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A Convergent Approach to Heterocycle Synthesis via Silver Ion Mediated α-Keto Imidoyl Halide–Arene Cyclizations. An Application to the Synthesis of the Erythrinane Skeleton†

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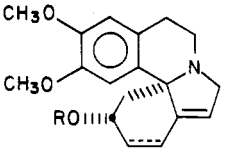
α-Keto imidoyl halides formed by the reaction of representative 2-phenylethyl and related isocyanides with acyl halides undergo facile cyclization induced by silver salts to provide the corresponding heterocycles in good to excellent yield. An efficient synthesis of the erythrinane skeletal system which relies upon the sequential utilization of this method followed by an azomethine ylide [3 + 2] cycloaddition reaction is described.

The polycondensed framework of the erythrina alkaloids **1** has remained a challenging target for efficient chemical synthesis.[1] In an earlier report, we described the successful utilization of the intramolecular azomethine ylide [3 + 2] cycloaddition reaction (e.g., **2** → **3**) for the synthesis of the physostigmine ring system.[2,3] We subsequently



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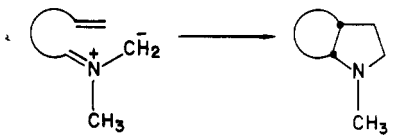
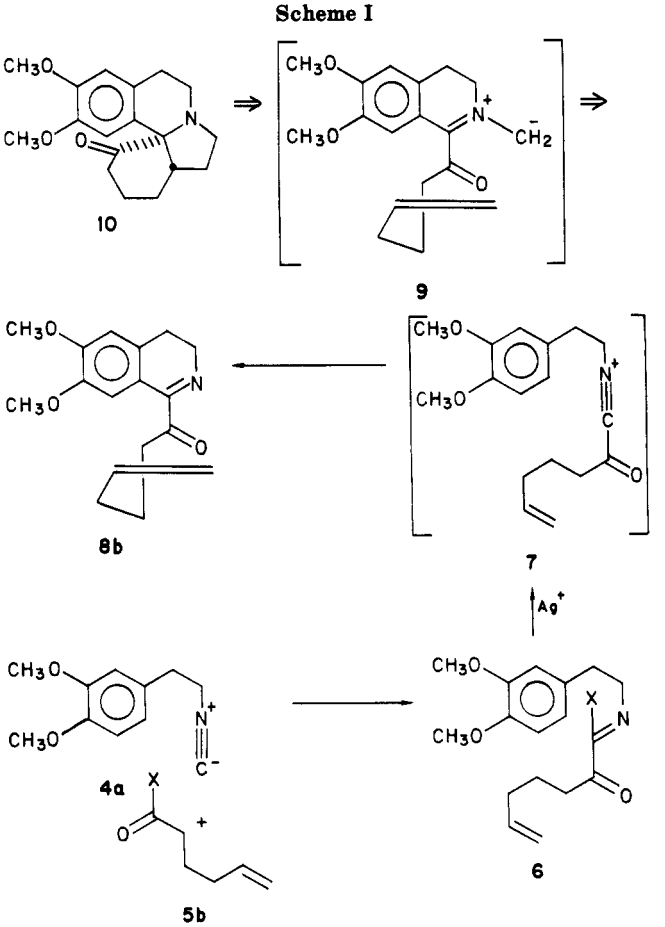


2 **3**

revealed that heteroannulations involving "nonstabilized" azomethine ylides are frequently restricted to substrates lacking hydrogens α to the iminium moiety.[3,4] In light of this constraint, we chose to investigate the intramolecular cyclization of α-keto iminium ylides (e.g., **9**) as a means for constructing the erythrinane skeleton.[5,6] Unfortunately, there existed a diminuative number of general methods for the synthesis of 1-acyldihydroisoquinolines of the type required for this purpose. In principle, the cyclization of an appropriately substituted arene onto a highly reactive acylnitrilium cation (e.g., **7** → **8**) would provide a convenient pathway to these intermediates. The required cations **7** were expected to be accessible via the

Scheme I



silver cation mediated ionization of α-keto imidoyl halides prepared by the reaction of organic isonitriles with acyl

† This manuscript is dedicated to the memory of Professor Robert V. Stevens.

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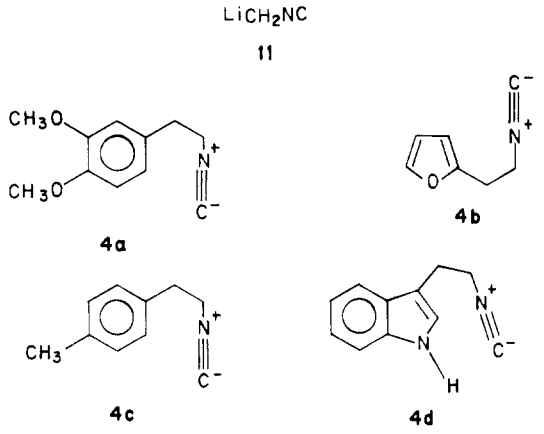
halides (Scheme I). Herein we report our observations on the preparative scope and limitations of this new method for heterocycle synthesis and describe its application to the elaboration of the erythrinane skeletal system.

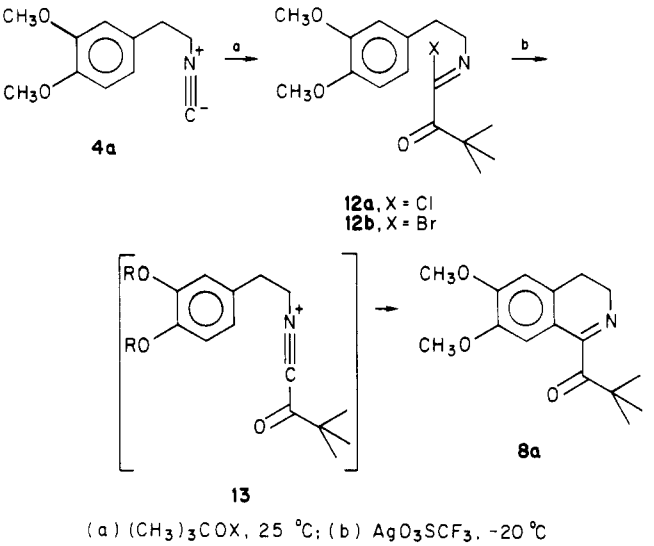
I. α-Keto Imidoyl Halide Heteroannulations

The isonitriles utilized in our studies were accessible by two highly complementary and general methods. Relatively simple isonitriles (e.g., **4a** and **4b**) were advantageously prepared by the dehydration of the corresponding formamide with $POCl_3$ in the presence of Et_3N.[7,8] Alternatively, the requisite isonitriles could be acquired by way of nucleophilic displacement reactions involving lithiomethyl isocyanide (**11**).[9] The isonitriles **4c** and **4d**[10]



were prepared by the action of **11** on the appropriate organic substrate. To this end, exposure of gramine methiodide[11] to 2.2 equiv of **11** in THF at −78 °C followed by careful protonation using AcOH furnished 2-(3-indoyl)-ethyl isocyanide (**4d**) in 64% yield. The isonitrile **4c** was similarly prepared in 71% isolated yield by treatment of α-bromo-*p*-xylene with lithiomethyl isocyanide (**11**) in THF (−78 °C → 0 °C) followed by flash chromatography.[12]

Organic isonitriles have been known to react with electrophilic species for many years.[13,14] However, despite the apparent nucleophilicity of the isonitrile moiety, the utilization of this functional group in carbon–carbon bond-forming operations has remained quite limited. We have found that acyl bromides and chlorides react with representative isonitriles to privide the corresponding α-keto imidoyl halides in high yield at temperatures as low as 0 °C.[15,16] As expected, acyl bromides were found to react with somewhat greater facility than acyl chlorides in the above context.[18] The product selectivity of the isonitrile–acyl halide insertion reaction was found to be coupled to both solvent polarity and reaction temperature. Treatment of 2-(3,4-dimethoxyphenyl)ethyl isocyanide (**4a**) in CH_2Cl_2, ether, or toluene solution with either trimethylacetyl bromide (0 °C, 0.5 h) or trimethylacetyl chloride (25 °C, 18 h) afforded the anticipated imidoyl halides **12a,b** in >90% yield.[17,18] In contrast, exposure of

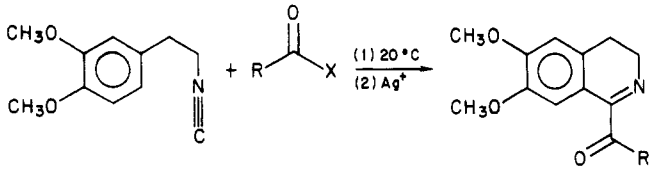


the isonitrile **4a** to trimethylacetyl chloride in acetonitrile or nitromethane furnished the imidoyl chloride **12a** in modest to low yields (NMR). The cyclization of **12a** or **12b** to the dihydroisoquinoline **8a** could be accomplished under several sets of reaction conditions. Under the mildest of these, the crude adducts **12a** or **12b** formed in the above manner were treated directly with 1.1 equiv of silver fluoroborate or silver triflate (CH_2Cl_2, −20 °C, 18 h), to afford the dihydroisoquinoline **8a** (82% overall from **4a**).

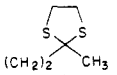
Efforts to effect the silver ion mediated cyclization of imidoyl chlorides such as **12a** at initial temperatures above 0 °C led to the production of intractable product mixtures. It is of interest that no detectable quantity (HPLC, capillary GC, and 300 MHz NMR) of the isomeric 1-acyl-7,8-dimethoxydihydroisoquinoline was formed under these reaction conditions. As an alternative to the use of silver salts, the cyclization of **12b** could be achieved, albeit in lower yield, in the presence of a catalytic quantity of CF_3SO_3H (CH_2Cl_2, 0 °C, 71%) or $SnCl_4$ (1 equiv, CH_2Cl_2, −78 °C → 0 °C, 31%). The formation of 1-acyldihydroisoquinolines under the ionizing set of reaction conditions involving silver salts can be rationalized by invoking transient acylnitrilium cations (e.g., **13**) as intermediates.[19] In contrast, the cyclization of the α-keto imidoyl halides **12a** or **12b** in the presence of Brønsted or Lewis acids presumably proceed via the corresponding protonated or coordinated halo iminium derivatives. The preparative generality of the above sequence with regard to the acyl

(1) An elegant synthesis of the erythrinane skeleton which utilizes a thionium ion cyclization has recently been published: Tamura, Y.; Maeda, H.; Akai, S.; Ishibashi, H. *Tetrahedron Lett.* **1982**, *23*, 2209.
(2) Smith, R.; Livinghouse, T. *J. Org. Chem.* **1983**, *48*, 1554.
(3) Smith, R.; Livinghouse, T. *Tetrahedron* **1985**, *41*, 3559.
(4) The failure of certain nonstabilized azomethine ylides to under internal [3 + 2] cycloadditions with nonactivated dipolarophiles has also been noted by others: Padwa, A.; Haffmans, G.; Tomas, M. *J. Org. Chem.* **1984**, *49*, 3314. Vedejs, E.; West, F. G. *J. Org. Chem.* **1983**, *48*, 4773.
(5) The successful utilization of "stabilized" azomethine ylides in intramolecular [3 + 2] cycloaddition reactions has recently been described: Confalone, P. N.; Huie, E. M. *J. Am. Chem. Soc.* **1984**, *106*, 7175 and references therein.
(6) An alternative method for the pyrolytic generation of stabilized azomethine ylides has appeared: DeShong, P.; Kell, D. A.; Sidler, D. R. *J. Org. Chem.* **1985**, *50*, 2309.
(7) Ugi, I.; Meyr, R.; Lipinski, M.; Bodesheim, F.; Rosendahl, F. K. *Org. Synth.* **1961**, *41*, 13.
(8) van Leusen, A. M.; Schut, J. *Tetrahedron Lett.* **1976**, 285.
(9) Schollkopf, U. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 339.
(10) Westling, M.; Livinghouse, T. *Tetrahedron Lett.* **1985**, *26*, 5389.
(11) Geissman, T. H.; Armen, H. *J. Am. Chem. Soc.* **1952**, *74*, 3916.
(12) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(13) Havlike, A.; Wald, M. M. *J. Am. Chem. Soc.* **1955**, *77*, 5171.
(14) Nef, J. U. *Justus Liebigs Ann. Chem.* **1982**, *270*, 267.
(15) The first examples of this reaction were reported by Ugi.[16] The reaction conditions employed in this early account were far harsher than necessary (benzene, reflux) and the product yields were lowered as a consequence.
(16) Ugi, I.; Fetzer, U. *Chem. Ber.* **1961**, *94*, 1116.
(17) It should be emphasized that the presence of trace contaminants in impure samples of organic isonitriles lead to greatly diminished yields of α-keto imidoyl halides.
(18) The greater reactivity of acyl bromides permits the desired insertion reactions to be conducted at temperatures as low as 0 °C. In some instances this characteristic has proven advantageous.
(19) We presently have no definitive evidence for the intermediacy of acylnitrilium cations in the silver ion mediated cyclization of **8a**.

Table I



4a 5 8a-e

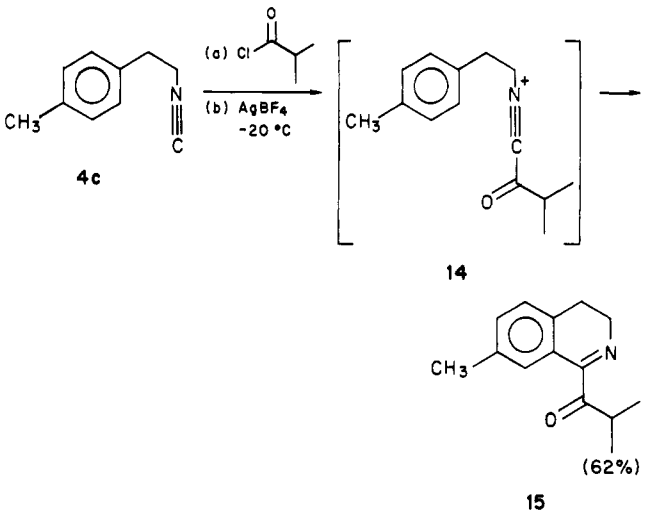
	acyl chloride 5 R	cyclization conditions	isolated % yield
a	$C(CH_3)_3$	$Ag^+O_3SC_3^-$	82
		HO_3SCF_3	71
		$SnCl_4$[a]	31
b	$(CH_2)_3CH{=}CH_2$	$Ag^+O_3SCF_3^-$	87
c	$(CH_2)_3C{\equiv}CH$	$Ag^+O_3SCF_3^-$	75
d		$Ag^+BF_4^-$	61
e	SC_2H_5[b]	$Ag^+O_3SCF_3^-$	57
f	OCH_3[c]		0

[a] In our hands the attempted cyclization of the imidoyl chloride **8a** using numerous alternative Lewis acids (e.g., $TiCl_4$, TiF_4, $AlCl_3$, $EtAlCl_2$, $BF_3{\cdot}OEt_2$, $Zn(OTf)_2$, or $Mg(OTf)_2$) afforded very poor yields of the dihydroisoquinoline **8a**. [b] In this instance it was necessary to employ an excess of the pure acyl chloride to achieve the preparation of the imidoyl chloride. [c] The formation of imidoyl chloride was not observed even when this acyl chloride was employed as the reaction solvent.

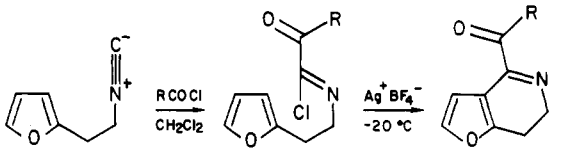
moiety was subsequently demonstrated by utilizing a variety of representative acyl chlorides **5a–f** (Table I).[20,21]

The foregoing examples illustrate the exceptionally mild nature of these cyclization conditions with regard to both reaction temperature and, more significantly, functional group compatibility. The participation of electron-rich aromatic nuclei in Bischler–Napieralski and related cyclization reactions is well known.[22] 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%).[22] The isonitrile **4c** was therefore prepared (p-$CH_3C_6H_4CH_2Br$, $LiCH_2NC$, THF) with the intent of providing a more lucid indication of the synthetic generality of "acylnitrilium ion" cyclizations. It is significant that treatment of **4c** with isobutyroyl chloride followed by exposure of the resultant imidoyl chloride to silver fluoborate at −20 °C furnished the dihydroisoquinoline **15** in 62% isolated yield.[23]

The well-known susceptability of the furan nucleus toward acid-catalyzed polymerization has traditionally stifled the successful utilization of these species in Bischler–Napieralski-type cyclizations.[24] As a direct consequence of this potential limitation, cyclization reactions involving 2-(2-furyl)ethyl isocyanide (**4b**) with representative acyl halides were examined. In complete accord with our prior observations, sequential treatment of **4b** with trimethylacetyl chloride followed by silver fluoborate (CH_2Cl_2–

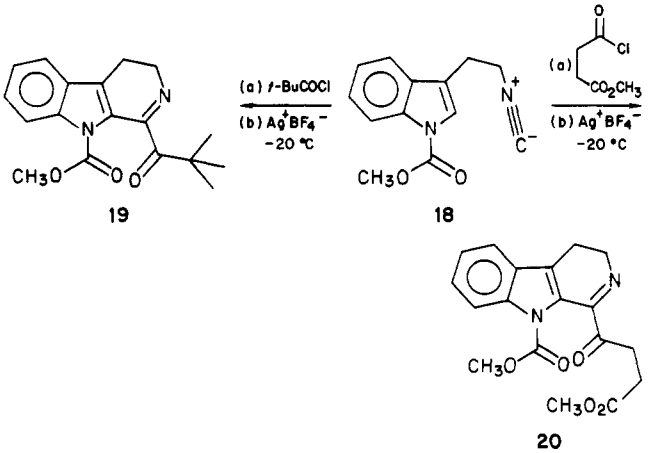


CH_3NO_2, −20 °C) afforded the furanodihydropyridine **17a** in 63% isolated yield. Similarly, exposure of **4b** to benzoyl bromide followed by silver fluoborate gave the furanodihydropyridine **17b** in 49% isolated yield.



4b 16a, R = $C(CH_3)_3$; 16b, R = C_6H_5 17a, R = $C(CH_3)_3$; 17b, R = C_6H_5

The isocarboline nucleus represents an essential structural subunit within the myriad of alkaloids belonging to the corynanthine, eburnia, and rauwolfia families, among others. The utility of α-keto imidoyl halide heterocycle annulations for the elaboration of functionalized isocarboline derivatives was readily 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 **4d** in conjunction with acyl halides. To circumvent this difficulty, **4d** was converted into the corresponding N-carbomethoxy derivative **18** via treatment with 1 equiv of n-BuLi followed by methyl chloroformate (99.5% isolated yield). Treatment of the N-carbomethoxytryptophyl



isocyanide (**18**) with 1 equiv of trimethylacetyl chloride (CH_2Cl_2, 25 °C, 18 h) followed by the addition of silver fluoborate (1.05 equiv, −20 °C, 3 h) secured the isocarboline **19** in 67% yield after purification. In a further example, acylation of **18** with β-carbomethoxypropionyl chloride followed by silver ion promoted cyclization at −20 °C furnished the isocarboline derivative **20** (60%).

(20) All new compounds exhibited satisfactory NMR and IR spectra as well as elemental (C, H) analyses or exact mass.

(21) In none of these instances could any detectable quantity of isomeric 7,8-dimethyldihydroisoquinolines be detected (capillary GC, HPLC, and 300-MHz ^1H NMR).

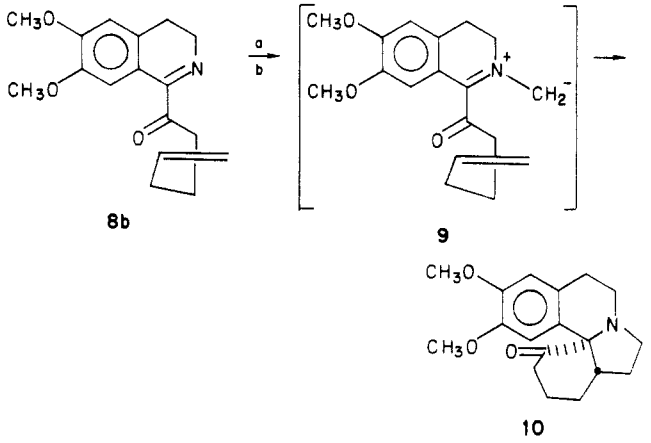
(22) Whaley, W. M.; Govindachari, T. R. In "Organic Reactions"; Adams, R., Ed., John Wiley: New York, 1951; Vol. 6, p 74.

(23) The successful participation of the nonactivated 4-methylphenyl moiety in this cyclization reaction strongly suggests that other carbon-centered nucleophiles (e.g., *typical alkenes and conjugated dienes*) may well be suitable partners in acylnitrilium ion annulations. These possibilities are currently being investigated.

(24) The cyclization of 2-(2-furyl)ethyl amides has been accomplished in low to moderate yield through the use of modified Bischler–Napieralski reaction conditions: Herz, W.; Tocker, S. *J. Am. Chem. Soc.* **1955**, *77*, 3554.

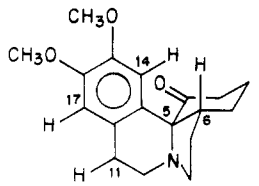
II. Synthesis of the Erythrinane Skeleton

In a previous account, we described the failure of *nonstabilized* azomethine ylides to undergo intramolecular [3 + 2] cycloadditions leading to the erythrinane skeleton.[3] In sharp contrast to our prior results, the internal cyclization of α-keto iminium ylides derived from the 1-acyldihydroisoquinolines **8b** and **8c** proceeded without incident. Accordingly, alkylation of the 1-acyldihydroisoquinoline **8b** with trimethylsilylmethyl triflate followed by the exposure of the resultant dihydroisoquinolinium salt to CsF (1,2-DME, 65 °C) furnished the erythrinane **10** directly in 70% overall yield.[25] No additional isomeric species derived from the intramolecular cyclization of the dipole **9** were detected by capillary GC, HPLC, or 300-MHz NMR.



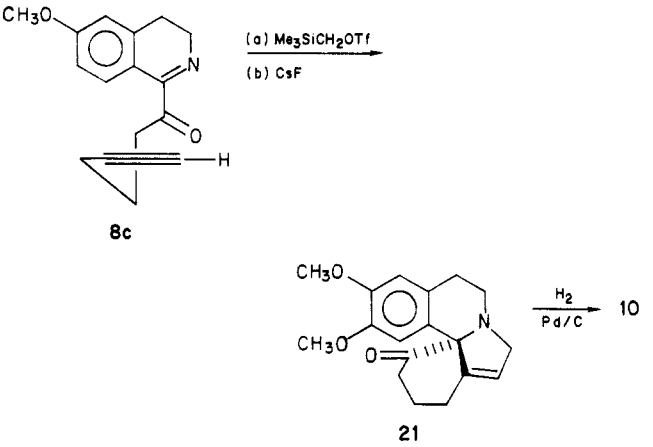
(a) $Me_3SiCH_2O_3SCF_3$; (b) CsF

Support for the existance of the cis-fused perhydroindole ring junction within **10** 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 (structure I). 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 was observed in *both* C_6D_6 and $CDCl_3$. Similarly, a pronounced NOE was observed between H_{14} and H_6. These data are consistant only with the existance of the indicated cis relationship between the C_5 aryl substituent and the proton at C-6 (structure I).[26]

An indication of the potential generality associated with α-keto iminium ylide [3 + 2] cycloadditions was provided by an example involving an acetylenic dipolarophile. To this end, sequential treatment of the 1-acyldihydroisoquinoline **8c** with trimethylsilylmethyl triflate followed by exposure of the resultant salt to CsF (inverse addition, diglyme, 110 °C) afforded the unsaturated erythrinane **21** in 42% isolated yield. The structure of the unsaturated erythrinane **21** was subsequently correlated to that of the corresponding saturated derivative **10** via reduction. Hydrogenation of **21** over 10% palladium on charcoal (1 atm H_2, EtOH) provided a single product which was identical in all respects (300-MHz NMR, IR, and mass spectrum) to the erythrinane **10** which had arisen from the cyclization of the azomethine ylide **9**.



α-Keto imidoyl halide–arene cyclizations provide a highly convergent means for the assembly of structurally diverse heterocycles. The complementarity of this method to the α-keto iminium ylide [3 + 2] cycloaddition reaction has been demonstrated by a concise synthesis of the erythrinane skeletal system. The application of these strategies to the preparation of other representative alkaloid ring systems will be the topics of future accounts from these laboratories.

Experimental Section

Melting points were determined on a electrothermal capillary melting point apparatus and are uncorrected. Infrared spectra were run on a Beckman Model 4250 infrared spectrometer. ^1H NMR spectra were obtained on Varian HFT-80 and Nicolet NT-300 spectrometers. ^{13}C NMR spectra were recorded on a Nicolet NT-300 spectrometer. Microanalyses were performed at M-H-W Laboratories, Phoenix, Az. Mass spectra were determined with a AEI MS-30 mass spectrometer at an ionizing voltage of 70 eV.

2-(2-Furyl)ethylformamide. A one-necked flask was charged with 5.18 g (47 mmol) of β-(2-furyl)ethyl amine[24] in 25 mL of ethyl formate. This mixture was refluxed for 12 h and the excess ethyl formate was then removed under reduced pressure. Distillation of the residue at 114 °C (0.12 torr) provided 5.5 g (85%) of β-(2-furyl)ethylformamide as a colorless liquid: NMR ($CDCl_3$/Me_4Si) δ 2.88 (2 H, t, J = 6.4 Hz, CH_2), 3.57 (2 H, t, J = 6.4 Hz, CH_2), 6.11 (1 H, m, Ar CH), 6.33 (1 H, m, Ar CH), 7.38 (1 H, m, Ar CH), 8.20 (1 H, s, NCHO); IR (CCl_4) cm^{-1} 3300 (NH), 3150–2800 (CH envelope), 1670 (C=O).

The following constitutes a typical procedure for the preparation of an organic isonitrile by the dehydration of the corresponding formamide.

2-(2-Furyl)ethyl Isocyanide (4b). An oven-dried, three-necked flask equipped with a thermometer, addition funnel, nitrogen inlet adapter, and magnetic stirring bar was charged with

(25) The structure assigned to the erythrinane **10** was fully supported by proton decoupling experiments and nuclear Overhauser difference spectroscopy.

(26) These NOE data are also in accord for the alternative chair conformer of the *cis*-perhydroindole nucleus.

135 mL of THF, 9.50 g (68 mmol) of β-(2-furyl)ethyl formamide and 47.6 mL (342 mmol) of triethylamine. The reaction mixture was cooled to 10 °C and 11.5 g (75 mmol) of phosphorous oxychloride in 7 mL of THF was added at a rate so that the reaction temperature remained below 16 °C. After the addition was complete, the mixture was stirred for an additional 45 min at 0–5 °C. The reaction mixture was then quenched with 340 mL of ice water and stirring was continued for an additional 2 h. The mixture was then extracted with 3 × 150 mL of ether, washed with brine, and dried over Na_2SO_4. The solvent was evaporated and the residue was purified by chromatography on 100 g of silica gel with 25% ether–pentane for elution to yield 6.88 g (84%) of the isocyanide **4b** as a colorless liquid: NMR ($CDCl_3/Me_4Si$) δ 3.025 (2 H, t of t, J = 6.0, 0.7 Hz, CH_2), 3.65 (2 H, t of t, J = 6.0, 1.9 Hz, CH_2), 6.19 (1 H, m, Ar CH), 6.32 (1 H, m, Ar CH), 7.34 (1 H, m, Ar CH); ^{13}C NMR (75.46 MHz, $CDCl_3$) δ 156.72, 150.12, 141.99, 110.39, 107.36, 40.41, 28.37; IR (CCl_4) cm^{-1} 3160 (Ar CH), 3040–2820 (CH envelope), 2155 (N≡C). Anal. Calcd for C_7H_7NO: C, 69.41; H, 5.82. Found: C, 69.52; H, 5.76.

2-(3,4-Dimethoxyphenyl)ethyl isocyanide (4a) was prepared in a similar manner: mp 52–53 °C; NMR ($CDCl_3/Me_4Si$) δ 2.93 (2 H, t with fine structure, J = 7.05 Hz, CH_2), 3.59 (2 H, t with fine structure, J = 7.05 Hz, CH_2), 3.87 (3 H, s, CH_3O), 3.89 (3 H, s, CH_3O), 6.81 (3 H, m, Ar CH); ^{13}C NMR (75.46 MHz, $CDCl_3$) δ 156.29, 148.92, 148.11, 129.10, 120.66, 111.74, 111.26, 55.86 (2 C, degenerate), 43.24, 35.29; IR (CCl_4) cm^{-1} 3100–2815 (CH envelope), 2149 (N≡C). Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85. Found: C, 69.05; H, 6.88.

The following constitutes a typical procedure for the preparation of an organic isonitrile via nucleophilic displacement with lithiomethyl isocyanide (**11**).

2-(3-Indolyl)ethyl Isocyanide (4d). An oven-dried, three-necked flask equipped with an addition funnel, nitrogen inlet adaptor, rubber septum, and magnetic stirring bar was charged with 2.75 mL (14.0 mmol) of n-butyllithium (5.1 M in hexane) and 35 mL of THF. The reaction mixture was cooled to −78 °C and a solution of 0.784 mL (14.0 mmol) of methyl isocyanide in 70 mL of THF was added to the butyllithium solution at a rate so that the temperature remained below −60 °C. The resultant white suspension was stirred for an additional 10 min and then transferred via cannula to a flame-dried flask containing a vigorously stirred mixture of 2.211 g (7.0 mmol) of gramine methiodide[11] in 100 mL of THF at −78 °C. After stirring at −78 °C for 1 h, 0.80 mL (14.0 mmol) of AcOH in 10 mL of THF was slowly added. The reaction mixture was then treated with 25 mL of 10% $KHCO_3$, extracted with 3 × 100 mL of ether, and dried over 3A powdered sieves. The solvents were evaporated and the crude mixture was purified by chromatography on alumina (activity 2.5) with 20% ethyl acetate–hexane for elution to furnish 0.76 g (64%) of the isocyanide **4d** as an off-white solid: mp 73–74.5 °C; NMR ($CDCl_3/Me_4Si$) δ 3.08 (2 H, apparent t, J = 6.51, Hz, CH_2), 3.56 (2 H, apparent t, J = 6.51 Hz, CH_2), 6.97 (1 H, s, NH), 7.16 (2 H, m, Ar CH), 7.29 (1 H, d, J = 7.8 Hz, Ar CH), 7.50 (1 H, d, J = 7.8 Hz, Ar CH), 8.10 (1 H, s, NH); ^{13}C NMR (75.46 MHz, $CDCl_3$) δ 155.34, 136.08, 126.58, 122.63, 122.11, 119.48, 118.05, 111.41, 110.62, 42.29, 25.64; IR (CCl_4) cm^{-1} 3150–2810 (CH envelope), 2150 (N≡C). Anal. Calcd for $C_{11}H_{10}N_2$: C, 78.08; H, 5.36. Found: C, 78.18; H, 5.27.

2-(4-Methylphenyl)ethyl isocyanide (4c) was prepared in a similar manner (71%) by the reaction of 1.1 equiv of **11** with α-bromo-p-xylene: NMR ($CDCl_3/Me_4Si$) δ 2.32 (3 H, s, CH_3), 2.91 (2 H, apparent t, J = 7.0 Hz, CH_2), 3.54 (2 H, t of t, J = 7 and 1.75 Hz, CH_2), 7.11 (4 H, Ar CH); ^{13}C NMR (75.46 MHz, $CDCl_3$) δ 156.14, 136.65, 133.47, 129.26, 128.63, 128.59, 128.42, 42.99, 35.10, 20.97; IR (CCl_4) cm^{-1} 3100–2830 (CH envelope), 2140 (N≡C). Anal. Calcd for $C_{10}H_{11}N$: C, 82.72 H, 7.64. Found: C, 82.93 H, 7.67.

2-[3-(1-Carbomethoxyindolyl)]ethyl Isocyanide (18). An oven-dried, three-necked flask equipped with a nitrogen inlet adaptor, thermometer, rubber septum, and magnetic stirring bar was charged with 0.400 g (2.35 mmol) of the isocyanide **4d** in 15 mL of THF and cooled to −78 °C. To this mixture was added 0.88 mL (2.35 mmol) of butyllithium (2.67 M in hexane), and the resultant solution was subsequently stirred at −78 °C for 20 min. Methyl chloroformate 0.364 mL (4.70 mmol) was then added and the reaction mixture allowed to warm to 0 °C for 2 h. The reaction was then quenched with 20 mL of H_2O and extracted with 3 × 50 mL of ether, and the combined organic fractions were dried over 3A powdered sieves. The solvent was evaporated to yield 0.534 g (99.5%) of the isocyanide **18** as an off-white solid: mp 98°–99 °C; NMR ($CDCl_3/Me_4Si$) δ 3.09 (2 H, t, J = 6.8 Hz, CH_2), 3.70 (2 H, t, J = 6.8 Hz, CH_2), 4.03 (3 H, s, CH_3O), 7.41 (4 H, m, Ar CH), 8.19 (1 H, apparent d, J = 7.6 Hz, Ar CH); ^{13}C NMR (75.46 MHz, $CDCl_3$) δ 156.71, 151.27, 135.57, 129.56, 125.22, 123.38, 123.06, 118.41, 116.33, 115.48, 53.93, 41.39, 25.51; IR (CCl_4) cm^{-1} 3100–2810 (CH envelope), 2150 (N≡C); 1722 (C=O). Anal. Calcd for $C_{13}H_{12}N_2O_2$: C, 68.41, H, 5.30. Found: C, 68.24 H, 5.35.

4,4-(Ethylenedithio)pentanoic Acid. An oven-dried, one-necked flask equipped with a rubber septum and magnetic stirring bar was charged with 150 mL of CH_2Cl_2, 5.77 g (40.0 mmol) of ethyl 4-ketopentanoate, and 5.65 g (60.0 mmol) of 1,2-ethanedithiol. The reaction mixture was treated with 1 mL of boron trifluoride etherate and stirred for 12 h at 25 °C. The mixture was subsequently diluted with 50 mL of 5% NaOH, the organic layer was extracted with H_2O and dried with $MgSO_4$, and the solvents were evaporated. The crude dithiolane so obtained was refluxed with 8.2 mL of 5 N NaOH for 0.5 h, and the reaction was then evaporated to near dryness. To the residue was added 6 mL of H_2O, and the resultant solution was again evaporated to near dryness. The residue was diluted with 44 mL of H_2O, 110 mL of ether, and neutralized with 2 N HCl at 0 °C. The mixture was extracted with 3 × 50 mL of ether, and the combined organic layers were washed with brine and then dried with Na_2SO_4. The solvents were evaporated to yield 5.77 g (75.2%) of 4,4-(ethylenedithio)pentanoic acid as a white solid: mp 48.5–50 °C; NMR ($CDCl_3/Me_4Si$) δ 1.79 (3 H, s, CH_3), 2.24 (2 H, t, J = 7.8 Hz, CH_2), 2.67 (2 H, t, J = 7.8 Hz, CH_2), 3.33 (4 H, m, overlapping CH_2CH_2); ^{13}C NMR (75.46 MHz, $CDCl_3$) δ 179.73, 65.93, 40.41, 39.31, 33.07, 31.84; IR (CCl_4) cm^{-1} 3050 (COOH), 2930 (CH), 1713 (C=O). Anal. Calcd for $C_7H_{12}O_2S_2$: C, 43.72; H, 6.29. Found: C, 43.80 H, 6.29.

The following represent typical procedures for the formation and silver ion mediated cyclization of α-keto imidoyl chlorides.

1-Hex-5-en-1-oyl-6,7-dimethoxy-3,4-dihydroisoquinoline (8b). An oven-dried, round-bottomed flask equipped with a nitrogen inlet adaptor, rubber septum, and a magnetic stirring bar was charged with 440 mg of 2-(3,4-dimethoxyphenyl)ethyl isocyanide (**4a**) (2.3 mmol) and 306 mg of 5-hexenoyl chloride (**23**) (2.3 mmol) dissolved in 6 mL of CH_2Cl_2. The reaction mixture was stirred for 7 h at 25 °C, cooled to −20 °C, and treated with 0.62 g of silver triflate (2.4 mmol). The suspension was then stirred in the dark at −20 °C for a further 3 h. The reaction mixture was treated with 0.4 mL of triethylamine (2.8 mmol) at −20 °C, followed by 6 mL of 10% aqueous $KHCO_3$. The mixture was stirred for 0.5 h at 25 °C and filtered through a bed of diatomaceous earth using 50 mL of CH_2Cl_2. The filtrate was then extracted with 30 mL of H_2O and the organic layer was washed with brine and dried over Na_2SO_4. After filtration, the solvents were removed in vacuo and the crude residue was submitted to flash chromatography on silica gel (30% ethyl acetate–hexane for elution). The solvents were evaporated to yield 574 mg of the olefinic dihydroisoquinoline **8b** (87%) as a white crystalline solid: mp 54–56 °C; NMR ($CDCl_3$–Me_4Si) δ 1.79 (apparent tt, 2 H, J = 7.4 Hz, CH_2), 2.14 (br dt, 2 H, J 6.53, 6.75 Hz, CH_2), 2.66 (m, 2 H, CH_2), 3.02 (t, 2 H, J = 7.40 Hz, CH_2), 3.81 (m, 2 H, CH_2), 3.89 (s, 3 H, CH_3O), 3.92 (s, 3 H, CH_3O), 4.98 (m, 1 H, J = 1.70, 10.22 Hz, vinyl CH), 5.04 (m, 1 H, J = 6.75, 17.20 Hz, vinyl), 5.83 (ddt, 1 H, J = 6.75, 10.22, 17.20 Hz, vinyl CH), 6.69 (s, 1 H, Ar CH), 7.39 (s, 1 H, Ar CH); ^{13}C NMR (75.46 MHz, $CDCl_3$) δ 203.19, 162.69, 151.14, 147.21, 138.09, 131.71, 118.63, 115.08, 110.57, 110.02, 56.05, 55.92, 47.53, 38.13, 33.17, 25.35, 22.89; IR (CCl_4) cm^{-1} 3010–2810 (CH envelope), 1701 (C=O), 1610 (C=N). Anal. Calcd for $C_{17}H_{21}O_3N$: C, 71.06; H, 7.36. Found: C, 70.93; H, 7.24.

The benzylic multiplet (δ 2.66) was shown to exhibit non-first-order coupling to the vicinal methylene (δ 3.81) on the basis of proton decoupling experiments. Specifically, irradiation of the signal at δ 3.81 resulted in the simplification of the signal at δ 2.66 to a singlet and vice versa.

1-Hex-5-yn-1-oyl-6,7-dimethoxy-3,4-dihydroisoquinoline (8c). An oven-dried flask equipped with a nitrogen inlet adaptor, rubber septum, and a magnetic stirring bar was charged with 0.478 g (2.5 mmol) of 2-(2,3-dimethoxyphenyl)ethyl isocyanide (**4a**),

0.324 g (2.5 mmol) of 5-hexynoyl chloride, and 7 mL of CH_2Cl_2. After being stirred for 14 h at 25 °C, the resultant red solution was cooled to −20 °C and treated with 0.642 g (2.5 mmol) of silver triflate. After being stirred at −20 °C for 12 h, the reaction mixture was treated with 20 mL of 10% $KHCO_3$ and extracted with 3 × 50 mL of CH_2Cl_2. The organic layer was then dried over 3A powder sieves and the solvents were evaporated. The residue was subsequently purified by chromatography on silica gel with 30% ethyl acetate–hexane for elution to afford 0.532 g (75%) of the dihydroisoquinoline **8c** as a white solid: mp 91–93 °C; NMR ($CDCl_3/Me_4Si$) δ 1.92 (2 H, apparent tt, J = 7.13 Hz, CH_2), 1.97 (1 H, t, J = 2.65 Hz, acetylenic CH), 2.31 (2 H, dt, J = 7.05, 2.65 Hz, propargylic CH), 2.66 (2 H, m, CH_2), 3.16 (2 H, t, J = 7.3 Hz, CH_2), 3.82 (2 H, m, CH_2), 3.89 (3 H, s, CH_3O), 3.92 (3 H, s, CH_3O), 6.69 (1 H, s, Ar CH), 7.42 (1 H, s, Ar CH); ^{13}C NMR (75.46 MHz, $CDCl_3$) δ 202.49, 162.38, 151.18, 147.23, 131.72, 118.59, 110.73, 110.03, 83.76, 68.93, 56.06, 55.91, 47.55, 37.55, 25.34, 22.53, 17.93; IR (CCl_4) cm^{-1} 3320 (acetylenic CH), 3020–2820 (CH envelope), 2280 (C≡C), 1708 (C=C). Anal. Calcd for $C_{17}H_{19}O_3N$: C, 71.54; H, 6.71. Found: C, 71.63; H, 6.55.

1-(2,2-Dimethylpropanoyl)-3,4-dihydrofurano[3,2-*c*]pyridine (17a). An oven-dried flask equipped with a nitrogen inlet adaptor, rubber septum, and magnetic stirring bar was charged with 4 mL of CH_2Cl_2, 0.242 g (2 mmol) of 2-(2-furyl)ethyl isocyanide (**4b**), and 0.253 g (2.1 mmol) of trimethylacetyl chloride. After being stirred for 18 h at 25 °C, the yellow solution was cooled to −20 °C and treated with 2.54 mL (2.2 mmol) of 0.865 M silver fluoborate in nitromethane. After being stirred at −20 °C for 12 h, the reaction mixture was sequentially treated with 0.21 mL of triethylamine and 10 mL of 10% $KHCO_3$. The reaction mixture was then extracted with 3 × 25 mL of CH_2Cl_2 and dried over 3A powdered sieves, and the solvents were evaporated. The residue was subsequently purified by chromatography on alumina (activity 2.5) with 30% ethyl acetate–hexane for elution to afford 0.259 g (63.2%) of the dihydropyridine **17a** as a colorless oil: NMR ($CDCl_3/Me_4Si$) δ 1.34 (9 H, s, $C(CH_3)_3$), 2.80 (2 H, apparent t, J = 8.90 Hz, CH_2), 4.06 (2 H, apparent t, J = 8.90 Hz, CH_2), 6.60 (1 H, s, Ar CH), 7.28 (1 H, s, Ar CH); ^{13}C NMR (75.46 MHz, $CDCl_3$) δ 206.80, 159.68, 158.02, 141.48, 113.07, 107.83, 48.42, 43.97, 27.08 (3 C, degenerate), 20.69; IR (CCl_4) cm^{-1} 3070–2780 (CH envelope), 1695 (C=O), 1620 (C=N); high resolution mass spectrum calcd for $C_{12}H_{15}NO_2$ M^+ = 205.1088, found M^+ = 205.1092.

The following heterocycles were prepared in an analogous manner.

1-(2,2-Dimethylpropanoyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (8a): mp 93–94.5 °C; NMR ($CDCl_3/Me_4Si$) δ 1.29 (9 H, s, $C(CH_3)_3$), 2.71 (2 H, m, CH_2), 3.76 (2 H, m, CH_2), 3.83 (3 H, s, OCH_3), 3.92 (3 H, s, OCH_3), 6.69 (1 H, s, Ar CH), 6.70 (1 H, s, Ar CH); ^{13}C NMR (75.46 MHz, $CDCl_3$) δ 166.29, 151.35, 147.47, 130.85, 118.78, 110.53, 109.12, 56.07, 55.97, 46.67, 44.07, 37.56, 26.94 (3 C, degenerate), 25.31; IR (CCl_4) cm^{-1} 3090–2800 (CH envelope), 1700 (C=O), 1609 (C=N). Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69. Found: C, 69.83; H, 7.58.

1-(Carbothioethoxy)-6,7-dimethoxy-3,4-dihydroisoquinoline (8b): mp 67–68.5 °C; NMR ($CDCl_3/Me_4Si$) δ 1.32 (3 H, t, J = 8.0 Hz, CH_3), 2.70 (2 H, m, CH_2), 2.98 (2 H, q, J = 8.0 Hz, CH_2), 3.88 (2 H, m, CH_2), 3.91 (3 H, s, CH_3O), 3.93 (3 H, s, CH_3O), 6.70 (1 H, s, Ar CH), 7.59 (1 H, s, Ar CH); ^{13}C NMR (75.46 MHz, $CDCl_3$) δ 194.41, 160.52, 151.46, 147.32, 131.87, 118.15, 110.40, 110.04, 56.06, 55.93, 47.56, 25.24, 23.28, 14.36; IR (CCl_4) cm^{-1} 3020–2810 (CH envelope), 1674 (C=O). Anal. Calcd for $C_{14}H_{17}NO_3S$: C, 60.19; H, 6.13. Found: C, 60.12; H, 6.19.

1-(2-Methylpropanoyl)-7-methyl-3,4-dihydroisoquinoline (15): NMR ($CDCl_3/Me_4Si$) δ 1.18 (6 H, d, J = 6.9 Hz, CH_3), 2.34 (3 H, s, CH_3), 2.70 (2 H, m, CH_2), 3.71 (1 H, septet, J = 6.9 Hz, CH), 3.84 (2 H, m, CH_2), 7.09 (1 H, d, J = 7.3 Hz, Ar CH), 7.19 (1 H, d, J = 7.3 Hz, Ar CH), 7.31 (1 H, s, Ar CH); ^{13}C NMR (75.46 MHz, $CDCl_3$) δ 206.35, 164.45, 136.53, 134.59, 131.86, 127.41, 127.24, 126.06, 47.68, 35.99, 25.22, 21.22, 17.63 (2 C, degenerate); IR ($CDCl_3$) cm^{-1} 3162 (Ar CH), 3090–2800 (CH envelope), 1708 (C=O). Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96. Found: C, 78.16; H, 8.07.

1-Benzoyl-3,4-dihydrofurano[3,2-*c*]pyridine (17b): NMR ($CDCl_3/Me_4Si$) δ 2.90 (2 H, apparent t, J = 8.8 Hz, CH_2), 4.18 (2 H, apparent t, J = 8.8 Hz, CH_2), 6.73 (1 H, br s, Ar CH), 7.20–7.91, (6 H, Ar envelope); ^{13}C NMR (75.46 MHz, $CDCl_3$) δ 191.80, 160.07, 158.40, 141.80, 135.00, 133.31, 130.58(×2), 128.16(×2), 113.19, 107.68, 48.91, 20.82; IR (CCl_4) cm^{-1} 3150–2800 (CH envelope), 1710 (C=O); high resolution mass spectrum calcd for $C_{14}H_{11}NO_2$ M^+ = 225.0786, found M^+ = 225.0796.

1-[4,4-(Ethylenedithio)pentanoyl]-6,7-dimethoxy-3,4-dihydroisoquinoline (8d). An oven-dried Schlenk tube equipped with a rubber septum and magnetic stirring bar was charged with 3 mL of dry toluene, 1 μL of DMF, and 0.192 g (1 mmol) of 4,4-(ethylenedithio)pentanoic acid. To this mixture was added 0.190 g (1.5 mmol) of oxalyl chloride. After the evolution of gas had ceased, the volatile compounds were evaporated and 0.191 g (1 mmol) of 2-(3,4-dimethoxyphenyl)ethyl isocyanide (**4a**) in 2 mL of CH_2Cl_2 was added. After being stirred at room temperature for 18 h, the reaction was cooled to −20 °C and treated with 1.16 mL (1 mmol) of a solution of silver fluoborate in CH_3NO_2 (0.865 M). The reaction mixture was stirred at −20 °C for 12 h and then quenched with 10 mL of 10% $KHCO_3$. The aqueous phase was then extracted with 3 × 25 mL of CH_2Cl_2. The organic fractions were combined and dried with Na_2SO_4 and the solvents were evaporated. The resultant dark oil was chromatographed on silica gel with 30% ethyl acetate–hexane for elution, yielding 0.22 g (61%) of the dihydroisoquinoline **8d** as a pale yellow solid: mp 74–75 °C; NMR ($CDCl_3/Me_4Si$) δ 1.83 (3 H, s, CH_3), 2.35 (2 H, t, J = 7.3 Hz, CH_2), 2.66 (2 H, t, J = 7.3 Hz, CH_2), 3.29 (2 H, m, CH_2), 3.34 (4 H, br s, CH_2CH_2), 3.83 (2 H, m, CH_2), 3.89 (3 H, s, CH_3O), 3.92 (3 H, s, CH_3O), 6.69 (1 H, s, Ar CH), 7.41 (1 H, s, Ar CH); ^{13}C NMR (75.46 MHz, $CDCl_3$) δ 202.35, 162.58, 151.09, 147.15, 131.73, 118.64, 110.69, 109.97, 66.42, 56.05, 55.94, 47.60, 40.20, 38.78, 36.60, 32.92, 25.37; IR (CCl_4) cm^{-1} 3025–2800 (CH envelope), 1703 (C=O), 1608 (C=N). Anal. Calcd for $C_{18}H_{23}NO_3S_2$: C, 59.15; H, 6.34. Found: C, 58.92; H, 6.36.

1-(2,2-Dimethylpropanoyl)-9-carbomethoxy-3,4-dihydropyrido[3,4-*b*]indole (19). An oven-dried flask equipped with a nitrogen inlet adaptor, rubber septum, and magnetic stirring bar was charged with 2 mL of CH_2Cl_2, 0.088 g (0.386 mmol) of the isocyanide **18**, and 0.047 g (0.386 mmol) of trimethylacetyl chloride. After being stirred for 18 h at 25 °C, the reaction mixture was cooled to −20 °C and treated with 0.079 g (0.405 mmol) of silver fluoborate dissolved in 1 mL of CH_3NO_2. After being stirred at −20 °C for 12 h, the reaction mixture was quenched with 10 mL of 10% $KHCO_3$, extracted with 3 × 25 mL of CH_2Cl_2, and dried over 3A powdered sieves, and the solvents were evaporated. The residue was subsequently purified by chromatography on silica gel with 30% ethyl acetate–hexane for elution to afford 0.081 g (67%) of the isocarboline **19** as an off-white solid: mp 113.5–115 °C; NMR ($CDCl_3/Me_4Si$) δ 1.44 (9 H, s, $C(CH_3)_3$), 2.77 (2 H, apparent t, J = 8 Hz, CH_2), 3.93 (2 H, apparent t, J = 8 Hz, CH_2), 3.98 (3 H, s, CH_3O), 7.28 (1 H, m, Ar CH), 7.41 (1 H, m, Ar CH), 7.55 (1 H, d, J = 7.8 Hz, Ar CH), 8.00 (1 H, d, J = 8.5 Hz, Ar CH); ^{13}C NMR (75.46 MHz, $CDCl_3$) δ 206.85, 158.49, 158.31, 151.70, 136.46, 127.94, 127.54, 127.26, 123.44, 120.01, 115.97, 54.22, 46.88, 43.64, 27.03, 19.06; IR ($CDCl_3$) cm^{-1} 3160 (Ar CH), 3010–2800 (CH envelope), 1745 (C=O), 1735 (C=O). Anal. Calcd for $C_{18}H_{20}N_2O_3$: C, 69.21; H, 6.45. Found: C, 69.24; H, 6.51.

1-(3-Carbomethoxypropanoyl)-9-carbomethoxy-3,4-dihydropyrido[3,4-*b*]indole (20) was prepared similarly: mp 110–111 °C; NMR ($CDCl_3/Me_4Si$) δ 2.71 (2 H, t, J = 7.0 Hz, CH_2), 2.78 (2 H, m, CH_2), 3.41 (2 H, t, J = 7.0 Hz, CH_2), 3.71 (3 H, s, CH_3O), 3.94 (3 H, s, CH_3O), 3.95 (2 H, m, CH_2), 7.30 (1 H, m, Ar CH), 7.44 (1 H, m, Ar CH), 7.56 (1 H, d, J = 8.1 Hz, Ar CH), 8.07 (1 H, d, J = 8.1 Hz, Ar CH); ^{13}C NMR (75.46 MHz, $CDCl_3$) δ 199.28, 173.14, 158.49, 151.41, 136.98, 127.84, 127.47, 126.98, 126.77, 123.46, 120.06, 115.69, 54.05, 51.78, 47.40, 32.94, 27.59, 19.21; IR ($CDCl_3$) cm^{-1} 3160 (Ar CH), 3090–2810 (CH envelope), 1735 (C=O), 1710, (C=O). Anal. Calcd for $C_{18}H_{18}N_2O_5$: C, 63.15; H, 5.30. Found: C, 63.19; H, 5.39.

4-Oxo-15,16-dimethoxyerythrinane (10). A flame-dried, round-bottomed flash equipped with a nitrogen inlet adaptor, rubber septum, and magnetic stirring bar was charged with 600 mg of anhydrous CsF (4.0 mmol) and 5 mL of 1,2-DME. In a separate flask, 250 mg of the dihydroisoquinoline **8b** (0.87 mmol) was alkylated with 410 mg of trimethylsilylmethyl triflate (1.74 mmol) in 3 mL of CH_2Cl_2 for 48 h at 25 °C. After removal of the CH_2Cl_2, the excess trimethylsilylmethyl triflate was evaporated in vacuo. The residue was dissolved in 2 mL of 1,2-DME and

added over 2 h via a mechanical syringe to the CsF suspension maintained at 65 °C. The reaction mixture was stirred at 65 °C for an additional 12 h, treated with 15 mL of H_2O, and extracted with 25 mL of CH_2Cl_2. The organic layer was washed with brine and dried over Na_2SO_4. After filtration, the solvents were evaporated and the crude mixture was chromatographed on Brockmann 3 neutral alumina (40% ethyl acetate–hexane for elution) to give 211 mg (70%) of the tetracyclic erythrinane **10** as an oil: NMR ($CDCl_3/SiMe_4$) δ 1.58 (m, 2 H, CH_2), 1.87 (m, 3 H, overlapping CH_2), 2.19 (m, 1 H, CH_2), 2.31 (m, 1 H, CH_2), 2.36 (m, 1 H, CH_2), 2.74 (m, 1 H, CH), 2.90 (m, 2 H, overlapping CH_2), 3.00 (m, 2 H, CH_2), 3.26 (ddd, 1 H, J = 9.3, 7.0, 7.0 Hz, CH_2), 3.83 (s, 3 H, CH_3), 3.85 (s, 3 H, CH_3), 6.55 (s, 1 H, Ar CH), 6.60 (s, 1 H, Ar CH); IR cm^{-1} (film) 3100–2900 (CH envelope), 1710 (C=O). Anal. Calcd for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69. Found: C, 71.92; H, 7.76.

4-Oxo-6,7-didehydro-15,16-dimethoxyerythrinane (21). A flame-dried, round-bottomed flask equipped with a nitrogen inlet adaptor, rubber septum, and magnetic stirring bar was charged with 300 mg of CsF (2.0 mmol) and 4 mL of diglyme. In a separate flask, 161 mg of the dihydroisoquinoline **8c** (0.57 mmol) was alkylated with 267 mg of trimethylsilylmethyl triflate (1.14 mmol) in 3 mL of CH_2Cl_2 for 48 h at 25 °C. After removal of the CH_2Cl_2, the excess trimethylsilylmethyl triflate was evaporated in vacuo. The residue was dissolved in 2 mL of diglyme and added over 2 h via a mechanical syringe to the CsF suspension maintained at 110 °C. The reaction mixture was stirred at 110 °C for an additional 12 h, treated with 15 mL of H_2O, and extracted with 25 mL of CH_2Cl_2. The organic layer was washed with brine and dried over Na_2SO_4. After filtration, the solvents were evaporated and the crude mixture was chromatographed on Brockmann 3 neutral alumina (40% ethyl acetate–hexane for elution) to give 71 mg (42%) of the tetracyclic erythrinane **21** as an oil: NMR ($CDCl_3/SiMe_4$) δ 1.83 (1 H, m, CH_2), 2.23 (1 H, m, CH_2), 2.48 (1 H, ddd, J = 14.3, 3.8, 3.8 Hz, CH_2), 2.79 (6 H, complex m, CH_2), 3.41 (1 H, d with fine splitting, J = 12.5 Hz, CH_2), 3.79 (1 H, d with fine splitting, J = 12.8, CH_2), 3.85 (2 H, m, CH_2), 3.86 (3 H, s, CH_3O), 3.89 (3 H, s, CH_3O), 5.71 (1 H, br s, vinyl CH), 6.66 (1 H, s, Ar CH), 7.01 (1 H, s, Ar CH); IR (film) cm^{-1} 3150–2860 (CH envelope), 1715 (C=O); high resolution mass spectrum calcd for $C_{18}H_{21}NO_3$ M^+ = 299.1516, found M^+ = 299.1522.

Hydrogenation of 4-Oxo-6,7-didehydro-15,16-dimethoxyerythrinane (21). To an oven-dried, round-bottomed flask equipped with an gas inlet adapter and magnetic stirring bar was added 2 mg of 10% palladium on charcoal. The system was purged with nitrogen and charged with 5.0 mg of the erythrinane **21** (0.017 mmol) in 4 mL of absolute EtOH. The system was flushed with hydrogen and the mixture was stirred under a hydrogen atmosphere for 3 h at 25 °C. The reaction mixture was subsequently filtered through Celite and the solvent was evaporated to give a quantitative yield of a single hydrogenated product.

The hydrogenation product was shown to be identical with the erythrinane **10** in all respects (300-MHz NMR, IR, and mass spectra, capillary GC, and HPLC).

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Registry No. **4a**, 63609-01-8; **4a** (formamide), 14301-36-1; **4b**, 100571-63-9; **4b** (formamide), 98547-33-2; **4c**, 100571-65-1; **4c** (formamide), 100571-66-2; **4d**, 100571-64-0; **4d** (formamide), 6502-82-5; **5** (X = Cl, R = $CH(CH_3)_2$), 79-30-1; **5** (X = Cl, R = C_6H_5), 98-88-4; **5** (X = Cl, R = $(CH_2)_2CO_2Me$), 1490-25-1; **5a**, 3282-30-2; **5b**, 36394-07-7; **5c**, 55183-45-4; **5d**, 78283-59-7; **5e**, 2941-64-2; **8a**, 100571-70-8; **8b**, 100571-68-4; **8c**, 100571-69-5; **8d**, 100571-71-9; **8d** (acid), 54717-84-9; **8e**, 100571-72-0; (±)-**10**, 100571-78-6; **15**, 100571-73-1; **17a**, 100571-74-2; **17b**, 100571-75-3; **18**, 100571-67-3; **19**, 100571-76-4; **20**, 100571-77-5; (±)-**21**, 100571-79-7; $EtO_2C(CH_2)_2COMe$, 539-88-8; $HS(CH_2)_2SH$, 540-63-6; 2-(2-furyl)ethylamine, 1121-46-6.

Stereoselective Reductions of a Vinylogous Urethane Structure in a Highly Substituted Indolo[2,3-*a*]quinolizidine

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Stereoselective reductions of the vinylogous urethane **1** are described. Reduction of **1** with sodium cyanoborohydride in acetic acid gave a 81:19 mixture of isomers **2** and **3**; tributyltin hydride in 0.7 M trifluoroacetic acid solution in methylene chloride reversed the ratio of **2–3** to 17:83. Reduction of **1** with triethylsilane in trifluoroacetic acid yielded a mixture of isomers **2**, **3**, and **4** in a ratio of 19:17:64. The structure and stereochemistry of **4** were established by X-ray crystallography.

The indolo[2,3-*a*]quinolizidine system is part of the carbon skeleton of many indole alkaloids, e.g., ajmalicin or corynanthein. For the selective generation of the stereocenters in the quinolizidine substructure the reduction of the double bond of a vinylogous urethane moiety seems suitable. This reduction generates two new stereocenters and thereby determines the nature of the annelation of the rings in the quinolizidine. However, the usual reagent (sodium borohydride in acetic acid)[1,2] for this reduction often shows little stereoselectivity or produces an undesired isomer. New reducing agents offering a greater degree of control upon the stereochemical outcome of this reduction thus seem desirable.

Results and Discussion

We describe here a study on the stereoselective reduction of the vinylogous urethane **1**. The use of various reducing agents led to the formation of the isomers **2–4** (Scheme I) in varying ratios (Table I).

We decided to use the vinylogous urethane **1** as a model compound because it has the same ring system as several indole alkaloids and can be obtained in a simple two-step synthesis (Scheme II). The 1,4-dihydropyridine derivative **5** was prepared in 42% yield from tryptamine, benzaldehyde, and ethyl propiolate.[3] Acid-catalyzed cyclization

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