 4 h	86%	95 : 5	-
2	Cl	-	66 °C / 10 h	50%	3 : 97	(93:2:5)
3	Cl	$H_2CCCH_3CO_2Na$	66 °C / 2 h	82%	0 : 100	(93:3:4)
4	OH	EtO_2CCl	66 °C / 3 h	62%	0 : 100	(>95:5)
5	OH	$(PhO)_2P(O)N_3$	25 °C / 4 h	47%	0 : 100	(>95:5)

[a]Values represent isolated yields of the major product.

The reaction of imine **83** with crotonic acid derivatives gave unexpected results (eq 32). The reaction of the imine with crotonoyl chloride and TEA gave several products. The formation of unwanted products could be due to the competition between *N*-acylation and removal of a proton from the β-methyl group to form a vinyl ketene. The formed vinyl ketene can give rise to various products. Vinyl ketene formation from crotonoyl chloride in the presence of TEA has been previously reported by Hickmott.[21] Use of a weaker base was expected to inhibit the formation of vinyl ketene. By using pyridine instead of TEA, enamide **88** was obtained in 25% yield (entry 1, Table XIV). The reaction of imine **83**

with crotonyl chloride gave enamide **88** as the major product (entry 2). Surprisingly, the reaction of imine **83** with crotonic anhydride gave only lactam **89** in 77% yield (entry 3). In the case of imine **52**, reaction of crotonic anhydride gave considerable amount of enamide (**72**:**73**, 36:64, entry 3, Table VI). The increase in amount of lactam **89** formation clearly indicated that the bulky *N*-isopropyl substituent favored the lactam formation over the formation of enamide **88**. The reaction of imine **83** with crotonic acid, activated by ethyl chloroformate, also gave lactam **89** as the major product (entry 4).



83 **88** **89**

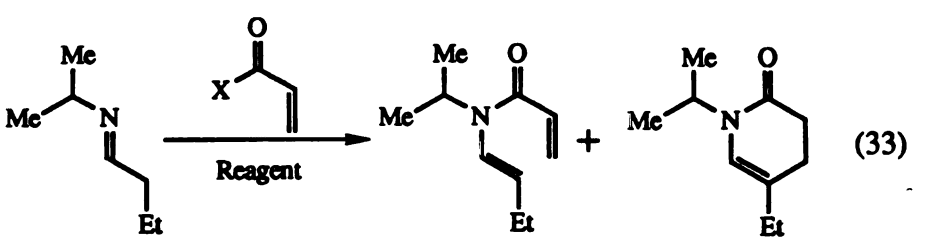
Table XIV. The Reaction of Imine **83** with Crotonic Acid Derivatives.

Entry	X	Reagent	(Temp/Time)	Yields[a]	88 : 89	(a : b)
1	Cl	Pyridine	66 °C / 4 h	25%	100 : 0	-
2	Cl	-	66 °C /10 h		69 : 31	
3	Cl	$H_3CHCCHCO_2Na$	66 °C /10 h	77%	0 : 100	(>95:5)
4	OH	EtO_2CCl	66 °C /12 h	66%	4 : 96	(89:11)

[a]Values represent isolated yields of the major product.

In order to study the ability of sterically hindered acyclic imine in controlling the formation of lactam *vs* enamide, annulation of imine **90** was carried out with acrylic and crotonic acid derivatives. Imine **90** was prepared from the condensation of butyraldehyde and isopropylamine in 68%. The results of the reaction of imine **90** with acrylic and crotonic acid derivatives (eq 33 and 34) are given in Tables XV and XVI, respectively. Enamides **91** and **93** were obtained as the major products from the reactions of imine **90**

with the corresponding acid chlorides and TEA (entry 1, Tables XV and XVI). In the absence of TEA, the reaction of imine **90** with acryloyl chloride gave a 65:35 ratio of **91** to **92** (entry 2, Table XV). This product distribution clearly shows the formation of more lactam as compared to that of the reaction of acryloyl chloride and imine **60** (**61**:**62**, 96:4, entry 2, Table II). Without the addition of TEA, reaction of crotonyl chloride with **90** gave a 30:70 ratio of **93** to **94** (entry 2, Table XVI). The formation of more lactam **94** clearly shows the influence of bulky substituent on the imine **90**. The reaction of acrylic anhydride with imine **90** gave a 7:93 mixture of **91** to **92** in 27% yield, which shows an increase in lactam formation over the reaction of **60** with acrylic anhydride (**61**:**62** 15:85, entry 3, Table II). Treatment of crotonic anhydride with **90** gave a 6:94 mixture of **93** to **94** in 47% yield which shows a tremendous increase in lactam formation over the ratio of 63:37 (entry 2, Table VII) obtained from the reaction of imine **60** and crotonic anhydride. These results clearly show the presence of a bulky isopropyl substituent on the nitrogen influenced the formation of lactam over the formation of enamide.

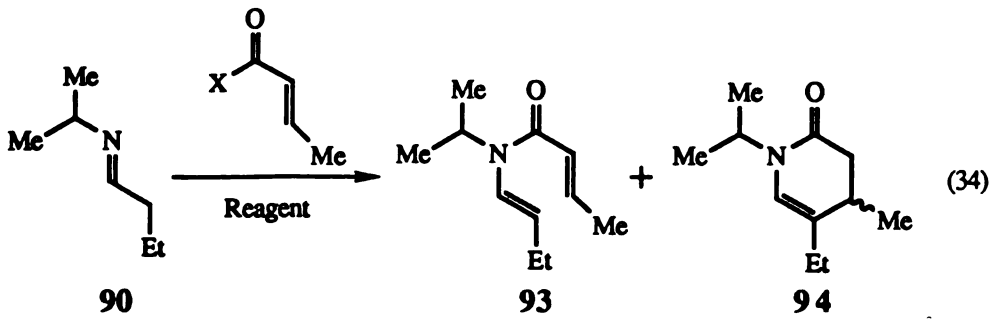


90 **91** **92** (33)

Table XV. The Reaction of Imine **90** with Acrylic Acid Derivatives.

Entry	X	Reagent	(Temp/Time)	Yields[a]	91 : 92
1	Cl	TEA	66°C / 5 h	49%	100 : 0
2	Cl	-	66°C /12 h	-	65 : 35
3	Cl	H_2CCHCO_2Na	66°C / 2 h	27%	7 : 93

[a]Values represent isolated yields of the major product.



90 93 94 (34)

Table XVI. The Reaction of Imine **90** with Crotonic Derivatives.

Entry	X	Reagent	(Temp/Time)	Yields[a]	93 : 94
1	Cl	TEA	66 °C / 6 h	37%	100 : 0l
2	Cl	-	66 °C /12 h	-	30 : 70
3	Cl	$H_3CHCCHCO_2Na$	66 °C /1 2 h	47%	6 : 94

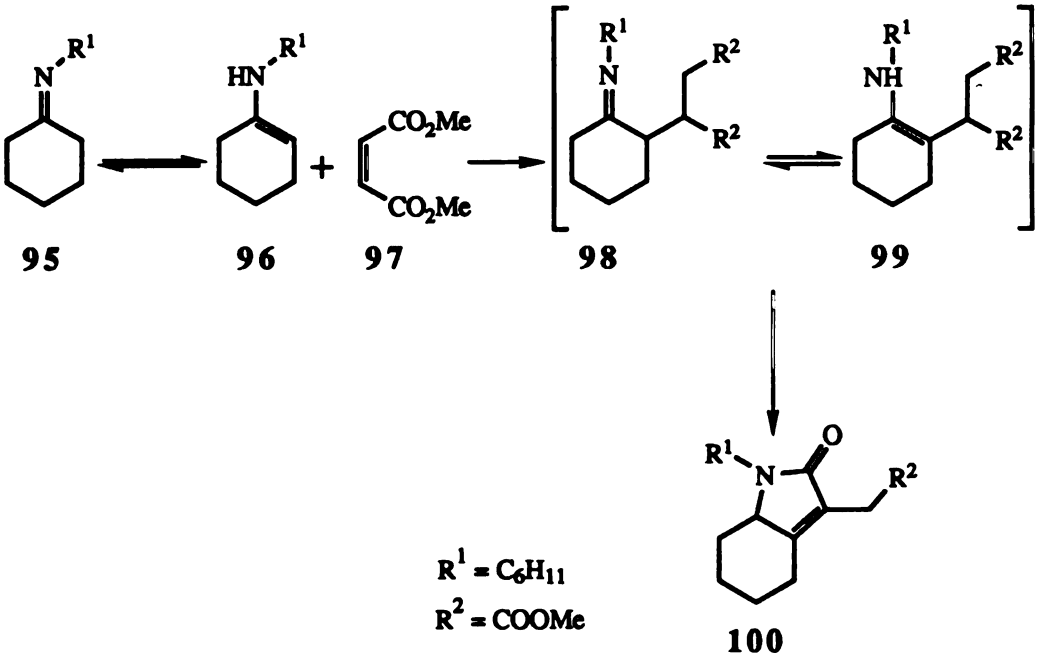
[a]Values represent isolated yields of the major product.

f) Mechanistic Discussion of Aza-Annulation

The mechanism of the aza-annulation reaction has not been fully investigated, and there are number of pathways possible for this annulation process. In general, options can be divided into two different pathways, those that acylate first at nitrogen, *N*-acylation, and those that undergo initial conjugate addition to form the carbon-carbon bond, initial *C*-alkylation. Hickmott proposed a mechanism for the formation of lactam **8** and enamide **9** from imine **7** with acryloyl chloride (Scheme I). According to Hickmott, the enamine tautomer **13** undergoes *N*-acylation to give the intermediate **14** which, after [3,3] sigmatropic rearrangement, gives ketene **15**. The loss of proton from **14** gives neutral enamide **9**. Attack of nitrogen on the ketene carbon of **15** gives lactam **8**. Both are competitive processes. In the presence of TEA, enamide **9** would be the major product because of the removal of proton from **14** by TEA. Since enamide **9** cannot be converted into lactam **8** under thermal, protic and Lewis acidic conditions, enamide **9** is not likely to be intermediate in lactam formation.

On the other hand, initial Michael type adduct formation from the enamine tautomer and α,β-unsaturated derivatives can undergo intramolecular *N*-acylation to give lactams. In the reaction of imine **35** with methyl acrylate,[11] Takahashi observed an initial Michael type addition, *C*-alkylation, followed by *N*-acylation to give lactam **33** (eq 11). The mono and bis Michael addition products **36** and **37** were isolated as the major products, and **36** was converted to lactam **38** upon heating. Pfau[22] reported that the reaction of imine **95** with dimethyl maleate (**97**) gave lactam **100** *via* the enamine tautomer **96** (Scheme III). The intermediates **98** and **99** were not isolated. Both Takahashi and Pfau did not observe any *N*-acylated amide products. The *C*-alkylation of the imine in the form of the enamine tautomer with α,β-unsaturated esters has been confirmed by the isolation of the mono and bis *C*-alkylation products.[11]

Scheme III. Reaction of Imine **95** with Dimethyl Maleate.



During our investigation on aza-annulation of imines, we observed that the reaction of imines with α,β-unsaturated acid chlorides and TEA gave only enamides (except the

reaction of imine **83** with crotonoyl chloride and TEA). In the absence of TEA, the reaction of imines with α,β-unsaturated acid chlorides gave a mixture of enamide and lactam, and the enamide to lactam ratio varied with imines and α,β-unsaturated acid chlorides. These results show a competition between initial *N*-acylation and *C*-alkylation. The presence of TEA favors the initial *N*-acylation to give an intermediate similar to **14**, and removal of the proton by TEA gives enamide which cannot not be converted into lactam. In the absence of TEA, the initial *C*-alkylation occurs faster than *N*-acylation to give lactam as the major product after intramolecular *N*-acylation.

The reaction of imine **35** with methyl acrylate gave *C*-alkylated Michael adduct products **36** and **37** and lactam **38**. No enamide was observed. The difference between α,β-unsaturated acid chloride and a methyl acrylate is their reactivity towards *N*-acylation. The acid chloride is a better acylating agent than the ester. Since the better acylating agent (α,β-unsaturated acid chloride) gives a mixture of lactam and enamide and the poorer acylating agent (methyl acrylate) gives a mixture of Michael adduct and lactam, the products distribution could be controlled by adjusting the acylating ability of the α,β-unsaturated acid derivatives. As expected from these arguments, the reaction of imine with relatively poor acylating agents such as anhydrides and acids, in the presence of acid activating reagents, gave lactams as the major product. However, from these results, we could not make any conclusion about initial *N*-acylation versus *C*-alkylation.

Further, steric effects due to the substituents on the nitrogen and substituents on the acylating agent (eg. β-methyl group in crotonic acid derivatives) could be used to control both *N*-acylation or *C*-alkylation. Bulky groups on the nitrogen would be expected to disfavor the *N*-acylation and substituents on the β-position of the α,β-unsaturated acid derivatives would be expected to disfavor the *C*-alkylation. The reaction of imine **83**, having a sterically hindered isopropyl group on the nitrogen, provided us with some insight into the mechanism. The reaction of imine **83** with both acrylic and methacrylic acid derivatives gave >95% of the lactams (**85** and **87**). Unexpectedly, crotonic anhydride

gave only lactam **89** from the reaction with imine **83**. Usually crotonic anhydride gave roughly a 60:40 mixture of uncyclized enamide and lactam. The formation of lactam as the major product clearly indicates that the lactam is formed from the initial *C*-alkylation followed by intramolecular *N*-acylation. In the reaction of crotonic anhydride with imine **83**, *C*-alkylation is more favorable than *N*-acylation because of the steric hinderance due to the bulky isopropyl group on the nitrogen. The effect of the bulky *N*-isopropyl group on the lactam formation was further confirmed from the reaction of imine **90** with crotonic anhydride. Treatment of imine **90** with crotonic anhydride gave a 6:94 mixture of enamide to lactam in 47% yield and demonstrated significant improvement over the 63:37 formation of the analogous **74**:**75**. Since the reaction of crotonic anhydride with other imines (**23** and **52**) did not favor either *C*-alkylation or *N*-acylation due to the β methyl group, nearly equal amounts of lactams and enamides were obtained. In the case of crotonoyl chloride, *N*-acylation was faster than *C*-alkylation because of the steric effect due to the β-methyl group; hence, the enamide was the major product.

From the above results, it can be concluded that the lactam was formed by initial *C*-alkylation followed by intramolecular *N*-acylation.

CONCLUSION

Lactams or enamides were selectively prepared in high yields by reaction of the imine made from cyclohexanone and acrylic or methacrylic acid derivatives. Acid activating reagents DPPA and ethyl chloroformate with α,β-unsaturated acids were better alternatives to the anhydrides and acid chlorides. Treatment of imines with crotonic acid derivatives produced more enamides. Enamides were selectively hydrolysed from a mixture of enamide and lactam. Annulation of the acyclic imine, made from butyraldehyde, with α,β-unsaturated anhydrides gave lactams in moderate yields. The acyclic imine was sensitive to carboxylic acids and gave aldol type condensation products. Reaction of α,β-unsaturated derivatives with bulky *N*-isopropyl group substituted imine favored the *C*-

alkylation and gave more lactams. In most of the cases, the β-substituted α,β-unsaturated acid derivative favored the *N*-acylation and gave more uncyclized enamides.

EXPERIMENTAL SECTION

General Methods. All reactions were carried out performing standard inert atmosphere techniques to exclude moisture and oxygen. Acrylic acid, methacrylic acid, methacrylic anhydride, crotonic anhydride, methacryloyl chloride, and crotonoyl chloride were purchased from Aldrich Chemical Co., and distilled before use. Acryloyl chloride was purchased from Fluka and used without purification. Aldrithiol-2 (2,2'-dipyridyl disulfide), and 2-chloro-1-methylpyridinium iodide were purchased from Aldrich Chemical Co. and used without purification. Diphenylphosphoryl azide (DPPA) was prepared according to a literature procedure.[23] Unless specified, concentration of mixtures was performed using a Buchii rotary evaporator.

General Procedure for the Preparation of Ketimines: A mixture of the primary amine (313 mmol) and ketone (250 mmol) in 750 mL of benzene was heated at reflux until >90% of the H_2O had been azeotropically removed from the reaction mixture with a Dean-Stark trap. After draining the H_2O from the Dean-Stark apparatus, the trap was filled with 4Å molecular sieves, and the reaction was heated for up to an additional 24 h to produce complete imine formation. The solution was then cooled to ambient temperature, concentrated, and distilled under vacuum using a vigereux column to give the corresponding imine.

23: (bp 92 °C, <1 mmHg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.59-1.83 (m, 6H), 2.34 (t, 4H, J = 5.8 Hz), 4.50 (s, 2H), 7.15-7.30 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 25.6, 26.5, 27.3, 28.7, 39.6, 53.6, 126.1; IR (neat) 3085, 3062, 3028, 1660, 1495, 1452, 1346 cm^{-1}.

52: (bp 75 °C, 6 mmHg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (d, 6H, J = 6.7 Hz), 1.59 (m, 4H), 1.68 (m, 2H), 1.85 (m, 1H), 2.24 (m, 4H), 3.06 (d, 2H, J = 6.7 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 19.9, 25.2, 26.1, 27.0, 27.9, 28.9, 39.2, 57.5, 171.9; IR (neat) 2930, 2862, 1660, 1469, 1449 cm^{-1}.

65: (bp 77 °C, 15 mmHg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (d, 6H, *J* = 6.7 Hz), 1.71 (m, 2H), 1.77 (m, 2H), 1.92 (m, 1H), 2.12 (m, 2H), 2.31 (m, 2H), 2.97 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.5, 23.9, 24.6, 28.7, 29.4, 36.0, 61.7, 179.9; IR (neat) 2958, 2858, 1678, 1466 cm^{-1}.

76: (bp 66 °C, 14 mmHg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.55-1.72 (m, 6H), 2.21 (t, 2H, *J* = 6.2 Hz), 2.40 (s, 6H), 2.47 (t, 2H, *J* = 6.2 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 25.9, 26.5, 27.4, 28.6, 35.9, 47.5, 170.1; IR (neat) 2858, 2815, 2771, 1635, 1468, 1449 cm^{-1}.

83: (bp 68 °C, 20 mmHg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09 (d, 6H, *J* = 6.3 Hz), 1.58-1.66 (m, 4H), 1.66-1.75 (m, 2H), 2.20-2.30 (m, 4H), 3.68 (sept, 1H, *J* =6.3 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 23.9, 26.1, 27.4, 27.8, 28.8, 40.1, 48.8, 170.4; IR (neat) 1660, 1450, 1377 cm^{-1}.

General Procedure for the Preparation of Aldimines: A mixture of amine (137 mmol), butyraldehyde (9.86 g, 137 mmol), and potassium carbonate (37.90 g, 274 mmol) in 200 mL Et_2O was stirred for 12 h at ambient temperature. The solution was then removed from the insoluble material via cannula and distilled using a vigereux to give the corresponding imine.

60: (78% yield, bp 53 °C, 25 mmHg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.81 (d, 6H, *J* = 6.4 Hz), 0.87 (t, 3H, J = 7.4 Hz), 1.48 (sext, 2H, J = 7.4 Hz), 1.82 (non, 1H, *J* = 7.4 Hz), 2.14 (td, 2H, *J* = 7.4, 5.0 Hz), 3.10 (d, 2H, *J* = 6.7 Hz), 7.5 (t, 1H, *J* = 5.0 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.8, 18.6, 19.6, 28.3, 36.9, 68.9, 164.4; IR (neat) 2958, 2875, 2828, 1674, 1469 cm^{-1}.

90: (68% yield, bp 108°C): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, 3H, *J* = 7.4 Hz), 1.11 (d, 6H, *J* = 6.4 Hz), 1.51 (sext, 2H, *J* = 7.4 Hz), 2.6 (dt, 2H, *J* = 5.2, 7.4 Hz), 3.23 (sept, 1H, *J* = 6.4 Hz), 7.61 (t, 1H, *J* = 5.2 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.1, 19.1, 23.7, 37.1, 60.7, 161.6; IR (neat) 2969, 2935, 2874, 2830, 1669, 1466 cm^{-1}.

General Procedure for the Preparation of Enamides: To 40 mL of dry THF were added the imine (8.0 mmol) and NEt_3 (1.21 g, 12.0 mmol) at 0 °C. The appropriate α,β-unsaturated acid chloride (9.6 mmol) was added slowly to this solution at 0 °C. After the addition was complete, the reaction was carried out under the conditions listed in the Tables. Solids were removed from the mixture by filtration, and were then washed thoroughly with Et_2O. The combined filtrate was concentrated, and the corresponding enamide was isolated by Kugelrohr distillation.

53: (bp 70-80 °C, <1 mmHg): ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (d, 6H, *J* = 6.9 Hz), 1.60 (m, 2H), 1.72 (m, 2H), 1.87 (m, 1H), 2.06 (m, 2H), 2.13 (m, 2H), 3.32 (bd, 2H, *J* = 7.2 Hz), 5.51-5.59 (m, 2H), 6.30 (dd, 1H, *J* = 16.9, 2.4 Hz), 6.46 (dd, 1H, *J* = 16.9, 10.0 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.2, 21.7, 22.9, 24.9, 27.3, 28.3, 52.4, 127.3, 128.3, 129.4, 138.7, 166.1; IR (neat) 2961, 2934, 1651, 1618 cm^{-1}; HRMS calcd for $C_{13}H_{21}NO$ m/z 207.1623, found m/z 207.1629.

24: (mp 67-68 °C): ^1H NMR (300 MHz, $CDCl_3$) δ 1.52 (m, 2H), 1.64 (m, 2H), 1.94-2.06 (m, 4H), 4.67 (s, 2H), 5.39 (m, 1H), 5.61 (dd, 1H, *J* = 9.7, 2.7 Hz), 6.38 (dd, 1H, *J* = 16.9, 2.7 Hz), 6.49 (dd, 1H, *J* = 16.9, 9.7 Hz), 7.20-7.28 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.5, 22.7, 24.7, 28.7, 49.7, 127.1, 127.3, 128.2, 128.5, 128.6, 128.7, 137.9, 165.2; IR (KBr) 3068, 3030, 2940, 2855, 1645, 1611, 1414 cm^{-1}; HRMS calcd for $C_{16}H_{19}NO$ m/z 241.1466, found m/z 241.1475.

84: (bp 70-80 °C, <1 mmHg): ^1H NMR (300 MHz, $CDCl_3$) δ 1.15, (d, 6H, *J* = 6.8 Hz), 1.62 (m, 2H), 1.71 (m, 2H), 2.06 (m, 2H), 2.16 (m, 2H), 4.66 (sept, 1H, *J* = 6.8 Hz), 5.55 (dd, 1H, *J* = 3.3, 9.2 Hz), 5.59 (m, 1H), 6.31 (dd, 1H, *J* = 16.8, 3.3 Hz), 6.40 (dd, 1H, *J* = 16.8, 9.2 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.8, 21.4, 22.8, 25.0, 31.8, 46.4, 126.6, 129.5, 129.7, 136.0, 164.7; IR (neat) 2975, 2936, 2881, 2860, 1652, 1614, 1448, 1438 cm^{-1}; HRMS calcd for $C_{12}H_{19}NO$ m/z 193.1466, found m/z 193.1467.

77: (bp 50-60 °C, <1 mmHg): ^{1}H NMR (300 MHz, $CDCl_3$, Mixture of rotational isomers, -30°C) δ 1.50-1.64 (m, 2H), 1.64-1.75 (m, 2H), 2.04-2.23 (m, 4H), 2.47 (s, 3H), 2.84 (bs, 3H), 5.46-5.64 (m, 2H), 6.25-6.36 (m), 7.14 (dd, *J* = 17.3, 10.3 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.2, 21.3, 22.2, 22.3, 24.52, 24.53, 27.5, 29.1, 43.2, 45.0, 126.4, 127.2, 127.4, 127.7, 128.9, 129.5, 132.3, 136.9, 164.6, 166.6. IR (neat) 2979, 2939, 2885, 2860, 1661, 1618, 1448, 1437 cm^{-1}; HRMS calcd for $C_{11}H_{18}N_2O$ m/z 194.1419, found m/z 194.1425.

68: (bp 65-75 °C, <1 mmHg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (d, 6H *J* = 6.7 Hz), 1.55 (m, 2H), 1.66 (m, 2H), 1.85 (m, 1H), 1.90 (t, 3H, J=1.4 Hz), 2.06 (m, 4H), 3.28 (d, 2H, *J* = 7.5 Hz), 5.00-5.08 (m, 2H), 5.50 (m, 1H): ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.1, 20.6, 21.5, 22.7, 24.8, 26.9, 27.9, 52.1, 115.1, 125.6, 138.6, 142.3, 171.9; IR (neat) 3009, 2872, 2842, 1645, 1615 cm^{-1}; HRMS calcd for $C_{14}H_{23}NO$ m/z 221.1779, found m/z 221.1785.

79: (bp 110-120 °C, <1 mmHg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (m, 2H), 1.56 (m, 2H), 1.92-1.99 (m, 7H), 4.65 (s, 2H), 5.08 (m, 1H), 5.17 (m, 1H), 5.33 (m, 1H), 7.22-7.28 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.5, 21.4, 22.6, 24.7, 28.4, 49.8, 116.0, 126.3, 127.1, 128.2, 128.4, 137.9, 138.7, 141.7, 171.6; IR (neat) 3088, 3066, 3008, 2935, 1648, 1619, 1496, 1453 cm^{-1}; HRMS calcd for $C_{17}H_{21}NO$ m/z 255.1612, found m/z 255.1615.

86: (bp 60-70 °C, <1 mmHg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14 (d, 6H, *J* = 6.8 Hz), 1.53 (m, 2H), 1.61 (m, 2H), 1.89 (t, 3H, J=1.3 Hz), 1.99-2.12 (m, 4H), 4.52 (m, 1H), 4.87-5.00 (m, 2H), 5.49 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.8, 21.3, 22.7, 24.8, 31.3, 46.3, 114.1, 128.3, 136.5, 142.6, 171.3; IR (neat) 2974, 2934, 2882, 2860, 1649, 1628, 1450, 1408 cm^{-1}; HRMS calcd for $C_{13}H_{21}NO$ m/z 207.1623, found m/z 207.1625.

72: (bp 65-75 °C, <1 mmHg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (d, 6H *J* = 6.7 Hz), 1.60 (m, 2H), 1.71 (m, 2H), 1.82 (dd, 3H, *J* = 1.7, 6.9 Hz), 1.85 (m, 1H),

2.05 (m, 2H), 2.13 (m, 2H), 3.28 (m, 2H), 5.58 (m, 1H), 6.14 (dq, 1H, *J* =15.1, 1.7 Hz), 6.87 (dq, 1H, *J* = 15.1, 6.9 Hz): ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 18.1, 20.1, 21.6, 22.8, 24.8, 27.2, 28.2, 52.2, 123.0, 127.4, 138.4, 140.4, 165.8; IR (neat) 2874, 1670, 1649, 1446 cm^{-1}. Anal. Calcd for $C_{14}H_{23}NO$: C, 75.97; H, 10.47; N, 6.33. Found: C, 76.62; H, 10.26; N, 6.34.

81: (mp 70-71 °C): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.53 (m, 2H), 1.64 (m, 2H), 1.83 (dd, 3H, *J* = 6.9, 1.7 Hz), 1.96 (m, 2H), 2.02 (m, 2H), 4.65 (s, 2H), 5.38 (m, 1H), 6.15 (dq, 1H, *J* = 15.1, 1.7 Hz), 6.94 (dq, 1H, *J* = 15.1, 6.9 Hz), 7.17-7.28 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 17.7, 21.1, 22.3, 24.3, 28.3, 49.5, 122.3, 126.6, 127.8, 127.9, 128.2, 137.8, 140.6, 165.1; IR (KBr) 3046, 3032, 2858, 1661, 1615, 1494 cm^{-1}; HRMS calcd for $C_{17}H_{21}NO$ m/z 255.1612, found m/z 255.1623.

88: (bp 65-75 °C, <1 mmHg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13 (d, 6H, *J* = 6.9 Hz), 1.61 (m, 2H), 1.71 (m, 2H), 1.82 (dd, 3H, *J* = 6.9, 1.8 Hz), 2.04 (m, 2H), 2.16 (m, 2H), 4.66 (sept, 1H, J=6.9 Hz), 5.57 (m, 1H), 6.05 (dd, 1H, *J* = 15.1, 1.6 Hz), 6.87 (dq, 1H, *J* =15.1, 6.9 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 18.0, 21.0, 21.5, 22.9, 25.0, 31.8, 46.1, 123.6, 129.4, 136.1, 140.1, 165.0; IR (neat) 2973, 2935, 2841, 1662, 1626, 1477 cm^{-1}; HRMS calcd for $C_{13}H_{21}NO$ m/z 207.1623, found m/z 207.1625.

66: (bp 60-70 °C, <1 mmHg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (d, 6H, *J* = 6.7 Hz), 1.86 (m, 1H), 1.90 - 2.05 (m, 2H), 2.39 (m, 4H), 3.35 (d, 2H, *J* = 7.5 Hz), 5.49 (m, 1H), 5.57 (dd, 1H, *J* = 10.2, 2.2 Hz), 6.33 (dd, 1H, *J* = 16.9, 2.2 Hz), 6.52 (dd, 1H, *J* = 10.2, 16.9 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.0, 22.3, 27.4, 30.3, 32.6, 52.2, 126.9, 129.1, 142.4, 165.6; IR (neat) 3020, 2965, 2931, 1644, 1611 cm^{-1}; HRMS calcd for $C_{12}H_{19}NO$ m/z 193.1466, found m/z 193.1469.

61: (bp 55-65 °C, <1 mmHg): ^{1}H NMR (300 MHz, $CDCl_3$, 2:1 *E*:*Z* mixture of isomers) δ 0.86 (d, 6H, *J* = 6.4 Hz, both isomers), 0.99 (t, 3H, *J* = 7.4 Hz, both), 2.05 (m, 2H, both), 3.36 (bd, 2H, *J* =7.3 Hz, minor), 3.44 (bd, 2H, *J* = 7.3 Hz, major),

5.00-5.22 (m, 1H, both), 5.63-5.70 (m, 1H, both), 6.25 (d, 1H, J = 17.0 Hz, major), 6.37 (m, 1H, minor), 6.39 (d, 1H, J = 12.9 Hz, major), 6.62 (dd, 1H, J = 16.8, 10.3 Hz, both), 7.24 (bd, 1H, J = 14.8 Hz, minor); ^{13}C NMR (75.5 MHz, $CDCl_3$ (major)) δ 13.8, 19.7, 23.1 26.0, 50.9, 119.4 126.7, 127.1 128.3, 165.2. (minor) 14.1, 19.7, 23.3, 26.8, 51.4, 114.5, 125.0, 127.5, 128.3, 164.4; IR (neat) 2964, 2930, 2875, 1646, 1612 cm^{-1}; HRMS calcd for $C_{11}H_{19}NO$ m/z 181.1467, found m/z 181.1473.

70: (bp 50-60 °C, <1 mmHg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (d, 6H, J = 6.8 Hz), 0.98 (t, 3H, J = 7.4 Hz), 1.96 (dd, 3H, J = 1.1, 1.6 Hz), 1.97-2.14 (m, 3H), 3.48 (d, 2H, J = 7.5 Hz), 5.01 (m, 1H), 5.08 (t, 1H, J =1.1 Hz), 5.25 (t, 1H, J = 1.4 Hz), 6.60 (bd, 1H, J =12.6 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.6, 20.1, 20.4, 23.6, 26.0, 49.2, 113.2, 116.9, 128.1, 140.8, 171.5; IR (neat) 2963, 2932, 2874, 1670, 1649, 1454 cm^{-1}; HRMS calcd for $C_{12}H_{21}NO$ m/z 195.1623, found m/z 195.1629.

74: (bp 50-60 °C, <1 mmHg): ^{1}H NMR (300 MHz, $CDCl_3$, 2:1 *E*:*Z* mixture of isomers) δ 0.86 (d, 6H, J = 6.3 Hz, major), 0.88 (d, 6H, J = 6.3 Hz, minor), 1.00 (t, 3H, J=7.3 Hz, both), 1.86 (dd, 3H, J =1.6, 6.8 Hz, both), 1.93-2.12 (m, 3H, both), 3.35 (bd, 2H, J=5.3 Hz, minor), 3.44 (d, 2H, J = 7.8 Hz, major), 4.98-5.20 (m, 1H, both), 6.24-6.56 (m, 1H, both), 6.74-7.00 (m, 1H, both), 7.24 (bd, 1H, J = 14.2 Hz, minor); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.5, 18.2, 20.1, 23.7, 26.4, 51.0, 118.5, 122.6, 127.3, 141.6, 165.8; IR (neat) 3031, 2963, 2874, 1653, 1628, 1448 cm^{-1}; HRMS calcd for $C_{12}H_{21}NO$ m/z 195.1623, found m/z 195.1627.

91: (bp 75-85 °C, 10 mmHg): ^{1}H NMR (300 MHz, $CDCl_3$, 93:7 ratio of *E*:*Z* isomers) δ 1.05 (t, 3H, J =7.5 Hz), 1.11 (d, 6H, J = 6.8 Hz), 2.14 (m, 2H), 4.77 (sept, 1H, J = 6.8 Hz), 5.47 (dt, 1H, J = 13.7, 6.9 Hz), 5.55 (dd, 1H, J = 10.3, 2.2 Hz), 5.93 (bd, 1H, J = 13.7 Hz), 6.28 (dd, 1H, J = 16.9, 2.2 Hz), 6.55 (dd, 1H, J = 16.9, 10.3 Hz) ; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.6, 19.9, 23.3, 45.4, 123.1, 126.2, 129.9, 135.9, 165.1; IR (neat) 2972, 2934, 2876, 1651, 1614, 1462, 1414 cm^{-1}; HRMS calcd for $C_{10}H_{17}NO$ m/z 167.1310, found m/z 167.1309.

93: (bp 90-100 °C, 7 mmHg): ^{1}H NMR (300 MHz, $CDCl_3$, 93:7 ratio of *E*:*Z* isomers) δ 1.02 (t, 3H, *J* = 7.5 Hz), 1.07 (d, 6H, *J* = 7.4 Hz), 1.79 (dd, 3H, *J* = 6.9, 1.5 Hz), 2.12 (m, 2H), 4.74 (sept, 1H, *J* = 6.9 Hz), 5.46 (dt, 1H, *J* = 13.7, 6.9 Hz), 5.90 (bd, 1H, *J* = 13.7 Hz), 6.22 (dq, 1H, *J* = 15.1, 1.5 Hz), 6.81 (dq, 1H, *J* = 15.1, 6.9 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.3, 17.5, 19.6, 22.9, 44.9, 123.0, 123.7, 135.0, 139.5, 165.2; IR (neat) 2971, 2935, 2875, 2855, 1667, 1626, 1448 cm^{-1}; HRMS calcd for $C_{11}H_{19}NO$ m/z 181.1466, found m/z 181.1460.

General Procedure for the Reaction of Imines with Acid Chloride: The α,β-unsaturated acid chloride (8.8 mmol) in 15 mL of dry THF was slowly added to the imine (6.8 mmol) in THF (30 mL) at reflux and the mixture was maintained at reflux for the required reaction time (see Tables). After the reaction was complete, the solution was washed with 25 mL of saturated aqueous $NaHCO_3$ solution. The aqueous layer was then extracted with 4 x 40 mL of Et_2O, and the organic fractions were combined and dried over Na_2SO_4. Following removal of solvents, the residue was purified by flash column chromatography (eluent: 20:80 Et_2O:petroleum ether, 40:60 Et_2O:petroleum ether, or 50:50 Et_2O:petroleum ether). The solvents were removed, and the residue was distilled under vacuum to give lactam or a mixture of enamide and lactam.

General Procedure for the Reaction of Imines with Acrylic Anhydride: To a suspension of NaH (0.43 g, 17.9 mmol) in 35 mL of THF at -78 °C was slowly added acrylic acid (0.87 g, 12.1 mmol). The mixture was warmed to ambient temperature and then stirred for 1 h. Acryloyl chloride (0.84 g, 9.3 mmol) was then added to the solution of sodium acrylate, and the reaction mixture was stirred for an additional 1 h at ambient temperature. The resulting solution of acrylic anhydride was transferred to a 100 mL flask containing the imine (7.2 mmol), and the original flask was rinsed with an additional 25 mL of THF.[24] After the reaction was carried out under the conditions listed in the Tables, the solution was washed with 30 mL of saturated $NaHCO_3$ solution. The aqueous layer was then extracted with 4 x 50 mL of Et_2O, and the organic fractions were

combined and dried over Na_2SO_4. After removal of solvents, the residue was purified by flash column chromatography (eluent: 50:50 Et_2O:petroleum ether), and the resulting lactam was distilled under vacuum.

General Procedure for the Reaction of Imines with Methacrylic Anhydride or Crotonic Anhydride: To a solution of imine (6.5 mmol) in 44 mL of THF was added methacrylic anhydride or crotonic anhydride (8.5 mmol), and the mixture was heated at reflux for the required reaction time (see Tables). After the reaction was complete, the solution was washed with 25 mL of saturated aqueous $NaHCO_3$ solution. The aqueous layer was then extracted with 4 x 40 mL of Et_2O, and the organic fractions were combined and dried over Na_2SO_4. Following removal of solvents, the residue was purified by flash column chromatography (eluent: 20:80 Et_2O:petroleum ether or 40:60 Et_2O:petroleum ether). The solvents were evaporated and the residue was distilled under vacuum to give the lactam.

General Procedure for the Reaction of Imines with Acrylate Derivatives Activated by EtO_2CCl (The Mixed Anhydride Method): To a cooled solution (-30°C to -25°C) of α,β-unsaturated acid (8.5 mmol) in 43 mL of THF were added TEA (0.9 g, 8.5 mmol) and ethyl chloroformate (0.92 g, 8.5 mmol). After the mixture was stirred for 1 h at this temperature, the imine (6.5 mmol) was added and stirred for an additional 1 h. The reaction mixture was then stirred at the appropriate temperature for the required time. After the reaction was complete, the solution was washed with 25 mL of saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with 4 x 40 mL of Et_2O, and the organic fractions were combined and dried over Na_2SO_4. Following concentration of the solution, the residue was purified by flash column chromatography (eluent: 20:80 Et_2O:petroleum ether, 40:60 Et_2O:petroleum ether, or 50:50 Et_2O:petroleum ether). The solvents were evaporated and the residue was distilled under vacuum to give lactam.

General Procedure for the Reaction of Imines with Acrylate Derivatives Activated by DPPA: To a solution of imine (6.5 mmol) in 30 mL THF at 0 °C were added TEA (0.86 g, 8.5 mmol) and DPPA (2.34 g, 8.5 mmol) and the mixture was stirred for 30 min. The α,β-unsaturated acid (8.5 mmol) was added slowly and the reaction mixture was stirred for 30 min at 0 °C, followed by stirring under the conditions listed in the Tables. After the reaction was complete, the solution was concentrated and the residue was extracted with 50 mL of $CHCl_3$ and the organic layer was washed with 30 mL of 10% HCl. The resulting aqueous layer was further extracted with 3 x 25 mL of $CHCl_3$, and the combined organic layers were subsequently washed with 35 mL of saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with 4 x 25 mL of $CHCl_3$. The combined organic layers were washed with 50 mL of H_2O, and this aqueous layer was then extracted with 4 x 25 mL of $CHCl_3$. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated to give a crude residue. The crude residue was purified by flash column chromatography (eluent: 20:80 Et_2O:petroleum ether, 40:60 Et_2O:petroleum ether, or 50:50 Et_2O:petroleum ether). The solvents were evaporated and the residue was distilled under vacuum to give the corresponding lactam.

General Procedure for the Reaction of Imines with Acrylate Derivatives Activated by MCPI: To 75 mL of dry THF were added MCPI (3.0 g, 11.7 mmol), imine (9.8 mmol), α,β-unsaturated acid (11.7 mmol), and TEA (2.4 g, 23.5 mmol). The solution was heated to reflux for the corresponding reaction time (see Tables). After the reaction was complete, the solution was concentrated and the crude product was purified by flash column chromatography (eluent: 20:80 Et_2O:petroleum ether, 40:60 Et_2O:petroleum ether, or 50:50 Et_2O:petroleum ether). The solvents were evaporated and the residue was distilled under vacuum to give the lactam or a mixture of enamide and lactam.

General Procedure for the Reaction of Imines with Acyl Imidazole: To a solution of acryloyl chloride (0.77 g, 8.5 mmol) in 20 mL of dry THF was slowly

added imidazole (1.2 g, 17.0 mmol) in 30 mL THF and the resulting solution was stirred for 1 h at ambient temperature. Imine (6.5 mmol) was added into the reaction mixture and heated at reflux for the corresponding reaction time (see Table I). After the reaction was complete, the solution was washed with 30 mL of saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with 4 x 30 mL of Et_2O and the organic fractions were dried over Na_2SO_4. Following concentration of the solution, the residue was purified by flash column chromatography (eluent 50:50 Et_2O:petroleum ether). The solvents were evaporated and the residue was distilled under vacuum to give lactam.

54: (bp 75-85 °C, <1 mmHg): ^1H NMR (300 MHz, $CDCl_3$, mixture of isomers) δ 0.83 (d, 3H, *J* = 6.7 Hz, **54b**), 0.84 (d, 6H, *J* = 6.7 Hz, **54a**), 0.85 (d, 3H, *J* = 6.7 Hz, **54b**), 1.20-2.20 (m, both), 2.42 (dd, 2H, *J* = 6.5, 8.4 Hz, **54a**), 2.48 (dd, 1H, *J* = 6.0, 12.8 Hz, **54b**), 2.58 (ddd, 1H, *J* = 17.7, 5.6, 2.0 Hz, **54b**), 3.40 (d, 2H, *J* = 7.4 Hz, **54a**), 3.55 (d, 2H, *J* = 7.4 Hz, **54b**), 5.03 (m, 1H, **54b**); ^{13}C NMR (75.5 MHz, $CDCl_3$, major) δ 19.8, 22.0, 22.8, 25.2, 25.4, 28.3, 29.0, 32.0, 46.7, 116.3, 131.8, 170.9, (minor) d 20.0, 20.2, 21.4, 24.5, 26.1, 27.4, 30.6, 32.9, 35.1, 48.5, 104.4, 138.6, 169.3; IR (neat) 3014, 2875, 1634, 1405 cm^{-1}. Anal. Calcd for $C_{13}H_{21}NO$: C, 75.31; H, 10.21; N, 6.76. Found: C, 75.18; H, 10.04; N, 6.74.

26: (bp 120-130 °C, <1 mmHg): ^1H NMR (300 MHz, $CDCl_3$) δ 1.40-1.50 (m, 2H, **26a**), 1.50-1.60 (m, 2H, **26a**), 1.60-1.75 (m, **26b**), 1.80-2.00 (m, **26b**), 2.03 (m, 4H, both), 2.14 (t, 2H, *J* = 7.8 Hz, **26a**), 2.55-2.80 (m, 2H, both), 4.61 (d, 1H, *J* = 16.0 Hz, **26b**), 4.84 (s, 2H, **26a**), 4.96 (m, 1H, **26b**), 5.21 (d, 1H, *J* = 16.0 Hz, **26b**), 7.05-7.30 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$, both isomers) δ 21.3, 21.9, 22.8, 24.4, 25.3, 25.4, 27.5, 29.0, 30.4, 31.7, 32.9, 35.0, 43.7, 46.4, 105.4, 115.3, 126.2, 126.3, 126.6, 126.7, 128.4, 128.5, 131.4, 137.7, 138.6, 138.7, 169.3, 170.4; IR (neat) 3087, 3064, 3030, 2932, 2858, 2839, 1669, 1641, 1496, 1454 cm^{-1}; HRMS calcd for $C_{13}H_{21}NO$ m/z 241.1466, found m/z 241.1473.

85: (bp 70-80 °C, <1 mmHg): ^{1}H NMR (300 MHz, $CDCl_3$, major isomer) δ 1.40 (d, 6H, *J* = 6.9 Hz), 1.50-1.70 (m, 4H), 1.93-2.09 (m, 4H), 2.09-2.18 (m, 2H), 2.33 (m, 2H), 3.97 (sept, 1H, *J* = 6.9 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$ mixture of isomers) δ 20.5, 22.2, 23.2, 25.2, 26.3, 29.1, 33.2, 46.8, 116.4, 132.3, 171.1; IR (neat) 3019, 2972, 2937, 1639, 1428, 1419 cm^{-1}; HRMS calcd for $C_{12}H_{19}NO$ m/z 193.1466, found m/z 193.1464.

78: (bp 55-65 °C, <1 mmHg): ^{1}H NMR (300 MHz, $CDCl_3$, major isomer) δ 1.50-1.69 (m, 4H), 1.95-2.08 (m, 4H), 2.13-2.23 (m, 2H), 2.41 (m, 2H), 2.81 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.3, 23.0, 24.7, 25.3, 28.8, 33.0, 43.3, 112.4, 134.1, 169.4; IR (neat) 2935, 2888, 1685, 1651, 1441 cm^{-1}; HRMS calcd for $C_{11}H_{18}N_2O$ m/z 194.1419, found m/z 194.1415.

69a: (bp 75-85 °C, <1 mmHg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (d, 3H, *J* = 6.7 Hz), 0.85 (d, 3H, *J* = 6.7 Hz), 1.15 (d, 3H, *J* = 6.9 Hz), 1.45-2.22 (m, 11H), 2.43 (m, 1H), 3.19 (dd, 1H, *J* = 13.8, 6.9 Hz), 3.60 (dd, 1H, *J* = 13.8, 7.9 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 15.5, 19.9, 20.0, 22.2, 23.0, 25.5, 28.4, 29.3, 33.5, 35.6, 47.1, 115.0, 131.0, 173.3; IR (neat) 2959, 2934, 2870, 2831, 1668, 1458 cm^{-1}; HRMS calcd for $C_{14}H_{23}NO$ m/z 221.1779, found m/z 221.1777.

80: (bp 120-130 °C, <1 mmHg): ^{1}H NMR (300 MHz, $CDCl_3$, major isomer) δ 1.23 (d, 3H, J = 6.9 Hz), 1.42-1.66 (m, 4H), 1.94-2.10 (m, 4H), 2.15 (dd, 1H, *J* =16.0, 6.5 Hz), 2.59 (m, 1H), 4.73 (d, 1H, *J* = 16.2 Hz), 4.97 (d, 1H, *J* = 16.2 Hz), 7.10-7.32 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$, mixture of isomers) δ 15.2, 21.6, 22.4, 25.0, 28.7, 33.2, 35.0, 43.6, 114.0, 125.8, 126.2, 128.1, 130.5, 138.3, 173.1; IR (neat) 3087, 3062, 3032, 2931, 2867, 2832, 1665, 1495, 1453 cm^{-1}; HRMS calcd for $C_{17}H_{21}NO$ m/z 255.1612, found m/z 255.1619.

87: (mp 56-57 °C): ^{1}H NMR (300 MHz, $CDCl_3$, major isomer) δ 1.08 (d, 3H, *J* =6.9 Hz), 1.37 (d, 3H, *J* = 6.9 Hz), 1.39 (d, 3H, J= 6.9 Hz), 1.44 - 2.22 (m, 10H), 2.32 (m, 1H), 3.95 (sept, 1H, *J* = 6.9 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 15.1, 20.5, 20.6,

22.3, 23.3, 26.4, 29.5, 33.4, 36.3, 46.9, 115.6, 131.8, 173.7; IR (KBr) 2966, 2931, 1664, 1451, 1418 cm^{-1}; HRMS calcd for $C_{13}H_{21}NO$ m/z 207.1623, found m/z 207.1630.

73a: (bp 75-85 °C, <1 mmHg): ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (d, 3H, *J* = 6.8 Hz), 0.88 (d, 3H, *J* = 6.8 Hz), 0.98 (d, 3H, *J* = 7.1 Hz), 1.35 - 1.90 (m, 5H) 1.95-2.20 (m, 5H), 2.26 (dd, 1H, *J* = 15.6, 4.2 Hz), 2.56 (dd, 1H, *J* = 15.6, 6.4 Hz), 3.09 (dd, 1H, *J* = 13.9, 7.0 Hz), 3.71 (dd, 1H, *J* = 13.9, 7.5); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 16.8, 20.1, 20.4, 22.2, 23.0, 25.6, 27.3, 28.6, 30.6, 39.2, 46.9, 120.0, 130.3, 169.7; IR (neat) 2957, 2870, 2837, 1670, 1639, 1466, 1435 cm^{-1}. Anal. Calcd for $C_{14}H_{23}NO$: C, 75.97; H, 10.47; N, 6.33. Found: C, 75.97; H, 10.30; N, 6.40.

82: (bp 120-130 °C, <1 mmHg): ^1H NMR (300 MHz, $CDCl_3$, major isomer) δ 1.00 (d, 3H, *J* = 7.1 Hz), 1.30 - 2.30 (m, 9H), 2.39 (dd, 1H, *J* = 15.6, 4.3 Hz), 2.70 (dd, 1H, J = 15.6, 6.5 Hz), 4.70 (d, 1H, *J* = 16.0 Hz), 5.03 (d, 1H, 16.0 Hz), 7.10-7.32 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 16.7, 21.7, 22.4, 25.0, 26.7, 30.4, 38.6, 43.4, 119.2, 126.2, 126.3, 128.0, 129.7, 138.4, 169.5; IR (neat) 3087, 3062, 3031, 2932, 2862, 2836, 1665, 1641, 1496 cm^{-1}; HRMS calcd for $C_{17}H_{21}NO$ m/z 255.1612, found m/z 255.1622.

89: (bp 70-80 °C, <1 mmHg): ^1H NMR (300 MHz, $CDCl_3$, major isomer) δ 0.92 (d, 3H, *J* = 7.1 Hz), 1.38 (d, 3H, *J* = 6.9 Hz), 1.40 (d, 3H, J= 6.9 Hz), 1.30-2.20 (m, 9H), 2.15 (dd, 1H, J=3.5, 15.4 Hz), 2.51 (dd, 1H, *J* =15.4, 6.2 Hz), 3.95 (sept, 1H, *J* = 6.9 Hz): ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 16.5, 20.0, 20.5, 22.3, 23.2, 26.4, 27.4, 30.5, 40.2, 46.7, 121.1, 130.9, 170.2; IR (neat) 2960, 2933, 2866, 1666, 1418 cm^{-1}; HRMS calcd for $C_{13}H_{21}NO$ m/z 207.1623, found m/z 207.1627.

67: (bp 65-75 °C, <1 mmHg): ^1H NMR (300 MHz, $CDCl_3$, mixture of isomers) δ 0.83-0.89 (m, 6H), 1.37-1.53 (m, 1H), 1.73-2.24 (m), 2.30-2.82 (m), 3.29 (d, 2H, *J* =7.6 Hz, **36a**), 3.38 (dd, 1H, *J* = 7.0, 13.4 Hz, **36b**), 3.56 (dd, 1H, *J* = 8.2, 13.4 Hz, **36b**), 4.78 (m, 1H, **36b**). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.0, 20.1, 20.2, 21.0,

21.7, 26.2, 27.1, 28.4, 29.9, 30.4, 31.2, 32.0, 32.8, 33.2, 41.9, 50.1, 102.9, 115.6, 137.0, 144.1, 169.4, 170.1; IR (neat) 3010, 2963, 2934, 2903, 2872, 2849, 1688, 1660, 1633, 1466, 1406 cm^{-1}. Anal. Calcd for $C_{12}H_{19}NO$: C, 74.57; H, 9.91; N, 7.25. Found: C, 74.13; H, 9.95; N, 7.19.

62: (bp 55-65 °C, <1 mmHg): ^1H NMR (300 MHz, $CDCl_3$) δ 0.84 (d, 6H, J = 6.7 Hz), 0.98 (t, 3H, *J* = 7.4 Hz), 1.88 (m, 1H), 2.00 (m, 2H), 2.14 (t, 2H, *J* = 7.9 Hz), 2.44 (t, 2H, *J* = 7.9 Hz), 3.20 (d, 2H, *J* = 7.5 Hz), 5.68 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.5, 20.0, 24.2, 26.9, 27.9, 31.6, 53.4, 121.5, 124.4, 169.5; IR (neat) 2964, 2842, 1639 cm^{-1}. Anal. Calcd for $C_{11}H_{19}NO$: C, 72.88; H, 10.56; N, 7.72. Found: C, 72.85; H, 9.87; N, 7.72.

71: (bp 55-65 °C, <1 mmHg): ^1H NMR (300 MHz, $CDCl_3$) δ 0.86 (d, 6H, *J* = 6.7 Hz), 1.01 (t, 3H, *J* = 7.4 Hz), 1.18 (d, 3H, *J* = 7.0 Hz), 1.83 - 2.08 (m, 4H), 2.26 (ddd, 1H, *J* = 6.7, 16.4, 1.0 Hz), 2.48 (d quint, 1H, *J* = 10.4, 7.0 Hz), 3.15 (dd, 1H, *J* = 13.4, 7.4 Hz), 3.30 (dd, 1H, *J* = 13.4, 7.6 Hz), 5.70 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.4, 15.9, 19.9, 20.0, 26.9, 27.8, 32.1, 35.3, 53.4, 120.1, 123.6, 172.6. IR (neat) 2964, 2932, 2872, 1662, 1458 cm^{-1}; HRMS calcd for $C_{12}H_{21}NO$ m/z 195.1623, found m/z 195.1623.

75: (bp 55-65 °C, <1 mmHg): ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (d, 6H, *J* = 6.7 Hz), 1.02 (m, 6H), 1.92 (m, 1H), 2.04 (m, 2H), 2.23-2.36 (m, 2H), 2.58 (m, 1H), 3.01 (dd, 1H, J = 13.4, 7.1 Hz), 3.46 (dd, 1H, J = 13.4, 7.7 Hz), 5.63 (t, 1H, *J* = 0.8 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.7, 17.7, 19.9, 20.0, 24.8, 27.9, 29.8, 39.1, 53.2, 122.9, 125.9, 168.4; IR (neat) 2964, 2930, 2873, 1679, 1467, 1456, 1414 cm^{-1}; HRMS calcd for $C_{12}H_{21}NO$ m/z 195.1623, found m/z 195.1630.

92: (bp 85-95 °C, 3 mmHg): ^1H NMR (300 MHz, $CDCl_3$) δ 1.03 (t, 3H, *J* = 7.4 Hz), 1.13 (d, 6H, *J* = 6.8 Hz), 2.07 (bq, 2H, *J* = 7.4 Hz), 2.18 (bt, 2H, *J* = 8.1 Hz), 2.48 (dd, 2H, *J* = 7.3, 8.7 Hz), 4.87 (sept, 1H, *J* = 6.8 Hz), 5.85 (quint, 1H, *J* = 1.2 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.4, 20.4, 23.5, 27.1, 31.6, 42.9, 117.7, 122.0,

168.1; IR (neat) 2968, 2934, 2898, 2877, 2842, 1657, 1463, 1437, 1410 cm^{-1}; HRMS calcd for $C_{10}H_{17}NO$ m/z 167.1310, found m/z 167.1309.

94: (bp 95-105 °C, 3 mmHg): ^1H NMR (300 MHz, $CDCl_3$) δ 0.97 (d, 3H, *J* = 6.9 Hz), 1.04 (t, 3H, *J* = 7.4 Hz), 1.10 (d, 3H, *J* = 6.9 Hz), 1.13 (d, 3H, *J* = 6.9 Hz), 2.02-2.11 (m, 2H), 2.26 (m, 1H), 2.26 (dd, 1H, *J* = 3.8, 16.6 Hz), 2.57 (dd, 1H, *J* = 16.6, 7.4 Hz), 4.87 (sept, 1H, *J* = 6.9 Hz), 5.76 (t, 1H, J = 1.4 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.7, 17.5, 20.0, 20.6, 25.2, 29.1, 39.3, 42.8, 116.5, 127.3, 167.6; IR (neat) 2965, 2932, 2876, 1671, 1463, 1410 cm^{-1}; HRMS calcd for $C_{10}H_{19}NO$ m/z 181.1466, found m/z 181.1462.

General Procedure for the Isomerization of Double Bonds and Hydrolysis of Enamides: To a solution containing a mixture of enamide and lactam or mixture of double bond isomers (1 mmol in 10 mL of methanol) was added p-toluenesulfonic acid (0.2 mmol) and the reaction mixture was heated at reflux or stirred at ambient temperature until either the enamide was hydrolyzed or isomerization demonstrated no further change.

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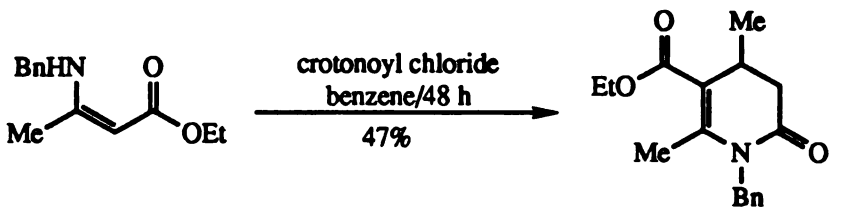
(24) In order to avoid aldol type condensation products in the reaction with aldimine **62**, acrylic anhydride was first transferred to a schlenk flask followed by addition of the imine to the acrylic anhydride solution.

CHAPTER 2

AZA-ANNULATION OF ENAMINES

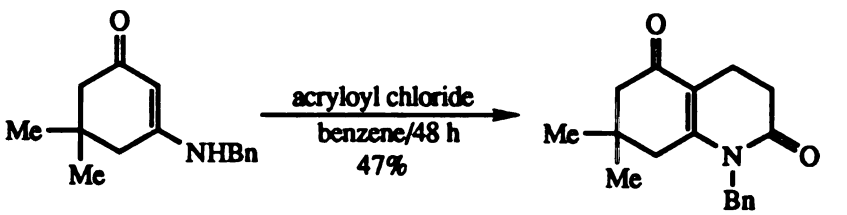
INTRODUCTION

In contrast to the isolation of a mixture of enamide and lactam from the reaction of an imine and acryloyl chloride,[1] Hickmott isolated only the six-membered lactam **102** in 47% yield from the reaction of enamino ester **101** and crotonyl chloride (eq 1).[2] Under the same reaction conditions, enamino ketone **103** also gave only bicyclic lactam **104** in 47% yield (eq 2).



(1)

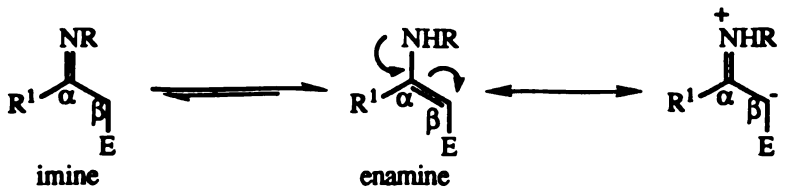
101 **102**



(2)

103 **104**

The absence of uncyclized enamide in the reaction of enamino ester **101** or enamino ketone **103** with α,β-unsaturated acid chlorides could be explained on the basis of the stable enamine tautomer. In the case of the imine **105** with an electron withdrawing group (E) in the β-position, the equilibrium favors the enamine tautomer **106** because of the conjugation of the enamine double bond with electron withdrawing group (E) (eq 3). Since the β-carbon of the enamine is more nucleophilic than the nitrogen as shown in **107**, initial *C*-alkylation occurs faster than the *N*-acylation during the annulation reaction. Hence the initial *C*-alkylation followed by intramolecular *N*-acylation would give only lactam.



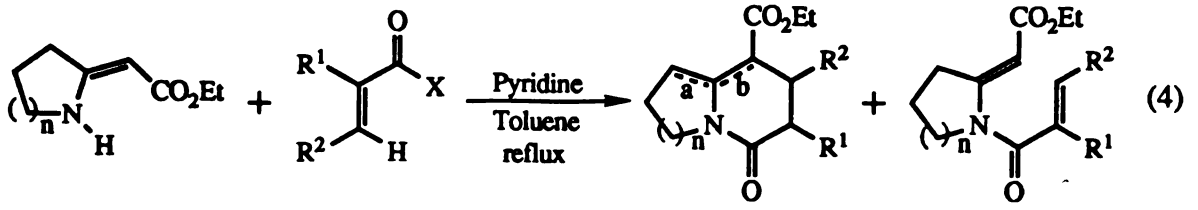
(3)

105 **106** **107**

Following Hickmott's earlier reports, several research groups have investigated the reactions of enamines with a variety of α,β-unsaturated acid derivatives. These results help us to understand the limitation and usefulness of this annulation. Selected examples of the reactions of enamines with various acid derivatives are discussed.

a) Reaction of Enamines with α,β-Unsaturated Acid Chlorides

Lhommet studied the reaction of cyclic enamino esters **108** and **109** with various α,β-unsaturated acid chlorides (eq 4) and the results are shown in Table XVII.[3] The reaction of acryloyl chloride with enamino ester **108** gave only lactam **110** (entry 1) and the reaction methacrolyl chloride and crotonyl chloride with **108** gave the corresponding enamides **114** and **115** as the major product (entry 2 and 3). The formation of uncyclized enamides **114** and **115** as the major product could be due the presence of pyridine in the reaction mixture. The reaction of enamino ester **109** with acryloyl chloride, methacryloyl chloride and crotonyl chloride gave the corresponding lactams **116** to **118** (entries 4 to 6), and the lactams were isolated as a mixture of double bond isomers. Lhommet increased the scope of this methodology by preparing several valuable substituted indolizidinone and quinolizidinone skeletons in a simple and elegant manner. These indolizidinone and quinolizidinone compounds could be used to synthesise various biologically active alkaloids.



(4)

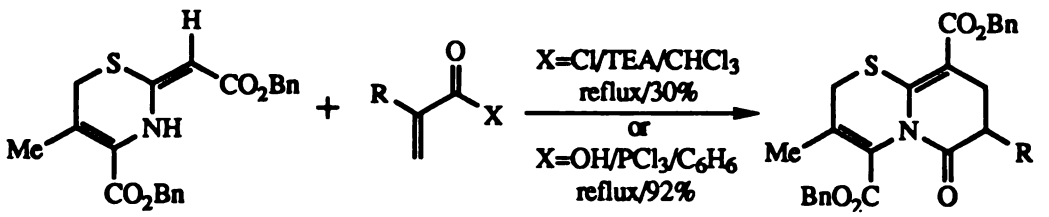
n=1 **108**	n=1, R^1= H	R^2 = H	**110**		**113**
n=2 **109**	n=1, R^1= Me	R^2 = H	**111**		**114**
	n=1, R^1= H	R^2 = Me	**112**		**115**
	n=2, R^1= H	R^2 = H	**116**		**119**
	n=2, R^1= Me	R^2 = H	**117**		**120**
	n=2, R^1= H	R^2 = Me	**118**		**121**

Table XVII. Reaction of Enamino Esters **108** and **109** with α,β-Unsaturated Acid Chlorides and Esters.

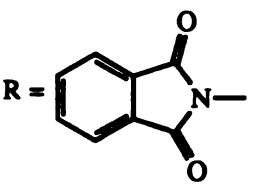
Entry	n	R^1	R^2	X	yield	Compounds	Ratio	(a : b)
1	1	H	H	Cl	72%	110 : 113	100 : 00	0 : 100
2	1	Me	H	Cl	64%	111 : 114	30 : 70	0 : 100
3	1	H	Me	Cl	72%	112 : 115	0 : 100	0 : 100
4	2	H	H	Cl	82%	116 : 119	100 : 00	70 : 30
5	2	Me	H	Cl	68%	117 : 120	100 : 00	80 : 20
6	2	H	Me	Cl	68%	118 : 121	100 : 00	60 : 40
7	1	H	H	OEt	75%	110 : 113	100 : 00	0 : 100
8	1	Me	H	OEt	72%	111 : 114	100 : 00	0 : 100
9	1	H	Me	OEt	63%	112 : 115	100 : 00	0 : 100
10	2	H	H	OEt	82%	116 : 119	100 : 00	65 : 35
11	2	Me	H	OEt	68%	117 : 120	100 : 00	92 : 08
12	2	H	Me	OEt	68%	118 : 121	100 : 00	52 : 48

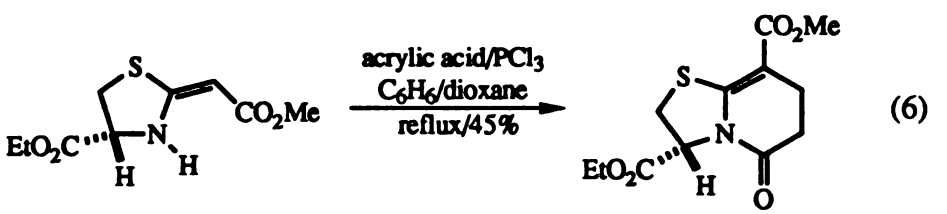
Treatment of the enamino ester **122** with acid chloride of 2-phthalimidoacrylic acid (**123a**) gave the bicyclic lactam **124** in 30% yield.[4] Lactam **124** is analogous to a β-lactam antibiotics. The yield of this reaction was improved to 92% by refluxing **122** with

123b and PCl_3 (eq 5). Isolation of compound **124** shows the use of the aza-annulation reaction to prepare six-membered lactams with an amino group α to the amide carbonyl group in a single step from the corresponding enamino ester. Under the above reaction conditions, reaction of enamino ester **125** with acrylic acid in the presence of PCl_3 gave lactam **126** in 45% yield (eq 6).[4]



122 **123a** X=Cl **123b** X=OH **124**





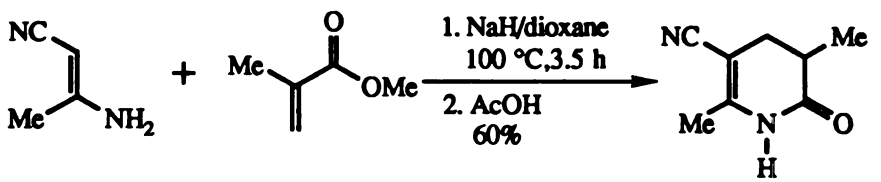
125 **126**

b) Reaction of Enamines with α,β-Unsaturated Esters

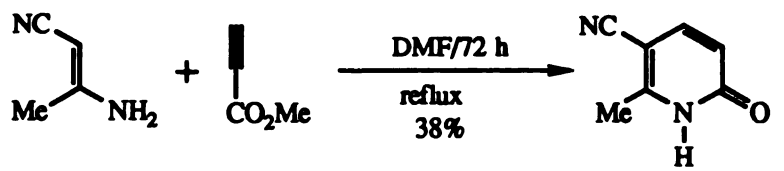
Lhommet studied the reaction of enamino esters **108** and **109** with various α,β-unsaturated esters (eq 4) and the results are shown in Table XVII.[3] In the reaction of enamino esters **108** and **109** with α,β-unsaturated esters, NaH was used as a base to favor the intramolecular *N*-acylation. Only bicyclic lactams **110** to **112** and **116** to **118** were obtained in moderate to good yield from the reaction of enamino esters **108** and **109** with all α,β-Unsaturated esters (entries 7 to 12). Lactams **116** to **118** were isolated as a

mixture of double bond isomers. Since the preparation of α,β-unsaturated esters are easier than the corresponding acid chlorides, use of α,β-unsaturated esters is an alternative to carry out annulation reactions.

Singh and his co-workers isolated lactam **128** in 60% yield from the reaction of enamino nitrile **127** with methyl methacrylate (eq 7).[5] Treatment of **127** with methyl propiolate gave pyridinone **129** in 38% yield (eq 8). Lactams **128** and **129** were formed *via* initial *C*-alkylation followed by intramolecular *N*-acylation. Even though the yield of the formation of compound **129** was low, use of methyl propiolate in this annulation opened a new door to prepare various substituted aromatic nitrogen heterocycles in a single step from the corresponding acyclic enamines.



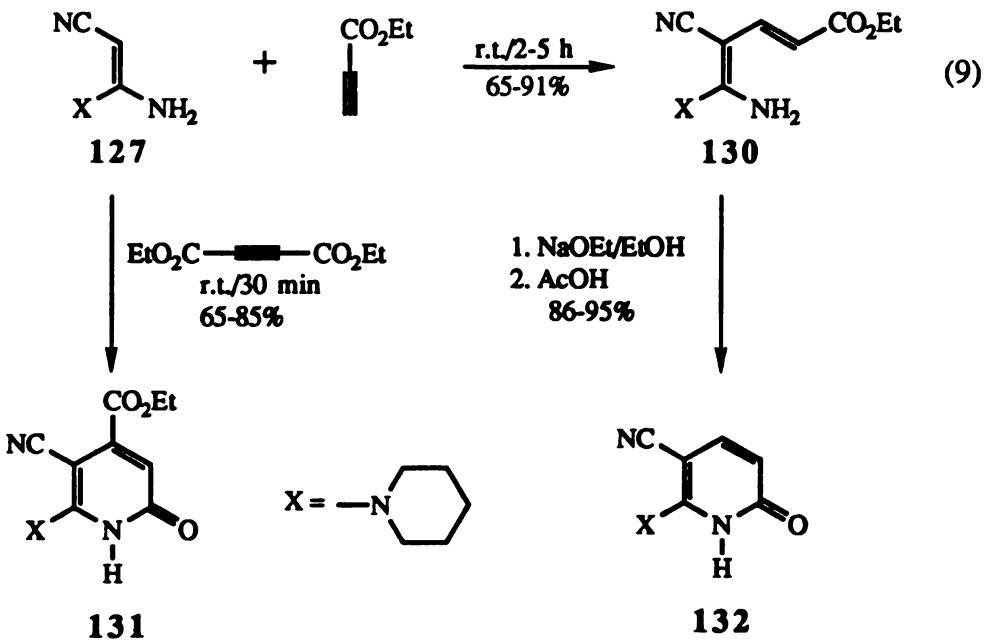
127 **128** (7)



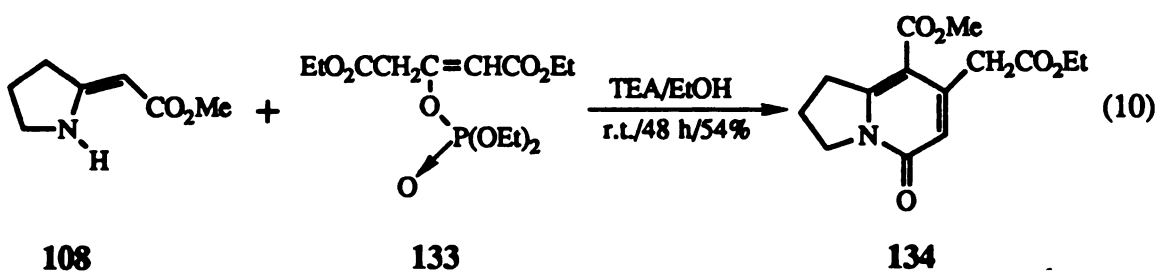
127 **129** (8)

The Maccioni group reported the isolation of the intermediate dienamino ester **130** from the reaction of **127** and ethyl propiolate (eq 9).[6] Dienamino ester **130** was a stable compound, did not undergo cyclization under normal conditions, and was cyclized into **132** by heating with sodium ethoxide in ethanol. On the other hand, reaction of diethyl acetylenedicarboxylate with **127** gave compound **131** without isolation of any *C*-alkylation product. As mentioned in the previous example, use of methyl propiolate and

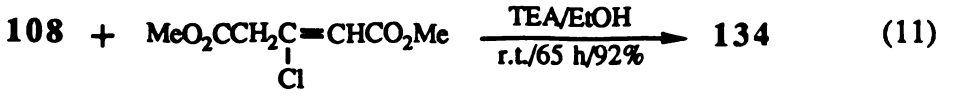
diethyl acetylenedicarboxylate as acylating agents provided substituted aromatic nitrogen heterocycles in good yields and increased the usefulness of this annulation reaction.



Danishefsky used this annulation as one of the key steps in the synthesis of the anti tumor alkaloid camptothecin.[7] Enamino ester **108** was reacted with enol phosphate **133** to give pyridone **134** (eq 10). The yield of this reaction has been increased from 54% to 92% by using readily available dimethyl-3-chloroglutoconate (**135**) in the presence of triethylamine (eq 11).[8] Compounds **133** and **135** are precursors of allene functionality and generate allene *in situ* with TEA.



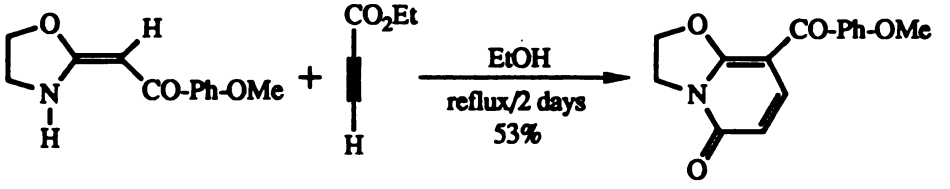
108 **133** **134**



(11)

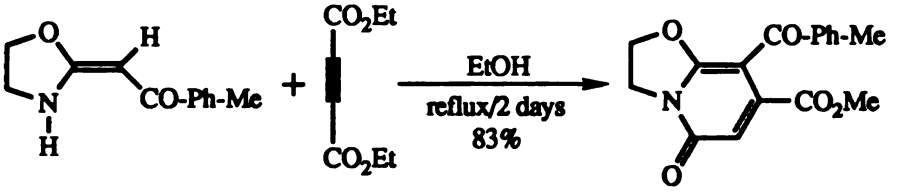
135

Huang prepared lactam **137** in 53% yield from the annulation of heterocyclic ketene *N,O*-acetal **136** with ethyl propiolate.[9] Only the more reactive 4-methoxy benzoyl substituted ketene *N,O*-acetal **136** reacted with ethyl propiolate to give the lactam **137** in moderate yield (eq 12). Reaction of other benzoyl substituted ketene *N,O*-acetals with ethyl propiolate gave only a trace of products. On the other hand, other benzoyl substituted ketene *N,O*-acetals such as *p*-methyl benzoyl substituted ketene *N,O*-acetal **138** gave **139** in 83% yield with diethyl acetylenedicarboxylate (eq 13). The rate of the reaction was very slow and the yields were moderate to high.



(12)

136 **137**

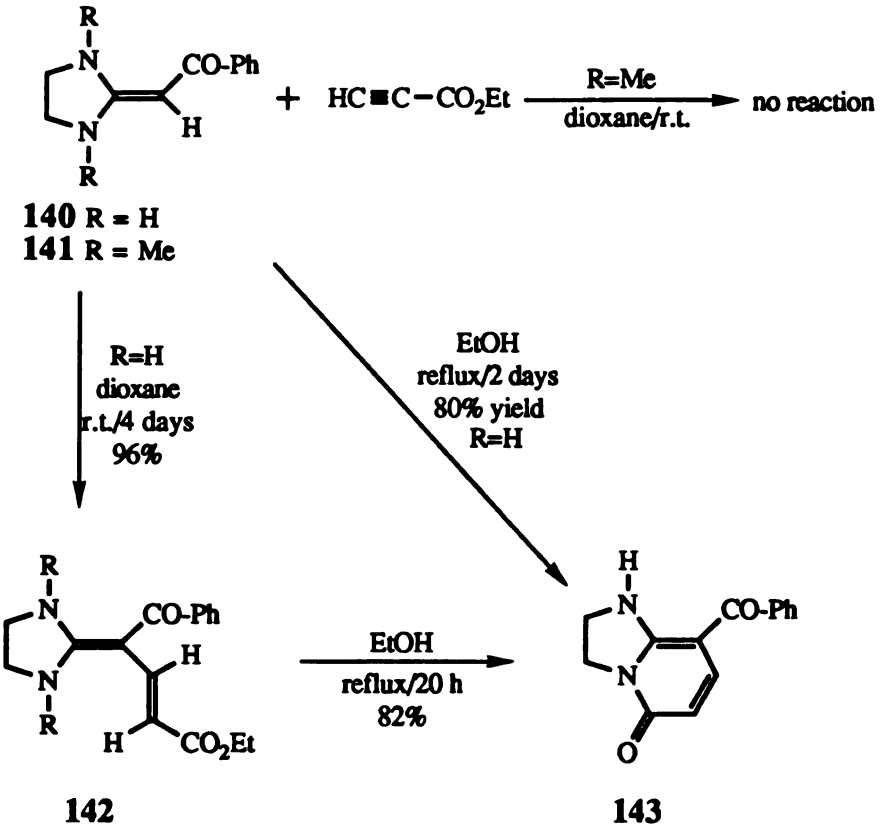


(13)

138 **139**

Huang also investigated the annulation of ketene aminals with ethyl propiolate (eq 14).[10] Compound **141** (R=Me) failed to react with ethyl propiolate, and resulted in the recovery of starting material. On the other hand, reaction of compound **140** (R=H) with ethyl propiolate readily gave the *C*-alkylated product **142**, which was cyclized in refluxing ethanol to give lactam **143**. The lactam **143** was also directly prepared in one

step by refluxing **140** with ethyl propiolate in ethanol. Polar protic solvents gave the cyclized product directly without the isolation of any intermediate.

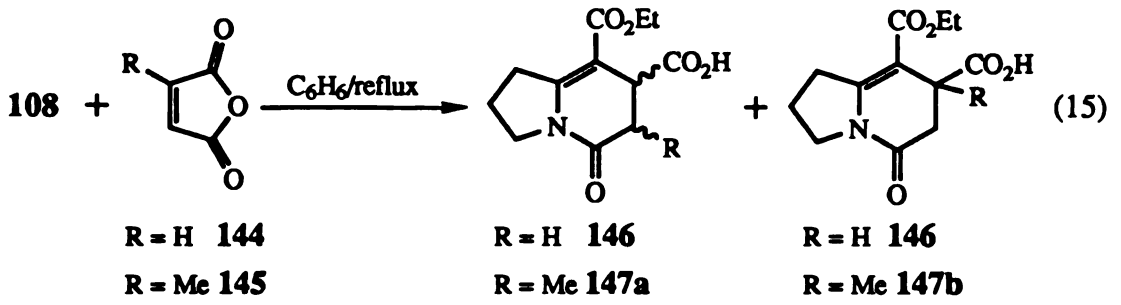


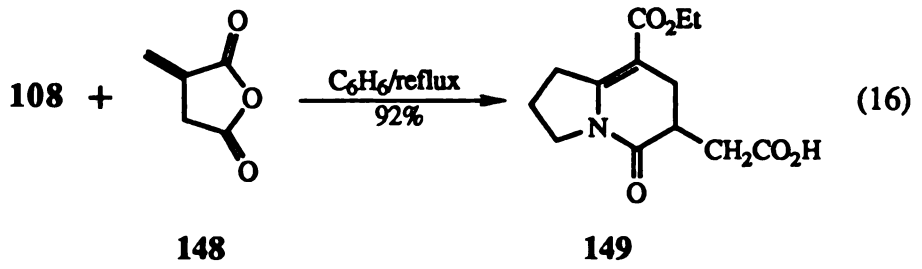
(14)

c) Reaction of Enamines with α,β-Unsaturated Anhydrides

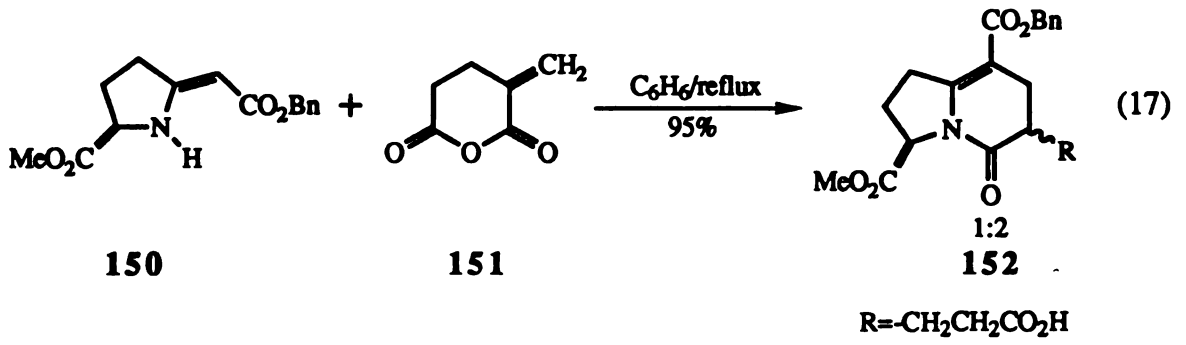
Nagasaka and his coworkers used the enamino ester **108** as an useful precursor to prepare a variety of fused heterocyclic compounds (eq 15).[11] Lactam **146** was prepared in 97% yield from the reaction of **108** and maleic anhydride (**144**) in refluxing benzene. In the case of 2-substituted maleic anhydride **145**, the annulation reactions required longer reaction times and gave lactams in low yield as a mixture of regioisomers **147a** and **147b**. The low reactivity could be due to the steric effect of the methyl group during the initial C-C bond formation. Annulation of **108** with itaconic anhydride (**148**) gave lactam **149** in 92% yield (eq 16). These reactions demonstrate the use of cyclic α,β-

unsaturated anhydrides as annulating agent in aza-annulation to prepare six-membered lactams in high yield.



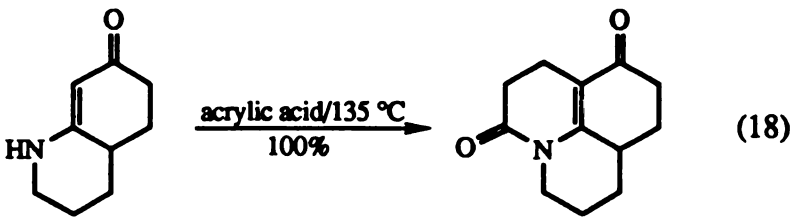


In extension of the use of cyclic anhydrides as the annulating agent, Danishefsky reacted α-methyleneglutaric anhydride (**151**) with enamino ester **150**, prepared from D,L-pyroglutamic acid, to give compound **152** in 95% yield. The compound **152** was used to the total synthesis of the enzyme inhibitor A58365A (eq 17).[12]



d) Reaction of Enamines with α,β-Unsaturated Acids

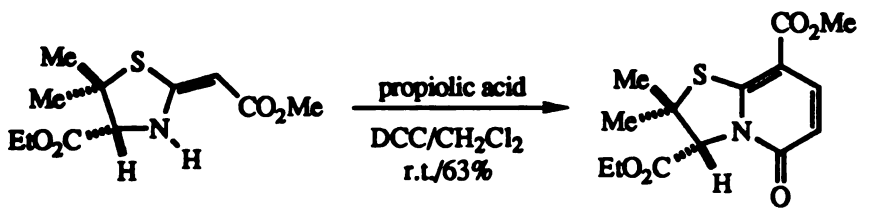
Wiesner used the aza-annulation reaction as the key step toward the synthesis of lycopodium alkaloid annotinine. The key intermediate **154** was obtained in quantitative yield by heating the enamino ketone **153** with a 15% excess of acrylic acid at 135 °C (eq 18).[13] The use of acrylic acid as the annulating agent required higher temperature and solvent was not used. However these conditions cannot be used in the presence of other sensitive functional groups.



(18)

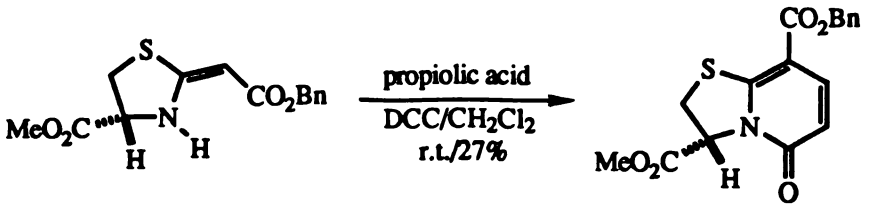
153 **154**

Young prepared bicyclic lactams **156** and **158** in 63 and 27% yields respectively from the annulation of the cyclic enamino esters **155** and **157** respectively with propiolic acid in the presence of acid activating reagent DCC (eq 19 and 20).[4] Young showed the use of acid activating reagent DCC in this annulation. Use of acid in the presence of acid activating agents eliminates the conversion of acids to the corresponding acid chlorides, esters or anhydrides.



(19)

155 **156**



(20)

157 **158**

Even though several reactions of enamines with various α,β-unsaturated acid derivatives have been reported, no one has systematically investigated the aza-annulation of enamines. Hence, we wanted to thoroughly study this reaction with the following aims:

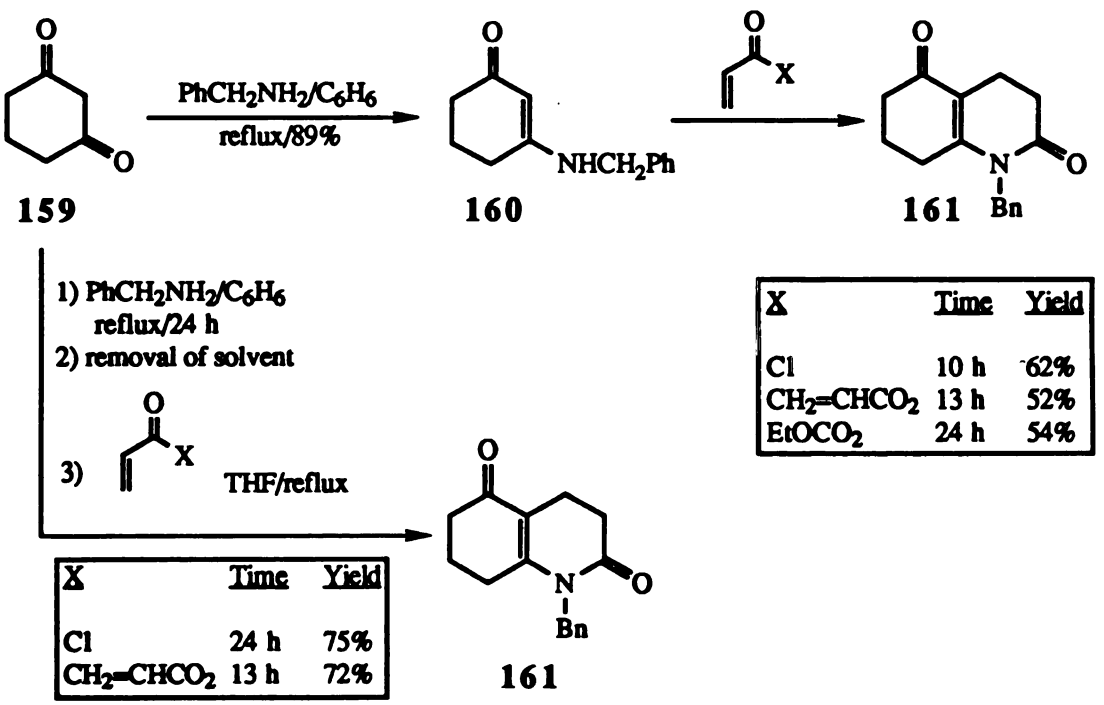
1) To optimize the reaction conditions of the annulation to prepare lactam in high yield under mild conditions and to extend this annulation methodology to various enamines conjugated with a variety of electron withdrawing groups.

2) To study the cis and trans selectivity of catalytic hydrogenation of the double bond of the lactams prepared from the reaction of enamines and acryloyl chloride. Since numerous alkaloids have saturated six-membered nitrogen heterocycles, hydrogenation of the annulated lactam would show the importance of this methodology in alkaloid synthesis.

RESULTS AND DISCUSSION

In order to study the aza-annulation of enamines conjugated with electron withdrawing groups, enamino ketone **160** was chosen for our initial studies. Enamino ketone **160** was prepared in 89% yield from the condensation of 1,3-cyclohexanedione **159** and benzylamine.[14] Purified enamino ketone **160** was reacted with various acrylic acid derivatives and the results are given in Scheme IV. Reaction of **160** with acrylic acid derivatives (acryloyl chloride, acrylic anhydride and acrylic acid in the presence of ethyl chloroformate) gave only bicyclic lactam **161** in moderate yields (52-62%).

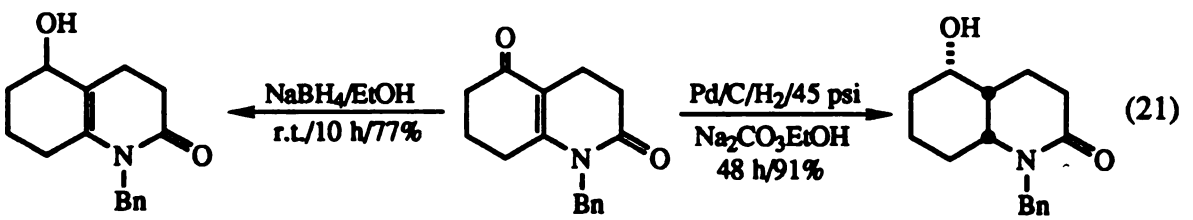
Scheme IV. Reaction of Enamino Ketone **160** with Acrylic Acid Derivatives.



Since the enamine formation is an efficient process, the crude enamino ketone **160** obtained after the removal of the solvent was directly treated with acrylic acid derivatives without further purification. For the two-step process, both acryloyl chloride and acrylic

anhydride gave lactam **161** in good yields (75 and 72% respectively). Since the two-step one pot reaction (enamine formation and annulation) was efficient and gave lactams in good yield, these conditions were used as the general annulation procedure to prepare six-membered lactams directly from the corresponding ketones. Further, acryloyl chloride is a readily available inexpensive reagent which serves as the annulating agent for the annulation process. This two-step one-pot annulation procedure using acryloyl chloride as the annulating reagent was employed in most of the annulation reactions unless otherwise noted.

Having optimized the aza-annulation conditions, attention was then focused on finding suitable conditions for the stereoselective reduction of the tetra substituted emamine double bond to either cis or trans lactams. The cis or trans lactam lends itself nicely as a precursor in organic synthesis. Reaction of lactam **161** with $NaBH_4$ did not reduce the enamine double bond, but reduced the ketone and gave alcohol **162** in 77% yield (eq 21).



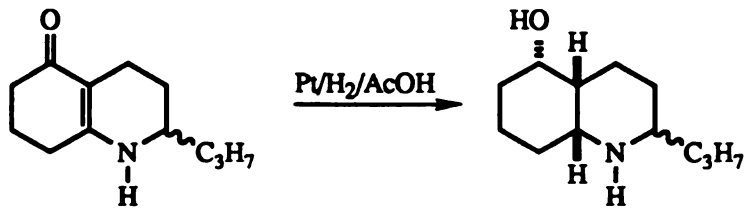
(21)

162 **161** **163**

(85:5:10)

Catalytic hydrogenation of the lactam **161** over 10% Pd on carbon gave a considerable amount of unwanted side products. Hydrogenation of compound **161** in ethanol in the presence of 3.5 equivalent of Na_2CO_3 under 45 psi of H_2 atmosphere gave cis fused hydroxy lactam **163** as the major product along with a trace of its hydroxyl epimer (5%) and trans isomer (10%) in 91% yield.[15] The stereochemistry of alcohol **163** was confirmed both by comparison with similar reactions in the literature and by

chemical transformations. Habermehl reported isolation of alcohol **165** from the catalytic hydrogenation of enamino ketone **164** with Pt in acetic acid (eq 22).[16]



(22)

164 **165**

In order to confirm the configuration of alcohol **163** by chemical transformations, compound **163** was oxidized to a 90:10 mixture of cis and trans ketone **166** in 93% yield using Swern oxidation (eq 23).[17] The ketone **166** was then reacted with $NaBH_4$ to give alcohol **163** along with a trace of its epimer (3%) and trans isomer (12%) in 92% yield. Attack of the hydride ion would be expected from the least hindered side, top side, of the cis fused ring to avoid steric hindrance as shown in Fig 1. As expected, during $NaBH_4$ reduction of **166**, the hydride ion was delivered from the sterically unhindered top side of the ring to give the alcohol **163** as the major product along with a small amount of its epimer.

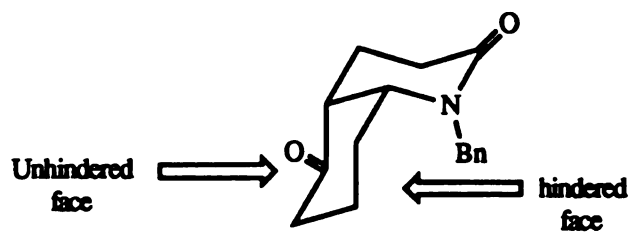
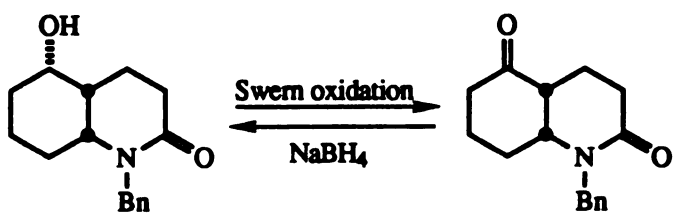


Fig 1. Structure of Compound **166**



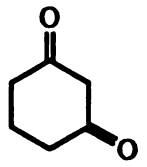
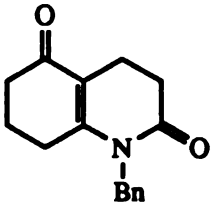
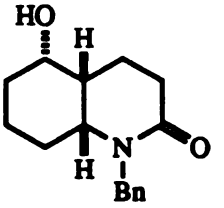
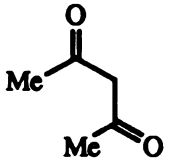
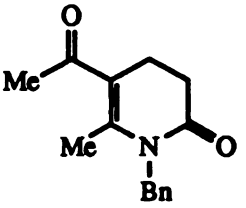
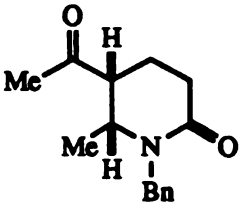
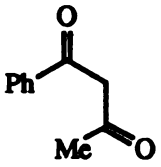
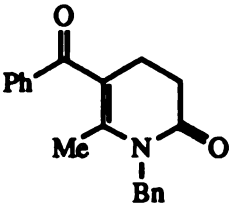
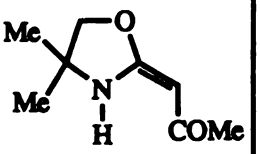
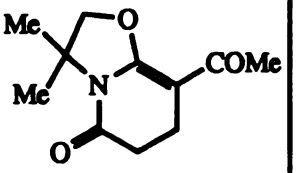
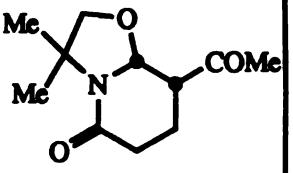
(23)

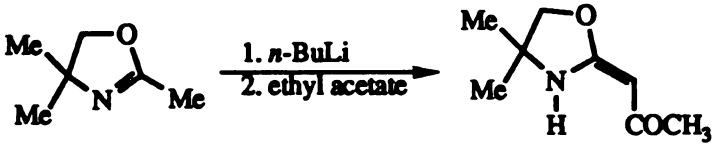
163 **166**

The isomer and epimer ratios of the compounds **163** and **166** were determined by the ^1H NMR spectroscopy. Since both alcohol **163** and ketone **166** have asymmetric centers, the benzylic methylene protons are non-equivalent and give an AB pattern in the ^1H NMR spectrum. The AB pattern due to the benzylic methylene protons was used to determine isomer and epimer ratio of the compounds. A similar observation was also reported by Hickmott.[2]

Having optimized the aza-annulation and hydrogenation conditions, this methodology was extended to a variety of enamines. Initially, acyclic symmetrical ketone **167**, non symmetrical ketone **170**, and cyclic enamino ketone **173** were chosen, and the results of annulation and hydrogenation are shown in Table XVIII. Aza-annulation of acetylacetone (**167**) gave lactam **168** in 84% yield (entry 2). On catalytic hydrogenation, lactam **168** gave a 65:35 mixture of cis and trans lactams **169** in 87% yield. The poor selectivity was believed to arise from the epimerization of the asymmetric center, α to the keto group, by Na_2CO_3 present in the reaction mixture. However, hydrogenation of lactam **168** in the absence of Na_2CO_3, also gave similar selectivity. Annulation of the unsymmetrical 1,3-diketone, benzoylacetone (**170**) regiospecifically gave lactam **171** in 79% yield (entry 3). Absence of the regioisomer could be explained on the basis of steric effects due to the phenyl group in the starting ketone. Unfortunately, the hydrogenation of the lactam **171** gave a mixture of products. The cyclic enamino ketone **173** was prepared using Meyer's procedure from the corresponding imine, 2,4,4-trimethyl-2-oxazoline (**172**), and ethyl acetate.[18] Reaction of **173** with acryloyl chloride gave lactam **174** in 64% yield (entry 4). Hydrogenation of the lactam **174** gave a 61:39 mixture of cis and trans lactam **175** in 34% yield. Aza-annulation of enamino ketones gave lactams in moderate to high yield, but the catalytic hydrogenation of the lactams **168**, **171** and **174** gave poor selectivity.

Table XVIII. Aza-Annulation of Enamino Ketones.

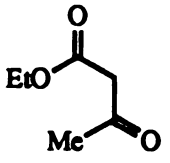
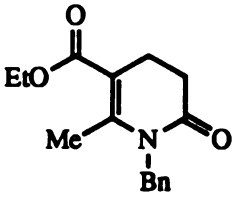
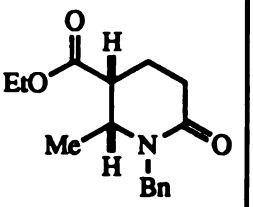
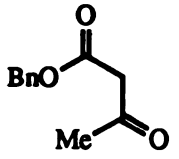
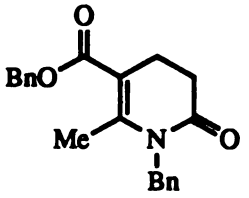
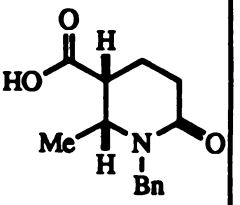
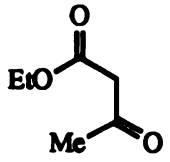
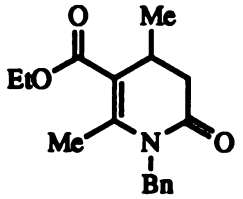
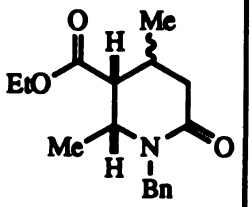
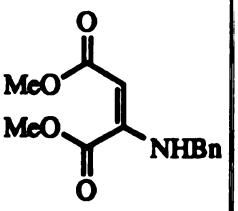
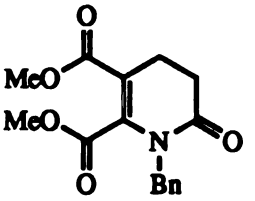
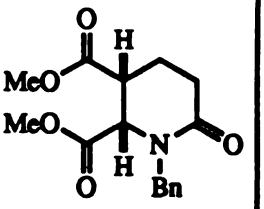
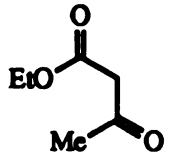
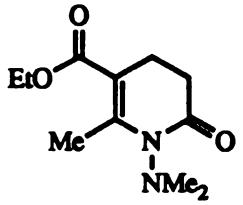
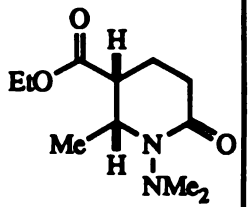
Entry	Diketone	Annulated product	Yield	Hydrogenated product	Yield (cis:trans)
1	 **159**	 **161**	75%	 **163**	91% (85:10:5)
2	 **167**	 **168**	84%	 **169**	87% (65:35)
3	 **170**	 **171**	79%	Mixture of products	—
4	 **173**	 **174**	64%	 **175**	34% (61:39)



172 **173** (24)

In developing this methodology, the annulation was extended to various enamino esters which were prepared from β-keto esters and a primary amines. The results of the annulation of various acyclic β-keto esters and hydrogenation of the lactams are shown in Table XIX. Annulation of ethyl acetoacetate (**176**) gave lactam **177** in 94% yield (entry 1). Catalytic hydrogenation of **177** gave a >98:<2 mixture of cis and trans lactams **178** in 91% yield. Lactam **180** was obtained in 91% yield from the annulation of benzyl acetoacetate (**179**) and hydrogenation of lactam **180** gave a 96:4 mixture of cis and trans acids **181** in 91% yield (entry 2). In order to avoid the formation of sodium salt of acid **181**, hydrogenation was carried out without the addition of Na_2CO_3. High cis stereoselectivity upon hydrogenation of lactams **178** and **181** encouraged us to extend these annulation and hydrogenation processes to other β-keto esters. The intermediate crude enamino ester **102**, derived from **176** and benzylamine, was treated with crotonyl chloride to give the lactam **103** in 75% yield (entry 3). Hydrogenation of lactam **103** was sluggish and gave a 86:14 mixture of diastereomers **182** in 53% yield. The enamino ester **183**, prepared from the reaction of dimethyl acetylenedicarboxylate and benzylamine, was treated with acryloyl chloride to give lactam **184** in 84% yield (entry 4).[19] Hydrogenation of lactam **184** stereospecifically gave only cis lactam **185** in 80% yield. Changing from benzylamine to *N,N*-dimethylhydrazine did not affect either the yield of the annulation product or selectivity of hydrogenation. The crude enamino ester prepared from **176** and *N,N*-dimethylhydrazine was treated with acryloyl chloride to provide lactam **186** in 75% yield (entry 5). Catalytic hydrogenation of lactam **186** was highly stereoselective and gave a >98:<2 mixture of cis and trans lactam **187** in 87% yield. In this methodology, annulation of acyclic enamino esters gave lactams in high yield and hydrogenation of the lactams stereoselectively gave cis lactams as the major product. This procedure is one of the simplest ways to prepare cis substituted piperidine skeletons.

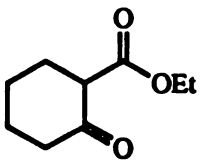
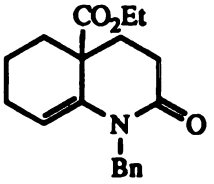
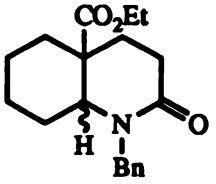
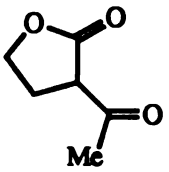
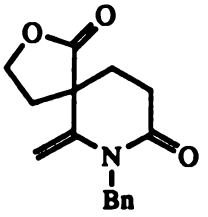
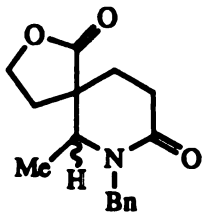
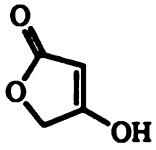
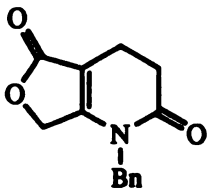
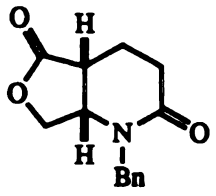
Table XIX. Aza-Annulation of Acyclic Enamino Esters.

Entry	β-Ketoester	Annulated product	Yield	Hydrogenated product	Yield (cis:trans)
1	 **176**	 **177**	94%	 **178**	91% (>98:<4)
2[a]	 **179**	 **180**	91%	 **181**	91% (96:4)
3	 **176**	 **103**	75%	 **182**	53% (86:14)
4[b]	 **183**	 **184**	84%	 **185**	80% (100:0)
5	 **176**	 **186**	75%	 **187**	87% (>98:<2)

a) Hydrogenation was carried out without Na_2CO_3. b) Hydrogenation was carried out in methanol without Na_2CO_3.

The results obtained from the annulation of β-keto esters prompted us to carry out aza-annulation on various cyclic β-keto esters **188, 191, 194.** The results of annulation of β-keto esters and hydrogenation of the annulated products are shown in Table XX.

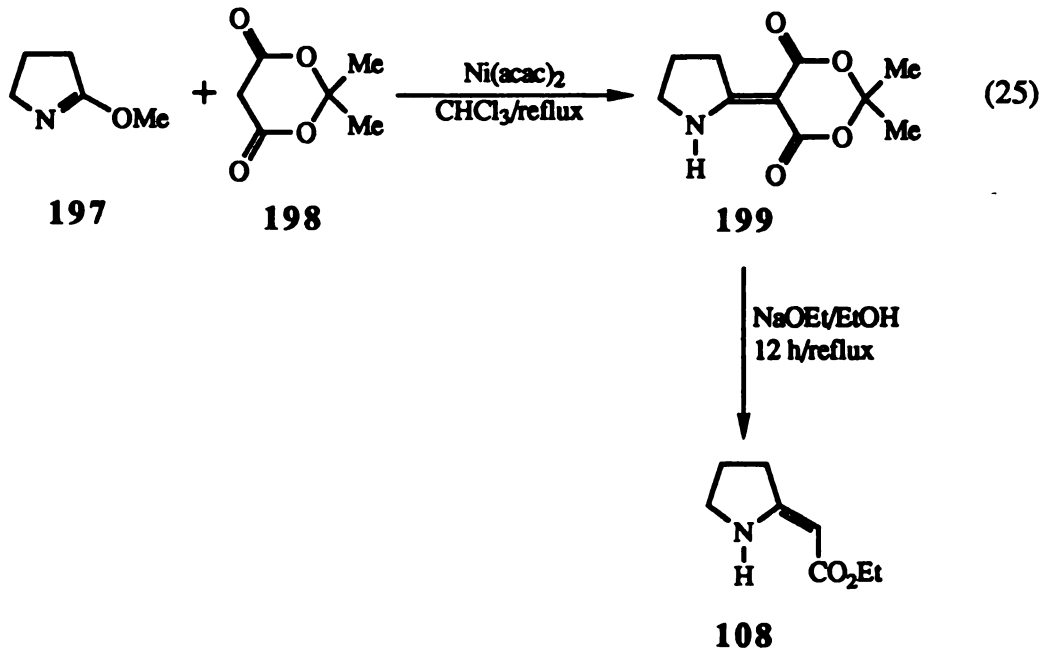
Table XX. Aza-Annulation of Cyclic Enamino Esters.

Entry	Ketoester	Annulated product	Yield	Hydrogenated product	Yield (cis:trans)
1	 **188**	 **189**	89%	 **190**	85% (56:44)
2	 **191**	 **192**	84%	 **193**	83% (91:9)
3	 **194**	 **195**	43%	 **196**	83% (95:5)

Annulation of ethyl 2-cyclohexanone carboxylate **(188)** gave lactam **189** with an angular quaternary ester group in 89% yield (entry 1). Catalytic hydrogenation of lactam **189** was not very selective and gave lactam **190** as a 56:44 mixture of two diastereomers in 85% yield. The spiro lactam **192** was obtained in 84% yield from the annulation of 2-

acetyl butyrolactone (**191**) (entry 2). The enamine double bond was exo cyclic, and hydrogenation of the lactam **192** gave a 91:9 mixture of two diastereomers of **193** in 83% yield. The absolute configuration of the major and minor diastereomers was not determined. Annulation of tetronic acid (**194**) gave lactam **195** in 43% yield (entry 3). The isolation of the lactam **195** in low yield was due to the formation of a side product. Attempts to avoid the formation of the side product or to increase the yield of the reaction were not made. Hydrogenation of the lactam **195** gave a 95:5 mixture of cis and trans compounds **196** in 83% yield. Even though the lactams **190, 193** and **196** were obtained from moderate to high yield, the hydrogenation of lactams **189** and **192** was not selective as expected.

The aza-annulation was extended to prepare various indolizidinone derivatives from the corresponding cyclic enamino esters. Cyclic enamino esters **108** and **200** were chosen for aza-annulation. Enamino ester **108** was prepared using Lhommet's procedure as shown in eq 25.[20]

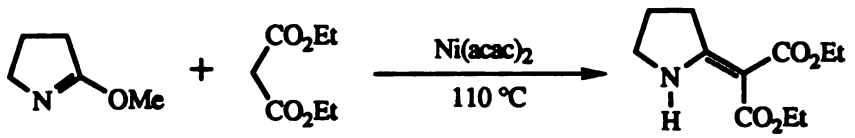


197 **198** **199** **108** (25)

The results of the annulation of enamino esters **108** and **200** are given in Table XXI. The reaction of **108** with acryloyl chloride gave lactam **110** in 87% yield (entry 1). Hydrogenation of the lactam **110** gave a 95:5 mixture of cis and trans lactam **201** in 95% yield. This sequence of annulation of enamino ester **108** followed by hydrogenation of the lactam provided the thermodynamically less stable cis fused indolizidinone skeleton.

Lhommet's inability to prepare lactam **113** from the reaction of enamino ester **108** and crotonoyl chloride prompted us to re investigate the same reaction using our annulation conditions. Under our annulation conditions, the reaction of crotonyl chloride with **108** gave a mixture of products with bicyclic lactam **112** as the major product in 45% yield. A 90:10 mixture of diastereoisomers **202** was obtained in 28% yield upon hydrogenation of the lactam **112**. Isolation of only enamide **115** by Lhommet could be due to the presence of pyridine in the reaction mixture. Presence of pyridine probably initiated the initial *N*-acylation over *C*-alkylation to avoid the steric hindrance due to the β-methyl group in crotonyl chloride. In the absence of base, *C*-alkylation is faster than *N*-acylation and gives the lactam as the major product.

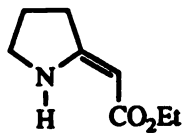
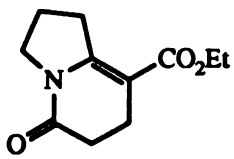
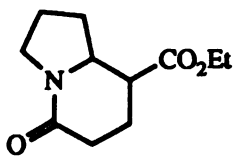
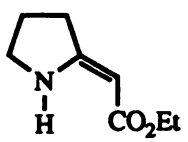
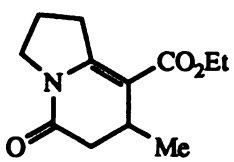
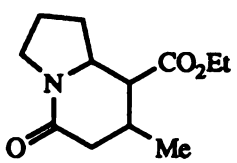
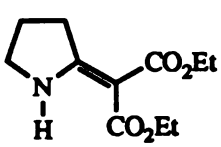
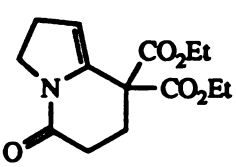
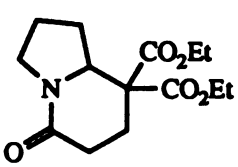
The enamino diester **200** was prepared from the condensation of lactim-ether **197** and diethyl malonate in the presence of catalytic amount of $Ni(acac)_2$ (eq 26).[21] Reaction of enamino ester **200** with acryloyl chloride gave indolizidinone **203** with a quaternary carbon in 75% yield. Hydrogenation of lactam **203** gave compound **204** in 85% yield. Since the enamino diester **200** gave lactam **203**, the structurally similar enamino diester **199** was expected to give a spiro compound after annulation. Treatment of **199** with acryloyl chloride did not give any expected product, and only starting material was recovered.



(26)

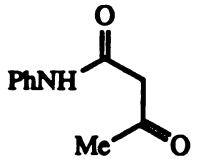
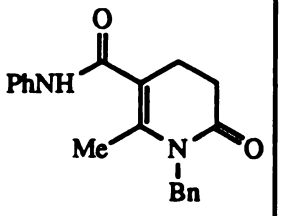
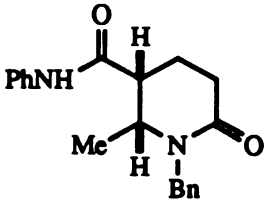
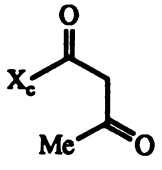
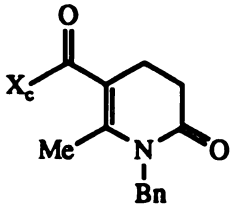
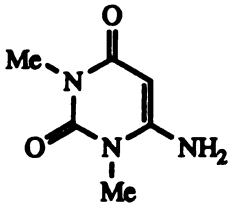
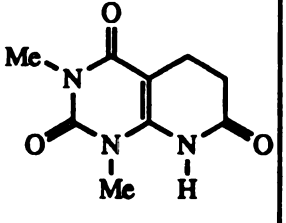
197 **200**

Table XXI. Aza-Annulation of Cyclic Enamino Esters.

Entry	Enaminoester	Annulated product	Yield	Hydrogenated product	Yield (cis:trans)
1	 **108**	 **110**	87%	 **201**	95% (95:5)
2	 **108**	 **112**	45%	 **202**	28% (90:10)
3	 **200**	 **203**	75%	 **204**	85%

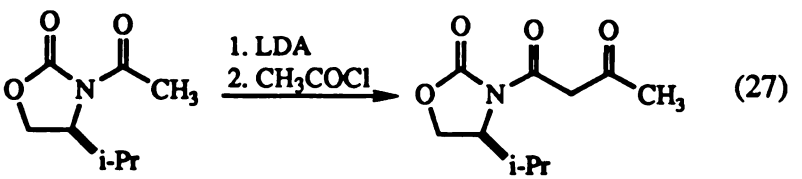
Annulation was also carried out with β-keto amides (Table XXII). Annulation of keto amide **205** gave lactam **206** in 53% yield (entry 1). The low yield of the lactam was due to the formation of a side product. Hydrogenation of **206** gave a 95:5 mixture of cis and trans lactam **207** in 56% yield. Excellent cis stereoselectivity on hydrogenation prompted us to carry out the annulation on an enamine conjugated with a chiral amide, and to study the diastereoselectivity of hydrogenation of the annulated product. Evan's chiral oxazolidone imide, commonly used in organic synthesis, was employed as the chiral auxiliary. Preparation of the required β-keto oxazolidone imide **209** is shown in equation 27.[22]

Table XXII. Aza-Annulation of Enamino Amides.

Entry	Ketone	Annulated product	Yield	Hydrogenated product	Yield (cis:trans)
1	 **205**	 **206**	53%	 **207**	56% (95:5)
2	 **209**	 **210**	93%		
3	 **211**	 **212**	79%		

Compound **208** was prepared from valinol using Evan's procedure.[23] The enolate generated from **208** using LDA was treated with acetyl chloride to give **209** in 44% yield (eq 27).[24] Under annulation conditions, lactam **210** was isolated in 93% yield from **209**. Lactam **210** was hydrogenated under the optimized conditions. The hydrogenation was

very slow, and even after 48 h, only a trace of the reduced product was observed by ^1H NMR spectroscopy. Since lactam **210** was almost inert to hydrogenation, further studies on this compound **210** were not pursued.



(27)

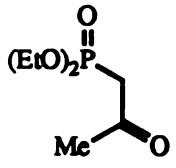
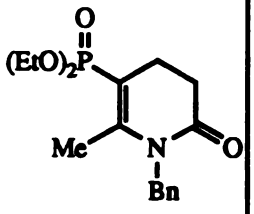
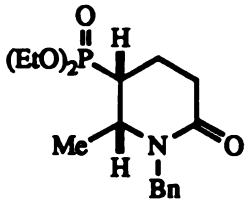
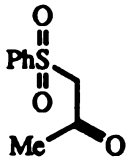
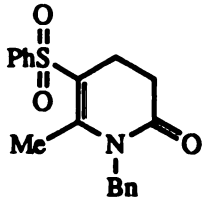
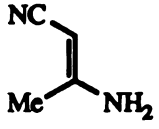
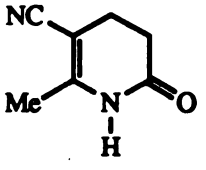
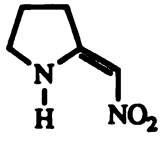
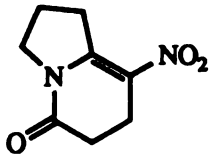
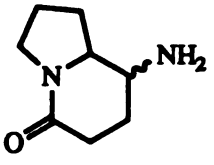
208 **209**

Reaction of the commercially available 1,6-dimethyl 2-amino uracil (**211**) with acryloyl chloride gave lactam **212** in 79% yield. Since the enamine functionality possesses a primary amine, formation of uncyclized enamide was also expected. However, only lactam **212** was isolated without any trace of uncyclized enamide. In compound **211**, the enamine carbon is more nucleophilic than the corresponding nitrogen, and favors the *C*-alkylation followed by intramolecular *N*-acylation.

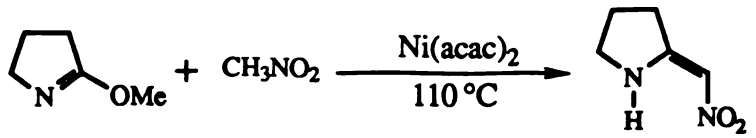
Aza-annulation methodology was also extended to other ketones with electron withdrawing groups such as a phosphate, sulfone, nitrile or nitro group in the β position. The results are given in the Table XXIII. Lactam **214** was obtained in 72% yield from diethyl-(2-oxopropyl)-phosphate (**213**). Hydrogenation of the lactam **214** gave a 78:22 mixture of cis and trans compounds **215** in 67% yield. Under the annulation conditions, β-keto sulfone **216** gave lactam **217** in 69% yield and only starting material was recovered when reduction of the double bond was attempted. Reaction of the commercially available enamino nitrile **127** with acryloyl chloride gave only lactam **218** in 82% yield. Hydrogenation of lactam **218** gave only a trace of reduced product even after extended exposure to the hydrogenation conditions. The cyclic enamino nitro compound **219** was prepared from the condensation of lactim-ether **197** and nitromethane in the presence of catalytic amount of $Ni(acac)_2$ (eq 28).[25] After the removal of the

methanol by product, the crude compound **219** was treated with acryloyl chloride to give lactam **220** in 38% yield (from the starting lactim-ether **197**). The presence of $Ni(acac)_2$ catalyst did not affect the annulation. Catalytic hydrogenation of lactam **220** gave a mixture of cis and trans of amino compounds and the ratio could not be determined.

Table XXIII. Aza-Annulation of Various Enamines.

Entry	Ketone	Annulated product	Yield	Hydrogenated product	Yield (cis:trans)
1	 **213**	 **214**	72%	 **215**	67% (78:22)
2	 **216**	 **217**	69%	No reaction	
3	 **127**	 **218**	82%	Trace of product	
4	 **219**	 **220**	38%[a]	 **221**	

a) yield from the starting lactim-ether **197**.



(28)

197 219

CONCLUSION

As planned, annulation reaction conditions were optimized to prepare six-membered lactams in high yield under mild conditions from the corresponding ketones. Preparation of lactams in high yield under mild conditions involving two steps one pot reaction shows the superiority of this methodology compared to other previously reported annulation conditions. Annulation was carried out on enamines conjugated with many electron withdrawing groups such as ester, ketone, amide, nitrile, sulfone, phosphate and nitro compounds. In general, the aza-annulation reaction can be performed on any enamine conjugated with an electron withdrawing group to give a six-membered lactam without any uncyclized enamide.

The stereoselectivity of the catalytic hydrogenation of the carbon-carbon double bond in lactams were studied. Catalytic hydrogenation gave a mixture of cis and trans lactams and the cis to trans selectivity depended on the nature of the electron withdrawing groups present in the lactam. Both ester and amide gave excellent cis selectivity. Other electron withdrawing groups, such as phosphate and ketones, gave poor selectivity. Aza-annulation, followed by hydrogenation of the annulated lactam, is one of the simplest ways to prepare cis substituted piperidine compounds and thermodynamically less stable 5,6-cis indolizidinones from readily available starting materials. Because of its simple and elegant nature, this methodology is expected to play a major role in alkaloid synthesis.

EXPERIMENTAL SECTION

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 either nitrogen or argon. Benzene, toluene, and tetrahydrofuran (THF) were distilled from sodium/benzophenone immediately prior to use. Triethylamine, dichloromethane and pyridine were heated at reflux over calcium hydride for a minimum of 12 h, and then distilled immediately prior to use. 1,3-Cyclohexanedione was obtained from Aldrich Chemical Co., and recrystallized from benzene prior to use. Benzylamine, acetoacetanilide and acryloyl chloride were obtained from Fluka and used without further purification. Acrylic acid, crotonyl chloride, diethyl-(2-oxopropyl)-phosphonate, benzyl acetoacetate, *N*,*N*-dimethyl hydrazine, ethyl 2-cyclohexanonecarboxylate and 2-acetylbutyrolactone were obtained from Aldrich Chemical Co., and used without further purification. *n*-Butyllithium (2.5 M in hexane) was purchased from Aldrich Chemical Co. Benzoyl acetone, tetronic acid, 3-aminocrotonitrile, 2,4,4-trimethyl-2-oxazolone, phenyl sulfonyl acetone and 6-amino-1,3-dimethyluracil were purchased from Lancaster and used without further purification.

NMR Spectra were obtained on a Varian Gemini 300 instrument with $CDCl_3$ as the solvent. ^1H NMR spectral data are reported as follows: chemical shifts relative to residual $CHCl_3$ (7.24 ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, sept = septet, b = broad), coupling, and integration. ^{13}C signals are reported in ppm relative to the residual $CHCl_3$ (77.0 ppm). Infrared spectra were recorded on a Nicolet 42 FT-IR instrument.

Preparation Enamino ketone 160. A mixture of benzylamine (19.11 g, 178.4 mmol) and 1,3-cyclohexanedione (**159**) (20.0 g, 178.4 mmol) in 1600 mL of benzene was heated at reflux for 24 h. The water generated during the condensation was azeotropically removed from the reaction mixture using a molecular sieves (4-Å) filled

modified Dean-Stark trap, developed in this laboratory. The reaction mixture was then cooled to room temperature, and concentrated to give the crude product. This crude product was crystallized from ethyl acetate to give enamino ketone **160** in 89% yield.

Reaction of Enamino Ketone 160 with a Mixed Anhydride. To a cooled solution (-30 °C to -25 °C) of acrylic acid (0.47g, 6.5 mmol) in 35 mL of THF were added TEA (0.65 g, 6.46 mmol) and ethyl chloroformate (0.69 g, 6.5 mmol). After the mixture was stirred for 1 h at this temperature, the enamino ketone **160** (1.00 g, 5.0 mmol) was added and stirred for an additional 30 min. The reaction mixture was then heated at reflux for 24 h. Then the solution was washed with 25 mL of saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with 4 x 40 mL of methylene chloride, and the organic fractions were combined and dried over Na_2SO_4. Following concentration of the solution, the residue was purified by flash column chromatography (eluent: 75:25 CH_2Cl_2-EtOAc). The solvents were removed, and the residue was distilled under vacuum to give lactam **161** in 54% yield.

Reaction of Enamino Ketone 160 with Acrylic Anhydride. To a suspension of NaH (0.30 g, 12.6 mmol) in 30 mL of THF at -78 °C was slowly added acrylic acid (0.61 g, 8.4 mmol). The mixture was warmed to ambient temperature, and stirred for 1h. Acryloyl chloride (0.59 g, 6.5 mmol) was then added to the solution of sodium acrylate, and the reaction mixture was stirred for an additional 1 h at ambient temperature. The resulting solution of acrylic anhydride was transferred *via* cannula to a 100 mL flask containing the enamino ketone **160** (1.00 g, 5.0 mmol) in 10 mL of THF. The flask was and then rinsed with an additional 15 mL of THF. The reaction mixture was heated at reflux for 13 h, cooled to room temperature and then washed with 30 mL of saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with 4 x 50 mL of CH_2Cl_2, and the organic fractions were combined and dried over Na_2SO_4. After filtration and removal of solvents, the residue was purified by flash column chromatography (eluent:

70:30 CH_2Cl_2-EtOAc). The solvents were removed, and the residue was distilled under vacuum to give lactam **161** in 52% yield.

Preparation of Lactam 161 from Cyclohexanedione (159) Using Acrylic Anhydride. A mixture of ketone (**159**) (0.64 g, 5.7 mmol) and benzylamine (0.58 g, 5.4 mmol) was taken up in 35 mL of benzene and heated at reflux for 24 h. The water generated was azeotropically removed from the reaction mixture using a modified Dean-Stark trap filled with 4-Å molecular sieves. The reaction mixture was then cooled to room temperature, and concentrated to give crude enamino ketone **160**. The yellow solid was placed in a 100 mL flask and dissolved in 10 mL of THF. The acrylic anhydride (7.04 mmol), prepared using the above procedure, was transferred into the flask and then was washed over with an additional 15 mL of THF. The reaction mixture was heated at reflux for 13 h, cooled to room temperature and washed with 25 mL of saturated $NaHCO_3$. The aqueous layer was then extracted with 4 x 50 mL of CH_2Cl_2. The organic fractions were combined and dried over Na_2SO_4. After removal of solvents, the residue was purified by flash column chromatography (eluent: 70:30 CH_2Cl_2-EtOAc). The solvents were removed, and the residue was distilled under vacuum to give lactam **161** in 72 % yield.

Reaction of Enamino Ketone 160 with Acryloyl Chloride. To a solution of enamino ketone **160** (2.0 g, 9.9 mmol) in 70 mL of THF was added acryloyl chloride (1.18 g, 12.9 mmol), and the reaction mixture was heated at reflux for 10 h. The reaction mixture was cooled to room temperature and washed with 50 mL of saturated aqueous $NaHCO_3$ solution. The aqueous layer was then extracted with 4 x 100 mL of CH_2Cl_2, and the organic fractions were combined and dried over Na_2SO_4. After removal of solvents, the residue was purified by flash column chromatography (eluent: 80:20 CH_2Cl_2:EtOAc). The solvents were removed, and the residue was distilled under vacuum to give lactam **161** in 62% yield.

Preparation of Lactam 161 from 1,3-Cyclohexanedione (159) Using Acryloyl Chloride. A mixture of benzylamine (25.2 g, 235.2 mmol) and ketone **159** (27.7 g, 247.0 mmol) was taken in 1500 mL of benzene and heated at reflux for 24 h. The water generated was azeotropically removed from the reaction mixture using a modified Dean-Stark trap filled with 4-Å molecular sieves. The reaction mixture was then cooled to room temperature, concentrated to give crude enamino ketone **160**. The crude enamino ketone was redissolved in 1570 mL of THF, and acryloyl chloride (27.7 g, 306.0 mmol) was slowly added to the reaction mixture. The reaction mixture was then heated at reflux for 24 h. Solvent was removed, and the residue was taken up in 400 mL of CH_2Cl_2 and washed with 100 mL of saturated $NaHCO_3$. The aqueous layer was extracted with 4 x 100 mL CH_2Cl_2. The organic fractions were combined and dried over Na_2SO_4. After removal of solvents, the residue was purified by flash column chromatography (eluent: 80:20 CH_2Cl_2-EtOAc). The solvents were removed, and the residue was distilled under vacuum to give lactam in 76% yield.

Hydrogenation of Lactam 161. A mixture of Lactam **161** (1.06 g, 4.2 mmol) and sodium carbonate (1.53 g, 14.5 mmol) in 70 mL of absolute ethanol was hydrogenated (45 psi) over 10% Pd on carbon for 18 h. The catalyst and sodium carbonate were removed by filtration. The solid was washed several times with CH_2Cl_2, and the washings and filtrates were combined, and solvent was removed to give a viscous crude residue. The crude residue was transferred to a silica gel column. The less polar impurities were removed by flushing the column with a 80:20 mixture of CH_2Cl_2-EtOAc. Elution of the column with a 1:1 mixture of CH_2Cl_2:MeOH followed by removal of solvents gave alcohol **163** as a white gummy solid in 91% yield. Compound **163** was solidified by triturating with a minimum amount of Et_2O.

Reduction of Lactam with $NaBH_4$. To a solution of lactam **161** (0.72 g, 2.8 mmol) in 20 mL of EtOH and 5 mL of MeOH at 0 °C was slowly added $NaBH_4$ (1.1 g, 28.2 mmol). The reaction mixture was warmed to room temperature, and stirred for 10 h.

Water (25 mL) was added to the reaction mixture and stirred for 30 min. The reaction mixture was extracted with 5 x 50 mL of CH_2Cl_2, and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated to give a crude residue. The crude residue was purified by flash column chromatography (eluent: 60:40 EtOAc-CH_2Cl_2). The solvents were evaporated to give alcohol **162** in 77% yield.

Oxidation of Alcohol 163. To a cooled solution (-70 to -60 °C) of oxalyl chloride (5.8 g, 45.7 mmol) in 85 mL of CH_2Cl_2 was slowly added DMSO (7.14 g, 91.3 mmol) in 19 mL of CH_2Cl_2 and stirred at this temp for 10 min. To this reaction mixture was slowly added alcohol (7.90 g, 30.4 mmol) in 77 mL of CH_2Cl_2 and stirred at -60 °C for 45 minutes. TEA (18.5 g, 182.7 mmol) was added and stirred for 20 min at this temperature, and the reaction was warmed to room temperature over a period of 30 min and stirred for an additional 30 min. Then 180 mL of H_2O was added and stirred for 1 h. The aqueous layer was extracted with 5 x 100 mL of CH_2Cl_2. The combined organic layers were washed with 200 mL of H_2O. The organics were dried (Na_2SO_4), filtered, and concentrated to give a crude residue, which was purified by flash column chromatography (eluent 75:25 CH_2Cl_2-EtOAc). The solvents were evaporated to give ketone **166** as a viscous product in 93% yield. This ketone **166** was solidified by triturating with a minimum amount of Et_2O.

Reduction of Ketone 166 with $NaBH_4$. To a solution of the ketone **166** (0.66 g, 2.6 mmol) in 21 mL of MeOH at 0 °C was added $NaBH_4$ (0.97 g, 25.63 mmol). The reaction mixture was stirred for 12 h at room temperature. Solvent was removed to give a solid which was taken up in 30 mL of CH_2Cl_2 and 20 mL of H_2O and stirred for 2 h. The aqueous layer was then extracted with 4 x 30 mL of CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to give a crude residue, which was purified by column chromatography (eluent: first 20:80 EtOAc-CH_2Cl_2. second, 1:1 MeOH-CH_2Cl_2). The solvents were removed to give the alcohol **163** in 92% yield.

General Procedure for Aza-Annulation. A mixture of the primary amine (12 mmol), ketone (10 mmol) and *p*-TsOH (0.01g, 0.05 mmol) in 66 mL of benzene was heated at reflux for 12 to 24 h. The water generated during the condensation was azeotropically removed from the reaction mixture using a modified Dean-Stark trap filled with 4-Å molecular sieves. The reaction progress was monitored by ^{1}H NMR spectroscopy. After enamine formation was complete, the reaction mixture was cooled to room temperature, and concentrated to give the corresponding crude enamine. The crude enamine was taken up in 66 mL of THF and the appropriate α,β-unsaturated acid chloride (13 mmol) was added slowly at room temperature. The reaction mixture was heated at reflux until the disappearance of starting materials was complete (6-24 h). Disappearance of starting material was monitored by ^{1}H NMR spectroscopy. The reaction mixture was washed with 25 mL of saturated aqueous $NaHCO_3$ solution, and the aqueous layer was extracted with 4 x 40 mL of CH_2Cl_2. The organic fractions were combined and dried over Na_2SO_4. Following concentration of the solution, the residue was purified by flash column chromatography. The solvents were evaporated to give the corresponding lactam.

General Procedure for Hydrogenation of the Annulation Products. In most of the hydrogenation reactions, this general procedure was used unless otherwise noted. A mixture of lactam (2.00 mmol) and sodium carbonate (0.74 g, 7.0 mmol) in 27 mL of absolute EtOH was hydrogenated (45 psi) over 10% Pd on carbon (0.2 g) for 12-48 h. The catalyst and sodium carbonate were removed by filtration. The solid was washed several times with CH_2Cl_2, and the washings were combined, and solvents were removed to give a viscous residue. The crude residue was redissolved in CH_2Cl_2 and refiltered. Concentration of the filtrate and washings gave the corresponding lactam.

Preparation of Enamino Ester 183. To a cooled solution (0-5 °C) of dimethyl acetylenedicarboxylate (1.42 g, 10.0 mmol) in 50 mL of benzene was slowly added benzylamine (1.1 g, 10 mmol). The reaction mixture was stirred at room temperature for

12 h. The removal of solvent gave the crude enamino ester which was carried on to the annulation reaction without further purification.

Preparation of Enamino Nitro Compound 219. A mixture of lactim-ether **197** (6.5 g, 65.7 mmol), nitromethane (4.8 g, 78.8 mmol), and $Ni(acac)_2$ (0.1 g, 0.4 mmol) was heated at 110 °C for 48 h. Removal of the solvent gave the crude cyclic enamino nitro compound which was used for annulation without further purification.

General Procedure for the Reaction of Enamines 108, 200, 219 with α,β-Unsaturated Acid Chlorides. To a solution of enamine (10 mmol) in 66 mL of THF was added the appropriate α,β-unsaturated acid chloride (13 mmol). The reaction mixture was heated at reflux until complete disappearence of starting materials (6-24 h), as monitored by ^1H NMR spectroscopy. The reaction mixture was washed with 25 mL of saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with 4 x 40 mL of CH_2Cl_2, and the organic fractions were combined and dried over Na_2SO_4. Following concentration of the solution, the residue was purified by flash column chromatography. The solvents were evaporated to give the corresponding lactam.

102: (mp 84-85 °C) ^1H NMR (300 MHz, $CDCl_3$) δ 1.06 (d, J = 7.1 Hz, 3 H), 1.27 (t, J = 7.1 Hz, 3 H), 2.34 (s, 3 H), 2.48 (dd, J = 15.7, 2.2 Hz, 1 H), 2.71 (dd, J = 15.7, 6.6 Hz, 1 H), 3. 01 (dquint, J = 6.9, 1.8 Hz, 1 H), 4.16 (q, J = 7.1 Hz, 2 H), 4.78 (d, J = 16.2 Hz, 1 H), 5.22 (d, J = 16. 2 Hz, 1 H), 7.13-7.33 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.8, 16.2, 17.6, 26.6, 37.8, 44.6, 59.8, 113.5, 126.1, 126.8, 128.3, 137.3, 146.6, 167.1, 170.0; IR (KBr) 3034, 2980, 2959, 1678, 1615, 1383, 1124 cm^{-1}; HRMS calcd for $C_{17}H_{21}NO_3$ m/z 287.1520, found m/z 287.1521.

110: (mp 45-47 °C) ^1H NMR (300 MHz, $CDCl_3$) δ 1.29 (t, J = 7.1 Hz, 3 H), 1.97 (quint, J = 7.6 Hz, 2H), 2.51 (m, 2 H), 2.65 (m, 2H), 3.14 (tt, J = 15.4, 1.8 Hz, 2 H), 3.72 (t, J = 7.2 Hz, 2 H), 4.19 (q, J = 7.1 Hz, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.9, 20.7, 20.9, 30.4, 31.2, 45.4, 59.5, 100.4, 152.5, 166.5, 168.9; IR (KBr) 2980, 1689, 1634,

1385, 1294, 1265, 1200, 1129 cm^{-1}; HRMS calcd for $C_{11}H_{15}NO_3$ m/z 209.1051, found m/z 209.1068.

112: ^1H NMR (300 MHz, $CDCl_3$) δ 1.04 (d, *J* = 7.1 Hz, 3 H), 1.30 (t, *J* = 7.1 Hz, 3 H), 1.98 (quint, *J* = 7.5 Hz, 2 H), 2.39 (dd, *J* = 16.4, 1.7 Hz, 1 H), 2.62 (dd, *J* = 16.4, 7.1 Hz, 1 H), 3.04 (m, 1 H), 3.14 (td, *J* = 7.7, 3.3 Hz, 2 H), 3.63-3.83 (m, 2 H), 4.20 (m, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.3, 19.1, 21.2, 27.3, 31.6, 38.2, 45.6, 59.7, 106.2, 151.7, 166.6, 168.7; IR (KBr) 2967, 1676, 1626, 1383, 1300, 1237, 1116 cm^{-1}.

161: (bp 190-200 °C, <1mm Hg): ^1H NMR (300 MHz, $CDCl_3$) δ 1.93 (quint, *J* = 6.4 Hz, 2 H), 2.33 (t, *J* = 6.5 Hz, 2 H), 2.46 (t, *J* = 6.5 Hz, 2H), 2.63 (s, 4 H), 5.0 (s, 2 H), 7.08-7.35 (m, 5 H); ^{13}C NMR (75.5 MHz. $CDCl_3$) δ 16.7, 21.3, 26.0, 30.6, 35.5, 44.4, 116.1, 125.5, 127.0, 128.5, 136.6, 154.6, 170.6, 195.8; IR (neat) 3063, 3032, 2953, 1690, 1649, 1615, 1389, 1296, 1177, 1130 cm^{-1}.

163: ^1H NMR (300 MHz, $CDCl_3$) δ 1.15 (qt, *J* = 13.4, 3.6 Hz, 1 H), 1.38 (dquint *J* = 12.9, 3.8 Hz, 2 H), 1.56-2.05 (m, 6 H), 2.22 (m, 1 H), 2.49 (ddd, *J* = 18.3, 11.6, 7.5 Hz, 1 H), 2.67 (dd, *J* = 18.3, 5.6 Hz, 1 H), 3.17 (dt, *J* = 11.8, 4.4 Hz, 1 H), 3.73 (dt, *J* = 11.8, 4.7 Hz, 1 H), 3.96 (d, *J* = 15.1 Hz, 1 H), 5.34 (d, *J* = 15.1 Hz, 1 H), 7.20-7.35 (m, 5 H); ^{13}C NMR (75.5 MHz. $CDCl_3$) δ 14.6, 20.9, 25.5, 28.4, 30.8, 40.3, 47.4, 56.3, 70.3, 126.8, 127.1, 128.2, 137.1, 169.7; IR (KBr) 3397, 3055, 2942, 1622, 1476, 1454, 1265 cm^{-1}.

166; ^1H NMR (300 MHz, $CDCl_3$) δ 1.51 (m, 1 H), 1.77-1.89 (m, 2 H), 1.89-2.05 (m, 1 H), 2.07-2.52 (m, 4 H), 2.57 (dd, *J* = 10.4, 7.1 Hz, 1 H), 2.63-2.76 (m, 2 H), 3.56 (ddd, *J* =10, 5, 5 Hz, 1 H), 4.03 (d, *J* = 15.1 Hz, 1 H), 5.39 (d, *J* = 15.1 Hz, 1H), 7.19-7.33 (m, 5 H); ^{13}C NMR (75.5 MHz. $CDCl_3$) δ 20.7, 21.1, 25.8, 30.3, 37.6, 47.1, 49.6, 56.7, 127.0, 127.1, 128.3, 136.6, 168.7, 209.9; IR (KBr) 3056, 2955, 1711, 1638, 1472, 1453, 1420, 1265 cm^{-1}.

168: ^1H NMR (300 MHz, $CDCl_3$) δ 2.26 (s, 6 H), 2.65 (s, 4H), 5.02 (s, 2 H), 7.12-7.35 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 15.8, 21.8, 29.4, 30.9, 44:3, 117.0,

125.7, 126.8, 128.3, 137.0, 145.9, 170.3, 198.6; IR (neat) 3030, 1690, 1669, 1591, 1383, 1186 cm^{-1}; HRMS calcd for $C_{15}H_{17}NO_2$ m/z 243.1259, found m/z 243.1260.

169: ^1H NMR (300 MHz, $CDCl_3$, mixture of isomers) δ 1.09 (d, *J* = 6.5 H, 1.2 H, minor), 1.24 (d, *J* = 6.5 Hz, 1.8 Hz, major), 1.93 (s, 1.8 H, major), 1.96-2.16 (m, 2.0 H, both), 2.08 (s, 1.2 H, minor), 2.39-2.70 (m, 2.6 H, both), 2.79 (dt, *J* = 12.6, 4.1 Hz, 0.4 H, minor), 3.78-3.88 (m, 1 H, both), 3.94 (d, *J* = 15.1 Hz, 0.4 H, minor), 4.03 (d, 15.1 Hz, 0.6 H, major), 5.28 (d, *J* = 15.1 Hz, 0.6 H, major), 5.36 (d, *J* = 15.1 Hz, 0.4 H, minor), 7.20-7.39 (m, 5 H, both); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.4, 17.2, 19.5, 19.8, 27.5, 28.1, 29.3, 29.9, 46.9, 47.7, 51.0, 52.2, 126.9, 127.0, 127.3, 127.7, 128.1, 128.2, 136.8, 136.9, 168.7, 168.9, 206.3, 207.1; IR (neat) 2975, 1711, 1638, 1474, 1453, 1161 cm^{-1}; HRMS calcd for $C_{15}H_{19}NO_2$ m/z 245.1415, found m/z 245.1422.

171: (mp 70-72 °C) ^1H NMR (300 MHz, $CDCl_3$) δ 1.92 (t, *J* = 1.4 Hz, 3 H), 2.62 (m, 2 H), 2.72 (m, 2 H), 5.04 (s, 2 H), 7.16-7.73 (m, 10 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 17.0, 23.1, 31.2, 44.2, 117.4, 125.8, 126.8, 128.2, 128.3, 128.4, 132.3, 137.2, 138.1, 142.8, 170.3, 196.7; IR (KBr) 3029, 2967, 1682, 1655, 1605, 1576, 1451, 1385, 1364 cm^{-1}; HRMS calcd for $C_{20}H_{19}NO_2$ m/z 305.1415, found m/z 305.1402.

174: (mp 94-96 °C) ^1H NMR (300 MHz, $CDCl_3$) δ 1.61 (s, 6 H), 2.37 (s, 3 H), 2.49 (m, 2 H), 2.61 (m 2 H) 4.20 (s, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 19.0, 24.0, 30.2, 32.2, 60.1, 80.3, 91.3, 158.3, 169.6, 194.1; IR (KBr) 2978, 2853, 1707, 1645, 1605, 1402, 1350, 1151 cm^{-1}

175: δ 1 ^1H NMR (300 MHz, $CDCl_3$, cis) δ 1.50 (s, 3 H), 1.51 (s, 3 H), 1.81 (m, 1 H), 1.96 (m, 1 H), 2.29 (s, 3 H), 2.32-2.51 (m, 2 H), 2.71 (ddd, *J* = 12.4, 8.8, 3.9 Hz, 1 H), 3.56 (dd, *J* = 8.8, 0.7 Hz, 1 H), 3.84 (d, *J* = 8.8 Hz, 1 H), 4.79 (d, *J* = 8.8 Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.9, 23.1, 24.1, 30.3, 31.0, 51.8, 59.4, 78.6, 88.5, 166.2, 206.8; IR (neat) 2969, 2874, 1717, 1651, 1464, 1443, 1363 cm^{-1}.

Diagnostic Peaks for trans Isomer: ^{1}H NMR (300 MHz, $CDCl_3$, trans) δ 2.24 (s, 3 H), 3.37 (q, *J* = 4.67 H, 1 H), 5.0 (d, *J* = 4.67 Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 19.6, 23.2, 23.6, 29.1, 32.3, 46.0, 53.0, 59.2, 78.5, 88.0, 167.2, 206.7.

177: (mp 75-77 °C) ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29 (t, *J* = 7.1 Hz, 3 H), 2.35 (t, *J* = 1.4 Hz, 3 H), 2.57-2.71 (m, 4 H), 4.18 (q, *J* = 7.1 Hz, 2 H), 5.03 (s, 2 H), 7.10-7.35 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.8, 16.0, 20.8, 30.9, 44.4, 59.9, 109.0, 125.7, 126.7, 128.3, 137.1, 148.0, 167.0, 171.0; IR (KBr) 2984, 2959, 2845, 1684, 1617, 1377, 1269, 1184, 1120 cm^{-1}; HRMS calcd for $C_{16}H_{19}NO_3$ m/z 273.1364, found m/z 273.1363.

178: (mp 51-53 °C) ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14 (d, *J* = 6.5 Hz, 3 H), 1.23 (t, *J* = 7.1 Hz, 3 H), 2.02-2.20 (m, 2 H), 2.50 (ddd, *J* = 18.3, 10.5, 8.5 Hz, 1 H), 2.63 (ddd, *J* = 18.3, 6.6, 3.0 Hz, 1 H), 2.81 (dt, *J* = 12.0, 4.8 Hz, 1 H), 3.82 (m, 1 H), 3.99 (d, *J* = 15.1 Hz, 1 H), 4.14 (q, *J* = 7.1 Hz, 2 H), 5. 28 (d, *J* = 15.1 Hz, 1 H), 7.23-7.37 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.7, 14.6, 17.7, 30.0, 43.4, 47.8, 51.7, 60.4, 126.9, 127.3, 128.2, 136.9, 168.6, 171.0; IR (KBr) 3032, 2978, 1732, 1643, 1497, 1474, 1453 cm^{-1}; HRMS calcd for $C_{16}H_{21}NO_3$ m/z 275.1521 found m/z 275.1508.

180: (mp 64-66 °C) ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.25 (t, *J* = 1.4 Hz, 3 H), 2.49 (m, 2 H), 2.59 (m, 2 H), 4.91 (s, 2 H), 5.05 (s, 2 H), 6.99-7.28 (m, 10 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 16.1, 20.8, 30.9, 44.5, 65.7, 108.5, 125.7, 126.8, 127.7, 127.8, 128.2, 128.4, 135.8, 137.1, 148.9, 166.7, 170.6; IR (KBr) 3034, 2953, 1703, 1682, 1618, 1387, 1368, 1269 cm^{-1}; HRMS calcd for $C_{21}H_{21}NO_3$ m/z 335.1521, found m/z 335.1533.

181 (mp 134-136 °C): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (d, *J* = 6.6 Hz, 3 H), 2.01-2.19 (m, 2 H), 2.55 (td, J = 18.5, 9.8 Hz, 1 H), 2.67 (m, 1 H), 2.80 (m, 1 H), 3. 84 (m, 1 H), 3.97 (d, *J* =15.1 Hz, 1 H), 5.29 (d, *J* = 15.1 Hz, 1 H), 7.20-7.35 (m, 5 H), 10.19 (bs, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.6, 17.3, 29.5, 43.1, 48.1, 51.7, 127.2, 127.4, 128.3, 136.2, 170.2, 174.0; IR (KBr) 3034, 2971, 1736, 1601, 1489, 1453, 1437, 1233, 1167 cm^{-1}; HRMS calcd for $C_{14}H_{17}NO_3$ m/z 247.1208, found m/z 247.1299.

182: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 (d, *J* = 6.9 Hz, 3 H), 1.20 (d, *J* = 6.7 Hz, 3 H), 1.27 (t, *J* = 7.1 Hz, 3 H), 2.27 (m, 1 H), 2.49-2.68 (m, 2 H), 2.77 (t, *J* = 4.7 Hz, 1 H), 3.67 (m, 1 H), 4.19 (q, *J* = 7.1 Hz, 2 H), 4.40 (d, *J* = 15.7 Hz, 1 H), 5.10 (d, *J* = 15.7 Hz, 1 H), 7.20-7.34 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.9, 17.6, 18.5, 28.4, 36.2, 45.6, 50.1, 52.5, 60.0, 126.4, 126.7, 128.0, 137.4, 170.1, 170.4; IR (neat) 3063, 3028, 2978, 2934, 1728, 1644, 1497, 1449, 1412, 1292 cm^{-1}.

184: (mp 86-88 °C) ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.50-2.62 (m, 4 H), 3.52 (s, 3 H), 3.60 (s, 3H), 4.67 (s, 2 H), 7.05-7.21 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 19.6, 29.9, 46.4, 51.7, 52.3, 108.3, 126.7, 127.1, 128.0, 136.1, 142.6, 163.5, 165.1, 169.3; IR (KBr) 3038, 2955, 1736, 1692, 1628, 1458, 1441, 1381, 1300 cm^{-1}; HRMS calcd for $C_{16}H_{17}NO_5$ m/z 303.1106, found m/z 303.1120.

185: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.98-2.22 (ddd, *J* = 8.1, 10.7, 15.5 Hz, 2 H), 2.49 (m, 1 H), 2.67 (ddd, *J* = 18.2, 6.9, 2.2 Hz, 1 H), 2.90 (dt, *J* = 12.9, 4.7 Hz, 1 H), 3.62 (s, 3 H), 3.65 (s, 3 H), 3.91 (d, *J* = 15.0 Hz, 1 H), 4.32 (dd, *J* = 4.1, 1.3 Hz, 1 H), 5.28 (d, *J* = 15.0 Hz, 1 H), 7.19-7.33 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 19.5, 29.9, 42.0, 49.2, 51.8, 52.2, 59.1, 127.3, 127.9, 128.2, 135.7, 169.0, 169.5, 170.3; IR (neat) 3011, 2955, 1748, 1655, 1414, 1311, 1209 cm^{-1}; HRMS calcd for $C_{16}H_{19}NO_5$ m/z 305.1262, found m/z 303.1210.

186: (bp 95-105 °C, <1 mm Hg) ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (t, *J* = 7.1 Hz, 3 H), 2.41 (t, *J* = 1.5 Hz, 3 H), 2.42-2.48 (m, 2 H), 2.51-2.58 (m, 2 H), 2.85 (s, 6 H), 4.19 (q, *J* = 7.1 Hz, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.8, 15.0, 20.6, 32.0, 43.0, 56.6, 106.4, 151.3, 167.0, 169.8; IR (neat) 2980, 2896, 1696, 1620, 1541, 1379, 1273 cm^{-1}.

187: (mp 40-42 °C) ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15 (d, *J* = 6.4 Hz, 3 H), 1.26 (t, *J* = 7.1 Hz, 3 H), 1.85-1.95 (m, 2 H), 2.28 (ddd, *J* = 18.1, 10.2, 9.1 Hz, 1 H), 2.43 (ddd, *J* = 18.1, 5.1, 4.9 Hz, 1 H), 2.78 (m, 1 H), 2.84 (s, 6 H), 3.89 (quint, *J* = 6.1 Hz, 1 H), 4.08-4.25 (m, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.7, 14.7, 17.1, 31.5, 43.2 (b),

44.2, 56.3, 60.4, 168.2, 170.8; IR (KBr) 2977, 2951, 1734, 1649, 1404, 1233, 1169 cm^{-1}; HRMS calcd for $C_{11}H_{20}N_2O_3$ m/z 228.1473, found m/z 228.1480.

189: (mp 72-74 °C): ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (t, *J* = 7.15 Hz, 3 H), 1.37 (m, 1 H), 1.49 (ddd, *J* = 13.8, 13.0, 2.5 Hz, 1 H), 1.66 (m, 1 H), 1.78 (td, *J* = 13.3, 5.7 Hz, 1 H), 2.03 (dddd, *J* = 17.9, 9.3, 6.3, 3.0 Hz, 1 H), 2.16 (m, 1 H), 2.25-2.38 (m, 2 H), 2.49 (ddd, *J* = 6.1, 12.8, 18.4 Hz, 1 H), 2.70 (ddd, *J* = 18.4, 5.8, 1.5 Hz, 1 H), 4.18 (q, *J* = 7.1 Hz, 2 H), 4.63 (d, *J* = 15.9 Hz, 1 H), 5.18 (dd, *J* = 5.1, 3.0 Hz, 1 H), 5.33 (d, *J* =15.9 Hz, 1 H), 7.20-7.34 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.8, 18.1, 23.8, 29.6, 30.3, 34.4, 46.0, 47.3, 60.8, 107.6, 125.9, 126.2, 127.9, 136.5, 137.2, 167.8, 173.6; IR (KBr) 3063, 2980, 1719, 1669, 1644, 1451, 1404, 1373 cm^{-1}; HRMS calcd for $C_{19}H_{23}NO_3$ m/z 313.1677, found m/z 313.1692.

190: ^1H NMR (300 MHz, $CDCl_3$, mixture of isomers) δ 1.25 (t, *J* = 7.1 Hz, 3 H, major) 1.27 (t, *J* = 7.1 Hz, 3 H minor), 1.33-1.59 (m, 1 H, both), 1.60-1.84 (m, 2 H, both), 1.85-2.1 (m, 2 H, both), 2.1-2.37 (m, 2 H, both), 2.38-2.56 (m, 1 H, both), 2.58-2.75 (m, 1 H, both), 3.26 (dd, *J* = 12.1 Hz, 0.56 H, major), 4.12-4.26 (m, 2 H, both), 4.47 (d, *J* = 15.9 Hz, 0.56 H, major), 4.63 (d, *J* = 15.9 Hz, 0.44 H, minor), 5.08-5.20 (m, 1 H minor), 5.32 (d, *J* = 15.9 Hz, 0.56 H, major), 7.18-7.35 (m, 5 H, both); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.8, 18.2, 21.8, 23.8, 24.5, 25.7, 29.7, 30.4, 32.3, 34.5, 35.9, 45.0, 46.0, 47.4, 47.5, 60.2, 60.9, 62.1, 107.8, 125.9, 126.2, 126.4, 128.0, 136.6, 137.2, 137.8, 168.0, 169.8, 172.7, 173.8.

192: ^1H NMR (300 MHz, $CDCl_3$) δ 1.85 (ddd, *J* = 13.4, 6.3, 3.1 Hz, 1 H), 2.22 (ddd, *J* = 12.8, 9.8, 8.2 Hz, 1 H), 2.34 (ddd, *J* = 12.8, 6.5, 2.5 Hz, 1 H), 2.43 (ddd, *J* = 12.0, 13.5, 6.0 Hz, 1 H), 2.63 (ddd, 18.1, 12.0, 6.2 Hz, 1 H), 2.93 (ddd, *J* = 18.1, 6.0, 3.3 Hz, 1 H), 4.16 (dt, *J* = 9.8, 6.6 Hz, 1 H), 4.24 (d, 3.1 Hz, 1 H), 4.38 (ddd, *J* = 9.2, 8.2, 2.6 Hz, 1 H), 4.54 (d, *J* = 3.1 Hz, 1 H), 4.93 (d, *J* = 15.7 Hz, 1 H), 5.03 (d, *J* = 15.7 Hz, 1 H, 7.15-7.34 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 27.3, 28.5, 33.8, 46.3, 47.3, 64.9,

94.2, 126.1, 126.7, 128.2, 136.1, 142.4, 167.7, 176.7; IR (neat) 3032, 2942, 1775, 1673, 1620, 1456, 1186, 1028 cm^{-1}.

193: ^1H NMR (300 MHz, $CDCl_3$, major isomer) δ 1.25 (d, *J* = 6.6 Hz, 3 H), 1.49 (m, 1 H), 1.67 (ddd, *J* = 13.0, 6.8, 2.8 Hz, 1 H), 1.87 (ddd, *J* = 12.9, 9.6, 8.7 Hz, 1H), 2.25-2.42 (m, 2H), 2.54 (m, 1H), 3.19 (qd, *J* = 6.6, 1.6 Hz, 1 H), 3.44-3.60 (m, 2H), 3.99 (td, J = 9.2, 2.8 Hz, 1 H), 5.48 (d, J = 14.3 Hz, 1 H), 7.12-7.26 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 15.2, 23.7, 27.5, 32.4, 45.6, 47.2, 52.4, 64.1, 127.6, 128.3, 128.6, 136.3, 167.6, 176.9; IR (KBr) 2973, 2946, 1763, 1644, 1495, 1472, 1455, 1219 cm^{-1}; HRMS calcd for $C_{16}H_{19}NO_3$ m/z 273.1364, found m/z 273.1374.

195: (mp 115-117 °C) ^1H NMR (300 MHz, $CDCl_3$) δ 2.64 (m, 2 H), 2.85 (td, *J* = 8.0, 1.1 Hz, 2 H), 4.65 (t, *J* = 2.0 Hz, 2 H), 4.81 (s, 2H), 7.16-7.40 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 15.5, 30.2, 45.6, 64.9, 102.4, 126.5, 127.9, 128.8, 135.0, 159.7, 169.1, 170.8; IR (KBr) 3038, 2982, 2959, 1746, 1695, 1664, 1435, 1275, 1196 cm^{-1}; HRMS calcd for $C_{14}H_{13}NO_3$ m/z 243.0895, found m/z 243.0896.

196 : ^1H NMR (300 MHz, $CDCl_3$) δ 2.01 (m, 1 H), 2.31 (m, 1 H), 2.41 (m, 1 H), 2.47-2.59 (m, 1 H), 2.97 (m, 1 H), 4.18-4.26 (m, 4 H), 5.13 (d, *J* = 15.1 Hz, 1 H), 7.19-7.39 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 19.2, 29.1, 37.4, 47.4, 55.0, 70.8, 127.3, 127.4, 128.5, 135.8, 169.1, 176.0; IR (KBr) 3032, 2959, 2946, 2922, 1788, 1644, 1470, 1451, 1362, 1163 cm^{-1}; HRMS calcd for $C_{14}H_{15}NO_3$ m/z 245.1051, found m/z 245.1050.

201: ^1H NMR (300 MHz, $CDCl_3$) δ 1.23 (t, *J* = 7.1 Hz, 3 H), 1.63-1.85 (m, 2 H), 1.87-2.05 (m, 3 H), 2.16 (m, 1 H), 2.37 (ddd, *J* = 17.9, 7.6, 2.6 Hz, 1 H), 2.52 (ddd, *J* = 17.9, 10.8, 7.4 Hz, 1 H), 2.96 (q, *J* = 4.2 Hz, 1 H), 3.47-3.54 (m, 2 H), 3.66 (quint, *J* = 5.3 Hz, 1 H), 4.12 (qd, *J* = 7.1, 1.4 Hz, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.7, 21.6, 23.4, 27.8, 29.2, 40.0, 44.6, 58.5, 59.9, 168.1, 171.1; IR (neat) 2977, 2880, 1730, 1640, 1460, 1414, 1327, 1302, 1177 cm^{-1}.

202: ^{1}H NMR (300 MHz, $CDCl_3$, major isomer) δ 1.13 (d, *J* = 6.51 Hz, 3 H), 1.25 (t, *J* = 7.1 Hz, 3 H), 1.43-2.54 (m, 7 H), 2.87 (t, *J* = 4.0 Hz, 1 H), 3.43-3.61 (m, 2 H), 3.70 (dt, *J* = 5.8, 5.2 Hz, 1 H), 4.16 (qd, *J* = 7.1, 1.8 Hz, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.9, 18.6, 21.7, 29.5, 30.3, 35.8, 44.6, 46.8, 59.2, 59.8, 168.4, 170.2; IR (neat) 2964, 2878, 1728, 1628, 1458, 1412, 1387, 1302, 1175 cm^{-1}.

203: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27 (t, *J* = 7.1 Hz, 6 H), 2.34-2.40 (m, 4 H), 2.62 (m, 2 H), 3.91 (dd, *J* = 9.2, 8.6 Hz, 2 H), 4.25 (q, *J* = 7.1 Hz, 4 H), 5.25 (t, *J* = 2.7 Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.4, 26.2, 26.4, 28.2, 44.2, 54.4, 61.8, 109.6, 135.6, 164.9, 167.6; IR (neat) 2982, 2869, 1736, 1667, 1647, 1439, 1414, 1372 cm^{-1}.

204: ^{1}H NMR (300 MHz, $CDCl_3$) δ); 1.24 (t, *J* = 7.1 Hz, 3 H), 1.26 (t, *J* = 7.1 Hz, 3 H), 1.65-1.98 (m, 2 H), 2.02-2.29 (m, 3 H), 2.42-2.60 (m, 3 H), 3.45-3.55 (m, 2 H), 3.85 (dd, *J* = 9.7, 6.8 Hz, 1 H), 4.14-4.26 (m, 4 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.3, 13.4, 21.5, 28.1, 28.2, 28.4, 44.9, 54.9, 60.9, 61.2, 167.3, 167.6, 169.0; IR (neat) 2980, 2883, 1734, 1649, 1460, 1414, 1370, 1252 cm^{-1}.

206: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.92 (t, *J* = 1.5 Hz, 3 H), 2.62 (m, 2 H), 2.72 (m, 2 H), 5.04 (s, 2 H), 7.19-7.71 (m, 10 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 16.0, 22.0, 30.9, 44.4, 113.3, 119.8, 124.1, 125.7, 126.9, 128.4, 128.6, 137.1, 137.4, 140.3, 167.0, 170.1; IR (KBr) 3029, 2969, 1680, 1655, 1605, 1385, 1364, 1281 cm^{-1}; HRMS calcd for $C_{20}H_{20}N_2O$ m/z 304.1575, found m/z 304.1530.

207: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (d, *J* = 6.5 Hz, 3 H), 2.00 (m, 1 H), 2.31 (m, 1 H), 2.52 (ddd, *J* = 18.2, 10.9, 7.7 Hz, 1 H), 2.68 (ddd, *J* = 18.2, 7.7, 1.6 Hz, 1 H), 2.80 (ddd, *J* = 12.7, 4.5, 3.7 Hz, 1 H), 3.82 (quint, *J* = 6.1 Hz, 1 H), 4.01 (d, *J* = 15.1 Hz, 1 H), 5.29 (d, *J* = 15.1 Hz, 1 H), 7.08-7.49 (m, 10 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.7, 18.1, 29.9, 45.4, 48.1, 52.9, 119.6, 124.2, 127.3, 127.4, 128.3, 128.6, 136.9, 137.1, 168.8, 168.9; IR (KBr) 3298, 3132, 3065, 2980, 1661, 1645, 1599, 1541, 1497, 1443 1240 cm^{-1}.

212: (mp 222-225 °C) ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.62 (m, 2 H), 2.80 (m, 2 H), 3.37 (s, 3 H), 3.54 (s, 3 H), 9.29 (bs, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 16.8, 27.9, 29.4, 29.9, 88.7, 144.0, 150.7, 161.1, 172.6; IR (KBr) 3289, 3048, 2957, 1715, 1667, 1634, 1507 cm^{-1}; HRMS calcd for $C_9H_{11}N_3O_3$ m/z 209.0800, found 209.0803 m/z 303.1120.

214: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29 (dt, J = 7.1, 0.6 Hz, 6 H), 2.30 (m, 3 H), 2.51 (m, 2 H), 2.60 (m, 2 H), 4.03 (m, 4 H), 5.00 (s, 2 H), 7.09-7.33 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$, includes C-P coupling) δ 15.8, 15.9, 16.9, 17.0, 21.3, 21.4, 31.0, 31.1, 44.2, 61.0, 61.1, 102.3, 104.9, 125.6, 126.7, 128.3, 137.0, 149.2, 149.5, 170.4; IR (neat) 3065, 3033, 2982, 2938, 2905, 1688, 1624, 1389, 1366, 1252, 1233, 1024 cm^{-1}; HRMS calcd for $C_{17}H_{24}NO_4P$ m/z 337.1443, found m/z 337.1443.

215: ^{1}H NMR (300 MHz, $CDCl_3$, mixture of isomers) δ 1.14 -1.34 (m, 9 H), 1.90- 2.72 (m, 5 H), 3.68 (m, 1 H), 3.85-4.15 (m, 5 H), 5.14 (d, J = 14.8 Hz, 0.24 H, minor isomer), 5.31 (d, J = 14.8 Hz, 0.76 H, major isomer), 7.19-7.33 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$, mixture of isomers) δ 15.7, 16.2, 16.3, 16.9, 17.0, 18.7, 18.8, 21.7, 21.8, 30.4, 30.5, 30.6, 30.9, 36.3, 37.2, 38.3, 39.1, 47.8, 47.9, 50.6, 50.9, 51.0, 61.7, 61.8, 61.9, 62.0, 127.2, 127.3, 127.8, 128.3, 128.4, 128.5, 137.2, 168.6, 169.8.

217: (mp 110-112 °C) ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.36 (t, J = 1.6 Hz, 3 H), 2.60 (m, 2 H), 2.74 (m, 2 H), 4.98 (s, 2H), 7.04-7.83 (m, 10 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 15.6, 21.3, 30.8, 44.6, 117.6, 125.5, 126.1, 127.0, 128.4, 128.8, 132.6, 136.5, 141.8, 147.6, 169.4; IR (KBr) 3061, 3032, 2957, 1688, 1622, 1449, 1360, 1302, 1173 cm^{-1}; HRMS calcd for $C_{19}H_{19}NO_3S$ m/z 341.1086, found m/z 341.1060.

218: (mp 211-213 °C) ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.17 (s, 3 H), 2.57 (s, 4 H), 7.96 (m, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 18.6, 21.9, 29.4, 84.6, 118.5, 148.4, 170.9; IR (KBr) 3212, 3139, 2205, 1690, 1653, 1373, 1327 cm^{-1}; HRMS calcd for $C_7H_8N_2O$ m/z 136.0636 found m/z 136.0645.

220: (mp 98-100 °C) ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.10 (quint, *J* = 7.7 Hz, 2 H), 2.73 (t, *J* = 8.4 Hz, 2 H), 3.06 (tt, *J* = 8.4, 1.7 Hz, 2 H) 3.46 (tt, *J* = 7.7, 1.8 Hz, 2 H), 3.83 (t, *J* = 7.5 Hz, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.4, 21.3, 30.1, 33.0, 46.6, 124.3, 153.2, 167.7; IR (KBr) 2968, 2907, 1688, 1640, 1474, 1339, 1302, 1258 cm^{-1}; HRMS calcd for $C_8H_{10}N_2O_3$ m/z 182.0691, found m/z 182.0715.

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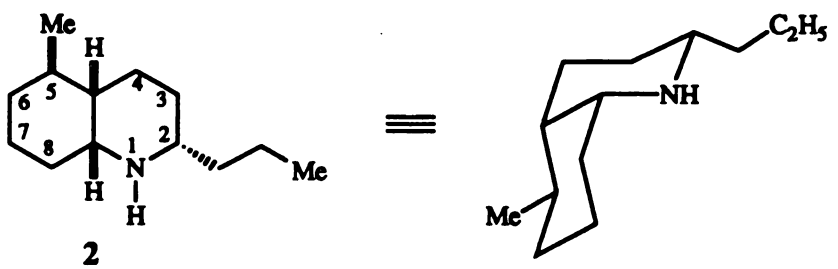
CHAPTER III

TOTAL SYNTHESIS OF (±)-5-EPIPUMILIOTOXIN C 195A AND APPROACHES TO THE SYNTHESIS OF (±)-PUMILIOTOXIN C 195A

INTRODUCTION

In order to demonstrate the use of the recently developed aza-annulation methodology in alkaloid synthesis, we targeted the total synthesis of several simple alkaloids. Since octahydroquinolone skeletons can be readily prepared in high yield using the aza-annulation methodology pumiliotoxin C 195A (2), a *cis* decahydroquinoline alkaloid, was selected as our target alkaloid.

Pumiliotoxin C 195A is one of the physiologically active alkaloids belonging to the family *Dendrobatidae*, and was isolated from the skin extracts of *Dendrobates pumilio*, a strikingly colored Panamanian frog.[1] The absolute stereochemistry of pumiliotoxin C 195A, ([2S, 4aS, 5R, 8aR] 5-methyl-2-*n*-propyl-*cis* decahydroquinoline) was determined by a single crystal X-ray analysis of its hydrochloride salt.[2]



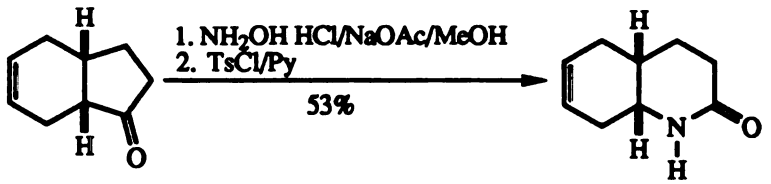
2

(±) Pumiliotoxin C 195A

Pumiliotoxin C is a relatively non-toxic compound. Higher concentrations of this alkaloid are required to have pharmacological effects on biological systems. "At higher concentrations of 80-320 μM, *dl*-pumiliotoxin C initially potentiated and then blocked indirect elicited twitch of the rat striated muscle preparations".[3] The impossibility of isolation of more than milligram quantities of this alkaloid (16 mg from 250 frogs), together with the pharmacological activity makes this alkaloid an attractive target for a total synthesis.

A successful syntheses of pumiliotoxin C 195A deals with the construction of the *cis*-decahydroquinoline ring system and elaboration of the correctly oriented side chains at carbons C-2 and C-5. In pumiliotoxin C 195A (2), the two side chains are equatorially oriented in the most stable cis-decahydroquinoline conformation. Further, the cis fused hydroquinoline intermediates are expected to show great stereoselective nucleophilic additions or catalytic hydrogenations because of the approach of reagents being restricted exclusively to the convex face of the molecule.

Several total synthesis of pumiliotoxin C have been reported,[4] and these routes have been reviewed.[3, 5] Most of the synthetic routes provided racemic pumiliotoxin C, but some asymmetric synthesis have also been reported. One of the first syntheses of (±)-pumiliotoxin C was reported by Inubushi in 1975.[4d] The cis fused decahydroquinolone ring **223** was prepared through the Beckmann rearrangement of cis tetrahydroindenone **222** (eq 1). After a series of chemical transformations, **223** was converted into **2**. This method required sixteen steps to prepare **2** from **222**.

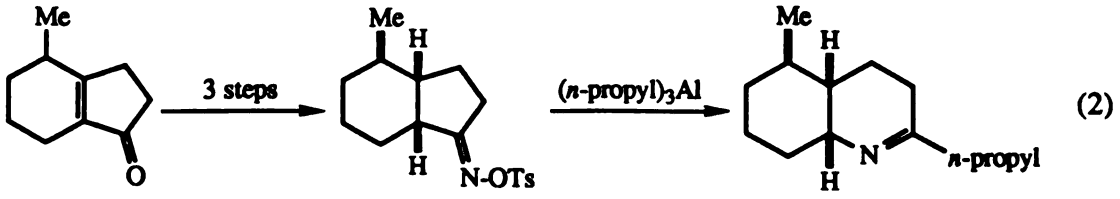


(1)

222 **223**

Yamamoto synthesized **2** to demonstrate the ability of organoaluminum reagents to induce the Beckmann rearrangement of oxime derivatives, as well as, to capture the well known intermediate iminocarbocation by the nucleophile, which was originally attached to aluminum.[4e] The precursor for Beckmann rearrangement (**225**) was prepared from **224** in three steps (eq 2). Catalytic hydrogenation of the tetrasubstituted C=C was used to obtain the cis fused ring. In the presence of 3 equivalents of tri-*n*-propylaluminum compound **225** was subjected to the Beckmann rearrangement

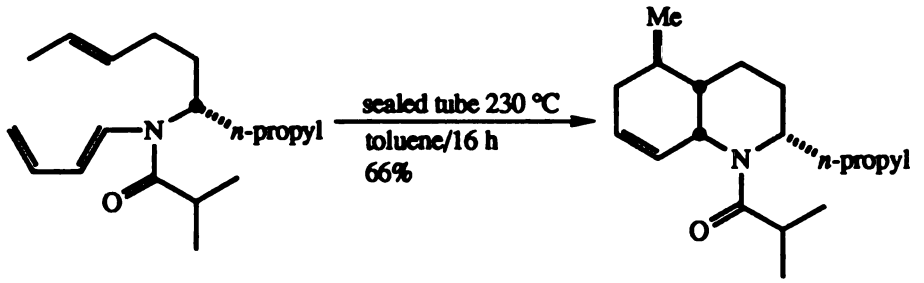
conditions to give imine **226** which upon reduction with DIBAL gave **2** in 60% yield. This methodology is an excellent way to prepare C-2 alkyl substituted cyclic amines.



(2)

224 **225** **226**

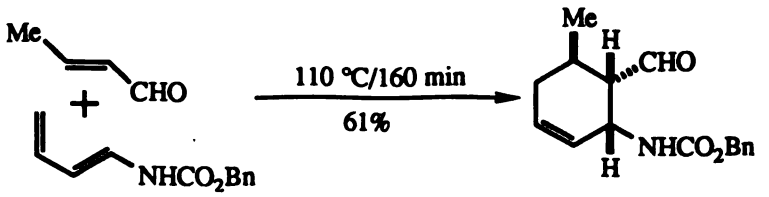
The Diels-Alder reaction has been used as a popular route for constructing the required cis ring junction of the decahydroquinoline system. Oppolzer used an intramolecular Diels-Alder reaction to establish the four stereocenters in a single step.[4a] Heating triene amide **227**, prepared from chiral (S)-norvaline, gave **228** in 60% yield, which after hydrogenation and deprotection, gave natural 2-(S) pumiliotoxin C (eq 3). This route was efficient, and afforded 97% enantiomerically pure (-)-pumiliotoxin C.



(3)

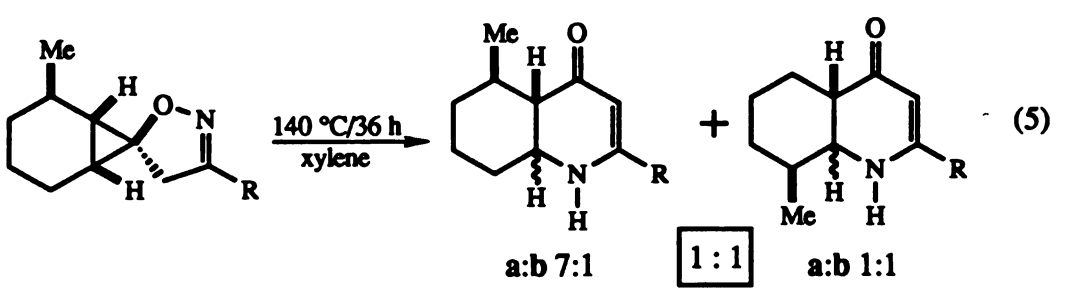
227 **228**

Overman generated the cis ring fusion and the C-5 methyl stereochemistry through an intermolecular Diels-Alder reaction.[4c] Heating the protected aminobutadiene **229** with crotonal at 110 °C gave the endo adduct **230** in 61% yield (eq 4). Further elaboration of **230** gave (±)-pumiliotoxin C. This short and convenient route provided racemic **2** in 56% overall yield from the diene **229**.



229 230 (4)

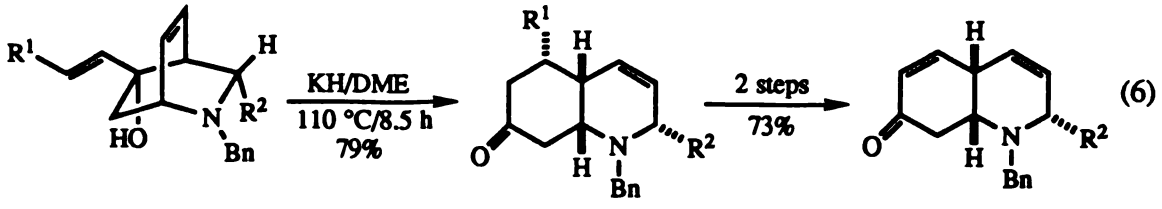
Brandi used the thermal rearrangement of 5-spirocyclopropane isooxazoline as the key reaction to establish both the cis fusion and the C-5 methyl stereochemistry.[4f] Heating compound **231** at 140 °C in xylene gave a 1:1 mixture of regioisomers **232** and **233** (eq 5). After tedious time consuming separations, **232** was isolated from the other stereo-and regioisomers and carried on to **2**.



(5)

231 232 233

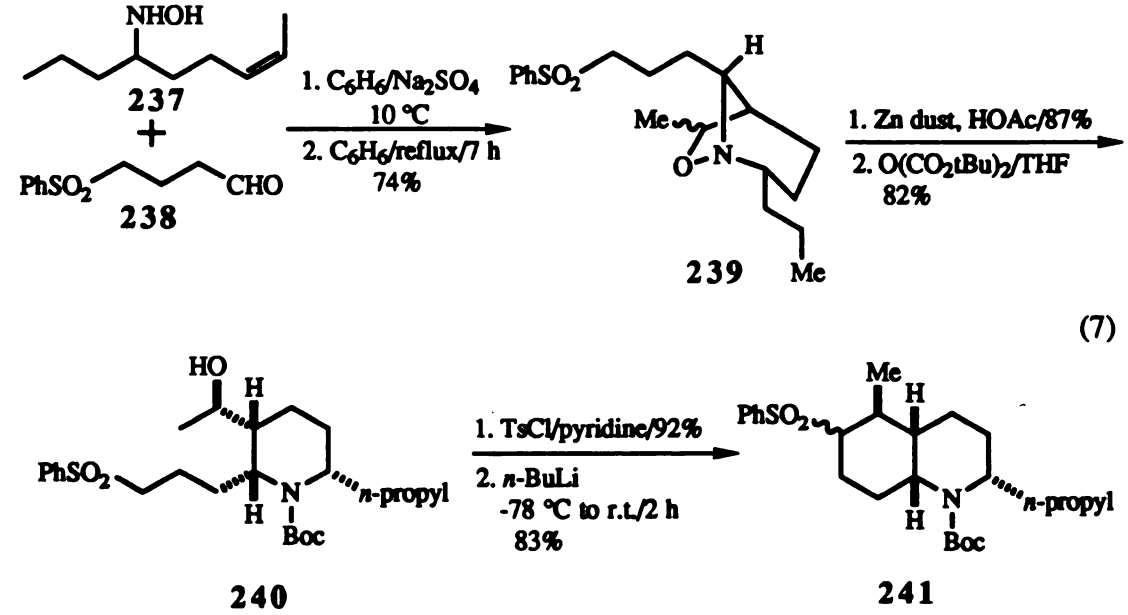
Polniaszek used an anionic oxy-cope rearrangement to prepare the cis fused hydroquioline skeleton.[4g] The anionic oxy-cope rearrangement of the alcohol **234** in DME gave **235** in 79% yield (eq 6). An assumption was made that the presence of the bulky phenyldimethylsilyl group influenced the C-2 stereochemistry. Compound **235** was converted into **236** in two steps, which after conjugate addition and further transformations yielded **2**.



234 235 236

R^1= $PhMe_2Si$ R^2=*n*-propyl

The synthesis of **2** by LaBel involved the intramolecular cycloaddition of a nitrone.[4h] The nitrone obtained from the reaction of hydroxl amine **237** and aldehyde **238** underwent intramolecular cycloaddition to give **239**, which upon reduction with zinc dust gave the cis 2,3,6-trisubstituted piperidine structure (eq 7). Conversion of alcohol **240** into the tosylate followed by intramolecular alkylation gave **241**. After removal of the sulfone group, **241** was converted to **2**.



237 + 238 → 239 → 240 → 241

From this literature survey, it can be seen that a variety of methodologies have been used to prepare the cis fused decahydroquinoline skeleton. Since we demonstrated

the use of aza-annulation in preparing octahydroquinolones in reasonably high yields, we undertook the total synthesis of (±)-pumiliotoxin C with the following goals:

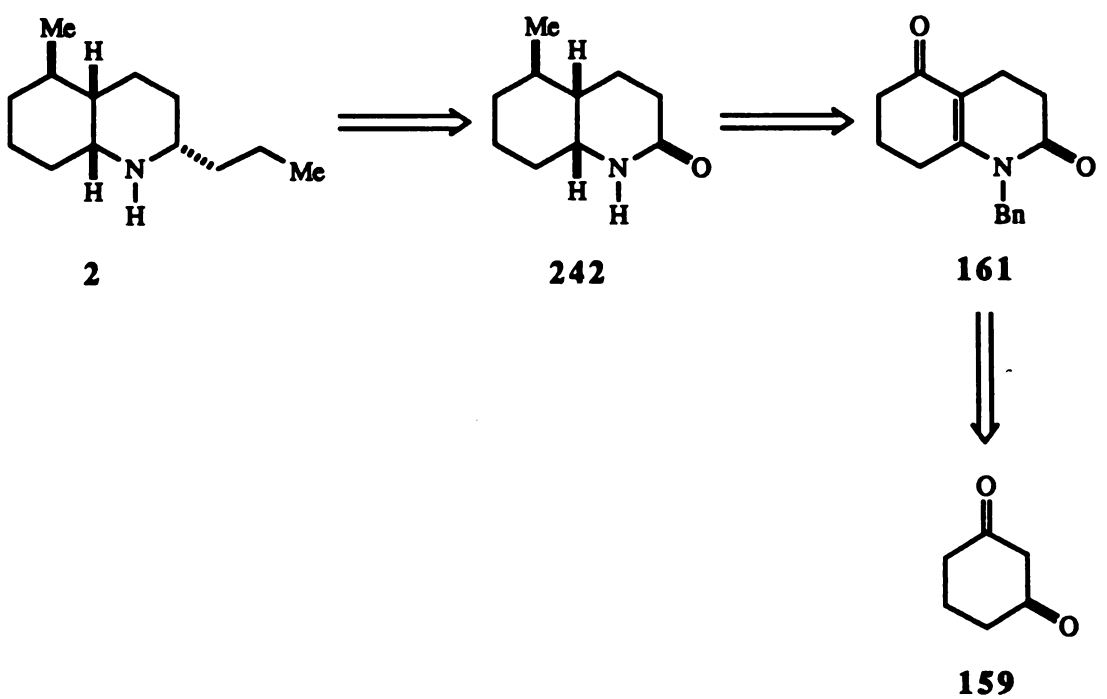
1) To utilize the aza-annulation methodology as the key reaction for the preparation of a suitable octahydroquinolone skeleton.

2) To functionalize the octahydroquinolone for further elaboration .

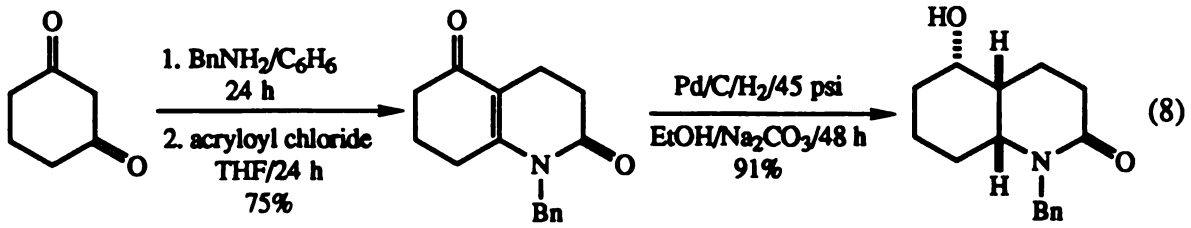
RESULTS AND DISCUSSION

The planned retrosynthetic analysis of (±)-pumiliotoxin C is shown in Scheme V. (±)-Pumiliotoxin C (**2**) should be readily available from **242** after functionalization of the amide carbonyl group using Oppolzer's procedure.[4m] The lactam **242** could be prepared from **161** after stereoselective reduction of the enamine double bond and transformation of the ketone functionality into the C-5 methyl group with correct stereochemistry followed by debenzylation. The keto lactam **161** is a typical aza-annulation product which had been prepared from readily available diketone **159**.

Scheme V. Retrosynthetic Analysis of (±)-Pumiliotoxin C.



As previously reported,[6] compound **161** was prepared in good yields from diketone **159** (eq 8). Under the established conditions, catalytic hydrogenation of **161** stereoselectively gave the cis alcohol **163** in 91% yield with a trace of its hydroxyl epimer and trans isomer.[6] With cis alcohol **163** in hand, possible pathways for the introduction of the methyl group at C-5 with correct stereochemistry were explored.

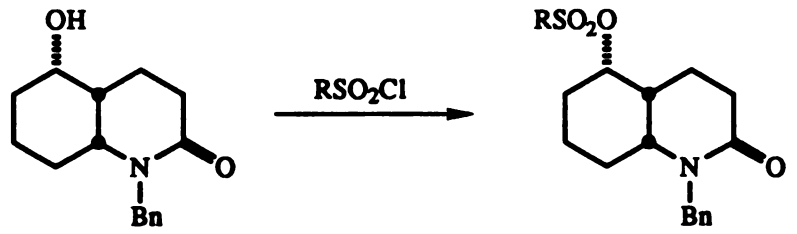


(8)

159 **161** **163**

a) S_N2 Displacement Reaction Approach

Based on literature precedent, the transformation of alcohol **163** into a better leaving group would facilitate S_N2 displacement with a methyl nucleophile to introduce the C-5 methyl group with correct stereochemistry.[7] Better leaving groups such as a mesylate and a tosylate were selected. Both mesylate **243** and tosylate **244** were prepared in 90% and 70% yields respectively from alcohol **163** (eq 9).



(9)

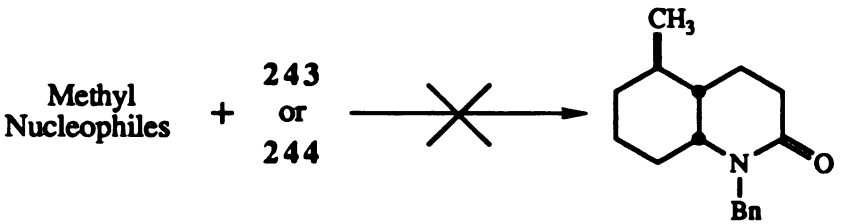
163

243 R=CH_3

244 R=*p*-$CH_3C_6H_4$

Both mesylate **243** and tosylate **244** were treated with a variety of methyl copper and methyl Grignard reagents (eq 10). Unfortunately, the desired product (**245a**) was not obtained, and either starting material or the elimination product **246** was recovered. Even

though several S_N2 displacement reactions of simple secondary tosylates with various copper reagents have been reported, both **243** and **244** failed to undergo S_N2 displacement possibly due to the steric hindrance exhibited in the cis decahydroquinolone system.[7]



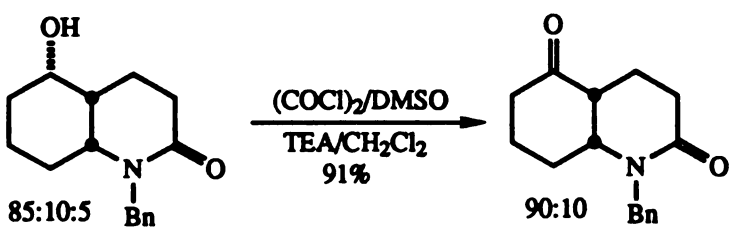
(10)

245a

246

b) Wittig Reaction Approach

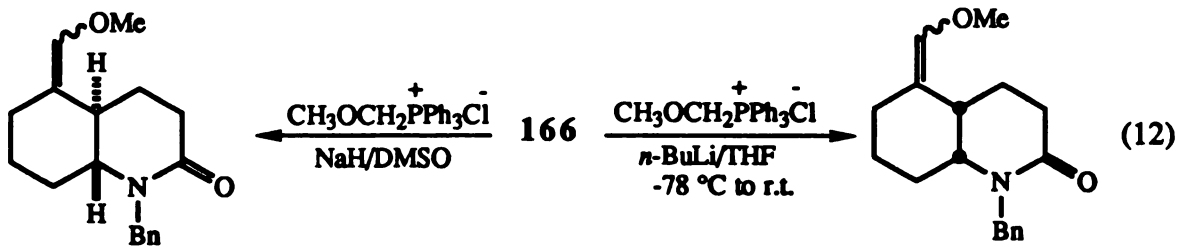
Since alcohol **163** could not be transformed into **245** *via* S_N2 displacement of mesylate **243** or tosylate **244** with methyl nucleophiles, different approaches were examined. Next, our attention was focused on a Wittig reaction to introduce the C-5 methyl group. In order to carry out the Wittig reaction, alcohol **163** was converted into ketone **166** in 91% yield using the Swern oxidation (eq 11).



(11)

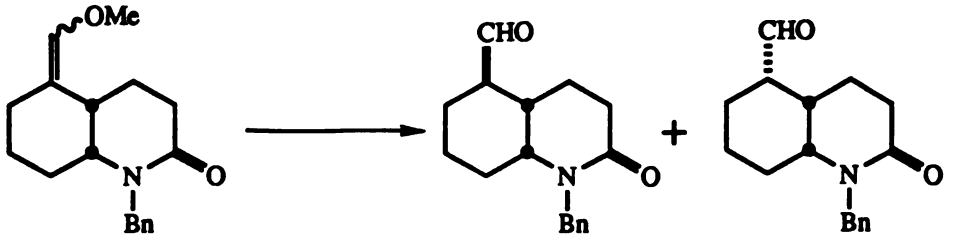
163 **166**

Reaction of the ylide, prepared from (methoxymethyl)triphenylphosphonium chloride and sodium hydride in dimethyl sulfoxide, with ketone **166** gave the enol ether of trans lactam **247a** in low yields (eq 12).[8] Under the reaction conditions, the cis lactam was isomerized to the trans lactam. In order to avoid this isomerization, the ylide was prepared using *n*-BuLi and reacted with ketone **166** at -78 °C. Under these modified conditions the formation of enol ether **247a** was avoided to a larger extent, and **247b** was obtained as the major product.



247a **247b** (12)

Without further purification, crude enol ether **247b** was submitted to hydrolysis under acidic conditions to give an aldehyde. Since the C-5 substituent in pumiliotoxin C is equatorially oriented, the hydrolysis of the enol ether **247b** was expected to give the desired aldehyde **248a** as the major product along with a trace of the undesired epimer. In order to find suitable conditions that enhance the formation of the desired aldehyde **248a** the enol ether was submitted to different hydrolysis conditions (eq 13).[9] Unfortunately, the optimum condition for the hydrolysis of enol ether **247b** with *p*-TsOH in refluxing aqueous dioxane gave a 1:1 mixture of the aldehydes **248a** and **248b** (eq 13).[9a] When the mixture of aldehydes **248a** and **248b** was submitted to epimerization conditions using sodium carbonate in methanol, significant change in the epimer ratio was not observed.

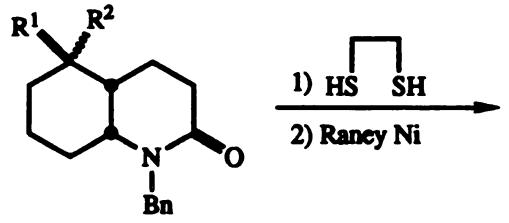


(13)

247b **248a** **248b**

H_2O/H_2SO_4/THF	45	55
HCl/THF	38	62
H_2O/HCOOH	42	58
H_2O/*p*-TsOH/Dioxane	47	53

Since a single aldehyde could not be obtained from the hydrolysis of enol ether **247b**, the mixture of crude aldehydes **248a** and **248b** was carried on to the next reaction. In order to reduce the aldehydes to the corresponding methyl groups, aldehydes **248a** and **248b** were reacted with ethanedithiol in the presence of BF_3:Et_2O to give dithianes, which upon desulfurization with Raney nickel, gave a 42:58 mixture of methyl lactams **245a** and **245b** in 47% yield from ketone **166** (eq 14).



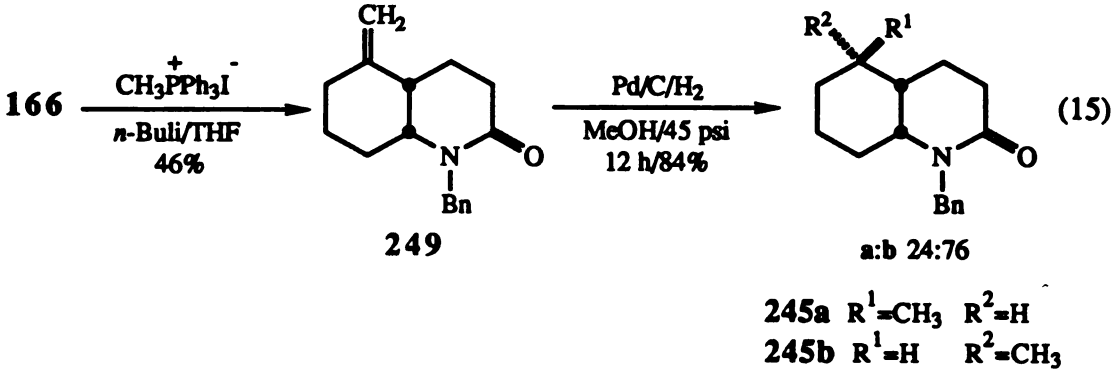
(14)

248a R^1=CHO R^2=H
248b R^2=H R^2=CHO

245a R^1=CH_3 R^2=H
245b R^2=H R^2=CH_3

In another approach, ketone **166** was reacted with the ylide prepared from methyltriphenylphoshonium iodide to give **249** in 46% yield. The trans lactam obtained along with crude **249** were separated by column chromatography. Catalytic hydrogenation of **249** over Pd/C gave **245** in 84% yield with a 24:76 mixture of epimers

245a and **245b** (eq 15). As expected from the model studies, the hydrogen was delivered from sterically less hindered top face of the decahydroquinoline system to give lactam **245b** as the major product. Since **245a** could not be obtained as a single epimer with nucleophilic displacement reaction or Wittig reaction approach, other methods were investigated.



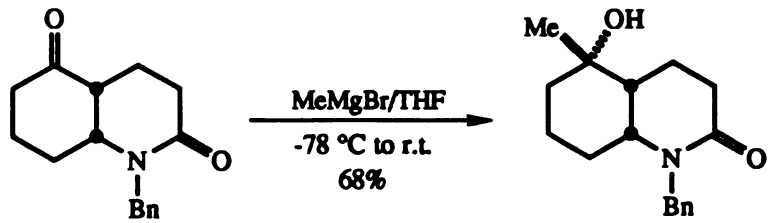
(15)

c) Radical Deoxygenation Approach

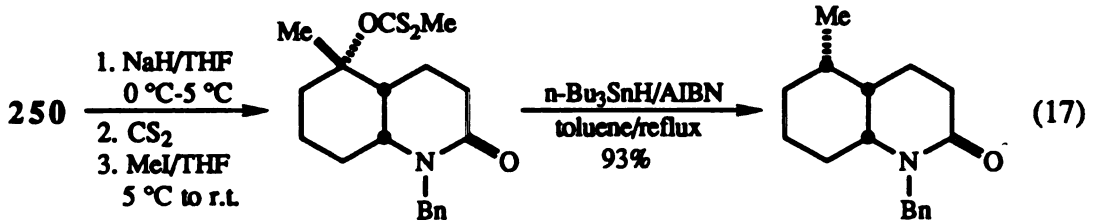
In the process of finding various approaches to introduce the C-5 methyl group, replacement of an -OH group by a hydrogen using deoxygenation of an alcohol attracted our attention. Several methods have been reported for the deoxygenating of alcohols.[10] Among the possible methods, deoxygenation of tertiary alcohol xanthates[11] and deoxygenation of the diethyl phosphate of 3° alcohols[12] were simple and efficient. Kochetkov examined the deoxygenation of various tertiary alcohol xanthates, and observed inversion of stereochemistry (50% to 98%) in the deoxygenated products.[11] Ireland reported that the deoxygenation of diethyl phosphates of a 3° alcohol by a lithium ethylamine solution gave the deoxygenated product in good yield with retention of configuration.[12]

In order to examine the stereochemical outcome of the deoxygenation of a 3° alcohol in a cis decahydroquinolone system, **250** was prepared in 68% yield from the reaction of ketone **166** and methyl magnesium bromide (eq 16). The minor epimer was

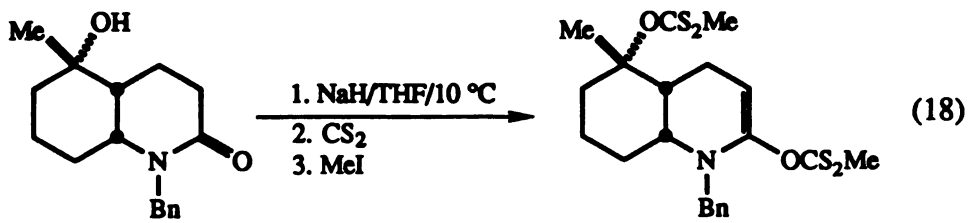
separated by column chromatography. Initial attempts to make the phosphate from alcohol **250** and diethylchlorophosphate using Ireland's procedure provided a mixture of products, and reduction of the crude reaction mixture with lithium in liquid ammonia did not give the desired product **245a**. Next, deoxygenation of the 3° alcohol xanthate was examined. Xanthate **251** was prepared using Kochetkov's procedure (eq 17).[11] During the xanthate preparation, the temperature of the reaction mixture had to remain below 5 °C to avoid undesired side reactions. When the temperature was increased above 10 °C prior to addition of CS_2, dixanthate **252** was obtained as a single product (eq 18).



166 **250** (16)

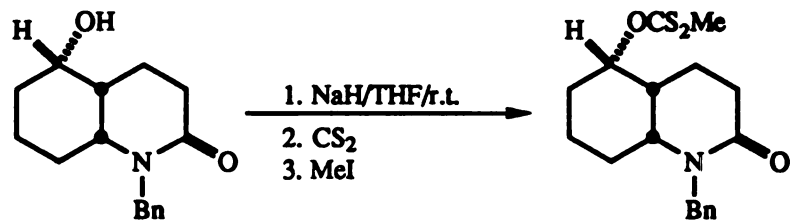


251 **245b** (17)



250 **252** (18)

The xanthate at C-2 in **252** could have formed from the reaction of the amide enolate, generated during the reaction, with CS_2 and MeI. Dixanthate formation was closely examined through a comparative experiment. Alcohol **163** was treated with NaH, CS_2 and MeI both at 5 °C and at room temperature (eq 19). Only the mono xanthate **253** was isolated at both temperatures. The only difference between these two alcohols is the fact that one is a 3° alcohol and other is a 2° alcohol. From the above experiment, it was evident that the 3° alkoxide formed at higher temperatures was basic enough to generate the amide enolate which reacted with CS_2 and MeI to give xanthate **252**. However, in the case of the 2° alcohol, the 2° alkoxide formed was not basic enough to generate an amide enolate, and hence, only the mono xanthate was observed.

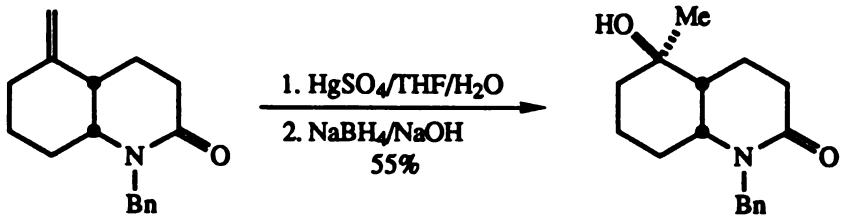


163 **253** (19)

Deoxygenation was carried out by heating xanthate **251** at reflux in toluene with tributyltin hydride and a catalytic amount of the radical initiator AIBN (eq 17). Surprisingly, deoxygenation of xanthate **251** gave the undesired epimer **245b** as the major product (>95%) in 93% yield. The ease of hydrogen radical approach, the themodynamic stability of the intermediate radical and other stereoelectronic factors had an appreciable influence in the stereoselective formation of **245b**.

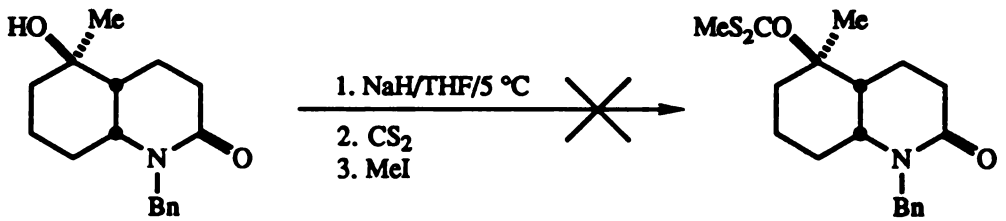
The stereoselectivity observed during the deoxygenation of xanthate **251** prompted us for the preparation of lactam **245a**. Deoxygenation of 3° alcohol **254** *via* xanthate **255** was expected to give lactam **245a** which could be transformed into (±)-pumiliotoxin C. Based on this assumption, alcohol **254** was prepared in 55% yield from

oxymercuration of **249** (eq 20). Attempts to prepare xanthate **255** were unsuccessful, and as a result, pure **245a** could not be prepared (eq 21).



(20)

249 **254**



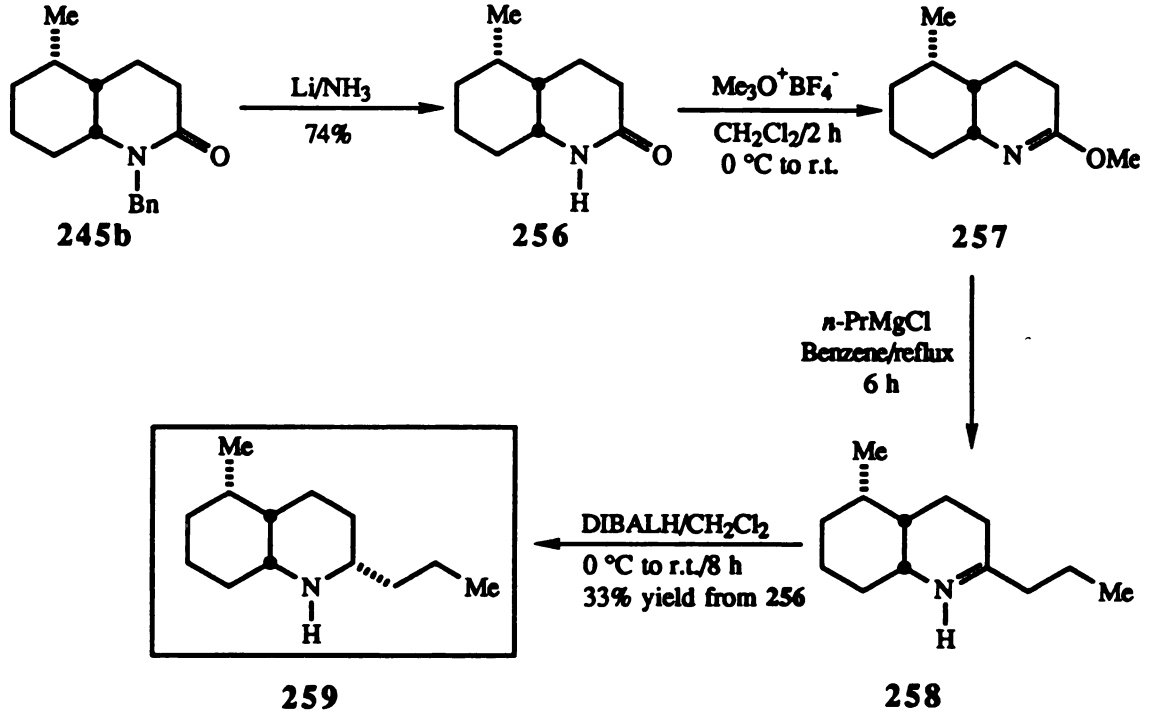
(21)

254 **255**

Since lactam **245a** could not be prepared as a single compound, we decided to transform lactam **245b** into (±)-5-epipumiliotoxin C (**259**). The total synthesis of (±)-5-epipumiliotoxin C (**259**) from compound **245b** is shown in Scheme VI. Reductive debenzylation of lactam **245b** in liquid ammonia with lithium metal at -33 °C gave decahydroquinolone **256** in 74% yield. Lactam **256** was converted to imine **258** using Oppolzer's conditions.[4m] Treatment of lactam **256** with trimethyloxonium tetrafluoroborate in the presence of a catalytic amount of Hunig's base gave lactim-ether **257**. Without purification, crude **257** was treated with propylmagnesium chloride in refluxing benzene to give imine **258**. Catalytic hydrogenation of imine **258** gave a mixture of products, but the reduction of crude imine **258** with DIBALH using Yamamoto's procedure[4e] gave (±)-5-epipumiliotoxin C (**259**) in 33% yield from lactam **245b**. Even though all of the attempts to introduce a C-5 methyl group with the correct

stereochemistry failed, the unexpected stereoselective formation of **245b** by the radical deoxygenation method allowed us to complete the total synthesis of unnatural (±)-5-epipumiliotoxin C. (±)-5-Epipumiliotoxin C was obtained in 7.3 overall yield from readily available diketone **159**.

Scheme VI. Total Synthesis of (±)-5-Epipumiliotoxin C.



CONCLUSION

Application of the aza-annulation methodology in alkaloid synthesis has been demonstrated by the total synthesis of (±)-5-epipumiliotoxin C. Aza-annulation was used as the key reaction for construction of the octahydroquinolone ring skeleton, and the octahydroquinolone was transformed into unnatural (±) 5-epipumiliotoxin C after several transformations. Catalytic hydrogenation of the octahydroquinolone was used to stereoselectively establish the cis ring fusion. The use of radical deoxygenation for stereo

chemical inversion has been utilized for the introduction of the C-5 methyl group. In general, aza-annulation of 1,3-cyclohexanedione followed by catalytic hydrogenation of the annulated lactam is one of the simplest and more economical methods for the construction of a cis-decahydroquinolone skeleton, which can be used as a common precursor for the preparation of several other cis-decahydroquinoline alkaloids. Further studies are required to prepare (±)-pumiliotoxin C from the octahydroquinolone skeleton.

EXPERIMENTAL SECTION

General Methods. All reactions were carried out under an atmosphere of either nitrogen or argon. Benzene, toluene, tetrahydrofuran (THF), and Et_2O were distilled from sodium/benzophenone immediately prior to use. Triethylamine, dichloromethane and pyridine were heated at reflux over calcium hydride for a minimum of 12 h, and then distilled immediately prior to use. 1,3-Cyclohexanedione was obtained from Aldrich Chemical Co. and recrystallized from benzene prior to use. Benzylamine and acryloyl chloride were obtained from Fluka, and used without further purification. A solution of DIBALH (1.0 M in hexane) was prepared from neat DIBALH obtained from Aldrich Chemical Co. Methylmagnesium bromide (3.0 M in Et_2O), propylmagnesium chloride (2.0 M in Et_2O), BF_3:Et_2O and trimethyloxonium tetrafluoroborate were purchased from Aldrich Chemical Co. Acrylic acid, methanesulfonyl chloride, and ethyl chloroformate were purchased from Aldrich Chemical Co. and distilled before use. Compounds **161**, **163** and **166** were prepared as described in Chapter II.

NMR Spectra were obtained on a Varian Gemini 300 instrument with $CDCl_3$ as the solvent. ^1H spectral data are reported as follows: chemical shifts relative to residual $CHCl_3$ (7.24 ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, sept = septet, b = broad), coupling, and integration. ^{13}C chemical shifts are reported relative to residual $CHCl_3$ (77.0 ppm). Infrared spectra were recorded on a Nicolet 42 FT-IR instrument.

Preparation of Mesylate (243). To a solution of alcohol (1.26 g, 4.8 mmol) and TEA (0.98 g, 9.7 mmol) in 45 mL of CH_2Cl_2 at 0 °C was added freshly distilled methanesulfonyl chloride (1.66 g, 14.5 mmol) and stirred for 3 h at this temperature. The temperature was raised to ambient temperature and stirred for an additional 3 h. Saturated $NaHCO_3$ (60 mL) was added and stirred for 30 min. The aqueous layer was then extracted with 4 x 50 mL of CH_2Cl_2, and the combined organic fractions were dried

over Na_2SO_4. After removal of solvents, the residue was purified by flash column chromatography (eluent: 80:20 CH_2Cl_2-EtOAc). The solvents were removed to give mesylate **243** in 82% yield. The mesylate was directly used for subsequent reactions without further characterization.

Preparation of Tosylate (244). To a solution of alcohol (0.9 g 3.47 mmol) in 13 mL of pyridine at 0 °C was added *p*-toluenesulfonyl chloride (0.99 g, 5.2 mmol) . The reaction mixture was stirred at 25 °C for 24 h. The solvent was removed, and the residue was taken in 40 mL of CH_2Cl_2 and washed successively with 25 mL of 10% aqueous HCl solution, 25 mL of saturated $NaHCO_3$, and 25 mL of brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated to give a crude residue, which was purified by flash column chromatography (eluent 15:85 EtOAc-CH_2Cl_2). The solvents were evaporated to give tosylate **244** in 77% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 (qt, *J* = 13.5, 3.7 Hz, 1 H), 1.33 (dq, *J* = 3.7, 13.4 Hz, 1 H), 1.55 (dq, *J* = 4.0, 12.6 Hz, 1 H), 1.58-1.79 (m, 2 H), 1.79-1.93 (m, 3 H), 2.25 (m, 1 H), 2.36 (dd, J = 18.1, 9.5 Hz, 1 H), 2.46 (s, 3 H), 2.58 (ddd, *J* = 17.9, 4.1, 3.9 Hz, 1 H), 3.13 (dt, *J* = 11.9, 4.3 Hz, 1 H), 3.94 (d, *J* = 15.3 Hz, 1 H), 4.53 (dt, *J* = 11.9, 5.0 Hz, 1 H), 5.28 (d, *J* = 15.3 Hz, 1 H), 7.15 (m, 2 H), 7.24-7.38 (m, 5 H), 7.77 (d, *J* = 8.2 Hz, 2 H); ^{13}C NMR (75.5 MHz. $CDCl_3$) δ 15.2, 20.5, 21.2, 25.1, 25.9, 30.3, 38.4, 47.5, 55.8, 80.4, 127.0, 127.1, 128.2, 129.4, 133.8, 136.8, 144.5, 168.9; IR (KBr) 3088, 3067, 3032, 2953, 2245, 1632, 1497, 1474, 1453, 1362, 1227, 1190, 1177, 1098 cm^{-1}.

Preparation of Compound 246 from Tosylate (244). To a solution of *t*-BuOK (0.11 g, 0.9 mmol) in 4 mL of DMSO was added the tosylate **244** (0.3g, 0.7 mmol) The reaction mixture was heated at 70 °C for 8 h. H_2O (10 mL) was added to the reaction mixture which was stirred for an additional 15 min. The reaction mixture was extracted with 4 x 20 mL of Et_2O, and the combined organic layers were washed with 2 x 20 mL of H_2O. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated to give a crude residue. The crude residue was purified by flash column chromatography

(eluent 50:50 Et_2O-Petroleum ether). The solvents were evaporated to give **246** in 72% yield: ^1H NMR (300 MHz, $CDCl_3$) δ 1.17-1.34 (m, 1 H), 1.39 (m, 1 H), 1.78 (m, 1 H), 1.99 (m, 2 H), 2.19 (m, 1 H), 2.26-2.45 (m, 3 H), 2.64 (m, 1 H), 3.78 (m, 1 H), 4.28 (d, *J* = 15.3 Hz, 1 H), 5.20 (d, *J* = 15.3 Hz, 1 H), 5.55 (m, 1 H); ^{13}C NMR (75.5 MHz. $CDCl_3$) δ 20.6, 24.2, 29.0, 33.6, 45.7, 45.8, 55.5, 55.6, 123.2, 126.6, 127.1, 128.1, 132.9, 137.2, 170.4; IR (KBr) 3087, 3061, 3029, 2946, 2861, 2840, 1646, 1495, 1449, 1420, 1358, 1279, 1196, 1157 cm^{-1}.

Preparation of Alcohol (250). To a solution of ketone **166** (1.42 g, 5.5 mmol) in 45 mL of THF at -78 °C was added dropwise 3.0 M solution of methylmagnesium bromide (3.70 mL, 11.07 mmol) and stirred at -78 °C for 1 h and at 0 °C for 5 h. The reaction mixture was then quenched with 25 mL of saturated NH_4Cl solution and stirred for 15 min. The aqueous layer was then extracted with 4 x 50 of CH_2Cl_2, and the organic fractions were combined and dried (Na_2SO_4). After removal of solvents, the residue was purified by flash column chromatography (eluent 40:60 CH_2Cl_2-EtOAc). The solvents were evaporated to give alcohol **250** in 71% yield: ^1H NMR (300 MHz, $CDCl_3$) δ 1.21 (s, 3 H), 1.26 (m, 1 H), 1.32-1.49 (m, 2 H), 1.54 (dd, *J* = 13.1, 4.2 Hz, 1 H), 1.65-1.96 (m, 4 H), 2.06 (m, 1 H), 2.46 (m, 1 H), 2.64 (dd, *J* = 18.1, 5.8 Hz, 1 H), 3.30 (dt, *J* = 12.0, 4.2 Hz, 1 H), 4.05 (d, *J* = 15.2 Hz, 1 H), 5.12 (d, *J* = 15.2 Hz, 1 H), 7.16-7.36 (m, 5 H); ^{13}C NMR (75.5 MHz. $CDCl_3$) δ 16.6, 20.7, 26.0, 27.2, 30.9, 33.6, 45.2, 48.0, 56.1, 71.2, 126.7, 126.9, 128.1, 137.1, 169.7; IR (KBr) 3392, 3088, 3063, 3030, 2938, 2868, 1620, 1496, 1453, 1416, 1359, 1129, 1123 cm^{-1}.

Preparation of Compounds 245a and 245b from Ketone (166): To a suspension of (methoxymethyl)triphenylphosphonium chloride (5.0 g, 14.6 mmol) in 55 mL of THF at -78 °C was added a 2.5 M solution of *n*-BuLi (5.85 mL, 14.6 mmol). The reaction was stirred at this temperature for 15 min, and then warmed to 0 °C for an additional hour. The reaction mixture was then cooled to -78 °C, and the ketone **166** (2.05 g, 9.7 mmol) in 7 mL of THF was added and stirred at -78 °C for 2 h, at -45 °C for

7 h , at -20 °C for 2 h, at 0 °C for 2 h and at room temperature for 4 h. The reaction mixture was then quenched with 35 mL of saturated NH_4Cl solution, and the aqueous layer was extracted with 4 x 50 mL of CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated to give crude enol ether **247**. The crude enol ether **247** was added to a solution of 96 mL of dioxane, 27 mL of H_2O and *p*-TsOH (0.46 g, 2.4 mmol). The reaction mixture was heated at reflux for 12 h, cooled, and saturated $NaHCO_3$ was added and stirred for another 30 minutes. The aqueous layer was extracted with 4 x 25 mL of CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated to give a mixture of crude aldehydes **248a** and **248b**. The crude aldehydes were filtered through a silica gel column (eluent 80:20 CH_2Cl_2-EtOAc). After removal of the solvents, the crude aldehydes were used for further reaction. To a solution of ethanedithiol (2.75 g, 29.2 mmol) and aldehydes **248a** and **248b** (9.7 mmol) in 190 mL of $CHCl_3$ at 0 °C was slowly added BF_3:OEt_2 (0.69 g, 4.9 mmol). The reaction mixture was stirred for 12 h at room temperature, 100 mL of 5% $NaHCO_3$ was added and the reaction mixture was stirred for 20 min. The organic layer was washed with 50 mL of H_2O and the combined aqueous layers were washed with 2 x 50 mL of $CHCl_3$. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated to give the crude dithiane. The crude dithiane was added to a suspension of 48.8 g of Raney nickel in 240 mL of EtOH, and heated at reflux for 12 h. The reaction mixture was cooled, filtered, and concentrated to give a crude residue. The residue was purified by flash column chromatography (eluent 55:45 Et_2O-petroleum ether). The solvents were evaporated to give a mixture of **245a** and **245b** in 47% yield from ketone **266**.

Preparation of Compound 249. To a suspension of methyltriphenylphosphonium iodide (4.04 g, 10 mmol) in 35 mL of THF at -78 °C was added a 2.5 M solution of *n*-BuLi (4.00 mL, 10 mmol) and stirred at this temperature for 15 min and stirred at room temperature for 1 h. The reaction mixture was then cooled to -78 °C, and ketone **166** (1.71 g, 6.7 mmol) in 6 mL of THF was added slowly and stirred

at -78 °C for 8 h, at -45 °C for 2 h, at 0 °C for 2 h and at room temperature for 4 h. Saturated ammonium chloride (25 mL) was added, and the mixture was stirred for 20 min. The aqueous layer was extracted with 4 x 40 mL of methylene chloride. The combined organic layers were dried (MgSO4), filtered, and concentrated to give a crude residue. This residue was purified by flash column chromatography (eluent 60:40 Et_2O-Petroleum ether). The solvents were evaporated to give **249** as a viscous liquid in 46% yield: ^1H NMR (300 MHz, $CDCl_3$) δ 1.17 (m, 1 H), 1.45-1.65 (m, 2 H), 1.82 (dq, *J* = 13.2, 3.5 Hz, 1 H), 2.01 (dq, *J* = 13.2, 3.4 Hz, 1 H), 2.07-2.14 (m, 2 H), 2.16-2.29 (m, 1 H), 2.44-2.59 (m, 2 H), 2.64 (dt, *J* = 13.0, 4.5 Hz, 1 H), 3.21 (dt, *J* = 12.1, 4.4 Hz, 1 H), 3.98 (d, *J* = 15.2 Hz, 1 H), 4.68 (d, *J* = 1.5 Hz, 1 H), 4.74 (d, *J* = 1.5 Hz, 1 H), 5.29 (d, *J* = 15.2 Hz, 1 H), 7.19-7.34 (m, 5 H); ^{13}C NMR (75.5 MHz. $CDCl_3$) δ 22.7, 24.7, 26.4, 29.8, 31.1, 43.5, 47.4, 57.9, 109.6, 126.7, 127.2, 128.1, 137.3, 149.0, 168.9; IR (KBr) 3067, 2940, 2882, 2861, 1640, 1495, 1468, 1453, 1418, 1360 cm^{-1}.

Hydrogenation of Compound 249. Compound **249** (0.59 g, 2.3 mmol) was taken up in 60 mL of MeOH and was hydrogenated at 45 psi over 10% palladium on carbon (0.2 g) for 12 h. Removal of the catalyst by filtration followed by concentration gave a 26:74 mixture of **245a** and **245b** in 84% yield.

Preparation of Xanthate (251). To a suspension of NaH (1.13 g, 47.2 mmol) in 22 mL of THF at 0 °C was slowly added tertiary alcohol **250** (2.58 g, 9.4 mmol) in 27 mL of THF. The flask was washed with additional 3 mL of THF, and the washing was added to the reaction mixture, which was stirred at 0-3 °C for 30 min. Then carbon disulfide (3.59 g, 47.2 mmol) was slowly added, and the reaction was stirred at 0-3 °C for 45 min. To this reaction mixture was slowly added methyl iodide (6.7 g, 47.2 mmol), and the reaction mixture was stirred this temperature for 30 min and at room temperature for 12 h. The reaction mixture was then cooled to 0 °C and quenched by slow addition of water. The aqueous layer was extracted with 4 x 30 mL of EtOAc. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated to give a crude residue, which was

purified by flash column chromatography using Et_2O as the eluent. The solvent was evaporated to give xanthate **251** in 76% yield. The xanthate was directly used for deoxygenation without further characterization.

Deoxygenation of Xanthate (251). A mixture of xanthate **251** (2.47 g, 6.8 mmol), tributyltin hydride (3.95 g, 13.6 mmol) and AIBN (0.223 g 1.36 mmol) in 27 mL of toluene was heated at reflux for 5 h. The reaction mixture was cooled to room temperature, and poured out on a silica gel column. The mixture was first eluted with petroleum ether and then 70:30 petroleum ether:Et_2O and finally flushed with Et_2O. Evaporation of the ether fractions gave the crude deoxygenated product. The crude was purified by flash column chromatography (eluent 90:10 Et_2O-petroleum ether). The solvents were evaporated to give **245b** as a viscous liquid in 93% yield: ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (d, J = 6.9 Hz, 3 H), 1.01-1.25 (m, 2 H), 1.26-1.43 (m, 2 H), 1.52-1.95 (m, 6 H), 2.42 (ddd, J = 18.2, 10.9, 8.1 Hz, 1 H), 2.59 (ddd, J = 18.2, 6.1, 1.9 Hz, 1 H), 3.12 (ddt, J = 11.3, 0.7, 3.6 Hz, 1 H), 3.92 (d, J = 15.1 Hz, 1 H), 5.31 (d, J = 15.1 Hz, 1 H), 7.13-7.33 (m, 5 H); ^{13}C NMR (75.5 MHz. $CDCl_3$) δ 15.0, 18.7, 24.1, 26.0, 27.8, 30.8, 33.9, 39.2, 47.2, 58.1, 126.6, 127.1, 128.1, 137.4, 169.5; IR (KBr) 3063, 3029, 2930, 2861, 1638, 1453, 1358, 1227 cm^{-1}.

Preparation of Lactam (256). Compound **245b** (1.89 g 7.3 mmol) in 20 mL of THF was added to liquid ammonia (150- 200 mL) at -78 °C. Small pieces of lithium rod were added slowly to generate a dark blue color. The dry ice bath was removed, and the reaction mixture was stirred for 2 h at -33 °C. The reaction mixture was then cooled to -78 °C and quenched by adding solid NH_4Cl. Ammonia was evaporated overnight to give a white solid. The white solid was dissolved in methanol and transferred into a round bottom flask. The solvent was removed to give a residue, and the residue was redissolved in CH_2Cl_2 and filtered to remove the insoluble inorganic salts. The filtrate was evaporated to give crude lactam **256** which was purified by flash column chromatography (eluent ethyl acetate). The solvent was evaporated to give **256** in 74%

yield: ^{1}H NMR (300 MHz, CDCl 3) δ 0.95 (d, J = 6.9 Hz, 3 H), 1.03 (m, 1 H), 1.17-1.50 (m, 3 H), 1.61-1.76 (m, 5 H), 1.94 (m, 1 H), 2.28 (ddd, J = 18.1, 10.4, 8.2 Hz, 1 H), 2.44 (ddd, J = 17.9, 4.2, 3.5 Hz, 1 H), 3.30 (dq, J = 11.5, 4.1 Hz, 1 H), 6.21 (bs, 1 H); ^{13}C NMR (75.5 MHz. $CDCl_3$) δ 14.6, 18.9, 23.9, 27.8, 30.1, 30.8, 33.8, 38.0, 53.7, 171.8; IR (KBr) 3193, 3087, 2926, 2877, 2855, 1653, 1495, 1416, 1302, 1227 cm^{-1}.

Preparation of (±)-5-Epipumiliotoxin C (259). To a solution of trimethyloxonium tetrafluoroborate (0.613 g, 4.1 mmol) and *N*-ethyl-diisopropylamine (2 drops) in 3 mL of CH_2Cl_2 at 0 °C was added lactam (0.35 g, 2.1 mmol) in 1 mL of CH_2Cl_2. The the reaction mixture was stirred at room temperature for 2 h, cooled to 0 °C, and 5 mL of saturated $NaHCO_3$ was added. The reaction mixture was stirred at 0 °C for 10 min and the aqueous layer was extracted with 3 x 10 mL of CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and filtered. The solvent was removed to give crude lactim-ether **257**. Without further purification, **257** was immediately transformed into (±)-5-epipumiliotoxin C.

To a 1M solution of propylmagnesium chloride in Et_2O (8.3 mL, 8.3 mmol) was added 6.5 mL of dry benzene. The Et_2O was removed by heating the reaction mixture at 80 °C under a stream of nitrogen. After the removal of Et_2O, the reaction mixture was cooled to 45 °C, and **257** in 2 mL of benzene was added slowly. The flask was washed with an additional 2 mL of benzene and the washing was added to the reaction flask. The reaction mixture was heated at reflux for 6 h, cooled to 0 °C, and then 10 mL of saturated aqueous $NaHCO_3$ was added. The aqueous layer was extracted with 3 x 10 mL of CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated to give crude imine **258**.

To a solution of crude **258** in 21 mL of CH_2Cl_2 at 0 °C was added a 1 M solution of DIBALH (10 mL, 10 mmol) in hexane and stirred at 0 °C for 2 h and at room temperature for 6 h. The reaction mixture was then cooled to 0 °C and quenched with 30 mL of MeOH and 15 mL of 15 % aq NaOH and stirred at room temperature for 30 min.

The aqueous layer was then extracted with 3 x 20 mL of CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated to give a crude residue, which was purified by flash column chromatography (eluent 80:20:2 Et_2O-MeOH-NH_4OH). The solvents were evaporated to give (±)-5-epipumiliotoxin C (259) as a viscous liquid in 33% yield for the three step-sequence. ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, J = 6.9 Hz, 3 H), 0.98 (d, J = 6.9 Hz, 3 H), 1.14-1.76 (m, 17 H), 2.74 (m, 1 H), 2.84 (m, 1 H); ^{13}C NMR (75.5 MHz. $CDCl_3$) δ 13.8, 19.1, 19.5, 21.3, 29.2, 30.9, 32.2, 34.1, 38.6, 39.6, 52.7, 55.2, 55.3; IR (neat) 2953, 2930, 2870, 1456, 1377, 1137.

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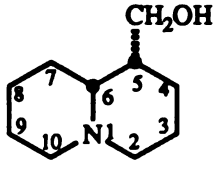
CHAPTER IV

TOTAL SYNTHESIS OF (±)-LUPININE AND (±)-TASHIROMINE

INTRODUCTION

a) Lupinine

Lupinine (3), one of the simplest lupin alkaloids, was initially isolated from yellow lupin seeds by Cassola[1] in 1835, and was obtained in pure form by Baumert[2] in 1881. Lupinine is present in numerous plants of the Lupinus family such as *Lupinus luteus*, *Lupinus niger* and *Lupinus palmeri*.[3] The absolute configuration of (-)-lupinine (5R, 6R)-1-hydroxymethylquinolizidine was established by a number of methods. 1) Degradation of (-)-lupinine to the optically active 4-methylnonane has the same sign of rotation as the optically active 4-methylnonane obtained from natural sources.[4] 2) During the chemical synthesis of *dl*-lupinine, establishment of asymmetric centers at C-5 and C-6 by catalytic hydrogenation using platinum showed the cis relationship of the C-5 and C-6 asymmetric centers.[5] 3) Spectroscopic methods have also been used to confirm the absolute configuration of (-)-lupinine.[6] Lupinine has little medicinal value, however the *p*-aminobenzoate derivative has been shown to possess a marked local anesthetic action.[7]

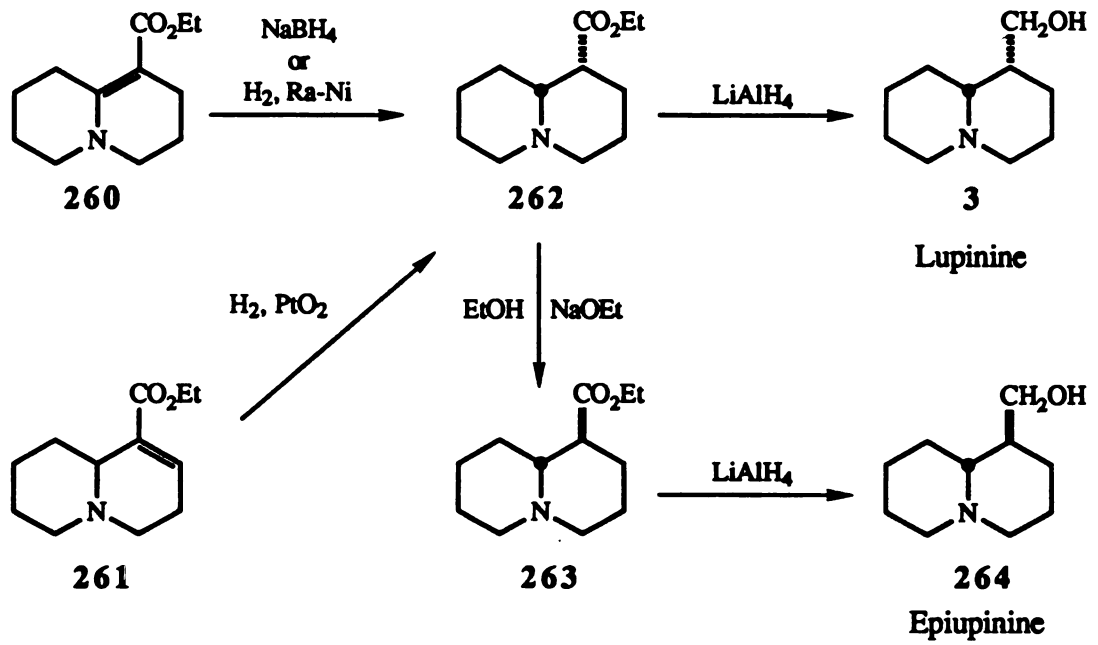


3

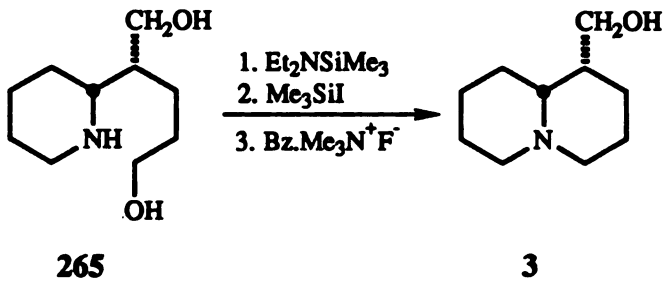
Since lupinine (3) is a simple quinolizidine alkaloid. This has been a target of choice for demonstrating the applicability of developed methodology. Lupinine has been prepared through several routes, and in most of the syntheses, the relative stereochemistry of the two asymmetric centers has been established by reduction of either **260** or **261** to give **262** (Scheme VII).[8] Subsequent reduction of **262** with $LiAlH_4$ was then used to prepare lupinine (3). Alternatively, epimerization of **262** to **263**, the more thermodynamically stable isomer, followed by reduction to **264** provided a route to

epilupinine (264). In most of the reported total synthesis of lupinine, at least one of the two heterocycle rings was already present in the starting material.

Scheme VII. General Routes for the Establishment of Lupinine (3) Stereochemistry.



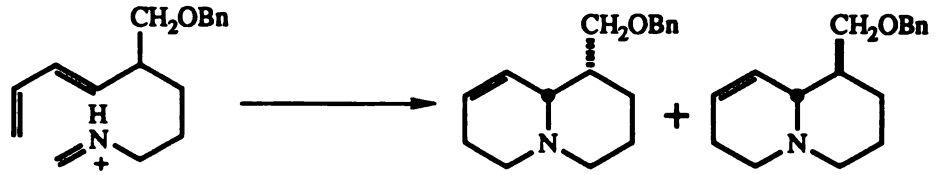
In some cases, the two asymmetric centers were established, as in **265**, prior to the second ring formation which was then cyclized from the intermediate amino alcohol (eq 1).[9]



(1)

An intramolecular immonium ion based Diels-Alder reaction has also been used to establish both stereocenters and quinolizidinine rings from the corresponding

immonium salt (eq 2).[10] Compound **266** readily gave a separable mixture of Diels-Alder adducts **267** and **268** in 82% yield in a ratio of 1:1.6.

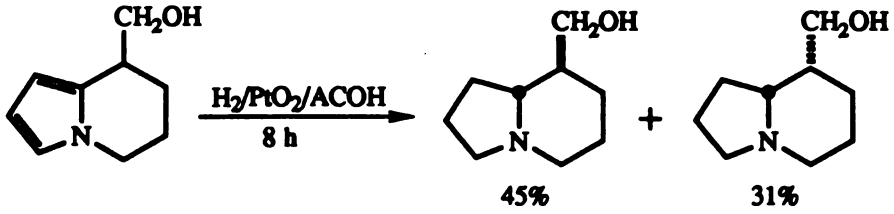


266 **267** **268** (2)

b) Tashiromine

Tashiromine (**269**), an indolizidine alkaloid, was isolated along with ammodendrine and seven other lupin alkaloids from the Maackia species, *Maackia.tashiroi*. *Maackia.tashiroi* is a deciduous shrub distributed widely in subtropical Asia.[11]

The stereochemistry of tashiromine was assigned by comparing ^{1}H NMR and ^{13}C NMR chemical shifts with epilupinine (**3**) and its cis diastereomer, lupinine (**264**).[11] Synthetic samples of (±)-tashiromine (**269**) and its diastereomer, (±)-epitashiromine (**270**), were prepared by catalytic hydrogenation of cyclohexapyrrole **271** (eq 3). The synthetic and natural alkaloids were chromatographically and spectroscopically indistinguishable.

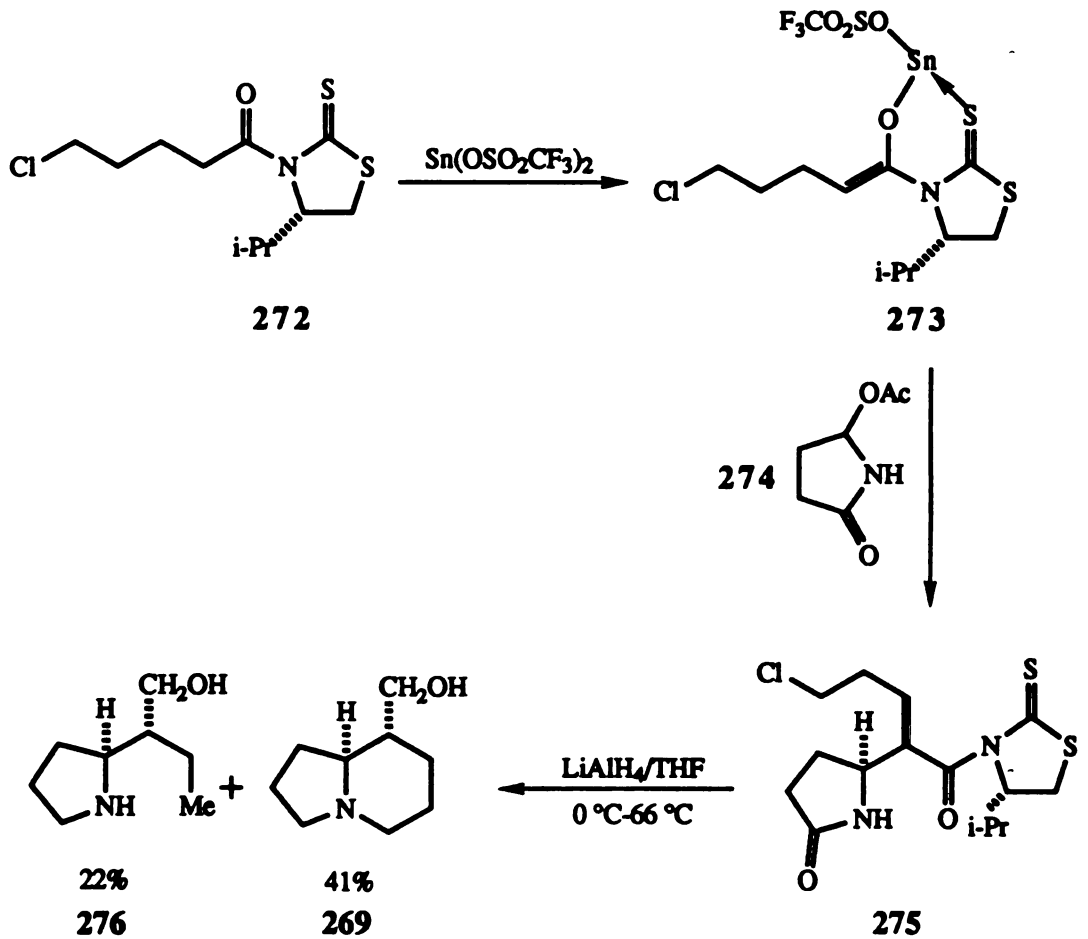


271 **269** **270** (3)

An asymmetric synthesis of (-)-tashiromine has been reported by Nagao and coworkers.[12] The synthesis of **269** involves a highly diastereoselective alkylation of cyclic acyl imine **274** with a chiral tin (II) enolate **273**, prepared from **272**, to give **275**

(Scheme VIII). Reduction of **275**, followed by intramolecular annulation gave a mixture of **276** and (-)-tashiromine (**269**). This is a short and comparatively efficient synthesis and can be used to prepare various bicyclic alkaloids.

Scheme VIII. Asymmetric Synthesis of (-)-Tashiromine.



In order to demonstrate the use of our aza-annulation methodology in indolizidine and quinolizidine alkaloids synthesis, total synthesis of both (±)-lupinine and (±)-tashiromine were undertaken with the following goals:

1) To utilize the aza-annulation methodology as the key step to prepare six-membered lactams in high yield.

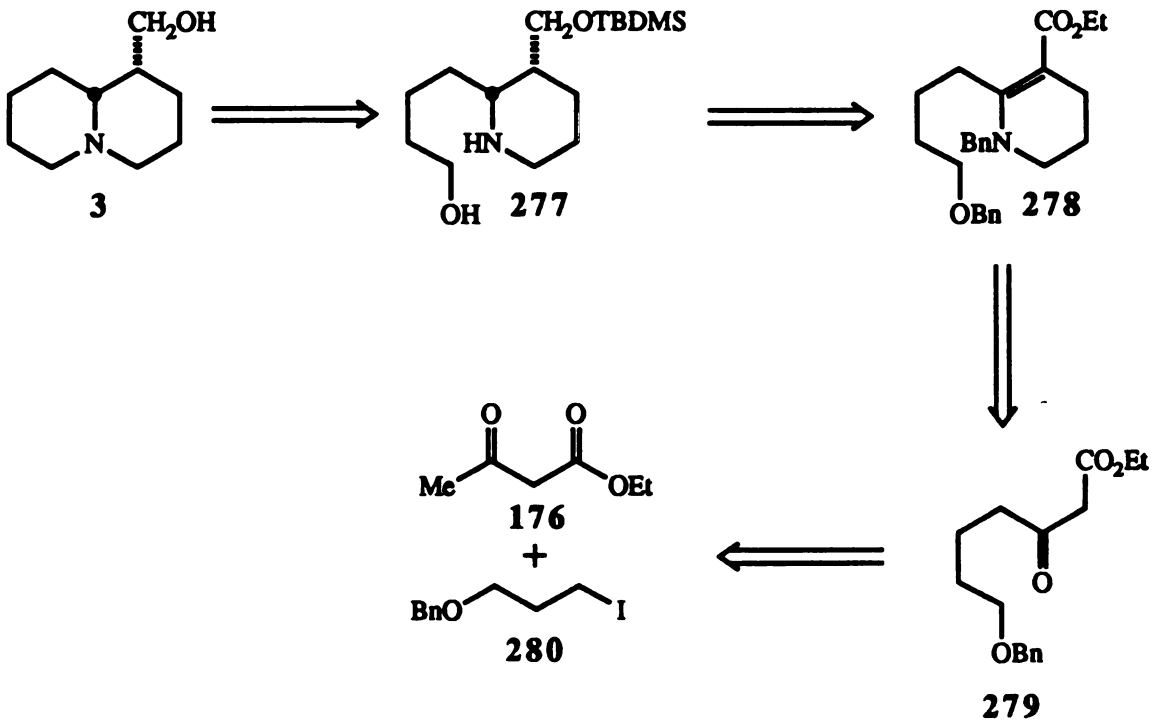
2) To utilize catalytic hydrogenation to generate cis stereocenters from the annulated product.

RESULTS AND DISCUSSION

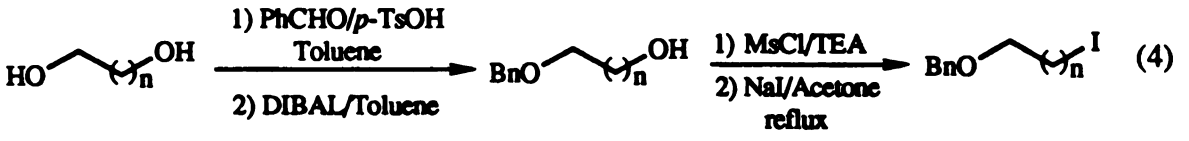
a) Total Synthesis of (±)-Lupinine (3)

The retrosynthetic analysis of (±)-lupinine is shown in Scheme IX. We hoped to prepare **3** from the amino alcohol **277** *via* formation of a C-N bond followed by desilylation. Compound **277** could be synthesized from **278** after reduction of the enamine double bond, reduction of amide and ester functionality, protection of primary alcohol and debenzylation. Lactam **278** could be readily obtained from aza-annulation of the suitably tethered β-keto ester **279**. β-Keto ester **279** should be readily prepared from ethyl acetoacetate (**176**) and iodide **280**. The retrosynthetic analysis of **3** shows the importance of aza-annualtion methodology in the preparation of six-membered lactams from acyclic substrates.

Scheme IX. Retrosynthetic Analysis of (±)-Lupinine (3).



The total synthesis of (±)-lupinine is shown in Scheme X. The required iodide was prepared according to commonly used procedures (eq 4). The monoptotected alcohol **284** was prepared from the corresponding diol **282** using Takano's procedure.[13] The alcohol **284** was converted into iodide **280** through the formation of a mesylate.[14]



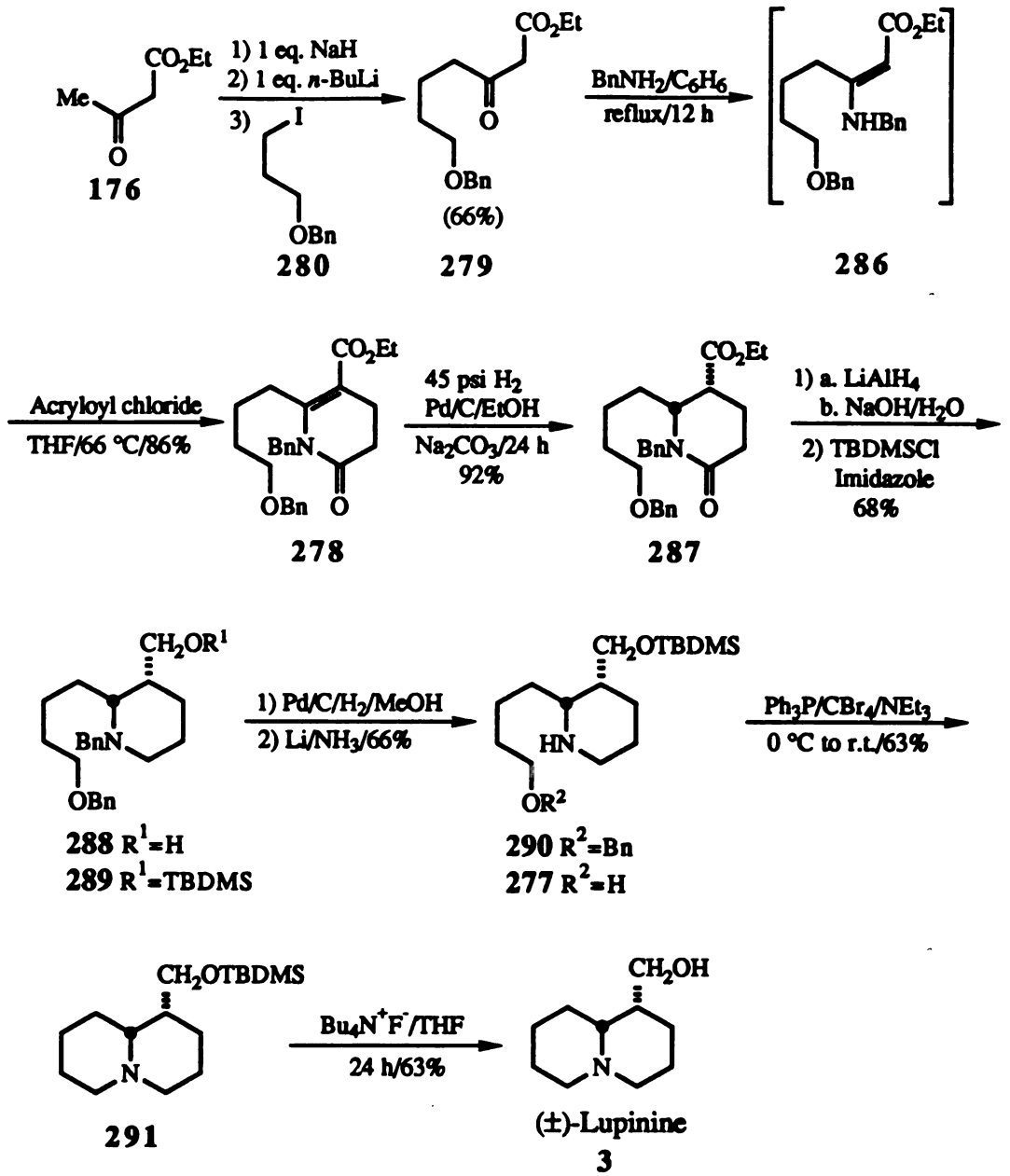
(4)

281 n=1 **283** n=1 **285** n=1

282 n=2 **284** n=2 **280** n=2

Alkylation of the dianion of ethyl acetoacetate (**176**) with iodide **280** at room temperature gave the β-keto ester **279** in 66% yield.[15] Condensation of β-keto ester **279** with $BnNH_2$ in benzene with a catalytic amount of *p*-TsOH, assisted by the azeotropic removal of H_2O, gave the enamino ester **286**. After removal of benzene, crude enamino ester **286** was taken up in THF and treated with acryloyl chloride to give the annulated product **278** in 86% yield in two-step procedure from β-keto ester **279**. Catalytic hydrogenation of **278** in the presence of Na_2CO_3 stereoselectively reduced the double bond to give lactam **287** (cis:trans, >95:<5) in 92% yield. The presence of Na_2CO_3 is crucial during the catalytic hydrogenation to avoid loss of *O*-benzyl protecting group. Both the amide and the ester of **287** were reduced with excess $LiAlH_4$ to give alcohol **288**, which was protected as TBDMS ether **289** in 76% yield for the two step sequence. Catalytic hydrogenation of **289** deprotected only the *N*-benzyl group to give **290**. Even after the addition of formic acid,[16] hydrogenation for several days, and increasing the amount Pd/C, the *O*-benzyl group was still present. The *O*-benzyl group was finally removed using liquid NH_3 and lithium metal at -33 °C to give the amino alcohol **277**.

Scheme X. The Total Synthesis of (±)-Lupinine (3).

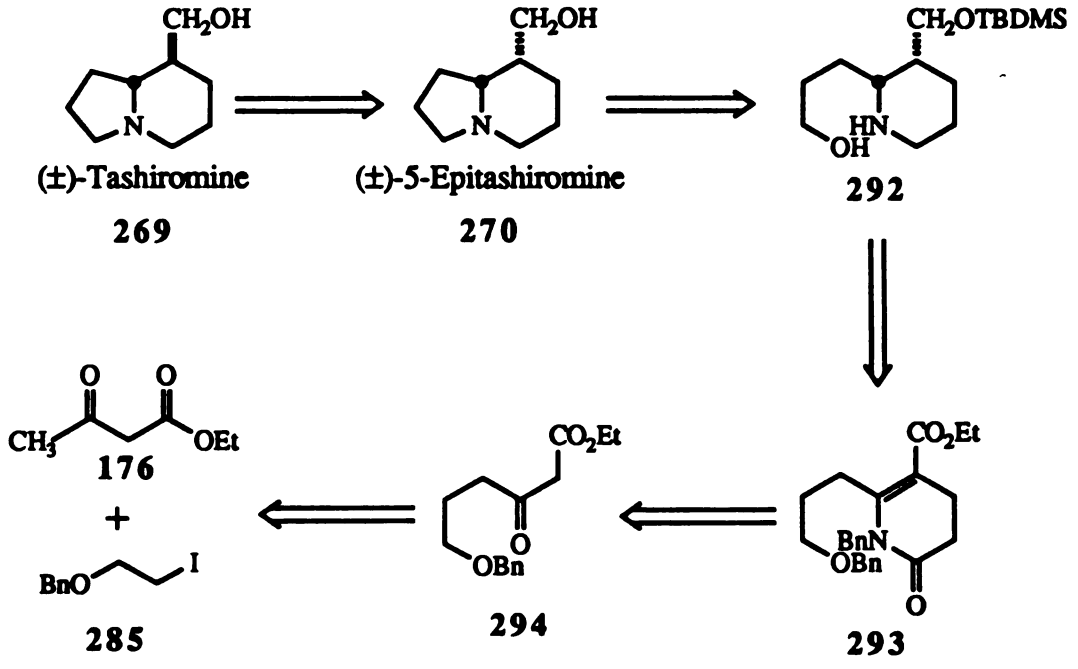


Using Kibayashis's coupling procedure, compound **277** was converted to **291** in 63% yield.[17] Deprotection of **291** with TBAF gave (±)-lupinine (**3**) in 63 % yield. The overall yield for this synthesis was 9.3%. The spectral data of **3** was consistent with published ^{1}H and ^{13}C spectral data.[18]

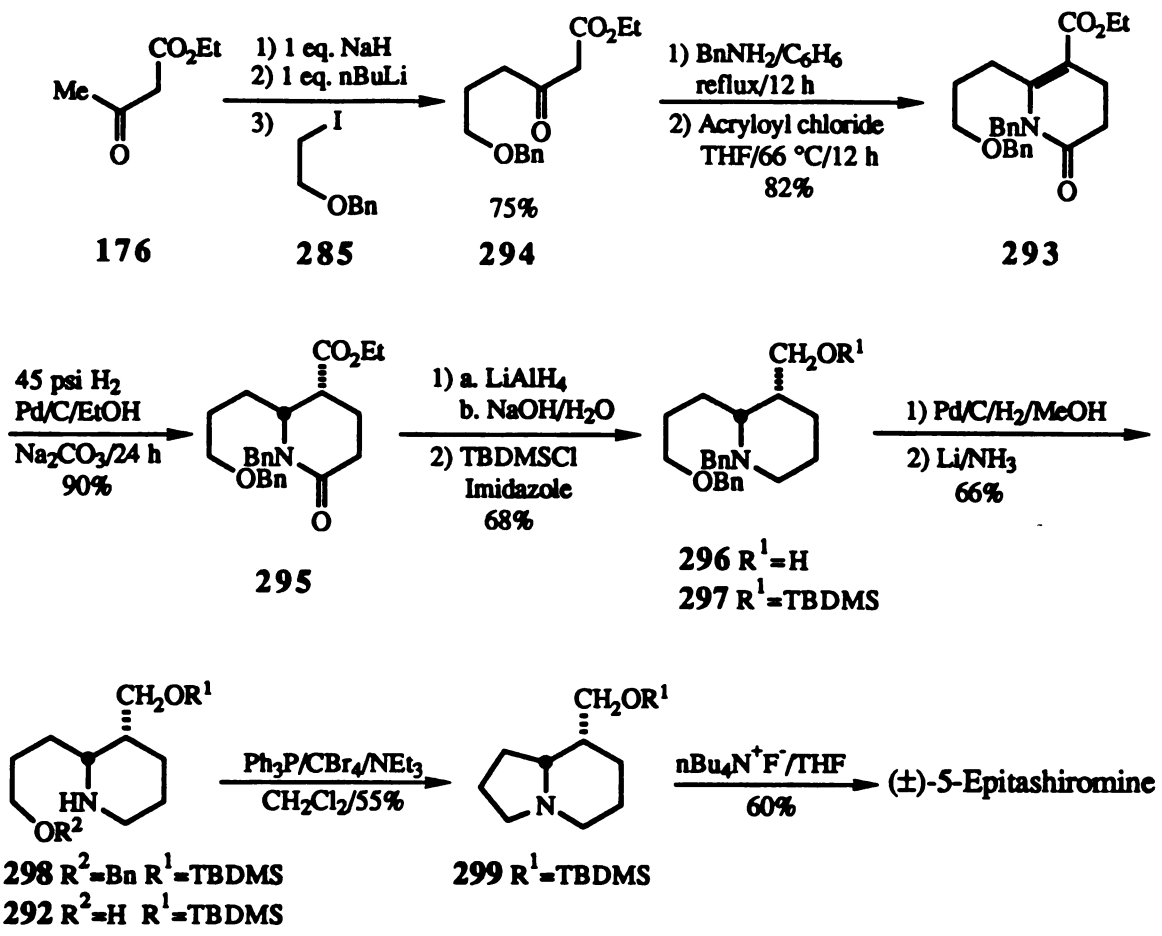
b) Total Synthesis of (±)-Tashiromine

The retrosynthetic analysis of (±)-tashiromine (**269**) is shown in Scheme XI. According to the retrosynthetic scheme, thermodynamically more stable **269** should be available from epitashiromine (**270**) after epimerization of the C-5 stereocenter. Epitashiromine (**270**) could be obtained from **292** *via* C-N bond formation and deprotection. Compound **292** could be synthesized from **293** after reduction of the enamine double bond, ester and amide groups, protection of the primary alcohol and debenzylation. Lactam **293** could be readily obtained after aza-annulation of suitably tethered β-keto ester **294**. The β-keto ester **294** should be readily prepared from ethyl acetoacetate (**176**) and iodide **285**.

Scheme XI. Retrosynthetic Analysis of (±)-Tashiromine (**269**).



Scheme XII. Total Synthesis of (±)-5-Epitashiromine

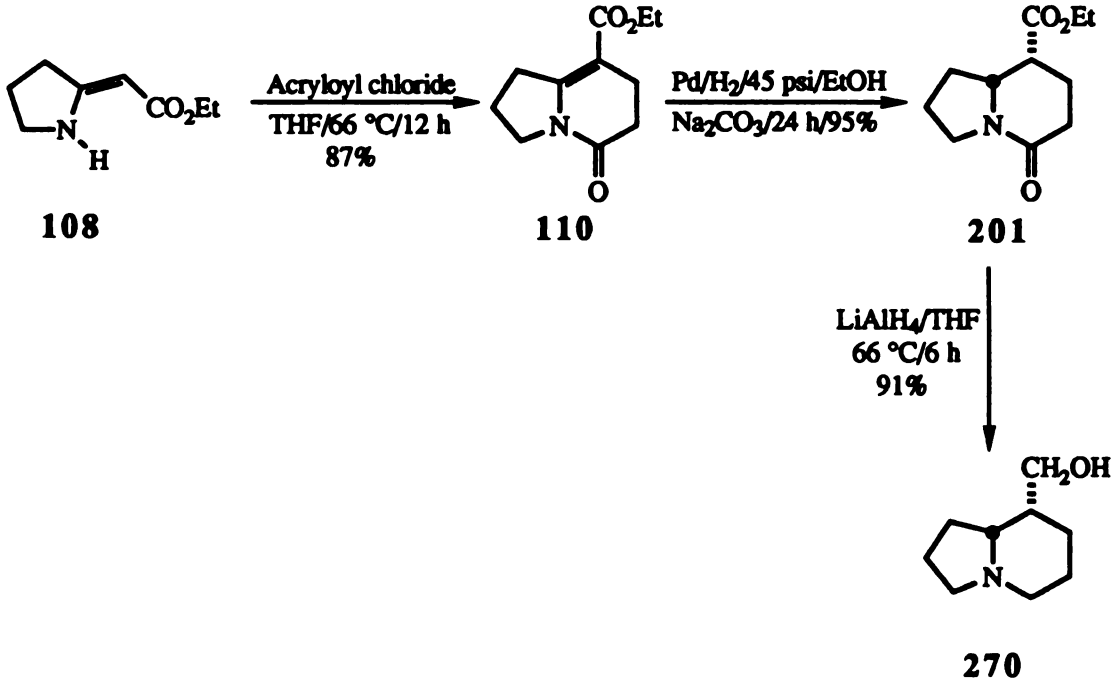


According to the retrosynthetic analysis, (±)-5-epitashiromine was initially prepared. The total synthesis (±)-5-epitashiromine is shown in Scheme XII. The iodide **285** was prepared from ethylene glycol as shown in eq 4. Alkylation of the dianion of **176** with iodide **285** gave β-keto ester **294** in 75% yield. Aza-annulation of the β-keto ester gave lactam **293** in 82% yield. Catalytic hydrogenation of **293** in the presence of Na_2CO_3 stereoselectively reduced the double bond to give **295** (cis:trans, >98:2) in 90% yield. Reduction of both amide and ester functional groups in **295** with excess $LiAlH_4$ gave the corresponding amino alcohol **296**, which was protected as the TBDMS ether **297** in 68% yield for the two-step sequence. Catalytic hydrogenation followed by Li/NH_3 reduction gave amino alcohol **292** in 66% yield. Compound **292** was converted to **299**

through the use of $PPh_3/CBr_4/NEt_3$. Final removal of the TBDMS group on **299** gave (±)-epitashiromine in 60% yield. The spectral data of epitashiromine was consistent with published ^1H and ^{13}C spectral data.[11]

The synthesis of (±)-epitashiromine was also approached through a simpler and more efficient route (Scheme XIII). Instead of the aza-annulation of an acyclic enamino ester, annulation was carried out on cyclic enamino ester **108** to give indolizidinone **110** in 87% yield. Catalytic hydrogenation **110** stereoselectively gave **201** (cis:trans, 95:5) in 95% yield.[19] Reduction of **201** with excess of $LiAlH_4$ gave (±)-epitashiromine in 91% yield. In this process, epitashiromine could be prepared on a large scale with a minimal number of steps. The overall for the synthesis of (±)-5-epitashiromine from **108** was 75%.

Scheme XIII. Alternate Synthesis of (±)-5-Epitashiromine.

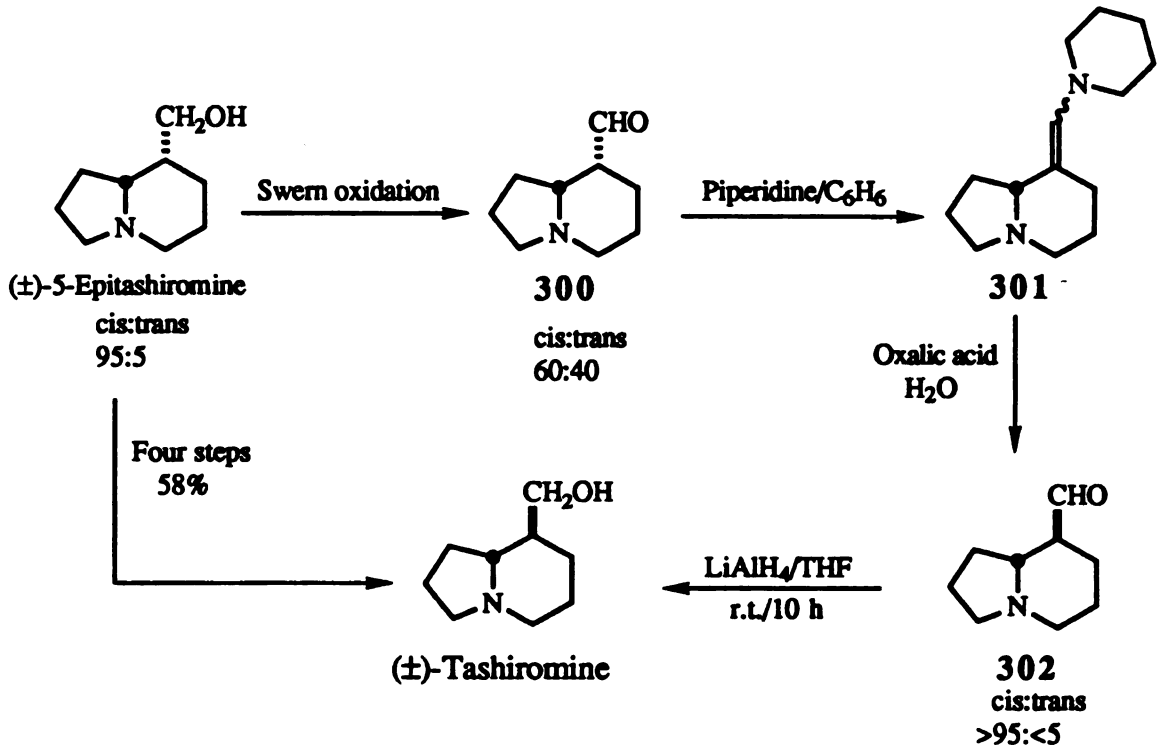


108 **110** **201** **270**

Once epitashiromine was prepared, attention was focussed on possible ways to convert (±)-5-epitashiromine (**270**) to (±)-tashiromine (**269**). In the case of **270**, the 5-

hydroxymethyl is in a less stable axial position, and in **269** the 5-hydroxymethyl is in a more stable equatorial position. The transformation of **270** to tashiromine (**269**) is shown in Scheme XIV.

Scheme XIV. Conversion of (±)-5-Epitashiromine to (±)-Tashiromine.



In order to epimerize the C-5 position in **270**, the axial hydroxymethyl group to equatorial hydroxymethyl, compound **270** was submitted to Swern oxidation conditions to give aldehyde **300**. Under the oxidation conditions, a considerable amount of the cis aldehyde was epimerized giving a 60:40 mixture of cis and trans isomers. Enamine **301** was prepared from the condensation of crude **300** and piperidine in benzene assisted by the azeotropic removal of H_2O. After removal of benzene, the crude enamine **301** was hydrolyzed using oxalic acid and H_2O to give trans aldehyde **302** as the major product along with a trace of cis aldehyde.[20] Reduction of the aldehyde with $LiAlH_4$ gave (±)-tashiromine in 58% overall yield from (±)-5-epitashiromine.

CONCLUSION

Total synthesis of (±)-lupinine, (±)-5-epitashiromine and (±)-tashiromine demonstrated the efficiency of the aza-annulation for the transformation of suitably tethered acyclic β-keto esters to bicyclic indolizidine or quinolizidine compounds. This is one of the few approaches to prepare (±)-lupinine from an acyclic precursor. The key transformations were the high yielding condensation and subsequent aza-annulation of the resulting β-enamino ester. The less stable cis stereocenters were selectively established by catalytic hydrogenation of the annulated lactams. Formation of the second ring by making C-N bond from an alcohol and an amine using $Ph_3P/TEA/CBr_4$ showed the effectiveness of this reaction. This methodology opens a new door for the preparation of a variety of alkaloids with different ring sizes.

EXPERIMENTAL SECTION

General Methods. All reactions were carried out under an atmosphere of either nitrogen or argon. Toluene and tetrahydrofuran (THF) were distilled from sodium/benzophenone immediately prior to use. Triethylamine and dichloromethane were heated at reflux over calcium hydride for a minimum of 12 h, and then distilled immediately prior to use. Benzylamine and acryloyl chloride were obtained from Fluka and used without further purification. TBDMSCl was obtained from Huls Co. Solutions of DIBALH (1.0 M in hexane), and DIBALH (1.0 M in toluene) were prepared from neat DIBALH obtained from Aldrich Chemical Co. *n*-Butyllithium (2.5 M in hexane) and $LiAlH_4$ (1 M in THF) were purchased from Aldrich Chemical Co. Methanesulfonyl chloride was purchased from Aldrich Chemical Co., and distilled before use.

NMR Spectra were obtained on Varian Gemini 300 instrument with $CDCl_3$ as the solvent. Data are reported as follows: chemical shifts relative to residual $CHCl_3$ (7.24 ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, sept = septet, b = broad), integration, and coupling. Infrared spectra were recorded on a Nicolet 42 FT-IR instrument.

General Procedure for the Preparation of Monoprotected Alcohols (283 and 284): A mixture of the desired diol (150 mmol), benzaldehyde (17.51 g, 165.0 mmol), and *p*-TsOH (0.144 g, 0.8 mmol) was taken up in 90 mL of toluene, and heated at reflux for 12 h using a modified Dean-Stark trap apparatus to azeotropically remove H_2O. The reaction mixture was then cooled to 0 °C, and an additional 135 mL of toluene was added. To the cooled reaction mixture was slowly added 3 M solution of DIBALH (62.5 mL, 187.5 mmol) in toluene and stirred at room temperature for 24 h. The reaction was cooled to 0 °C and quenched with dropwise addition of 90 mL of MeOH followed by 90 mL of 15% NaOH solution, and the solution was stirred for 1.5 h at room temperature. The aqueous layer was extracted with 5 x 200 mL of Et_2O, dried (Na_2SO_4), filtered,

concentrated, and distilled under vacuum to give the corresponding monoprotected alcohol.

General Procedure for the Conversion of Alcohols to Iodides (285 and 280): To a cooled (0 °C) solution of alcohol (124.20 mmol) and TEA (52.40 g, 496.7 mmol) in 1250 mL of Et_2O was added methanesulfonyl chloride (42.70 g, 372.6 mmol) and stirred at 0 °C for 2 h and then at room temperature for 10 h. The reaction mixture was then washed with 500 mL of saturated aqueous NH_4Cl solution, and the aqueous layer was extracted with 3 x 500 mL of Et_2O. The combined organic layers were washed with 1000 mL of H_2O, dried ($MgSO_4$), filtered, and the solvent was removed to give crude mesylate which was used without further purification.

The crude mesylate and sodium iodide (83.8 g, 559.00 mmol) were taken up in 620 mL of acetone and heated at reflux for 24 h. The reaction was cooled to ambient temperature, and 500 mL of Et_2O and 500 mL of H_2O were added. The aqueous layer was extracted with 2 x 500 mL of Et_2O, and the combined organic layer was washed with 500 mL of saturated $Na_2S_2O_3$ and 500 mL of saturated NaCl solution. The organic layer was dried (Na_2SO_4), filtered, concentrated and distilled under vacuum to give the corresponding iodides.

General Procedure for the Alkylation of Ethyl Acetoacetate (176): To a cooled (~ -20 °C) suspension of NaH (0.67 g, 28.0 mmol) in 28 mL of THF was dropwise added a solution of ethyl acetoacetate (3.65 g, 28.0 mmol) in 6 mL of THF. The reaction mixture was stirred at this temperature until all of the sodium hydride was consumed (~15 min). To this clear solution was slowly added 2.5 M *n*-BuLi solution (11.20 mL, 28.0 mmol) in hexane to give an orange solution which was stirred at 0 °C for 15 min. A solution of the iodide (23.34 mmol) in 6 mL of THF was added dropwise, and the flask was rinsed with an additional 1 mL of THF. The solution was stirred at 0 °C for 1.5 h, and the temperature was allowed to warm to room temperature and stirred for an additional 12 h. The reaction mixture was quenched with 30 mL of saturated aqueous NH_4Cl solution and

the aqueous layer was extracted with 4 x 50 mL of Et_2O. The combined organic layers were dried (Na_2SO_4), filtered and concentrated to give a crude residue. The crude residue was purified by flash column chromatography (eluent: 80:20 hexane-Et_2O or 85:15 petroleum ether-Et_2O).

279: ^1H NMR (300 MHz. $CDCl_3$) δ 1.28 (t, J = 7.1 Hz, 3 H), 1.56-1.77 (m, 4 H), 2.57 (t, J = 7.1 Hz, 2 H), 3.42 (s, 2 H), 3.48 (t, J = 6.1 Hz, 2 H), 4.19 (q, J = 7.1 Hz, 2 H), 4.49 (s, 2 H), 7.26-7.35 (m, 5 H); ^{13}C NMR (75.5 MHz. $CDCl_3$) δ 14.1, 20.3, 29.0, 42.6, 49.2, 61.3, 69.9, 72.9, 127.5, 127.6, 128.4, 138.5, 167.3, 202.7; IR (neat) 3065, 3032, 2982, 2940, 2863, 1746, 1717, 1647, 1455, 1412, 1368, 1316, 1028 cm^{-1}; HRMS calcd for $C_{16}H_{22}NO_4$ m/z 278.1517, found m/z 278.1512.

294: ^1H NMR (300 MHz. $CDCl_3$) δ 1.27 (t, J = 7.1 Hz, 3 H), 1.92 (quint, J = 6.1 Hz, 2 H), 2.67 (t, J = 7.1 Hz, 2 H), 3.44 (s, 2 H), 3.50 (t, J = 6.1 Hz, 2 H), 4.19 (q, J = 7.1 Hz, 2 H), 4.48 (s, 2 H), 7.27-7.39 (m, 5 H); ^{13}C NMR (75.5 MHz. $CDCl_3$) δ 13.6, 23.2, 39.3, 48.9, 60.9, 68.6, 72.4, 127.1, 127.2, 127.9, 137.9, 166.8, 202.2; IR (neat) 3065, 3032, 2982, 2936, 2865, 1743, 1715, 1647, 1455, 1368, 1314 cm^{-1}.

General Procedure for Aza-Annulation: A mixture of benzylamine (1.90 g, 17.7 mmol), the corresponding β-keto ester (16.07 mmol) and *p*-TsOH (0.152 g, 0.80 mmol) in 107 mL of benzene was heated at reflux for 12 h. The generated H_2O was azeotropically removed from the reaction mixture using modified Dean-Stark trap apparatus filled with 4-Å molecular sieves. The reaction mixture was then cooled to room temperature and concentrated to give the crude enamino ester which was used for annulation without further purification. Acryloyl chloride (1.89 g, 20.9 mmol) was added to a solution of the crude enamino ester in 107 mL of THF, and the reaction mixture was heated at reflux for 12 h. After the reaction was complete, the solution was washed with 40 mL of saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with 4 x 30 mL of CH_2Cl_2, and the combined organic layers were dried (Na_2SO_4), filtered and concentrated to give the crude residue. The crude residue was purified by flash column

chromatography (eluent: 65:35 hexane-Et_2O or 60:40 petroleum ether-Et_2O). The solvents were evaporated to give the corresponding lactam.

278: ^1H NMR (300 MHz. $CDCl_3$) δ 1.29 (t, *J* = 7.1 Hz, 3 H), 1.50-1.70 (m, 4 H), 2.54-2.70 (m, 4 H), 2.77 (bt, *J* = 7.5 Hz, 2 H), 3.46 (t, *J* =6.2 Hz, 2 H), 4.18 (q, *J* = 7.1 Hz, 2 H), 4.50 (s, 2 H), 5.10 (bs, 2 H), 7.10 (bd, *J* = 7.1 Hz, 2 H), 7.20-7.38 (m, 8 H); ^{13}C NMR (75.5 MHz. $CDCl_3$) δ 13.9, 20.8, 25.4, 28.1, 28.9, 31.1, 44.0, 59.9, 69.3, 72.5, 109.4, 125.7, 126.7, 127.1, 127.2, 127.9, 128.3, 137.3, 138.0, 152.0, 166.7, 171.2; IR (neat) 3088, 3063, 3031, 2978, 2938, 2861, 1688, 1617, 1497, 1455, 1372, 1271, 1119 cm^{-1}; HRMS calcd for $C_{26}H_{31}NO_4$ m/z 421.2252, found m/z 421.2262.

293: ^1H NMR (300 MHz. $CDCl_3$) δ 1.28 (t, *J* = 7.1 Hz, 3 H), 1.81 (m, 2 H), 2.57 (m, 2 H), 2.66 (m, 2 H), 2.86 (m, 2 H), 3.55 (t, *J* = 5.9 Hz, 2 H), 4.16 (q, *J* = 7.1 Hz, 2 H), 4.49 (s, 2 H), 5.06 (s, 2 H), 7.07 (bd, *J* = 8.1 Hz, 2 H), 7.18-7.38 (m, 8 H); ^{13}C NMR (75.5 MHz. $CDCl_3$) δ 13.8, 20.8, 25.6, 28.8, 31.1, 43.7, 59.9, 69.1, 72.6, 109.3, 125.8, 126.6, 127.2, 127.3, 127.9, 128.2, 137.4, 138.0, 151.9, 166.8, 171.2; IR (neat) 3088, 3063, 3032, 2978, 2855, 1688, 1617, 1497, 1455, 1372, 1271 cm^{-1}.

General procedure for the Hydrogenation of Lactams: A solution of the lactam (6.2 g, 14.72 mmol), and Na_2CO_3 (5.42 g, 51.51 mmol) in 196 mL of EtOH was hydrogenated at 45 psi over 10% Pd/C (1.5 g) for 24 h. The catalyst and Na_2CO_3 were removed by filtration, and the residue was washed with CH_2Cl_2. The combined filtrate and washings were concentrated to give a crude residue, which was redissolved in CH_2Cl_2 and filtered. Concentration of the filtrate and washings gave the corresponding reduced lactam as a viscous liquid.

287: ^1H NMR (300 MHz. $CDCl_3$) δ 1.20 (t, *J* = 7.2 Hz, 3 H), 1.30-1.71 (m, 6 H), 2.00-2.24 (m, 2 H), 2.46-2.68 (m, 2H), 2.75 (dt, *J* = 12.6, 4.6 Hz, 1 H), 3.43 (t, *J* = 6.2 Hz, 2 H), 3.71 (q, *J* = 5.2 Hz, 1 H), 3.90 (d, *J* = 15.1 Hz, 1 H), 3.98-4.18 (m, 2 H), 4.49 (s, 2 H), 5.41 (d, *J* = 15.1 Hz, 1 H), 7.22-7.40 (m, 10 H); ^{13}C NMR (75.5 MHz. $CDCl_3$) δ 13.6, 18.2, 24.0, 29.4, 29.5, 31.4, 43.6, 49.3, 56.4, 60.5, 69.3, 72.5, 127.0, 127.1, 127.2,

127.4 127.9, 128.2, 136.8, 138.0, 169.1, 171.2; IR (neat) 3088, 3063, 3030, 2940, 2865, 1732, 1646, 1497, 1452, 1234, 1163 cm^{-1}; HRMS calcd for $C_{26}H_{33}NO_4$ m/z 423.2409, found m/z 423.2446.

295: ^1H NMR (300 MHz. $CDCl_3$) δ 1.20 (t, *J* = 7.1 Hz, 3 H), 1.55-1.74 (m, 4 H), 2.00-2.24 (m, 2 H), 2.53 (dd, *J* = 18.4, 8.8 Hz, 1 H), 2.64 (ddd, *J* = 18.4, 8.3, 3.3 Hz, 1 H), 2.76 (dt, *J* = 12.4, 4.6 Hz, 1 H), 3.38-3.43 (m, 2 H), 3.75 (bq, *J* = 4.5 Hz, 1 H), 3.91 (d, *J* = 15.1 Hz, 1 H), 4.04-4.15 (m, 2 H), 4.48 (s, 2 H), 5.40 (d, *J* = 15.1 Hz, 1 H), 7.20-7.39 (m, 10 H); ^{13}C NMR (75.5 MHz. $CDCl_3$) δ 13.6, 18.3, 27.3, 28.1, 29.4, 43.6, 49.2, 56.3, 60.5, 69.4, 72.5, 126.9, 127.2, 127.4, 127.9, 128.2, 136.8, 137.9, 169.1, 171.1; IR (neat) 3031, 2955, 1732, 1644, 1468, 1453, 1237 cm^{-1}.

General Procedure for the Preparation of Silyl Ethers: To a solution of the lactam (14.81 mmol) in 59 mL of THF at 0 °C was slowly added 1.0 M solution of $LiAlH_4$ solution (59.25 mL, 59.25 mmol) in THF, and the reaction mixture was heated at reflux for 12 h. The solution was cooled to 0 °C and quenched by the sequential addition of 2.3 mL of H_2O, 2.3 mL of 15% w/v aqueous NaOH, and 6.9 mL of H_2O. After stirring for 1 h at room temperature, the aluminum salts were removed by filtration, and the combined filtrate and washings were dried (Na_2SO_4), filtered and concentrated to give the crude alcohol, which was used without purification.

A mixture of the crude alcohol (14.81 mmol), imidazole (2.52 g, 37.03 mmol) and *tert*-butyldimethylsilyl chloride (2.68 g, 17.77 mmol) in 23 mL of DMF was stirred at room temperature for 12 h. The reaction mixture was washed with 25 mL of saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with 4 x 30 mL of Et_2O, and the organic fractions were washed with 50 mL of H_2O and dried over $MgSO_4$. Following concentration of the solution, the residue was purified by flash column chromatography (eluent: 40:60 Et_2O-hexane or 200:800:13 Et_2O-petroleum ether-NH_4OH). The solvents were evaporated to give the corresponding silyl ether.

289: ^{1}H NMR (300 MHz. $CDCl_3$) δ 0.03 (s, 3 H), 0.04 (s, 3 H), 0.87 (s, 9 H), 1.01-1.42 (m, 4 H), 1.43-1.69 (m, 6 H), 2.09 (m, 1 H), 2.43 (dt, *J* = 13.2, 3.3 Hz, 1 H), 2.62 (td, *J* = 12.6, 3.3 Hz, 1 H), 2.74 (m, 1 H), 3.40-3.50 (m, 2 H), 3.73 (s, 2 H), 4.51 (s, 2 H), 7.20-7.37 (m, 10 H); ^{13}C NMR (75.5 MHz. $CDCl_3$) δ -5.8, -5.7, 17.8, 21.7, 22.9, 23.6, 24.1, 25.5, 29.7, 38.6, 45.5, 57.8, 58.6, 64.6, 70.2, 72.5, 126.1, 127.0, 127.2, 127.6, 127.9, 128.2, 138.3, 140.3; IR (neat) 3087, 3063, 3029, 2932, 2857, 2795, 1495, 1472, 1360, 1256, 1103 cm^{-1}; HRMS calcd for $C_{30}H_{47}NO_2Si$ m/z 481.3376, found m/z 481.3351.

297: ^{1}H NMR (300 MHz. $CDCl_3$) δ -0.1 (s, 3 H), 0.1 (s, 3 H), 0.84 (s, 9 H), 1.10-1.42 (m, 2 H), 1.46-1.80 (m, 6 H), 2.07 (m, 1 H), 2.36-2.50 (m, 1 H), 2.56-2.78 (m, 2 H), 3.41 (m, 4 H), 3.72 (s, 2 H), 4.46 (s, 2 H), 7.22-7.34 (m, 10 H); ^{13}C NMR (75.5 MHz. $CDCl_3$) δ -5.8, -5.7, 17.8, 20.2, 21.4, 22.8, 25.5, 27.4, 38.3, 45.3, 57.7, 58.1, 64.7, 70.3, 72.3, 126.2, 127.0, 127.2, 127.6, 127.9, 128.3, 138.4, 140.2; IR (neat) 3087, 3063, 3029, 2928, 2857, 1495, 1472, 1362, 1256, 1101 cm^{-1}.

General Procedure for the Preparation of Amino Alcohols: A solution of silyl ether (5.874 g, 11.81 mmol) in 120 mL of MeOH was hydrogenated at 45 psi over 10% Pd-C (2.3 g), for 24 h. The catalyst was removed by filtration, and the combined filtrate and washings were concentrated to give the crude deprotected amine, which was used for Li/NH_3 reduction with out further purification.

The crude amine in 35 mL of THF was added to liquid ammonia (300-350 mL) at -78 °C. Small pieces of lithium rod were added slowly to generate a dark blue color. The dry ice bath was removed, and the reaction mixture was stirred for 2 h at -33 °C. The reaction mixture was then cooled to -78 °C and quenched by adding solid NH_4Cl. Ammonia was evaporated overnight to give a white solid. The white solid was dissolved in MeOH and transferred into a round bottom flask. The solvent was removed to give a residue, and the residue was re dissolved in CH_2Cl_2 and filtered to remove the insoluble inorganic salts. The filtrate was evaporated to give the crude amino alcohol which was

purified by flash column chromatography (eluent: 15:85 MeOH-CH_2Cl_2 or 10:90 MeOH-CH_2Cl_2). The solvent was evaporated to give amino alcohol.

277: ^1H NMR (300 MHz. $CDCl_3$) δ 0.07 (s, 3 H), 0.08 (s, 3 H), 0.89 (s, 9 H), 1.48-1.81 (m, 6 H), 1.82-1.98 (m, 2 H), 2.20-2.50 (m, 3 H), 3.10-3.20 (m, 2 H), 3.48 (m, 1 H), 3.59-3.80 (m, 4 H), 8.44 (bs, 1 H), 9.64 (bs, 1 H); ^{13}C NMR (75.5 MHz. $CDCl_3$) δ -6.0, -5.9, 17.6, 19.6, 21.8, 22.0, 25.4, 25.5, 31.2, 37.2, 41.0, 55.6, 61.0, 61.7; IR (neat) 3357, 2934, 2858, 2812, 1584, 1472, 1258, 1094 cm^{-1}; HRMS calcd for $C_{16}H_{37}NO_2Si$ m/z 303.2593, found m/z 303.2523.

292: ^1H NMR (300 MHz. $CDCl_3$) δ 0.05 (s, 3 H), 0.07 (s, 3 H), 0.87 (s, 9 H), 1.51-1.62 (m, 2 H), 1.68-2.0 (m, 5 H), 2.26-2.38 (m, 1 H), 3.06-3.22 (m, 2 H), 3.53-3.83 (m, 6 H), 8.73 (bs, 1 H), 9.60 (bs, 1 H); ^{13}C NMR (75.5 MHz. $CDCl_3$) δ -6.0, -5.9, 17.6, 19.8, 21.7, 23.2, 25.4, 28.4, 37.5, 40.6, 55.3, 61.1, 61.9; IR (KBr) 3449, 3248, 2955, 2856, 2804, 1584, 1471, 1258, 1092 cm^{-1}.

General Procedure for the Preparation of Bicyclic Compounds (291 and 299): To a solution of amino alcohol (0.614 mmol), and CBr_4 (0.255 g, 0.768 mmol) in 2.5 mL of CH_2Cl_2 at 0 °C was added Ph_3P (0.242 g, 0.921 mmol), and the reaction mixture was stirred at this temperature for 1 h. TEA (1.043 g, 9.824 mmol) was then added at 0 °C and stirred for 30 min and the reaction was allowed to warm to room temperature and stirred for an additional 30 min. The solvent was then removed to give a crude solid, which was washed with 5 x 25 mL of petroleum ether. Following concentration of the petroleum ether washings, the residue was purified by flash column chromatography (eluent: 100:1.5 Et_2O-NH_4OH or 20:80:1.3 petroleum ether-Et_2O-NH_4OH). The solvents were evaporated to give the corresponding bicyclic compounds.

291: ^1H NMR (300 MHz. $CDCl_3$) δ 0.05 (s, 6 H), 0.89 (s, 9 H), 1.15-1.35 (m, 2 H), 1.36-1.59 (m, 4 H), 1.65-1.81 (m, 3 H), 1.87-2.04 (m, 3 H), 2.76-2.86 (m, 2 H), 3.71 (t, J = 9.8 Hz, 1 H), 3.82 (dd, J = 9.8, 5.2 Hz, 1 H); ^{13}C NMR (75.5 MHz. $CDCl_3$) δ -5.7,

17.8, 20.6, 24.8, 25.1, 25.5, 25.6, 29.2, 40.7, 56.6, 57.2, 60.5, 64.3; IR (neat) 2932, 2857, 2803, 2759, 1472, 1464, 1445, 1256 cm^{-1}.

299: ^1H NMR (300 MHz. $CDCl_3$) δ 0.04 (s, 6 H), 0.88 (s, 9 H), 1.16-2.26 (m, 12 H), 2.93-3.03 (m, 2 H), 3.64 (dd *J* = 10.0, 8.2 Hz, 1 H), 3.78 (dd, *J* = 10.0, 5.4 Hz, 1 H); ^{13}C NMR (75.5 MHz. $CDCl_3$) δ -5.8, 17.8, 20.2, 21.1, 24.8, 25.2, 25.5, 37.9, 52.9, 54.5, 60.8, 65.2.

General Procedure for the Deprotection of Silyl Ethers (291 and 299): To a solution of silyl ether (0.335 g, 1.112 mmol) in 4 mL of THF was added 2.2 ml of 1 M solution of TBAF (2.2 mmol) in THF, and stirred at room temperature for 24 h. The reaction mixture was then washed with 5 mL of 10% aqueous NaOH. The aqueous layer was extracted with 4 x 15 mL of EtOAc,. and the combined organic layers were dried over (Na_2SO_4), filtered, and concentrated to give a crude residue. The crude residue was purified by flash column chromatography (eluent: 90:10:1.5 Et_2O-MeOH-NH_4OH or 80:20:1.5 Et_2O-MeOH-NH_4OH) to give the corresponding alcohol.

3: ^1H NMR (300 MHz. $CDCl_3$) δ 1.25 (m, 1 H), 1.46-1.64 (m, 6 H), 1.66-1.94 (m, 4 H), 1.95-2.22 (m, 3 H), 2.78-2.85 (m, 2 H), 3.67 (d, *J* = 10.9 Hz, 1 H), 4.11 (ddd, *J* = 10.9, 3.7, 1.7 Hz, 1 H); ^{13}C NMR (75.5 MHz. $CDCl_3$) δ 22.8, 24.6, 25.5, 29.6, 31.1, 38.3, 57.1, 65.0, 65.6; IR (neat) 3370, 2934, 2859, 2807, 2764, 1445, 1352 cm^{-1}.

270: ^1H NMR (300 MHz. $CDCl_3$) δ 1.45-1.63 (m, 2 H), 1.64-1.91 (m, 6 H), 1.92-2.13 (m, 3 H), 2.21-2.32 (m, 1 H), 2.94-3.03 (m, 1 H), 3.05-3.13 (m, 1 H), 3. 71 (dd, *J* = 10.8, 1.2 Hz, 1 H), 4.14 (ddd, *J* = 10.8, 4.2, 1.2 Hz, 1 H); ^{13}C NMR (75.5 MHz. $CDCl_3$) δ 20.7, 22.9, 25.6, 29.6, 35.7, 53.4, 54.4, 64.5, 66.5; IR (neat) 3370, 2934, 2787, 2730, 1447, 1379, 1327 cm^{-1}.

Preparation of (±)-5-Epitashiromine (270) from Lactam (201): To a solution of lactam **201** (1.11 g, 5.23 mmol) in 26 mL of THF at 0 °C was slowly added 1 M solution of $LiAlH_4$ (13.10 mL, 13.10 mmol) and the solution was heated at reflux for 6 h. The reaction mixture was cooled to 0 °C, and quenched by the sequential addition of 0.5 mL

of H_2O, 0.5 mL of 15% w/v aqueous NaOH, and 1.5 mL of H_2O. After stirring for 1 h at room temperature, the aluminum salts were removed by filtration, and the combined filtrate and washings were dried (Na_2SO_4), filtered and concentrated to give (±)-5-epitashiromine (**292**) in 91% yield.

Conversion of (±)-5-Epitashiromine (292) to Tashiromine (269): To a cooled (-65 to -70 °C) solution of oxalyl chloride (0.9105 g, 7.173 mmol) in 13 mL of CH_2Cl_2 was slowly added a solution of DMSO (1.821 g, 14.35 mmol) in 3 mL of CH_2Cl_2. The reaction mixture was stirred at this temperature for 10 min. A solution of the alcohol in 12 mL of CH_2Cl_2 was added slowly, and the reaction was stirred for 45 min at -50 to -60 °C. TEA (2.90 g, 28.69 mmol) was added to the reaction mixture and stirred at 50 to -60 °C for 20 min, and the temperature was allowed to warm to room temperature, and stirred at this temperature for an additional 1 h. At this point, 30 mL of H_2O was added and stirred for 1 h. The aqueous layer was extracted with 4 x 25 mL of CH_2Cl_2 and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated to give the crude aldehyde. A mixture of crude aldehyde (4.78 mmol), piperidine (0.45 g, 5.26 mmol) and *p*-TsOH (0.005 g, 0.024 mmol) in 32 mL of benzene was heated at reflux for 10 h using a modified Dean-Stark trap filled with 4-A molecular sieves to azeotropically remove H_2O. The solution was then cooled to room temperature and concentrated to give the crude enamine **301**. To a solution of **301** in 8 mL of CH_2Cl_2 was added a solution of oxalic acid dihydrate (0.63 g) in 5 mL of H_2O. The reaction mixture was stirred at room temperature for 4 h and heated at reflux for 1 h. The reaction was cooled to room temperature, and 10 mL of H_2O, 15 mL of CH_2Cl_2 and 10 mL of 15% aq NaOH were added and stirred for 30 min. The aqueous layer was extracted with 4 x 20 mL of CH_2Cl_2, and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated to give the crude aldehyde. To a solution of the crude aldehyde (4.78 mmol) in 19 mL of THF at 0 °C, was slowly added 1 M solution of $LiAlH_4$ (7.20 mL, 7.20 mmol) in THF and the solution was stirred at room temperature for 6 h. The solution

was cooled to 0 °C and quenched by the sequential addition of 0.27 mL of H_2O, 0.27 mL of 15% w/v aqueous NaOH, and 0.82 mL of H_2O. After stirring for 1 h at room temperature, the aluminum salts were removed by filtration, and the combined filtrate and washings were dried (Na_2SO_4), filtered, and concentrated to give a crude residue, which was purified by flash column chromatography (eluent: 85:15:2 Et_2O-MeOH-NH_4OH). The solvents were evaporated to give (±)-tashiromine (**269**) in 58% yield from (±)-5-epitashiromine (**292**).

269: ^1H NMR (300 MHz. $CDCl_3$) δ 1.01 (qd, J = 12.7, 4.7 Hz, 1 H), 1.36-1.97 (m, 10 H), 2.03 (q, J = 9.0 Hz, 1 H), 2.98-3.10 (m, 2 H), 3.44 (dd, J = 10.8, 6.3 Hz, 1 H), 3.67 (dd, J = 10.8, 4.6 Hz, 1 H); ^{13}C NMR (75.5 MHz. $CDCl_3$) δ 20.2, 24.6, 27.2, 28.5, 44.1, 52.2, 53.7, 64.6, 66.0; IR (neat) 3374, 2932, 2793, 1462, 1445, 1385, 1331, 1279 cm^{-1}.

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