INTRAMOLECULAR [4+1] PYRROLINE ANNULATION AS A GENERAL METHOD FOR THE SYNTHESIS OF PYRROLIZIDINE ALKALOIDS.

by

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in

Chemistry

APPROVED:

Tomas Hudlicky, Chairman

J. F. Wolfe

J. G. Mason

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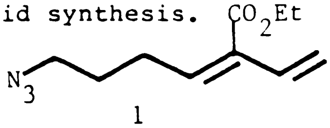
(ABSTRACT)

A general methodology for the synthesis of pyrrolizidine alkaloids has been developed. The two key steps in the sequence were the synthesis of the dienic azide system **1** and its regioisomer **2** by utilizing the vinylogous Reformatsky reaction, and the intramolecular additions of the azide moiety across the activated dienes with subsequent pyrolyses to provide the pyrrolizidines of type **3**. This study broadened the scope of the vinylogous Reformatsky reaction to include the preparation of alkaloid synthons and introduced the heteroatom equivalent of the carbenoid [4+1] annulation as a method of alkaloid synthesis.



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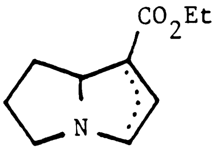

3

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TABLE OF CONTENTS

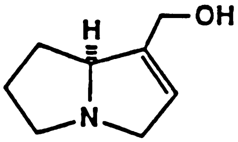
I. INTRODUCTION

Pyrrolizidine alkaloids are among the most targeted natural products being synthesized. These alkaloids, some of which are shown in Scheme 1, all posses a common azabicyclo[3,3,0]octane system with oxygenation occurring in both rings of the fused system.

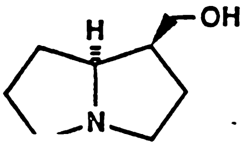
These alkaloids have been found mainly in the plant kingdom in the Boraginaceae, Leguminosae and Composite plant families.[1] These simple ring fused alkaloids possess a wide variety of biological activities ranging from anti-inflammatory and antiviral properties to hepatoxcities and carcinogenesis.[2] Although the pyrrolizidine alkaloids, all possess the same gross structure, they differ radically in their biological activity, leading one to the conclusion that the activity is dependent upon the substitution pattern of the ring system.

The less oxygenated species, such as supinidine **4** and isoretronecanol **5** have been the most frequently studied as targets for total synthesis. The total syntheses, whether complete or formal have been accomplished using many different strategies with a varying degree of generality. It was with the idea of the generation a general method for the synthesis of the pyrrolizidine alkaloids that the work herein is discussed, the problem was first approached as a model study in which a synhtesis of a pyrrolizidine skeleton, a bicyclic system without any substitution, was constructed. This was eventually abandoned for the direct-approach, in which the supinidine precursor, **3a**, was the target. It is within the context of a generalized approach to the pyrrolizidine alkaloids that the work described herein is presented.

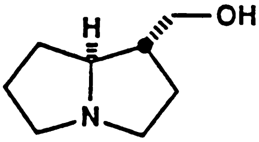
Table 1



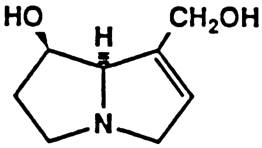
4 , supinidine



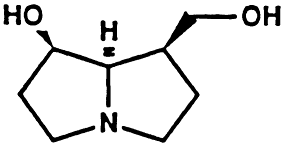
5 , isoretronecanol



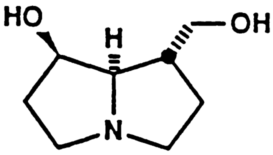
6 , trachelanthamidine



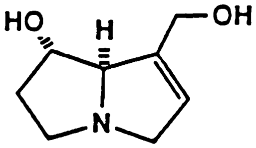
7 retronecine



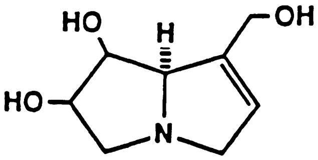
8 platynecine



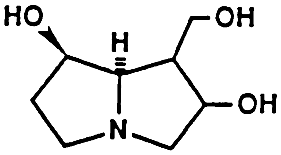
9 hastanecine



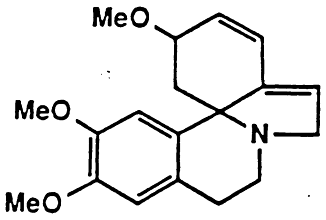
10 heliotridine



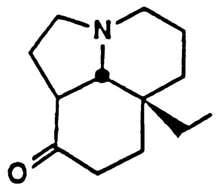
11 crotanecine



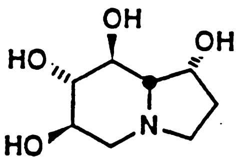
12 rosmarinecine



13 erysotrine



14 aspidospermine precursor

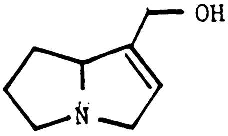


15 castanospermine

II. HISTORICAL

A. Isolation and Characterization

In 1936 G. P. Menshikov[3] isolated and characterized an alkaloid from Lindelofia anchusoides and named it isoretronecanol **5**. Again, in 1945 Menshikov[4] isolated alkaloids from Trachelanthus koulkovi. One of the alkaloids, that he named trachelanthamidine, had the structure **6**. This structure was again proven correct by Menshikov[5] in 1949. In 1949, G. P. Menshikov and E. L. Gurevich[6] isolated several alkaloids from the plant family Bornginaceae (Heliotropium supinium). One of the alkaloids was found to have the structure 4, and named supinidine. This structure was proven correct again in 1958 by F. L. Warren and M. E. Von Klemperer[7].



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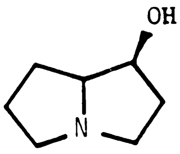
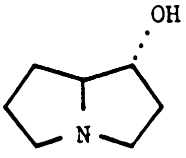


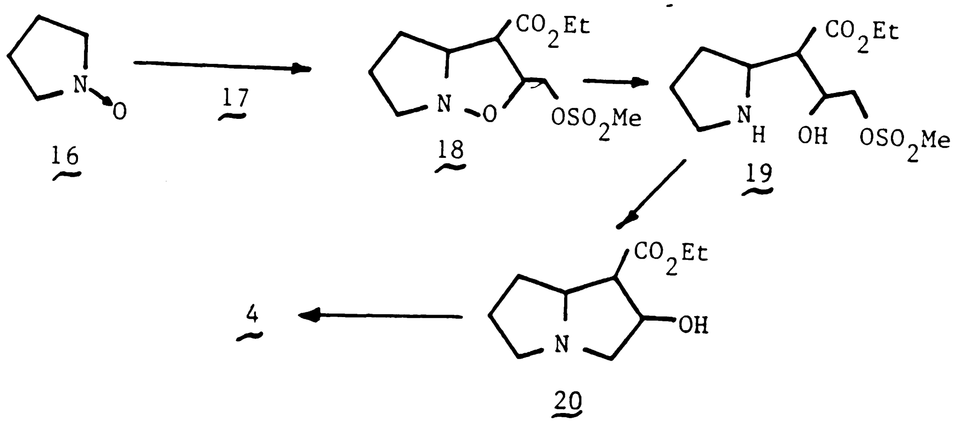
5



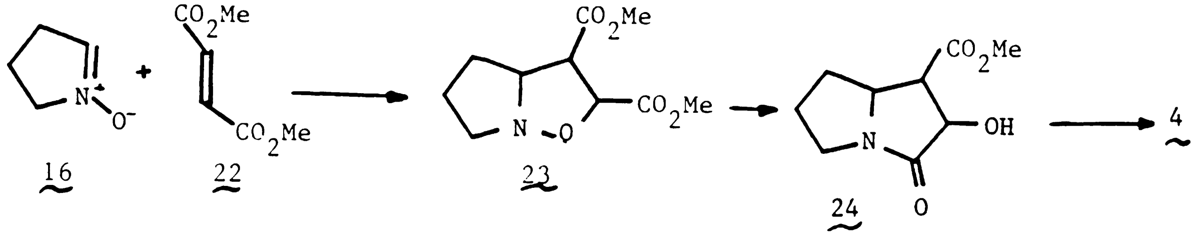
6

B. Synthesis of Supinidine, Isoretronecanol and Trachelanthamidine

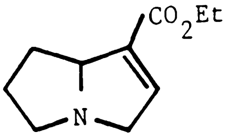
The first synthesis of supinidine **4** was accomplished in 1971 by Tufariello[8]. Using pyrroline oxide **16** as a starting material, reaction with δ-hydroxycrotonate **17** yielded, after protection, the isoxazolidine **18**. Subsequent hydrogenolytic cleavage led to pyrrolizidine **20** via amino alcohol **19**. Dehydration and reduction led to supinidine **4**.



In 1975 Tufariello[9] again synthesized supindine in a similiar fashion. The addition of nitrone **16** to a symmetrical dipolaraphile **22** yielded aminoether **23.** Subsequent hydrogenolytic cleavage and condensation led to **24** whose dehydration and reduction yielded supinidine **4.**

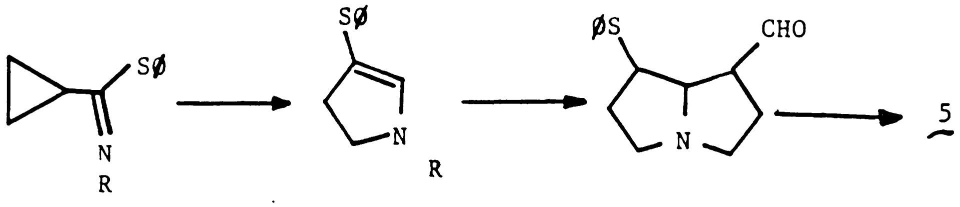


The methodologies involved in the synthesis of the pyrrolizidines closely related to supinidine **4,** isoretronecanol **5** and trachelanthamidine **6** overlap in many instances since **5** and **6** can be prepared from supinidine precursor **3a.**



3a

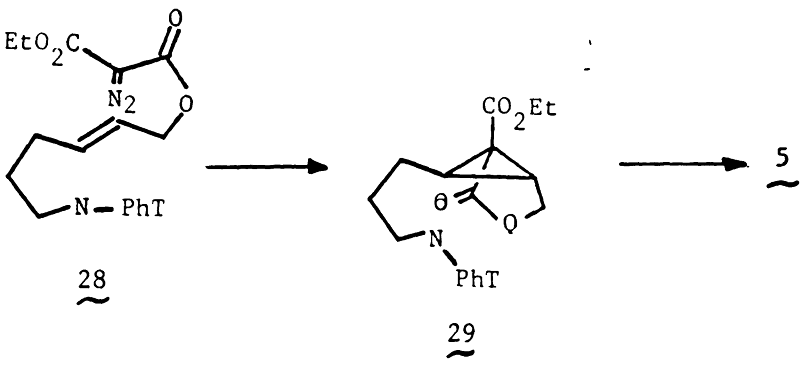
In 1976 R. V. Stevens[10] et. al employed an acid catalyzed rearrangement of a cyclopropyl imine **25** to pyrroline **26** as the key transformation in the synthesis of (dl)-isoretronecanol **5**. This synthetic effort was especially noteworthy due to its potential as a general methodology. Pyrroline **26** was transformed via an acid catalized cyclization (with an ammonium cation intermediate) to give the isoretronecanol precursor **27**.



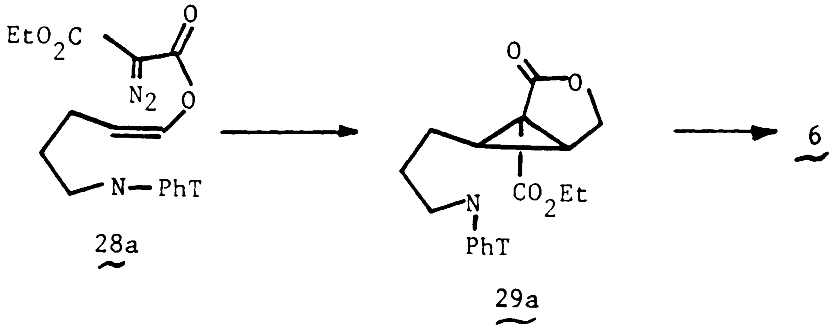
25 26 27

R= $(CH_2)_3CH(OEt)_2$

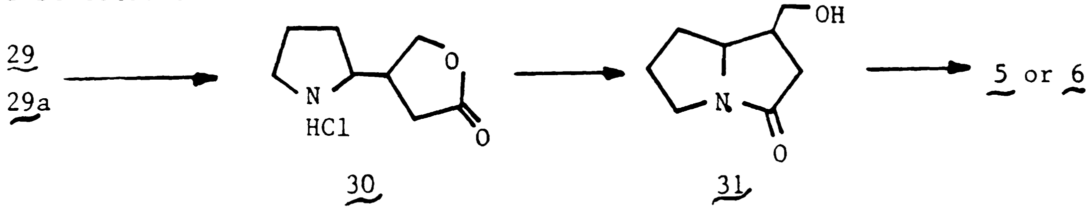
Danishefsky[11] published a synthesis of both C-4 epimers, **5** and **6**, in 1977 by utilization of a carbenoid addition to the olefin in **28** and **28a** to give **29** and **29a**.



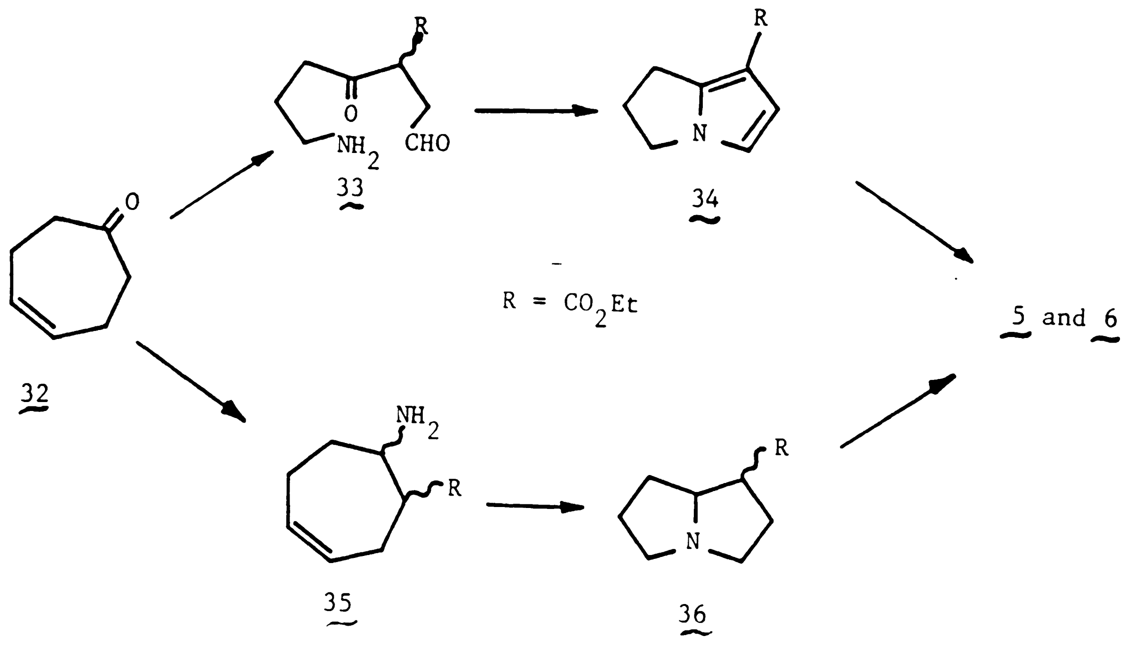
PhT = pthalimide



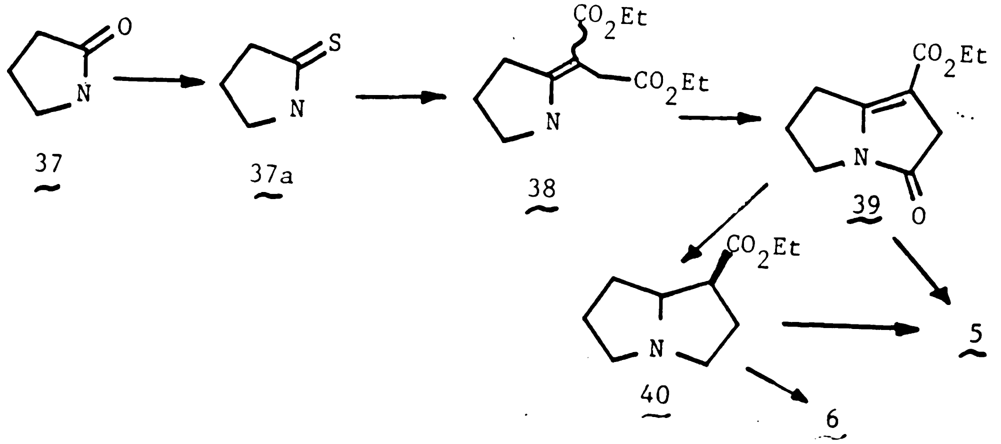
In this synthesis the substitution pattern of the olefin (whether Z or E) determined the product obtained. The Z olefin in **28a** gave trachelanthamidine **6** unequivocally while the E olefin led to isoretronecanol **5**. Once the cyclopropane was obtained, its intramolecular nucleophillic ring opening gave pyrroline **30**, which, upon methoxide treatment, yielded the γ-lactam **31** which was then elaborated to either 5 or **6** with base depending upon the original olefin substitution.



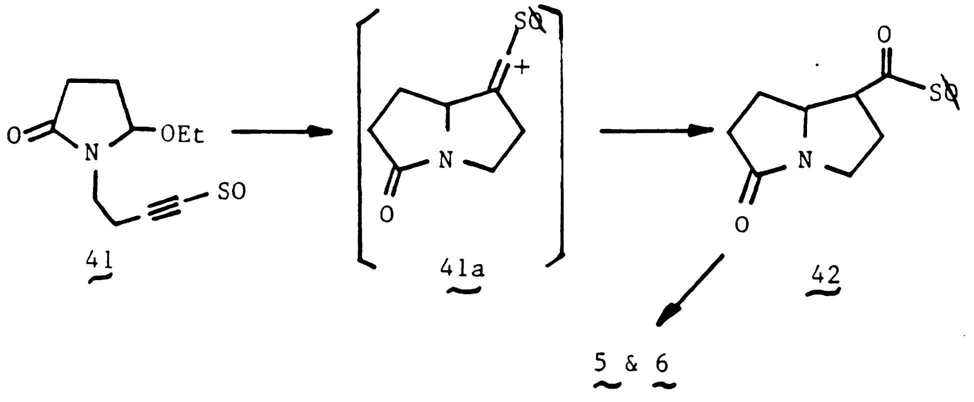
In the same year, Borch[12], employed a substituted cycloheptenone **32**, which upon ozonolysis of the olefin gave keto-aldehyde **33.** This substance underwent a slow cyclization to **34** which gave a mixture of **5** and **6** upon hydrogenation. In this synthetic effort **32** was also transformed into **35** via reductive amination of **32** on treatment with OsO_4-$NaIO_4$, subsequent $NaBH_3CN$ reductive cyclization gave **36.** Upon reduction with $LiAlH_4$ **17** was than transformed into 5 and **6** depending on the C_4 stereochemistry of the starting material involved.



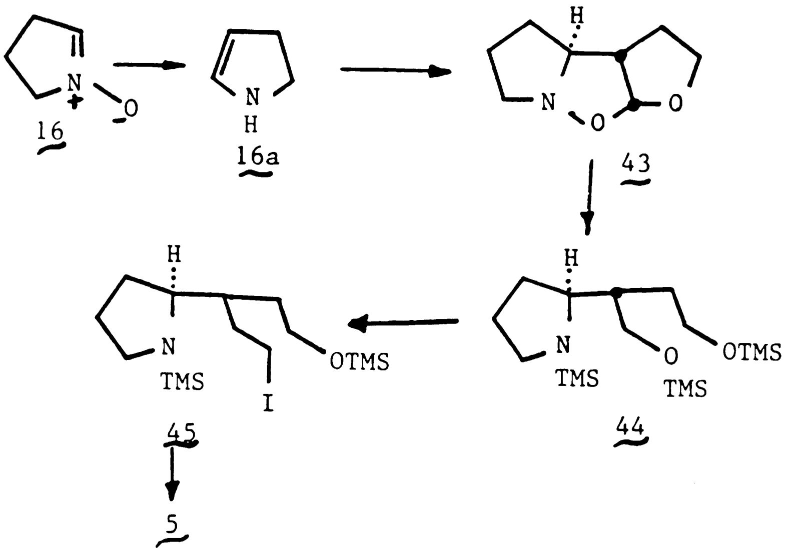
(dl)-Isoretronecanol and (dl)-trachelanthamidine were the targets of Pinnick in 1978. Pinnicks' route[13] used pyrrolidone as a starting material which was converted via thiopyrrolidone **37** into diester **38.** This material underwent hydride cyclization to give lactam **39,** which can be taken directly to **5.** Compound **39** was also reduced to **40** which can be transformed to **5,** or under heating with base will epimerize C-4 which was then elaborated to **6.**



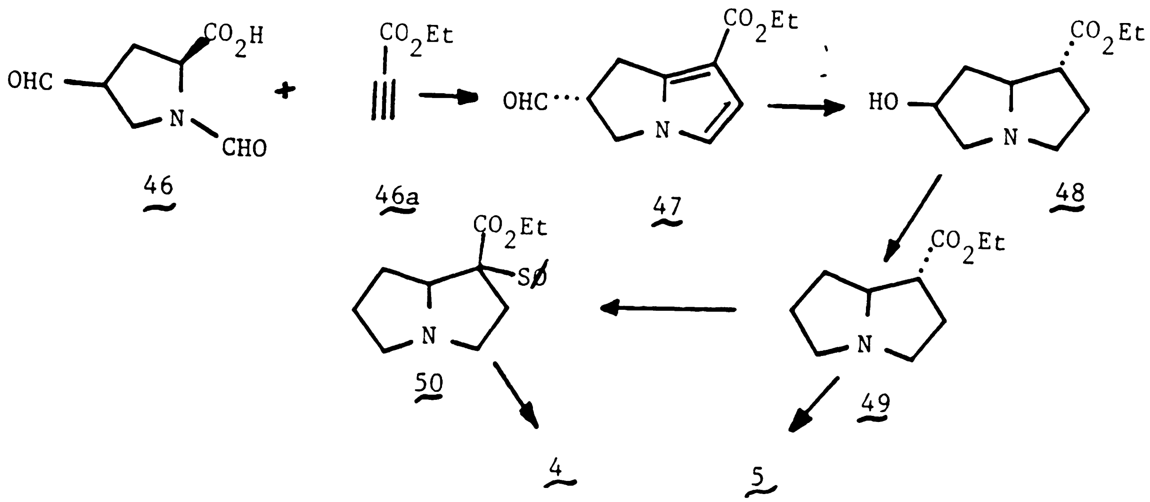
Speckamp[14] in 1979 employed the use of a reductive cyclization of phenylthioacetylene imide **41** to obtain the amide **42**, as a precursor to trachelanthamidine and isoretronecanol. The reaction of **41** to **42** was accomplished through an acid mediated cyclization with the cationic species **41a** as an intermediate. Reduction of **42** with $LiAlH_4$ proceeded to either **5** or **6** depending on the sterochemistry at C-4.



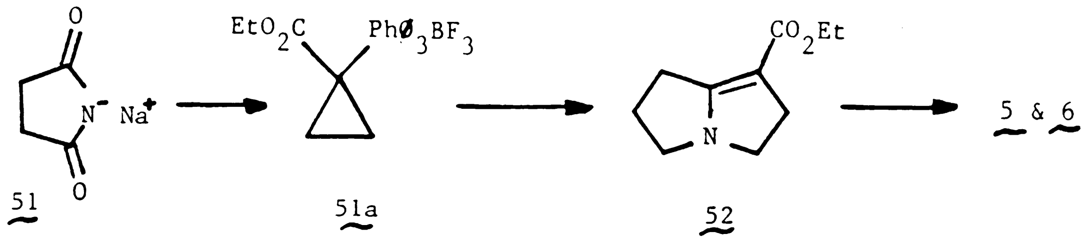
In 1979 a Japanese group headed by Iwashita[15] synthesized (dl)-isoretonecanol through utilization a 1,3-dipolar addition of pyrroline oxide **16** to dihydrofuran **16a.** The resulting amino ether **43** was reduced with $LiAlH_4$ to afford an aminodiol which was silylated to give **44.** This compound was treated with TMSI to give the C-4 iodide **45** (not isolated), which upon treatment with $\phi Me_3N^+F^-$ was transformed into isoretonecanol **5.**



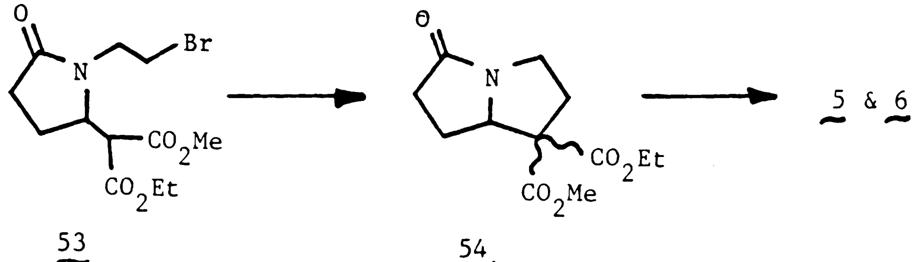
In 1979 Robins & Sakdavat[16] used another 1,3 dipolar addition of the formyl derivative **46** to ethyl propiolate **46a** to synthesize (+) isoretronecanol and (+)-supindine. The 1,3 dipolar addition gave diene **47** which upon hydrogenation and removal of the formal group gave the saturated ester **48.** The alcohol was removed via its conversion to chloride formation followed by reduction with H_2 and Raney Nickel to give ester **49** which was reduced to (+)-isoretronecanol and also converted to supinidine via formation and elimination of the C-4 phenylselenyl intermediate **50**



In 1980 Muchowski and Nelson[17] synthesized isoretronecanol via nucleophillic opening of a cyclopropane and subsequent intramolecular Wittig cyclization. Sodium succinimide **51** opening of carbethoxycyclopropyltriphenylphosphonium tetrafluoborate **51a** with subsequent intramolecular Wittig reaction led to pyrroline **52** which was hydrogenated and reduced with $LiAlH_4$ to give isoretronecanol and trachelanthamidine.

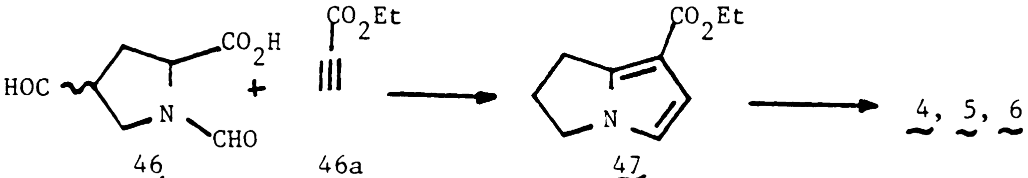


Kraus[18] in 1980 used an intramolecular alkylation as a key step in the synthesis of isoretronecanol and trachelanthamidine. Amide ester **53** underwent anionic intramolecular alkylation to give **54** whose decarboxylation, and reduction gave **5** and **6**.



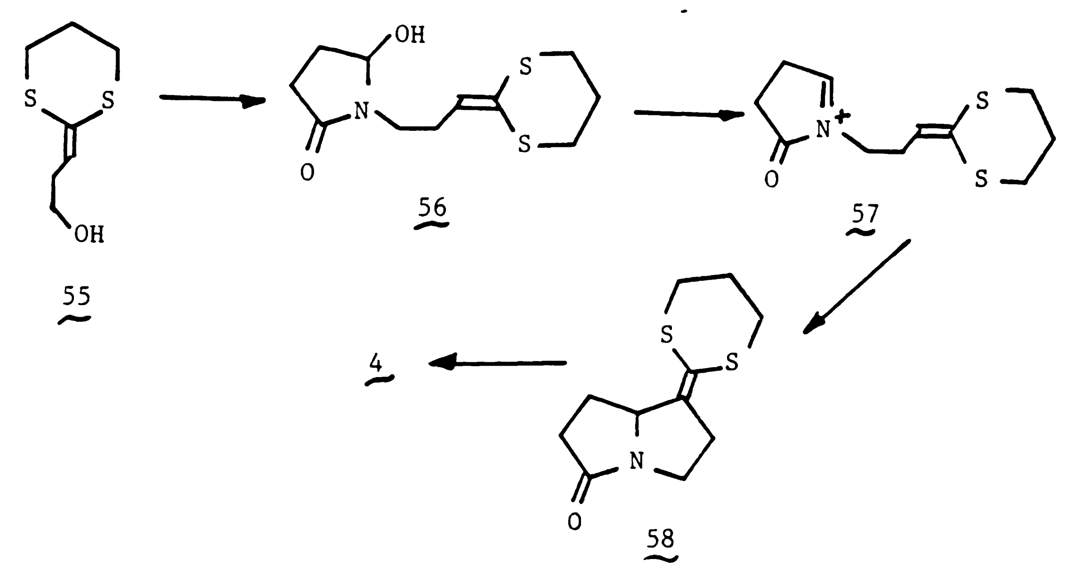
53 54

In 1981 Robins[19] again prepared **4, 5,** and **6** through 1,3 dipolar addition which he used in an earlier synthesis of supinidine. In this synthesis stereospecific hydrogenation was utilized for a chiral synthesis of **4, 5,** and **6.**



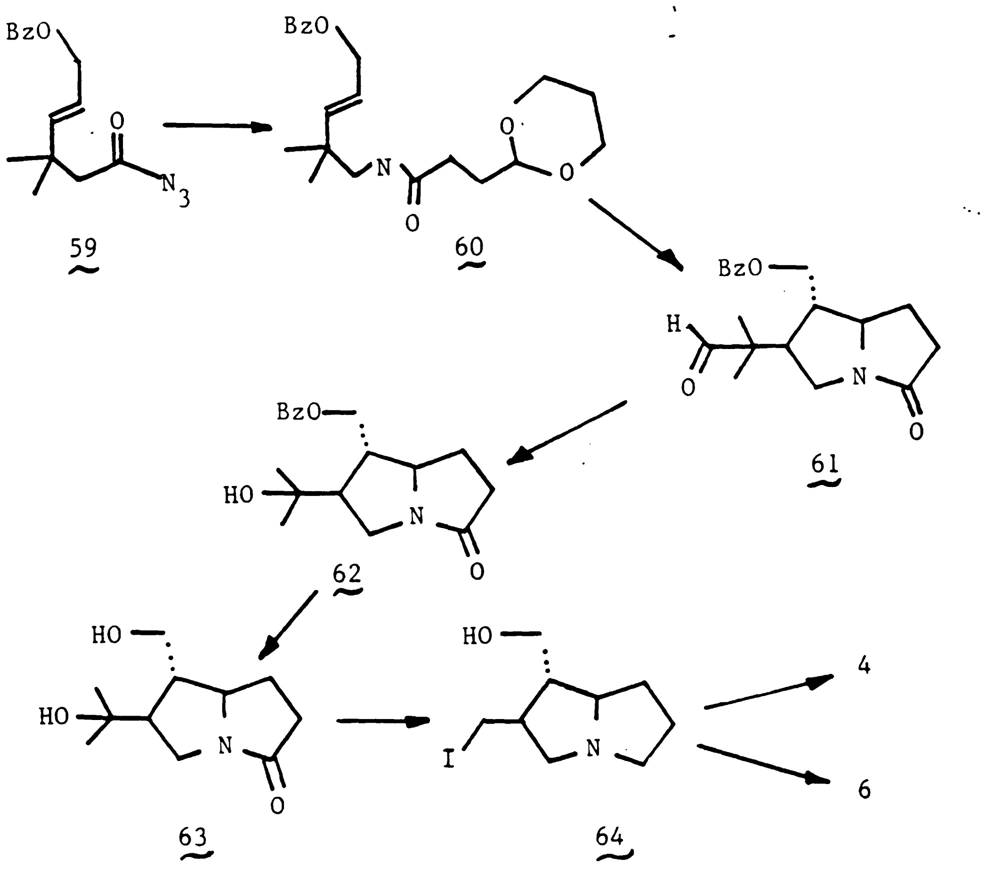
46 46a 47

In 1982 Chamberlin[20] prepared supinidine using a ketene thioacetal group **55** as a key intermediate through a Mitsunobu coupling[21] of **55** with

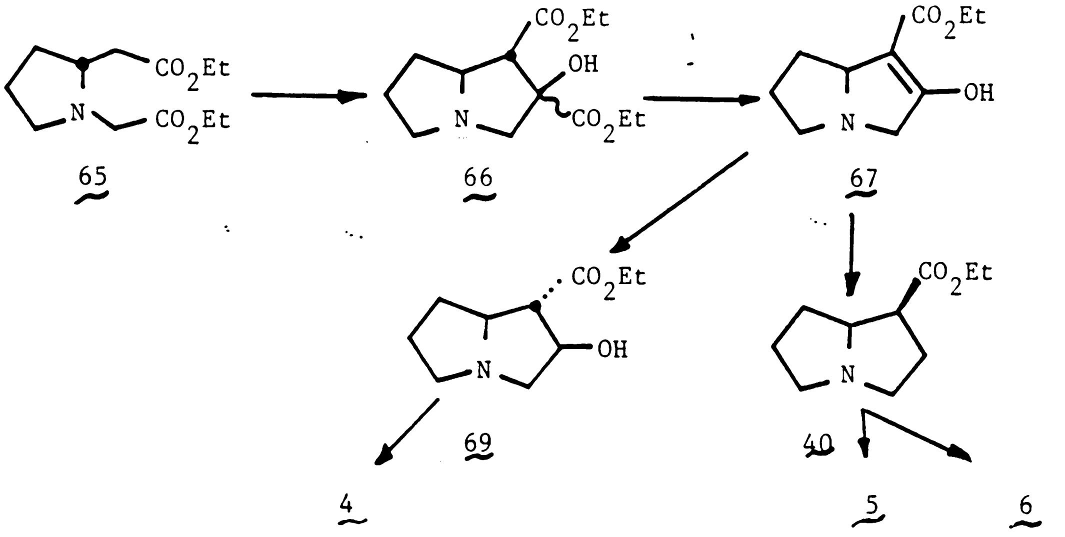


succinimide and reduction with $NaBH_4$ to give **56.** The cyclization step **56** → **58** was accomplished through an acyliminium ion **57.** The cyclization product **58** was transformed into supinidine by anionic double bond isomerization, thioacetal removal and reduction with $LiAlH_4$.

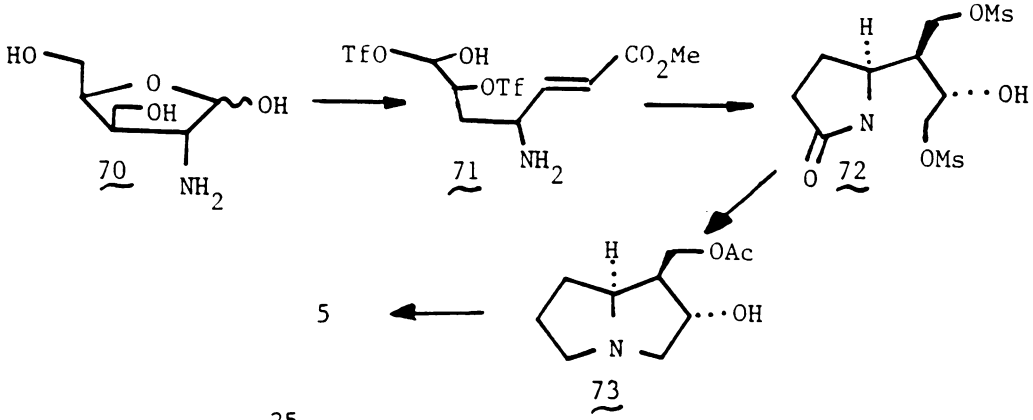
Hart[22] in 1982 used an N-acyliminium ion rearrangement-cyclization to synthesize trachelanthamidine and supinidine. Acyl azide **58** underwent a Curtius rearrangement followed by a Grignard reaction to give acetal **60.** Stirring of **60** in formic acid for an extended period of time gave **61** and **62.** Formate **61** was transformed into **62** by saponification. Modification of the C-3 substituent by hydrogenation and selective acylation gave **63.** Treatment with mercuric oxide and iodine gave a mixture of C-2 iodides **64.** These were converted into trachelanthamidine by treatment with tri-n-butyltin hydride followed by $LiAlH_4$ reduction. Supinidine resulted from dehydrohalogenation of the C-2 iodides and subsequent allylic acetate reduction with $LiAlH_4$.



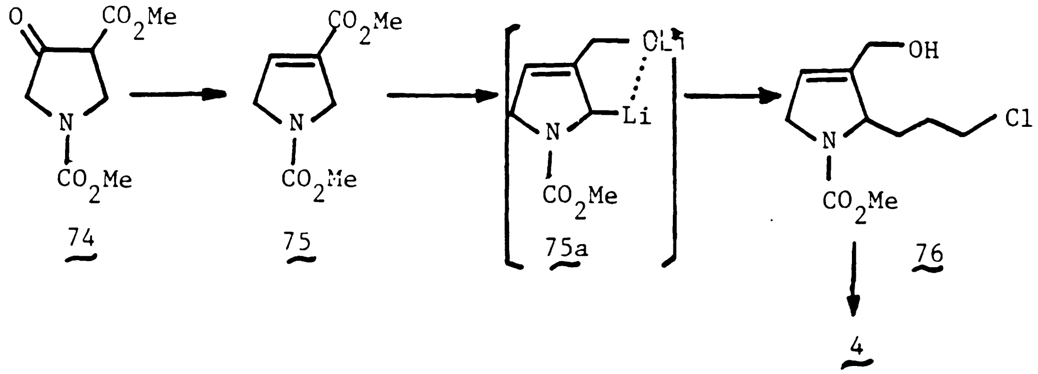
A Dieckmann cyclization was the key step in the chiral synthesis of (-)-**4**, (-)-**5** and (-)-**6** by Benn[23] in 1982. Diester **65** (from homolegation of s-pyroline (N-Cbz)) was cyclized to **66** under equilibrium conditions with sodium ethoxide. Treatment of **66** with acetic acid gave the unsaturated pyrrolizidine ester **67** which was then transformed into **40** under hydrogenation conditions. Reduction of **40** gave trachelanthamidine **5** while epimerization and subsequent reduction gave isoretranecanol **6.** Sodium cyanoborohydride reduction of **67** gave alcohol **69** which gave (-)-supinidine via the elimination of its mesylate.



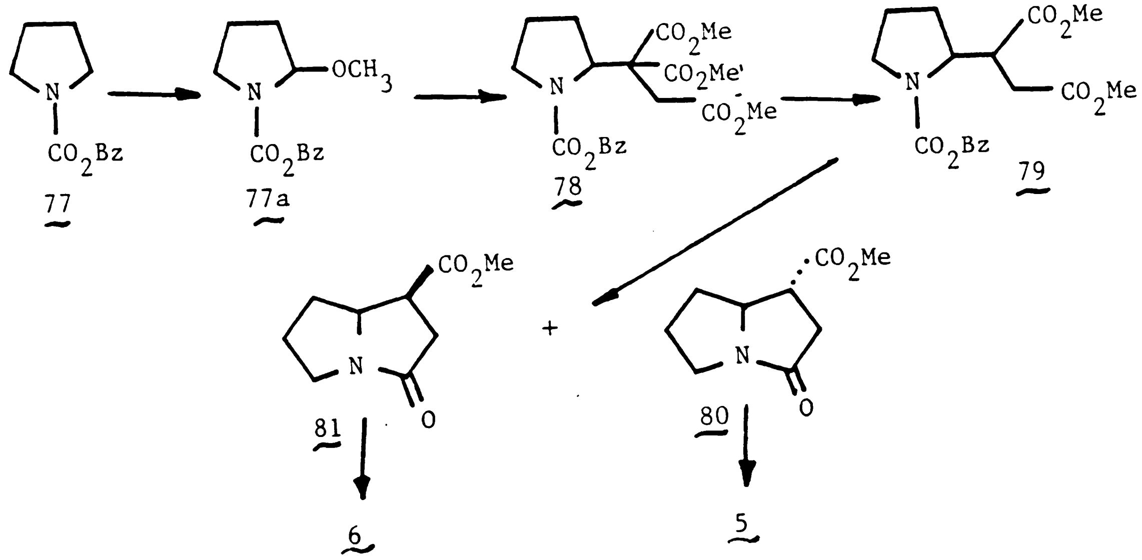
In 1983, Tatsuta[24] used D-glucasamine as a starting material and furanose **70** as a key intermediate. The sugar **70** was tritylated at C-2 and subjected to Wittig conditions to give **71** reduction, removal of the trityl group and mesylation of **71** afforded dimesylate **72**. Borane reduction gave the monoacetate **73**. Elimination, hydrogenation and deprotection of the acetate led to isoretronecanol **5**.



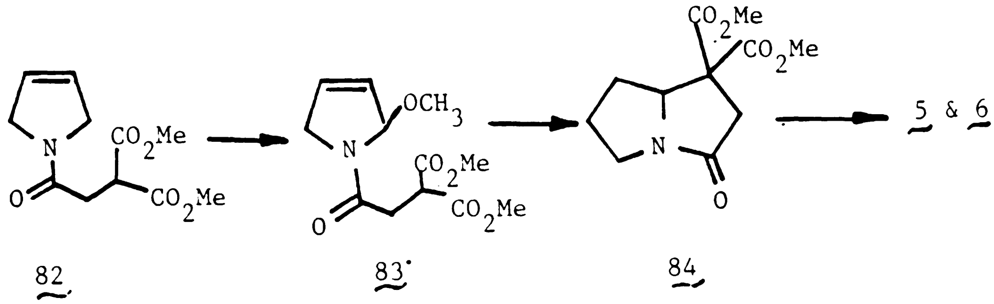
In 1983 MacDonald[25] used a 1,2 vicinal annulation to synthesize (dl)-supinidine. Reduction of pyrrolidine **74** followed by protection and subsequent elimination gave crystalline pyrroline **75**. Reduction of the ester moiety followed by alkylation gave **76**. Regioselective alkylation was thought to occur because of the ability for chelation between lithium and the alcohol in structure **75a**. N-decarbomethoxylation and in-situ cyclization afforded supinidine **4**.



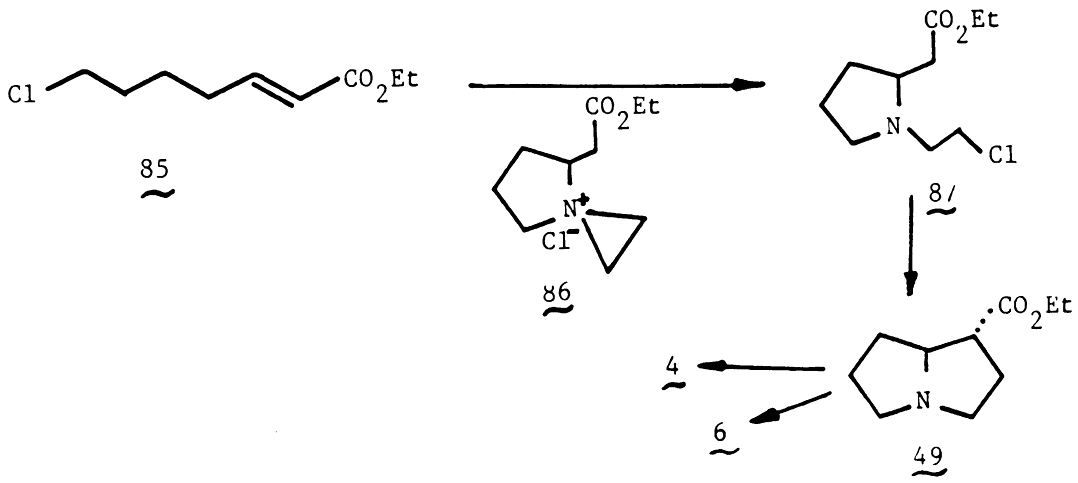
In 1984 Shono[26] and co-workers utilized pyrrolidine as a starting material in the synthesis of **5** and **6**. The benzyl carbonate of pyrrolidine **77** was α-methoxylated using aniodic oxidation to give **77a**. Acid catalyzed generation of a carbomethoxyiminium ion and a carbon-carbon bond formation with a triester gave **78** which was hydrolyzed, decarboxylated, and esterified to give diester **79**. This material was hydrogenated and the free amine cyclized in situ to give two isomers, **80** and **81**, which were isolated by distillation. $LiAlH_4$ reduction gave **5** and **6**.



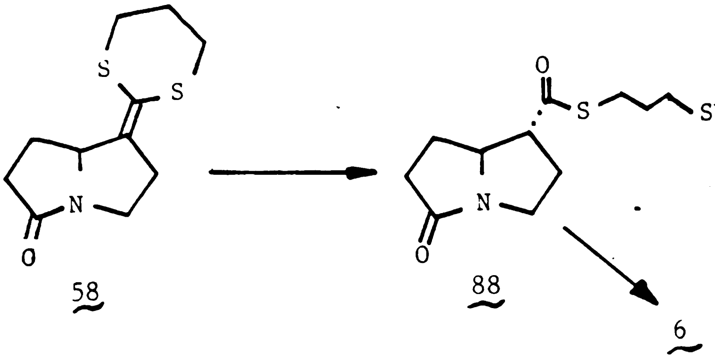
In 1984 anodic oxidation was used in a synthesis of **5** and **6** by Wistrand[27]. Starting with pyrrolidine, acylation gave **82**, which was subjected to anodic oxidation to provide **83**. Treatment of **83** with $AlCl_3$ gave pyrrolizidine **84** which after decarbomethoxylation and subsequent treatment with $LiAlH_4$ reduction gave **5** and **6**.



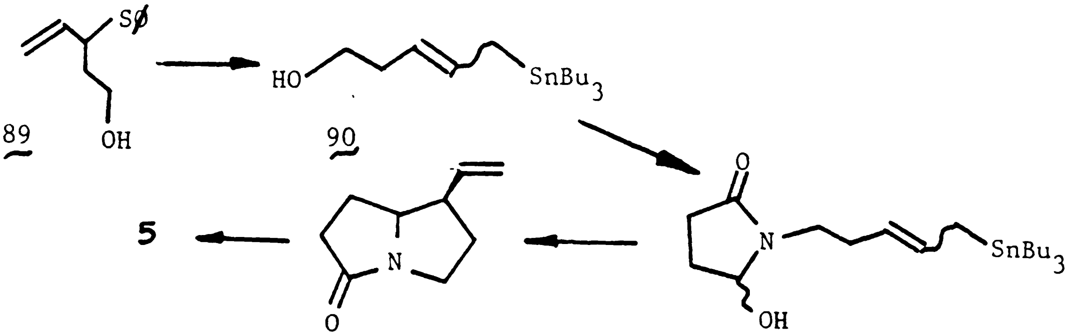
Kametani[28] used an intramolecular cyclization in order to prepare (dl)-trachelanthamidine and (dl) supindine. The α,β-unsaturated chloroester **85** was treated with an excess of aziridine to yield the pyrrolidine **87** through the proposed intermediate ammonium salt **86**. Intramolecular alkylation using LDA provided pyrrolizidine **49**. The attainment of which constitutes a formal synthesis of trachelanthamidine. Ester **49** was also phenylselenated via the procedure of Robins[11] and eliminated to give (dl) supindine.



In 1984 Chamberlin[29] synthesized (dl)-supinidine and (dl)-trachelanthamidine utilizing a method developed earlier in his group[13]. In Chamberlin's earlier synthesis the key step was an acyliminium ion cyclization of **57** to give thioacetal **58**. The synthesis of supinidine was the same as before while in the synthesis of trachelanthamidine, thioacetal **58** was stirred with perchloric acid to give **88**, which upon $LiAlH_4$ reduction gave trachelanthamidine **5**.

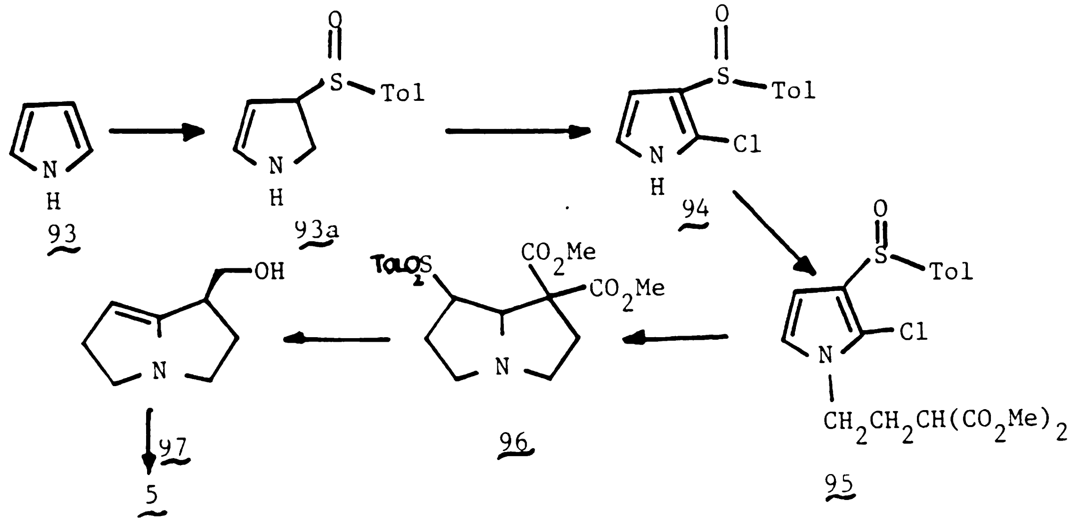


In 1985, Keck[30] employed a "two electron" cyclization of allylstannane in the synthesis of isoretronecanol. Alcohol **89** was transformed into stannane **90** via the procedure of Veno[30a]. Mitsunobu coupling with succinimide and subsequent reduction gave the hydroxylactam **91**. Treatment with methane sulfonylchloride and triethylamine led to pyrrolizidine **92** from which to (dl)-isoretronecanol was obtained after oxidative cleavage of the olefin and reduction with $LiAlH_4$.

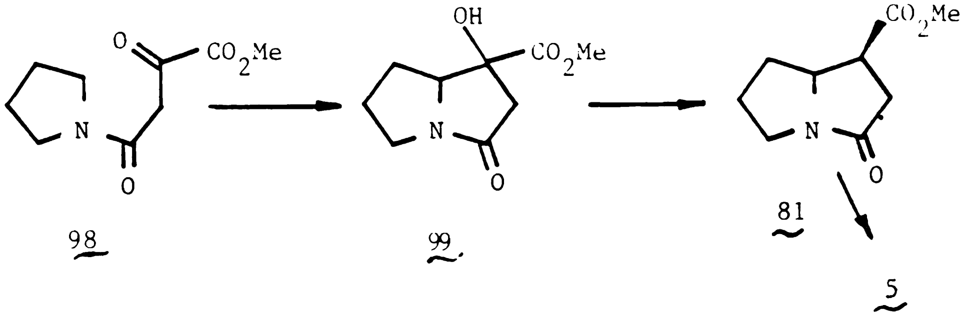


89 90 91 92

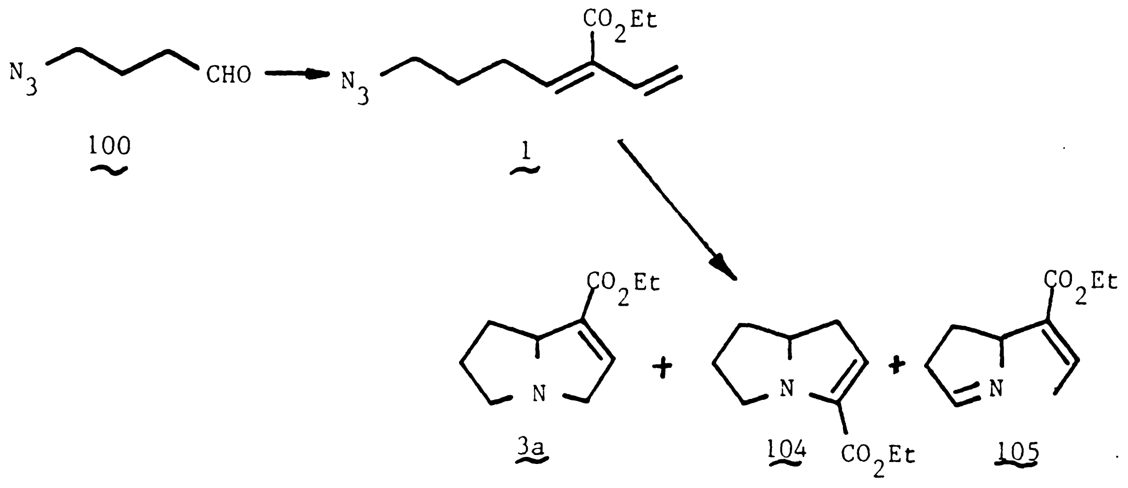
Greenhouse[31] utilized pyrrole in a 1985 publication dealing with the synthesis of (dl)-isoretronecanol. Pyrrole was treated with toluenesulfonyl chloride to give a mixture of C-2 and C-3 substituted pyrroles. Both C-2 & C-3 were taken to the C-3 substituted pyrrole **93** upon treatment with acid. After treatment with oxayl chloride and subsequent oxidation **93** was transformed into **94**. The anion of **94**, formed with sodium hydride, was treated with spiro[2,5]5,7 dioxa, 6,6-dimethyloctan-4,8-dione to give, after transesterification, the chlor-N-substituted diester pyrrole **95**. Cyclization to **96** occurred after the formation of the malonate anion followed by reflux. Basic hydrolysis, decarboxylation and esterification gave **97**. Reduction with $LiAlH_4$ and hydrogenation furnished (dl)isoretronecanol **5**.



In 1985, Gramain[32] used a key photochemical step in the synthesis of isoretronecanol. α-pyruvate **98** derived from acyl pyrrole was irradiated with a medium pressure mercury lamp to give lactam **99** whose dehydration and hydrogenation led to **81**. Reduction with $LiAlH_4$ gave isoretronecanol.

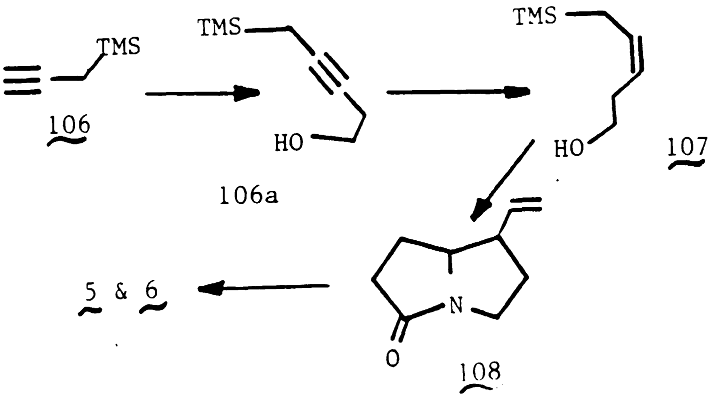


In 1985 Hudlicky[33] reported the formal synthesis of (dl)-supinidine via an intramolecular [4+1] pyrroline annulation. Dienic azide **1** was pyrrolyzed resulting in pyrrolizidine **3a, 104,** and imine **105.** Dienic azide **1** was obtained from azido aldehyde **100.** The attainment of pyrrolizidene **3a** represented a formal synthesis of supinidine.

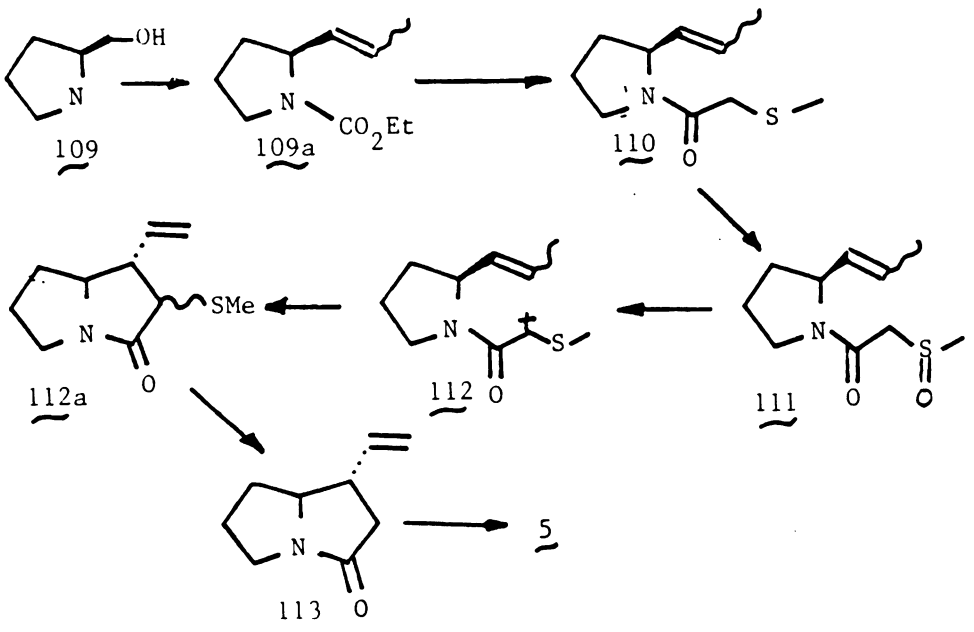


Also in 1985 Pearson[34] reported on the formal synthesis of (±) supinidine. Like Hudlicky[33], Pearson used the intramolecular additional of azide to a diene to give pyrrolizidines **3a, 104** and imine **105** under pyrrolytic conditions.

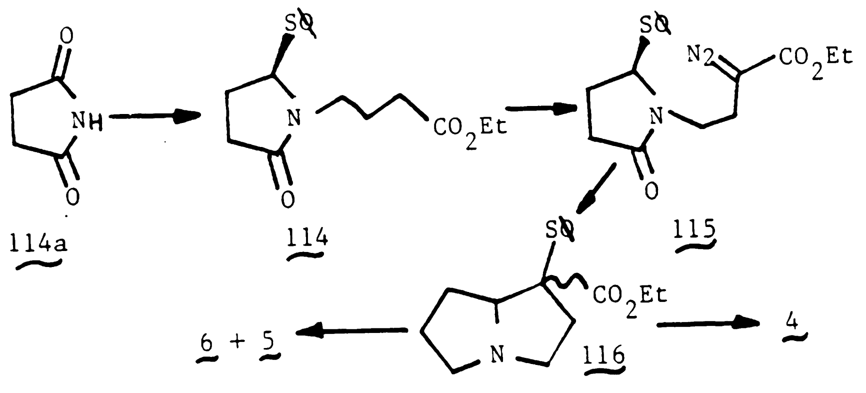
In 1985 Speckamp[35] utilized an acylic TMS alcohol as a intermediate in the synthesis of **5** and **6.** Starting with the TMS allylic acetylene **106** alkylation with oxirane gave **106a** which was reduced to give **107.** Condensation of **107** with pyrrolidine gave, after trifluoroacetic acid cyclization, the pyrrolizidine **108.** Ozonloysis and reduction with lithium aluminum hydride ga0ve **5** and **6.**



In 1986 Ishibashi[36] synthesized optically active trachelanthamidine by starting with optically active prolinol **109.** N-ethoxycarbonylation followed by Swern oxidation[37] and Wittig reaction (with ethylidenetriphyenylphosphorance) gave n-ethoxyolefin **109a.** Deprotection and N-acylation gave sulfide **110,** which was oxidized to give the sulfoxide **111.** Cyclization occurred with trifluoroacetic anhydride. A suspected intermediate was cation **112.** The resultant amide olefin **112a** was oxidized with $NaIO_4$ and reduced with aluminum amalgam to afford the lactam **113.** Oxidative cleavage with $OsO_4/NaIO_4$ and reduction with $LiAlH_4$ yielded (-)trachelanthamidine.

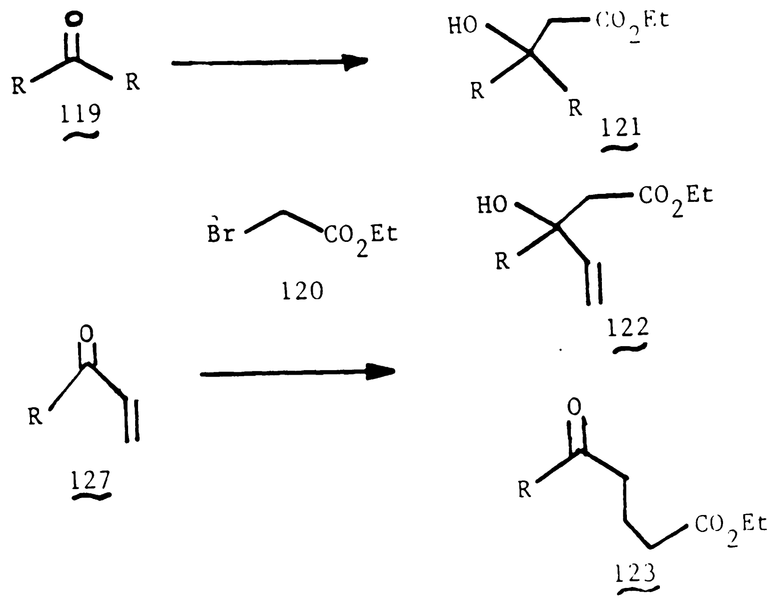


Also in 1986 Kametani[38] synthesized (dl)-supindinde, (dl)-isoretronecanol and (dl)-trachelanthamidine starting with succimide **(114a)**. N-alkylation, reduction with $NaBH_4$ and thiophenol treatment yielded the lactam **114**. Diazotization, preceeded by treatment with ethylformate, gave the diazo sulphide **115**, which upon heating in benzene gave pyrrolizidine **116**. Oxidative elimination and reduction gave (dl)-supindine while treatment with raney nickel gave the lactams **117** and **118** which represent a formal synthesis of (dl)-trachelanthamidine and (dl)-isoretronecenol.



C. The Reformatsky Reaction

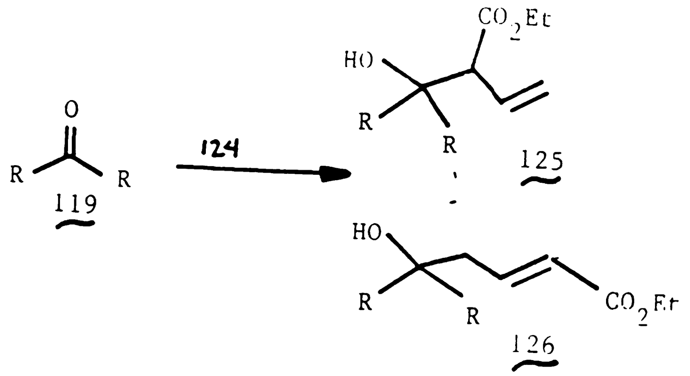
The Reformatsky Reaction[39] is a facile method of carbon carbon bond formation, first reported for the addition of bromoesters to both saturated ketones and α,β unsaturated ketones[39a].



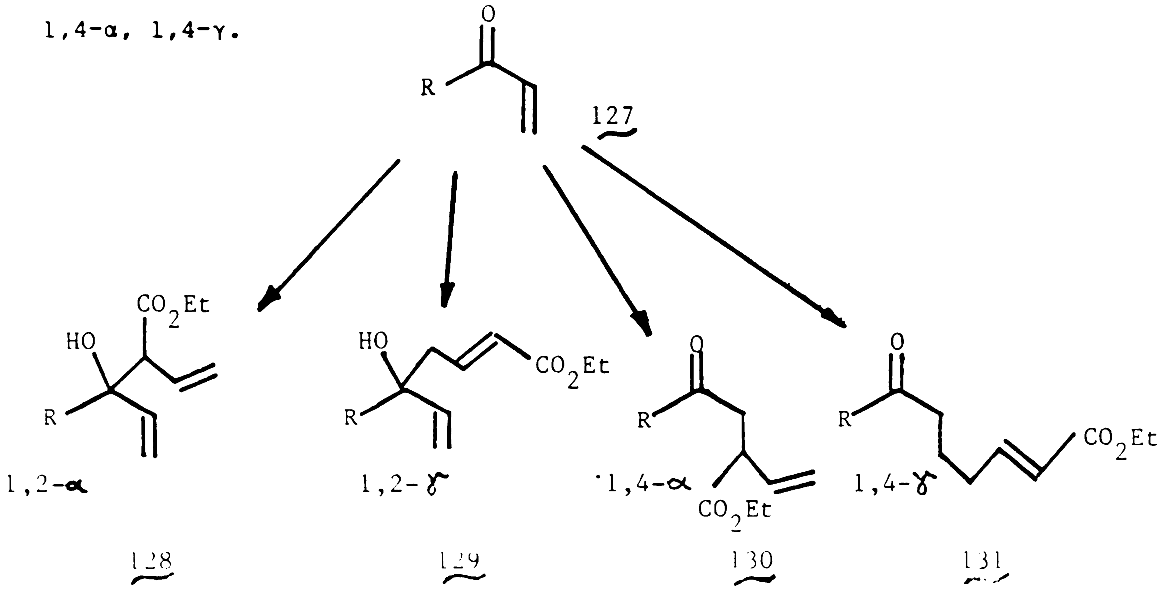
In the late 1970's the use of this reaction was extended to include the use of vinylogous substrate **124** in its addition to carbonyl compounds. The vinylogous substrate (ehtyl 4-bromocrotonate) was found

124

to add in ether an α addition mode or a γ addition mode to ketones and aldehydes[40a].



The mode of addition was found to be in direct correlation to the hardness/softness of the metal catalyst and to the polarity of the solvent used in the reaction medium. After extensive investigation Hudlicky and co-workers found that the use of a Zn-Cu couple[40a] in diethylether with a trace of acid, led exclusively to the α adduct. Later investigations by Hudlicky[40b] revealed that additions of bromocrotonate across α,β unsaturated ketones and aldehydes resulted in the selective preparation of all four possible products, 1,2-α, 1,2-γ, 1,4-α, 1,4-γ.

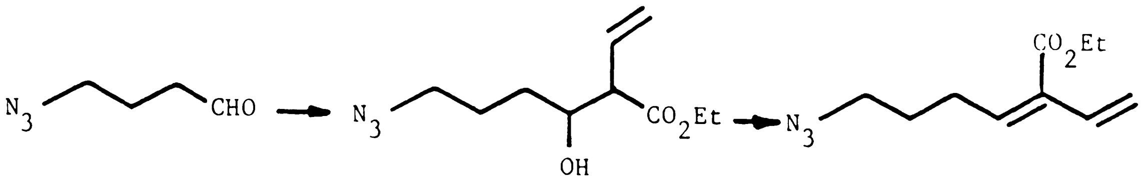


Naturally the conditions to obtain 1 of 4 possible products are more complicated than the simple saturated ketone case. The addition of the crotonate unit across a saturated ketone in a controlled manner offers a valuable tool to workers in the synthetic community because:

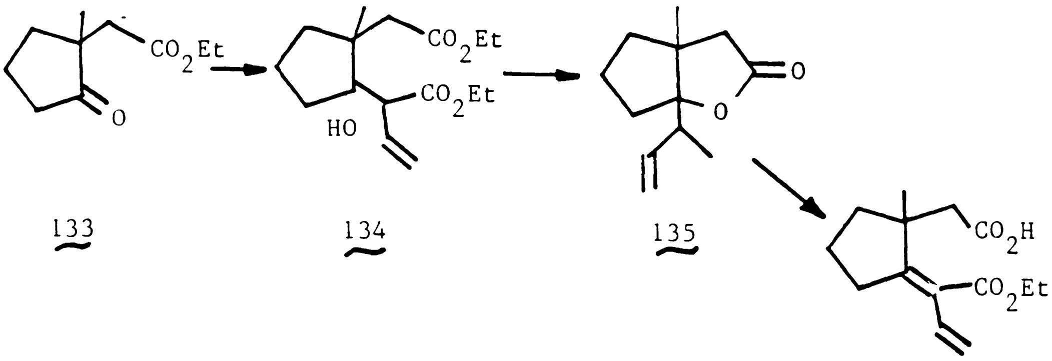
(1) - it represents a facile carbon-carbon bond formation

(2) - manipulation to gain either α or γ addition is controlled by simply changing catalyst and solvent.

The addition of bromocrotonate to ketones and aldehydes has been used successfully in several syntheses. Hudlicky has used the reaction in synthetic work in the area of terpenes[40c] and heterocycles[33]. In both of these syntheses the Reformatsky reaction was used as a prelude to a diene moiety being placed in the synthetic scheme.



100 132 1



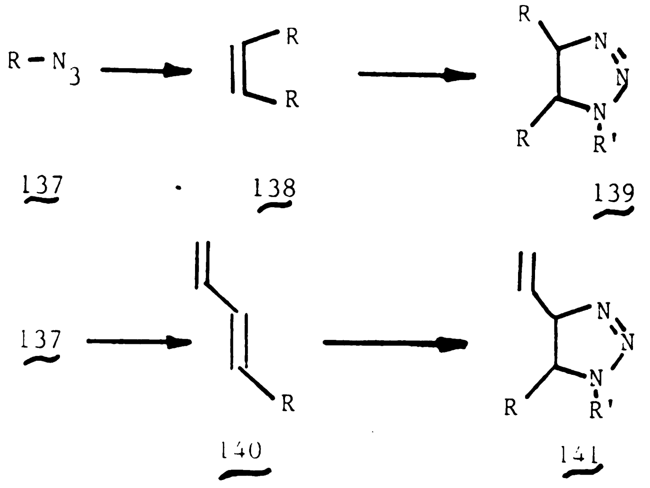
133 134 135 136

In the heterocyclic case the alcohol produced was protected and later eliminated with base to give the requisite diene system. In the terpene case, however, the alkoxide was trapped intramolecularly as the lactone. Lactone cleavage under basic conditions yielded the dienic system.

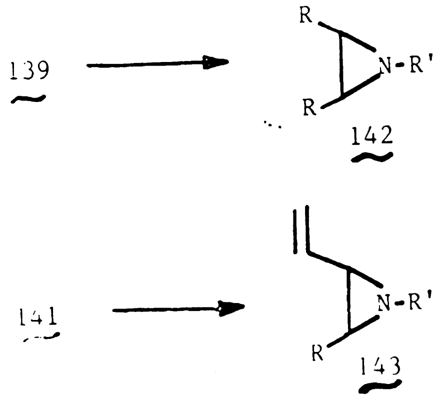
In both cases the diene system produced major synthetic intermediates which, until the advent of the Reformatsky reaction were somewhat difficult to obtain.

D. Azide Additions to Olefins

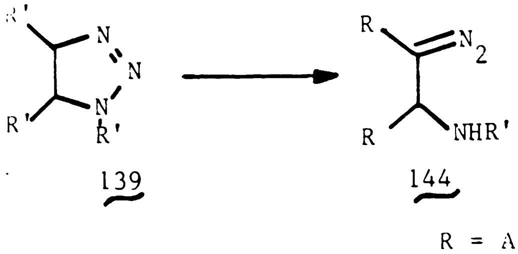
The cycloaddition of organic azides to olefins, either isolated or conjugated, have some precedent in organic chemistry[41]. The cycloaddition can be viewed as a 1,3 dipolar addition to the olefin to give the highly labile triazolenes **139** and **141** [42].



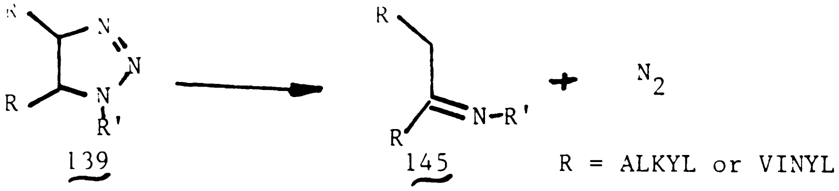
The decomposition of this highly labile species can follow several mechanistic pathways. Loss of nitrogen leads to the aziridine[43] **142** or the corresponding vinylaziridine **143**.



The triazolene can also decompose in such a manner as to generate aminodiazocompounds[44] **144.**

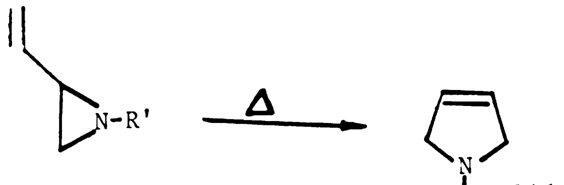


A third pathway that is possible is the formation of an imine[45] **145.**



E. <u>Vinylaziridine, pyrroline rearrangement.</u>

The vinylaziridines have several possibilities for rearrangement, two specific cases being thermolytic[46] and nucleophillic[47] cleavage. In both cases the resultant product is a pyrroline, albeit they proceed through two dissimiliar pathways. Although the thermolytic cleavage can generally be reguarded as a [1,3]-sigmatropic shift, the intermediates can be viewed as diradicals such as **171** and **172,** azomethine ylides such as **173** and **174** or it can be thought of as a concerted reaction. The nucleophillic ring opening is postulated to proceed through an anionic intermediate such as **147.**



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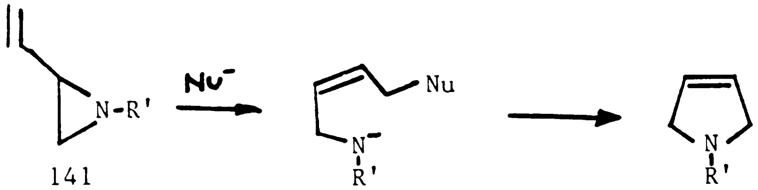
146



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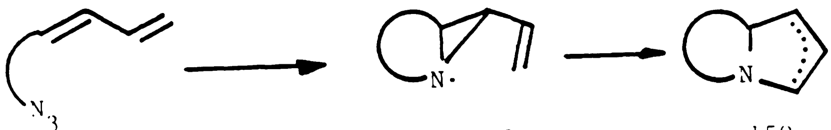
147

146

III. DISCUSSION

A. Introduction

The synthesis of the "simple" pyrrolizidines have been undertaken with a wide range of methodologies as seen in the historical section. Although the protocol has been set for some very elegant syntheses of these alkaloids, it seemed that a very general method of synthesis for these and other pyrroline type alkaloids was lacking. It became apparant that by coupling the Reformatsky reaction and the methodology developed concerning azide additions across dienes one has a lucrative entry into any alkaloids that contain a five membered heterocyclic ring, such as the pyrrolizidines. The first thrust of this investigation utilizing the coupled methodology the attempted synthesis of the pyrrolizidine skeleton **155**. After this approach did not work satisfactoraly, the direct approach was tried. The first series, one in which an OTHP diene was an intermediate turned out to be less successful than utilizing an azido olefin as an early intermediate.

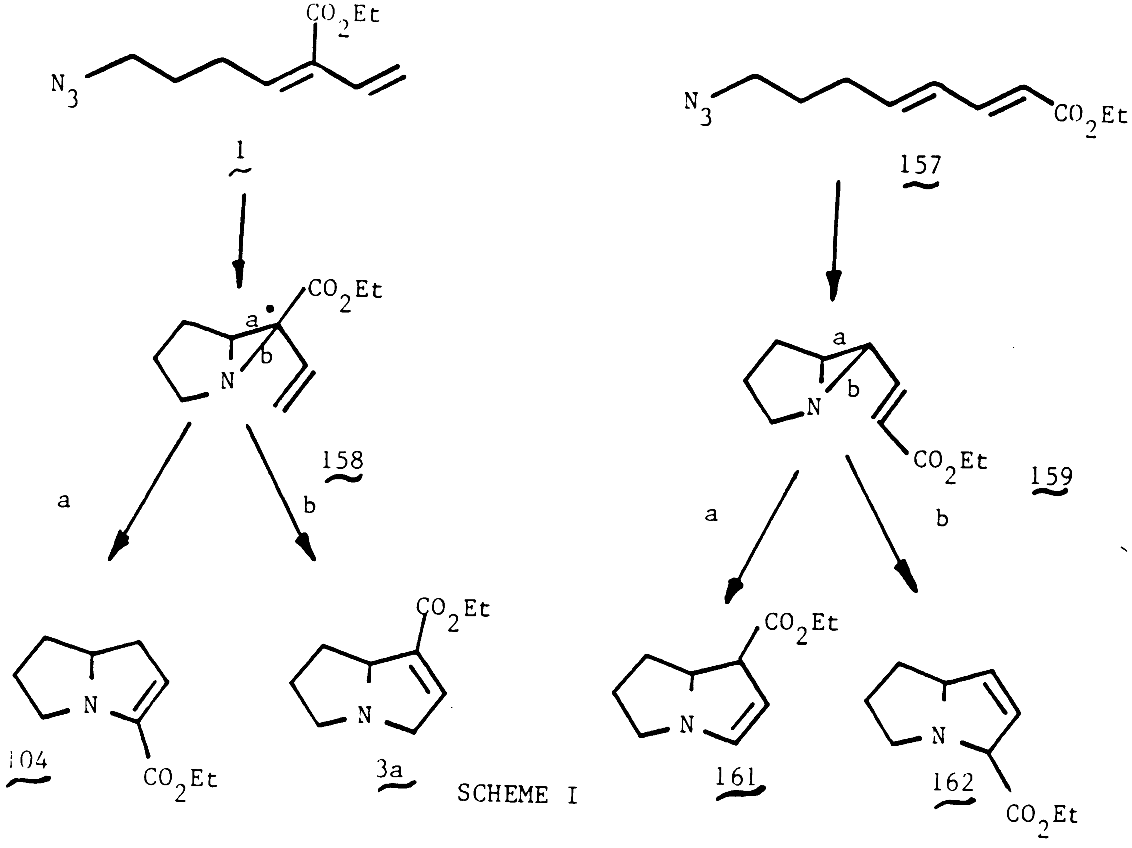


148 149 150

B. Results

In the initial studies directed toward synthesis of **155**, using a modified procedure of Hudlicky[48], azido heptadiene **153** was produced via a bis allylic alcohol followed by claisen rearrangement, reduction and SN_2 displacement of the mesylate with N_3^-.

As a result of the early results, it was obvious that the unactivated dienes not conclusive to the coupled methodology. The next step was to prepare azido esters **102** and **157** which bear an electron-withdrawing substituent at either one of two relevant positions in the diene system, thus activating the dienes. The substitution patterns of these two dienes later became important in controlling the topology of pyrrolines **104** and **3a.** Working on the assumption that the two dienes would lead to the vinylaziridines **158** and **159,** it was recognized the fact that there exists two bonds in the vinylazaridines (a and b) that are activated toward cleavage. Controlling this ring scission (either diradical or nucleophilic) facillitated the projected conversion of either vinylaziridine to the two pyrrolines **3a** and **104.** (Scheme 1)



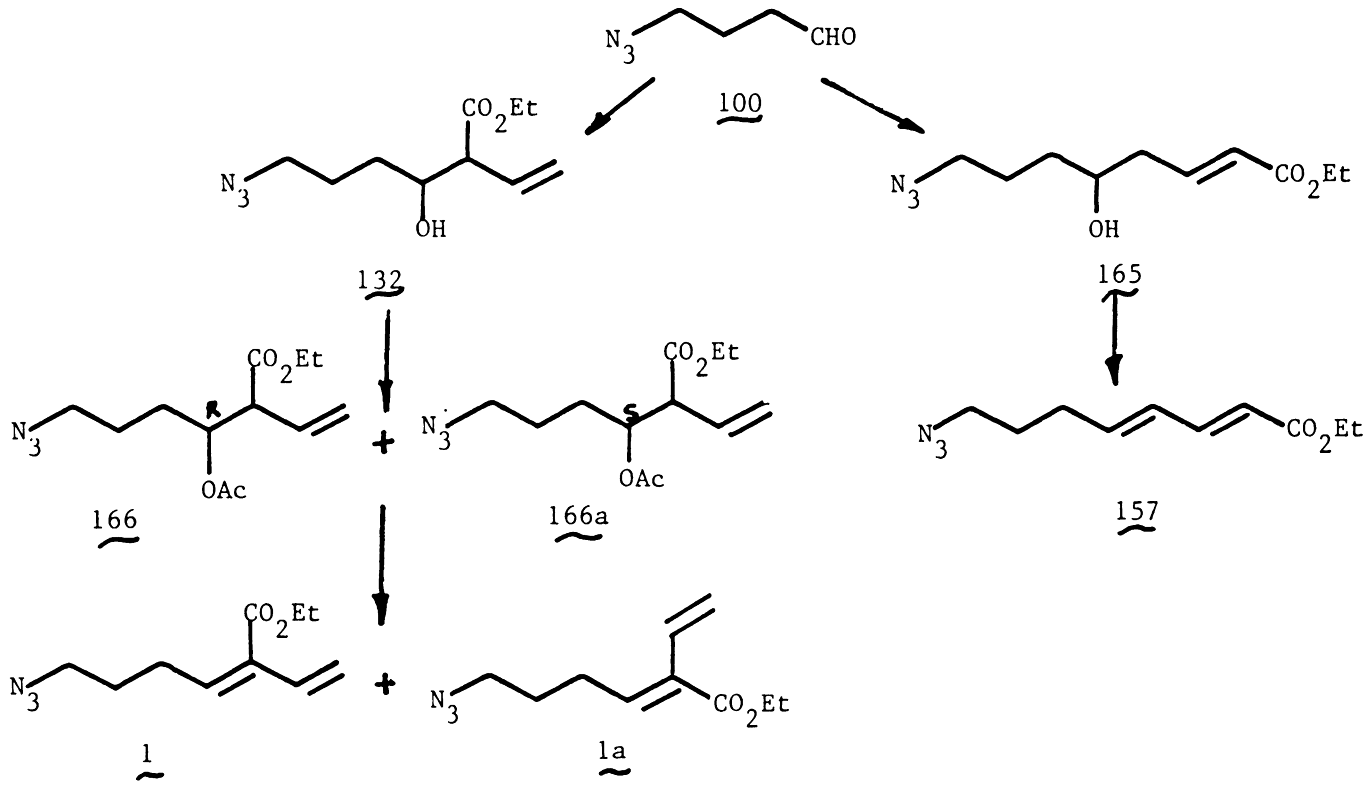
SCHEME I

Thus, thermolytic cleavage of bond a in **158** would yield a preponderance of **104** while nucleophillic ring opening and subsequent closure would yield a majority of **3a.** 1,3 disposition of the ester group giving, vinylaziridine **159,** would lend itself to the same type of ring scissions yielding pyrrolines **161** and **162.** These pyrrolines can than be transformed to **3a** and **104** respectively by olefin isomerization.

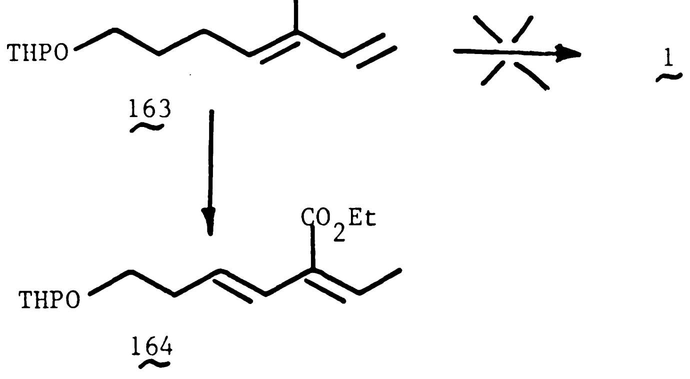
Preparation of Azido dienes 1 and 157.

Due to the 1,3 disposition of the ester groups in the dienes, we were able to use the regioselectivity of the Reformatsky reaction in the synthesis of both ester regioisomers. The requisite dienes **1** and **157** were prepared as shown in Scheme (II). Pent-4-en-tol was converted to azido aldehyde **100** by mesylation, azide displacement and ozonolysis. This procedure proved vastly superior to a preparation which utilized pent-4-enyl bromide (see Experimental Section). Aldehyde **100** was purified by Kugelrohr distillation at ambient temperature under high vacuum and immediately used in the next step. Although **100** could not be stored without decomposition, the azido group proved suprisingly inert to subsequent manipulation. This greatly simplified the synthesis of **1** and **157**; in the original plan (azide addition last) OTHP either protected diene **163** was a key intermediate and this proved especially cumbersome, in view of the number of isomers produced during its synthesis. Another problem connected with the OTHP ether was the amount of olefin isomerization **163** → **164** that occurred during subsequent steps.

Exposure of aldehyde **100** to ethyl-4-bromocrotonate in the presence of zinc-copper couple containing traces of acetic acid led to the formation of the α-adduct **132** as a mixture of erythro and threo isomers

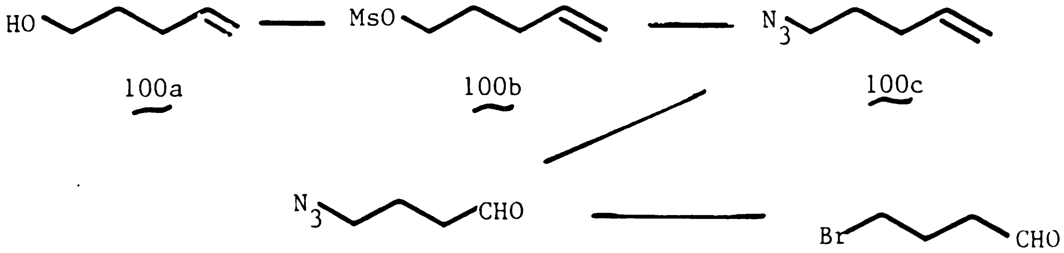


N3
CHO
100
CO2Et
OH
132
165
CO2Et
OAc
166
R
S
166a
157
1
1a



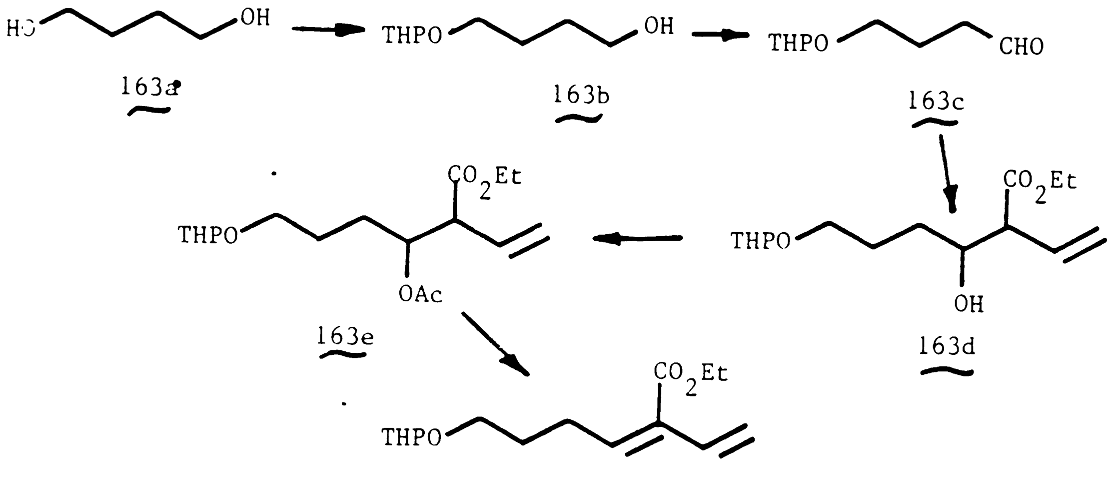
CO2Et
THPO
163
1
164

Preparation of Azido Aldehyde 100



100a 100b 100c 100 100d

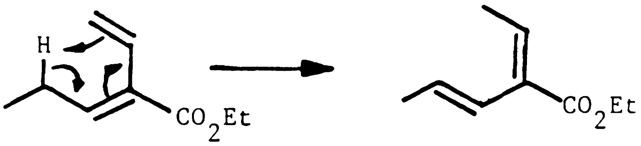
Preparation of OTHP diene 163



163a 163b 163c 163d 163e 163

(1.1:1)(R:S) in exceptional yields. Because these alcohols decomposed during purification the crude reaction mixtures were immediately subjected to acetylation to give the more stable acetates **166.** Purification if the acetates on silica-gel (hexane/ethylacetate) yeilded pure erythro and threo isomers **166** and **166a.**

Initially, elimination of the acetates was carried out on a mixture of isomers to afford a mixture of geometric diene isomers **1** and **1a.** The elimination of the acetates to provide the requisite dienes **1** and **1a** were originally performed on a mixture of the acetates. The experimental conditions for the elimination reaction had to be closely monitered since over exposure of the reaction to base resulted in double bond isomerization to give to more stable diene **168.** The more stable dienes were probably the result of a [1,5] sigmatropic shift of the E diene.

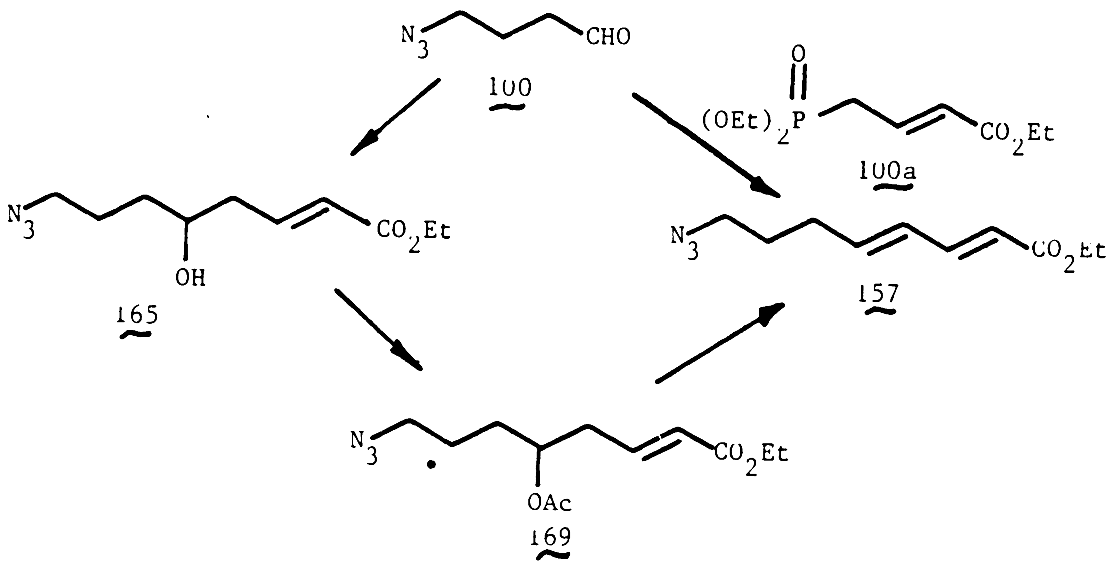


167
E - diene

168

The best conditions for elimination (DBU/DME, 0°C, 5 min) produced a 2.5:1 E/Z ratio of dienes **1.** It was suspected that the elimination of the acetates would not be stereospecific. This supposition was supported because with similar cases in the terpene series, mixtures of E and Z dienes were obtained after elimination of stereochemically pure acetates. Upon investigation it was found that the isomeric ratio of dienes was indeed independent of the steric integrity of the acetates. In order to try and manipulate the diene E/Z ratio, several leaving groups and various elmination criteria were tried, the results of which are in Table 1.

The γ-adduct, diene **157**, was available via two methods. (Scheme III). The first was the use of the Reformatsky reaction in a γ-addition mode; utilization of zinc and dry benzene as the reaction medium.



Scheme III

Table 1. Conditions of elimination for the formation of azidodienes.

Substrate	Conditions	Products[a]		
		102a(E)	102(Z)	168
mixture of erythro/threo	neat DBU, 0°, 1 min.	-	-	100
(1.1:1)	DME/DBU, R. T., > 15 min.	-	-	100
R = Ac	DBU/DME, 0°, 5 min.	2.5	1	<1%
	DME/DBU, 5 min. 0°			
	Isomer A	4	1	-
	Isomer B	1	1	-
R= Ms	DME/DBU, 6 min., 0°C	7	1	-
	DME/DBU, >10 min., 0°C	1.75	1	1
= Ts	DME/DBU, 7 min., 0°	>20	1	-
	DME/DBU, >30min., 0°	1	-	1

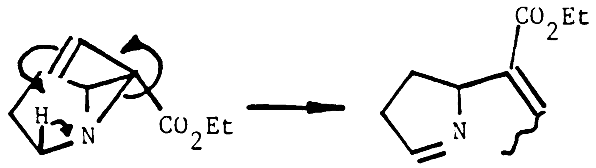
a) Ratios were determined by ^{1}H-NMR (270 MHz). The isolated yields (chromatography) were >80%.

The second, a one step method, was the Horner-Emmons modified Wittig reaction of the phosphonate ester **100a** of ethyl 4-bromocrotonate with aldehyde **100**. This gave the thru conjugated diene in 70% yield.

Both the vinylacrylate **102** and the conjugated diene **157** were now available to test their cycloadditions.

<u>Cycloadditions in the α Series.</u>

Exposure of diene **102** (mixture of E&Z isomers) to thermolytic conditions ranging from refluxing THF to flash vacuum pyrolysis (Table 2) provided imine **105** in over 90% yield, the reaction mixtures also contained traces of pyrrolines **104** & **3a**. The imine **105** can be viewed



140   105

as the product of a 1,5 homodienyl proton shift occuring from the endo isomer of the vinyl aziridine **140**. It was suspected that the initial steric integrity of the diene system did not affect the amount of imine obtained. This was confirmed by pyrrolyzing homogenous E diene and

Table 2. Results and Product Distribution of Thermolyses.

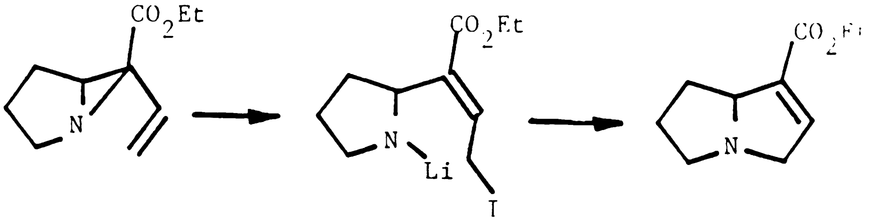
Starting Material	Conditions	Products[a]			
α-series		158	105	3a	104
1 (**a** and **b**)	0°, 1 week	10	10	-	-
	80°, 0.2 mm Hg, Kugelrohr	85	15	-	<1
	550°, 10^{-5} mm Hg, flash vac. pyr.	-	51	9	40
	450°, 0.25 mm Hg	8	45	5	42
158	550°, 10^{-5} mm Hg, flash vac. pyr.	-	45	10	45
	LiI/acetone, reflux	-	<10	91	-
158	550°, 0.6 x 10^{-3} mm Hg	-	>90	-	trace
105	550°, 10^{-5} mm Hg, flash vac. pyr.	-	67	7	26
1[b]	90°, 0.6 mm Hg	35	5	-	-
1	550°, 10^{-5} mm Hg, flash vac. pyr.	-	51	9	40
1[b]	550°, 10^{-5}mm Hg, flash vac. pyr.	-	50	10	40
105	500, 10^{-4}mm Hg	-	85	4	11
γ-series		Products			
		159	161	162	
157	450°, 10^{-5}mm Hg	60	24	<5	
159	450°, 10^{-5}mm Hg	-	90	<5	

a) Ratios were determined by ^{1}H-NMR (270MHz).

b) ~50% of this mixture contained isomerized diene **168** resulting from [1,5] hydrogen shift.

obtaining the same mixture of products as obtained by pyrrolyzing a mixture of E/Z dienes. It was postulated that although the formation of the triazolene may have been stereospecific, the loss of N_2 is not and yielded a mixture of vinylaziridines. A possible pathway operating during theromlysis is presented in Fig. 2. It should be noted that the triazolenes were detected by NMR but not characterized because of their lability.

Vinylaziridine **158** was also transformed to pyrrolizidine **3a** upon nucleophillic ring opening. LiI in acetone or NaI in DME opened the vinylaziridine in a fashion consistent with that previously reported in the literature[47] with the proposed lithio salt **170** as an intermediate



158 170 3a

Thus the synthesis of pyrrolizidine **3a** was accomplished in a quantitative fashion via nucleophilic ring opening, while pyrroline **104** was the preponderant pyrrolizidine obtained by pyrrolysis.

The reversibility of the [1,5] homodienyl shift was investigated by pyrrolysis of the imine in the temperature ranges in which the pyrrolizidines were produced. Products of this pyrrolysis were similar to the products obtained by pyrrolysis of diene **102**. However, the ratios of **105**, **3a**, and **104** were different for each experiment and proved impossible to standardize. This could be contributed to the amount of imine **105a** in the samples since this would be inert to the retro [1,5] sigmatropic rearrangement.

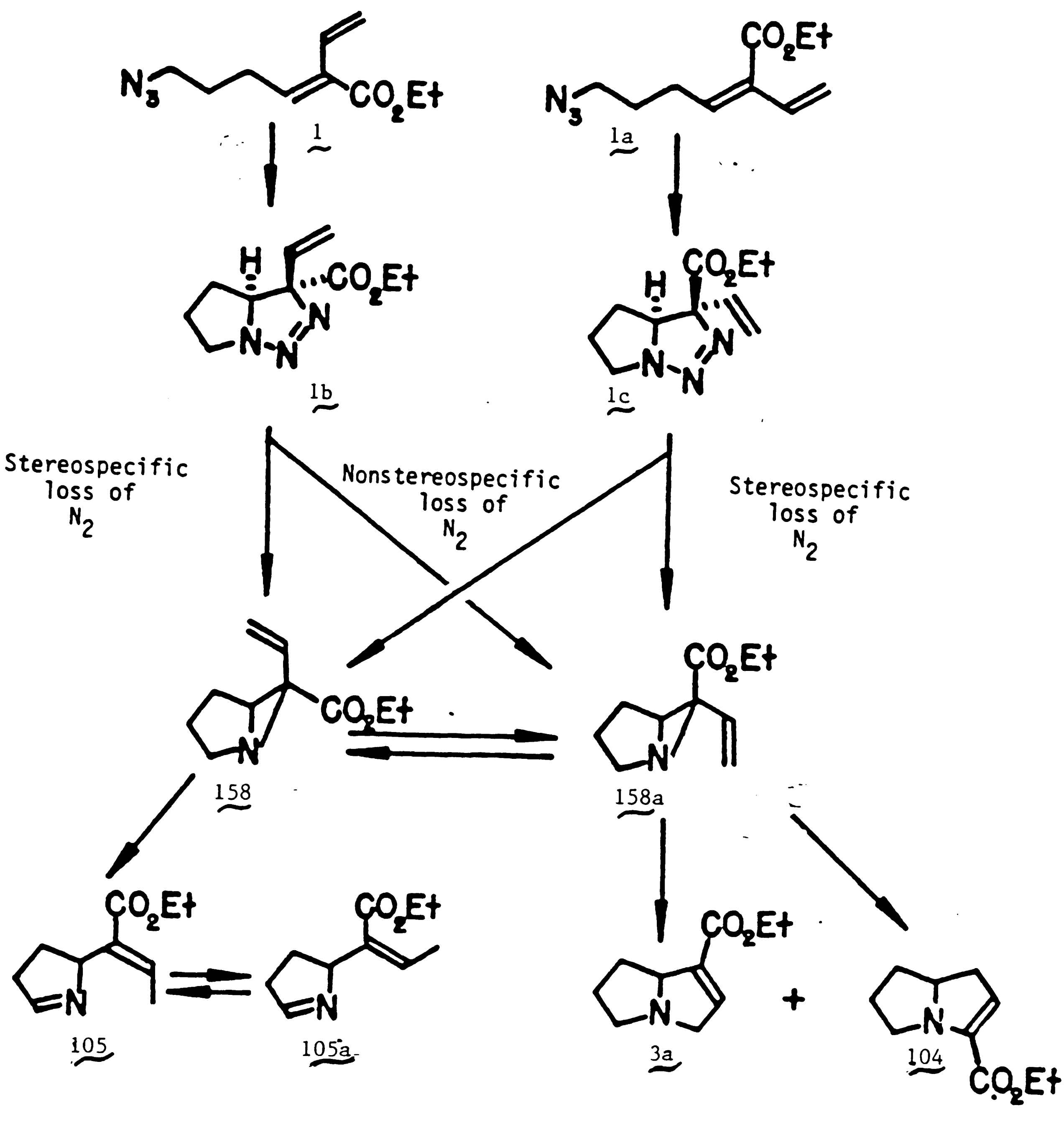
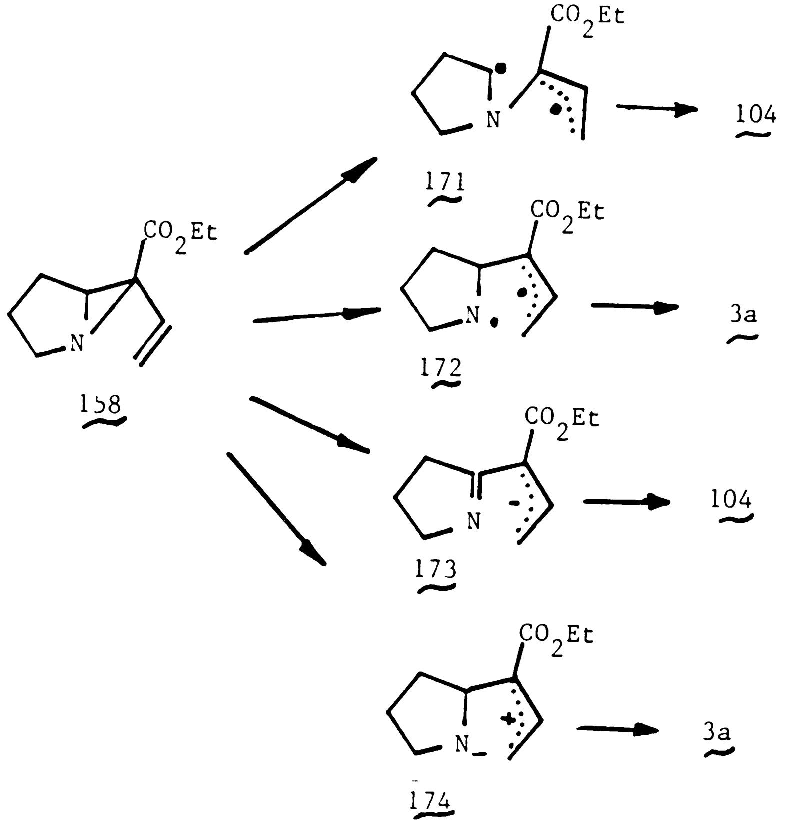


Fig. 2. Probable mechanistic pathway in the decomposition of azidodienes.

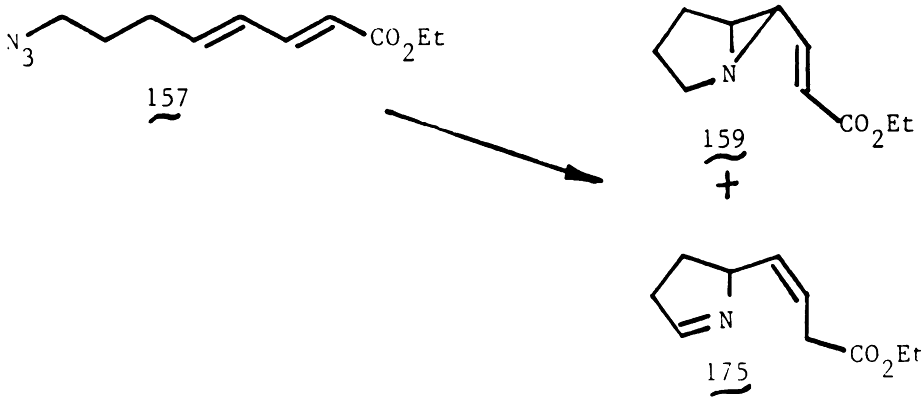
The mechanism of the pyrroline formation needs to be investigated further in order to clearly define its pathway. Four possible intermediates, two diradical and two zwitterionic, seem to be available. From the relative stabilities of the four intermediate species it would seem that diradical **172** and azomethine **173** are the two most likely to be in preponderance during the α-series pyrrolysis.



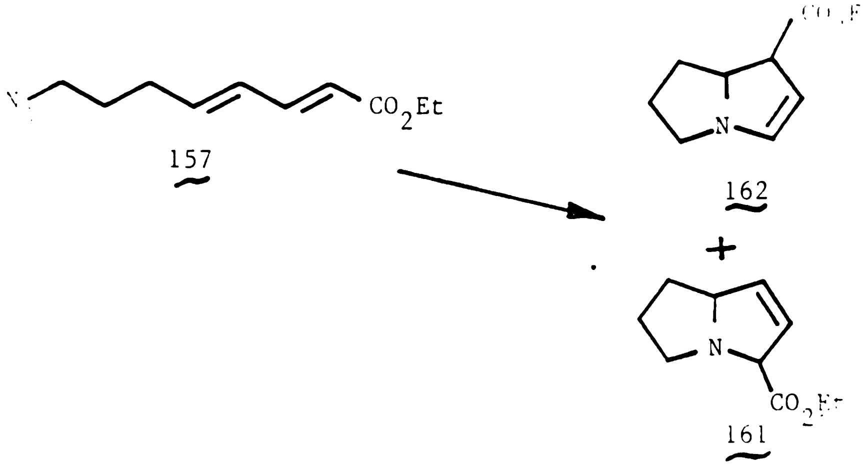
Cycloaddition in the γ-series.

Having completed the pyrrolysis of the vinylacrylate **102**, we next turned to the pyrrolysis of the fully conjugated system **157**. The most attractive feature of this system was its sterochemical homogeniety, only the E, E form was produced in the base catalyzed removal of acetates or in the Horner-Emmons modified Wittig reaction. Consequently

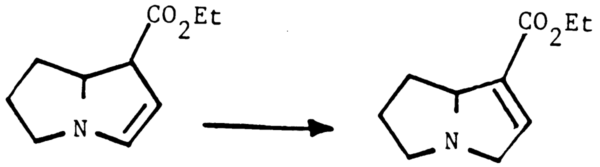
Consequently the reactions in this series were considerably cleaner than the corresponding α-series. Refluxing the diene **157** led to the vinylaziridine **159** in good yield. The only impurity was a small amount of imine **175.** This was a product of prolonged reflux periods, or purification although its yields were negligible when compared to those of imine **105** in the α series.



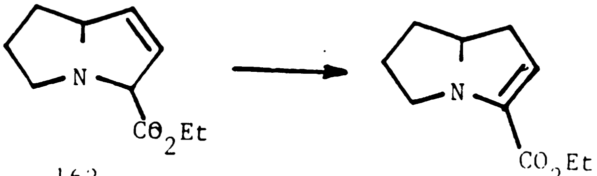
Pyrrolysis of diene **157** at 450°C produced pyrroline **161** and a small amount of **162.**



This mixture of pyrrolines was than subjected to isomerization to yield pyrrolizidine **3a** and **104.**



161 3a



162 104

C. Conclusion

The assumption that diene activation was essential for successful [4+1] addition was proven by the poor results obtained in the pyrrolysis of the non substituted azido dienes and the subsequent cycloaddition of the substituted dienes. The cycloaddition of the vinylacrylate **102** and the fully conjugated dienic ester **157** have been shown to give the appropriate vinylaziridines **158** and **159**. These vinylaziridines, the two series differing by a 1,3-disposition of the ester group, were shown to give pyrrolizidines **3a** & **104** by either nucleophillic ring opening or thermolytic cleavage of the aziridine moiety. Excellent selectivity, to give either 2 or 4 substituted pyrrolines, depending on the mode of ring scission, in conjunction with the vinylazidine used shows the enormous flexibility of the methodology employed. Thus the major product of the α series of the Reformatsky reaction under nucleophillic conditions was pyrrolizidine **3a** while under thermolytic conditions pyrrolzidine **104** was obtained as the major product. By contrast, in the γ series the 4-

substituted pyrrolizidine was the major product under thermolytic conditions.

This shows that by starting with the same azido aldehyde one can achieve either the 2 or 4 substituted pyrrolizidines depending upon two criteria; (1st) the type of addition of 4-ethylbromocrotonate and (2nd) the type of ring opening used upon the respective vinyl aziridine.

Thus supinidine has been synthesized in a regioselective manner via two mutually reinforcing convergent approaches.[50]

EXPERIMENTAL

Melting and boiling points are uncorrected (average local atmospheric conditions: P=706 mm Hg; R.T.=21°C; relative humidity=63%). All non-hydrolytic reactions were performed under nitrogen atmosphere unless noted otherwise. Solvents for both reactions and purifications were distilled from appropriate media; (see guidelines in Gordon, A. J.; Ford, R. A. "The Chemist's Companion"; Wiley: New York, 1972). All glassware used in small scale reactions and during final purification was successively washed in chromic acid and isopropanol/KOH baths. Infrared spectra were recorded on Perkin Elmer 283B spectrophotometer using polystyrene film as an external standard (1601 cm^{-1}). ^{1}H-NMR spectra were recorded on the following instruments: Varian EM-390 (90 MHz), IBM NR-80 (80 MHz), IBM WP-200 (200 MHz) and IBM WP-270 (270 MHz). ^{13}C-NMR spectra were recorded at 20, 50, or 67.5 MHz on NR-80, WP-200, and WP-270 spectrometers respectively. Two-dimensional NMR studies were performed on the IBM WP-200 instrument. All spectra were calibrated with TMS, $CHCl_3$, or $CDCl_3$. All carbon assignments are based on either INEPT sequences or SFORD partially decoupled spectra. Mass spectral measurements (low and high resolution, exact mass peak matching) were determined on a VG 7070 instrument.

The purity of all compounds was ascertained by high-field ^{1}H-NMR combined with chromatographic criteria: analytical TLC, gas chromatography, or high-pressure, reversed-phase chromatography. Most intermediates were not stable enough to obtain elemental analysis.

5-methanesulfonyloxypent-l-ene (**100b**)

5-Hydroxy-l-pentene (45 g, 0.523 mol) and triethylamine (158.67 g, 0.57 mol) were stirred at 0°C under an inert atmosphere for 30 min. To this mixture a solution of methanesulfonyl chloride (179.73 g, 1.57 mol) in methylene chloride (150 ml) was added dropwise. After addition at 0°C, stirring was continued at room temperature for 18 h. The reaction was quenched with $NaHCO_3$ solution followed by aqueous workup and extraction with methylene chloride. Removal of solvent in vacuo yielded a dark orange oil, **20b**[31] (75.18 g, 95%), suitable for use in the next step: IR (neat) 1350, 1080 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 90 MHz) δ 1.85 (p, 2H, J=7Hz), 2.1 (t, 2H, J=7Hz), 4.2 (t, 2H, J=7Hz), 5.0 (m, 2H), 5.5-6.0 (m, 1H); ^{13}C-NMR ($CDCl_3$, 67.5 MHz) δ 27.7 (CH_2), 28.8 (CH_3), 36.6 (CH_2), 69.1 (CH_2), 115.2 (CH_2), 136.4 (CH).

5-Azidopent-l-ene (**100c**)

Mesyl olefin **20b** (75.56 g, 0.477 mol) and DMF (150 ml) were stirred at room temperature for 10 min under an inert atmosphere. To this solution, sodium azide (37.24 g, 0.572 mol) was added and stirring continued, by means of a mechanical stirrer, for 38 h. Aqueous workup and removal of ether by distillation through 30-cm Vigreaux column yielded **20c**[7c] (27 g, 52%): IR (neat) 2180, 1650 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 90 MHz) δ 1.7 (p, 2H, J=7Hz), 2.1 (q, 2H, J=7Hz), 3.27 (t, 2H, J=7Hz), 5.0 (m, 2H), 5.6-6.0 (m, 1H).

4-Bromobutanal (**100d**)

Ozone was bubbled through a solution of 5-bromo-l-pentene (Aldrich)(1 g, 6.7 mmol), in dry methylene chloride (50 ml) and dry MeOH (25 ml) at -78°C until a blue color persisted. This was followed by bubbling of O_2 until the solution remained clear. Addition of dimethyl sulfide (4.9 g, 67 mmol) at 0°C was followed by stirring at room temperature for 24 h. Aqueous workup afforded **24c** (0.91 g, 90%) as a clear colorless oil: IR(neat) 1730 cm^{-1}; ^1H -NMR ($CDCl_3$, 90 MHz) δ 2.2(m, 2H), 2.7 (t, 2H, J=7Hz), 3.5 (t, 2H, J=7Hz), 9.9 (s, 1H).

<u>4-Azidobutanal (**100**)</u>

<u>A. By Ozonolysis of **100c**</u>: Ozone was bubbled through a solution of azido olefin **100b** (17.4 g, 0.159 mol) and methylene chloride (70 ml) at -78°C until a blue color persisted. This was followed by O_2 until the solution remained clear. Addition of dimethyl sulfide (98.7 g, 1.59 mol) at 0°C was followed by stirring at room temperature for 24 h. The solution was diluted with ether; subsequent aqueous workup and removal of ether and methylene chloride by distillation through a 21-cm Vigreaux column yielded a gold oil, **100** (12.4 g, 70%).

<u>B. By Azide Displacement of **100c**</u>: 4-Bromobutanal (1.76 g, 11 mmol) and DMF (20 ml) were stirred at room temperature for 10 min under an inert atmosphere. To this stirring solution, sodium azide (916 mg, 13 mmol) was added in one portion. Stirring was continued under an inert atmosphere for 12.5 h. An aqueous workup followed by extraction with ether and removal of solvent by distillation through a 21-cm Vigreaux column yielded a gold oil, **100** (1 g, 70%): IR (neat) 2100, 1730 cm^{-1}; ^1H-NMR ($CDCl_3$, 90 MHz) δ 1.85 (p, 2H, J=7Hz), 2.5 (t, 2H, J=7Hz), 3.30 (t, 2H, J= 7Hz); ^{13}C -NMR ($CDCl_3$) δ 21.3 (CH_2), 40.5 (CH_2), 50.4 (CH_2), 200.7 (C).

<u>7-Azido-4-hydroxy-3-carboethoxyhept-1-ene (**132**)</u>

<u>A. Reformatsky method</u>: To dry, powdered zinc (1.5 g, 21.2 mmol) a saturated solution of $Cu(OAc)_2$ in acetic acid (25 ml) was added and stirring continued for 0.5 h. The resulting zinc-copper couple was rinsed with diethyl ether until no acetic acid was detected by NMR analysis of eluent. Anhydrous ether (25 ml) was added, and stirring at room temperature continued for several minutes. A solution of 5-azidobutanal (2 g, 17.64 mmol), ethyl 4-bromocrotonate (3.14 g, 21.2 mmol), and anhydrous ether (25 ml) was added dropwise via addition funnel until half of the solution has been added. If the reaction started, addition and stirring continued; if there were no initiation, several crystals of I_2 were added to inititate the reaction, followed by continued addition and stirring. After addition was complete, the temperature was brought to reflux for 2.5 h. The reaction was quenched with saturated NH_4Cl solution followed by aqueous workup to yield 3.6 g (90%) of a clear, gold oil. Partial purification by filtration of the oil through a 5-cm plug of silica gel yielded 3.4 g (85%) of **132** as a clear, colorless oil. This compound was used immediately in the next step because of its instability. **132**: IR (neat) 3500, 2100, 1730, 6640 cm^{-1}; ^1H-NMR ($CDCl_3$, 270 MHz) δ 1.3 (t, 3H, J=7Hz), 1.5-1.95 (m, 4H), 2.75 (d, 0.33H, J=6 Hz), 2.8 (d, 0.67H, J= 3 Hz), 3.1 (m, 1H), 3.35 (br t, 2H) 3.9 (m, 1H), 4.2 (q, 2H, J=7Hz), 5.3 (m, 2H), 5.8-6.0 (m, 1H).

<u>B. Lithium Dienolate Method</u>: Diisopropylamine (1.247 ml, 8.9 mmol) was stirred at 0°C under N_2, and <u>n</u>-butyllithium (3.71 ml, 8.9 mmol) was added dropwise. The mixture was stirred for 25 min and then

10 ml THF (freshly distilled) was added to obtain a 0.9 M solution of LDA. The mixture was cooled to -78°C, freshly distilled HMPA (1.71 ml, 9.8 mmol) was added, and the mixture stirred for 30 min. Ethyl crotonate (1.11 ml, 8.9 mmol) was added and, after 15 min, followed with 4-azidobutanal (0.957 g, 8.47 mmol). Stirring was continued for 3.5 h (completion indicated by TLC) at -78°C with warming to -50° during this period. The reaction mixture was diluted with 40 ml ether (at -50°C) and quenched with 45 ml saturated NH_4Cl solution. The aqueous layer was extracted with cold ether (2 x 10 ml). The combined organic layers were washed with 10 ml cold water, 3M HCl (1 x 10 ml then 1 x 5 ml), and saturated NaCl solution (3 x 5 ml), then dried over Na_2SO_4. Removal of the solvent afforded 1.743 g (91%) of **132** of purity suitable for use in the next step.

<u>7-Azido-4-acetoxy-3-carboethoxyhept-1-ene (**166**)</u>

Azido alcohol **22a** (40 mg, 0.176 mmol) was stirred at 0°C with pyridine (13.9 mg, 0.176 mmol) for 10 min. To this solution acetic anhydride (71.8 mg, 0.70 mmol) was added dropwise, followed by addition of 4-dimethylaminopyridine (4 mg, 0.035 mmol). The reaction mixture was stirred for 12 h, during which time the ice melted and the mixture warmed to room temperature. The reaction was quenched with saturated $NaHCO_3$ solution followed by an aqueous workup to yield 37 mg (85%) of **166**, a clear, gold oil. Separation of isomers was performed on silica gel using gradient elution (hexane, 95:5, 90:10 ...70:30 hexane/EtOAc). The reaction was scaled up to 1 g for preparative runs, in which a mixture of isomers was used.

Isomer A: IR (neat) 2100, 1740, 1720 (shoulder) cm^{-1}; ^1H-NMR

($CDCl_3$, 270 MHz) δ 1.26 (t, 3H, J=7Hz), 1.60 (m, 4H), 2.04, (s, 3H), 3.25 (dd, 1H, J= 6 Hz, 10 Hz) 3.32 (m, 3H), 4.12 (q, 2H, J= 7 Hz), 5.28 (m, 2H), 5.80 (m, 1H); ^{13}C-NMR ($CDCl_3$, 67.5 MHz) δ 13.9 (CH_3), 20.7 (CH_3), 24.3 (CH_2), 28.7 (CH_2), 50.9(CH_2), 54.8 (CH), 60.8 (CH_2), 72.7 (CH), 120.1 (CH_2), 131.5 (CH), 169.9 (C), 170.7 (C).

Isomer B: IR (neat) 2980, 2940, 2100, 1740, 1720 (shoulder) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 1.25 (t, 3H, J= 7Hz), 1.68 (m, 4H), 2.05 (s, 3H), 3.24 (t, 1H, J= 6Hz) 3.28 (m, 3H), 4.16 (q, 2H), 5.20 (t, 3H), 5.88 (m, 1H); ^{13}C-NMR ($CDCl_3$, 67.5 MHz) δ 13.8 (CH_3), 20.5 (CH_3), 24.7 (CH_2), 29.1 (CH_2), 50.7 (CH_2), 54.4 (CH), 60.7 (CH_2), 72.2 (CH), 119.5 (CH_2), 131.7 (CH), 169.8 (C), 170.6 (C).

3-Carboethoxy-7-azidohept-1,3-diene (**1,a**)

A solution of azido acetates **166** (2:1 mixture of diastereomers) (253 mg, 1 mmol) in 3 ml of dry DME was cooled to 0°. Diazabicycloundecane (DBU)(167.2 mg, 1.1 mmol) was added at intervals via syringe (20 μm/20 sec). After 7 min, the reaction was quenched with saturated NH_4Cl solution and extracted with Et_2O (3 x 20 ml). Filtration of Et_2O solution through a plug of silica (1 x 0.5 cm) and evaporation gave 200 mg (96%) of diene **13**, shown to be a mixture of E and Z isomers (2:1). An analytically pure sample was obtained by flash chromatography on silica gel (hexane/Et_2O, 9:1) to give 61% recovery of 13: IR(neat) 3100, 2100, 1720, 1640, 1300 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 1.20 (t, 3H, J=7Hz), 1.65 (p, 2H, J=7Hz), 2.34 (q, 2H, J=7Hz), 3.25(t, 2H, J=7Hz), 4.16 (q, 2H, J=7Hz, E isomer), 4.20 (q, 2H, J=7Hz, Z isomer), [5.34 (dd, 1H, J=20 Hz, 1 Hz), 5.5 (dd, 1H, J= 30Hz, 1Hz), 6.41

(dd, 1H, J=30Hz, 10 Hz), 6.65 (t, 1H, J=7Hz), E isomer], [5.08 (d, 1H, J=15 Hz), 5.22 (d, 1H, J= 20Hz), 5.84 (t, 1H, J=7Hz), 6.25 (dd, 1H, J=20, 8Hz), Z isomer]; ^{13}C-NMR ($CDCl_3$, 67.5 MHz) δ 14.1 (CH_3), [25.7 (CH_2), E isomer; 26.8 (CH_2), Z isomer], 28.2 (CH_2), 50.8 (CH_2), 60.5 (CH_2), [115.1 (CH_2), 119.7(CH), 128.9 (CH), 140.9 (C), E isomer], [117.0 (CH_2), 119.0 (CH), 135.1 (CH), 137.0 (C), Z isomer], 165.8 (C); mass spectrum (70 eV, m/e (rel int.)) 209 (M^+)(1), 181 (M^+-nitrogen) (30), 152 (55), 136 (40), 108 (B), 106 (90), 91 (38), 80 (B), 79 (92), 65 (40), 53 (65).

Calculated for $C_{10}H_{15}O_2N_3$: 209.1164 Found: 209.1146

3-Carboethoxy-7-azidohept-2,4-diene (**168**).

These compounds were easily prepared by allowing the above reaction mixture to warm to room temperature. After 15 min of stirring, the reaction was quenched and worked up as described above. The ratio of E and Z isomers of **168** varied with reaction times. The isomerized dienes were contaminants in the preparation of dienes **1** if the times of the reaction were not most carefully monitored. **102:** IR (neat) 2100, 1720 (broad) cm^{-1}.

1-Carboethoxy-7-azidohept-1-en-4-ol (**165**)

A. By Reformatsky method

Azido aldehyde **100** (0.62 g; 5.5 mmol) and ethyl 4-bromocrotonate (1.1 g) in 2 ml of benzene were added to dry zinc (2 eq) in benzene (5 ml) over 5 min. Reaction was initiated with a crystal of iodine. The yellow-green mixture was brought to reflux, and after 4 h the reaction was quenched with NH_4Cl solution. Extraction with ether and evaporation gave 1.1 g (86.6%) of oil. Further purification by rapid filtration of an ether solution through a plug of silica (2x4 cm) gave 95 mg (72%) of **165**: IR (neat) 3500, 2120, 1730, 1660, 1640 cm^{-1}; ^1H-NMR ($CDCl_3$, 270 MHz) δ 1.2 (t, 3H, J=7Hz), 1.5-2.0 (m, 4H), 2.3 (br dd, 2H), 3.15 (br t, 2H), 3.9 (dd, 1H, J=16, 7Hz), 4.05 (q, 2H, J=7Hz), 5.8 (d, 1H, J=16Hz), 6.85 (m, 1H).

<u>1-Carboethoxy-7-azidohept-1,3-diene (**157**).</u>

<u>A. By Wittig reaction</u>: In a flame-dried flask under nitrogen was placed a solution of ethyl 1-carboethoxy-4-diethylphosphonylcrotonate (2.214 g, 8.85 mmol) (prepared from ethyl 4-bromocrotonate and triethyl phosphite)[25] in dry THF (4 ml), and the mixture was cooled to -78°C. To this solution was added <u>n</u>-BuLi in hexane (3.5 ml of 2.5 <u>M</u> solution, 8.85 mmol), and the orange solution was stirred for 30 min at -78°C. 4-Azidobutanal (1 g, 8.85 mmol) was added and stirring continued for 2 h at -78°C. The reaction mixture was warmed to -50°C (30 min) and the reaction quenched with saturated NH_4Cl solution. Extraction with ether (3x50 ml), drying (Na_2SO_4), and evaporation gave 1.38 g (75%) of oil **157**: IR (neat) 2110, 1720, 1650, 1630, cm^{-1}. ^1H-NMR ($CDCl_3$, 270 MHz) δ 1.28 (t, 3H, J=7Hz) 1.75 (p, 2H, J=7Hz), 2.27 (q, 2H, J=7Hz), 3.31 (t, 2H, J=7Hz), 4.2 (q, 2H, J=7Hz), 5.82 (d, 1H, J=16Hz) 6.16 (m, 2H), 7.28 (dd, 1H, J=16.4Hz) ; ^{13}C-NMR ($CDCl_3$, 67.5 MHz) δ 14.3 (CH_3), 28.0 (CH_2), 29.9 (CH_2), 50.7 (CH_2), 60.2 (CH_2), 120.2 (CH), 129.5 (CH), 141.9 (CH), 144.3 (CH), 167.1 (C); mass spectrum (70 eV, m/e (rel. int.)) 209 (M^+)(5), 181 (5), 149 (20), 108 (B), 97 (20), 80 (42), 67 (20), 55 (30).

Calculated for $C_{10}H_{15}N_3O_2$: 209.1164 Found: 209.1284

B. By elimination of acetate of **165**

The acetate of **165** was prepared in a manner identical to that described for **166** (^{1}H-NMR, δ 2.09 (s, 3H)). Elimination with DBU/DME at 0° for 45 min gave 81% yield of diene **157**, identical to that prepared by method A above.

Ethyl 2-[-5-(3H-4,5-dihydropyrrolyl)crotonate (**105**)

Azido dienes **102** (2:1 mixture of *E* and *Z* isomers) (200 mg, 0.97 mmol) were refluxed in 20 ml of dry THF for 4 h. Evaporation of solvent and a quick filtration through silica gel (hexane/EtOAc, 4:1) yielded 144 mg (85%) of imine **105** (Rf=0.29; EtOAc/hexane, 80:20). (Traces of vinylaziridine **158** and pyrrolines **104** and **3a** were detectable in the ^{1}H-NMR spectrum of crude product.) **105:** IR (neat) 1710, 1650, 1630 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 1.25 (t, 3H, J=7Hz), 1.8-2.2(m, 2H), 1.9(d, 3H, J=6Hz), 2.5-3.0(m, 2H), 4.15(q, 2H, J=7Hz), 5.08 (m, 1H), 6.95(q, 1H, J=6Hz), 7.65 (br d, 1H, J=2Hz); ^{13}C-NMR ($CDCl_3$, 67.5 MHz) δ 14.0 (CH_3, double intensity), 26.0 (CH_2), 38.0 (CH_2), 59.9 (CH_2), 69.7(CH), 133.9 (C), 138.9 (CH), 166.5 (C), 167.0 (CH); mass spectrum (70 eV, m/e (rel. int.)) 181 (M+)(45), 166 (20), 152 (65), 136 (70), 108 (90), 107 (95), 106 (B), 96 (75), 79 (40), 68 (52), 54 (25).

Calculated for $C_{10}H_{15}O_2N$: 181.1102 Found: 181.1098

2β-Carboethoxy-2-vinyl-3α-bicyclo-[3.1.0]-1-azahexane (**158**)

A sample of azido dienes **102** (100 mg) was distilled in a Büchi Kugelrohr apparatus at 80-90°C and 0.2 mm Hg over 30 min. The distillate (85 mg, 92%) was shown to contain imine **105** (13%), vinylaziridine **158** (85%), and traces of pyrroline **2**. Chromatography (silica gel/EtOAc) afforded pure **15b** (R_f=0.24, EtOAc; R_f=0.93, $CHCl_3$:MeOH, 1:1): IR (neat) 1730, 1640 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 1.27 (t, 3H, J= 7Hz), 1.7-2.2 (m, 4H), 2.9 (m, 1H), 3.2 (m, 1H), 4.12 (q, 2H, J=7Hz), 5.5 (m, 2H), 5.78 (dd, 1H, J=18, 8Hz); ^{13}C-NMR($CDCl_3$, 67.5 Mhz) δ 14.0 (CH_3), 24.9 (CH_2), 46.0(C), 50.2(CH_2), 51.5(CH), 60.2(CH_2), 61.2(CH_2), 123.3(CH_2), 127.2(CH) 167.0(C); mass spectrum (70eV, m/e (rel. int)) 181 (M+)(35), 166(10), 152(50), 149(30), 136(30), 108(60), 97(25), 83(40), 80(50), 69(65), 57(B).

Calculated for $C_{10}H_{15}O_2N$: 181.1104 Found: 181.1102

4-Carboethoxy-3,4-dehydropyrrolizidine (**3a**).

A. From azido dienes **102** by thermolysis. A sample of dienes **102** (210 mg, 1 mmol) was evaporated through a Vycor tube (1x50cm; base-washed, not conditioned with $PbCO_3$) at 450°C and 10^{-5} mm Hg. The time of this distillation was kept to ~2 min by gentle warming of the flask containing the dienes. The condensate was recovered from the trap cooled with liquid N_2 and analyzed by ^{1}H-NMR. It was shown to contain imines **105** (51%), pyrrolizidine **3a** (9%), and pyrrolizidine **104** (40%). The crude product (190 mg, 94%) was purified by flash chromatography (chloroform on alumina) to give pure **3a** (R_f=0.51, $CHCL_3$:MeOH, 1:1, R_f=0.49, $CHCl_3$:MeOH:NH_4OH, 55:45:2): ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 1.25 (t, 3H, J=7Hz), 1.5-3.0 (m, 6H),3.4 (m, 2H) 4.15 (q, 2H, J=7Hz), 4.3 (m, 1H), 6.65 (br dd, 1H). The spectral and chromatographic parameters were identical to those previously reported for this substance.[51]

B. By LiI opening of **158**.

Vinylaziridine **158** (7 mg) was dissolved in acetone containing 25 mg LiI and the mixture refluxed for 8-10 hr. Aqueous workup and extraction with methylene chloride gave 6 mg of pyrolizidine **3a** contaminated with material resembling imine **105**. Pyrrolizidine 3a proved to be a rather sensitive material. Although isolated several times by chromatography, we were unable to obtain analytically pure samples. All spectra were contaminated with decomposition products of unknown composition.

2-Carboethoxy-2,3-dehydropyrrolizidine (**104**).

The condensate from the pyrolysis of **102** was chromatographed on silica gel with hexane/EtOAc (20:80). Pyrrolizidine **104** (R_f=0.51, EtOAc/hexane, 80:20) was obtained as a clear oil, which decomposed within two weeks of storage. **104**: IR (neat) 1720, 1600 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 1.27 (t, 3H, J=7Hz) 1.5 (m, 1H), 1.75 (m, 2H), 1.95 (m, 1H), 2.45 (m, 1H), 2.72 (m, 1H), 2.98 (m, 1H), 3.25 (m, 1H), 3.96 (m, 1H), 4.16 (q, 2H, J=7Hz), 6.84 (t, 1H, J=2Hz); ^{13}C-NMR ($CDCl_3$, 67.5 MHz) δ 14.2 (CH_3), 25.5 (CH_2), 32.7 (CH_2), 35.7 (CH_2), 52.2 (CH_2), 60.4 (CH_2), 64.5 (CH), 117.2 (CH), 144.7 (C), 162.4 (C); mass spectrum (70 eV, m/e (rel. int.)) 181 (M^+)(72), 179 (30), 152 (42), 134 (25), 108 (B), 80 (75).

Calculated for $C_{10}H_{15}O_2N$: 181.1102 Found: 181.1112

2-[1-(2-Carboethoxyvinyl)]-bicyclo-[3.1.0]-1-azahexane (**159**).

Azido diene **157** (0.980 g, 47 mmol) was refluxed in dry toluene for 4 h, during which time a stoichiometric volume of nitrogen was expelled from the reaction mixture. Removal of solvent *in vacuo* without heating afforded 0.8 g of **157** (94%), which could be used in the next step. The crude product was contaminated with imine **159a** (>8%). Attempts to purify **157** by flash chromatography led to extended decomposition or transformation of **157** to **159a**. Flash chromatography of crude mixture yielded 122 mg (14%) of analytically pure **159**: IR (neat) 1730, 1660, 1590, cm^{-1}; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 1.2 (t, 3H, J=7Hz), 1.4-2.1 (m, 5H), 2.4 (dd, 1H, J=4.1 Hz), 3.0 (m, 2H), 4.1 (q, 2H), 5.92 (d, 1H, J=16Hz), 6.6 (dd, 1H, J=16, 6Hz); ^{13}C-NMR ($CDCl_3$, 67.5 MHz) δ 13.5 (CH_3), 19.5 (CH_2), 25.4 (CH_2), 36.9 (CH), 48.8 (CH), 52.0 (CH_2), 59.4 (CH_2), 120.5 (CH), 147.3 (CH), 165.4 (C); mass spectrum (70 eV, m/e (rel. int.)) 181 (M^+_(5), 177(2), 152(4), 124(10), 108(B), 84(3). Calculated for $C_{10}H_{15}NO_2$: 181.1102 Found: 181.1064.

4-Carboethoxy-4α-pyrrolizidine (**162**)

Chromatographed vinylaziridine **159** (90 mg, 0.49 mmol) was evaporated through a horizontally situated hot tube (1x40cm) at 450°C and 10^{-5} mm Hg, and the condensate collected in a trap cooled with liquid H_2. The total time of evaporation was kept under 2 min. by gently warming the indicated the presence of only pyrroline **162** (H NMR 54.6 Cd, 1H, J=5.5Hz) 5.85 (M, 1H)) and trace amounts of pyrroline **161** in a ratio of at least 95:5. Thin layer chromatography showed a clean conversion of **159** (R_f = .75 Al_2O_3, $CHCl_3$) to **162** (R_f = .38, al_2O_3, $ChCl_3$). Because of the instability of enamines of this type no purification was attempted.

2-[4-hydroxybutoxy]-terrahydropyran (**163b**)

1,4 butanediol (Aldrich) (3g; .033 moles) was stirred at room temperature with dihydropyran (Aldrich) (2.8g, .033 moles). Ten drops of phosphoric acid was added and stirring continued for 18 hours.

Aqueous workup yielded 4.5 g (80%) of **163b**.

2-[4-butanol,oxy]-tetrahydropyran (**163c**)

Pyridiniumchlorochromate (905 mg, 4.2 mmol) was stirred with sodium acetate (68.4 mg, 8.4x15$^{3.}$ mol) and 5 ml of dry methylene chloride. To this stirring solution the THP-Aldehyde (**163b**) (500 mg, 2.8 mmol) was added bolous and stirring continued for 1.5 hours. The resulting material was plug filtered and extracted with diethylether. Solvent evaporation and column chromatograph (hex/Et_2O) yielded (**163c**) (85%, 410 mg).

7-tetrahydropyran, 4-hydroxy,3-ethoxyhept-1-ene (**163d**).

To dry powdered zinc (65 mg, 1.002 mmol) a saturated solution of $Cu(OAc)_2$ in acetic acid (5 mls) was added and stirring continued for 5 hours. The resulting ZnCu couple was rinsed with diethyl ether until no acetic acid was present by NMR. Anhydrous ethyl ether was added and stirring continued for several minutes. A solution of ethylether 2 mls and (**163c**) (115 mg, .668 mmol) 4-ethylbromocrotonate (118 mg, 801 mmol) dropwise via addition funnel. If the reaction started addition and stirring continued; if no reaction occurred, several crystals of I_2 were added, followed by continued addition and stirring. After addition was complete the temperature was brought to reflux Gr 2.5 hrs. The reaction was quenched with NH_4Cl following by aqueous workup to give (**163d**) (150 mg, 88%). This compound was immediately used in the next step due to instability.

<u>7-tetrahydropyran-4-Acetoxy-3,ethoxyl,heptal-ene (**163c**)</u>

Hydroxy olefin (50 mg, .174 mmol) was stirred with Acetic Anhydride (2 mls) and triethylamine (26 mg, .261 mmol) at 0°C for several minutes. Dimethylaminopyridine (10 mol%) was added and stirring continued for 12 hours. Aqueous workup with $NaHCO_3$ (SAT'd. Solution) yielded (**183c**) (95%, 54mg).

<u>7-tetrahydropyran-3-ethyoxyhepta 1,3-diene (**163**)</u>

Acetoxyl olefin (50 mg, 152 mmol) was stirred with THF (3 mls) at 0°C for several minutes. Diazobicycloundecane (35 mg; 23 mmol) was added dropwise over 15 h. Solution was brought to room temperature and quenched with NH_4Cl. Aqueous workup with cold dilute HCl wash yielded 163 (90%, 36 mg).

REFERENCES

1. Warren, F. L.; Fortschritte Der Chemie Organischer Naturstoffe, 1955, 12, 198.

2. For reviews of the pyrrolizidine alkaloids and their biological properties see:

   a) Robins, D. J., Adv. Heterocyclic Chem., 1979, 24, 247.

   b) Culvenor, C. C., Bull, L. B., Dick, A. T. "The Pyrrolizidine Alkaloids"; North Holland: Amsterdam, 1968.

   c) Warren, F. L. Fortsch. Chem. Org. Natur. 1966, 23, 329; ibid. 1955.

   d) Warren, F. L. Alkaloids (N.Y.) 1970, 12, 245.

   e) Warren, F. L. in "The Alkaloids, Chemistry & Physiology"; Manske, R. H. F., Ed.; Academic Press: New York, 1970; Vol. XII, p. 319.

   f) MacLean, E. K. Pharm. Rev. 1970, 22, 429.

   g) Letendre, L.; Smithson, W. A.; Gilchrist, G. S.; Bergert, E. O.; Hoagland, C. H.; Ames, M. M.; Powis, G.; Korach, J. S. Cancer 1981, 47, 437.

3. Menshikov, G. P.; Zhaonovich, E. S.; J. of Gen. Chem. (Russian) 1963, 69, 110

4. Menshikov, G. P.; Zhur. Obshehei. Khim., 1946, 16, 1311

5. Menshikov, G. P.; Shadanovich, Y.; Ber. 1936, 69, B, 1799.

6. Menshikov, G. P., Gurevich, E. L., Zhur Obshchei Khim 1949, 19, 1382

7. Warren, F. L.; Klemperer, M. E. V.; J. Chem. Soc. 1958, 4574

8. Tufariello, J. J.; Tette, J. P.; J. Chem. Soc. D 1971, 10, 469

9. Tufariello, J. J.; Tette, J. P.; J. Org. Chem., 1975, 40, 3866

10. Stevens, R. V.; Luh, Y.; Shen, J. T., Tetrahedron Lett., 1976, 42, 3799.

11. Danishefsky, S.; McKee R.; Singh, R. K.; J. Am. Chem. Soc., 1977, 99, 4783.

12. Borch, R. F.; Bartholomeus, C. H.; J. Org. Chem., 1977, 42, 1225.

13. Pinnick, H. W.; Chang, Y-H, J. Org. Chem., 1978, 43, 4662.

14. Speckamp, W. N.; Nossin, P. M. M., Tetrahedron Lett., 1979, 4411.

15. Iwashita, T.; Kasumi, T.; Kakisawa, H., Chem. Lett (Japan) 79, 1337.

16. Robins, D. J.; Sakdarat, S., J. Chem. Soc. Chem. Comm. 1979, 1181.

17. Muchowski, J. M.; Nelson, P. H.; Tetrahedron Letters, 1980, 21, 4585.

18. Kraus, G. A.; Nenenschwander, K., Tetradehron Lett., 1980, 21 3841.

19. Robins, D. J.; Sakdarat, S., J. Chem. Soc., Perkin Transactions 1, 1981, 909.

20. Chamberlin, A. R.; Chung, J. Y. L., Tetrahedron Letter, 82, 23, 2619.

21. Mitsunobu, O.; Wada, M.; Sawo, T.; J. Amer. Chem. Soc., 1972, 94, 679.

22. Hart, D. J.; Yang, T-K, Tetrahedron Letter, 1982, 23, 2761.

23. Benn, M.; Rveger, H.; Heterocycles, 1982, 19, 1677.

24. Tatsuta, K.; Takahashi, H.; Amemiya, Y., J. Am. Chem. Soc., 1983, 105, 4096.

25. MacDonald, T. L.; Narayanan, B. A., J. Org. Chem., 1983, 48, 1131.

26. Shono, T.; Matsumura, Y.; Vchida, K.; Tsubata, K.; Makino A., J. Org. Chem., 1984, 49, 300.

27. Wistrand, L. G.; Ekstrom, M.; Blum, Z. Acta, Chemica Scandinavaci B, 1984, 38, 297.

28. Kametani, T.; Higashiyama, K.; Otomasu, H.; Honda, T., Heterocycle, 1984, 22 729.

29. Chamberlin, A. R.; Nguyen, H. D.; Chung, Y. L., J. Org. Chem., 1984, 49, 1682.

30. Keck, G.; Enhdm, E. J., Tetrahedron Letter, 1985, 26, 3311.

31. Greenhouse, R.; Ortiz, C., Tetrahedron Letter, 1985, 26, 2831.

32. Gramain, J. C.; Remuson, R.; Vallee, D., J. Org. Chem., 1985, 50, 710.

33. Hudlicky, T.; Frazier, J. O.; Kwart, L., Tetrahedron Letter, 1985, 26, 3523

34. Pearson, W. H., Tetrahedron Letter, 1985, 26, 3527.

35. Tufariello, W. H., J. Org. Chem. 1975, 40, 3866.

36. Ishibashi, H.; Ozeki, H.; Ikeda M.; J. Chem. Soc. Chem. Comm., 1986, 654.

37. Khuddus, Swern D., J. Am. Chem. Soc. 1973, 95, 8393.

38. Kametani, T.; Yukawa, H.; Honda, T.; J. Chem. Soc. Chem. Comm., 1986, 651.

39. Reformatsky, R. N.; Ber, 1887, 20, 1210

Reviews: a) Rathke, M. W., Org. React., 1975, 22, 423.

b) Gaudemar, M., Organomet. Chem. Rev. A 1972, 8, 123.

40a. Hudlicky, T.; Rice, L. E.; Boston, M. C.; Finklea, H. O.; Suder, B. J.; Frazier, J. O.; J. Org. Chem. 1984, 49, 1845.

40b. Hudlicky, T.; Natchus, M. G.; Kwart, L. K.; Colwell, B. L.; J. Org. Chem.; 1985, 50, 4300.

40c. Short, R. P. Disseration, VPI&SU, 1985.

41. For General Reference see:

a) Lwowski, W.; Ed. "Nitrenes"; Interscience: NY, 1970.

b) Scriven, E. F. V.; Ed. "Azides and Nitrenes"; Academic Press: NY, 1984.

42. a) Logothetis, A. L.; J. Am. Chem. Soc., 1965, 87, 749.

b) Henery-Logan, K .P.; Clark, R. A.; Tetrahedron Letters, 1968, 7, 801.

c) Broeckx, W.; et al. Tetrahedron Letters, 1971, 27, 3527.

d) Scheiner, P., Tetrahedron Letters, 1967, 24, 349.

e) Figeys, H. P.; Jammar, R.; Tetrahedron Letters, 1981, 22, 637.

43. a) Logothetis, A. L.; J. Am. Chem. Soc., 1965, 87, 749.

b) Henery-Logan, K. R.; Clark, R. A., Tetrahedron Letters, 1968, 7, 801.

44. a) Schultz, A. G.; McMahon, W. G.; J. Org. Chem., 1984, 49, 1676.

b) Logothetis, A. L.; J. Am. Chem. Soc.; 1965, 87, 749.

45. a) Schultz, A. G.; Ravichandran, R.; J. Org. Chem., 1980, 45, 5009.

b) Kozikowski, A. P.; Greco, M. N.; J. Org. Chem., 1984, 49, 2310.

c) Smolinsky, G., J. Am. Chem. Soc., 1961, 83, 4483.

d) Henery-Logan, K. R.; Clark, R. A., Tetrahedron Letters, 1968, 7, 801.

e) Harvey, G. R.; Ratts, K. W., J. Org. Chem., 1966, 31, 3907.

46. a) Rees, C. W.; Atkinson, R. S., J. Chem. Soc. Chem. Comm., 1967, 1232.

b) Vessieve, R.; Gelas-Mialhe, Y.; Borel, D., Can. J. Chem., 1976, 54, 1590.

c) Pommolet, J. C.; Chuche, J., Can. J. Chem., 1976, 54, 1571.

d) Lwowski, N.; Rice, S. N.; Mishra, A., J. Org. Chem., 1968, 33, 481.

47. a) Muxfeldt, H.; Schneider, R. S.; Mooberry, J.B.; J. Am. Chem. Soc., 1966, 88, 3670.

b) Schultz, A. G.; McMahon, W. G., J. Org. Chem., 1984, 49, 1676.

48. Hudlicky, T., Kutchan, T., Wilson, S. R., MaO, D. T., J. Am. Chem.Soc., 1980, 102, 6351.

49. Naguta, W., Adv. Heterocycle Chem., 1972, 1, 5-29.

50. a) Hudlicky, T.; Frazier, J. O.; Kwart, L.; Tetrahedron Letters, 1985, 3523

b) Hudlicky, T.; Frazier, J. O.; Seoane, G.; Tiedje, M.; Seoane, A.; Kwart, L.; Beal, C., J. Amer. Chem. Soc., 1986, 108, 3755.

51. Robins, D. J.; Sakdarat, S., J. Chem. Soc. Chem. Comm. 1979, 1181.

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