

RECENT ADVANCES IN THE SYNTHESIS OF PYRROLIZIDINES

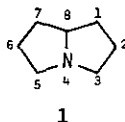
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Abstract— This review briefly summarizes some recent advances in the synthesis of pyrrolizidines.

1. INTRODUCTION

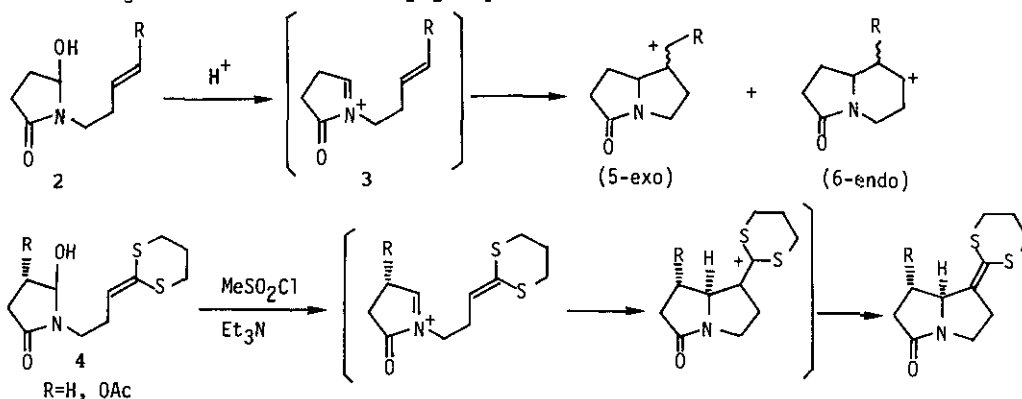
Pyrrolizidines have increasingly attracted the attention of synthetic organic chemists, in part due to their relatively simple structural features and a wide range of pharmacological activities. Since a comprehensive review of the pyrrolizidine chemistry by Robins had appeared in 1979,¹ major progress in the synthesis of this heterocyclic system has been made. Meanwhile several reviews²⁻⁶ appeared but most of them (with one exception of ref. 6) are concerned with the pyrrolizidine alkaloids. This review focuses on the synthetic methods of the pyrrolizidine ring system including dehydro derivatives and covers from 1978 up to mid-1987. The numbering of the system is as shown in 1. The currently accepted name for 1 in Chemical Abstracts is hexahydro-1H-pyrrolizine; the systematic name is 1-azabicyclo[3.3.0]octane.

2. C₁-C₈ BOND FORMATION

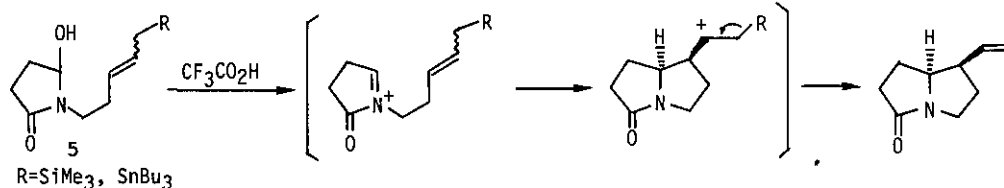
A variety of new methods involving the C₁-C₈ bond formation have been developed during the last decade.

Perhaps, the most versatile approach is based on the acid-catalyzed cyclization of the N-acyliminium ions 3, mainly developed by Speckamp and co-workers.⁷ The N-acyliminium ion precursors, hydroxylactams 2 can be prepared most conveniently by controlled sodium borohydride reduction of the corresponding N-substituted succinimides. The key cyclization step was usually accomplished by treatment of

the hydroxylactams **2** with acids such as formic acid, trifluoroacetic acid, or methanesulfonic acid. One of the major problems encountered in this intramolecular reaction of the N-acyliminium ions **3** with alkenes or alkynes is the regiochemistry of the cyclization. In principle, ring closure of the N-acyliminium ion can take place in two possible directions, 6-endo and 5-exo. Generally the formation of the six-membered rings (endo-ring closure) is in preference to five (exo-ring closure). This problem has been overcome by introducing a cation-stabilizing group onto the alkenes and alkynes.

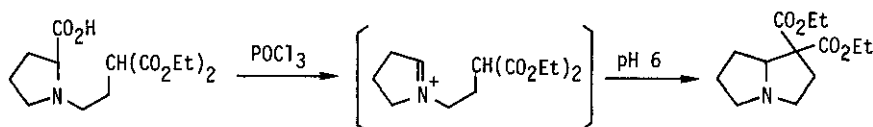


Dithioacetal (**4**, R=H),⁸ phenyl (**2**, R=Ph),⁹ phenylthio (**2**, R=SPh),¹⁰ and chloro (**2**, R=Cl) groups¹² are found to be effective for this purpose. Cyclization of **5** (R=SiMe₃,¹¹ SnBu₃¹²) proceeded with high regio- and stereo-selectivities to give the 5-oxopyrrolizidine with an exo-1-vinyl group. Synthesis of an optically

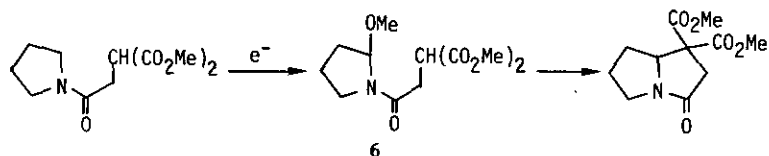


active pyrrolizidine derivative using the dithioacetal **4** (R=OAc) has been achieved via a stereoselective cyclization directed by an acetoxy substituent.^{8c}

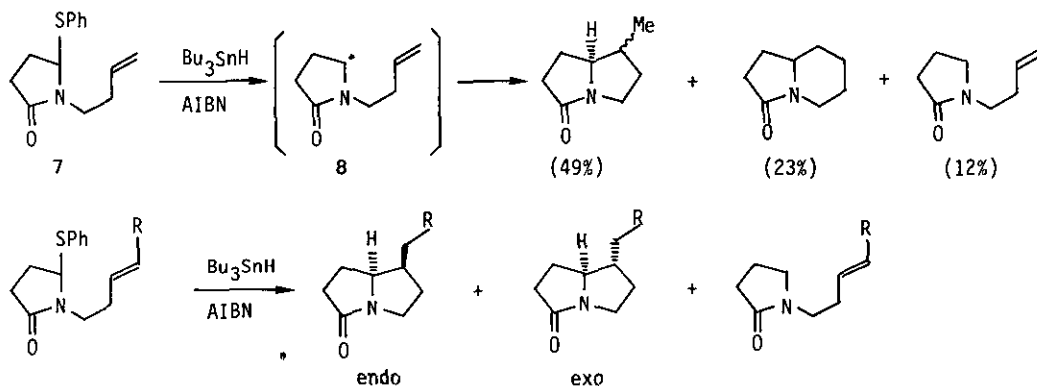
Rapoport and coworkers¹³ utilized an iminium ion generated by decarboxylation of an α -amino acid, which cyclized at pH 6 to give the pyrrolizidine ring system.



Zoltan and coworkers¹⁴ utilized an intramolecular cyclization of the electrochemically prepared N-acyliminium ion precursor **6**.



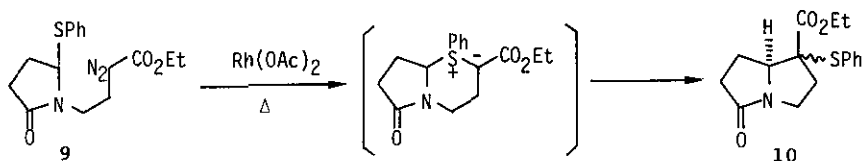
An alternative promising approach to the pyrrolizidines, developed by Hart and coworkers,¹⁵ utilizes cyclization of α -acylamino radicals 8. These radicals can be easily generated by treatment of 5-phenylthio-, 5-methylthio-, or 5-phenylselenyl-substituted 2-pyrrolidinones (e.g., 7) with tributyltinhydride in the presence of α, α' -azobisisobutyronitrile (AIBN). Here again, the same regio-chemical problem as one encountered in the cationic cyclization arises. The pyrrolizidine formation can be increased by introduction of appropriate substituents on the alkenes. Some examples are shown below. Another interesting feature of this radical cyclization is very high endo-stereoselectivity. The exact reason for this preference is not clear. Radical cyclization of silylated alkenyl and allenyl derivatives has been reported to proceed with high regio- and stereo-chemical selectivities.^{16,17}



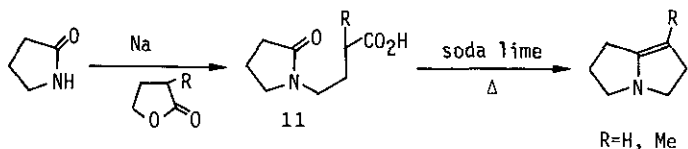
| R | Yield (%) (endo/exo) | Yield (%) |
|---------------------------------|----------------------|-----------|
| H (=7) | 49 (11:1) | 12 |
| CO ₂ Bu ^t | 81 (9:1) | 0 |
| CN | 85 (9:1) | 0 |

In a variant of these cationic or radical cyclization reactions, Kametani and coworkers¹⁸ developed an intramolecular carbenoid displacement reaction, which involves insertion of the carbenoid into the C-S bond. Heating the diazo compound 9 in benzene in the presence of a catalytic amount of rhodium acetate gave the 5-

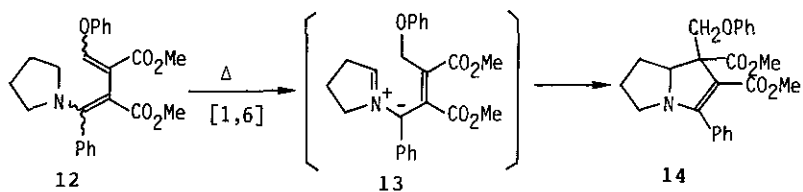
oxopyrrolizidine **10**.



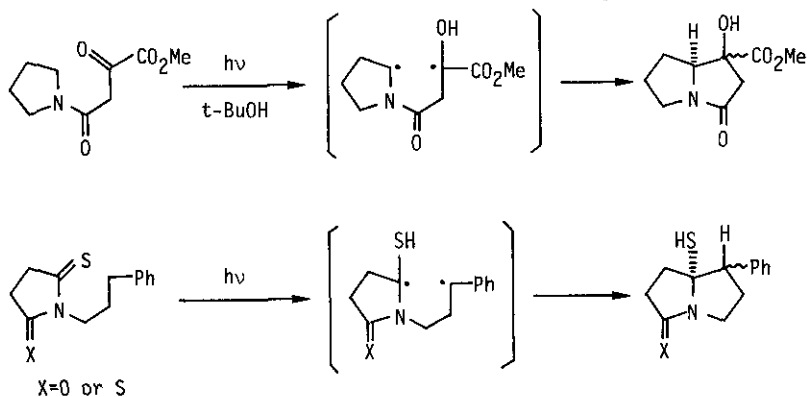
Miyano and coworkers¹⁹ found that heating of readily available 4-(2-oxopyrrolidin-1-yl)butanoic acids **11** with soda lime gave rise to $\Delta^{1(8)}$ -dehydropyrrolizidines. Although the mechanistic details of this reaction remain to be established, this method appears to be of considerable practical importance.

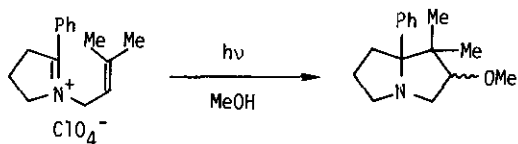


An interesting approach to the pyrrolizidine ring system, developed by Reinhoudt and coworkers,²⁰ utilizes an electrocyclic reaction as a key step. 1-(1-Pyrrolidinyl)-1,3-butadienes **12** having an electron-withdrawing group at C-3, underwent a thermal rearrangement to pyrrolizidine derivatives **14**. This thermal rearrangement involves a concerted antarafacial [1,6] hydrogen shift followed by disrotatory electrocyclic reaction of the resulting 1,5-dipolar species **13**.

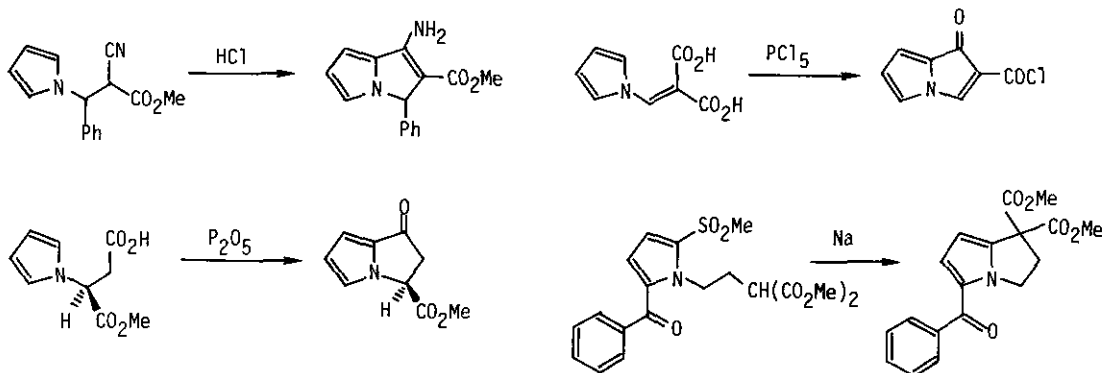


Several photochemical approaches have been reported.²¹⁻²³ However, all of these approaches suffer from a lack of stereoselectivity.





Intramolecular electrophilic and nucleophilic substitution reactions at the 2-position on the pyrrole ring have often been used.²⁴⁻²⁷ Some typical examples are shown below.

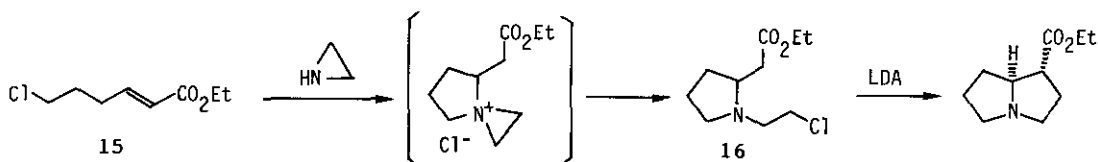


An intramolecular carbenoid insertion reaction on the pyrrole ring has been examined but the yield is poor.²⁸

3. C₁-C₂ BOND FORMATION

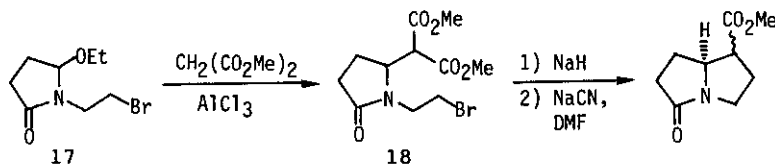
The C₁-C₂ bond formation approach using an intramolecular alkylation is one of the standard methods for the synthesis of the pyrrolizidines.

One interesting approach to the precursor, N-(2-chloroethyl)pyrrolidine 16, developed by Kametani and coworkers,²⁹ is based on the ring opening reaction of an aziridinium salt. Treatment of the α,β-unsaturated ester 15 with an excess of aziridine gave directly N-(2-chloroethyl)pyrrolidine 16 which, upon treatment with lithium diisopropylamide (LDA), underwent an intramolecular alkylation to yield the pyrrolizidine ester.



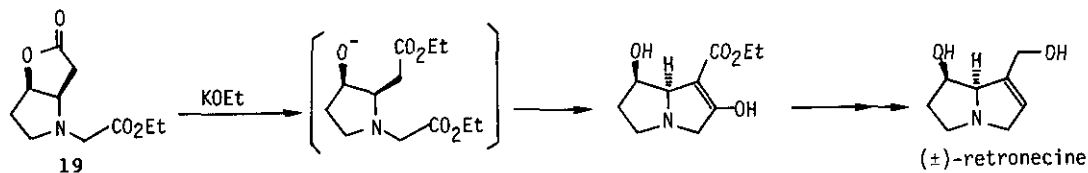
A promising short synthesis of the precursor, N-(2-bromoethyl)-2-pyrrolidinone 18, involving amidoalkylation of 17 with dimethyl malonate in the presence of

aluminium chloride, has been described by Kraus and Neuenschwander.³⁰ Cyclization of 18 with sodium hydride followed by decarbomethoxylation gave the 5-oxopyrrolizidine ester.

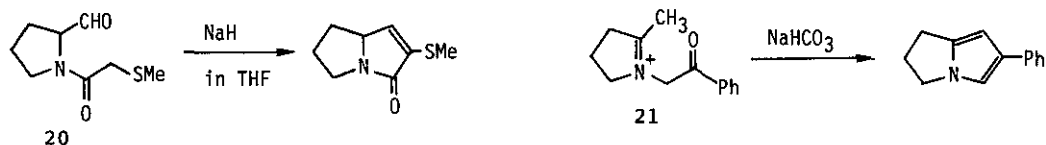


The intramolecular alkylation approach is also applicable to the pyrrole derivative.³¹

A Dieckmann condensation has been extensively used for the construction of the pyrrolizidine ring system. Since Geissman and Waiss³² reported the conversion of the lactone 19 into (\pm)-retronecine in 1962, various groups devoted much effort to improve the overall yields from this lactone and the related compounds to the pyrrolizidine alkaloids.³³⁻³⁹ The chiral synthesis of the key intermediates, starting from L-proline or 4-hydroxy-L-proline,³⁴ D-glucose,³⁵ D-erythrose,³⁶ L-diethyl tartrate,³⁷ and R-³⁸ and S-malic acids³⁹, is also noteworthy.



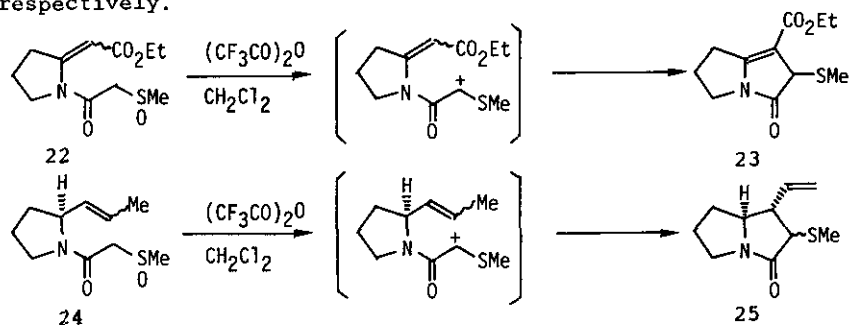
An intramolecular aldol condensation has also been used. Treatment of the pyrrolidine-2-aldehyde 20 with sodium hydride afforded the pyrrolizidone derivative.⁴⁰ Similarly, base treatment of the 2-methyl-1-pyrrolinium salt 21 provided a pyrrolizine derivative.⁴¹



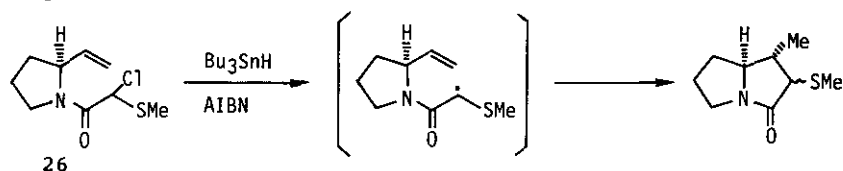
Both Dieckmann and intramolecular aldol condensations have successfully been employed for the synthesis of the pyrrolizines from the pyrrole derivatives.^{42,43}

An alternative route to the pyrrolizidine ring system, developed by our group,^{44,45} is based on cationic olefin cyclization of thionium ion intermediates. Treatment of N-(methylsulfinylacetyl)pyrrolidine derivatives 22 and 24 under Pummerer reaction conditions gave directly the 3-oxopyrrolizidines 23 and

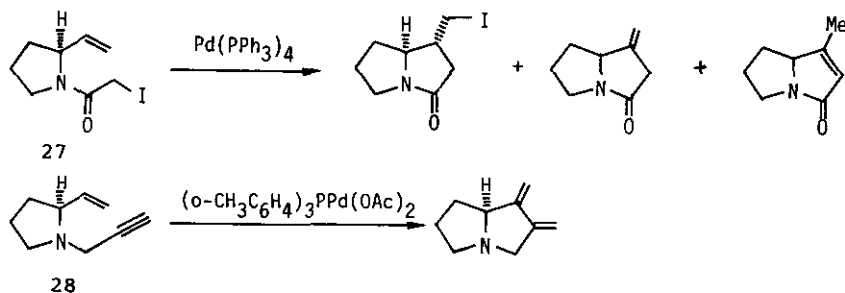
25, respectively.



A variant of this approach involves cyclization of the radical generated by treatment of N-(methylthiochloroacetyl)-2-vinylpyrrolidine 26 with tributyltinhydride in the presence of AIBN.⁴⁶

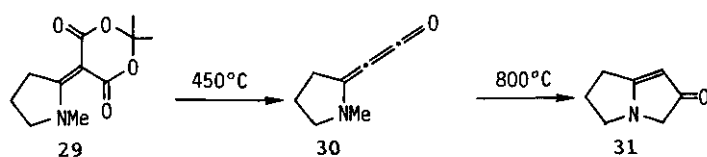


Two recent noteworthy C_1-C_2 bond forming approaches to pyrrolizidines involve palladium-mediated cyclization of N-iodoacetyl-2-vinylpyrrolidine 27⁴⁷ and N-propargyl-2-vinylpyrrolidine 28.⁴⁸

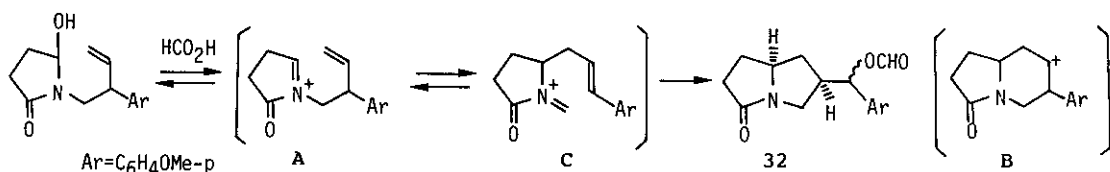


4. C_2-C_3 BOND FORMATION

Only one example involving the direct C_2-C_3 bond formation approach has been reported.⁴⁹ Pyrolyzing the Meldrum's acid derivative 29 at $450^\circ C$ gave a reactive methyleneketene intermediate 30 which, on further increase of the temperature ($800^\circ C$), was transformed into the pyrrolizinone derivative 31.



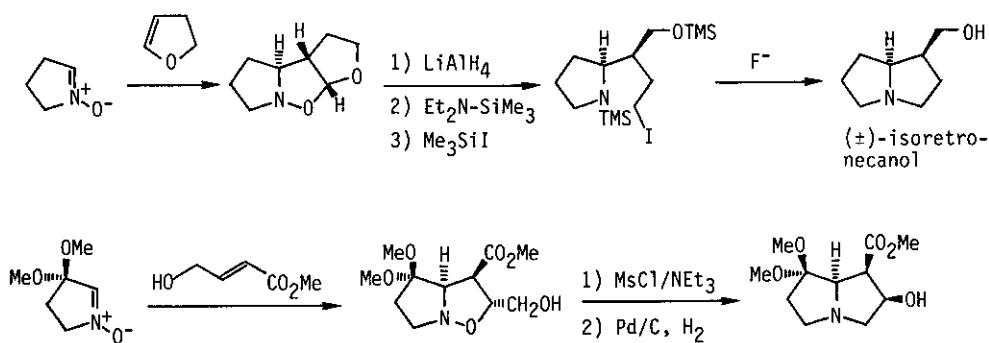
An interesting approach developed independently by Speckamp⁵⁰ and Hart,⁵¹ involves an aza-Cope rearrangement-cyclization of the N-acyliminium ions. As described earlier, cyclization of the N-acyliminium ions **A** of the 2-aza-1,5-hexadienyl type generally affords the six-membered ring **B**. However, when a substituent (i.e., gem-dimethyl, methoxy, phenyl, or vinyl) is present at C-3 or C-4 of the initially formed N-acyliminium ions **A**, the rearranged ion **C** cyclizes preferentially to a 5-membered ring **32**. This rearrangement (**A**→**C**) is now well established to proceed by a 2-aza-Cope rearrangement.



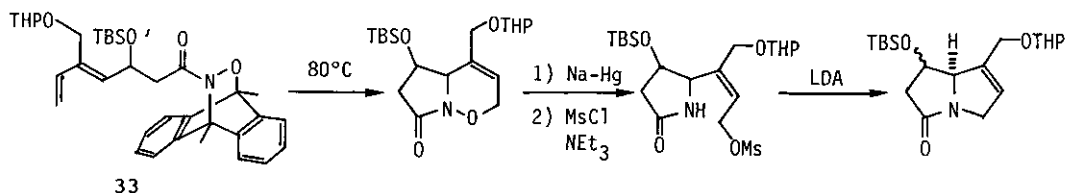
5. C₃-N BOND FORMATION

One of the earliest approaches to pyrrolizidines involves construction of the second five-membered ring on a pyrrolidine by C₃-N bond formation using an intramolecular N-alkylation or N-acylation.

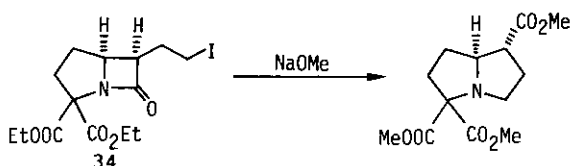
Several new approaches to the precursors for the N-alkylation approach, 2-(3-halo- or 3-mesyloxy-propyl)pyrrolidines have been described. Particularly noteworthy is the use of 1,3-dipolar cycloaddition of nitrones for stereospecific introduction of the desired functional group.⁵²⁻⁵⁴ Two examples are shown below.



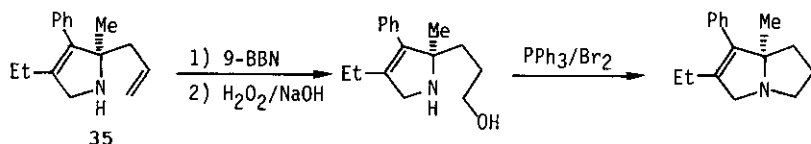
Keck and Nickell⁵⁵ utilized an intramolecular [4+2] cycloaddition reaction of an acylnitroso compound generated by thermolysis of **33**. This approach, however, suffers from a lack of stereoselectivity in the crucial cycloaddition step.



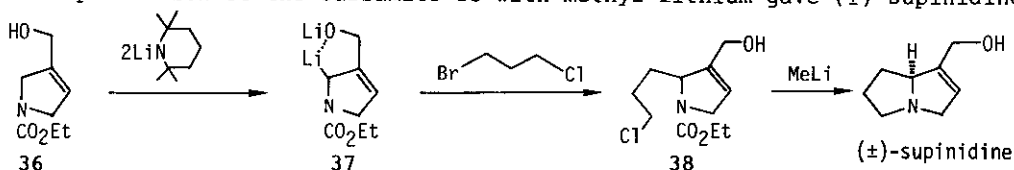
Cavagna and coworkers⁵⁶ utilized a ring opening reaction of a suitably functionalized β -lactam **34** with base or acid for the construction of the pyrrolizidine ring system.



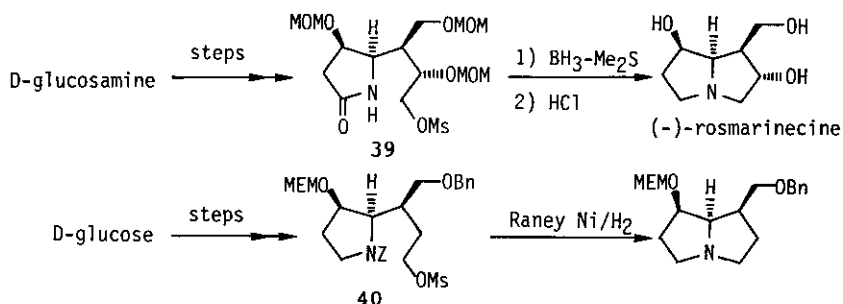
Hydroboration-oxidation of the alkene **35** followed by treatment of the resulting alcohol with triphenylphosphine-bromine furnished the pyrrolizidine derivative.⁵⁷



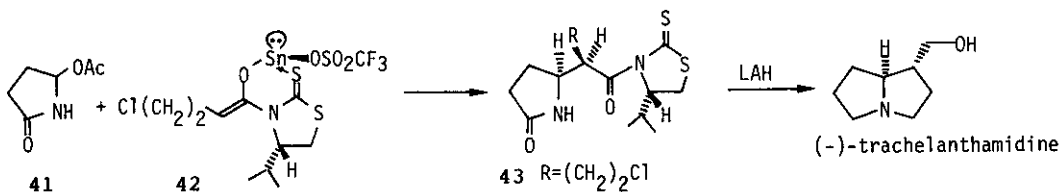
McDonald and Narayanan⁵⁸ found that pyrrolinealcohol **36** underwent regioselective lithiation to give a dianion **37** which could be alkylated to afford the carbamate **38**. Deprotection of the carbamate **38** with methyl lithium gave (\pm)-supinidine.



The chiral syntheses of the intermediates **39** and **40** from D-glucosamine⁵⁹ and D-glucose,⁶⁰ respectively, are also noteworthy. Both the syntheses are stereoselective, but nonetheless, quite lengthy.

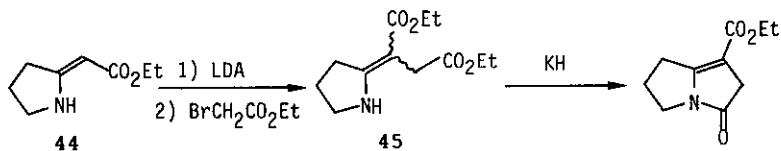


Recently Nagao and coworkers⁶¹ have developed an ingenious method for alkylation of 5-acetoxy-2-pyrrolidinone **41** using chiral Sn (II) enolate **42** which furnished the 5-alkylated pyrrolidinone **43**. This reaction proceeded with high diastereoselectivity ($\geq 97\%$ de). Treatment of compound **43** with excess LAH affords directly (-)-trachelanthamide (99% ee).

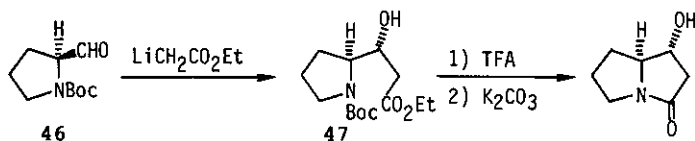


An alternative C₃-N bond formation approach is based on an intramolecular N-acylation of pyrrolidine-2-propionates, giving 3-oxopyrrolizidines. A variety of the methods for the syntheses of such precursors have been developed in the last decade.

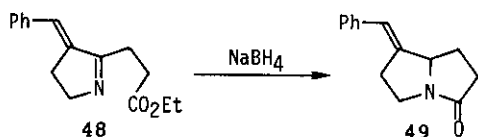
Reaction of the anion of **44** with ethyl bromoacetate gave the diester **45** which cyclized under basic conditions to afford the 5-oxopyrrolizidine.⁶²

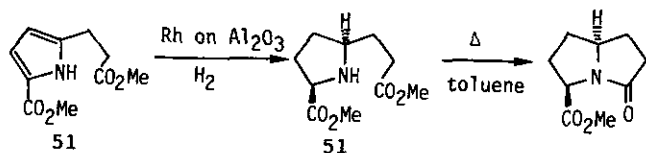


Aldol reaction of the aldehyde **46** with ethyl lithioacetate proceeded stereoselectively to give **47**, which, after deprotection, underwent cyclization to give a 3-oxopyrrolizidine.⁶³

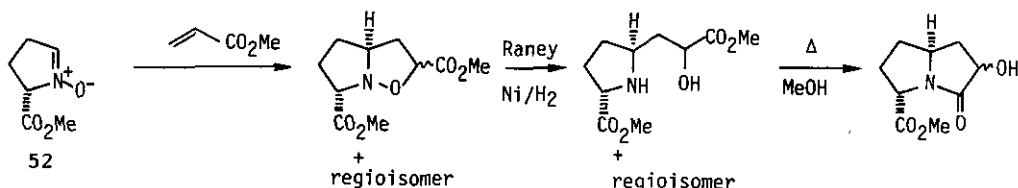


Reduction of the pyrroline ester **48** with sodium borohydride proceeded with concomitant cyclization giving the lactam **49**. Catalytic hydrogenation of pyrrole diester **50** over rhodium-on-alumina gave the pyrrolidine ester **51**, which cyclized in refluxing toluene to furnish the 5-oxopyrrolizidine ester.⁶⁵

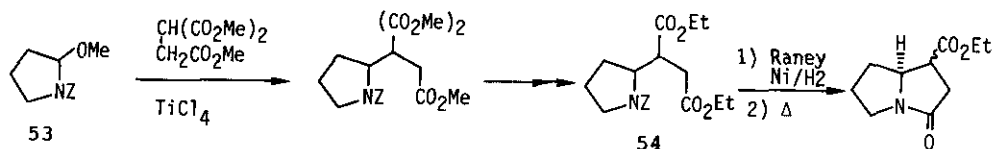




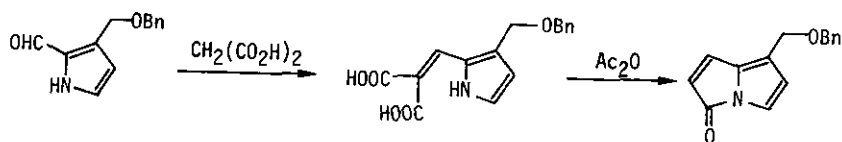
1,3-Dipolar cycloaddition of the nitrene 52 with methyl acrylate has been used for introduction of a propionic ester residue to the pyrrolidine ring.^{66,67}



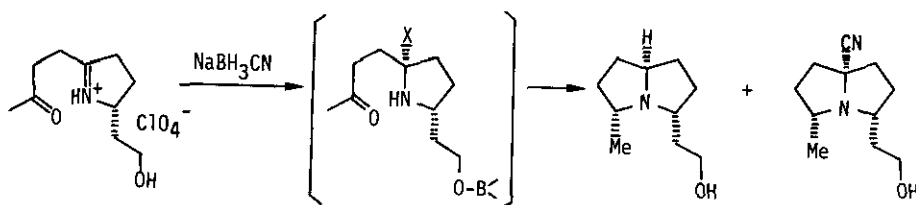
One versatile approach to the pyrrolizidine precursor, developed by Shono and coworkers,⁶⁸ commences from electrochemically prepared methyl 2-methoxy-pyrrolidine-1-carboxylate 53. The methoxyl group of 53 can be easily replaced by active methylene groups or vinyl ethers in the presence of TiCl_4 . Hydrogenolysis of the N-carbamate 54 with Raney nickel followed by distillation of the resulting aminoester gave the 3-oxopyrrolizidine ester.



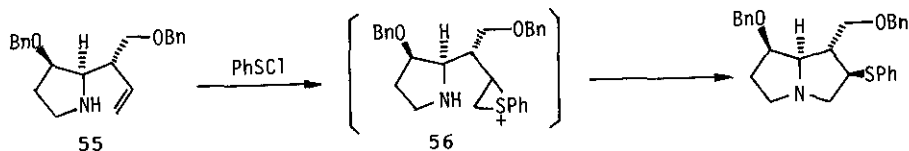
Cyclization of (pyrrol-2-ylmethylene)malonic acid, malononitrile, or malonyl chloride has been used to prepare 3-oxo-3H-pyrrolizine derivatives.^{69,70,70a}



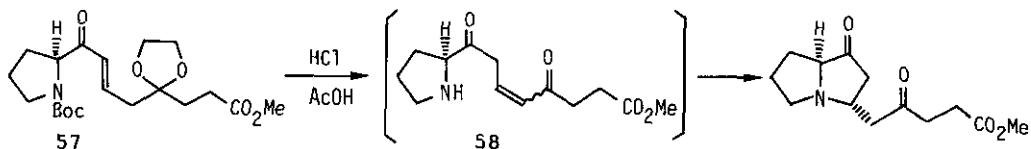
An alternative synthesis of pyrrolizidines utilizes an intramolecular reductive amination as a key step.^{71,72} This reaction is highly stereoselective.



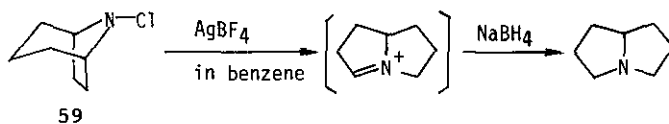
A promising approach, developed by Kametani and coworkers,⁷³ is based on the so-called "sulfenocycloamination" of the ω -alkenylamines 55. This ring closure is believed to involve a sulfonium ion 56. Similar cyclization also takes place by using phenylselenenyl bromide.⁷⁴



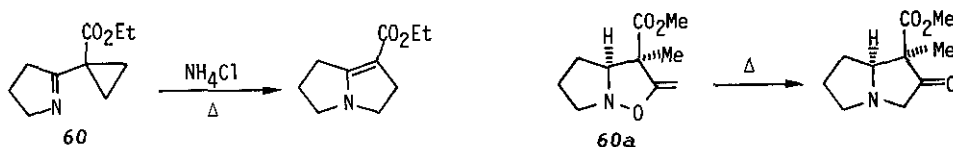
An entirely different approach, which utilizes an intramolecular Michael reaction of the enone 57, has been developed by Heathcock and von Geldern.⁷⁵ This reaction probably involves prior isomerization of the double bond to the isomeric enone 58 which may undergo a 5-exo-Trig type cyclization.



A synthesis of pyrrolizidine itself developed by Schell and coworkers,⁷⁶ utilizes an interesting silver ion-induced rearrangement of N-chloronortropane 59. Treatment of 59 with silver tetrafluoroborate in benzene followed by sodium borohydride reduction of the resulting iminium ion gave pyrrolizidine in high yield. The use of an aprotic solvent is crucial for high yield rearrangement of the chloramine.



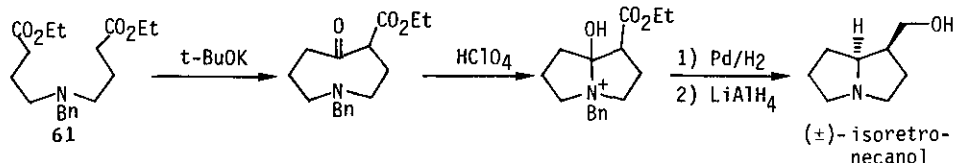
Two alternative syntheses utilizing a thermal rearrangement as a key step have been reported. Heating the imine 60 in refluxing xylene containing a catalytic amount of ammonium chloride yielded the pyrrolizidine derivative.⁷⁷ An exo-methylene substituted isoxazolidine 60a, prepared by 1,3-dipolar cycloaddition of a nitron with a carbomethoxy substituted allene, underwent to rearrange upon thermolysis to the 2-oxopyrrolizidine ester.^{77a}



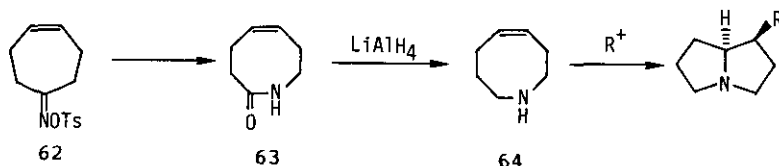
6. N-C₈ BOND FORMATION

This approach requires the preparation of eight-membered ring intermediates.

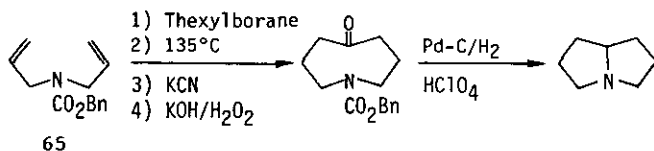
One of the early routes to the precursor, originally developed by Leonard,⁷⁸ utilizes a high-dilution Dieckmann condensation of the diester **61**.



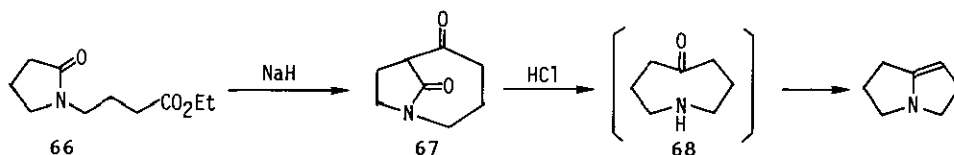
A more recent approach to the precursor, developed by Wilson and Sawicki,⁷⁹ is based on the Beckmann rearrangement of 4-cycloheptenone oxime **62**. Lithium aluminium hydride reduction of the resulting lactam **63** gave the amine **64**, which was treated with various electrophiles (Br₂, I₂, HgCl₂, PhSeBr, and PhSBr) to afford 1-substituted pyrrolizidines in high yields with high endo-stereoselectivity.



An interesting approach to 5-azacyclooctanone derivatives involves the hydroboration-carbon monoxide insertion of the diallylamine **65**. Unfortunately, the overall yield is not satisfactory.⁸⁰

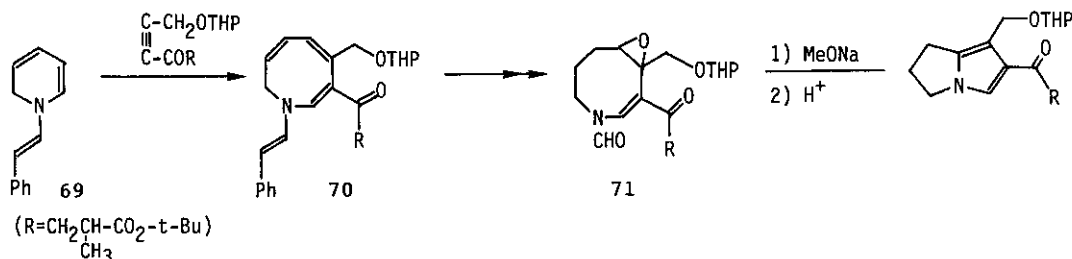


A Dieckmann condensation of the pyrrolidone ester **66** gave the ketoamide **67** which was hydrolyzed with acid to give Δ^{1,8}-dehydropyrrolizidine, presumably via 5-azacyclooctanone **68**.⁸¹

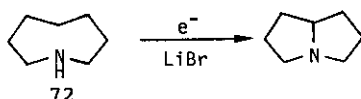


A cycloaddition reaction of 1,2-dihydropyridine **69** with acetylenic esters or ketones has been used for the preparation of the 1,8-dihydroazocine derivative

70.⁸² The dihydroazocine was then converted to the 1-formyl-4,5-epoxyazocine 71 which, upon treatment with sodium methoxide followed by acid, underwent rearrangement to form a dihydropyrrolizine.



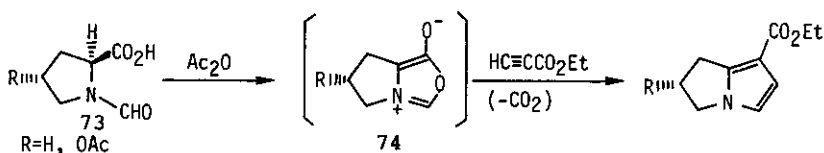
An interesting electrochemical transannular cyclization of azacyclooctane 72 in the presence of halide ion to pyrrolizidine has been reported.⁸³



7. $\text{C}_1\text{-C}_8/\text{C}_2\text{-C}_3$ BOND FORMATION

This approach uses a 1,3-dipolar cycloaddition reaction for construction of the second five-membered ring.

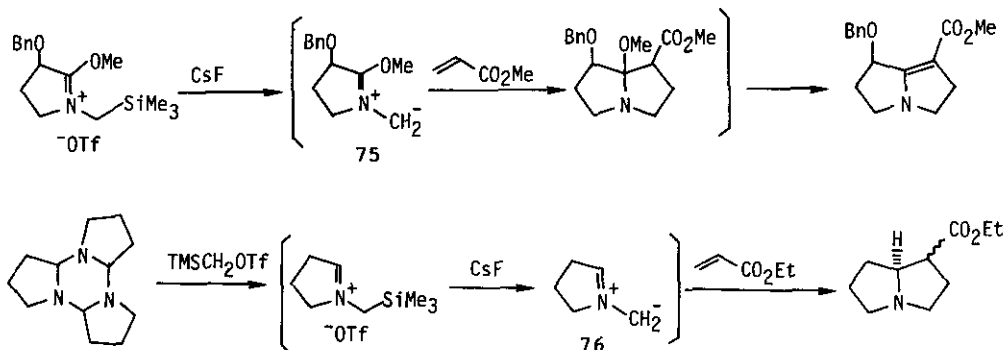
One of the approaches involves a 1,3-dipolar cycloaddition of alkynes or alkenes to mesoionic oxazolones 74 derived from N-acylprolines 73. This reaction can be accomplished simply by heating a solution of 73 and an alkyne in acetic anhydride to produce a dihydropyrrolizine in good yields. This method was



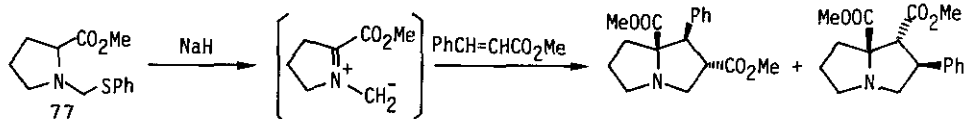
first reported in 1970 by Huisgen and coworkers.⁸⁴ The small number of steps involved, good yields, and high regioselectivity make this approach quite attractive for the pyrrolizidine synthesis. In fact, many applications of this approach have recently been reported.⁸⁵⁻⁸⁹ An interesting application, based on this strategy, is a synthesis of optically active pyrrolizidine which uses (-)-4-hydroxy-L-proline as the starting material.⁸⁹

In an alternative approach, Vedejs and coworkers⁹⁰ utilized the 1,3-dipolar cycloaddition of the imidate ylide 75, generated by desilylation from a (trimethylsilylmethyl)iminium salt. Mison and coworkers⁹¹ utilized a similar

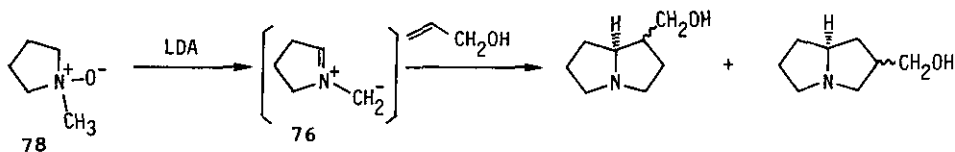
approach for the synthesis of the pyrrolizines. Sekiya and coworkers^{92b} generated the imidate ylide **76** by treating the trimer of 1-pyrroline with trimethylsilylmethyl triflate followed by desilylation of the resulting trimethylsilylmethyliminium salt. The 1,3-dipolar cycloaddition of these ylides with acrylates is highly regioselective.



A variant of this approach involves a base-promoted generation of the imidate ylide **77**,^{92a} which underwent cycloaddition with alkenes to give pyrrolizidines.

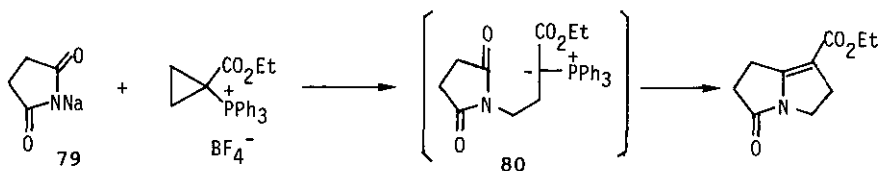


The ylide intermediate was shown to be generated by treating N-methylpyrrolidine N-oxide **78** with lithium diisopropylamide (LDA).⁹³ Trapping with various simple alkenes, it provides the corresponding pyrrolizidines. For example, 2-propen-1-ol gave the four possible regio- and stereo-isomers.

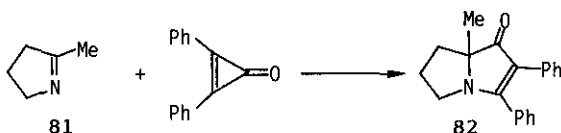


8. C₁-C₈/C₃-N BOND FORMATION

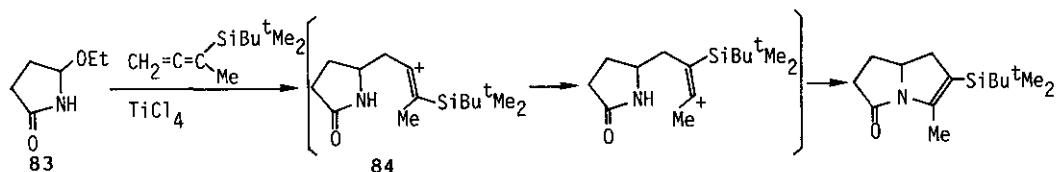
Several one-step syntheses involving [3+2] annulation reaction have been reported. The reaction of sodium succinimide with carbethoxycyclopropyltriphenylphosphonium tetrafluoroborate **79** gave directly $\Delta^{1(8)}$ -dehydropyrrolizidine.^{94,94a} This reaction is believed to involve nucleophilic ring opening of the cyclopropyl phosphonium salt **79** to give an unisolable stabilized ylide **80** which subsequently underwent an intramolecular Wittig reaction.



The reaction of diphenylcyclopropenone with 2-substituted 1-pyrrolines **81** gave rise to the pyrrolizinone **82** in good yields.⁹⁵

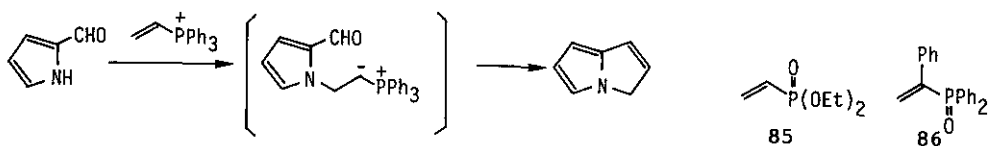


A versatile route based on [3+2] annulation of allenylsilanes to N-acyliminium ions, was developed by Danheiser and coworkers.⁹⁶ For example, addition of a (tert-butyldimethylsilyl)allene to 5-ethoxy-2-pyrrolidinone **83** in the presence of titanium tetrachloride produced the pyrrolizinone derivative. This reaction is assumed to proceed via regiospecific electrophilic substitution of the N-acyliminium ion derived from **83** at C-3 of the allenylsilane which produces a vinyl cation **84** stabilized by hyperconjugative interaction with adjacent carbon-silicon bond. A 1,2-cationic silyl group shift then occurs affording an isomeric vinyl cation, which is intercepted by the nucleophilic nitrogen atom to generate the pyrrolizinone ring system.

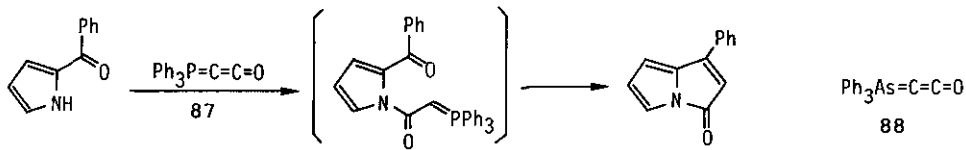


9. C₁-C₂/C₃-N BOND FORMATION

The reaction of pyrrole-2-aldehyde with vinylphosphonium bromide in the presence of sodium hydride is a well-known entry to the 3H-pyrrolizines.^{97,98a} Recently, this reaction has been extended to vinylphosphonates **85**^{98b,c} and phosphine oxides **86**.^{98b,c}

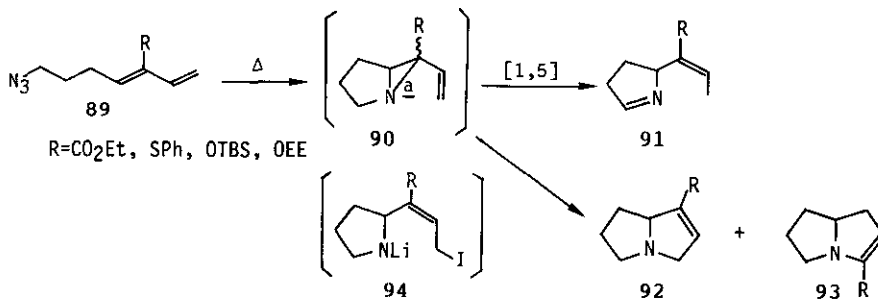


In a variant of this approach, cumulative ylides **87**⁹⁹ and **88**¹⁰⁰ have also been used as versatile synthons for the preparation of the pyrrolizinone skeleton.

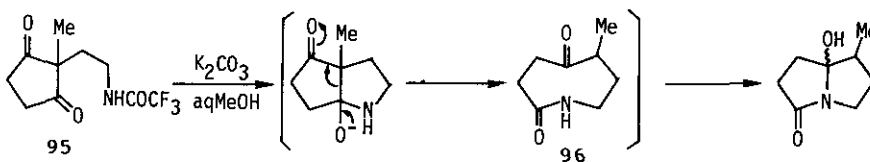


10. C₈-N/C₃-N BOND FORMATION

An interesting approach to pyrrolizidines is based on an intramolecular "[4+1] pyrroline annulation" of ω -azidodienes **89**.^{101a,102a} The exposure of the diene (**89**, R=CO₂Et)(mixture of E and Z isomers) to conditions of thermal decomposition ranging from refluxing THF to flash pyrolysis gave uniformly high yields of the undesired imine **91**. The reaction mixtures contained isomeric pyrrolizines **92** and **93** only as minor products. Subsequently, in order to circumvent the undesired pathways, two methods have been developed. Pearson and coworkers^{101a} found that the introduction of a hetero-substituent (SPh, OTBS, or OEE) onto the diene moiety facilitates cleavage of bond a of a possible intermediate aziridine **90** to produce the desired pyrrolizine. Another modification, developed by Hudlicky and coworkers,^{102b} consists of refluxing the ω -azidodiene (**89**, R=CO₂Et) in acetone containing LiI. The nucleophile-assisted ring opening of the vinylaziridine **90** has been thought to occur via an intermediate **94**, which furnishes the pyrrolizine **92**.

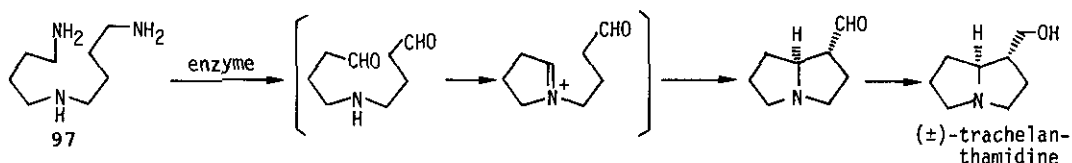


An interesting rearrangement of the cyclopentane-1,3-dione **95** has been described by Ban and coworkers.¹⁰³ This reaction is considered to take place via azacyclo-octanedione intermediate **96**.

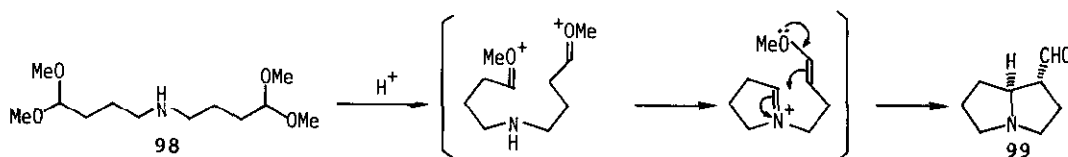


11. C₁-C₈/C₈-N BOND FORMATION

Two syntheses of (±)-trachelanthamidine, which are patterned along the suggested biogenetic pathway, were published by two groups. Robins¹⁰⁴ used homospermidine 97 as starting material which was converted into (±)-trachelanthamidine by the sequence of enzymic oxidations with diamine oxidase, non-enzymic cyclization under physiological conditions, and reduction by a coupled dehydrogenase system.



Takano and coworkers¹⁰⁵ utilized the amino-diacetal 98 which was treated with methanolic hydrochloric acid to give the Mannich base 99. This base was directly reduced with sodium borohydride to yield (±)-trachelanthamidine.



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