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C-Acylnitrilium Ion Initiated Cyclizations in Heterocycle Synthesis

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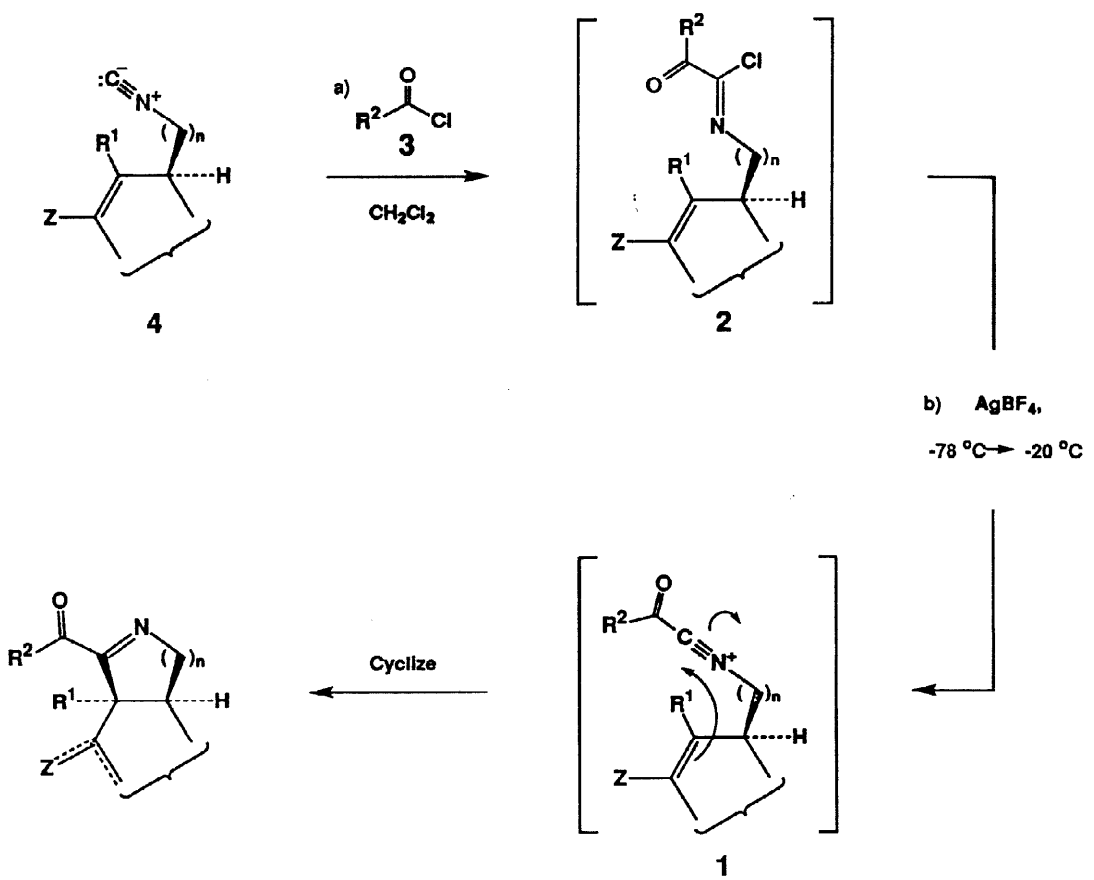
1. Background and Strategic Considerations.

Cyclization reactions initiated by nitrogen-stabilized carbocations have continued to play a central role in synthetic approaches to numerous natural and unnatural heterocycles. Among the cationic species which have been employed for this purpose, iminium[1] and *N*-acyliminium ions[2] have proven particularly useful for effecting selective carbon-carbon bond formation. Analogous cyclizations initiated by nitrilium ions are considerably more obscure and often proceed inefficiently.[3] The latter processes are frequently complicated by the methods used to generate the parent nitrilium ion and various side reactions (e.g., facile proton loss α- to the nitrilium moiety) that these intermediates undergo.

Recently, we required a general and exceedingly mild method for the construction of nitrogenous heterocycles of variable ring size. In principle, this objective could be met in a highly convergent manner by invoking the cyclization of a *C*-acylnitrilium ion **1** derived from an α-ketoimidoyl halide (e.g., **2**) bearing an internal carbon nucleophile. These intermediates, in turn, were expected to be readily accessible by the reaction of an acyl halide **3** with the requisite isonitrile **4** (Scheme 1).

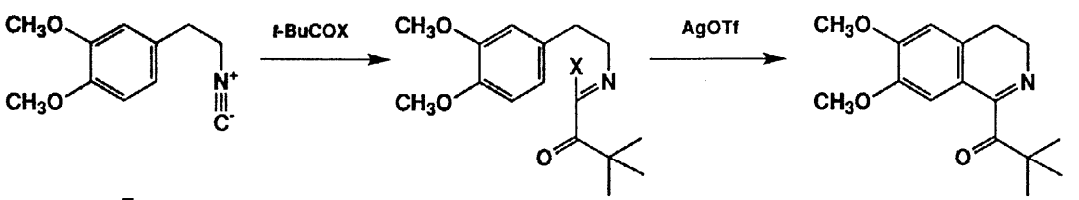


Scheme 1

The synthetic advantages inherent to acylnitrilium ion initiated cyclizations include (1) a high level of convergence with respect to the introduction of peripheral 2-acyl moieties, (2) the flexibility to construct heterocycles of varied ring size, (3) the presence of an endocyclic imine within the product that can serve as a site for further functionalization, and (4) the exceptionally mild reaction conditions ($AgBF_4$ or AgOTf, $ClCH_2CH_2Cl/CH_2Cl_2$, −78→ 0 °C) that are employed for effecting cyclization (Scheme 1).

2. Applications to the Synthesis of 2-Acyl-3,4-dihydroisoquinolines and the Erythrinane Skeleton.[4,5]

Accounts concerned with the reactions of isonitriles with electrophilic species have remained surprisingly few in number.[6,7] We have found that acyl bromides and chlorides react with representative isonitriles to provide the corresponding α-ketoimidoyl halides in ca. 90% yield at temperatures as low as 0 °C.[8a,b] As expected, acyl bromides were found to react with somewhat greater facility than acyl chlorides in the above context.[9] Treatment of 3,4-dimethoxyphenethyl isocyanide **5** in CH_2Cl_2 with either trimethylacetyl bromide (0 °C, 0.5 h) or trimethylacetyl chloride (25 °C, 18 h) afforded the anticipated imidoyl halides **6a** or **6b** in quantitative yield. The cyclization of **6a** or **6b** to the dihydroisoquinoline **7** could be easily accomplished under several sets of reaction conditions. Under the mildest of these, the crude adducts **6a** or **6b** formed in the above manner were treated directly with 1.1 equiv. of AgOTf (CH_2Cl_2, -20 °C →20 °C,12 h) to afford the dihydroisoquinoline **7** (82% overall from **5**). Significantly, no detectable quantity (HPLC, capillary GC) of the isomeric 1-acyl-7,8-dimethoxydihydroisoquinoline was formed under these reaction conditions.



5 **6a: X = Br** **6b: X = Cl** **7**

Alternatively, the cyclization of **6b** could be achieved in lower yield in the presence of a catalytic quantity of CF_3SO_3H (CH_2Cl_2, 0 °C) or $SnCl_4$ (1 equiv, CH_2Cl_2, -78 °C→ 0 °C). The formation of 1-acyldihydroisoquinolines under the ionizing set of reaction conditions involving silver salts can be rationalized by invoking a *C*-acylnitrilium ion (e.g., **14**) as an intermediate. In contrast, the cyclization of α-ketoimidoyl halides in the presence of Brønsted or Lewis acids presumably proceeds via the corresponding protonated or complexed haloiminum derivatives. The generality of the foregoing annulation sequence was subsequently investigated by the utilization of a variety of acyl chlorides (e.g., **8a-e**). The results of this study are summarized in **Table 1**.

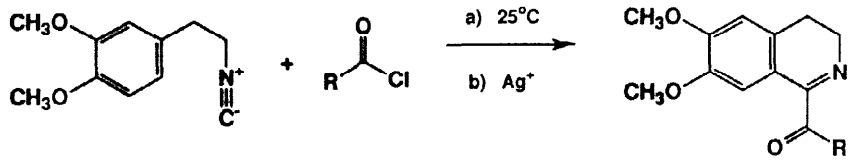
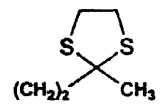
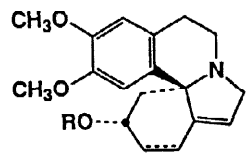


Table 1. 5 8 7a-e

	Acyl Chloride 8 (R)	Cyclization Conditions	Isolated Yield (%)
a	$C(CH_3)_3$	AgOTf	82
		TfOH	71
		$SnCl_4$	31
b	$(CH_2)_3CH{=}CH_2$	AgOTf	87
c	$(CH_2)_3C{\equiv}CH$	AgOTf	75
d		$AgBF_4$	61
e	SC_2H_5	AgOTf	57
f	OCH_3	--------	0

Heterocycle annulations reliant upon the nucleophilic interception of chemically activated α-ketomidoyl halides should facilitate the synthesis of numerous alkaloids. Accordingly, the execution of this type of cyclization involving alternative carbon-based nucleophiles (e.g., indole and other heteroaromatic nuclei, as well as electron rich double bonds) was subsequently examined (*vide infra*).



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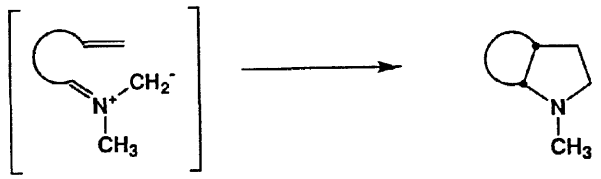
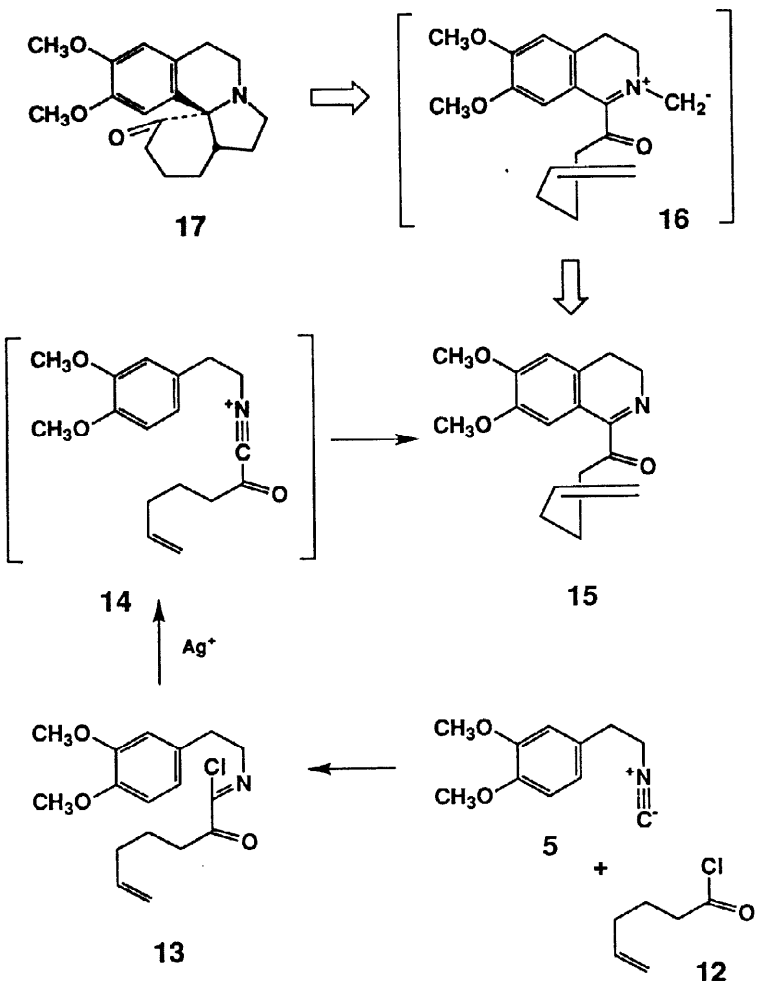


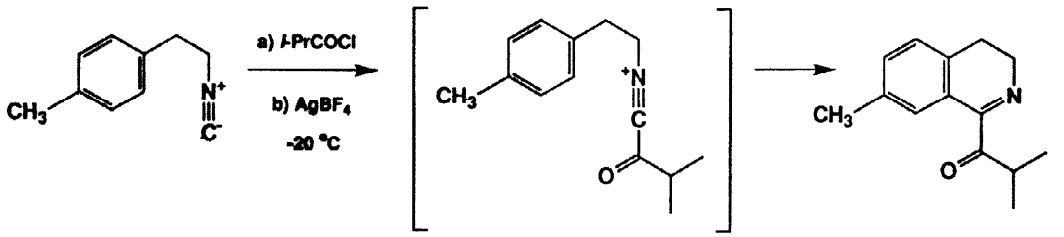
9 10

The polycondensed framework of the erythrina alkaloids **11** has remained a challenging target for efficient chemical synthesis.[10] As part of a parallel study, we described the successful utilization of the intramolecular azomethine ylide [3 + 2] cycloaddition reaction (e.g., **9**→**10**) for the synthesis of the physostigmine ring system.[11,12] We subsequently discovered that heteroannulations involving "nonstabilized" azomethine ylides are frequently restricted to substrates lacking hydrogens α- to the iminium moiety.[12,13] In light of this constraint, we chose to investigate the intramolecular cyclization of α-ketoiminium ylides (e.g., **16**) as a means for constructing the erythrinane skeleton.[14,15] The cyclization of an appropriately substituted arene onto a highly reactive acylnitrilium cation (e.g., **14**→**15**) was expected to provide a convenient pathway to the 1-acyldihydroisoquinoline precursors to these transient 1,3-dipoles. The required cations **14** were expected to be accessible via the silver cation mediated ionization of α-ketoimidoyl halides prepared by the reaction of organic isonitriles with acyl halides (Scheme 2). Prior to embarking on the synthesis of the tetracyclic erythrinane core, additional studies on the preparative scope and limitations of *C*-acylnitrilium ion-arene cyclizations were undertaken. The results of these studies and the application of this method to the elaboration of the erythrinane skeletal system are described below.



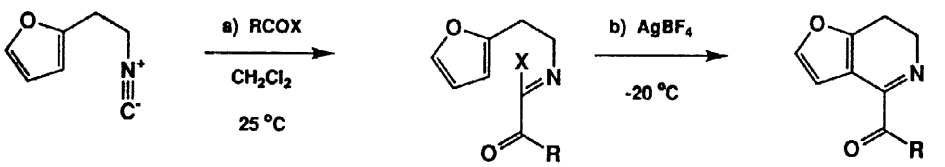
Scheme 2

The participation of electron-rich aromatic nuclei in Bischler-Napieralski and related cyclization reactions is well known. In contrast, cyclizations involving nonactivated aromatic species usually require exceptionally harsh reaction conditions (P_2O_5, 110 °C) and proceed only in low yield (ca. 0-15%).[16] The isonitrile **18** was therefore prepared (*p*-$CH_3C_6H_4CH_2Br$, $LiCH_2NC$, THF) with the intent of providing a more lucid illustration of the synthetic generality of acylnitrilium ion cyclizations. In this connection, it is significant that treatment of **18** with isobutyroyl chloride followed by exposure of the resultant imidoyl chloride to silver fluoroborate at -20 °C furnished the dihydroisoquinoline **20** in 62% isolated yield.



18 **19** **20**

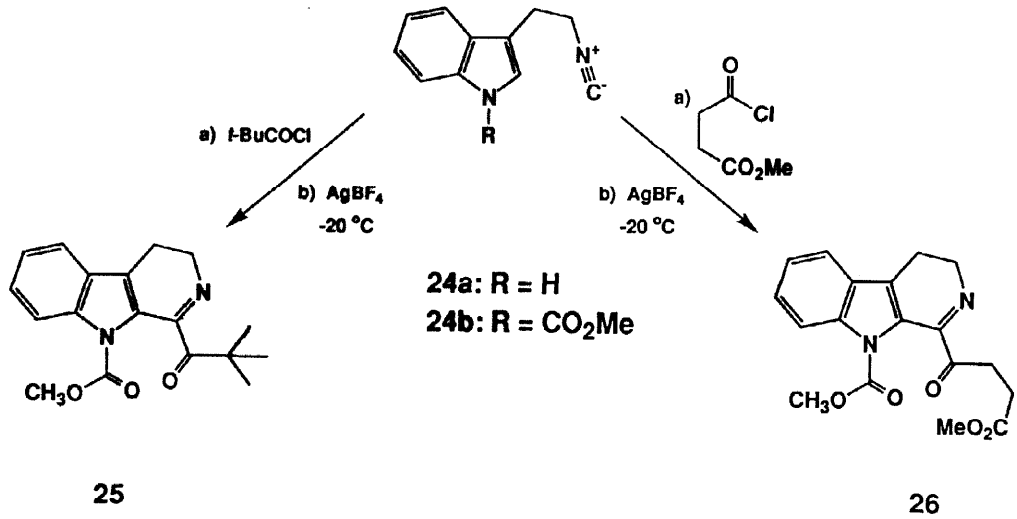
The well-known susceptability of the furan nucleus toward acid-catalyzed polymerization has traditionally disfavored the successful utilization of these species in Bischler-Napieralski-type cyclizations.[17] As a direct consequence of this potential limitation, cyclization reactions involving 2-(2-furyl)ethyl isocyanide (**21**) with representative acylhalides were examined. In complete accord with our prior observations, sequential treatment of **21** with trimethylacetyl chloride followed by silver fluoroborate (CH_2Cl_2, CH_3NO_2, -20 °C) afforded the furanodihydropyridine **23a** in 63% isolated yield. Similarly, exposure of **21** to benzoyl bromide followed by silver fluoroborate gave the furanodihydropyridine **23b** in 49% isolated yield.



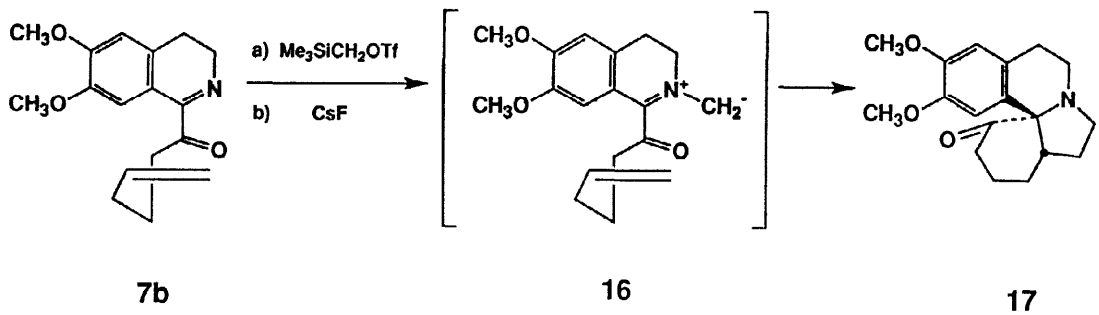
21 **22a: R = *t*-Bu** **23a: R = *t*-Bu**
22b: R = Ph **23b: R = Ph**

The isocarboline nucleus represents an essential structural subunit within the myriad of alkaloids belonging to the corynanthe, eburnia, and rauwolfia families, among others. The utility of α-ketoimidoyl halide heterocycle annulations for the elaboration of functionalized isocarboline derivatives was subsequently demonstrated by the following study. The extreme sensitivity of the electron-rich indole nucleus to trace amounts of hydrogen halides precluded the direct utilization of the isonitrile **24a** in conjunction with acyl halides. To circumvent this difficulty, **24a** was converted into the corresponding *N*-carbomethoxy derivative **24b** via treatment with 1 equiv of *n*-BuLi followed by methyl chloroformate (99% isolated yield). Treatment of the *N*-carbomethoxytryptophyl isocyanide (**24b**) with 1 equiv of trimethylacetyl chloride (CH_2Cl_2, 25 °C, 18 h)

followed by the addition of silver tetrafluoroborate (1.05 equiv, -20 °C, 3 h) secured the isocarboline **25** in 67% yield after purification. In a related example, acylation of **24b** with β-carbomethoxypropionyl chloride followed by silver ion promoted cyclization at –20 °C furnished the isocarboline derivative **26** (60%).

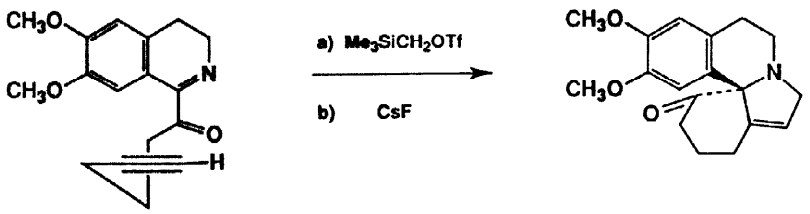


As part of an earlier investigation, we had noted the failure of *nonstabilized* azomethine ylides to undergo intramolecular [3 + 2] cycloadditions leading to the erythrinane skeleton.[12] In sharp contrast to our prior results, the internal cyclization of α-ketoiminium ylides derived from the 1-acyldihydroisoquinolines **7b** and **7c** proceeded without incident. Alkylation of the 1-acyldihydroisoquinoline **7b** with trimethylsilylmethyl triflate followed by the exposure of the resultant dihydroisoquinolinium salt to CsF (1,2-DME, 65 °C) furnished the erythrinane **17** directly in 70% overall yield.[18] No additional isomeric species derived from the intramolecular cyclization of the dipole **16** were detected by capillary GC, HPLC, or NMR.



An indication of the potential generality associated with α-ketoiminium ylide [3 + 2] cycloadditions was provided by an example involving an acetylenic dipolarophile. To this end, sequential treatment of the 1-acyldihydroisoquinoline **7c** with trimethylsilylmethyl triflate followed by exposure of the resultant salt to CsF (inverse addition, diglyme, 110 °C) afforded the unsaturated erythrinane **27** in 42% isolated yield. The structure of the unsaturated erythrinane **27** was subsequently correlated to that of the corresponding saturated derivative

17 via reduction. Hydrogenation of 27 over 10% palladium on charcoal (1 atm H_2, EtOH) provided a single product which was identical in all respects (NMR, IR, and mass spectrum) to the erythrinane 17 which has arisen from the cyclization of the azomethine ylide.



7c **27**

Support for the existence of the *cis*-fused perhydroindole ring junction within **17** was provided by nuclear Overhauser enhancement difference (NOED) spectroscopy and proton-decoupling experiments. The C-6 methine proton was determined to be a multiplet possessing apparent non-first-order coupling centered at 2.51 ppm (C_6D_6) by a series of decoupling studies. Specifically, these studies revealed that the proton assigned as H-6 was coupled to four vicinal protons in the aliphatic region (δ 1.82-1.93) and lacked a geminal partner (Figure 1). The C-11 benzylic protons were similarly assigned as multiplets with a geminal coupling of 15 Hz at 2.05 and 2.27 ppm, respectively. The chemical shift of the "peripheral" C-17 aryl proton was found to be strongly influenced by solvent anisotropic effects [δ 6.39 (C_6D_6), δ 6.59 ($CDCl_3$)] whereas the chemical shift of the "internal" C-14 proton was relatively less solvent dependent [δ 6.58 (C_6D_6), δ 6.47 ($CDCl_3$)]. We next implemented the utilization of NOED spectroscopy. A significant positive NOE between H_{17} and the equatorial proton at C-11 and H_6 was observed in *both* C_6D_6 and $CDCl_3$. These data are consistent only with the existence of the indicated cis relationship between C-5 aryl substituent and the proton at C-6 (Figure 1).

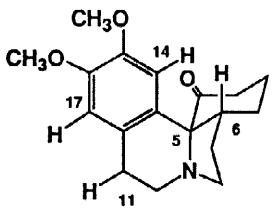
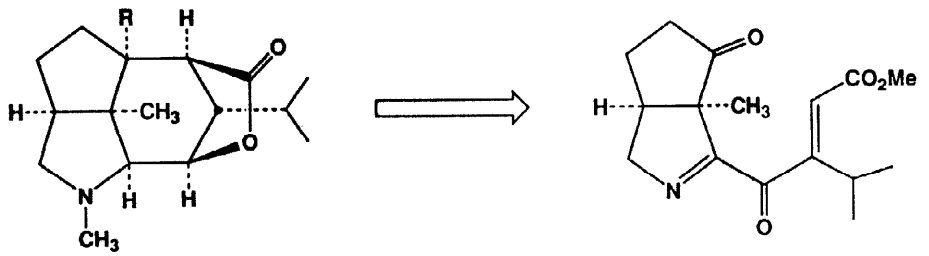


Figure 1

3. Acylnitrilium Ion-Silyloxyalkene Cyclizations. Applications to the Synthesis of Δ^1-Pyrrolines.[19,20]

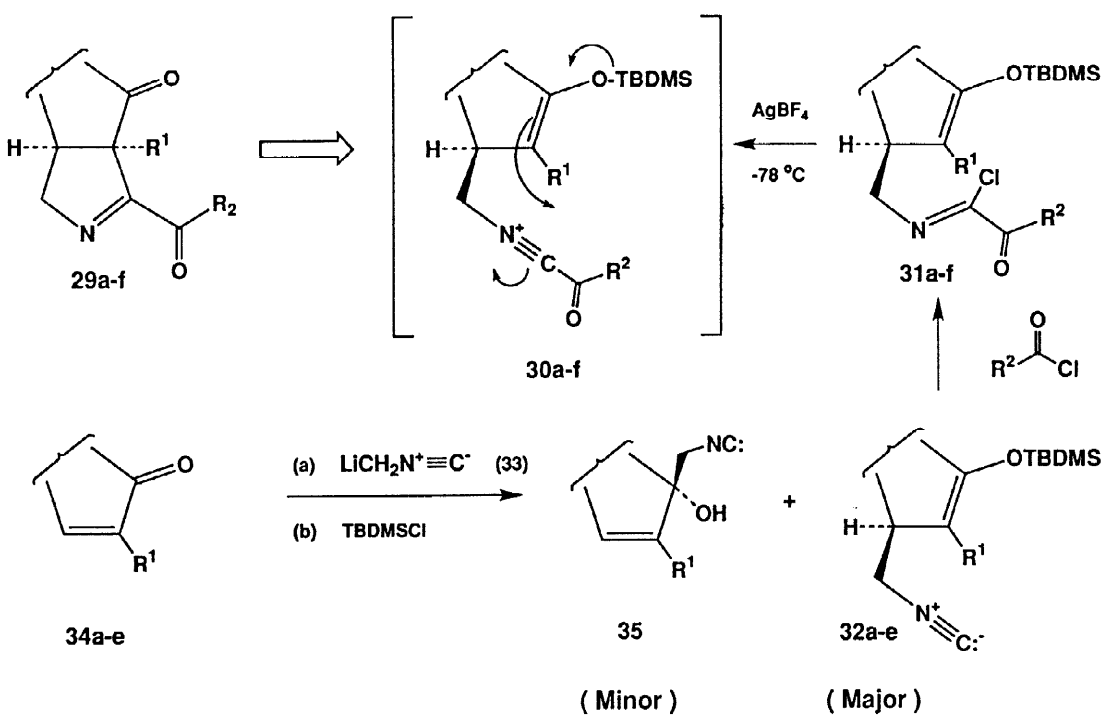
As part of a unified synthetic approach to the *Orchidaceae* alkaloids[26], we required large quantities of the Δ^1-pyrroline **29g**. It was predicted that **29g** and related Δ^1-pyrrolines might be synthesized in a highly convergent manner by the silver ion induced cyclization of α-ketoimidoyl chlorides (e.g., **31a-f**) formed by the direct combination of acyl chlorides with isocyanomethylsilyl enol ethers (e.g., **32a-e**).[8b] The requisite isocyanomethylsilyl enol ethers **32a-e**, in turn, were expected to be available by sequential 1,4- addition of isocyanomethylithium (**33**)[21] to the corresponding α,β-unsaturated ketones **34a-e** followed by enolate silylation. Curiously, there were no reports detailing the reactions of isocyanomethyllithium (**33**) or its organometallic derivatives with enones present in the literature at the time we began these investigations.



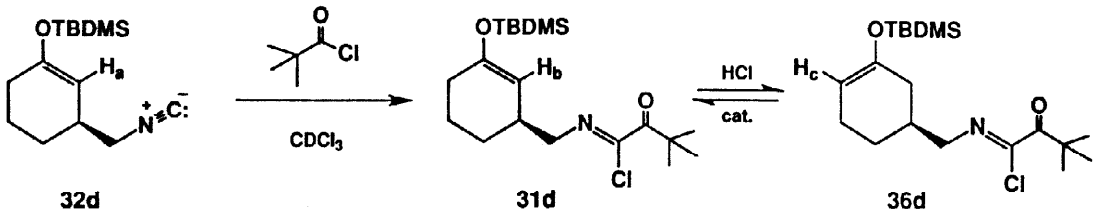
Dendrobine **(28a) : R = H**
Dendramine **(28b) : R = OH**

29g

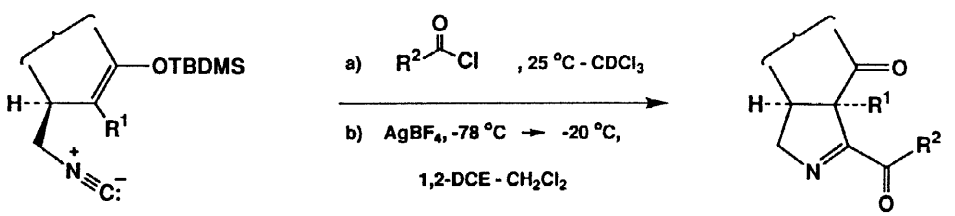
We initially conducted a detailed study of the parameters which govern 1,2- vs 1,4- regioselectivity for this nucleophilic addition reaction. It was ultimately determined that reasonable to excellent selectivity favoring the desired 1,4- mode of addition could be achieved by simply complexing isocyanomethyllithium with TMEDA or HMPA prior to reaction with the enone.[20,22] It is noteworthy that alternative organometallic derivatives of isocyanomethyllithium proved far less effective for 1,4-addition.[22] It was subsequently found that 1,4- addition of complexed isocyanomethyllithium was extendable to a wide range of substrate enones. It was also discovered that the rate of reaction of the enolates derived from 1,4- addition with *t*-butyldimethylchlorosilane was significantly faster than the corresponding silylation of the tertiary alkoxides derived from 1,2-addition. Accordingly, simple hydrolysis of the reaction mixture resulting from sequential nucleophilic addition of $LiCH_2NC$:, followed by silylation, provided the desired isocyanomethylsilyl enol ethers **32a-e** admixed with small amounts of tertiary alcohols **35** which could be conveniently separated by flash chromatography. A compilation of the isocyanomethylsilyl enol ethers **32a-e** which were prepared by this direct procedure appears in **Table 2.**



The acylative cyclization of the isocyanomethylsilyl enol ethers **32c** and **32d** initially appeared more problematic than the acylnitrilium ion initiated cyclizations of substrates bearing aryl terminators (*vide supra*).[4,5] The reason for the inefficiency of cyclization was readily revealed by following the course of the reaction of **32d** with trimethylacetyl chloride by ^{1}H NMR. By way of this technique, the extent of acylation was easily monitored by following the disappearance of the signal attributable to C*H*$_2$-NC: (δ 3.14) and the development of the corresponding methylene signal associated with the α-ketoimidoyl chloride product **31d** (δ 3.45). During the course of acylation, the disappearance of the vinyl proton H$_a$ (δ 4.73) occurred with simultaneous development of a new signal attributable to H$_b$ (δ 4.69) *and* an unexpected vinyl resonance H$_c$ assigned to the positional isomer **36d** (δ 4.71). The isomerization of **31d**→**36d** was presumably caused by trace amounts of adventitious HCl present in the reaction medium. It was readily determined that pyridine or, more conveniently, powdered 4 Å molecular sieves effectively suppressed silyl enol ether isomerization in substrates of this type.[23] As expected, isocyanomethylsilyl enol ethers which possess tetrasubstituted alkene moieties were *not* found to undergo facile isomerization under the conditions which are typically employed (25 °C) to achieve isonitrile acylation.

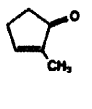
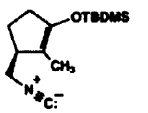
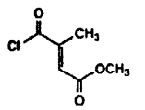
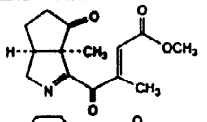
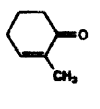
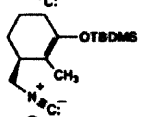
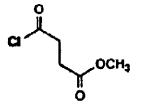
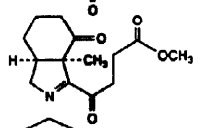
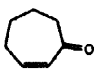
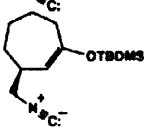
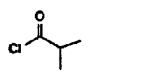
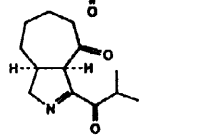
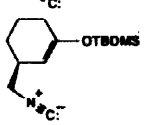
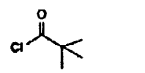
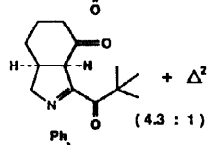
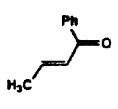
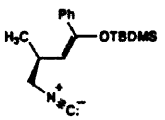
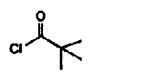
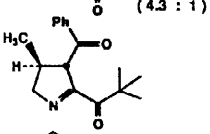
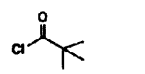
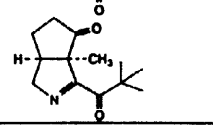


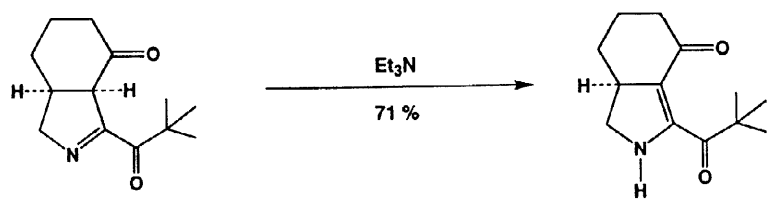
The cyclization of the crude α-ketoimidoyl chlorides obtained in the above manner was achieved by their addition to 1.10 - 1.35 equiv of $AgBF_4$[24] in CH_2Cl_2-$ClCH_2CH_2Cl$ (1:1) at -78 °C followed by warming to -20 °C. An immediate precipitation of AgCl was observed at -78 °C suggesting the rapid generation of the transient acylnitrilium ion intermediates **30a-f**. Subsequent cyclization of **30a-f** occurred at < -20 °C to afford the corresponding Δ^1-pyrrolines **29a-f** in 85-95 % *crude* yield and in a high state of chemical purity as assessed by ^{1}H NMR. The Δ^1-pyrrolines **29a-f** prepared in this manner could be purified with modest recoveries when subjected to chromatography on untreated silica gel.[19] However, the efficient purification of these compounds could be achieved either by reverse phase (C-18) chromatography or radial flash chromatography using silica gel disks that had been pretreated with gaseous Me_3N. The results obtained from a series of Δ^1-pyrroline forming cyclizations are collected in **Table 2**. The Δ^1-pyrroline **29d** was found to be quite sensitive to base catalyzed isomerization. Accordingly, exposure of **29d** to Et_3N (1 equiv) in CH_2Cl_2 led to the formation of the corresponding Δ^2-pyrroline **37** in 71% isolated yield.



32a-e 29a-f

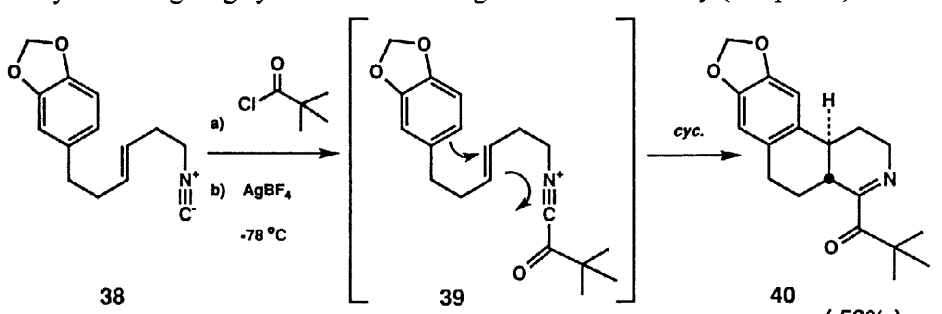
Table 2.

	enone 34	isonitrile 32	yield %	acyl chloride	pyrroline 29	yield %
a			71			86
b			70			88
c			68			78
d			67			73
e			79			81
f	34a	32a				87



29d 37

We had previously shown that acylnitrilium ions are sufficiently electrophilic to undergo facile cyclization with nonactivated arenes at –20 °C (*vide supra*).[5] The use of *simple* alkenes as nucleophilic addends in acylnitrilium ion initiated heteroannulations would be of considerable synthetic interest. To explore this possibility, the unsaturated isonitrile **38** was sequentially acylated ($(CH_3)_3CCOCl$, 25 °C, 6 h) and then subjected to $AgBF_4$-mediated cyclization (CH_2Cl_2-CH_3NO_2, -78 °C). As had been desired, the tetrahydropyridine **40** was obtained as the major cyclized product in 53% isolated yield.[25] The extension of this methodology to the synthesis of naturally occurring ring systems was investigated in a later study (see part v).



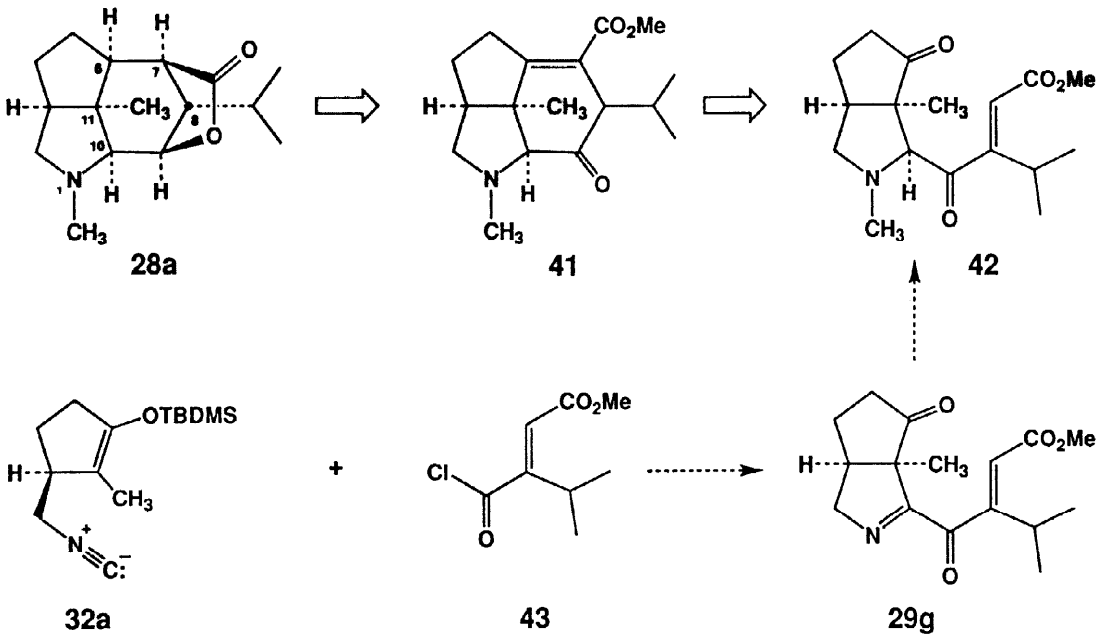
38 39 40 (53%)

The examples presented above clearly indicate the utility of acylnitrilium ion initiated cyclizations for the synthesis of polyfunctional azacycles. The application of this methodology to the synthesis of the *Orchidaceae* alkaloids was subsequently undertaken.

4. Stereocontrolled Total Synthesis of (±)-Dendrobine.[26]

The *Orchidaceae* alkaloid dendrobine (**28a**) is the most abundant of the sesquiterpene bases isolated from the ornamental orchid "Jinchai Shihu" (Dendrobium mobile LINDL)[27]. This alkaloid is the principle component of the Chinese Folk medicine "Chin-Shih-Hu"[28] and has been shown to exhibit antipyretic and hypotensive activity.[29] The intricate molecular architecture of the isoprenoid *Orchidaceae* alkaloids is elaborated upon a densely clustered array of seven stereogenic centers. Consequently, this family of compounds continues to represent a major challenge for efficient chemical synthesis.

Our approach to this molecule was designed around the possibility that the correct relative stereochemistry at C-6 and C-7 of **28a** might arise as a consequence of syn delivery of hydrogen onto the convex face of the prospective intermediate **41**. Intermediate **41**, in turn, was envisaged to arise via an intramolecular reductive aldol or phosphite anion driven Horner-Wadsworth-Emmons type coupling reaction involving the γ-ketoenoate **42**. Dissection of the Δ^1-pyrroline **29g** corresponding to **42** implicated the isocyanosilyl enol ether **32a** and the acyl chloride **43**, which could potentially be united in a highly convergent manner by way of the acylnitrilium ion-silyloxyalkene cyclization described above[19,20] (Scheme 3). The successful realization of this overall strategy, which culminated in an *unusually* efficient (eight linear steps, 6.2% cumulative yield) total synthesis of dendrobine (**28a**) is detailed below.

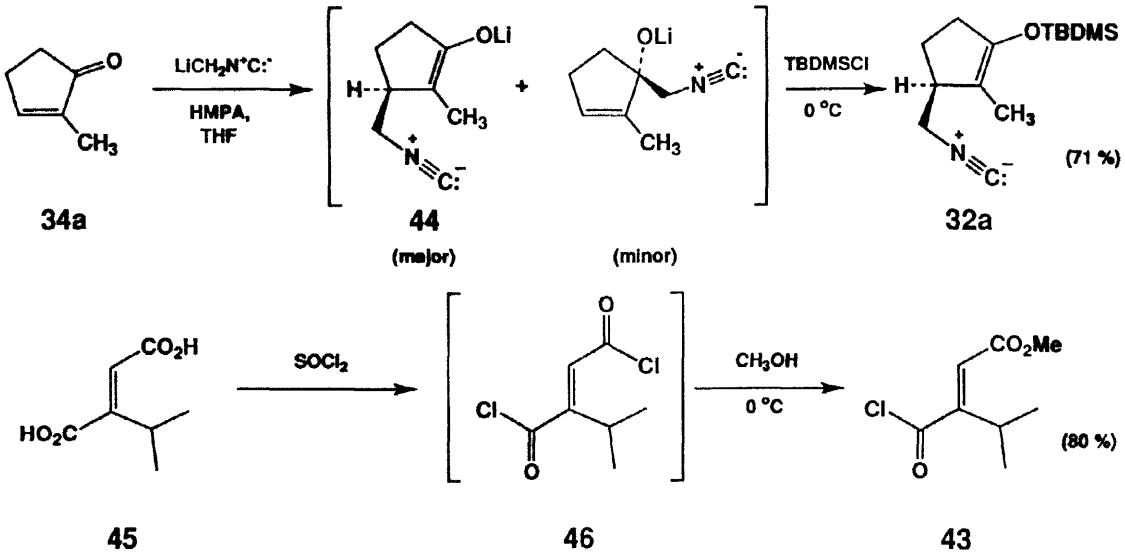


Scheme 3

4.1. *Synthesis of the Cyclization Substrate 42.*

The point of departure for our synthetic effort was 2-methylcyclopent-2-en-1-one (**34a**). This substance possesses all of the carbons required for the intact B ring of the *Orchidaceae* alkaloids. Exposure of **34a** to 1.17 equiv of isocyanomethyllithium[20] in the presence of HMPA (THF, -78 °C) led to regioselective 1,4-addition to

afford a solution of the corresponding enolate **44** along with a small amount of the tertiary alkoxide resulting from 1,2-addition.[22] Direct treatment of this mixture with *tert*-butyldimethylchlorosilane (-78 °C→0 °C) led to *selective* trapping of the less hindered enolate **44** to provide isocyanosilyl enol ether **32a** in 71% overall yield after chromatography. The requisite acyl chloride **43** was prepared in an exceedingly straightforward manner from the known 2-butenedioic acid **45**[30]. Accordingly, treatment of **45** with thionyl chloride gave the corresponding acyl chloride **46** which was directly treated with methanol under carefully controlled reaction conditions. We were gratified to find that the methanolysis of **46** proceeded with complete specificity for esterification of the less sterically encumbered carbonyl to furnish **43** in 80% overall yield (Scheme 4).

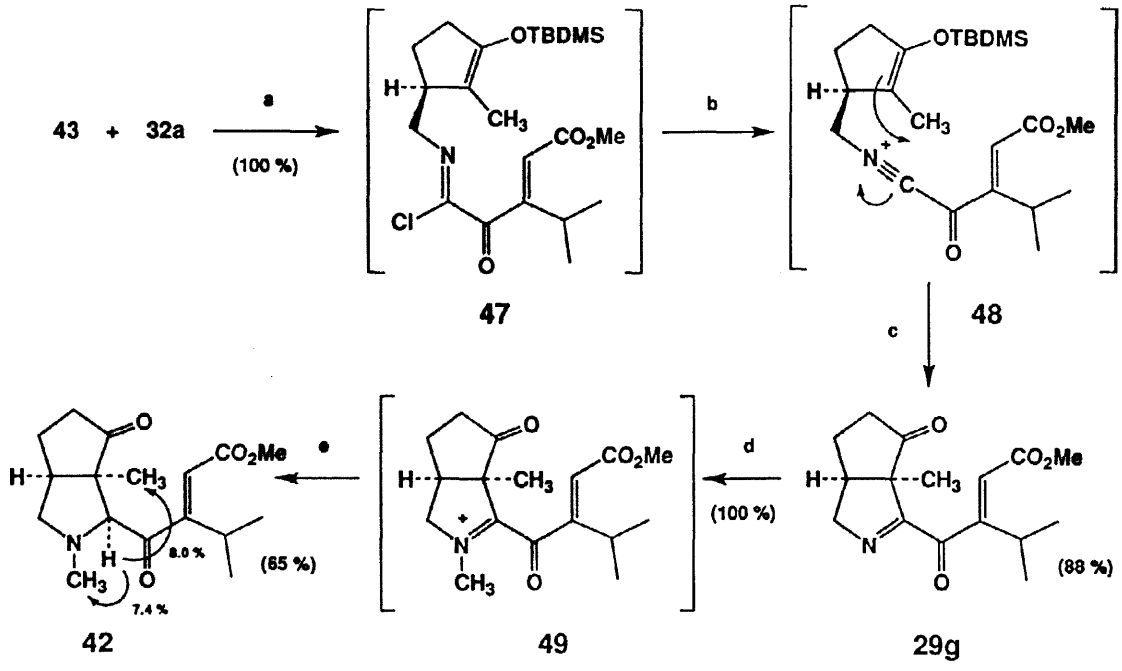


Scheme 4

With abundant quantities of the essential precursors **43** and **32a** in hand, we were suitably positioned for the execution of the crucial acylnitrilium ion-initiated heteroannulation. The reaction of isonitrile moieties with acyl chlorides is typically quite rapid, even at 25 °C.[5] However, due to the sterically congested nature of the chlorocarbonyl function of **43**, a slightly elevated temperature (40 °C) was required for the facile acylation of **32a**. To this end, exposure of **32a** to 1.17 equiv of **43** (CH_2Cl_2, reflux 3.5 h) in the presence of 4 Å molecular sieves (for the sequestration of adventitious HCl) provided the α-ketoimidoyl chloride **47** quantitatively. Direct transfer of the solution of **47** to a solution of 1.45 equiv. of $AgBF_4$ in 1:1 $ClCH_2CH_2Cl$ - CH_2Cl_2 at -78 °C followed by warming to -20 °C resulted in the generation of the transient acylnitrilium ion **48** and its ultimate cyclization to the essential Δ^1-pyrroline **32a** in *88% yield.* It should be emphasized that the gratifyingly high yield obtained in the case of **32a** is quite representative for acylnitrilium ion-initiated heteroannulations (*vide supra*).[31]

In principle, the stereoselective conversion of Δ^1-pyrroline **32a** to the contrathermodynamic 2-acylpyrrolidine **42** should be most readily accomplished by a consecutive *N*-methylation - hydride reduction sequence. The successful implementation of this experimental protocol initially proved quite challenging. Although *N*-methylation of **32a** could be achieved quantitatively via the agency of $CH_3O_3SCF_3$, initial attempts

to effect *selective* reduction of the corresponding iminium salt **49** with the usual types of reagents [e.g., $(Ph_3P)_2CuBH_4$,[32] $NaBH_3CN$, etc.] gave capricious results. It was ultimately discovered that the direct reduction of **49** to **42** could be realized in a highly stereocontrolled manner (selectivity = 50:1) by employing potassium tri(*tert*-butoxy)borohydride[33] as the reducing agent at -78 °C . To our knowledge this is the first example of an iminium cation reduction employing this useful reagent.[34] Evidence for the relative stereochemistry of **42** was provided by nuclear Overhauser difference (NOED) spectroscopy. Specifically, irradiation of the C-10 methine led to an 8.0% enhancement in the signal corresponding to the C-11 methyl substituent and a 7.4% enhancement of the *N*-methyl singlet (Scheme 5).



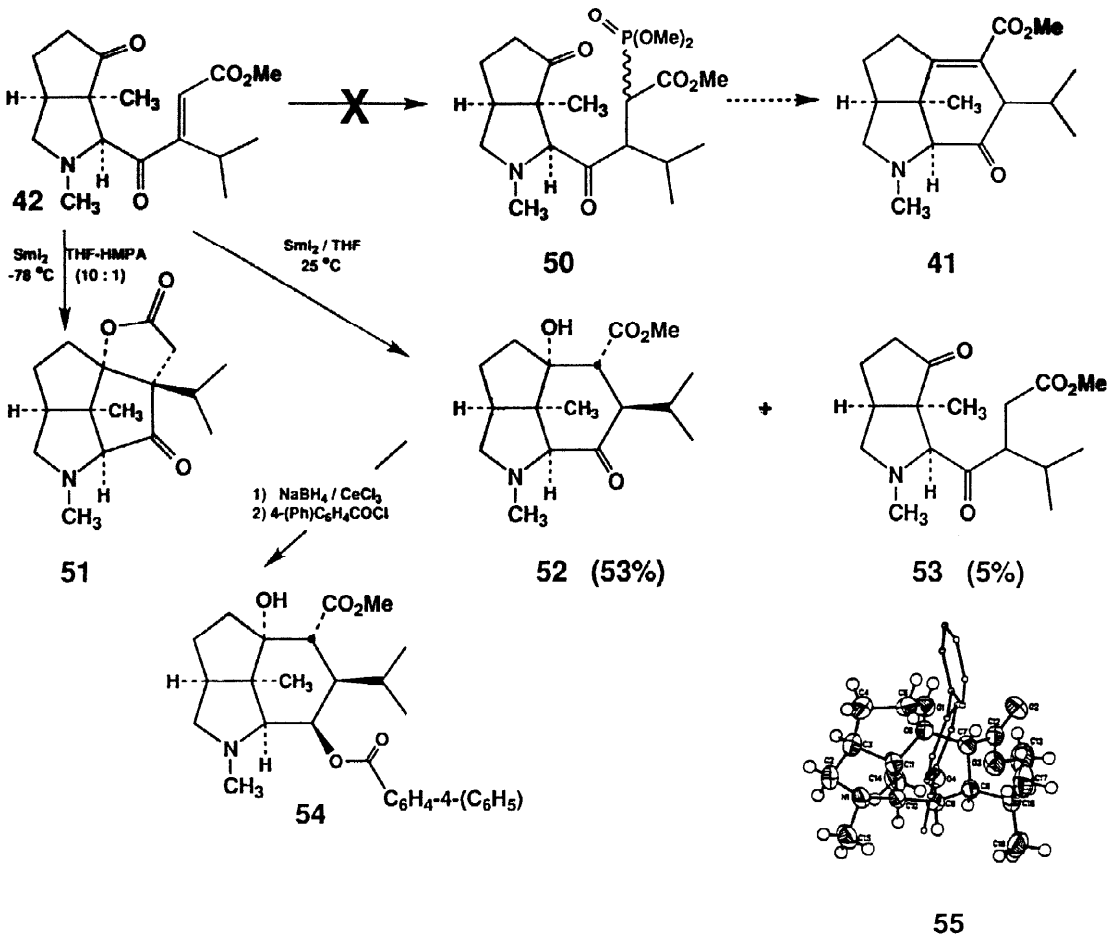
Scheme 5

(a) 4-Å sieves, 40 °C ; (b) $AgBF_4$, -78 °C ; (c) -78 °C → -20 °C ; (d) $CH_3O_3SCF_3$; (e) $K^+HB^-(O\text{-}t\text{-}Bu)_3$

4.2. Studies on the Cyclization of the Octahydrocyclopenta[c]pyrrole 42. Samarium Iodide Mediated Closure of Ring C.

Having achieved the synthesis of 2-acylpyrrolidine **42** in three overall steps from 2-methylcyclopent-2-en-1-one (**34a**), our attention was directed toward the essential task of effecting the annulation of ring C. It was our original intention to employ a phosphite anion driven Horner-Wadsworth-Emmons coupling reaction for this purpose. Unfortunately, the γ-ketoenoate moiety of **42** proved inert toward 1,4-addition of phosphite-derived reagents under a wide range of reaction conditions. Even trimethylaluminum promoted addition of dimethyl phosphite[35] was ineffective in this regard. In a series of elegant papers, Enholm,[36] Curran,[37] and Molander[38] had described several provocative applications of samarium (II) iodide-promoted ketyl-alkene couplings. These cyclization procedures typically lead to the preferential formation of five membered rings, as would be expected for free radical cyclizations.[39] It was our hope, however, that the steric deceleration created by the presence of the obstructive isopropyl substituent at C-2 of the acyl moiety would override this inherent

kinetic preference. Unfortunately, treatment of **42** with SmI_2 in THF-HMPA (10:1) at -78 °C led to the exclusive formation of the tetracyclic γ-lactone **51** formally derived from the 5-exo mode of ring closure. Through experimentation, it was rapidly established that the mode selectivity of cyclization was *strongly* coupled to reaction temperature. Consequently, addition of **42** to SmI_2 (4 equiv) in THF at 25 °C provided **52** as the exclusive cyclized product in 53% yield after chromatography. In addition, 5% of the reduction product **53** was formed in this reaction (Scheme 6). The relative stereochemistry of **52** was readily established by single crystal X-ray diffraction analysis of the derivative **54** prepared by sequential Luche reduction[40] and 4-phenylbenzoylation of the C-9 carbonyl. The results of this study are depicted in representation **55**. The stereochemical outcome of the Sm (II) mediated annulation is consistent with both a chelation controlled diyl cyclization and an intramolecular aldol condensation involving a samarium (III) enolate intermediate. Experiments were not conducted which would have distinguished between these two mechanistic possibilities.

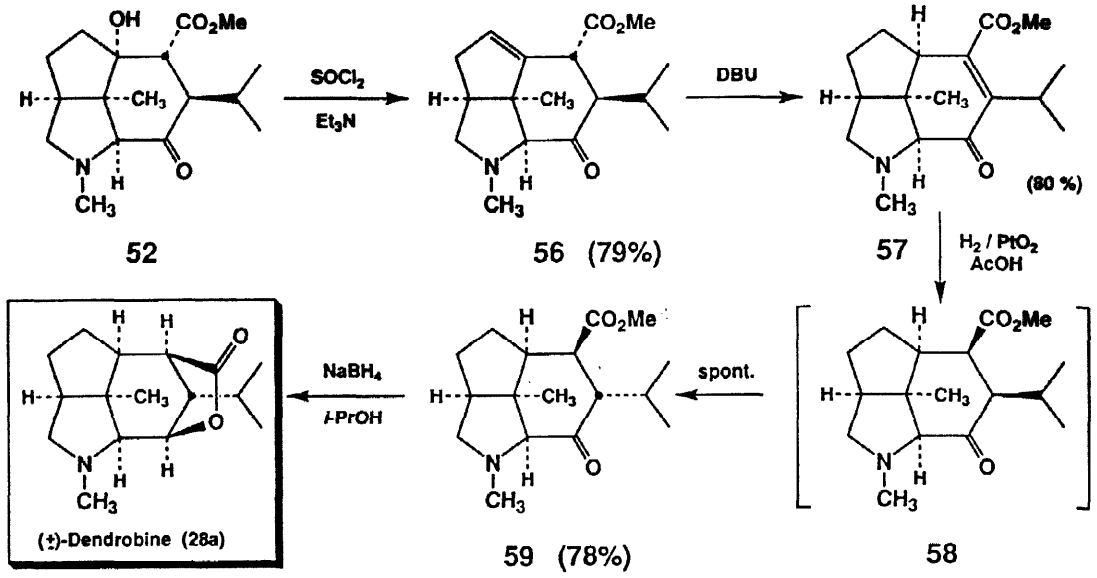


Scheme 6

4.3. Conversion of 16 into (±)-Dendrobine (28a).

The direct conversion of **42** to **52**, although quite pleasing in a practical sense, presented the obvious strategic obstacles of correcting the oxidation state at C-6 and the stereochemical incongruencies at C-7 and C-8. These transformations were expediently achieved as follows. Treatment of **52** with $SOCl_2$ (3 equiv) and

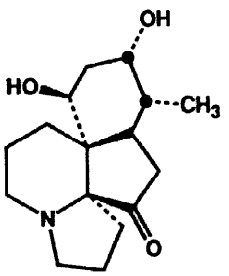
Et_3N (30 equiv) in EtOAc (0 °C→25 °C) led to regiospecific dehydration in the Hofmann sense to provide the β,γ-enoate **56** in 79% yield. The regiochemical preference observed for this reaction is not surprising in light of the sterically shielded nature and low kinetic acidity of the hydrogen at C-7. Isomerization of **56** to γ-ketoenoate **57** was cleanly achieved in 81% yield by exposure to DBU (4 equiv) in refluxing dioxane. Reduction of the tetra substituted double bond within **57** was most readily accomplished by hydrogenation over PtO_2 in AcOH at 40 psi pressure (25 °C). Fortuitously under these conditions, the anticipated cis isomer **58**, which was initially produced via syn hydrogenation, underwent quantitative isomerization to furnish the required trans isomer **59** directly in 78% yield. Presumably, AcOH is sufficiently acidic to promote the observed epimerization at C-8. Final reduction of **59**, according to the procedure of Roush[41] ($NaBH_4$, *i*-PrOH, 20 °C), gave (±)-dendrobine (**28a**) in 58% yield after recrystallization. Synthetic (±)-dendrobine (**28a**), mp 129-131 °C (lit.[29] mp 130-132 °C), prepared in this manner was identical in all respects (300 MHz ^1H and ^{13}C NMR spectra) except optical rotation to an authentic sample of the natural material, which was kindly provided by Professor K. Yamada.



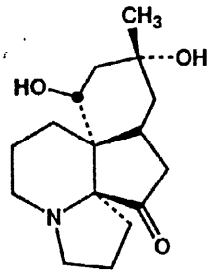
Scheme 7

5. C-Acylnitrilium Ion Initiated Spiroannulations.[42]

Alkaloids belonging to the *Lycopodium* family have remained an enduring challenge for efficient chemical synthesis. Although a number of these alkaloids possess intriguing pharmacology,[43] the ongoing interest in total synthesis would appear to be stimulated at least as much by the structural complexity of these substances as the attendant strategic imperatives for skeletal construction. Despite the continuing activity in this area, relatively little progress has been reported with regard to the synthesis of the irregular alkaloids belonging to the serratinane subgroup. With the exception of (±)-serratinine **61**[44] and the corresponding 8-deoxy derivative,[45] each of which have been synthesized once previously, no completed syntheses of alkaloids in this category have appeared.

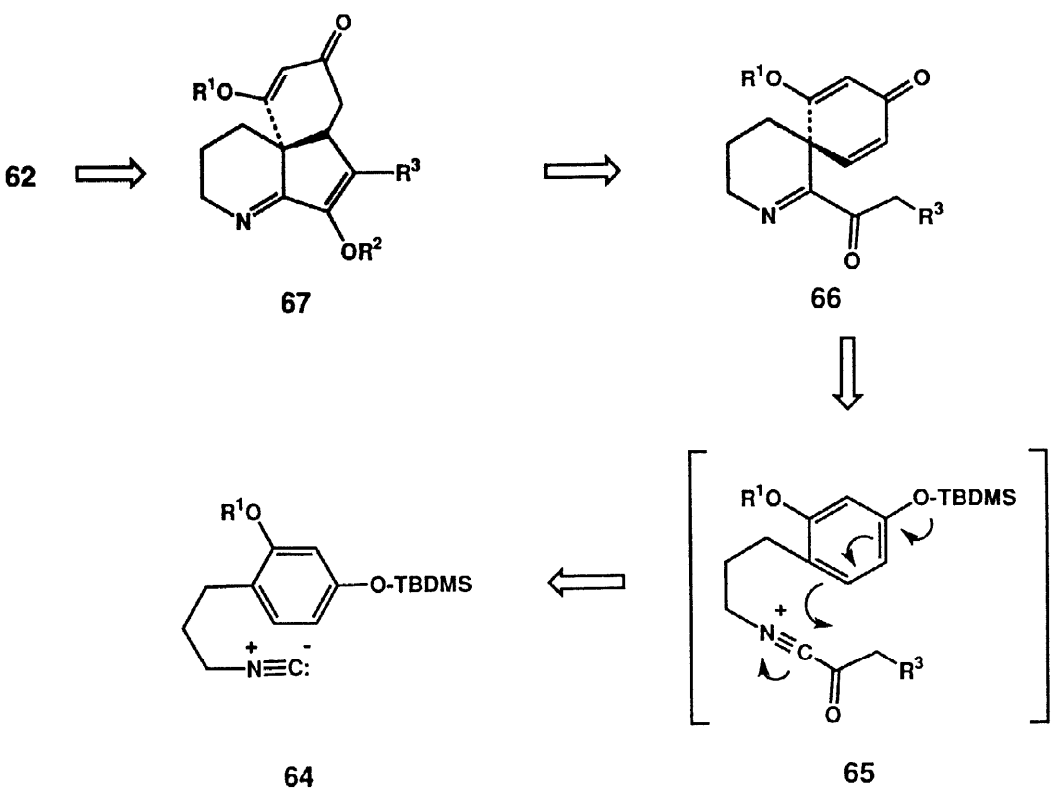


61



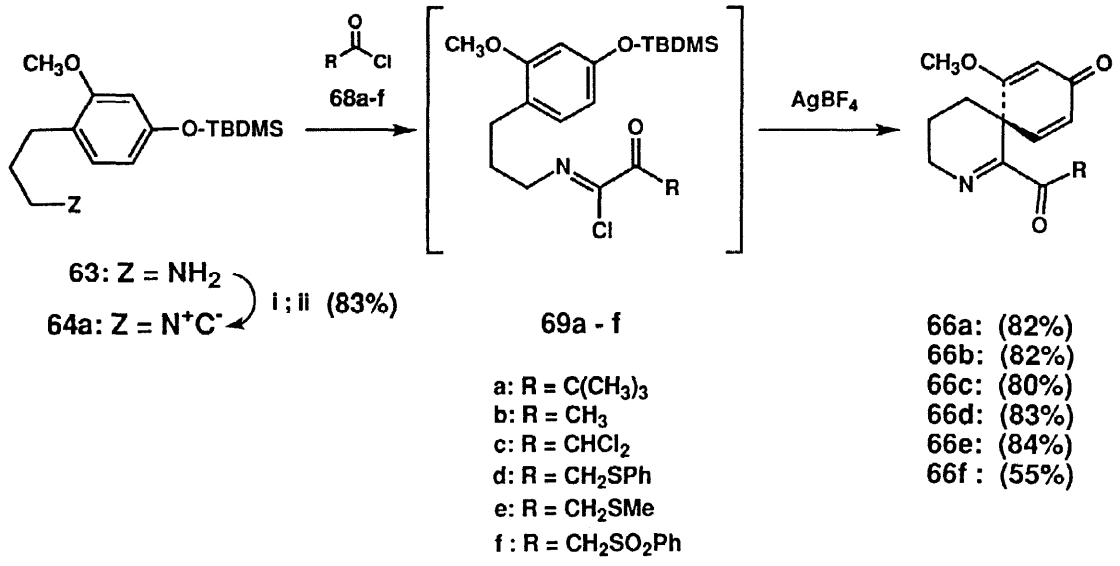
62

As described above, we had previously shown that cyclizations initiated by acylnitrilium ions could provide access to a wide variety of heterocyclic systems. Our interest in (±)-serratine **62**[46] was stimulated by the possibility that the essential tricyclic core of this *Lycopodium* alkaloid could be derived from a simple arene nucleus *via* sequential utilization of an acylnitrilium ion-initiated spiroannulation and intramolecular 1,4-addition (Scheme 8). Below we detail the successful implementation of this strategy.



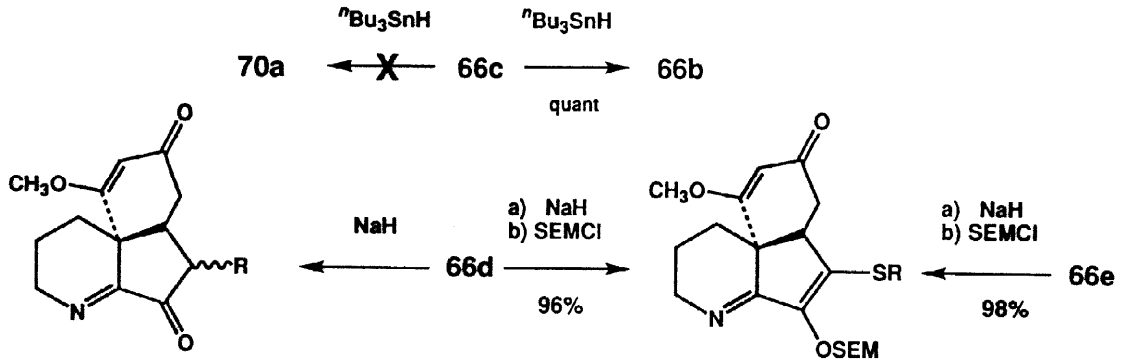
Scheme 8

The key isonitrile **64a** that was employed in this investigation was prepared by sequential formylation/dehydration (i. EtOCHO; ii. $POCl_3$-Et_3N, THF, 0 °C) of 3-[-4-(*t*-butyldimethylsilyloxy)-2-methoxyphenyl]propanamine **63**. Acylation of **64a** with the acyl chlorides **68a-f** (CH_2Cl_2, rt) was found to proceed in close analogy with previous examples to provide the intermediate α-ketoimidoyl chlorides **69a-f** in *ca.* quantitative yield (NMR). Exposure of **69a-f** to $AgBF_4$ (1.5 equiv) in $ClCH_2CH_2Cl$-CH_2Cl_2 (1:1) at -70 °C resulted, without exception, in the immediate precipitation of AgCl signaling the generation of the corresponding transient acylnitrilium ions. In contrast to most of the examples previously described in this review, cation interception by the pendant carbon centered nucleophile did not occur rapidly at -78 °C. Optimally, preformed solutions of the reactive intermediates were subsequently warmed to -20 °C and maintained at this temperature for 20 h to induce spirocyclization. By way of this procedure, the spiro[cyclohexa-2,5-diene-1,3'-(3',4',5',6'-tetrahydropyridin)]-ones **66a-e** could be obtained on a preparative scale in 80-84% purified yield. It is of interest that cyclization of **69f** under an analogous set of reaction conditions resulted in only a modest yield (55%) of the desired spirocyclic intermediate **66f**. Presumably, the enhanced propensity of the β-ketosulfonyl moiety of **69f** to enolize was responsible for the degradation of spirocyclization efficiency in this instance. In this connection, the successful conversion of **69b-f** to **66b-f** constitutes the first reasonably comprehensive series of acylnitrilium ion cyclizations involving substrates that possess readily enolizable sites α- to the carbonyl function.



The predisposition of the spirocyclic intermediates **66b-e** to undergo intramolecular 1,4-addition was subsequently examined. Several attempts to convert **66c** to the corresponding tricycle **70a** *via* free-radical intermediates under reductive conditions (Bu_3SnH)[47] led only to the production of **66b** albeit in excellent (>90%) yield. By way of contrast, base-mediated cyclization of **66d** and **66e** gave more encouraging results. In an initial experiment, exposure of **66d** to NaH (1.1 equiv) in DMF [0 °C (10 min)→25 °C (8 h)] followed by protonolysis (AcOH, 1.1 equiv) afforded the unstable α-phenylthioketone **70b** in good yield. We suspected that the observed instability of **70b** might be a consequence of initial tautomerization involving the sensitive α-keto

imine moiety. Accordingly, this bifunctional array was derivatized by alkylative protection *in situ*. To this end, cyclization of **66d** (NaH-DMF, 0 °C→25 °C) followed by enolate interception [SEM-Cl (1.1 equiv), -60 °C→25 °C] furnished the tricyclic imine **67d** in 96% purified yield. Cyclization of **66e** in a similar manner provided **67e** in 98% yield.[48] Although **66f** could be induced to undergo an analogous cyclization, **66b** proved resistant toward base mediated intramolecular Michael addition.

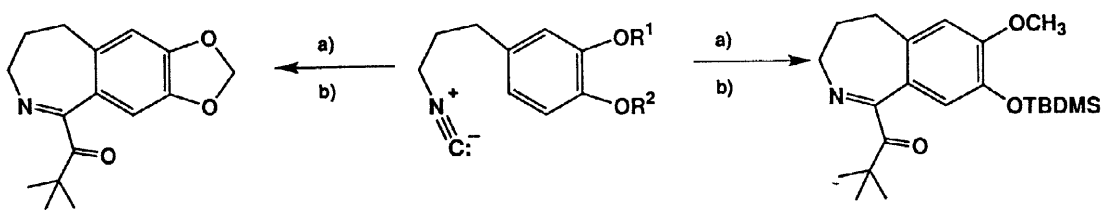


70a: R = H
70b: R = SPh

67d: R = Ph
67e: R = Me

At least three features of the preceding cyclizations are worthy of comment. These studies have shown that a variety of functionally varied α-keto imidoyl chlorides can serve as effective precursors to synthetically viable acylnitrilium ions; intramolecular capture of the enolates derived from **66d** and **66e** by the least substituted (and most electrophilic) cyclohexadienone β-carbon is completely selective; and the *in situ* enolate trapping protocol gives rise to the functionally well differentiated intermediates **67d** and **67e**. Studies directed toward the stereodefined annulation of the serratinane D ring and the completion of the synthesis of (±)-serratine (**62**) are continuing.

In a parallel series of experiments, it was shown that the presence of a 4-silyloxy moiety on the arene nucleus is essential for successful spirocyclization. Consequently, cyclization of **64b** under an analogous set of reaction conditions led exclusively to the 2-acylbenzazepine **71b** in 61 % yield. As expected, acylative cyclization of **64c** provided the 2-acylbenzazepine **71c** as the exclusive product in 71 % yield.[20]



71c (71 %)

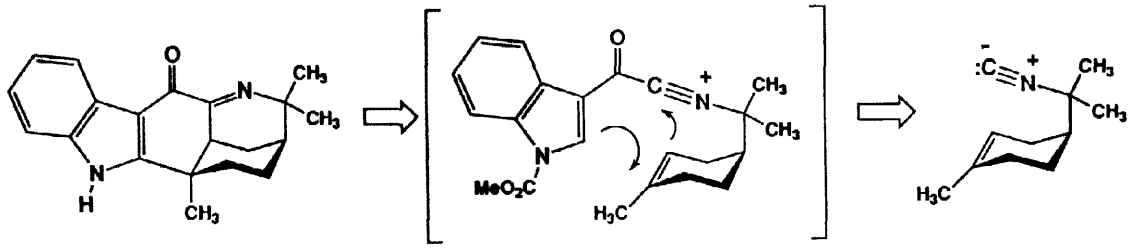
64b: R^1=CH$_3$; R^2=TBDMS
64c: R^1, R^2= CH$_2$

71b (61 %)

a) Me_3CCOCl, 25 °C, $CDCl_3$ b) $AgBF_4$, -78 °C → -20 °C 1,2-DCE-CH_2Cl_2

6. Monocyclizations Involving *C*-Acylnitrilium Ions and Simple Alkenes.[49]

Our interest in the prospective use of an acylnitrilium ion initiated alkene-cascade cyclization for the synthesis of the *Aristotelia* alkaloid (+)-makonine (**72**)[50] (Scheme 9) prompted our examination of prototypical cyclizations between these cations and simple, unactivated alkenes. The results of this study are described below.



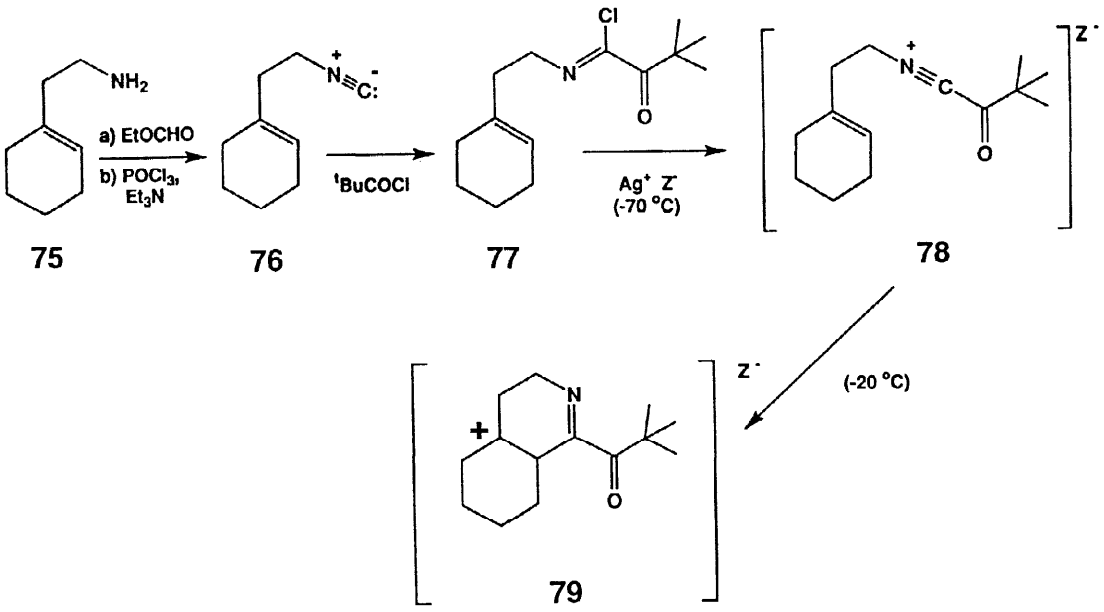
72 **73** **74**

Scheme 9

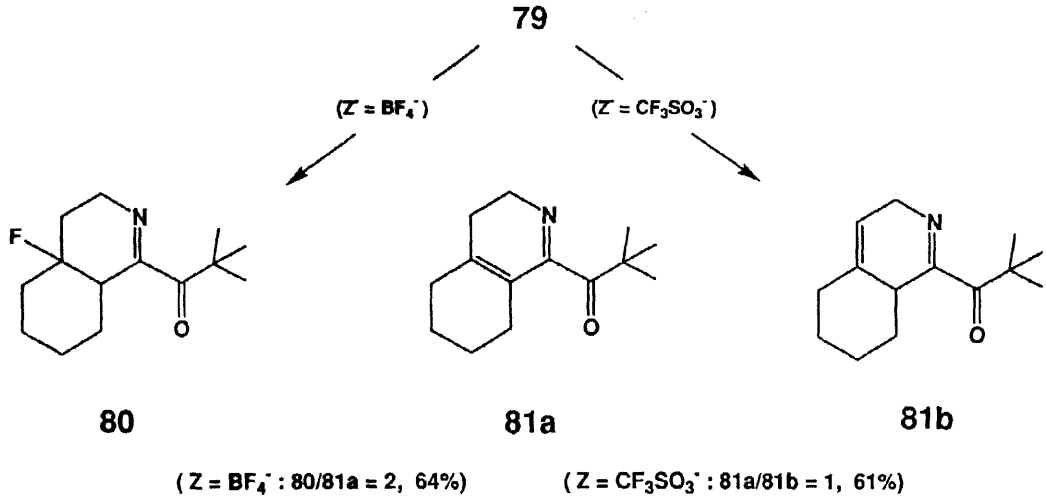
The isonitriles employed in this investigation were prepared from the corresponding amines by sequential *N*-formylation/dehydration. Accordingly, formylation of amine **75** (EtOCHO, reflux, 5 h) followed by dehydration ($POCl_3$–Et_3N, THF, 0 °C) furnished isocyanide **76** in 82% yield after distillation.

6.1. Cyclization Studies.

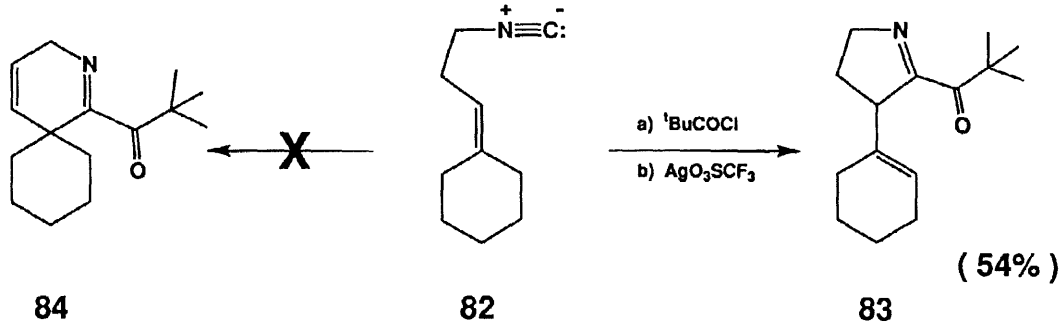
The initial conversion of compound **76** into the corresponding α-keto imidoyl chloride **77** was achieved by treatment with trimethylacetyl chloride (TMAC) (1.05 equiv) as described previously.[20] Whereas ionization of **77** could be readily achieved by exposure to $AgBF_4$ (1.10 equiv) in analogy with previous examples [CH_2Cl_2 ($CH_2Cl)_2$, −70 °C], subsequent cyclization of the resulting acylnitrilium ion **78** took an unexpected course. When the reaction mixture was warmed to −20 °C, cyclization of **78** proceeded by way of the tertiary carbonium ion **79** to provide **80**[51] and **81a** (**80**/**81a** = 2) in 64% isolated yield.



75 **76** **77** **78** **79**

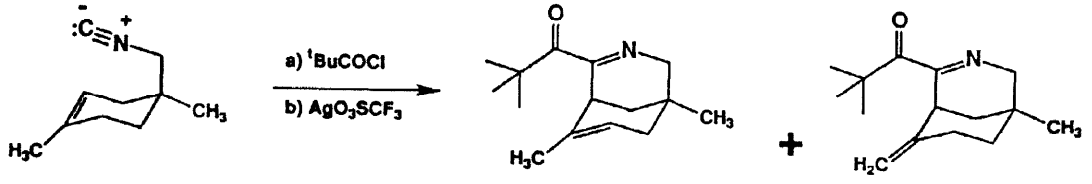


The formation of **80** could be completely suppressed by the use of AgO_3SCF_3 for generation of the initial acylnitrilium cation. Accordingly, treatment of **77** with AgO_3SCF_3 (1.10 equiv, CH_2Cl_2, –70 °C → –40 °C) provided the isomeric hexahydroisoquinolines **81a** and **81b** [**81a/81b** = 1 (NMR)] in 61% overall yield from the isocyanide **76**. Exposure of this mixture to silica gel resulted in quantitative conversion of **81b** into **81a** which could be isolated in analytically pure form in 61% yield. As expected, the regiochemistry of the foregoing cyclizations (fused *vs* spiro) would appear to be governed by the relative stabilities of the respective post-cyclization carbocations. A similar outcome was observed in the acylative cyclization of 3-cyclohexylidene-1-isocyanopropane (**82**).[52] Sequential reaction of **82** with TMAC (1.05 equiv) followed by ionization/cyclization of the resulting α-ketoimidoyl chloride [AgO_3SCF_3 (1.10 equiv), CH_2Cl_2,–70 °C→ –40 °C] provided the 3,4-dihydro-2*H*-pyrrole **83** to the exclusion of the corresponding spirocycle **84** in 54% yield after chromatography. Not surprisingly, conformational restriction of the 3-(1-cyclohexenyl) substituent precluded facile isomerization of the nonconjugated alkene within **83** (*vide supra*).



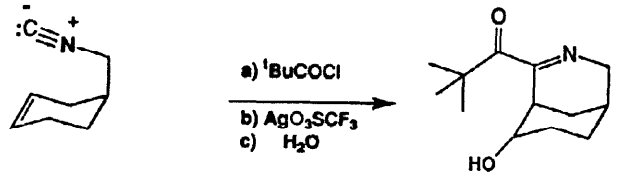
As a prelude to the intended synthesis of (+)-makonine (**72**), we next turned our attention to the construction of bicyclic ring systems via acylnitrilium ion-alkene cyclizations. Reaction of 4-(isocyanomethyl)-2,4-dimethyl-1-cyclohexene (**85**)[53] with TMAC (1.05 equiv) followed by Ag^+ mediated cyclization [AgO_3SCF_3 (1.10 equiv), CH_2Cl_2,–70 °C→ –40 °C] secured the azabicyclo[3·3·1]nonanes **86a** and **86b** [**86a/86b** = 1.5 (NMR)] in 51% yield after chromatography.[54] Presumably **86a** and **86b** arise as a consequence of divergent

proton elimination from a common carbocationic intermediate. In contrast to this result, acylation/cyclization of the 1,2-disubstituted alkene containing isonitrile **87** (vide supra) furnished the bicyclic alcohol **88** as the only major product after an aqueous quench albeit in low (33%) isolated yield.[55] In this instance, a series of DEPT and ^{1}H–^{13}C HETCOR experiments was used to unambiguously establish the connectivity of the core heterocycle and rule out the isomeric [3·2·2] ring system. The regioselectivity of cyclization in the case of **88** is likely a reflection of preferential 6-membered ring formation.



85 **86a** **86b**

(86a/86b = 1.5; 51%)



(33%)

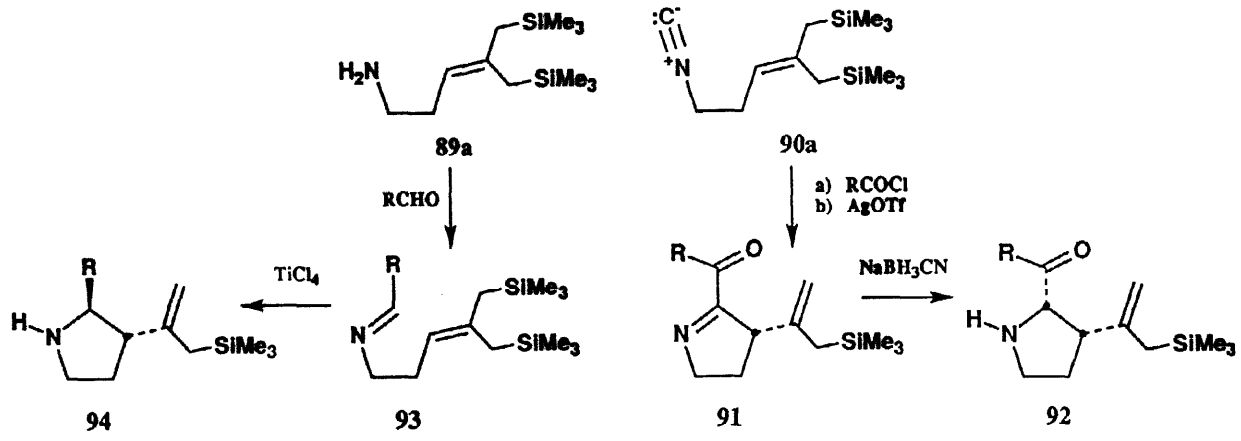
87 **88**

The preceding examples clearly show that even isolated, unactivated alkenes can serve as suitable terminators for cyclizations involving acylnitrilium ions. Although cyclization efficiencies are lower than in previous examples, these results indicate that isolated alkenes in various settings might serve as effective cationic relay moieties for cascade type annulations.

7. 2-Propylidene-1,3-bis(silane) Terminated Cyclizations.[56]

In principle, a variety of alternative carbon-based nucleophiles could be utilized in conjunction with *C*-acylnitrilium ions for the synthesis of structurally diverse heterocycles in a stereocontrolled manner. We had previously shown that 2-propylidene-1,3-bis(silane) moieties could serve as highly effective terminators in *trans*-selective cyclizations initiated by metalloiminium ions.[57] In addition to high regio- and stereochemical control, another appealing aspect connected with the use of the 2-propylidene-1,3-bis(silane) terminator resides in the simultaneous liberation of a functionalizable allylsilane moiety upon monocyclization.[58-60] The comparatively high nucleophilicity of 2-propylidene-1,3-bis(silane)s raised the issue of the prospective compatibility of these terminators with reaction conditions which are required for the initiation of the foregoing cyclization sequences.[61] Despite this initial concern, the facile generation of *C*-acylnitrilium ions tethered to 2-propylidene-1,3-bis(silane)s and the stereocontrolled coupling[62] of these components to furnish highly functionalized Δ^{1}-pyrrolines was found to be highly successful. We subsequently demonstrated that the product

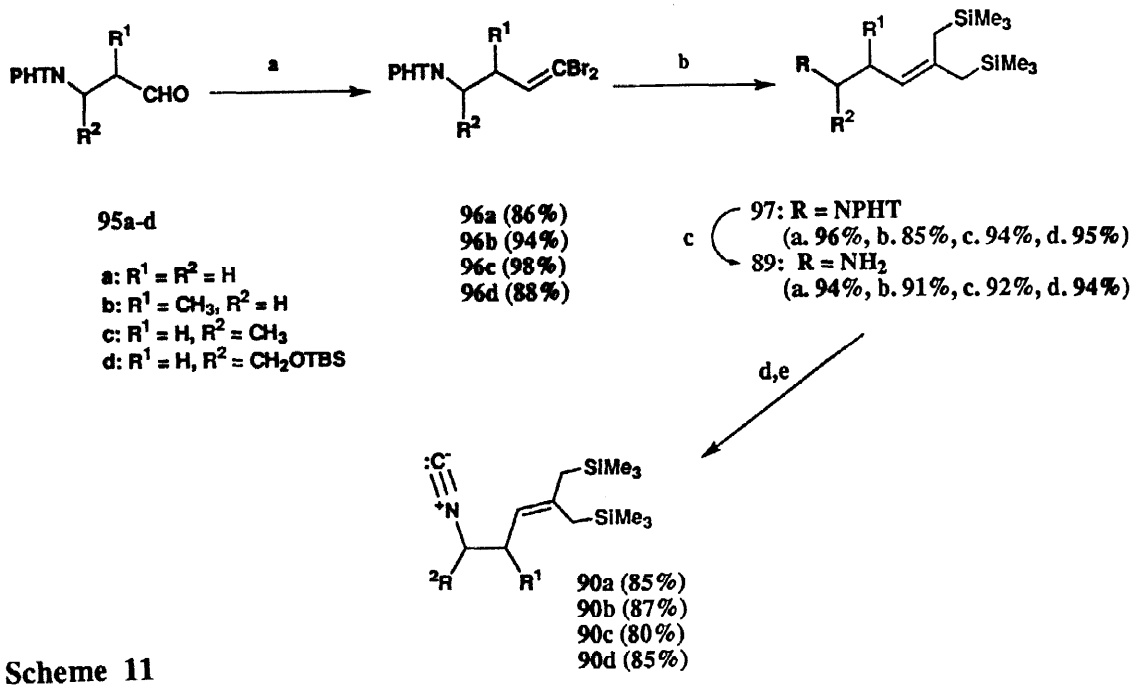
Δ^1-pyrrolines are convertible to a set of 2,3-*cis*-pyrrolidine derivatives which stereochemically compliments that available from the corresponding metalloiminium cyclizations (Scheme 10).



Scheme 10

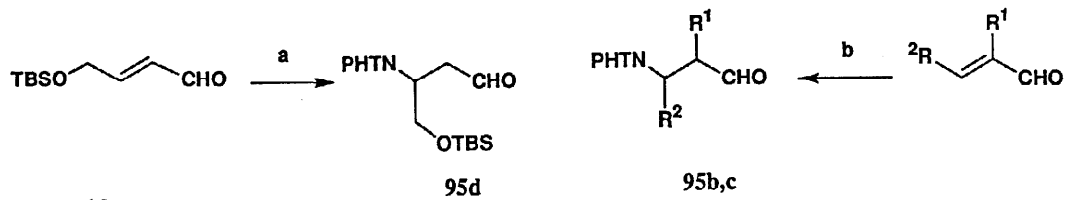
7.1. Isonitrile Synthesis

We began this investigation by developing methods for the synthesis of 2-propylidene-1,3-bis(silane) bearing isonitriles. Treatment of imide **95a**[63] with CBr_4 and Ph_3P (CH_2Cl_2, 0 °C) provided imide **96a** in 86% isolated yield. Exposure of **96a** to $(Me_3SiCH_2)_2Zn$ (1.5 equiv, prepared from $Me_3SiCH_2MgCl + ZnCl_2$ *in situ*) in the presence of 7 mol % $PdCl_2(PPh_3)_2$ (THF, rt) furnished **97a** in 96% yield after purification which, upon PHT cleavage with $N_2H_4 \bullet H_2O$ (EtOH, reflux), afforded amine **89a** (78% *overall* from **95a**). Sequential *N*-formylation of **89a** (EtOCHO) followed by dehydration of the corresponding formamide ($POCl_3$-Et_3N, THF, 0 °C) furnished **90a** in 85% overall yield (Scheme 11). Gratifyingly, products resulting from electrophilic desilylation were not observed during the course of the formylation-dehydration sequence. Isonitriles **90b-d** were efficiently synthesized in an analogous manner from imides **95b-d** which were prepared, in turn, by either DBU or sodium ethoxide mediated addition of phthalimide to the requisite α,β-unsaturated aldehydes (5% DBU, PHT, DMF, rt *or* 10%, NaOEt, PHT, EtOH, rt) (Scheme 12). For the sterically hindered amine **89d**, optimal conversion to the corresponding formamide was effected using formic acetic anhydride[64] (Et_2O, -78 °C).



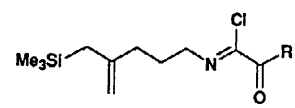
Scheme 11

(a) CBr_4, Ph_3P, CH_2Cl_2, 0 °C; (b) $(TMSCH_2)_2Zn$, (1.5 equiv), $PdCl_2(Ph_3P)_2$ (7 mol %), THF, rt; (c) $N_2H_4 \bullet H_2O$, EtOH, reflux; (d) EtOCHO, reflux or CH_3CO_2CHO, Et_2O, -78 °C for **89d** (e) $POCl_3/Et_3N$, THF, 0 °C.



Scheme 12

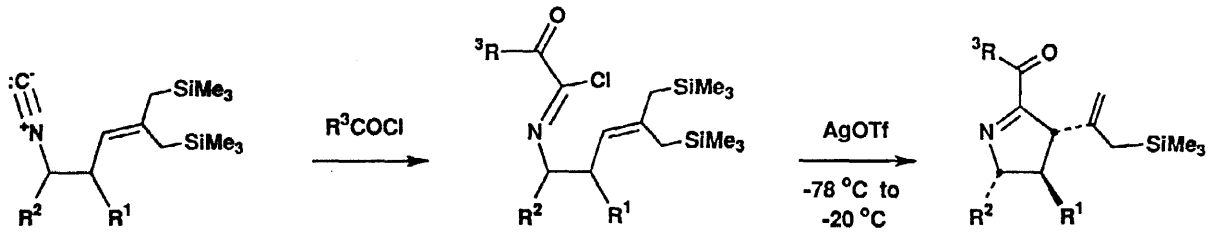
[a](a) 5% DBU, PHT, DMF, rt. (b) 10% NaOEt, PHT, EtOH, rt.



99

7.2. Cyclization Studies

The acylative cyclization of **90a** with a variety of simple as well as functionalized acyl chlorides was subsequently examined. Treatment of **90a** with various acyl chlorides (1.1 equiv, CH_2Cl_2, rt) resulted in *chemospecific* functionalization of the isonitrile moiety to generate the corresponding α-ketoimido chlorides **98a-e** in quantitative yields as determined by ^{1}H-NMR. Immediate exposure of the unpurified adducts **98a-e** to AgO_3SCF_3 (1.5 equiv, $CH_2Cl_2/ClCH_2CH_2Cl$, −78 °C → −20 °C) led to smooth cyclization to provide the 2-acyl-Δ^1-pyrrolines **91a-e** in 61% to 91% isolated yields after neutralization of the reaction mixture by careful inverse addition to vigorously stirred aqueous $KHCO_3$ at 0 °C followed by chromatographic purification (**Table 3**). It is noteworthy in a preparative context that quenching via *direct* addition of $KHCO_{3(aq.)}$ sometimes led to the formation of products derived from the protodesilylation of the pendant allylsilane moiety. In addition, the use of $AgBF_4$ (-78 °C) in place of AgO_3SCF_3 resulted in diminished yields (<20-70%) of the desired Δ^1-pyrrolines with protodesilylated materials of type **99** frequently being isolated.

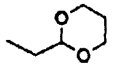


90a: $R^1 = R^2 = H$
90b: $R^1 = CH_3$, $R^2 = H$
90c: $R^1 = H$, $R^2 = CH_3$
90d: $R^1 = H$, $R^2 = CH_2OTBS$

98a-l

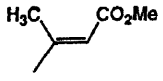
91a-l

Table 3. Acylative Cyclizations of Isonitrile 90a.

Pyrroline	R^3COCl (-R^3)	Yield[1] (%)	Pyrroline	R^3COCl (-R^3)	Yield[1] (%)
91a	-$C(CH_3)_3$	82	91d	-$CH_2CH_2CH_2Cl$	61
91b	-$CH(CH_3)_2$	68	91e		91
91c	-$CH_2CH(CH_3)_2$	77			

[1]All yields are from **90a** and correspond to isolated, chromatographically purified products.

Table 4. Stereocontrolled Acylative Cyclizations of Isonitriles 90b - 90d.

Pyrroline	R^3COCl (-R^3)	Isonitrile	$3_{trans} : 3_{cis}$[2]	Yield[1] (%)
91f	-$C(CH_3)_3$	90b	>50 : 1	41
91g	-CH_2CH_3	90b	>50 : 1	40
91h	-$C(CH_3)_3$	90c	1 : 4.6	90(65[3])
91i	-CH_2CH_3	90c	1 : 3.8	78(49[3])
91j	-$C(CH_3)_3$	90d	1 : 2.6	87(56[3])
91k	-$CH_2CH_2CO_2Me$	90d	1 : 4.5	77(48[3])
91l		90d	1 : 3.0	76(47[3])

[1]All yields from the isonitrile correspond to isolated, chromatographically purified products. [2]Obtained from integration of the expanded olefinic region of 300 ^1H NMR spectra of crude Δ^1-pyrrolines. [3]Isolated yield of chromatographically purified *cis*-isomer from isonitrile.

7.3. Diastereoselective Cyclizations

In principle, the cyclization of isonitriles possessing sites of resident asymmetry could give rise to 2-acyl-Δ^1-pyrrolines with a high degree of substrate derived stereocontrol.[65] To investigate this possibility, the isonitriles **90b-d** were prepared (*vide supra*) and subjected to AgO_3SCF_3 mediated acylative cyclization. Silver ion induced cyclizations of representative α-ketoimidoyl chlorides **98f** and **98g** derived from **90b** [AgO_3SCF_3 (1.5 equiv), CH_2Cl_2-$ClCH_2CH_2Cl$, -78 °C → -20 °C] were found to proceed with excellent levels of internal stereoselection [*trans* : *cis* ≥ 50:1 (NMR)] but with lower overall efficiency than observed for acyl chloride derivatives of **90a**. By way of contrast, cyclization of α-ketoimidoyl chlorides derived from **90c** and **90d** gave rise to Δ^1-pyrrolines **91h-l** in 76% to 90% isolated yields, but with diminished stereoselectivity in favor of the *cis* isomers (**Table 4**). In these instances, the major diastereomers **91h-l**$_{cis}$ could be readily separated by column chromatography on silica gel in 65%, 49%, 56%, 48% and 47% isolated yields from the isonitrile respectively. The stereochemical outcome of the foregoing cyclizations can be rationalized on the basis of conformational control involving minimization of non-bonded interactions. Accordingly, *trans* selective cyclization of *C*-acylnitrilium ions **100f** and **100g** corresponding to isonitrile **90b** should occur via a conformer in which energetically unfavorable $A^{1,3}$-interactions are suppressed. In the case of the *C*-acylnitrilium ions **100h-l** derived from isonitriles **90c** and **90d**, the origin of the comparatively lower levels of 1,3-stereoinduction favoring the corresponding *cis*-Δ^1-pyrrolines **91h-l** can be ascribed to the avoidance of a less profound allylic through space interaction (**Figure 2**). In all of the preceding examples, stereochemical assignments were based on rigorous NOE spectroscopic studies. Several representative NOE enhancements for the Δ^1-pyrrolines **91f**, **91k**, and **91h** are shown in **Figure 3**. For the *cis*-Δ^1-pyrrolines, the observance of a large NOE interaction from the C-3 and C-5 methine hydrogens to the *same* hydrogen of the centrally located C-4 methylene was particularly diagnostic. Analogous experiments performed on the minor *trans* isomers revealed NOE enhancements that complimented these stereochemical assignments.[66]

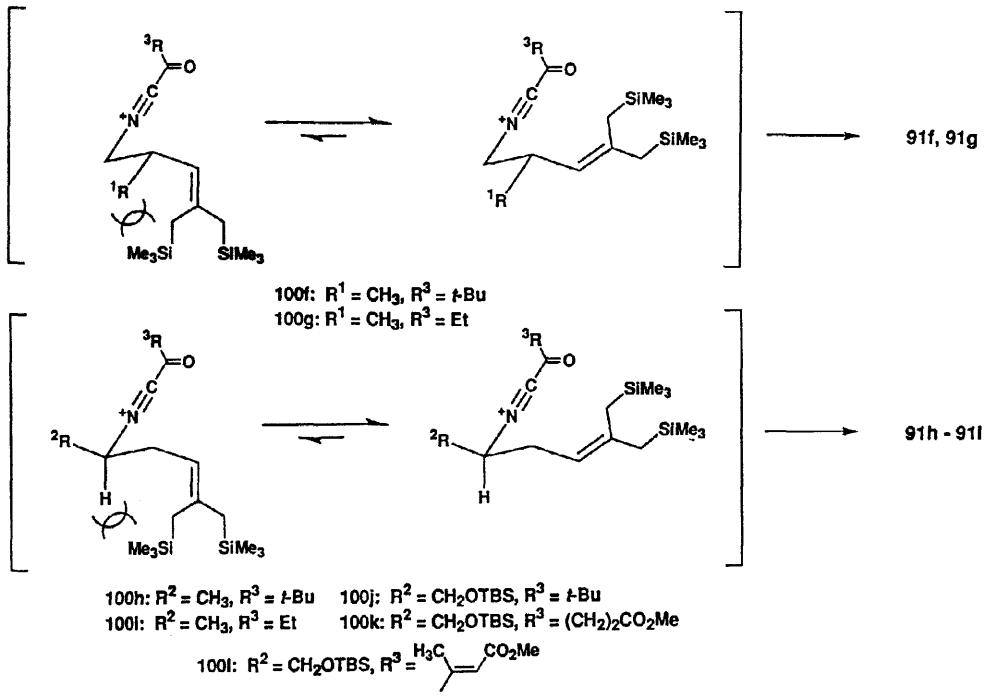


Figure 2

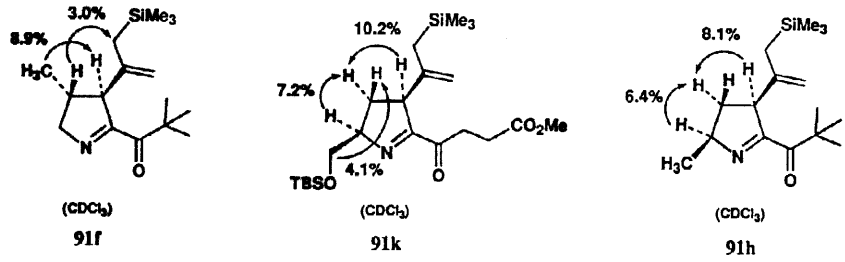
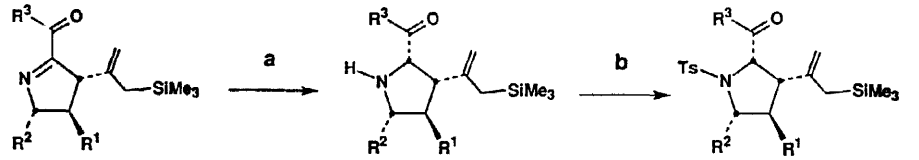


Figure 3

7.4. Diastereoselective Reductions

Reduction of the imine moiety of the foregoing Δ^1-pyrrolines could be readily accomplished by treatment with $NaBH_3CN$ (4.00 equiv) and TFA (1.05 equiv) in CH_3OH at −78 °C. As expected, kinetic delivery of hydride occurred predominantly in an *anti* sense with respect to the 2-(trimethylsilylmethyl)ethylidene substituent to provide crude *cis*-pyrrolidines **92a-c**$_{cis}$ which were not purified but immediately subjected to *N*-tosylation [TsCl, DMAP, CH_2Cl_2, −78 °C→ −20 °C] to furnish the sulfonamide derivatives **101a-c**$_{cis}$. In this fashion, higher overall yields of pure materials were obtained and, for the case of **101b**, removal of the minor diastereomer was readily accomplished by fractional crystallization from petroleum ether. In addition, the basic pyrrolidines **92a-c** were safeguarded against potential epimerization at the labile C-2 stereocenter.[67] As before, stereochemical assignments were based on a series of NOE experiments **(Figure 4)**. The anti approach of hydride in the reduction step was clearly evident in the large (9.2-13.1%) NOE enhancement between the C-1 and C-2 methine hydrogens. The results of these spectroscopic studies are consistent with and, therefore, serve to support the initial stereochemical assignments of pyrrolines **91f-91i.**



91a
91f$_{trans}$
91j$_{cis}$

92a
92b
92c

101a (55%; 1,2-*c*:*t* = 22:1)
101b (63%; 1,2-*c*:*t* = 4.4:1)
101c (67%; 1,2-*c*:*t* > 50:1)

a: $R^1 = R^2 = H$, R^3 = *t*-Bu
b: $R^1 = CH_3$, $R^2 = H$, R^3 = *t*-Bu
c: $R^1 = H$, $R^2 = CH_2OTBS$, R^3 = *t*-Bu

a) $NaBH_3CN$ (4.00 equiv), TFA (1.05 equiv), CH_3OH, -78 °C; (b) TsCl (1.2 equiv), DMAP (1.3 equiv), CH_2Cl_2, -78 °C → -20 °C.

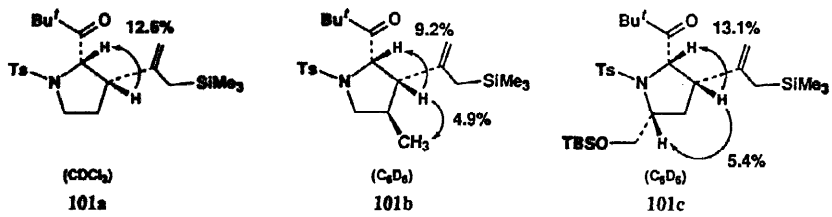


Figure 4

In summation, the foregoing study has shown that *C*-acylnitrilium ion-2-propylidene-1,3-bis(silane) cyclizations are useful for providing a range of functionally diverse Δ^1-pyrrolines in a highly convergent manner. The product Δ^1-pyrrolines may be readily isolated in stereochemically pure form in reasonable to good overall yield. Subsequent reduction of these unsaturated heterocycles can provide rapid access to the corresponding *cis*-2-acylpyrrolidines which bear synthetically useful allylsilane moieties. In addition, the flexible and efficient synthesis of requisite amino-2-propylidene 1,3-bis(silane)s could, in principle, be extended to longer carbon chain homologs enabling the preparation of larger ring heterocycles by this methodology. As we have shown in this account, *C*-acylnitrilium ion initiated cyclizations provide an efficient and highly versitile avenue to a wide variety of functionalized heterocycles. The application of this method to additional challenges of synthetic interest will be described in the future.

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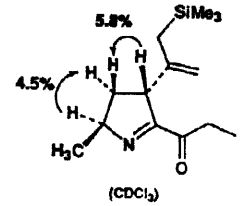

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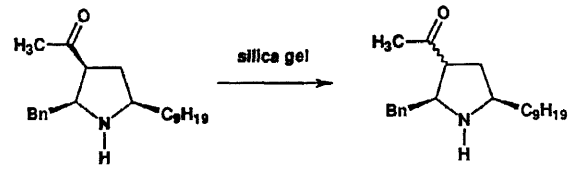

Biographical sketch

Thomas S. Livinghouse

Thomas S. Livinghouse was born in Los Angeles, California on December 8, 1954. He was awarded a Bachelor of Science degree in Chemistry with honors from U.C.L.A. in 1976 and subsequently completed a Masters Degree under the guidance of Orville L. Chapman at U.C.L.A. in 1977. After receiving his Ph.D. in 1980 from Robert V. Stevens at Rice University, he conducted research as a National Institutes of Health Postdoctoral Fellow in the laboratories of William S. Johnson at Stanford University. From 1981-1987, Dr. Livinghouse served as an Assistant Professor at the University of Minnesota in Minneapolis. In 1987, he was appointed an Associate Professor and moved, along with his research group, to Montana State University. In 1991, he was promoted to the rank of Professor. Professor Livinghouse has been the recipient of numerous awards and is a past fellow of the Alfred P. Sloan Foundation, the Alexander von Humboldt Foundation and the Japan Society for the Promotion of Science. In 1997, he served as chairman of the 16th International Congress of Heterocycle Chemistry. His current research interests include the development of new carbo- and heteroannulation strategies based on cationic, radical and metal-mediated cyclizations. In addition, the Livinghouse group is actively engaged in ligand design and catalysis.