ACCOUNTS OF CHEMICAL RESEARCH

VOLUME 10 NUMBER 6 JUNE, 1977

General Methods of Alkaloid Synthesis

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Received February 11, 1977

Synthetic chemists have always marveled at Nature's ability to elaborate a fantastic variety of structurally diverse and frequently very complex substances from a few relatively simple starting materials. Plants, for example, manufacture thousands of alkaloids from carbon dioxide—a one-carbon synthon! The total synthesis of alkaloids has occupied a central role in natural products chemistry for many years. Landenberg[1] is credited with having synthesized the first alkaloid, coniine, in 1886. This was followed at the turn of the century by syntheses of atropine, nicotine, and papaverine.[2] Subsequent progress in alkaloid synthesis was rather slow to develop until 1944, when R. B. Woodward[3] announced his landmark synthesis of quinine. In 1952, Gates[4] published the first synthesis of morphine, and shortly thereafter Woodward[5] announced that strychnine had been conquered. These accomplishments served as milestones for contemporary organic synthesis and have been followed by many other notable achievements which have contributed to "the art and science" of organic chemistry as a whole. Nevertheless, until quite recently,[6,7] few systematic studies have been employed to synthesize a wide variety of structurally diverse alkaloids. With these thoughts in mind, my students and I initiated in 1966 a research program aimed at developing and exploiting just such methodology.

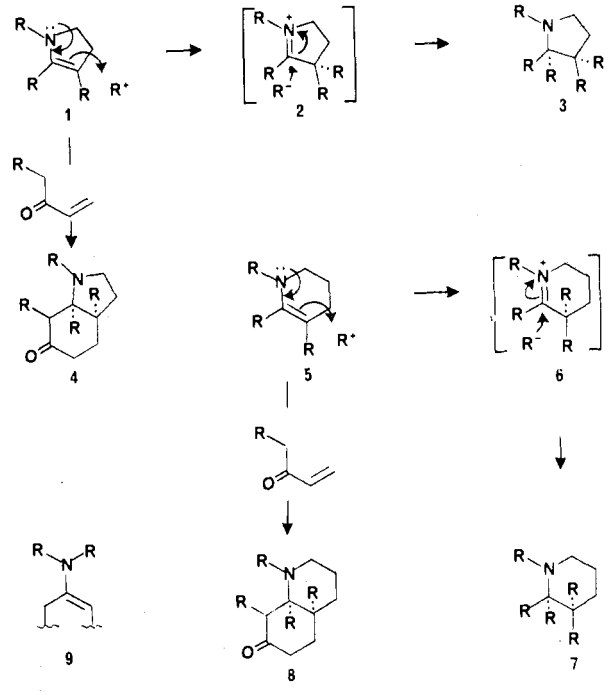
The following partial compilation of alkaloid families and some typical representatives thereof underscores the diverse nature of these nitrogenous plant products.

Alkaloid Families

Pyridine (**12**, **14**, **16**)	Indolizidine (**47**, **52**, **53**)
Pyrrolidine (**14**, **17**)	Aspidosperma (**54**, **55**)
Sceletium (**23a**, **24**, **25**, **30**)	Quinazoline (**79**)
Amaryllidaceae (**33**, **34**)	Hasubanan (**86**)
Pyrrolizidine (**41**, **42**)	Erythrina (**89**, **90**)

In spite of the obvious gross structural differences between members of these families, it occurred to us

Scheme I



that an *impressive number of them might be generated from only two relatively simple synthons* (**1** and **5**). Although the synthesis and chemistry of exocyclic enamines (**9**) had been developed continuously for well over two decades,[8] it seemed remarkable to us that from the standpoint of alkaloid synthesis their *endo*cyclic counterparts (**1** and **5**) had been largely ignored. As a consequence of their biosynthesis, it is interesting to

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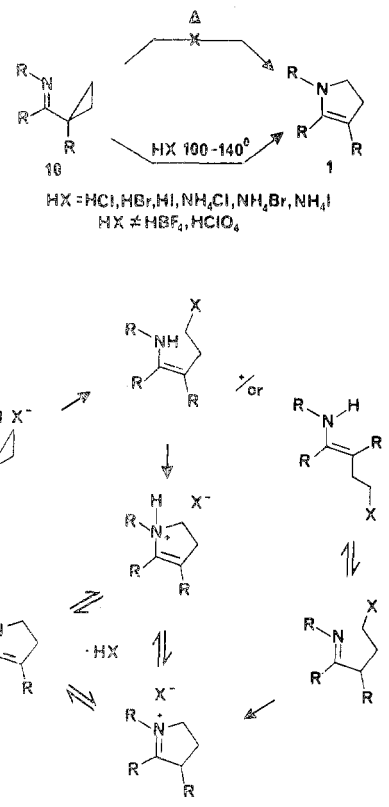
† Contribution No. 3813.

(1) A. Landenburg, *Chem. Ber.*, **19**, 439, 2578 (1886).
(2) For an interesting account of this early work, see *Alkaloids*, **1** (1950).
(3) R. B. Woodward and W. E. Doering, *J. Am. Chem. Soc.*, **66**, 849 (1944); **67**, 860 (1945).
(4) M. Gates and G. Tschudi, *J. Am. Chem. Soc.*, **74**, 1109 (1952).
(5) R. B. Woodward, *Experentia, Suppl.*, **No. 2**, 213 (1955); R. B. Woodward, M. P. Cava, W. D. Ollis, A. Hunger, H. V. Daeniker, and K. Schenker, *Tetrahedron*, **19**, 247 (1963).
(6) E. Wenkert, *Acc. Chem. Res.*, **1**, 78 (1968), and subsequent papers.
(7) T. Kametani and K. Fukumoto, *Acc. Chem. Res.*, **9**, 319 (1976); see also W. Oppolzer, *Tetrahedron Lett.*, 1001 (1974), and references cited therein.
(8) "Enamines: Synthesis, Structure, and Reactions", A. G. Cook, Ed., Marcel Dekker, New York and London, 1969.

Scheme II

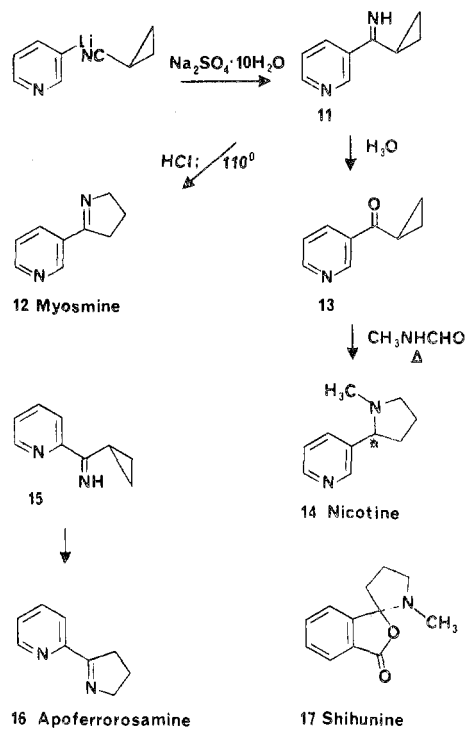


note that in those alkaloids where a pyrrolidine (or pyrroline) ring is discernible, one almost invariably finds nuclear "substitution" on only one side of the molecule; the other side is usually devoid of any substituents (see **3**). By analogy with their exocyclic counterparts, we reasoned that endocyclic enamines **1** and **5** should react with various electrophilic reagents on the β carbon. It should be noted further that such a process simultaneously renders the α carbon electrophilic and therefore susceptible to capture by nucleophilic reagents, as depicted in **2** and **6**. In this fashion we anticipated that the substitution pattern noted above might readily be elaborated. Further scrutiny of these alkaloids reveals that many of them incorporate either a hydroindolone (**4**) or a hydroquinolone (**8**) moiety into their nucleous. It is interesting to note that in the case of aspidospermine (**54**) both moieties are discernible. We felt that annulation[9] of endocyclic enamines **1** and **5** with methyl vinyl ketone, or some derivative thereof, might provide a facile entry into these fused ring systems. These thoughts set the stage for a remarkably general approach to alkaloid synthesis (see Scheme I).

The initial task was to develop some reliable and convenient method for the synthesis of endocyclic enamines **1** and **5**. Of the various methods for the synthesis of 2-pyrrolines (**1**) which were considered, the thermally induced rearrangement of appropriately substituted cyclopropyl imines (**10**) captured our imagination, and we were pleased to discover that an example of the proposed rearrangement had been reported by J. B. Cloke in 1929.[10] The novelty of this methodology and its potential broad utility prompted a careful examination of the crucial rearrangement step.

(9) For a recent review, see: M. Jung, *Tetrahedron*, **32**, 3 (1976).
(10) J. B. Cloke, *J. Am. Chem. Soc.*, **51**, 1174 (1929); cf. also J. B. Cloke, L. H. Baer, J. M. Robbins, and G. E. Smith, *ibid.*, **67**, 2155 (1945), and references cited therein.

Scheme III

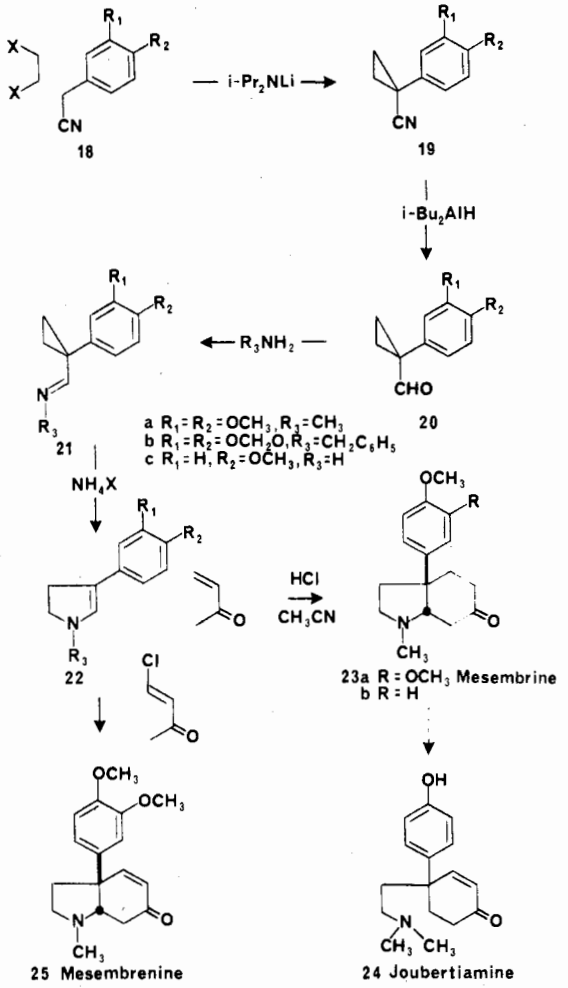


It soom became apparent that *this rearrangement is not a purely thermal process—an acid catalyst is required.* Scheme II summarizes our observations to date. Catalytic amounts of anhydrous halohydrogen acids induce the rearrangement upon heating. Later we learned that ammonium halides are also effective and, in general, provide superior yields of cleaner product. By contrast, fluoroborate or perchlorate salts fail to catalyze the rearrangement under similar conditions, proving that the gegenion must be nucleophilic. These observations are consistent with the mechanism outlined in Scheme II.

Our initial experiments were aimed at very modest targets in order to test the efficacy of the proposed methodology. Thus, condensation of 3-lithiopyridine and cyclopropanecarbonitrile, followed by careful quenching, provided cyclopropyl imine **11**.[11] Conversion of this intermediate to its hydrochloride salt and heating afforded myosmine (**12**). Similarly, apoferrorosamine (**16**) was generated from cyclopropyl imine **15**.[11] Other groups have recently reported the application of similar methodology to prepare labeled nicotine (**14**)[12] and the unusual alkaloid shihunine (**17**)[13] (see Scheme III). Armed with these encouraging results, we focused our attention on the somewhat more complex *Sceletium* or Mesembrine alkaloids. The requisite cyclopropyl imines (**21a–c**) were prepared by bisalkylation of the appropriately substituted benzyl cyanide (**18a–c**). Eventually, we learned that the combination of ethylene dichloride as the alkylating agent and slightly more than 2 equiv of lithium diisopropylamide as the base gave superior yields of the cyclopropanecarbonitriles **19a–c**. Similarly, we learned with experience that these substances could be selec-

(11) R. V. Stevens and M. C. Ellis, *Tetrahedron Lett.*, 5185 (1967); R. V. Stevens, M. C. Ellis, and M. P. Wentland, *J. Am. Chem. Soc.*, **90**, 5576 (1968).
(12) R. A. Comes, M. T. Core, M. D. Edmonds, W. B. Edwards, and R. W. Jenkins, Jr., *J. Labelled Compd.*, **9**, 253 (1973).
(13) E. Breuer and S. Zbaida, *Tetrahedron*, **31**, 499 (1975).

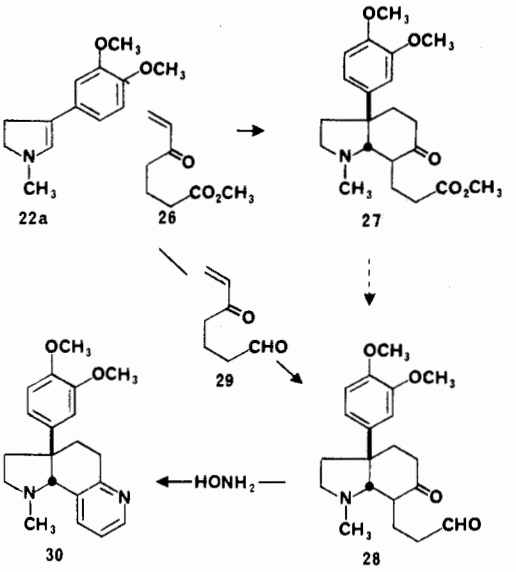
Scheme IV



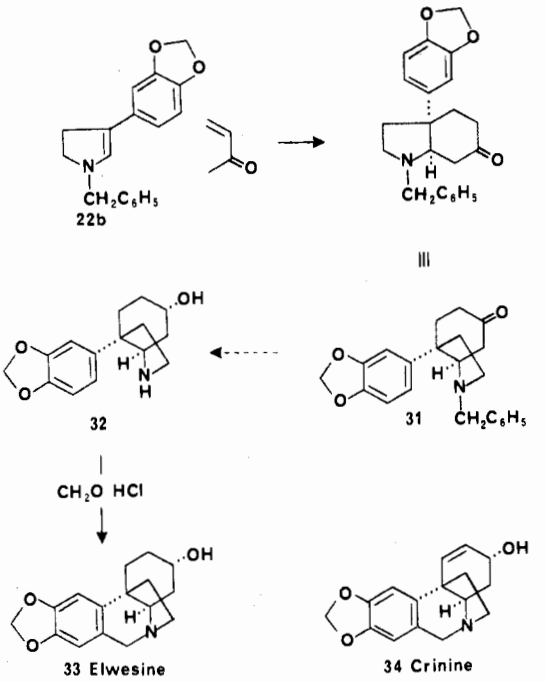
tively reduced in high yield to the corresponding aldehydes **20** by employing diisobutylaluminum hydride. Treatment of these aldehydes with an appropriate primary amine completes a three-stage synthesis of the cyclopropyl imines **21a–c**. Rearrangement of each of these substances as described above afforded the 2-pyrrolines **22a–c** in high yield. We were now in a position to test the crucial annulation step and soon discovered that heating **22a** and methyl vinyl ketone in refluxing ethylene glycol afforded a 55% yield of (±)-mesembrine (**23a**).[14,15] Almost simultaneously with these reports, two other groups[16] disclosed similar findings. The additional observation[16b] that these annulations are strongly catalyzed by anhydrous HCl in CH_3CN vastly increased the practical utility of the annulation step and paved the way for efficient syntheses of mesembrenine (**25**)[16b] and joubertiamine (**24**) and its derivatives,[17] as outlined in Scheme IV.

After the work described above had been completed, the structure of Sceletium alkaloid A-4 (**30**) appeared and provided an additional opportunity to test this methodology. Thus, annulation of **22a** with methyl 5-oxohept-6-enoate (**26**) afforded indolone (**27**) in high yield.[18a] The oxidation state of the ester side chain was adjusted to that of an aldehyde (**28**), which reacted smoothly with hydroxylamine to afford Sceletium A-4 (**30**). Alternatively, aldehyde **28** can be prepared directly from enamine **22a** and **29**[18] (see Scheme V).

Scheme V



Scheme VI



Many Amaryllidaceae alkaloids such as elwesine (**33**) and crinine (**34**) also incorporate a hydroindolone nucleus into their skeletons. Annulation of **22b** with methyl vinyl ketone afforded **31**. Catalytic reduction and debenzylation of this intermediate afforded carbinolamine **32**, which underwent Pictet–Spengler cyclization to yield elwesine (**33**)[19] (see Scheme VI).

The pyrrolizidine alkaloids, e.g., isoretronecanol (**41**) and platynecine (**42**), provide a somewhat different

(14) All of the compounds reported herein are racemic.

(15) R. V. Stevens and M. P. Wentland, *Tetrahedron Lett.*, 2613 (1968); R. V. Stevens and M. P. Wentland, *J. Am. Chem. Soc.*, **90**, 5580 (1968); (b) R. V. Stevens, P. M. Lesko, and R. Lapalme, *J. Org. Chem.*, **40**, 3495 (1975).

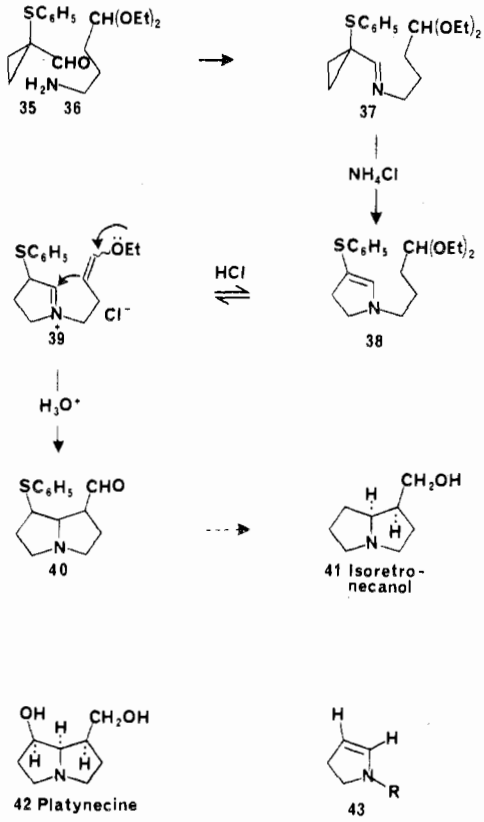
(16) (a) S. L. Keely, Jr., and F. C. Tahk, *J. Am. Chem. Soc.*, **90**, 5580 (1968); (b) T. J. Curphey and H. L. Kim, *Tetrahedron Lett.*, 1441 (1968).

(17) R. V. Stevens and J. T. Lai, *J. Org. Chem.*, **37**, 2138 (1972).

(18) (a) R. V. Stevens, P. M. Lesko, and R. Lapalme, *J. Org. Chem.*, **40**, 3495 (1975); (b) C. P. Forbes, J. D. Michau, T. van Ree, A. Wiechers, and M. Woudenberg, *Tetrahedron Lett.*, 935 (1976).

(19) R. V. Stevens, L. E. DuPree, Jr., and P. L. Loewenstein, *J. Org. Chem.*, **37**, 977 (1972); R. V. Stevens and L. E. DuPree, Jr., *Chem. Commun.*, 1585 (1970).

Scheme VII

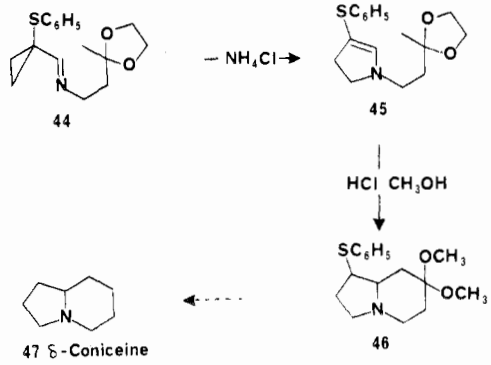


challenge to the general methodology. The opening moves are the same as described above, mainly condensation of aldehyde **35** and amine **36** to afford cyclopropyl imine **37**. This substance rearranged smoothly to pyrroline **38** upon heating in xylene in the presence of suspended ammonium chloride.[20] Treatment of **38** with anhydrous HCl gas establishes an equilibrium ultimately leading to intermediate **39**[21] which cyclizes to afford pyrrolizidine **40** (after aqueous workup). It should be noted that the unusual 3-phenylthio-2-pyrroline intermediate **38** serves as a relatively stable equivalent synthon of the unsubstituted enamine **43** which is notoriously unstable.[8] Having served its ordained mission to stabilize enamine **38**, the sulfur was now removed with Raney nickel and the aldehyde reduced to afford isoretronecanol (**41**). It should be noted also that the sulfur in **40** is judiciously placed for possible conversion (via the Pummerer rearrangement) to platynecine (**42**) (see Scheme VII).

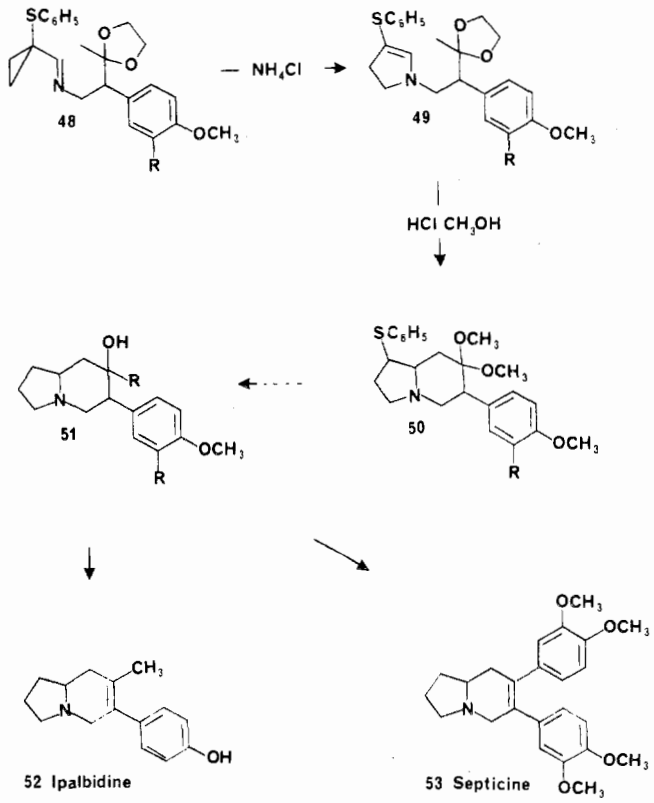
Application of this particular variation to the indolizidine alkaloids δ-coniceine[20] (**47**), ipalbidine (**52**), and septicine (**53**)[22] illustrated further the utility of the 3-phenylthio-2-pyrroline synthon in the synthesis of functionalized indolizidine and pyrrolizidine nuclei (see Schemes VIII and IX).

Thus far in our discussion we have been concerned only with the synthesis and chemistry of 2-pyrrolines (**1**). The Aspidosperma alkaloids, e.g., aspidospermine (**54**) and vindoline (**55**), afforded us the opportunity to examine the chemistry of the next higher homologue, **59**, a tetrahydropyridine. Once again, general methodology for the synthesis of such intermediates was sought, and the acid-catalyzed rearrangement of various cyclobutyl imines (**58**) was therefore examined.[23] However, in contrast to the cyclopropyl imine rearrangement, this reaction proved to be sluggish and much less general. Alternative solutions were therefore sought. One such alternative has been provided by Evans[24] and is outlined in Scheme X (**60** → **61** → **59**).

Scheme VIII



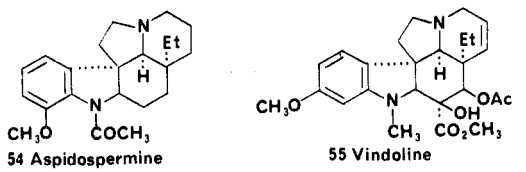
Scheme IX

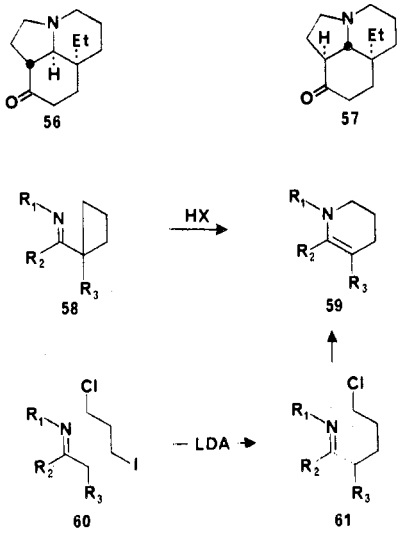


An alternative method was devised for endocyclic enamine **63** which utilized a carefully controlled reduction of lactam **62** with diisobutylaluminum hydride, followed by a basic workup.[25] Selective reductions to provide endocyclic enamines have subsequently been shown to be quite general.[26] Treatment of this endocyclic enamine (**63**) with methyl vinyl ketone afforded the cis-fused hydroquinolone **64a**, and subsequent debenzylation yielded **64b**. It is not known if this

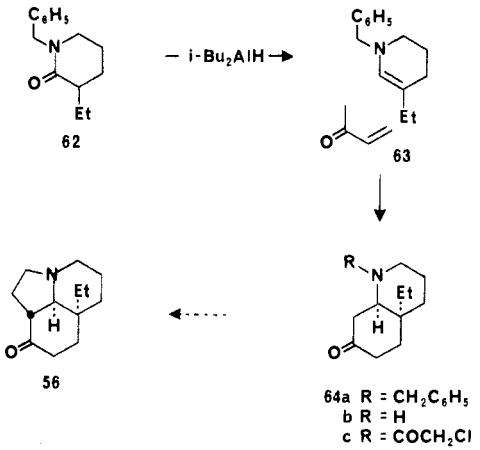
(20) R. V. Stevens, Y. Luh, and J. T. Shev, *Tetrahedron Lett.*, 3799 (1976).
(21) Cyclizations of this type were first reported by: E. Wenkert, K. G. Dave, and R. V. Stevens, *J. Am. Chem. Soc.*, 90, 6177 (1968).
(22) R. V. Stevens and Y. Luh, *Tetrahedron Lett.*, in press.
(23) R. V. Stevens and J. T. Sheu, *J. Chem. Soc., Chem. Commun.*, 682 (1975).
(24) D. A. Evans, *J. Am. Chem. Soc.*, **92**, 7593 (1970).
(25) R. V. Stevens, R. K. Mehra, and R. L. Zimmerman, *Chem. Comm.*, 1968 (1969).
(26) F. Bohlmann, H. J. Mueller, and D. Schumann, *Chem. Ber.*, 106, 3026 (1973).

Scheme X

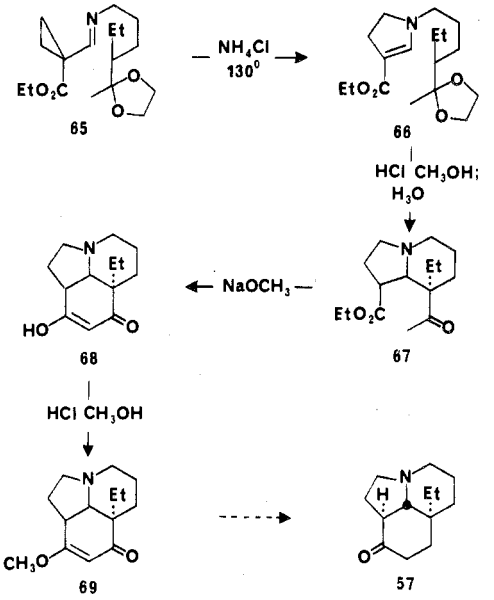




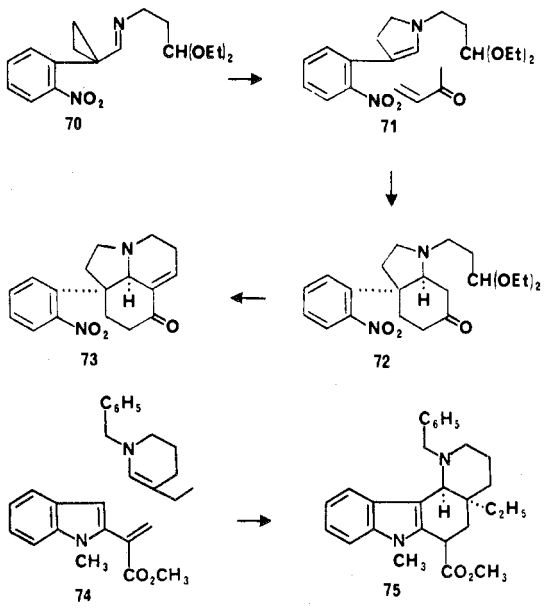
Scheme XI



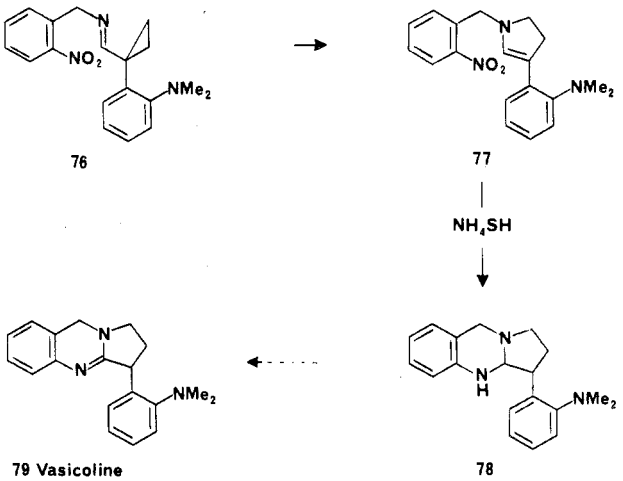
Scheme XII



Scheme XIII



Scheme XIV

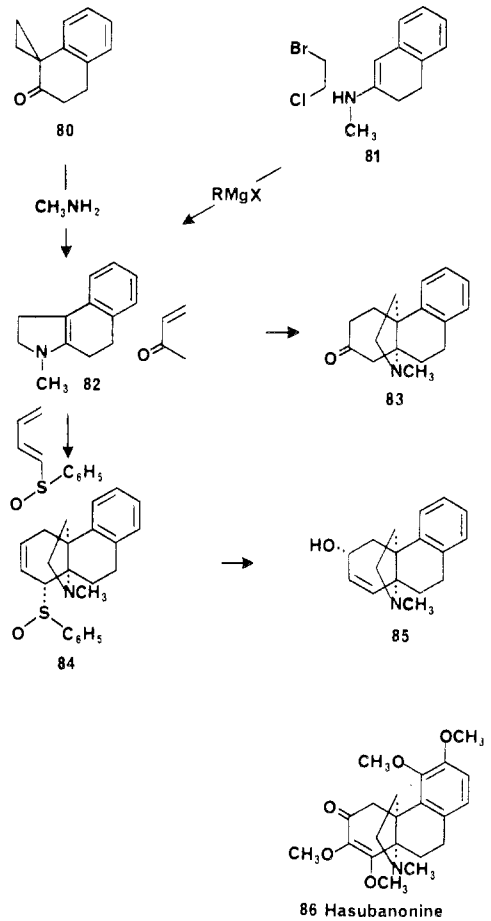


stereochemical result is due to kinetic or thermodynamic control. In either event, **64b** proved to be identical with a substance prepared previously by Stork[27] and converted into tricyclic ketone **56** and, thereafter, into aspidospermine (**54**) (see Scheme XI).

The stereoisomeric tricyclic ketone **57** has also been converted into aspidospermine by Ban and his collaborators.[28] This substance became the target of a fundamentally different approach designed to test further the efficacy of the cyclopropyl imine rearrangement. To this end, cyclopropyl imine **65** was prepared[29] and rearranged to **66**. Exposure of this substance to anhydrous HCl, followed by aqueous workup, gave keto ester **67** as a mixture of diastereomers. Treatment of this mixture with base followed by methanolic HCl afforded predominantly enol ether **69** as a nicely crystalline substance whose conversion to Ban's tricyclic ketone (**57**) proceeded along traditional lines (see Scheme XII).

(27) G. Stork and J. Dolfini, *J. Am. Chem. Soc.*, **85**, 2872 (1963).
(28) Y. Ban, Y. Sato, I. Inove, M. Nagai, T. Oishi, M. Terashima, O. Yonemitsu, and Y. Kanoako, *Tetrahedron Lett.*, 2261 (1965).
(29) R. V. Stevens, J. M. Fitzpatrick, M. Kaplan, and R. L. Zimmerman, *Chem. Commun.*, 857 (1971).

Scheme XV



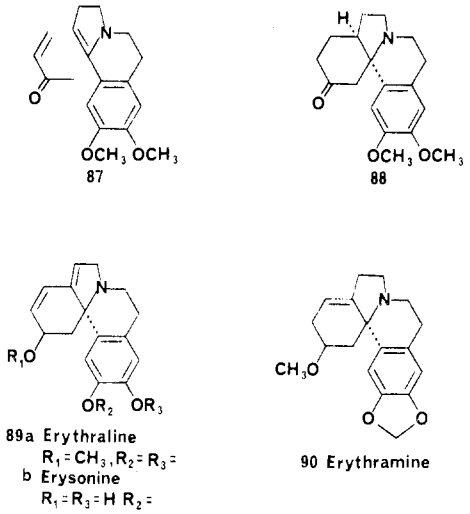
As gratifying and illuminating as the results just cited were to us, they may prove not to be the ultimate test of this methodology. Scheme XIII shows the application of *both* the cyclopropyl imine rearrangement (**70** to **71**) *and* the annulation sequence (**71** to **72**) as a means of attaching the requisite aryl group to this basic tricyclic nucleus (**73**).[30] Further deployment of intermediate **73** in the synthesis of certain Aspidosperma alkaloids can be anticipated. In this connection, mention should also be made of Ziegler's brilliant pseudoannulation of endocyclic enamine **74** to afford **75**[31].

Scheme XIV outlines a further test of the cyclopropyl imine rearrangement as a method of approach to vasicoline (**79**).[32]

(30) Unpublished results: R. L. Zimmerman, Ph.D. Thesis, Rice University, Houston, Texas.

(31) F. E. Ziegler and E. B. Spitzner, *J. Am. Chem. Soc.*, **95**, 7146 (1973).

Scheme XVI



No account of this methodology would be complete without mention of the synthesis and annulation of endocyclic enamine **82** as a device for elaborating the basic skeleton (**83**) of hasubanonine (**86**).[33] Of special note is the generation of allylic alcohol **85** via the elegant sequence **82** to **84**[34] (see Scheme XV).

The annulation of endocyclic enamine **87** with methyl vinyl ketone to afford the basic skeleton (**88**) of several of the Erythrina alkaloids (**89**, **90**) brings to a close our experimental observations to date.[35] The use of other annulating agents can be anticipated to provide new, improved syntheses of these substances (see Scheme XVI).

Epilogue

Within the space allotted, I have attempted to show the genesis of a concept and its development to a state of some maturity. Although much remains to be done, we believe a firm foundation for future developments has been laid.

It remains for me to acknowledge with heartfelt thanks the contributions of my collaborators. Their names are cited in the appropriate references. I am also most grateful to the National Science Foundation and the Robert A. Welch Foundation for financial support.

(32) Unpublished results: Dr. Arthur Howard, Rice University.

(33) (a) S. L. Keely, Jr., A. J. Martinez, and F. C. Tahk, *Tetrahedron Lett.*, 2763 (1969); (b) D. A. Evans, C. A. Bryan, and G. M. Wahl, *J. Org. Chem.*, **35**, 4122 (1970).

(34) D. A. Evans, C. A. Bryan, and C. L. Sims, *J. Am. Chem. Soc.*, **94**, 2891 (1972).

(35) R. V. Stevens and M. P. Wentland, *Chem. Commun.*, 1104 (1968).