123754-18-7; (+)-**32**, 123754-19-8; (+)-**33**, 123754-20-1; (+)-**34**, 123754-21-2; (+)-**35**, 123754-22-3; (+)-**36**, 123808-92-4; (+)-**37**, 123808-93-5; (*S*)-valinol, 2026-48-4; levulinic acid, 123-76-2; (*R*)-valinol, 4276-09-9.

Supplementary Material Available: Experimental details for (*S*)-**23** and all ^{1}H NMR spectra for all intermediates and ^{13}C NMR spectra for capnellenes (30 pages). Ordering information is given on any current masthead page.

Total Synthesis of (±)-Vallesamidine

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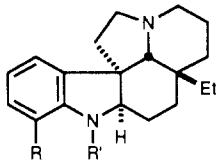
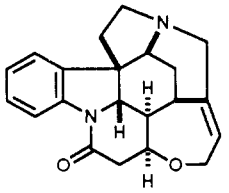
This article reports full details of a project aimed at providing synthetic access to the 2,2,3-trialkylindoline alkaloids such as vallesamidine (**4**). The basic strategy was to preassemble the tricyclic portion containing the nonindolic nitrogen and to form the indoline ring at a late stage in the synthesis. An approach summarized in the retrosynthetic analysis summarized in Scheme III failed because enones **48** and **50** do not undergo 1,4-addition of nitrogen nucleophiles. However, the retrosynthesis summarized in Scheme X did lead to a successful synthesis of (±)-**4**. The synthesis requires seven steps from 2-ethylcyclopentanone [→ **54** → **56** → **66** → **68** → **71** → **74** → (±)-**4**] and delivers the alkaloid in 19% overall yield. Pivotal steps in the synthesis are the lactam annelation process in which **56** reacts with *o*-nitrocinnamic acid to yield **66** and the NBS-mediated cyclization of amino lactam **68** to the pentacyclic bromo lactam **70**. Four of the seven steps involve the formation of skeletal (C–C or C–N) bonds and only three are functional-group transformations.

Much research has been devoted to the synthesis of 2,3,3-trialkylindoline alkaloids, typified by the *Aspidosperma*[3] and *Strychnos*[4] alkaloids aspidospermine (**1**) and strychnine (**3**). Far less attention has been given to 2,2,3-trialkylindoline alkaloids such as vallesamidine (**4**)[5-8] and andrangine (**5**).[9-11] We therefore set out to explore some novel synthetic routes to these types of alkaloids and chose vallesamidine (**4**) as the synthetic target. This report outlines the background information, the retrosynthetic analyses, the results of several synthetic approaches, and the eventual total synthesis of the alkaloid.[12]



1: R = MeO, R' = Ac
2: R = H, R' = Me



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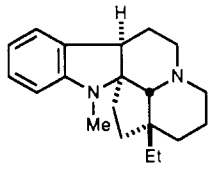

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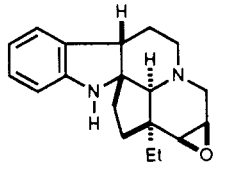
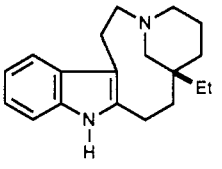


5

Vallesamidine (**4**) was isolated in 1965 from *Vallesia dichotoma* (Ruiz et Pav).[5] On the basis of chemical and physical data, it appeared to be isomeric with *N*-methylaspidospermidine (**2**); however, because of the amount of material available, a definite structure could not be assigned. Djerassi et al.[13] subsequently determined the molecular structure and absolute configuration of vallesamidine by X-ray diffraction. This work, which confirmed speculations by Kutney et al.,[14] was the first determination of the absolute configuration of an alkaloid related to aspidospermine (**1**).

The aspidospermine skeleton can be generated by oxidative cyclization of quebrachamine (**6**).[13,14] Vallesamidine differs from aspidospermine in that C-19 is attached to the indoline ring at C-2 rather than at C-12, suggesting that the biosynthesis of *Aspidosperma* alkaloids involves quebrachamine-type intermediates and that vallesamidine may be regarded as the product of an "abnormal" cyclization, generating the same stereochemistry at carbons 2, 12, and 19 as the "normal" (*Aspidosperma*) cyclizations.[6]



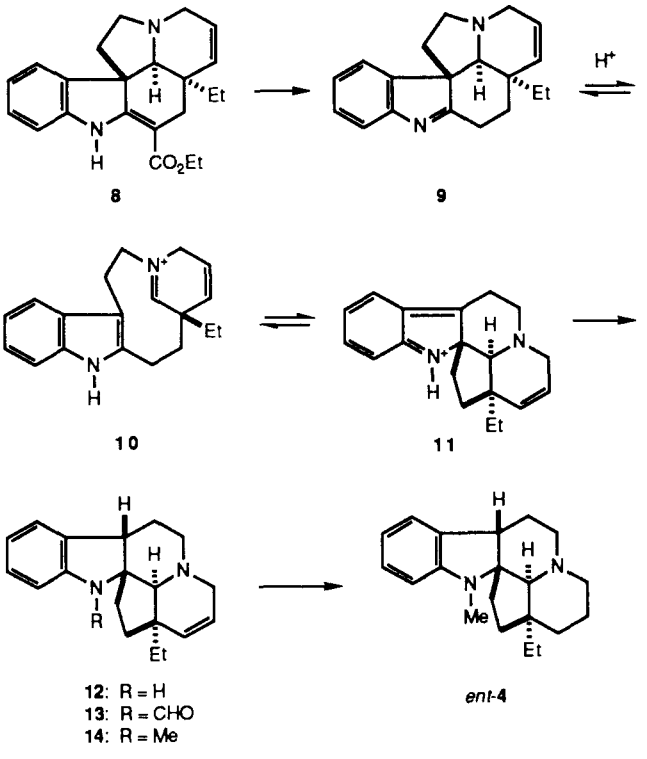
6

Vallesamidine is a structurally unique compound that does not belong to any one particular class of alkaloids. In addition to being related to the *Aspidosperma*[3] alkaloids, it is structurally related to the *Schizozygia* alkaloids (e.g. schizozygine (**7**)).[15-18] The only other compound having the same skeletal system is andrangine (**5**).[10] The absolute configurations of vallesamidine and andrangine

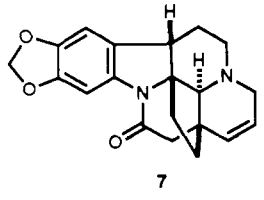
(1) Current address: Burroughs Wellcome Company, 3030 Cornvallis Road, Research Triangle Park, NC 27709.
(2) Current address: Abbott Laboratories, Abbott Park, IL 60064.
(3) For a review see: Cordell, G. A. In *The Alkaloids*; Manske, R. H. F., Rodrigo, R., Eds.; Academic Press: New York, 1979; Vol. XVII, pp 199–384.
(4) For a review see: Smith, G. F. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1960; Vol. VIII, pp 591–671.
(5) Walser, A.; Djerassi, C. *Helv. Chim. Acta.* **1965**, *48*, 391.
(6) Brown, S. H.; Djerassi, C.; Simpson, P. G. *J. Am. Chem. Soc.* **1968**, *90*, 2445.
(7) Levy, J.; Mauperin, P.; Doe, M.; Le Men, J. *Tetrahedron Lett.* **1971**, 1003.
(8) Laronze, J.-Y.; Laronze-Fontaine, J.; Levy, J.; Le Men, J. *Tetrahedron Lett.* **1974**, 491.
(9) Cave, A.; Bruneton, J. *Tetrahedron Lett.* **1973**, 5081.
(10) Kan, C.; Das, B. C.; Husson, H.-P.; Potier, P. *Bull. Soc. Chim. Fr.* **1974**, *12*, 2839.
(11) Bruneton, J.; Bouquet, A.; Cave, A. *Phytochemistry* **1974**, *13*, 1963.
(12) For a preliminary account of a part of this work, see: Dickman, D. A.; Heathcock, C. H. *J. Am. Chem. Soc.* **1989**, *111*, 1528.
(13) Brown, S. H.; Djerassi, C.; Simpson, P. G. *J. Am. Chem. Soc.* **1968**, *90*, 2445.
(14) Kutney, J. P.; Piers, E. *J. Am. Chem. Soc.* **1964**, *86*, 953.
(15) Renner, U.; Kerweisz, P. *Experientia* **1963**, *19*, 244.
(16) Renner, U. *Lloydia* **1964**, *27*, 406.
(17) Renner, U.; Fritz, H. *Helv. Chim. Acta* **1965**, *48*, 308.
(18) Wenkert, E.; Wickberg, B. *J. Am. Chem. Soc.* **1965**, *87*, 1580.

0022-3263/90/1955-0798$02.50/0

Scheme I



are different, implying that the two alkaloids differ biogenetically.

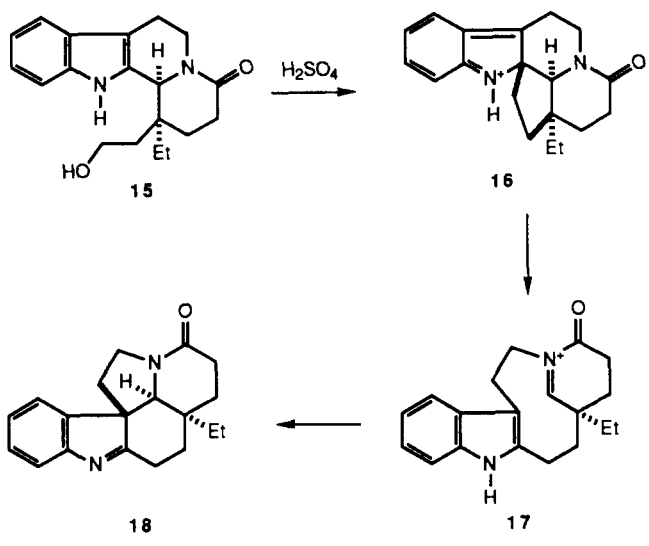


7

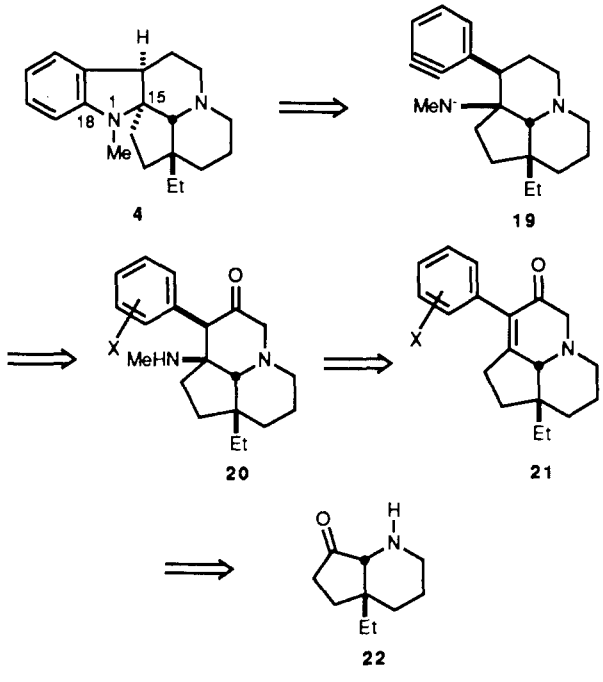
To date there has been only one synthesis of vallesamidine, summarized in Scheme I. Tabersonine (8)[19] was converted, via indoline 9, into 2,2,3-trialkylindoline 12 in 24% yield.[7] The *N*(a)-formyl derivative 13 was reduced to obtain *N*(a)-methylindoline 14, which was hydrogenated to obtain the enantiomer of natural vallesamidine. The key rearrangement in this synthesis presumably occurs by fragmentation of the conjugate acid of 9 to the quebrachamine-type ion 10, which cyclizes at C-2 of the indole ring to provide an ion (11) that is reduced to 12.

One possible way to make 2,2,3-trialkylindolines is intramolecular alkylation at C-2 of a 2,3-dialkylindole. However, because of the ease of fragmentation to quebrachamine-type intermediates (cf. Scheme I), this route is not generally applicable. For example, in Harley–Mason's 1967 aspidospermine synthesis,[20] the interesting skeletal rearrangement shown in Scheme II was used advantageously. Treatment of hydroxy lactam 15 with 40% sulfuric acid or boron trifluoride etherate at 100 °C gives the indolenine lactam 18, presumably by initial formation of the carbocation 16, followed by fragmentation to an immonium ion (17) that attacks the indole at C-3 to give the aspidospermine skeleton. Similar rearrangements have been employed in syntheses of eburnamine, 3-methylaspidospermine,[21] and (±)-vindoline.[22] These precedents

Scheme II



Scheme III

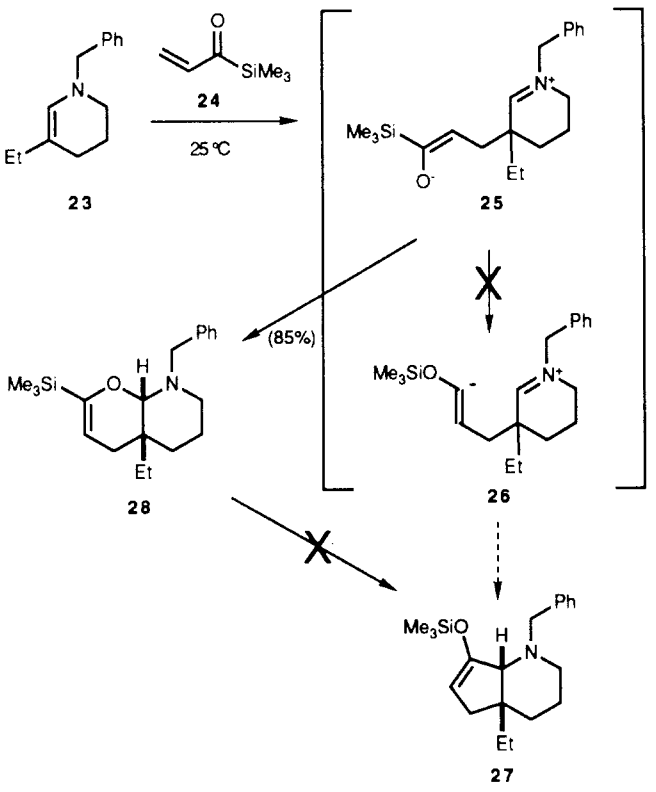


show that when a cation is formed at the C-3 position, quebrachamine-type intermediates are generated and cyclize to the more stable aspidospermine alkaloids.

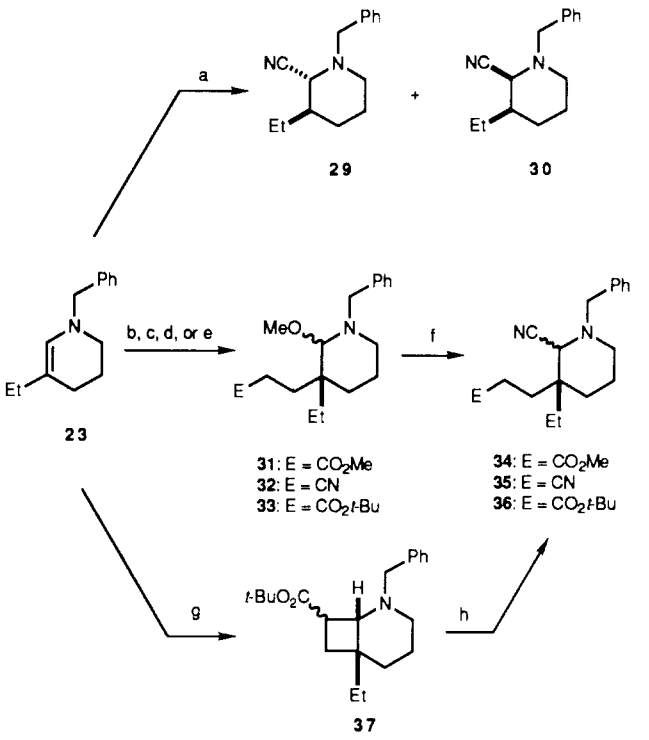
Because of the problem outlined in the foregoing discussion, we have investigated synthetic approaches wherein the indole heterocyclic ring is not formed until a late stage in the synthesis (Scheme III). We envisioned the construction of a tricyclic diamine bearing a pendant haloaryl group (**20**).[23] Formation of the N-1,C-18 indoline bond would be accomplished by intramolecular attack of an amine anion on a benzyne intermediate (e.g., **19**), a cyclization that has been explored by Bunnett[24,25] and Huisgen.[26,27]

(19) Plat, M.; Le Men, J.; Janot, M.-M.; Wilson, J. M.; Budzikiewicz, H.; Durham, L. J.; Nakagawa, Y.; Djerassi, C. *Tetrahedron Lett.* **1962**, 271.
(20) Harley-Mason, J.; Kaplan, M. *Chem. Commun.* **1967**, 915.
(21) Barton, J. E. D.; Harley-Mason, J. *Tetrahedron Lett.* **1965**, 298.
(22) Feldman, P. L.; Rapoport, H. *J. Org. Chem.* **1986**, *51*, 3882.
(23) For an earlier, unsuccessful approach to compounds like **20**, see: Norman, M. H.; Heathcock, C. H. *J. Org. Chem.* **1987**, *52*, 226.
(24) Bunnett, J. F.; Hrutfiord, B. F. *J. Am. Chem. Soc.* **1958**, *80*, 2021, 4745.
(25) Bunnett, J. F.; Hrutfiord, B. F. *J. Am. Chem. Soc.* **1961**, *83*, 1691.
(26) Huisgen, R.; Konig, H. *Chem. Ber.* **1959**, *92*, 203, 249.
(27) Huisgen, R.; Konig, H.; Bleeker, N. *Chem. Ber.* **1959**, *92*, 424.

Scheme IV



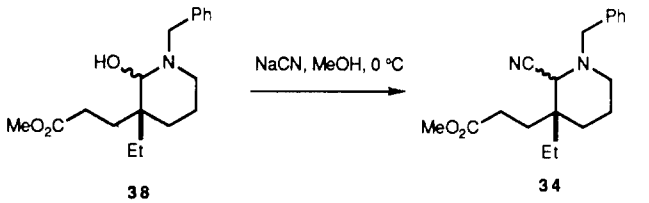
Scheme V[a]



[a] (a) Methyl acrylate, NaCN, CH_3CN, reflux; (b) methyl acrylate, MeOH, reflux; (c) acrylonitrile, MeOH, reflux; (d) *tert*-butyl acrylate, MeOH, reflux; (e) *tert*-butyl acrylate, MeOH, 7–15 kbar, 24 h; (f) NaCN, MeOH, 0 °C; (g) *tert*-butyl acrylate, *t*-BuOH, reflux; (h) NaCN, MeOH, reflux.

Our initial starting material was enamine **23**, prepared in four steps and 80% overall yield from butyraldehyde.[28] The first attempt to fuse a cyclopentanone ring to **23** employed acylsilane **24**, prepared by the method of Danheiser.[29] It was hoped that reaction of enamine **23** with acylsilane **24** would give **25**, which might undergo Brook rearrangement to give **26**. This dipolar species would be expected to close, providing enol silane **27** (Scheme IV). This, however, is not the case. Reaction of **23** with **24** results not in formation of enol silane **27**, but rather gives vinylsilane **28** in excellent yield. The stereochemistry of **28** is assigned by analogy to reactions of methyl vinyl ketone with similar enamines, which give the cis-fused products.[30] Attempts to promote rearrangement of **28** to enol silane **27** were not successful; only starting material was recovered when **28** was treated with TAS-F or TAS-HF_2 in THF or sodium methoxide in methanol.

Five-membered ring annelation of enamine **23** by reaction with an electrophilic olefin and trapping the resulting immonium ion with an external nucleophile was more successful (Scheme V). However, all attempts to accomplish this transformation in a one-pot process resulted only in formation of a mixture of cyanamines **29** and **30** (82:18 ratio). The major diastereomer is assigned the trans configuration by ^{13}C NMR spectrometry.[31] Dinitrile **35** and nitrile esters **34** and **36** were prepared by two-step sequences. The preparation of methyl ester **34** by this method is straightforward. Treatment of a concentrated solution (1.2 M) of enamine **23** with 1.5 equiv of methyl acrylate in absolute methanol gives **31** in essentially quantitative crude yield. In this reaction, methanol acts as the trapping agent driving the reaction to completion. The initial product is taken up in methanol and treated with sodium cyanide to provide nitrile ester **34** in 73% overall yield from enamine **23**. Attempts to purify **31** by column chromatography resulted in hydrolysis to hemiaminal **38**. Treatment of **38** with sodium cyanide in methanol also gives nitrile ester **34**.



Compound **32** was prepared by heating a solution of enamine **23** with excess acrylonitrile in absolute methanol. Treatment of **32** directly with sodium cyanide affords dinitrile **35**. Although **35** is obtained in 76% yield, an annoying side reaction (1,4-addition of methanol to acrylonitrile forming β-methoxypropionitrile) is a complicating side reaction that cannot be avoided. Because of this side reaction, concentration and purification problems make the preparation of dinitrile **35** impractical on a large scale.

Preparation of the *tert*-butyl ester **36** was accomplished in three ways. Reaction of enamine **23** with *tert*-butyl acrylate in refluxing methanol gives ester **33** in low yield, due to an unidentified side reaction which could not be avoided, under thermal conditions. As a result, compound **36** is obtained in only 33% overall yield from **23**. If *tert*-butyl alcohol rather than methanol is used for the reaction of **23** with *tert*-butyl acrylate, cyclobutane **37** is

(28) Norman, M. H.; Heathcock, C. H. *J. Org. Chem.* **1988**, *53*, 3370.
(29) Danheiser, R. L.; Szczepanski, S. W.; Tsai, Y.-M.; Okano, K.; Fink, D. M. *Org. Synth.* **1987**, *66*, 14.
(30) (a) Ziegler, F. E.; Kloek, J. A.; Zoretic, P. A. *J. Am. Chem. Soc.* **1969**, *91*, 2342. (b) Ziegler, F. E.; Spitzner, E. B. *J. Am. Chem. Soc.* **1973**, *95*, 7146. (c) Stevens, R. V.; Mehra, R. K.; Zimmerman, R. L. *J. Chem. Soc., Chem. Commun.* **1969**, 877.
(31) (a) Jokela, R.; Taminen, T.; Lounsamea, M. *Heterocycles* **1985**, *23*, 1707. (b) Wehrli, F. W.; Wirthlin, T. *Interpretation of ^{13}C NMR Spectra*; Heyden and Sons, Ltd.: Philadelphia, PA, 1978; p 45.

obtained in 31% yield. Compound **37** reacts with sodium cyanide in hot methanol to give ester nitrile **36** as a crude product in 69% yield. However, preparation of **36** by this method is unsatisfactory both because of the to low overall yield (ca. 20%) and because of irreproducibility in the reaction of **37** with cyanide. In some cases, this reaction is accompanied by transesterification with methanol, leading to methyl ester **34**.

The problems encountered in the thermal reaction and in the cyclobutane approach are essentially eliminated by the use of high-pressure conditions. Enamine **23** reacts with 1.5 equiv of *tert*-butyl acrylate in methanol at 7 kbar for 24 h to give **33** in 97% yield.[32] The methoxy group is easily exchanged with cyanide ion to give *tert*-butyl ester **36** in 64% overall yield.

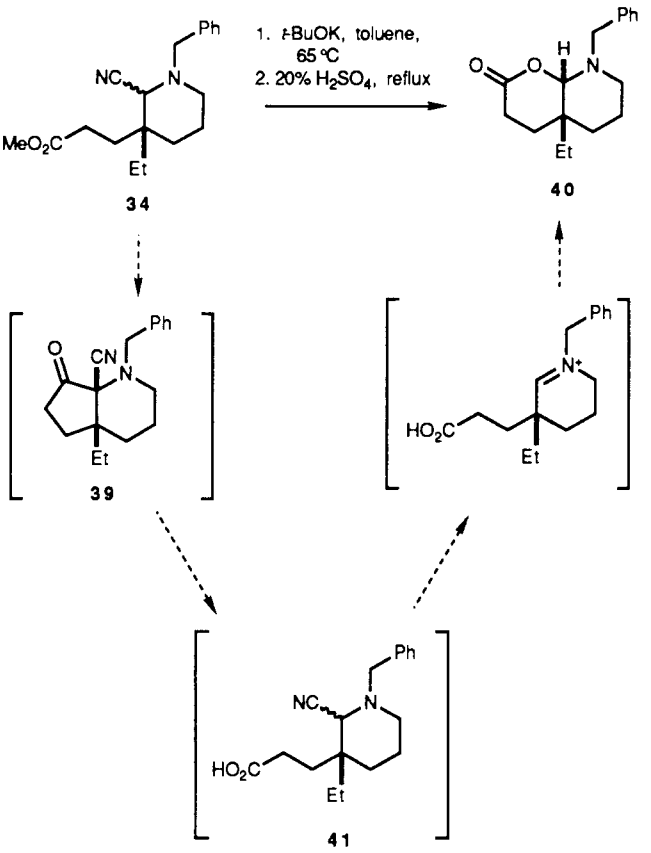
Thorpe–Ziegler cyclization of dinitrile **35** to form the cyclic nitrile enamine could not be accomplished. Treatment of **35** with potassium *tert*-butoxide in toluene or *tert*-butyl alcohol gave mixtures of cyclized products. Because this cyclization did not proceed cleanly and because of the problems encountered in the preparation of **35**, the dinitrile approach to amino ketone **22** was not pursued further.

Initial attempts to cyclize nitrile ester **34** resulted in hydrolysis of the methyl ester to the corresponding nitrile acid and indicated that a critical feature in the Thorpe–Ziegler/Dieckmann cyclizations of these substrates is that the reagents must be very dry. In order to assure this, ester nitrile **34** is taken up in toluene (freshly distilled from CaH_2), and the solvent is removed with a rotary evaporator, thus removing any water by azeotripic evaporation. In this way, hydrolysis of the methyl ester is avoided. Cyclization of ester nitrile **34** with potassium *tert*-butoxide or sodium methoxide in dry toluene gives an unstable product that decomposes upon attempted chromatographic purification (Scheme VI). Treatment of the crude material with refluxing 20% aqueous sulfuric acid gives lactone **40**, which may arise from the hydrolysis of nitrile ketone **39** formed by addition of the nitrile anion to the ester. Under the hydrolytic conditions, attack may occur at the carbonyl group, resulting in ring-opening to nitrile acid **41**, which eliminates cyanide and closes to give lactone **40**.

These problems were solved by employing the *tert*-butyl ester analogue (**36**) because the bulky *tert*-butyl group inhibits nucleophilic attack on the ester and permits the ester enolate to add to the nitrile function. Thus, the reaction of **36** with potassium *tert*-butoxide in dry toluene at 65 °C provides the crystalline β-amino α,β-unsaturated ester **42** in 65% yield (Scheme VII).

Various conditions were investigated to effect the hydrolysis and decarboxylation of **42**, including 2 N hydrochloric acid in ethyl acetate, trifluoroacetic acid in methylene chloride, catalytic sulfuric acid in acetic acid, and aqueous sulfuric acid. All of the conditions employed gave mixtures of the desired amino ketone **43** and amino lactone **40**. Best results are obtained by treating **42** with refluxing 20% sulfuric acid. Under these conditions, the **43**:**40** ratio is >50:1 and bicyclic ketone **43** is isolated in 55% yield. At lower acid concentrations more of lactone **40** is formed. For example, the **43**:**40** ratio is 3:1 with 10% sulfuric acid and 2:1 with 5% sulfuric acid. Amino lactone **40** may be formed by the C=O extrusion mechanism suggested in Scheme VII or by a retro-Thorpe–Ziegler/Dieckmann reaction followed by elimination of cyanide as previously suggested for the methyl ester. Because ester enamine **42** is relatively unstable, it is best hydrolyzed and decarboxylated immediately upon workup. Amino ketone **40** is obtained in 50% overall yield from nitrile ester **36** in this manner.

Scheme VI



Because of the buffering effect of the basic nitrogen, ketalization of amino ketone **43** is very slow. With *p*-toluenesulfonic acid as catalyst in refluxing toluene, ketal formation is complete only after 6 days. However, if the more soluble 2-naphthalenesulfonic acid is used as catalyst, ketalization is complete in 15 h and ethylene ketal **44** is obtained in 78% yield (Scheme VIII).

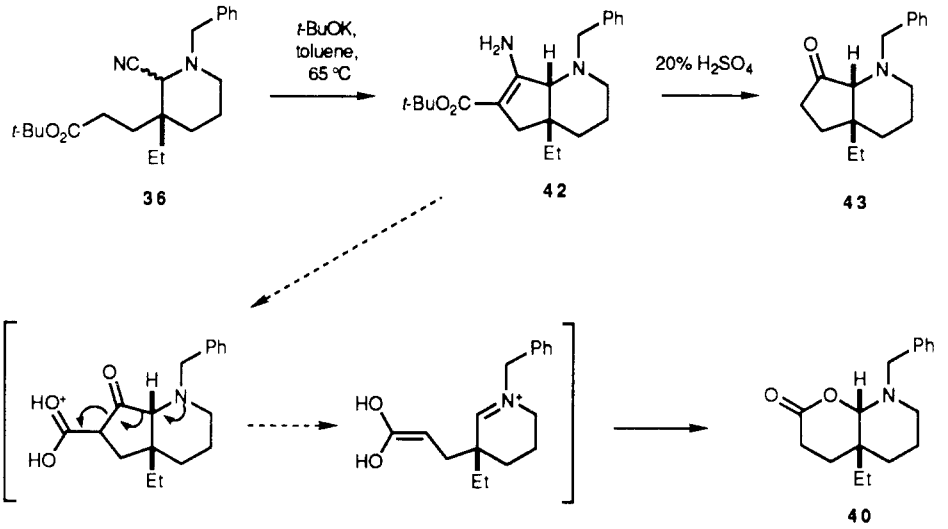
Debenzylation of amino ketal **44** is best accomplished by treatment of its hydrochloride salt with hydrogen over 10% palladium on carbon in absolute methanol; secondary amine **45** is obtained in 98% yield. Compound **45** reacts with α-chloro ketone **46**[33] in dry acetonitrile in the presence of Hunig's base to give ketal ketone **47** in 73% yield (Scheme VIII). Treatment of **47** with refluxing 1.4 N hydrochloric acid promotes deketalization, intramolecular aldol condensation, and dehydration, giving tricyclic enone **48** in 59% yield.

The next task in the projected synthesis of vallesamidine by this route involves the introduction of methylamine or its equivalent to the β-position of the enone. However, direct Michael addition of methylamine, sodium azide, or trimethylsilyl azide to **48** failed, presumably because of steric hindrance. Although enone **48** seems to be too sterically hindered for Michael addition, a less hindered enone might undergo Michael addition with a nucleophile such as *O*-chloroaniline and therefore provide an alternative access to a substance such as **20** (Scheme III). To this end, tricyclic enone **50** was synthesized by reaction of **45**

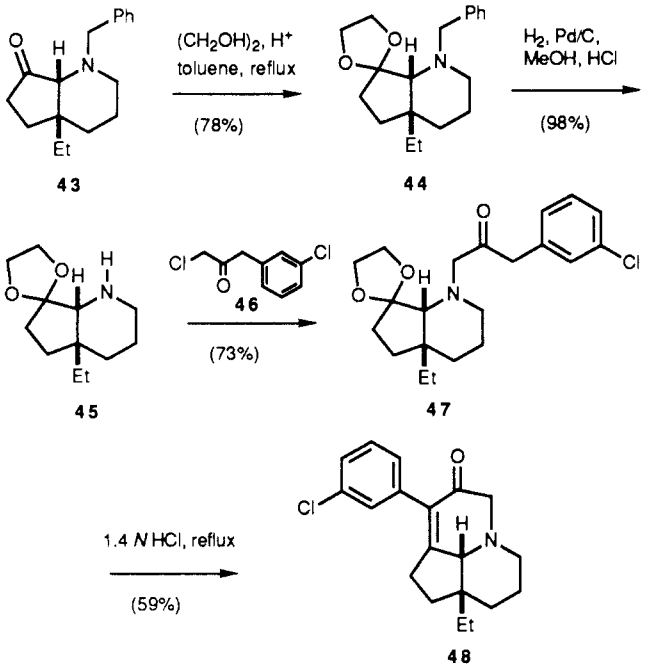
(32) For the previous use of high pressure conditions for enamine Michael additions, see: Dauben, W. G.; Kozikowski, A. D. *J. Am. Chem. Soc.* **1974**, *96*, 3664.

(33) Bordwell, F. G.; Scamehorn, R. G.; Springer, W. R. *J. Am. Chem. Soc.* **1969**, *91*, 2087.

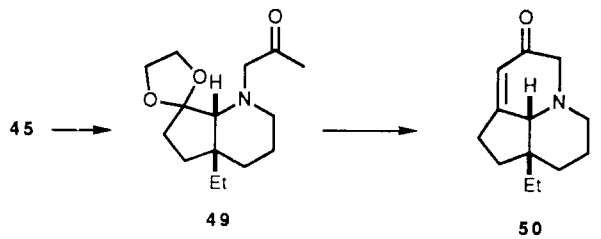
Scheme VII



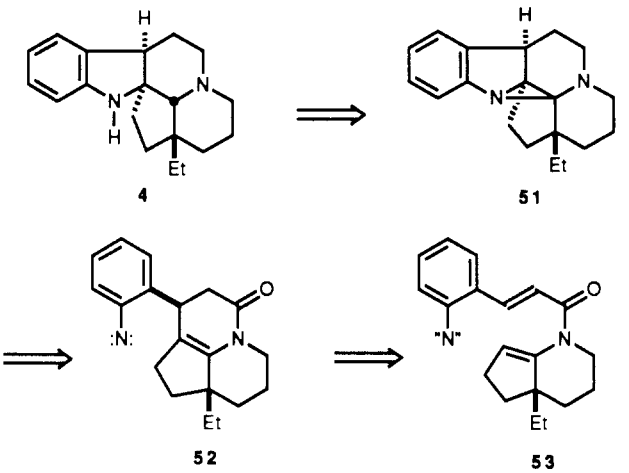
Scheme VIII



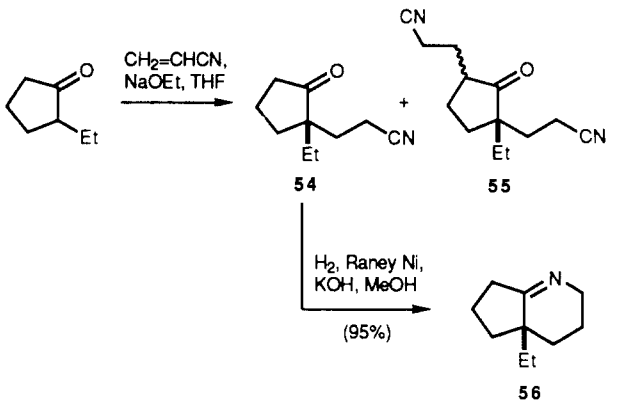
Scheme IX



Scheme X



Scheme XI



with chloroacetone to give **49**. Treatment of this substance with 1.4 N HCl as previously described provides enone **50** (Scheme IX). Unfortunately, all attempts to effect Michael addition of 2-chloroaniline to enone **50** failed.

Other less direct methods to introduce a methylamino group at the β-position of enone **48** were considered.[34] However, because the synthesis of **48** from available starting materials already requires 13 steps, and several more synthetic manipulations would be required to complete the synthesis, this approach was abandoned and a more direct route was sought. The synthetic plan summarized in Scheme X emerged as an attractive possibility. In this approach, the N-1,C-15 indoline bond would be formed by intramolecular reaction of an enamide with a nitrene (e.g., **52**) or its equivalent.

The synthesis begins with 2-ethylcyclopentanone,[35] which is cyanoethylated by addition of sodium ethoxide

(34) For a review of allylic amine syntheses by [3,3] sigmatropic rearrangements of imidate esters, see: Overman, C. E. *Acc. Chem. Res.* **1980**, *13*, 218.

(35) Stork, G.; Dowd, S. *J. Am. Chem. Soc.* **1963**, *85*, 2872.

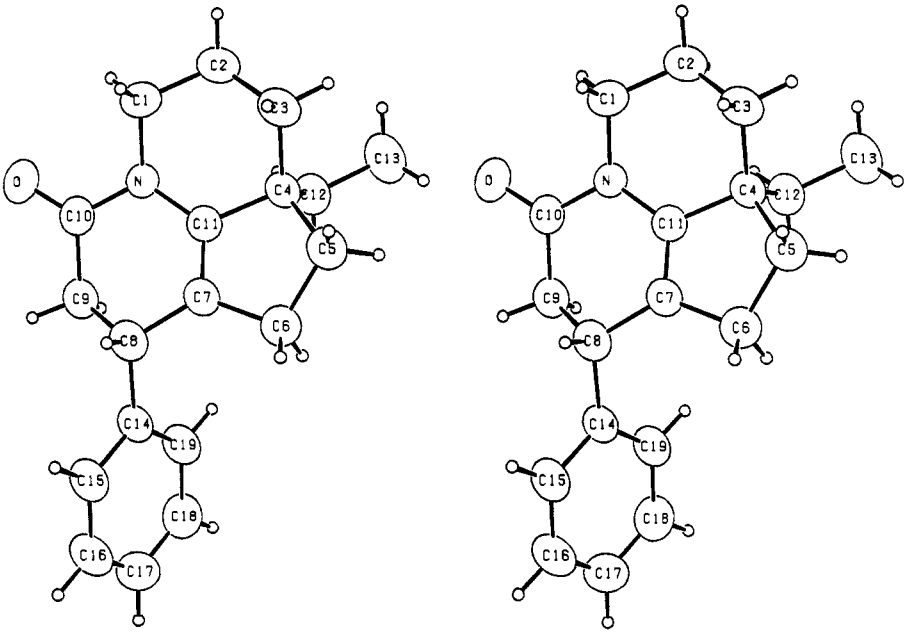


Figure 1. ORTEP stereoscopic representation of the X-ray crystal structure of compound **59**.

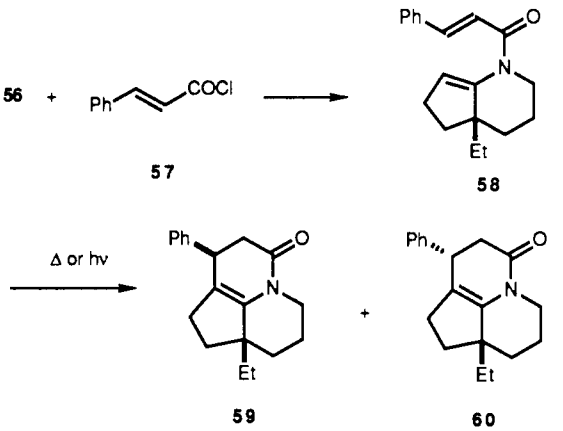
and acrylonitrile to give **54**, the product arising from the more stable enolate. Cyano ketone **54** is accompanied by its further cyanoethylation product, **55**. The amount of **55** is minimized by slow addition of 0.5 equiv of acrylonitrile to 1 equiv of 2-ethylcyclopentanone. Under these conditions, **54** is formed in 58% yield based on unrecovered ketone (Scheme XI). Reductive cyclization of **54** to imine **56** is accomplished by stirring the compound under **56** psi of hydrogen with a slurry of unactivated Raney nickel powder in methanolic KOH for 20 h. This reaction is worth noting, since the reductive conversion of cyano ketones to imines is uncommon.[36]

Initial attempts to convert bicyclic imine to a lactam of type **52** centered around the use of a electrocyclic reaction of enamide **58**, which is formed in 88% yield by reaction of cinnamoyl chloride with **56** in the presence of triethylamine. Attempts to cyclize enamide **58** under thermal or acid-catalyzed conditions give mostly decomposition products and a small amount (5%) of cyclized products **59** and **60** in a 2:1 ratio (Scheme XII). The structure of **59** was determined by single-crystal X-ray analysis (Figure 1).

Because of the inefficient nature of the acid-catalyzed cyclization of enamide **58**, photochemical conditions were explored. Evaluation of several different wavelengths and solvents showed that the yield of unsaturated lactams is greatest using 254-nm light. Interestingly, isomer **60** is favored over **59** and the diastereoselectivity of the photochemical ring closure is solvent dependent. In hexanes or methanol, **60** is favored over **59** in a ratio of 2:1. When benzene, a solvent that absorbs light near 254 nm, is employed as solvent, the **60**:**59** ratio is 94:6.

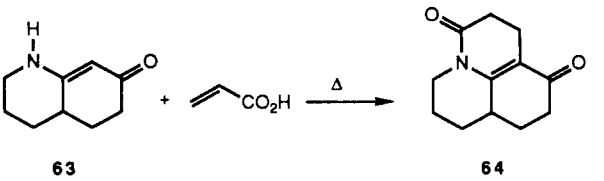
If we consider the dipolar resonance structure of enamide **58**, cyclization should occur in the photochemically preferred 6π-conrotatory sense (Scheme XIII). The initial cyclization product must be **61**. As depicted in the insert in Scheme XIII, **61** would result from a conformation in which the styrene group is located on the face of the enamide cis to the ethyl group. The actual conratatory closure would have to occur in the manner depicted, since the alternative motion would entail serious nonbonded

Scheme XII



interactions of the two vinyl hydrogens in the transition state. If the reactive conformation were the one in which the styrene unit is on the face trans to the ethyl group, the sterically permitted conrotatory closure would provide **62** and thence unsaturated lactam **59**. Indeed, molecular mechanics calculations of the energies of conformations **58a** and **58b** show that the former is more stable than the latter by approximately 4.5 kcal/mol.[37]

Having been thwarted in attempts to use unsaturated enamide **58** as a precursor to lactam **59**, we turned to other possible annelation methods. An attractive literature precedent for transformation of imine **56** into unsaturated lactam **59** is found in the work of Wiesner and Poon,[38] who discovered that vinylogous amide **63** reacts with excess acrylic acid to give enamide **64** in quantitative yield.

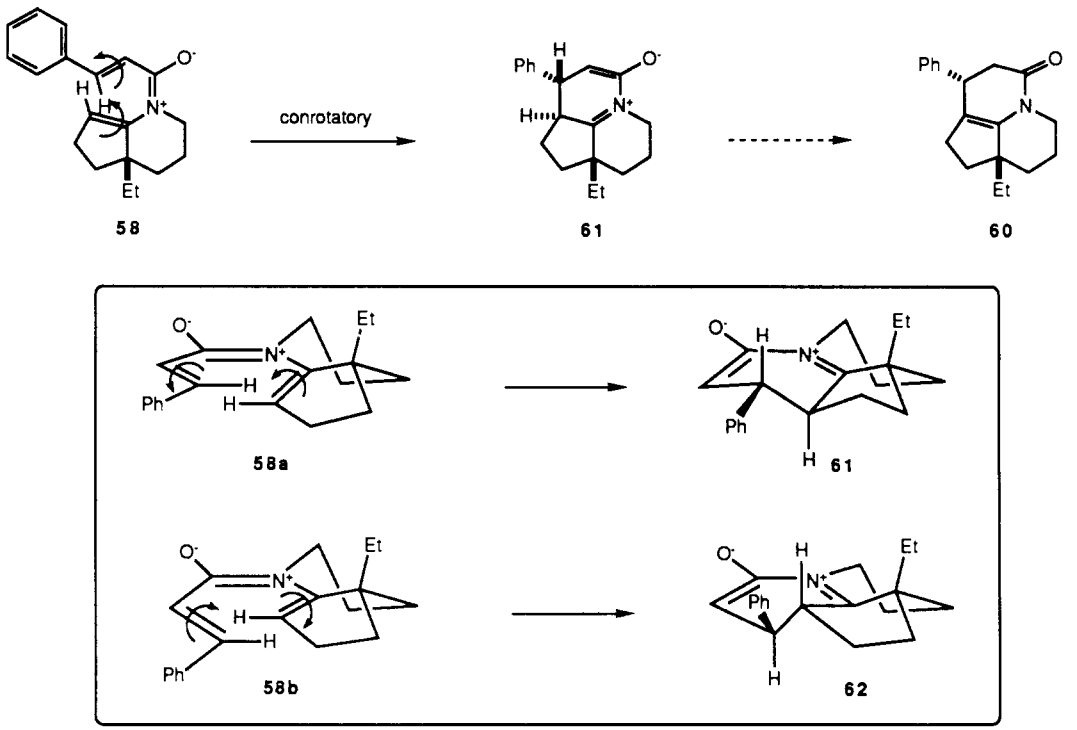


(36) Belleau, B. *Can. J. Chem.* **1957**, *35*, 651.

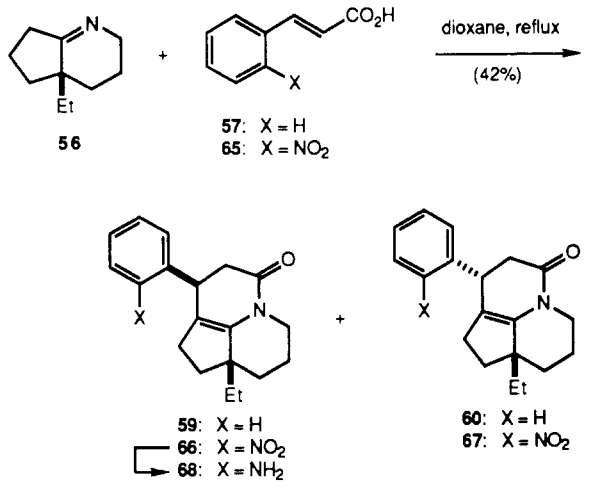
(37) Calculations were carried out with Still's Macromodel program (version 1.5) using the basic Allinger MM2 force field.

(38) Wiesner, K.; Poon, L. *Tetrahedron Lett.* **1967**, 4937.

Scheme XIII



Scheme XIV



The logical extension of this precedent, reaction of imine **56** with cinnamic acid (**57**), proceeds in 65% yield at 145 °C and with the desired stereochemistry, the ratio of **59** to **60** being 6:1 (Scheme XIV). Enamide **58** is not observed during the course of the reaction by ^{1}H NMR spectrometry, thin-layer chromatography, or capillary gas chromatography. Furthermore, when **58** is treated with cinnamic acid in decahydronaphthalene at 145 °C, cyclization occurs only to an extent of 5% after 72 h and the ratio of **59** to **60** is only 2:1. This experiment effectively rules out **58** as an intermediate in the reaction of **56** with **57**.

Since enamide **58** has been eliminated as an intermediate, we believe that the reaction of **56** and **57** proceeds by Michael reaction of **57** with the enamine tautomer of **56** (Scheme XV). If we make the reasonable assumption that cinnamic acid reacts on the face trans to the angular ethyl group, then the observed major product **59** would arise from a transition state as depicted in the Newman projection A, which appears to minimize steric interactions. The minor isomer, **60**, presumably results from transition state conformation B.

With the desired selective transformation to form lactam **59** in hand, further modification of the aromatic ring system was necessary to incorporate a nitrogen atom at the ortho position. To this end, the lactam annelation reaction was investigated with *o*-amino-, *o*-azido-, and *o*-acetamido-, and *o*-nitrocinnamic acids. In addition, we investigated the use of methyl *o*-nitrocinnamate with ammonium chloride as catalyst. Of these various reagents and conditions, the use of *o*-nitrocinnamic acid (**65**) worked best. Optimization of the reaction conditions showed that the highest yields and cleanest product was obtained if a 1:1 ratio of *o*-nitrocinnamic acid and its ammonium salt were used. Thus, reaction of **56** with 1.25 equiv of *o*-nitrocinnamic acid and 1.25 equiv of the corresponding ammonium salt in refluxing dioxane (100 °C) for 90 h gives **66** in 42% yield, based on the fact that 20% of the imine is recovered (Scheme XIV). Because of the lower reaction temperature, the lactam annelation reaction with *o*-nitrocinnamic acid appears to be more stereoselective than that with cinnamic acid; the **66**:**67** ratio is greater than 20:1. A major side product of the reaction is *o*-nitrotoluene (7–10%) and a minor one is indole. Both of these products are formed during the reaction regardless of whether or not *o*-nitroammonium cinnamate is present.

The next requirement of our synthetic plan was formation of the indoline ring. Direct activation of the nitro group with triethyl phosphite according to the procedure of Cadogan[39] was unsuccessful. However, reduction with hydrogen in the presence of Adam's catalyst provides aniline **68** in quantitative yield (Scheme XIV). Care must be taken in the handling of **68**, since it is prone to rearrangement under acidic conditions, yielding an epimeric mixture of quinolines (**69**).

(39) Cadagan, J. I. G.; Cameron-Wood, M.; Machie, R. U.; Searle, J. G. *J. Chem. Soc.* **1965**, 4831.

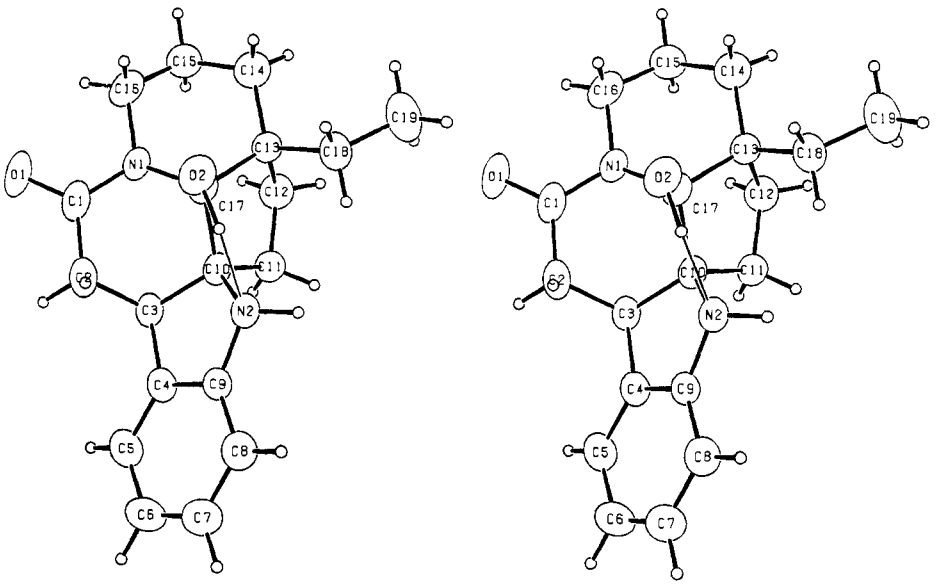
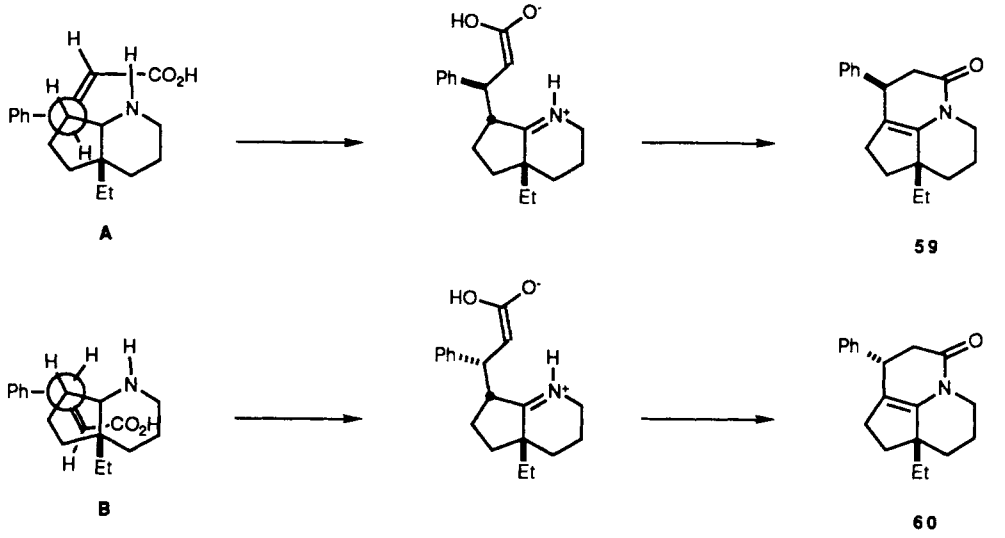
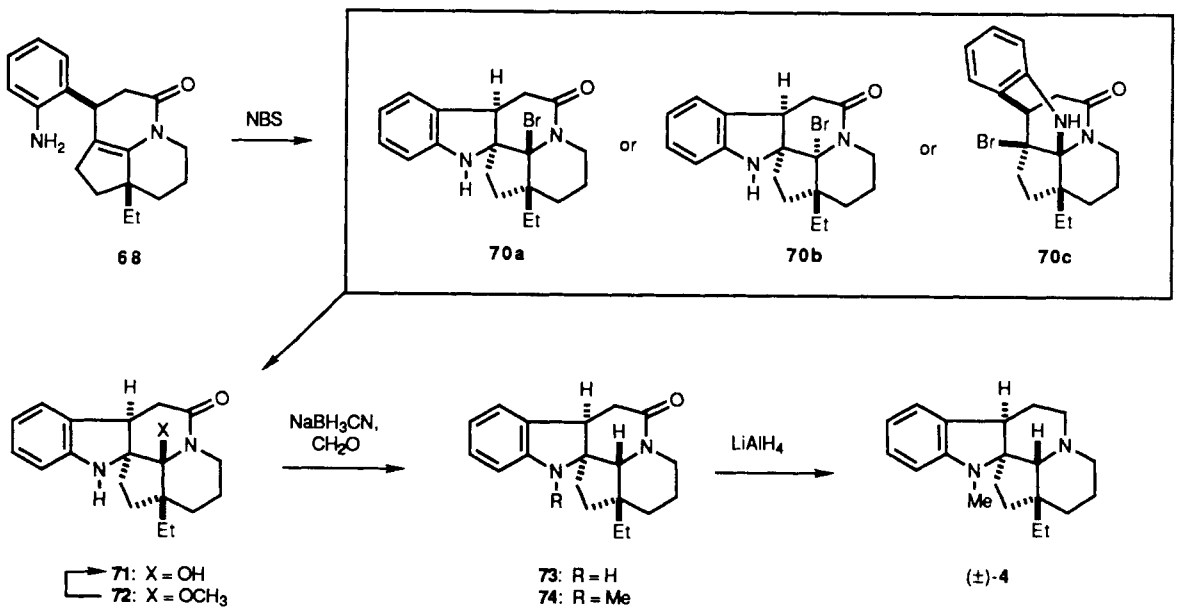


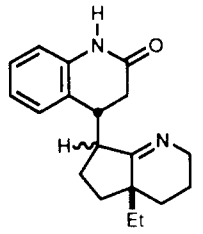
Figure 2. ORTEP stereoscopic representation of the X-ray crystal structure of compound **71**.

Scheme XV



Scheme XVI





69

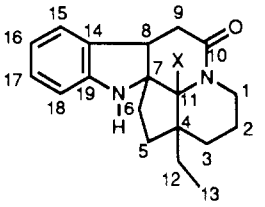
Treatment of aniline **68** with *N*-bromosuccinimide gives rise to a relatively unstable bromo lactam whose exact structure still has not been rigorously proven (Scheme XVI). The bromo lactam is converted into hydroxy lactam **71** by hydrolysis in refluxing aqueous acetone. The stereostructure of **71** is rigorously established by X-ray analysis (Figure 2). If the hydrolysis is carried out with silver nitrate in aqueous methanol, the product is a mixture of the hemihydrate of hydroxy lactam **71** (77%) and methoxy lactam **72** (20%). Methyl ether **72** is converted quantitatively into **71** by reaction with aqueous acetic acid.

Structures that have been considered for the intermediate bromo lactam are **70a**, **70b**, and **70c** (Scheme XVI). Compounds **70a** and **70b** would result from initial bromination of the aniline nitrogen, followed by nucleophilic displacement of bromide by the enamide double bond. The resulting acylimmonium ion would then react with bromide to give **70a** or **70b**. Alternatively, electrophilic attack of NBS on the enamide double bond (perhaps via an intermediate *N*-bromoaniline) could give an acylimmonium ion that would react with the aniline nitrogen to give **70c**. Although the bromo lactam is a solid, attempts to obtain a crystal suitable for X-ray analysis have been unsuccessful. The ^{1}H NMR spectrum of the bromo lactam is rather different from those of **71** and **72**, both in the chemical shifts and coupling constant patterns shown by analogous protons. Furthermore, although the ^{13}C NMR spectra of the three compounds are reasonably similar (Table I), there are significant differences. A particularly striking difference is seen in the resonance of C-19, which is shifted upfield by 10-11 ppm in the bromo lactam, relative to the analogous carbon in **71**, **72**, and **73**. The observed chemical shift for C-19 in the bromo lactam is unusual for indoline alkaloids.[40] For further comparison, the analogous resonances in vallesamidine (**4**) and andrangine (**5**)[9] occur at 151.4 and 149.5 ppm, respectively. This marked difference may signal that the intermediate bromo lactam has an unexpected structure, such as **70c**. However, the shifts of the sp^3 quaternary resonances (78.5 and 80.8 ppm) seem more consistent with a structure such as **70a** or **70b** than with **70c**.

Molecular mechanics calculations of structures **70a** and **70b** indicate that the isomer with bromine cis to the ethyl group is more stable than the isomer with bromine and ethyl trans by 6.2 kcal/mol.[37] If the bromine atom were trans to the ethyl group (e.g., **70b**), it is expected that equilibration to the more stable isomer **70a** could be induced to occur. However, treatment of the bromo lactam with excess lithium bromide in refluxing THF results in no change. Thus, of the two diastereomeric structures **70a** and **70b**, the former is more probable. On balance, however, we confess that the exact nature of the bromo lactam remains a mystery.

Hydroxy lactam **71** is converted into lactam **74** in 90% yield by treatment with sodium cyanoborohydride in aqueous acetic acid followed by addition of formalin solution. If the two-stage reduction is interrupted prior to addition of formalin, the intermediate *N*-demethyllactam **73** may be obtained. Lactam **74** is converted into (±)-vallesamidine by lithium aluminum hydride in refluxing THF. The synthesis requires seven steps from 2-ethylcyclopentanone and proceeds in 19% overall yield. Four of the seven steps involve the formation of skeletal (C–C or C–N) bonds and only three are functional group transformations.

Table I. ^{13}C NMR Shifts of Alcohol 71, Ether 72, and the Bromo Lactam (70a, 70b, or 70c)



C	73[a]	71[a]	72[a]	70a–c[b]
1	40.23 (2)	39.48 (2)	40.54 (2)	42.93
2	18.93 (2)	18.80 (2)	19.16 (2)	18.55
3	33.18 (2)	28.29 (2)	30.87 (2)	33.14
4	44.87 (0)	48.59 (0)	49.10 (0)	45.81
5	29.62 (2)	27.02 (2)	28.30 (2)	27.31
6	36.65 (2)	36.71 (2)	36.46 (2)	36.15
7	76.03 (0)	76.20 (0)	74.96 (0)	78.54
8	46.76 (1)	48.32 (1)	47.57 (1)	44.61
9	38.90 (2)	39.32 (2)	39.74 (2)	37.89
10	172.52 (0)	174.37 (0)	173.41 (0)	170.92
11	70.13 (1)	91.60 (0)	95.95 (0)	80.00
12	32.99 (2)	27.52 (2)	28.57 (2)	27.60
13	8.44 (3)	7.95 (3)	7.79 (3)	10.16
14	130.28 (0)	130.62 (0)	130.69 (0)	128.39
15	124.02 (1)	124.18 (1)	123.73 (1)	123.16
16	119.24 (1)	121.38 (1)	119.04 (1)	118.13
17	128.04 (1)	128.25 (1)	128.06 (1)	127.28
18	109.55 (1)	111.39 (1)	110.08 (1)	112.58
19	148.89 (0)	147.72 (0)	149.17 (0)	137.52

[a] Carbon type as determined by DEPT: (0) = quaternary, (1) = methine, (2) = methylene, (3) = methyl. [b] Carbon type not determined.

Experimental Section

General. Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. Benzene and tetrahydrofuran (THF) were distilled from sodium/benzophenone immediately prior to use. Dimethoxyethane (DME) and *tert*-butyl alcohol were distilled from sodium. Toluene, dimethylformamide (DMF), dimethyl sulfoxide (DMSO), triethylamine, pyridine, and acetonitrile were distilled from calcium hydride prior to use. Dichloromethane was dried over and distilled from phosphorus pentoxide. All reactions involving air- or moisture-sensitive compounds were performed under a nitrogen atmosphere. Gravity column chromatography was done with Merck silica gel 60 (70–230 mesh ASTM), and flash chromatography[41] was done with MN silica gel 60 (230–400 mesh ASTM). Thin-layer chromatography (TLC) was performed with Analtech silica gel FG TLC plates (250 μm). ^{1}H NMR spectra were meausred at 250, 300, or 500 MHz; resonances for minor diastereomers are given in brackets. ^{1}H NMR and ^{13}C NMR spectra were measured as $CDCl_3$ solutions and infrared spectra were measured as $CHCl_3$ solutions unless otherwise noted; coupling constants are given in hertz.

1-(Phenylmethyl)-3-ethyl-1,4,5,6-tetrahydropyridine (23) and (1-oxo-2-propenyl)trimethylsilane (24) were prepared by published procedures.[28,29]

(40) Shamma, M.; Hindenlang, D. M. *Carbon-13 NMR Shift Assignments of Amines and Alkaloids*; Plenum: New York, 1979.

(41) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

***cis*-(±)-4a-Ethyl-4a,5,6,7,8,8a-hexahydro-8-(phenylmethyl)-2-(trimethylsilyl)-4*H*-pyrano[2,3-*b*]pyridine (28).** A mixture of *N*-(phenylmethyl)-3-ethyl-1,4,5,6-tetrahydropyridine (**23**) (0.1560 g, 0.775 mmol) and (1-oxo-2-propenyl)trimethylsilane (**24**) (0.1491 g, 1.160 mmol, 1.5 equiv) was stirred at room temperature for 0.5 h. The light yellow product was purified by column chromatography on flash silica gel (12 g) with 20:1 hexanes/ethyl acetate as eluant to provide 0.2177 g (85%) of **28** (single diastereomer) as a colorless oil. IR: 1635, 1255, 1095, 995, 850 cm^{-1}. ^1H NMR: δ 0.12 (s, 9), 0.75 (t, 3, J = 7.6), 1.22 (m, 3), 1.35–2.00 (m, 5), 2.44 (dm, 1, J = 11.1), 2.71 (dt, 1, J = 11.4, 3.6), 3.69 (d, 1, J = 13.6), 3.87 (d, 1, J = 13.6), 4.02 (s, 1), 4.82 (dd, 1, J = 5.2, 2.4), 7.27 (m, 5). ^{13}C NMR: δ −2.43, 6.59, 21.15, 25.43, 28.35, 32.67, 33.56, 45.43, 58.53, 90.45, 106.98, 126.64, 128.04, 128.83, 139.69, 157.17. Anal. Calcd for $C_{20}H_{31}NSiO$: C, 72.89; H, 9.48; N, 4.25. Found: C, 72.66; H, 9.47; N, 4.22.

***trans*-(±)- and *cis*-(±)-1-(Phenylmethyl)-2-cyano-3-ethylhexahydropyridine (29 and 30).** A mixture of enamine **23** (0.129 g, 0.638 mmol), methyl acrylate (0.0514 g, 0.597 mmol, 0.93 equiv), sodium cyanide (0.0337 g, 0.687 mmol, 1.08 equiv), and absolute methanol (2.0 mL) was refluxed under N_2 for 24 h. The solvent was removed with a rotary evaporator to give a sticky, white solid that was purified by column chromatography on silica gel (7.5 g) with 20:1 hexanes/ethyl acetate as eluant to afford 0.132 g (90%) of **29** and **30** as colorless oils.

Cis Diastereomer 30 (R_f = 0.29 in 20:1 hexanes/ethyl acetate), 8.3 mg (18%). IR (film): 2240 (weak), 1460 cm^{-1}. ^1H NMR: δ 0.79 (t, 3, J = 7.3), 1.63 (m, 7), 2.50 (dt, 1, J = 11.6, 3.0), 2.73 (br dd, 1, J = 11.6, 3.4), 3.47 (d, 1, J = 13.3), 3.51 (br s, 1), 3.73 (d, 1, J = 13.3), 7.33 (m, 5). ^{13}C NMR: δ 11.72, 20.50, 23.06, 24.48, 38.84, 49.97, 55.04.

Trans Diastereomer 29 (R_f = 0.25 in 20:1 hexanes/ethyl acetate), 38.2 mg (82%). IR (film): 2240 (weak), 1460 cm^{-1}. ^1H NMR: δ 0.88 (t, 3, J = 7.4), 1.24 (m, 4), 1.63 (m, 3), 2.37 (dt, 1, J = 11.9, 3.2), 2.79 (br d, 1, J = 11.9), 3.59 (d, 1, J = 13.3), 3.69 (d, 1, J = 13.3), 3.73 (s, 1), 7.35 (m, 5). ^{13}C NMR: δ 11.07, 24.75, 25.89, 26.72, 40.04, 49.17, 57.60, 60.47, 115.31, 127.41, 128.40, 128.80, 137.08. Mass spectrum (70 eV): m/z 91 (base), 228 (parent). Anal. Calcd for $C_{15}H_{20}N_2$: C, 78.90; H, 8.83; N, 12.27. Found: C, 78.88; H, 8.91; 12.06.

Methyl (±)-3-(2′-Cyano-3′-ethyl-1′-(phenylmethyl)hexahydropyridin-3′-yl)propanoate (34): (a) From Enamine 23. A solution of methyl acrylate (0.195 g, 2.27 mmol, 1.5 equiv) and enamine **23** (0.305 g, 1.52 mmol) in 1.2 mL of absolute methanol was heated at reflux for 19 h in an oil bath. The solvent was removed with a rotary evaporator to afford 0.480 g (99%) of **31** as an orange oil in a 1:1 mixture of diastereomers. The crude **31** (0.480 g, 1.50 mmol) was dissolved in absolute methanol (2.0 mL), and sodium cyanide (0.223 g, 4.55 mmol) was added. The solution was stirred at room temperature for 10 min and quenched with water (4.0 mL). Saturated brine was added to the resulting milky mixture until the solution became clear. The aqueous solution was extracted with ethyl acetate (3 × 5 mL). The organic extracts were combined, dried over $MgSO_4$, filtered, and concentrated to give 0.448 g of crude material. The orange residue was purified by flash chromatography (20 g) with 15:1 hexanes/ethyl acetate as eluant to yield 0.348 g (73% from **23**) of **34** as a light yellow oil (1:1 ratio of diastereomers). IR (film): 2220 (weak), 1740, 1455 cm^{-1}. ^1H NMR:[42] δ 0.65 (t, 3, J = 7.5), 0.78 (t, 3, J = 7.5), 1.18–2.23 (m, 10), 2.82 (br d, 1, J = 10.3), 3.33 (s, 1), 3.49 (m, 1), 3.65 (s, 3), 3.69 (s, 3), 3.70 (d, 1, J = 13.1), 7.32 (m, 5). ^{13}C NMR: δ 6.59, 6.95, 20.52, 22.80, 25.05, 27.56, 27.94, 29.23, 30.01, 30.24, 31.24, 37.80, 37.83, 49.24, 51.68, 59.82, 60.02, 60.37, 115.24, 115.27, 127.59, 128.44, 128.46, 128.84, 136.99, 173.47, 173.89. Anal. Calcd for $C_{19}H_{26}N_2O_2$: C, 72.58; H, 8.33; N, 8.91. Found: C, 72.42; H, 8.35; N, 8.76.

(b) From 38. A solution of compound **38** (0.0259 g, 0.0848 mmol) and sodium cyanide (0.012 g, 0.25 mmol) in 0.5 mL of absolute methanol was stirred at room temperature for 10 min. The solution was diluted with 5 mL of water, saturated brine was added until the milky mixture became clear, and the solution was extracted with ethyl acetate. The extracts were dried over $MgSO_4$, filtered, and concentrated to give 35.2 mg of crude material that was purified by chromatography on silica gel (1.7 g) with 15:1 hexanes/ethyl acetate as eluant to afford 0.0188 g (71%) of **34** as a colorless oil (1:1 mixture of diastereomers). This material was spectrally identical with that obtained by method a.

(±)-1-(Phenylmethyl)-2-cyano-3-ethyl-3-(2-cyanoethyl)-hexahydropyridine (35). Enamine **23** (0.0556 g, 0.276 mmol), acrylonitrile (0.040 mL, 0.032 g, 0.607 mmol, 2.2 equiv), and absolute methanol (0.25 mL) were placed in a 0.5-mL Wheaton vial and heated at 75 °C in an oil bath for 24 h. An additional portion of acrylonitrile (0.090 mL, 0.073 g, 1.37 mmol, 5.0 equiv) was added, and the resulting solution was heated at 80–90 °C for 60 h. The solvent was removed to afford 99.8 mg of crude **32**. A solution of this material and sodium cyanide (0.0680 g, 1.38 mmol, 5.0 equiv) in 1.0 mL of methanol was stirred for 10 min at room temperature. The mixture was diluted with water and extracted with ethyl acetate (2 × 10 mL). The organic extracts were dried over $MgSO_4$, filtered, and concentrated to give 81.3 mg of an orange oil that was purified by chromatography on silica gel (3.5 g) with 15:1 hexanes/ethyl acetate as eluant to yield 0.0588 g (76% based on **23**) of **35** as a colorless oil as a 2:1 mixture of diastereomers. IR: 2260, 2220 cm^{-1}. ^1H NMR: δ 0.65 (t, 3, J = 7.5), [0.78 (t, 3, J = 7.5)], 1.21 (t, 2, J = 7.0), 1.25–2.15 (m, 7), 2.21 (m, 1), 2.45 (dt, 1, J = 12.0, 3.3), [2.48 (dt, 1, J = 12.0, 3.3)], 2.83 (dm, 1, J = 10.5), [3.27 (s, 1)], 3.33 (s, 1), [3.48 (m, 1)], 3.50 (d, 1, J = 13.1), 3.72 (d, 1, J = 13.1), 7.35 (m, 5). ^{13}C NMR: δ (6.53), 6.90, 11.01, (11.16), 20.28, (20.42), 22.57, (25.86), (28.69), 29.76, (29.85), 31.79, (37.91), 38.05, 49.08, (49.17), 59.17, (59.34), (60.14), 60.27, (114.65), 114.91, 119.25, (119.53), 127.66, (127.79), 128.57, (128.57), 128.80, 136.64, (136.67). Anal. Calcd for $C_{18}H_{23}N_3$: C, 76.83; H, 8.24; N, 14.93. Found: C, 76.55; H, 8.34; N, 14.67.

1,1-Dimethylethyl (±)-3-(2′-Cyano-3′-ethyl-1′-(phenylmethyl)hexahydropyridin-3′-yl)propanoate (36): (a) From Enamine 23 under High-Pressure Conditions. Two 17-mm Teflon tubes clamped on one end were each charged with enamine (0.5028 g, 2.498 mmol), *tert*-butyl acrylate (0.4802 g, 3.474 mm, 1.5 equiv), and absolute methanol (1.30 mL). The tubes were clamped shut, placed in a high-pressure apparatus[43] and pressurized at 7 kbar for 24 h. The combined reaction mixtures from the two tubes were concentrated to give 1.6953 g (97%) of crude **33** as a light orange oil, as a 1:1 mixture of diastereomers. The crude material was taken up in absolute methanol (5.0 mL) and cooled to 0 °C. To the cooled solution was added powdered sodium cyanide (0.4870 g, 9.936 mmol, 2.0 equiv), and the resulting mixture was stirred at 0 °C for 0.5 h. After dilution with water (5.0 mL) the milky solution was extracted with ethyl acetate (3 × 10 mL). The organic extracts were dried over $MgSO_4$ and concentrated to give 1.6098 g of a crude orange oil that was purified by chromatography on flash silica (65 g) with 15:1 hexanes/ethyl acetate as eluant to provide 1.1325 g (64%) of **36** as a viscous, colorless oil in a 1:1 diastereomeric ratio. IR (film): 1735, 1460, 1375, 1160 cm^{-1}. ^1H NMR:[40] δ 0.66 (t, 3, J = 7.5), 0.78 (t, 3, J = 7.5), 1.25–2.10 (m, 6), 1.42 (s, 9), 1.47 (s, 9), 2.43 (dt, 1, J = 12.1, 3.1), 2.80 (m, 1), 3.33 (s, 1), 3.49 (d, 1, J = 13.3), 3.69 (d, 1, J = 13.3), 3.70 (d, 1, J = 13.2), 7.32 (m, 5). ^{13}C NMR: δ 6.63, 7.01, 20.56, 22.84, 25.08, 27.98, 28.06, 28.91, 29.31, 29.33, 30.04, 30.28, 31.30, 37.77, 37.85, 49.24, 49.30, 59.97, 60.05, 60.38, 80.25, 80.40, 115.32, 127.55, 128.43, 128.45, 128.83, 137.08, 172.37, 172.79. Anal. Calcd for $C_{22}H_{32}N_2O_2$: C, 74.12; H, 9.05; N, 7.86. Found: C, 74.45; H, 9.15; N, 7.55.

(b) From Enamine 23 under Thermal Conditions. *tert*-Butyl acrylate (0.0963 g, 0.752 mmol, 1.1 equiv), enamine **23** (0.1376 g, 0.6835 mmol), and absolute methanol (0.50 mL) were placed in a 0.50-mL Wheaton vial and heated in an oil bath at 120 °C for 24 h. After concentration, the resulting orange oil was taken up in absolute methanol (2.5 mL), and the solution was cooled to 0 °C. Sodium cyanide (0.1675 g, 3.42 mmol, 5.0 equiv) was added, and the solution was allowed to stir at 0 °C for 1 h. The mixture was diluted water (3.0 mL) and extracted with ethyl acetate (3 × 3 mL). The organic extracts were dried over $MgSO_4$ and concentrated to give 202.1 mg of an orange oil that was purified by column chromatography on silica gel (7 g) with 15:1 hexanes/ethyl acetate as eluant to yield 80.8 mg (33%) of **36** as

(42) It was not possible to assign various multiplets to given diastereomers.

(43) DeShong, P.; Dicken, C. M.; Perez, J. J.; Shoff, R. M. *Org. Prep. Proc. Int.* **1982**, *14*, 369.

a colorless oil (1:1 diastereomeric ratio). This material was identical spectrally with that obtained by method a.

(c) From Cyclobutane 37 under Thermal Conditions. A solution of cyclobutane **37** (0.0341 g, 0.1035 mmol) and sodium cyanide (0.0254 g, 0.517 mmol, 5.0 equiv) in 1.0 mL of methanol was refluxed for 1 h. The mixture was diluted with water and extracted with ethyl acetate. The extracts were dried over $MgSO_4$ and concentrated to give 23.0 mg of crude material. ^1H NMR indicated approximately 50% conversion. The crude material was taken up in absolute methanol (1.0 mL), sodium cyanide (0.040 g) was added, and the mixture was heated at reflux for 2 h and worked up as before to give 0.0216 g (69%) of crude **36**, identical spectrally with that obtained by methods a and b.

1,1-Dimethylethyl (±)-6-Ethyl-2-(phenylmethyl)-2-azabicyclo[4.2.0]octane-8-carboxylate (37). A mixture of enamine (0.1546 g, 0.7680 mmol), *tert*-butyl acrylate (0.1476 g, 1.152 mmol, 1.5 equiv), and dry CH_3CN (0.40 mL) was heated at 105 °C in an oil bath for 72 h. Additional portions of *tert*-butyl acrylate (0.0984 g, 0.7686 mmol, 1.0 equiv) were added after 15 and 42 h of heating. The solvent was removed to give 0.2217 g of an orange oil that was purified by flash chromatography with 20:1 hexanes/ethyl acetate as eluant to provide 0.0779 g (31%) of a single diastereomer of **37** as a light yellow oil. IR (film): 1725, 1460, 1370, 1150 cm^{-1}. ^1H NMR: δ 0.86 (t, 3, J = 7.5), 1.44 (s, 9), 1.55 (m, 7), 1.79 (m, 1), 2.26 (m, 1), 2.57 (dm, 1, J = 11.7), 3.23 (q, 1, J = 8.7), 3.40 (d, 1, J = 8.3), 3.42 (d, 1, J = 13.7), 3.70 (d, 1, J = 3.7), 7.28 (m, 5). ^{13}C NMR: δ 8.72, 22.52, 28.07, 30.21, 30.99, 31.09, 35.36, 39.41, 46.76, 58.45, 66.54, 79.70, 126.67, 128.07, 128.43, 139.21, 174.82. Mass spectrum (70 eV): m/z 329 (parent), 186 (base). Anal. Calcd for $C_{21}H_{31}NO_2$: C, 76.55; H, 9.48; N, 4.24. Found: C, 76.60; H, 9.57; N, 4.32.

Methyl (±)-3-(2′-Hydroxy-3′-ethyl-1′-(phenylmethyl)-hexahydropyridin-3′-yl)propanoate (38). Enamine **23** (0.109 g, 0.544 mmol), methyl acrylate (0.052 g, 0.598 mmol, 1.1 equiv), and absolute methanol (0.50 mL) were placed in a Teflon tube that was then sealed at both ends with pinch clamps and placed in a high-pressure apparatus under 7 kbar of pressure for 16 h. The solvent was removed to give 0.166 g of **31** (1:1 mixture of diastereomers). The material was purified by chromatography on silica gel (8 g) with 1:1 hexanes/ethyl acetate as eluant. During chromatography, hydrolysis of the methyl aminal **31** resulted to provide 0.124 g (75%) of **38** (1:1 mixture of diastereomers) as a light yellow oil. IR (film): 3505 (broad), 1740, 1455 cm^{-1}. ^1H NMR:[40] δ 0.75 (t, 3, J = 7.6), 0.79 (t, 3, J = 7.6), 1.33 (m, 5), 1.65 (m, 3), 1.88 (m, 1), 2.17 (m, 3), 2.42 (br d, 0.5, J = 5.1), 2.46 (d, 0.5, J = 2.6), 2.64 (tt, 1, J = 12.0, 3.4), 3.59 (d, 1, J = 3.5), 3.63 (s, 3), 3.65 (d, 1, J = 3.5), 3.70 (s, 3), 3.74 (s, 1), 3.80 (s, 1), 3.97 (d, 1, J = 5.6), 4.08 (d, 1, J = 5.6). ^{13}C NMR: δ 6.75, 6.98, 14.08, 15.16, 20.78, 20.85, 23.26, 25.96, 27.16, 27.26, 27.72, 28.14, 29.38, 39.43, 39.67, 44.35, 51.54, 58.64, 60.29, 65.72, 86.73, 86.78, 126.67, 126.74, 128.05, 128.11, 128.37, 128.42, 139.35, 139.54, 174.70, 175.17. Mass spectrum (70 eV): m/z 305 (parent), 91 (base). Anal. Calcd for $C_{18}H_{27}NO_3$: C, 70.78; H, 8.91; N, 4.58. Found: C, 70.44; H, 9.00; N, 4.39.

(±)-4a-Ethyloctahydro-8-(phenylmethyl)-2*H*-pyrano[2,3-*b*]pyridin-2-one (40). A solution of compound **34** (0.1055 g, 0.3355 mmol) and dry toluene (2.0 mL) was concentrated under vacuum. Fresh toluene (1.0 mL) and potassium *tert*-butoxide (0.1506 g, 1.340 mmol, 4.0 equiv) were added, and the solution was stirred at room temperature under N_2 for 9 h. Water (2.0 mL) was added to the thick mixture, and the resulting aqueous solution was extracted with ethyl acetate (3 × 3 mL). The organic extracts were dried over $MgSO_4$, filtered, and concentrated to give 0.1239 g of a light yellow oil. This material was filtered through flash silica gel (5.5 g) with 9:1 hexanes/ethyl acetate followed by straight ethyl acetate as eluants. The crude material was taken up in a mixture of 0.25 mL of concentrated H_2SO_4, and 0.75 mL of water and the resulting solution was heated at 80 °C for 22 h. After being cooled to room temperature, the reaction mixture was made basic by the addition of saturated K_2CO_3. The basic solution was extracted with ethyl acetate (3 × 3 mL). The organic extracts were dried over $MgSO_4$ and concentrated to give 0.0464 g of an orange oil. This material was purified by flash chromatography with ether as eluant to yield 0.0286 g (35%) **40** as a single diastereomer. IR (film): 1730 cm^{-1}. ^1H NMR: δ 0.82 (t, 3, J = 7.6), 1.22–2.00 (m, 8), 2.47 (m, 2), 2.58 (br dd, 1, J = 11.7, 5.2), 2.77 (dt, 1, J = 12.1, 3.2), 3.79 (d, 1, J = 13.9), 3.96 (d, 1, J = 13.9), 4.79 (s, 1), 7.30 (m, 5). ^{13}C NMR: δ 6.93, 22.22, 24.85, 26.77, 28.20, 28.95, 34.50, 44.21, 58.00, 99.40, 127.04, 128.21, 128.50, 138.22, 173.06. Mass spectrum (70 eV): m/z 273 (parent), 91 (base). Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.43; H, 8.33; N, 4.99.

1,1-Dimethylethyl *cis*-(±)-7-Amino-4a-ethyl-2,3,4,4a,5,7a-hexahydro-1-(phenylmethyl)-1*H*-1-pyrindine-6-carboxylate (42). A solution of aminonitrile **36** (0.1061 g, 0.2980 mmol) in dry toluene (2.0 mL) was concentrated to fully dry the sample. Fresh toluene (1.0 mL) and potassium *tert*-butoxide (0.1336 g, 1.19 mmol, 4.0 equiv) were added, and the resulting mixture was heated in an oil bath at 65 °C. After 15 min, the solution became sufficiently thick to stop the magnetic stirring bar. An additional portion of toluene (1.0 mL) was added, and heating was continued for 12 h. The mixture was allowed to cool to room temperature and diluted with 5.0 mL of water (5.0 mL), and the aqueous solution was extracted with ethyl acetate (2 × 10 mL). The organic extracts were washed with saturated brine, dried over $MgSO_4$, and concentrated to give 0.1077 g of a dark orange oil. The crude material was purified by bulb-to-bulb distillation at reduced pressure (bp 150–160 °C, 0.25 Torr) to give 0.0689 g (65%) of a single diastereomer of **42** as a viscous yellow oil that slowly crystallized to give light yellow crystals, mp 138–140 °C. IR: 3495, 3380, 1670, 1645, 1535 cm^{-1}. ^1H NMR: δ 0.88 (m, 1), 0.94 (t, 3, J = 7.3), 1.06 (br d, 1, J = 13.5), 1.40–2.00 (m, 7), 1.48 (s, 9), 2.14 (d, 1, J = 13.5), 2.65 (m, 2), 3.43 (s, 1), 3.99 (s, 2), 7.33 (m, 5). ^{13}C NMR: δ 9.44, 15.77, 28.60, 29.85, 30.53, 38.71, 41.04, 47.17, 58.76, 70.26, 78.23, 92.53, 127.05, 128.28, 128.50, 140.07, 168.20. Anal. Calcd for $C_{22}H_{32}N_2O_2$: C, 74.12; H, 9.05; N, 7.86. Found: C, 73.86; H, 9.13; 7.68.

***cis*-(±)-4a-Ethyloctahydro-1-(phenylmethyl)-7*H*-1-pyrindin-7-one (43): (a) From *tert*-Butyl Ester 36.** A solution of nitrile ester **36** (0.1158 g, 0.3248 mmol) in dry toluene (2.0 mL) was concentrated to dryness to fully dry the sample. Fresh toluene (2.0 mL) and potassium *tert*-butoxide (0.1458 g, 1.299 mmol, 4.0 equiv) were added, and the reaction mixture was stirred at room temperature under N_2 for 6 h. The mixture was diluted with water (3.0 mL), and the solution was extracted with ethyl acetate (3 × 3 mL). The organic extracts were dried over $MgSO_4$ and concentrated to give 0.1077 g of a crude viscous yellow oil. A mixture of the crude enamine ester **42** in 3.0 mL of 20% H_2SO_4 was heated at reflux for 45 min, during which time the sticky solid slowly went into solution. The mixture was cooled to 0 °C in an ice bath and made basic by the addition of saturated K_2CO_3. The solution was extracted with ethyl acetate (5 × 30 mL). The extracts were dried over $MgSO_4$ and concentrated to give 54.9 mg of a crude orange oil that was purified by column chromatography on flash silica gel (2.5 g) with 15:1 hexanes/ethyl acetate as eluant to give 0.0546 g (66%) of **43** as a light yellow oil. IR: 1740, 1455, 1160 cm^{-1}. ^1H NMR: δ 0.84 (t, 3, J = 7.5), 1.21 (m, 1), 1.35–1.83 (m, 7), 2.19 (m, 2), 2.48 (dt, 1, J = 11.4, 4.1), 2.60 (dt, 1, J = 11.4, 3.0), 2.73 (s, 1), 4.02 (d, 1, J = 14.0), 4.09 (d, 1, J = 14.0), 7.27 (m, 5). ^{13}C NMR: δ 7.90, 21.54, 28.12, 28.16, 29.03, 33.50, 40.67, 48.14, 58.53, 72.51, 126.67, 128.03, 128.48, 139.81, 220.90. Anal. Calcd for $C_{17}H_{23}NO$: C, 79.33; H, 9.01; N, 5.44. Found: C, 79.30; H, 9.10; N, 5.42.

(b) From Enamine Ester 42. A mixture of enamine ester **42** (0.1446 g, 0.4056 mmol) and 20% H_2SO_4 (2.50 mL) was refluxed for 1 h; the solid went into solution after 10 min. The mixture was cooled in an ice bath and made basic by the slow addition of saturated K_2CO_3. The solution was extracted with ethyl acetate (4 × 5 mL). The extracts were dried over $MgSO_4$ and concentrated to give 82.2 mg of an orange oil that was a 9:1 mixture of bicyclic ketone **43** and lactone **40** as determined by integration of the ^1H NMR signals at 2.73 and 4.79 ppm, respectively. The crude material was purified by column chromatography on flash silica gel (3.5 g) with 12:1 hexanes/ethyl acetate as eluant to give 0.0573 g (55%) of **43** as a colorless oil.

Analogous acid hydrolysis of enamine ester **42** with (0.1061 g, 0.2976 mmol) with acetic acid (1.0 mL), water (1.0 mL), and concentrated H_2SO_4 (2 drops) gave 0.0575 g of a crude orange oil that was a 2:1 mixture of bicyclic ketone **43** and lactone **40**. Acid hydrolysis of **42** (0.1185, 0.3324 mmol) with 10% H_2SO_4 gave 0.0718 g of an orange oil that was a 3:1 mixture of bicyclic ketone **43** and lactone **40**. In each case, the material isolated was identical

spectrally with that obtained by method a.

***cis*-(±)-4a-Ethyloctahydro-1-(phenylmethyl)-7*H*-1-pyrindin-7-one Ethylene Ketal (44).** A solution of bicyclic ketone **43** (0.1631 g, 0.6337 mmol), ethylene glycol (0.1966 g, 3.168 mmol, 5.0 equiv), and 2-naphthalenesulfonic acid (0.2867 g, 1.267 mmol, 2.0 equiv), in 2.0 mL of toluene was refluxed under a Dean–Stark trap for 15 h, during which time the mixture separated into two phases. After the mixture was cooled to room temperature, saturated K_2CO_3 was added and the resulting white emulsion was extracted with ethyl acetate (6 × 5 mL). The organic extracts were dried over $MgSO_4$ and filtered. The solvent was removed to give 0.2019 g of a reddish oil that was purfied by column chromatography on flash silica gel (9.0 g) with 15:1 hexanes/ethyl acetate as eluant to give 0.1485 g (78%) of **44** as a colorless oil. IR (film): 2950, 1460, 1170 cm^{-1}. ^1H NMR: δ 0.83 (t, 3, J = 7.5), 1.25–1.65 (m, 7), 1.70–2.05 (m, 3), 2.45 (dm, 1, J = 11.2), 2.89 (s, 1), 3.00 (dt, 1, J = 11.2, 3.5), 3.76 (m, 2), 4.05 (m, 4), 7.26 (m, 5). ^{13}C NMR: δ 8.55, 21.05, 26.80, 29.97, 31.84, 34.92, 41.40, 46.12, 58.82, 62.72, 64.37, 71.26, 119.53, 126.28, 127.87, 128.05, 141.32. Anal. Calcd for $C_{19}H_{27}NO_2$: C, 75.71; H, 9.03; N, 4.65. Found: C, 75.71; H, 8.96; N, 4.61.

***cis*-(±)-4a-Ethyloctahydro-7*H*-1-pyrindin-7-one Ethylene Ketal (45).** A mixture of ketal **44** (5.50 g, 18.24 mmol), absolute methanol (30 mL), 10% palladium on carbon (0.237 g), and concentrated HCl (1.9 mL) was stirred under H_2 for 16 h, then filtered through a plug of Celite with the aid of ether. The filtrate was washed with saturated K_2CO_3, dried over $MgSO_4$, and concentrated to yield 3.80 g (98%) of **45** as a colorless oil. IR (film): 3380, 1460, 1110 cm^{-1}. ^1H NMR: δ 0.83 (t, 3, J = 7.5), 1.25–1.65 (m, 8), 1.75–2.10 (m, 3), 2.52 (ddd, 1, J = 11.6, 8.2, 3.5), 2.60 (s, 1), 3.03 (m, 1), 3.91 (m, 4). ^{13}C NMR: δ 7.80, 21.35, 28.80, 29.52, 30.46, 33.37, 41.39, 43.21, 63.87, 64.03, 66.03, 117.77. Anal. Calcd for $C_{12}H_{21}NO_2$: C, 68.21; H, 10.02; N, 6.63. Found: C, 68.10; H, 10.09; N, 6.57.

3-Chlorophenylethanoyl Chloride. A mixture of 3-chlorophenylacetic acid (5.00 g, 29.3 mmol), 80 mL of dry benzene, and $SOCl_2$ (4.28 mL, 6.97 g, 58.6 mmol, 2.0 equiv) was refluxed for 2 h. The reflux condenser was removed and a distillation head was attached. The benzene and excess $SOCl_2$ were distilled at atmospheric pressure to leave a red liquid as the pot residue. This material was purified by bulb-to-bulb distillation under reduced pressure to yield 4.94 g (89%) of the acid chloride as a burgundy liquid. IR (film): 1795, 1480, 970 cm^{-1}. ^1H NMR: δ 4.15 (s, 2), 7.16 (m, 1), 7.27 (m, 1), 7.32 (m, 2). ^{13}C NMR: δ 52.37, 127.70, 128.43, 129.65, 130.18, 132.97, 134.72, 171.39. Anal. Calcd for $C_8H_6Cl_2O$: C, 51.04; H, 3.19. Found: C, 50.71; H, 2.92.

1-Chloro-3-(3′-chlorophenyl)-2-propanone (46). To 3-chlorophenylacetyl chloride (4.94 g, 26.02 mmol) was added 232.0 mL of a 0.28 M solution of diazomethane in ether. The red-burgundy color of the acid chloride dissipated immediately upon the addition of the diazomethane. The resulting light yellow solution was stirred at room temperature for 4 h and cooled to 0 °C with an ice bath, and gaseous HCl was bubbled through the solution for 5–10 min. After the slow addition of 100 mL of water, the organic layer was separated, and the aqueous phase was extracted with ether (3 × 25 mL). The organic extracts were combined, washed with saturated $NaHCO_3$, dried over $MgSO_4$, and concentrated to give 3.76 g of a crude amber oil. This material was purified by bulb-to-bulb distillation at reduced pressure followed by column chromatography on flash silica gel (90 g) with 9:1 hexanes/ethyl acetate as eluant to give 2.10 g (40%) of **46** as a light yellow oil, bp 90–93 °C (0.22–0.25 Torr) [lit.[32] mp 32–35 °C]. IR (film): 1740 cm^{-1}. ^1H NMR: δ 3.89 (s, 2), 4.12 (s, 2), 7.11 (m, 1), 7.23 (m, 1), 7.28 (m, 2). ^{13}C NMR: δ 46.61, 47.70, 127.54, 127.63, 129.54, 130.01, 134.57, 199.19. Anal. Calcd for $C_9H_8Cl_2O$: C, 53.44; H, 3.95. Found: C, 53.46; H, 3.89.

***cis*-(±)-1-(3-Chlorophenyl)-3-(4′a-ethylhexahydrospiro-[1,3-dioxolane-2,7′-[7*H*-1]pyrindin]-1′(2′*H*)-yl)-2-propanone (47).** A solution of ketal amine **45** (0.0978 g, 0.3947 mmol), α-chloro ketone **46** (0.0801 g, 0.4219 mmol, 1.07 equiv), diisopropylethylamine (0.075 mL, 0.0561 g, 0.4342 mmol, 1.1 equiv), and dry acetonitrile (0.60 mL) was refluxed for 40 min. The mixture was allowed to cool to room temperature, diluted with ethyl acetate, washed with saturated K_2CO_3, dried over $MgSO_4$, and concentrated to give 0.1532 g of an orange oil that was purified by flash chromatography with 6:1 hexanes/ethyl acetate as eluant to give 0.1092 g (73%) of **47** as a light orange oil. IR (film): 1720, 1600, 1470 cm^{-1}. ^1H NMR: δ 0.88 (t, 3, J = 7.5), 1.44 (m, 6), 1.75 (m, 3), 2.02 (m, 1), 2.34 (ddd, 1, J = 10.9, 4.7, 2.1), 2.87 (s, 1), 3.05 (dt, 1, J = 11.6, 3.2), 3.31 (d, 1, J = 16.6), 3.61 (d, 1, J = 16.6), 3.68–4.12 (m, 6), 7.10 (m, 1), 7.24 (m, 3). ^{13}C NMR: δ 8.53, 20.91, 25.99, 29.97, 31.69, 34.58, 41.39, 45.58, 47.94, 62.52, 64.18, 64.60, 71.28, 119.07, 126.81, 127.59, 129.59, 129.62, 134.12, 136.58, 209.60. Anal. Calcd for $C_{21}H_{28}ClNO_3$: C, 66.74; H, 7.47; N, 3.71. Found: C, 66.67; H, 7.42; N, 3.87.

***cis*-(±)-1-(3-Chlorophenyl)-7a-ethyl-6,7,7a,8,9,9b-hexahydro-3*H*-cyclopenta[*ij*]quinolizin-2(5*H*)-one (48).** Ketal ketone **47** (0.506 g, 0.2707 mmol) was taken up in 21 mL of 1.4 N HCl, and the resulting solution was heated at reflux for 105 min. The reaction mixture was cooled to room temperature and neutralized by the addition of 5% aqueous NaOH. The solution was extracted with CH_2Cl_2 (3 × 20 mL). The organic extracts were dried over K_2CO_3 and concentrated to provide a crude yellow oil that was purified by flash chromatography with 2:1 hexanes/ethyl acetate as eluant to give 0.249 g (59%) of **48** as a light yellow oil. IR: 1675 cm^{-1}. ^1H NMR: δ 0.93 (t, 3, J = 7.5), 1.09 (dt, 1, J = 13.5, 3.4), 1.58 (m, 6), 1.96 (septet, 1, J = 7.6), 2.50 (m, 2), 2.72 (m, 2), 3.43 (d, 1, J = 17.2), 3.72 (d, 1, J = 17.2), 3.85 (s, 1), 7.06 (m, 1), 7.16 (m, 1), 7.28 (m, 2). ^{13}C NMR: δ 8.97, 21.10, 26.33, 27.10, 28.77, 33.46, 42.78, 46.99, 62.94, 68.87, 127.50, 127.58, 129.28, 129.38, 133.03, 133.91, 135.43, 162.81, 194.93. Mass spectrum (70 eV): m/z 315 (parent), 84 (base). HRMS: Calcd for $C_{19}H_{22}NO^{37}Cl$ 317.1362, found 317.1358; calcd for $C_{19}H_{22}NO^{35}Cl$ 315.1392, found 315.1381.

***cis*-(±)-3-(4′a-Ethylhexahydrospiro[1,3-dioxolane-2,7′-[7*H*-1]pyrindin]-1′(2′*H*)-yl)-2-propanone (49).** A solution of ketal amine **45** (0.482 g, 2.82 mmol), α-chloroacetone (0.211 g, 2.28 mmol, 1.00 equiv), diisopropylethylamine (0.324 g, 2.51 mmol, 1.10 equiv), and acetonitrile (7 mL) was refluxed for 3 h. The mixture was allowed to cool to room temperature and partitioned between 75 mL of CH_2Cl_2 and 30 mL of 5% aqueous NaOH. After two additional 20-mL extractions with CH_2Cl_2, the combined organic layers were dried over K_2CO_3 and concentrated to give a yellow oil, which was purified by flash column chromatography to give 0.480 g (80%) of **49**. IR (film): 1718 cm^{-1}. ^1H NMR (250 MHz): δ 0.85 (t, 3, J = 7.5), 1.35–2.03 (m, 10), 2.17 (s, 3), 2.38–2.45 (m, 1), 2.86 (s, 1), 2.98–3.16 (m, 1), 3.28 (d, 1, J = 16.9), 3.57 (d, 1, J = 16.9), 3.70–4.05 (m, 4). ^{13}C NMR: δ 8.45, 20.92, 26.13, 26.94, 29.82, 31.71, 34.60, 41.24, 47.75, 62.59, 64.23, 65.68, 71.23, 109.49, 211.43. Anal. Calcd for $C_{15}H_{25}NO_3$: C, 67.39; H, 9.42; N, 5.24. Found: C, 67.07; H, 9.48; N, 5.25.

***cis*-(±)-7a-Ethyl-6,7,7a,8,9,9b-hexahydro-3*H*-cyclopenta-[*ij*]quinolizin-2(5*H*)-one (50).** Ketal **49** (0.160 g, 0.598 mmol) was taken up in 1.4 N HCl (5 mL), and the resulting solution was refluxed under N_2 for 3 h. The mixture was cooled to ambient temperature, neutralized with 20 mL of 5% NaOH, and extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were dried over K_2CO_3 and concentrated to provide a crude yellow oil that was purified by flash chromatography with 3% methanol in CH_2Cl_2 to yield 0.065 g (53%) of **50** as an oil. IR (film): 1670 cm^{-1}. ^1H NMR (250 MHz): δ 0.91 (t, 3, J = 7.5), 0.89–1.03 (m, 1), 1.40–1.81 (m, 6), 1.87–2.03 (m, 1), 2.51–2.68 (m, 4), 3.26 (d, 1, J = 17.0), 3.56 (d, 1, J = 17.0), 3.64 (s, 1), 6.01 (s, 1). ^{13}C NMR: δ 8.81, 20.91, 25.99, 27.03, 28.57, 33.26, 42.38, 46.62, 62.47, 68.16, 121.75, 167.53, 196.74. Anal. Calcd for $C_{13}H_{19}NO$: C, 76.05; H, 9.33; N, 6.82. Found: C, 75.84; H, 9.25; N, 6.70.

(±)-2-Ethyl-2-(2′-cyanoethyl)cyclopentanone (54). A mixture of 91.72 g (0.817 mol) of 2-ethylcyclopentanone, 1.5 L of THF, and 55.02 g (0.809 mol, 0.9 equiv) of $NaOC_2H_5$ was stirred vigorously with a magnetic Teflon-coated stirring bar at room temperature while a solution of 26.89 mL (21.67 g, 0.408 mol, 0.5 equiv) of acrylonitrile in 27 mL of THF was added at a rate of 0.19 mL/min with a syringe pump. After 2.5 h, the solution was filtered through a Celite-covered fritted filter. The solvent was removed in vacuo, and the remaining oil was taken up in 250 mL of CH_2Cl_2. The solution was washed with two 150-mL portions of water, and the organic layer was dried over K_2CO_3. After concentration, 2-ethylcyclopentanone (44.48 g, 0.396 mol) was recovered by distillation at 70 °C under aspirator vacuum. The remaining oil was distilled at 107–117 °C to afford 39.80 g (57% based on recovered ketone) of **54** as a light yellow oil. IR (film): 2263, 1739 cm^{-1}. ^1H NMR (250 MHz): δ 0.85 (t, 3, J = 7.4),

1.44–1.56 (m, 2), 1.79–2.01 (m, 6), 2.25–2.48 (m, 4). ^{13}C NMR: δ 8.05, 12.13, 18.33, 26.19, 29.31, 32.93, 37.77, 50.62, 119.59, 221.24. Anal. Calcd for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.34; H, 8.77; N, 8.27. The pot residue contained 23.1 g (13%) of **55**, a mixture of cis and trans isomers.

(±)-4a-Ethyl-3,4,4a,5,6,7-hexahydro-2*H*-1-pyrindine (56) [RN 118895-50-4]. Nitrile **54** (13.85 g, 83.84 mmol), KOH (9.19 g), Raney Nickel powder (5.68 g), and methanol (150 mL) were placed in a 250-mL pressure bottle and shaken for 20 h under 56 psi of H_2 in a Parr apparatus. The mixture was filtered through Celite, and the filtrate was concentrated to a green oil, which was partitioned between 200 mL of CH_2Cl_2 and 500 mL of water. The aqueous phase was extracted with two 75-mL portions of CH_2Cl_2, and the combined organic layers were dried over K_2CO_3. The excess solvent was removed with a rotary evaporator to give 12.09 g (95%) of **56** as a pale green oil. IR (film): 1685 cm^{-1}. ^{1}H NMR (250 MHz): δ 0.83 (t, 3, J = 7.4), 1.05–1.82 (m, 8), 1.90–2.02 (m, 2), 2.18–2.36 (m, 1), 2.45–2.63 (m, 1), 3.43–3.68 (m, 2). ^{13}C NMR: δ 7.80, 17.58, 17.91, 24.63, 27.76, 32.26, 35.20, 42.07, 48.54, 182.35. Anal. Calcd for $C_{10}H_{17}N$: C, 79.41; H, 11.33; N, 9.26. Found: C, 79.24; H, 11.16; N, 9.24.

(±)-(*E*)-4a-Ethyl-2,3,4,4a,5,6-hexahydro-1-(1-oxo-3-phenyl-2-propenyl)-1*H*-1-pyrindine (58). A solution of cinnamoyl chloride (2.298 g, 13.79 mmol), triethylamine (2.40 mL, 1.74 g, 17.22 mmol, 1.25 equiv), and imine **56** (2.190 g, 14.47 mmol, 1.050 equiv) in 50 mL of CH_2Cl_2 was stirred at 25 °C for 0.25 h. After concentration in vacuo the resulting yellow solid was purified by flash column chromatography (10:1 hexanes/ethyl acetate) to obtain 3.430 g (88%) of **58** as a yellow solid, mp 104 °C. IR (KBr): 1656, 1621, 1400 cm^{-1}. ^{1}H NMR (250 MHz): 0.93 (t, 3, J = 7.3), 1.38–1.85 (m, 6), 1.95–2.14 (m, 2), 2.27–2.53 (m, 3), 2.75–2.88 (m, 1), 4.53–4.67 (m, 1), 6.99 (d, 1, J = 15.7), 7.31–7.55 (m, 5), 7.66 (d, 1, J = 15.7). ^{13}C NMR: δ 8.93, 20.93, 26.67, 28.17, 35.13, 36.63, 44.34, 47.36, 119.12, 119.25, 127.58, 128.63, 129.21, 135.43, 140.84, 145.22, 166.08. Anal. Calcd for $C_{19}H_{23}NO$: C, 81.10; H, 8.24; N, 4.98. Found: C, 81.14; H, 8.17; N, 4.93.

***cis*- and *trans*-(±)-1-Phenyl-7a-ethyl-1,2,5,6,7,7a,8,9-octahydro-2*H*-cyclopenta[*ij*]quinolizin-3-one (59 and 60). (a) By Acid-Catalyzed Cyclization of Enamide 58.** A mixture of 0.125 g (0.444 mmol) of enamide **58**, 0.082 g (0.553 mmol, 1.25 equiv) of cinnamic acid, and 5 mL of decalin was heated at 145 °C under N_2. After 72 h, much decomposition had taken place and the ratio of **58**:**59**:**60** was 94:2:4 by GLPC analysis. Column chromatography (20:1 hexanes/ethyl acetate) gave 5 mg of a mixture of **59** and **60**, which could be separated from one another by crystallization from heptane due to the fact that **60** is an oil and **59** is a solid, mp 104 °C.

Compund 59. IR (film): 1682 cm^{-1}. ^{1}H NMR (500 MHz): δ 0.891 (t, 3, J = 7.5), 1.214–1.264 (m, 1), 1.412–1.564 (m, 3), 1.646–1.817 (m, 2), 1.948–2.151 (m, 3), 2.197–2.382 (m, 1), 2.611 (dd, 1, J = 1.23, 15.38), 2.918–2.978 (m, 1), 3.018 (dt, J = 8.73, 15.38), 3.473 (dd, 1, J = 1.23, 8.73), 3.996–4.037 (m, 1), 7.070–7.087 (m, 2), 7.185–7.215 (m, 1), 7.262–7.290 (m, 2). ^{13}C NMR: δ 8.96, 19.59, 26.97, 28.59, 32.64, 36.47, 38.28, 40.16, 41.28, 45.53, 117.07, 126.75, 126.81, 128.80, 141.81, 142.06, 169.64. Anal. Calcd for $C_{19}H_{23}NO$: C, 81.10; H, 8.24; N, 4.98. Found: C, 80.81; H, 8.40; N, 4.69.

Compound 60. IR ($CDCl_3$): 1645 cm^{-1}. ^{1}H NMR (500 MHz): δ 0.907 (t, 3, J = 7.43), 1.213–1.273 (m, 1), 1.483–1.581 (m, 3), 1.712–1.813 (m, 3), 1.930–1.986 (m, 2), 2.098–2.168 (m, 1), 2.679–2.750 (m, 2), 2.980–3.040 (m, 1), 3.764–3.804 (m, 1), 3.971–4.013 (m, 1), 7.154–7.171 (m, 2), 7.225–7.264 (m, 1), 7.305–7.335 (m, 2). ^{13}C NMR: δ 9.00, 19.42, 27.47, 28.46, 32.40, 36.06, 39.90, 40.99, 41.73, 45.64, 117.22, 126.70, 127.79, 128.56, 141.74, 142.27, 170.86. Anal. Calcd for $C_{19}H_{23}NO$: C, 81.10; H, 8.24; N, 4.98. Found: C, 81.21; H, 8.30; N, 4.98.

(b) By Ultraviolet Irradiation of 58. A solution of 0.031 g (0.110 mmol) of **58** in 6 mL of degassed benzene (6 mL) was irradiated through quartz with 254-nm light under N_2 in a Rayonet reactor. After 10 h the starting material was consumed and the reaction mixture was concentrated and purified by flash column chromatography to yield 0.013 g (42%) of a 94:6 ratio of **59** and **60** as determined by GLPC and 500-MHz ^{1}H NMR spectroscopy.

(c) Lactam 60 from Thermal Reaction of Imine 56 with Cinnamic Acid. A solution of 0.245 g (1.620 mmol) of imine **56** and 0.3 g (2.025 mmol, 1.25 equiv) of cinnamic acid in 0.5 mL of decalin was heated at 145 °C in an oil bath; reaction was complete after 5 h. The mixture was purified by flash column chromatography (15% ethyl acetate/hexanes) to obtain 0.298 g (65%) of compounds **59** and **60** in a ratio of 6:1 as determined by capillary gas chromatography and 500-MHz ^{1}H NMR spectroscopy.

***cis*-(±)-7a-Ethyl-1,2,5,6,7,7a,8,9-octahydro-1-(2-nitrophenyl)-3*H*-cyclopenta[*ij*]quinolizin-3-one (66) [RN 119009-93-7].** A solution of 1.00 g (6.61 mmol) of imine **56**, 1.60 g (8.28 mmol, 1.25 equiv) of *o*-nitrocinnamic acid, and 1.74 g (8.29 mmol, 1.25 equiv) of ammonium *o*-nitrocinnamate in 30 mL of dioxane was degassed, placed under an argon atmosphere, and heated at reflux for 90 h, at which time the reaction had only proceeded to approximately 60% completion by 500-MHz ^{1}H NMR spectroscopy. The reaction mixture was diluted with 300 mL of $CHCl_3$, washed with 300 mL of saturated K_2CO_3 solution, and dried over K_2CO_3. Concentration gave a black oil, from which 0.195 g of imine **56** was removed by bulb-to-bulb distillation (bath temperature 80 °C, 0.15 Torr). The remainder of the oil was chromatographed on flash silica to obtain 0.725 g of **66**, mp 136 °C (42% based on unrecovered 56), 0.065 g of *o*-nitrotoluene (7.2%), and 0.03 g of indole.

Lactam 66. IR (KBr): 1665 cm^{-1}. ^{1}H NMR (500 MHz): δ 0.920 (t, 3, J = 7.43), 1.224–1.284 (m, 1), 1.465–1.648 (m, 3), 1.726–1.803 (m, 3), 1.941–2.007 (m, 2), 2.071–2.140 (m, 1), 2.682 (dd, 1, J = 13.91, 15.51), 2.954 (dd, 1, J = 5.94, 15.51), 3.045–3.105 (m, 1), 3.946–3.988 (m, 1), 4.351 (dd, 1, J = 5.88, 13.91), 7.344–7.401 (m, 2), 7.593 (dt, 1, J = 1.25, 7.65), 7.790 (dd, 1, J = 1.24, 8.15). ^{13}C NMR: δ 9.02, 19.31, 27.54, 28.30, 31.88, 34.72, 36.04, 40.82, 40.90, 45.76, 114.44, 124.14, 127.46, 129.78, 132.67, 136.72, 143.25, 150.03, 169.44. Anal. Calcd for $C_{19}H_{22}N_2O_3$: C, 69.92; H, 6.79; N, 8.58. Found: C, 69.88; H, 6.85; N, 8.57.

***cis*-(±)-1-(2-Aminophenyl)-7a-ethyl-1,2,5,6,7,7a,8,9-octahydro-3*H*-cyclopenta[*ij*]quinolizin-3-one (68) [RN 118895-51-5].** A mixture of 1.54 g (4.715 mmol) of **66**, 0.043 g of PtO_2, and 65 mL of methanol were shaken in a Parr apparatus under 56 psi of H_2 for 1.5 h, filtered through Celite, and concentrated to give 1.39 g (99%) of **68** as a yellow solid, mp 129–130 °C. IR (KBr): 3490, 3385, 3272, 1650 cm^{-1}. ^{1}H NMR (500 MHz): δ 0.898 (t, 3, J = 7.43), 1.184–1.254 (m, 1), 1.404–1.484 (m, 1), 1.504–1.583 (m, 1), 1.598–1.697 (m, 2), 1.703–1.746 (m, 1), 1.896–2.014 (m, 3), 2.213–2.278 (m, 1), 2.626 (dd, 1, J = 6.09, 15.82), 2.974–3.067 (m, 2), 4.60–4.82 (br s, 2), 3.876 (dd, 1, J = 6.07, 14.53), 3.956–3.998 (m, 1), 6.658 (dd, 1, J = 1.03, 7.96), 6.744 (t, 1, J = 7.46), 6.978 (dd, 1, J = 1.36, 7.59), 7.060 (dt, 1, J = 1.53, 7.76). ^{13}C NMR: δ 8.78, 19.06, 26.83, 27.97, 31.44, 35.65, 35.67 (br), 37.54 (br), 40.86, 45.43, 115.92, 116.18, 118.50, 125.10, 127.37, 128.97, 142.44, 144.07, 170.91. Anal. Calcd for $C_{19}H_{24}N_2O$: C, 76.99; H, 8.16; N, 9.45. Found: C, 76.77; H, 8.10; N, 9.29.

(±)-1-Demethyl-19-hydroxyvallesamidin-10-one (71) [RN 118895-52-6] and (±)-1-Demethyl-19-methoxyvallesamidin-10-one (72) [118895-53-7]. To a vigorously stirring solution of 0.610 g (2.057 mmol) of **68** in 110 mL of CH_2Cl_2 was added 0.366 g (2.056 mmol, 1.0 equiv) of *N*-bromosuccinimide in one portion. The mixture was stirred at 25 °C for 15 min and was then concentrated without warming (rotary evaporator) to obtain an amorphous yellow solid (referred to in the text as structures **70a**, **70b**, or **70c**). IR ($CDCl_3$): 1632, 650 cm^{-1}. ^{1}H NMR (500 MHz): δ 1.025 (t, 3, J = 7.25), 1.455–1.553 (m, 2), 1.735–1.813 (m, 2), 1.894–1.935 (m, 2), 1.973–2.038 (m, 1), 2.164 (dd, 1, J = 7.37, 13.56), 2.287–2.350 (m, 1), 2.496 (d, 1, J = 18.55), 2.532–2.586 (m, 1), 2.809–2.871 (m, 1), 3.464 (dd, 1, J = 7.52, 18.32), 3.628 (d, 1, J = 7.45), 4.365–4.420 (m, 1), 4.620 (br s, 1), 6.413 (d, 1, J = 7.90), 6.660 (t, 1, J = 7.42), 6.936 (d, 1, J = 7.40), 7.023 (dt, 1, J = 1.27, 7.43). ^{13}C NMR: δ 10.16, 18.55, 27.31, 27.60, 33.14, 36.15, 37.89, 42.93, 44.61, 45.81, 78.54, 80.00, 112.58, 118.13, 123.16, 127.28, 128.39, 137.52, 170.92.

To the foregoing solid was added a solution of 0.419 g (2.468 mmol, 1.2 equiv) of $AgNO_3$ in a mixture of 300 mL of water and 100 mL of methanol. The reaction mixture was stirred at 25 °C for 45 min, and the resulting gray mixture was partitioned in a 2-L separatory funnel containing brine (500 mL) and $CHCl_3$ (300 mL). The aqueous layer was extracted with an additional 200-mL portion of $CHCl_3$, and the combined organic layers were washed with brine and dried over K_2CO_3. Concentration gave a yellow solid that was chromatographed on flash silica, previously deactivated by washing with 10% triethylamine, 40% hexanes,

and 50% $CHCl_3$. Elution with a 1:1:2 mixture of $CHCl_3$, ethyl acetate, and hexanes gave the 0.510 g (77%) of the hemihydrate of **71** and 0.141 g (20%) of **72**, which was quantitatively converted into **71** by stirring with 60% aqueous acetic acid.

Compound 71. Mp: 208 °C (from acetonitrile). IR (KBr): 3380, 3320, 1651 cm^{-1}. ^1H NMR (500 MHz): δ 0.900 (t, 3, J = 7.49), 1.212–1.285 (m, 1), 1.469–1.552 (m, 2), 1.636–1.689 (m, 3), 1.746–1.880 (m, 3), 2.121–2.182 (m, 1), 2.351 (dd, 1, J = 13.41, 15.56), 2.528 (dd, 1, J = 4.70, 15.62), 2.812–2.871 (m, 1), 3.254 (dd, 1, J = 4.73, 13.38), 3.897 (s, 1), 4.410–4.450 (m, 1), 4.693 (s, 1), 6.776 (d, 1, J = 7.75), 6.875 (t, 1, J = 7.44), 7.091–7.132 (m, 2). ^{13}C NMR: δ 7.95, 18.80, 27.02, 27.52, 28.29, 36.71, 39.32, 39.48, 48.32, 48.59, 76.20, 91.60, 111.39, 121.38, 124.18, 128.25, 130.62, 147.72, 174.37. Anal. Calcd for $C_{19}H_{24}N_2O_2 \cdot {}^1/_2H_2O$: C, 71.00; H, 7.84; N, 8.72. Found: C, 71.30; H, 7.57; N, 8.58. FAB HRMS: calcd for $C_{19}H_{25}N_2O_2$ (MH^+) m/z 313.1916, found 313.1907.

Compound 72. Oil. ^1H NMR (500 MHz): δ 0.885 (t, 3, J = 7.45), 1.443–1.725 (m, 7), 1.719–1.787 (m, 1), 1.801–1.835 (m, 1), 1.911–1.986 (m, 1), 2.562 (dd, 1, J = 12.32, 15.52), 2.659 (dd, 1, J = 5.92, 15.59), 2.679–2.725 (m, 1), 3.147 (s, 3), 3.181 (dd, 1, J = 5.94, 12.23), 4.156 (br s, 1), 4.486–4.573 (m, 1), 6.675 (d, 1, J = 7.61), 6.736 (t, 1, J = 7.42), 7.041–7.131 (m, 2). ^{13}C NMR: δ 7.79, 19.16, 28.30, 28.57, 30.87, 36.46, 39.74, 40.54, 47.57, 49.10, 51.07, 74.96, 95.95, 110.08, 119.04, 123.73, 128.06, 130.69, 149.17, 173.41.

(±)-1-Demethylvallesamidin-10-one (73) and (±)-Vallesamidin-10-one (74) [RN 118895-54-8]. A solution of 0.510 g (1.576 mmol) of hydroxy lactam **71** in a mixture of 40 mL of acetic acid and 20 mL of water was vigorously stirred at 25 °C while 1.53 g (24.34 mmol, 15.5 equiv) of $NaBH_3CN$ was added slowly. After 30 min the temperature was increased to 50 °C, and heating was continued for 2 h. Workup at this point afforded lactam **73**, mp 225 °C. For preparation of **74**, the reaction mixture was cooled to 25 °C and 1.5 mL of aqueous formalin solution was added, followed by 0.510 g (8.16 mmol, 5.15 equiv) of $NaBH_3CN$. The solution was stirred at 25 °C overnight and poured into a separatory funnel containing 600 mL of saturated K_2CO_3 (600 mL) and extracted with three 200-mL portions of $CHCl_3$. The combined organic layers were dried over K_2CO_3 and concentrated to give a yellow solid. Purification of the solid by filtration through a 5-g plug of silica gel using 1:1:2 $CHCl_3$/ethyl acetate/hexanes provided 0.440 g (90%) of **74**, mp 121–122 °C.

Compound 73. IR ($CDCl_3$): 3600–3150, 1641 cm^{-1}. ^1H NMR (500 MHz): δ 0.960 (t, 3, J = 7.45), 1.504–1.642 (m, 8), 1.766–1.822 (m, 1), 1.869–1.923 (m, 1), 1.976–2.044 (m, 1), 2.407 (dd, 1, J = 12.25, 14.69), 2.528 (dd, 1, J = 4.63, 15.36), 2.531–2.589 (m, 1), 3.203 (dd, 1, J = 4.58, 12.12), 3.382 (s, 1), 4.396–4.423 (m, 1), 6.626 (d, 1, J = 7.73), 6.745 (t, 1, J = 7.27), 7.045–7.087 (m, 2). ^{13}C NMR: δ 8.44, 18.93, 29.62, 32.99, 33.18, 36.65, 38.90, 40.23, 44.87, 46.76, 70.13, 76.03, 109.55, 119.24, 124.02, 128.04, 130.28, 148.89, 172.52. Anal. Calcd for $C_{19}H_{24}N_2O$: C, 76.99; H, 8.16; N, 9.45. Found: C, 76.70; H, 8.19; N, 9.35.

Compound 74. IR ($CDCl_3$): 1633 cm^{-1}. ^1H NMR (500 MHz): δ 0.930 (t, 3, J = 7.12), 1.200–1.264 (m, 1), 1.403–1.912 (m, 9), 2.345 (dd, 1, J = 12.40, 16.26), 2.436 (dd, 1, J = 5.38, 16.25), 2.537–2.628 (m, 1), 2.764 (s, 3), 3.061 (dd, 1, J = 5.36, 11.78), 3.463 (br s, 1), 4.603–4.657 (m, 1), 6.443 (d, 1, J = 7.74), 6.98 (t, 1, J = 7.23), 7.055 (d, 1, J = 7.0), 7.107 (dt, 1, J = 1.20, 7.67). ^{13}C NMR: δ 9.03, 17.39, 26.51, 28.65, 29.60, 29.64, 34.43, 35.18, 38.06, 45.33, 46.26, 69.04, 77.99, 107.27, 118.18, 123.08, 127.81, 131.99, 149.99, 169.75. Anal. Calcd for $C_{20}H_{26}N_2O$: C, 77.38; H, 8.44; N, 9.02. Found: C, 77.18; H, 8.31; N, 8.89.

(±)-Vallesamidine (4) [RN 53648-26-3]. A solution of 0.410 g (1.316 mmol) of **74** (0.410 g, 1.316 mmol) in 30 mL of THF was treated with 0.300 g (7.905 mmol) of $LiAlH_4$. The mixture was heated at reflux for 2.5 h, cooled to 25 °C, diluted with 30 mL of diethyl ether, and quenched by sequential addition of 0.3 mL of water, 0.3 mL of 15% aqueous NaOH, and 0.6 mL of water. The resulting slurry was filtered through Celite and concentrated to give a light brown oil, which was purified by flash column chromatography (1:3 ethyl acetate/hexanes) to give 0.360 g (92%) of (±)-vallesamidine (**4**) as a light yellow oil. IR (film) 2950, 1600 cm^{-1}. ^1H NMR (500 MHz): δ 0.892 (t, 3, J = 7.40), 1.389–1.913 (m, 12), 2.216–2.28 (m, 2), 2.260 (s, 1), 2.782 (s, 3), 2.802–2.882 (m, 3), 6.419 (d, 1, J = 7.72), 6.653 (t, 1, J = 7.34), 7.022 (d, 1, J = 7.05), 7.063 (t, 1, J = 7.65). ^{13}C NMR: δ 9.10, 18.40, 26.52, 27.49, 30.27, 31.07, 31.19, 35.41, 44.27, 44.44, 49.89, 50.40, 73.02, 78.92, 107.50, 117.51, 122.82, 127.12, 134.83, 151.36. Anal. Calcd for $C_{20}H_{28}N_2$: C, 81.03; H, 9.52; N, 9.45. Found: C, 81.39; H, 9.67; N, 9.22. The IR, ^1H NMR, and ^{13}C NMR spectra were identical with those of an authentic sample of vallesamidine kindly supplied by Professor Carl Djerassi of Stanford University.

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Registry No. (±)-**4**, 53648-26-3; **23**, 19716-82-6; **24**, 51023-60-0; (±)-**28**, 124286-71-1; (±)-**29**, 124286-72-2; (±)-**30**, 124286-73-3; (±)-*cis*-**31**, 124286-74-4; (±)-*trans*-**31**, 124286-64-2; (±)-*cis*-**32**, 124286-75-5; (±)-*trans*-**32**, 124286-96-0; (±)-*cis*-**33**, 124286-76-6; (±)-*trans*-**33**, 124286-67-5; (±)-*cis*-**34**, 124286-77-7; (±)-*trans*-**34**, 124286-65-3; (±)-*cis*-**35**, 124286-78-8; (±)-*trans*-**35**, 124286-66-4; (±)-*cis*-**36**, 124286-79-9; (±)-*trans*-**36**, 124316-03-6; **37**, 124286-80-2; (±)-*cis*-**38**, 124286-81-3; (±)-*trans*-**38**, 124286-68-6; (±)-**40**, 124286-82-4; (±)-**42**, 124286-83-5; (±)-**43**, 124286-84-6; (±)-**44**, 124286-85-7; (±)-**45**, 124286-86-8; **46**, 24253-17-6; (±)-**47**, 124286-87-9; (±)-**48**, 124286-88-0; (±)-**49**, 124286-89-1; (±)-**50**, 124286-90-4; (±)-**54**, 118895-49-1; (±)-*cis*-**55**, 124286-97-1; (±)-*trans*-**55**, 124286-98-2; (±)-**56**, 118895-50-4; **57**, 17082-09-6; (±)-**58**, 124286-91-5; (±)-**59**, 124286-92-6; (±)-**60**, 124286-93-7; **65**, 1013-96-3; **65**·NH_3, 124286-69-7; (±)-**66**, 119009-93-7; (±)-**68**, 124286-94-8; (±)-**79a**, 124375-88-8; (±)-**70b**, 124286-70-0; (±)-**70c**, 124316-35-4; (±)-**71**, 118895-52-6; (±)-**72**, 118895-53-7; (±)-**73**, 124286-95-9; (±)-**74**, 118895-54-8; CH_2=$CHCO_2Me$, 96-33-3; CH_2=CHCN, 107-13-1; CH_2=$CHCO_2Bu$-*t*, 1663-39-4; 3-$ClC_6H_4CH_2CO_2H$, 1878-65-5; 3-$ClC_6H_4CH_2COCl$, 41904-39-6; CH_3COCH_2Cl, 78-95-5; (±)-2-ethylcyclopentanone, 64847-88-7.

Supplementary Material Available: X-ray crystallographic data for compounds **59** and **71**, including experimental details, general temperature factor expressions, thermal and positional parameters for non-hydrogen atoms, bond lengths, bond angles, and torsional angles (20 pages). Ordering information is given on any current masthead page.