THE AROMATIC 3-AZA-COPE REARRANGEMENT AND AZA-ANNULATION REACTION AS SYNTHETIC TOOLS FOR THE CONSTRUCTION OF NITROGEN HETEROCYCLES

By

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ABSTRACT

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Conditions for the aromatic 3-aza-Cope rearrangement were developed for which the reaction occurred at a reasonable rate, at practical temperatures and with adequate reproducibility and regiospecifity. The catalyst systems BF_3-Et_2O in toluene, $ZnCl_2$ in xylenes, and $AlCl_3$ in xylenes efficiently accelerated the 3-aza-Cope rearrangement of *N*-allylaniline substrates accessing a convenient method for C-C bond formation between *N*-alkyl substituents and an *o*-aromatic ring carbon. This versatile rearrangement yielded products which could potentially act as precursors to a variety of indole alkaloids substituted in the indole 6-membered ring portion.

Stereochemically complex hydroxylated piperidine alkaloids were efficiently accessed through use of the aza-annulation. The C-4 and C-5 substituent pattern was determined through initial substrate preparation. After aza-annulation, the stereochemistry at these positions could then be controlled through choice of reduction conditions. Trans stereochemistry at C-4 relative to C-5 was efficiently incorporated to an extent of >98:2 through use of the Baeyer-Villiger oxidation. Stereospecific cis hydroxylation at the C-2 and C-3 positions was then accessed through selenation followed by oxidation with OsO_4. D-mannonolactam and deoxymannojirimycin were prepared from propargyl alcohol using this methodology.

The aza-annulation was then shown to constitute a quick and efficient method of building up highly functionalized 6-membered nitrogen heterocycles for potential use in the preparation of peptide mimics. DDQ oxidation of these functionalized heterocycles provided the corresponding functionalized pyridone ring systems. This methodology thus may provide a rapid and efficient route into the formation of peptide mimics with functionalization possible at the C-2, C-4, and C-5 positions.

To my parents Joan and Guenter

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF SCHEMES

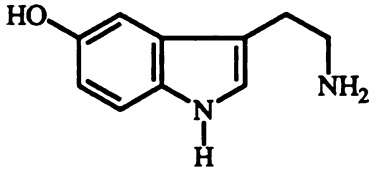
LIST OF ABBREVIATIONS

Ac	Acetyl
Bn	Benzyl
BuLi (*n*-BuLi)	*n*-Butyllithium
C_6H_6	Benzene
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DMSO	Dimethylsulfoxide
Et	Ethyl
G. C.	Gas Chromatography
hr (s)	Hour (s)
LHMDS	Lithium Bis(trimethylsilyl)amide
LDA	Lithium Diisopropylamide
M	Molar
m	Meta
Me	Methyl
m-CPBA (MCPBA)	*m*-Chloroperoxybenzoic Acid
ML_n	Generalized Lewis Acid
NBS	*N*-Bromosuccinimide
NOE	Nuclear Overhauser Effect
o	Ortho
P	Generalized Protecting Group
p	Para
PCC	Pyridinium Chlorochromate
Ph	Phenyl
RT	Room Temperate
THF	Tetrahydrofuran
TMS	Trimethylsilyl
TLC	Thin Layer Chromatography
Ts (Tos)	*p*-Toluenesulfonyl
p-TsOH	*p*-Toluenesulfonic Acid

CHAPTER I.
REFINEMENT OF THE LEWIS ACID-PROMOTED 3-AZA-COPE REARRANGEMENT OF *N*-ALKYL-*N*-ALLYLANILINES: A VERSATILE ROUTE TOWARD THE PREPARATION OF INDOLES SUBSTITUTED IN THE BENZENE RING PORTION.

Introduction.

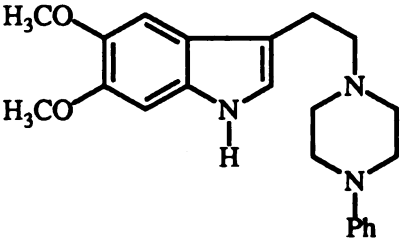
Indoles substituted in the benzene ring portion occupy an important role in indole alkaloid synthesis. Examples of these alkaloids are serotonin (**I-1**) and oxypertine (**I-2**).



Serotonin

(a neurotransmitter)

I-1

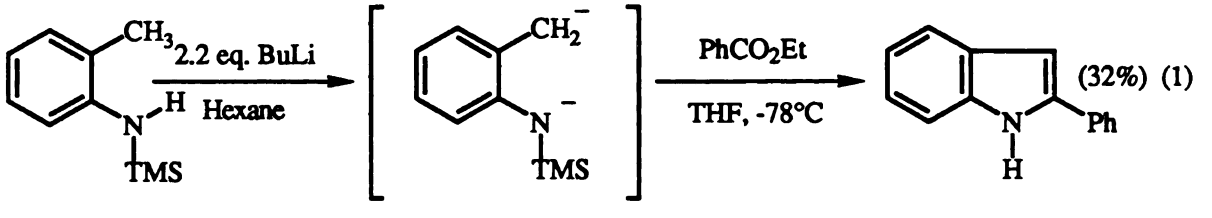


Oxypertine

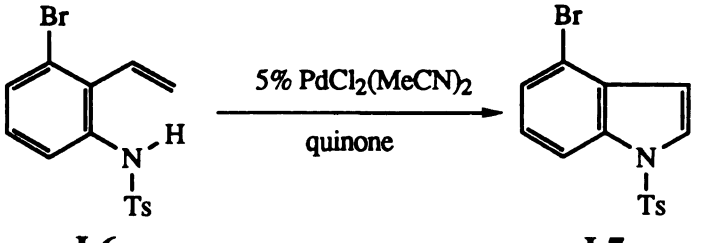
(a tranquilizer)

I-2

Preparation of these types of indoles have been executed by a variety of methods.[1] Many of these methods began with various *o*-substituted anilines (eqs. 1-3).[2-4] Preparation of these *o*-substituted anilines was also approached *via* a wide variety of methodologies (eqs. 4 and 5).[5,6]

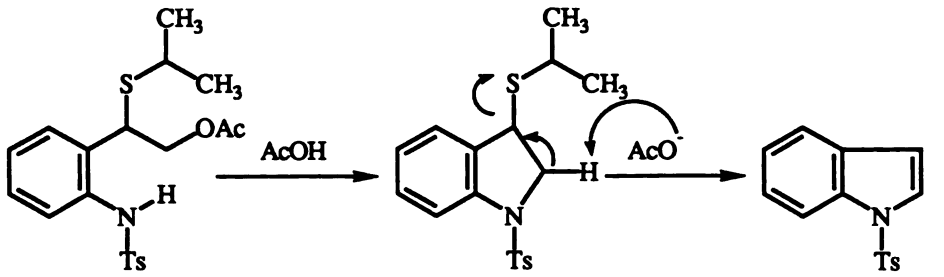


I-3 **I-4** **I-5**

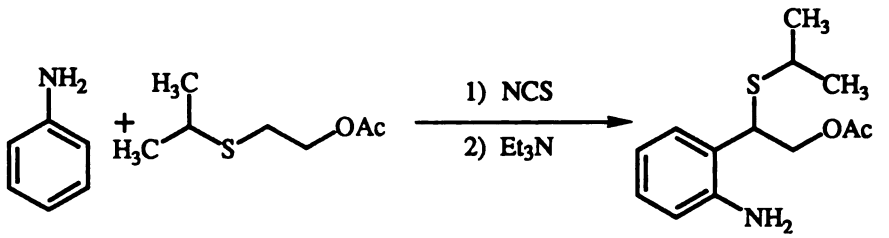


(15%) (2)

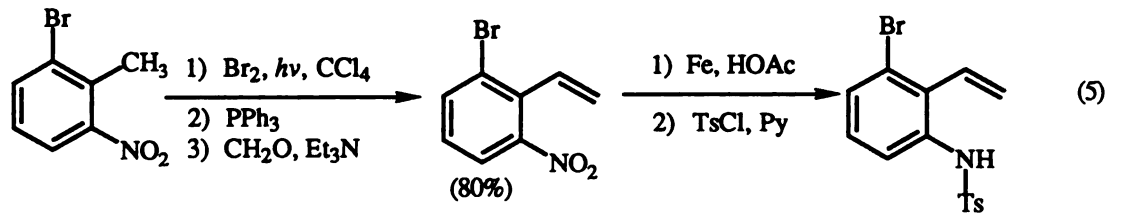
I-6 **I-7**



I-8 I-9 I-10

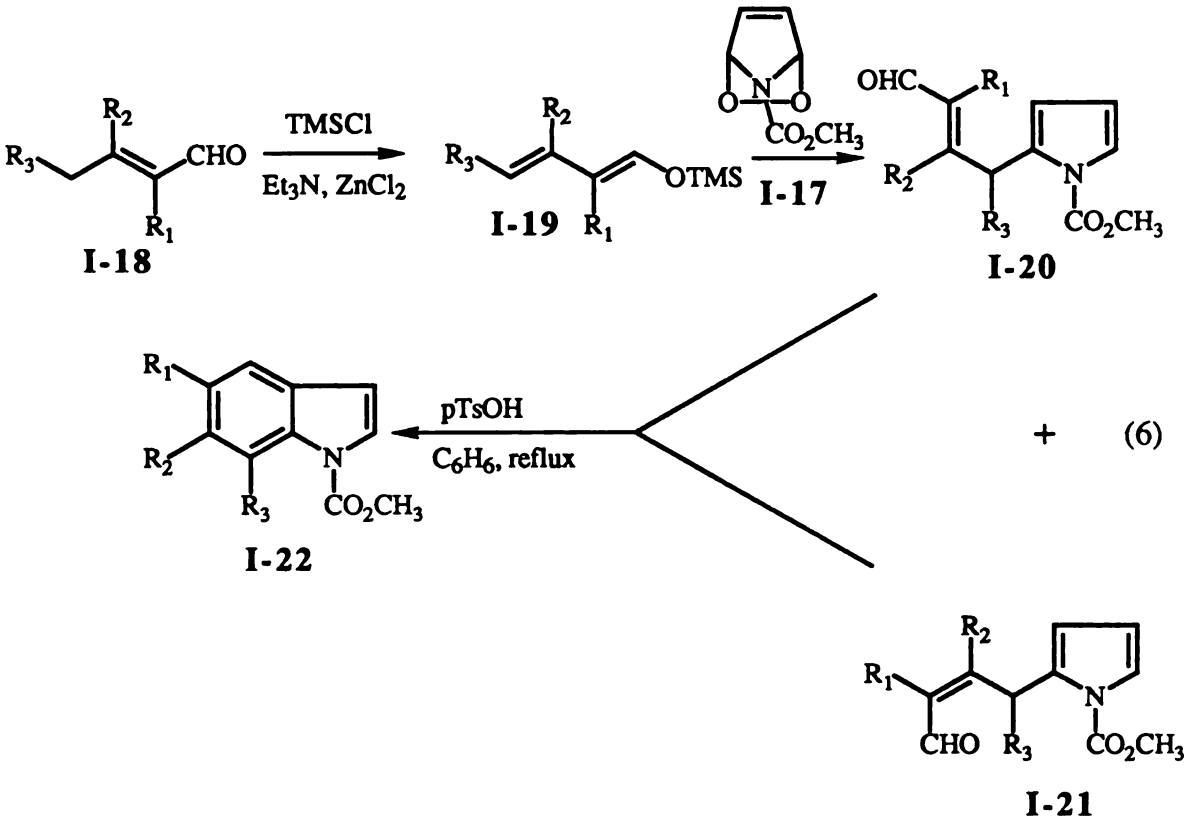


I-11 I-12 I-13



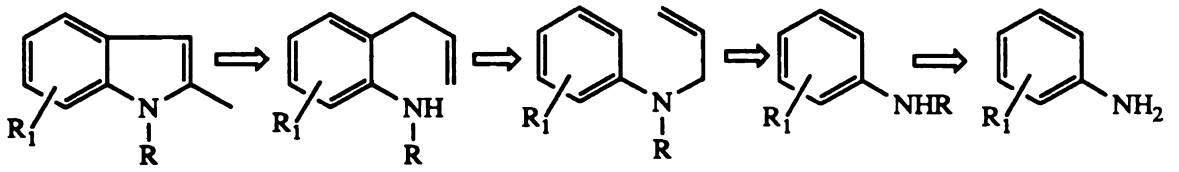
I-14 I-15 I-16

The major disadvantages of these methods are either low overall yields from aniline to indole or lack of aniline substituent availability. A compromise between the benzene portion substituent pattern of the indole and overall yield of reaction is particularly evident in the synthesis outlined in equation 6.[7] Yields for this synthesis range from 40% to 45% not including the formation of the endo-peroxide pyrrole (**I-17**).



In order to ascertain a more efficient route toward the formation of substituted indole frameworks, the aromatic 3-aza-Cope rearrangement (aromatic-amino-Claisen rearrangement) for the *o*-allylation of anilines has been examined. Specifically, it was hoped that conditions for the 3-aza-Cope reaction could be developed so that the reaction would occur at a reasonable rate, at practical temperatures and with adequate reproducibility and regiospecifity. These improved conditions would allow for the convenient and versatile preparation of indoles substituted in the benzene ring portion as illustrated retrosynthetically in Scheme I-1.

Scheme I-1. Retrosynthetic Analysis of Substituted Indole Preparation from Substituted Anilines



I-23 **I-24** **I-25** **I-26** **I-27**

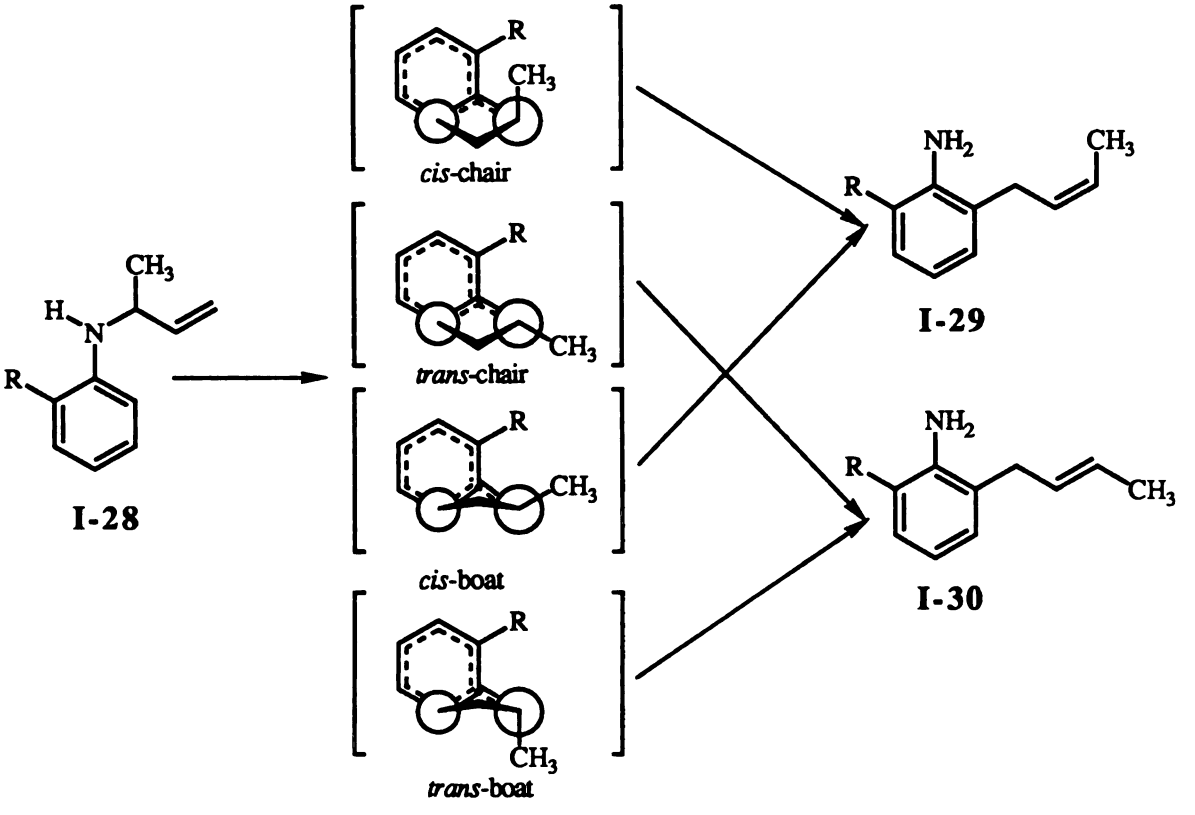
R represents any appropriate *N*-protecting group and R_1 represents any desired substituent.

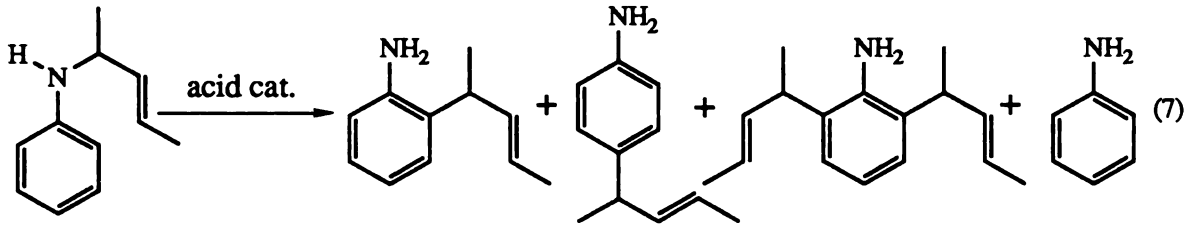
Aromatic 3-aza-Cope rearrangement.

The aromatic 3-aza-Cope rearrangement, a [3,3]-sigmatropic rearrangement of *N*-allyl-*N*-arylamines, has received less attention than its counterpart, the aromatic-Claisen rearrangement, probably because of the drastic conditions required and the tendency toward side reactions.[8] Thermal rearrangements of *N*-allylaniline occur at 200 - 350°C with cleavage to arylamines sometimes being the dominant reaction.[9] Analogous rearrangements of the oxygen counterparts occur in the temperature range of 150 - 225°C.[8]

The nature of the rearrangement was examined extensively by Jolidon and Hanson and found to be similar to the aromatic oxy-Claisen rearrangement.[9] Futhermore, in rearrangements using mixtures of deuterated and non-deuterated reactants (one reactant with the aromatic ring deuterated at the *m*-positions and the other with the terminal allyl positions deuterated), the formation of cross products was not observed. Also in this study, the [3,3] nature of the reaction was examined through steric interactions arising in the rearrangement of *o*-substituted-*N*-allylanilines. Scheme I-2 gives the possible transition state conformations of a [3,3]-type process. As substituents of increased bulk were used, steric interaction between them and the crotyl methyl group increased in the *cis*-chair transition state conformation (top). A corresponding decrease in the amount of **I-29** resulted. Evidence that the Lewis acid catalyzed rearrangement follows the same mechanism is available.[11] Extensive studies of Lewis acid catalyzed rearrangements were executed by Abdrakhmanov, *et al.*.[12,13] In one study, the rearrangement of *N*-(α-methylcrotyl)aniline (**I-31**, eq. 7) was monitored by Gas Chromatography (G. C.) relative to an internal standard. The results of this study are shown in Table I-1.

Scheme I-2. Possible Transition State Conformations for *o*-Substituted-*N*-allylanilines





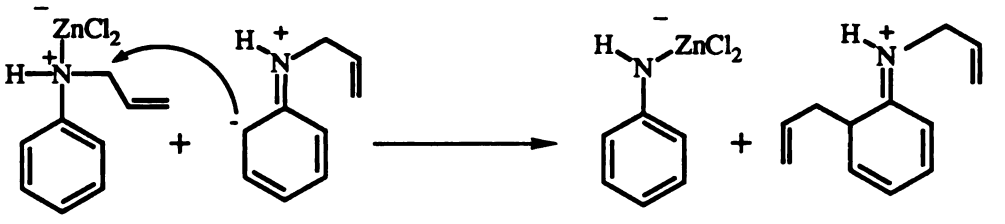
I-31 **I-32** **I-33** **I-34** **I-35**

Table I-1. Study of Acid Catalyzed Rearrangements of **I-31**[12]

Entry	Acid Catalyst / Equivalents	Solvent (130°C)	Time (min.) 90% conv.	% I-32[a]	% I-33[a]	% I-34[a]	% I-35[a]
1	Aniline-HCl / 1:1	Aniline	360	87	11	0	NA
2	Aniline-HCl / 1:1	1-Octanol	200	74	3	12	NA
3	Aniline-HCl / 1:1	DMSO	180	40	6	6	NA
4	Aniline-HCl / 1:1	C_6H_5-NO_2	180	62	4	8	20
5	Aniline-HCl / 1:2	C_6H_5-NO_2	260	68	4	11	15
6	Aniline-HCl / 1:3	C_6H_5-NO_2	380	72	3	12	12
7	$ZnCl_2$ / 1:10	C_6H_5-NO_2	60	90	7	0	1
8	$AlCl_3$ / 1:10	C_6H_5-NO_2	25	68	3	18	5
9	$CoCl_2$ / 1:10	C_6H_5-NO_2	30	55	6	13	15
10	$SnCl_4$ / 1:10	C_6H_5-NO_2	10	62	12	0	10
11	$TiCl_4$ / 1:10	C_6H_5-NO_2	60	48	4	0	17
12	BF_3-etherate / 1:10	C_6H_5-NO_2	20	68	10	0	9
13	$ZnCl_2$ / 1:1	C_6H_5-Cl	20	75	5	0	10
14	$ZnCl_2$ / 1:1	xylene	60	65	7	0	10

[a] Values represent G.C. yields relative to an internal standard.

Inconsistencies exist between the results of Abdrakhmanov and those reported by Jolidon and Hansen. In particular, the recovery of **I-34** and **I-35** by Abdrakhmanov indicated bond cleavage prior to bond making, a less [3,3]-like process. Furthermore, explanation as to how more **I-34** than **I-35** could be formed in some cases was difficult since the second substituent on **I-34** had to have come from **I-31**, **I-32**, or **I-33**. Decomposition mechanisms have been postulated.[14] One sequence is shown in equation 8.

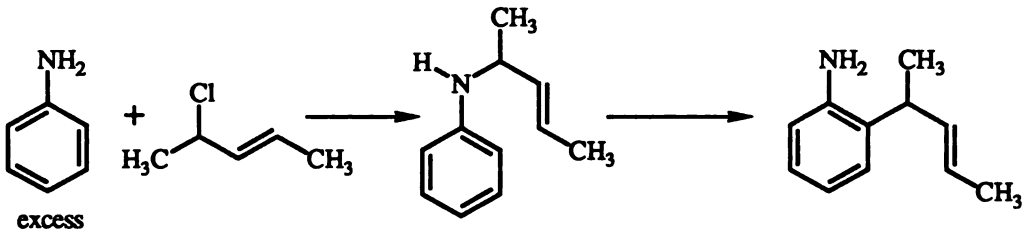


I-36 I-37 I-38 I-39 (8)

Substituent effects on the aromatic portion of the substrate have also been examined in some depth. For the rearrangement of *o*- and *m*-substituted anilines, the amount of resulting *p*-product (similar to **I-33**) was found to be significantly higher.[15] For example, in *m*-toluidines (*m*-methylanilines), the ratio of *o*- to *p*-rearrangement products was found to be 2.5 : 1 as opposed to 7 : 1 in the unsubstituted case. For *o*-chloroaniline, the ratio was 3 : 1. The only exception to this trend was *m*-anisidine (*m*-methoxyaniline) which yielded the *o*-product only. Reaction rates for all substituted anilines were reported slower. Rates of reaction of *p*-substituted-*N*-allylanilines in H_2SO_4 at 60°C were as follows: *p*-H (k_{rel}=1), *p*-CH_3 (k_{rel}=0.5), *p*-Cl (k_{rel}=0.5), *p*-OCH_3 (k_{rel}=0.2). With the *p*-CN substituent, cleavage was the principle reaction. Krowicki, *et al.*, also studied the effects of substituents on the aromatic ring.[16] For the rearrangement of *N*-methyl-*N*-(α-methylallyl)aniline under conditions of refluxing ethanol / water with an HCl catalyst for 8 hours the following isolated yields were obtained: *p*-H (95%), *p*-CH_3 (95%), *p*-OCH_3 (92%), *m*-CH_3 (45%), *m*-OCH_3 (24%). Under conditions of 180 - 230°C in concentrated HCl, *N*-allylanisidines simply decomposed.[17]

N-Substitution has been reported to give increased yields and faster rates of rearrangement under milder conditions.[15] Rates of reaction for both the thermal and acid catalyzed rearrangements increased in the order of *N*-H < *N*-CH_3 , *N*-*t*-butyl.[9]
Rearrangement yields vary greatly depending on the reaction conditions and substituent pattern of the migrating group. The most favorable conditions were reported by Krowicki *et al.*[1] and Abdrakhmanov[12,13] although yields reported by Abdrakhmanov were by G. C. only. The fact that the yields given were by G. C. only was significant in that isolated yields have sometimes been found to be far less than G. C. yields (for example: 70% yield by G. C. vs. 29% isolated for the Bronsted catalyzed rearrangement of *N*-methyl-*N*-(α-methylallyl)aniline and 88% G. C. vs. 57% isolated for a similar rearrangement of *N*-allylaniline).[9] To exemplify the variety of yields obtained in seemingly similar reactions, the following illustrations have been included. Reported yields for $ZnCl_2$ catalyzed rearrangements range from 42% isolated for *N*-allylaniline in refluxing xylenes for 3

hours with 0.7 equivalents of catalyst to 23% isolated for **I-32** under conditions of 1 equivalent of $ZnCl_2$ in refluxing xylenes.[18] For the rearrangement of **I-31** to **I-32** the yields range from 65% under conditions of 1.1 equivalent of $ZnCl_2$ in xylenes at 130°C for 1 hour by G. C.[13] to 97% with 1.1 equivalents of $ZnCl_2$ at 130°C in nitrobenzene by G. C. The highest overall yield found for an acid catalyzed rearrangement was for the reaction shown in equation 9.[19] This reaction, which was run with a "large excess" of aniline, was reported to have provided a 100% isolated yield of **I-42** after 4 hours at 120°C or 3 hours at 184°C. The authors attributed the high yield to the catalytic activity of aniline-HCl, checking their hypothesis by running the reaction without excess aniline (no reaction) and then adding aniline-HCl which gave 100% isolated yield. For analogous reactions run without excess aniline and under conditions of thermal and acid catalysis, the authors obtained 20 - 40% yields.

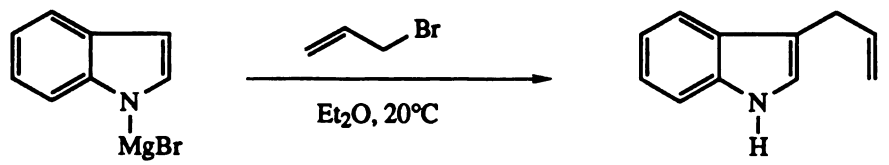


(9)

I-35 **I-40** **I-41** **I-42**

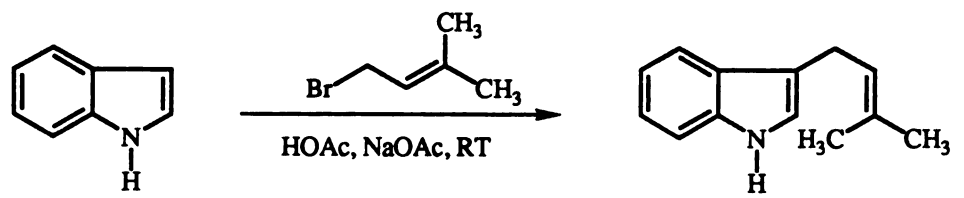
Aza-annelation of *N*-Allylindoles.

The [3,3]-rearrangement of *N*-allylindoles is far less studied than the [3,3]-rearrangement of *N*-allylanilines. This is probably due to the higher energy required to overcome the strained transition state and the variety of other methods available to achieve the same transformation (eqs 10-12).[20-22]



(10)

I-43 **I-44**



(11)

I-45 **I-46**

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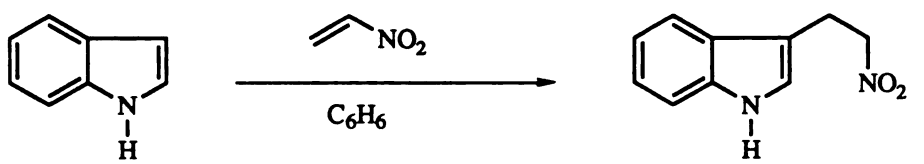
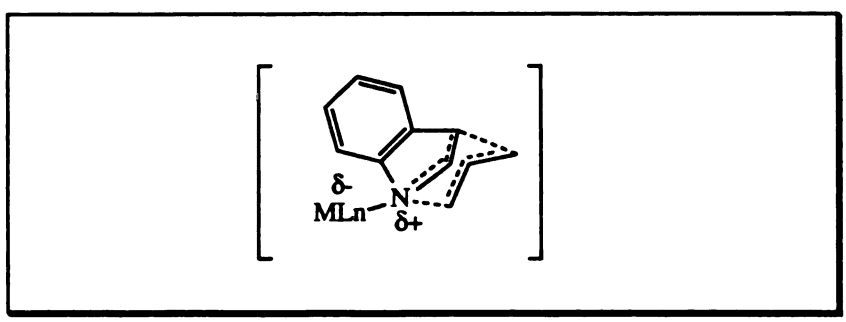


I-45 I-47 (12)

Thermal rearrangements of *N*-allylindole (**I-59**) to 3-allylindole (**I-44**) occur at elevated temperatures (405 - 470°C).[23] The requirement for higher temperature is consistent with the greater strain the transition state (**I-48**) must endure (Figure I-1). Under conditions of 1 equivalent of $AlCl_3$ in refluxing benzene for 2 hours, **I-59** rearranged to **I-44** in 58% isolated yield while the crotyl analog rearranged in 43% isolated yield.[24]

Figure I-1. Transition State **I-48**



I-48

There exists support for use of the aromatic 3-aza-Cope rearrangement as an efficient synthetic tool in the preparation of *o*-substituted anilines. This same [3,3]-process may then be used in the 3-allylation of indoles from **I-59**. In the former case, once the *o*-allylaniline is formed, ring closure may be executed to form the corresponding indole oxidatively *via* aldehyde formation followed by acid catalyzed ring closure.[25] Ring closure may also be affected directly using $Hg(OAc)_2$[26] or light[16] followed by aromatization with Mn(II)[27] or DDQ.[28] The 3-aza-Cope rearrangement could thus constitute an efficient route to indole alkaloids substituted in the benzene portion. The primary obstacles that must be overcome are: finding a general and efficient catalyst system, improving reaction yield reproducibility, and increasing overall reaction yield.

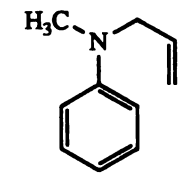
Results and Discussion.

Substrates for the aromatic 3-aza-Cope rearrangement were cleanly prepared by *N*-alkylation through the methodology of Tweede and Allabashi.[29] Since previous rearrangements were executed using only a small variety of spectator (protective) *N*-substituents, a variety of substrates (Figure I-2, I-3, and I-4) were synthesized. Preparation of these substrates were as indicated in Scheme I-1. The protecting group or equivalent was added to the aniline or aniline derivative and the product then isolated. The protected aniline was then allowed to react with the alkyl bromide to provide the *N*-allylanilines. The specific syntheses were as follows: *N*-methyl-*N*-allyl aniline (**I-49**) was prepared in 91% yield by allylating *N*-methyl aniline. *N*-Allyl-*N*-benzyl aniline (**I-50**) was prepared in 3 steps from **I-35** by condensation first of **I-35** with benzaldehyde to form *N*-benzylidine aniline (**I-51**) which was subsequently reduced to *N*-benzyl aniline (**I-52**) with $LiAlH_4$. Substrate **I-52** was allylated to give **I-50** in 54% overall yield. *N*-tosyl-*N*-allyl aniline (**I-53**) was prepared by the reaction of **I-35** with tosyl chloride to yield the *N*-tosyl aniline (**I-54**) which was then allylated to provide **I-53** in 40% overall yield. *N*-allyl acetaniline (**I-55**) was prepared *via* preparation first of acetaniline (**I-56**) from **I-35**, followed by allylation in 50% overall yield. Preparation of **I-57** in 20% overall yield from *m*-nitro aniline was accomplished by methylation of **I-74** to give *N*-methyl-*m*-nitroaniline (**I-58**) which was then allylated to provide **I-57**. Preparation of **I-59**, by allylation of **I-45**, was accomplished in 75% yield.

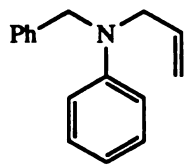
The *p*-methoxy substrates were prepared in similar fashion from *p*-anisidine (Figure I-3). *N*-Methyl-*N*-allyl-*p*-methoxy aniline (**I-60**) was prepared in 42% overall yield *via N*-methyl-*p*-methoxy aniline (**I-61**). *N*-Benzyl-*N*-allyl-*p*-methoxy aniline (**I-62**) was prepared in 28% overall yield in 3 steps by preparation first of *N*-benzylidine-*p*-methoxy aniline (**I-63**), reduction of **I-63** to *N*-benzyl-*p*-methoxy aniline (**I-64**) followed by allylation.

The *m*-methoxy substrates (Figure I-4) were prepared from *m*-methoxy aniline (**I-66**), which was prepared as outlined in Scheme I-3.[30] *N*-methyl-*N*-allyl-*m*-methoxy aniline (**I-67**) was prepared by formation first of *N*-methyl-*m*-methoxy aniline (**I-68**) followed by alkylation in 50% overall yield. *N*-benzyl-*N*-allyl-*m*-methoxy aniline (**I-69**) was prepared in similar fashon *via N*-benzyl-*m*-methoxy aniline (**I-70**) or *via N*-benzylidine-*m*-methoxyaniline (**I-71**) followed by alkylation in 72% overall yield. *N*-isobutyl-*N*-allyl-*m*-methoxy aniline (**I-72**) was prepared via *N*-isobutyl-*m*-methoxy aniline (**I-73**) in 62% overall yield.

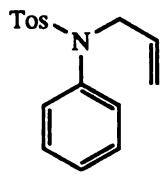
Figure I-2. Substrates Prepared for Acid Catalyzed Rearrangement



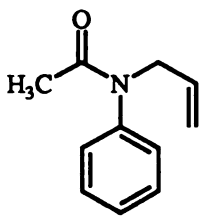
I-49



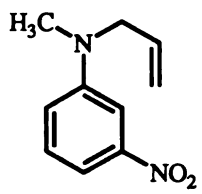
I-50



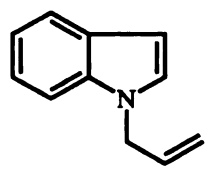
I-53



I-55

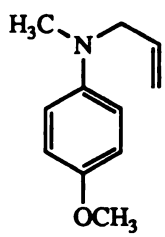


I-57

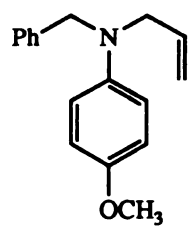


I-59

Figure I-3. *N*-Substituted-*p*-methoxy Substrates

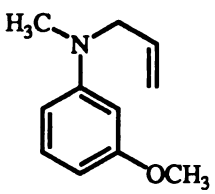


I-60

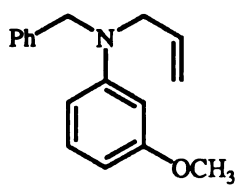


I-62

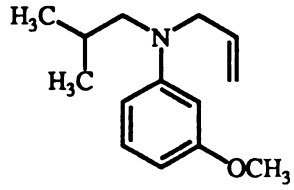
Figure I-4. *N*-Substituted-*m*-methoxy Substrates



I-67

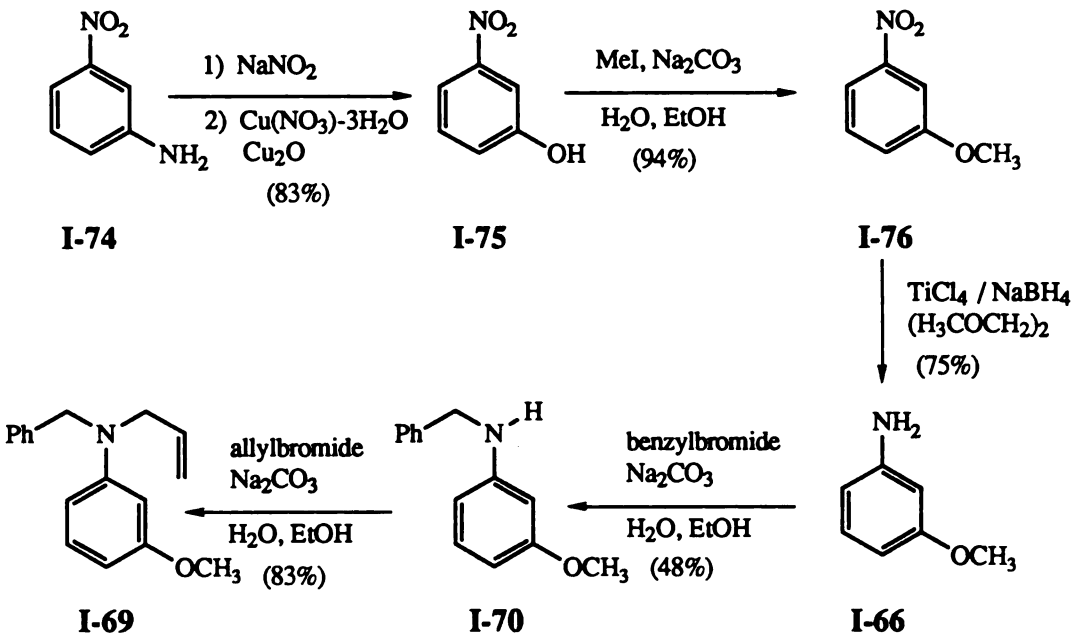


I-69

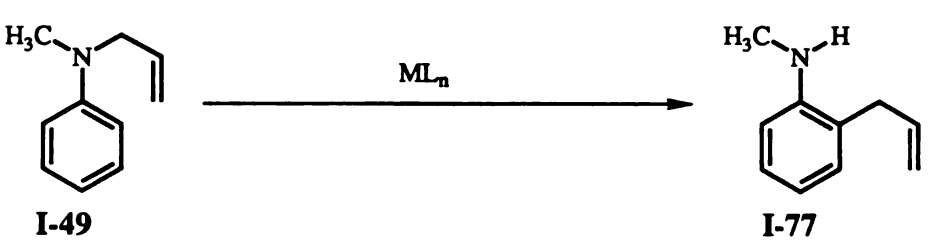


I-72

Scheme I-3. Preparation of *N*-Benzyl-*N*-allyl-*m*-methoxyaniline.



Acid catalyzed rearrangement of the substrates **I-49, I-50, I-53, I-55, I-57,** and **I-59** were then explored with emphasis being placed on the rearrangement of **I-49** (eq 13). Initial studies of the rearrangement of **I-49** focused on the optimization of conditions using the well studied catalyst $ZnCl_2$. $ZnCl_2$ molarities were varied from 0.36 to 3.0 M under conditions of refluxing xylenes (140°C) and 1.2 equivalents of catalyst. Rearrangement of **I-49** to the *o*-allyl product (**I-77**) occurred in 45% isolated yield at 0.5 M (Table I-2). Compound **I-49** was then subjected to rearrangements using a variety of acid catalysts. These catalysts exhibited a wide range of activities as indicated in Table I-3.



I-49 **I-77** (13)

Table I-2. Effect of Varying $ZnCl_2$ Molarities on Maximum % **I-77** in the Reaction Mixture in the Rearrangement of **I-49**

Entry	$ZnCl_2$[a] molarity	Time (hours)	% of **I-77**[b]
1	0.36	16	27
2	0.5	16	52
3	1.0	16	51
4	2.0	16	37
5	3.0	40	17

[a] Reactions were executed using 1.2 equiv of catalyst relative to **I-49**. [b] Values represent % of the reaction mixture as **I-77**, as indicated by G.C. without an internal standard.

Table I-3. Results of the Acid Catalyzed Rearrangement of **I-49**

Entry	Catalyst[a]	Time (hours)	% yield of **I-77**[b]
1	$TiCl_4$	20	46
2	$MgBr_2$	44	38
3	HBF_4	48	33
4	*bis*-t-Cl-AlMe[c]	24	28
5	*bis*-d-Ph-AlMe[d]	72	27
6	$FeCl_3$	4	24
7	$AlMe_2Cl$	24	22
8	H_2SO_4	24	17
9	$MeAlCl_2$	44	16
10	$EtAlCl_2$	14	8
11	HCl	No rxn.[e]	0
12	$AlMe_2Cl$	No rxn.[e]	0
13	$SnCl_4$	No rxn.[e]	0
14	$FeBr_3$	Dest of SM[f].	0

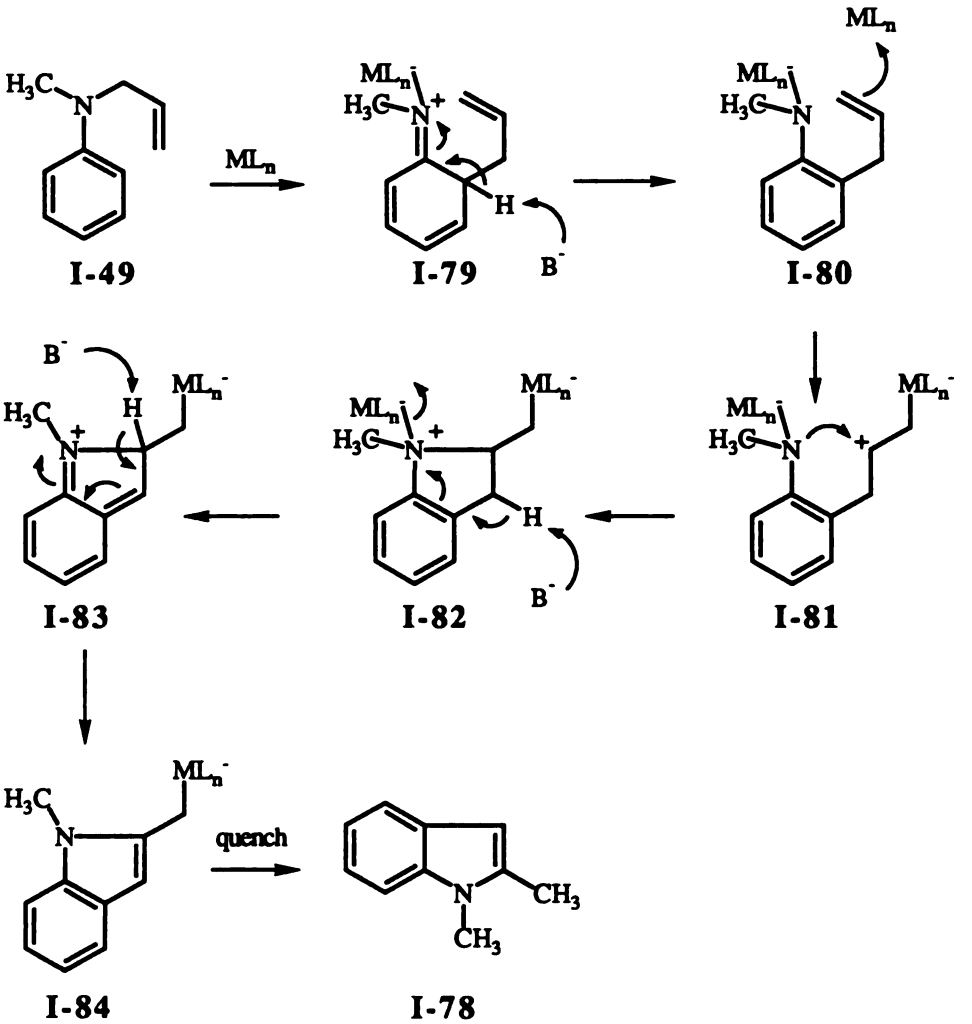
[a] Reactions were executed using 1.2 equiv of catalyst relative to **I-49**. [b] Values represent G.C. yields relative to an internal standard. [c] *bis*-t-Cl-AlMe represents *bis*-(2,4,6-trichlorophenoxy)methylaluminum. [d] *bis*-d-Ph-AlMe represents *bis*-(2,6-diphenylphenoxy)methylaluminum. [e] No rxn. indicates that less than 2% of the starting material was consumed over 48 hours. [f] Dest of SM indicates complete destruction of starting material with less than 2% yield of any single isolable product.

Table I-4. Effect of Solvent Reflux Temperature on the Rearrangement of **I-49**

Entry	Catalyst[a]	Solvent[b]	Time (hours)	% yield of **I-77**[c]
1	$AlCl_3$	xylene	8	88
2	$AlCl_3$	toluene	24	52
3	BF_3-Et_2O	xylene	24	49
4	BF_3-Et_2O	toluene	44	79
5	$ZnCl_2$	decalin	16	0[d]
6	$ZnCl_2$	xylene	16	52
7	$ZnCl_2$	toluene	24	17
8	HBF_4	xylene	2	11
9	HBF_4	toluene	48	33
10	$FeCl_3$	xylene	4	24
11	$FeCl_3$	toluene	4	2
12	HCl	decalin	24	9
13	HCl	xylene	No rxn[e]	0
14	HCl	toluene	No rxn.[e]	0
15	$FeBr_3$	xylene	Dest of SM[f]	0
16	$FeBr_3$	toluene	8	3

[a] Reactions were executed using 1.2 equiv of catalyst relative to **I-49**. [b] Temperatures at reflux for the solvents used were: 190°C for decalin, 140°C for xylene and 111°C for toluene. [c] Values represent G.C. yields of **I-77** relative to an internal standard. [d] Product **I-78** was formed. See text and Scheme IV for explanation. [e] No rxn. indicates that less than 2% of the starting material was consumed over 48 hours. [f] Dest of SM indicates complete destruction of starting material with less than 2% yield of any single isolable product.

Scheme I-4. Possible Mechanism for the Formation of **I-78** from **I-49**

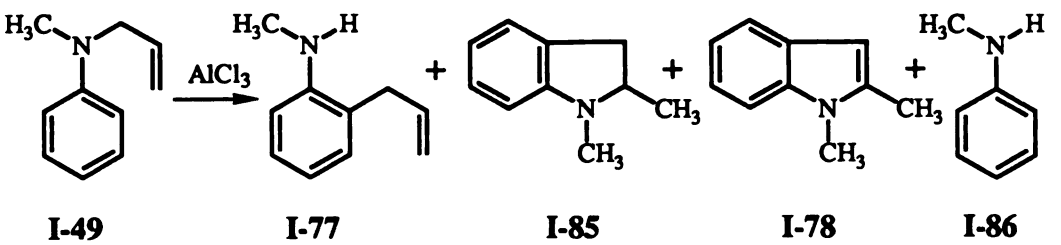


The effect of temperature was examined by running similar reactions in refluxing xylenes (140°C), toluene (111°C) or decalin (190°C) as indicated in Table I-4. These results indicated that, in general, xylenes exhibited the optimum solvent conditions for the catalysts examined. Notable exceptions were those of BF_3-etherate, which provided an increase in yield from 49% at 24 hours in xylenes to 79% at 40 hours in toluene, and of HBF_4 which provided an increase in yield from 11% at 2 hours in xylenes to 33% at 48 hours in toluene. Another interesting result obtained from these experiments was the formation of 1,2-dimethylindole (**I-78**) as the sole product in 30% isolated yield from $ZnCl_2$ catalyzed reaction of **I-49** under conditions of refluxing decalin for 16 hours. A possible mechanism for this conversion is indicated in Scheme I-4.

Since $AlCl_3$ in xylenes gave the highest yield of **I-77**, the next variable explored was the equivalents of $AlCl_3$ relative to **I-49** (Table I-5). These experiments yielded interesting results in that lower equivalents of $AlCl_3$ tended to promote cyclization to the 1,2-dimethyl-2,3-dihydroindole (**I-85**) and even aromatization to **I-78**. Decomposition to *N*-methylaniline (**I-86**) was also noted (eq. 14).

Although G.C. yields for the rearrangement of **I-49** to **I-77** were extremely promising, isolation of **I-77** proved to be challenging as expected from the results of Jolidon and Hanson.[9] Products of the test reactions were generally isolated by quenching the acid *in situ* with an excess of 15% aqueous sodium hydroxide. Quenching was followed by repeated washing with 15% aqueous sodium hydroxide, saturated aqueous sodium chloride and water. Solvent removal was then affected by rotary evaporation, and the resulting product mixture chromatographed on silica with petroleum ether. Isolated yields of **I-77** for the three most effective acid catalysts are given in Table I-6. Reaction yield consistency remains problematic at times, especially for the $AlCl_3$ catalyzed systems.

Rearrangements of **I-50**, **I-53**, and **I-55** were also examined using a variety of catalysts. For the other substrates, a more limited number of catalysts was examined as indicated (Tables I-7 - I-9).



(14)

I-49 **I-77** **I-85** **I-78** **I-86**

Table I-5. Effect of Varying Equivalents of $AlCl_3$ on the Rearrangement of **I-49**

Entry	Equivalents of $AlCl_3$[a]	Time (hours)	% **I-77**[b]	% **I-85**[b]	% **I-78**[b]	% **I-86**[b]
1	1.5	2	38	0	0	0
2	1.5	4	22	0	0	0
3	1.5	8	9	0	0	0
4	1.2	4	49	0	0	0
5	1.2	8	88	0	0	2
6	1.2	24	71	0	0	3
7	1.2	30	66	0	0	5
8	0.75	2	58	0	0	0
9	0.75	4	68	1	0	0
10	0.75	8	70	6	0	0
11	0.75	24	23	32	5	0
12	0.75	48	4	37	9	1
13	0.75	72	1	42	12	3
14	0.5	2	36	0	0	0
15	0.5	4	51	2	0	0
16	0.5	8	72	6	0	4
17	0.5	24	3	71	9	5
18	0.25	2	18	0	0	0
19	0.25	4	33	1	0	0
20	0.25	8	55	11	0	0
21	0.25	24	9	56	9	0
22	0.25	48	3	40	13	0
23	0.25	72	2	29	22	0

[a] Rearrangements were run 0.5 M of **I-49** with 1.2 equiv. of Lewis acid at reflux in xylenes. [b] Yieldswere determined by G.C. analysis of the crude reaction mixture relative to an internal standard.

Table I-6. Optimized Yields for the Rearrangement of **I-49**

Entry	Catalyst[a]	% yield of **I-77** by G. C.[b]	% yield of **I-77** isolated
1	$AlCl_3$	88	46
2	BF_3-etherate	79	58
3	$ZnCl_2$	52	45

[a] Rearrangements were run 0.5 M of substrate with 1.2 equiv. of Lewis acid at reflux in toluene (111°C, Et_2O-BF_3) or xylenes (140°C $ZnCl_2$). [b] Yields were determined by G. C. analysis of the crude reaction mixture relative to an internal standard.

Table I-7. Results of the Acid Catalyzed Rearrangement of **I-53**

Entry	Catalyst[a]	Solvent (at reflux)	Time (hours)	% *o*-prod[b]
1	$AlCl_3$	xylenes	1	33
2	$ZnCl_2$	xylenes	No rxn[c]	0
3	BF_3-etherate	toluene	Dest of SM[d]	0
4	$AlMe_2Cl$	xylenes	24	11

[a] Rearrangements were run 0.5 M of **I-53** with 1.2 equiv. of Lewis acid. [b] Yields were determined by G. C . analysis of the crude reaction mixture relative to an internal standard. [c] No reaction indicates that less than 2% of the starting material had been consumed over 48 hours. [d] Dest. of SM indicates complete destruction of starting material with less than 2% of any single product formed.

Table I-8. Results of the Acid Catalyzed Rearrangement of **I-50** to **I-87**

Entry	Catalyst[a]	Solvent (at reflux)	Time (hours)	% *o*-prod **I-87**[b]
1	$AlCl_3$	xylenes	2	75
2	$AlMe_2Cl$	xylenes	2	0
3	BF_3-etherate	toluene	24	0
4	HF	xylenes	72	13
5	H_3PO_4	xylenes	24	0

[a] Rearrangements were run 0.5 M of **I-50** with 1.2 equiv. of Lewis acid. [b] Yields were determined by G. C. analysis of the crude reaction mixture relative to an internal standard.

Table I-9. Results of the Acid Catalyzed Rearrangement of **I-55**

Entry	Catalyst[a]	Solvent (at reflux)	Time (hours)	% *o*-prod[b]
1	$AlCl_3$	xylenes	2	1
2	BF_3-etherate	toluene	2	10
3	$ZnCl_2$	xylenes	No rxn[c]	0
4	$TiCl_4$	xylenes	No rxn	0
5	$AlMe_3$	xylenes	2	8
6	$AlMe_2Cl$	xylenes	No rxn	0
7	H_2SO_4	xylenes	No rxn	0
8	*bis*-d-Ph-AlMe[d/]	xylenes	No rxn	0

[a] Rearrangements were run 0.5 M of **I-55** with 1.2 equiv. of Lewis acid or 0.1 - 0.3 equiv. using the Lewis acid $TiCl_4$. [b] Yields were determined by G. C. analysis of the crude reaction mixture relative to an internal standard. [c] *B*is-d-Ph-AlMe represents the *bis*-(2,6-diphenylphenoxy) methylaluminum. [d] No rxn indicates that less than 2% of starting material had been consumed within 48 hours.

Results of the acid catalyzed rearrangements of **I-59** were particularly promising in lieu of the strained transition state. Isolated yields of **I-44** along with the corresponding G. C. yields are indicated in Table I-10.

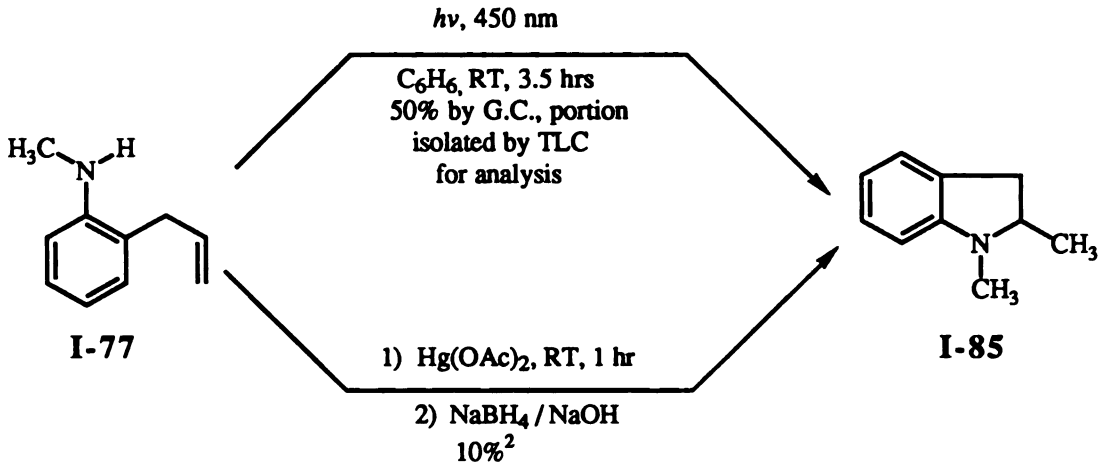
Table I-10. Results of the Acid Catalyzed Rearrangement of **I-57**

Entry	Catalyst[a]	Solvent	Time (hours)	%yield **I-44**[b]	% iso yield of **I-44**
1	$AlCl_3$	xylenes	8	88	54
2	$ZnCl_2$	xylenes	No rxn[c]	0	-
3	BF_3-etherate	toluene	4	5	-
4	$AlMe_2Cl$	xylenes	24	30	20
5	$TiCl_4$	xylenes	8	3	-
6	$AlMeCl_2$	xylenes	24	23	5
7	*bis*-d-Ph-AlMe[b]	xylenes	No rxn	0	-
8	$FeCl_3$	toluene	No rxn	0	-

[a] Rearrangements were run 0.5 M of **I-57** with 1.2 equiv. of Lewis acid or 0.1 - 0.3 equiv using the Lewis acid $TiCl_4$. [b] Ratios were determined by G. C. analysis of the crude reaction mixture relative to an internal standard. [c] *Bis*-d-Ph-AlMe represents *bis*-(2,6-diphenylphenoxy)methylaluminum. [d] No rxn. indicates that less than 2% of the substrate had been consumed within 48 hours.

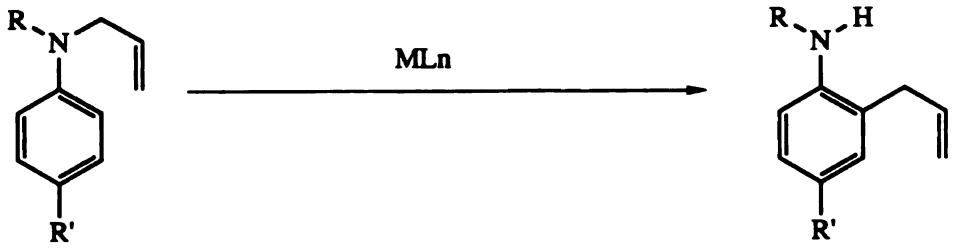
At this time, several initial attempts to achieve ring closure of **I-77** were attempted. Photocyclization (Hg arc lamp, C_6H_6)[16] yielded the desired **I-85** in 50% yield as determined by G. C. (a portion isolated for analysis by preparative TLC). Ring closure initiated by action of $Hg(OAc)_2$ gave 10% isolated yield of the same product (Scheme I-5).[26]

Scheme I-5. Ring Closure of **I-77**



A potentially promising route to ring closure could be through the use of $KMnO_4$ / $NaIO_4$.[31] Subsequent aromatization could then be achieved using Mn(II)[27] or DDQ.[28]

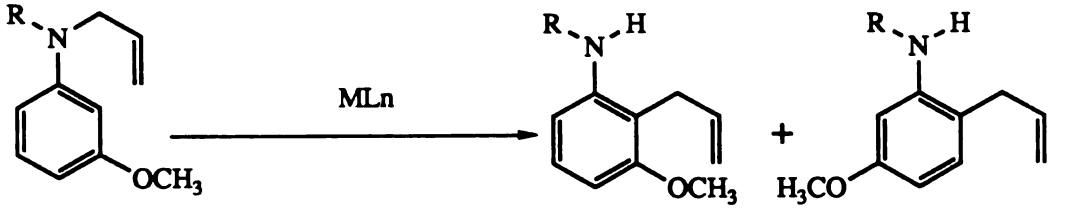
To determine the scope and generality of the aromatic aza-Cope rearrangement, several other aniline substrates were examined: **I-60, I-62, I-67, I-69** and **I-72** (eq 14, 15). Results for rearrangement of **I-49, I-50, I-53, I-57, I-60, I-62, I-67, I-69, I-72** and **I-81** using the most favorable catalyst conditions are indicated in the summary tables I-11 - I-13:



(14)

I-50 R = CH_2Ph, R' = H
I-60 R = Me, R' = OMe
I-62 R = CH_2Ph, R' = OMe

I-87 R = CH_2Ph, R' = H
I-88 R = Me, R' = OMe
I-89 R = CH_2Ph, R' = OMe



(15)

I-67 R = Me
I-69 R = CH_2Ph
I-72 R = iBu

I-90 R = Me
I-92 R = CH_2Ph
I-94 R = iBu

I-91 R = Me
I-93 R = CH_2Ph
I-95 R = iBu

Table I-11. $AlCl_3$ Catalyzed Rearrangements of Various Nitrogen and Aromatic Substituted Anilines[a]

ring substitution	*N*-isobutyl hrs. G.C. / iso.[b]	*N*-methyl hrs. G.C. / iso.[b]	*N*-benzyl hrs. G.C. / iso.[b]	*N*-tosyl hrs. G.C. / iso.[b]
unsubstituted		08 88 / 68	02 35 / 15	48 33 / 0
p-methoxy		04 0 / 0	01 11 / Cni[c]	04 0 / Dsm[d]
m-methoxy	04 0 / dsm	24[e] 0 / Dsm	01[e] 18 / Cni	08[e] 0 / Dsm
m-nitro		04 0 / Dsm		

[a] Rearrangements were run 0.5 M of substrate with 1.2 equiv. of Lewis acid at reflux in toluene (111°C, Et_2O-BF_3) or xylenes (140°C $ZnCl_2$). [b] Yieldswere determined by G.C. analysis of the crude reaction mixture relative to an internal standard. [c] Cni indicates no isolable products. [d] Dsm indicates destruction of starting material. [e] Yield is inclusive of both *o*-regioisomers formed.

Table I-12. $ZnCl_2$ Catalyzed Rearrangement of Various Nitrogen and Aromatic Substituted Anilines[a]

ring substitution	*N*-isobutyl hrs. G.C. / iso.	*N*-methyl hrs. G.C.[b] / iso.	*N*-benzyl hrs. G.C.[b] / iso.	*N*-tosyl hrs. G.C.[b] / iso.
unsubstituted		16 52 / 45	24 30 / 15	48 0 / No rxn[e]
p-methoxy		16 66 / 58	24 57 / 53	48 0 / Dsm[c]
m-methoxy	06[d] 98 / 98	08[d] 77 / 70	24[d] 64 / 57	48 0 / Dsm
m-nitro		48 0 / No rxn		

[a] Rearrangements were run 0.5 M of substrate with 1.2 equiv. of Lewis acid at reflux in toluene (111°C, Et_2O-BF_3) or xylenes (140°C, $ZnCl_2$). [b] Yields were determined by G.C. analysis of the crude reaction mixture relative to an internal standard. [c] Dsm indicates destruction of starting material. [d] Yields are inclusive of both *o*-regioisomers formed. [e] No rxn indicates no reaction.

Table I-13. BF_3-etherate Catalyzed Rearrangement of Various Nitrogen and Aromatic Substituted Anilines[a]

ring substitution	*N*-isobutyl hrs. G.C. / iso.	*N*-methyl hrs. G.C.[b] / iso.	*N*-benzyl hrs. G.C.[b] / iso.	*N*-tosyl hrs. G.C.[b] / iso.
unsubstituted		48 79 / 58	24 0 / Cni[c]	48 0 / Dsm[d]
p-methoxy		72 61 / 55	48 42 / 35	48 0 / Dsm
m-methoxy	24[e] 89 / 80	48[e] 99 / 99	48[e] 47 / 38	48[e] 0 / Dsm
m-nitro		24 0 / Dsm		

[a] Rearrangements were run 0.5 M of substrate with 1.2 equiv. of Lewis acid at reflux in toluene (111°C, Et_2O-BF_3) or xylenes (140°C $ZnCl_2$). [b] Yields were determined by G.C. analysis of the crude reaction mixture relative to an internal standard. [c] Cni indicates no isolable products. [d] Dsm indicated destruction of starting material. [e] Yields are inclusive of both *o*-regioisomers formed.

For the **I-67**, **I-69**, and **I-72**, rearrangement resulted in the formation of *o*-allyl regioisomers (Table I-14). Rearrangement to the position *para* to the *m*-methoxy group was always preferred. HCl catalyzed rearrangement in refluxing ethanol according to the method of Krowicki[2] yielded regioisomer ratios of 2.1 : 1.0 for **I-72** after 60 hours (78%

conversion), 2.8 : 1.0 for **I-67** after 60 hours (26% conversion) and 2.7 : 1.0 for the **I-69** after 60 hours (22% conversion).

Table I-14. *O*-Allyl Regioisomer Product Ratios for the *N*-Substituted *m*-Methoxy Substrates Under Conditions of Varying Acid Catalysis.

	Lewis Acid Catalyst	
product ratio	$ZnCl_2$	BF_3-etherate
I-95 : I-94	2.7 : 1.0	2.6 : 1.0
I-91 : I-90	1.8 : 1.0	1.9 : 1.0
I-93 : I-92	2.5 : 1.0	2.6 : 1.0

For the nitrogen substituents examined, the rearrangement appears to be promoted by bulky *N*-substituents (probably through ground state destabilization). This finding correlates well with previous work.[15] Rearrangement in the presence of the benzyl substituent is retarded though, and the *N*-tosyl substrate (**I-53**) did not rearrange. Substituents on the aniline aromatic ring promoted rearrangement in the order of *m*-methoxy > *p*-methoxy > unsubstituted >> *m*-nitro. This supports the notion of greater ring reactivity being associated with electron releasing substituents.

For regioisomers obtained where *m*-substituted anilines underwent rearrangement, the two *o*-allyl products were generally obtained in the ratio of 2.0-3.0 : 1.0. Bulkier *N*-substituents promoted somewhat greater selectivity than non bulky substituents. This correlation was opposite that observed under conditions of HCl catalysis described earlier. Also, HCl catalyzed reactions did not go to completion after 84 hours.

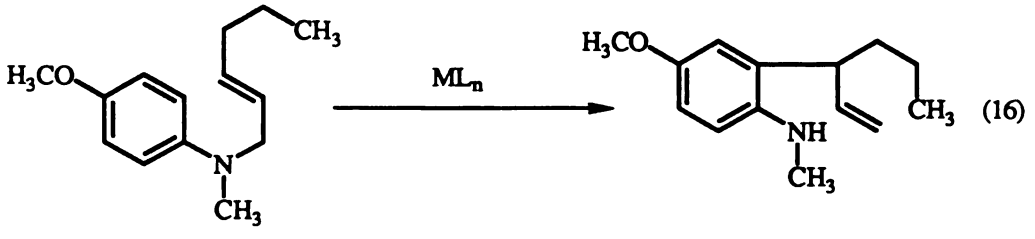
Comparison of relative rearrangement rates of the non-activated substrate **I-49** (eq 13) *vs* the activated **I-67** (eq 15) was carried out through direct competition of 1.0 equiv of each substrate with 1.8 equiv of Lewis acid (Table I-15). Results of this study indicated that **I-67** reacted approximately 1.5 times faster when the rearrangement was promoted by Et_2O-BF_3 and approximately 3.0 times faster when promoted by $ZnCl_2$.

Table I-15. Competitive Lewis Acid-Promoted 3-Aza-Cope Rearrangement of **I-49** and **I-67**

		product formation[b] (%)		
catalyst	condns[a] (time (hours))	**I-90 + I-91**	**I-77**	**(I-90 + I-91) : I-77**
Et_2O-BF_3	2.0	24	15	62:38
	4.0	33	22	60:40
	6.0	49	30	62:38
	8.0	55	33	63:37
$ZnCl_2$	0.5	17	7	71:29
	1.0	36	10	78:22
	1.5	47	15	76:24
	2.0	55	18	75:25

[a] Rearrangements were run 0.5 M of substrate with 1.5 equiv. of Lewis acid at reflux in toluene (111°C, Et_2O-BF_3) or xylenes (140°C $ZnCl_2$) with 1.8 equiv of Lewis acid. [b] Yields were determined by G. C. analysis of the crude reaction mixture relative to an internal standard.

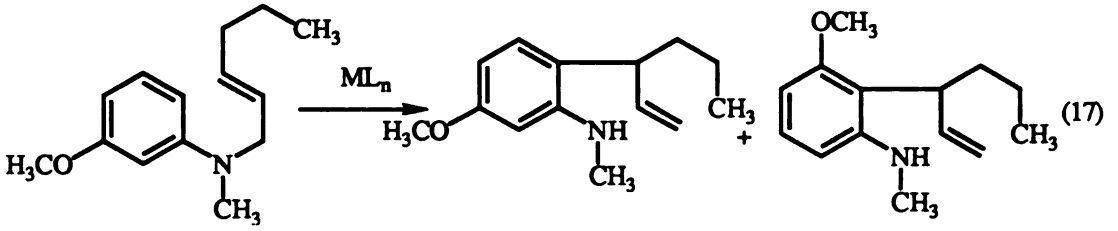
In order to establish a potential route to methoxy-substituted natural products, the rearrangement of several substrates containing unsymmetrical allylic substituents was examined. *N*-((*E*)-2-Hexen-1-yl)-*N*-methyl-*m*-methoxyaniline (**I-100**) and *N*-((*E*)-2-hexen-1-yl)-*N*-methyl-*p*-methoxyaniline (**I-97**) were prepared by standard procedures in 72 and 73% yields from their respective methoxy substituted-*N*-methyl anilines and 1-bromo-2-hexene (**I-98**). Bromination of 2-hexene-1-ol with NBS provided **I-98** in 68% yield.[32]



(16)

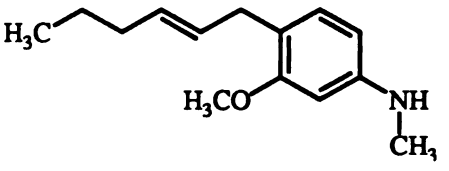
I-97 **I-99**

Rearrangement of **I-97** provided **I-99** in 50% yield with $ZnCl_2$ in xylenes at 140°C and in 79% yield with BF_3-Et2O at 111°C (eq 16). For the meta-substituted aniline substrate (**I-100**), a mixture of regioisomers was obtained (eq 17).



I-100 **I-101** **I-102**

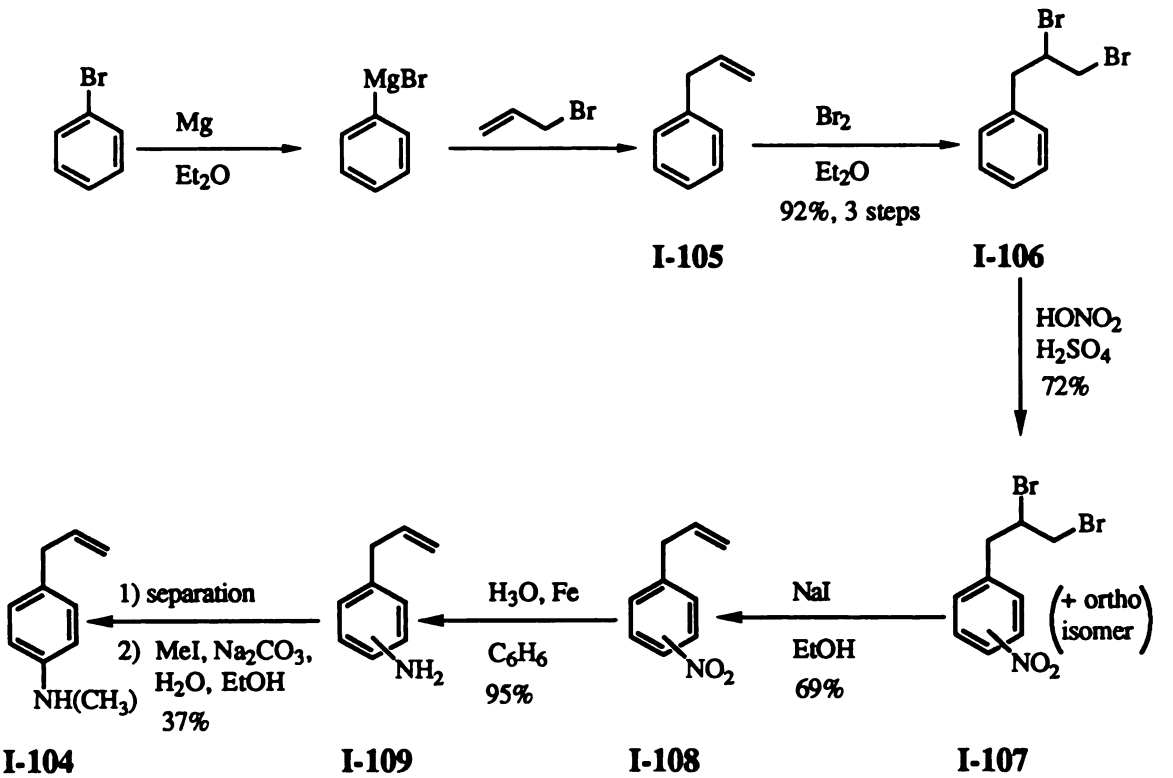
Selectivities for the rearrangement of **I-100** under conditions of BF_3-Et_2O and $ZnCl_2$ were higher than for **I-67**, as was expected based on the bulkier allyl substituent. For the BF_3-Et_2O promoted system, a regioselectivity of 75:25 was obtained for **I-101** and **I-102**. For the $ZnCl_2$ system, a regioselectivity of 83:17 was obtained for the same products. Yields for these reactions were 75% and 70% respectively. Another product isolated from both of these reactions in 11% was **I-103**.



I-103

To determine whether any *N*-methyl-*p*-allylaniline (**I-104**) was formed during the aromatic 3-aza-Cope rearrangement of **I-49**, **I-104** was prepared by standard methodologies. The preparation of **I-104** was executed by Grignard reaction of bromobenzene with allylbromide to provide allylbenzene (**I-105**).[33] The alkene was then masked using Br_2 in diethyl ether at -78°C to give **I-106** in 92% overall yield. Nitration of **I-106** gave **I-107** (72% yield), and debromination gave *p*-allylnitrobenzene (**I-108**) with some *o*-product present (69% yield).[33, 34] The nitro group was then reduced to the corresponding amine using acid activated iron to give **I-109** in 95% yield.[35] The *o*-, and *p*-isomers were then separated by chromatography and the *p*-isomer *N*-methylated to give the desired product, **I-104** (Scheme I-6).[29] Overall yield for the conversion of bromobenzene to **I-104** was 16%.

Scheme I-6. Synthesis of *N*-Methyl-*p*-allylaniline.



It was determined that in no rearrangement of **I-49** to **I-104** occurred in greater than 2%.

Conclusion.

It was hoped that conditions for the 3-aza-Cope reaction could be developed under which the 3-aza-Cope rearrangement would occur at a reasonable rate, at practical temperatures and with adequate reproducibility and regiospecifity. The catalyst systems BF_3-Et_2O in toluene and $ZnCl_2$, and $AlCl_3$ in xylene efficiently accelerated the 3-aza-Cope rearrangement of *N*-allylaniline substrates accessing a convenient method for C-C bond formation between *N*-alkyl substituents and an ortho aromatic ring carbon. This versatile rearrangement yields products which may potentially act as precursors to a variety of indole alkaloids substituted in the benzene ring portion.

Experimental Section.

General Methods.

All reactions were carried out using standard inert atmosphere techniques to exclude moisture and oxygen, and reactions were performed under an atmosphere of nitrogen. Benzene, toluene and diethyl ether were distilled from sodium/benzophenone immediately prior to use. Xylenes and decalin were heated over calcium hydride for a minimum of 12 hr and then distilled prior to use. $LiAlH_4$ (1 *M* in THF) was obtained from Aldrich Chemical Co. Unless specified, concentration of mixtures was performed using a Büchi rotary evaporator.

Gas chromatographic (G. C.) analyses were carried out on one of two instruments. For lower molecular weight compounds gas chromatographic analysis was carried out isothermally on a Perkin-Elmer 8500 instrument using a 50 meter RSL-200 capillary column (5% methylphenyl silicon) and an FID detector at 200 °C oven temperature, 220 °C injector temperature, and 300 °C detector temperature. Helium gas pressure was set at 15 psi with a flow rate of 2 mL/min. For higher molecular weight compounds, gas chromographic analysis was carried out on a Hewlett-Packard 5880A series gas chromatograph fitted with a 30 meter silica capillary column and a flame ionization detector. For these analysis injector and detector temperatures were set at 250 °C and the column oven temperature was programmed: 40 °C, 2 min., 10 °C/min. ramp to 200 °C. All reactions were monitored by G. C. and the reactions terminated either when the starting material had been consumed or no further reaction appeared to continue. For reactions in which a Dean-Stark trap was used, the trap was filled with molecular sieves to a level below that of returning solvent turbulence. These were changed during reactions in which additional reagent was added after the reactions initiation. Molecular sieves were activated by heating in a 150 °C oven for at least 24 hours prior to use. NMR spectra were obtained on a VXR-300 spectrometer using $CDCl_3$ with 0.1% TMS as an internal standard δ (0.00 ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, sept = septet), integration and coupling. Infrared spectra were recorded on a Nicolet 42 FT-IR instrument.

Formation of 1-Bromo-2-hexene (I-98). 2-Hexene-1-ol (2.00 g, 20 mmol) and triphenylphosphine (6.29 g, 24 mmol) were added to 60 mL of CH_2Cl_2 and cooled to 0°C. Using a solids addition funnel, NBS (4.27 g, 24 mmol) was slowly added over a period of 1 h. The reaction was allowed to warm to room temperature. After 14 h, the solvent was removed and the solid mass extracted with low boiling petroleum ether (10 X 50 mL) with vigorous mixing. Solvent removal gave a clear, colorless oil (2.23 g, 68%

yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, J = 7.3 Hz, 3H), 1.41 (sext, J = 7.3 Hz, 2H), 2.04 (q, J = 6.7 Hz, 2H), 3.94 (d, J = 6.0 Hz, 2H), 5.60-5.80 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.49, 21.90, 33.40, 33.99, 126.40, 136.26; IR (oil/NaCl) 3032, 2961, 2874, 1661, 1464 cm^{-1}

General Method for *N*-Alkylation of primary anilines. The aniline (2.0-50 mmol, 4.0 equiv) and the alkyl bromide or alkyl iodide (1.0 equiv) were taken up in a 4:1 ethanol/water mixture (0.5 M relative to the aniline) along with Na_2CO_3 (0.6 equiv). After stirring at room temperature for 14 h, the EtOH was removed under reduced pressure and the crude oil purified by flash column chromatography (silica, 230-400 mesh; eluent - 5:95 Et_2O:low boiling petroleum ether). The solvents were evaporated and the mono- and dialkylated aniline by-products isolated.

***N*-Tosylaniline (I-54).** (30% Yield, mp 101 - 103 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.32 (s, 3H), 7.14 (m, 7H), 7.65 (s-br, 1H), 7.73, (d, J = 8.4 Hz, 2H); ^{13}C (75 MHz, $CDCl_3$) δ 21.41, 121.19, 124.98, 127.21, 129.15, 129.53, 129.58, 135.83, 136.59, 143.77; IR (KBr) 3052, 3059, 2899, 1483, 1339, 1159, 914, 756 cm^{-1}.

***N*-Methyl-*m*-nitroaniline (I-58).** (20% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.89 (d, J = 2.7 Hz, 3H), 4.19 (s-br, 1H), 6.86 (ddd, J = 8.4, 2.7, 0.9 Hz, 1H), 7.26 (t, J = 8.1 Hz, 1H), 7.36 (t, J = 2.4 Hz, 1H), 7.50 (ddd, J = 8.1, 2.1, 0.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.42, 105.67, 111.65, 118.40, 129.55, 149.39, 149.95; IR (oil/NaCl) 3410 (broad), 3000, 2800, 1541, 1343, 1094, 779, 729, 667 cm^{-1}.

***N*-Methyl-*p*-methoxyaniline (I-60).** (65% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.73 (s, 3H), 3.44 (bs, 1H), 3.70 (s, 3H), 6.50-6.56 (m, 2H), 6.74-6.80 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.30, 55.55, 113.39, 114.68, 143.59, 151.82; IR (oil/NaCl) 3405 (broad), 3058, 2988, 2832, 2811, 1620, 1514, 1466 cm^{-1}.

***N*-Methyl-*m*-methoxyaniline (I-68).** (73% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.74 (s, 3H), 3.67 (bs, 1H), 3.73 (s, 3H), 6.12 (t, J = 2.4 Hz, 1H), 6.18 (ddd, J = 8.1, 2.4, 0.9 Hz, 1H), 6.25 (ddd, J = 8.1, 2.4, 0.9 Hz, 1H), 7.06 (t, J = 8.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.44, 54.82, 98.08, 102.07, 105.42, 129.70, 150.65, 160.68; IR (oil/NaCl) 3413 (broad), 2994, 2836, 2811, 1617, 1499 cm^{-1}.

***N*-Benzyl-*m*-methoxyaniline (I-70).** (87% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.70 (s, 3H), 4.01 (bs, 1H), 4.25 (s, 2H), 6.15 (t, J = 2.4 Hz, 1H), 6.21 (ddd, J = 7.8, 2.4, 0.6 Hz, 1H), 6.26 (ddd, J = 8.4, 2.4, 0.9 Hz, 1H), 7.04 (t, J = 8.1 Hz, 1H), 7.20-7.38, (m, 5H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 48.14, 54.90, 98.74, 102.52, 105.84, 127.10, 127.38, 128.51, 129.87, 139.25, 149.45, 160.70; IR (oil/NaCl) 3416 (broad), 3029, 2836, 1615, 1495 cm^{-1}.

Formation of *N*-Benzylidene aniline (I-51) from the Condensation of Aniline and Benzaldehyde. To benzene (100 mL) were added aniline (9.31 g, 100.0 mmol), benzaldehyde (1.10 g, 100.0 mmol) and *p*-toluenesulfonic acid (0.33 g, 1.7 mmol). The reaction flask was fitted with a Dean-Stark trap containing 4 Å molecular sieves, and the solution heated at reflux for 14 h. After cooling the mixture, the volatiles were removed under reduced pressure and the imine recrystallized from low boiling petroleum ether to give *N*-benzyliminaniline (16.60 g, 92.0 mmol) in 92% yield. (mp 50-52 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15-7.22 (m, 3H), 7.31-7.45 (m, 5H), 7.84-7.90 (m, 2H), 8.39 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 120.77, 125.81, 128.63, 128.69, 129.03, 131.22, 136.14, 151.98, 160.15; IR (KBr) 3061, 2892, 1626, 1591, 1451 cm^{-1}.

Reduction of *N*-Benzylidene-aniline (I-51) to Benzylaniline (I-52). To a suspension of $LiAlH_4$ (10.36 g, 280.0 mmol) in Et_2O (56 mL) at 0 °C, was slowly added **I-51** (5.00 g 27.6 mmol). The mixture was heated at reflux for 72 h, after which the solution was cooled to 0 °C and quenched by the addition of water (10 mL), followed by 15% aqueous NaOH (10 mL), and water (30 mL). After stirring for 2 h, the solution was filtered through Na_2SO_4 and the solvent removed under reduced pressure at room temperature. The resulting oil was purified by flash column chromatography (silica, 230-400 mesh; eluent - 10:90 Et_2O:low boiling petroleum ether). The solvents were evaporated to give **I-52** (7.92 g, 210.0 mmol) in 75% yield: (mp 34-37 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.77 (bs, 1H), 4.09 (s, 2H), 6.46 (dd, J = 8.4, 0.9 Hz, 2H), 6.63 (tt, J = 7.2, 0.9 Hz, 1H), 7.10-7.18 (m, 2H), 7.20-7.35 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 48.15, 112.72, 117.42, 127.10, 127.39, 128.51, 129.15, 139.34, 148.03; IR (oil/NaCl) 3420 (broad), 3027, 2843, 1603, 1507, 1453 cm^{-1}.

Formation of *N*-Benzylidene-*p*-methoxyaniline (I-63) from the Condensation of *p*-Methoxyaniline and Benzaldehyde. To 100 mL of benzene were added *p*-methoxyaniline (1.79 g, 14.6 mmol), benzaldehyde (1.54 g, 14.6 mmol) and *p*-toluenesulfonic acid (0.05 g, 0.1 mmol). The reaction flask was fitted with a Dean-Stark trap containing 4 Å molecular sieves, and the solution was heated at reflux for 14 h. After cooling the mixture to room temperature, the volatiles were removed under reduced pressure, and the imine purified by flash column chromatography (silica, 230-400 mesh; eluent - 10:90 Et_2O:low boiling petroleum ether). The solvents were evaporated and the solvents removed under reduced pressure to give **I-63** (2.30g, 10.9 mmol) in 75% yield: (mp 70-71 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.79 (s, 3H), 6.87-6.95 (m, 2H), 7.18-7.26 (m, 2H), 7.40-7.47 (m, 3H), 7.83-7.91 (m, 2H), 8.45 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.38, 114.29, 122.13, 128.49, 128.63, 130.93, 136.38, 144.79, 158.23; IR (KBr) 3054, 2955, 2879, 2838, 1622, 1507 cm^{-1}.

Reduction of *N*-Benzylidene-*p*-methoxyaniline (I-63) to *N*-Benzyl-*p*-methoxyaniline (I-64). To a suspension of $LiAlH_4$ (4.04 g, 109.1 mmol) in Et_2O (20 mL) at 0 °C, was slowly added **I-63** (2.30 g, 10.9 mmol). The mixture was heated at reflux for 72 h, after which the solution was cooled to 0 °C and quenched by the addition of water (10 mL), 15% aqueous NaOH (10 mL), and water (30 mL). After stirring for 2 h, the solution was filtered through Na_2SO_4 and the solvent removed under reduced pressure. The oil was then purified by flash column chromatography (silica, 230-400 mesh; eluent - 20:80 Et_2O:low boiling petroleum ether). The solvents were evaporated and the aniline distilled under vacuum to give **I-64** (1.63 g, 7.8 mmol) in 71% yield.(mp 46-49 °C); ^1H NMR (300 MHz, $CDCl_3$) δ 3.70 (s, 3H), 3.75 (bs, 1H), 4.24 (s, 2H), 6.53-6.60 (m, 2H), 6.72-6.79 (m, 2H), 7.20-7.37 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 49.08, 55.66, 113.98, 114.78, 127.04, 127.42, 128.47, 139.60, 142.34, 152.04; IR (KBr) 3376 (broad), 2998, 2950, 2832, 1514 cm^{-1}.

Formation of Acetanilide (I-56) from Aniline and Acetic anhydride. To an acidified 50 °C aqueous solution of aniline (0.91 g, 9.7 mmol, 0.3 *M*) was rapidly added acetic anhydride (1.38 g, 13.5 mmol) followed immediately by addition of sodium acetate (2.25 g, 1.1 mmol) in water (60 mL). The mixture was cooled to 0 °C for 15 min and the white crystals collected by vacuum filtration. The crystals were then dissolved in methylene chloride, dried and the solvent removed under reduced pressure to give (1.10 g, 8.3 mmol) 85% of the desired **I-56**.(mp 113-115 °C); ^1H NMR (300 MHz, $CDCl_3$) δ 2.12 (s, 3H), 7.07 (td, J = 7.3, 1.2 Hz, 1H), 7.27 (td, J = 8.4, 1.8 Hz, 2H), 7.51 (dd, J = 7.3, 1.2 Hz, 2H), 8.37 (s-br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.24, 120.13, 124.15, 128.76, 147.91, 169.04; IR (KBr) 3295, 3195, 3059, 1665, 1599, 1557, 1435, 1323, 760, 694 cm^{-1}.

General Method for the *N*-Allylation of Secondary Anilines. The aniline (2.0-50.0 mmole, 1.0 equiv) and the alkyl bromide or alkyl chloride (1.2-4.0 equiv) were taken up in a 4:1 ethanol:water mixture (0.5 M relative to the aniline) along with Na_2CO_3 (0.6 equiv). After stirring at room temperature for 14 h the ethanol was removed under reduced pressure and the crude oil purified by flash column chromatography (silica, 230-400 mesh; eluent 5:95 Et_2O:low boiling petroleum ether). The solvents were evaporated and the di-alkylated anilines distilled under vacuum.

***N*-Allyl-*N*-methylaniline (I-49).** (91% yield, bp 107-110°C <1.5 mmHg): ^1H (300 MHz, $CDCl_3$) δ 2.78 (s, 3 H), 3.76 (dt, J = 5.0, 1.7 Hz, 2H), 5.05 (dq, J = 17.0, 1.7 Hz, 1H), 5.07 (dq, J = 10.4, 1.7 Hz, 1H), 5.73 (ddt, J = 17.0, 10.4, 5.0 Hz, 1H), 6.60-6.68 (m, 3H), 7.11-7.19 (m, 2H); ^{13}C (75.5 MHz) ($CDCl_3$) δ 37.57, 54.86, 112.16,

115.70, 116.17, 128.82, 133.60, 149.81; IR (oil/NaCl) 3063, 3027, 2980, 2897, 2815, 1644, 1599, 1449 cm^{-1}.

***N*-Allyl-*N*-benzylaniline (I-50).** (85% yield); ^1H NMR (300 MHz, $CDCl_3$) δ 3.85-3.91 (m, 2H), 4.43 (s, 2H), 5.10 (dq, *J* = 10.5, 1.8 Hz, 1H), 5.12 (dq, *J* = 17.4, 1.8 Hz, 1H), 5.78 (ddt, *J* = 17.4, 10.5, 4.8 Hz, 1H), 6.59-6.68 (m, 3H), 7.06-7.24 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.81, 53.76, 112.24, 116.06, 116.43, 126.41, 126.63, 128.40, 128.99, 133.52, 138.76, 148.73; IR (KBr) 3062, 3028, 2862, 1599, 1509 cm^{-1}.

***N*-Allyl-*N*-tosylaniline (I-53).** (87% yield, mp 66-68 °C); ^1H NMR (300 MHz, $DCDl_3$) δ ,2.41 (s, 3H), 4.17 (dt, *J* = 6.3, 1.4 Hz, 2H), 5.04 (sext, *J* = 0.9 Hz, 1H), 5.06 (dq, *J* = 17.1, 1.4 Hz, 1H), 5.73 (ddt, *J* = 17.1, 10.2, 6.3 Hz, 1H), 7.04 (m, sH), 7.26 (m, 5H), 7.48 (dt, *J* = 8.7, 2.1, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.46, 53.43, 118.68, 127.62, 128.76, 129.35, 132.74, 135.32, 139.02, 143.36; IR (KBr) 3068, 2928, 1493, 1183, 1038, 918, 696, 670 cm^{-1}.

***N*-Allyl-*N*-acetanilide (I-55).** (75% yield, mp 44-46 °C); ^1H NMR (300 MHz, $CDCl_3$) δ 1.86 (s, 3H), 4.38 (d, *J* = 6.3 Hz, 2H), 5.04 (s, 1H), 5.10 (d, *J* = 7.8 Hz, 1H), 5.87 (ddt, *J* = 17.1, 10.2, 6.3 Hz, 1H), 7.17 (d, *J* = 6.9 Hz, 2H), 7.36 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.47, 51.77, 117.53, 127.64, 127.86, 129.34, 132.95, 142.78; IR (KBr) 3009, 2938, 1645, 1593, 1501, 1399, 1277, 1009, 939, 916, 708 cm^{-1}.

***N*-Allyl-*N*-methyl-*m*-nitroaniline (I-57).** (99% yield); ^1H NMR (300 MHz, $CDCl_3$) δ 3.01 (s, 3H), 3.97 (dt, *J* = 4.8, 1.8 Hz, 2H), 5.13 (dq, *J* = 16.8, 1.8 Hz, 1H), 5.17 (dq, *J* = 17.1, 1.8 Hz, 1H), 5.81 (ddt, *J* = 17.1, 10.5, 1.8 Hz, 1H), 6.93 (ddd, *J* = 8.1, 2.4, 0.6 Hz, 1H), 7.28 (tt, *J* = 8.4, 1.2 Hz, 1H), 7.48 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 38.17, 54.81, 106.02, 110.55, 116.54, 117.56, 129.47, 132.25, 149.31, 149.74; IR (oil/NaCl) 3088, 2909, 2826, 1530, 1375, 1348, 1003, 735, 673 cm^{-1}.

***N*-Allyl-*N*-methyl-*p*-methoxyaniline (I-60).** (66% yield, bp <4 mmHg 80-86 °C); ^1H NMR (300 MHz, $CDCl_3$) δ 2.83 (s, 3H), 3.72 (s, 3H), 3.80 (dt, *J* = 5.3, 1.7 Hz, 2H), 5.14 (dq, *J* = 10.5, 1.7 Hz, 1H), 5.16 (dq, *J* = 17.4, 1.7 Hz, 1H), 5.82 (ddt, *J* = 17.4, 10.5, 5.3 Hz, 1H), 6.67-6.73 (m, 2H), 6.77-6.84 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 38.54, 55.55, 56.44, 114.54, 114.59, 116.26, 134.20, 144.38, 151.64; IR (oil/NaCl) 3077, 2936, 2832, 2809, 1642, 1516 cm^{-1}.

***N*-Allyl-*N*-benzyl-*p*-methoxyaniline (I-62).** (75% yield, bp <4 mmHg 128-139 °C); ^1H NMR (300 MHz, $CDCl_3$) δ 3.72 (s, 3H), 3.92 (dt, *J* = 5.1, 1.8 Hz, 2H), 4.46 (s, 2H), 5.16 (dq, *J* = 10.2, 1.8 Hz, 1H), 5.17 (dq, J = 17.2, 1.8 Hz, 1H), 5.87 (ddt, J = 17.2, 10.2, 5.1 Hz, 1H), 6.64-6.71 (m, 2H), 6.74-6.80 (m, 2H), 7.18-7.33 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 53.78, 54.82, 55.66, 114.35, 114.63, 116.33, 126.71, 126.80, 128.46, 134.17, 139.25, 143.61, 151.53; IR (oil/NaCl) 3085, 2934, 2832, 1512 cm^{-1}.

***N*-Allyl-*N*-methyl-*m*-methoxyaniline (I-67).** (68% yield, bp <4 mmHg 83-87 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.91 (s, 3H), 3.76 (s, 3H), 3.88 (dt, *J* = 5.1, 1.8 Hz, 2H), 5.13 (dq, *J* = 10.8, 1.8 Hz, 1H), 5.14 (dq, *J* = 17.1, 1.8 Hz, 1H), 5.82 (ddt, *J* = 17.1, 10.8, 5.1 Hz, 1H), 6.22-6.29 (m, 2H), 6.30-6.36 (m, 1H), 7.07-7.15 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 37.96, 54.95, 55.16, 98.90, 101.09, 105.50, 116.01, 129.66, 133.66, 150.79, 160.65; IR (oil/NaCl) 3085, 2998, 2938, 2836, 1609, 1503 cm^{-1}.

***N*-Allyl-*N*-benzyl-*m*-methoxyaniline (I-69).** (83% yield, bp <4 mmHg 130-137 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.68 (s, 3H), 3.96 (dt, *J* = 4.8, 1.8 Hz, 2H), 4.50 (s, 2H), 5.16 (dq, *J* = 10.5, 1.8 Hz, 1H), 5.17 (dq, *J* = 17.1, 1.8 Hz, 1H), 5.85 (ddt, *J* = 17.1, 10.5, 4.8 Hz, 1H), 6.22-6.35 (m, 3H), 6.32 (ddd, *J* = 8.4, 2.1, 0.8 Hz, 1H), 7.06 (t, *J* = 8.4 Hz, 1H), 7.17-7.31 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 53.03, 53.89, 54.88, 98.91, 101.19, 105.46, 116.21, 126.46, 126.71, 128.48, 129.71, 133.50, 138.77, 150.26, 160.63; IR (oil/NaCl) 3085, 3936, 2836, 1612, 1501, 1453 cm^{-1}.

***N*-Allyl-*N*-isobutyl-*m*-methoxyaniline (I-72).** (80% yield, bp <4 mmHg 35-36 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (d, *J* = 6.6 Hz, 6H), 2.06 (sept, *J* = 6.6 Hz, 1H), 3.06 (d, *J* = 7.2 Hz, 2H), 3.73 (s, 3H), 3.91 (dt, *J* = 4.8, 1.8 Hz, 2H), 5.09 (dq, *J* = 16.8, 1.8 Hz, 1H), 5.10 (dq, *J* = 11.1, 1.8 Hz, 1H), 5.78 (ddt, *J* = 16.8, 11.1, 4.8 Hz, 1H), 6.18-6.32 (m, 3H), 7.04-7.11 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.33, 27.30, 53.96, 54.82, 58.93, 98.83, 100.27, 105.39, 115.82, 129.51, 133.82, 149.98, 160.58; IR (oil/NaCl) 2955, 2870, 2836, 1611, 1576, 1499 cm^{-1}.

***N*-(*E*-2-hexene)-*N*-methyl-*p*-methoxyaniline (I-97).** (73% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, *J* = 7.4 Hz, 3H), 1.36 (sext, *J* = 7.4 Hz, 2H), 1.98 (q, *J* = 7.4 Hz, 2H), 2.78 (s, 3H), 3.70 (s, 3H), 3.73 (bd, *J* = 5.4 Hz, 2H), 5.43 (dtt, *J* = 15.3, 5.7, 1.1 Hz, 1H), 5.56 (dtt, *J* = 15.3, 5.7, 1.1 Hz, 1H), 6.67-6.73 (m, 2H), 6.76-6.82 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.46, 22.29, 34.22, 38.21, 55.41, 55.78, 114.41, 114.81, 125.66, 132.91, 144.55, 151.60; IR (oil/NaCl) 2957, 2932, 2872, 2832, 1620, 1562, 1464 cm^{-1}.

***N*-(*E*-2-hexene)-*N*-methyl-*m*-methoxyaniline (I-100).** (72% yield); ^{1}H NMR (300MHz, $CDCl_3$) δ 0.86 (t, *J* = 7.4 Hz, 3H), 1.36 (sext, *J* = 7.4 Hz, 2H), 1.98 (q, *J* = 7.4 Hz, 2H), 2.85 (s, 3H), 3.74 (s, 3H), 3.81 (dd, *J* = 5.4, 0.9 Hz, 2H), 5.42 (m, 1H), 5.55 (m, 1H), 6.21-6.28 (m, 2H), 6.31-6.36 (m, 1H), 7.09 (td, *J* = 8.0, 0.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.48, 22.29, 34.20, 37.57, 54.41, 54.80, 98.91, 100.97, 105.58, 125.18, 129.55, 132.63, 150.88, 160.59; IR (oil/NaCl) 2959, 2872, 2836, 1607, 1503, 1456 cm^{-1}.

Formation of *N*-Isobutyl-*m*-methoxyaniline (I-72) by a Modified *N*-alkylation Procedure. The aniline (4.00 g, 35.5 mmol) and isobutyl bromide (2.22 g, 16.2 mmol) were taken up in a 4:1 ethanol:water mixture (65 mL) along with Na_2CO_3 (1.02 g, 9.7

mmol). After stirring at reflux for 48 h the ethanol was removed under reduced pressure and the crude oil purified by flash column chromatography (silica, 230-400 mesh; eluent - 10:90 Et_2O:low boiling petroleum ether). The solvents were evaporated and product distilled under vacuum to give (1.21 g, 6.3 mmol) 78% yield of the **I-72**. ^1H NMR (300 MHz, $CDCl_3$) δ 0.96 (d, J = 6.7 Hz, 6H), 1.86 (nonet, J = 6.7 Hz, 1H), 2.89 (d, J = 6.7 Hz, 2H), 3.72 (bs, 1H), 3.77 (s, 3H), 6.14 (t, J = 2.4 Hz, 1H), 6.18-6.26 (m, 2H), 7.05 (t, J = 8.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.40, 27.95, 51.72, 54.94, 98.50, 101.95, 105.81, 129.83, 149.93, 160.80; IR (oil/NaCl) 3407 (broad), 2957, 2870, 2836, 1617, 1497 cm^{-1}.

General Method for *N*-Alkylation of Indole and Acetanilide. The indole or acetanilide (10.0 mmol, 1.0 equiv) was added to a previously prepared mixture of crushed KOH (40.0 mmol, 4.0 equiv) in DMSO (20 mL) and allowed to stir 45 min at room temperature. After cooling the mixture in an ice bath for several minutes, the alkyl bromide or alkyl iodide (20.0 mmol, 2.0 equiv) was then added. After stirring at room temperature for 1 h, a large excess of water was added and the product mixture extracted with Et_2O. The Et_2O was then removed under reduced pressure and the crude oil purified by flash column chromatography (silica, 230-400 mesh; eluent - 5:95 Et_2O:low boiling petroleum ether). The solvents were evaporated and the alkylated anilines distilled under vacuum or recrystallized.

***N*-Allylacetanilide (I-55).** (75% yield, mp 44-46 °C); ^1H NMR (300 MHz, $CDCl_3$) δ 1.86 (s, 3H), 4.30 (d, J = 6.3 Hz, 2H), 5.04 (s, 1H), 5.10 (d, J = 7.8 Hz, 1H), 5.87 (ddt, J = 17.1, 10.2, 6.3 Hz, 1H), 7.17 (d, J = 6.9 Hz, 2H), 7.36 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.47, 51.77, 117.53, 127.64, 127.86, 129.34, 132.95, 142.78; IR (KBr) 3008, 1645, 1593, 1501, 1399, 1277, 1009, 916, 708, 662 cm^{-1}.

***N*-Allylindole (I-59).** (73% yield); ^1H NMR (300 MHz, $CDCl_3$) δ 4.87 (dt, J = 7.0, 1.5 HZ, 2H), 5.43 (dq, J = 17.1, 1.5 Hz, 1H), 5.57 (dq, J = 10.5, 1.5 Hz, 1H), 6.29 (ddt, J = 21.0, 10.5, 5.3 Hz, 1H), 7.08 (dd, J = 3.0, 0.8 Hz, 1H), 7.42 (d, J = 3.0 Hz, 1H), 7.74 (m, 3H), 8.25 (d, J = 8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 48.13, 101.07, 109.40, 116.49, 119.18, 120.68, 121.23, 127.52, 128.48, 133.22, 135.83; IR (oil/NaCl) 3086, 2859, 1645, 1511, 1465, 1316, 1259, 1013, 992, 924, 737, 718 cm^{-1}.

***m*-Nitroanisole (I-76).** (54% yield, mp 35-38 °C); ^1H NMR (300 MHz, $CDCl_3$) δ 3.88 (s, 3H), 7.32 (ddd, J = 8.4, 2.7, 0.9 Hz, 1H), 7.43 (t, J = 8.1 Hz, 1H), 7.73 (t, J = 2.4 Hz, 1H), 7.82 (ddd, J = 7.2, 2.1, 1.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.83, 108.15, 115.75, 121.27, 121.36, 129.93, 121.01, 149.27, 160.16; IR (KBr) 2832, 1530, 1352, 1250, 1042, 801, 739, 671 cm^{-1}.

Formation of *m*-Nitrophenol (I-75) from *m*-Nitroaniline. To a stirred mixture of *m*-nitroaniline (2.87 g, 20.8 mmol) in 35% aqueous sulfuric acid (50 mL), 50 g of ice was added followed by sodium nitrite (1.70 g, 25.0 mmol) in water (20 mL). After 5 min several crystals of urea were added and the mixture then allowed to continue stirring for an additional 5 min. A solution of cupric nitrate (466.50 g, 2050 mmol) in water (900 mL), and cupric oxide (2.80 g, 19.6 mmol) were then added and the solution allowed to warm to room temperature. After 1 h the dark green mixture was extracted with Et_2O (15 X 50 mL). The solvent was removed under reduced pressure and the solid recrystallized from Et_2O/low boiling petroleum ether to give a yellow solid (2.40 g, 20.1 mmol) in 83% yield. (mp 95-97 °C); ^1H NMR (300 MHz, $CDCl_3$) δ 7.21 (dd, J = 8.1, 1.8 Hz, 1H), 7.40 (t, J = 9.0 Hz, 1H), 7.63 (m, 2H), 9.21 (s-br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 110.64, 115.02, 122.71, 131.07, 149.98, 158.86, 207.29; IR (KBr) 3391 (broad), 1522, 1350, 1300, 1078, 818, 739, 673 cm^{-1}.

Formation of *m*-Nitroanisole (I-76) from *m*-Nitrophenol (I-75) Using K_2CO_3 in Acetone. *m*-Nitrophenol (0.50 g, 3.6 mmol) and methyl iodide (0.27 g, 7.2 mmol) were added to a stirred mixture of K_2CO_3 (1.02 g, 7.2 mmol) in dry acetone (7.2 mL). After stirring for 14 h at room temperature, the mixture was filtered and the solvents removed under reduced pressure. The crude oil was purified by flash column chromatography (silica, 230-400 mesh; eluent - 10:90 Et_2O:low boiling petroleum ether). The solvents were evaporated to give the desired product (0.32 g, 0.3 mmol) in 58% yield. Spectroscopic data was identical to that reported for the product obtained by the general *N*-alkylation of Indole and Acetanilide procedure.

Formation of *m*-Nitroanisole (I-76) from *m*-Nitrophenol (I-75) Using Na_2CO_3 in Aqueous Ethanol. *m*-Nitrophenol (0.50 g, 3.6 mmol) and methyliodide (2.04 g, 14.4 mmol) were taken up in 7.2 mL of a 4:1 ethanol/water mixture along with Na_2CO_3 (0.76 g, 7.2 mmol). After stirring at room temperature for 14 h the ethanol was removed under reduced pressure, the crude oil purified by flash column chromatography (silica, 230-400 mesh; eluent - 5:95 Et_2O:low boiling petroleum ether). The solvents were evaporated to give *m*-nitroanisole (0.54 g, 3.5 mmol) in 98% yield. Spectroscopic data was identical to that reported for the product obtained by the general *N*-alkylation of Indole and Acetanilide procedure.

Formation of *m*-Methoxyaniline (I-70) from *m*-Nitroanisole (I-76). To a mixture of $TiCl_4$ (1.19 mL, 11.0 mmol) and $NaBH_4$ (1.25 g, 33.0 mmol) in dimethoxyethane (40 mL) was slowly added a solution of *m*-nitroanisole (1.53 g, 10.0 mmol) in dimethoxyethane (10 mL) at 0 °C. After 14 h at room temperature the reation mixture was cooled to 0 °C and quenched by carefull addtion of excess water. Extraction

of the reaction mixture with Et_2O followed by solvent removal at reduced pressure afforded a crude oil which was purified by flash column chromatography (silica, 230-400 mesh; eluent - 5:95 Et_2O:low boiling petroleum ether). The solvents were evaporated to give *m*-methoxyaniline (1.84 g, 15.0 mmol) in 75 % yield. ^1H NMR (300 MHz, $CDCl_3$) δ 3.66 (s-br, 2H), 3.74 (s, 3H), 6.21 (t, J = 2.4 Hz, 1H), 6.29 (dddd, J = 15.9, 8.4, 2.4, 0.9 Hz, 2H), 7.05 (t, J = 8.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 54.95, 100.93, 103.79, 107.79, 129.99, 147.74, 160.63; IR (oil/NaCl) 3372 (broad), 3002, 2838, 1603, 1496, 1461, 1208, 1173, 1159, 1037, 739, 689 cm^{-1}.

In a separate reaction acetone was allowed into the reaction mixture during quenching affording *N*-isopropyl-*m*-methoxyaniline. ^1H NMR (300 MHz, $CDCl_3$) δ 1.18 (d, J = 6.0 Hz, 6H), 3.47 (s-br, 1H), 3.85 (p, J = 6.3 Hz, 1H), 3.74 (s, 3H), 6.13 (t, J = 2.1 Hz, 1H), 6.18 (dd, J = 8.1, 2.7 Hz, 1H), 6.23 (dd, J = 8.1, 2.7 Hz, 1H), 7.05 (t, J = 8.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.88, 44.09, 54.89, 99.02, 101.83, 106.28, 129.85, 148.80, 160.75; IR (oil/NaCl) 3395 (broad), 2967, 2872, 2836, 1617, 1512, 1497, 1211, 830, 756, 689 cm^{-1}.

Alternate Method for the Formation of *N*-Tosylaniline (I-54) from Aniline and Tosyl Chloride. Aniline (2.50 g, 26.9 mmol) and tosyl chloride (5.65 g, 29.6 mmol) were added to chlorobenzene (54 mL) and heated at reflux for 18 h. After cooling, the solvent was removed under reduced pressure to give a solid. Recrystallization of the solid from Et_2O/low boiling petroleum ether under aspirator vacuum gave *N*-tosylaniline (4.40 g, 17.7 mmol) in 66% yield. Spectroscopic data was identical to that reported for the **I-54** obtained by the general *N*-alkylation procedure.

General Method for the Lewis Acid Catalyzed Rearrangement of *N*-Allyl-*N*-alkylanilines. The aniline (0.5-2.0 mmol, 1.0 eq) and the catalyst (0.6-2.4 mmol, 1.2 eq) were added to dry xylenes or toluene (0.5 *M* relative to the aniline) at -78 °C along with an internal standard of decalin. The reaction was heated to the appropriate temperature and allowed to react as described in the text. The reaction was then quenched at 0 °C by addition of a 15% aqueous NaOH solution and the organics concentrated. The crude products were isolated and purified by flash column chromatography (silica, 230-400 mesh; eluent, 5:95 Et_2O:low boiling petroleum ether).

Formation of *N*-Methyl-*o*-allylaniline (I-77) by Acid Catalyzed Rearrangement of *N*-Allyl-*N*-methylaniline (I-49). (45% yield): ^1H NMR (300 MHz) ($CDCl_3$) δ 2.83 (s, 3 H), 3.26 (bd, J = 6.1 Hz, 2H), 3.73 (bs, 1H), 5.08 (dq, J = 16.7, 1.8 Hz, 1H), 5.10 (dq, J = 10.4, 1.8 Hz, 1H), 5.93 (ddt, J = 16.7, 10.4, 6.1 Hz, 1 H), 6.63 (d, J = 8.2 Hz, 1H), 6.70 (td, J = 7.4, 1.1 Hz, 1H), 7.03 (dd, J = 7.4, 1.1 Hz, 1H), 7.12 (td, J = 7.4, 1.6 Hz, 1H); ^{13}C (75.5 MHz) ($CDCl_3$) δ 30.54, 36.21, 109.73, 115.97, 116.93,

123.39, 127.59, 129.47, 135.95, 147.22; IR (oil/NaCl) 3436 (broad), 3075, 2978, 2894, 2815, 1634, 1605, 1514, 1466 cm^{-1}.

Formation of *o*-Allyl-*N*-benzylaniline (I-87) by Acid Catalyzed Rearrangement of *N*-Allyl-*N*-benzylaniline (I-50). ^1H NMR (300 MHz, $CDCl_3$) δ 3.34 (bd, *J* = 6.3 Hz, 2H), 4.10 (bs, 1H), 4.34 (s, 2H), 5.07 (dq, *J* = 16.8, 1.7 Hz, 1H), 5.11 (dq, *J* = 10.5, 1.7 Hz, 1H), 5.95 (ddt, *J* = 16.8, 10.5, 6.3 Hz, 1H), 6.62 (d, *J* = 7.4 Hz, 1H), 6.70 (td, *J* = 7.4, 0.9 Hz, 1H), 7.06 (dd, *J* = 7.4, 1.2 Hz, 1H), 7.12 (td, *J* = 7.4, 1.5 Hz, 1H), 7.22-7.37 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.50, 48.13, 110.69, 116.29, 117.34, 123.49, 127.12, 127.35, 127.68, 128.57, 129.78, 135.93, 139.41, 146.11; IR (oil/NaCl) 3440 (broad), 3031, 2888, 2843, 1633, 1603, 1510 cm^{-1}.

Formation of *o*-Allyl-*N*-methyl-*p*-methoxyaniline (I-88) by Acid Catalyzed Rearrangement of *N*-Allyl-*N*-methyl-*p*-methoxyaniline (I-60). ^1H NMR (300 MHz, $CDCl_3$) δ 2.81 (s, 3H), 3.25 (dt, *J* = 6.0, 1.7 Hz, 2H), 3.37 (bs, 1H), 3.74 (s, 3H), 5.07 (dq, *J* = 17.1, 1.7 Hz, 1H), 5.12 (dq, *J* = 10.2, 1.7 Hz, 1H), 5.93 (ddt, *J* = 17.1, 10.2, 6.0 Hz, 1H), 6.58 (d, *J* = 8.7 Hz, 1H), 6.70 (d, *J* = 3.0 Hz, 1H), 6.76 (dd, *J* = 8.7, 3.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.37, 36.31, 55.70, 110.96, 112.02, 116.23, 116.50, 125.45, 135.76, 141.65, 151.81; IR (oil/NaCl) 3422 (broad), 2938, 2832, 2808, 1638, 1514, 1464 cm^{-1}.

Formation of *o*-Allyl-*N*-benzyl-*p*-methoxyaniline (I-89) by Acid Catalyzed Rearrangement of *N*-Allyl-*N*-benzyl-*p*-methoxyaniline (I-62). ^1H NMR (300 MHz, $CDCl_3$) δ 3.29 (dt, *J* = 6.0, 1.5 Hz, 2H), 3.72 (s, 3H), 3.78 (bs, 1H), 4.28 (s, 2H), 5.06 (dq, *J* = 17.1, 1.5 Hz, 1H), 5.11 (dq, *J* = 10.5, 1.5 Hz, 1H), 5.94 (ddt, *J* = 17.1, 10.5, 6.0 Hz, 1H), 6.57 (d, *J* = 8.4 Hz, 1H), 6.67 (d, *J* = 3.0 Hz, 1H), 6.66-6.73 (m, 1H), 7.21-7.37 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.46, 48.89, 55.65, 111.94, 112.02, 116.39, 116.55, 125.50, 127.05, 127.39, 128.51, 135.69, 139.67, 140.34, 151.93; IR (oil/NaCl) 3430 (broad), 3063, 2936, 2832, 1636, 1509, 1466 cm^{-1}.

Formation of *N*-Methyl-2-allyl-3-methoxyaniline (Minor Isomer, I-90) and *N*-Methyl-2-allyl-*5*-methoxyaniline (Major Isomer, I-91) by Acid Catalyzed Rearrangement of *N*-Allyl-*N*-methyl-*m*-methoxyaniline (I-67). Minor Isomer: ^1H NMR (300 MHz, $CDCl_3$) δ 2.84 (s, 3H), 3.38 (dt, *J* = 6.0, 1.9 Hz, 2H), 3.78 (bs, 1H), 3.80 (s, 3H), 5.02 (dq, *J* = 17.4, 1.8 Hz, 1H), 5.03 (dq, *J* = 9.3, 1.8 Hz, 1H), 5.88 (ddt, *J* = 17.4, 9.3, 6.0 Hz, 1H), 6.35 (d, *J* = 8.4 Hz, 1H), 6.38 (d, *J* = 8.4 Hz, 1H), 7.14 (t, *J* = 8.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.90, 31.04, 55.78, 100.66, 103.68, 114.76, 125.90, 127.67, 136.05, 148.70, 157.60; IR (oil/NaCl) 3438 (broad), 3077, 2939, 2836, 2815, 1601, 1591, 1478 cm^{-1}. Major Isomer: ^1H NMR (300 MHz, $CDCl_3$) δ 2.82 (s, 3H), 3.21 (dt, *J* = 6.0, 1.8 Hz, 2H), 3.77 (bs, 1H), 3.79 (s, 3H), 5.05 (dq, *J* = 16.8, 1.8 Hz,

1H), 5.08 (dq, J = 10.8, 1.8 Hz, 1H), 5.91 (ddt, J = 16.8, 10.8, 6.0 Hz, 1H), 6.19-6.27 (m, 2H), 6.93 (d, J = 8.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.62, 35.69, 55.10, 97.19, 100.74, 115.79, 116.31, 130.17, 136.53, 148.51, 159.83; IR (oil/NaCl) 3438 (broad), 3077, 2938, 2834, 2809, 1617, 1520 cm^{-1}.

Formation of *N*-Benzyl-2-allyl-3-methoxyaniline (Minor Isomer, I-92) and *N*-Benzyl-2-allyl-*5*-methoxyaniline (Major Isomer, I-93) by Acid Catalyzed Rearrangement of *N*-Allyl-*N*-benzyl-*m*-methoxyaniline (I-69). Minor Isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.42 (dt, J = 6.0, 1.8 Hz, 2H), 3.79 (s, 3H), 4.16 (bs, 1H), 4.34 (s, 2H), 5.01 (dq, J = 16.8, 1.8 Hz, 1H), 5.02 (dq, J = 11.0, 1.8 Hz, 1H), 5.89 (ddt, J = 16.8, 11.0, 5.4 Hz, 1H), 6.32 (bd, J = 8.4 Hz, 1H), 6.37 (d, J = 8.4 Hz, 1H), 7.06 (t, J = 8.4 Hz, 1H), 7.21-7.36 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.02, 48.35, 55.77, 100.81, 104.50, 114.97, 127.06, 127.30, 127.65, 128.55, 128.62, 135.93, 139.61, 147.43, 157.90; IR (oil/NaCl) 3440 (broad), 2936, 2836, 1634, 1599, 1476 cm^{-1}. Major Isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.25 (dt, J = 6.0, 1.8 Hz, 2H), 3.72 (s, 3H), 4.13 (bs, 1H), 4.31 (s, 2H), 5.05 (dq, J = 17.1, 1.8 Hz, 1H), 5.09 (dq, J = 10.5, 1.8 Hz, 1H), 5.93 (ddt, J = 17.1, 10.5, 6.0 Hz, 1H), 6.19-6.27 (m, 2H), 6.95 (d, J = 8.1 Hz, 1H), 7.20-7.37 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.82, 48.12, 55.04, 97.96, 101.16, 115.95, 116.22, 127.15, 127.38, 128.57, 130.32, 136.41, 139.21, 147.22, 159.68; IR (oil/NaCl) 3438 (broad), 3063, 2834, 1617, 1586, 1520, 1466 cm^{-1}.

Formation of *N*-Isobutyl-2-allyl-3-methoxyaniline (Minor Isomer, I-94) and *N*-Isobutyl-2-allyl-*5*-methoxyaniline (Major Isomer, I-95) by Acid Catalyzed Rearrangement of *N*-Allyl-*N*-Isobutyl-*m*-methoxyaniline (I-72). Minor Isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (d, J = 6.6 Hz, 6H), 1.89 (nonet, J = 6.6 Hz, 1H), 2.92 (d, J = 6.6 Hz, 2H), 3.39 (dt, J = 5.7, 1.8 Hz, 2H), 3.79 (s, 3H), 3.83 (bs, 1H), 5.03 (dq, J = 10.8, 1.8 Hz, 1H), 5.06 (dq, J = 16.8, 1.8 Hz, 1H), 5.88 (ddt, J = 16.8, 10.8, 5.7 Hz, 1H), 6.31 (d, J = 8.2 Hz, 1H), 6.33 (d, J = 8.2 Hz, 1H), 7.09 (t, J = 8.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.57, 28.00, 28.13, 51.89, 55.76, 100.17, 104.03, 110.84, 114.91, 127.58, 136.30, 147.90, 157.67; IR (oil/NaCl) 3430 (broad), 3076, 2959, 2870, 2836, 1635, 1601, 1476 cm^{-1}. Major Isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.98 (d, J = 6.7 Hz, 6H), 1.91 (nonet, J = 6.7 Hz, 1H), 2.91 (d, J = 6.7 Hz, 2H), 3.24 (dt, J = 6.3, 1.8 Hz, 2H), 3.79 (s, 3H), 3.83 (bs, 1H), 5.06-5.16 (m, 2H), 5.93 (ddt, J = 17.7, 9.6, 6.3 Hz, 1H), 6.17-6.24 (m, 2H), 6.94 (d, J = 8.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.58, 27.84, 36.14, 51.59, 55.12, 97.42, 100.43, 115.88, 116.08, 130.33, 136.82, 147.74, 159.79; IR (oil/NaCl) 3432 (broad), 3079, 2957, 2870, 2834, 1617, 1588, 1520 cm^{-1}.

Formation of *N*-Methyl-2-(2-vinylpentane)-3-methoxyaniline (Minor Isomer, I-102), *N*-Methyl-2-(2-vinylpentane)-*5*-methoxyaniline (Major Isomer, I-101) as well

as *N*-Methyl-3-methoxy-4-(2-*E*-hexene)-aniline (*E*-Isomer, I-103) by Acid Catalyzed Rearrangement of *N*-*trans*-2-Hexene-*N*-methyl-*m*-methoxyaniline (I-100). Minor Isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, *J* = 7.2 Hz, 3H), 1.07-1.37 (m, 2H), 1.70-1.89 (m, 2H), 2.77 (s, 3H), 3.77 (s, 3H), 3.98-4.17 (m, 2H), 5.07 (dt, *J* = 6.6, 2.4 Hz, 1H), 5.12 (d, *J* = 2.4 Hz, 1H), 6.11 (m, 1H), 6.30 (bd, *J* = 8.1 Hz, 2H) 6.37 (bd, J = 8.1 Hz, 1H), 7.10 (t, *J* = 8.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$), δ 14.18, 21.11, 31.06, 32.49, 37.58, 55.78, 100.89, 104.45, 113.37, 114.28, 127.58, 141.64, 148.91, 158.10; IR (oil/NaCl) 3426 (broad), 2919, 2848, 1588, 1476 cm^{-1}. Major Isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (t, *J* = 7.4, 3H), 1.21-1.48 (m, 2H), 1.62-1.81 (m, 2H), 2.82 (s, 3H), 3.15 (bq, *J* = 7.4 Hz, 1H), 3.79 (s, 3H), 3.87 (bs, 1H), 5.01 (dt, *J* = 11.7, 1.4 Hz, 1H), 5.06 (dt, *J* = 10.5, 1.4 Hz, 1H), 5.81(ddt, *J* = 17.7, 10.5, 7.4 Hz, 1H), 6.22 (d, *J* = 2.4 Hz, 1H), 6.28 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.98 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.09, 20.75, 30.80, 35.48, 43.19, 55.04, 97.49, 100.92, 114.13, 120.41, 127.59, 141.76, 148.28, 159.31; IR (oil/NaCl) 3438 (broad), 3077, 2959, 2930, 2872, 2836, 2807, 1615, 1586, 1463 cm^{-1}. *E*-Isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.4 Hz, 3H), 1.37 (sext, *J* = 7.4 Hz, 2H), 1.97 (bq, *J* = 7.4 Hz, 2H), 2.82 (s, 3H), 3.20 (d, *J* = 7.4 Hz, 2H), 3.62 (bs, 1H), 3.79 (s, 3H), 5.43 (dtt, *J* = 15.0, 6.5, 1.4 Hz, 1H), 5.43 (dtt, *J* = 15.0, 6.5, 1.4 Hz, 1H), 6.13-6.20 (m, 2H), 6.94 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.69, 22.69, 31.03, 32.21, 34.66, 55.25, 96.26, 104.09, 118.56, 129.13, 130.07, 130.70, 149.03, 158.03; IR (oil/NaCl) 3413 (broad), 2957, 2930, 2872, 2836, 1618, 1516, 1464 cm^{-1}.

Formation of *N*-Methyl-2-(2-vinylpentane)-4-methoxyaniline (I-99) by Acid Catalyzed Rearrangement of *N*-Methyl-*N*-(*trans*-2-hexene)-*p*-methoxyaniline (I-97). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (t, *J* = 7.4 Hz, 3H), 1.22-1.48 (m, 2H), 1.62-1.81 (m, 2H), 2.80 (s, 3H), 3.26 (bq, *J* = 7.4 Hz, 2H), 3.47 (bs, 1H), 3.75 (s, 3H), 5.02 (dt, *J* = 17.1, 1.4 Hz, 1H), 5.06 (dt, *J* = 10.2, 1.4 Hz, 1H), 5.81 (ddd, *J* = 17.1, 10.2, 7.4 Hz, 1H), 6.57-6.66 (m, 1H), 6.71-6.76 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.03, 20.65, 31.54, 35.52, 43.50, 55.61, 111.10, 111.38, 114.24, 114.49, 129.87, 141.09, 141.35, 152.04; IR (oil/NaCl) 3413 (m-broad), 3077, 2957, 2872, 2832, 2809, 1647, 1510, 1458 cm^{-1}.

Formation of 1,2-Dimethyl-2,3-dihydroindole (I-85) by Photochemical Ring Closure of *o*-Allyl-*N*-methylaniline (I-77). *o*-Allyl-*N*-methylaniline (0.12 g, 0.82 mmol) and Argon degassed thiophene free benzene (41 mL) were placed in a pyrex tube and subjected to a 450 Watt medium pressure Hg lamp. After 3.5 h the solvent was removed under reduced pressure. The reaction had gone 50% to completion by G.C. The resulting oil was separated by preparative TLC (silica) to give the desired product. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (d, *J* = 6.3 Hz, 3H), 1.71 (s, 3H), 2.59 (dd, *J* = 15.3, 10.5 Hz, 1H),

3.08 (dd, J = 15.3, 8.1 Hz, 1H), 3.39 (qt, J = 2.4, 1.5 Hz, 1H), 6.45 (d, J = 7.8 Hz, 1H), 6.65 (td, J = 7.4, 0.9 Hz, 1H), 7.06 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.7, 33.7, 37.4, 62.8, 107.1, 117.8, 124.0, 127.3, 129.2; IR (oil/NaCl) 3073, 2921, 2815, 1605, 1586, 1514, 1466, 1312, 1264, 1065, 914, 748, 648 cm^{-1}.

Formation of 1,2-Dimethyl-2,3-dihydroindole (I-85) by $Hg(OAc)_2$ Catalyzed Ring Closure of *o*-Allyl-*N*-methylaniline (I-77). *o*-Allyl-*N*-methylaniline (1.42 g, 9.66 mmol) was added to anhydrous methanol (48.3 mL) followed by addition of $Hg(OAc)_2$ (3.69 g, 11.59 mmol) at room temperature. After 1 h the reaction mixture was cooled to 0 °C and reduced by careful addition of $NaBH_4$ (2 equiv, 0.5 *M* solution) in NaOH (2 *N*). After 20 h the reaction mixture was extracted repeatedly with Et_2O and the organics concentrated under reduced pressure. The crude oil was purified by flash column chromatography (silica, 230-400 mesh; eluent - 1:99 Et_2O:low boiling petroleum ether). The solvents were evaporated to give the desired product (0.14 g, 0.9 mmol) in 10% yield.

Formation of 2,3-Dibromopropylbenzene (I-106). To Mg turnings (15.29 g, 636.94 mmol) in dry Et_2O (40.0 mL) was slowly added a solution of bromobenzene (10.00 g, 63.69 mmol) in dry Et_2O (23.7 mL). The Grignard reagent was allowed to form over an hour at room temperature (the solution turned dark brown). The solution was transfered *via* cannula to a dry flask. The temperature was lowered to 0°C and allylbromide (9.35 g, 76.43 mmol) was added dropwise *via* syringe. The reaction was allowed to warm to room temperature. After 14 h the reaction was quenched by addition of water. The organics were collected and the aqueous layer washed with 4 portions of ether (20.0 mL).

The organics were dried, collected and cooled to -78°C. To this mixture was added Br_2 (12.23 g, 76.43 mmol) dropwise. The solution was allowed to stirr for 1 h and remained red. Solvent removal under reduced pressure gave an orange oil. The crude oil was purified by flash column chromatography (silica, 230-400 mesh; eluent -5:95 Et_2O:low boiling petroleum ether). The solvents were evaporated to yield the desired product as a clear oil (16.28 g, 92% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.13 (dd, J = 14.5, 8.3 Hz, 1 H), 3.51 (dd, J = 14.5, 4.8 Hz, 1 H), 3.63 (dd, J = 10.5, 8.9 Hz, 1 H), 3.85 (dd, J = 10.3, 4.2 Hz, 1 H), 4.37 (m, 1 H), 7.24-7.37 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.02, 42.00, 52.39, 127.18, 128.48, 129.48, 136.83; IR (oil/NaCl) 3106, 3031, 2938, 1497, 1431, 1252, 1219, 1142 cm^{-1}.

Formation of 2,3-Dibromopropyl-*p*-nitrobenzene (I-107). To a mixture of 70% HNO_3 (26.6 mL) and 98% H_2SO_4 (33.7 mL) was added 2,3-Dibromopropylbenzene (16.28 g, 58.58 mmol) dropwise at -15°C. The reaction was then allowed to warm to 0°C

over 45 min. After an additional 15 min the reaction was cooled again to -15°C and quenched by partitioning between water and ether. The organics were collected, dried and the solvent removed under reduced pressure to give oils. The crude oils were purified by flash column chromatography (silica, 230-400 mesh; eluent - Et_2O:low boiling petroleum ether). The solvents were evaporated to give the desired pure product. (13.66 g, 72% yield); ^1H NMR (300 MHz, $CDCl_3$) δ 3.21 (dd, *J* = 14.6, 8.6 Hz, 1 H), 3.62 (t, *J* = 10.2 Hz, 1 H), 3.67 (dd, *J* = 14.6, 4.2 Hz, 1 H), 3.90 (dd, *J* = 10.7, 4.2 Hz, 1 H), 4.37 (m, 1 H), 7.42-7.51 (m, 2 H), 8.14-8.24 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.31, 41.42, 50.74, 123.58, 130.38, 135.91, 144.13; IR (oil/NaCl) 3079, 2973, 2855, 1607, 1520, 1435, 1346, 1250 cm^{-1}.

Formation of *p*-Allylnitrobenzene (I-108). To a solution of 2,3-dibromopropyl-*p*-nitrobenzene (3.00 g, 9.28 mmol) in EtOH (92.8 mL) was added NaI (2.78 g, 18.58 mmol) as a single portion at room temperature. The reaction was heated at reflux for 1.5 h. NaI (2.78 g, 18.58 mmol) was again added in small portions. After 6 h total, the reaction was allowed to cool to room temperature and stir for 14 h. The solvent was removed under reduced pressure and the residue partitioned between $CHCl_3$ and aqueous 50% saturated sodium bicarbonate solution. The organics were collected, dried and the solvent removed under reduced pressure to give an oil. The crude oil was purified by flash column chromatography (silica, 230-400 mesh; eluent - low boiling petroleum ether). The solvents were evaporated to yield the desired product as a clear oil (1.05 g, 6.43 mmol) in 69% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 3.49 (d, *J* = 6.6 Hz, 2 H), 5.12 (dq, *J* = 16.9, 1.6 Hz, 1 H), 5.16 (dq, *J* = 10.2, 1.6 Hz, 1 H), 5.94 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1 H), 7.32-7.37 (m, 2 H), 8.10-8.70 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 39.86, 117.37, 121.28, 123.64, 129.35, 135.44, 147.77; IR (oil/NaCl) 3081, 2853, 1640, 1605, 1518, 1346 cm^{-1}.

Preparation of *p*-Allylaniline (I-109). To a solution of *p*-allylnitrobenzene (0.55 g, 3.37 mmol) in benzene (20.0 mL) was added activated Fe (5.00 g, 89.28 mmol) and water (2.0 g, 111.11 mmol). The reaction was brought to reflux. After 2 h a trace of HCl was added to the reaction along with a several drops of water. After 12 h the reaction was quenched by partitioning between water and Et_2O. The organics were separated, dried and the solvents removed under reduced pressure to yield an oil. The crude oil was purified by flash column chromatography (silica, 230-400 mesh; eluent - Et_2O:low boiling petroleum ether). The solvents were evaporated to yield the desired product as an oil (0.43 g, 95% yield); ^1H NMR (300 MHz, $CDCl_3$) δ 3.28 (d, *J* = 6.6 Hz, 2 H), 3.56 (s-br, 2 H), 5.02 (dq, *J* = 10.3, 1.7 Hz, 1 H), 5.04 (dq, *J* = 17.1, 1.7 Hz, 1 H), 5.94 (ddt, *J* = 17.1, 10.3, 6.7 Hz, 1 H), 6.61-6.65 (m, 2 H), 6.95-7.00 (m, 2 H); ^{13}C NMR (75 MHz,

$CDCl_3$) δ 39.36, 115.06, 115.25, 129.34, 130.02, 138.18, 144.45; IR (oil/NaCl) 3436 (broad), 3355 (broad), 3218 (broad), 3077, 3004, 2897, 1624, 1516, 1435, 1273 cm^{-1}.

Formation of *N*-Methyl-*p*-allylaniline (I-104). The *p*-allylaniline (0.20 g, 1.50 mmol) and MeI (0.05 g, 0.38 mmol) were taken up in a 4:1 ethanol:water mixture (3.0 mL) along with Na_2CO_3 (0.02 g, 0.22 mmol). After stirring at room temperature for 14 h the ethanol was removed under reduced pressure and the crude oil purified by flash column chromatography (silica, 230-400 mesh; eluent - 5:95 Et_2O:low boiling petroleum ether). The solvents were evaporated to give a clear colorless oil. (0.06 g, 37% yield); ^1H NMR (300 MHz, $CDCl_3$) δ 2.82 (s, 3 H), 3.28 (d, J = 6.9 Hz, 2 H), 3.60 (s-br, 1 H), 5.01 (dq, J = 10.2, 1.7 Hz, 1 H), 5.04 (dq, J = 16.8, 1.7, 1 H), 5.95 (ddt, J = 16.8, 10.2, 6.9, 1 H), 6.54-6.59 (m, 2 H), 6.99-7.03 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.96, 39.37, 112.58, 114.93, 128.69, 129.29, 138.37, 147.69; IR (oil/NaCl) 3413 (broad), 2977, 2893, 2813, 1615, 1522, 1318, 1264, 1063 cm^{-1}.

References.

1) Katritzky, A. R.; Rees, C. W. Comprehensive Heterocyclic Chemistry, Vol. 4; Pergamon Press: 1984.
2) Smith, A. B., III; Visnick, N.; Haseline, J. N.; Spanger, P. A. *Tetrahedron*, **1986**, *42*, 2959.
3) Harrington, P. J.; Hegedus, L. S.; Mc Daniel, K. F. *J. Am. Chem. Soc.* **1987**, 109, 4335.
4) Murai, Y.; Masuda, G.; Inoue, S.; Sato, K. *Heterocycles*, **1991**, *32*, 1377.
5) Murai, Y.; Masuda, G.; Inoue, S.; Sato, K. *Heterocycles*, **1991**, *32*, 1377.
6) Harrington, P. J.; Hegedus, L. S. *J. Org. Chem.* **1984**, *49*, 2657.
7) Muratake, H.; Natsume, M. *Heterocycles* **1989**, *29*, 783.
8) Lutz, R. *Chem. Rev.* **1984**, *84*, 205.
9) Jolidon, S.; Hansen, H.-J. *Helv. Chim. Acta.* **1977**, *60*, 978.
10) Frater, G.; Habish, A.; Hansen, H.-J.; Schmid, H. *Helv. Chim. Acta.* **1969**, *52*, 335.
11) Schmid, M.; Hansen, H.-J.; Schmid, H. *Helv. Chim. Acta.* **1973**, *56*, 105.
12) Abdrakhmanov, I. B.; Sharafutdinov, V. M.; Tolstikov, G. A. *Zhur. Org. Chem.* **1984**, 163.
13) Abdrakhmanov, I. B.; Fakhretdinov, R. N.; Khusnutdinov, R. N.; Dzhemilev, U. M. *Zhur. Org. Chem.* **1982**, 2325.
14) Hurd, C. D.; Jenkins, W. W. *J. Org. Chem.* **1957**, *22*, 1418.

15) Abdrakmanov, I. B.; Sharafutdinov, V. M.; Nigmatullin, N. G.; Sagitdinov, I. A.; Tolstikov, G. A. *Zhur. Org. Chem.* **1982**, 1278.

16) Krowicki, K.; Paillous, N.; Riviere, M.; Lattes, A. *J. Hetero. Chem.* **1976**, *13*, 555.

17) Bader, A. R.; Bridgwater, R.J.; Freeman, P. R. *J. Am. Chem. Soc.* **1961**, *83*, 3319.

18) Takamatsu, N.; Inoue, S.; Kishi, Y. *Tetrahedron Lett.* **1971**, *48*, 4661.

19) Abdrakhmanov, I. B.; Sharafutdinov, V. M.; Sagitdinov, I. A.; Tolstikov, G. A *Zhur. Org. Chem* **1978**, 2350.

20) Brown, J. B.; Henbest, H. B.; Jones, E. R. H. *J. Chem. Soc.* **1952**, 3172.

21) Casnati, G.; Francioni, M.; Guareschi, A.; Pochini, A. *Tetrahedron Lett.* **1969**, 29, 2485.

22) Büchi, G.;Mak, C.-P. *J. Org. Chem.* **1977**, *42*, 1784.

23) Jolidon, S.; Hanison, H.-J. *J. Org. Chem.* **1974**, *39*, 846.

24) Inada, S.; Nagai, K.; Takayanagi, Y.; Okazaki, M. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 833.

25) Aristoff, P. A.; Johnson, P. O.; Harrison, A. W. *J. Am .Chem. Soc.* **1985**, *107*, 7967.

26) Katayama, H.; Tachikoma, Y.; Takatsu, N.; Kato, A. *Chem. Pharm. Bull.* **1983**, *31*, 2220.

27) Ketcha, D. *Tetrahedron Lett.* **1988**, *29*, 2151.

28) Tao, X.; Nichiyama, S.; Yamamura, S. *Chem. Lett.* **1991**, 1785.

29) Tweedie, V.; Allibashi, J. *J. Org. Chem.* **1960**, *26*, 3676.

30) (a) Cohen, T.; Dietz Jr., A. G.; Miser, J. R. *J. Org. Chem.* **1977**, *42*, 2053. (b) Johnstone, R. A. W.; Rose, M. E. *Tetrahedron* **1979**, *35*, 2169. (c) Kano, S.; Tanaka, Y.; Sugino, E.; Satsoshi, H. *Synthesis* **1980**, 695.

31) Aristoff, P. A.; Johnson, P. D.; Harrison, A. W. *J. Am. Chem. Soc.* **1985**, *107*, 7967.

32) Bose, A. K.; Lal, B. *Tetrahedron Lett.* **1973**, *33*, 3937.

33) (a) Hobbs, C. F.; Hamman, W. C. *J. Org. Chem.* **1970**, *35*, 4188. (b) Gough, R.G.; Dixon, J. A. *J. Org. Chem.* **1968**, *33*, 2148

34) Robertson, G. R. *Org. Syn.* **1932**, *I*, 389.

35) Hazlet, S. E.; Dornfield, C. A. *J. Am. Chem. Soc.* **1944**, *60*, 1781.

CHAPTER II.
AZA-ANNULATION AS A ROUTE TO HYDROXYLATED ALKALOIDS: THE TOTAL SYNTHESES OF D-MANNONOLACTAM AND DEOXYMANNOJIRIMYCIN

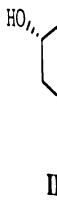
Introduction.

Naturally occurring piperidine alkaloids exhibit a wide variety of biological activities.[1] Although found in a number of organisms, these alkaloids possess alike stereochemical arrays similar to those found in simple sugars such as glucose (**II-1**), D-mannose (**II-2**), and fucose (**II-3**) (Figure II-1). For example, deoxymannojirimycin (**II-4**), with stereochemistry similar to **II-2**, is an inhibitor of both bovine α-L-fucosidase and mannosidase I for glycoprotein processing. D-mannonolactam (**II-7**) inhibits both α-D-mannosidase and α-D-glucosidase.[2] Deoxynojirimycin (**II-4**), stereochemically similar to **II-1**, has exhibited selective inhibition of α-glucosidases I, and II without effective inhibition of α-mannosidase.[3] The more lipophilic alkaloids, prosopinine (**II-5**) and cassine (**II-8**) are also very biologically active.[4] A convergent route to these alkaloids would thus be beneficial.

While compounds **II-6** and **II-7** have been prepared from their sugar analogs,[5] an efficient and convergent synthesis of these compound types from simple organic molecules has not been previously reported (Scheme II-1). Key to the preparation of any of the aforementioned alkaloids is the construction of the piperidine ring of the type represented by **II-11** (Figure II-2). In **II-11**, particular attention to the stereochemistry of C-4 relative to C-5 is critical. Protected hydroxyl functionality at C-4 and C-6 must also be incorporated. Further stereochemical features at C-2 and C-3 must then be incorporated efficiently and specifically relative to the first two. Adding the tether to C-1 could then be executed if desired. It is the objective of this work to use the aza-annulation in the design of a convergent route toward the preparation of these highly active compounds.

Figur

(gl

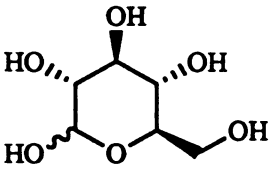


D

(deoxy

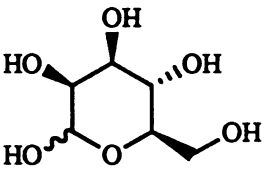
(D-ma

Figure II-1. Hydroxylated Piperidine Alkaloids and Stereochemically Similar Sugars



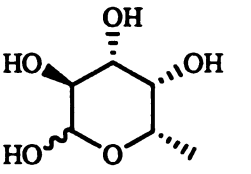
II-1

(glucose)



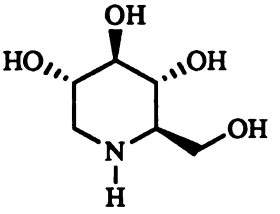
II-2

(D-mannose)



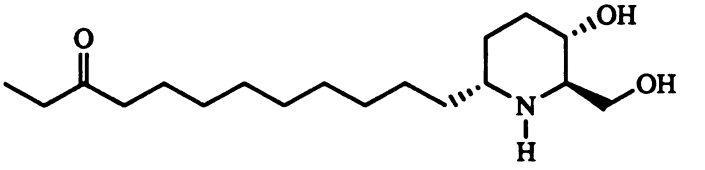
II-3

(fucose)



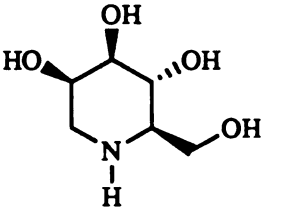
II-4

(deoxynojirimycin)



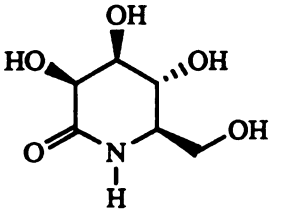
II-5

(prosopinine)



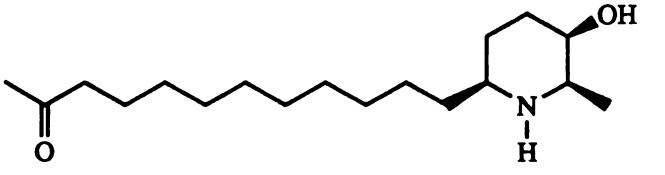
II-6

(deoxymannojirimycin)



II-7

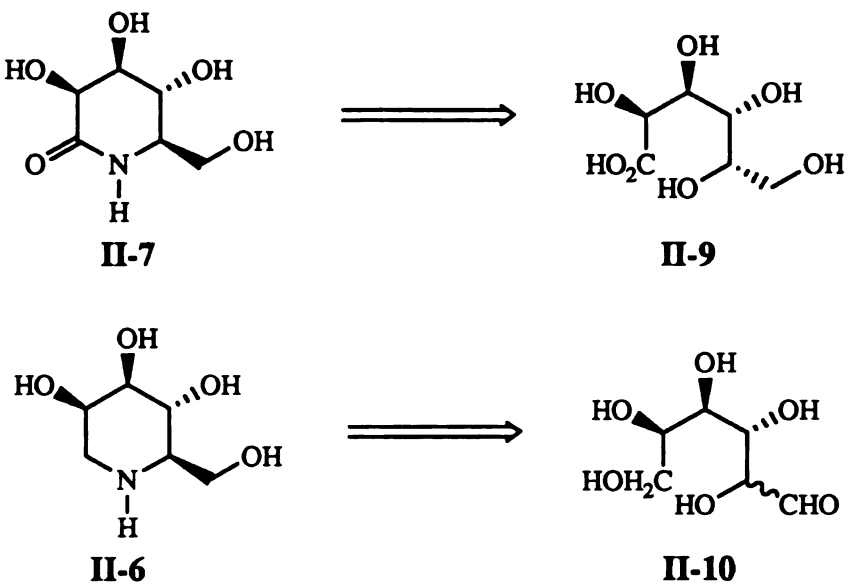
(D-mannonolactam)



II-8

(cassine)

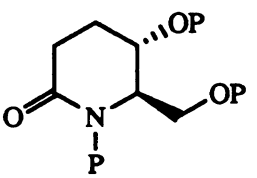
Scheme II-1. Preparation of **II-6** and **II-7** from Sugar Analogs



II-7 **II-9**

II-6 **II-10**

Figure II-2. Alkaloid Precursor Target



II-11

Results and Discussion.

The initial piperidine ring system was prepared via aza-annulation.[6] Desired substitution at C-5 as well as at C-4 was incorporated at the onset, in the preparation of the initial ß-diketone, ß-ketoester, or acetylenic ester. In the simplest instance, benzylamine was added to acetoacetone to form the enamine which was annulated with acryloyl chloride to give **II-12** in 94% yield (Scheme II-2). Reduction of **II-12** to **II-13** was afforded in 81% yield using Pd/C and H_2. Baeyer-Villiger oxidation of **II-13** (epimerized to an equilibrium 24:76 ratio of cis:trans isomeric products) yielded **II-14** in 45% yield. Subsequent hydrolysis of **II-14** provided **II-15** in 89% yield. Of particular interest were the development of predictable conditions for cis-hydrogenation of **II-12** and development of an efficient method for the oxidation of **II-13** to **II-14**.

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II-12

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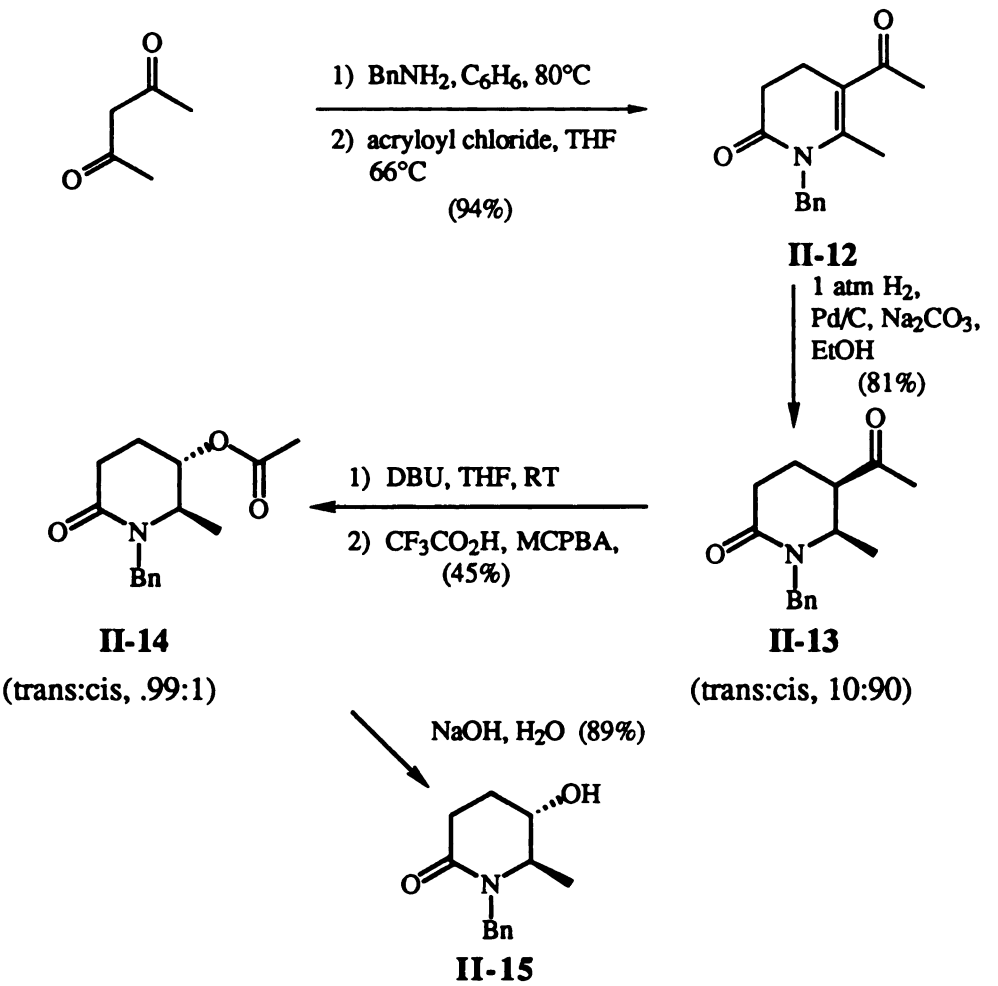
Scheme II-2. Preparation of Initial Precursor Analog **II-15**



Examination of a variety of oxidation conditions had been initiated prior to optimization of the hydrogenation conditions.[7] A series of oxidations were attempted using **II-12**, which was a mixture of isomers at the reduced double bond (trans:cis, 10:90). Conditions and percent reaction mixture as product are given in Table II-1.

Table II-1. Baeyer-Villiger Oxidation Studies on cis **II-13**

Entry[ref]	Conditions[a]	time (hours)	% rxn. mix as prod.[b]
1[7a]	MCPBA, NaOAc, $CHCl_3$, reflux	96	4
2[7b]	Fe_2CO_3, benzaldehyde, C_6H_6, O_2, RT	96	1
3[7c]	H_2O_2, Ac_2O, NaOAc, 0°C to RT	120	0
4[7d, 7e]	MCPBA, $NaHCO_3$, CH_2Cl_2, RT	120	8
5[7f]	MCPBA, CH_2Cl_2, RT	120	18
6[7g]	MCPBA (2.6 eq), CF_3COOH, CH_2Cl_2, RT	120	35
7[7h]	MCPBA, glacial HOAc, CH_2Cl_2, RT	120	33
8[7g]	MCPBA (2.6 eq), CF_3COOH, CH_2Cl_2, reflux	72	51
9[7g]	MCPBA (5.2 eq), CF_3COOH, CH_2Cl_2, reflux	72	60
10[7g]	MCPBA, H_2SO_4, HOAc, CH_2Cl_2, reflux	48	12
11[7g]	t-BuOH, CF_3COOH, CH_2Cl_2, RT	24	0
12[7g]	t-BuOH, CH_2Cl_2, reflux	24	0
13[7g]	MCPBA (10.4 eq), CF_3COOH, CH_2Cl_2, reflux	24	34

[a] Starting material was a mixture of isomers with a cis:trans ratio of 90:10. [b] The percent reaction mixture as product was determined by G. C. without an internal standard.

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1[7g]	
2[7g]	
3[7g]	
4[7g]	
5[7g]	
6[7g]	

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Since none of these sets of conditions yielded satisfactory results, and since all prepared **II-13** had been consumed, more **II-12** was reduced. Reduction of **II-12** under more dilute conditions resulted in a product isomer ratio of 24:76 cis:trans (Table II-3). Again, a series of oxidations was attempted. These yielded greatly improved results, even under similar conditions (Table II-2).

Table II-2. Baeyer-Villiger Oxidation Studies on trans Substrate **II-13**

Entry[ref]	Conditions[a]	Time (hours)	% rxn. as prod[b](iso)
1[7g]	MCPBA (5.2 eq), CF_3COOH, CH_2Cl_2, reflux	24	86 (41%)
2[7g]	MCPBA (5.2 eq), CF_3COOH, CH_2Cl_2, reflux	10	75 (45%)
3[7g]	MCPBA (2.6 eq), CF_3COOH, CH_2Cl_2, reflux	7.5	66 (43%)
4[7g]	MCPBA (2.6 eq), CF_3COOH, CH_2Cl_2, reflux	10	67 (20%)
5[7g]	MCPBA (5.2 eq), CF_3COOH, $CHCl_3$, reflux	14	89 (18%)
6[7g]	MCPBA (5.2 eq), CF_3COOH, CH_2Cl_2, reflux	24	52 (22%)

[a] Starting material was a mixture of isomers with a cis:trans ratio of 24:76.[b] The percent reaction mixture as product was determined by G. C. without an internal standard.

Because it appeared that the primarily trans substrate yielded superior results, a series of reduction conditions were examined to try to maximixe the portion of trans **II-13** formed (Table II-3). The greatest percentage trans achieved was 76%. This represented the approximate thermodynamic product distribution, as exhibited by several equilibration studies. Several other sets of oxidation conditions were then attempted but yielded inferior results to those indicated in Table II-2 (Table II-4).

Table

Entry	
1	
2	
3	
4	
5	

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Entry(ref)	
1[7g]	
2[7g]	
3[7i]	
4[7j]	
5[7k]	
6[7l]	
7[7i]	
8[7j]	

[a] T

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Table II-3. Various Conditions Used in the Palladium Mediated Reduction of **II-12**

Entry	g Pd : mmol reactant	Molarity (substrate)	**II-13** cis:trans ratio[a]
1	1.0 : 1	0.25	61 : 39
2	0.2 : 1	0.50	83 : 17
3	0.1 : 1	0.50	69 : 31
4	0.1 : 1	0.10	24 : 76
5	0.1 : 1	0.05	32 : 68

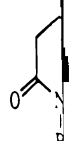
[b] The cis to trans product ratio was determined by ^{1}H NMR.

Table II-4. Continued Baeyer-Villiger Oxidation Studies of **II-13** to **II-14**

Entry(ref)	Ratio *cis* : *trans*	Conditions	Time (hours)	% rxn. as prod[a](iso)
1[7g]	28 : 72	MCPBA (5.2 eq), CF_3COOH, CH_2Cl_2, RT	24	62 (41%)
2[7g]	54 : 46	MCPBA (5.2 eq), CF_3COOH, CH_2Cl_2, RT	24	63 (32%)
3[7i]	24 : 76	MCPBA (5.2 eq), Na_2HPO_4, CH_2Cl_2, RT	36	23
4[7j]	24 : 76	MCPBA (5.2 eq), pTsOH, CH_2Cl_2, RT	84	88 (18%)
5[7k]	24 : 76	MCPBA (5.2 eq), $NaHCO_3$, CH_2Cl_2, RT	12	9
6[7l]	24 : 76	MCPBA (5.2 eq), Li_2CO_3, CH_2Cl_2, RT	84	30
7[7i]	24 : 76	MCPBA (5.2 eq), Na_2HPO_4, CH_2Cl_2	84	16
8[7j]	53 : 47	MCPBA (5.2 eq), pTsOH, CH_2Cl_2, reflux	60	68

[a] The percent reaction mixture as product was determined by G. C. without an internal standard.

To further indicate the role substrate structure might have been responsible for the relatively low oxidation yields, compound **II-16** was reduced to **II-17** (62% yield) and then oxidized to **II-18** (Scheme II-3). Yield of the oxidation was 67%.



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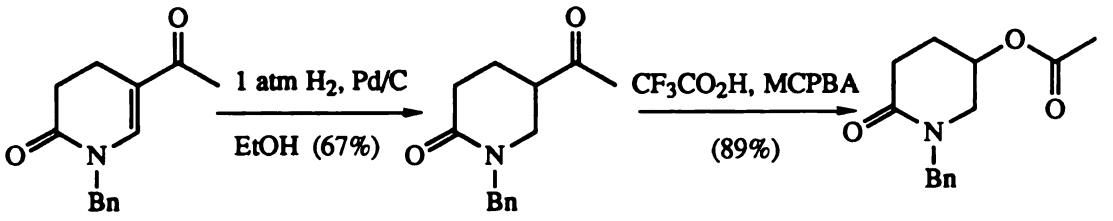
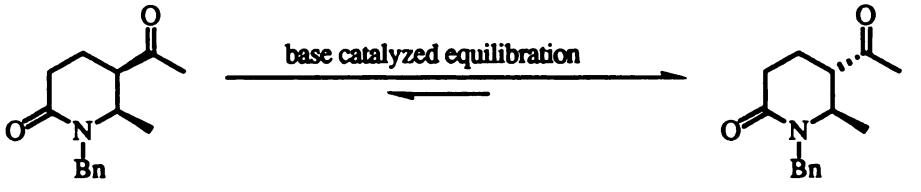
Scheme II-3. Oxidation of Achiral Substrate Surrogate



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

Efficient base catalyzed equilibration of cis **II-13** to trans **II-13** yielded a product mixture that was consistently 30% cis to 70 % trans (Figure II-3). Baeyer Villiger oxidation yielded only trans **II-14** as detectable by NMR. Confirmation of stereochemistry was achieved by comparison to known compounds[8] and by comparison of the final products to purchased standards.

Figure II-3. Epimirization of Model Compound **II-13**

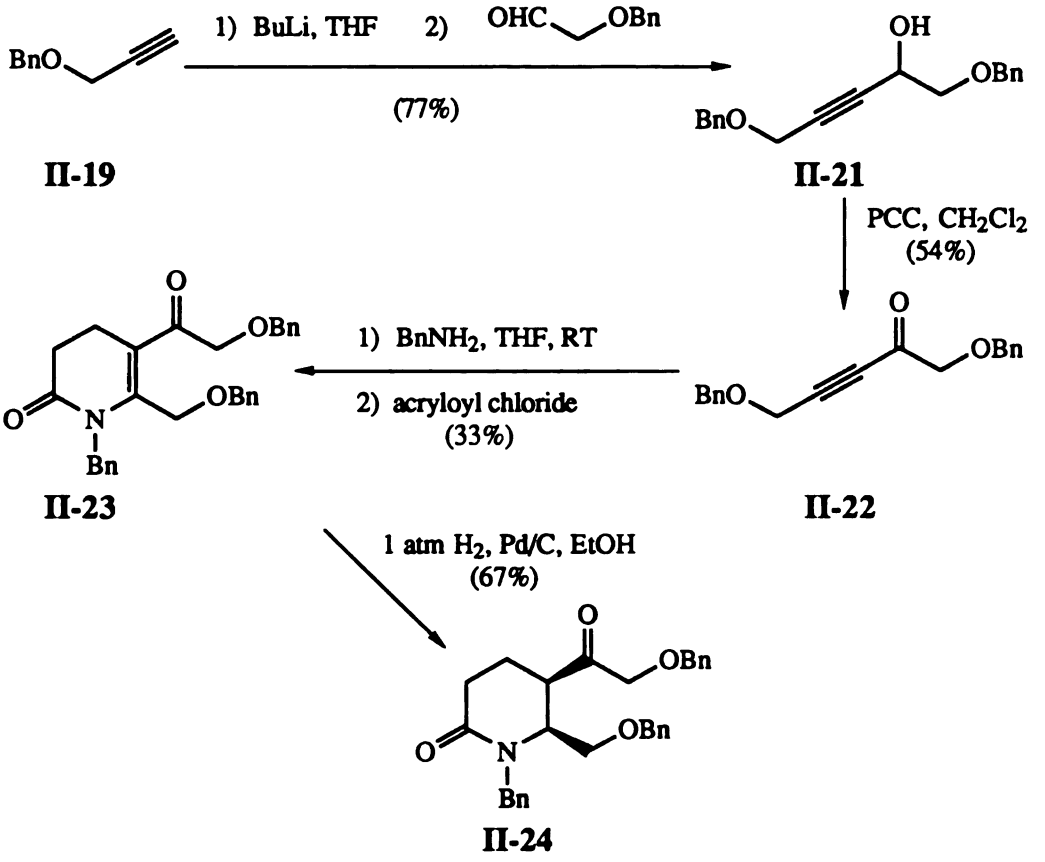


II-13 (cis) **II-13** (trans)

69% cis : 31% trans	LHMDS, THF, -78°C - RT, 12 hrs	28% cis : 72% trans
61% cis : 39% trans	DBU, THF, -78°C - RT, 12 hrs	30% cis : 70% trans

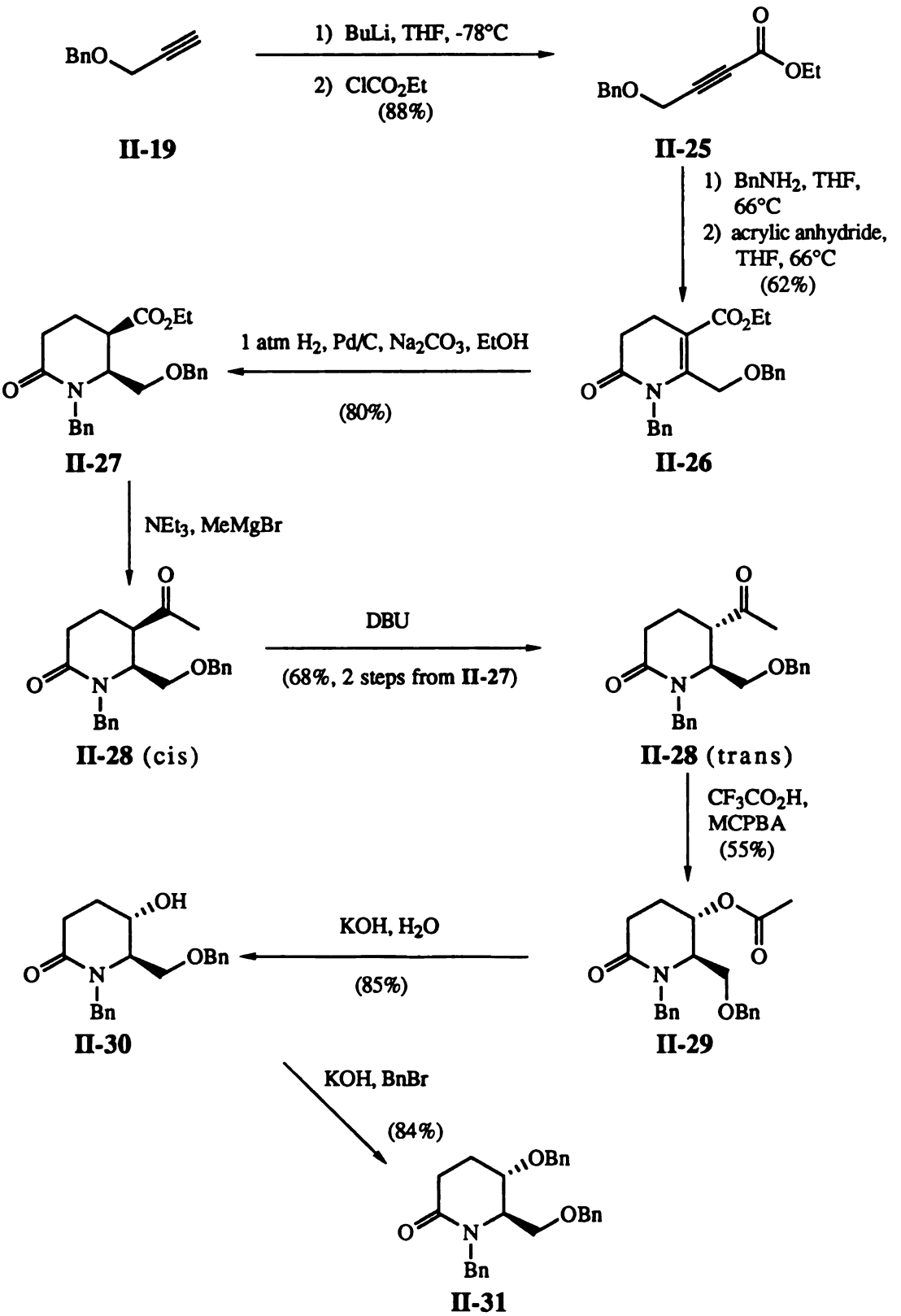
Extension of this methodology toward the preparation of compounds of the type indicated by structure **II-11** was then executed. Initially, propargyl alcohol was deprotonated and protected using benzyl bromide to afford **II-18** in 90% yield. Deprotonation of the alkyne using BuLi, followed by reaction with **II-20**, gave the alcohol **II-21**. Oxidation of **II-21** with PCC provided **II-22** in 54% yield.[9] Aza-annulation of **II-22** in the usual manner provided **II-23** in 33% yield. Hydrogenation of **II-23** provided **II-24** in 67% yield (Scheme II-4).

Scheme II-4. Preparation of Alkaloid Precursor **II-24**



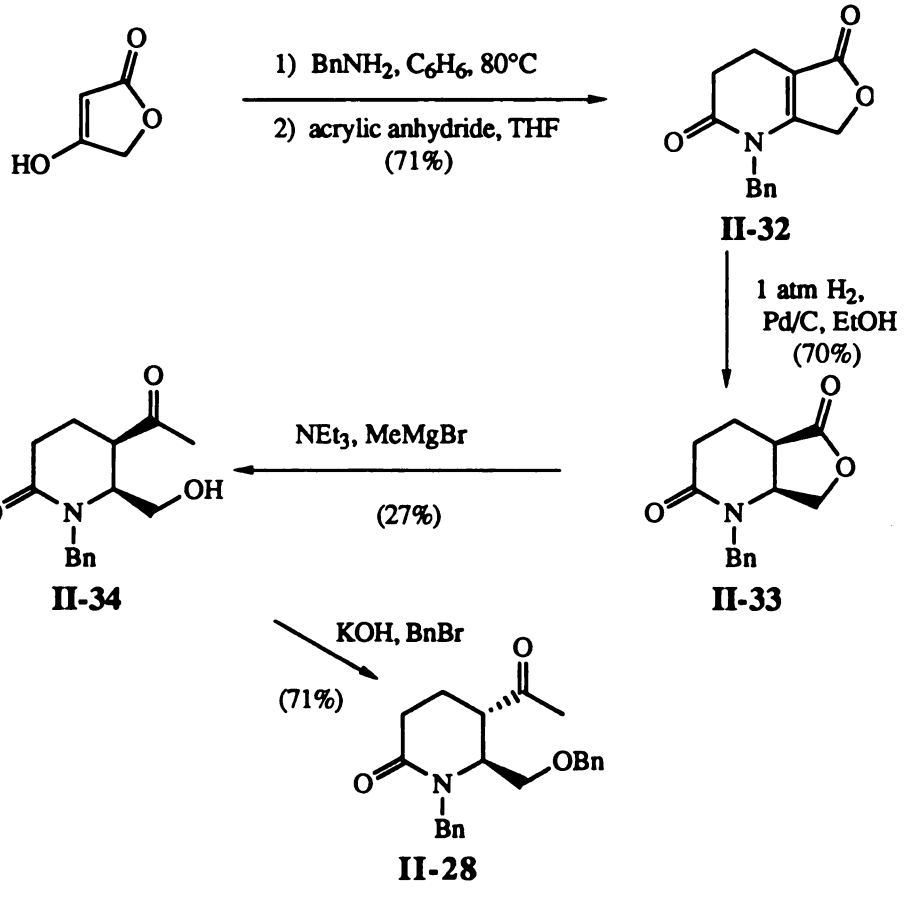
A more efficient route toward compounds of the type indicated by **II-11** was initiated by acylation of **II-19** with ethylchloroformate by action of BuLi to provide **II-25** in 88% yield. Aza-annulation of **II-25** provided **II-26** in 35% yield using acryloyl chloride and in 62% yield using freshly prepared acrylic anhydride. Reduction of **II-26** afforded **II-27** in 80% yield and in a cis to trans ratio of 98:2. To prepare **II-28** for use in the Baeyer-Villiger oxidation, a modified Grignard reaction was used. Epimerization at the position α to the ketone of cis **II-28** with DBU afforded **II-28** in a cis to trans ratio of 17:83. Overall yield for the 2 steps was 61%. Oxidation of **II-28** provided **II-29** in 56% yield. Subsequent hydrolysis gave **II-30** in 85% yield. Protection of **II-30** was executed using benzyl bromide to provide **II-31** in 84% yield (Scheme II-5).[10]

Scheme II-5. Preparation of Alkaloid Precursor II-31



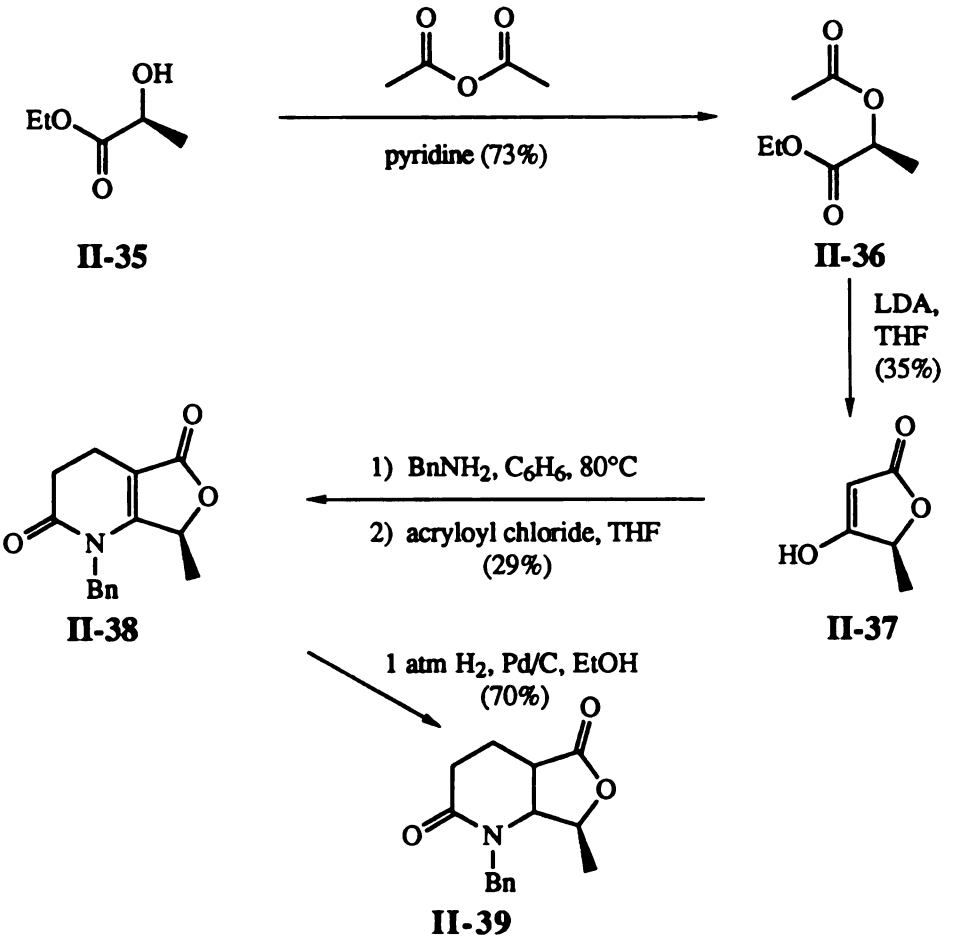
An alternative route to the preparation of **II-31** could be accessed from tetronic acid (Scheme II-6). Annulation of tetronic acid using benzylamine and acrylic anhydride afforded **II-32** in 71% yield. Reduction of **II-32** provided **II-33** in 83% yield. Use of the modified Grignard procedure to open the lactone yielded **II-34** in 27% yield. Protection of the C-6 alcohol using benzyl bromide was executed in 71% yield providing **II-28** as a mixture of cis and trans isomers in the ratio of 20:80 respectively.

Scheme II-6. Alternate Route to Alkaloid Precursor Preparation



This alternate route was significant in that it could possibly allow access to a variety of natural products with stereochemistry incorporated at C-6 (Scheme II-7). Alkylation of **II-35** (prepared from the respective carboxylic acid) provided **II-36** in 80% yield. The tetronic acid derivative, **II-37**, was then prepared in 35% yield.[11] Aza-annulation of **II-37** in the usual fashion using acryloyl chloride afforded **II-38** in 29% yield. Reduction of **II-38** provided **II-39** in 70% yield as a mixture of isomers in the ratio of 70:30 .

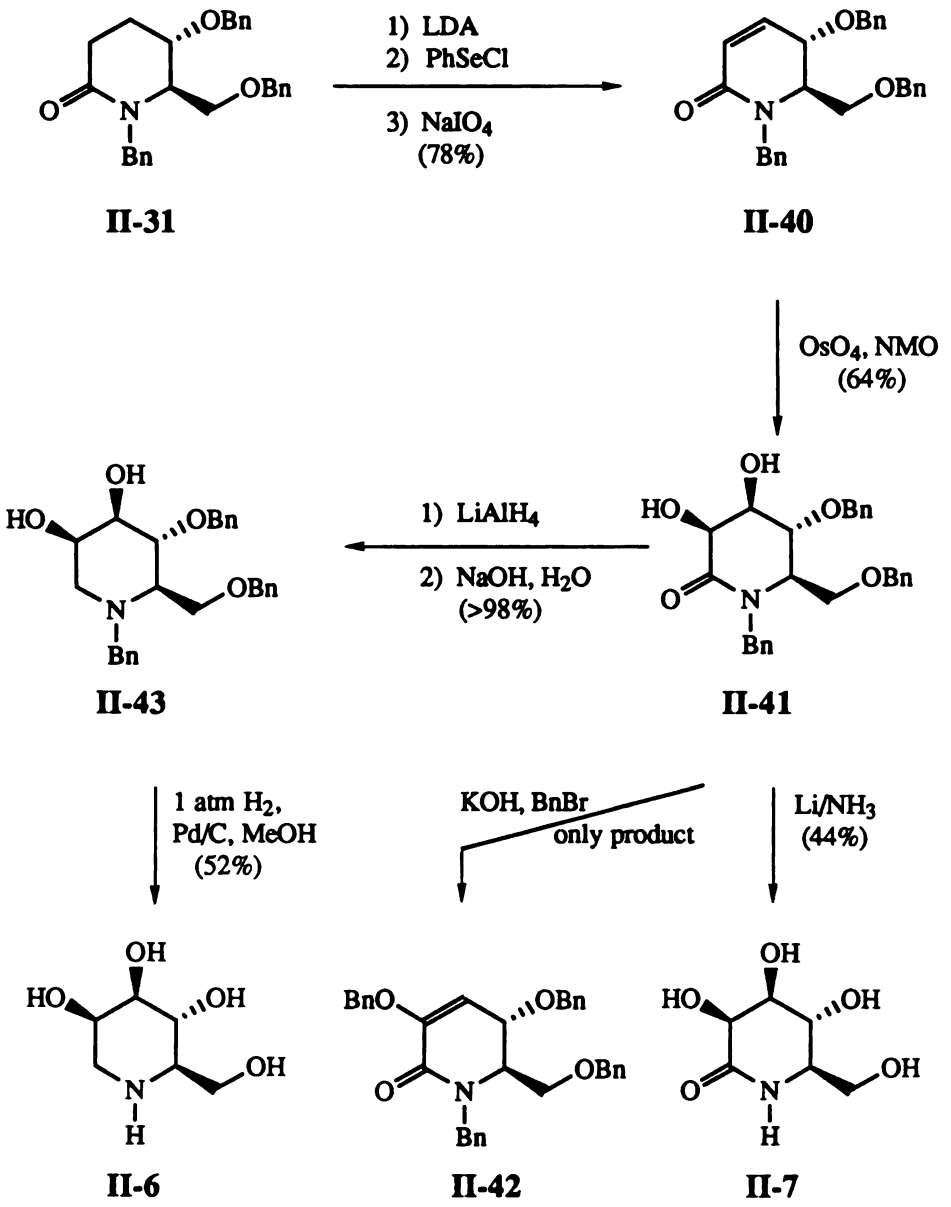
Scheme II-7. Use of Alternate Route to Introduce Chiral Center



II-35 **II-36** **II-37** **II-38** **II-39**

As a synthetic equivalent to **II-11**, **II-31** proved to be a versatile substrate for the preparation of alkaloids. For example, the preparation of **II-5** from **II-31** was executed in 29% overall yield.[10] Preparation of **II-6**, and **II-7** were then executed from **II-31** as outlined in Scheme II-8. Selenation of **II-31** followed by $NaIO_4$ oxidation provided **II-40** in 78% yield.[12] Stereospecific cis-dihydroxylation of **II-40** using OsO_4 in NMO gave **II-41** in 64% yield.[13] Attempted protection of **II-41** with benzyl bromide using KOH afforded **II-42** as the sole product. Direct reduction of the diol using $LiAlH_4$ provided **II-43** in near quantative yield. Reductive removal of the protecting groups from **II-43** using Pd/C, H_2, and with a trace of acid afforded **II-6** in 52% yield.[14] Preparation of **II-7** from **II-41** was executed smoothly by Li/NH_3 reduction in 44% yield.[15] Yields for the preparation of **II-5**, **II-6**, and **II-7** from **II-18** were 3% overall for each (Scheme II-8). DQ-COSY spectra of **II-6** and **II-7** are shown in Figure II-4 and Figure II-5, respectively.

Scheme II-8. Preparation of **II-6** and **II-7** fom Alkaloid Precursor



Conclusion.

Stereochemically complex hydroxylated piperidine alkaloids can be efficiently accessed through use of the aza-annulation. The C-4 and C-5 substituent pattern may be incorporated at the onset by aza-annulation substrate manipulation. The stereochemistry at these positions may then be controlled through choice of reduction conditions. Trans stereochemistry at C-4 relative to C-5 may be efficiently incorporated to an extent of >98:2 through use of the Baeyer-Villiger oxidation. Subsequent incorporation of cis stereochemistry at the C-2 and C-3 positions may then be accessed through use OsO_4 cis hydroxylation. Comparison of **II-6** with a purchased standard of the same compound showed that all four stereocenters were incorporated as initially predicted from asymmetric starting materials.

Figure II-4. DQ-COSY Spectra of **II-6**

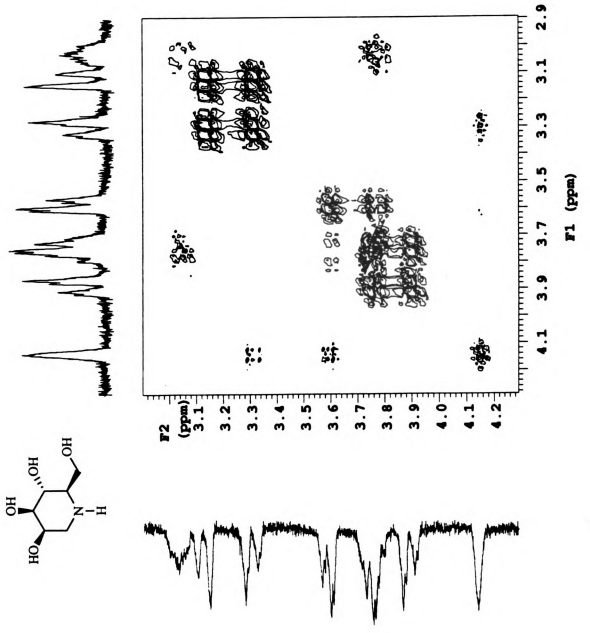
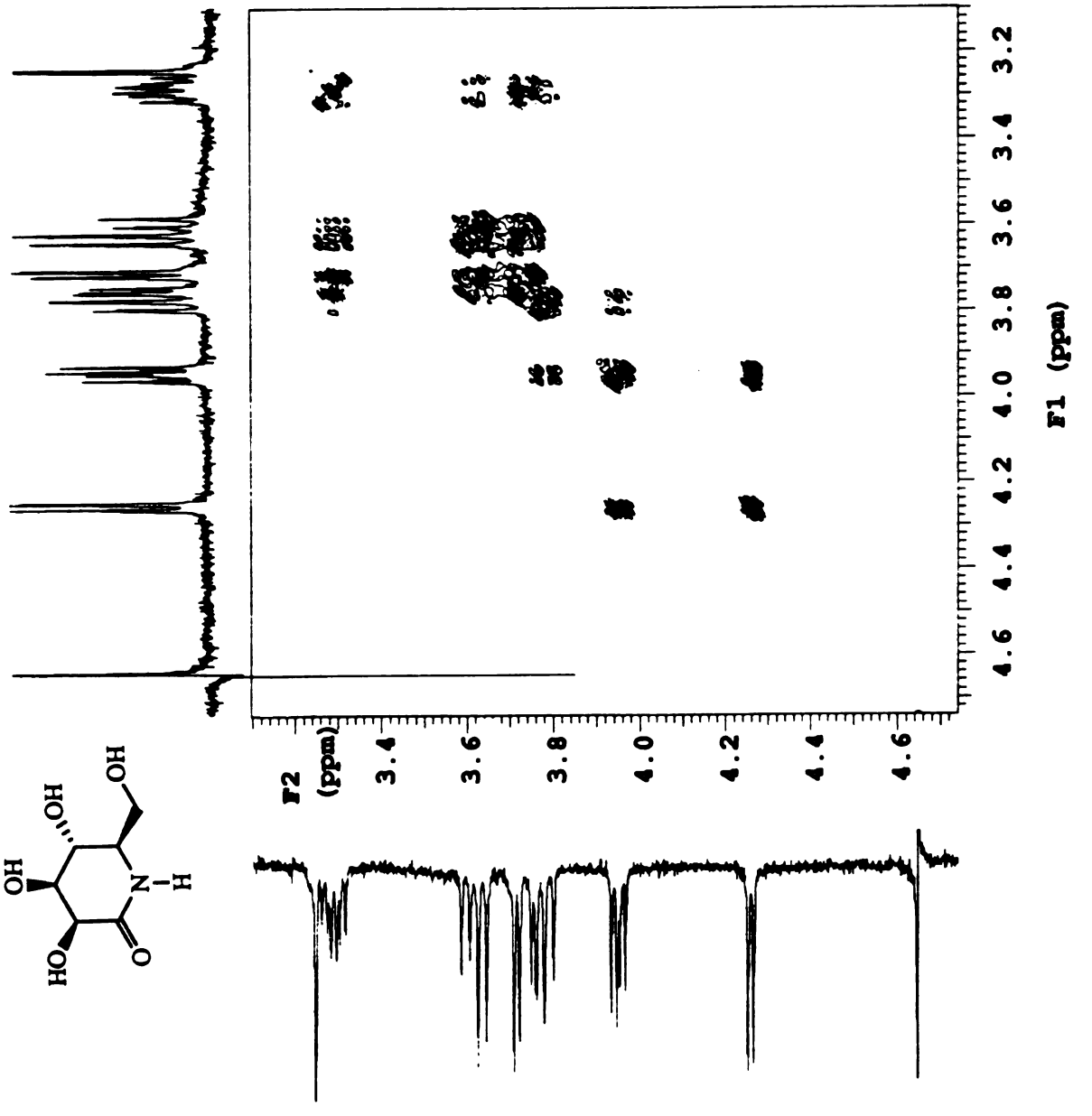


Figure II-5. DQ-COSY Spectra of II-7



Experimental Section.

General Methods. All reactions were carried out using standard inert atmosphere techniques to exclude moisture and oxygen, and reactions were performed under an atmosphere of nitrogen. Benzene, toluene and ether were distilled from sodium/benzophenone immediately prior to use. Xylenes and decalin were heated over calcium hydride for a minimum of 12 h and then distilled prior to use. $LiAlH_4$ (1 *M* in THF) was obtained from Aldrich Chemical Co. Unless specified, concentration of mixtures was performed using a Buchi rotary evaporator.

For reactions in which a Dean-Stark trap was used, the trap was filled with molecular sieves to a level below that of returning solvent turbulence. These were changed during reactions in which additional reagent was added after the reactions initiation. Molecular sieves were activated by heating in a 150 °C oven for at least 24 h prior to use.

Formation of II-12. To 2,4-pentanedione (25.00 g, 250.00 mmol) in C_6H_6 (500.0 mL) was added benzylamine (47.50 g, 250.00 mmol) and a catalytic amount of *p*-TsOH at room temperature. The reaction was fitted with a Dean - Stark trap, filled with molecular sieves to a level below that of returning solvent turbulence, and heated at reflux. After 12 h the reaction was cooled to room temperature and the solvent removed under reduced pressure. THF (500.0 mL) and acryloyl chloride (38.45 g, 425.00 mmol) were then added and the reaction again heated at reflux. After 14 h the reaction was cooled to room temperature and the solvent removed under reduced pressure. The reaction mixture was then chromatographed (silica, 230-400 mesh; eluent - 90:10 Et_2O:petroleum ether). The solvents were evaporated to give a clear, colorless oil (54 g, 94% yield); ^1H NMR (300 MHz, $CDCl_3$) δ 2.21 (s, 3 H), 2.24 (s, 3 H), 2.53-2.68 (m, 4 H), 5.00 (s, 2 H), 7.12 (bd, *J* = 2.0, 2 H), 7.16-7.34 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.72, 21.81, 29.33, 30.84, 44.22, 116.95, 125.65, 126.67, 128.28, 137.08, 145.83, 170.11, 198.32; IR (oil/NaCl) 3031, 2969, 2843, 1669, 1590, 1383, 1275, 1186 cm^{-1}.

Formation of II-13. To **II-12** (10.00 g, 56.50 mmol) in EtOH (565.0 mL) was added Na_2CO_3 (20.96 g, 197.74 mmol) and 10% Pd/C (5.65 g). The reaction vessel was purged with N_2 and then flushed with and maintained under an atmosphere of H_2. After stirring for 16 h, the reaction mixture was filtered through a fine scintered glass funnel and the solvent removed under reduced pressure. The resulting crude oil was purified by flash column chromatography (silica, 230-400 mesh; eluent - Et_2O). The solvents were evaporated to give a clear, colorless oil (8.19. g, 81% yield, 90:10 *cis*:*trans*). ^1H NMR (300 MHz, $CDCl_3$) (*cis* isomer) δ 1.07 (d, *J* = 6.6 Hz, 3 H), 2.06 (s, 3 H), 1.92-2.17 (m, 4 H), 2.48 (ddd, *J* = 18.3, 10.4, 8.0 Hz, 1 H), 2.61 (ddd, *J* = 18.3, 7.4, 2.0 Hz, 1 H), 2.79 (dt, *J* = 12.6, 4.2 Hz, 1 H), 3.84 (m, 1 H), 3.96 (d, *J* = 15.2 Hz, 1

H), 5.31 (d, J = 15.2 Hz, 1 H), 7.22-7.36 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) (*cis* isomer) δ 14.52, 17.33, 28.08, 29.96, 47.74, 51.03, 51.14, 127.04, 127.36, 128.28, 136.97, 168.67, 206.25; IR (oil/NaCl) 2975, 1713, 1640, 1163 cm^{-1}; HRMS calcd for $C_{15}H_{19}NO_2$ *m/z* 245.1416, found *m/z* 245.1415.

Isomerization of II-13. To **II-13 cis** (0.20 g, 1.12 mmol) in THF (2.24 mL) was added DBU (0.09 g, 0.56 mmol) at room temperature. After 16 h the reaction was terminated by addition of an equal volume of water. The organics were seperated and the solvent removed under reduced pressure. The resulting crude oil was purified by flash column chromatography (silica, 230-400 mesh; eluent - Et_2O). The solvents were evaporated to give a clear, colorless oil (0.20 g, >99% yield, 72% *trans*); ^1H NMR (300 MHz, $CDCl_3$) (*trans* isomer) δ 1.22 (d, J = 6.6 Hz, 1 H), 1.89 (s, 3 H), 1.91-2.12 (m, 3 H), 2.35-2.63 (m, 3 H), 3.82 (m, 1 H), 4.01 (d, J = 15.2 Hz, 1 H), 5.23 (d, J = 15.2 Hz, 1 H), 7.22-7.34 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) (*trans* isomer) δ 19.53, 19.86, 27.47, 29.39, 46.98, 51.14, 52.26, 126.93, 127.78, 128.10, 136.97, 168.87, 207.05; IR (oil/NaCl) 2975, 1713, 1640, 1163 cm^{-1}.

Formation of II-14. To **II-13** (76% *trans*) (1.00 g, 5.60 mmol) in CH_2Cl_2 (11.2 mL) was added *m*-CPBA (5.00 g, 29.20 mmol) and CF_3COOH (0.60 g, 5.60 mmol) at room temperature. The reaction was heated at reflux. After 14 h, the reaction was cooled to room temperature and the solvent removed under reduced pressure. The resulting slurry was brought up in a minimum amount of Et_2O and purified by flash chromatography (silica, 230-400 mesh; eluent - Et_2O). The solvents were evaporated to give a clear, colorless oil (4.5 g, 41% yield, 100% *trans*) (mp = 66-67 °C); ^1H NMR (300 MHz, $CDCl_3$) δ 1.24 (d, J = 6.7 Hz, 3 H), 1.89 (s, 3 H), 1.97 (m, 1 H), 2.16 (dddd, J = 14.7, 11.4, 7.5, 2.7 Hz, 1 H), 2.51 (ddd, J = 18.3, 7.5, 2.1 Hz, 1 H), 2.66 (ddd, J = 18.3, 11.4, 7.5 Hz, 1 H), 3.46 (qt, J = 6.7, 2.0 Hz, 1 H), 3.80 (d, J = 15.3 Hz, 1 H), 4.88 (dt, J = 3.9, 2.1 Hz, 1 H), 5.46 (d, J = 15.3 Hz, 1 H), 7.20-7.37 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.80, 20.75, 21.03, 26.81, 47.18, 54.38, 70.07, 127.19, 127.72, 128.32, 136.95, 168.57, 169.89; IR (oil/NaCl) 2975, 2942, 1736, 1634, 1482, 1246, 1179 cm^{-1}; HRMS calcd for $C_{15}H_{19}NO_3$ *m/z* 261.1365, found *m/z* 261.1363.

Formation of II-15. To **II-14** (0.10 g, 0.56 mmol) in water (0.6 mL) was added crushed NaOH (0.04 g, 1.12 mmol) at room temperature. The reaction was heated at approximately 50°C. After 12 h, the product was extracted from the reaction mixture with 6 portions of $CHCl_3$ (1.0 mL each). The organics were combined, dried, and the solvent removed under reduced pressure. the product was recrystallized from Et_2O:low boiling petroleum ether giving white crystals. (0.06 g, 89% yield) (mp = 110-113 °C); ^1H NMR (300 MHz, $CDCl_3$) δ 1.18 (d, J = 6.6 Hz, 3 H), 1.88 (m, 1 H), 1.95-2.12 (m, 2

H), 2.42 (ddd, J = 18.0, 7.3, 2.8 Hz, 1 H), 2.71 (ddd, J = 18.0, 10.8, 7.3 Hz, 1 H), 3.34 (m, 1 H), 3.83 (dt, J = 4.8, 2.8 Hz, 1 H), 3.95 (d, J = 15.2 Hz, 1 H), 5.35 (d, J = 15.2 Hz, 1 H), 7.20-7.35 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.37, 24.05, 26.92, 47.42, 57.96, 68.45, 127.23, 127.78, 128.56, 137.33, 169.42; IR (oil/NaCl) 3289, 3023, 2890, 1609, 1453, 1175, cm^{-1}; HRMS calcd for $C_{13}H_{17}NO_2$ *m/z* 219.1259, found *m/z* 219.1245.

Formation of II-17. To **II-16** (0.24 g, 1.05 mmol) in EtOH (10.5 mL) was added Na_2CO_3 (0.39 g, 3.67 mmol) and 10% Pd/C (0.10 g). The reaction vessel was purged with N_2 and then flushed with and maintained under an atmosphere of H_2. After stirring for 16 h, the reaction mixture was filtered through a fine scintered glass funnel and the solvent removed under reduced pressure. The resulting crude oil was purified by flash column chromatography (silica, 230-400 mesh; eluent - Et_2O). The solvents were evaporated to give a clear, colorless oil (0.15 g, 62% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.79-1.94 (m, 2 H), 2.14 (s, 3 H), 2.49 (ddd, J = 16.8, 10.4, 6.4 Hz, 1 H), 2.59 (ddd, J = 17.8, 6.4, 4.4 Hz, 1 H), 2.79 (tdd, J = 9.9, 5.3, 3.8 Hz, 1 H), 3.29 (ddd, J = 12.6, 5.3, 1.4 Hz, 1 H), 3.41 (dd, J = 12.3, 9.3 Hz, 1 H), 4.47 (d, J = 14.7 Hz, 1 H), 4.73 (d, J = 14.7 Hz, 1 H), 7.22-7.36 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.79, 28.01, 30.96, 46.58, 47.17, 50.07, 127.40, 128.05, 128.52, 136.70, 168.63, 207.21; IR (oil/NaCl) 3032, 2932, 2876, 1713, 1642, 1495, 1455, 1262, 1167, cm^{-1}.

Formation of II-18. To **II-17** (0.10 g, 0.43 mmol) in CH_2Cl_2 (0.86 mL) was added *m*-CPBA (0.39 g, 2.25 mmol) and CF_3COOH (0.05 g, 0.43 mmol) at room temperature. The reaction was heated at reflux. After 14 h, the reaction was cooled to room temperature and the solvent removed under reduced pressure. The resulting slurry was brought up in a minimum amount of Et_2O and purified by flash column chromatography (silica, 230-400 mesh; eluent - Et_2O). The solvents were evaporated to give a clear, colorless oil (0.07 g, yield = 67%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.01 (s, 3 H), 2.02-2.08 (m, 2 H), 2.52 (ddd, J = 17.9, 6.0, 5.3 Hz, 1 H), 2.67 (ddd, J = 17.9, 9.6, 7.1 Hz, 1 H), 3.26 (ddd, J = 13.2, 3.9, 1.3 Hz, 1 H), 3.43 (dd, J = 13.2, 3.9 Hz, 1 H), 4.49 (d, J = 14.7 Hz, 1 H), 4.71 (d, J = 14.7 Hz, 1 H), 5.12 (dq, J = 3.9, 3.6 Hz, 1 H), 7.21-7.36 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.97, 25.49, 27.86, 49.80, 50.46, 66.17, 127.49, 127.99, 128.60, 136.56, 168.73, 170.18; IR (oil/NaCl) 3063, 2959, 2873, 1738, 1646, 1491, 1365, 1421, 1238, 1182, 1075 cm^{-1}.

Formation of 22. To **II-19** (0.43 g, 2.95 mmol) in THF (8.56 mL) was added BuLi (1.41 mL, 2.5 M) at -78 °C). After stirring for 10 min, **II-20** (0.53 g, 3.53 mmol) was added, and the reaction allowed to warm to room temperature. After 10 min at room temperature, the reaction was quenched by addition of water. The reaction was extracted

with EtOAc (5 X 10 mL) and the organics dried and concentrated. The resulting oil was brought up in a minimum amount of Et_2O and purified by flash chromatography (silica, 230-400 mesh; eluent - 1:1 petroleum ether:Et_2O). The solvents were evaporated to give **II-21** as a clear, colorless oil.(0.67 g, 77% yield).

To **II-21** (0.43 g, 1.45 mmol) in CH_2Cl_2 (14.50 mL) was added PCC (0.63 g, 2.91 mmol) at room temperature. After 14 h, the reaction was repeatedly extracted with Et_2O and the organics combined and concentrated. The resulting oil was brought up in a minimum amount of Et_2O and purified by flash column chromatography (silica, 230-400 mesh; eluent - 1:1 petroleum ether:Et_2O). The solvents were evaporated to give **II-22** as a clear, colorless oil.(0.23 g, 54% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 4.19 (s, 2 H), 4.28 (s, 2 H), 4.56 (s, 2 H), 4.61 (s, 2 H), 7.25-7.78 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.72, 56.75, 71.97, 73.24, 75.49, 83.12, 90.58, 127.80, 127.90, 127.92, 127.95, 128.33, 136.51, 136.77, 184.23; IR (oil/NaCl) 3065, 1694, 1455, 1352, 1211, 1173, 1028 cm^{-1}.

Formation of II-23. To **II-22** (0.60 g, 2.04 mmol) in THF (4.0 mL) was added $BnNH_2$ (0.19 g, 2.04 mmol) at room temperature. The reaction was heated at reflux. After 12 h the reaction was cooled to room temperature and acryloyl chloride (0.31 g, 3.47 mmol) added. The reaction was again heated at reflux. After 14 h the reaction was cooled to room temperature and the solvent removed under reduced pressure. The reaction mixture was then chromatographed (silica, 230-400 mesh; eluent - 10:90 Et_2O:petroleum ether). The solvents were evaporated to give a clear, colorless oil (0.30 g, 33% yield); ^1H NMR (300 MHz, $CDCl_3$) δ 2.48-2.61 (m, 4 H), 4.21 (s, 2 H), 4.31 (s, 2 H), 4.54 (s, 4 H), 5.08 (s, 2 H), 6.98 (dd, J = 7.5, 1.5 Hz, 2 H), 7.18-7.37 (m, 13 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.53, 30.78, 44.47, 63.68, 72.72, 73.41, 74.46, 119.82, 126.08, 127.78, 127.91, 127.96, 128.04, 128.15, 128.43, 128.50, 128.65, 136.91, 137.59, 137.72, 144.55, 170.53, 198.97; IR (oil/NaCl) 3031, 1678, 1605, 1497, 1455, 1306, 1277, 1068 cm^{-1}.

Formation of II-24. To **II-23.**, (0.15 g, 0.34 mmol) in EtOH (3.4 mL) was added Na_2CO_3 (0.13 g, 1.19 mmol) and 10% Pd/C (0.034 g). The reaction vessel was purged with N_2 and then flushed with and maintained under an atmosphere of H_2. After stirring for 16 h, the reaction mixture was filtered through a fine scintered glass funnel and the solvent removed under reduced pressure. The resulting crude oil was purified by flash column chromatography (silica, 230-400 mesh; eluent - Et_2O). The solvents were evaporated to give a clear, colorless oil (0.10 g, 67% yield); ^1H NMR (300 MHz, $CDCl_3$) (isomer ratio 70:30) δ (major isomer, diagnostic peaks) 3.12 (dt, J = 12.9, 3.9 Hz, 1 H), 3.88 (d, J = 16.2 Hz, 1 H), 4.00 (d, J = 16.2 Hz, 1 H), 5.25 (d, J = 15 Hz, 1 H), (minor

isomer, diagnostic peaks) 3.26 (dt, J = 6.6, 4.8 Hz, 1 H), 3.63 (d, J = 16.8 Hz, 1 H), 3.81 (d, J = 16.8 Hz, 1 H), 5.19 (d, J = 15 Hz, 1 H), ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.54, 20.03, 29.85, 30.09, 44.08, 45.81, 48.17, 49.13, 55.15, 55.74, 67.64, 69.91, 73.03, 73.06, 73.16, 73.22, 73.77, 74.74, 127.30, 127.35, 127.54, 127.64, 127.69, 127.70, 127.73, 127.78, 127,85, 127.90, 128.16, 128.29, 128.34, 128.36, 128.43, 128.50, 136.81, 137.03, 137.08, 137.25, 137.33, 169.44, 170.21, 206.33, 207.68; IR (oil/NaCl) 3031, 1717, 1645, 1453, 1100 cm^{-1}.

Formation of II-25. To benzyl protected propargyl alcohol (1.20 g, 8.19 mmol) in THF (16.38 mL) was added BuLi (3.28 mL, 2.5 M in Hexane) at -78°C. After 10 min ethyl chloroformate (0.89 g, 8.19 mmol) was added dropwise. The reaction was slowly warmed to 0°C (until a deep red color began to form) and was promptly quenched by addition of water. The organics were separated and the solvent removed under reduced pressure. The resulting crude oil was purified by flash column chromatography (silica, 230-400 mesh; eluent - petroleum ether). The solvents were evaporated to give a clear, colorless oil (1.61 g, 91% yield); ^1H NMR (300 MHz, $CDCl_3$) δ 1.29 (t, J = 7.2 Hz, 3 H), 4.22 (q, J = 7.2 Hz, 2 H), 4.25 (s, 2 H), 4.59 (s, 2 H), 7.22-7.40 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.78, 56.53, 61.90, 71.81, 78.07, 82.94, 127.87, 127.90, 128.29, 136.59, 152.87; IR (oil/NaCl) 3032, 2984, 2872, 2236, 1713, 1248 cm^{-1}.

Formation of II-26. To **II-25** (1.61 g, 7.37 mmol) in THF (14.74 mL) was added $BnNH_2$ (0.70 g, 7.37 mmol) at room temperature. The reaction was heated at reflux. After 12 h the reaction was cooled to room temperature and acryloyl chloride (0.70 g, 7.74 mmol) added. The reaction was again heated at reflux. After 14 h the reaction was cooled to room temperature and the solvent removed under reduced pressure. The reaction mixture was then chromatographed (silica, 230-400 mesh; eluent - 10:90 Et_2O:petroleum ether). The solvents were evaporated to give a white solid (1.61 g, 35% yield) (mp = 84 - 87 °C); ^1H NMR (300 MHz, $CDCl_3$) δ 1.27 (t, J = 7.0 Hz, 3 H), 2.49-2.58 (m, 2 H), 2.62-2.71 (m, 2 H), 4.17 (q, J = 7.0 Hz, 2 H), 4.57 (s, 2 H), 4.60 (s, 2 H), 5.12 (s, 2 H), 6.97-7.03 (m, 2 H), 7.16-7.39 (m, 8 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.16, 21.69, 30.82, 44.51, 60.76, 63.56, 72.65, 113.54, 126.06, 126.97, 127.93, 128.07, 128.42, 128.63, 137.61, 137.90, 146.08, 166.71, 170.92; IR (oil/NaCl) 2984, 1682, 1636, 1269, 1130 cm^{-1} HRMS calcd for $C_{23}H_{25}NO_4$ *m/z* 379.1784, found *m/z* 379.1777.

Formation of II-27. To **II-26** (2.50 g, 6.85 mmol) in EtOH (68.50 mL) was added Na_2CO_3 (2.54 g, 23.97 mmol) and 10% Pd/C (0.69g). The reaction vessel was purged with N_2 and then flushed with and maintained under an atmosphere of H_2. After stirring for 16 h, the reaction mixture was filtered through a fine scintered glass funnel and the solvent removed under reduced pressure. The resulting crude oil was purified by flash

column chromatography (silica, 230-400 mesh; eluent - 70:30 Et_2O:petroleum ether). The solvents were evaporated to give a clear, colorless oil (1.66 g, 66% yield, 90:10 *cis*:*trans*). ^1H NMR (300 MHz, $CDCl_3$) (*cis* isomer) δ 1.13 (t, J = 7.2 Hz, 3 H), 2.03 (m, 1 H), 2.21 (ddt, J = 9.9, 7.8, 12.9 Hz, 1 H), 2.49 (ddd, J = 18.3, 10.0, 8.3 Hz, 1 H), 2.59 (ddd, J = 18.3, 7.8, 1.8 Hz, 1 H), 2.79 (dt, J = 15.0, 9.0 Hz, 1 H), 3.53 (d, J = 5.4 Hz, 2 H), 3.88-4.08 (m, 3 H), 4.15 (d, J = 15.2 Hz, 1 H), 4.37 (s, 2 H), 5.23 (d, J = 15.2 Hz, 1 H), 7.17-7.37 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) (*cis* isomer) δ 13.82, 19.18, 30.07, 42.40, 49.16, 56.17, 60.65, 68.62, 73.15, 127.19, 127.44, 127.59, 127.67, 128.19, 128.42, 137.22, 137.31, 169.56, 171.06; IR (oil/NaCl) 2959, 2870, 1734, 1645, 1173 cm^{-1}; HRMS calcd for $C_{23}H_{27}NO_4$ *m/z* 381.1940, found *m/z* 381.1988.

Formation of II-28. To MeMgBr (2.27 mL, 3.0 *M* in THF) in C_6H_6 (19.1 mL) was added NEt_3 (2.06 g, 20.44 mmol) at 0°C. After 10 min **II-27** (1.25 g, 3.41 mmol) in C_6H_6 (5.0 mL) was added with vigorous stirring. After 3 h at 0°C the reaction was quenched by addition of an equal volume of 3 *M* aqueous HCl. The organics were separated and the solvent removed under reduced pressure. The resulting crude oil was purified by flash column chromatography (silica, 230-400 mesh; eluent - Et_2O). The solvents were evaporated to give a clear, colorless oil (0.56 g, 61% yield); ^1H NMR (300 MHz, $CDCl_3$) (*cis* isomer) δ 1.87 (m, 1 H), 2.02 (s, 3 H), 2.12 (m, 1 H), 2.32-2.64 (m, 2 H), 2.71 (dt, J = 13.2, 4.1 Hz, 1 H), 3.42 (dd, J = 9.9, 7.5 Hz, 1 H), 3.50 (dd, J = 9.9, 4.1 Hz, 1 H), 3.94 (m, 1 H), 4.05 (d, J = 15.0 Hz, 1 H), 4.30 (d, J = 1.8 Hz, 2 H), 5.28 (d, J = 15.0 Hz, 1 H), 7.16-7.36 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) (*cis* isomer) δ 18.07, 28.30, 29.82, 48.85, 49.63, 55.82, 67.89, 72.90, 127.12, 127.34, 127.49, 128.03, 128.11, 128.29, 136.91, 137.04, 169.23, 205.36; IR (oil/NaCl) 3088, 2924, 1713, 1644, 1161, 1101 cm^{-1}; HRMS calcd for $C_{22}H_{25}NO_3$ *m/z* 351.1835, found *m/z* 351.1818.

Isomerization of trans II-28. To **cis II-28** (0.2 g, 0.74 mmol) in THF (1.48 mL) was added DBU (0.06 g, 0.37 mmol) at room temperature. After 16 h the reaction was terminated by addition of an equal volume of water. The organics were separated and the solvent removed under reduced pressure. The resulting crude oil was purified by flash column chromatography (silica, 230-400 mesh; eluent - Et_2O). The solvents were evaporated to give a clear, colorless oil (0.20 g, >99% yield, 83% *trans*); ^1H NMR (300 MHz, $CDCl_3$) (*trans* isomer) δ 1.89 (s, 3 H), 1.95 (m, 1 H), 2.04 (m, 1 H), 2.44 (dt, J = 17.7, 6.5 Hz, 1 H), 2.58 (ddd, J = 17.7, 7.5, 6.5 Hz, 1 H), 2.95 (dt, J = 6.5, 4.8 Hz, 1 H), 3.42-3.52 (m, 2 H), 3.94 (m, 1 H), 4.10 (d, J = 15.0 Hz, 1 H), 4.37 (d, J = 1.5 Hz, 2 H), 5.14 (d, J = 15.0 Hz, 1 H), 7.16-7.36 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) (*trans* isomer) δ 19.93, 27.27, 29.58, 47.78, 47.98, 55.17, 69.36, 72.81, 127.01,

127.30, 127.45, 127.53, 127.82, 128.12, 136.91, 137.15, 169.86, 207.06; IR (oil/NaCl) 3088, 2924, 1713, 1644, 1161, 1101 cm^{-1}.

Formation of II-29. To **II-28** (83% *trans*) (1.15 g, 4.24 mmol) in CH_2Cl_2 (8.48 mL) was added MCPBA (3.66 g, 21.22 mmol) and CF_3COOH (4.24 g, 0.48 mmol) at room temperature. The reaction was heated at reflux. After 14 h, the reaction was cooled to room temperature and the solvent removed under reduced pressure. The resulting slurry was brought up in a minimum amount of Et_2O and purified by flash chromatography (silica, 230-400 mesh; eluent - Et_2O). The solvents were evaporated to give a clear, colorless oil (0.60 g, 60% yield, 100% *trans*); ^1H NMR (300 MHz, $CDCl_3$) δ 1.88 (s, 3 H), 1.94 (m, 1 H), 2.17 (dddd, *J* = 13.8, 10.8, 7.8, 3.0 Hz, 1 H), 2.51 (ddd, *J* = 18.3, 7.6, 2.7 Hz, 1 H), 2.63 (ddd, *J* = 18.3, 10.8, 7.6 Hz, 1 H), 3.45-3.60 (m, 3 H), 3.92 (d, *J* = 15.3 Hz, 1 H), 4.43 (d, *J* = 12.0 Hz, 1 H), 4.50 (d, *J* = 12.0 Hz, 1 H), 5.16 (m, 1 H), 5.39 (d, *J* = 15.3 Hz, 1 H), 7.18-7.40 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.86, 22.30, 27.00, 48.12, 58.52, 67.97, 68.74, 73.31, 127.37, 127.63, 127.92, 128.01, 128.44, 128.50, 136.91, 137.31, 169.72, 169.96; IR (oil/NaCl) 3063, 2934, 2869, 1738, 1647, 1240, 1181 cm^{-1}; HRMS calcd for $C_{22}H_{25}NO_4$ *m/z* 367.1784, found *m/z* 367.1768.

Formation of II-30. To **II-29** (0.30 g, 1.05 mmol) in water (1.05 mL) was added crushed KOH (0.2 g, 0.52 mmol) at room temperature. The reaction was heated at approximately 50°C. After 12 h, the product was extracted from the reaction mixture with 6 portions of $CHCl_3$ (2 mL each). The organics were combined and the solvent removed under reduced pressure. The resulting crude oil was purified by flash column chromatography (silica, 230-400 mesh; eluent - Et_2O). The solvents were evaporated to give a clear, colorless oil (0.22 g, 85% yield); ^1H NMR (300 MHz, $CDCl_3$) δ 1.81 (m, 1 H), 2.00 (dddd, *J* = 12.6, 9.9, 6.9, 3.0, 1 H), 2.37 (ddd, *J* = 18.3, 6.9, 4.8 Hz, 1 H), 2.64 (ddd, *J* = 16.8, 9.3, 6.9 Hz, 2 H), 3.39 (m, 1 H), 3.40 (s, 1 H), 3.51 (m, 1 H), 4.07 (d, *J* = 15.3 Hz, 1 H), 4.10 (bs, 1 H), 4.37 (d, *J* = 12.0 Hz, 1 H), 4.43 (d, *J* = 12 Hz, 1 H), 5.18 (d, *J* = 15.3 Hz, 1 H), 7.16 - 7.38 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.16, 27.37, 48.09, 62.13, 65.65, 69.42, 73.27, 127.15, 127.58, 127.71, 127.86, 128.45, 128.46, 137.23, 137.44, 170.28; IR (oil/NaCl) 3364 (broad), 3063, 2928, 1617, 1453, 1181, 1101 cm^{-1}; HRMS calcd for $C_{20}H_{23}NO_3$ *m/z* 325.1678, found *m/z* 325.1666.

Formation of II-31. To **II-30** (0.50 g, 2.05 mmol) in Et_2O (4.10 mL) was added crushed KOH (0.23 g, 4.10 mmol) and molecular sieves (0.40 g) at room temperature. After 5-10 min of stirring BnBr (0.39 g, 2.26 mmol) was added. After 3 h the reaction was quenched by addition of excess water. The reaction mixture was extracted

with 10 portions of Et_2O (4 mL each), the organics combined and solvent removed under reduced pressure. The resulting crude oil was purified by flash column chromatography (silica, 230-400 mesh; eluent - Et_2O). The solvents were evaporated to give a white solid (0.57 g, 84% yield) (mp = 60 - 63 °C); ^1H NMR (300 MHz, $CDCl_3$) δ 1.91-2.02 (m, 2 H), 2.40 (ddd, *J* = 18.0, 6.2, 3.9 Hz, 1 H), 2.69 (ddd, *J* = 18.0, 10.4, 8.5 Hz, 1 H), 3.39 (dd, *J* = 9.9, 7.2 Hz, 1 H), 3.52 (dd, *J* = 9.9, 3.9 Hz, 1 H), 3.65 (m, 1 H), 3.83 (dd, *J* = 6.2, 3.9 Hz, 1 H), 3.99 (d, *J* = 15.3 Hz, 1 H), 4.26 (d, *J* = 12.0 Hz, 1 H), 4.35 (d, *J* = 12.0 Hz, 1 H), 4.37 (d, *J* = 12.0 Hz, 1 H), 4.41 (d, *J* = 12.0 Hz, 1 H), 5.36 (d, *J* = 15.3 Hz, 1 H), 7.14-7.36 (m, 15 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.18, 27.22, 47.69, 58.37, 69.16, 69.77, 71.79, 73.03, 126.87, 127.07, 127.28, 127.37, 127.56, 127.65, 128.05, 128.21, 128.26, 137.06, 137.36, 137.85, 169.93; IR (oil/NaCl) 3088. 3030, 2867, 1642, 1453, 1096 cm^{-1}; HRMS calcd for $C_{27}H_{29}NO_3$ *m/z* 415.2148, found *m/z* 415.2142.

Formation of II-32 Using Acryloyl Chloride. To tetronic acid (2.00 g, 20.00 mmol) in C_6H_6 (40.0 mL) was added benzylamine (1.95 g, 18.18 mmol) and a catalytic amount of *p*-TsOH at room temperature. The reaction was fitted with a Dean - Stark trap and heated at reflux. After 12 h the reaction was cooled to room temperature and the solvent removed under reduced pressure. THF (40.0 mL) and acryloyl chloride (2.80 g, 30.91 mmol) were then added. The reaction was again heated at reflux. After 14 h the reaction was cooled to room temperature and the solvent removed under reduced pressure. The reaction mixture was then chromatographed (silica, 230-400 mesh; eluent - Et_2O). The solvents were evaporated to give a white solid (3.08 g, 70% yield) (mp = 121-124°C); ^1H NMR (300 MHz, $CDCl_3$) δ 2.58 (bt, *J* = 8.1 Hz, 2 H), 2.80 (bt, *J* = 8.1 Hz, 2 H), 4.65 (t, *J* = 2.0 Hz, 2 H), 4.78 (s, 2 H), 7.16-7.21 (m, 2 H), 7.24-7.36 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.54, 30.26, 45.58, 64.98, 102.21, 126.53, 127.77, 128.73, 135.25, 159.97, 169.18, 170.94; IR (solid/KBr) 3071, 2961, 2869, 1738, 1698, 1665, 1437, 1277, 1138 cm^{-1}; HRMS calcd for $C_{14}H_{13}NO_3$ *m/z* 243.0896, found *m/z* 243.0880.

Formation of II-32 Using Acrylic Anhydride. To tetronic acid (2.00 g, 20.00 mmol) in C_6H_6 (40.0 mL) was added benzylamine (1.95 g, 18.18 mmol) and a catalytic amount of *p*-TsOH at room temperature. The reaction was fitted with a Dean - Stark trap and heated at reflux. After 12 h the reaction was cooled to room temperature and the solvent removed under reduced pressure. THF (40.0 mL) and acrylic anhydride (3.15 g, 30.91 mmol) (Acrylic anhydride was prepared immediately prior to use by adding NaH (1.8 equiv) to acrylic acid (1.2 equiv) at -78°C and allowing the mixture to warm to room temperature followed by the addition of acryloyl chloride (1.0 equiv) and allowing the

mixture to stir for 1 h. This mixture was transfered *via* cannula.) were then added. The reaction was again heated at reflux. After 14 h the reaction was cooled to room temperature and the solvent removed under reduced pressure. The reaction mixture was then chromatographed (silica, 230-400 mesh; eluent - Et_2O). The solvents were evaporated to give a white solid (3.13 g, 71% yield).

Formation of II-33. To **II-32** (0.46 g, 1.96 mmol) in EtOH (30.0 mL) and MeOH (15.0 mL) was added Na_2CO_3 (0.72 g, 6.86 mmol) and 10% Pd/C (0.40 g). The reaction vessel was purged with N_2 and then flushed with and maintained under an atmosphere of H_2. After stirring for 16 h, the reaction mixture was filtered through a fine scintered glass funnel and the solvent removed under reduced pressure. The resulting crude solid was purified by flash column chromatography (silica, 230-400 mesh; eluent - Et_2O). The solvents were evaporated to give a white solid (0.38 g, 79% yield, >98:2 *cis:trans*). ^1H NMR (300 MHz, $CDCl_3$) (*cis* isomer) δ 2.01 (m, 1 H), 2.30 (m, 1 H), 2.41 (m, 1 H), 2.52 (m, 1 H), 2.98 (m, 1 H), 4.18-4.30 (m, 4 H), 5.13 (d, J = 15.0 Hz, 1 H), 7.14-7.42 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) (*cis* isomer) δ 19.88, 29.68, 37.85, 47.94, 55.20, 71.23, 127.93 (2), 128.97, 136.15, 169.49, 176.09; IR (solid/KBr) 3071, 2961, 2862, 1738, 1698, 1665, 1437, 1277, 1196 cm^{-1}.

Formation of II-34. To MeMgBr (1.77 mL, 3.0 M in THF) in C_6H_6 (3.0 mL) was added NEt_3 (1.61 g, 15.92 mmol) at 0°C. After 10 min **II-33** (0.65 g, 2.65 mmol) in C_6H_6 (2.3 mL) was added with vigorous stirring. After 3 h at 0 °C the reaction was quenched by addition of an equal volume of 3 *M* aqueous HCl. The organics were separated and the solvent removed under reduced pressure. The resulting crude oil was purified by flash column chromatography (silica, 230-400 mesh; eluent - 95:5 Et_2O:MeOH). The solvents were evaporated to give a clear, colorless oil (0.17 g, 25% yield, >98:2 *cis:trans*); ^1H NMR (300 MHz, $CDCl_3$) (*cis* isomer) δ 1.90 (m, 1 H), 1.91 (s, 3 H), 2.10 (m, 1 H), 2.40 (dt, J = 17.7, 6.8 Hz, 1 H), 2.54 (dt, J = 17.7, 6.8 Hz, 1 H), 3.03 (dt, J = 6.6, 4.8 Hz, 1 H), 3.57 (dd, J = 11.6, 3.8 Hz, 2 H), 3.65 (dd, J = 11.4, 6.3 Hz, 1 H), 3.82 (m, 1 H), 3.92 (bs, 1 H), 4.08 (d, J = 15.0 Hz, 1 H), 5.19 (d, J = 15.0 Hz, 1 H), 7.21 (bd, J = 7.8 Hz, 2 H), 7.20-7.34 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) (*cis* isomer) δ 20.11, 25.58, 29.86, 47.49, 48.03, 57.15, 61.87, 127.45, 127.91, 128.54, 136.91, 171.06, 207.88; IR (oil/NaCl) 3374, 3088, 2942, 1711, 1613, 1455, 1256, 1169 cm^{-1}.

Formation of Preparation of Ethyl 2(S)-acetoxypropanoate (II-36). To a solution of S-ethyl lactate (2.0 g, 16.96 mmol) in pyridine (14.75 mL), was added acetic anhydride (1.88 g, 18.42 mmol) at 0 °C. The reaction was allowed to stirr at room temperature. After 12 h the reaction was poured into a mixture of crushed ice (100 mL)

and HCl (7 mL). The mixture was extracted with Et_2O, and the ether extracts washed with water followed by brine. The organics were dried, and the solvent removed under reduced pressure to give a colorless oil. The crude oil was purified by flash column chromatography (silica, 230-400 mesh; eluent - Et_2O:low boiling petroleum ether). The solvents were evaporated to give the product pure as a clear oil (5.2 g, 44.44 mmol) in 80% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 1.27 (t, J = 7.2 Hz, 3H), 1.47 (d, J = 7.2 Hz, 3H), 2.11 (s, 3H), 4.19 (q, J = 7.2 Hz, 2H), 5.03 (q, J = 7.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.66, 16.46, 20.14, 60.85, 68.29, 169.82, 170.38; IR (oil/NaCl) 2990, 2878, 1744, 1451, 1373, 1240, 1134, 1101, 1020, 735 cm^{-1}.

Formation of 4-Hydroxy-5(S)-methyl-2-furanone((S)-γ-Methyltetronic Acid) (II-37). To a solution of lithium bis(trimethylsilyl)amide (15 mmol, 1M in THF) in THF (40 mL) was added Ethyl 2(S)-acetoxypropanoate (**II-36**) (1.00 g, 6.29 mmol) in THF (40 mL) at -78 °C. The reaction was kept at -78 °C for 1 h and then poured into 2 *M* HCl (60 mL). The two layers were separated and the aqueous layer washed with EtOAc. The combined organics were dried and the solvents removed under reduced pressure. The oil was brought into CH_2Cl_2, dried and the solvent removed to provide a solid. The solid was then recrystallized from EtOAc-low boiling petroleum ether to yield the desired product pure (0.25 g, 2.2 mmol) in 35% yield. (mp. 108-111 °C); ^1H NMR (300 MHz, $CDCl_3$) δ 1.54 (d, J = 7.2 Hz, 3H), 4.93 (q, J = 6.8 Hz, 1H), 5.09 (s, 1H), 11.92 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.33, 77.32, 88.18, 178.13, 185.04; IR (oil/NaCl) 2942, 2708, 1709, 1599, 1279, 1238, 909 cm^{-1}.

Formation of II-38. To **II-37** (2.00 g, 20.00 mmol) in C_6H_6 (40.0 mL) was added benzylamine (1.95 g, 18.18 mmol) and a catalytic amount of *p*-TsOH at room temperature. The reaction was fitted with a Dean - Stark trap and heated at reflux. After 12 h the reaction was cooled to room temperature and the solvent removed under reduced pressure. THF (40.0 mL) and acryloyl chloride (2.80 g, 30.91 mmol) were then added. The reaction was again heated at reflux. After 14 h the reaction was cooled to room temperature and the solvent removed under reduced pressure. The reaction mixture was then chromatographed (silica, 230-400 mesh; eluent - Et_2O). The solvents were evaporated to give pure **II-38** in 29% yield; ^1H NMR (300 MHz, $CDCl_3$) δ 1.49 (d, J = 6.7 Hz, 3H), 2.51-2.71 (m, 2H), 2.72-2.91 (m, 2H), 4.50 (d, J = 16.2 Hz, 1H), 4.86 (qd, J = 6.7, 1.4 Hz, 1H), 5.25 (d, J = 16.2 Hz, 1H), 7.14 (d, J = 6.3 Hz, 2H), 7.27-7.39 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.78, 19.42, 30.85, 45.87, 73.19, 103.99, 126.25, 128.03, 129.11, 135.48, 142.26, 163.78, 169.98; IR (KBr) 2982, 2853, 1748, 1669, 1451, 1424, 1319, 1148, 1038, 773 cm^{-1}.

Formation of II-39. To **II-38** (0.46 g, 1.96 mmol) in EtOH (30.0 mL) and MeOH (15.0 mL) was added Na_2CO_3 (0.72 g, 6.86 mmol) and 10% Pd/C (0.40 g). The reaction vessel was purged with N_2 and then flushed with and maintained under an atmosphere of H_2. After stirring for 16 h, the reaction mixture was filtered through a fine scintered glass funnel and the solvent removed under reduced pressure. The resulting crude solid was purified by flash column chromatography (silica, 230-400 mesh; eluent - Et_2O). The solvents were evaporated to give pure **II-39** in 70% yield. ^1H NMR (300 MHz, $CDCl_3$) (diagnostic peaks for the two isomers are designated A and B) δ (A) 1.31 (d, *J* = 6.6 Hz, 3H), 2.58 (m, 1H), 3.08 (m, 1H), 3.58 (d, *J* = 15.0 Hz, 1H), 4.58 (qd, *J* = 6.6, 1.8 Hz, 1H), 4.01 (d, *J* = 15.0 Hz, 1H), 5.37 (d, *J* = 15.6 Hz, 1H), (B) 1.44 (d, *J* = 6.9 Hz, 3H), 2.52 (m, 1H), 2.01 (m, 1H), 3.79 (dd, *J* = 8.7, 1.8 Hz, 1H), 4.28 (dd, *J* = 9.9, 6.9 Hz, 2H), 5.67 (d, *J* = 15.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.49, 20.04, 20.33, 21.80, 29.57, 30.60, 37.21, 38.69, 47.73, 49.06, 56.05, 60.54, 78.95, 80.41, 127.95, 128.92, 128.96, 135.97, 169.50, 170.82, 175.95, 176.05.

Formation of II-40. To **II-31** (1.00 g, 2.41 mmol) in THF (16.1 mL) was added BuLi (1.06 mL, 2.5 M in THF) at -78 °C. After 10 min, phenylselenium chloride (0.51 g, 2.65 mmol) in THF (8.0 mL) was added and the reaction allowed to warm to 0 °C. After 3 min the reaction was quenched by addition of an equal volume of water. The mixture was extracted with 4 portions of Et_2O (10.0 mL) and the organics dried and concentrated under reduced pressure. The residue was brought up in MeOH:THF:HOH (16.0:8.0:1.0 mL) and $NaIO_4$ (1.55 g, 7.23 mmol) added. After 14 h the reaction was diluted with an equal volume of water and the mixture extracted with 10 portions of Et_2O (10.0 mL). The organics were separated, dried, and the solvent removed under reduced pressure. The resulting crude solid was purified by recrystallization from Et_2O:low boiling pet ether to give white crystals. (0.78 g, 78% yield) (mp = 98-99 °C); ^1H NMR (300 MHz, $CDCl_3$) δ 3.34 (t, *J* = 9.2 Hz, 1 H), 3.48 (dd, *J* = 9.6, 5.0 Hz, 1 H), 3.84 (m, 1 H), 4.00 (d, *J* = 15.5 Hz, 1 H), 4.08 (dd, *J* = 5.9, 1.4 Hz, 1 H), 4.27 (d, *J* = 12.0 Hz, 1 H), 4.33 (d, *J* = 12.0 Hz, 1 H), 4.40 (d, *J* = 12.0 Hz, 1 H), 4.45 (d, *J* = 12.0 Hz, 1 H), 5.37 (d, *J* = 15.5 Hz, 1 H), 6.15 (d, *J* = 9.6 Hz, 1 H), 6.47 (ddd, *J* = 9.6, 5.9, 1.1 Hz, 1 H), 7.10-7.15 (m, 2 H), 7.19-7.38 (m, 13 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 48.07, 57.40, 68.07, 68.60, 70.11, 73.24, 127.32, 127.52, 127.69, 127.75, 127.87, 128.04, 128.24, 128.29, 128.44, 128.51, 134.59, 136.91, 137.40, 137.52, 162.29; IR (oil/NaCl) 3088, 2870, 1669, 1611, 1455, 1262, 1146, 1092 cm^{-1}.

Formation of II-41. To **II-40** (0.10 g, 0.24 mmol) in *t*-BuOH (1.4 mL) was added NMO (excess) and OsO_4 (0.96 mL, 0.05 M in *t*-BuOH) at room temperature. After 3 h the reaction was quenched by addition of excess Na_2SO_3. Solvent was removed under

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reduced pressure till the reaction color began to turn grey. The resulting mixture was purified by repeated flash column chromatography (silica, 230-400 mesh; eluent - Et_2O to 50:50 Et_2O:EtOH) till the resulting product fractions were clear and colorless. The solvents were evaporated to give a white solid (0.07 g, 64% yield) (mp = 95-98 °C); ^1H NMR (300 MHz, $CDCl_3$) δ 2.96 (d, *J* = 1.8 Hz, 1 H), 3.61-3.78 (m, 3 H), 3.84 (d, *J* = 1.2 Hz, 1 H), 3.97 (t, *J* = 3.1 Hz, 1 H), 4.32 (d, *J* = 15.6, 1 H), 4.37 (td, *J* = 3.6, 2.1 Hz, 1 H), 4.41 (s, 2 H), 4.42 (m, 1 H), 4.44 (d, *J* = 12.0 Hz, 1 H), 4.50 (d, *J* = 12.0 Hz, 1 H), 5.27 (d, *J* = 15.6 Hz, 1 H), 7.11-7.21 (m, 4 H), 7.21-7.39 (m, 11 H); ^{13}C NMR (75 MHz, $CDCl_3$) 47.56, 58.98, 68.11, 68.85, 69.57, 71.48, 73.13, 75.21, 127.39, 127.55, 127.65, 127.74, 127.83, 128.23, 128.35, 128.41, 128.53, 136.83, 137.19, 137.43, 171.20 δ ; IR (oil/NaCl) 3409, 3088, 3031, 2869, 1645, 1455, 1250, 1074 cm^{-1}; HRMS calcd for $C_{27}H_{29}NO_5$ *m/z* 447.2046, found *m/z* 447.2046.

Formation of II-7. To **II-41** (0.06 g, 0.13 mmol) was added NH_3 (3.9 mL) and Li metal at -78°C, until the solution turned a persistent deep blue. After 3 h at reflux the reaction was cooled to -78°C and quenched by the addition of NH_4Cl. The reaction was then allowed to warm to room temperature allowing for NH_3 removal. The reaction was extracted with 10 portions of a solution of $CHCl_3$:MeOH (2:1, 2.0 mL) and filtered through cotton. Solvent removal under reduced pressure then under flat vacuum resulted in a solid which was dissolved in a minimum amount of MeOH and purified by flash column chromatography (silica, 230-400 mesh; eluent - 90:10 $CHCl_3$:MeOH). The solvents were evaporated to give a white solid (0.01 g, 44% yield) (mp = 163-168 °C); ^1H NMR (300 MHz, $CDCl_3$) δ 3.23 (td, *J* = 6.3, 3.9 Hz, 1 H), 3.59 (dd, *J* = 11.9, 5.9 Hz, 1 H), 3.68 (dd, *J* = 11.7, 5.1 Hz, 1 H), 3.72 (t, *J* = 6.2 Hz, 1 H), 3.89 (dd, *J* = 5.7, 3.9 Hz, 1 H), 4.20 (d, *J* = 3.9 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) 57.30, 61.11, 67.20, 68.14, 71.94, 173.17 δ ; IR (oil/NaCl) 3287, 3063, 2941, 2890, 2834, 1609, 1453, 1281, 1175, 1032 cm^{-1}.

Formation of II-43. To **II-41** (0.07 g, 0.16 mmol) in Et_2O (1.6 mL) was added excess LAH at room temperature. After 3 h the reaction was quenched at 0°C *via* slow addition of 15% NaOH until all visible LAH had been consumed. The reaction was filtered, dried and the solvent removed under reduced pressure. The resulting crude oil was purified by flash column chromatography (silica, 230-400 mesh; eluent - Et_2O). The solvents were evaporated to give a clear, colorless oil (0.07 g, >99% yield); ^1H NMR (300 MHz, $CDCl_3$) (*cis* isomer) δ 2.21 (dd, *J* = 12.2, 1.5 Hz, 1 H), 2.38 (dt, *J* = 8.7, 2.6 Hz, 1 H), 2.82 (s-broad, 2 H), 2.91 (dd, *J* = 12.2, 4.4 Hz, 1 H), 3.27 (d, *J* = 12.9 Hz, 1 H), 3.55 (dd, *J* = 8.4, 3.3 Hz, 1 H), 3.64 (t, *J* = 8.6 Hz, 1 H), 3.73 (m, 1 H), 3.76 (dd, *J* = 10.4, 2.6 Hz, 1 H), 3.83 (dd, *J* = 10.4, 2.6 Hz, 1 H), 4.16 (d, *J* = 13.2 Hz, 1 H), 4.45

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(s, 1 H), 4.56 (d, J = 11.1 Hz, 2 H), 4.90 (d, J = 11.1 Hz, 1 H), 7.20-7.40 (m, 15 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 54.71, 56.67, 64.76, 66.87, 68.10, 73.26, 74.61, 75.90, 78.42, 127.16, 127.65, 127.74, 127.79, 127.97, 127.99, 128.40, 128.94, 137.85, 138.52, 138.60; IR (oil/NaCl) 3422, 3063, 2923, 1495, 1453, 1098 cm^{-1}; HRMS calcd for $C_{27}H_{31}NO_4$ *m/z* 433.2253, found *m/z* 433.2253.

Formation of II-6. To **II-43** (0.08 g, 0.18 mmol) in EtOH (1.8 mL) was added 10% Pd/C (0.18 g) and conc HCl (1.8 mL). The reaction flask was purged with N_2 and then flushed with and maintained under an atmosphere of H_2 and allowed to stir at room temperature. After 14 h the reaction mixture was filtered and the solvent removed under reduced pressure. The crude solid was recrystallized from MeOH:Et_2O to give a white solid. (0.01 g, 33% yield) (mp = 184-186 °C); ^1H NMR (300 MHz, $CDCl_3$) δ 3.00 (ddd, J = 9.9, 6.6, 3.0 Hz, 1 H), 3.10 (dd, J = 13.8, 1.3 Hz, 1 H), 3.27 (dd, J = 13.8, 3.0 Hz, 1 H), 3.55 (dd, J = 9.6, 3.0 Hz, 1 H), 3.70 (dd, J = 12.3, 6.0 Hz, 1 H), 3.74 (t, J = 6.8 Hz, 1 H), 3.85 (dd, J = 12.3, 3.5 Hz, 1 H), 4.10 (m, 1 H).

References.

1) (a) Fairbanks, A. J.; Carpenter, N. C.; Fleet, G. W. J.; Ramsden, N. G.; de Bello, I. C.; Winchester, B. G.; Al-Daher, S. S.; Nagahashi, G. *Tetrahedron* **1992**, *48*, 3365. (b) Sharon, N. Lis, H. *Sci. Amer.* **1993**, 82 (c) Fuhrmann, U.; Bause, E.; Legler, G.; Ploegh, H. *Nature* **1984**, *307*, 755.

2) Evans, S. V.; Fellows, L. E.; Shing, T. K. M.; Fleet, G. W. J. *Phytochemistry* **1985**, *24*, 1953.

3) (a) Truscheit, E.; Frommer, W.; Junge, B.; Muller, L.; Schmidt, D. D.; Wingender, W. *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 744. (b) Fellows, L. E. *Chem. Ber.* **1987**, *23*, 842.

4) (a) Fr. Patent; FR 1524395, *[CA 71:91733w]*. (b) Bourrinet, P.; Quevauviller, A. *Ann. Pharm. Fr.* **1968**, *26*, 787, *[CA 71: 29012g]*. (c) Bourrinet, P.; Queviller, A. *Compt. Rend. Soc. Biol.* **1968**, *162*, 1138, *[CA 70:95233k]*.

5) (a) Fleet, G. W. J.; Ramsden, N. G.; Witty, D. R. *Tetrahedron* **1989**, *45*, 319. (b) Fleet, G. W. J.; Ramsden, N. G.; Witty, D. R. *Tetrahedron* **1989**, *45*, 327.

6) Paulvannan, K.; Stille, J. R. *J. Org. Chem.* **1992**, *57*, 5319.

7) (a) Daniewski, A. R.; Kiegiel, J. *Synthesis* **1987**, *70*, 5. (b) Murahashi, S-I.; Oda, Y.; Naota, T. *Tetrahedron Lett.* **1992**, *33*, 7557. (c) Daniewski, A. R.; Warchol, T. *Liebigs Ann. Chem.* **1992**, 965. (d) Miki, Y.; Ohta, M.; Hachiken, H.; Takemura, S. *Synthesis* **1989**, 312. (e) Wender, P. A.; Tebbe, M. J. *Synthesis* **1991**, 1089. (f) Conversations with Paulvannan, K. (g) Canan, Koch, S. S.;

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Chamberlin, R. *Synth. Commun.* **1989**, *19*, 829. (h) Hassal, C. H. *Organic Reactions* **1943**, *3*, 73. (i) Wilson, S. R.; Di Grandi, M. J. *J. Org. Chem.* **1991**, *56*, 4766. (j) Siginome, H.; Yamada, S. *J. Org. Chem.* **1985**, *50*, 2489. (k) Baxter, A. J. C.; Holmes, A. B. *JCS Perkin I* **1977**, 2343. (l) Warasaki, K.; Sakakura, T.; Uchimura, T.; Guedin-Vuong, D. *J. Am. Chem. Soc.* **1984**, *106*, 2954.

8) Paulvannan, K.; Stille, J. R. *Tetrahedron Lett.* **1993**, *34*, 6673.

9) (a) Kurth, M. J.; O'Brian, M. J.; Hope, H.; Yanuck, M. *J. Org. Chem.* **1985**, *50*, 2626. (b) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, *31*, 2647.

10) Cook, G. R.; Beholz, L. G.; Stille, J. R. *Tetrahedron Lett.* **1994**, *35*, 1669.

11) (a) Fryuk, M. D.; Dosnich, B. *J. Am. Chem. Soc.* **1978**, *100*, 5491. (b) Brandage, S.; Flodman, L.; Norberg, A. *J. Org. Chem. Soc.* **1984**, *49*, 927.

12) (a) Clive, D. L. J. *Tetrahedron* **1978**, *34*, 1049. (b) Reich, H. J. *Acc. Chem. Res.* **1979**, *12*, 22.

13) (a) Nishiyama, S.; Yamamura, S.; Hasegawa, K.; Sakoda, M.; Harada, K. *Tetrahedron Lett.* **1991**, *32*, 6753. (b) Guillerm, G.; Varkados, M.; Auvin, S.; Legoffis, F. *Tetrahedron Lett.* **1987**, *28*, 535.

14) The physical data for **II-6** were consistent with those reported, 5b

15) The physical data for **II-7** were consistent with those reported, 5a

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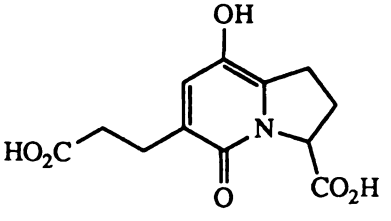
CHAPTER III
AZA-ANNULATION AS A ROUTE TOWARD THE PREPARATION OF PEPTIDE MIMICS

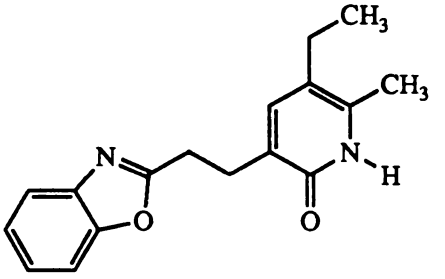
Introduction.

There has recently been increased interest in the preparation of peptide mimics, as these compounds have been used in the modification of an increasing number of biological processes. Compounds such as A58365A (**III-1**) act as effective angiotension converting enzyme (ACE) inhibitors, effective for the treatment of hypertension.[1] L-696,229 (**III-2**), another peptide mimic, constitutes one of the latest in HIV-reverse transcriptase inhibitors (Figure III-1).[2] Other peptide mimics have been implicated for use as potential anti-cancer agents.[3]

Figure III-1. Several Important Peptide Mimics



III-1
(A58365A)



III-2
(L-696,229)

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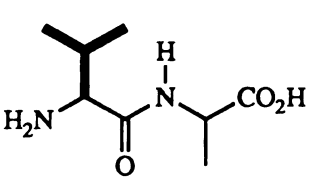
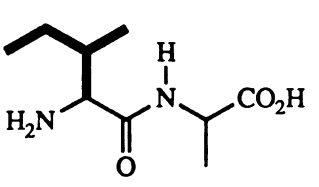
In the design of a peptide mimic, a known peptide possessing some function acts as the target for the design. A peptide surrogate is then designed to mimic the original peptide but differ from it significantly enough to disrupt normal enzyme function and elicit some desired response. An example of this method of design was executed by Rapoport (Figure III-2).[4] In this work, several dipeptides were targeted and 5-membered ring analogs of them prepared. In each instance, the first amino acid side chain was tethered into the ring.

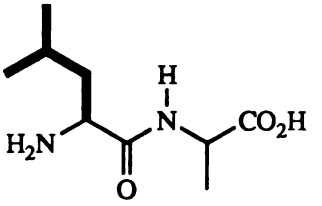
Figure III-2. Examples of Peptide Surrogate Design



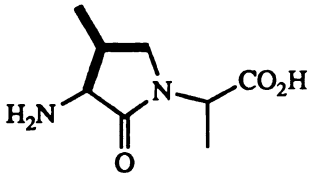
III-3
(Val-Ala)



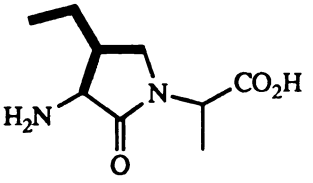
III-5
(Ile-Ala)



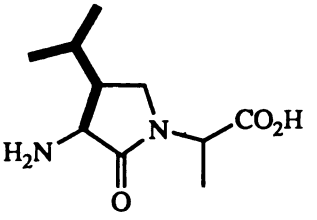
III-7
(Leu-Ala)



III-4



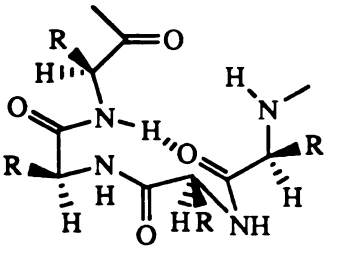
III-6



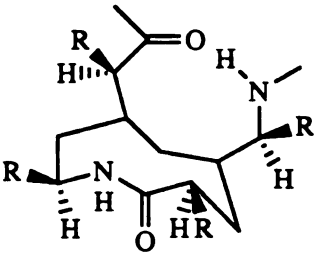
III-8

Extremely important to peptide function is the peptides secondary structure. One common structural unit is the β-turn. In natural peptides, the β-turn is four amino acid units long. In β-turn mimics, the turn can be comprised of a variety of structural units. Any structure that effectively mimics the topography of the targeted β-turn may be used. An example of a conformationally restricted β-turn mimic is presented in Figure III-3.[5]

Figure III-3. β-Turn Mimic



III-9
(β-turn)

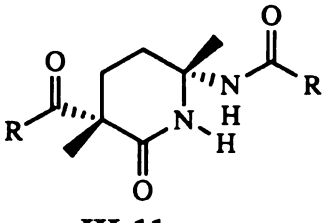


III-10
(β-turn mimic)

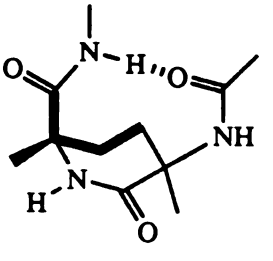
Many conformationally restricted β-amino acids have also been prepared as peptide mimics.[6-8] Generally, these peptide surrogates are resistant to enzymatic cleavage as well as fixed in geometry, making them effective probes of enzyme function. Incorporation of conformationally restricted β-amino acid segments into linear bioactive peptides can give information concerning the linear peptides active conformation.[7] Further, conformationally restricted β-amino acids may be highly biologically active without further modification.

An example of a piperidinone β-turn mimic is shown in Figure III-4.[8] When incorporated into short peptides, the β-amino acid adopts the conformation shown at the right. Pyridinone β–amino acids and their derivatives, such as **III-1**, would exhibit significantly altered external topography, thus potentially inhibiting enzyme function. These pyridinone β-amino acids are also very stable.

Figure III-4. Piperidinone Peptide Mimic



III-11



III-11
(3-D conformation)

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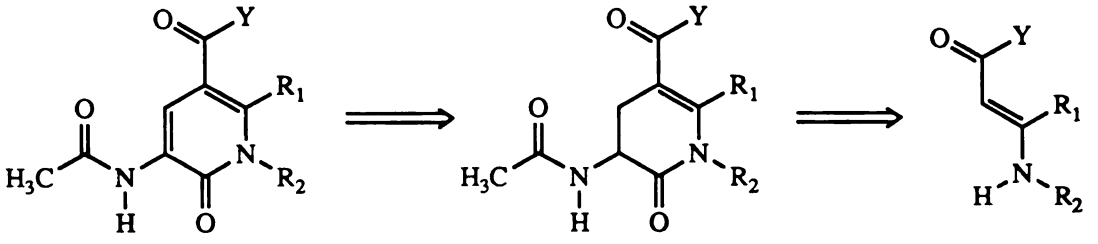
The objective of the current work was to examine ways to employ the aza-annulation as a tool for accessing conformationally restricted 6-membered-ring peptide mimics.[6] The general strategy for approaching functionalized pyridinone systems is indicated in Scheme III-1.

Scheme III-1. General Strategy for Functionalized Pyridinone Formation



III-12 **III-13** **III-14**

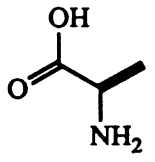
To this end, a variety of substrates were prepared and annulated, exploring the scope and generality of the aza-annulation methodology toward peptide mimic formation. The prepared piperidinone β-amino acid mimics were then oxidized yielding the corresponding pyridinone β-amino acids.

Results and Discussion.

As precursors of pyridones substituted at the C-4 position and especially the C-5 position, functionalized β–ketoesters, β–ketoamides, or acetylinic esters were prepared. These reacted with benzylamine or the amine salt of phenyl glycine ethyl ester to provide compounds with a structure similar to **III-14**.[10] These were then annulated using the mixed anhydride of 2-acetamidoacrylic acid, accessing structures similar to **III-13**.[9] DDQ oxidation of these compounds provided compounds similar to **III-12**.[11] The amino acids used as models for preparation of the β-amino acid analogs by aza-annulation were: alanine (**III-15**), proline (**III-16**), aspartic acid methyl ester (**III-17**), benzyl protected serine (**III-18**), and phenylalanine (**III-19**). The aza-annulated derivative types are represented by structures **III-20** - **III-24** (Figure III-5).

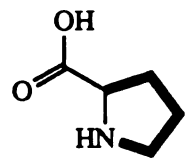
Initially, the β-ketoester **III-25** was annulated. Reaction of **III-25** with benzylamine and 2-acetamidoacrylic acid cleanly afforded **III-27** in 91% yield. DDQ oxidation provided **III-28** in 73% yield (Scheme III-2). Annulation of enaminoester **III-29** with 2-acetamidoacrylic acid provided **III-30** in 77% yield. Oxidation of **III-30** with DDQ gave **III-31** in 73% yield (Scheme III-3).

Figure III-5. Aza-annulation β-Amino Acid Analogs



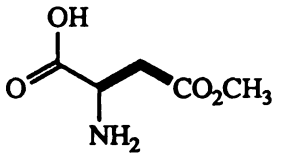
III-15

(alanine)



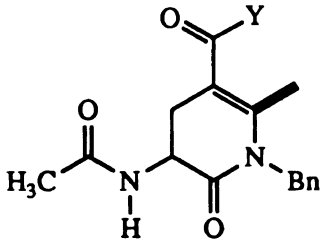
III-16

(proline)

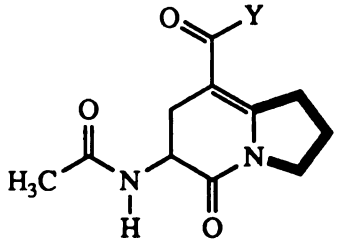


III-17

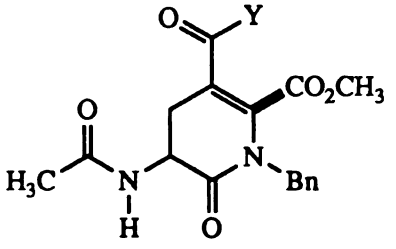
(aspartic acid methyl ester)



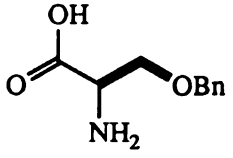
III-20



III-21

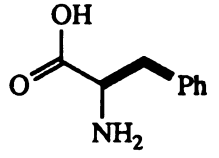


III-22



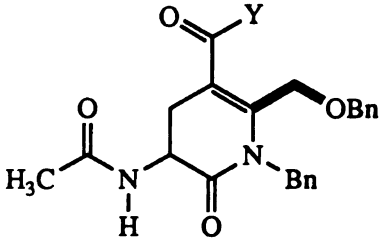
III-18

(benzyl protected serine)

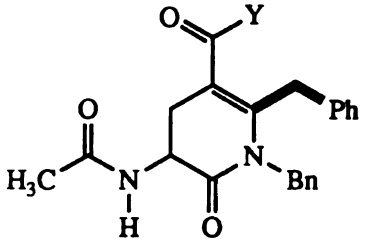


III-19

(phenylalanine)

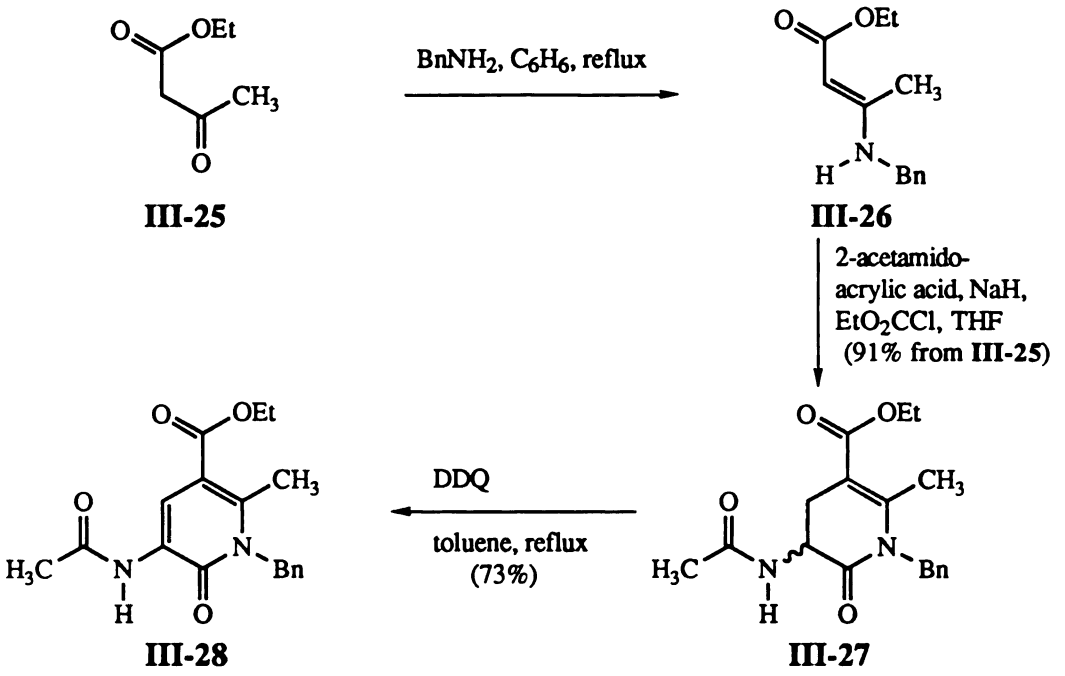


III-23

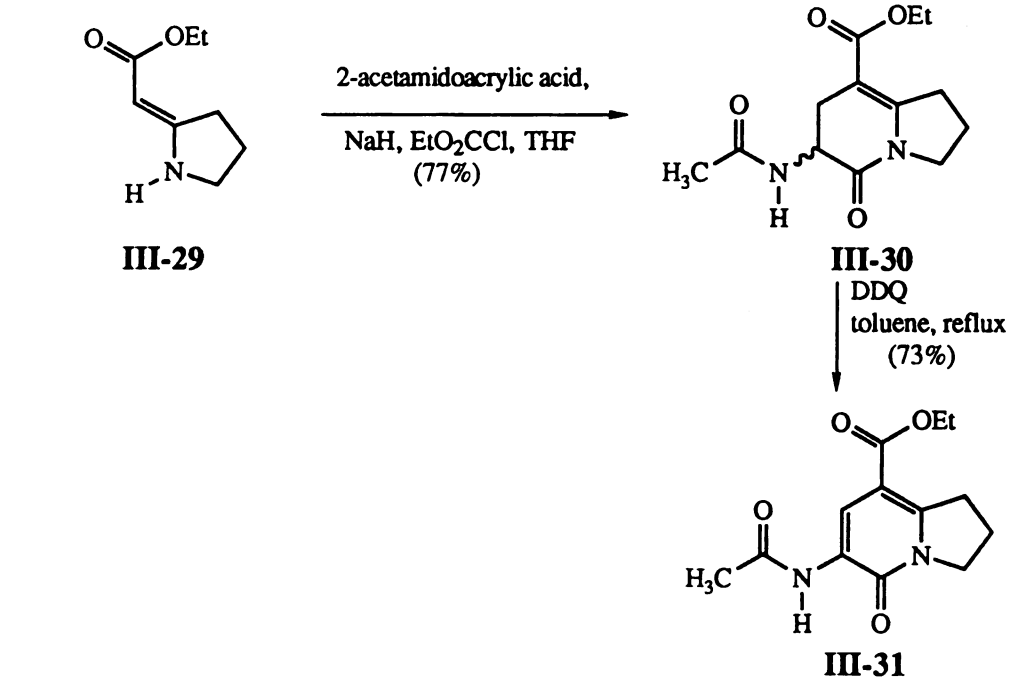


III-24

Scheme III-2. Aza-annulation of β-ketoester **III-25**

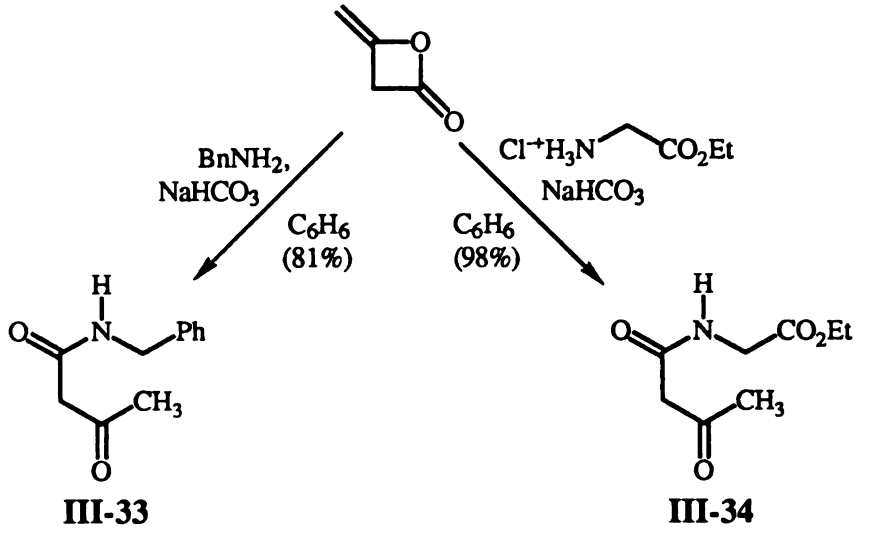


Scheme III-3. Aza-annulation of Enamino Ester **III-29**



Several β-ketoamide substrates were smoothly prepared by reaction of diketene with benzyl amine or the amine salt of glycine ethyl ester (Scheme III-4). Reaction of diketene with benzyl amine, using $NaHCO_3$ as a base, provided **III-33** in 81% yield while reaction with the amine salt of glycine ethyl ester provided **III-34** in 98% yield.

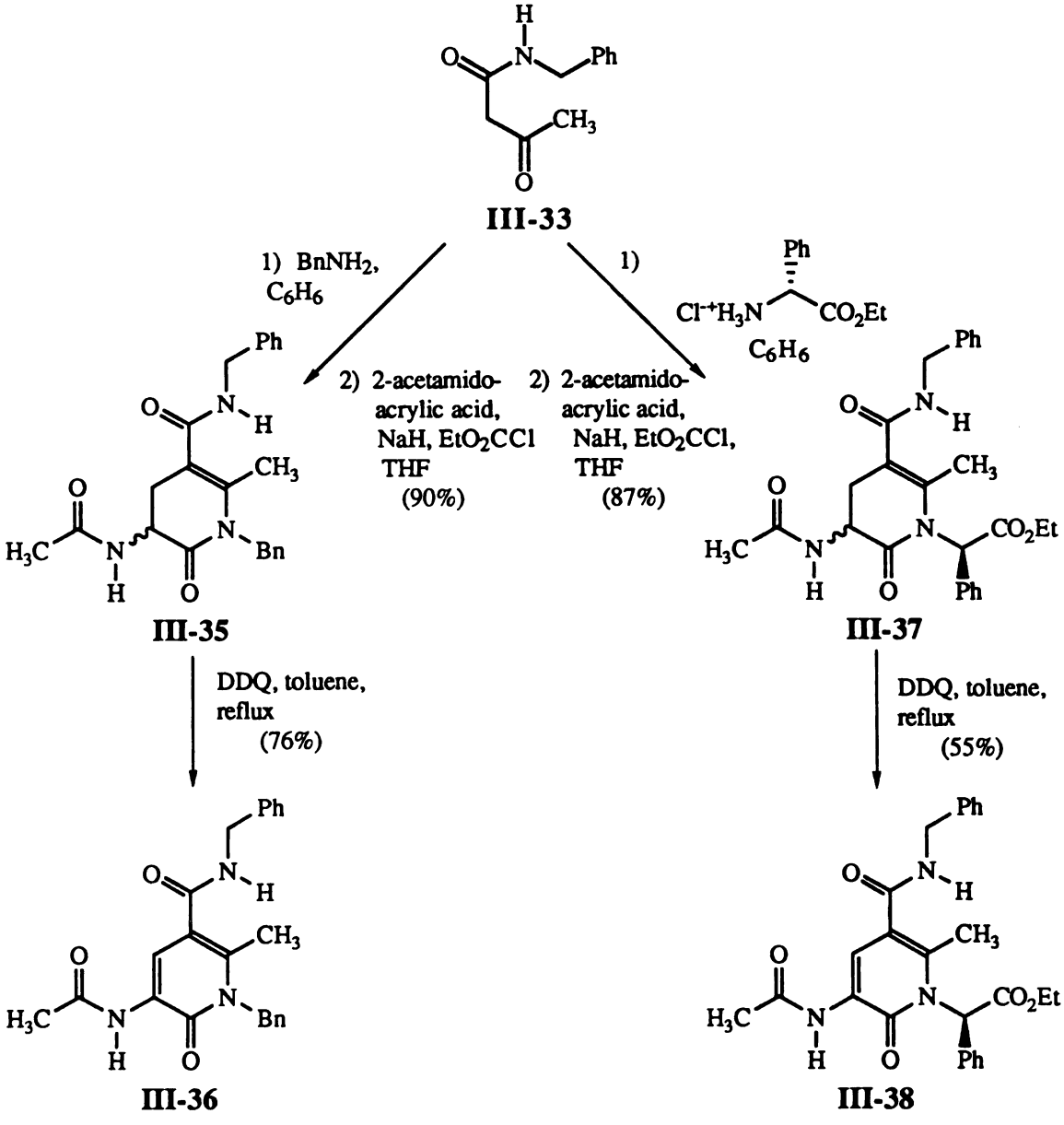
Scheme III-4. Preparation of β–keto amide substrates



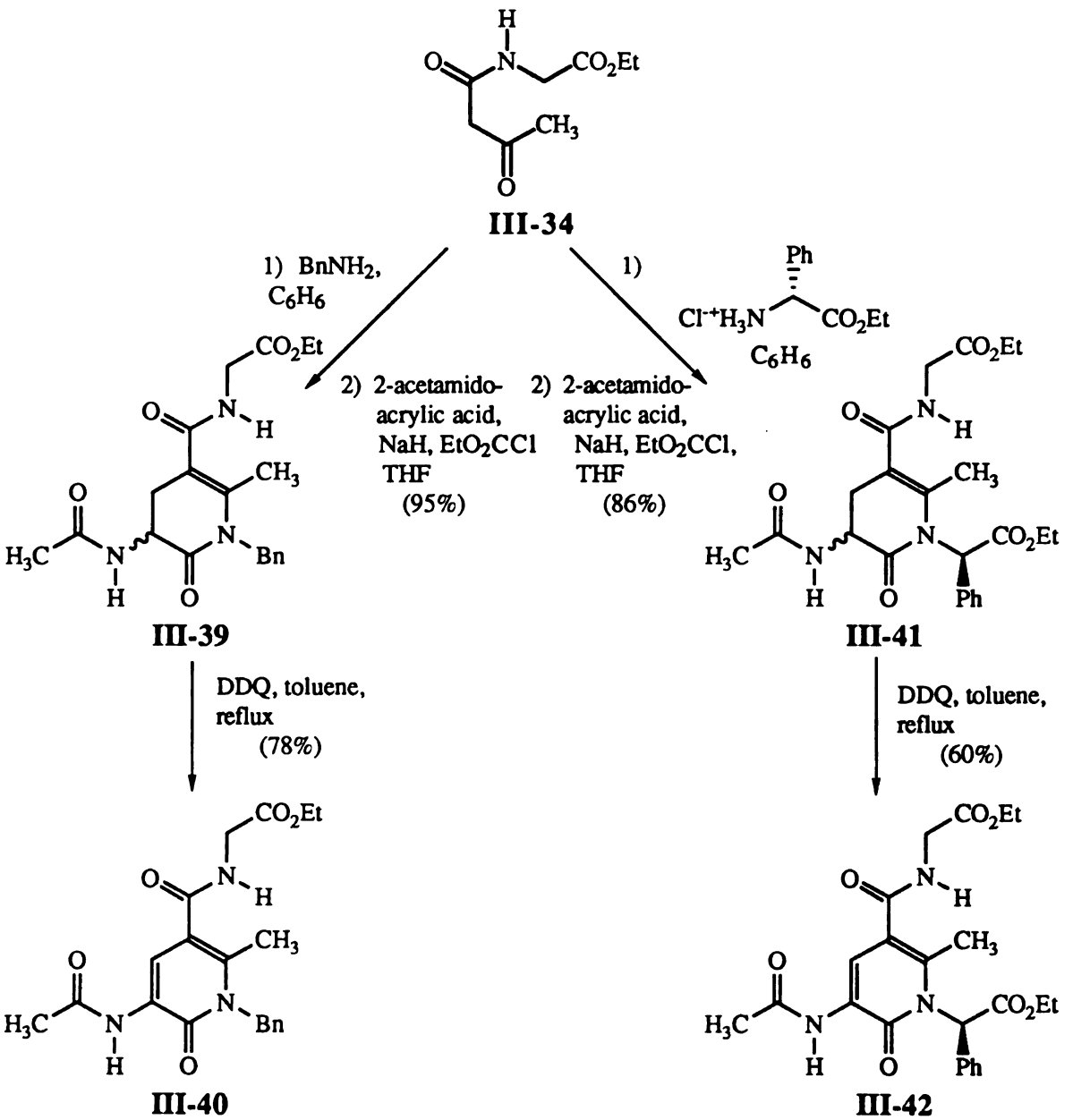
Aza-annulation of **III-33** and **III-34** were executed as described[7] using benzyl amine or the amine salt of phenylglycine ethylester (Scheme III-5 and III-6). Oxidation provided the corresponding peptide analog types. Annulation of **III-33** with benzyl amine gave **III-35** in 90% yield. Subsequent oxidation with DDQ afforded **III-36** in 76% yield. Similar reaction of **III-33** with the amine salt of phenylglycine ethylester provided **III-37** as a mixture of diastereomers in a ratio of 51:49 in 87% yield. DDQ oxidation gave **III-38** in 55% yield. For the annulation substrate **III-34**, reaction with benzyl amine provided **III-39** in 95% yield. DDQ oxidation afforded **III-40** in 78% yield. Annulation of **III-34** with the protected phenylglycine salt gave **III-41** as a mixture of diastereomers in a ratio of 51:49 in 86% yield. Oxidation of **III-41** provided **III-42** in 60% yield.


H3C
H3C

Scheme III-5. Aza-annulation of β-ketoamide **III-33**

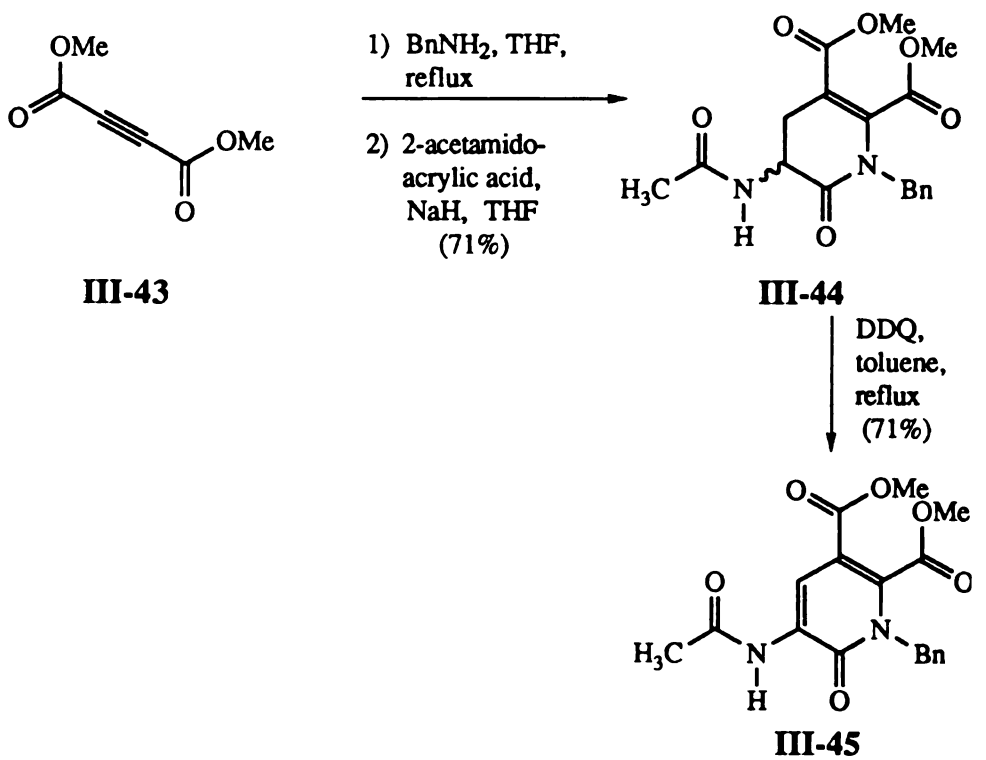


Scheme III-6. Aza-annulation of β-ketoamide **III-34**



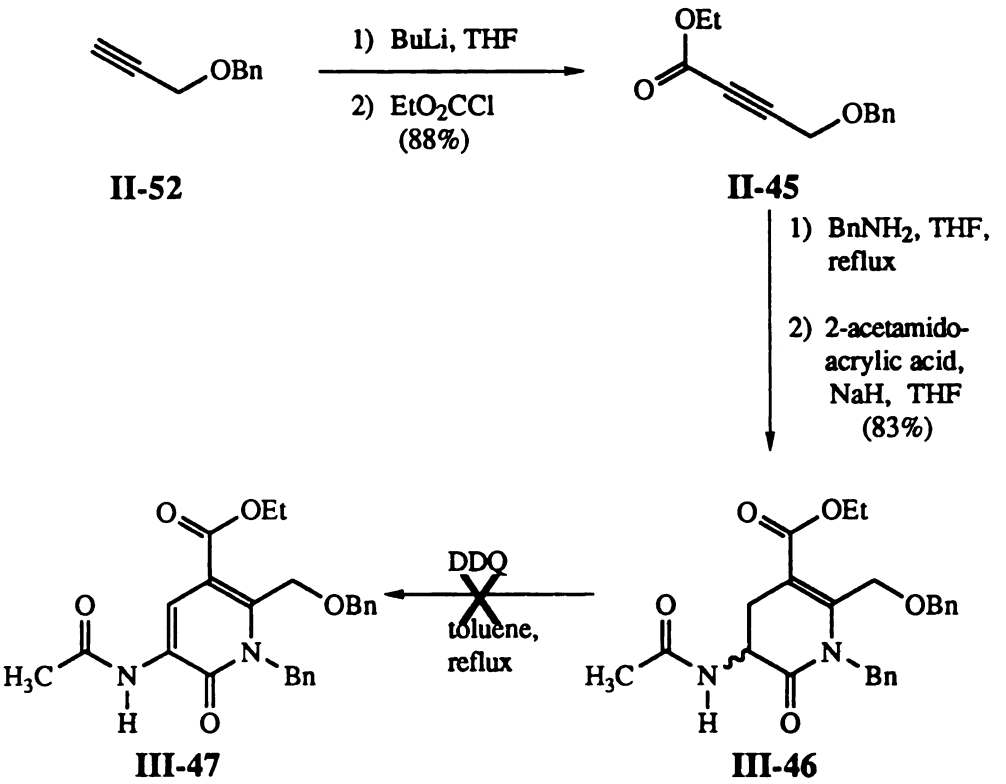
To effect placement of functionality at the C-5 position, aza-annulation using acetylenic esters was executed (Scheme III-7, III-8, and III-9). Annulation of **III-43** with benzyl amine gave **III-48** in 71% yield. Subsequent DDQ oxidation gave **III-45** in 71% yield. Ethyl ester **II-45** (prepared as described in chapter II) was annulated in 83% yield providing **III-46**. DDQ oxidation of **III-46** failed, giving recovery starting material.[11] Substrate **III-49** (prepared in similar fashon to **II-25** in 94% yield) was annulated using benzyl amine to provide **III-50** in 61% yield. The stereochemical conformation about the double bond was determined using NOE.[12] The expected isomer comprised 8% of the product mixture.

Scheme III-7. Aza-annulation of Acetylenic Ester **III-43**

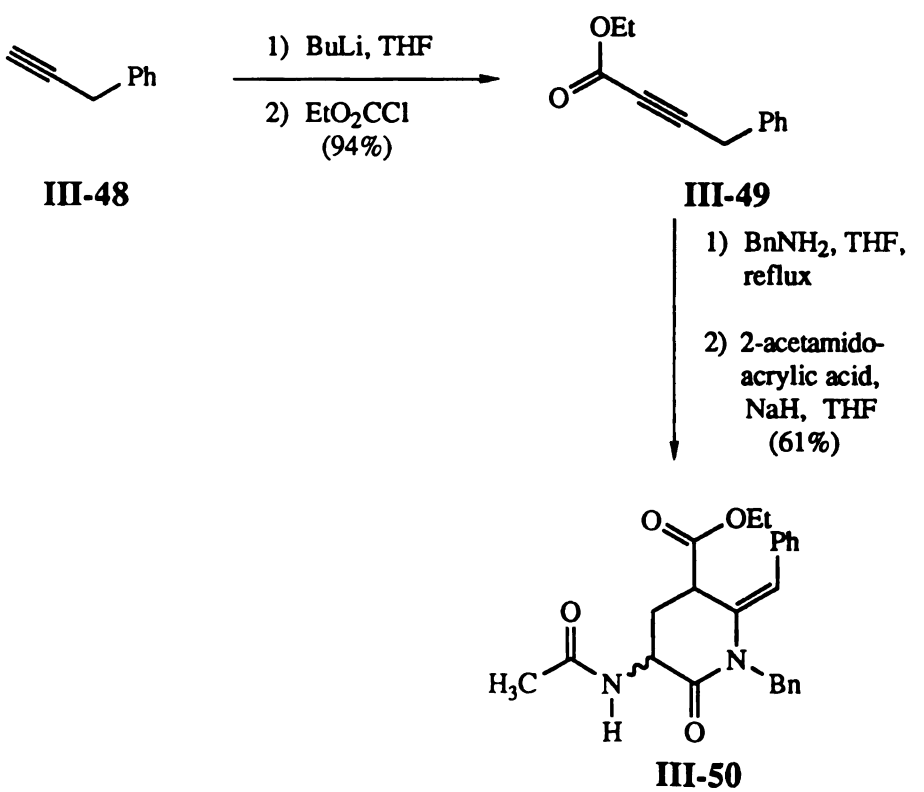


III-43 **III-44** **III-45**

Scheme III-8. Aza-annulation of Acetylenic Ester **II-45**

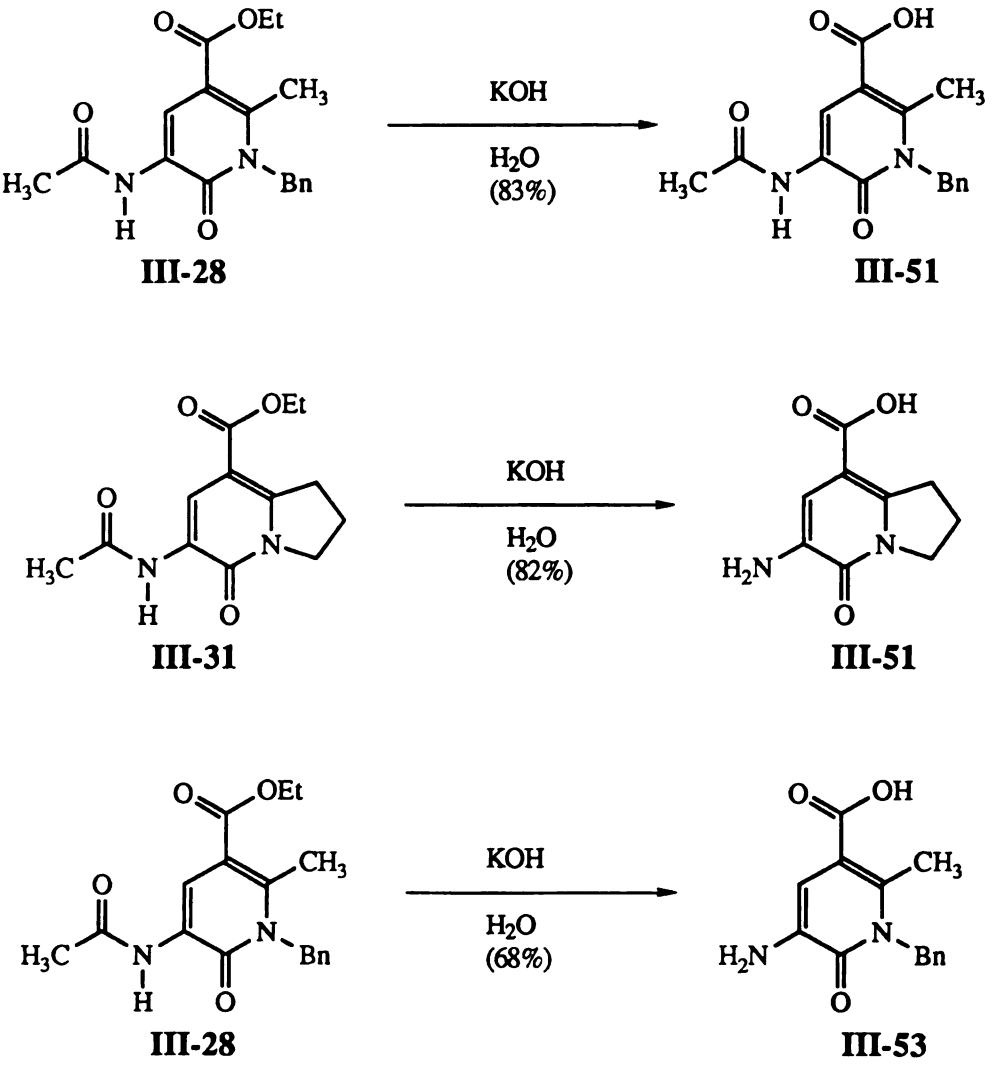


Scheme III-9. Aza-annulation of Acetylenic Ester **III-49**

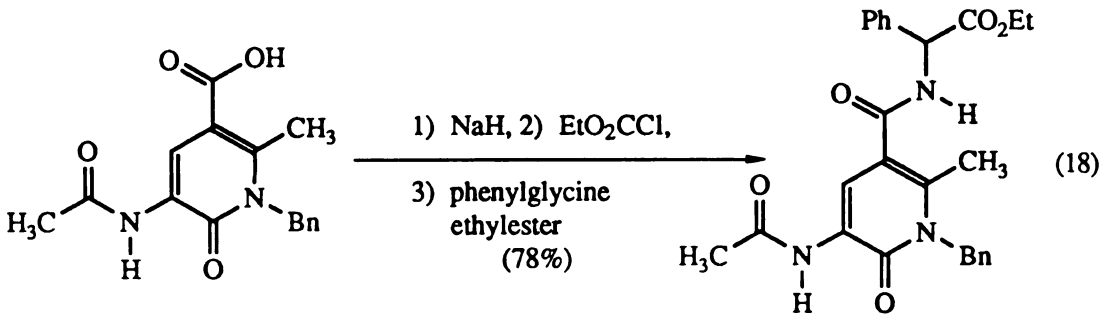


Hydrolysis of **III-28** and **III-31** prepared the substrates for acylation of the amine or alkylation of the carboxylic acid. Treatment of **III-28** with aqueous KOH cleanly hydrolyzed the ester leaving the amide intact to provide **III-51** in 83% yield. Hydrolysis of **III-31** under similar conditions provided **III-49** in 82% yield. To deprotect the amine of **III-28**, KOH in 30% H_2O_2 was used to give **III-53** in 75% yield (Scheme III-10).

Scheme III-10. Hydrolysis of **III-28** and **III-31**



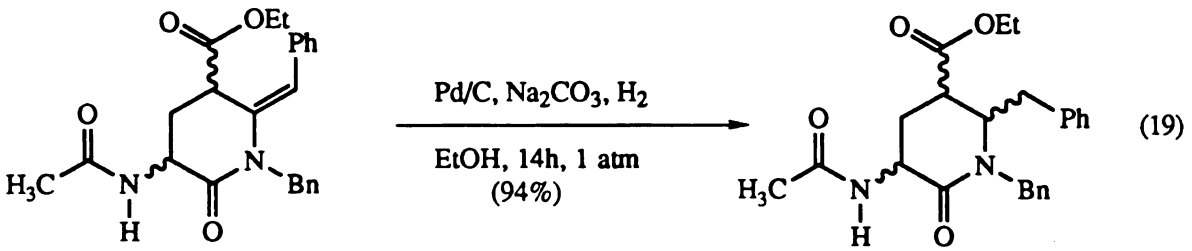
The versatility of compounds such as **III-52** was demonstrated by alkylation of the free carboxylic acid. Alkylation of **III-52** with phenylglycine ethyl ester provided **III-54** in 78% yield (eq 18).



(18)

III-52 **III-54**

Hydrogenation of **III-50** under conditions of Pd/C, Na_2CO_3, and H_2 at one atmosphere resulted in the formation of **III-55** as a mixture of diastereomers in a ratio of 96:4 in 94% yield (eq 19). Attempted DDQ oxidation of **III-50** failed.[9]



(19)

III-50 **III-55**

Conclusion.

The aza-annulation constitutes a quick and efficient method of building up highly functionalized 6-membered nitrogen heterocycles. Oxidation of these heterocycles provide the corresponding functionalized pyridone ring. The aza-annulation methodology thus constitutes a rapid and efficient route for the formation of peptide mimics with functionalization possible at the C-2, C-4, and C-5 positions. In the current work, the aza-annulation methodology was used to prepare a series of extended, 6-membered ring amino acid analogs.[14] These analogs constitute conformationally modified protein segments that may be incorporated into peptide mimics.

Experimental Section.

General Methods. All reactions were carried out using standard inert atmosphere techniques to exclude moisture and oxygen, and reactions were performed under an atmosphere of nitrogen. Benzene, toluene and ether were distilled from sodium/benzophenone immediately prior to use. Xylenes and decalin were heated over calcium hydride for a minimum of 12 h and then distilled prior to use. $LiAlH_4$ (1 *M* in THF) was obtained from Aldrich Chemical Co. Unless specified, concentration of mixtures was performed using a Büchi rotary evaporator.

Gas chromatographic (GC) analyses were carried out on one of two instruments. For lower molecular weight compounds gas chromatographic analysis was carried out isothermally on a Perkin-Elmer 8500 instrument using a 50 meter RSL-200 capillary column (5% methylphenyl silicon) and an FID detector at 200 °C oven temperature, 220 °C injector temperature, and 300 °C detector temperature. Helium gas pressure was set at 15 psi with a flow rate of 2 mL/min. For higher molecular weight compounds, gas chromographic analysis was carried out on a Hewlett-Packard 5880A series gas chromatograph fitted with a 300 meter silica capillary column and a flame ionization detector. For these analysis injector and detector temperatures were set at 250 °C and the column oven temperature was programmed: 40 °C, 2 min., 10 °C/min. ramp to 200 °C. All reactions were monitored by GC and the reactions terminated either when the starting material had been consumed or no further reaction appeared to continue. For reactions in which a Dean-Stark trap was used, the trap was filled with molecular sieves to a level below that of returning solvent turbulence. These were changed during reactions in which additional reagent was added after the reactions initiation. Molecular sieves were activated by heating in a 150 °C oven for at least 24 hours prior to use. NMR spectra were obtained on a VXR-300 spectrometer using $CHCl_3$ with 0.1% TMS as an internal standard δ (0.00 ppm), CD_3OD, Acetone-d_6, or DMSO-d_6, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sept = septet), integration and coupling. Infrared spectra were recorded on a Nicolet 42 FT-IR instrument.

General Method for the Formation of β-Ketoamides. Diketene (5.0-30.0 mmol, 1.0 equiv) and the amine or amine hydrocloride salt (1.0 equiv) were taken up in benzene (0.5 M relative to the amine) along with an excess of $NaHCO_3$ (2.0 equiv) at 0 °C. After stirring at room temperature for 14 h, the reaction mixture was filtered and the solvent removed under reduced pressure to yield the product as a solid. Recrystallization from $Et_2O/CHCl_3$ yielded the product as white leaflets.

III-34: (1.74 g, 9.35 mmol, 99% yield); mp 52-53 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (t, *J* = 7.1 Hz, 3 H), 2.28 (s, 3 H), 3.50 (s, 2 H), 4.04 (d, *J* = 5.4 Hz, 2 H), 4.20 (q, *J* = 7.2 Hz, 2 H), 7.61 (bs, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.84, 30.36, 41.11, 49.63, 61.13, 166.16, 169.41, 203.54; IR (KBr) 3353, 2986, 1754, 1715, 1673, 1543, 1418, 1401, 1321, 1175 cm^{-1}; HRMS for $C_8H_{13}NO_4$ *m/z* 187.0845, found *m/z* 187.0844.

III-33: (3.59 g, 18.80 mmol, 81% yield); mp 100-102 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.24 (s, 3 H), 3.42 (s, 2 H), 4.44 (d, *J* = 6.0 Hz, 2 H), 7.25-7.40 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.90, 43.46, 49.56, 127.42, 127.62, 128.62, 137.88, 165.38, 204.35; IR (KBr) 3249, 3085, 1715, 1640, 1443, 1410, 1190, 1163 cm^{-1}; HRMS for $C_{11}H_{13}NO_2$ *m/z* 191.0146, found *m/z* 191.0982.

General Method for the Aza-Annulation of β–Ketoamides and β–Ketoesters. A mixture of the primary amine or primary amine salt (0.5-5.0 mmol, 1.0 equiv) and the B-ketoamide (1.0 equiv) were taken up in benzene (0.5 M relative to the amine) along with BF_3-etherate (0.5 equiv) and fitted with a modified Dean-Stark trap which passes returning solvent through molecular sieves. After the reaction had gone to completion, as indicated by ^{1}H NMR, the solvent was removed under reduced pressure and the crude enamine brought up in THF (0.1 M relative to the enamine). The sodium salt of 2-acetamidoacrylic acid (1.3 equiv) was added at -78 °C and the reaction allowed to stir at rt for 14 h, or longer if ^{1}H NMR suggested the reaction not complete. Sat. aq. $NaHCO_3$ (excess) was added, and the mixture was extracted 4 times with EtOAc. The combined organic fractions were dried over Na_2SO_3, filtered, and the solvent evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica, 230-400 mesh, eluent, Et_2O:EtOAc:MeOH)

III-27: (0.56 g, 1.70 mmol, 74% yield); mp 132-135 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (t, *J* = 7.2 Hz, 3 H), 2.06 (s, 3 H), 2.27 (tq, *J* = 15.9, 2.6 Hz, 1 H), 2.37 (d, *J* = 2.1 Hz, 3 H), 3.40 (dd, *J* = 15.9, 6.3 Hz, 1 H), 4.17 (q, *J* = 7.2 Hz, 2 H), 4.55 (dt, *J* = 14.7, 6.0 Hz, 1 H), 4.78 (d, *J* = 16.1 Hz, 1 H), 5.22 (d, *J* = 16.1 Hz, 1 H), 6.61 (bd, *J* = 5.1 Hz, 1 H), 7.11 (d, *J* = 6.9 Hz, 2 H), 7.22-7.36 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.14, 16.11, 23.15, 27.69, 45.80, 48.96, 60.51, 109.12, 126.04, 127.41, 127.63, 128.83, 136.73, 147.35, 166.68, 170.12; IR (KBr) 3299, 2986, 1686, 1389, 1248, 1163 cm^{-1}; HRMS for $C_{18}H_{22}N_2O_4$ *m/z* 330.1580, found *m/z* 330.1572.

III-30: (1.27 g, 4.77 mmol, 74% yield); mp 150-151 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29 (t, *J* = 7.2 Hz, 3 H), 2.03 (quint, *J* = 7.3 Hz, 2 H), 2.07 (s, 3 H), 2.29 (tt, *J* = 15.6, 2.9 Hz, 1 H), 3.16 (td, *J* = 7.7, 2.1 Hz, 2 H), 3.40 (dd, *J* = 16.2, 7.5 Hz, 1 H), 3.68 (dt,

J = 11.4, 7.3 Hz, 1 H), 3.79 (dt, *J* = 11.4, 7.2 Hz, 1 H), 4.19 (q, *J* = 7.2 Hz, 2 H), 4.54 (dt, J = 14.4, 7.2, 1 H), 6.39 (d, *J* = 5.7 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.33, 21.59, 23.17, 27.99, 31.20, 46.17, 49.60, 60.15, 100.82, 152.30, 166.41, 167.89, 170.23; IR (KBr) 3281, 2984, 2849, 1690, 1642, 1545, 1399, 1248, 1173, 1109 cm^{-1}; HRMS for $C_{13}H_{18}N_2O_4$ *m/z* 266.1267, found *m/z* 266.1260.

III-39: (1.06 g, 2.74 mmol, 95% yield); mp 71-74 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (t, *J* = 7.1 Hz, 3 H), 2.00 (s, 3 H), 2.16 (d, *J* = 2.2 Hz, 3 H), 2.46 (btd, *J* = 15.3, 2.2 Hz, 1 H), 2.96 (dd, *J* = 15.3, 6.5 Hz, 1 H), 3.95 (dd, *J* = 18.1, 5.6 Hz, 1 H), 4.04 (dd, *J* = 18.1, 5.6 Hz, 1 H), 4.14 (q, *J* = 7.2 Hz, 2 H), 4.59 (dt, *J* = 15.3, 6.5 Hz, 1 H), 4.67 (d, *J* = 16.7 Hz, 1 H), 5.13 (d, *J* = 16.7 Hz, 1 H), 6.91 (t, *J* = 5.6 Hz, 1 H), 7.05-7.13 (m, 3 H), 7.19-7.34 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.84, 15.79, 22.78, 28.31, 41.18, 45.42, 48.74, 61.09, 111.95, 125.82, 127.12, 128.58, 136.78, 139.74, 168.09, 169.34, 169.69, 170.25; IR (KBr) 3285, 2984, 1744, 1657, 1584, 1543, 1319, 1190 cm^{-1}; HRMS for $C_{20}H_{25}N_3O_5$ *m/z* 387.1794, found *m/z* 387.1789.

III-35: (0.78 g, 2.06 mmol, 90% yield); mp 82-85 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.92 (s, 3 H), 2.07 (d, *J* = 2.3 Hz, 3 H), 2.41 (btd, *J* = 15.3, 2.3 Hz, 1 H), 2.93 (dd, *J* = 15.5, 6.4 Hz, 1 H), 4.35 (dd, *J* = 14.7, 5.5 Hz, 1 H), 4.43 (dd, *J* = 14.7, 5.5 Hz, 1 H), 4.54 (dt, *J* = 15.0, 6.4 Hz, 1 H), 4.63 (d, *J* = 16.4 Hz, 1 H), 5.05 (d, *J* = 16.4 Hz, 1 H), 6.80 (bt, *J* = 5.7 Hz, 1 H), 6.98 (bd, *J* = 6.3 Hz, 1 H), 7.07 (d, *J* = 6.6 Hz, 2 H), 7.16-7.30 (m, 8 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.87, 22.79, 28.51, 43.44, 45.45, 48.78, 112.45, 125.86, 127.15, 127.57, 128.39, 128.61, 136.82, 138.02, 139.12, 167.80, 169.27, 170.21; IR (KBr) 3289, 3002, 1734, 1659, 1584, 1543, 1321, 1248 cm^{-1}; HRMS for $C_{23}H_{25}N_3O_3$ *m/z* 391.1896, found *m/z* 391.1895.

III-41: (mixed diastereomers, ratio 49:51); (0.52 g, 1.13 mmol, 86% yield); mp 77-80 °C; ^{1}H NMR (300 MHz, $CDCl_3$, characteristic peaks) δ (major isomer) 2.03 (s, 3 H), 2.12 (d, *J* = 1.5 Hz, 3 H), 2.45 (btq, *J* = 9.0, 1.5 Hz, 1 H), 2.77 (ddd, *J* = 7.8, 3.3, 1.5 Hz, 1 H), 5.62 (s, 1 H), 6.17 (bt, *J* = 2.9 Hz, 1 H), (minor isomer) 2.02 (s, 3 H), 2.24 (d, *J* = 1.5 Hz, 3 H), 2.33 (btq, *J* = 9.0, 1.5 Hz, 1 H), 3.10 (ddd, *J* = 9.0, 3.3, 1.5 Hz, 1 H), 5.68 (s, 1 H), 6.13 (bt, *J* = 2.9 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.97, 16.29, 16.56, 22.75, 22.98, 28.16, 28.26, 41.35, 41.42, 46.44, 49.04, 59.71, 59.91, 60.78, 61.32, 61.80, 62.35, 100.38, 113.15, 113.52, 167.73, 127.71, 127.77, 127.99, 128.04, 128.09, 128.20, 128.34, 133.26, 134.22, 134.44, 139.46, 139.49, 140.42, 167.92, 168.04, 168.47, 169.04, 169.30, 169.35, 169.40, 169.74, 169.79, 170.22, 170.30, 171.05; IR (KBr) 3277, 2986, 1744, 1655, 1541, 1204 cm^{-1}; HRMS for $C_{23}H_{29}N_3O_7$ *m/z* 459.2006, found *m/z* 459.2011.

III-37: (mixed diastereomers, ratio 49:51); (0.36 g, 0.80 mmol, 87% yield); mp 83-85 °C; ^{1}H NMR (300 MHz, $CDCl_3$, characteristic peaks) δ (major isomer) 2.01 (s, 3 H), 2.22 (d, J = 1.2 Hz, 3 H), 2.30 (bdt, J = 9.2, 1.5 Hz, 1 H), 5.67 (s, 1 H), 5.92 (m, 1 H), (minor isomer) 2.02 (s, 3 H), 2.10 (d, J = 1.2 Hz, 3 H), 2.43 (btd, J = 9.2, 1.5 Hz, 1 H), 5.59 (s, 1 H), 5.95 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.87, 16.22, 16.50, 20.86, 22.78, 28.17, 28.33, 40.42, 43.46, 46.47, 48.94, 59.82, 61.67, 111.05, 113.61, 114.01, 117.30, 126.02, 127.06, 127.17, 127.50, 127.55, 127.71, 127.95, 128.21, 128.37, 128.41, 128.52, 134.26, 134.42, 137.88, 137.95, 138.52, 139.39, 167.46, 167.64, 168.02, 168.43, 169.22, 169.61, 170.13, 170.18; IR (KBr) 3297, 3007, 1742, 1651, 1532, 1217 cm^{-1}; HRMS for $C_{26}H_{29}N_3O_5$ *m/z* 463.2107, found *m/z* 463.2150.

General Method for the Formation of Acetylenic Esters. To benzyl protected propargyl alcohol (10-50 mmol, 1.0 equiv) in THF (0.5 M relative to the alcohol) was added BuLi (1.0 equiv, 2.5 M in Hexane) at -78 °C. After 10 min ethyl chloroformate (1.5 equiv) was added dropwise. The reaction was slowly warmed to 0 °C (only until a deep red color began to form for the case of **II-25**, after which time it was promptly quenched) and then to rt. After 14 h, the reaction was quenched by addition of water. The organics were separated and the solvent removed under reduced pressure. The resulting crude oil was purified by flash column chromatography (silica, 230-400 mesh; eluent - petroleum ether). The solvents were evaporated to give a clear, colorless oil.

II-25: (1.61 g, 7.45 mmol, 91% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29 (t, J = 7.2 Hz, 3 H), 4.22 (q, J = 7.2 Hz, 2 H), 4.25 (s, 2 H), 4.59 (s, 2 H), 7.22-7.40 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.78, 56.53, 61.90, 71.81, 78.07, 82.94, 127.87, 127.90, 128.29, 136.59, 152.87; IR (oil/NaCl) 3032, 2984, 2872, 2236, 1713, 1248 cm^{-1}.

III-49: (3.06 g, 16.28 mmol, 94% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (t, J = 7.1 Hz, 3 H), 3.73 (s, 2 H), 4.23 (q, J = 7.1 Hz, 2 H), 7.25-7.40 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.00, 24.97, 61.87, 74.84, 86.20, 127.16, 127.99, 128.69, 134.07, 153.67; IR (oil/NaCl) 2984, 2238, 1709, 1255 cm^{-1}.

General Method for the Aza-Annulation of Acetylenic Esters. A mixture of the primary amine (0.5-5.0 mmol, 1.0 equiv) and the acetylenic ester (1.0 equiv) were taken up in THF (0.5 M relative to the amine) along with BF_3-etherate (0.5 equiv) and allowed to heat at rt. After the reaction had gone to completion, as indicated by ^{1}H NMR, the solvent was removed under reduced pressure and the crude enamine brought up in THF (0.1 M relative to the enamine). The sodium salt of 2-acetamidoacrylic acid (1.3 equiv) was added at -78 °C and the reaction allowed to stir at rt for 14 h, or longer if ^{1}H

NMR suggested the reaction not complete. Sat. aq. $NaHCO_3$ (excess) was added, and the mixture was extracted 4 times with EtOAc. The combined organic fractions were dried over Na_2SO_3, filtered, and the solvent evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica 230-400 mesh, eluent, Et_2O:EtOAc:MeOH)

III-44: (3.60 g, 10.00 mmol, 71% yield); mp 151-154 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 2.05 (s, 3 H), 2.34 (dd, *J* = 16.3, 15.6 Hz, 1 H), 3.42 (dd, *J* = 16.3, 7.0 Hz, 1 H), 3.67 (s, 3 H), 3.73 (s, 3 H), 4.63 (ddd, *J* = 15.6, 7.0, 5.6 Hz, 1 H), 4.65 (d, *J* = 15.6 Hz, 1 H), 4.94 (d, *J* = 15.6 Hz, 1 H), 6.51 (bd, *J* = 5.6 Hz, 1 H), 7.16-7.22 (m, 2 H), 7.25-7.36 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.07, 26.41, 47.81, 48.43, 52.24, 52.90, 108.95, 127.13, 127.79, 128.56, 135.77, 141.88, 163.32, 165.05, 169.21, 170.14; IR (KBr) 3306, 2953, 1742, 1705, 1634, 1534, 1437, 1248 cm^{-1}; HRMS for $C_{18}H_{20}N_2O_6$ *m/z* 360.1322, found *m/z* 360.1308.

III-46: (3.32 g, 7.61 mmol, 83% yield); mp 97-99 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, *J* = 7.2 Hz, 3 H), 2.03 (s, 3 H), 2.29 (td, *J* = 16.0, 2.0 Hz, 1 H), 3.39 (dd, *J* = 16.0, 6.6 Hz, 1 H), 4.16 (q, *J* = 7.2 Hz, 2 H), 4.31 (dd, *J* = 12.9, 2.0 Hz, 1 H), 4.45 (dt, *J* = 15.0, 6.0 Hz, 1 H), 4.54 (d, *J* = 12.0 Hz, 1 H), 4.60 (d, *J* = 12.0 Hz, 1 H), 4.80 (d, *J* = 16.5 Hz, 1 H), 5.00 (d, *J* = 12.9 Hz, 1 H), 5.41 (d, *J* = 16.5 Hz, 1 H), 6.73 (bd, *J* = 5.7 Hz, 1 H), 6.98-7.02 (m, 2 H), 7.17-7.38 (m, 8 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 13.97, 22.99, 28.00, 45.62, 48.50, 60.90, 63.07, 72.50, 112.97, 125.91, 127.16, 127.87, 128.32, 128.64, 137.12, 137.39, 145.35, 165.91, 170.07; IR (KBr) 3310, 3011, 2936, 1673, 1632, 1497, 1392, 1372, 1217 cm^{-1}; HRMS for $C_{25}H_{28}N_2O_5$ *m/z* 436.1998, found *m/z* 436.2064.

III-50: (mixed isomers, ratio 92:8); (2.64 g, 6.5 mmol, 61% yield); ^1H NMR (300 MHz, $CDCl_3$) δ 1.14 (t, *J* = 7.1 Hz, 3 H), 1.79 (ddd, *J* = 13.1, 11.1, 6.6, 1 H), 2.03 (s, 3 H), 2.80 (ddd, *J* = 13.1, 9.4, 7.0 Hz, 1 H), 3.85-4.87 (m, 3 H), 4.47 (dt, *J* = 11.1, 6.3 Hz, 1 H), 4.77 (d, *J* = 15.4 Hz, 1 H), 5.23 (d, *J* = 15.4 Hz, 1 H), 6.46 (s, 1 H), 6.84 (d, *J* = 5.8 Hz, 1 H), 7.13-7.38 (m, 5 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 13.84, 23.00, 29.05, 40.78, 48.71, 51.43, 61.38, 121.37, 127.32, 127.47, 128.40, 128.51, 128.90, 134.38, 135.82, 137.00, 169.53, 170.00, 171.91; IR (KBr) 3330, 2982, 1734, 1671, 1496, 1410, 1244, 1184 cm^{-1}.

General Method for the DDQ Oxidation of Aza-Annulation Products. A mixture of the aza-annulation product (0.5-50.0 mmol, 1.0 equiv) and DDQ (1.5 equiv) were taken up in tolune (0.1 M with respect to the aza-annulation product). After heating at reflux for 14 h the solvent was removed under reduced pressure and the crude product was

purified by flash column chromatography (silica, 230-400 mesh, eluent, Et_2O: EtOAc) or recrystallized ($CHCl_3$:EtOAc). For compounds derived from *B*-ketoamides, the oxidation was repeated to give the indicated yields.

III-28: (0.029 g, 0.088 mmol, 58% yield); mp 176-178 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.37 (t, *J* = 7.1 Hz, 3 H), 2.19 (s, 3 H), 2.68 (s, 3 H), 4.30 (q, *J* = 7.1 Hz, 2 H), 5.47 (s, 2 H), 7.09 (d, *J* = 6.7 Hz, 2 H), 7.26-7.35 (m, 3 H), 8.30 (bs, 1 H), 8.91 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.19, 16.91, 24.63, 48.33, 61.15, 110.44, 122.64, 125.77, 126.05, 127.64, 128.94, 135.22, 145.30, 158.40, 165.88, 169.02; IR (KBr) 3308, 2982, 1713, 1638, 1516, 1192 cm^{-1}; HRMS for $C_{18}H_{20}N_2O_4$ *m/z* 328.1423, found *m/z* 328.1411.

III-31: (0.039 g, 0.150 mmol, 78% yield); mp 225-226 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.33 (t, *J* = 7.1 Hz, 3 H), 2.18 (s, 3 H), 2.21 (quint, *J* = 7.7 Hz, 2 H), 3.50 (t, *J* = 7.7 Hz, 2 H), 4.16 (t, *J* = 7.7 Hz, 2 H), 4.28 (q, *J* = 7.1 Hz, 2 H), 8.14 (bs, 1 H), 8.85 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.31, 20.99, 24.63, 33.04, 49.43, 60.78, 106.11, 122.55, 126.13, 149.57 156.83, 164.86, 168.80; IR (KBr) 3297, 2982, 2936, 1715, 1684, 1636, 1532, 1196, 1100 cm^{-1}; HRMS for $C_{13}H_{16}N_2O_4$ *m/z* 264.1110, found *m/z* 264.1108.

III-40: (0.31 g, 0.15 mmol, 80% yield); mp = 177-180 °C; ^1H NMR (300 MHz, Acetone-d_6) δ 1.21 (t, *J* = 7.1 Hz, 3 H), 2.11 (s, 3 H), 2.48 (s, 3 H), 4.10 (d, *J* = 6.0 Hz, 2 H), 4.13 (q, *J* = 7.1 Hz, 2 H), 5.54 (s, 2 H), 7.14-7.17 (m, 2 H), 7.24-7.56 (m, 3 H), 8.01 (t, *J* = 6.0 Hz, 1 H), 8.54 (s, 1 H), 9.04 (s, 1 H); ^{13}C NMR (75 MHz, Acetone-d_6) δ 14.42, 17.22, 24.38, 42.21, 48.85, 61.47, 108.55, 122.56, 127.30, 129.21, 129.52, 129.62, 137.19, 145.59, 158.65, 168.80, 170.10, 170.28; IR (KBr) 3277, 3032, 1748, 1671, 1644, 1512, 1210, 1003 cm^{-1}; HRMS for $C_{20}H_{23}N_3O_5$ *m/z* 385.1638, found *m/z* 385.1623.

III-36: (0.21 g, 0.56 mmol, 76% yield); mp 180-181 °C; ^1H NMR (300 MHz, Acetone-d_6) δ 2.10 (s, 3 H), 2.42 (s, 3 H), 4.55 (d, *J* = 6.0 Hz, 2 H), 5.51 (s, 2 H), 7.12-7.16 (m, 2 H), 7.19-7.56 (m, 8 H), 8.18 (t, *J* = 6.0 Hz, 1 H), 8.54 (s, 1 H), 8.96 (s, 1 H); ^{13}C NMR (75 MHz, Acetone-d_6) δ 17.28, 24.36, 44.20, 48.79, 108.50, 122.42, 127.30, 127.83, 128.13, 128.45, 129.21, 129.51, 129.60, 136.99, 137.25, 145.43, 158.59, 168.47, 169.97; IR (KRr) 3299, 3067, 3034, 2880, 1705, 1634, 1507, 1476, 1248, 1003 cm^{-1}; HRMS for $C_{23}H_{23}N_3O_3$ *m/z* 389.1739, found *m/z* 389.1762.

III-42: (0.32 g, 0.70 mmol, 60% yield); mp = 204-205 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.24 (t, *J* = 7.2 Hz, 3 H), 1.28 (t, *J* = 7.2 Hz, 3 H), 2.17 (s, 3 H), 2.49 (s, 3 H), 4.13-4.29 (m, 6 H), 6.14 (s, 1 H), 6.55 (bs, 1 H), 7.26-7.48 (m, 5 H), 8.32 (s, 1 H), 8.55 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.08, 17.53, 24.54, 41.88, 61.74,

62.17, 62.65, 112.68, 115.71, 121.15, 126.60, 128.08, 128.59, 128.92, 132.86, 134.72, 140.19, 157.78, 167.40, 167.67, 169.65; IR (KBr) 3314, 2986, 1744, 1645, 1524, 1217, 1082, 1003 cm^{-1}; HRMS for $C_{23}H_{27}N_3O_7$ *m/z* 457.1849, found *m/z* 457.1853.

III-38: (0.16 g, 0.35 mmol, 55% yield); mp = 155-156 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.24 (t, *J* = 7.2 Hz, 3 H), 2.18 (s, 3 H), 2.50 (s, 3 H), 4.26 (q, *J* = 7.2 Hz, 2 H), 4.57 (dd, *J* = 5.6, 1.7 Hz, 2 H), 6.12 (s, 1 H), 6.19 (m, 1 H), 7.19-7.43 (m, 10 H), 8.27 (s, 1 H), 8.53 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.10, 17.52, 24.67, 44.28, 62.11, 62.69, 116.21, 120.69, 126.86, 127.73, 127.85, 128.15, 128.54, 128.62, 128.85, 133.01, 137.69, 139.77, 140.51, 167.20, 167.38, 169.27; IR (KBr) 3280, 2960, 2920, 1736, 1647, 1516, 1455, 1217 cm^{-1}; HRMS for $C_{26}H_{27}N_3O_5$ *m/z* 461.1951, found *m/z* 461.1901.

III-45: (0.21 g, 0.59 mmol, 71% yield); mp = 128-129 °C; ^1H NMR (300 Hz, $CDCl_3$) δ 2.19 (s, 3 H), 3.79 (s, 3 H), 3.85 (s, 3 H), 5.26 (s, 2 H), 7.19-7.32 (m, 5 H), 8.34 (bs, 1 H), 8.84 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.67, 50.44, 52.62, 53.41, 109.06, 120.06, 127.36, 128.04, 128.61, 128.83, 134.77, 138.14, 157.02, 163.12, 164.18, 169.23; IR (KBr) 3374, 3021, 2955, 1728, 1691, 1645, 1516, 1437, 1215 cm^{-1}.

General Method for the Hydrolysis of Esters and Amides. A mixture of the oxidation product (0.5-2.0 mmol, 1.0 equiv) and KOH (20.0 equiv) were taken up in H_2O (for hydrolysis of esters) or 30% H_2O_2 (for hydrolysis of amides) (0.1 M with respect to the oxidation product). After 14 to 38 h, the reaction was extracted with $CHCl_3$, filtered, neutralizated with HCl, and the carboxcylic acid collected by filtration or the amines collected by solvent removal under reduced pressure followed by extraction with MeOH or acetone. The products were then recrystallized (MeOH:$CHCl_3$ or MeOH:Et_2O).

III-51: (0.48 g, 2.03 mmol, 61% yield); mp >260 °C; ^1H NMR (300 MHz, Acetone-d_6) δ 2.07 (s, 3 H), 2.70 (s, 3 H), 5.55 (s, 2 H), 7.17 (d, *J* = 6.9 Hz, 1 H), 7.26-7.35 (m, 4 H), 8.98 (s, 1 H); ^{13}C NMR (75 MHz, Acetone) δ 17.09, 24.32, 48.52, 106.25, 123.00, 127.10, 128.14, 129.62, 130.55, 133.29, 137.24, 158.84, 167.42, 171.53; IR (KBr) 3277, 3031, 1692, 1622, 1603, 1553, 1387, 1190 cm^{-1}.

III-52: (0.061 g, 0.314 mmol, 82% yield); ^1H NMR (300 MHz, DMSO-d_6) δ 2.03 (quint, *J* = 7.6 Hz, 2 H), 3.25 (t, *J* = 7.6 Hz, 2 H), 3.95 (t, *J* = 7.6 Hz, 2 H), 6.91 (s, 1 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 21.09, 32.45, 48.73, 111.03, 128.51, 129.14, 135.41, 143.12, 156.81; IR (KBr) 3364, 1698, 1615, 1536, 1117 cm^{-1}.

III-53: (0.047 g, 0.183 mmol, 61% yield); mp 205-206 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 2.46 (s, 3 H), 5.46 (s, 2 H), 7.07-7.54 (m, 5 H), 8.02 (s, 1 H); ^{13}C NMR

(75 MHz, DMSO-d_6) δ 16.83, 30.74, 115.41, 127.05, 128.34, 129.37, 129.86, 133.98, 135.86, 137.69, 160.60, 169.74; IR (KBr) 2928, 1709, 1640, 1549, 1455, 1256, 1024 cm^{-1}.

Formation of III-54: To a solution of **II-52** (0.20 g, 0.848 mmol) in THF (8.48 mL) was added NaH (0.92 g, 0.848 mmol) at -78 °C. To the reaction was added EtO_2CCl (0.081 mL, 0.848 mmol) followed by phenylglycine ethyl ester (0.183 g, 0.848 mmol). The reaction was allowed to warm to room temperature and stirr for 2 hr. Sat. aq. $NaHCO_3$ (excess) was added, and the mixture was extracted 4 times with EtOAc. The combined organic fractions were dried over Na_2SO_3, filtered, and the solvent evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica, 230-400 mesh, eluent, Et_2O:EtOAc:MeOH). (0.29 g, 0.66 mmol, 78% yield); mp 209-210 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.22 (t, *J* = 7.1 Hz, 3 H), 2.17 (s, 3 H), 2.42 (s, 3 H), 4.17 (dq, *J* = 10.7, 7.1 Hz, 1 H), 4.25 (dq, *J* = 10.7, 7.1 Hz, 1 H), 5.38 (s, 2 H), 5.63 (d, *J* = 7.1 Hz, 1 H), 6.98 (d, *J* = 7.1 Hz, 1 H), 7.09 (d, *J* = 6.5 Hz, 2 H), 7.25-7.44 (m, 8 H), 8.37 (s, 1 H), 8.55 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.90, 16.88, 24.43, 48.53, 57.22, 61.99, 126.20, 126.31, 127.33, 127.63, 128.49, 128.57, 128.84, 128.96, 135.02, 135.89, 140.32, 157.95, 166.84, 169.61, 170.58; IR (KBr) 3324, 3019, 1736, 1636, 1514, 1217 cm^{-1}.

Formation of III-55. To **III-50** (0.24 g, 1.05 mmol) in EtOH (10.5 mL) was added Na_2CO_3 (0.39 g, 3.67 mmol) and 10% Pd/C (0.10 g). The reaction vessel was purged with N_2 and then flushed with and maintained under an atmosphere of H_2. After stirring for 16 h, the reaction mixture was filtered through a fine scintered glass funnel and the solvent removed under reduced pressure. The resulting crude oil was purified by flash column chromatography (silica, 230-400 mesh; eluent - Et_2O). The solvents were evaporated to give a white solid which was recrystallized fron EtOAc (mixture of diastereomers, ratio 96:4), (0.23 g, 0.99 mmol, 94% yield). mp 202-205 °C; ^1H NMR (300 MHz, $CDCl_3$) (major diastereomer) δ 1.16 (t, *J* = 7.2 Hz, 3 H), 2.00 (s, 3 H), 2.32 (q, *J* = 13.7 Hz, 1 H), 2.55 (m, 1 H), 2.93 (dt, *J* = 13.7, 4.4 Hz, 1 H), 3.21 (dd, *J* = 13.7, 7.4 Hz, 1 H), 3.29 (d, *J* = 15.2 Hz, 1 H), 3.90 (dq, *J* = 10.8, 7.1 Hz, 1 H), 4.01 (dq, *J* = 10.8, 7.1 Hz, 1 H), 4.07 (m, 2 H), 5.24 (d, *J* = 15.2 Hz, 1 H), 7.00 (dd, *J* = 7.5, 1.9 Hz, 2 H), 7.12 (d, *J* = 6.4 Hz, 1 H), 7.21-7.34 (m, 8 H); ^{13}C NMR (75 MHz, $CDCl_3$) (major diastereomer) δ 13.92, 22.87, 25.69, 37.30, 42.80, 49.65, 50.81, 58.76, 60.95, 126.77, 127.37, 127.47, 128.51, 128.57, 129.34, 136.80, 138.09, 169.14, 170.45, 170.52; IR (solid/NaCl) 3297, 3067, 3009, 1732, 1642, 1541, 1455, 1217 cm^{-1}.

References.

1) Jones, J. H. In *Amino Acids and Peptides*. The Royal Society of Chemistry, London, 1991, Vol. 22. pp 161-7, and references therein.
2) Houpis, I. N.; Molina, A.; Lynch, J.; Reamer, R. A.; Volante, R. P.; Reider, P. J. *J. Org. Chem.* **1993**, *58*, 3176.
3) Liskamp, R. M. J. *Angew. Chem. Int. Engl.* **1994**, *33*, 305.
4) Wolf, J.-P.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 3164.
5) Kahn, M.; Chen, B. *Tetrahedron Lett.* **1987**, *28*, 1623.
6) Paulvannan, K.; Stille, J. R. *Tetrahedron Lett.* **1993**, *34*, 8197.
7) Nagai, U.; Sato, K.; Nakamura, R.; Kato, R. *Tetrahedron* **1993**, *49*, 3577.
8) Kemp, D. S.; McNamara, P. E. *J. Org. Chem.* **1984**, *49*, 2286.
9) For a sample of other aza-annulation uses see: (a) Paulvannan, K.; Stille, J. R. *J. Org. Chem.* **1992**, *57*, 5319. (b) Paulvannan, K.; Stille, J. R. *Tetrahedron Lett.* **1993**, *34*, 6673. (c) Cook, G. R.; Beholz, L. G.; Stille, J. R. *Tetrahedron Lett.* **1994**, *35*, 1669.
10) (a) In a procedure developed by Nancy Barta, of Michigan State University, the amine of an amine salt could be freed by mixing it with $NaHCO_3$ in C_6H_6 followed by filtration or the amine salt could be used directly in the condensation with 0.5 equiv of BF_3-etherate as catalyst. (b) In a procedure developed by Carol Walters, of Michigan State University, formation of the mixed anhydride during annulation could be efficiently executed by adding the acrylate salt to the enamine, followed by addition of ethylchloroformate.
11) (a) Sano, T.; Horiguchi, Y.; Tsuda, Y.; Itatani, Y. *Heterocycles* **1978**, *9*, 161. (b) Kozikowski, A. P.; Xia, Y.; Rajarathnam Reddy, E.; Tukmantel, W.; Hanin, I.; Tang, X. C. *J. Org. Chem.* **1991**, *56*, 4637. (c) Walker, D.; Hiebert, J. D. *Tetrahedron* **1966**, 153. (d) Modifications on described DDQ oxidation procedure attempted to provide increased yield included: 6 hour addition of DDQ, use of increased equivilants of DDQ, use of dioxane and mixed xylenes as solvent, use of pTsOH as catalyst in all three solvents, and use of triethyl amine as catalyst in all three solvents. None of these modifications provided an increased yield. (e) Attempted oxidation of **III-46** using Pd/C in refluxing diglyme or EtOAc resulted in no reaction. Fu, P. P.; Harvey, R. G. *Chem. Rev.* **1978**, *78*, 317. Attempted oxidation of **III-46** using SeO_2 with HOAc also yielded no product formation. Nagaoka, H. Schmid, H. Kishi, Y.; Kishi, I. *Tetrahedron Lett.* **1981**, *22*, 899.

12) NOE studies on **III-50** indicated that the stereochemistry of the double bond of the major isomer was *E* (NOE enhancements between the vinyl proton and *N*-benzyl protons were 3.3% and 1.6% when the vinyl proton was irradiated. NOE enhancement between the vinyl proton and the benzylidine protons was 9.7% when the vinyl proton was irradiated).

13) DDQ oxidation of **III-50** under optimum conditions (see reference 8 and text) provided a mixture of products consisting of **III-50** (20%), the analog of **III-50** with the double bond isomerized into the ring (80%), and possibly a trace of the fully oxidized analog of **III-50**. The composition of the reaction mixture was determined by ^{1}H NMR. Characteristic peaks of the double bond isomerized product were: 2.49 (td, J = 15.9, 3.0 Hz, 1 H), 3.55 (dd, J = 15.9, 6.3 Hz, 1 H), 4.63 (dt, J = 15.1, 6.3 Hz, 1 H).

14) Compounds **III-27, III-28, III-30, III-35, III-36, III-37, III-39, III-40, III-41, III-44, III-45, III-46, III-54,** and **III-55** were submitted for biological testing.

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Lewis Acid-Promoted 3-Aza-Cope Rearrangement of *N*-Alkyl-*N*-allylanilines

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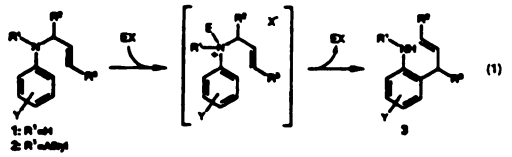
The 3-aza-Cope rearrangement of *N*-alkyl-*N*-allylaniline substrates, which required 250 °C to proceed thermally, was promoted by Lewis acid reagents at 111–140 °C. Systematic studies of this reaction were performed to examine a number of reaction variables such as concentration, the stoichiometry of the Lewis acid with the substrate, the optimum temperature for rearrangement, and the type of Lewis acid reagent. Of the many Lewis acids investigated, $ZnCl_2$ (140 °C) and Et_2O-BF_3 (111 °C) were the most generally successful reagents for promoting the aromatic 3-aza-Cope rearrangement. With respect to substrate variation, the presence of a methoxy substituent para to the *N*-allyl group slowed the reaction slightly, while a meta substituent accelerated the rate of [3,3] rearrangement and produced moderate site selectivity on the aromatic ring. Lewis acid-promoted rearrangement of an unsymmetrically substituted allyl moiety resulted in [3,3] sigmatropic rearrangement to give the 1-hexen-3-yl substituent on the aromatic ring. Overall, both $ZnCl_2$ and Et_2O-BF_3 were shown to efficiently accelerate the regiospecific 3-aza-Cope rearrangement of *N*-alkyl-*N*-allylanilines for the purpose of forming a carbon–carbon bond between a secondary alkyl substituent and an aromatic ring.

Introduction

The aromatic 3-aza-Cope rearrangement of *N*-allylaniline substrates **1** and **2** has been of interest for some time as a route to the formation of 2-substituted aniline and indole products, but the utility of this reaction has been greatly limited (eq 1).[1] The severe conditions (200–



(1)

350 °C) required for thermal rearrangement, which produced low yields of 2-allylanilines (**3**) and significant amounts of products resulting from removal of the allyl group, have restricted the utility of this reaction and presented an enormous challenge to synthetic organic chemists.[2] Approaches to overcoming these barriers have focused around one common theme—charge acceleration of the rearrangement process by reaction of *N*-allylaniline substrates with electrophilic reagents through generation of a quaternary intermediate.

The electrophile sources most commonly used for charge acceleration of the aromatic 3-aza-Cope rearrangement have been Brønsted acids, which typically promote rearrangement at temperatures of 140–150 °C. Polyphosphoric acid has been used to promote charge-accelerated 3-aza-Cope rearrangement, but effective use of this reagent was limited to the *N*-crotyl derivatives (R^3 = Me) of **1** and **2**.[4] Two other proton sources, HCl and H_2SO_4, were studied more extensively and have shown greater versatility in promoting this [3,3] sigmatropic rearrangement. The use of HCl to promote the rearrangement of **1** to **3** was achieved by treatment of **1** with either HCl[5b] or $PhNH_2$·HCl.[5] Similarly, the treatment of **2** with HCl also gave 2-allylaniline derivatives.[4,6] Rearrangement of both **1** and **2** was promoted effectively with 2 N H_2SO_4.[7] A drawback to the use of strong protic acids has been the tendency of these reagents to produce formation of indole and indoline products from **3**, thus reducing the overall effectiveness of this reaction.[3,4,7c] Generation of the analogous quaternary ammonium salts (E, R^1 = alkyl) produced similar charge acceleration of the aromatic 3-aza-Cope rearrangement at 140 °C; however, significant amounts of substrate deallylation usually occurred.[7d,e,8]

The use of Lewis acids for charge acceleration of the 3-aza-Cope rearrangement appears to be a promising alternative to the use of protic acids. As early as 1957,[5b] $ZnCl_2$ was found to promote the transformation of **1** to **3**, and subsequent examples have produced 37–78% yields of **3**.[5b,d,8a,9] Treatment with Et_2O-BF_3 was also an effective method of promoting [3,3] rearrangement of **1** at 140

(1) For reviews that include a discussion of the aromatic 3-aza-Cope rearrangement, see: (a) Bennett, G. B. *Synthesis* **1977**, 589. (b) Heimgartner, H.; Hansen, H.-J.; Schmid, H. *Adv. Org. Chem.* **1979**, *9*, Part 2, 655. (c) Lutz, R. P. *Chem. Rev.* **1984**, *84*, 205. (d) Przheval'skii, N. M.; Grandberg, I. I. *Russ. Chem. Rev.* **1987**, *56*, 477.

(2) (a) Carnahan, F. L.; Hurd, C. D. *J. Am. Chem. Soc.* **1930**, *52*, 4586. (b) Hurd, C. D.; Jenkins, W. W. *J. Org. Chem.* **1957**, *22*, 1418.

(3) (a) Hyre, J. R.; Bader, A. R. *J. Am. Chem. Soc.* **1958**, *80*, 437. (b) Bader, A. R.; Bridgwater, R. J.; Freeman, P. R. *J. Am. Chem. Soc.* **1961**, *83*, 3319.

(4) Krowicki, K.; Pailloux, N.; Riviere, M.; Lattes, A. *J. Heterocycl. Chem.* **1976**, *13*, 555.

(5) (a) Abdrakmanov, I. B.; Sharafutdinov, V. M.; Sagitdinov, I. A.; Tolstikov, G. A. *Zh. Org. Chem.* **1979**, *15*, 2601. (b) Abdrakhmanov, I. B.; Fakhrutdinov, R. N.; Khusnutdinov, R. N.; Dzhemilev, U. M. *Zh. Org. Chem.* **1981**, *17*, 2804. (c) Abdrakmanov, I. B.; Sharafutdinov, V. M.; Nigmatullin, N. G.; Sagitdinov, I. A.; Tolstikov, G. A. *Zh. Org. Chem.* **1982**, *18*, 1466. (d) Abdrakhmanov, I. B.; Sharafutdinov, V. M.; Tolstikov, G. A. *Zh. Org. Chem.* **1984**, *20*, 620. (e) Abdrakhmanov, I. B.; Sharafutdinov, V. M.; Tolstikov, G. A. *Zh. Org. Chem.* **1984**, *20*, 663.

(6) de Sequi-Sannes, G.; Riviere, M. M.; Lattes, A. *Tetrahedron Lett.* **1974**, 2073.

(7) (a) Jolidon, S.; Hansen, H.-J. *Chimia* **1976**, *30*, 21. (b) Jolidon, S.; Hansen, H.-J. *Chimia* **1976**, *30*, 23. (c) Jolidon, S.; Hansen, H.-J. *Helv. Chim. Acta* **1977**, *60*, 978. (d) Katayama, H.; Takatsu, N. *Chem. Pharm. Bull.* **1981**, *29*, 2465. (e) Katayama, H.; Tachikoma, Y.; Takatsu, N.; Kato, A. *Chem. Pharm. Bull.* **1983**, *31*, 2220.

(8) (a) Schmid, M.; Hansen, H.-J.; Schmid, H. *Helv. Chim. Acta* **1973**, *56*, 105. (b) Katayama, H. *Chem. Pharm. Bull.* **1978**, *26*, 2027.

(9) Takamatsu, N.; Inoue, S.; Kishi, Y. *Tetrahedron Lett.* **1971**, *48*, 4661.

0022-3263/93/1958-5095$04.00/0

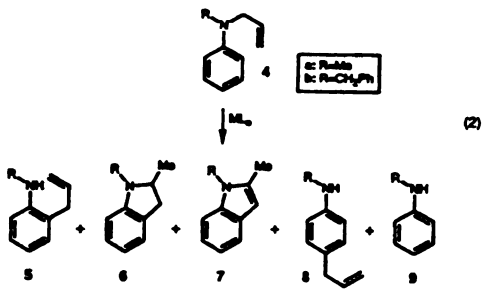
°C,[9d,10] and the use of Et_2O-BF_3 was the only example of a Lewis acid-promoted 3-aza-Cope rearrangement of 2.[7d,e] Other catalysts, such as $AlCl_3$, $FeCl_3$, $SnCl_4$, and $TiCl_4$, were less effective at promoting the rearrangement of 1.[5b,d] A striking feature of studies of the Lewis acid-promoted rearrangement of substrates 2 has been the varying success reported for very similar substrates. Typically, the origin of these differences is a sensitivity of this system to one or many of the reaction conditions.

Our recent investigations in the area of the aliphatic 3-aza-Cope rearrangement have led to the development of proton[11] and Lewis acid[12] charge-accelerated rearrangement of *N*-alkyl-*N*-allylenamines at temperatures ranging from 40 to 110 °C. Organoaluminum complexes were particularly efficient and versatile in promoting the 3-aza-Cope rearrangement, and a recent report of an aromatic Claisen rearrangement accelerated by an organoaluminum reagent provided additional optimism for the ability of organoaluminum complexes to promote the aromatic 3-aza-Cope rearrangement.[13] Herein, we report the systematic investigation of the aromatic 3-aza-Cope rearrangement of *N*-alkyl-*N*-allylanilines promoted by Lewis acids.

Results and Discussion

An investigation of a number of reaction variables was performed by studying the effect of the relative amount of Lewis acid, concentration of the reaction, reaction time, and the temperature at which rearrangement would occur. The nature of the nitrogen "spectator" substituent on the *N*-allylaniline substrate, as well as substitution on the aromatic ring and the allyl group, were used to probe the features of this reaction.

Studies were initiated by monitoring the rearrangement of 4a (eq 2) in the presence of varying amounts of $AlCl_3$, a catalyst that was effective for the rearrangement of 1.



The 3-aza-Cope rearrangement of 4a gave 5a in all cases, but the relative amount of $AlCl_3$ was critical to the selectivity of the reaction (Table I). Treatment of 4a with 1.5 equiv of Lewis acid produced rapid disappearance of starting material, low amounts of 5a, and further destruction of 5a over time.[14] With the use of 1.2 equiv, the reaction was slowed to a useful rate, and optimal generation of 5a was observed. Problems associated with subsequent [3,3] rearrangement to the para position were not encountered. When less than a stoichiometric amount of $AlCl_3$ was used, significant quantities of byproducts, resulting from cyclization of 5a, were produced during the time necessary to drive the rearrangement to >95% completion. Examination of other Lewis acids showed similar patterns, and in each case, 1.2 equiv of Lewis acid was the optimum amount of reagent.

Another Lewis acid reported to promote the rearrangement of 1, $ZnCl_2$, showed a greater sensitivity toward reaction conditions and was used to probe the effect of substrate concentration on the product distribution (Table II). Acceleration of the rearrangement with $ZnCl_2$ at concentrations greater than 1.0 M resulted in the generation of substantial quantities of 6a and 7a, and reaction concentrations from 0.5 to 1.0 M were found to be optimal. For all subsequent rearrangements described, reactions were performed at 0.5 M of substrate with 1.2 equiv of the corresponding Lewis acid.

Once general reaction conditions were established, a survey of Lewis acids revealed that $AlCl_3$, $ZnCl_2$, and Et_2O-BF_3 were the most effective reagents for promoting [3,3] rearrangement of 4a to 5a (Table III). Treatment of 4a with $TiCl_4$ or $MgBr_2$ produced consumption of 4a, but in both cases, 6a (10–12%) and 7a (2%) were formed concurrently under these reaction conditions. Alkylaluminum complexes, including the methylaluminum bis(4-bromo-2,6-di-*tert*-butylphenoxide) reagent used for the aromatic Claisen rearrangement, produced disappointing results by slow consumption of 4a, presumably to meth-

Table I. Effects of the Amount of $AlCl_3$ on the 3-Aza-Cope Rearrangement of 4a

		yield[b] (%)				
			product formation[c]			
equiv[a]	time (h)	4a	5a	6a	7a	9a
1.5	2	12	38	0	0	0
	4	0	22	0	0	0
	8	0	9	0	0	0
1.2	4	50	49	0	0	0
	8	8	88	0	0	2
	24	6	71	0	0	3
0.75	4	28	68	1	0	0
	8	16	70	6	0	0
	24	11	23	32	5	0
	48	9	4	37	9	1

[a] Rearrangements were run 0.5 M 4a at reflux in xylenes (140 °C). [b] Values represent GC yields of volatile, nonoligomeric products (ref 14). [c] Formation of no greater than 1% 8a was observed.

Table II. Effects of Reaction Concentration on the 3-Aza-Cope Rearrangement of 4a Promoted by 1.2 Equiv of $ZnCl_2$

	yield[b] (%)				
		product formation[c]			
condns[a] (M, 4a)	4a	5a	6a	7a	9a
3.0	1	7	19	35	5
2.0	16	37	18	15	7
1.0	19	51	4	6	5
0.75	22	52	4	6	4
0.5	28	53	4	4	3
0.36	69	27	2	0	0

[a] Rearrangements were run at reflux in xylenes (140 °C) for 16 h. In each case, longer reaction times produced lower yields. [b] Values represent % yields as determined by GC analysis (ref 14). [c] Formation of no greater than 1% 8a was observed.

(10) George, C.; Gill, E. W.; Hudson, J. A. *J. Chem. Soc., Chem. Commun.* **1990**, 74.
(11) Cook, G. R.; Stille, J. R. *J. Org. Chem.* **1991**, *56*, 5578.
(12) Cook, G. R.; Barta, N. S.; Stille, J. R. *J. Org. Chem.* **1992**, *57*, 461.
(13) Maruoka, K.; Sato, J.; Banno, H.; Yamamoto, H. *Tetrahedron Lett.* **1990**, *31*, 377.
(14) Product distribution and yields for these compounds were determined by capillary gas chromatographic analysis of the quenched reaction mixture (H_2O, NaOH) using internal standards and correcting for detector response.

Table III. Efficiency of Lewis Acids on the 3-Aza-Cope Rearrangement of 4a

reagent[a]	condns: temp (°C)	condns: time (h)	product formation 5a; yield (%)
$AlCl_3$	140	8	88
$ZnCl_2$	140	16	53
Et_2O-BF_3	111	44	79
Et_2O-BF_3	140	24	49
$TiCl_4$	140	16	46
$MgBr_2$	140	40	38
$(ArO)_2AlMe$[c]	140	72	28
$FeCl_3$	140	4	24
Me_2AlCl	140	24	22
$MeAlCl_2$	140	44	16

[a] Rearrangements were run 0.5 M of 4a with 1.2 equiv of Lewis acid at reflux in toluene (111 °C) or xylenes (140 °C). [b] Values represent GC yields of 5a (ref 14). [c] ArO = 4-bromo-2,6-di-*tert*-butylphenoxy.

Table IV. Lewis Acid-Promoted 3-Aza-Cope Rearrangement of 4 and 10

substrate	reagent (1.2 equiv)	condns[a] (time(h))	yield (%) isolated[b] (GC)[c]
4a	$AlCl_3$	8	68 (88)
	$ZnCl_2$	16	45 (52)
	Et_2O-BF_3	48	58 (79)
4b	$AlCl_3$	2	15 (35)
	$ZnCl_2$	24	15 (30)
	Et_2O-BF_3	24	13 (28)
10a	$ZnCl_2$	16	58 (66)
	Et_2O-BF_3	72	55 (61)
10b	$ZnCl_2$	24	53 (57)
	Et_2O-BF_3	48	35 (42)

[a] Rearrangements were run 0.5 M of 4a with 1.2 equiv of Lewis acid at reflux in toluene (111 °C, Et_2O-BF_3) or xylenes (140 °C, $AlCl_3$, and $ZnCl_2$). [b] Overall isolated yields of 5 and 11. [c] Reference 14.

ylated and oligomeric products, without generation of significant amounts of 5a–9a. In general, these trends were opposite those observed for the aliphatic 3-aza-Cope rearrangement, in which the organoaluminum species were the most efficient reagents, and the metal halides typically used for Freidel–Crafts alkylation produced very poor results.[12] The temperature at which the aromatic 3-aza-Cope rearrangement occurred was also critical to the success of the reaction. The use of decalin (180 °C) resulted in the formation of 6a and 7a as the major products in poor yield, and the use of toluene (111 °C) did not provide a high enough temperature at reflux to promote conversion of 4a to products. Interestingly, the use of Et_2O-BF_3 was the one exception, and rearrangement in toluene at reflux was more efficient than reaction in xylene.

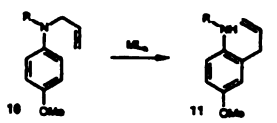
The three optimum catalysts, $AlCl_3$, $ZnCl_2$, and Et_2O-BF_3, were each used in the studies of substrate variability. Under the optimum conditions for rearrangement, 5a was isolated from the reaction mixture in 45–68% yield (Table IV). The reaction of Lewis acids with 4b, having an *N*-benzyl group instead of an *N*-methyl substituent, produced much poorer results. Under similar reaction conditions, a 35% yield was the best that could be obtained from any of the catalysts with 4b. The disappearance of 4b without formation of the desired products was suspected to result from reaction of nucleophiles at the benzylic position and concomitant displacement of a quaternary nitrogen during the vigorous reaction conditions. Treatment of the analogous allyl acetamide and sulfonamide substrates with these Lewis acids did not result in [3,3] rearrangement products.

Table V. Lewis Acid-Promoted 3-Aza-Cope Rearrangement of 12

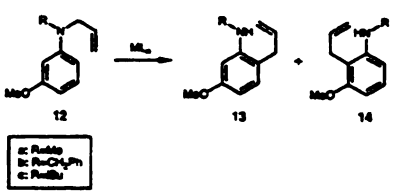
substrate	reagent (1.2 equiv)	condns[a] (time (h))	product formation (%): 13:14[b]	product formation (%): yield[c] (GC)[d]
12a	$ZnCl_2$	8	64:36	70 (77)
	Et_2O-BF_3	48	66:34	99 (99)
12b	$ZnCl_2$	24	71:29	57 (64)
	Et_2O-BF_3	48	72:28	38 (47)
12c	$ZnCl_2$	6	73:27	98 (98)
	Et_2O-BF_3	24	72:28	80 (89)

[a] Rearrangements were run 0.5 M of 4a with 1.2 equiv of Lewis acid at reflux in toluene (111 °C, Et_2O-BF_3) or xylenes (140 °C, $ZnCl_2$). [b] Ratios of 13:14 were determined by GC analysis of the crude reaction mixture. For substrates b and c, ratios were confirmed by ^1H NMR analysis. [c] Overall isolated yield as the mixture of 13 and 14. [d] Reference 14.

Rearrangement of substrates containing a methoxy substituent on the aromatic ring provided useful insight into the nature of this Lewis acid-promoted transformation (eqs 3 and 4, Tables IV and V). The most noticeable



(3)



(4)

difference observed with these substrates was that $AlCl_3$ produced rapid disappearance of 10 and 12, without the generation of any of the typical [3,3] rearrangement products.[15] Due to the slight deactivation at the position meta to the methoxy substituent, substrate 10 rearranged more slowly than the analogous unsubstituted substrate 4. However, even though the substituent deactivated the position at which carbon–carbon bond formation occurred, standard conditions for the rearrangement promoted with $ZnCl_2$ and Et_2O-BF_3 led to comparable or higher isolated yields of 11.

Rearrangement of substrate 12, having a methoxy substituent meta to the allylamine substituent, introduced the possibility of regioisomer formation. Depending on the ortho position at which rearrangement took place, two different products resulted, and in each case, reaction occurred at a position activated by the ortho and para directing methoxy substituent (eq 4). Unfortunately, regioselectivity was only moderate, ranging from 64:36 to 73:27 for 13:14, and the product ratio showed little dependence on the Lewis acid used. Formation of the para product analogous to 8a was not observed. Activation of the aromatic ring by the methoxy substituent had beneficial effects. Not only did rearrangement to products

(15) The treatment of methyl phenyl ethers with $AlCl_3$ and soft nucleophiles has been reported to cleave the methyl ether to produce phenolic products. Node, M.; Nishide, K.; Fuji, K.; Fujita, E. *J. Org. Chem.* **1980**, *45*, 4275. Similar problems have been reported with the use of Et_2O-BF_3.[3b]

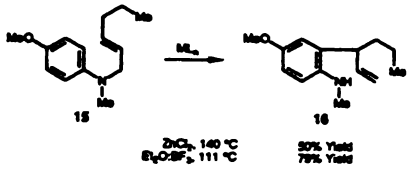
Table VI. Competitive Lewis Acid-Promoted 3-Aza-Cope Rearrangement of 4a and 12a

reagent	condns[a] (time (h))	product formation[b] (%) 13a + 14a	5a	(13a + 14a):5a
Et_2O-BF_3	2	24	15	62:38
	4	33	22	60:40
	6	49	30	62:38
	8	56	33	63:37
$ZnCl_2$	0.5	17	7	71:29
	1.0	36	10	78:22
	1.5	47	15	76:24
	2.0	56	18	75:25

[a] Rearrangements were run 0.5 M of 4a with 1.5 equiv of Lewis acid at reflux in toluene (111 °C, Et_2O-BF_3) or xylenes (140 °C, $ZnCl_2$) with 1.8 equiv of Lewis acid. [b] Ratios were determined by GC analysis of the crude reaction mixture (ref 14).

occur in shorter time periods, but higher product yields resulted due to the increased rate of the transformation of 12 to 13 and 14 relative to the competitive formation of byproducts. As was observed in the reaction of 10, $AlCl_3$ resulted in consumption of 12 without producing 13 or 14.[15] Comparison of relative reaction rates was observed by the direct competition of 1.0 equiv each of 4a and 12a promoted by 1.8 equiv of Lewis acid. Results from this study showed that formation of 13a and 14a was approximately 1.5 times faster than that of 5a when promoted by Et_2O-BF_3 and roughly 3.0 faster in the presence of $ZnCl_2$ (Table VI).[16]

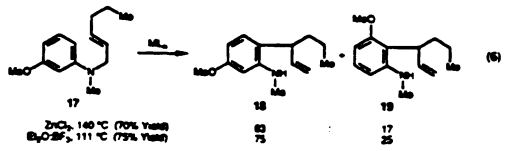
A final set of substrates was examined in order to determine the regioselectivity of the rearrangement with an unsymmetrical allylic substituent, enhance regioselective reaction on the aromatic ring, and establish a potential route to a methoxy-substituted variety of naturally occurring alkaloids. These substrates were prepared with an unsymmetrical *N*-((*E*)-2-hexen-1-yl) substituent on the aniline (eq 5). Rearrangement of 15 with $ZnCl_2$ at



(5)

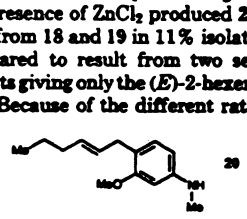
140 °C or Et_2O-BF_3 at 111 °C produced 16 in 50% and 79% isolated yields, respectively. Compared to the analogous rearrangement of 10a, the use of $ZnCl_2$ was similar, while the reaction promoted by Et_2O-BF_3 was far more efficient. In both reactions, only [3,3] rearrangement was evident from analysis of the reaction products; carbon–carbon bond formation resulting from [1,3] rearrangement of the substrate through a nonconcerted pathway was not observed. Most importantly, these reagents efficiently promoted the regiospecific 3-aza-Cope rearrangement of *N*-alkyl-*N*-allylanilines and produced carbon–carbon bond formation between an aromatic ring and a secondary alkyl substituent.

The rearrangement of the corresponding substrate having a methoxy substituent meta to the amine, 17, produced results similar to those observed for the rearrangement of 12a and 15a (eq 6). As was observed for



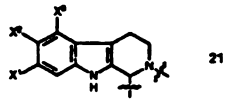
(6)

12a, a mixture of regioisomers was obtained. In the case of 17, however, slightly increased product selectivities of 75:25 and 83:17 for 18:19 were obtained for rearrangement with Et_2O-BF_3 and $ZnCl_2$, respectively. However, in contrast to previous rearrangement with the *N*-allyl substituents, further [3,3] Cope rearrangement of 18 and/or 19 in the presence of $ZnCl_2$ produced 20, which could be separated from 18 and 19 in 11% isolated yield. This product appeared to result from two sequential [3,3] rearrangements giving only the (*E*)-2-hexen-1-yl aromatic substituent. Because of the different rates at which 20



20

was generated from 18 versus 19, the regioselectivity ratio based on the direct observation of product distribution might not directly reflect the actual selectivity of the relative reaction rates. The similarities in structure of 16, 18, and 19 to the indole alkaloids 21 such as acricine (X^1



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$= X^3 = H$, $X^2 = OMe$),[17] reserpinine ($X^1 = OMe$, $X^2 = X^3 = H$),[17] ochropposinine ($X^1 = X^2 = OMe$, $X^3 = H$),[18] and mitragynaline ($X^1 = X^2 = H$, $X^3 = OMe$)[19] are striking and provide some intriguing possibilities for future application of this methodology.

Summary

Systematic studies of the aromatic 3-aza-Cope rearrangement have been used to examine a number of reaction variables, and results have shown that reaction conditions having a substrate concentration of 0.5 M and treatment with 1.2 equiv of Lewis acid were optimum for obtaining the desired product. Of the many Lewis acids investigated, $ZnCl_2$ (140 °C) and Et_2O-BF_3 (111 °C) were the most generally successful reagents for promoting the 3-aza-Cope rearrangement. The presence of a methoxy substituent para to the *N*-allyl group slowed the reaction slightly, while a meta substituent greatly accelerated the rate of rearrangement to the position ortho or para to the methoxy group. In this case, site selectivity on the aromatic ring was moderate. Rearrangement of an unsymmetrically substituted allyl moiety resulted in regioselective [3,3] rearrangement to produce a 1-hexen-3-yl substituent on the aromatic ring. Overall, both $ZnCl_2$ and Et_2O-BF_3 were demonstrated to efficiently accelerate the regiospecific 3-aza-Cope rearrangement of *N*-alkyl-*N*-allylanilines for

(16) These values illustrate the presence of this general trend, but the accuracy of these values is somewhat limited by the differing efficiencies of these reactions.

(17) Holscher, P.; Knolker, H.-J.; Winterfeldt, E. *Tetrahedron Lett.* 1990, *31*, 705.
(18) Fujii, T.; Obba, M.; Tachinami, T.; Miyajima *Chem. Pharm. Bull.* 1990, *38*, 1200.
(19) Houghton, P. J.; Latiff, A.; Said, I. M. *Phytochem.* 1991, *30*, 347.

the purpose of forming a carbon–carbon bond between a secondary alkyl substituent and an aromatic ring.

Experimental Section

General Methods. All reactions were carried out performing standard inert atmosphere techniques to exclude moisture and oxygen.[20] Benzene, toluene, tetrahydrofuran (THF), and Et_2O were distilled from sodium/benzophenone immediately prior to use. Xylenes and decalin were heated over calcium hydride for a minimum of 12 h and then distilled prior to use. Petroleum ether (35–60 °C boiling range) was used without further purification. $LiAlH_4$ (1 M in THF) was obtained from Aldrich Chemical Co. 1-Bromo-2-hexene[21] and all secondary alkylanilines were prepared by literature methods.[22] Compound 8a was prepared through an independent route.[23]

For reactions in which a Dean-Stark trap was used, the trap was filled with 4-Å molecular sieves to a level below that of returning solvent turbulence. The sieves were changed during reactions in which additional reagent was added during the course of the reaction. Molecular sieves were activated by heating in a 150 °C oven for at least 24 h prior to use. Unless specified, concentration of mixtures after workup was performed using a Büchi rotary evaporator.

General Method for the *N*-Allylation of Secondary Anilines.[22] The aniline (2.0–50.0 mmol, 1.0 equiv) and the alkyl bromide or alkyl chloride (1.2–4.0 equiv) were taken up in a 4:1 EtOH/H_2O mixture (0.5 M relative to the aniline) along with Na_2CO_3 (0.6 equiv). After stirring at room temperature for 14 h, the EtOH was removed under reduced pressure and the crude oil purified by flash column chromatography (silica, 230–400 mesh; eluent 5:95 Et_2O/petroleum ether). The solvents were evaporated and the dialkylated anilines distilled under vacuum.

***N*-Allyl-*N*-methylaniline (4a):** 91% yield; bp 107–110 °C, <1.5 mmHg; ^1H (300 MHz, $CDCl_3$) δ 2.78 (s, 3H), 3.76 (dt, J = 5.0, 1.7 Hz, 2H), 5.05 (dq, J = 17.0, 1.7 Hz, 1H), 5.07 (dq, J = 10.4, 1.7 Hz, 1H), 5.73 (ddt, J = 17.0, 10.4, 5.0 Hz, 1H), 6.60–6.68 (m, 3H), 7.11–7.19 (m, 2H); ^{13}C (75.5 MHz, $CDCl_3$) δ 37.57, 54.86, 112.16, 115.70, 116.17, 128.82, 133.60, 149.81; IR (oil/NaCl) 3063, 3027, 2980, 2897, 2815, 1644, 1599, 1449 cm^{-1}; HRMS calcd for $C_{10}H_{13}N$ m/z 147.1049, found m/z 147.1010.

***N*-Allyl-*N*-benzylaniline (4b):** 85% yield; ^1H NMR (300 MHz, $CDCl_3$) δ 3.85–3.91 (m, 2H), 4.43 (s, 2H), 5.10 (dq, J = 10.5, 1.8 Hz, 1H), 5.12 (dq, J = 17.4, 1.8 Hz, 1H), 5.78 (ddt, J = 17.4, 10.5, 4.8 Hz, 1H), 6.59–6.68 (m, 3H), 7.06–7.24 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.81, 53.76, 112.24, 116.06, 116.43, 126.41, 126.63, 128.40, 128.99, 133.52, 138.76, 148.73; IR (KBr) 3062, 3028, 2862, 1599, 1509 cm^{-1}; HRMS calcd for $C_{16}H_{17}N$ m/z 223.1362, found m/z 223.1382.

***N*-Allyl-*N*-methyl-4-methoxyaniline (10a):** 66% yield; bp 80–86 °C, <4 mmHg; ^1H NMR (300 MHz, $CDCl_3$) δ 2.83 (s, 3H), 3.72 (s, 3H), 3.80 (dt, J = 5.3, 1.7 Hz, 2H), 5.14 (dq, J = 10.5, 1.7 Hz, 1H), 5.16 (dq, J = 17.4, 1.7 Hz, 1H), 5.82 (ddt, J = 17.4, 10.5, 5.3 Hz, 1H), 6.67–6.73 (m, 2H), 6.77–6.84 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 38.54, 55.55, 56.44, 114.54, 114.59, 116.26, 134.20, 144.38, 151.64; IR (oil/NaCl) 3077, 2936, 2832, 2809, 1642, 1516 cm^{-1}; HRMS calcd for $C_{11}H_{15}NO$ m/z 177.1154, found m/z 177.1148.

***N*-Allyl-*N*-benzyl-4-methoxyaniline (10b):** 75% yield; bp 128–139 °C, <4 mmHg; ^1H NMR (300 MHz, $CDCl_3$) δ 3.72 (s, 3H), 3.92 (dt, J = 5.1, 1.8 Hz, 2H), 4.46 (s, 2H), 5.16 (dq, J = 10.2, 1.8 Hz, 1H), 5.17 (dq, J = 17.2, 1.8 Hz, 1H), 5.87 (ddt, J = 17.2, 10.2, 5.1 Hz, 1H), 6.64–6.71 (m, 2H), 6.74–6.80 (m, 2H), 7.18–7.33 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 53.78, 54.82, 55.66, 114.35, 114.63, 116.33, 126.71, 126.80, 128.46, 134.17, 139.25, 143.61, 151.53; IR (oil/NaCl) 3085, 2934, 2832, 1512 cm^{-1}; HRMS calcd for $C_{17}H_{19}NO$ m/z 253.1468, found 253.1453.

***N*-Allyl-*N*-methyl-3-methoxyaniline (12a):** 68% yield; bp 83–87 °C, <4 mmHg; ^1H NMR (300 MHz, $CDCl_3$) δ 2.91 (s, 3H), 3.76 (s, 3H), 3.88 (dt, J = 5.1, 1.8 Hz, 2H), 5.13 (dq, J = 10.8, 1.8 Hz, 1H), 5.14 (dq, J = 17.1, 1.8 Hz, 1H), 5.82 (ddt, J = 17.1, 10.8, 5.1 Hz, 1H), 6.22–6.29 (m, 2H), 6.30–6.36 (m, 1H), 7.07–7.15 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 37.96, 54.95, 55.16, 98.90, 101.09, 105.50, 116.01, 129.66, 133.66, 150.79, 160.65; IR (oil/NaCl) 3085, 2998, 2938, 2836, 1609, 1503 cm^{-1}; HRMS calcd for $C_{11}H_{15}NO$ m/z 177.1154, found m/z 177.1156.

***N*-Allyl-*N*-benzyl-3-methoxyaniline (12b):** 83% yield; bp 130–137 °C, <4 mmHg; ^1H NMR (300 MHz, $CDCl_3$) δ 3.68 (s, 3H), 3.96 (dt, J = 4.8, 1.8 Hz, 2H), 4.50 (s, 2H), 5.16 (dq, J = 10.5, 1.8 Hz, 1H), 5.17 (dq, J = 17.1, 1.8 Hz, 1H), 5.85 (ddt, J = 17.1, 10.5, 4.8 Hz, 1H), 6.22–6.35 (m, 3H), 6.32 (ddd, J = 8.4, 2.1, 0.8 Hz, 1H), 7.06 (t, J = 8.4 Hz, 1H), 7.17–7.31 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 53.03, 53.89, 54.88, 98.91, 101.19, 105.46, 116.21, 126.46, 126.71, 128.48, 129.71, 133.50, 138.77, 150.26, 160.63; IR (oil/NaCl) 3085, 3936, 2836, 1612, 1501, 1453 cm^{-1}; HRMS calcd for $C_{17}H_{19}NO$ m/z 253.1468, found m/z 253.1465.

***N*-Allyl-*N*-isobutyl-3-methoxyaniline (12c):** 80% yield; bp 35–36 °C, <4 mmHg; ^1H NMR (300 MHz, $CDCl_3$) δ 0.92 (d, J = 6.6 Hz, 6H), 2.06 (sept, J = 6.6 Hz, 1H), 3.06 (d, J = 7.2 Hz, 2H), 3.73 (s, 3H), 3.91 (dt, J = 4.8, 1.8 Hz, 2H), 5.09 (dq, J = 16.8, 1.8 Hz, 1H), 5.10 (dq, J = 11.1, 1.8 Hz, 1H), 5.78 (ddt, J = 16.8, 11.1, 4.8 Hz, 1H), 6.18–6.32 (m, 3H), 7.04–7.11 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.33, 27.30, 53.96, 54.82, 58.93, 98.83, 100.27, 105.39, 115.82, 129.51, 133.82, 149.98, 160.58; IR (oil/NaCl) 2955, 2870, 2836, 1611, 1576, 1499 cm^{-1}; HRMS calcd for $C_{14}H_{21}NO$ m/z 219.1624, found m/z 219.1634.

***N*-((*E*)-2-Hexen-1-yl)-*N*-methyl-4-methoxyaniline (15):** 73% yield; ^1H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, J = 7.4 Hz, 3H), 1.36 (sext, J = 7.4 Hz, 2H), 1.98 (q, J = 7.4 Hz, 2H), 2.78 (s, 3H), 3.70 (s, 3H), 3.73 (bd, J = 5.4 Hz, 2H), 5.43 (dtt, J = 15.3, 5.7, 1.1 Hz, 1H), 5.56 (dtt, J = 15.3, 5.7, 1.1 Hz, 1H), 6.67–6.73 (m, 2H), 6.76–6.82 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.46, 22.29, 34.22, 38.21, 55.41, 55.78, 114.41, 114.81, 125.66, 132.91, 144.55, 151.60; IR (oil/NaCl) 2957, 2932, 2872, 2832, 1620, 1562, 1464 cm^{-1}; HRMS calcd for $C_{14}H_{21}NO$ m/z 219.1624, found m/z 219.1618.

***N*-((*E*)-2-Hexen-1-yl)-*N*-methyl-3-methoxyaniline (17):** 72% yield; ^1H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, J = 7.4 Hz, 3H), 1.36 (sext, J = 7.4 Hz, 2H), 1.98 (q, J = 7.4 Hz, 2H), 2.85 (s, 3H), 3.74 (s, 3H), 3.81 (dd, J = 5.4, 0.9 Hz, 2H), 5.42 (m, 1H), 5.55 (m, 1H), 6.21–6.28 (m, 2H), 6.31–6.36 (m, 1H), 7.09 (td, J = 8.0, 0.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.48, 22.29, 34.20, 37.57, 54.41, 54.80, 98.91, 100.97, 105.58, 125.18, 129.55, 132.63, 150.88, 160.59; IR (oil/NaCl) 2959, 2872, 2836, 1607, 1503, 1456 cm^{-1}; HRMS calcd for $C_{14}H_{21}NO$ m/z 219.1624, found m/z 219.1639.

General Method for the Lewis Acid-Promoted Rearrangement of *N*-Allyl-*N*-alkylanilines. The aniline (0.5–2.0 mmol, 1.0 equiv) and the catalyst (0.6–2.4 mmol, 1.2 equiv) were added to dry xylenes or toluene (0.5 M relative to the aniline) at −78 °C along with an internal standard of decalin. The reaction was heated to the appropriate temperature and allowed to react as described in the text. The reaction was then quenched at 0 °C by addition of a 15% aqueous NaOH solution, and the organic fractions were combined, separated, dried over $MgSO_4$, and concentrated. The crude products were isolated and purified by flash column chromatography (silica, 230–400 mesh; eluent, 5:95 Et_2O/petroleum ether). Yields for these reactions are provided in the tables.

***N*-Methyl-2-allylaniline (5a):** ^1H NMR (300 MHz, $CDCl_3$) δ 2.83 (s, 3H), 3.26 (bd, J = 6.1 Hz, 2H), 3.73 (bs, 1H), 5.08 (dq, J = 16.7, 1.8 Hz, 1H), 5.10 (dq, J = 10.4, 1.8 Hz, 1H), 5.93 (ddt, J = 16.7, 10.4, 6.1 Hz, 1H), 6.63 (d, J = 8.2 Hz, 1H), 6.70 (td, J = 7.4, 1.1 Hz, 1H), 7.03 (dd, J = 7.4, 1.1 Hz, 1H), 7.12 (td, J = 7.4, 1.6 Hz, 1H); ^{13}C (75.5 MHz, $CDCl_3$) δ 30.54, 36.21, 109.73, 115.97, 116.93, 123.39, 127.59, 129.47, 135.95, 147.22; IR (oil/

(20) For more detailed General Experimental procedures from these labs, see ref 12.

(21) Prepared from 2-hexen-1-ol by treatment with NBS/PPh_3: (a) Trippett, S. *J. Chem. Soc.* **1962**, 2337. (b) Boss, A. K.; Lai, B. *Tetrahedron Lett.* **1973**, 3937.

(22) Prepared by a modification of the method described in: Tweedie, V.; Allibashi, J. *J. Org. Chem.* **1969**, *35*, 3676.

(23) Compound 8a was prepared from allyl benzene by the following sequence: (a) Br_2, −78 °C (92%);[24] (b) HNO_3, H_2SO_4, 0 °C (72%);[25] (c) NaI, EtOH (69%);[26] (d) H_2O, Fe (95%);[27] (e) MeI, Na_2CO_3 (37%).[22]

(24) Rolston, J. H.; Yates, K. *J. Am. Chem. Soc.* **1969**, *91*, 1469.

(25) Robertson, G. R. *Organic Syntheses*; Wiley: New York, 1932; Collect. Vol. I, p 389.

(26) Julian, P. L.; Karpel, W. J. *J. Am. Chem. Soc.* **1950**, *72*, 362.

(27) Haslet, S. E.; Dornfield, C. A. *J. Am. Chem. Soc.* **1944**, *60*, 1781.

NaCl) 3436 (broad), 3075, 2978, 2894, 2815, 1634, 1605, 1514, 1466 cm^{-1}; HRMS calcd for $C_{10}H_{13}N$ *m/z* 147.1049, found *m/z* 147.0994.

N-Benzyl-2-allylaniline (5b): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.34 (bd, J = 6.3 Hz, 2H), 4.10 (bs, 1H), 4.34 (s, 2H), 5.07 (dq, J = 16.8, 1.7 Hz, 1H), 5.11 (dq, J = 10.5, 1.7 Hz, 1H), 5.95 (ddt, J = 16.8, 10.5, 6.3 Hz, 1H), 6.62 (d, J = 7.4 Hz, 1H), 6.70 (td, J = 7.4, 0.9 Hz, 1H), 7.06 (dd, J = 7.4, 1.2 Hz, 1H), 7.12 (td, J = 7.4, 1.2 Hz, 1H), 7.22–7.37 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.50, 48.13, 110.69, 116.29, 117.34, 123.49, 127.12, 127.35, 127.68, 128.57, 129.78, 135.93, 139.41, 146.11; IR (oil/NaCl) 3440 (broad), 3031, 2888, 2843, 1633, 1603, 1510 cm^{-1}; HRMS calcd for $C_{16}H_{17}N$ *m/z* 223.1362, found *m/z* 223.1373.

N-Methyl-2-allyl-4-methoxyaniline (11a): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.81 (s, 3H), 3.25 (dt, J = 6.0, 1.7 Hz, 2H), 3.37 (bs, 1H), 3.74 (s, 3H), 5.07 (dq, J = 17.1, 1.7 Hz, 1H), 5.12 (dq, J = 10.2, 1.7 Hz, 1H), 5.93 (ddt, J = 17.1, 10.2, 6.0 Hz, 1H), 6.58 (d, J = 8.7 Hz, 1H), 6.70 (d, J = 3.0 Hz, 1H), 6.76 (dd, J = 8.7, 3.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.37, 36.31, 55.70, 110.96, 112.02, 116.23, 116.50, 125.45, 135.76, 141.65, 151.81; IR (oil/NaCl) 3422 (broad), 2938, 2832, 2808, 1638, 1514, 1464 cm^{-1}; HRMS calcd for $C_{11}H_{15}NO$ *m/z* 177.1154, found *m/z* 177.1161.

N-Benzyl-2-allyl-4-methoxyaniline (11b): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.29 (dt, J = 6.0, 1.5 Hz, 2H), 3.72 (s, 3H), 3.78 (bs, 1H), 4.28 (s, 2H), 5.06 (dq, J = 17.1, 1.5 Hz, 1H), 5.11 (dq, J = 10.5, 1.5 Hz, 1H), 5.94 (ddt, J = 17.1, 10.5, 6.0 Hz, 1H), 6.57 (d, J = 8.4 Hz, 1H), 6.67 (d, J = 3.0 Hz, 1H), 6.66–6.73 (m, 1H), 7.21–7.37 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.46, 48.89, 55.65, 111.94, 112.02, 116.39, 116.55, 125.50, 127.06, 127.39, 128.51, 135.69, 139.67, 140.34, 151.93; IR (oil/NaCl) 3430 (broad), 3063, 2936, 2832, 1636, 1509, 1466 cm^{-1}; HRMS calcd for $C_{17}H_{19}NO$ *m/z* 253.1468, found *m/z* 253.1468.

N-Methyl-2-allyl-5-methoxyaniline (12a): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.82 (s, 3H), 3.21 (dt, J = 6.0, 1.8 Hz, 2H), 3.77 (bs, 1H), 3.79 (s, 3H), 5.05 (dq, J = 16.8, 1.8 Hz, 1H), 5.08 (dq, J = 10.8, 1.8 Hz, 1H), 5.91 (ddt, J = 16.8, 10.8, 6.0 Hz, 1H), 6.19–6.27 (m, 2H), 6.93 (d, J = 8.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.62, 35.69, 55.10, 97.19, 100.74, 115.79, 116.31, 130.17, 136.53, 148.51, 159.83; IR (oil/NaCl) 3438 (broad), 3077, 2938, 2834, 2809, 1617, 1520 cm^{-1}; HRMS calcd for $C_{11}H_{15}NO$ *m/z* 177.1154, found *m/z* 177.1145.

N-Methyl-2-allyl-3-methoxyaniline (13a): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.84 (s, 3H), 3.38 (dt, J = 6.0, 1.9 Hz, 2H), 3.78 (bs, 1H), 3.80 (s, 3H), 5.02 (dq, J = 17.4, 1.8 Hz, 1H), 5.03 (dq, J = 9.3, 1.8 Hz, 1H), 5.88 (ddt, J = 17.4, 9.3, 6.0 Hz, 1H), 6.35 (d, J = 8.4 Hz, 1H), 6.38 (d, J = 8.4 Hz, 1H), 7.14 (t, J = 8.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.90, 31.04, 55.78, 100.66, 103.68, 114.76, 125.90, 127.67, 136.05, 148.70, 157.60; IR (oil/NaCl) 3438 (broad), 3077, 2939, 2836, 2815, 1601, 1591, 1478 cm^{-1}; HRMS calcd for $C_{11}H_{15}NO$ *m/z* 177.1154, found *m/z* 177.1142.

N-Benzyl-2-allyl-5-methoxyaniline (13b): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.25 (dt, J = 6.0, 1.8 Hz, 2H), 3.72 (s, 3H), 4.13 (bs, 1H), 4.31 (s, 2H), 5.05 (dq, J = 17.1, 1.8 Hz, 1H), 5.09 (dq, J = 10.5, 1.8 Hz, 1H), 5.93 (ddt, J = 17.1, 10.5, 6.0 Hz, 1H), 6.19–6.27 (m, 2H), 6.95 (d, J = 8.1 Hz, 1H), 7.20–7.37 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.82, 48.12, 55.04, 97.96, 101.16, 115.95, 116.22, 127.15, 127.38, 128.57, 130.32, 136.41, 139.21, 147.22, 159.68; IR (oil/NaCl) 3438 (broad), 3063, 2834, 1617, 1586, 1520, 1466 cm^{-1}; HRMS calcd for $C_{17}H_{19}NO$ *m/z* 253.1468, found *m/z* 253.1492.

N-Benzyl-2-allyl-3-methoxyaniline (14b): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.42 (dt, J = 5.4, 1.8 Hz, 2H), 3.79 (s, 3H), 4.16 (bs, 1H), 4.34 (s, 2H), 5.01 (dq, J = 16.8, 1.8 Hz, 1H), 5.02 (dq, J = 11.0, 1.8 Hz, 1H), 5.89 (ddt, J = 16.8, 11.0, 5.4 Hz, 1H), 6.32 (bd, J = 8.4 Hz, 1H), 6.37 (bd, J = 8.4 Hz, 1H), 7.06 (t, J = 8.4 Hz, 1H), 7.21–7.36 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.02, 48.35, 55.77, 100.81, 104.50, 114.97, 127.06, 127.30, 127.65, 128.55, 128.62, 135.93, 139.61, 147.43, 157.90; IR (oil/NaCl) 3440 (broad), 2936, 2836, 1634, 1599, 1476 cm^{-1}; HRMS calcd for $C_{17}H_{19}NO$ *m/z* 253.1468, found *m/z* 253.1436.

N-Isobutyl-2-allyl-5-methoxyaniline (13c): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.98 (d, J = 6.7 Hz, 6H), 1.91 (nonet, J = 6.7 Hz, 1H), 2.91 (d, J = 6.7 Hz, 2H), 3.24 (dt, J = 6.3, 1.8 Hz, 2H), 3.79 (s, 3H), 3.83 (bs, 1H), 5.06–5.16 (m, 2H), 5.93 (ddt, J = 17.7, 9.6, 6.3 Hz, 1H), 6.17–6.24 (m, 2H), 6.94 (d, J = 8.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.58, 27.84, 36.14, 51.59, 55.12, 97.42, 100.43, 115.88, 116.08, 130.33, 136.82, 147.74, 159.79; IR (oil/NaCl) 3432 (broad), 3079, 2957, 2870, 2834, 1617, 1588, 1520 cm^{-1}; HRMS calcd for $C_{14}H_{21}NO$ *m/z* 219.1624, found *m/z* 219.1641.

N-Isobutyl-2-allyl-3-methoxyaniline (14c): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (d, J = 6.6 Hz, 6H), 1.89 (nonet, J = 6.6 Hz, 1H), 2.92 (d, J = 6.6 Hz, 2H), 3.39 (dt, J = 5.7, 1.8 Hz, 2H), 3.79 (s, 3H), 3.83 (bs, 1H), 5.03 (dq, J = 10.8, 1.8 Hz, 1H), 5.06 (dq, J = 16.8, 1.8 Hz, 1H), 5.88 (ddt, J = 16.8, 10.8, 5.7 Hz, 1H), 6.31 (d, J = 8.2 Hz, 1H), 6.33 (d, J = 8.2 Hz, 1H), 7.09 (t, J = 8.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.57, 28.00, 28.13, 51.89, 55.76, 100.17, 104.03, 110.84, 114.91, 127.58, 136.30, 147.90, 157.67; IR (oil/NaCl) 3430 (broad), 3076, 2959, 2870, 2836, 1635, 1601, 1476 cm^{-1}; HRMS calcd for $C_{14}H_{21}NO$ *m/z* 219.1624, found *m/z* 219.1622.

N-Methyl-2-(1-hexen-3-yl)-4-methoxyaniline (16): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (t, J = 7.4 Hz, 3H), 1.22–1.48 (m, 2H), 1.62–1.81 (m, 2H), 2.80 (s, 3H), 3.26 (bq, J = 7.4 Hz, 2H), 3.47 (bs, 1H), 3.75 (s, 3H), 5.02 (dt, J = 17.1, 1.4 Hz, 1H), 5.06 (dt, J = 10.2, 1.4 Hz, 1H), 5.81 (ddd, J = 17.1, 10.2, 7.4 Hz, 1H), 6.57–6.66 (m, 1H), 6.71–6.76 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.03, 20.65, 31.54, 35.52, 43.50, 55.61, 111.10, 111.38, 114.24, 114.49, 129.87, 141.09, 141.35, 152.04; IR (oil/NaCl) 3413 (m-broad), 3077, 2957, 2872, 2832, 2809, 1647, 1510, 1458 cm^{-1}; HRMS calcd for $C_{14}H_{21}NO$ *m/z* 219.1624, found *m/z* 219.1487.

N-Methyl-2-(1-hexen-3-yl)-5-methoxyaniline (18): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (t, J = 7.4, 3H), 1.21–1.48 (m, 2H), 1.62–1.81 (m, 2H), 2.82 (s, 3H), 3.15 (bq, J = 7.4 Hz, 1H), 3.79 (s, 3H), 3.87 (bs, 1H), 5.01 (dt, J = 17.7, 1.4 Hz, 1H), 5.06 (dt, J = 10.5, 1.4 Hz, 1H), 5.81 (ddd, J = 17.7, 10.5, 7.4 Hz, 1H), 6.22 (d, J = 2.4 Hz, 1H), 6.28 (dd, J = 8.4, 2.4 Hz, 1H), 6.98 (d, J = 8.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.09, 20.75, 30.80, 35.48, 43.19, 55.04, 97.49, 100.92, 114.13, 120.41, 127.59, 141.76, 148.28, 159.31; IR (oil/NaCl) 3438 (broad), 3077, 2959, 2930, 2872, 2836, 2807, 1615, 1586, 1463 cm^{-1}; HRMS calcd for $C_{14}H_{21}NO$ *m/z* 219.1624, found *m/z* 219.1650.

N-Methyl-2-(1-hexen-3-yl)-3-methoxyaniline (19): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, J = 7.2 Hz, 3H), 1.07–1.37 (m, 2H), 1.70–1.89 (m, 2H), 2.77 (s, 3H), 3.77 (s, 3H), 3.98–4.17 (m, 2H), 5.07 (dt, J = 6.6, 2.4 Hz, 1H), 5.12 (d, J = 2.4 Hz, 1H), 6.11 (m, 1H), 6.30 (bd, J = 8.1 Hz, 2H), 6.37 (bd, J = 8.1 Hz, 1H), 7.10 (t, J = 8.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.18, 21.11, 31.06, 32.49, 37.58, 55.78, 100.89, 104.45, 113.37, 114.28, 127.58, 141.64, 148.91, 158.10; IR (oil/NaCl) 3426 (broad), 2919, 2848, 1588, 1476 cm^{-1}; HRMS calcd for $C_{14}H_{21}NO$ *m/z* 219.1624, found *m/z* 219.1635.

N-Methyl-4-((*E*)-2-hexen-1-yl)-3-methoxyaniline (20): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, J = 7.4 Hz, 3H), 1.37 (sext, J = 7.4 Hz, 2H), 1.97 (bq, J = 7.4 Hz, 2H), 2.82 (s, 3H), 3.20 (d, J = 7.4 Hz, 2H), 3.62 (bs, 1H), 3.79 (s, 3H), 5.43 (dtt, J = 15.0, 6.5, 1.4 Hz, 1H), 5.55 (dtt, J = 15.0, 6.5, 1.4 Hz, 1H), 6.13–6.20 (m, 2H), 6.94 (d, J = 7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.69, 22.69, 31.03, 32.21, 34.66, 55.25, 96.26, 104.09, 118.56, 129.13, 130.07, 130.70, 149.03, 158.03; IR (oil/NaCl) 3413 (broad), 2957, 2930, 2872, 2836, 1618, 1516, 1464 cm^{-1}.

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Supplementary Material Available: ^{1}H and ^{13}C NMR spectra of all compounds in the Experimental Section (46 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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Aza-Annulation as a Route To Hydroxylated Alkaloid Lipids. The Synthesis of (±)-Prosopinine.

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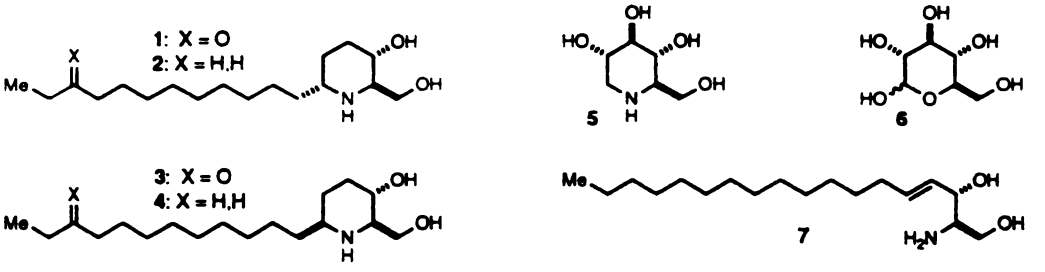
Abstract: The total synthesis of (±)-prosopinine is described. Aza-annulation was used to generate the six-membered nitrogen heterocycle, stereochemical control was achieved through the use of the δ-lactam template, and homologation of the lactam introduced the alkyl chain substituent on the piperidine ring.

Prosopinine (**1**) and prosophylline (**3**) are naturally occurring alkaloids isolated from the leaves of the African mimosa *Prosopis africana* Taub. These intriguing molecules possess a variety of antibiotic and anesthetic properties due to the blend of physiologically important structural features.[1] The polar head group of this class of lipids consists of a piperidine ring with similarities to the alkaloid deoxynorjirimycin (**5**), a potent α-glucosidase inhibitor with demonstrated antitumor activity and inhibition of syncytia formation in HIV-1.[2] Each of these compounds, in turn, have hydroxyl functionality with the same stereochemistry found at C-4 and C-6 of glucose (**6**). The tail portion of naturally occurring **1** and **3** produces a striking resemblance to the membrane lipid sphingosine (**7**). Previous synthetic efforts directed toward the preparation of *Prosopis* alkaloids have resulted in the synthesis of desoxoprosopinine (**2**),[3] prosophylline (**3**),[4] and desoxoprosophylline (**4**).[3a,3b,3e]

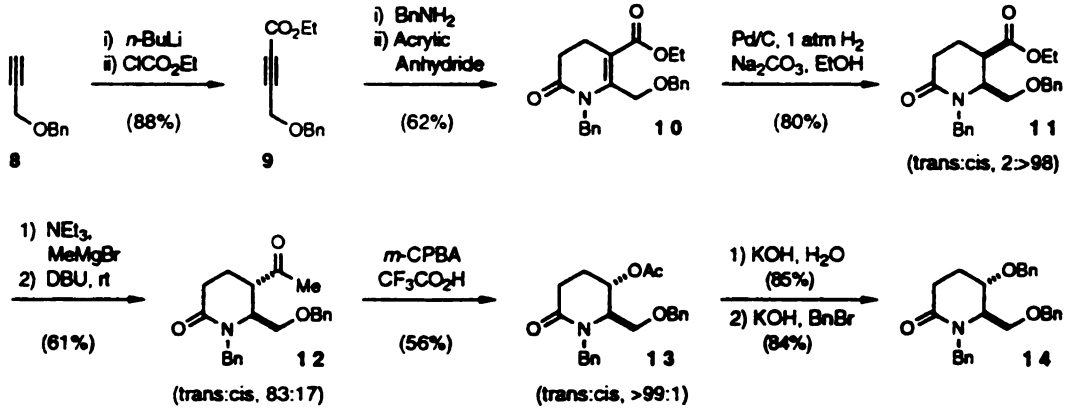


Our approach to the synthesis of prosopinine involved five phases. Of initial importance was the construction of the six-membered nitrogen heterocycle, which involved the synthesis of the corresponding δ-lactam with the use of recently developed aza-annulation methodology.[5] Once prepared, this versatile δ-lactam intermediate served as a framework for the introduction of the correct relative stereochemistry of the -OH and -CH_2OR substituents. The third phase of the synthesis addressed the homologation necessary for the stereochemically controlled transformation of the lactam carbonyl to the alkyl chain substituent. The preparation of the tail portion, and subsequent Wittig coupling of this fragment with the hydroxylated piperidine head group, completed the synthesis.

1670

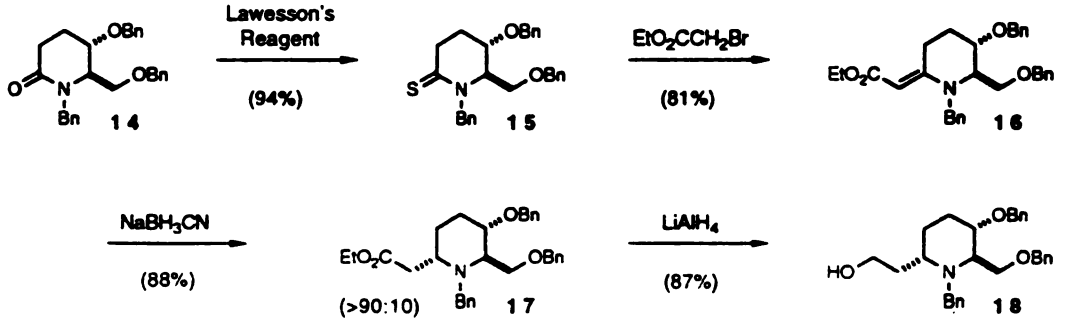
The first facet of this synthesis, the construction of the six-membered nitrogen heterocycle, was accomplished through aza-annulation methodology for the formation of **10** (Scheme I). Deprotonation and ethoxycarboxylation of **8** generated **9**, the substrate required for the two step annulation procedure. Conjugate addition of $BnNH_2$ to **9** produced the corresponding β-enamino ester intermediate, which led to the formation of **10** when treated with acrylic anhydride. Analogous use of acryloyl chloride was less effective for the transformation of **9** to **10** (35%).

Scheme I. Synthesis and Use of The δ-Lactam Template for The Formation of **14**.



The δ-lactam template provided a means through which the relative stereochemistry of the ring substituents could be controlled in the next stage of this synthesis. Catalytic hydrogenation of **10** was performed in the presence of Na_2CO_3, which prevented the deprotection of the hydroxyl group, to stereoselectively give the reduced δ-lactam **11**.[6] Transformation of **11** to **12** was accomplished through the use of $MeMgBr/NEt_3$,[7] and base catalyzed epimerization at the position α to the ketone produced an equilibrium 83:17 trans:cis ratio of **12**. The subsequent Bacyer-Villiger oxidation produced only the trans isomer **13** under these conditions, with efficiency of the reaction directly proportional to the original trans:cis ratio of **12**.[8] Hydrolysis of the acetyl group, followed by benzyl protection of the resultant hydroxyl group, gave **14**.

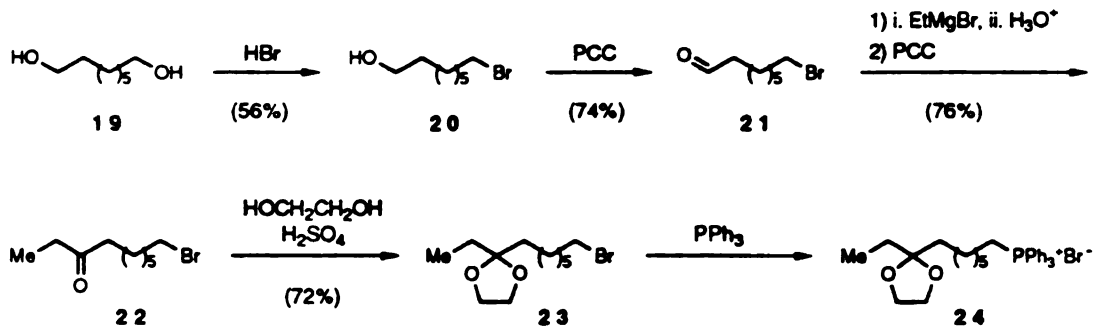
Scheme II. Homologation of The Lactam Carbonyl.



The next segment of this synthesis centered around the homologation of the lactam carbonyl in a stereoselective manner that would accommodate subsequent elaboration of the molecule (Scheme II). Conversion of **14** to the thiolactam **15**,[9] followed by alkylation and Eschenmoser contraction,[10] gave the vinylogous carbamate **16**. Hydride reduction selectively produced **17**, with the stereochemical configuration of **1** rather than **3**, and $LiAlH_4$ reduction of the ester functionality gave **18**.

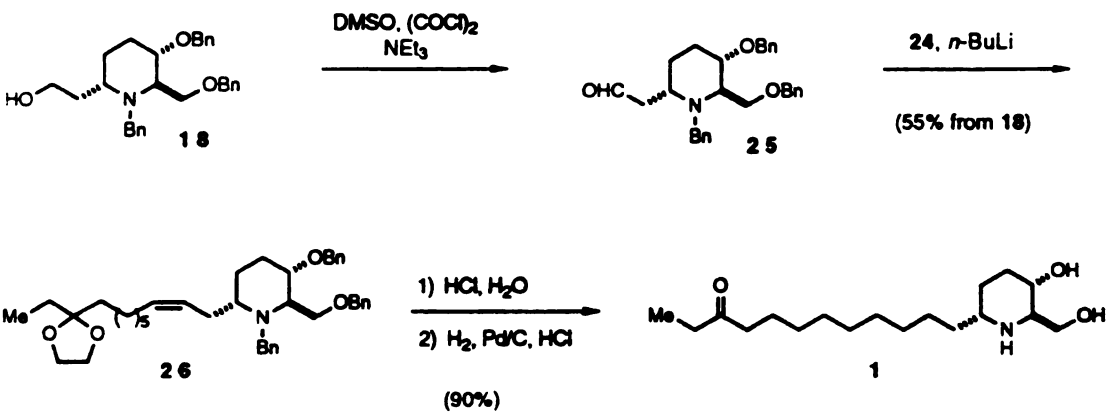
Preparation of the phosphonium salt **24**, required for Wittig coupling with the aldehyde derived from **18**, is illustrated in Scheme III. Monobromination of **19** produced **20**,[11] which was oxidized to the corresponding aldehyde, **21**. Addition of EtMgBr, followed by oxidation gave **22**, which was subsequently protected as dioxolane **23**. Treatment with PPh_3 resulted in generation of the corresponding phosphonium salt **24**.

Scheme III. Synthetic Preparation of the Aliphatic Wittig Reagent.



Extension of the aliphatic chain was performed by Swern oxidation of **18** to **25**, followed by Wittig olefination to give **26** as an 85:15 mixture of cis and trans isomeric alkenes, respectively. The synthesis of prosopinine was completed by deprotection of the carbonyl followed by hydrogenation of the alkene with concomitant removal of the benzyl protecting groups to give **1** in 3% overall yield from **8**.[12]

Scheme IV. Wittig Homologation to Attach the Aliphatic Chain.



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REFERENCES AND NOTES

1. (a) Ratle, G.; Monseur, X.; Das, B.; Yassi, J.; Khuong-Huu, Q.; Goutarel, R. *Bull. Soc. Chim. Fr.* **1966**, 2945, *[CA 66:18779h]*. (b) Bourrinet, P.; Quevauviller, A. *C. R. Soc. Biol.* **1968**, *162*, 1138, *[CA 70:95233k]*. (c) Fr. Patent; FR 1524395 *[CA 71:91733w]*. (d) Bourrinet, P.; Quevauviller, A. *Ann. Pharm. Fr.* **1968**, *26*, 787, *[CA 71:29012g]*. (e) Khuong-Huu, Q.; Ratle, G.; Monseur, X.; Goutarel, R. *Bull. Soc. Chim. Belges* **1972**, *81*, 425. (f) Khuong-Huu, Q.; Ratle, G.; Monseur, X.; Goutarel, R. *Bull. Soc. Chim. Belges* **1972**, *81*, 443.
2. For information on nojirimycin and related hydroxylated piperidines, see the following articles and the references cited within: (a) van den Brock, L. A. G. M.; Vermaas, D. J.; Heskamp, B. M.; van Boeckel, C. A. A.; Tan, M. C. A. A.; Bolscher, J. G. M.; Ploegh, H. L.; van Kemenade, F. J.; de Goede, R. E. Y.; Miedema, F. *Recl. Trav. Chim. Pays-Bas* **1993**, *112*, 82. (b) Fairbanks, A. J.; Carpenter, N. C.; Fleet, G. W. J.; Ramsden, N. G.; de Bello, I. C.; Winchester, B. G.; Al-Daher, S. S.; Nagahashi, G. *Tetrahedron* **1992**, *48*, 3365. (c) Fleet, G. W. J.; Fellows, L. E.; Winchester, B. Plagiarizing Plants: Aminosugars as a Classs of Glycosidase Inhibitors, In: *Bioactive Compounds from Plants*, p 112-125, Wiley, Chichester (Ciba Foundation Symposium 154) **1990**. (d) Legler, G. *Adv. in Carbohydr. Chem. and Biochem.* **1990**, *48*, 319.
3. (a) Saitoh, Y.; Moriyama, Y.; Takahashi, T. *Tetrahedron Lett.* **1980**, *21*, 75. (b) Saitoh, Y.; Moriyama, Y.; Hirota, H.; Takahashi, T.; Khuong-Huu, Q. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 488. (c) Holmes, A. B.; Thompson, J.; Baxter, A. J. G.; Dixon, J. *J. Chem. Soc., Chem. Commun.* **1985**, 37. (d) Ciufolini, M. A.; Hermann, C. W.; Whitmire, K. H.; Byrne, N. E. *J. Am. Chem. Soc.* **1989**, *111*, 3473. (e) Tadano, K.; Takao, K.; Nigawara, Y.; Nishino, E.; Takagi, I.; Maeda, K.; Ogawa *Synlett* **1993**, 565.
4. Natsume, M.; Ogawa, M. *Heterocycles* **1981**, *16*, 973.
5. (a) Paulvannan, K.; Stille, J. R. *J. Org. Chem.* **1992**, *57*, 5319. (b) Paulvannan, K.; Schwarz, J. B.; Stille, J. R. *Tetrahedron Lett.* **1993**, *34*, 215. (c) Paulvannan, K.; Stille, J. R. *Tetrahedron Lett.* **1993**, *34*, 6673.
6. (a) Barth, W.; Paquette, L. A. *J. Org. Chem.* **1985**, *50*, 2438. (b) Kazmierczak, F.; Helquist, P. *J. Org. Chem.* **1989**, *54*, 3988.
7. Kikkawa, I.; Yorifugi, T. *Synthesis* **1980**, 877.
8. Canan Koch, S. S.; Chamberlin, R. *Synth. Commun.* **1989**, *19*, 829.
9. Jain, S.; Sujatha, K.; Rama Krishna, K. V.; Roy, R.; Singh, J.; Anand, N. *Tetrahedron* **1992**, *48*, 4985.
10. (a) Hart, D. J.; Kanai, K. *J. Am. Chem. Soc.* **1983**, *105*, 1255. (b) Hart, D. J.; Hong, W.-P.; Hsu, L.-Y. *J. Org. Chem.* **1987**, *52*, 4665.
11. Kang, S.-K.; Kim, W.-S.; Moon, B.-H. *Synthesis*, **1985**, 1161.
12. The physical data for **1** were consistent with those reported for **1** and **2**,[1,3,4] and were as follows: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05 (t, J = 7.3 Hz, 3 H), 1.23-1.41 (m, 13 H), 1.44-1.61 (m, 5 H), 1.66 (m, 1 H), 1.74 (m, 1 H), 2.07 (bs, 3 H), 2.39 (t, J = 7.5 Hz, 2 H), 2.41 (q, J = 7.3 Hz, 2 H), 2.76 (m, 1 H), 2.87 (dt, J = 5.5, 7.7 Hz, 1 H), 3.53 (ddd, J = 4.0, 5.6, 6.9 Hz, 1 H), 3.61 (dd, J = 5.4, 10.5 Hz, 1 H), 3.65 (dd, J = 7.8, 10.5 Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 7.8, 23.9, 26.3, 27.4, 28.6, 29.2, 29.3, 29.4, 29.6, 33.9, 35.8, 42.4, 49.7, 58.1, 62.3, 68.1, 212.0.

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Construction of Hydroxylated Alkaloids (±)-Mannonolactam, (±)-Deoxymannojirimycin, and (±)-Prosopinine through Aza-Annulation

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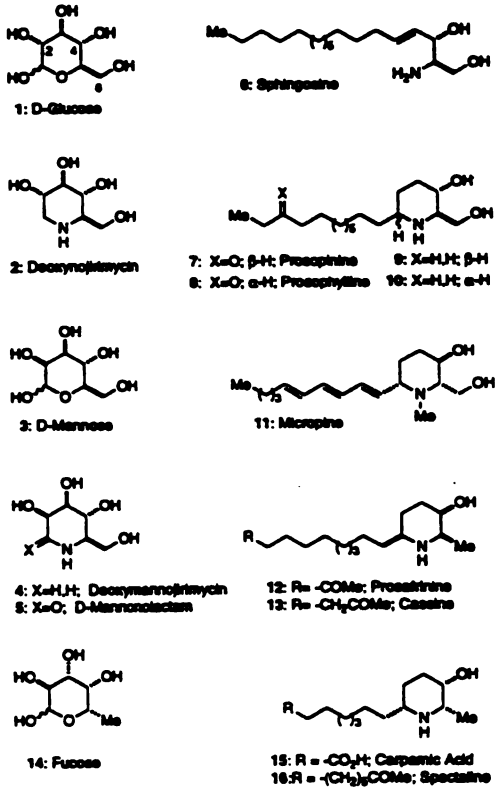
The aza-annulation of β-enamino carbonyl substrates with acrylate derivatives provides an efficient and convenient route for the regioselective construction of δ-lactams. This two-step ring-forming sequence involved initial generation of the benzyl enamine through either a condensation or conjugate addition reaction with $BnNH_2$, followed by aza-annulation with acryloyl chloride or acrylic anhydride. Controlled by the rigid framework of the intermediate lactam, introduction of ring substituents was accomplished with high relative stereoselectivity. The carbonyl functionality, which was necessary to direct the regioselectivity of the aza-annulation reaction, was then transformed into a protected hydroxyl substituent through Baeyer–Villiger oxidation. The resultant δ-lactam product was used as a valuable intermediate in the synthesis of three natural products. Subsequent modification of this δ-lactam gave the naturally occurring α-mannosidase inhibitors (±)-mannonolactam and (±)-deoxymannojirimycin, while synthesis of the alkaloid (±)-prosopinine was accomplished through homologation of the lactam carbonyl.

Introduction

Hydroxylated piperidine alkaloids are found frequently in living systems,[1] and the wide range of potent physiological effects stems from their ability to mimic carbohydrate substrates in a variety of enzymatic processes.[2] With the pivotal role that carbohydrates play in biological processes such as cell recognition and differentiation, these alkaloids have become important synthetic targets.[3] Important structure–activity relationships for these molecules center around the stereochemical configuration of hydroxyl functionality which are β to the nitrogen. Due to the prominance of D-glucose (1) and D-mannose (3) in biological processes, many alkaloids mimic the C-4 and C-6 structural features of these carbohydrates (Chart 1).

Polyhydroxylated piperidine alkaloids exhibit selective inhibition of a number of biologically important pathways, including the binding and processing of glycoproteins.[4] For example, compound 4 has been shown to inhibit α-L-fucosidase, α-D-mannosidase, and α-D-glucosidase activity,[5] while the analogous lactam 5 inhibited both α-D-mannosidase and α-D-glucosidase.[5a] The piperidine alkaloid 2 has exhibited selective inhibition of α-glucosidases I and II without effective inhibition of α-mannosidase,[2,7] and this glucose analog has potential for use in the therapy

Chart 1



[a] Abstract published in *Advance ACS Abstracts*, Xxxxxxxxx YY, ZZZZ.

(1) or reviews that include piperidine alkaloids, see: (a) Wang, C.-L. J.; Wuonola, M. A. *Org. Prep. Proc. Int.* **1992**, *24*, 585. (b) Pinder, A. R. *Nat. Prod. Rep.* **1992**, *9*, 491. (c) Pinder, A. R. *Nat. Prod. Rep.* **1992**, *9*, 17. (d) Pinder, A. R. *Nat. Prod. Rep.* **1990**, *7*, 447. (e) Numata, A.; Ibuka, T. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1987; Vol. 31, Chapter 6. (f) Fodor, G. B.; Colasanti, B. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1985; Vol. 3, Chapter 1.

(2) or more specific information on hydroxylated piperidines, see the following articles and the references cited within: (a) van den Broek, L. A. G. M.; Vermaas, D. J.; Heskamp, B. M.; van Boeckel, C. A. A.; Tan, M. C. A. A.; Boland, J. G. M.; Plough, H. L.; van Kemenade, F. J.; de Goede, R. E. Y.; Miedema, F. *Recl. Trav. Chim. Pays-Bas* **1993**, *112*, 82. (b) Winchester, B.; Fleet, G. W. J. *Glycobiology* **1992**, *2*, 199. (c) Fairbanks, A. J.; Carpenter, N. C.; Fleet, G. W. J.; Ramsden, N. G.; Cenci de Bello, I.; Winchester, B. G.; Al-Daher, S. S.; Nagahashi, G. *Tetrahedron* **1992**, *48*, 3365. (d) Fleet, G. W. J.; Fellows, L. E.; Winchester, B. Plagiarizing Plants: Aminosugars as a Class of Glycosidase Inhibitors In *Bioactive Compounds from Plants*; Wiley: Chichester (Ciba Foundation Symposium 154), 1990; pp 112–125. (e) Legler, G. *Adv. Carbohydr. Chem. Biochem.* **1990**, *48*, 319.

(3) a) Sharon, N.; Lis, H. *Sci. Am.* **1993**, *268*, 82. (b) Sharon, N.; Lis, H. *Science* **1989**, *246*, 227. (c) Karlsson, K.-A. *Trends Pharm. Sci.* **1991**, *12*, 265.

(4) Ibsen, A. D. *Ann. Rev. Biochem.* **1967**, *56*, 497.

0022-3263/xx/1900-0001$04.50/0

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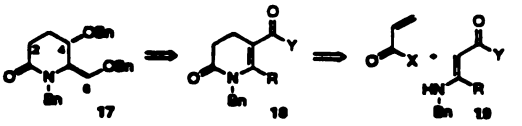
of diabetes mellitus, hyperlipoproteinemia, cancer, and arthritis.[8] Interestingly, when compared to 2, synthetic derivatives such as *N*-butyl-2 and *N*-decyl-2 show pronounced antiviral activity through inhibition of syncytia formation in HIV-1.[2a,9]

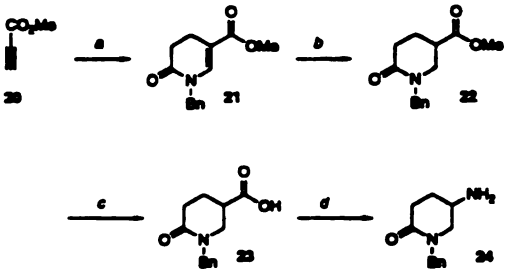
Naturally occurring heterocyclic amines with long aliphatic appendages, such as the *Prosopis* (7 and 8) and *Cassia* alkaloids (12, 13, 15, and 16), have also been reported.[1] These compounds are found throughout the world and have received increasing attention as medicinal agents due to the variety of pharmacological properties they exhibit.[10] The *Prosopis* alkaloids 7 and 8 are particularly intriguing because they contain a blend of physiologically important structural features.[11] At one end of the molecule is the polar head group with a configuration of hydroxyl substituents similar to that found in 2 and 4, while a lipophilic tail portion resembles that of the membrane lipid sphingosine (6). Similar mixtures of alkyl chain "tail" and carbohydrate "head" structural features are found in penaresidines A and B, which display potent ATPase-activating properties, and BAY R 1005, which shows promise for immunization of patients with defective T-lymphocytes such as patients with AIDS.[12] In each of these molecules, the alkyl chain serves to (1) facilitate transfer across membranes, (2) anchor the active compound in the membrane with the polar portion protruding, or (3) interact with the hydrophobic portion of the enzymes to which these compounds bind.

Our approach to the construction of several hydroxylated piperidines utilized the aza-annulation reaction for efficient construction of nitrogen heterocycle 18 from β-enamino carbonyl derivative 19 (Scheme 1).[13] The heterocycle was then used as a framework to control the relative stereochemistry of the C-4 and C-5 ring substituents in the generation of 17.[14] From this versatile intermediate, the naturally occurring alkaloids (±)-mannonolactam (5), (±)-deoxymannojirimycin (4), and (±)-prosopinine (7) were prepared.

Scheme 1. General Approach for Formation of δ-Lactams by Aza-Annulation/Hydrogenation



Scheme 2. Heterocycle Formation through Conjugate Addition/Aza-Annulation[a]



[a] Reagents and conditions: (a) (i) $BnNH_2$, C_6H_6, rt, (ii) acryloyl chloride, THF, 66 °C (53%); (b) 3 atm of H_2, PdC, EtOH (86%); (c) (i) NaOH, H_2O, (ii) HCl, H_2O (90%); (d) (i) DPPA, NEt_3, *t*-BuOH, (ii) HCl, (iii) NaOH, H_2O (24%).

Results and Discussion

Method Development. The use of ketone and ester functionality as electron-withdrawing substituents was found to significantly enhance the efficiency and selectivity of the aza-annulation reaction (Scheme 1; Y = Me, OEt).[13] However, several key transformations were required to adapt this methodology to the synthesis of hydroxylated alkaloids. Of initial importance was the need for additional methods of enamine preparation that were compatible with the subsequent aza-annulation reaction. In conjunction with these studies, aza-annulation was explored as a route to 19 in which R ≠ Me, followed by subsequent stereoselective introduction of the C-5 substituent. In addition, methods for conversion of the C-4 carbonyl substituent to a hydroxyl group and homologation of the resulting lactam carbonyl were required.

One approach to the desired δ-lactam products involved the combination of three fragments, an acetylenic ester, a primary amine, and an acrylate derivative, to produce the desired heterocycles (Scheme 2). Conjugate addition of $BnNH_2$ to 20 generated the intermediate β-enamino ester, which gave the corresponding six-membered nitrogen heterocycle 21 upon aza-annulation with acryloyl chloride. A variety of reagents, which included $Me_2CuCNLi_2$, $Me_2CuCNLi_2/BF_3$-OEt_2, $Me_2CuBrLi_2$, and $MeCu$-BF_3, were employed for possible introduction of a methyl substituent

(5) a) Fuhrmann, U.; Bause, E.; Legler, G.; Ploegh, H. *Nature* **1984**, *307*, 755. (b) Elbein, A. D.; Legler, G.; Tlusty, A.; McDowell, W.; Schwarz, R. *Arch. Biochem. Biophys.* **1984**, *235*, 579. (c) Legler, G.; Jülich, E. *Carbohydr. Res.* **1984**, *128*, 61. (d) Niwa, T.; Tsuruoka, T.; Goi, H.; Kodama, Y.; Itoh, J.; Inouye, S.; Yamada, Y.; Niida, T.; Nobe, M.; Ogawa, Y. *J. Antibiot.* **1984**, *37*, 1579. (e) Evans, S. V.; Fellows, L. E.; Shing, T. K. M.; Fleet, G. W. J. *Phytochemistry* **1985**, *24*, 1953.

(6) a) Ishida, N.; Kumagai, K.; Niida, T.; Hamamoto, K.; Shomura, T. *J. Antibiotics* **1967**, *A20*, 62. (b) Inouye, S.; Tsuruoka, T.; Ito, T.; Niida, T. *Tetrahedron* **1968**, *24*, 2125.

(7) a) Niwa, T.; Inouye, S.; Tsuruoka, T.; Koaze, Y.; Niida, T. *Agric. Biol. Chem.* **1970**, *34*, 966. (b) Truscheit, E.; Frommer, W.; Junge, B.; Müller, L.; Schmidt, D. D.; Wingender, W. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 744. (c) Fuhrmann, U.; Bause, E.; Ploegh, H. *Biochim. Biophys. Acta* **1983**, *825*, 95. (d) Murao, S.; Miyata, S. *Agric. Biol. Chem.* **1980**, *44*, 219. (e) Fellows, L. E. *Chem. Br.* **1987**, *23*, 842.

(8) trumb. A.; Effenberger, F.; Fischer, P. *J. Org. Chem.* **1990**, *55*, 3026 and references cited therein.

(9) arpea, A.; Fleet, G. W. J.; Dwek, R. A.; Petursson, S.; Namgoong, S. K.; Ramsden, N. G.; Jacob, G. S.; Rademacher, T. W. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 9229.

(10) base compounds are found in Africa (8), Pakistan (juliflorimine), Philippines (11), and South America (13); they exhibit a variety of pharmacological properties (prosopinine (7) and prosopine: anesthetic, analgesic, and antibiotic activities;[11] carpaine, the macrolactone dimer of 15: antituberculotic and antitumor activity, effects on the brain and cardiovascular system, hemolytic effects, and hypotensive effects).[1]

(11) a) Fr. Pat. FR 1524395; *Chem. Abstr.* **1969**, *71*, 91733w. (b) Bourrinet, P.; Quevauviller, A. *Ann. Pharm. Fr.* **1968**, *26*, 787; *Chem. Abstr.* **1969**, *71*, 29012g. (c) Bourrinet, P.; Quevauviller, A. *C. R. Soc. Biol.* **1968**, *162*, 1138; *Chem. Abstr.* **1969**, *70*, 95233K.

(12) a) Penaresidine A and B: Kobayashi, J.; Cheng, J.-F.; Ishibashi, M.; Wälchli, M. R.; Yamamura, S.; Ohizumi, Y. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1135. (b) BAY R 1005: Lockhoff, O. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1611.

(13) a) Paulvannan, K.; Stille, J. R. *J. Org. Chem.* **1992**, *57*, 5319. (b) Paulvannan, K.; Schwarz, J. B.; Stille, J. R. *Tetrahedron Lett.* **1993**, *34*, 215. (c) Paulvannan, K.; Stille, J. R. *Tetrahedron Lett.* **1993**, *34*, 6673. (d) Paulvannan, K.; Stille, J. R. *J. Org. Chem.* **1994**, *59*, 1613. (e) Paulvannan, K.; Stille, J. R. *Tetrahedron Lett.* **1993**, *34*, 8197.

(14) or continuity, the carbohydrate numbering system was used in this manuscript when referring to the pyridones.

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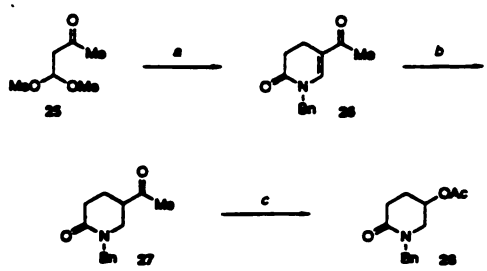
Scheme 3. Formation and Oxidation of 27[a]



[a] Reagents and conditions: (a) (i) H_2O, TsOH, C_6H_6, (ii) $BnNH_2$, C_6H_6, 80 °C, (iii) acryloyl chloride, THF, 66 °C (23%); (b) 1 atm of H_2, Pd/C, EtOH (87%); (c) CF_3CO_3H, *m*-CPBA (89%).

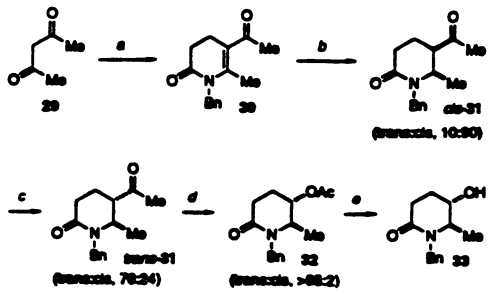
β to the ester, but conjugate addition to the vinylogous carbamate 21 was not observed.[15]

In order to explore modification of the carboxyl substituent at C-4, 21 was reduced through catalytic hydrogenation to give 22, and selective hydrolysis of the ester produced the corresponding β-amino acid derivative 23. Attempts at oxidative decarboxylation with the use of established methods were not successful for selective introduction of the C-4 hydroxyl due to the formation of complex product mixtures.[16] However, a similar oxidative procedure for introduction of an amino group resulted in partial success. Treatment of 23 with DPPA/NEt_3 in *t*-BuOH, followed by hydrolysis of the intermediate *tert*-butylcarbamate, provided amine 24 in low yield.[17] Optimization of this transformation was not pursued.

Related studies were performed with the corresponding methyl ketone derivative 26 (Scheme 3). Hydrolysis of 25 produced the corresponding aldehyde, which was condensed with $BnNH_2$ and treated with acryloyl chloride to give 26. The low yield obtained for this three-step process resulted from self-condensation of the intermediate aldehyde. As found for 21, conjugate addition of nucleophiles to vinylogous imide 26 did not proceed under established conditions.[14] Baeyer–Villiger oxidation of 27 to 28 generated very promising results for the introduction of an oxygen substituent at C-4.[18] However, the inability to introduce substituents at the position β to the ester or ketone group required that the C-5 substituent be in place prior to aza-annulation.

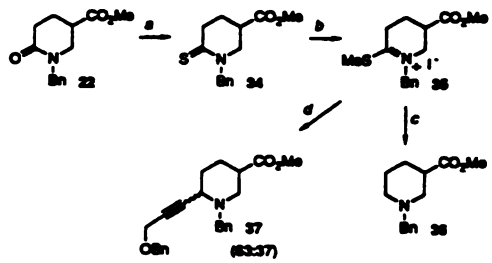
As previously reported,[13d] 29 was condensed with $BnNH_2$ and treated with acryloyl chloride to produce the corresponding aza-annulation product 30, and catalytic hydrogenation generated 31 as a 10:90 mixture of trans and cis isomers (Scheme 4).[19] In order to access alkaloids 12 and 16, a variety of conditions were used to affect the desired Baeyer–Villiger oxidation of *cis*-31.[18] However, 32 was the only acetate derivative generated under these conditions. Epimerization of 31, by treatment with DBU, generated an equilibrium ratio of trans/cis isomeric products (76:24), and oxidation of this predominantly trans substrate mixture resulted in the formation of 32 in 45% yield. When compared to the successful oxidation of 27, steric constraints imposed by the cis methyl substituent prevented efficient Baeyer–Villiger oxidation of *cis*-31, while *trans*-31 was transformed to the corresponding ester. Hydrolysis of the acetate resulted in deprotection of the hydroxyl group to generate 33.

Scheme 4. Formation and Oxidation of 31[a]



[a] Reagents and conditions: (a) (i) $BnNH_2$, C_6H_6, 80 °C, (ii) acryloyl chloride, THF, 66 °C (94%); (b) 1 atm of H_2, Pd/C, Na_2CO_3, EtOH (81%); (c) DBU; (d) CF_3CO_3H, *m*-CPBA (45%); (e) NaOH, H_2O (74%).

Scheme 5. Homologation of the Lactam Carbonyl[a]



[a] Reagents and conditions: (a) Lawesson's reagent (90%); (b) MeI; (c) (i) $PrMgBr$, (ii) $NaBH_4$, (72% from 34); (d) (i) $BnOCH_2C{\equiv}CLi$, (ii) $NaBH_4$ (45%) from 34).

The final stage of method development focused on homologation of the lactam carbonyl, which was necessary in order to append lipophilic tail segments to the alkaloid portion of these molecules. Initial studies of lactam carbonyl homologation were performed with 22 (Scheme 5). Lawesson's reagent provided an extremely efficient method for the transformation of 22 to thiolactam 34, and subsequent *S*-methylation generated the corresponding imidate salt 35.[20] Treatment of 35 with a carbon nucleophile, to generate the intermediate iminium species,

(15) a) ($Me_2CuCNLi_2$) Dodd, D. S.; Oehlschlager, A. C. *Tetrahedron Lett.* **1991**, *32*, 3643. (b) ($Me_2CuBrLi_2$) Bertz, S. H.; Dabbagh, G. *Tetrahedron* **1989**, *45*, 425. (c) Lipshutz, B. H. *Synthesis* **1987**, 325. (d) ($MeCu\cdot BF_3$) Yamamoto, Y.; Yamamoto, S.; Yatagai, H.; Ishihara, Y.; Maruyama, K. *J. Org. Chem.* **1982**, *47*, 119. (e) ($Me_2CuCNLi_2$) Lipshutz, B. H.; Wilhelm, R. S.; Floyd, D. M. *J. Am. Chem. Soc.* **1981**, *103*, 7672.

(16) a) Fang, F. G.; Danishefsky, S. J. *Tetrahedron Lett.* **1989**, *30*, 3621. (b) Kienzle, F.; Holland, G. W.; Jernow, J. L.; Kwoh, S.; Rosen, P. *J. Org. Chem.* **1973**, *38*, 3440. (c) Barton, D. H. R.; Costen, I. H.; Sammes, P. G. *J. Chem. Soc., Perkin Trans. I* **1973**, 599. (d) Denney, D. B.; Sherman, N. *J. Org. Chem.* **1965**, *30*, 3760.

(17) a) Mostowicz, D.; Belzecki, C.; Chmielewski, M. *Synthesis* **1991**, 273. (b) Sato, M.; Katagiri, N.; Takayama, K.; Hirose, M.; Kaneko, C. *Chem. Pharm. Bull.* **1989**, *37*, 665. (c) Eaton, P. E.; Ravi Shankar, B. K.; Price, G. D; Pluth, J. J.; Gilbert, E. E.; Alster, J. Sandus, O. *J. Org. Chem.* **1984**, *49*, 185. (d) Hanfliger, W.; Klöppner, E. *Helv. Chim. Acta.* **1982**, *65*, 1837. (e) Chantegrel, B.; Gelin, S. *Synthesis* **1981**, 315.

(18) a) Canan Koch, S. S.; Chamberlin, R. *Synth. Commun.* **1989**, *19*, 829. (b) Wilson, S. R.; Di Grandi, M. J. *J. Org. Chem.* **1991**, *56*, 4766. (c) Suginome, H.; Yamada, S. *J. Org. Chem.* **1985**, *50*, 2489. (d) Baxter, A. J. G.; Holmes, A. B. *J. Chem. Soc., Perkin Trans. I* **1977**, 2343. (e) Narasaki, K.; Sakakura, T.; Uchimaru, T.; Guédin-Vuong, D. *J. Am. Chem. Soc.* **1984**, *106*, 2954.

(19) he addition of Na_2CO_3 produced optimum results for cis selectivity, and prevented the removal of the benzyl protection of hydroxyl groups, when present. (a) Barth, W.; Paquette, L. A. *J. Org. Chem.* **1968**, *50*, 2438. (b) Kazmierczak, F.; Heiquist, P. *J. Org. Chem.* **1989**, *54*, 3968.

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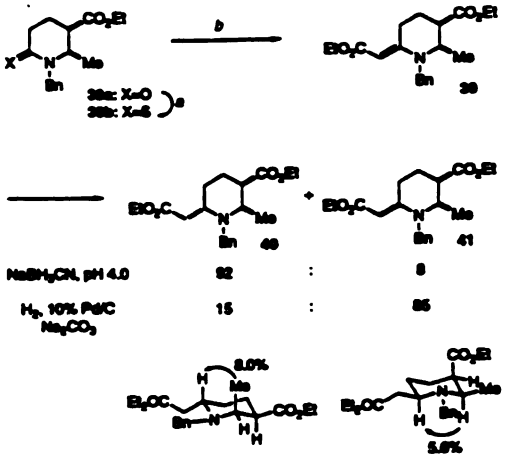
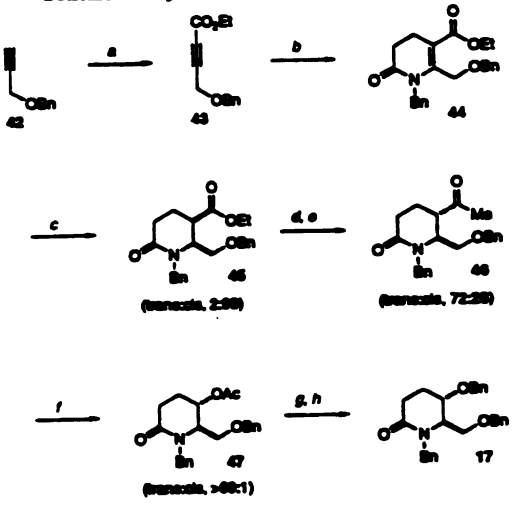
Scheme 6. Homologation of 38[a]



[a] Reagents and conditions: (a) Lawesson's reagent (80%); (b) (i) EtO_2CCH_2Br, (ii) NEt_3, PPh_3 (79%).

Scheme 7. Synthesis of Intermediate 17[a]



[a] Reagents and conditions: (a) (i) BuLi, (ii) $ClCO_2Et$, (88%); (b) (i) $BnNH_2$, THF, 66 °C, (ii) acrylic anhydride, THF, 66 °C (62%); (c) 1 atm of H_2, Pd/C, Na_2CO_3, EtOH (80%); (d) NEt_3, MeMgBr; (e) DBU (68%, 2 steps from 45); (f) CF_3CO_3H, *m*-CPBA (56%); (g) KOH, H_2O (85%); (h) KOH, BnBr (84%).

followed by $NaBH_4$ reduction, was used as a strategy for homologation of this system. With the use of PrMgBr, the reaction conditions resulted in formation of 36 as the only reaction product. In contrast, the addition of an acetylide followed by treatment with $NaBH_4$ gave 37 as a 63:37 ratio of diastereomers in 45% yield, with the balance of the substrate converted to 36.[21] Unfortunately, extension of this methodology to the homologation of the methyl-substituted derivative 38a was not effective.

An alternative route for carbonyl homologation of 38a was explored through the Eschenmoser contraction/sulfide extrusion procedure.[22] Thiolactam formation of 38b and alkylation with ethyl bromoacetate generated the corresponding thioimidate salt, and subsequent contraction/sulfide extrusion produced the corresponding vinylogous carbamate 39 (Scheme 6). Homologation of 38a through this sequence provided an efficient and attractive route to 39 as a single isomer. On the basis of steric constraints, this isomer was designated as the corresponding *E* alkene isomer. Reduction with $NaBH_3CN$ transformed 39 to a mixture of diastereomers 40 and 41, in a ratio of 92:8, while catalytic hydrogenation provided the complementary 15:85 ratio of these products.[23] Stereochemical assignments of 40 (8.0% enhancement) and 41 (5.6% enhancement) were established through NMR NOE techniques on each isomer by irradiation of the H and Me substituents α to the nitrogen (Scheme 6).

Applications to Alkaloid Synthesis. With the model studies complete for both construction and elaboration of 17, two separate approaches to 17 were explored in which different substrates for enamine formation were used. The first approach to 17 involved the conjugate addition of $BnNH_2$ for generation of the β-enamino ester species required for aza-annulation (Scheme 7).[24] The reaction of $BnNH_2$ with 43, prepared by deprotonation and ethoxycarboxylation of 42, led to the corresponding β-enamino ester intermediate.[25] Treatment with acrylic anhydride resulted in aza-annulation to generate 44 in 62% yield for the two-step process, while the use of acryloyl chloride produced less favorable results for this transformation (35% yield). Catalytic hydrogenation of 44 in the presence of Na_2CO_3 stereoselectively generated 45 without deprotection of the hydroxyl group,[19] and treatment with NEt_3 followed by MeMgBr gave the corresponding methyl ketone (46) as a 2:98 ratio of trans/cis products.[26] Base-catalyzed epimerization changed the trans/cis ratio to 72:28, and Baeyer–Villiger oxidation under optimized conditions gave 47 as a single diastereomer. Deprotection of the secondary hydroxyl group, followed by benzylation, provided the desired intermediate 17.

An alternative route to 17 involved condensation of $BnNH_2$ with tetronic acid (48) to form the required β-enamino ester intermediate (Scheme 8). Subsequent aza-annulation with acrylic anhydride (71%) or acryloyl chloride (70%) resulted in formation of the corresponding δ-lactam 49. Catalytic hydrogenation generated the cis-fused bicyclic system 50, and conversion of the lactone to methyl ketone 51 (2:>98, trans/cis) was performed under the same conditions used for the transformation of 45 to 46. Benzylation of the hydroxyl group under basic conditions resulted in formation of an equilibrium mixture

(20) sin, S.; Sujatha, K.; Rama Krishna, K. V.; Roy, R.; Singh, J.; Anand, N. *Tetrahedron* **1992**, *48*, 4985.

(21) a) Takahata, H.; Takahashi, K.; Wang, E.-C.; Yamazaki, T. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1211. (b) Tominaga, Y.; Kohra, S.; Hosomi, A. *Tetrahedron Lett.* **1987**, *28*, 1529.

(22) a) Hart, D. J.; Kanai, K. *J. Am. Chem. Soc.* **1983**, *105*, 1255. (b) Hart, D. J.; Hong, W.-P.; Hsu, L.-Y. *J. Org. Chem.* **1987**, *52*, 4665.

(23) ydrogenation of 39 at 1 atm H_2 only proceeded to ~50% conversion after 48 h. The crude products consisted of a mixture of 39, 40, and 41 (15:85, respectively), and a small amount of the *N*-debenzylated analog. Reduction at higher pressures (3 atm) resulted in nearly complete removal of the *N*-benzyl group and gave the deprotected analogs of 40 and 41 in the same 15:85 ratio, respectively.

(24) ook, G. R.; Beholz, L. G.; Stille, J. R. *Tetrahedron Lett.* **1994**, *35*, 1669.

(25) nalogous acylation of 42 with acetyl chloride, followed by conjugate addition of $BnNH_2$ in an attempt to access 44 by a more direct route, generated a mixture of both possible β-enamino ketone regioisomers.

(26) ikawa, I.; Yorifuji, T. *Synthesis* **1980**, 877.

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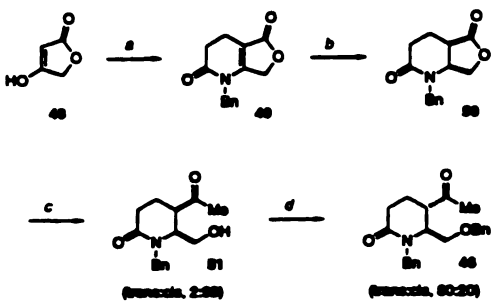
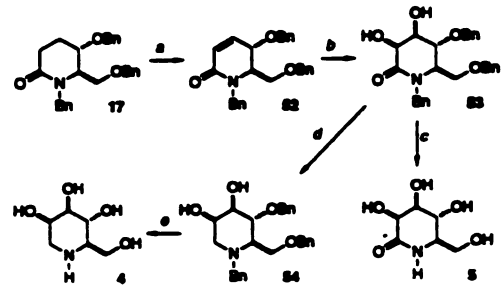
Scheme 8. Conversion of 48 to 46[a]



[a] Reagents and conditions: (a) (i) $BaNH_2$, C_6H_6, 80 °C, (ii) acrylic anhydride, THF, 66 °C (71%); (b) 1 atm of H_2, Pd/C, Na_2CO_3, EtOH (83%); (c) NEt_3, MeMgBr (27%); (d) KOH, BnBr (71%).

Scheme 9. Synthesis of Deoxymannojirimycin (4) and Mannolactam (5)[a]



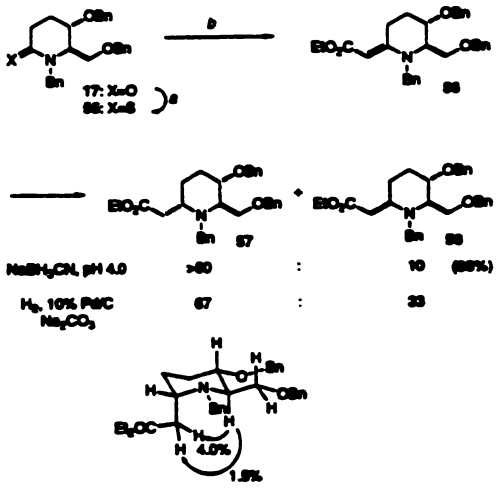
[a] Reagents and conditions: (a) (i) LDA, (ii) PhSeCl, (iii) $NaIO_4$ (78%); (b) OsO_4, NMO (64%); (c) Li/NH_3 (44%); (d) (i) $LiAlH_4$, (ii) NaOH, H_2O (>98%); (e) 1 atm of H_2, Pd/C, MeOH (52%).

of 46 (80:20, trans/cis). Although methods for a more efficient transformation of 50 to 51 were not fully pursued, this synthetic scheme provided an alternative route to 46, and ultimately to 17.

(±)-Mannonolactam (5) and (±)-Deoxymannojirimycin (4). The conversion of 17 to the tetrahydroxylated derivatives 4 and 5 was accomplished by introduction of the cis hydroxyl substituents through OsO_4 dihydroxylation (Scheme 9). Treatment of the anion of 17 with PhSeCl, followed by periodate oxidation and elimination of selenic acid, produced the α,β-unsaturated species 52.[27] Dihydroxylation gave 53, which was used for the syntheses of both 4 and 5.[28] Removal of the benzyl protecting groups from 53 generated 5 in 44% yield after recrystallization.[29] Stepwise reduction of the lactam carbonyl followed by deprotection with catalytic hydrogenation gave 4 in 52% yield, and white crystalline material was obtained in 33% yield after recrystallization.[30] Overall, the syntheses of 4 and 5 were both achieved in 3% overall yield from 42.

(±)-Prosopinine. Two representative *Prosopis* alkaloids, 7 and 8, isolated from the leaves of the African mimosa *Prosopis africana* Taub,[31] differ only in the stereochemistry of the carbon at which the alkyl chain and the heterocycle are connected. Although the synthesis of 7 has not been reported, synthetic efforts have resulted in the construction of desoxoprosopinine (9),[32] prosophylline (8),[33] and desoxoprosophylline (10).[32a,b,c] Due to the diastereomeric relationship of prosopinine (7) and prosophylline (8), our approach to the synthesis of these molecules was designed around the control of stereochemistry during homologation of the lactam. As observed during formation of 40 and 41, stereochemical control was a function of the reagent used for reduction of the iminium ion generated from 39 (Scheme 6).

Scheme 10. Homologation of 17[a]



[a] Reagents and conditions: (a) Lawesson's reagent (94%); (b) (i) EtO_2CCH_2Br, (ii) NEt_3, PPh_3 (81%).

Homologation of the lactam carbonyl of 17 was performed in the same manner described for 38 (Scheme 6).[34] Formation of the thiolactam, followed by the Eschenmoser contraction/sulfide extrusion procedure, gave 56 in good overall yield (Scheme 10).[22] Hydride reduction of 56 selectively produced 57 in a >90:10 ratio of the two possible diastereomers, with the stereochemistry of the major product similar to that of 7. In contrast to the results observed for 38, catalytic hydrogenation of 56 also produced 57 as the major diastereomer. In this case, lower product selectivity was obtained (67:33, 57/58), and selective formation of 58, the intermediate related in structure to 8, was not accomplished.

The final stages of the prosopinine synthesis required extension of the chain through Wittig methodology

(27) a) Clive, D. L. J. *Tetrahedron* **1978**, *34*, 1049. (b) Reich, H. J. *Acc. Chem. Res.* **1979**, *12*, 22.

(28) a) Nishiyama, S.; Yamamura, S.; Hasegawa, K.; Sakoda, M. Harada, K. *Tetrahedron Lett.* **1991**, *32*, 6753. (b) Guillerm, G.; Varkadas, M.; Auvin, S.; Le Goffic, F. *Tetrahedron Lett.* **1987**, *28*, 535.

(29) he physical data for 4 were consistent with those reported: Fleet, G. W. J.; Ramsden, N. G.; Witty, D. R. *Tetrahedron* **1989**, *45*, 319.

(30) he physical data for 5 were consistent with those reported:[29] Fleet, G. W. J.; Ramsden, N. G.; Witty, D. R. *Tetrahedron* **1989**, *45*, 327.

(31) a) Ratle, G.; Monsour, X.; Das, B. C.; Yassi, J.; Khuong-Huu, Q.; Goutarel, R. *Bull. Soc. Chim. Fr.* **1966**, 2945. (b) Khuong-Huu, Q.; Ratle, G.; Monsour, X.; Goutarel, R. *Bull. Soc. Chim. Belg.* **1972**, *81*, 425. (c) Khuong-Huu, Q.; Ratle, G.; Monsour, X.; Goutarel, R. *Bull. Soc. Chim. Belg.* **1972**, *81*, 443.

(32) a) Saitoh, Y.; Moriyama, Y.; Takahashi, T.; Khuong-Huu, Q. *Tetrahedron Lett.* **1980**, *21*, 75. (b) Saitoh, Y.; Moriyama, Y.; Hirota, H.; Takahashi, T.; Khuong-Huu, Q. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 488. (c) Holmes, A. B.; Thompson, J.; Baxter, A. J. G.; Dixon, J. *J. Chem. Soc., Chem. Commun.* **1985**, 37. (d) Cimfolini, M. A.; Hermann, C. W.; Whitmire, K. H.; Byrne, N. E. *J. Am. Chem. Soc.* **1989**, *111*, 3473. (e) Tadano, K.; Takao, K.; Nigawara, Y.; Nishimo, E.; Takagi, I.; Maeda, K.; Ogawa *Synlett* **1993**, 565.

(33) atsuma, M.; Ogawa, M. *Heterocycles* **1981**, *16*, 973.

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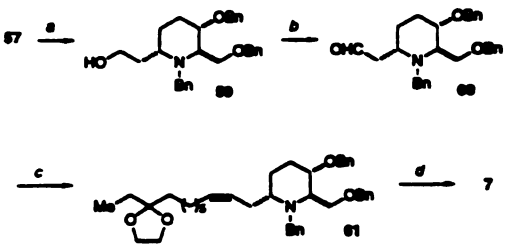
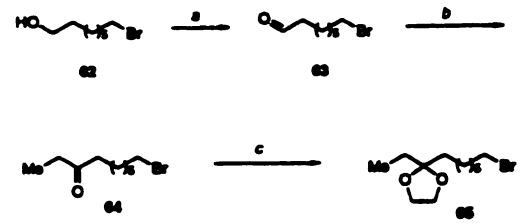
Scheme 11. Conversion of 57 to 7[a]



[a] Reagents and conditions: (a) (i) $LiAlH_4$, (ii) NaOH (87%); (b) DMSO, $(COCl)_2$, NEt_3; (c) 68, PPh_3, *n*-BuLi (55% from 59); (d) (i) HCl, H_2O, (ii) 3 atm of H_2, Pd/C, HCl (90%).

Scheme 12. Preparation of 65[a]



[a] Reagents and conditions: (a) PCC, CH_2Cl_2 (74%); (b) (i) EtMgBr, (ii) H_3O^+, (iii) PCC, CH_2Cl_2 (76% from 63); (c) $HOCH_2CH_2OH$, H_2SO_4 (72%).

(Scheme 11). Further reduction of 57 generated 59, which was then partially oxidized to the corresponding aldehyde 60. Chain extension of 60 with the ylide formed from 65 (Scheme 12) gave 61 as a 15:85 mixture of trans/cis alkene isomers on the alkyl appendage. Deprotection of the carbonyl, followed by reduction of the alkene and debenzylation during hydrogenation, gave 7 in 3% overall yield from 42.[34]

Summary. The aza-annulation of β-enamino ketone and ester substrates with either acryloyl chloride or acrylic anhydride has provided an efficient and convenient route for the regioselective construction of δ-lactams. This annulation procedure was performed in tandem with two different methods for enamine generation, through conjugate addition of $BnNH_2$ to an α,β-acetylenic ester or by condensation of $BnNH_2$ with a β-keto ester or ketone to form the desired δ-lactam. Once established, the δ-lactam framework was used to control the stereochemical preference of substituents on the ring, and the carbonyl functionality was transformed into a protected hydroxyl substituent. From δ-lactam 17, the naturally occurring α-mannosidase inhibitors (±)-mannonolactam and (±)-deoxymannojirimycin were prepared. In addition, homologation of the lactam carbonyl of 17 also provided a route to the alkaloid (±)-prosopinine.

Experimental Section

General Methods. All reactions were carried out by performing standard inert atmosphere techniques to exclude moisture and oxygen, and reactions were carried out under an atmosphere of either nitrogen or argon.[35] Azeotropic removal of H_2O was assisted by the use of 3- or 4-Å molecular sieves.[36] In each case, diastereomeric product ratios were determined by ^1H NMR.

(34) he physical and spectral data for 7 were consistent with those reported for 7 and 9.[16,21-23]

Formation of 21. $BnNH_2$ (10.72 g, 100 mmol) was added to a solution of 20 (8.41 g, 100 mmol) in Et_2O (100 mL) at 0 °C. After the solution was warmed to rt, the mixture was stirred for 12 h. The mixture was then concentrated and dissolved in THF (600 mL), and acryloyl chloride (9.92 g, 110 mmol) was added at rt. After being heated for 16 h at reflux, the solution was washed with saturated aqueous $NaHCO_3$ (200 mL), and the aqueous layer was extracted with 3 × 200 mL of Et_2O. The combined organic layers were dried ($MgSO_4$) and purified by chromatography (70:30 petroleum ether/Et_2O) to give 21 (13.12 g, 53 mmol) in 53% yield: ^1H NMR (300 MHz, $CDCl_3$) δ 2.61 (s, 4 H), 3.68 (s, 3 H), 4.71 (s, 2 H), 7.19–7.35 (m, 6 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 19.8, 30.7, 49.8, 51.5, 108.8, 127.6, 127.8, 128.8, 136.4, 139.4, 166.6, 169.6; IR (neat) 3080, 3065, 3032, 2951, 2905, 2849, 1690, 1649, 1439, 1377, 1294, 1254, 1184, 1121, 729, 700 cm^{-1}.

Formation of 26. Substrate 25 (1.32 g, 10 mmol) was dissolved in 20 mL of benzene, and TsOH (15 mg) and H_2O (20 mL) were added. After the mixture was stirred at rt for 12 h, the solution was extracted with 2 × 20 mL of benzene, and the combined organic layers were dried ($MgSO_4$). The solution was filtered, $BnNH_2$ (1.071 g, 10 mmol) was added, and the mixture was heated at reflux for 48 h. Concentration gave the crude enamine, which was dissolved in THF (60 mL). Acryloyl chloride (1.11 g, 10 mmol) was added, and the solution was heated at reflux. After 20 h, saturated aqueous $NaHCO_3$ (50 mL) was added, and the mixture was extracted with 4 × 40 mL of Et_2O. The combined organic fractions were dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by chromatography (40:60 petroleum ether/Et_2O) to give 26 (0.517 g, 2.3 mmol) in 23% yield: mp 72–75 °C (from petroleum ether/Et_2O); ^1H NMR (300 MHz, $CDCl_3$) δ 2.18 (s, 3 H), 2.55–2.66 (m, 4 H), 4.76 (s, 2 H), 7.15 (s, 1 H), 7.20–7.38 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 18.8, 24.7, 30.6, 49.9, 119.4, 127.5, 128.0, 128.9, 136.2, 140.3, 169.8, 194.8; IR (neat) 3067, 3065, 3032, 3006, 2967, 2928, 2904, 2849, 1694, 1636, 1373, 1292, 1184, 702 cm^{-1}; HRMS calcd for $C_{14}H_{15}NO_2$ *m/z* 229.1103, found *m/z* 229.1109.

General Method for the Hydrogenation of Enamides. A mixture of enamide (1 equiv), Na_2CO_3 (3.0 equiv),[19] and 10% Pd on carbon (0.1 g/mmol enamide) in EtOH (0.05–0.2 M) was stirred under an atmosphere of H_2 (1–3 atm) for 16–48 h. The solids were removed by filtration, the mixture was concentrated, and the crude product was purified by chromatography.

22: 5.23 g, 21.66 mmol, 98% yield; ^1H NMR (300 MHz, $CDCl_3$) δ 1.98 (ddt, *J* = 6.0, 13.5, 9.6 Hz, 1 H), 2.12 (m, 1 H), 2.45 (ddd, *J* = 6.3, 9.6, 17.8 Hz, 1 H), 2.59 (ddd, *J* = 5.2, 6.3, 17.8 Hz, 1 H), 2.76 (dddd, *J* = 3.9, 5.8, 9.9, 12.4 Hz, 1 H), 3.36 (ddd, *J* = 1.1, 5.8, 12.4 Hz, 1 H), 3.42 (dd, *J* = 8.5, 12.4 Hz, 1 H), 3.63 (s, 3 H), 4.50 (d, *J* = 14.7 Hz, 1 H), 4.67 (d, *J* = 14.7 Hz, 1 H), 7.20–7.36 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 23.8, 30.6, 38.9, 47.9, 50.0, 52.0, 127.4, 128.0, 128.5, 136.6, 168.8, 172.4; IR (neat) 3086, 3063, 3030, 2953, 2875, 1736, 1642, 1495, 1454, 1437, 1381, 1356, 1332, 1264, 1204, 1171, 1013, 727, 700 cm^{-1}; HRMS calcd for $C_{14}H_{17}NO_3$ *m/z* 247.1209, found *m/z* 247.1206.

27: 0.15 g, 0.65 mmol, 62% yield; ^1H NMR (300 MHz, $CDCl_3$) δ 1.79–1.94 (m, 2 H), 2.14 (s, 3 H), 2.49 (ddd, *J* = 16.8, 10.4, 6.4 Hz, 1 H), 2.59 (ddd, *J* = 17.8, 6.4, 4.4 Hz, 1 H), 2.79 (tdd, *J* = 9.9, 5.2, 3.8 Hz, 1 H), 3.29 (ddd, *J* = 12.6, 5.3, 1.4 Hz, 1 H), 3.41 (dd, *J* = 12.3, 9.3 Hz, 1 H), 4.47 (d, *J* = 14.7 Hz, 1 H), 4.73 (d, *J* = 14.7 Hz, 1 H), 7.22–7.36 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.79, 28.01, 30.96, 46.58, 47.17, 50.07, 127.40, 128.05, 128.52, 136.70, 168.63, 207.21; IR (oil/NaCl) 3032, 2932, 2876, 1713, 1642, 1495, 1455, 1262, 1167, cm^{-1}; HRMS calcd for $C_{14}H_{17}NO_2$ *m/z* 231.1259, found *m/z* 232.1251.

31: 8.19 g, 33.4 mmol, 81% yield, 90:10 (cis/trans); ^1H NMR (300 MHz, $CDCl_3$, cis isomer) δ 1.07 (d, *J* = 6.6 Hz, 3 H), 2.06 (s, 3 H), 1.92–2.17 (m, 4 H), 2.48 (ddd, *J* = 18.3, 10.4, 8.0 Hz, 1 H), 2.61 (ddd, *J* = 18.3, 7.4, 2.0 Hz, 1 H), 2.79 (dt, *J* = 12.6, 4.2 Hz, 1 H), 3.84 (m, 1 H), 3.96 (d, *J* = 15.2 Hz, 1 H), 5.31 (d, *J* =

(35) or more detailed general experimental procedures from these laboratories, see: Cook, G. R.; Barta, N. S.; Stille, J. R. *J. Org. Chem.* **1992**, *57*, 461.

(36) ehydration of condensation reactions was performed with the use of a modified Dean–Stark apparatus in which the cooled distillate was passed through either 3- or 4-Å molecular sieves prior to return of the solvent to the reaction mixture. Barta, N. S.; Paulvannan, K.; Schwarz, J. B.; Stille, J. R. *Synth. Commun.* **1994**, *24*, 583.

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15.2 Hz, 1 H), 7.22–7.36 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) (cis isomer) δ 14.52, 17.33, 28.08, 29.96, 47.74, 51.03, 51.14, 127.04, 127.36, 128.28, 136.97, 168.67, 206.25; IR (oil/NaCl) 2975, 1713, 1640, 1163 cm^{-1}; HRMS calcd for $C_{16}H_{19}NO_2$ *m/z* 245.1416, found *m/z* 245.1415.

45: 0.63 g, 1.65 mmol, 80% yield, 98:2 (cis/trans); ^{1}H NMR (300 MHz, $CDCl_3$) (cis isomer) δ 1.13 (t, *J* = 7.2 Hz, 3 H), 2.03 (m, 1 H), 2.21 (ddt, *J* = 9.9, 7.8, 12.9 Hz, 1 H), 2.49 (ddd, *J* = 18.3, 10.0, 8.3 Hz, 1 H), 2.59 (ddd, *J* = 18.3, 7.8, 1.8 Hz, 1 H), 2.79 (dt, *J* = 15.0, 9.0 Hz, 1 H), 3.53 (d, *J* = 5.4 Hz, 2 H), 3.88–4.08 (m, 3 H), 4.15 (d, *J* = 15.2 Hz, 1 H), 4.37 (s, 2 H), 5.23 (d, *J* = 15.2 Hz, 1 H), 7.17–7.37 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) (cis isomer) δ 13.82, 19.18, 30.07, 42.40, 49.16, 56.17, 60.65, 68.62, 73.15, 127.19, 127.44, 127.59, 127.67, 128.19, 128.42, 137.22, 137.31, 169.56, 171.06; IR (oil/NaCl) 2959, 2870, 1734, 1645, 1173 cm^{-1}; HRMS calcd for $C_{26}H_{31}NO_4$ *m/z* 381.1940, found *m/z* 381.1938.

50: 0.36 g, 1.48 mmol, 79% yield, >98:2 (cis/trans); mp 98–101 °C (from petroleum ether/Et_2O); ^{1}H NMR (300 MHz, $CDCl_3$) (cis isomer) δ 2.01 (m, 1 H), 2.30 (m, 1 H), 2.41 (m, 1 H), 2.52 (m, 1 H), 2.98 (m, 1 H), 4.18–4.30 (m, 4 H), 5.13 (d, *J* = 15.0 Hz, 1 H), 7.14–7.42 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) (cis isomer) δ 19.88, 29.68, 37.85, 47.94, 55.20, 71.23, 127.93 (2), 128.97, 136.15, 169.49, 176.09; IR (solid/KBr) 3032, 2969, 2946, 2922, 1788, 1644, 1470, 1451, 1362, 1163 cm^{-1}; HRMS calcd for $C_{14}H_{15}NO_3$ *m/z* 245.0996, found *m/z* 245.1054.

Hydrolysis of 22. A solution of **22** (3.00 g, 12.0 mmol) and NaOH (0.96 g, 24.0 mmol) in a mixture of THF (50 mL) and H_2O (200 mL) was stirred for 20 h at rt, and the mixture was adjusted to pH <3.0 by addition of concd HCl. The mixture was extracted with 3 × 75 mL of $CHCl_3$, and the combined organic layers were dried ($MgSO_4$) and concentrated to give **23** (2.52 g, 10.8 mmol) in 90% yield: mp 156–157 °C (from $CHCl_3$/Et_2O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.96 (m, 1 H), 2.13 (m, 1 H), 2.50 (ddd, *J* = 6.3, 9.3, 17.9 Hz, 1 H), 2.63 (dt, *J* = 17.9, 5.5 Hz, 1 H), 2.76 (m, 1 H), 3.38 (dd, *J* = 5.8, 12.5 Hz, 1 H), 3.43 (dd, *J* = 8.5, 12.5 Hz, 1 H), 4.43 (d, *J* = 14.6 Hz, 1 H), 4.74 (d, *J* = 14.6 Hz, 1 H), 7.16–7.35 (m, 5 H), 11.24 (bs, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 23.6, 30.4, 38.8, 48.0, 50.5, 127.6, 128.1, 128.7, 136.2, 170.0, 175.7; IR (neat) 3070, 3029, 2930, 2872, 2780, 2670, 2492, 1940, 1713, 1591, 1455, 1421, 1375, 1302, 1223, 980, 752, 698 cm^{-1}; HRMS calcd for $C_{12}H_{15}NO_3$ *m/z* 233.1052, found *m/z* 233.1039.

General Procedure for DBU Epimerization. To a 90:10 solution of *cis*-**31**/*trans*-**31** (0.20 g, 1.12 mmol) in THF (2.2 mL) was added DBU (0.09 g, 0.56 mmol), and the mixture was stirred at rt. After 16 h, the reaction was quenched by addition of 3 mL of H_2O. The organic layers were separated, concentrated, and purified by chromatography (Et_2O) to give **31**.

trans-**31**: 0.20 g, 0.82 mmol, >99% yield, 28:72 (cis/trans); ^{1}H NMR (300 MHz, $CDCl_3$) (trans isomer) δ 1.22 (d, *J* = 6.6 Hz, 1 H), 1.89 (s, 3 H), 1.91–2.12 (m, 3 H), 2.35–2.63 (m, 3 H), 3.82 (m, 1 H), 4.01 (d, *J* = 15.2 Hz, 1 H), 5.23 (d, *J* = 15.2 Hz, 1 H), 7.22–7.34 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) (trans isomer) δ 19.53, 19.86, 27.47, 29.39, 46.98, 51.14, 52.26, 126.93, 127.78, 128.10, 136.97, 168.87, 207.05; IR (oil/NaCl) 2975, 1713, 1640, 1163 cm^{-1}; HRMS calcd for $C_{16}H_{19}NO_2$ *m/z* 245.1416, found *m/z* 245.1415.

trans-**46** (from **51**): 0.20 g, 0.57 mmol, >99% yield, 17:83 (cis/trans); ^{1}H NMR (300 MHz, $CDCl_3$) (trans isomer) δ 1.89 (s, 3 H), 1.95 (m, 1 H), 2.04 (m, 1 H), 2.44 (dt, *J* = 17.7, 6.5 Hz, 1 H), 2.58 (ddd, *J* = 17.7, 7.5, 6.5 Hz, 1 H), 2.95 (dt, *J* = 6.3, 4.8 Hz, 1 H), 3.42–3.52 (m, 2 H), 3.94 (m, 1 H), 4.10 (d, *J* = 15.0 Hz, 1 H), 4.37 (d, *J* = 1.5 Hz, 2 H), 5.14 (d, *J* = 15.0 Hz, 1 H), 7.16–7.36 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) (trans isomer) δ 19.93, 27.27, 29.58, 47.78, 47.98, 55.17, 69.36, 72.81, 127.01, 127.30, 127.45, 127.53, 127.82, 128.12, 136.91, 137.15, 169.86, 207.06; IR (oil/NaCl) 3088, 2924, 1713, 1644, 1161, 1101 cm^{-1}; HRMS calcd for $C_{23}H_{25}NO_3$ *m/z* 351.1835, found *m/z* 351.1818.

General Procedure for Baeyer–Villiger Oxidation. To a solution of **27** (0.10 g, 0.43 mmol) in CH_2Cl_2 (1 mL) were added *m*-CPBA (0.39 g, 2.25 mmol) and CF_3COOH (0.05 g, 0.43 mmol) at rt, and the reaction was heated at reflux. After 14 h, the reaction was cooled and concentrated, and the resulting slurry was purified by chromatography (Et_2O) to give **28**.

28: 0.069 g, 0.28 mmol, 67% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.01 (s, 3 H), 2.02–2.08 (m, 2 H), 2.52 (ddd, *J* = 17.9, 6.0, 5.3 Hz, 1 H), 2.67 (ddd, *J* = 17.9, 9.6, 7.1 Hz, 1 H), 3.26 (ddd, *J* = 13.2, 3.9, 1.3 Hz, 1 H), 3.43 (dd, *J* = 13.2, 3.9 Hz, 1 H), 4.49 (d, *J* = 14.7 Hz, 1 H), 4.71 (d, *J* = 14.7 Hz, 1 H), 5.12 (dq, *J* = 3.8, 3.6 Hz, 1 H), 7.21–7.36 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.97, 25.49, 27.86, 49.80, 50.46, 66.17, 127.49, 127.99, 128.60, 136.56, 168.73, 170.18; IR (oil/NaCl) 3063, 2959, 2873, 1738, 1646, 1491, 1365, 1421, 1238, 1182, 1075 cm^{-1}.

32: 4.49 g, 17.2 mmol, 41% yield; mp 66–67 °C (from petroleum ether/Et_2O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (d, *J* = 6.9 Hz, 3 H), 1.89 (s, 3 H), 1.97 (m, 1 H), 2.16 (dddd, *J* = 14.7, 11.4, 7.5, 2.7 Hz, 1 H), 2.51 (ddd, *J* = 18.3, 7.5, 2.1 Hz, 1 H), 2.66 (ddd, *J* = 18.3, 11.4, 7.5 Hz, 1 H), 3.46 (qt, *J* = 6.7, 2.0 Hz, 1 H), 3.80 (d, *J* = 15.3 Hz, 1 H), 4.88 (dt, *J* = 3.9, 2.1 Hz, 1 H), 5.46 (d, *J* = 15.3 Hz, 1 H), 7.20–7.37 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.80, 20.75, 21.03, 26.81, 47.18, 54.38, 70.07, 127.19, 127.72, 128.32, 136.95, 168.57, 169.89; IR (NaCl) 2975, 2942, 1736, 1634, 1482, 1246, 1179 cm^{-1}; HRMS calcd for $C_{18}H_{23}NO_3$ *m/z* 261.1365, found *m/z* 261.1363.

47: 0.59 g, 1.63 mmol, 60% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.88 (s, 3 H), 1.94 (m, 1 H), 2.17 (dddd, *J* = 13.8, 10.8, 7.8, 3.0 Hz, 1 H), 2.51 (ddd, *J* = 18.3, 7.6, 2.7 Hz, 1 H), 2.63 (ddd, *J* = 18.3, 10.8, 7.6 Hz, 1 H), 3.45–3.60 (m, 3 H), 3.92 (d, *J* = 15.3 Hz, 1 H), 4.43 (d, *J* = 12.0 Hz, 1 H), 4.50 (d, *J* = 12.0 Hz, 1 H), 5.16 (m, 1 H), 5.39 (d, *J* = 15.3 Hz, 1 H), 7.18–7.40 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.86, 22.30, 27.00, 48.12, 58.52, 67.97, 68.74, 73.31, 127.37, 127.63, 127.92, 128.01, 128.44, 128.50, 136.91, 137.31, 169.72, 169.96; IR (oil/NaCl) 3063, 2934, 2869, 1738, 1647, 1240, 1181 cm^{-1}; HRMS calcd for $C_{26}H_{29}NO_4$ *m/z* 367.1784, found *m/z* 367.1768.

Formation of 33. To a solution of **32** (0.10 g, 0.383 mmol) in H_2O (0.6 mL) was added crushed NaOH (0.04 g, 1.12 mmol), and the reaction was heated at approximately 50 °C for 12 h. After this time, the product was extracted from the reaction mixture with 6 × 1 mL of $CHCl_3$. The organic layers were combined and dried, and the solvent was removed under reduced pressure. The product was recrystallized from Et_2O/petroleum ether to give **33** (0.062 g, 0.283 mmol) in 74% yield: mp 110–113 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (d, *J* = 6.6 Hz, 3 H), 1.88 (m, 1 H), 1.96–2.12 (m, 2 H), 2.42 (ddd, *J* = 18.0, 7.1, 2.8 Hz, 1 H), 2.71 (ddd, *J* = 18.0, 10.8, 7.4 Hz, 1 H), 3.34 (m, 1 H), 3.83 (dt, *J* = 4.8, 2.8 Hz, 1 H), 3.95 (d, *J* = 15.2 Hz, 1 H), 5.35 (d, *J* = 15.2 Hz, 1 H), 7.20–7.35 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.37, 24.05, 26.92, 47.42, 57.96, 68.45, 127.23, 127.78, 128.56, 137.33, 169.42; IR (oil/NaCl) 3289, 3023, 2890, 1609, 1453, 1175, cm^{-1}; HRMS calcd for $C_{13}H_{17}NO_2$ *m/z* 219.1259, found *m/z* 219.1245.

Preparation of Thioamides. Lawesson's reagent (0.5 equiv) was added to a solution of the lactam (1.0 equiv) in THF (0.4 M), and the mixture was stirred for 4–12 h. After evaporation of the solvent, the nonvolatile mixture was diluted with EtOAc (3 times the volume of THF), and the solution was washed sequentially with 3 portions of saturated aqueous $NaHCO_3$ (1/3 the volume of EtOAc) followed by 2 portions of saturated aqueous NaCl (1/3 the volume of EtOAc). The aqueous layers were combined and extracted with 2 portions of EtOAc (1/3 the volume of EtOAc). All organic layers were combined and then dried (Na_2SO_4). Purification by chromatography (Et_2O) afforded the pure thiolactam.

34: 5.36 g, 20.4 mmol, 99% yield; mp 63–65 °C (from Et_2O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.87 (ddt, *J* = 5.8, 13.7, 9.1 Hz, 1 H), 2.00 (dq, *J* = 13.7, 5.8 Hz, 1 H), 2.78 (m, 1 H), 2.97 (ddd, *J* = 6.3, 8.8, 18.2 Hz, 1 H), 3.14 (dt, *J* = 18.2, 5.8 Hz, 1 H), 3.42–3.56 (m, 2 H), 3.56 (s, 3 H), 5.12 (d, *J* = 14.5 Hz, 1 H), 5.40 (d, *J* = 14.5 Hz, 1 H), 7.18–7.29 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 23.0, 38.6, 40.3, 50.0, 52.0, 57.1, 127.6, 127.7, 128.5, 134.8, 172.0, 199.7; IR (neat) 3080, 3030, 2951, 2860, 1734, 1514, 1453, 1348, 1200, 1169, 1043, 704 cm^{-1}; HRMS calcd for $C_{14}H_{17}NO_2S$ *m/z* 263.0980, found *m/z* 263.0962.

38b: 2.28 g, 7.82 mmol, 99% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.17 (d, *J* = 6.6 Hz, 3 H), 1.18 (t, *J* = 7.1 Hz, 3 H), 1.93–2.13 (m, 2 H), 2.77 (ddd, *J* = 4.7, 5.8, 11.5 Hz, 1 H), 3.14 (dt, *J* = 8.5, 19.5 Hz, 1 H), 3.29 (ddd, *J* = 3.3, 6.6, 19.5 Hz, 1 H), 3.98 (dq, *J* = 5.8, 6.6 Hz, 1 H), 4.09 (q, *J* = 7.1 Hz, 2 H), 4.45 (d, *J* = 14.8 Hz, 1 H), 6.23 (d, *J* = 14.8 Hz, 1 H), 7.23–7.35 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0, 14.7, 18.3, 40.0, 43.5, 54.9, 55.8, 61.0, 127.5, 127.7, 128.7, 135.3, 170.8, 199.8; IR (neat) 3087, 3061, 2980, 2938, 1732, 1497, 1452, 1348, 1171, 961, 708 cm^{-1}; HRMS calcd for $C_{16}H_{21}NO_3S$ *m/z* 291.1293, found *m/z* 291.1341.

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. 55: 1.45 g, 3.36 mmol, 94% yield; mp 81–82 °C (from Et_2O); ^1H NMR (300 MHz, $CDCl_3$) δ 1.83–2.05 (m, 2 H), 3.10 (ddd, J = 4.4, 6.1, 19.0 Hz, 1 H), 3.30 (ddd, J = 7.1, 9.6, 19.0 Hz, 1 H), 3.49 (dd, J = 6.6, 10.2 Hz, 1 H), 3.58 (dd, J = 4.4, 10.2 Hz, 1 H), 3.85 (m, 1 H), 3.91 (m, 1 H), 4.24 (d, J = 11.8 Hz, 1 H), 4.35 (d, J = 11.8 Hz, 1 H), 4.40–4.50 (m, 3 H), 6.45 (d, J = 15.1 Hz, 1 H), 7.14–7.40 (m, 15 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.7, 37.3, 55.5, 61.1, 69.1, 70.0, 72.2, 73.3, 127.2, 127.4, 127.5, 127.6, 127.9, 128.2, 128.5, 135.2, 137.1, 137.7, 201.8; IR (neat) 3100, 3090, 3031, 2940, 2867, 1497, 1453, 1345, 1173, 1073, 1028, 733, 696 cm^{-1}; HRMS calcd for $C_{27}H_{29}NO_3S$ m/z 431.1919, found m/z 431.1887.

General Method for Eschenmoser Sulfide Contraction. The thiolactam (1.0 equiv) and $BrCH_2CO_2Et$ (1.2 equiv) were stirred in Et_2O (1 M) for 24–36 h. After removal of solvent, the thionium salt was dissolved in CH_3CN (0.2 M), and PPh_3 (1.2 equiv) was added. The mixture was allowed to stir for 10 min, NEt_3 (1.5 equiv) was added, and the solution was heated to reflux. After 26 h, the solids were removed by filtration, and the resultant solution was concentrated. Chromatography (90:10 to 70:30 petroleum ether/Et_2O) provided the pure enaminoesters.

39: 0.426 g, 1.23 mmol, 79% yield; mp 69–71 °C (from petroleum ether/Et_2O); ^1H NMR (300 MHz, $CDCl_3$) δ 1.12 (d, J = 6.4 Hz, 3 H), 1.18 (t, J = 7.0 Hz, 3 H), 1.24 (t, J = 7.0 Hz, 3 H), 1.89–2.11 (m, 2 H), 2.86–3.00 (m, 2 H), 3.62 (ddd, J = 3.1, 6.7, 18.7 Hz, 1 H), 3.80 (quint, J = 6.3 Hz, 1 H), 3.99 (dq, J = 3.4, 7.0 Hz, 2 H), 4.02 (dq, J = 3.4, 7.0 Hz, 1 H), 4.14 (q, J = 7.0 Hz, 2 H), 4.26 (d, J = 16.5 Hz, 1 H), 4.55 (d, J = 16.5 Hz, 1 H), 4.63 (s, 1 H), 7.17 (d, J = 7.0 Hz, 2 H), 7.22–7.37 (m, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0, 14.5, 14.6, 17.0, 25.4, 44.1, 54.0, 54.8, 58.2, 60.6, 85.7, 126.4, 127.1, 128.6, 136.1, 159.8, 168.6, 171.8; IR (neat) 3100, 3080, 3030, 2978, 2920, 2870, 1734, 1682, 1561, 1136, 1060, 1030, 966, 791, 727, 696 cm^{-1}; HRMS calcd for $C_{20}H_{27}NO_4$ m/z 345.1940, found m/z 345.1939.

56: 1.22 g, 2.51 mmol, 81% yield; ^1H NMR (300 MHz, $CDCl_3$) δ 1.17 (t, J = 7.1 Hz, 3 H), 1.85 (m, 1 H), 1.95 (m, 1 H), 2.95 (dt, J = 18.1, 6.2 Hz, 1 H), 3.41 (dd, J = 6.7, 9.7 Hz, 1 H), 3.50 (m, 1 H), 3.51 (dd, J = 4.5, 9.7 Hz, 1 H), 3.61 (ddd, J = 2.8, 4.4, 7.1 Hz, 1 H), 3.86 (ddd, J = 3.0, 4.4, 6.9 Hz, 1 H), 3.98 (dq, J = 3.8, 7.1 Hz, 1 H), 4.01 (dq, J = 3.8, 7.1 Hz, 1 H), 4.35 (d, J = 16.5 Hz, 1 H), 4.41 (s, 2 H), 4.43 (d, J = 14.6 Hz, 1 H), 4.52 (d, J = 14.6 Hz, 1 H), 4.53 (d, J = 16.5 Hz, 1 H), 4.60 (s, 1 H), 7.18–7.36 (m, 15 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.6, 22.2, 22.3, 53.9, 58.2, 62.5, 70.1, 70.2, 73.2, 73.3, 84.8, 126.6, 127.0, 127.4, 127.5, 127.6, 127.8, 128.3, 128.4, 128.5, 136.3, 137.6, 138.2, 161.7, 168.9; IR (neat) 3100, 3060, 3031, 2980, 2934, 2867, 1680, 1561, 1497, 1455, 1362, 1142, 1094, 1073, 735, 696 cm^{-1}; HRMS calcd for $C_{34}H_{35}NO_4$ m/z 485.2567, found m/z 485.2559.

Formation of 43. To a solution of 42 (1.20 g, 8.19 mmol) in THF (16 mL) was added BuLi (3.28 mL, 2.5 M in hexane) at −78 °C. After the mixture was stirred for 10 min, $ClCO_2Et$ (0.89 g, 8.19 mmol) was added dropwise. The reaction was slowly warmed to 0 °C (until a deep red color began to form) and was then promptly quenched by addition of H_2O. The organic phase was separated, and the solvent was removed under reduced pressure to produce a crude oil, which was purified by chromatography (petroleum ether) to give 43 (1.61 g, 7.39 mmol) in 91% yield: ^1H NMR (300 MHz, $CDCl_3$) δ 1.29 (t, J = 7.2 Hz, 3 H), 4.22 (q, J = 7.2 Hz, 2 H), 4.25 (s, 2 H), 4.59 (s, 2 H), 7.22–7.40 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.78, 56.53, 61.90, 71.81, 78.07, 82.94, 127.87, 127.90, 128.29, 136.59, 152.87; IR (oil/NaCl) 3032, 2984, 2872, 2236, 1713, 1248 cm^{-1}.

Aza-Annulation Procedure for Formation of 44. To a solution of 43 (1.61 g, 7.37 mmol) in THF (15 mL) was added $BnNH_2$ (0.70 g, 7.37 mmol) at rt, and the reaction was heated at reflux for 12 h. After the mixture was cooled to rt, acrylic anhydride (1.7 equiv) was added, and the reaction was heated at reflux for 14 h.[37] The solution was then cooled to rt and concentrated, and the crude product was purified by chromatography (10:90 Et_2O/petroleum ether) to give 44 (1.73 g, 4.56 mmol) in 62% yield: mp 84–87 °C (from Et_2O/petroleum ether); ^1H NMR (300 MHz, $CDCl_3$) δ 1.27 (t, J = 7.0 Hz, 3 H), 2.49–2.58 (m, 2 H), 2.62–2.71 (m, 2 H), 4.17 (q, J = 7.0 Hz, 2 H), 4.57 (s, 2 H), 4.60 (s, 2 H), 5.12 (s, 2 H), 6.97–7.03 (m, 2 H), 7.16–7.39 (m, 8 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.16, 21.69, 30.82, 44.51, 60.76, 63.56, 72.65, 113.54, 126.06, 126.97, 127.93, 128.07, 128.42, 128.63, 137.61, 137.90, 146.08, 166.71, 170.92; IR (NaCl) 2984, 1682, 1636, 1269, 1130 cm^{-1}; HRMS calcd for $C_{20}H_{25}NO_4$ m/z 379.1784, found m/z 379.1777.

General Procedure for Conversion of Ester to Methyl Ketone Functionality. To a solution of MeMgBr (2.27 mL, 3.0 M in THF) in benzene (19 mL) was added NEt_3 (2.06 g, 20.4 mmol) at 0 °C. After 10 min, a solution of 45 (1.25 g, 3.41 mmol) in benzene (5 mL) was added with vigorous stirring, and the mixture was stirred for 3 h at 0 °C. The reaction was quenched by addition of 25 mL of 3 M aqueous HCl. The organic layer was separated and concentrated, and the resulting crude oil was purified by chromatography (Et_2O) to give 46.

cis-46 (from 45): 0.56 g, 1.60 mmol, 61% yield; ^1H NMR (300 MHz, $CDCl_3$) (cis isomer) δ 1.87 (m, 1 H), 2.02 (s, 3 H), 2.12 (m, 1 H), 2.32–2.64 (m, 2 H), 2.71 (dt, J = 13.2, 4.1 Hz, 1 H), 3.42 (dd, J = 9.9, 7.5 Hz, 1 H), 3.50 (dd, J = 9.9, 4.1 Hz, 1 H), 3.94 (m, 1 H), 4.05 (d, J = 15.0 Hz, 1 H), 4.30 (d, J = 1.8 Hz, 2 H), 5.28 (d, J = 15.0 Hz, 1 H), 7.16–7.36 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) (cis isomer) δ 18.07, 28.30, 29.82, 48.86, 49.63, 55.82, 67.89, 72.90, 127.12, 127.34, 127.49, 128.03, 128.11, 128.29, 136.91, 137.04, 169.23, 206.36; IR (oil/NaCl) 3068, 2924, 1713, 1644, 1161, 1101 cm^{-1}; HRMS calcd for $C_{20}H_{25}NO_3$ m/z 351.1835, found m/z 351.1818.

51: 0.17 g, 0.65 mmol, 25% yield, >98:2 (cis/trans); ^1H NMR (300 MHz, $CDCl_3$) (cis isomer) δ 1.90 (m, 1 H), 1.91 (s, 3 H), 2.10 (m, 1 H), 2.40 (dt, J = 17.7, 6.8 Hz, 1 H), 2.54 (dt, J = 17.7, 6.8 Hz, 1 H), 3.03 (dt, J = 6.6, 4.8 Hz, 1 H), 3.57 (dd, J = 11.6, 3.8 Hz, 2 H), 3.65 (dd, J = 11.4, 6.3 Hz, 1 H), 3.82 (m, 1 H), 3.92 (ba, 1 H), 4.08 (d, J = 15.0 Hz, 1 H), 5.19 (d, J = 15.0 Hz, 1 H), 7.21 (bd, J = 7.8 Hz, 2 H), 7.20–7.34 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) (cis isomer) δ 20.11, 25.58, 29.86, 47.49, 48.03, 57.15, 61.87, 127.45, 127.91, 128.54, 136.91, 171.06, 207.88; IR (oil/NaCl) 3374, 3068, 2942, 1711, 1613, 1455, 1256, 1169 cm^{-1}; HRMS calcd for $C_{15}H_{19}NO_2$ m/z 261.1365, found m/z 261.1354.

Formation of 17. To a solution of 47 (0.30 g, 0.80 mmol) in H_2O (1.1 mL) was added crushed KOH (0.20 g, 0.52 mmol) at rt, and the reaction was heated at approximately 50 °C. After 12 h, the product was extracted from the reaction mixture with 6 × 2 mL of $CHCl_3$. The organic layers were combined and concentrated, and the resulting crude alcohol was purified by chromatography (Et_2O) to give an oil (0.22 g, 0.68 mmol) in 85% yield: ^1H NMR (300 MHz, $CDCl_3$) δ 1.81 (m, 1 H), 2.00 (dddd, J = 12.6, 9.9, 6.9, 3.0, 1 H), 2.37 (ddd, J = 18.3, 6.9, 4.8 Hz, 1 H), 2.64 (ddd, J = 16.8, 9.3, 6.9 Hz, 2 H), 3.39 (m, 1 H), 3.40 (s, 1 H), 3.51 (m, 1 H), 4.07 (d, J = 15.3 Hz, 1 H), 4.10 (ba, 1 H), 4.37 (d, J = 12.0 Hz, 1 H), 4.43 (d, J = 12 Hz, 1 H), 5.18 (d, J = 15.3 Hz, 1 H), 7.16–7.38 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.16, 27.37, 48.09, 62.13, 65.65, 69.42, 73.27, 127.15, 127.58, 127.71, 127.86, 128.45, 128.46, 137.23, 137.44, 170.28; IR (oil/NaCl) 3364 (br), 3063, 2928, 1617, 1453, 1181, 1101 cm^{-1}; HRMS calcd for $C_{20}H_{23}NO_3$ m/z 325.1678, found m/z 325.1666.

To a solution of the alcohol (0.50 g, 2.05 mmol) in Et_2O (4 mL) were added crushed KOH (0.23 g, 4.10 mmol) and molecular sieves (0.40 g) at rt. After 5–10 min of stirring, BnBr (0.39 g, 2.26 mmol) was added. The reaction was quenched after 3 h by addition of excess H_2O, and the mixture was extracted with 10 × 4 mL of Et_2O. The organic layers were combined and concentrated, and the resulting crude oil was purified by chromatography (Et_2O) to give 17 (0.57 g, 1.37 mmol) in 84% yield: mp 60–63 °C (from $CHCl_3$/Et_2O); ^1H NMR (300 MHz, $CDCl_3$) δ 1.91–2.02 (m, 2 H), 2.40 (ddd, J = 18.0, 6.2, 3.9 Hz, 1 H), 2.69 (ddd, J = 18.0, 10.4, 8.5 Hz, 1 H), 3.39 (dd, J = 9.9, 7.2 Hz, 1 H), 3.52 (dd, J = 9.9, 3.9 Hz, 1 H), 3.65 (m, 1 H), 3.83 (dd, J = 6.2, 3.9 Hz, 1 H), 3.99 (d, J = 15.3 Hz, 1 H), 4.26 (d, J = 12.0 Hz, 1 H), 4.35 (d, J = 12.0 Hz, 1 H), 4.37 (d, J = 12.0 Hz, 1 H), 4.41 (d, J = 12.0 Hz, 1 H), 5.36 (d, J = 15.3 Hz, 1 H), 7.14–7.36 (m, 15 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.18, 27.22, 47.69, 58.37, 69.16, 69.77, 71.79, 73.03, 126.87, 127.07, 127.28, 127.37, 127.56, 127.65, 128.05, 128.21, 128.26, 137.06, 137.36, 137.85, 169.93; IR

(37) crylic anhydride was prepared immediately prior to use by adding NaH (1.8 equiv) to acrylic acid (1.2 equiv) at −78 °C and allowing the mixture to warm to rt. Acryloyl chloride (1.0 equiv) was then added, and the mixture was stirred for 1 h. This mixture was transferred to the reaction vessel via cannula.

(38) ang. S.-K.; Kim, W.-S.; Moon, B.-H. *Synthesis* **1986**, 1161.

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(NaCl) 3088, 3030, 2867, 1642, 1453, 1096 cm^{-1}; HRMS calcd for $C_{21}H_{29}NO_3$ *m/z* 415.2148, found *m/z* 415.2142.

Formation of 52. To a solution of 17 (1.00 g, 2.41 mmol) in THF (16 mL) was added BuLi (1.06 mL, 2.5 M in THF) at −78 °C. After 10 min, PhSeCl (0.51 g, 2.65 mmol) in THF (8 mL) was added and the reaction mixture allowed to warm to 0 °C for 3 min. The reaction was quenched by addition of 25 mL of H_2O, and the mixture was extracted with 4 × 10 mL of Et_2O. The combined organic layers were concentrated under reduced pressure. The residue was taken up in MeOH/THF/H_2O (16:8:1, 25 mL), and $NaIO_4$ (1.55 g, 7.23 mmol) was added. After this mixture was stirred for 14 h, the reaction was diluted with 25 mL of H_2O, and the mixture was extracted with 10 × 10 mL of Et_2O. The organic layers were combined and concentrated to give a crude solid, which was purified by recrystallization from Et_2O/petroleum ether to give 52 (0.78 g, 1.88 mmol) in 78% yield: mp 98–99 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.34 (t, J = 9.2 Hz, 1 H), 3.48 (dd, J = 9.8, 5.0 Hz, 1 H), 3.84 (m, 1 H), 4.00 (d, J = 15.5 Hz, 1 H), 4.08 (dd, J = 5.9, 1.4 Hz, 1 H), 4.27 (d, J = 12.0 Hz, 1 H), 4.33 (d, J = 12.0 Hz, 1 H), 4.40 (d, J = 12.0 Hz, 1 H), 4.45 (d, J = 12.0 Hz, 1 H), 5.37 (d, J = 15.5 Hz, 1 H), 6.15 (d, J = 9.6 Hz, 1 H), 6.47 (ddd, J = 9.6, 5.9, 1.1 Hz, 1 H), 7.10–7.15 (m, 2 H), 7.19–7.38 (m, 13 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 48.07, 57.40, 68.07, 68.80, 70.11, 73.24, 127.32, 127.52, 127.69, 127.75, 127.87, 128.04, 128.24, 128.29, 128.44, 128.51, 134.59, 136.91, 137.40, 137.52, 162.29; IR (NaCl) 3088, 2870, 1669, 1611, 1455, 1262, 1146, 1092 cm^{-1}; HRMS calcd for $C_{27}H_{29}NO_3$ *m/z* 413.1991, found *m/z* 413.1999.

Formation of 53. To a solution of 52 (0.10 g, 0.24 mmol) in *t*-BuOH (1.4 mL) were added NMO (excess) and OsO_4 (0.96 mL, 0.05 M in *t*-BuOH) at rt. After 3 h, the reaction was quenched by addition of excess solid Na_2SO_3. Solvent was removed under reduced pressure until the reaction color began to turn gray. The resulting mixture was purified by chromatography (solvent gradient: Et_2O to 50:50 Et_2O/MeOH) to give 53 (0.069 g, 0.154 mmol) in 64% yield: mp 96–98 °C (from Et_2O/MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.96 (d, J = 1.8 Hz, 1 H), 3.61–3.78 (m, 3 H), 3.84 (d, J = 1.2 Hz, 1 H), 3.97 (t, J = 3.1 Hz, 1 H), 4.32 (d, J = 15.6, 1 H), 4.37 (td, J = 3.6, 2.1 Hz, 1 H), 4.41 (s, 2 H), 4.42 (m, 1 H), 4.44 (d, J = 12.0 Hz, 1 H), 4.50 (d, J = 12.0 Hz, 1 H), 5.27 (d, J = 15.6 Hz, 1 H), 7.11–7.21 (m, 4 H), 7.21–7.39 (m, 11 H); ^{13}C NMR (75 MHz, $CDCl_3$) 47.56, 58.98, 68.11, 68.85, 69.57, 71.48, 73.13, 75.21, 127.39, 127.55, 127.65, 127.74, 127.83, 128.23, 128.35, 128.41, 128.53, 136.83, 137.19, 137.43, 171.20 δ; IR (NaCl) 3409, 3088, 3031, 2869, 1645, 1455, 1250, 1074 cm^{-1}; HRMS calcd for $C_{27}H_{29}NO_5$ *m/z* 447.2046, found *m/z* 447.2046.

Formation of 5. To a solution of 53 (0.06 g, 0.13 mmol) in NH_3 (4 mL) was added Li metal at −78 °C until the solution turned a persistent deep blue. After 3 h at reflux, the solution was cooled to −78 °C and then the reaction was quenched by the addition of solid NH_4Cl. The mixture was then allowed to warm to rt. Once NH_3 removal was complete, the reaction mixture was extracted with 10 × 2 mL of a 2:1 solution of $CHCl_3$/MeOH and then filtered. Solvent removal under reduced pressure produced a solid, which was dissolved in a minimum amount of MeOH and purified by chromatography (90:10 $CHCl_3$/MeOH) to give 5 (0.010 g, 0.057 mmol) in 44% yield: mp 163–168 °C (from $CHCl_3$/Et_2O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.23 (td, J = 6.3, 3.9 Hz, 1 H), 3.59 (dd, J = 11.9, 5.9 Hz, 1 H), 3.68 (dd, J = 11.7, 5.1 Hz, 1 H), 3.72 (t, J = 6.2 Hz, 1 H), 3.89 (dd, J = 5.7, 3.9 Hz, 1 H), 4.20 (d, J = 3.9 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) 57.30, 61.11, 67.20, 68.14, 71.94, 173.17; IR (oil/NaCl) 3287, 3063, 2941, 2890, 2834, 1609, 1453, 1281, 1175, 1032 cm^{-1}; HRMS calcd for $C_5H_{11}NO_3$ *m/z* 177.0637, found *m/z* 176.0481.

Formation of 54. To a solution of 53 (0.07 g, 0.16 mmol) in Et_2O (1.6 mL) was added excess $LiAlH_4$ at rt. After 3 h, the reaction was quenched at 0 °C *via* slow addition of 15% aqueous NaOH until all visible $LiAlH_4$ had been consumed. The reaction was filtered, dried, and concentrated to give a crude oil, which was purified by chromatography (Et_2O) to give 54 (0.069 g, 0.16 mmol) in >98% yield: ^{1}H NMR (300 MHz, $CDCl_3$) (cis isomer) δ 2.21 (dd, J = 12.2, 1.5 Hz, 1 H), 2.38 (dt, J = 8.7, 2.6 Hz, 1 H), 2.82 (bs, 2 H), 2.91 (dd, J = 12.2, 4.4 Hz, 1 H), 3.27 (d, J = 12.9 Hz, 1 H), 3.55 (dd, J = 8.4, 3.3 Hz, 1 H), 3.64 (t, J = 8.6 Hz, 1 H), 3.73 (m, 1 H), 3.76 (dd, J = 10.4, 2.6 Hz, 1 H), 3.83 (dd, J = 10.4, 2.6 Hz, 1 H), 4.16 (d, J = 13.2 Hz, 1 H), 4.45 (s, 1 H), 4.56 (d, J = 11.1 Hz, 2 H), 4.90 (d, J = 11.1 Hz, 1 H), 7.20–7.40 (m, 15 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 54.71, 56.67, 64.76, 66.87, 68.10, 73.26, 74.61, 75.90, 78.42, 127.16, 127.65, 127.74, 127.79, 127.97, 127.99, 128.40, 128.94, 137.85, 138.52, 138.60; IR (oil/NaCl) 3422, 3063, 2923, 1495, 1453, 1096 cm^{-1}; HRMS calcd for $C_{27}H_{31}NO_4$ *m/z* 433.2253, found *m/z* 433.2253.

Formation of 4. To a solution of 54 (0.08 g, 0.18 mmol) in EtOH (2 mL) was added 10% Pd on carbon (0.18 g) and concd HCl (1.8 mL), and the mixture was placed under an atmosphere of H_2 and stirred at rt. After 14 h, the reaction mixture was filtered and the solvent removed under reduced pressure to give 4 (0.014 g, 0.094) as a crude solid (52% yield), which was recrystallized to give pure 4 (0.009 g, 0.059 mmol) in 33% yield: mp 184–186 °C (from MeOH/Et_2O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.00 (ddd, J = 9.9, 6.6, 3.0 Hz, 1 H), 3.10 (dd, J = 13.8, 1.3 Hz, 1 H), 3.27 (dd, J = 13.8, 3.0 Hz, 1 H), 3.55 (dd, J = 9.6, 3.0 Hz, 1 H), 3.70 (dd, J = 12.3, 6.0 Hz, 1 H), 3.74 (t, J = 6.8 Hz, 1 H), 3.85 (dd, J = 12.3, 3.5 Hz, 1 H), 4.10 (m, 1 H).

General Method for the $NaBH_3CN$ Reduction of Enaminoesters. To a solution of the enamino ester (1.0 equiv) and bromocresol green (trace amounts as an indicator) in MeOH (0.2 M) was added $NaBH_3CN$ (1.0 equiv). A 5% methanolic HCl solution was added dropwise until a yellow color persisted in solution. While the reaction mixture was stirred for 2 h, periodic addition of HCl was made to maintain a yellow color. The mixture was then diluted with CH_2Cl_2 (5 times the volume of MeOH), washed with 10% aqueous $NaHCO_3$ ($^1/_2$ the volume of CH_2Cl_2), and the organic phase was dried over Na_2SO_4. The solvent was evaporated and chromatography (70:30 petroleum ether/Et_2O) afforded the pure piperidines.

40 and 41: 0.110 g, 0.318 mmol, 100% yield, mixture of 40/41 (>90:10); ^{1}H NMR (300 MHz, $CDCl_3$) δ (major isomer) 0.98 (d, J = 6.9 Hz, 3 H), 1.13 (t, J = 7.1 Hz, 3 H), 1.14 (t, J = 7.1 Hz, 3 H), 1.37 (dq, J = 5.2, 12.4 Hz, 1 H), 1.56 (dq, J = 13.2, 3.0 Hz, 1 H), 1.72–1.92 (m, 2 H), 2.19 (dd, J = 7.4, 14.8 Hz, 1 H), 2.46 (dd, J = 6.9, 14.8 Hz, 1 H), 2.78 (dt, J = 4.9, 11.8 Hz, 1 H), 3.22 (dq, J = 4.7, 6.9 Hz, 1 H), 3.34 (m, 1 H), 3.67 (s, 2 H), 3.93–4.12 (m, 4 H), 7.12–7.31 (m, 5 H); (minor isomer) 0.93 (d, J = 7.0 Hz, 3 H), 1.19 (t, J = 7.3 Hz, 3 H), 1.20 (t, J = 7.3 Hz, 3 H), 1.62–1.77 (m, 3 H), 1.84 (m, 1 H), 2.34 (dd, J = 10.3, 14.2 Hz, 1 H), 2.65 (dd, J = 3.4, 14.2 Hz, 1 H), 2.73 (m, 1 H), 3.22–3.35 (m, 2 H), 3.75 (s, 2 H), 4.06 (q, J = 7.3 Hz, 2 H), 4.08 (q, J = 7.3 Hz, 2 H), 7.17–7.34 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (major isomer) 10.4, 14.1, 21.2, 28.2, 40.1, 41.5, 50.7, 51.9, 53.2, 60.1, 60.4, 126.6, 127.8, 128.2, 140.6, 172.1, 174.1; IR (neat) 3067, 3063, 3029, 2960, 2940, 2874, 2853, 1734, 1495, 1453, 1370, 1200, 1152, 1034, 733, 698 cm^{-1}; HRMS calcd for $C_{28}H_{29}NO_4$ *m/z* 347.2097, found *m/z* 347.2113.

57: 0.619 g, 1.27 mmol, 88% yield, mixture of isomers (>90:10); ^{1}H NMR (300 MHz, $CDCl_3$) δ (major isomer) 1.17 (t, J = 7.2 Hz, 3 H), 1.53–1.78 (m, 3 H), 1.99 (m, 1 H), 2.43 (dd, J = 8.7, 14.2 Hz, 1 H), 2.60 (dd, J = 5.3, 14.2 Hz, 1 H), 2.95 (dt, J = 7.0, 4.5 Hz, 1 H), 3.24 (m, 1 H), 3.54 (dt, J = 4.2, 7.5 Hz, 1 H), 3.71 (m, 3 H), 4.03 (m, 1 H), 4.04 (q, J = 7.2 Hz, 2 H), 4.36 (s, 2 H), 4.42 (d, J = 11.4 Hz, 1 H), 4.55 (d, J = 11.4 Hz, 1 H), 7.16–7.38 (m, 15 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (major isomer) 14.1, 24.7, 25.4, 33.9, 52.7, 59.2, 60.2, 68.8, 70.8, 72.9, 74.2, 126.5, 127.3, 127.4, 127.5, 127.6, 128.0, 128.2, 128.3, 128.4, 138.4, 138.8, 140.7, 172.6; IR (neat) 3067, 3063, 3031, 2980, 2936, 2865, 1732, 1495, 1452, 1368, 1290, 1157, 1096, 1028, 737, 698 cm^{-1}; HRMS calcd for $C_{34}H_{37}NO_4$ *m/z* 487.2723, found *m/z* 487.2708.

Reduction of 57 to 59. To a solution of 57 (0.167 g, 0.342 mmol) in Et_2O was added $LiAlH_4$ (0.1 g, 2.63 mmol), and the mixture was stirred for 2 h. The reaction was quenched by addition of H_2O (0.1 mL), 15% aqueous NaOH (0.1 mL), and H_2O (0.3 mL). After the mixture was stirred for 1 h, the solution was filtered, and the solvents were evaporated to give 59 (0.133 g, 0.298 mmol) in 87% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16 (m, 1 H), 1.27 (s, 1 H), 1.41 (m, 1 H), 1.68 (m, 1 H), 1.94 (m, 1 H), 2.09 (m, 1 H), 2.27 (m, 1 H), 2.91 (m, 1 H), 3.40 (dt, J = 2.2, 10.5 Hz, 1 H), 3.48–3.68 (m, 3 H), 3.62 (d, J = 13.2 Hz, 1 H), 3.74 (dd, J = 8.0, 9.9 Hz, 1 H), 3.86 (dd, J = 3.7, 9.9 Hz, 1 H), 4.11 (d, J = 13.2 Hz, 1 H), 4.41 (d, J = 11.5 Hz, 1 H), 4.46 (d, J = 12.1 Hz, 1 H), 4.58 (d, J = 12.1 Hz, 1 H), 4.61 (d, J = 11.5 Hz, 1 H), 7.20–7.38 (m, 15 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.6, 26.6, 30.9, 50.6, 54.4, 57.1, 62.9, 68.2, 70.4, 72.3, 73.3, 126.9, 127.3, 127.4,

MSC: jo940171k BATCH: jo6b22 USER: eap69 PAGE: 10
DIV: @xy1dr/data2/CLS_pj/GRP_jo/JOB_i12/DIV_jo940171k DATE: 04/22/94

127.6, 128.3, 129.0, 138.2, 138.7, 140.0; IR (neat) 3405, 3067, 3063, 3029, 2936, 2861, 1496, 1455, 1100, 1075, 733, 698 cm^{-1}; HRMS calcd for $C_{28}H_{39}NO_2$ *m/z* 445.9956, found *m/z* 445.2619.

Swern Oxidation of 59 to 60. To a solution of oxalyl chloride (0.057 g, 0.45 mmol) in CH_2Cl_2 at −70 °C was added a solution of DMSO (0.070 g, 0.90 mmol) in CH_2Cl_2 (1 mL). After 10 min, a solution of **59** (0.133 g, 0.297 mmol) in CH_2Cl_2 (2 mL) was added. The mixture was allowed to stir for 45 min at −65 °C, and then NEt_3 (0.182 g, 1.8 mmol) was added. After the mixture was stirred for 20 min at −65 °C, it was warmed to rt for 1 h. The mixture was quenched with 10% aqueous $NaHCO_3$ and then extracted with 3 × 10 mL of CH_2Cl_2. The solvents were evaporated and the aldehyde was used immediately without further purification.

Wittig Homologation of 60 to 61. A mixture of **45** (0.168 g, 0.6 mmol) and PPh_3 (0.157 g, 0.6 mmol) was heated at reflux in toluene (2 mL) for 48 h. After the solution was cooled to rt, the solvent was removed under vacuum and THF (2 mL) was added. A solution of BuLi (2.5 M in hexane, 0.24 mL, 0.6 mmol) was added to the phosphonium salt at −78 °C and the mixture was stirred for 15 min at −78 °C and then stirred for 1 h at rt. The resulting ylide solution was cooled to −78 °C and **60** (0.137 g, 0.296 mmol) in THF (1 mL) was added. After the mixture was warmed to −45 °C over 2 h, it was stirred at that temperature for an additional 1 h, warmed to 0 °C for 3 h, and stirred an additional 2 h at rt. The reaction was quenched with H_2O (10 mL) and then the solution extracted with 3 × 20 mL of CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated. The oil was purified by chromatography (90:10 to 80:20 petroleum ether/Et_2O) to give **61** (0.102 g, 0.163 mmol) in 55% yield (cis/trans 85:15): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, J = 7.4 Hz, 3 H), 1.20–1.38 (m, 8 H), 1.44–1.75 (m, 6 H), 1.88–2.20 (m, 4 H), 2.22–2.35 (m, 2 H) 2.58 (m, 1 H, trans isomer), 2.69 (m, 1 H), 2.83 (dt, J = 7.4, 3.8 Hz, 1 H, trans isomer), 3.01 (dt, J = 7.4, 4.3 Hz, 1 H), 3.54 (m, 1 H), 3.68–3.78 (m, 3 H), 3.91 (s, 4 H), 4.06 (d, J = 14.0 Hz, 1 H, trans isomer), 4.08 (d, J = 13.7 Hz, 1 H), 4.39 (s, 2 H), 4.42 (d, J = 11.5 Hz, 1 H), 4.43 (d, J = 11.5 Hz, 1 H, trans isomer), 4.55 (d, J = 11.5 Hz, 1 H, trans isomer), 4.56 (d, J = 11.5 Hz, 1 H), 5.21 (m, 1 H), 5.34 (m, 1 H), 7.16–7.41 (m, 15 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (cis isomer) 8.1, 23.7, 25.0, 25.4, 27.4, 29.1, 29.2, 29.4, 29.5, 29.6, 29.7, 29.8, 52.5, 55.0, 58.9, 64.9, 68.7, 70.8, 72.9, 74.6, 112.1, 126.4, 127.2, 127.3, 127.4, 127.6, 128.0, 128.3, 128.4, 131.1, 138.4, 138.8, 141.1; (trans isomer) 8.1, 23.5, 25.0, 27.2, 29.1, 29.2, 29.4, 29.5, 29.6, 29.7, 29.8, 52.4, 54.8, 58.8, 64.9, 68.7, 70.8, 72.9, 74.6, 112.0, 126.2, 126.9, 127.3, 127.4, 127.7, 127.8, 128.2, 128.3, 128.4, 131.3, 138.4, 138.9, 141.2; IR (neat) 3100, 3080, 3029, 2930, 2855, 1453, 1075, 733, 696 cm^{-1}; HRMS calcd for $C_{41}H_{59}NO$, *m/z* 625.4131, found *m/z* 625.4112.

Preparation of 7. To a solution of **61** (0.099 g, 0.158 mmol) in THF (8 mL) was added 10% aqueous HCl (4 mL). After the mixture was stirred for 2 h, saturated aqueous $NaHCO_3$ (10 mL) was added, and the mixture was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2CO_3) and concentrated. In preparation for hydrogenation, the residue was dissolved in EtOH (10 mL), and concd HCl (20 drops) was added. To this mixture was added 10% Pd on carbon (0.05 g), and the solution was stirred under H_2 (3 atm) for 24 h. The mixture was filtered and concentrated. The residue was dissolved in 20 mL of $CHCl_3$, washed with saturated aqueous $NaHCO_3$ and extracted with 4 × 20 mL of $CHCl_3$, and the combined organic layers were dried over Na_2SO_4. Filtration through basic alumina with $CHCl_3$ and MeOH, followed by removal of solvent, produced crystals, which were washed with a minimum amount of acetone and dried under vacuum to give **7** (0.045 g, 0.142 mmol) in 90% yield as white crystals: mp 88–89 °C (from acetone); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 (t, J = 7.3 Hz, 3 H), 1.23–1.41 (m, 13 H), 1.44–1.61 (m, 5 H), 1.66 (m, 1 H), 1.74 (m, 1 H), 2.07 (bs, 3 H), 2.39 (t, J = 7.5 Hz, 2 H), 2.41 (q, J = 7.3 Hz, 2 H), 2.76 (m, 1 H), 2.87 (dt, J = 5.5, 7.7 Hz, 1 H), 3.53 (ddd, J = 4.0, 5.6, 6.9 Hz, 1 H), 3.61 (dd, J = 5.4, 10.5 Hz, 1 H), 3.65 (dd, J = 7.8, 10.5 Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 7.8, 23.9, 26.3, 27.4, 28.6, 29.2, 29.3, 29.4, 29.6, 33.9, 35.8, 42.4, 49.7, 58.1, 62.3, 68.1, 212.0; IR (neat) 3320, 2926, 2855, 1717, 1460, 1377, 1275, 1119, 1073, 723 cm^{-1}; HRMS calcd for M-1 of $C_{28}H_{54}NO_2$ *m/z* 312.2540, found *m/z* 312.2540.

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Supplementary Material Available: Experimental procedures for **24**, **36**, **37**, **49**, **63**, **64**, and **65** and copies of ^{1}H NMR spectra of all compounds in the Experimental Section (49 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

USER: PAGE: 5 DATE: 04/18/94 TIME: 17:27:27
DIV: @xy2dir/data2/CLS_pj/GRP_simprt/JOB_simprt/DIV_simsoftin

Author Index Entries

MSC: jo940171k BATCH: jo6b22 VOLUME: 059 ISSUE: 012

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