RECENT ADVANCES IN THE SYNTHESIS OF PYRROLIZIDINES

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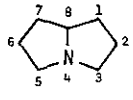
Abstract — This review briefly summarizes some recent advances in the synthesis of pyrrolizidines.

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 reviews[2-6] 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.



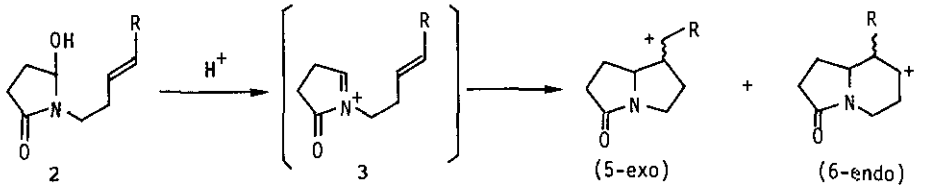
1

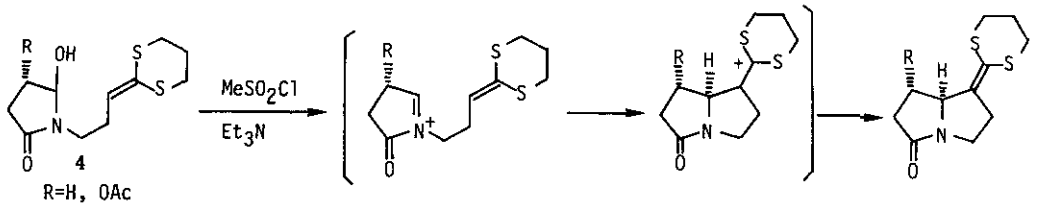
2. C_1-C_8 BOND FORMATION

A variety of new methods involving the C_1-C_8 bond formation have been developed during the last decade.

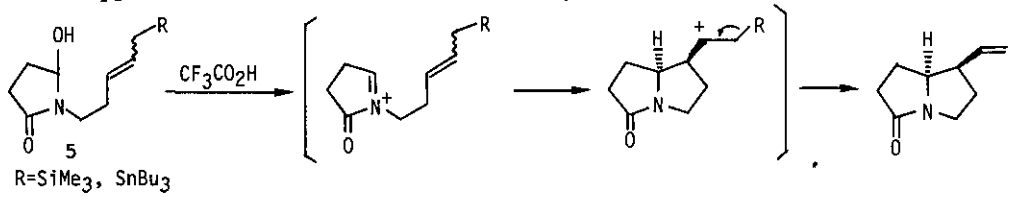
Perhaps, the most versatile approach is based on the acid-catalyzed cyclization of the N-acyliminium ions **3**, mainly developed by Speckamp and co-workers.[7] The N-acyliminium ion precursors, hydroxylactams **2** can be prepared most conveniently by controlled sodium borohydride reduction of the corresponding 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.



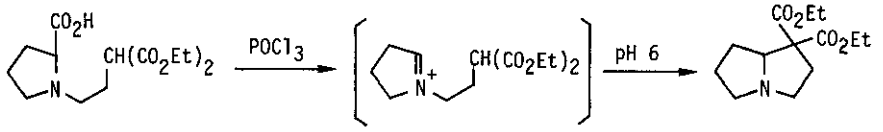


Dithioacetal (**4**, R=H),[8] phenyl (**2**, R=Ph),[9] phenylthio (**2**, R=SPh),[10] and chloro (**2**, R=Cl) groups[12] are found to be effective for this purpose. Cyclization of **5** (R=$SiMe_3$,[11] $SnBu_3$[12]) proceeded with high regio- and stereo-selectivities to give the 5-oxopyrrolizidine with an exo-1-vinyl group. Synthesis of an optically

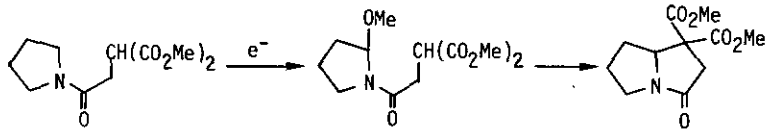


active pyrrolizidine derivative using the dithioacetal **4** (R=OAc) has been achieved via a stereoselective cyclization directed by an acetoxy substituent.[8c]

Rapoport and coworkers[13] utilized an iminium ion generated by decarboxylation of an α-amino acid, which cyclized at pH 6 to give the pyrrolizidine ring system.

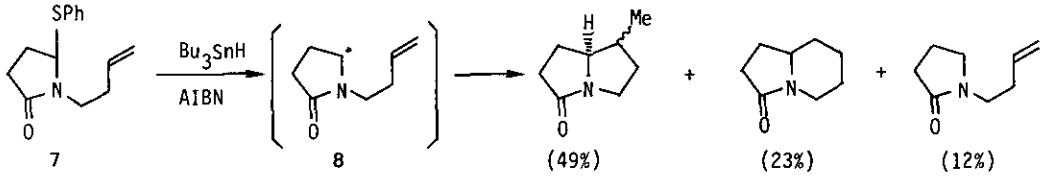


Zoltan and coworkers[14] utilized an intramolecular cyclization of the electrochemically prepared N-acyliminium ion precursor **6**.

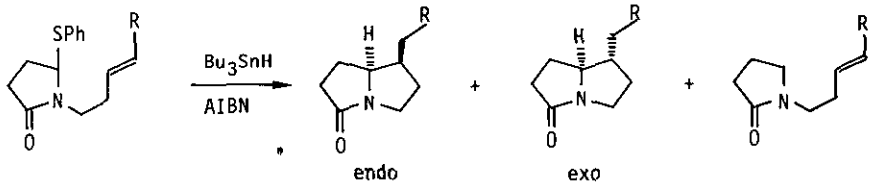


6

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 regiochemical 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]



7 8 (49%) (23%) (12%)

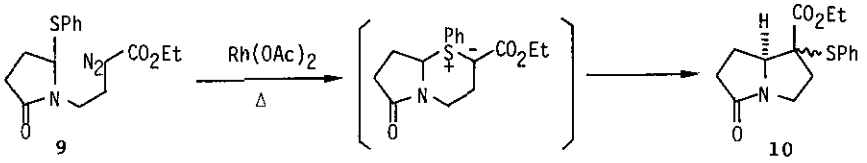


endo exo

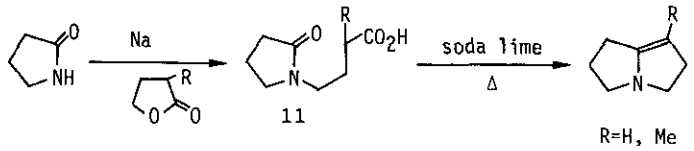
R	Yield (%) (endo/exo)	Yield (%)
H (=7)	49 (11:1)	12
CO_2Bu^t	81 (9:1)	0
CN	85 (9:1)	0

In a variant of these cationic or radical cyclization reactions, Kametani and coworkers[18] 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-

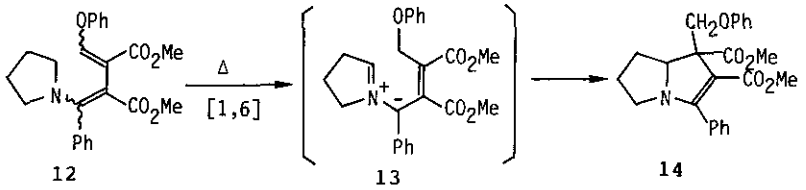
oxopyrrolizidine **10**.



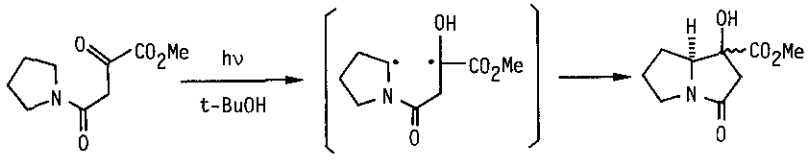
Miyano and coworkers[19] found that heating of readily available 4-(2-oxopyrrolidin-1-yl)butanoic acids **11** with soda lime gave rise to $\Delta^{1(8)}$-dehydropyrrolizidines. Although the mechanistic details of this reaction remain to be established, this method appears to be of considerable practical importance.

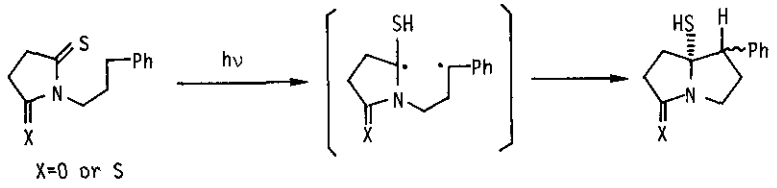


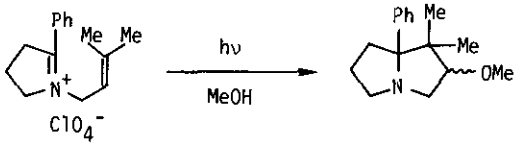
An interesting approach to the pyrrolizidine ring system, developed by Reinhoudt and coworkers,[20] utilizes an electrocyclic reaction as a key step. 1-(1-Pyrrolidinyl)-1,3-butadienes **12** having an electron-withdrawing group at C-3, underwent a thermal rearrangement to pyrrolizine derivatives **14**.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



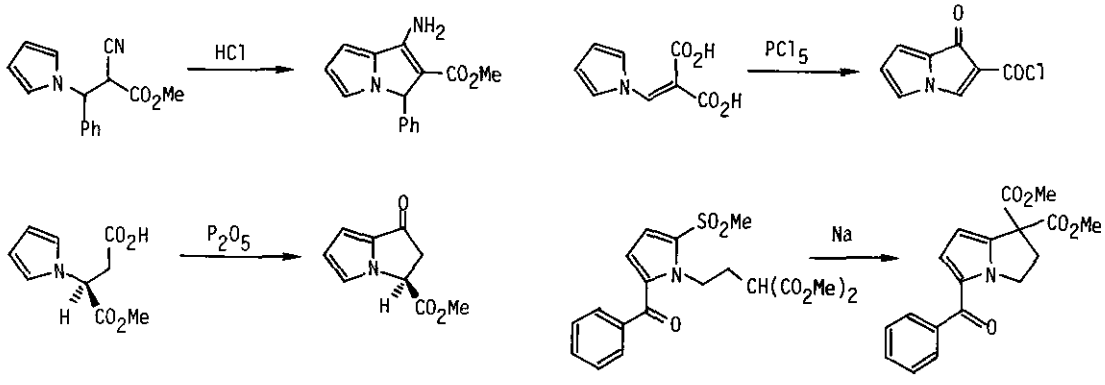
Several photochemical approaches have been reported.[21-23] However, all of these approaches suffer from a lack of stereoselectivity.







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.

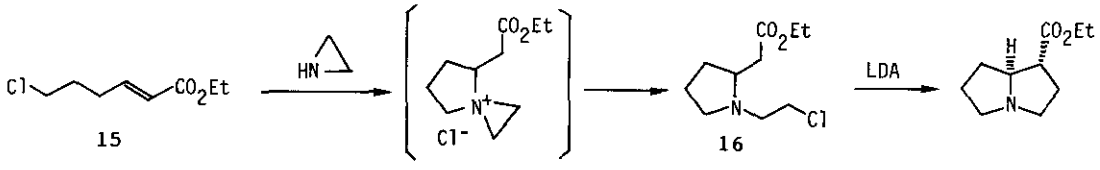


An intramolecular carbenoid insertion reaction on the pyrrole ring has been examined but the yield is poor.[28]

3. C_1-C_2 BOND FORMATION

The C_1-C_2 bond formation approach using an intramolecular alkylation is one of the standard methods for the synthesis of the pyrrolizidines.

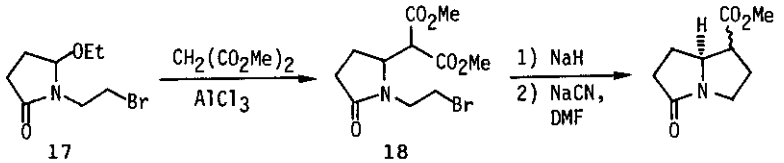
One interesting approach to the precursor, N-(2-chloroethyl)pyrrolidine **16**, developed by Kametani and coworkers,[29] is based on the ring opening reaction of an aziridinium salt. Treatment of the α,β-unsaturated ester **15** with an excess of aziridine gave directly N-(2-chloroethyl)pyrrolidine **16**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



15 16

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

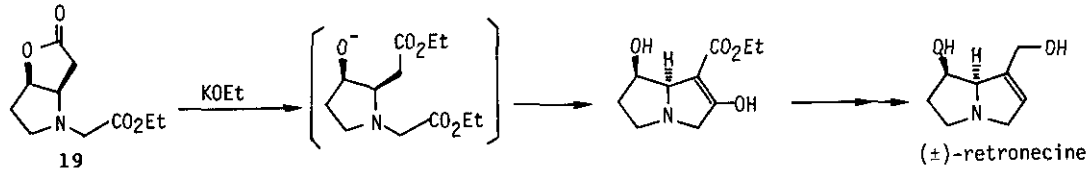
aluminium chloride, has been described by Kraus and Neuenschwander.[30] Cyclization of **18** with sodium hydride followed by decarbomethoxylation gave the 5-oxopyrrolizidine ester.



17 18

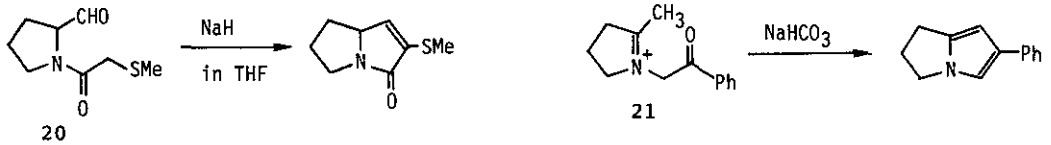
The intramolecular alkylation approach is also applicable to the pyrrole derivative.[31]

A Dieckmann condensation has been extensively used for the construction of the pyrrolizidine ring system. Since Geissman and Waiss[32] reported the conversion of the lactone **19** into (±)-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 acids[39], is also noteworthy.



19 (±)-retronecine

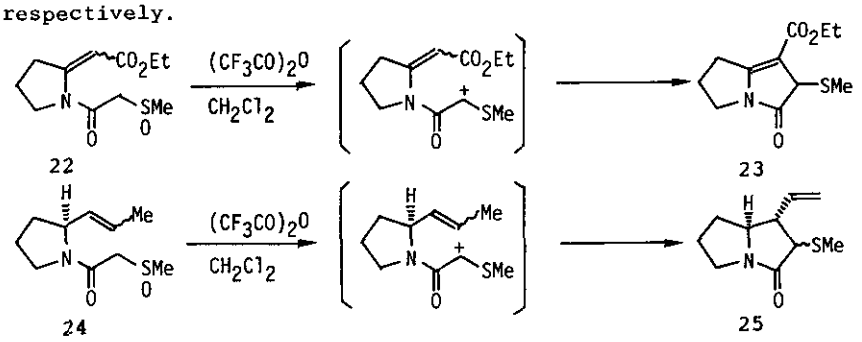
An intramolecular aldol condensation has also been used. Treatment of the pyrrolidine-2-aldehyde **20** with sodium hydride afforded the pyrrolizinone derivative.[40] Similarly, base treatment of the 2-methyl-1-pyrrolinium salt **21** provided a pyrrolizine derivative.[41]



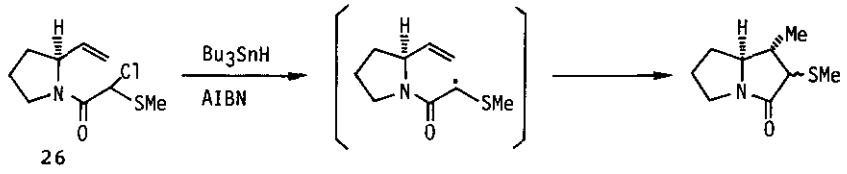
20 21

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

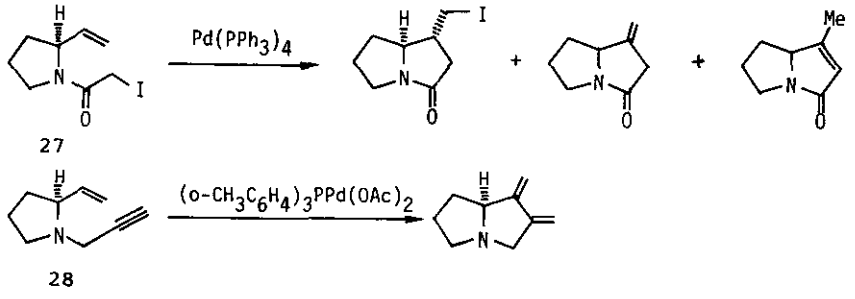
25, respectively.



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]

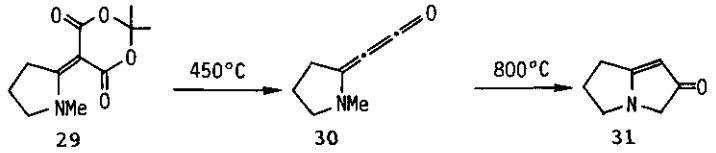


Two recent noteworthy C_1-C_2 bond forming approaches to pyrrolizidines involve palladium-mediated cyclization of N-iodoacetyl-2-vinylpyrrolidine **27**[47] and N-propargyl-2-vinylpyrrolidine **28**.[48]

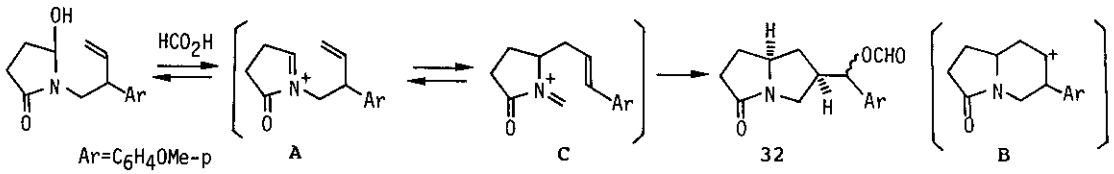


4. C_2-C_3 BOND FORMATION

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°C gave a reactive methyleneketene intermediate **30** which, on further increase of the temperature (800°C), was transformed into the pyrrolizinone derivative **31**.



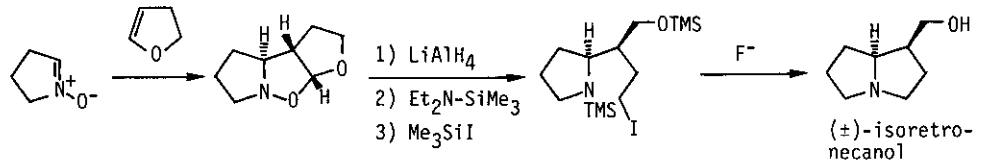
An interesting approach developed independently by Speckamp[50] and Hart,[51] involves an aza-Cope rearrangement-cyclization of the N-acyliminium ions. As described earlier, cyclization of the N-acyliminium ions **A** of the 2-aza-1,5-hexadienyl type generally affords the six-membered ring **B**. However, 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.

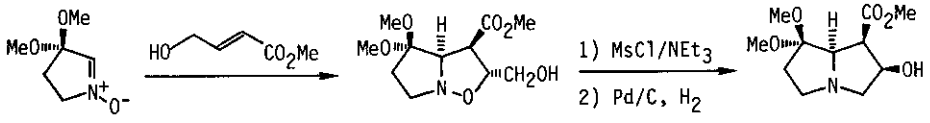


5. C_3-N BOND FORMATION

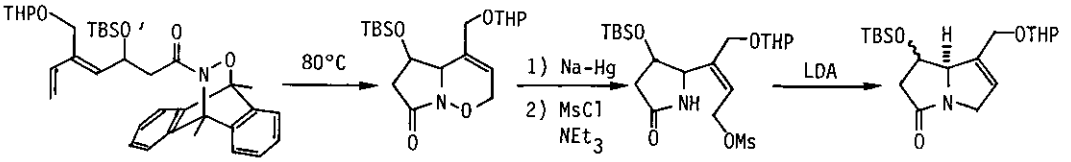
One of the earliest approaches to pyrrolizidines involves construction of the second five-membered ring on a pyrrolidine by C_3-N bond formation using an intramolecular N-alkylation or N-acylation.

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 Nickell[55] 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.



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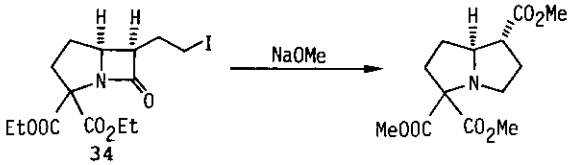
Cavagna and coworkers[56] utilized a ring opening reaction of a suitably functionalized β-lactam **34** with base or acid for the construction of the pyrrolizidine ring system.



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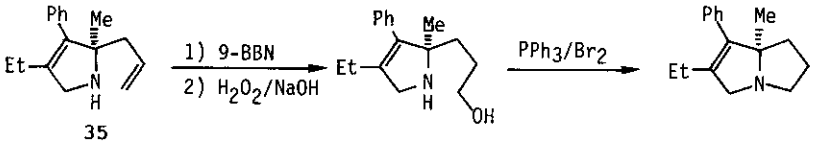
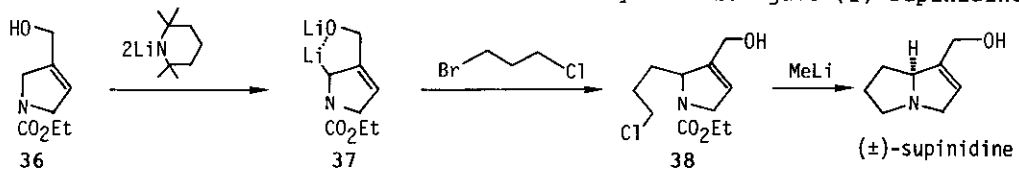
Hydroboration-oxidation of the alkene **35** followed by treatment of the resulting alcohol with triphenylphosphine-bromine furnished the pyrrolizidine derivative.[57]



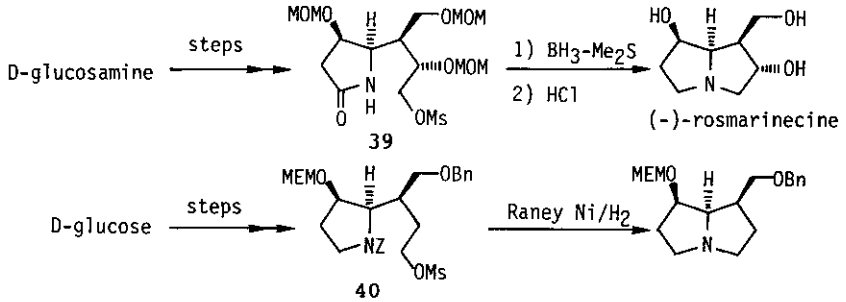
35

McDonald and Narayanan[58] 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 (±)-supinidine.



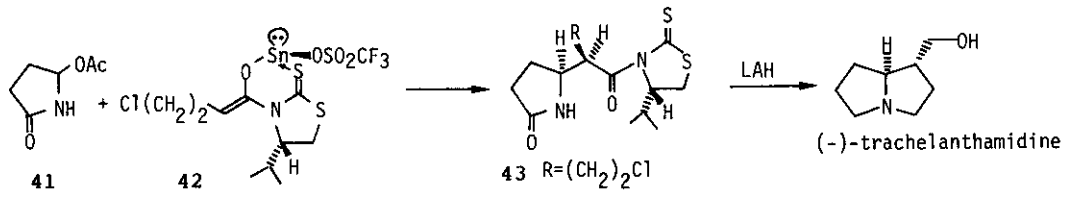
36 37 38

The chiral syntheses of the intermediates **39** and **40** from D-glucosamine[59] and D-glucose,[60] respectively, are also noteworthy. Both the syntheses are stereoselective, but nonetheless, quite lengthy.



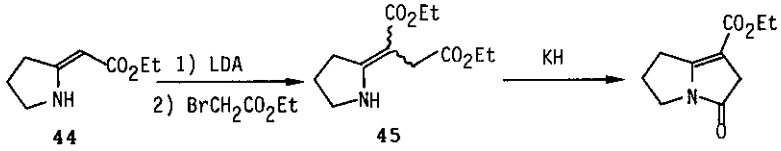
39 40

Recently Nagao and coworkers[61] have developed an ingeneous 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 (≥97% de). Treatment of compound **43** with excess LAH affords directly (-)-trachelanthamidine (99% ee).

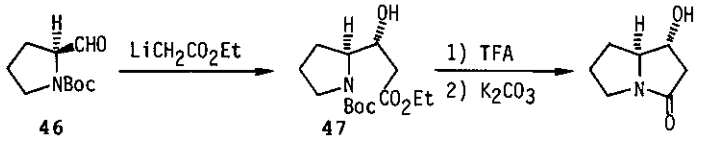


An alternative C_3-N bond formation approach is based on an intramolecular N-acylation of pyrrolidine-2-propionates, giving 3-oxopyrrolizidines. A variety of the methods for the syntheses of such precursors have been developed in the last decade.

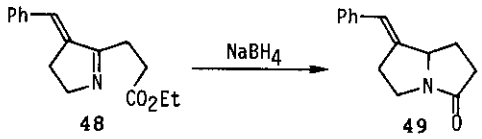
Reaction of the anion of **44** with ethyl bromoacetate gave the diester **45** which cyclized under basic conditions to afford the 5-oxopyrrolizidine.[62]

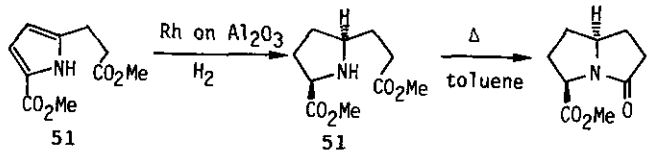


Aldol reaction of the aldehyde **46** with ethyl lithioacetate proceeded stereoselectively to give **47**, which, after deprotection, underwent cyclization to give a 3-oxopyrrolizidine.[63]



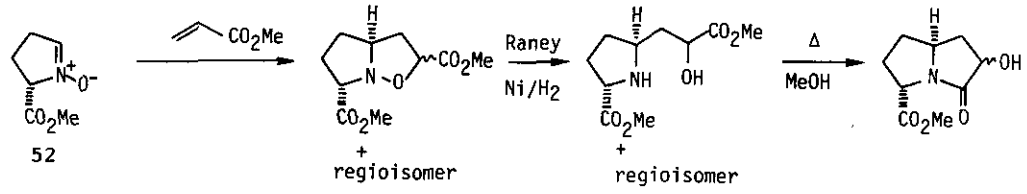
Reduction of the pyrroline ester **48** with sodium borohydride proceeded with concomitant cyclization giving the lactam **49**. Catalytic hydrogenation of pyrrole diester **50** over rhodium-on-alumina gave the pyrrolidine ester **51**, which cyclized in refluxing toluene to furnish the 5-oxopyrrolizidine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





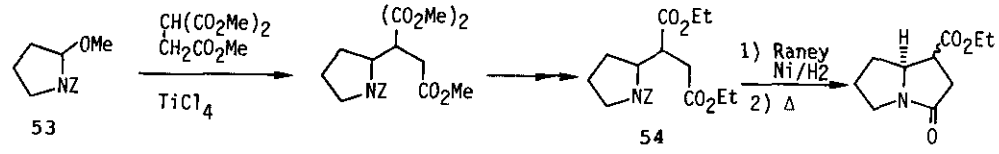
51 51

1,3-Dipolar cycloaddition of the nitrone **52** with methyl acrylate has been used for introduction of a propionic ester residue to the pyrrolidine ring.[66,67]



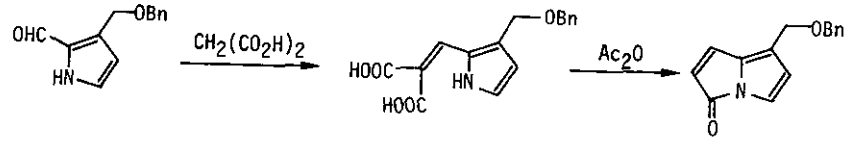
52 + regioisomer + regioisomer

One versatile approach to the pyrrolizidine precursor, developed by Shono and coworkers,[68] commences from electrochemically prepared methyl 2-methoxypyrrolidine-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.

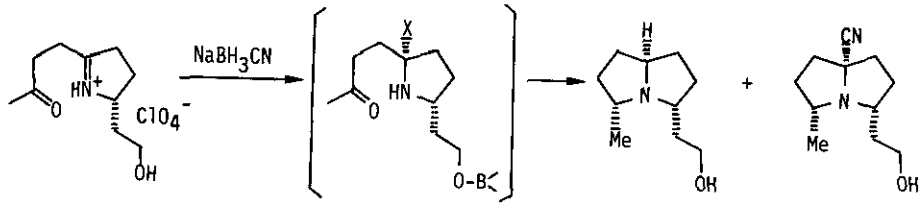


53 54

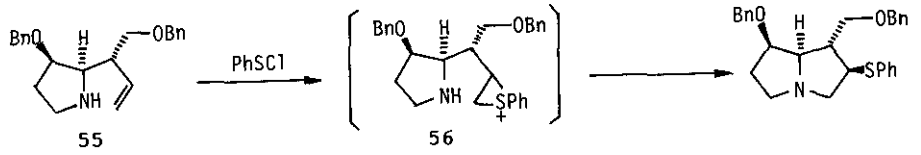
Cyclization of (pyrrol-2-ylmethylene)malonic acid, malononitrile, or malonyl chloride has been used to prepare 3-oxo-3H-pyrrolizine derivatives.[69,70,70a]



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

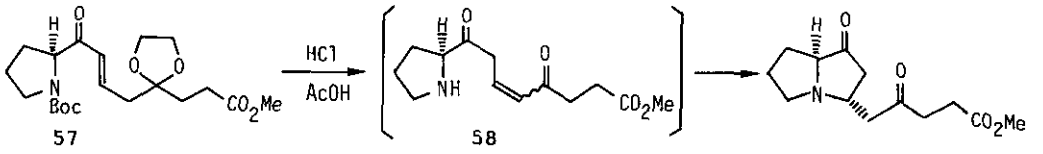


A promising approach, developed by Kametani and coworkers,[73] is based on the so-called "*sulfenocycloamination*" *of the* ω*-alkenylamines* **55**. This ring closure is believed to involve a sulfonium ion **56**. Similar cyclization also takes place by using phenylselenenyl bromide.[74]



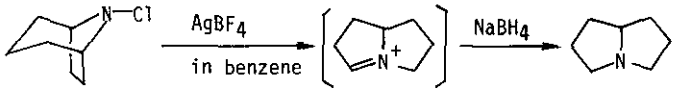
55 **56**

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.



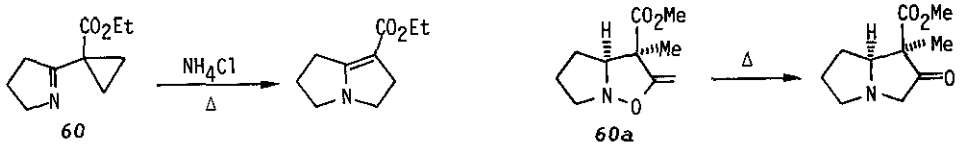
57 **58**

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*.



59

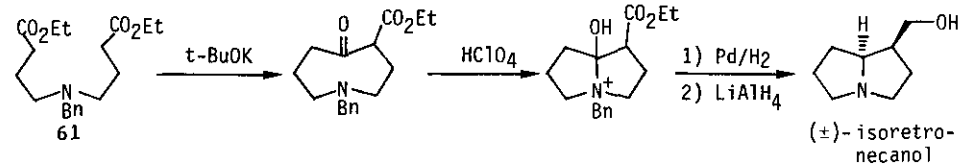
Two alternative syntheses utilizing a thermal rearrangement as a key step have been reported. Heating the imine **60** in refluxing xylene containing a catalytic amount of ammonium chloride yielded the pyrrolizidine derivative.[77] An exo-methylene substituted isoxazolidine **60a**, prepared by 1,3-dipolar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



60 ***60a***

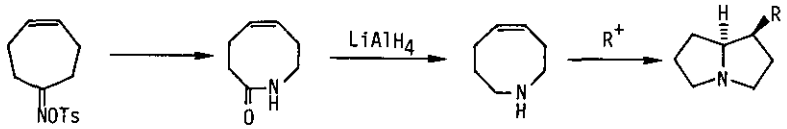
6. $N\text{-}C_8$ BOND FORMATION

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**.



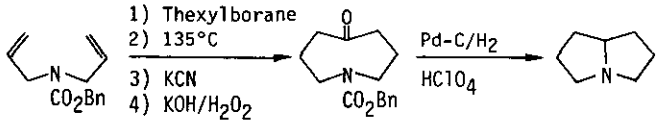
61

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 (Br_2, I_2, $HgCl_2$, PhSeBr, and PhSBr) to afford 1-substituted pyrrolizidines in high yields with high endo-stereoselectivity.



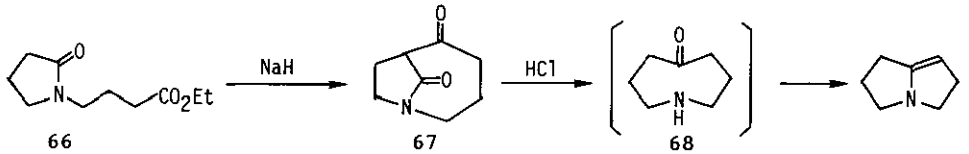
62 **63** **64**

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]



65

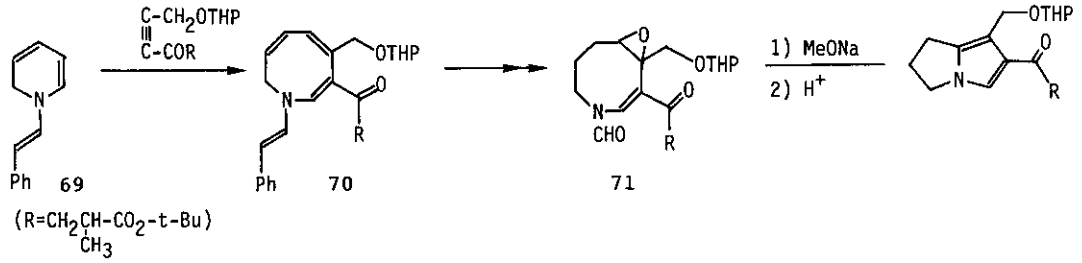
A Dieckmann condensation of the pyrrolidone ester **66** gave the ketoamide **67** which was hydrolyzed with acid to give $\Delta^{1,8}$-dehydropyrrolizidine, presumably via 5-azacyclooctanone **68**.[81]



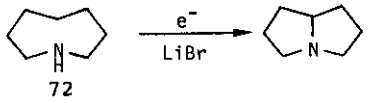
66 **67** **68**

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.



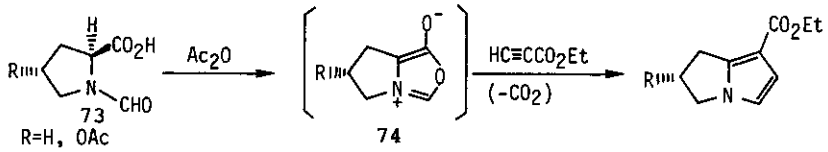
An interesting electrochemical transannular cyclization of azacyclooctane **72** in the presence of halide ion to pyrrolizidine has been reported.[83]



7. C_1-C_8/C_2-C_3 BOND FORMATION

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

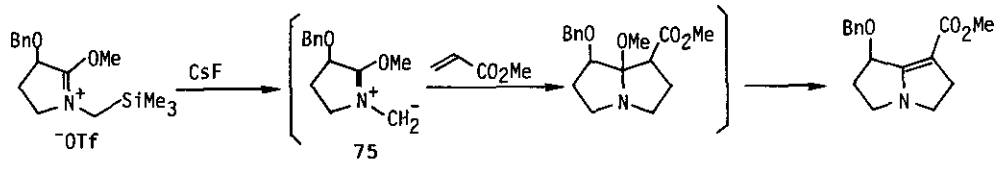
One of the approaches involves a 1,3-dipolar cycloaddition of alkynes or alkenes to mesoionic oxazolones **74** derived from N-acylprolines **73**. This reaction can be accomplished simply by heating a solution of **73** and an alkene or alkyne in acetic anhydride to produce a dihydropyrrolizine in good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

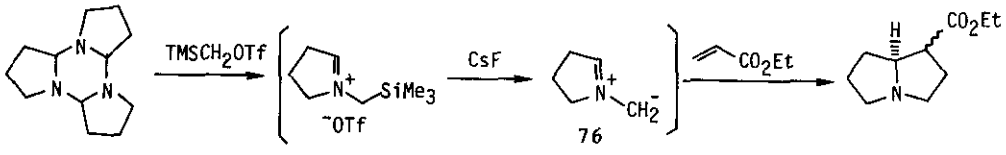


first reported in 1970 by Huisgen and coworkers.[84] The small number of steps involved, good yields, and high regioselectivity make this approach quite attractive for the pyrrolizidine synthesis. In fact, many applications of this approach have recently been reported.[85-89] An interesting application,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

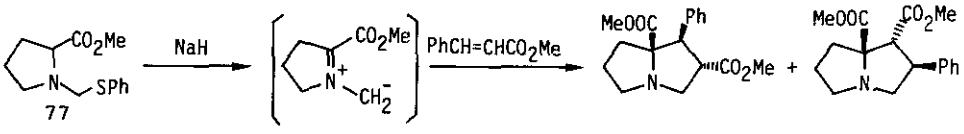
In an alternative approach, Vedejs and coworkers[90] utilized the 1,3-dipolar cycloaddition of the imidate ylide **75**, generated by desilylation from a (trimethylsilylmethyl)iminium salt. Mison and coworkers[91] utilized a similar

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.

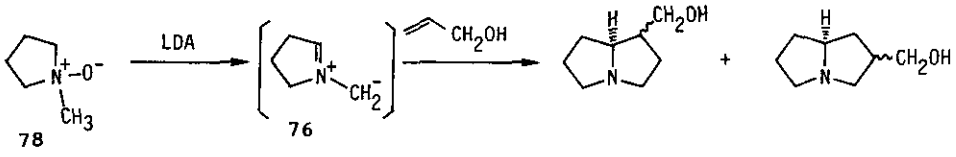




A variant of this approach involves a base-promoted generation of the imidate ylide **77**,[92a] which underwent cycloaddition with alkenes to give pyrrolizidines.

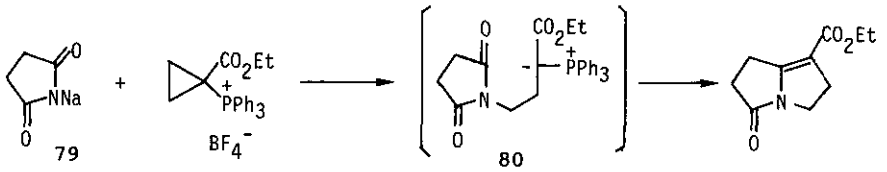


The ylide intermediate was shown to be generated by treating N-methylpyrrolidine N-oxide **78** with lithium diisopropylamide (LDA).[93] Trapping with various simple alkenes, it provides the corresponding pyrrolizidines. For example, 2-propen-1-ol gave the four possible regio- and stereo-isomers.



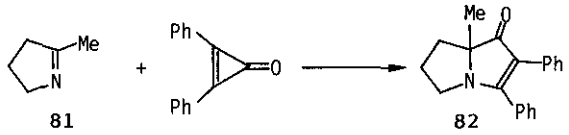
8. C_1-C_8/C_3-N BOND FORMATION

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.



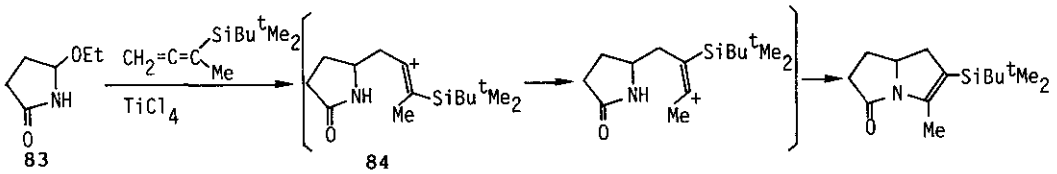
79 80

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



81 82

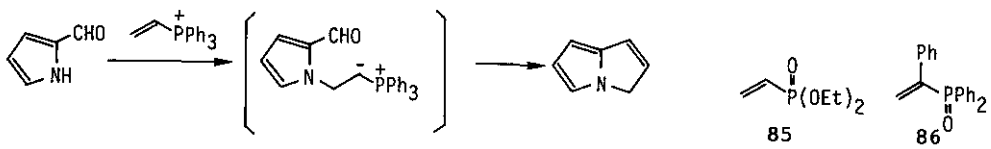
A versatile route based on [3+2] annulation of allenylsilanes to N-acyliminium ions, was developed by Danheiser and coworkers.[96] For example, addition of a (tert-butyldimethylsilyl)allene to 5-ethoxy-2-pyrrolidinone **83** in the presence of titanium tetrachloride produced the pyrrolizinone derivative. 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.



83 84

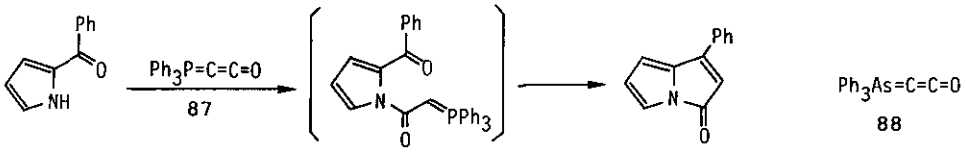
9. C_1-C_2/C_3-N BOND FORMATION

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]



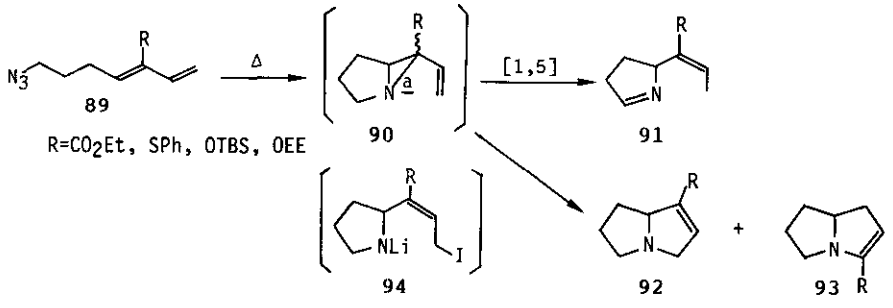
85 86

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.

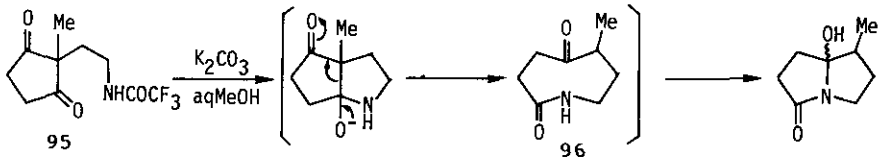


10. C_8-N/C_3-N BOND FORMATION

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=CO_2Et)(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=CO_2Et) 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**.

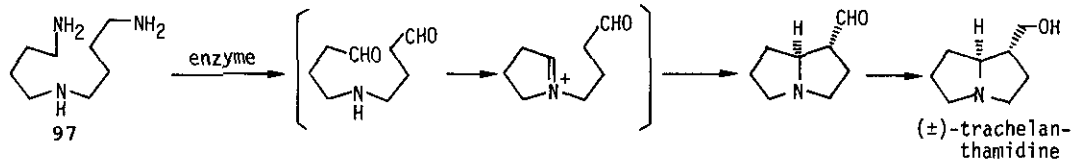


An interesting rearrangement of the cyclopentane-1,3-dione **95** has been described by Ban and coworkers.[103] This reaction is considered to take place via azacyclo-octanedione intermediate **96**.



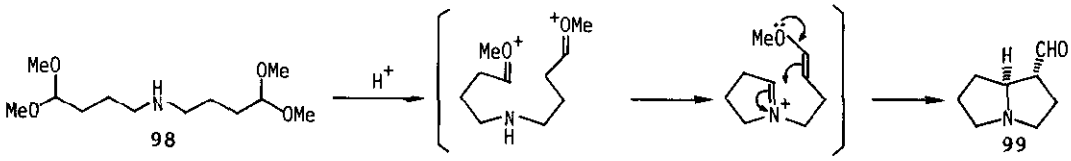
11. C_1-C_8/C_8-N BOND FORMATION

Two syntheses of (±)-trachelanthamidine, which are patterned along the suggested biogenetic pathway, were published by two groups. Robins[104] 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.



97

Takano and coworkers[105] 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.



98 **99**

REFERENCES

1. D.J. Robins, Adv. Heterocycl. Chem., 1979, **24**, 247.
2. D.J. Robins, Fortschr. Chem. Org. Naturst., 1982, **41**, 115.
3. K. Narasaka, J. Syn. Org. Chem., 1985, **43**, 464.
4. D.J. Robins, The Alkaloids (London), 1983, **13**, 65.
5. J.T. Wrobel, The Alkaloids (Academic Press), 1985, **26**, 327.
6. G. Hall, J.K. Sugden, and M.B. Waghela, Synthesis, 1987, 10.
7. a) W.N. Speckamp, Recl. Trav. Chem. Pays-Bas, 1981, **100**, 345; b) W.N. Speckamp, Tetrahedron, 1985, **41**, 4367.
8. a) A.R. Chamberlin and J.Y.L. Chung, Tetrahedron Lett., 1982, **23**, 2619; b) A. R. Chamberlin and J.Y.L. Chung, J. Am. Chem. Soc., 1983, **105**, 3653; c) A.R. Chamberlin, H.D. Nguyen, and J.Y.L. Chung, J. Org. Chem., 1984, **49**, 1682.
9. P.M.M. Nossin and W.N. Speckamp, Tetrahedron Lett., 1979, 4411.
10. A.W. Lochead, G.R. Proctor, and M.P.L. Caton, J. Chem. Soc., Perkin Trans. 1, 1984, 2477.
11. a) H. Hiemstra and W.N. Speckamp, Tetrahedron Lett., 1983, **24**, 1407; b) H. Hiemstra, M.H.A. Sno, R.J. Vijn, and W.N. Speckamp, J. Org. Chem., 1985, **50**,

4014.

12. G.E. Keck and E.J. Enholm, Tetrahedron Lett., 1985, **26**, 3311.
13. I.G. Csendes, Y.Y. Lee, H.C. Padgett, and H. Rapoport, J. Org. Chem., 1979, **44**, 4173.
14. B. Zoltan, E. Mikael, W.L. Goeran, Acta Chem. Scand., 1984, **38**, 297.
15. a) D.J. Hart and Y.-M. Tsai, J. Am. Chem. Soc., 1982, **104**, 1430; b) D.A. Burnett, J.-K. Choi, D.J. Hart, and Y.-M. Tsai, ibid., 1984, **106**, 8201; c) D.J. Hart and Y.-M. Tsai, ibid., 1984, **106**, 8209.
16. a) J.-K. Choi, D.J. Hart, and Y.-M. Tsai, Tetrahedron Lett., 1982, **23**, 4765; b) J.-K. Choi and D.J. Hart, Tetrahedron, 1985, **19**, 3959.
17. S. Kano, Y. Yuasa, K. Asami, and S. Shibuya, Chem. Lett., 1986, 735.
18. T. Kametani, H. Yukawa, and T. Honda, J. Chem. Soc., Chem. Commun., 1986, 651.
19. a) S. Miyano, T. Somehara, M. Nakao, and K. Sumoto, Synthesis, 1978, 701; b) S. Miyano, S. Fujii, O. Yamashita, N. Toraishi, K. Sumoto, F. Satoh, and T. Masuda, J. Org. Chem., 1981, **46**, 1737.
20. a) D.N. Reinhoudt, J. Geevers, and W.P. Trompenaars, Tetrahedron Lett., 1978, 1351; b) W. Verboom, G.W. Visser, W.P. Trompenaars, D.N. Reinhoudt, S. Harkema, and G.J. van Hummel, Tetrahedron, 1981, **37**, 3525; c) D.N. Reinhoudt, G.W. Visser, W. Verboom, P.H. Benders, and M.L.M. Pennings, J. Am. Chem. Soc., 1983, **105**, 4775.
21. J.-C. Gramain, R. Remusen, and D. Vallee, J. Org. Chem., 1985, **50**, 710.
22. M. Machida, K. Oda, and Y. Kanaoka, Tetrahedron Lett., 1985, **26**, 5173.
23. J.L. Stavinoha, P.S. Mariano, A. Leone-Bay, R. Swanson, and C. Bracken, J. Am. Chem. Soc., 1981, **103**, 3148.
24. a) R. Neidlein and G. Jeromin, J. Chem. Res. (S), 1980, 232; b) R. Neidlein and G. Jeromin, Chem. Ber., 1982, **115**, 714.
25. S.J. Box and D.F. Corbett, Tetrahedron Lett., 1981, **22**, 3293.
26. R. Neidlein and G. Jeromin, Chem. Ber., 1982, **115**, 706.
27. a) F. Franco, R. Greenhouse, and J.M. Muchowski, J. Org. Chem., 1982, **47**, 1682; b) C. Ortiz and R. Greenhouse, Tetrahedron Lett., 1985, **26**, 2831.
28. E. Galeazzi, A. Guzman, A. Pinedo, A. Saldana, D. Torre, and J.M. Muchowski, Can. J. Chem., 1983, **61**, 454.
29. a) T. Kametani, K. Higashiyama, H. Otomasu, and T. Honda, Heterocycles, 1984, **22**, 729; b) T. Kametani, K. Higashiyama, H. Otomasu, and T. Honda, Israel J. Chem., 1987, **27**, 57.

30. G.A. Kraus and K. Neuenschwander, Tetrahedron Lett., 1980, **21**, 3841.

31. a) J. Ackrell, F. Franco, R. Greenhouse, A. Guzman, and J.M. Muchowski, J. Het. Chem., 1980, **17**, 1081; b) H. Carpio et al., Can. J. Chem., 1982, **60**, 2295.

32. T.A. Geissman and A.C. Waiss, Jr., J. Org. Chem., 1962, **27**, 139.

33. a) K. Narasaka, T. Sakakura, T. Uchimaru, K. Morimoto, and T. Mukaiyama, Chem. Lett., 1982, 455; b) K. Narasaka, T. Sakakura, T. Uchimaru, and D. Guedin-Vuong, J. Am. Chem. Soc., 1984, **106**, 2954.

34. a) H. Rueger and M. Benn, Heterocycles, 1982, **19**, 23; b) H. Rueger and M. Benn, ibid., 1982, **19**, 1677; c) H. Rueger and M. Benn, ibid., 1983, **20**, 1331; V.K. Yadav, H. Rueger, and M. Benn, ibid., 1984, **22**, 2735.

35. M.K. Gurjar and V.J. Patil, Ind. J. Chem., 1985, **24**, 1282.

36. J.G. Buchanan, G. Singh, and R.H. Wightman, J. Chem. Soc., Chem. Commun., 1984, 1299.

37. K. Shishido, Y. Sukegawa, K. Fukumoto, and T. Kametani, Heterocycles, 1985, **23**, 1629.

38. H. Niwa, Y. Miyachi, O. Okamoto, Y. Uosaki, and K. Yamada, Tetrahedron Lett., 1986, **27**, 4605.

39. S. Saito, S. Matsumoto, S. Sato, M. Inaba, and T. Moriwake, Heterocycles, 1986, **24**, 2785.

40. M. Ikeda, S. Harada, A. Yamasaki, K. Kinouchi, and H. Ishibashi, Heterocycles, in press.

41. G. Dannhardt and R. Obergrusberger, Arch. Pharm. (Weinheim), 1978, **312**, 896.

42. E. Roeder, H. Wiedenfeld, and T. Bourauel, Justus Liebigs Ann. Chem., 1985, 1708.

43. J.M. Muchowski et al., J. Med. Chem., 1985, **28**, 1037.

44. H. Ishibashi, K. Sato, K. Maruyama, M. Ikeda, and Y. Tamura, Chem. Pharm. Bull., 1985, **33**, 4593.

45. H. Ishibashi, H. Ozeki, and M. Ikeda, J. Chem. Soc., Chem. Commun., 1986, 655.

46. H. Ishibashi, T. Sato, M. Irie, S. Harada, and M. Ikeda, Chem. Lett., 1987, 795.

47. M. Mori, N. Kanda, I. Oda, and Y. Ban, Tetrahedron, 1985, **41**, 5465.

48. B.M. Trost and S.-F. Chen, J. Am. Chem. Soc., 1986, **108**, 6053.

49. a) P. Lorencak, J.-C. Pommelet, J. Chache, and C. Wentrup, J. Chem. Soc., Chem. Commun., 1986, 369; b) H. Dhimane, J.-C. Pommelet, J. Chuche,

G. Lhommet, and M. Haddad, Tetrahedron Lett., 1987, **28**, 885.

50. a) P.M.M. Nossin and W.N. Speckamp, Tetrahedron Lett., 1981, **22**, 3289; b) P.M.M. Nossin, J.A.M. Hamersma, and W.N. Speckamp, ibid., 1982, **23**, 3807; c) H. Ent, H. de Koning, and W.N. Speckamp, ibid., 1985, **26**, 2109; d) H. Ent, H. de Koning, and W. N. Speckamp, ibid., 1985, **26**, 5105; e) H. Ent, H. de Koning, and W.N. Speckamp, J. Org. Chem., 1986, **51**, 1687.
51. a) D.J. Hart and T.-K. Yang, Tetrahedron Lett., 1982, **23**, 2761; b) D.J. Hart and T.-K. Yang, J. Chem. Soc., Chem. Commun., 1983, 135; c) D.J. Hart and T.-K Yang, J. Org. Chem., 1985, **50**, 235.
52. T. Iwashita, T. Kusumi, and H. Kakisawa, J. Org. Chem., 1982, **42**, 230.
53. a) J.J. Tufariello and G.E. Lee, J. Am. Chem. Soc., 1980, **102**, 373; b) J.J. Tufariello, H. Meckler, and K. Winzenberg, J. Org. Chem., 1986, **51**, 3556.
54. E. Roeder, H. Wiedenfeld, and E.-J. Jost, Arch. Pharm. (Weinheim), 1984, **317**, 403.
55. G.E. Keck and D.G. Nickell, J. Am. Chem. Soc., 1980, **102**, 3632.
56. F. Cavagna, A. Linkies, H. Pietsch, and D. Reuschling, Angew. Chem. Int. Ed. Engl., 1980, **19**, 129.
57. S.A. Abbas, A. Laurent, P. Mison, and N. Pellissier, Bull. Soc. Chim. Fr., 1986, 288.
58. T.L. McDonald and B.A. Narayanan, J. Org. Chem., 1983, **48**, 1129.
59. a) K. Tatsuta, S. Miyashita, K. Akimoto, and M. Kinoshita, Bull. Chem. Soc. Jpn., 1982, **55**, 3254; b) K. Tatsuta, H. Takahashi, Y. Amemiya, and M. Kinoshita, J. Am. Chem. Soc., 1983, **105**, 4096.
60. Y. Nishimura, S. Kondo, and H. Umezawa, J. Org. Chem., 1985, **50**, 5210.
61. Y. Nagao, W.-M. Dai, M. Ochiai, S. Tsukagoshi, and E. Fujita, J. Am. Chem. Soc., 1988, **110**, 289.
62. H.W. Pinnick and Y.-H. Chang, J. Org. Chem., 1978, **24**, 4662.
63. G.J. Hanson, J.S. Baran, and T. Lindberg, Tetrahedron Lett., 1986, **27**, 3577.
64. R.E. Gawley and S. Chemburkar, Tetrahedron Lett., 1986, **27**, 2071.
65. W.W. Turner, J. Het. Chem., 1986, **23**, 327.
66. a) J.E. Baldwin, M.F. Chan, G. Gallacher, P. Monk, and K. Pront, J. Chem. Soc., Chem. Commun., 1983, 250; b) J.E. Baldwin, M.F. Chan, G. Gallacher, M. Otsuka, P. Monk, and K. Prout, Tetrahedron, 1984, **40**, 4513.
67. H. Iida, Y. Watanabe, and C. Kibayashi, Chem. Pharm. Bull., 1985, **33**, 351.
68. T. Shono, Y. Matsumura, K. Uchida, K. Tsubata, and A. Makino, J. Org. Chem.,

1984, **49**, 300.

69. F. Bohlmann, W. Klose, and K. Nickisch, Tetrahedron Lett., 1979, 3699.

70. R. Neidlein and G. Jeromin, J. Chem. Res. (S), 1980, 233.

70a. H. McNab, J. Org. Chem., 1981, **46**, 2809.

71. D. Lathbury and T. Gallagher, J. Chem. Soc., Chem. Commun., 1986, 1017.

72. S. Takano, S. Otaki, and K. Ogasawara, J. Chem. Soc., Chem. Commun., 1983, 1172.

73. a) T. Ohsawa, M. Ihara, K. Fukumoto, and T. Kametani, Heterocycles, 1982, **19**, 1605; b) T. Ohsawa, M. Ihara, K. Fukumoto, and T. Kametani, ibid., 1982, **19**, 2075; c) T. Ohsawa, M. Ihara, K. Fukumoto, and T. Kametani, J. Org. Chem., 1983, **48**, 3644.

74. A. Toshimitsu, K. Terao, and S. Uemura, J. Org. Chem., 1986, **51**, 1724.

75. C.H. Heathcock and T.W. von Geldern, Heterocycles, 1987, **25**, 75.

76. a) F.M. Schell, R.N. Ganguly, K.S. Percell, and J.E. Parker, III, Tetrahedron Lett., 1979, 4925; b) F.M. Schell and R.N. Ganguly, J. Org. Chem., 1980, **45**, 4069.

77. H.W. Pinnick and Y.-H. Chang, Tetrahedron Lett., 1979, 837.

77a. A. Padwa, Y. Tomioka, and M.K. Venkataraman, Tetrahedron Lett., 1987, **28**, 755.

78. N.J. Leonard and T. Sato, J. Org. Chem., 1969, **34**, 1066.

79. a) S.R. Wilson and R.A. Sawicki, J. Org. Chem., 1979, **44**, 287; b) S.R. Wilson, R.A. Sawicki, and J.C. Hufman, J. Org. Chem., 1981, **46**, 3887.

80. a) M.E. Garst and J.N. Bonfiglio, Tetrahedron Lett., 1981, **22**, 2027; b) M.E. Garst, J.N. Bonfiglio, and J. Marks, J. Org. Chem., 1982, **47**, 1494.

81. Y. Arata, K. Tanaka, S. Yoshifuji, and S. Kanatomo, Chem. Pharm. Bull., 1979, **27**, 981.

82. L.V. Yerino, M.E. Osborn, and P.S. Mariano, Tetrahedron, 1982, **38**, 1579.

83. R.M. Elofson, F.F. Gadallah, and J.K. Laidler, Can. J. Chem., 1985, **63**, 1170.

84. a) H.O. Bayer, H. Gotthardt and R. Huisgen, Chem. Ber., 1970, **103**, 2356; b) H. Gotthardt and R. Huisgen, ibid., 1970, **103**, 2625.

85. W.K. Anderson and H.L. McPherson, Jr., J. Med. Chem., 1982, **25**, 84.

86. M. Forte, F. Orsini, and F. Pelizzoni, Gazz. Chim. Ital., 1985, **115**, 569.

87. D. Laduree, J.-C. Lancelot, and M. Robba, Tetrahedron Lett., 1985, **26**, 1295.

88. O. Yebdri and F. Texier, J. Het. Chem., 1986, **23**, 809.

89. a) D.J. Robins and S. Sakdarat, J. Chem. Soc., Chem. Commun., 1979, 1181; b)

D. Robins and S. Sakdarat, J. Chem. Soc., Perkin Trans. 1, 1981, 909.

90. a) E. Vedejs and G.R. Martinez, J. Am. Chem. Soc., 1980, **102**, 7993; b) E. Vedejs and F.G. West, J. Org. Chem., 1983, **48**, 4773; c) E. Vedejs, S. Larsen, and F.G. West, J. Org. Chem., 1985, **50**, 2170.

91. P.F. Belloir, L. Laurent, P. Mison, S. Lesniak, and R. Bartnik, Synthesis, 1986, 683.

92. a) N. Imai, Y. Terao, K. Achiwa, and M. Sekiya, Tetrahedron Lett., 1984, **25**, 1579; b) Y. Terao, N. Imai, K. Achiwa, and M. Sekiya, Chem. Pharm. Bull., 1982, **30**, 3167.

93. J. Chastanet and G. Roussi, Heterocycles, 1985, **23**, 653.

94. a) W. Flitsh and P. Wernsmann, Tetrahedron Lett., 1981, **22**, 719; b) W. Flitsch and P. Russkamp, Justus Liebigs Ann. Chem., 1983, 521.

94a. J.M. Muchowski and P.H. Nelson, Tetrahedron Lett., 1980, **21**, 4585.

95. a) T. Eicher and R. Rohde, Synthesis, 1985, 619; b) T. Eicher and D. Krause, ibid., 1986, 899.

96. R.L. Danheiser, C.A. Kwasigroch, and Y.-M. Tsai, J. Am. Chem. Soc., 1985, **107**, 7233.

97. E.E. Schweiser and K.K. Light, J. Am. Chem. Soc., 1964, **86**, 2744.

98. a) W. Flitsh and W. Lubisch, Chem. Ber., 1982, **115**, 1547; b) W. Flitsch and W. Lubisch, ibid., 1984, **117**, 1424; c) V. Batroff, W. Flitsch, D. Leaver, and D. Skinner, ibid., 1984, **117**, 1649.

99. a) W. Klose, K. Nickisch, and F. Bohlmann, Chem. Ber., 1980, **113**, 2694; b) K. Nickisch, W. Klose, E. Nordhoff, and F. Bohlmann, ibid., 1980, **113**, 3086.

100. H.J. Bestmann and R.K. Bansal, Tetrahedron Lett., 1981, **22**, 3839.

101. a) W.H. Pearson, Tetrahedron Lett., 1985, **26**, 3527; b) W.H. Pearson, J.E . Celebuski, Y.-F Poon, B.R. Dixon, and J.H. Glans, Tetrahedron Lett., 1986, **27**, 6301.

102. a) T. Hudlicky, J. O. Frazier, and L.D. Kwart, Tetrahedron Lett., 1985, **26**, 3523; b) T. Hudlicky, J.O. Frazier, G. Seoane, M. Tiedje, A. Seoane, L.D. Kwart, and C. Beal, J. Am. Chem. Soc., 1986, **108**, 3755.

103. T. Ohnuma, M. Tabe, K. Shiiya, Y. Ban, and T. Date, Tetrahedron Lett., 1983, **24**, 4249.

104. D.J. Robins, J. Chem. Soc., Chem. Commun., 1982, 1289.

105. S. Takano, N. Ogawa, and K. Ogasawara, Heterocycles, 1981, **16**, 915.

Received, 7th December, 1987