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Acylnitrilium Ions. Versatile New Intermediates for the Synthesis of Highly Functionalized Heterocycles.

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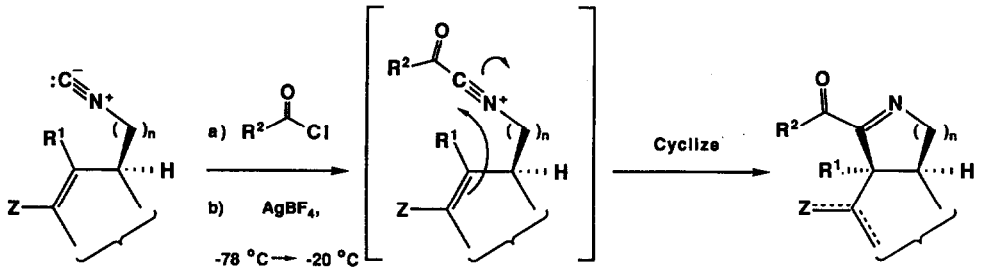
Abstract - Acylnitrilium ions, generated by the exposure of α-ketoimidoyl chlorides to $AgBF_4$, readily engage suitably disposed sites of molecular unsaturation in cyclization reactions leading to heterocyclic ring systems. This novel method for annulation is applicable to the construction of 5, 6, and 7 membered rings and is particularly useful for the synthesis of polyfunctional heterocycles possessing quaternary sites in the β-position to nitrogen.

INTRODUCTION

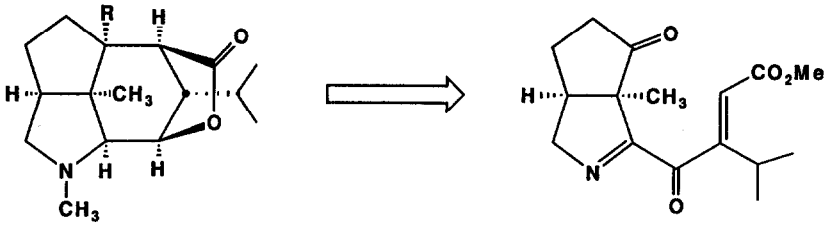
The diverse spectrum of biological, chemical, and physical properties possessed by nitrogen-containing heterocycles has elevated this category of compounds to a position of preeminence as synthetic objectives. Despite the number and intensity of investigations which have led to the development of numerous procedures for heteroannulation, several distinct challenges remain with respect to the elucidation of *general* methods for the convergent assembly of azacycles. Although representative methods for azacycle synthesis have been developed which utilize anionic[2-4], free radical[5-7], and cycloaddition[8-10] pathways, perhaps the most versatile procedures for achieving this goal involve cyclization reactions initiated by nitrogen stabilized cations. Among these, annulation reactions triggered by iminium[11] and acyliminium[12,13] ions have been exploited most extensively in total synthesis. Our interests in the development of general methods for alkaloid synthesis led us to propose the use of C-acylnitrilium ions as initiators for heterocyclization.[14-16] The synthetic advantages inherent to this new method for heteroannulation include: (1) a high level of convergence with respect to the introduction of peripheral 2-acyl moieties; (2) the flexibility to elaborate heterocycles of varied annular dimension; (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 ($AgBF_4$ - $ClCH_2CH_2Cl$, -78 °C → 0 °C) which are employed for effecting cyclization (eq 1). In this paper we will detail the application of acylnitrilium ion initiated cyclizations to the synthesis of Δ^1-pyrrolines and describe the first examples of cationic spiroannulations promoted by these reactive intermediates.



(eq. 1)

RESULTS

A. *Acylnitrilium Ion-Silyloxyalkene Cyclizations. Applications to the Synthesis of Δ^1-Pyrrolines.*

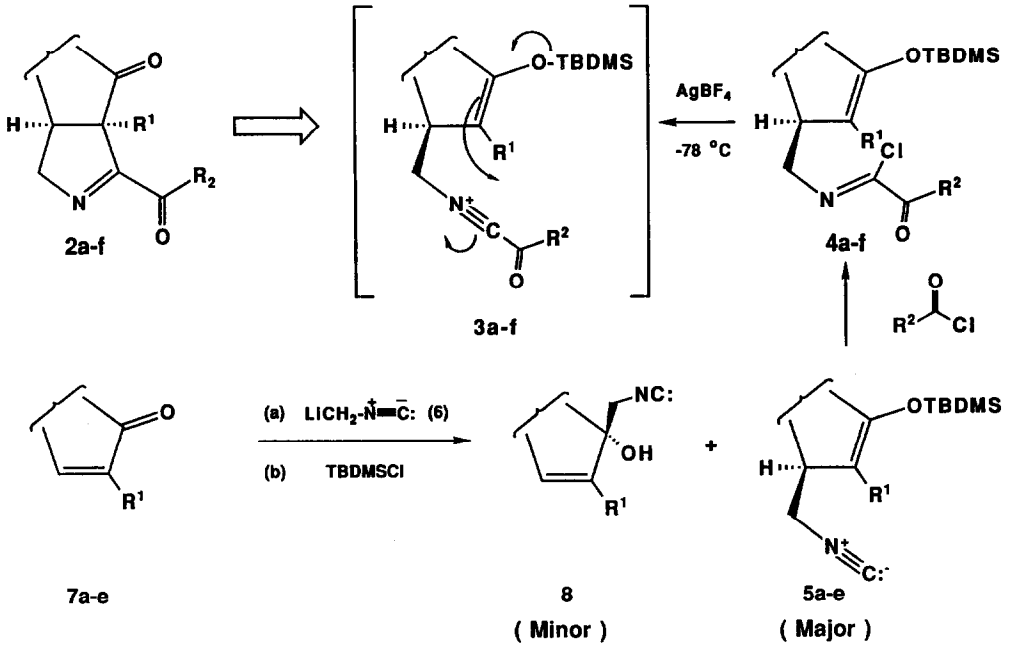


Dendrobine **(1a) : R = H**
Dendramine **(1b) : R = OH**

2g

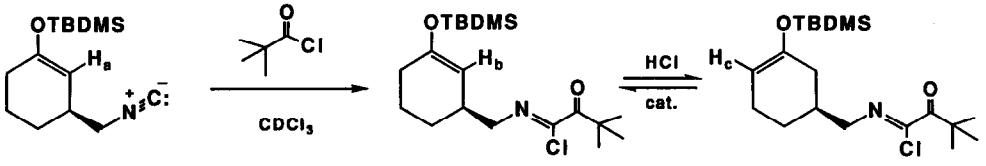
As part of a unified synthetic approach to the *Orchidaceae* alkaloids[17], we required large quantities of the Δ^1-pyrroline **2g**. It was predicted that **2g** and related Δ^1-pyrrolines might be synthesized in a highly convergent manner by the silver ion induced cyclization of α-ketoimidoyl chlorides (e.g., **4a-f**) formed by the direct combination of acyl chlorides with isocyanomethylsilyl enol ethers (e.g., **5a-e**).[18] The requisite isocyanomethylsilyl enol ethers **5a-e**, in turn, were expected to be available, at least in principle, by sequential 1,4- addition of isocyanomethylithium (**6**)[19] to the corresponding α,β-unsaturated ketones **7a-e** followed by enolate silylation. Curiously, there were no reports detailing the reactions of isocyanomethyllithium (**6**) or its organometallic derivatives with enones present in the literature at the time we began our investigations. Accordingly, we 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 optimally be

achieved by simply complexing isocyanomethyllithium with TMEDA or HMPA prior to reaction with the enone.[20] It is noteworthy that alternative organometallic derivatives of isocyanomethyllithium proved far less effective in this capacity.[20] Subsequent to this study it was 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 **5a-e** admixed with small amounts of tertiary alcohols **8** which could be conveniently separated by flash chromatography. A compilation of the isocyanomethylsilyl enol ethers **5a-e** which were prepared by this direct procedure appears in Table 1.



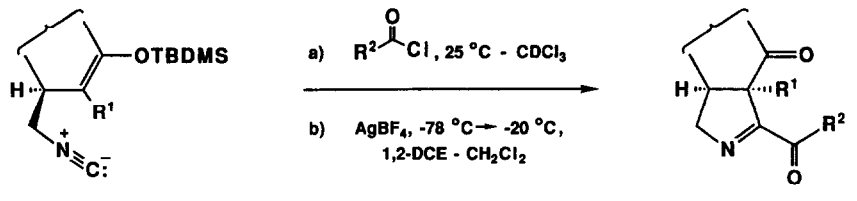
The acylative cyclization of the isocyanomethylsilyl enol ethers **5c** and **d** initially appeared more problematic than the acylnitrilium ion initiated cyclizations of substrates bearing aryl terminators reported previously.[14,15] The reason for the inefficiency of cyclization was readily revealed by following the course of the reaction of **5d** with trimethylacetyl chloride by ^1H NMR. By way of this technique, the extent of acylation was easily monitored by following the disappearance of the signal attributable to CH_2-NC: (δ 3.14) and the development of the corresponding methylene signal associated with the α-ketoimidoyl chloride product **4d** (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 **9d** (δ 4.71). The isomerization of **4d** ⇌ **9d** 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 silylenol ether isomerization in substrates of this type.[21] 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.



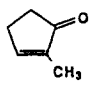
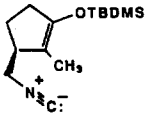
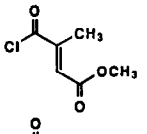
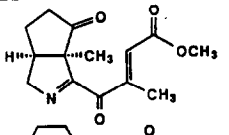
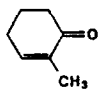
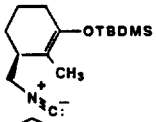
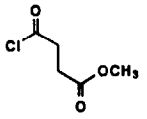
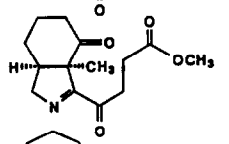
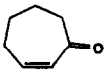
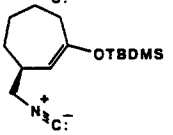
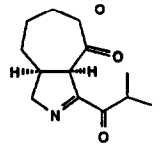
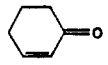
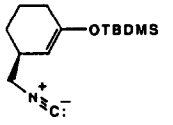
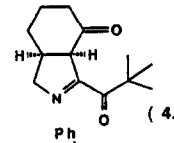
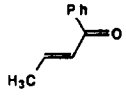
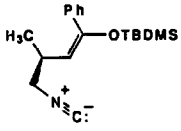
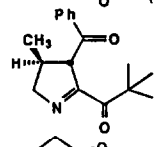
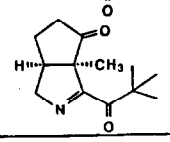
5d **4d** **9d**

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 $AgBF_4$[22] 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 intermediate **3a-f**. Subsequent cyclization of **3a-f** occured at <-20 °C to afford the corresponding Δ^1-pyrrolines **2a-f** in 85-95 *% crude* yield and in a high state of chemical purity as assessed by ^1H NMR. The Δ^1-pyrrolines **2a-f** prepared in this manner could be purified with modest recoveries when subjected to chromatography on untreated silica gel.[16] 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 1.

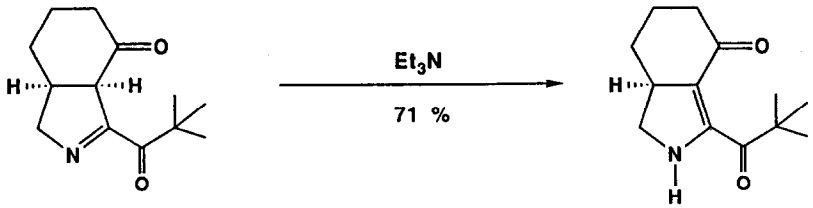


5a-e **2a-f**

Table 1. Synthesis of γ-Isocyanomethylsilyl Enol Ethers and Δ^1-Pyrrolines.

	enone 7	isonitrile 5	yield %	acyl chloride	pyrroline 2	yield %
a			71			86
b			70			83
c			68			78
d			67		 + 10 (4.3 : 1)	73
e			79			81
f	7a	5a				87

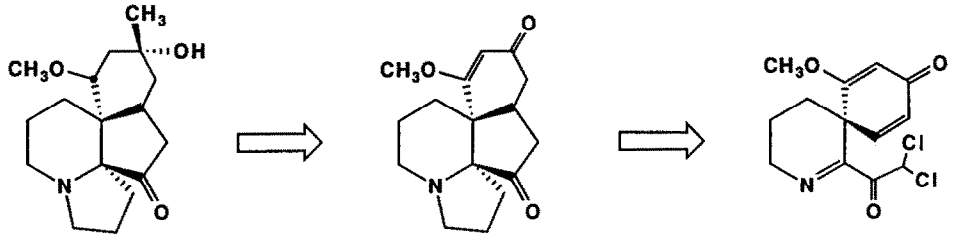
The Δ^1-pyrroline **2d** was found to be quite sensitive to base catalyzed isomerization. Accordingly, exposure of **2d** to Et_3N (1 equiv) in CH_2Cl_2 led to the formation of the corresponding Δ^2-pyrroline **10** in 71 % isolated yield.



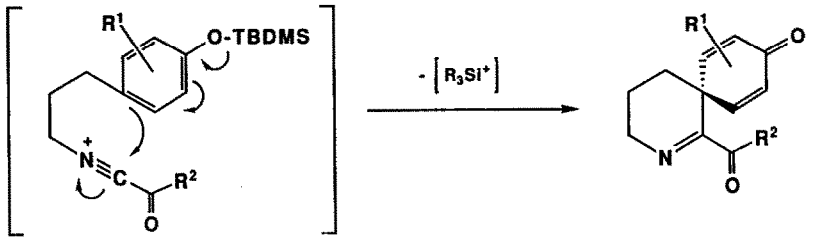
2d **10**

B. *Cationic Spiroannulations Promoted by Acylnitrilium Ions. Applications to the Synthesis of 3,3-Disubstituted Δ^1-Piperidienes.*

The irregular *Lycopodium* alkaloid serratine (**11**)[23] possesses a polycondensed tetracyclic core that contains five stereogenic centers. Our strategy for the synthesis of this unusual heterocyclic ring system is designed to rely on the modification of the tetracyclic intermediate **12** which, in turn, will hopefully derive from the Δ^1-piperidiene **13**. We felt that Δ^1-piperidienes of this general variety might be readily available by way of acylnitrilium ion initiated spiroannulations terminated by 4-*t*-butyldimethylsilyloxyphenyl moieties (eq 2). Herein we report the successful realization of cationic spiroannulations promoted by this new class of nitrogen stabilized carbocations.



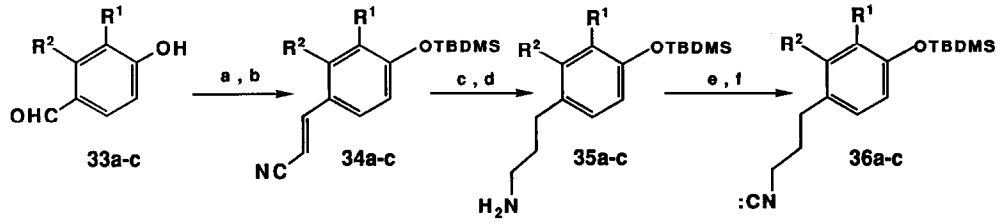
11 **12** **13**



(eq 2)

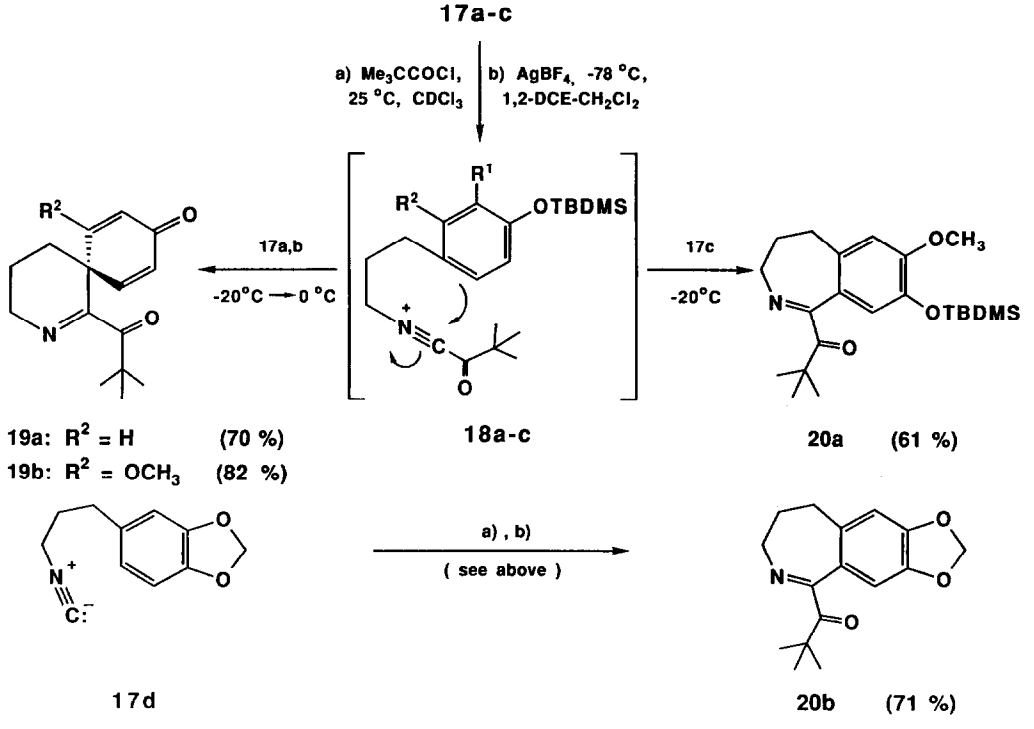
The precyclization intermediates **17a-c** which were required for this study were readily prepared by the following sequence of reactions. Silylation of the appropriate phenol **14a-c** (TBDMSCl / imidazole, DMF)[24] followed by condensation of the resulting silyl ether with the sodium derivative of diethylphosphonoacetonitrile gave the corresponding cinnamonitriles **15a-c** in high yield. Hydrogenation of **15a-c** (H_2, Pd/C) followed by nitrile reduction ($LiAlH_4$) provided the 3-(aryl)propanamines **16a-c**. Sequential formylation of **16a-c** (EtOCHO) and final dehydration of the formamide moiety (Et_3N-$POCl_3$, THF) furnished the isonitriles **17a-c**. The isonitrile **17d** was prepared in an analogous manner from 3,4-methylenedioxybenzaldehyde.

The acylative cyclization of the isonitriles **17a-d** was conducted by a procedure which was directly analogous to that used for the conversion of the isocyanomethylsilyl enol ethers **5a,e** to the Δ^1-pyrrolines **2a-f**. In the case of the substrates **17a** and **b**, acylnitrilium ion initiated cyclization led *exclusively* to spirocyclic products. Accordingly, acylation of the 3-(aryl)-1-isocyanopropanes **17a** and **b** with trimethylacetyl chloride ($CDCl_3$, 25 °C) followed by silver ion promoted cyclization ($AgBF_4$, $ClCH_2CH_2Cl$-CH_2Cl_2, -78 °C → -20 °C → 0 °C) delivered the spirocyclic Δ^1-piperidienes **19a** and **b** in 70 % and 82 % yield respectively after chromatographic purification. By way of contrast, cyclization of **17c** under an analogous set of reaction conditions led exclusively to the 2-acylbenzazepine **20a** in 61 % yield. As expected, acylative cyclization of **17d** provided the 2-acylbenzazepine **20b** as the exclusive product in 71 % yield.



(a: $R^1 = R^2 = H$; b: $R^1 = H$, $R^2 = OCH_3$; c: $R^1 = OCH_3$, $R^2 = H$)

[a) TBDMSCl - Imidazole ; b) $(EtO)_2POCH^-CN\ Na^+$; c) H_2 / Pd ; d) $LiAlH_4$; e) EtOCHO : f) $POCl_3$ / Et_3N]



In summary, acylnitrilium ion initiated cyclizations have proven an exceptionally versatile and highly convergent means for the synthesis of structurally diverse heterocycles. The present study has further revealed that the mode selectivity of cationic cyclization terminated by arene moieties is subject to control by remote substituent effects. Accordingly, either spirocyclic or fused 6 \ 7 ring systems can be efficiently prepared by the selection of the appropriate 3-(4-oxyphenyl)-1-isocyanopropane precursor. The application of this efficient heteroannulation procedure to the total synthesis of the *Orchidaceae* alkaloid dendrobine[17], the irregular *Lycopodium* alkaloids as well as related synthetic targets will be detailed in future accounts from these laboratories.

Acknowledgements. Support for this research by grants from the Alfred P. Sloan Foundation and the MONTS seed program administered by the National Science Foundation is gratefully acknowledged.

EXPERIMENTAL SECTION

General experimental details: Tetrahydrofuran (THF) and Et_2O were distilled from K and Na - benzophenone respectively. Dimethylformamide (DMF) was distilled from CaH_2 at 20 mm, while CH_2Cl_2, benzene, toluene, and diisopropylamine were distilled from CaH_2 at atmospheric pressure. The molarities indicated for organolithium reagents were established by titration with 2-butanol. ^1H NMR and ^{13}C NMR were measured at 250 and 63 and 300 and 75 MHz respectively, with Bruker WM-250 and Bruker AC-300 spectrometers. ^1H NMR chemical shifts are reported as δ values in ppm relative to TMS. ^1H NMR coupling constants are reported in Hz and refer to apparent multiplicities and not true coupling constants. Multiplicity is indicated as follows: s (singlet); d (doublet); t (triplet); q (quartet); m (multiplet); app d (apparent doublet); app t (apparent triplet); dd (doublet of doublets); etc. High-resolution mass spectra were measured on a VG Analytical 7070E spectrometer. Infrared spectra were recorded with a Nicolet 5DX FTIR spectrometer. TLC and column chromatography were done with E. Merck silica gel. Radial chromatography was done with a Harrison Research Chromatotron. All reactions were run under an argon or nitrogen atmosphere and concentrations were performed under reduced pressure with a Büchi rotary evaporator.

(E)-and (Z)-1-Isocyano-2-methyl-4-phenyl-4-(*t*-butyldimethylsilyloxy)but-3-ene (5e) An oven-dried, three-necked flask fitted with a thermometer, addition funnel, N_2 inlet adaptor, rubber septum and magnetic stirring bar was charged with 6.22 mL (16.5 mmol) of *n*-butyllithium (2.65 M in hexane), 30 mL of THF and cooled to -78 °C. To this solution was added 0.92 mL (16.5 mmol) of methyl isocyanide in 50 mL of THF at a rate so that the temperature did not exceed -60 °C. The resultant white suspension was stirred at -60 °C for 0.5 h and then 10 mL (66.25 mmol) of TMEDA in 10 mL of THF was added dropwise and stirring was continued for 0.5 h at -78 °C. A solution of 1.46 g (15 mmol) of 1-phenyl-2-buten-1-one in 50 mL of THF was then added dropwise at -78 °C and the resultant mixture was stirred at this temperature for 3.5 h. A solution of 2.25 g (15 mmol) of *t*-butyldimethylchlorosilane in 50 mL of THF was added dropwise and the mixture was allowed to warm slowly to room temperature. After stirring at room temperature for 12 h, the solvents were removed under reduced pressure. The residue was then triturated with hexane and the organic phase was washed sequentially with 75 mL of saturated NH_4Cl, 75 mL of H_2O, 75 mL of brine and then dried over Na_2SO_4. The solvent was removed *in vacuo* to yield 4.09 g (90.6 %) of the crude isonitrile as an oil. This material was subjected to chromatography on silica gel with 20 % ethyl acetate - hexane for elution to give 3.57 g (79 %) of the pure isonitrile **5f** as a colorless oil: ^1H NMR ($CDCl_3$) δ 7.41 (m, 2H, ArCH), 7.28 (m, 3H, ArCH), 4.88 (d, J=9.1 Hz, 1H, vinyl CH), 3.43 (dd with fine structure, J=14.4, 5.1 Hz, 1H, CH_2), 3.31 (dd with fine structure, J=14.4, 7.1 Hz, 1H, CH_2), 3.06 (m, 1H, CH), 1.19 (d,

J=6.8 Hz, 3H, CH_3), 0.99 (s, 9H, $C(CH_3)_3$), -0.04 (s, 3H, CH_3), -0.08 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 156.93 (C), 151.52 (C), 139.01 (C), 128.26 (CH), 128.11 (CH x 2), 126.50 (CH x 2), 11.74 (CH), 47.57 (CH_2), 30.61 (CH), 25.95 (CH x 3), 18.36 (C), 18.13 (CH_3), -3.76 (CH_3), -3.98 (CH_3); IR (film) 3080-2850 (C-H envelope), 2150 (C=N), 1645 (C=C) cm^{-1}. Anal. calcd. for $C_{18}H_{27}NOSi$: C, 71.71; H, 9.03. Found: C, 71.56; H, 9.26.

1-*t*-Butyldimethylsilyloxy-3-(Isocyanomethyl)-2-methylcyclopentene (5a) An oven-dried flask fitted with a thermometer, addition funnel, N_2 adaptor, rubber septum, and a magnetic stirring bar was charged with 4.5 mL (45.0 mmol) of *n*-BuLi (10 M in hexane), 120 mL of THF and cooled to -78 °C. To this solution was added 2.2 mL (42.0 mmol) of methyl isocyanide in 20 mL of THF at a rate so that the temperature did not exceed -60 °C. The resultant white suspension was stirred at -78 °C for 20 min and 20 mL of HMPA in 20 mL of THF was then added dropwise followed by 3.5 mL (36.0 mmol) of 2-methyl-cyclopent-2-en-1-one in 20 mL of THF while maintaining the temperature at -78 °C. The reaction mixture was stirred at -78 °C for 2 h then 6.2 g (42.0 mmol) of t-butyldimethylchlorosilane in 50 mL of pentane was added. The solution was then allowed to warm to 0 °C for 30 min. The reaction mixture was poured into saturated NH_4Cl. The organic layer was separated, washed with brine, and dried over anh. $MgSO_4$. After filtration through Florisil, the solvent was removed under reduced pressure to give the crude isonitrile **5c** as an oil, which was subjected to chromatography on silica gel with 2 % ethyl acetate - hexane for elution to afford 6.4 g (71 %) of the pure isonitrile **6** as a pale yellow oil: ^1H NMR ($CDCl_3$) δ 3.45 (ddt, J=14.67, 5.74, 1.73 Hz, 1H, CH_2), 3.30 (ddt, J=14.67, 6.42, 1.73 Hz, 1H, CH_2), 2.73 (br s, 1H, CH), 2.43 (m, 1H, CH_2), 2.34 (m, 1H, CH_2), 2.20 (m, 1H, CH_2), 1.70 (m, 1H, CH_2), 1.52 (t, J=1.02 Hz, 3H, CH_3), 0.94 (s, 9H, 3 x CH_3), 0.13 (s, 3H, CH_3), 0.12 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 156.45 (s), 149.89 (s), 11.03 (2), 45.15 (t), 44.8 (d), 32.24 (t), 25.62 (q), 24.10 (t), 18.02 (s), 9.87 (q), 4.10 (q), 4.04 (q); IR ($CDCl_3$) 2995, 2930, 2860, 2150, 1690, 1260, 845 cm^{-1}; mass spectrum m/e (EI): 251, 211, 194 167, 73, 59; high resolution mass spectrum calcd. for $C_{14}H_{25}NOSi$: M^+=251.1702. Found: M^+=251.1705.

1-*t*-Butyldimethylsilyloxy-3-(Isocyanomethyl)cyclohex-1-ene (5d) was prepared in a similar manner in 67 % isolated yield: ^1H NMR ($CDCl_3$) δ 4.73 (t, J=1.41 Hz, 1H, vinyl CH), 3.25 (dd, J=6.66, 1.58 Hz, 1H, CH_2), 3.24 (dd, J=6.64, 1.72 Hz, 1H, CH_2), 2.53 (br s, 1H, CH), 2.01 (m, 2H, CH_2), 1.78 (m, 2H, CH_2), 1.61 (m, 1H, CH_2), 1.31 (m, 1H, CH_2), 0.91 (s, 9H, $C(CH_3)_3$), 0.13 (s, 6H, CH_2); ^{13}C NMR ($CDCl_3$) δ 156.33 (C), 153.79 (C), 103.68 (CH), 47.04 (CH_2), 34.93 (CH), 29.73 (CH_2), 25.88 (CH_2), 25.63 (CH x 3), 20.79 (CH_2), 17.97 (C), -4.51 (CH_3), -4.74 (CH_3); IR (film) 2980-2860 (CH envelope), 2150 (C≡N), 1640 (C=C) cm^{-1}. Anal. calcd. for $C_{14}H_{25}NOSi$: C, 66.87; H, 10.02. Found: C, 66.66; H, 10.13.

1-*t*-Butyldimethylsilyloxy-3-(Isocyanomethyl)-2-methylcyclohex-1-ene (5b) was prepared in a similar manner in 70 % isolated yield: ^1H NMR ($CDCl_3$) δ 3.42 (d, J=14.75 Hz, 1H, CH_2), 3.27 (m, J=14.70 Hz, 1H, CH_2), 2.33 (br s, 1H, CH), 2.01 (br s, 2H, CH_2), 1.64 (m, 4H, CH_2), 1.57 (s, 3H, CH_3), 0.91 (s, 9H, $C(CH_3)_3$), 0.09 (s, 6H, CH_3); ^{13}C NMR ($CDCl_3$) δ 156.39 (C), 147.29 (C), 109.67 (C), 44.48 (CH_2), 39.53 (CH), 30.33 (CH), 25.82 (CH_3 x 3), 25.70 (CH_2), 19.99 (CH_2), 18.15 (C), 14.02 (CH_3), -3.78 (CH_3), -3.87 (CH_3); IR (film) 2980-2810 (CH envelope), 2140 (C≡N), 1680 (C=C) cm^{-1}; high resolution mass spectrum calcd. for $C_{15}H_{27}NOS$: M^+=265.4745. Found M^+=265.1855. Anal. calcd. for $C_{15}H_{27}NOSi$: C, 67.86; H, 10.25. Found: C, 67.63; H, 10.13.

1-*t*-Butyldimethylsilyloxy-3-(isocyanomethyl)cyclohept-1-ene (5c) was prepared in a similar manner in 68 % isolated yield: ^1H NMR ($CDCl_3$) δ 4.71 (d, J=4.12 Hz, 1H, vinyl CH), 3.25 (d, J=6.69 Hz, 2H, CH_2), 2.47 (br s, 1H, CH), 2.31 (dd, J=15.67, 10.07 Hz, 1H, CH_2), 2.12 (dd, J=15.72, 7.01 Hz, 1H, CH_2), 1.87 (m, 1H, CH_2), 1.53 (m, 5H, CH_2), 0.88 (s, 9H, $C(CH_3)_3$), 0.11 (s, 6H, CH_3); ^{13}C NMR ($CDCl_3$) δ 157.16 (C), 156.23 (C), 108.52 (CH), 47.63 (CH_2), 36.37 (CH), 35.22 (CH_2), 31.19 (CH_2), 28.87 (CH_2), 25.68 (3 x CH_3), 24.73 (CH_2), 17.96 (C), -4.42 (CH_3), -4.45 (CH_3); IR (film) 2955-2850 (CH

envelope), 2140 (C≡N), 1630 (C=C) cm^{-1}; high resolution mass spectrum calcd. for $C_{13}H_{19}NO_2$: M^+=221.30188. Found: M^+=221.1400.

3-Trimethylacetyl-3aα,4,5,6,7,7aα-hexahydro-1H-isoindol-4-one (2d) and 3-Trimethylacetyl-2,4,5,6,7,7a-hexahydro-1H-isoindol-4-one (10) An oven-dried NMR tube fitted with a rubber septum was purged with N_2 and was then charged with 0.1832 g (0.73 mmol) of 1-*t*-butyldimethylsilyloxy-3-(isocyanomethyl)cyclohex-1-ene (**5d**), 0.064 mL (0.80 mmol) of pyridine, 0.099 mL (0.80 mmol) of trimethylacetyl chloride, and 0.75 mL of $CDCl_3$. The reaction was monitored by NMR and was shown to be complete after 150 min. The α-ketoimidoyl chloride **4d** was formed quantitively: ^1H NMR ($CDCl_3$) δ 4.65 (br s, 1H, vinyl CH), 3.32 (m, 2H, CH_2), 2.41 (br s, 1H, CH), 1.82 (m, 2H, CH_2), 1.59 (m, 2H, CH_2), 1.49 (m, 2H, CH_2), 1.13 (s, 9H, $C(CH_3)_3$), 0.74 (s, 9H, $C(CH_3)_3$), 0.05 (s, 6H, CH_3). The reaction mixture was diluted with 3.0 mL of CH_2Cl_2, 3.0 mL of 1,2-dichloroethane, cooled to -78 °C and was then added dropwise, *via* cannula, to a stirred solution of 2.15 mL (1.09 mmol) of $AgBF_4$ (0.5095 M in 1,2-dichloroethane) and 2 mL of CH_2Cl_2 maintained at -78 °C. The reaction mixture was stirred for 8 h at -20 °C. It was then quenched with 15 mL of 10 % aq. $KHCO_3$ and extracted with 3 x 15 mL of CH_2Cl_2. The combined organic phases were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure leaving crude product mixture as an oil. Capillary GC indicated the presence of two compounds in a ratio of 5.3:1. The residue was subject to reverse phase chromatography on C18 with 20 % methanol - acetonitrile for elution to provide two fractions. The first fraction furnished 0.0952 g (59 %) of 3-trimethylacetyl-3aα,4,5,6,7,7aα-hexahydro-1H-isoindol-4-one (**2d**) as an oil: ^1H NMR ($CDCl_3$) δ 4.57 (br s, 1H, NH), 4.46 (dd, J=17.46, 5.43 Hz, 1H, CH_2), 3.99 (dd, J=17.46, 0.72 Hz, 1H, CH_2), 2.65 (app ddt, J=18.49, 6.08, 2.53 Hz, 1H, CH), 2.40 (m, 2H, CH_2), 1.92 (m, 2H, CH_2), 1.67 (m, J=6.96 Hz, 2H, CH_2), 1.30 (s, 9H, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$) δ 207.54 (C), 204.53 (C), 169.52 (C), 88.58 (C), 67.84 (CH_2), 50.66 (CH), 44.24 (C), 38.50 (CH_2), 29.51 (CH_2), 26.45 (CH_3 x 3), 24.60 (CH_2); IR (CCl_4) 3410 (N-H), 2980-2865 (C-H envelope), 1725 (C=O), 1695 (C=O) cm^{-1}; high resolution mass spectrum calcd. for $C_{13}H_{19}NO_2$: M^+=221.3019. Found: M^+=221.1416. The second fraction furnished 0.0221 g (13.7 %) of 3-trimethylacetyl-2,4,5,6,7,7a-hexahydro-1H-isoindol-4-one (**10**) as an oil: ^1H NMR ($CDCl_3$) δ 4.26 (ddd, J=19.88, 3.35, 1.53 Hz, 1H, CH_2), 4.06 (dd, J=19.89, 1.33 Hz, 1H, CH_2), 3.68 (dd, J=4.72, 1.98 Hz, 1H, CH), 2.53 (m, 2H, CH_2), 2.26 (m, 2H, CH and CH_2 superimposed), 2.04 (m, 1H, CH_2), 1.83 (m, 2H, CH_2), 1.27 (s, 9H, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$) δ 207.05 (C), 206.30 (C), 162.90 (C), 61.95 (CH_2), 52.88 (C), 52.73 (CH), 43.57 (CH_2), 29.21 (CH), 27.22 (CH_3 x 3), 26.41 (CH_2), 24.07 (CH_2); IR ($CDCl_3$) 2965-2860 (CH envelope), 1720 (C=O), 1685 (C=O), 1650 (C=N) cm^{-1}. Anal. calcd. for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65. Found: C, 70.41; H, 8.55. It should be noted that when pyridine was not present during the insertion reaction, the ratio of **2d** to **10** was 1:1.6.

3-(3-Carbomethoxypropanoyl)-3aα,4,5,6,7,7aα-hexahydro-3a-methyl-1H-isoindol-4-one (2b) An oven-dried NMR tube fitted with a rubber septum, was purged with N_2, and then charged with 0.2050 g (0.774 mmol) of 1-*t*-butyldimethylsilyloxy-3-(isocyanomethyl)-2-methylcyclohex-1-ene (**5b**), 0.50 mL of $CDCl_3$, and 0.1280 g (0.851 mmol) of 2-carbomethoxypropionyl chloride. The reaction was monitored by NMR and was found to be complete after 230 min to provide the α-ketoimidoyl chloride **4b** in quantitative yield: ^1H NMR ($CDCl_3$) δ 3.66 (dd, J=14.46, 3.86 Hz, 1H, CH_2), 3.52 (s, 3H, CH_3), 3.51 (dd, J=14.46, 8.79 Hz, 1H, CH_2), 3.08 (t, J=6.60 Hz, 2H, CH_2), 2.53 (app q, J=6.63 Hz, 2H, CH_2), 2.36 (br s, 1H, CH), 1.92 (br s, 2H, CH_2), 1.58 (s, 3H, CH_3), 1.57 (m, 4H, CH_2), 0.82 (s, 9H, $C(CH_3)_3$), 0.01 (s, 6H, CH_3). The reaction mixture was diluted with 3.5 mL of CH_2Cl_2, 3.5 mL of 1,2-dichloroethane, cooled to -78 °C and was then added dropwise, *via* cannula, to a solution of 2.28 mL (1.16 mmol) of $AgBF_4$ (0.5095 M in 1,2-dichloroethane), and 2.3 mL of CH_2Cl_2 maintained at -78 °C. The reaction mixture was stirred for 18 h at -20 °C. It was then quenched with 20 mL of 10 % aq. $KHCO_3$ and extracted with 3 x 20 mL of CH_2Cl_2. The combined organic phases were washed with brine and dried over Na_2SO_4. The solvents were removed *in vacuo* leaving 0.2817 g (89 % pure by capillary GC) of the crude pyrroline as an oil. This was subjected to radial chromatography (10 % ethyl acetate - toluene for elution) to give 0.1700 g (83 %) of the pure Δ^1-pyrroline **2b**: ^1H NMR ($CDCl_3$) δ 4.18 (dd,

J=17.66 Hz, 1H, CH_2), 3.83 (dd, J=17.67 Hz, 1H, CH_2), 3.62 (s, 3H, CH_3), 3.25 (dt, J=18.74, 6.60 Hz, 1H, CH_2), 3.10 (dt, J=18.75, 6.44 Hz, 1H, CH_2), 2.61 (t, J=6.46 Hz, 2H, CH_2), 2.42 (m, 2H, CH and CH_2 superimposed, as shown by COZY experiments), 2.22 (m, 1H, CH_2), 1.75 (m, 3H, CH_2), 1.45 (m, 1H, CH_2), 1.25 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 209.54 (C), 197.16 (C), 173.86 (C), 172.91 (C), 65.93 (CH_2), 63.39 (C), 51.82 (CH_3), 50.26 (CH), 39.53 (CH_2), 33.69 (CH_2), 27.61 (CH_2), 27.34 (CH_2), 27.34 (CH_2), 23.44 (CH_2), 18.77 (CH_3); IR (film) 2960-2840 (C-H envelope), 1760 (C=O), 1720 (C=O), 1680 (C=O), 1650 (C=N) cm^{-1}; high resolution mass spectrum calcd. for $C_{14}H_{19}NO_4$ M^+=265.3118. Found M^+=265.1313. Anal. calcd. for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22. Found: C, 63.15; H, 7.37.

1-(3-Carbomethoxy-2-methylpropenoyl)-3,3aα,4,5,6,6aα-hexahydro-6a-methylcyclopenta[c]pyrrol-6-one (**2a**) was prepared in a similar manner to provide 101.7 % of the crude pyrroline (96 % pure by capillary GC) as an oil. This was subjected to radial chromatography (5 % ethyl acetate - toluene for elution) to give 0.1953 g (86 %) of the pure pyrroline **2a**: ^1H NMR ($CDCl_3$) δ 6.48 (q, J=1.42 Hz, 1H, vinyl CH), 4.30 (dd, J=17.54, 6.99 Hz, 1H, CH_2), 4.05 (dd, J=17.54, 2.43 Hz, 1H, CH_2), 3.74 (s, 3H, CH_3), 2.70 (m, 1H, CH), 2.29 (m, 3H, CH_2), 2.23 (d, J=1.42 Hz, 3H, CH_3), 1.60 (m, 1H, CH_2), 1.34 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 213.48 (C), 193.02 (C), 170.11 (C), 166.00 (C), 149.17 (C), 130.34 (CH), 69.29 (C), 67.39 (CH_2), 51.86 (CH_3), 47.25 (CH), 36.90 (CH_2), 25.49 (CH_2), 18.91 (CH_3), 12.93 (CH_3); IR (film) 3050-2850 (C-H envelope), 1740 (C=O), 1730 (C=O), 1670 (C=O), 1635 (C=N), 1620 (C=C) cm^{-1}; high resolution mass spectrum calcd. for $C_{14}H_{17}NO_4$: M^+=263.2959. Found M^+=263.1195. Anal. calcd. for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51. Found: C, 63.77; H, 6.67.

1-Trimethylacetyl-3,3aα,4,5,6,6aα-hexahydro-6a-methylcyclopenta[c]pyrrol-6-one (**2f**) was prepared in a similar manner in 87 % isolated yield: ^1H NMR ($CDCl_3$) δ 4.21 (dd, J=17.28, 6.66 Hz, 1H, CH_2), 4.13 (dd, J=17.28, 2.07 Hz, 1H, CH_2), 2.56 (m, 1H, CH_2), 2.27 (m, 2H, CH_2), 2.13 (m, 1H, CH_2), 1.51 (m, 1H, CH_2), 1.30 (s, 3H, CH_3), 1.18 (s, 9H, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$) δ 214.06 (C), 206.56 (C), 170.58 (C), 69.51 (C), 67.11 (CH_2), 47.07 (CH_3), 44.14 (C), 37.03 (CH_2), 26.40 (3 x CH_3), 25.47 (CH_2), 19.05 (CH); IR ($CDCl_3$) 2980-2880 (CH envelope), 1740 (C=O), 1690 (C=O), 1620 (C=N) cm^{-1}; high resolution mass spectrum calcd. for $C_{13}H_{19}NO_2$: M^+=221.3019. Found M^+=221.1415. Anal. calcd. for $C_{13}H_{19}NO_2$: C, 70.55; H, 8.65. Found: C, 70.47; H, 8.69.

5-Trimethylacetyl-4-benzoyl-3-methyl-3β,4α-dihydro-2H-pyrrole (**2e**) was prepared in an analogous manner to afford 92 % of the crude pyrroline as an oil. This was subjected to reverse phase chromatography on C18 with 20 % methanol - acetonitrile for elution to give 0.1098 g (81 %) of the pure pyrroline **2e**: ^1H NMR ($CDCl_3$) δ 7.95 (m, 2H, ArCH), 7.58 (m, 1H, ArCH), 7.48 (m, 2H, ArCH), 4.63 (d with fine structure, J=5.49, 1.83 Hz, 1H, CH), 4.43 (ddd, J=17.28, 7.64, 2.12 Hz, 1H, CH_2), 3.84 (dd with fine structure, J=17.28, 4.91, 1.35 Hz, 1H, CH_2), 2.45 (m, J=7.05, 5.46 Hz, 1H, CH), 1.33 (s, 9H, $C(CH_3)_3$), 1.18 (d, J=7.00 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 204.27 (C), 198.94 (C), 170.49 (C), 136.44 (C), 133.45 (CH), 128.77 (CH x 2), 128.71 (CH x 2), 70.22 (CH_2), 63.54 (CH), 44.06 (C), 37.59 (CH), 26.88 (CH_3 x 3), 19.73 (CH_3); IR ($CDCl_3$) 3020-2840 (CH envelope), 1675 (C=O), 1665 (C=O), 1620 (C=N), 1595 (C=C Ar), 1580 (C=C Ar) cm^{-1}; high resolution mass spectrum calcd. for $C_{17}H_{21}NO_2$: M^+=271.3624. found M^+=271.1570. Anal. calcd. for $C_{17}H_{21}NO_2$: C, 75.24; H, 7.80. Found: C, 75.10; H, 7.67.

1-(2-Methylpropanoyl)-3,3aα,4,5,6,7,8,8aα-octahydrocyclohepta[c]pyrrol-8-one (**2c**) An oven-dried NMR tube fitted with a rubber septum was purged with N_2 and then charged with 0.2772 g (1.046 mmol) of 1-t-butyldimethylsilyloxy-3-(isocyanomethyl)cyclohept-1-ene (**5c**), 0.0919 mL (1.15 mmol) of pyridine, 0.1205 mL (1.15 mmol) of 2-methylpropanoyl chloride, and 0.70 mL of $CDCl_3$. The insertion reaction was monitored by NMR and was found to be complete after 210 min. The reaction mixture was then diluted with 4 mL of CH_2Cl_2, 4 mL of 1,2-dichloroethane, cooled to -78 °C and was added dropwise, *via* cannula to a solution of 3.079 mL (1.57 mmol) of $AgBF_4$ (0.5095 M in 1,2-dichloroethane), and 3 mL of CH_2Cl_2 maintained at -78 °C. The reaction mixture was stirred for 18 h at -20 °C. It was then quenched with 25 mL of 10 % aq. $KHCO_3$ and extracted with 3 x 25 mL of CH_2Cl_2. The combined

organic phases were washed with brine and dried over Na_2SO_4. The solvents were removed *in vacuo* leaving 0.1967 g of the crude pyrroline as an oil. This was subjected to reverse phase chromatography on C18 with 20 % methanol - acetonitrile for elution to give 0.1806 g (78 %) of the pure pyrroline **2c**: ^{1}H NMR ($CDCl_3$) δ 4.48 (d, J=7.10 Hz, 1H, CH), 4.35 (dt, J=20.85, 1.95 Hz, 1H, CH_2), 4.22 (dd, J=20.91, 4.32 Hz, 1H, CH_2), 3.73 (septet, J=6.92 Hz, 1H, CH), 2.73 (dd with fine structure, J=18.75, 4.41, 1.68 Hz, 1H, CH_2), 2.63 (dd with fine structure, J=18.81, 3.65, 1.67 Hz, 1H, CH_2), 2.28 (broad m, 1H, CH), 2.01 (m, 2H, CH_2), 1.70 (m, 2H, CH_2), 1.52 (m, 1H, CH_2), 1.31 (m, 1H, CH_2), 1.03 (d, J=6.92 Hz, 3H, CH_3), 1.01 (d, J=6.92 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 209.17 (C), 204.75 (C), 159.51 (C), 59.36 (CH_2), 55.49 (CH), 47.47 (CH_2), 33.97 (CH_2), 32.97 (CH), 30.76 (CH), 29.29 (CH_2), 23.16 (CH_2), 18.58 (CH_3); IR ($CDCl_3$) 2980-2860 (CH envelope), 1765 (C=O), 1750 (C=O), 1695 (C=N) cm^{-1}; high resolution mass spectrum calcd. for $C_{13}H_{19}NO_2$: M^+=221.30188. Found M^+= 221.1400.

7-Trimethylacetyl-8-azaspiroundeca-1,4,7-trien-3-one (19a) An oven-dried NMR tube fitted with a rubber septum was purged with Ar and then charged with 0.138 g (0.50 mmol) of 3-(4-*t*-butyldimethylsilyloxyphenyl)-1-isocyanopropane (**17a**), 0.068 mL (0.55 mmol) of trimethylacetyl chloride and 0.25 mL of $CDCl_3$. The insertion reaction was monitored by NMR and found to be complete after 180 min. The volatile components were then removed from the imidoyl chloride *in vacuo*. The crude imidoyl chloride was diluted with 2.25 mL CH_2Cl_2, 2.25 mL 1,2-dichloroethane and cooled to -78 °C. This solution was then added dropwise *via* syringe to a stirred solution of 1.50 mL (0.75 mmol) $AgBF_4$ (0.50 M in 1,2-dichloroethane) and 1.50 mL CH_2Cl_2 maintained at -78 °C. After the addition, the reaction mixture was stirred for 1 h at -78 °C and then maintained at -20 °C for 2 h. The reaction mixture was then warmed to 0 °C and was maintained at this temperature for 20 h whereupon it was quenched with 15 mL of 10 % aq. $KHCO_3$. The resulting white-gray slurry was subsequently filtered through a pad of celite. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (4 x 10 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel (20 % ethyl acetate - hexane for elution) to give the cyclized product (**19a**) (86 mg, 70 %) as a yellow crystalline solid: m.p. 51-54 °C; ^{1}H NMR ($CDCl_3$) δ 7.18 (d, J=8.4 Hz, 2H, CH), 6.98 (d, J=8.4 Hz, 2H, CH), 3.35 (m, 2H, CH_2), 2.77 (app t, J=7.4 Hz, 2H, CH_2), 1.96 (m, 2H, CH_2), 1.33 (s, 9H, 3 x CH_3); ^{13}C NMR ($CDCl_3$) δ 177.0, 156.1, 149.6, 137.0, 129.2, 121.5, 40.6, 38.9, 31.4, 30.4, 30.0, 26.2; IR(KBr) 3032, 2980, 2930, 2874, 1744, 1680, 1509, 1481, 1454, 1368, 1281, 1228, 1198, 1167, 1126 cm^{-1}; mass spectrum m/e (EI) 245, 161, 134, 107, 85, 57, 41; high resolution mass spectrum calcd. for $C_{15}H_{19}NO_2$: M^+=245.1416. Found: M^+=245.1410.

1-Methoxy-7-trimethylacetyl-8-azaspiroundeca-1,4,7-trien-3-one (19b) was prepared in a similar manner from 3-(2-methoxy-4-*t*-butyldimethylsilyloxyphenyl)-1-isocyanopropane (**17b**) in 82 % isolated yield: m.p. 138-141 °C; ^{1}H NMR ($CDCl_3$) δ 6.63 (d, J=9.9 Hz, 1H, CH), 6.19 (d, J=9.8 Hz, 1H, CH), 5.57 (s, 1H, CH), 3.65 (s, 3H, CH_3), 2.13 (m, 2H, CH_2), 1.75 (m, 4H, 2 x CH_2), 1.19 (s, 9H, 3 x CH_3); ^{13}C NMR ($CDCl_3$) δ 205.1, 187.2, 177.3, 161.5, 145.6, 127.5, 102.4, 55.6, 49.0, 46.3, 43.6, 33.8, 27.4, 17.9; IR(KBr) 3062, 2956, 1684, 1662, 1638, 1594, 1456, 1438, 1368, 1234, 1214, 1090, 1016, 930, 880 cm^{-1}; mass spectrum m/e (EI) 275, 191, 164, 137, 57, 41; high resolution mass spectrum calcd. for $C_{16}H_{21}NO_3$: M^+=275.1521. Found: M^+=275.1526.

1-(Trimethylacetyl)-7-methoxy-8-*t*-butyldimethylsilyloxy-4,5-dihydro-3H-2-benzazepine (20a) Sequential acylation (Me_3CCOCl)-$AgBF_4$ mediated cyclization of 3-(3-methoxy-4-*t*-butyldimethylsiloxyphenyl)-1-isocyanopropane (**17c**) in an analogous manner furnished 61 % of the 2-acylbenzazepine **20a**: ^{1}H NMR ($CDCl_3$) δ 6.82 (s, 1H, CH), 6.68 (s, 1H, CH), 3.81 (s, 3H, CH_3), 3.38 (app t, J=6.7 Hz, 2H, CH_2), 2.55 (app t, J=7.3 Hz, 2H, CH_2), 2.34 (m, 2H, CH_2), 1.25 (s, 9H, 3 x CH_3), 0.95 (s, 9H, 3 x CH_3), 0.11 (s, 6H, 2 x CH_3); ^{13}C NMR ($CDCl_3$) δ 209.4, 170.8, 152.2, 143.1, 134.5, 125.2, 120.2, 112.6, 55.4, 49.8, 43.7, 34.7, 30.6, 27.1, 25.7, 18.4, -4.6; IR(film) 2955, 2858, 1694, 1564, 1508, 1464, 1344, 1325, 1284, 1261, 1087, 907, 862, 840, 808, 784 cm^{-1}; mass spectrum m/e (EI) 389, 332, 304, 276, 248, 233, 204, 73, 57, 41; high resolution mass spectrum calcd. for $C_{22}H_{35}NO_3Si$: M^+=389.2386. Found: M^+=389.2386.

1-(Trimethylacetyl)-7,8-methylenedioxy-4,5-dihydro-3H-2-benzazepine (20b) Sequential acylation (Me_3CCOCl) - $AgBF_4$ mediated cyclization of 3-(3,4-methylenedioxyphenyl)-1-isocyanopropane (**17d**) in an analogous manner furnished 71 % of the 2-acylbenzazepine **20b**: ^1H NMR ($CDCl_3$) δ 6.82 (s, 1H, CH), 6.68 (s, 1H, CH), 5.94 (s, 2H, CH_2), 3.37 (app t, J=6.7 Hz, 2H, CH_2), 2.48 (app t, J=7.3 Hz, 2H, CH_2), 2.31 (m, 2H, CH_2), 1.25 (s, 9H, 3 x CH_3); ^{13}C NMR ($CDCl_3$) δ 209.0, 169.9, 148.7, 146.0, 135.3, 126.3, 109.3, 107.9, 101.3, 49.6, 43.9, 34.7, 30.6, 27.1; IR (film) 2954, 2864, 2362, 2338, 1686, 1654, 1596, 1558, 1540, 1506, 1484, 1362, 1240, 1040, 932, 882 cm^{-1}; mass spectrum m/e (EI) 273, 188, 160, 131, 103, 57, 41; high resolution mass spectrum calcd. for $C_{16}H_{19}NO_3$: M^+=273.1365. Found: M^+=273.1354.

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