1290, 1260, 1140, 1125, cm^{-1}; UV (EtOH) λ_{max} 246 nm (ϵ 20300), 357 (10500); ^1H NMR δ 7.72 (d, J = 9.0 Hz, 1 H), 7.96 (dd, J = 9.0 2.1 Hz, 1 H), 8.02 (s, 1 H), 8.19 (d, J = 2.1 Hz, 1 H), 10.1 (s, 2 H, exchangeable with D_2O); MS, m/e 376 (M^+), 269; exact mass calcd m/e 375.9146, found 375.9139; pKa (H_2O) 3.7, 9.65. Anal. Calcd for $C_{12}H_6Cl_2N_2O_4S_2$; C, 38.20; H, 1.60; N, 7.43. Found, C, 38.41; H, 1.55; N, 7.50.

2-(Aminosulfonyl)thioacetamide. A solution of 2-(aminosulfonyl)acetonitrile[14] (24 g, 0.2 mol) and triethylamine (50 mL) in pyridine (100 mL) was saturated with hydrogen sulfide gas over a period of 1 h. After removal of the volatile components by vacuum evaporation, the residue was dissolved in dioxane (50 mL). On standing at room temperature the product crystallized to give, after filtration and washing with Et_2O, 22.4 g (73%), mp 110–113 °C. An analytical sample, obtained by evaporative crystallization from Et_2O, had mp 115–117 °C. Anal. Calcd for $C_2H_6N_2O_2S_2$: C, 15.58; H, 3.92; N, 18.17. Found: C, 15.97; H, 3.80; N, 17.97.

UV Spectral Data for 1b, 1e, and 4. 1b: UV (EtOH) λ_{max} 272 nm (ϵ 22500), 370 (6700). **1e**: UV (EtOH) λ_{max} 262 nm (ϵ 24400), 365 (6900); **4**: UV (EtOH) λ_{max} 245 nm (ϵ 23500), 281.5 (22400).

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Registry No. 2a, 89566-24-5; **2a** (dipotassium salt), 89873-47-2; **2b**, 89873-37-0; **2c**, 89873-38-1; **3**, 89873-39-2; **5a**, 4563-33-1; **5b**, 19299-41-3; **5c**, 89873-40-5; **6a**, 85195-24-0; **6c**, 89873-41-6; **7**, 89873-42-7; **8**, 89873-43-8; **9**, 89873-44-9; **10**, 89873-45-0; **11**, 89873-46-1; diethyl oxalate, 95-92-1; methyl oxalyl chloride, 5781-53-3; 3,4-dichlorothiobenzamide, 22179-73-3; 1,3-dichloroacetone, 534-07-6; thiourea, 62-56-6; ammonia, 7664-41-7; ethyl oxalyl chloride, 4755-77-5; 2-(aminosulfonyl)thioacetamide, 89873-48-3; 2-bromo-1-(3,4-dichlorophenyl)ethanone, 2632-10-2; 2-(aminosulfonyl)acetonitrile, 41827-87-6; hydrogen sulfide, 7783-06-4; potassium *tert*-butoxide, 865-47-4.

Supplementary Material Available: ^{13}C chemical shift and coupling constant data for substituents other than thiazole in structures **1a–f**, **2a–c**, **3**, and **4**, along with ^{13}C NMR data for **5c** and **10** (4 pages). Ordering information is given on any current masthead page.

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Stereo- and Regioselective Total Synthesis of the Hydropyrido[2,1,6-*de*]quinolizine Ladybug Defensive Alkaloids[1a]

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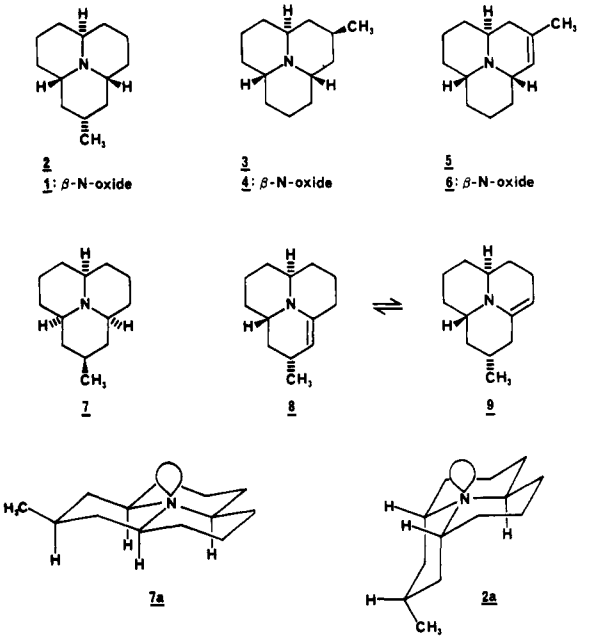
The stereo- and regioselective syntheses of the ladybug defensive alkaloids coccinelline (**1**), precoccinelline (**2**), (±)-hippodamine (**3**), (±)-convergine (**4**), (±)-hippocasine (**5**), (±)-hippocasine oxide (**6**), myrrhine (**7**), (±)-propyleine (**8**), and (±)-isopropyleine (**9**) are described starting from perhydroboraphenalene.

Ladybugs are well-known for their voracious appetites for such agricultural pests as aphids and scale insects;[2] in fact, they are commercially available for just this purpose.[3] Interestingly, ladybugs have few natural enemies, a fact suggested by the bright coloration of many ladybug species; this "aposematic coloration" warns potential predators of the existence of a chemical defense system.[4] When threatened, ladybugs secrete an oily, bitter tasting fluid from their joints which repulses ants, quail, and other creatures which might otherwise consume them. This phenomenon, referred to as "reflex bleeding", serves the ladybug as a highly effective means of protection.[5]

The first studies directed toward characterization of the actual ladybug defensive agents were reported by Tursch and co-workers in 1971.[6,7] A white, crystalline solid was isolated from methanol extracts of the European ladybug *Coccinella septempunctata*; this substance was shown to repel the ant *Myrmica rubra* at concentrations as low as 0.1–0.5% in water.[8] Spectral[9] and crystallographic[10]

Scheme I



(1) (a) Taken in part from the Ph.D. Dissertation of Mark E. Thompson, Yale University, 1981. (b) Address correspondence to this author at E. R. Squibb and Sons, Inc., POB 4000, Princeton, NJ 08540.
(2) Hagen, K. S. *Natl. Geographic* **1970**, *137*, 543–553.
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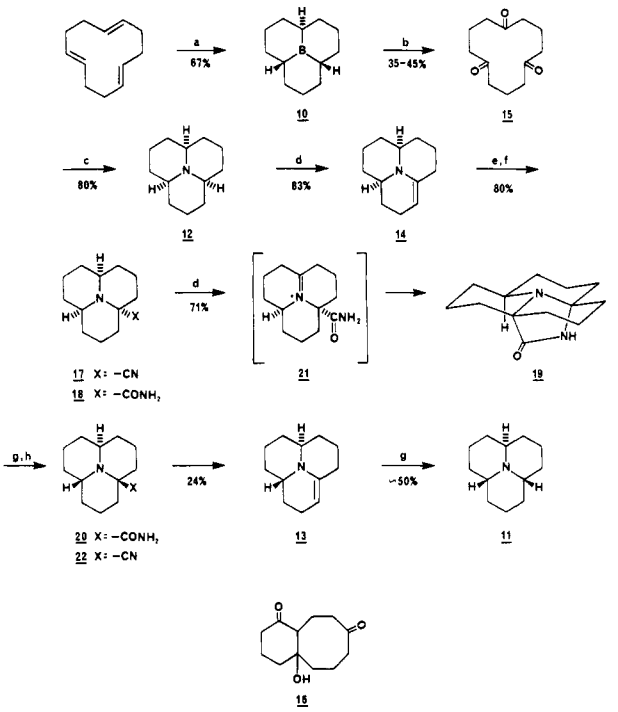
analyses revealed this compound, named coccinelline, possessed the *N*-oxide structure **1**, a methyl derivative of the perhydropyrido[2,1,6-*de*]quinolizine ring system. Along with coccinelline, a significant amount of the corresponding free base precoccinelline (**2**) was isolated. A number of different ladybug species have since been examined. To date, seven additional hydropyridoquinolizine alkaloids have been isolated and characterized:[7] hippodamine (**3**) and its *N*-oxide convergine (**4**) from *Hippodamia convergens*, *Anisosticta nonodecimpunctata*,[11] and *H. caseyi*,[12] hippocasine (**5**) and hippocasine oxide (**6**) from *H. caseyi*,[12] myrrhine (**7**) from *Myrrha octodecimpunctata*,[13] and propyleine (**8**) from *Propylaea quattuordecimpunctata*.[14] Propyleine has since been shown (vide infra) to be in equilibrium with isopropyleine (**9**) (Scheme I). Some of these compounds have been found in additional coccinellid species,[8,13,15] in the Australian soldier beetle *Chauliognathus pulchellus*,[16] and in the boll weevil *Anthonomus grandis*.[17]

Of all these structures, only myrrhine (**7**) possesses the thermodynamically more stable tricyclic skeleton with all three ring junction hydrogen atoms oriented cis to one another and trans to the preferred orientation of the nitrogen lone pair (see **7a**, Scheme I); if the nitrogen lone pair were cis to the hydrogen atoms, one of the rings would be forced into a skew boat conformation. Six of the remaining compounds possess the trans,cis,trans stereochemistry, with two hydrogen atoms cis to one another and trans to the remaining one. The preferred nitrogen lone pair orientation in these compounds is cis to two of the hydrogen atoms (see **2a**, Scheme I); again, nitrogen inversion would force one of the rings into a skew boat conformation. Examination of molecular models of the two remaining compounds **8** and **9** indicates that the nitrogen lone pair prefers to be cis to the ring junction hydrogen atom attached to the same ring that contains the double bond, assuming the nitrogen atom in **8** and **9** is not planar, as would seem to be the case.[18] In all cases the methyl substituent is either vinylic (**5** and **6**) or occupies the thermodynamically preferred equatorial position (quasiequatorial in the case of **8**).

The laboratory synthesis of myrrhine (**7**), (±)-hippodamine (**3**), and (±)-convergine (**4**) was first achieved by Ayer and co-workers in 1976.[19] The total synthesis of precoccinelline (**2**) and coccinelline (**1**) was reported later that same year by the Ayer group.[20] In 1979, Stevens announced the synthesis of **1** and **2** in an elegant demonstration of kinetic control in the Robinson–Schöpf reaction.[21] These interesting synthetic achievements had in common the construction of the tricyclic alkaloid framework from single six-membered ring or acyclic precursors.

Scheme II[a]



[a] a, $BH_3 \cdot Me_2S$; b, RuO_2, $NaIO_4$; c, NH_3, H_2, Pd/C; d, $Hg(OAc)_2$, EDTA; e, H^+, KCN; f, $H_2SO_4 \cdot SO_3$; g, H_2, Pd/C; h, $POCl_3$, pyridine.

Our approach to the ladybug defensive agents focused on a highly efficient and stereoselective construction of the parent perhydropyrido[2,1,6-*de*]quinolizine ring system starting from the readily available[22] perhydro-9b-boraphenalene **10**,[23,24] which possessed the three required rings but necessitated the organochemical equivalent of a transmutation of the elements. This approach has culminated in the laboratory preparation of all the known hydropyridoquinolizine ladybug alkaloids in a regio- and stereoselective manner.[25-27] Herein is provided an account of these efforts.

The initial stage of our investigation focused on conversion of perhydroboraphenalene **10**, prepared by hydroboration/equilibration of 1,5,9-cyclododecatriene[22] to the amines **11** and **12**, or preferably functionalized derivatives thereof, the enamines **13** and **14** (Scheme II). Two avenues of approach were studied. The first to bear fruit involved oxidation of **10** to the symmetrical triketone **15**.[23] Initial oxidation attempts using a variety of chromium(VI) reagents were frustrated due to formation of internal ketals and hemiketals.[28] The use of ruthenium tetraoxide cycled with sodium periodate[29] in aqueous acetone gave 35–45%

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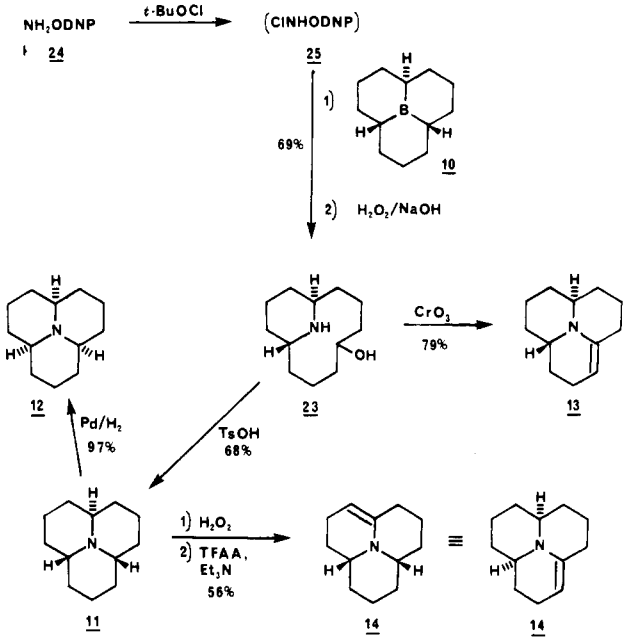
isolated yields of the very sensitive triketone **15**. Treatment of **15** in solution with trace acid or base resulted in rapid conversion to the hydroxy diketone **16**; in crystalline form, however, **15** is stable for years. In spite of its reactivity, **15** underwent reductive amination smoothly to produce the all-cis amine **12**, as attested by strong Bohlman bands[30] in the IR spectrum and only three lines in the proton decoupled ^{13}C NMR spectrum.

Having thus gained an efficient entry into the parent all-cis ring system, we endeavored to convert **12**, the thermodynamically preferred isomer, into its less stable partner, the trans,cis,trans amine **11**. A sequence involving the inversion of stereochemistry at one of the carbon atoms adjacent to the nitrogen atom was necessary. Oxidation of the amine to the known[31] enamine **14** was accomplished with mercuric acetate.[32] Catalytic reduction of **14** gave back the cis amine **12**, as expected; Clemmenson conditions, which in some cases give the opposite stereochemical results,[33] gave a mixture of **11** and **12**, so a more selective method for the synthesis of **11** was sought.

Hydrocyanation of enamine **14** gave amino nitrile **17**.[31] Attempts to introduce a double bond with mercuric acetate were not successful; **17** merely reverted to enamine **14**. The cyano group then was converted to the amide **18** with fuming sulfuric acid. This time, treatment with mercuric acetate gave the lactam **19**, hydrogenation of which gave the amide **20**; both reactions presumably occur via the immonium salt **21**. The steric course of the reduction can be rationalized by assuming hindrance of approach to the catalyst by the quasi-axial amido group, although the real reasons are probably more complex.[34] Dehydration of amide **20** gave the amino nitrile **22** admixed with the enamine **13**. Catalytic reduction of **13** gave the trans,cis,trans amine **11** as evidenced by the seven-line proton-decoupled ^{13}C NMR spectrum. Although somewhat lengthy and inefficient, this route did provide comparison samples of **11** and **13** which were useful later in the determination of the outcome of the second avenue of approach under investigation.

This approach involved the direct conversion of organoboranes to amines, for which numerous methods have been developed; all these methods involve the use of a nucleophilic nitrogen reagent carrying a single leaving group on the nitrogen atom, and thus only one alkyl group of the organoborane is transferred to the same nitrogen atom.[35] Conversion of perhydroboraphenalene to the corresponding tertiary amine requires the transfer of three alkyl groups of a single organoborane to the same nitrogen atom; this operation could conceivably be accomplished

Scheme III



with an appropriate reagent carrying three leaving groups affixed to nitrogen. Nitrogen trichloride, an obvious candidate, reacted exothermically with **10**, but only trace amounts of **11** and **12** were formed; presumably, free-radical processes, i.e., α-chlorination, intervened.[36] We then turned to reagents carrying two leaving groups on nitrogen (Scheme III). In situ generation of the very unstable *N*-chloro-*O*-(2,4-dinitrophenyl)hydroxylamine (**25**) followed by addition of perhydroboraphenalene (**10**) and subsequent peroxide oxidation gave the amino alcohol **23**.[24] Compelling evidence for the *trans*-piperidine structure was obtained by oxidation to the previously prepared trans enamine **13**.

The oxidation of **23** to **13** deserves further comment. Treatment of **23** with the Jones reagent[37] in acidic aqueous acetone worked well, but isolation of the product proved problematical. Addition of base to the reaction mixture resulted in formation of a thick, gelatinous precipitate of chromium hydroxide. This problem was overcome by the development, discussed in greater detail elsewhere,[38] of a Cr(II)-mediated complexation of Cr(III) in a base-soluble form.

With a two-step synthesis of enamine **13** from **10** in hand, we sought an alternate synthesis of the enamine **14** from **23**. Indeed, treatment of **23** with acid gave tertiary amine **11** (Scheme III).[24,39] Furthermore, mercuric acetate oxidation[32] of **11** or the modified Polonovski reaction[40] on the *N*-oxide of **11** gave **14** with greater than 98% stereoselectivity (Scheme III). The oxygen atom of the *N*-oxide of **11** presumably is cis to two of the ring junction hydrogen atoms (cf. the interconversion of precoccinelline and coccinelline[9] and of hippodamine and convergine[11,19]); formation of **14** in the Polonovski reaction indicates an antiperiplanar elimination, thus confirming LaLonde's observations.[41]

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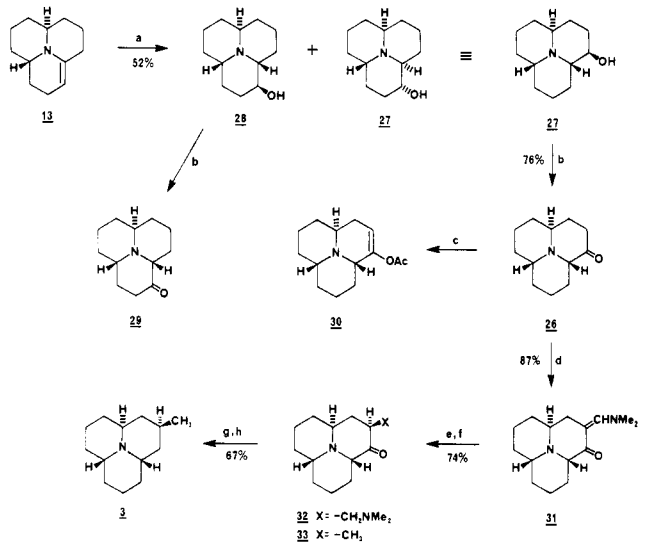
Scheme IV[a]



[a] a, $BH_3 \cdot Me_2S$, then H_2O_2, NaOH; b, CrO_3, H^+; c, $i\text{-}Pr_2NLi$, then Ac_2O; d, $MeOCH(NMe_2)_2$; e, $Li \cdot 4NH_3$, t-BuOH; f, H_2, Pd/C; g, $HSCH_2CH_2SH$, $BF_3 \cdot Et_2O$; h, Li, $H_2NCH_2CH_2NH_2$.

An alternate preparation of amine **12** was realized by isomerization of the trans,cis,trans amine **11** with palladium-on-carbon at 190°, presumably by a dehydrogenation–hydrogenation mechanism leading to the more stable isomer **12** (Scheme III).

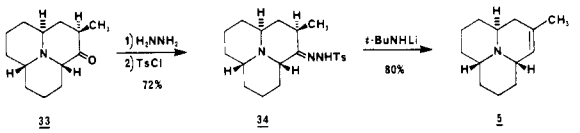
At this point, our initial endeavors to prepare the parent ring systems of the natural products were completed satisfactorily; either stereoisomer could be synthesized specifically in only a few steps. In addition, the vital intermediates **13** and **14** with appropriate stereochemistry and functionality for further elaboration to the ladybug defensive agents could be prepared efficiently with very high stereoselectivity in multigram quantities. We were then ready to address the synthesis of the natural products themselves.

Enamine **13** has the appropriate stereochemistry for conversion to all the ladybug alkaloids except myrrhine (**7**). At the outset, we envisaged the ketone **26**, obtainable from enamine **13** via hydroboration–oxidation, as a key intermediate (Scheme IV). A major attraction of this route was the potential preparation of six compounds from a common, late-stage intermediate.

In practice, hydroboration of enamine[42] **13** with borane–dimethyl sulfide followed by oxidation afforded a 95% crude yield of a 3:1 mixture of two alcohols, formed by attack of the borane from either face of enamine **13** (Scheme IV).[43] The major isomer showed a broad singlet at δ 3.61 ppm, typical of an axial alcohol, and was assigned structure **27**; this isomer had the appropriate stereochemistry for further transformation to the natural products mentioned above. The minor isomer **28** exhibited a triplet of doublets (J = 4, 11 Hz), as expected for an equatorial alcohol, at δ 3.99 ppm.

Oxidation of alcohol **27** occurred with Jones reagent[37] in acetic acid containing 1 equiv of sulfuric acid. Again, the Cr(II)-mediated workup procedure[38] allowed efficient isolation of amino ketone **26**. No epimerization at the enolizable center α to the nitrogen atom was noted.

Scheme V



Subsequently, it was discovered that the mixture of alcohols **27** and **28** obtained in the hydroboration reaction could be oxidized directly to a mixture of ketones **26** and **29**. Treatment of this mixture with catalytic sodium methoxide in methanol resulted in equilibration to a 9:1 mixture of **26** and **29**, the greater thermodynamic stability of **26** presumably a manifestation of the 2-alkyl ketone effect.[44]

The next step in the synthesis of the natural products required introduction of a methyl group adjacent to the carbonyl group. The kinetic enolate anion of ketone **26** was expected to lie in the desired direction;[45] indeed, this was demonstrated by formation of the enol acetate **30** (Scheme IV). However, attempts to trap the enolate with methyl iodide were unsuccessful, resulting only in formation of what appeared to be N-methylation products. Reaction with the Bredereck reagent[46] gave **31**; lithium bronze reduction[47] to **32** and subsequent catalytic hydrogenation gave methyl ketone **33**.

Conversion of **33** to hippodamine required reductive removal of the carbonyl group. The Huang–Minlon modification[48] of the Wolff–Kishner reduction resulted in formation of hippodamine and its methyl group epimer in a ratio of 2:1. Epimerization during such reductions is not uncommon.[49] Conventional Raney nickel desulfurization of the derived thioketal was slow and incomplete; successful removal of the thioketal group was accomplished with lithium in ethylenediamine.[50] Synthetic (±)-hippodamine (**3**), isomeric purity >98%, was identical with natural material[51] by ^1H NMR, IR, and MS. (±)-Convergine (**4**) was prepared by oxidation of **3** with peracid.[11]

Attention was next focused on conversion of methyl ketone **33** to hippocasine (**5**) (Scheme V). The Bamford-Stevens reaction appeared to be an interesting possibility.[52] Reaction of **33** with hydrazine in refluxing ethanol gave the hydrazone; immediate treatment with p-toluenesulfonyl chloride[53] gave tosylhydrazone **34**, which appeared to be a single isomer at the methyl group. Treatment of **34** with butyllithium resulted primarily in addition of the lithium reagent to the tosylhydrazone, a reaction known to occur when deprotonation is slow.[54] Lithium diisopropylamide[55] also gave a low yield. As this

(42) Borowitz, I. J.; Williams, G. J. *J. Org. Chem.* **1967**, *32*, 4157–4160. Barieux, J.-J.; Gore, J. *Bull. Soc. Chim. Fr.* **1971**, 1649–1657; **1971**, 3978–3985.

(43) Initial hydroboration studies were performed by Pamela Campbell and Joseph DiMaggio.

(44) Robins, P. A.; Walker, J. *J. Chem. Soc.* **1955**, 1789–1790. Klyne, W. *Experientia* **1956**, *12*, 119–124. Allinger, N. L.; Blatter, H. M. *J. Am. Chem. Soc.* **1961**, *83*, 994–995. Also see footnote 11, ref 26.

(45) Garst, M. E.; Bongfiglio, J. N.; Grudoski, D. A.; Marks, J. *Tetrahedron Lett.* **1978**, 2671–2674.

(46) Bredereck, H.; Effenberger, F.; Botsch, H. *Chem. Ber.* **1964**, *97*, 3397–3406. Bredereck, H.; Effenberger, F.; Simchen, G. *Ibid.* **1965**, *98*, 1078–1080.

(47) Mel'nikova, V. I.; Pivnitskii, K. K. *J. Org. Chem. USSR* (*Engl. Transl.*) **1972**, *8*, 2138–2144 and earlier papers. Mueller, R. H.; Gillick, J. G. *J. Org. Chem.* **1978**, *43*, 4647–4648.

(48) Huang-Minlon *J. Am. Chem. Soc.* **1946**, *68*, 2487–2488; **1949**, *71*, 3301–3303.

(49) Clarke, R. L. *J. Am. Chem. Soc.* **1961**, *83*, 965–968.

(50) Crossley, N. S.; Henbest, H. B. *J. Chem. Soc.* **1960**, 4413–4417.

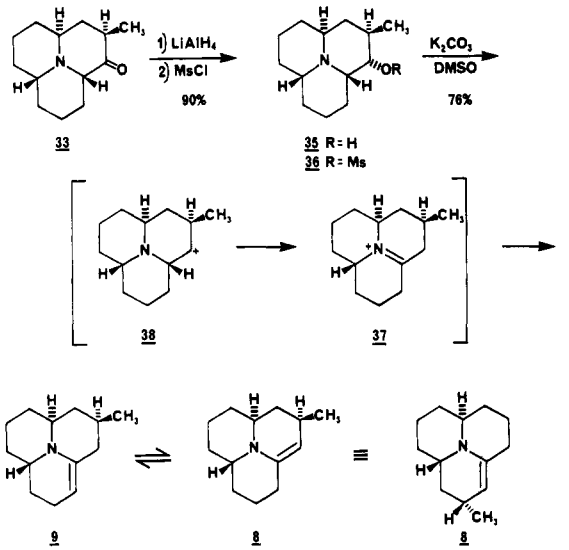
(51) Drs. Tursch and Daloze kindly provided spectra of hippodamine and propyleine/isopropyleine. Spectra of precoccinelline, coccinelline, and myrrhine and a sample of coccinelline hydrochloride were obtained from Drs. Tursch and Braekman. Professor Ayer provided spectra of hippodamine, hippocasine, hippocasine oxide hydrochloride, and myrrhine and a sample of convergine hydrochloride.

(52) (a) Bamford, W. R.; Stevens, T. S. *J. Chem. Soc.* **1952**, 4735–4740. (b) Review: Shapiro, R. H. *Org. React.* (*N.Y.*) **1976**, *23*, 405–507.

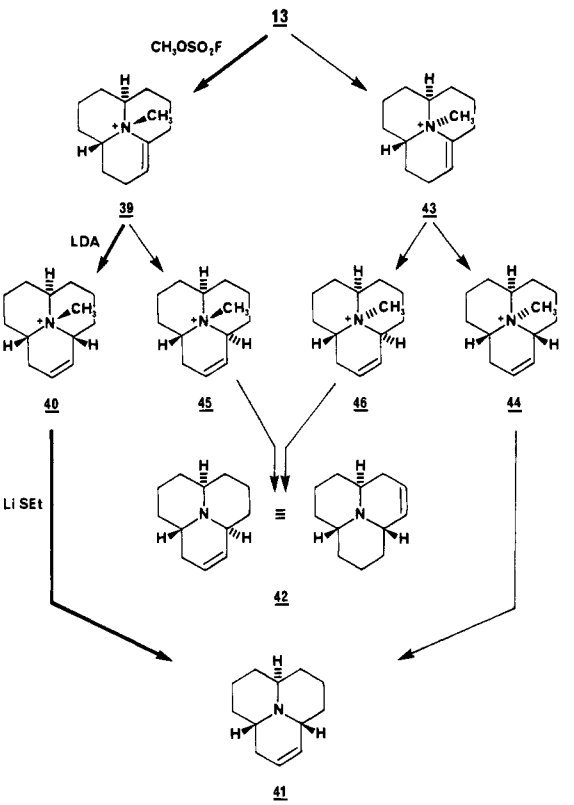
(53) Cf.: Hartzler, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 4527–4531.

(54) Reference 52b, p 423.

Scheme VI



Scheme VII



base can sometimes function as a hydride donor,[56] we next tried lithium *tert*-butylamide and were gratified to obtain (±)-hippocasine (**5**) in 80% yield; none of the regioisomer propyleine (**8**) was observed. (±)-Hippocasine oxide (**6**) was obtained on reaction with hydrogen peroxide and converted to its hydrochloride salt. Spectroscopic and TLC comparison of (±)-**6** and (±)-**6**·**HCl** showed them identical with the natural[51] materials.

The next natural product to be targeted was propyleine (**8**), also derivable from methyl ketone **33** provided a method could be found to achieve double bond regiochemistry opposite to that required in the conversion of **33** to hippocasine.

Reduction of **33** gave the equatorial alcohol **35** (Scheme VI). Conversion to the corresponding mesylate **36** proceeded in high yield. Clean elimination was effected by heating **36** with solid potassium carbonate in dimethyl sulfoxide; no hippocasine (**5**) was observed. The 60-MHz ^{1}H NMR spectrum and MS of the product were identical with those of natural material;[51] furthermore, the product was homogeneous by VPC and TLC. However, the 270-MHz ^{1}H NMR spectrum clearly showed the presence of two compounds in the ratio of 3:1; this was confirmed by the ^{13}C NMR spectrum, in which two pairs of olefinic resonances were present. The two compounds were assigned structures **8** (propyleine) and **9** (isopropyleine), with **9** as the major component. Evidence for these assignments has been presented previously.[27]

We suspect the elimination reaction of **36** occurs via an E1 mechanism, a 1,2-hydride shift in carbonium ion **38** giving the immonium salt **37** (as opposed to the less stable tertiary carbonium ion); subsequent deprotonation would give a mixture of **8** and **9** (Scheme VI).

Our next goal was the synthesis of precoccinelline (**2**) and coccinelline (**1**). Ketone **29** possessed the appropriate functionality for introduction of the methyl group. However, not only was **29** the minor product of hydroboration–oxidation of enamine **13**, it also could not be prepared by epimerization of the major, thermodynamically more stable product, ketone **26**. Thus an alternate route was sought starting from enamine **13**. Attempts to deprotonate the position γ (or "para") to the nitrogen atom by the use of strong bases such as *sec*-butyllithium or potassium *tert*-butoxide/*sec*-butyllithium were without success;[57] addition of methyl iodide to these reaction mixtures gave back starting enamine. We next turned our attention to the ene ammonium salt **39** with the hope that deprotonation would be more favored. Treatment of **39**, obtained from **13** by reaction with methyl fluorosulfate, with lithium diisopropylamide (THF, −78 to −20 °C) resulted in virtually complete isomerization to the allylic ammonium salt **40**, presumably via the allylic ylide (Scheme VII). Similar isomerizations of less complex ene ammonium salts with sodium hydroxide have been reported.[58] All attempts to trap the intermediate ylide with methyl iodide were unsuccessful. The methyl group of **40** was removed with lithium ethyl mercaptide in dimethylformamide[59] to afford the allylic amine **41**.

Chemical evidence for the structure of **41** was obtained by hydroboration–oxidation to give alcohol **28** as the major product, the same alcohol obtained previously as the minor product from hydroboration–oxidation of enamine **13**. This result established the stereochemistry of the allylic hydrogen atom in **40** but not the stereochemistry of the methyl group. A priori, either **41** or **42** could have been obtained by the methylation/isomerization/demethylation sequence. Depending on the stereochemistry of the methylation reaction and on the stereochemistry of protonation in the isomerization reaction, either or both **41** and **42** could have been produced, and each by two possible routes, as shown in Scheme VII. Methylation of enamine **12** could have given either **39** or **43**. Isomerization of either **39** to **40** or of **43** to **44** followed by demethylation would have led to **41**; alternatively, isomerization of either **39** to **45** or of **43** to **46** would have led to **42**. Molecular models

(55) Kolonko, K. J.; Shapiro, R. H. *J. Org. Chem.* **1978**, *43*, 1404–1408.
(56) Kowalski, C.; Creary, X.; Rollin, A. J.; Burke, M. C. *J. Org. Chem.* **1978**, *43*, 2601–2608.
(57) Ahlbrecht, H.; Eichler, J. *Synthesis* **1974**, 672–674. Martin, S. F.; DuPriest, M. T. *Tetrahedron Lett.* **1977**, 3925–3928.
(58) Saunders, M.; Gold, E. H. *J. Am. Chem. Soc.* **1966**, *88*, 3376–3381.
(59) Cf.: Hutchins, R. O.; Dux, F. J. *J. Org. Chem.* **1973**, *38*, 1961–1962. Bartlett, P. A.; Johnson, W. S. *Tetrahedron Lett.* **1970**, 4459–4462. Vaughan, W. R.; Baumann, J. B. *J. Org. Chem.* **1962**, *27*, 739–744.

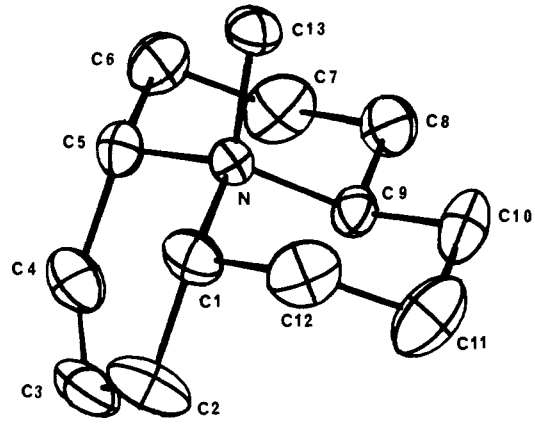
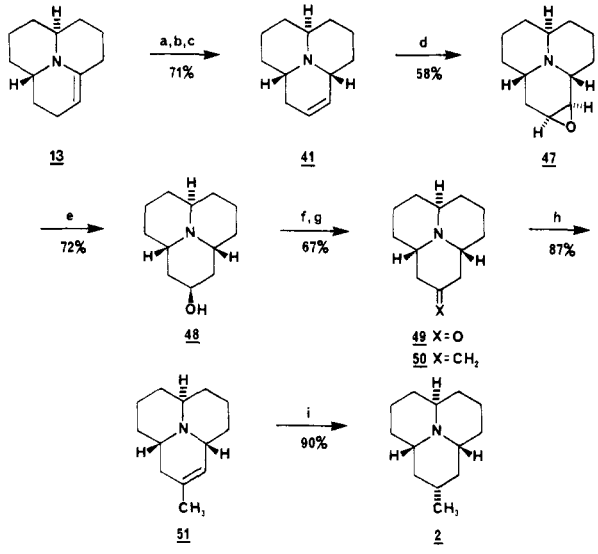


Figure 1. ORTEP[80] drawing of **40** (only one of two molecules in the asymmetric unit is portrayed); C2 and C4 are disordered with respect to the position of the double bond.

Scheme VIII[a]



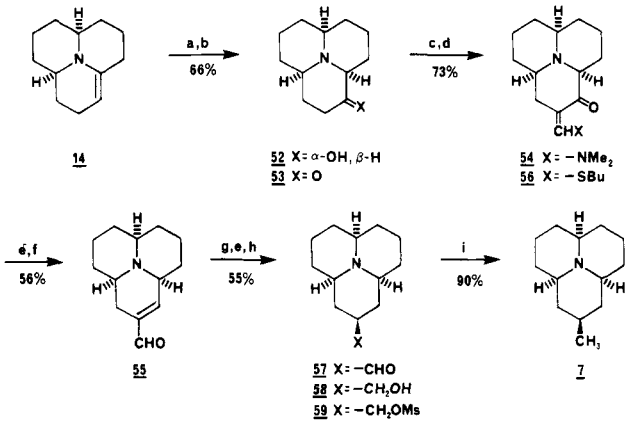
[a] a, FSO_3Me; b, *i*-Pr_2NLi, THF; c, LiSEt, DMF; d, H^+, CF_3CO_3H; e, Li, $H_2NCH_2CH_2NH_2$; f, CrO_3, H^+; g, $Ph_3P{=}CH_2$; h, TsOH, refluxing xylene; i, H_2, Pd/C.

indicate that **39**, **40**, and **46** can possess all-chair stereochemistries; however, in **43**, **44**, and **45** one of the rings is forced into a skew boat conformation. Thus initially it was hoped that the sequence **12** → **39** → **40** → **41** would obtain, as this sequence proceeds via all-chair stereochemistries. In fact, X-ray crystallographic analysis of the chloride salt of the product of isomerization showed it to possess structure **40** (Figure 1); consequently, the methylation product must possess structure **39**.

With an appropriately functionalized compound in hand, we could continue the synthesis of precoccinelline. Regiospecific derivatization of the allylic amine **41** was accomplished in a two-step sequence (Scheme VIII). Epoxidation of the trifluoroacetate salt of **41** (to prevent *N*-oxide formation) with peroxytrifluoroacetic acid occurred from the less hindered face of the double bond to give **47**.[60] All other attempts to functionalize the double bond—e.g., oxymercuration, Prevost reaction—were without success; presumably, protonation or complexation of the nitrogen atom resulted in strong deactivation of the double bond. Epoxide **47** was relatively inert to lithium aluminum hydride due to steric hindrance; forcing conditions gave a mixture of products. However, axial alcohol

(60) Fodor, G. *Tetrahedron* **1957**, *1*, 86–102.

Scheme IX[a]



[a] a, $BH_3{\cdot}Me_2S$, then H_2O_2, NaOH; b, CrO_3, H^+; c, $MeOCH(NMe_2)_2$; d, BuSH, TsOH; e, $LiAlH_4$; f, H_3O^+; g, $Li{\cdot}4NH_3$; h, MsCl, Et_3N; i, $LiBHEt_3$.

48 was obtained cleanly on treatment with lithium in ethylenediamine.[61] Oxidation then gave ketone **49**, previously prepared by Ayer and Furuichi[20] and by Stevens and Lee.[21] In our hands, reaction of **49** with methylmagnesium iodide and methyllithium was incomplete, presumably due to enolization. Conversion of **49** to the exocyclic methylene compound **50** was accomplished in high yield via a Wittig reaction.[21] Hydrogenation of **50** gave a 3:2 mixture of methyl group isomers, contrary to other reports,[21] with **2** predominating. Hydrogenation of the sterically more demanding **51**, prepared by isomerization of **50** with toluenesulfonic acid in refluxing xylene, gave precoccinelline (**2**) with greater than 97% stereoselectivity, as has been reported by Ayer and Furuichi.[20] Reaction of **2** with peracid gave coccinelline (**1**).[9] The synthetic and natural[51] materials were identical by spectral comparison.

Myrrhine (**7**) was the final ladybug alkaloid to be approached. Myrrhine differs significantly from all the others discussed so far in that it possesses the thermodynamically favored all-cis stereochemistry about the nitrogen atom. Enamine **14** was the chosen starting material. As in the synthesis of precoccinelline (**2**), the introduction of a methyl group at the carbon atom "para" to the nitrogen atom was required. Reaction of **14** with methyl fluorosulfate resulted in predominant C-alkylation; thus the methodology applied in the synthesis of **2** could not be extended to the synthesis of **7**. Methodology developed in the synthesis of hippodamine (**3**) was next attempted.

Hydroboration–oxidation of the enamine **14** gave alcohol **52** (Scheme IX); the all-cis stereochemistry about the nitrogen atom was apparent from the strong Bohlman bands[30] in the IR spectrum. The equatorial nature of the hydroxyl group was evident from the broadened triplet (J = 10 Hz) at δ 3.33 in the ^1H NMR spectrum. Oxidation to ketone **53** was accomplished with Jones reagent in acetic acid; again, the Cr(II)-mediated workup procedure proved valuable.[38] Reaction of **53** with the Bredereck reagent[46] gave enamino ketone **54** in high yield. All attempts to effect direct 1,2-reduction of **54** to the unsaturated aldehyde **55** were unsuccessful; 1,4-reduction occurred preferentially. In contrast, reduction of the thiomethylene compound **56**, prepared by treatment of **54** with butanethiol and acid,[62] with lithium aluminum hydride followed

(61) Hallsworth, A. S.; Henbest, H. B. *J. Chem. Soc.* **1957**, 4604–4608; **1960**, 3571–3575. Brown, H. C.; Ikegami, S.; Kawakami, J. H. *J. Org. Chem.* **1970**, *35*, 3243–3245.

(62) Martin, S. F.; Moore, D. R. *Tetrahedron Lett.* **1976**, 4459–4462.

by treatment with aqueous acid gave **55** via the intermediate alcohol.[63] Catalytic hydrogenation of **55** gave a mixture of aldehydes and saturated alcohols. However, reduction with lithium tetraamine[47] gave a good yield of aldehyde **57** along with its epimer in the thermodynamic 85:15 ratio. Conversion of the mixture of aldehydes to the alcohols by hydride reduction permitted purification of the desired equatorial hydroxymethyl compound **58** by crystallization. Subsequent mesylation to give **59** followed by reduction with lithium triethylborohydride[64] completed the synthesis of myrrhine (**7**), identical with the natural material[51] by spectroscopic comparison.

Experimental Section

Melting points are corrected; boiling points are uncorrected. Temperature ranges cited for bulb-to-bulb distillations refer to the oven temperature. Elemental analyses were performed by Spang Microanalytical Laboratory (Eagle Harbor, MI), Atlantic Microlab, Inc. (Atlanta, GA), or Dr. R. C. Rittner of Olin Corporation (New Haven, CT). ^{1}H NMR spectra were recorded of $CDCl_3$ solutions at 270 MHz on a Bruker HX-270 spectrometer unless otherwise indicated. Chemical shifts are reported as δ values in ppm downfield from internal Me_4Si. ^{13}C NMR spectra were taken of $CDCl_3$ solutions at 67.89 MHz on a Bruker HX-270 or at 20 MHz on a Varian CFT-20 spectrometer. Chemical shifts are reported as δ values in ppm downfield from Me_4Si or are referenced to the center line of the $CDCl_3$ triplet (δ 77.0). IR spectra were recorded on a Nicolet 5000 FT-IR or a Beckman 4250 spectrometer as $CHCl_3$ solutions unless noted otherwise. Low-resolution MS were obtained on a Hewlett-Packard 5985A GC-MS instrument at 70 eV; the instrument was equipped with a $^1/_4$ in. × 3 ft column packed with 3% OV-101 on Chromasorb G. The high-resolution MS was obtained at the department of chemistry, Cornell University. Analytical VPC was performed on either a Perkin-Elmer 880 chromatograph equipped with a flame-ionization detector or on a Varian Aerograph 1400 thermal conductivity instrument. Columns used were $^1/_8$ in. × 6 ft SS packed with either 5% OV-101 or 5% Carbowax 20M on 110/120 mesh Anakrom ABS. Preparative VPC was conducted on a Varian Aerograph 90-P thermal conductivity instrument with a $^1/_4$ in. × 6 ft SS column packed with 5% SE-30 on 60/70 Anakrom A. Analytical TLC was performed on flexible precoated silica gel or alumina plates (0.2 mm) with fluorescent indicator supplied by J. T. Baker Chemical Company. Preparative TLC was performed on 2 mm silica gel GF plates supplied by Analtech, Inc. Silica gel (100–200 mesh) obtained from Fisher Scientific Company was used for column chromatography.

THF, Et_2O, PhH, and DME were distilled from sodium benzophenone ketyl under N_2 immediately before use. CH_2Cl_2 was distilled from P_2O_5. $CHCl_3$, *i*-Pr_2NH, DMF, Et_3N, ethylenediamine, *t*-$BuNH_2$, *t*-BuOH, and Me_2SO were distilled from CaH_2 under N_2. Low temperatures were maintained with the following baths: −78 °C, *i*-PrOH/dry ice; −45 °C, CH_3CN/dry ice; 0 °C, ice/water. The temperatures cited refer to the external bath temperature.

(3aα,6aα,9aβ)-Dodecahydro-9b-boraphenalene (10). A procedure modified from that of Rotermund and Köster was used.[22] A 1-L round-bottomed flask was equipped with a 250-mL addition funnel and distillation take-off apparatus. The system was swept with dry N_2 and 160 mL of cyclooctane was added along with 100 mL of dry THF and 295 mL (1.60 mol) of distilled 1,5,9-cyclododecatriene. This solution was treated with 152 mL (1.60 mol) of borane–dimethyl sulfide complex, added dropwise over 2.5 h. As a result of the exothermic reaction, Me_2S began to distill out of the flask when less than half of the reagent had been added. After the addition was complete, the remainder of the Me_2S was distilled from the reaction mixture (40–60 °C). Two additional fractions were then collected; the first consisted mainly of THF (60–65 °C) and the second of cyclooctane (140–160 °C). The reaction mixture was then heated in an oil bath maintained at 215–220 °C for ca. 15 h. The desired product was isolated by vacuum distillation directly from the reaction flask. A forerun of colorless liquid was collected (25–45 °C (1.2 mm)) and then ca. 200 mL of organoborane **10** (85–95 °C (1.2 mm)) was obtained as a viscous yellow liquid. The product was stored under N_2 in a desiccator.

1,5,9-Cyclododecanetrione (15). A 250-mL three-necked flask was equipped with a thermometer, mechanical stirrer (glass blade), and a N_2 inlet. The flask was flushed with N_2; water (105 mL), acetone (75 mL), NaOAc (944 mg, 11.5 mmol), finely powdered $NaIO_4$ (29.8 g, 139 mmol), and 400 mg of RuO_2 were added. Finally, 4.04 g (23 mmol) of organoborane **10** was added via syringe.[65] The mixture was stirred vigorously with ice/water cooling when necessary to maintain the temperature between 15 and 30 °C. The black RuO_2 dissolved and the reaction mixture assumed a yellow-green color characteristic of RuO_4. This color persisted for 2 h, when the mixture turned black in color. The solid sodium iodate was removed by filtration through a medium porosity fritted glass funnel; the solid was washed well with 1:1 acetone–water. The filtrate was transferred to a separatory funnel and just enough $NaIO_4$ was added to the black filtrate to cause it to turn yellow-green again. Then 1 g of powdered charcoal was added and the mixture was shaken vigorously for 1 min. *i*-PrOH (3 mL) was then added and the mixture shaken again. The mixture was filtered through a medium porosity fritted glass funnel and the filtrate was extracted with five 40-mL portions of CH_2Cl_2. The combined extract was washed with two 50-mL portions of saturated aqueous $NaHCO_3$ solution and then dried over $MgSO_4$. Filtration and removal of the solvent in vacuo gave an oily, yellow-green solid. Ether (10 mL) was added[66] and the mixture was heated briefly on the steam bath with swirling.[67] After cooling to room temperature, the flask was placed in the freezer to complete crystallization. The solid was filtered off, washed with a little ether, and dried in vacuo to afford the triketone **15**, mp 87–90 °C. Yields ranged from 35% to 45%. An analytical sample (mp 90–91.5 °C) was prepared by recrystallization from ether: IR 1718, 1710 (shoulder) cm^{-1}; ^{1}H NMR[68] (60 MHz) δ 2.43 (12 H, t, J = 6 Hz), 1.96 (6 H, quintet, J = 6 Hz). Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.59; H, 8.69.

Octahydro-4a-hydroxybenzocyclooctene-1,8(2*H*,5*H*)-dione (16). The mother liquors from several preparations of triketone **15** were combined and the solvent removed. Crystallization from isopropyl acetate gave white crystals of hydroxy diketone **16**: IR 3580, 1685 cm^{-1}. The analytical sample, mp 187–189 °C, was obtained by recrystallization from acetone. Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.63; H, 8.63.

(3aα,6aα,9aα)-Dodecahydropyrido[2,1,6-*de*]quinolizine (12). A. By Reductive Amination of 15. 1,5,9-Cyclododecanetrione (**15**, 3.57 g) was weighed into a 500-mL Parr hydrogenation bottle. Then, in order, were added 380 mg of 10% Pd on carbon, 35 mL of *i*-PrOH, 57 mL of 2.2 M ammonia in *i*-PrOH (prepared by condensation of liquid NH_3 into cold *i*-PrOH; the concentration was determined by titration with 0.1 N HCl to the methyl red end point), and 1.0 mL of HOAc. The bottle was placed on a Parr apparatus, flushed with H_2, and charged to 60 psig with H_2. After 16 h, the mixture was filtered and the solvent was removed in vacuo; the residue was dissolved in a slight excess of dilute HCl and extracted with two 50-mL portions of ether. The water layer was basified with KOH and extracted with four 50-mL portions of CH_2Cl_2. The combined organic layer was

(63) Ireland, R. E.; Marshall, J. A. *J. Org. Chem.* **1962**, *27*, 1620–1627.
(64) Holder, R. W.; Matturro, M. G. *J. Org. Chem.* **1977**, *42*, 2166–2168. Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1973**, *95*, 1669–1671.

(65) Larger scale reactions appear to give lower yields owing to the instability of the product to longer reaction times and workup times. Several reactions may be set up an hour or so apart.
(66) Because the triketone is extremely sensitive to intramolecular aldol condensation, it is imperative that it be isolated with all due haste. The entire workup procedure (up until the addition of the ether) should be performed within 60 min or less. Once in crystalline form, the triketone is stable for years.
(67) All the solid may not dissolve; extended heating at this point will cause decomposition.
(68) The $CDCl_3$ should be passed through a 3-cm column of basic alumina (most conveniently in a disposable pipette plugged with cotton) before mixing with the triketone. The spectrum should then be run as soon as possible.

dried over $MgSO_4$ and filtered; the solvent was removed in vacuo and the residue was distilled bulb-to-bulb (ca. 85 °C (0.5 mm)) to afford 2.57 g (80% yield) of the *all-cis*-perhydroazaphenalene (**12**) as a colorless liquid which discolored slowly on exposure to air: IR (film) 2950, 2880, 2810, 2750, 1455, 1390, 1330, 1265, 1115, 1045 cm^{-1}; ^{13}C NMR δ 62.4 (3 C, d), 33.9 (6 C, t), 24.1 (3 C, t).

Anal. Calcd for $C_{12}H_{21}N$: C, 80.38; H, 11.80; N, 7.81. Found: C, 80.27; H, 11.75; N, 7.89.

B. By Isomerization of Amine 11. Trans amine **11** (16.2 g), 570 mg of 10% Pd on carbon, 40 mL of *i*-PrOH, and 1 mL of HOAc were placed in a stainless steel bomb. The bomb was flushed with H_2 and sealed. The bomb was heated and rocked at 190 °C for 21 h. After cooling, the contents of the bomb were removed and the catalyst was filtered off. Water was added and the mixture was extracted twice with 1:1 ether/hexane. The combined extract was dried (K_2CO_3, Na_2SO_4) and the solvent was removed in vacuo. The residue was distilled to afford 15.7 g of cis amine **12** (97% yield).

***cis*-(±)-1,2,3,3a,4,5,6,6a,7,8-Decahydropyrido[2,1,6-*de*]quinolizine (14). A. Via Mercuric Acetate Oxidation of 12.** To 70 mL of water were added 2.49 g (13.9 mmol) of cis amine **12**, 8.12 g (27.8 mmol) of EDTA, 6.63 g (22.0 mmol) of $Hg(OAc)_2$, 32.4 mL of 1.5 N (48.6 mmol) aqueous NaOH solution, and 1.4 mL of HOAc.[32] The mixture was stirred and refluxed under N_2 for 4.5 h. The mixture was cooled and 7.2 mL of 20% aqueous ammonium polysulfide was added. The resulting solid was removed by filtration through a Celite pad. The filtrate was made basic with NaOH and extracted with ether. The extract was washed once with saturated NaCl solution and dried over Na_2SO_4. The solvent was removed in vacuo and the residue was distilled bulb-to-bulb to give 2.04 g (83% yield) of enamine **14** as a colorless oil.

An alternate isolation procedure involved continuous extractive steam distillation. At the end of the reflux period, the reaction mixture was cooled and made basic with NaOH. Steam distillation utilizing a water recycling apparatus[69] gave a 78% yield of enamine **14** after bulb-to-bulb distillation. This method was considerably more convenient than the sulfide precipitation method.

B. Via the Modified Polonovski Reaction on 11. A solution of 3.4 g (19 mmol) of trans amine **11** in 22 mL of MeOH was cooled to 0 °C and 2 mL of 90% H_2O_2 was added over 5 min. The mixture was allowed to warm slowly to room temperature and was stirred for 12 h. Disappearance of the starting material was evident by TLC (silica, 10 mL of THF plus 3 drops of concentrated NH_4OH). Chloroform (60 mL) was added and, with ice/water cooling, excess peroxide was destroyed by the careful addition of 10% Pt on C. After 45 min, $MgSO_4$ was added. The solids were removed by filtration and washed with $CHCl_3$. The filtrate was concentrated in vacuo to afford a light brown semisolid. Trituration with EtOAc resulted in the isolation of 3.4 g (84% yield) of the *N*-oxide of **11**, presumably as the monohydrate, as a white solid.

The *N*-oxide (3.4 g, 16 mmol) was dissolved in 32 mL of dry dichloromethane under N_2. The solution was cooled to −78 °C and 4.5 mL (32 mmol) of trifluoroacetic anhydride was added over 10 min.[40] The mixture was allowed to warm to room temperature; after 12 h, 20 mL of 50% aqueous KOH solution was added at 0 °C. The water layer was extracted with three 50-mL portions of CH_2Cl_2. The combined organic layer was dried (K_2CO_3, Na_2SO_4) and concentrated in vacuo to give a dark brown oil. Bulb-to-bulb distillation (50–52 °C (0.15 mmHg)) yielded 1.9 g (56% from **11**) of the cis enamine **14** as a colorless oil which discolored on exposure to air. Analysis by VPC (OV-101, 130 °C) indicated a purity of ca. 98%: IR(film) 2930, 2840, 2800, 2775, 1645, 1445, 1320 cm^{-1}; ^1H NMR δ 4.42 (1 H, br d, J = 6 Hz), 2.54 (1 H, br t, J = 10 Hz), 2.28 (1 H, br t, J = 10 Hz), 1.94–1.18 (four sets of multiplets); ^{13}C NMR δ 142.6 (1 C), 98.2 (1 C), 59.9 (1 C), 58.4 (1 C), 34.2 (1 C), 33.1 (2 C), 32.6 (1 C), 30.2 (1 C), 24.0 (1 C), 23.3 (1 C), 21.9 (1 C); MS, m/e (relative intensity) 177 (M^+, 62), 176 (100), 162 (42), 149 (18), 148 (32), 135 (20), 134 (34), 120 (15).

Conversion to the known picrate salt, mp 127–128 °C (lit.[31] mp 128–129 °C) was accomplished with 1 equiv of picric acid in EtOH.

(69) For a description of the apparatus, see: Vogel, A. I. "Practical Organic Chemistry", 3rd ed.; Longman: London, 1956; pp 224–225.

(3aα,6aα,9aα)-Decahydropyrido[2,1,6-*de*]quinolizine-3a-(1*H*)carboxamide (18). Concentrated HCl (1.0 mL, 12 mmol) was added to a mixture of 2.04 g (11.5 mmol) of enamine **14**, 50 mL of ether, and 100 mL of water. KCN (2.25 g, 34.5 mmol) was added and the mixture was stirred at 25 °C for 17 h.[31] The water layer was extracted with four 50-mL portions of ether. The combined extract was dried (Na_2SO_4) and evaporated to give 2.11 g of the somewhat unstable amino nitrile **17** which was taken directly on to the next step.

The amino nitrile was added to 14 mL of fuming H_2SO_4 (30% SO_3) and the mixture was stirred mechanically at 50 °C for 50 h. The reaction mixture was added slowly and carefully to crushed ice and then basified with NaOH. The water layer was extracted with chloroform (seven 50-mL portions). The combined extract was evaporated and the residue was chromatographed on silica gel (5% THF in acetone) to give 1.92 g (80% from **14**) of the cis amide **18** as a light orange solid: IR 3540, 3415, 3000, 2940, 2870, 1675, 1585 cm^{-1}; ^1H NMR (100 MHz) δ 5.41 (2 H, br s), 3.25 (2 H, t, J = 11 Hz), 1.85 (2 H, d, J = 11 Hz), 1.8–1.1 (18 H); ^{13}C NMR δ 177.8 (1 C, s), 64.5 (1 C, d), 54.6 (2 C, d), 39.8 (2 C, t), 35.5 (2 C, t), 34.7 (2 C, t), 23.6 (1 C, t), 20.8 (2 C, t).

An analytical sample, mp 195–198 °C, was prepared by recrystallization from benzene.

Anal. Calcd for $C_{13}H_{22}N_2O$: C, 70.23; H, 9.97; N, 12.60. Found: C, 70.28, H, 9.97; N, 12.49.

(±)-Dodecahydro-9a,3a-(iminomethano)pyrido[2,1,6-*de*]quinolizin-12-one (19). To 2.63 g (11.8 mmol) of cis amide **18** were added 60 mL of water, 5.17 g (17.7 mmoles) of EDTA, 4.14 g (13.0 mmole) of $Hg(OAc)_2$, 27.7 mL of 1.5 N (41.5 mmol) aqueous NaOH solution, and 1.2 mL (21 mmol) of HOAc.[32] The mixture was stirred vigorously and refluxed. After 4 h the mixture was cooled and 6 mL of 20% aqueous ammonium polysulfide was added. The mixture was filtered through Celite. The filtrate was basified with NaOH and extracted with eight 50-mL portions of $CHCl_3$. The combined extract was dried over Na_2SO_4 and evaporated. The residue was dissolved in hot acetone and chromatographed on a silica gel (deactivated with 12 wt% water) column eluted with acetone to give lactam **19** as a tan solid. Recrystallization (three crops) from acetone gave 1.85 g (71% yield) of colorless lactam **19**: mp 146.5–147 °C; IR 3420, 3200, 3000, 2940, 2875, 2855, 1700 cm^{-1}; ^1H NMR (100 MHz) δ 6.40 (1 H, br s), 2.5–1.1 (19 H); ^{13}C NMR δ 180.3, 74.9, 67.5, 55.9, 35.8, 33.7, 32.7, 31.3, 31.1, 29.6, 22.1, 20.5, 18.1.

Anal. Calcd for $C_{13}H_{20}N_2O$: C, 70.87; H, 9.15; N, 12.72. Found: C, 70.91; H, 9.07; N, 12.77.

(3aα,6aα,9aβ)-(±)-Decahydropyrido[2,1,6-*de*]quinolizine-3a(1*H*)-carboxamide (20). A mixture of 1.25 g of lactam **19**, 500 mg of 10% Pt on C, 50 mL of MeOH, and 0.5 mL of HOAc was shaken for 60 h under 4 atm of H_2. The catalyst was removed by filtration and the solvent was evaporated. The residue was taken up in $CHCl_3$ and washed with dilute aqueous NaOH solution. The organic layer was dried over Na_2SO_4 and the solvent was evaporated to give 1.19 g (94% yield) of of the trans amide **20** as a white, crystalline solid: IR 3500, 3375, 3000, 2940, 2865, 1675, 1540 cm^{-1}; ^1H NMR (100 MHz) δ 7.40 (1 H, br s), 5.43 (1 H, br s), 4.70 (1 H, d, J = 10 Hz), 2.79 (1 H, t, J = 11 Hz), 1.9–1.1 (17 H), 0.92 (1 H, d, J = 10 Hz); ^{13}C NMR δ 180.5, 65.4, 54.9, 49.5, 37.7, 35.1, 34.3, 31.6, 22.9, 21.3, 21.1, 20.0, 19.7.

The analytical sample, mp 155–157 °C, was obtained by recrystallization from ether.

Anal. Calcd for $C_{13}H_{22}N_2O$: C, 70.23; H, 9.97; N, 12.60. Found: C, 70.26; H, 9.87; N, 12.62.

***trans*-(±)-1,2,3,3a,4,5,6,6a,7,8-Decahydropyrido[2,1,6-*de*]quinolizine (13). A. From Amide 20.** Trans amide **20** (985 mg, 4.4 mmol), 1.01 g (13.2 mmol) of $POCl_3$, 696 mg (8.8 mmol) of pyridine, and 34 mL of $CHCl_3$ were mixed and refluxed for 7 h. The mixture was stirred at 25 °C with aqueous $NaHCO_3$ solution. The organic layer was separated and dried over Na_2SO_4. Removal of the solvent gave 779 mg of a mixture of amino nitrile **22** and enamine **13** in ca. equal amounts. Chromatography on a silica gel (deactivated with 12 wt% water) column eluted with 1% concentrated NH_4OH in ether followed by bulb-to-bulb distillation gave 200 mg of enamine **13** as a colorless oil which discolored slowly on exposure to air: IR (film) 2940, 2875, 2800, 1650, 1445, 1320, 1070 cm^{-1}; ^1H NMR δ 4.66 (1 H, br d, J = 5 Hz), 2.99 (1 H, dd, J = 5, 10 Hz), 2.42 (1 H, br t, J = 10 Hz); ^{13}C NMR

δ 147.4 (s), 103.6 (d), 56.8 (d), 54.2 (d), 33.8 (t), 33.3 (t), 33.0 (t), 30.8 (t), 25.8 (t), 24.7 (t), 24.1 (t), 19.5 (t).

B. From Amino Alcohol 23. See ref 38.

(3aα,6aα,9aβ)-Dodecahydropyrido[2,1,6-*de*]quinolizine (11). A. From Enamine 13. To 50 mg of 10% Pt on C were added 0.065 mL of HOAc, 8 mL of MeOH, and 200 mg of the enamine **13**/nitrile **22** mixture. The reaction mixture was shaken under 4 atm of H_2 for 12 h. The catalyst was filtered off, and the solvent was removed. The residue was chromatographed on deactivated silica gel (12 wt% water) with 1% concentrated NH_4OH in ether to give 100 mg of the trans amine **11** after bulb-to-bulb distillation; 20 mg of cis amine **12** (formed by isomerization of **11** by the catalyst) was also obtained.

B. From Amino Alcohol 23. The crude amino alcohol **23** (12.2 g) was dissolved in 100 mL of xylene and a small amount of *p*-toluenesulfonic acid was added. The solution was refluxed under a Dean–Stark trap until no more water collected (ca. 3 h). After cooling to room temperature the solution was acidified with 10% aqueous HCl (50 mL). The water layer was separated and washed with five 30-mL portions of hexane and one 30-mL portion of ether. KOH pellets were added carefully with ice/water cooling until the aqueous layer was strongly basic. Extraction with ether (three 50-mL portions) and CH_2Cl_2 (three 50-mL portions) followed by drying over $MgSO_4$ and Na_2SO_4 and concentration in vacuo afforded the crude trans amine. Bulb-to-bulb distillation (50–53 °C, (0.12 mmHg)) gave 7.48 g (68%) of **11** as a colorless oil. Analysis by VPC indicated a purity of ca. 98%: IR (film) 2925, 2860, 1460, 1445, 1125 cm^{-1}; ^1H NMR δ 2.96 (2 H, br d, J = 10 Hz), 2.82 (1 H, br t, J = 11 Hz), 1.97–0.88 (18 H, four sets of multiplets); ^{13}C NMR δ 57.7 (2 C, d), 47.6 (1 C, d), 34.1 (2 C, t), 30.7 (2 C, t), 25.5 (1 C, t), 21.6 (2 C, t), 19.2 (2 C, t); MS, m/e (relative intensity) 179 (M^+, 41), 178 (91), 164 (25), 151 (17), 150 (66), 138 (16), 137 (100), 136 (81), 122 (29).

The analytical sample was prepared by conversion of amine **11** to the corresponding picrate, obtained as yellow plates, mp 198–200 °C.

Anal. Calcd for $C_{18}H_{24}N_4O_7$: C, 52.94; H, 5.92; N, 13.72. Found: C, 53.07; H, 5.78; N, 13.76.

***O*-(2,4-Dinitrophenyl)hydroxylamine (24).**[70] A mixture of 10.0 g (37.1 mmol) of ethyl *O*-(2,4-dinitrophenyl)acetohydroxamate[71] and 24 mL of 70% $HClO_4$ was stirred at room temperature for 30 min. The resulting clear yellow solution was diluted with 200 mL of ice-cold water; the resulting suspension was stirred for 5–10 min and then filtered. The collected solid was washed well with cold water.[70b] Crude product was recrystallized by dissolution in 30 mL of absolute EtOH with steam bath heating and vigorous swirling;[72] when all the solid had dissolved, the solution was protected from light, allowed to cool to room temperature, and then placed in the refrigerator at −5 °C for 1 h. The light yellow crystals were collected by filtration, washed with cold absolute EtOH, and dried in vacuo overnight. The yield of **24**, mp 110–112 °C (lit.[70] mp 112–113 °C), was 6.12 g (83%). The product was stored in the dark and used within three days of preparation.

(±)-*trans*-13-Azabicyclo[7.3.1]tridecan-5-ol (23).[24] A 250-mL three-necked flask containing a solution of 5.98 g (30.1 mmol) of **24** in 150 mL of dry CH_2Cl_2 was swept with N_2. The solution was cooled to −78 °C and a precipitate formed. To this rapidly stirred suspension was added 3.34 mL (30.1 mmol) of *tert*-butyl hypochlorite[73] in a steady stream. The cold bath was removed and the mixture allowed to warm slowly. As the temperature of the reaction mixture approached 0 °C, the solid gradually dissolved to yield a clear solution which was stirred for several minutes more until it had assumed a deep golden-yellow color. The −78 °C bath was replaced around the reaction flask; the mixture was observed closely for signs of solid formation (indicative of incomplete chlorination of **24**).[74] After several minutes at −78 °C, the solution was still homogeneous; 5.68 mL (30.1 mmol) of perhydroboraphenalene (**10**)[22] was added all at once to give an exothermic reaction with formation of a very dark red color. The cold bath was removed and the flask allowed to warm to room temperature. The solvent was removed in vacuo and the residue was stirred in 125 mL of 1 N aqueous NaOH solution and 100 mL of ether. The resulting thick suspension was cooled to 0 °C and treated with 5 mL of 30% H_2O_2 added over 5 min; the mixture was stirred for an additional 15 min. Excess oxidant was destroyed by the slow addition of saturated aqueous $NaHSO_3$ solution. Concentrated HCl (10 mL) was added slowly until the mixture was acidic. The layers were separated; the acidic water layer was washed with two 50-mL portions of ether and then made strongly basic by the careful addition of KOH pellets with ice/water cooling. The aqueous layer was extracted with CH_2Cl_2 (four 50-mL portions) and the combined organic layer was dried over $MgSO_4$ and concentrated in vacuo to yield 4.08 g (69%) of amino alcohol **23** as an orange oil. Purification could be achieved either by filtration through a short silica column with ether or by the Sharpless calcium chloride method[75] to give **23** as a yellow oil: IR (film) 3350, 2920, 2860, 1450, 1430, 1030 cm^{-1}; ^1H NMR (90 MHz) δ 4.18 (1 H, m), 3.20–2.36 (3 H, m), 2.20–0.70 (18 H); ^{13}C NMR δ 69.0, 53.7, 48.4, 37.7, 34.7, 33.9, 33.6, 31.5, 26.3, 23.7, 21.5, 21.4. The amino alcohol was typically carried on to the next step, preparation of either enamine **13** or amine **11**, without purification (vide supra).

(1α,3aβ,6aα,9aα)-(±)-Dodecahydropyrido[2,1,6-*de*]quinolizin-1-ol (27) and (1α,3aα,6aβ,9aα)-(±)-Dodecahydropyrido[2,1,6-*de*]quinolizin-1-ol (28).[42,43] A solution of the trans enamine **13** (6.75 g, 38.1 mmol) in 95 mL of dry THF was transferred to a flame-dried flask under N_2. The flask was cooled to 0 °C and 6.5 mL (68 mmol) of borane–dimethyl sulfide complex was added dropwise. After 8.5 h at 0–5 °C, the reaction mixture was allowed to warm to room temperature and was stirred for 12 h. Excess borane was quenched with 10 mL of absolute EtOH, the flask was cooled to 0 °C, and a solution of 12 ml of 30% H_2O_2 in 25 mL of 2.5 N aqueous NaOH was added over a period of 10 min. The mixture was stirred at room temperature for 1 h and then refluxed for 1.5 h. Solid $NaHSO_3$ was added with ice/water cooling to destroy the unconsumed peroxide. The solvent was removed in vacuo and the resulting aqueous solution was acidified with concentrated HCl. The water layer was washed with ether (two 20-mL portions) and then made strongly basic with KOH pellets. The water layer was extracted with ether; the combined extract was dried over $MgSO_4$ and concentrated in vacuo to afford 7.1 g (95%) of a colorless oil which was shown by VPC analysis (Carbowax 20M, 180 °C) to consist of a mixture of alcohols **27** and **28** in a ratio of ca. 3:1. By fractional crystallization from 2-butanone, it was possible to remove about 10% (200 mg) of the minor isomer **28** from the mixture. Recrystallization from 2-butanone followed by sublimation (100–110 °C (0.6 mmHg)) afforded pure **28** as a white solid: mp 178–178.5 °C; IR 3600, 2930, 2860, 1450, 1130, 1035 cm^{-1}; ^1H NMR δ 3.99 (1 H, td, J = 4, 11 Hz), 3.00 (1 H, br d, J = 8 Hz), 2.78 (1 H, br t, J = 10 Hz), 2.68 (1 H, br d, J = 10 Hz); MS, m/e (relative intensity) 195 (M^+, 32), 194 (35), 138 (64), 137 (59) 136 (100).

Anal. Calcd for $C_{12}H_{21}NO$: C, 73.80; H, 10.84; N, 7.17. Found: C, 73.89; H, 11.00; N, 7.12.

The major isomer **27** was obtained in pure form by continuous extractive steam distillation[69] from water into chloroform. Fractions were collected every few hours so that the progress of the separation could be monitored by VPC. The distillation was discontinued when the **27**:**28** ratio in the distillate approached ca. 90:10. The collected fractions were dried over Na_2SO_4 and concentrated in vacuo to give a pale yellow solid. Recrystallization from hexane afforded 3.9 g (52%) of stereoisomerically pure **27** as a white solid: mp 66.5–67.5 °C; IR 3450, 2970, 2855, 1445, 1110, 1000 cm^{-1}; ^1H NMR δ 3.61 (1 H, br s), 3.00 (1 H, br d, J = 9 Hz), 2.86 (3 H, m); MS, m/e (relative intensity) 195 (M^+, 33), 194 (39),

(70) (a) Sheradsky, T. *J. Heterocycl. Chem.* **1967**, *4*, 413–414. (b) Tamura, Y.; Minimikawa, J.; Sumoto, K.; Fujii, S.; Ikeda, M. *J. Org. Chem.* **1973**, *38*, 1239–1241.

(71) Ilvespää, A. O.; Marxer, A. *Helv. Chim. Acta* **1963**, *46*, 2009–2020.

(72) Excessive heating at this stage results in a lower quality, brownish product and should be avoided.

(73) Mintz, M. J.; Walling, C. "Organic Syntheses"; Wiley: New York, 1973; Collect. Vol. 5, pp 184–187.

(74) Incomplete reaction between **24** and the hypochlorite appears to occur when poor quality **24** is used; reaction can often be initiated by the addition of a drop of triethylamine, but the yield of final product is generally lower. This problem can be avoided by the use of good quality (i.e., no hint of a brownish tinge) reagent **24**.

(75) Sharpless, K. B.; Chong, A. O.; Scott, J. A. *J. Org. Chem.* **1975**, *40*, 1252–1257.

166 (34), 138 (56), 137 (48), 136 (100).

The analytical sample was prepared by sublimation (50–70 °C (0.5 mmHg)).

Anal. Calcd for $C_{12}H_{21}NO$: C, 73.80; H, 10.84; N, 7.17. Found: C, 73.90; H, 10.96; N, 7.26.

(3aα,6aβ,9aβ)-(±)-Decahydropyrido[2,1,6-*de*]quinolizin-1(2*H*)-one (2ε). A solution of 282 mg (1.40 mmol) of amino alcohol **27** and 0.090 mL (1.6 mmol) of concentrated H_2SO_4 in 3 mL of HOAc was treated at 20 °C with 1.0 mL of Jones reagent[37] added over 5 min. After 1 h, excess oxidant was destroyed by addition of 1 mL of *i*-PrOH. The solution was diluted with 10 mL of water and 2.5 g (8.5 mmol) of trisodium citrate dihydrate was added. A piece of freshly amalgamated mossy zinc was added and the mixture was stirred under a flow of N_2 for 15 min. With ice/water cooling, the solution was made strongly alkaline by the addition of 20% aqueous NaOH solution.[38] The water layer was extracted with ether (six 10-mL portions) and the combined extract was dried over $MgSO_4$ and concentrated in vacuo. Bulb-to-bulb distillation (70–74 °C (0.2 mmHg)) afforded 211 mg (76%) of amino ketone **26** as a colorless oil: IR (film) 2925, 2850, 1710, 1445, 1040 cm^{-1}; ^1H NMR δ 3.44 (1 H, br d, J = 13 Hz), 3.16 (1 H, br t, J = 11 Hz), 2.92 (1 H, br d, J = 11 Hz), 2.45 (1 H, m), 2.33 (1 H, br d, J = 13 Hz); MS, m/e (relative intensity) 193 (M^+, 14), 165 (44), 164 (62), 137 (100), 136 (90).

The analytical sample was prepared by preparative VPC (OV-101, 160 °C) followed by bulb-to-bulb distillation.

Anal. Calcd for $C_{12}H_{19}NO$: C, 74.57; H, 9.91; N, 7.25. Found: C, 74.52; H, 9.85; N, 7.13.

(3aα,6aβ,9aβ)-(±)-2-[(Dimethylamino)methylene]decahydropyrido[2,1,6-*de*]quinolizin-1(2*H*)-one (31). A mixture of 180 mg (0.90 mmol) of amino ketone **26** and 0.40 mL (2.6 mmol of bis(dimethylamino)methoxymethane[46] was heated under N_2 at 60–65 °C for 10 h. On cooling to room temperature, the brown reaction mixture solidified. Recrystallization from ether at −30 °C gave 194 mg (87%) of **31** as light tan needles. A second recrystallization from ether/acetone gave colorless crystals: mp 97–99 °C; IR 2925, 1645, 1530, 1420, 1315, 1130 cm^{-1}; ^1H NMR δ 7.46 (1 H, s), 3.44 (1 H, m), 3.08 (6 H, s), 2.98 (1 H, br d, J = 10 Hz), 2.78 (1 H, dd, J = 4, 13 Hz), 2.37 (1 H, m).

Anal. Calcd for $C_{15}H_{24}N_2O$: C, 72.54; H, 9.74; N, 11.28. Found: C, 72.62; H, 9.77; N, 11.28).

(2α,3aβ,6aα,9aα)-(±)-2-((Dimethylamino)methyl)decahydropyrido[2,1,6-*de*]quinolizin-1(2*H*)-one (32). The lithium bronze reagent was formed by distillation of 3–5 mL of NH_3 from Na into a dry three-necked flask containing 50 mg (7 mmol) of Li wire, cut into 2-cm pieces and washed with hexane. The flask had been equipped with a mechanical stirring apparatus, dry ice condenser, and an addition funnel and was maintained under N_2. When the reagent had formed, excess NH_3 was evaporated to leave a bronze-colored liquid. At room temperature, a solution of 859 mg (3.5 mmol) of enamino ketone **31** and 256 mg (3.5 mmol) of dry *t*-BuOH in 16 mL of dry THF was added in a steady stream with vigorous stirring.[47] The mixture was stirred vigorously for 30 min and then excess aqueous acetone (1:1, v/v) was added to destroy any remaining reagent. The solvents were removed in vacuo at or below room temperature. The aqueous layer was extracted with ether (four 20-mL portions). The combined extract was washed with brine, dried over $MgSO_4$, and evaporated to yield 855 mg (99%) of the β-amino ketone **32** as a very pale yellow solid. Crystallization from ether/hexane gave colorless crystals: mp 97–100 °C (prior softening); IR 2935, 2850, 2815, 2775, 1710, 1455, 1445 cm^{-1}; ^1H NMR δ 3.47 (1 H, dd, J = 2, 12 Hz), 3.25 (1 H, br t, J = 10 Hz), 2.93 (1 H, br d, J = 11 Hz), 2.65 (3 H, m), 2.20 (6 H, s).

Anal. Calcd for $C_{15}H_{26}N_2O$: C, 71.96; H, 10.47; N, 11.19. Found: C, 71.73; H, 10.32; N, 10.99.

(2α,3aβ,6aα,9aα)-(±)-Decahydro-2-methylpyrido[2,1,6-*de*]quinolizin-1(2*H*)-one (33). The β-amino ketone **32** (855 mg, 3.40 mmol) was stirred under 1 atm of H_2 with 93 mg of 10% Pd on C in 16 mL of EtOH containing 20 drops of HOAc. After 1 equiv of H_2 had been consumed (ca. 30 min), the catalyst was removed by filtration and rinsed with a little CH_2Cl_2. The filtrate was concentrated in vacuo and the resulting oil was diluted with 20 mL of ether, and dilute aqueous NaOH solution was added. The water layer was extracted with three 20-mL portions of ether and one portion of CH_2Cl_2. The combined extracts were dried over $MgSO_4$, filtered through Na_2SO_4, and concentrated in vacuo. Bulb-to-bulb distillation (73-80°C (0.1 mmHg)) afforded 533 mg (74% from **31**) of ketone **33** as a colorless oil which solidified at temperatures below 0 °C: IR (film) 2915, 2860, 1710, 1455, 1445 cm^{-1}; ^1H NMR δ 3.47 (1 H, dd, J = 3, 12 Hz), 3.26 (1 H, br t, J = 11 Hz), 2.94 (1 H, br d, J = 12 Hz), 2.57 (1 H, m), 1.04 (3 H, d, J = 6 Hz); MS, m/e (relative intensity) 207 (M^+, 7), 179 (23), 178 (25), 137 (100), 136 (35), 122 (16).

Analysis by VPC (OV-101, 160 °C) and GC–MS showed about 10% of another isomer which could be removed either at a later stage or by conversion of **33** to the corresponding picrate (1 equiv of picric acid, EtOH, reflux) followed by recrystallization from absolute EtOH, mp 181–183 °C dec.

Anal. Calcd for $C_{19}H_{24}N_4O_8$: C, 52.29; H, 5.54; N, 12.84. Found: C, 52.30; H, 5.58; N, 12.84.

Dithioethylene Ketal of 33. A solution of ketone **33** (170 mg, 0.81 mmol) in 2.5 mL of $CHCl_3$ under N_2 was treated with 0.14 mL (1.6 mmol) of ethanedithiol and 0.20 mL (1.6 mmol) of boron trifluoride etherate; the mixture was refluxed for 8 h.[76] The solution was diluted with ether and several milliliters of 20% aqueous NaOH solution was added. The water layer was extracted with six 10-mL portions of ether and the combined organic extract was dried over $MgSO_4$ and concentrated in vacuo. Bulb-to-bulb distillation (120–125 °C (0.01 mmHg)) afforded 190 mg (84%) of the thioketal of ketone **33** as a colorless oil: IR 2940, 2880, 1455, 1375, 1140, 1130 cm^{-1}; ^1H NMR δ 3.15 (4 H, br s), 3.06–2.75 (3 H, m), 1.06 (3 H, d, J = 6 Hz); MS, m/e (relative intensity) 283 (M^+, 1), 222 (2), 190 (2), 179 (5), 178 (5), 176 (2), 151 (3), 150 (3), 139 (10), 138 (100), 137 (20), 136 (7).

The analytical sample was obtained by preparative VPC (SE-30, 180 °C).

Anal. Calcd for $C_{15}H_{25}NS_2$: C, 63.55; H, 8.89; N, 4.94. Found: C, 63.84; H, 9.02; N, 4.85.

(±)-Hippodamine (3). A solution of 180 mg (0.64 mmol) of the thioketal of **33** in 5 mL of dry ethylenediamine was introduced into a 50-mL flask which had been flame-dried under N_2. To this solution was added 40 mg (6 mmol) Li wire, cut into 2-cm pieces and washed with hexane.[50] The mixture was stirred rapidly with a glass-coated stirring bar at room temperature for 1.5 h; many color changes were observed. When a dark blue color finally persisted, water was added slowly. The aqueous layer was extracted with six 10-mL portions of ether–hexane (1:1, v/v). The combined organic extract was washed with 20% aqueous NaOH solution (four 5-mL portions) and brine. After drying over $MgSO_4$ and Na_2SO_4, the solution was concentrated in vacuo to afford a cloudy oil which was distilled bulb-to-bulb (45–55 °C (0.1 mmHg)) to yield 99 mg (80%) of (±)-hippodamine (**3**) as a colorless oil. Analysis by VPC (OV-101, 130 °C) showed a purity of ca. 98%: IR (film) 2935, 2850, 1455, 1445, 1290, 1130 cm^{-1}; ^1H NMR δ 2.90 (2 H, br d, J = 12 Hz), 2.82 (1 H, br t, J = 11 Hz), 0.85 (3 H, d, J = 6 Hz); MS, m/e (relative intensity) 193 (M^+, 42), 192 (100), 178 (26), 164 (43), 151 (77), 150 (68), 137 (35), 136 (36).

The analytical sample was prepared by conversion to the corresponding picrate, mp 149–150 °C.

Anal. Calcd for $C_{19}H_{26}N_4O_7$: C, 54.02; H, 6.20; N, 13.26. Found: C, 53.99; H, 6.23; N, 13.26.

Synthetic hippodamine proved virtually identical with the natural material[51] by IR, ^1H NMR, and MS spectral comparison.

(±)-Convergine (4). A solution of 51 mg (0.26 mmol) of (±)-hippodamine (**3**) in 2 mL of CH_2Cl_2 was cooled to 0 °C and treated with a solution of 50 mg (0.30 mmol) of *m*-chloroperbenzoic acid (99+%) in 2 mL of CH_2Cl_2.[11,19] The mixture was stirred at 0 °C for 15 min and then at room temperature for 10 h. Aqueous NaOH solution (20%, 10 mL) was added and the water layer was extracted with several 10-mL portions of CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated in vacuo to give 47 mg of (±)-convergine (**4**) as a light tan solid: IR 3100, 2940, 2870, 2500, 1450, 1445, 1260, 944 cm^{-1}; ^1H NMR δ 3.41 (1 H, br t, J = 11 Hz), 3.20 (2 H, br s), 2.86 (1 H, m), 2.54 (1 H, td, J = 4, 12 Hz), 0.84 (3 H, d, J = 6 Hz); ^{13}C NMR δ 74.5, 73.9, 58.4, 35.8, 33.9, 27.9, 27.3 (2 C), 25.5, 24.4, 23.6, 21.4, 18.0.

(±)-Convergine was treated with anhydrous HCl in CH_2Cl_2 to give the corresponding hydrochloride as a white powder which

(76) Fieser, L. F. *J. Am. Chem. Soc.* **1954**, *76*, 1945–1947.

was recrystallized from ether–dichloromethane to give material with mp >210 °C dec (lit.[19] mp 225–230 °C dec); IR (KBr) 2950, 2860, 2730, 2555, 1510, 1460 cm^{-1}; ^1H NMR δ 4.66 (2 H, br d, J = 12 Hz), 3.74 (1 H, br t, J = 12 Hz), 2.73 (1 H, m), 2.41 (1 H, td, J = 5, 12 Hz), 0.96 (3 H, d, J = 6 Hz). Synthetic (±)-convergine·HCl was identical with natural material[51] by TLC (silica, 10 mL MeOH + 3 drops concentrated NH_4OH, R_f 0.51), IR, and ^1H NMR.

Tosylhydrazone of 33.[53] A mixture of 336 mg (1.60 mmol) of ketone **33** and 208 mg (6.40 mmol) of 95% hydrazine in 8 mL of absolute EtOH was stirred under N_2 at 20 °C. After 4 h, the reaction appeared complete by TLC (silica, 10 mL of THF plus 4 drops of concentrated NH_4OH). The solvent was removed in vacuo to yield a colorless oil which was dissolved in CH_2Cl_2 and filtered through Na_2SO_4. Removal of all volatile components in vacuo afforded an unstable white solid in nearly quantitative yield. This material was carried on without further purification: IR (KBr) 3395, 3230, 2935, 2865, 1645, 1460, 1450 cm^{-1}; ^1H NMR δ 5.02 (2 H, br s), 4.00 (1 H, dd, J = 3, 12 Hz), 3.09 (1 H, br t, J = 11 Hz), 3.03 (1 H, br d, J = 11 Hz), 2.45 (1 H, m), 1.06 (3 H, d, J = 6 Hz).

The crude hydrazone was dissolved in 3 mL of CH_2Cl_2. Under N_2, 0.34 mL (2.4 mmol) of Et_3N was added and the solution was cooled to 0 °C. A solution of 309 mg (1.62 mmol) of TsCl in 4 mL of CH_2Cl_2 was added over 2–3 min. The cold bath was removed after 15 min and the reaction mixture was stirred at 20 °C for 3 h. Additional CH_2Cl_2 was added and the organic layer was washed with two 5-mL portions of saturated $NaHCO_3$ solution and then with water. The organic layer was dried over $MgSO_4$ and concentrated in vacuo to give a brown foam. Purification was effected by column chromatography on 20 g of silica gel; elution with $CHCl_3$–MeOH (96:4, v/v) afforded 438 mg (72% from **33**) of tosylhydrazone **34** as a white foam: IR 3280, 3030, 2940, 2865, 1640, 1600, 1495, 1165 cm^{-1}; ^1H NMR δ 7.85 (2 H, d, J = 8 Hz), 7.39 (2 H, d, J = 8 Hz), 5.80 (1 H, br s), 3.73 (1 H, br d, J = 10 Hz), 3.03 (1 H, br t, J = 12 Hz), 2.92 (1 H, br d, J = 10 Hz), 2.42 (3 H, s), 1.03 (3 H, d, J = 6 Hz).

(±)-Hippocasine (5). Lithium *tert*-butylamide was prepared by treatment of 0.36 mL (3.4 mmol) of *tert*-butylamine in 6 mL of dry THF with 1.4 mL (2.6 mmol) of 1.9 M *n*-butyllithium in hexane at −78 °C under N_2. The mixture was warmed to room temperature over 30 min and then cooled again to −78 °C. A solution of 423 mg (1.13 mmol) of tosylhydrazone **34** in 8 mL of dry THF was added to the solution.[55] After 15 min, the cold bath was removed and the mixture was stirred at 20 °C for 7.5 h; a precipitate gradually formed. Water was added and the THF was removed in vacuo. The residue was taken up in ether and washed with four small portions of water. The organic layer was dried over $MgSO_4$ and concentrated to yield a light orange oil. Bulb-to-bulb distillation (60–65 °C (0.13 mmHg)) gave 173 mg (80%) of (±)-hippocasine (**5**) as a colorless oil: IR 2925, 2870, 1685, 1450, 850, 840, 810 cm^{-1}; ^1H NMR δ 5.36 (1 H, br s), 3.23 (1 H, br d, J = 10 Hz), 3.04 (2 H, m), 1.63 (3 H, s), 1.04 (1 H, br d, J = 11 Hz); MS, m/e (relative intensity) 191 (M^+, 47), 190 (97), 176 (100), 162 (50), 148 (41), 120 (28), 94 (22).

An analytical sample was prepared by conversion of **5** to the corresponding picrate. Recrystallization from 95% EtOH gave yellow needles, mp 137.5–139 °C.

Anal. Calcd for $C_{19}H_{24}N_4O_7$: C, 54.28; H, 5.75; N, 13.33. Found: C, 54.27; H, 5.79; N, 13.33.

The identity of synthetic material was confirmed by comparison of the ^1H NMR, IR, and MS spectra with those of natural material.[51]

(±)-Hippocasine Oxide (6). (±)-Hippocasine (**5**) (75 mg, 0.39 mmol) was dissolved in 6.5 mL of methanol. With stirring, 8 drops of 30% H_2O_2 was added; additional peroxide was added at the following intervals: 4 drops after 4.5 h, 2 drops after 16.5 h, and 2 drops after 27 h. The reaction appeared complete after a total time of 30 h (TLC: silica, 10 mL of THF plus 4 drops of concentrated NH_4OH). Chloroform (30 mL) was added and excess peroxide was destroyed by the careful addition of several milligrams of 10% Pt on C. After filtration, the solution was dried over Na_2SO_4 and concentrated in vacuo to give 88 mg (96%) of (±)-hippocasine oxide (**6**) as a colorless oil: ^1H NMR (60 MHz) δ 5.30 (1 H, br s), 3.8–3.2 (3 H, m), 1.70 (3 H, br s).

The *N*-oxide **6** was more fully characterized as the corresponding hydrochloride. Thus, a solution of 88 mg of **6** in 4 mL of acetone was treated with 3 drops of concentrated HCl at room temperature with occasional swirling. Within 2 min a white solid cyrstallized from solution. The supernatant was decanted to leave (±)-hippocasine oxide hydrochloride (103 mg, 99% yield); this material was recrystallized from EtOAc–MeOH (99:1, v/v) to give white, feather-like crystals: mp >210 °C dec (lit.[12] mp >220 °C dec); IR (KBr) 3420, 2945, 2540, 1695, 1508, 1465, 1445 cm^{-1}; ^1H NMR δ 5.35 (1 H, br s), 5.01 (1 H, br d, J = 11 Hz), 4.82 (1 H, br d, J = 12 Hz), 3.80 (1 H, m), 2.75 (1 H, m), 2.39 (1 H, m), 1.71 (3 H, br s); ^1H NMR (CD_3OD) δ 5.41 (1 H, br s), 4.28 (1 H, m), 4.01 (1 H, br d, J = 11 Hz), 3.85 (1 H, br d, J = 12 Hz), 1.75 (3 H, br s).

Synthetic and natural material proved identical by comparison of their IR and ^1H NMR spectra.[51]

(1α,2β,3aα,6aβ,9aβ)-(±)-Dodecahydro-2-methylpyrido[2,1,6-*de*]quinolizin-1-ol (35). A solution of ketone **33** (210 mg, 1.0 mmol) in 7 mL of dry ether was added to a stirred suspension of 132 mg (3.48 mmol) of $LiAlH_4$ in 10 mL of dry ether under N_2. After 4 h, excess hydride reagent was destroyed by the careful addition of saturated aqueous Na_2SO_4 solution with ice/water cooling. $MgSO_4$ was added and the supernatant was filtered through Na_2SO_4. Concentration in vacuo gave the amino alcohol **35** (202 mg, 96%) as a white powder. Analysis by VPC (OV-101, 180 °C) showed the presence of a minor (ca. 5%) isomer. Recrystallization from CH_2Cl_2–hexane afforded colorless needles: mp 172–173 °C; IR 3615, 3400, 2940, 2870, 1460, 1445, 1120, 1050 cm^{-1}; ^1H NMR δ 3.46 (1 H, dt, J = 10, 5 Hz), 3.02 (2 H, m), 2.86 (1 H, br t, J = 11 Hz), 0.98 (3 H, d, J = 6 Hz); MS, m/e (relative intensity) 209 (M^+, 42), 208 (67), 192 (23), 180 (30), 167 (24), 166 (27), 151 (26), 150 (49), 138 (100), 137 (81), 136 (74), 122 (24), 96 (26).

The analytical sample was prepared by sublimation (100–110 °C (0.3 mmHg)).

Anal. Calcd for $C_{13}H_{23}NO$: C, 74.59; H, 11.07; N, 6.69. Found: C, 74.62; H, 11.09; N, 6.66.

(1α,2β,3aα,6aβ,9aβ)-(±)-Dodecahydro-2-methylpyrido[2,1,6-*de*]quinolizin-1-ol, Methanesulfonate Ester (36). A flask containing 81 mg (0.39 mmol) of amino alcohol **35** in 2.5 mL of CH_2Cl_2 was swept with N_2 and maintained under a slight positive pressure. Triethylamine (0.082 mL, 0.58 mmol) was added and the flask was cooled to 0 °C. Methanesulfonyl chloride (0.033 mL, 0.43 mmol) was added; after 5 min, the cold bath was removed and the reaction mixture was stirred for 6 h. CH_2Cl_2 (30 mL) was added and the organic layer was washed with two 10-mL portions of saturated aqueous $NaHCO_3$ solution and three 5-mL portions of water. The organic layer was dried ($MgSO_4$, Na_2SO_4) and the solvent removed in vacuo to afford 105 mg (94%) of mesylate **36** as a very pale yellow solid. Recrystallization from CH_2Cl_2–hexane gave white crystals: mp 138–140 °C; IR 2935, 2860, 1460, 1450, 1355, 1175, 970, 950, 920 cm^{-1}; ^1H NMR δ 4.42 (1 H, dd, J = 6, 11 Hz), 3.36 (1 H, m), 3.00 (3 H, s), 2.94 (1 H, br t, J = 11 Hz), 1.00 (3 H, d, J = 6 Hz).

Anal. Calcd for $C_{14}H_{25}NO_3S$: C, 58.50; H, 8.77; N, 4.87. Found: C, 58.38; H, 8.80; N, 4.80.

(±)-Propyleine (8) and (±)-Isopropyleine (9). A mixture of 50 mg of mesylate **36** and 150 mg of anhydrous K_2CO_3 in 1.5 mL of dry Me_2SO was heated under N_2 at 120–125 °C for 2 h. The reaction mixture was cooled and then diluted with 50 mL of ether. The organic layer was washed with five 5-mL portions of water, dried over $MgSO_4$, and concentrated in vacuo to afford a pale yellow oil. Bulb-to-bulb distillation gave 25 mg (76%) of a colorless liquid. VPC analysis (OV-101, 160 °C) showed a single peak; TLC (silica, 10 mL of THF plus 4 drops of concentrated NH_4OH) indicated the product was homogeneous: IR (film) 2925, 2860, 2830, 1650, 1450, 1375, 1320, 1240, 1075 cm^{-1}; MS, m/e (relative intensity) 191 (M^+, 38), 190 (48), 177 (13), 176 (100), 149 (16), 148 (25), 134 (10). Comparison of the 60-MHz ^1H NMR spectra of natural[51] and synthetic material showed the spectra virtually superimposable. At 270 MHz, however, the ^1H NMR of synthetic material clearly showed the presence of two isomers in a ratio of 1:3; the minor isomer was eventually assigned the propyleine (**8**) structure and the major isomer the isopropyleine structure **9**. **8**: ^1H NMR δ 4.60 (1 H, br s), 0.97 (3 H, d, J = 6 Hz). **9**: ^1H NMR δ 4.75 (1 H, br s), 3.06 (1 H, dd, J = 5 Hz), 2.46

(1 H, tt, J = 3, 10 Hz), 0.90 (3 H, d, J = 6 Hz). All remaining protons appeared as several sets of complex multiplets between δ 2.10 and 0.88.

The ^{13}C NMR spectrum also displayed signals for the two isomers in a ratio of 1:3. **8**: δ 147.0, 111.4 with four identifiable additional upfield peaks, the remaining peaks apparently overlapping with those of **9**. **9**: δ 147.1, 103.9, 56.3, 54.4, 42.6, 41.6, 33.5, 32.5, 31.0, 25.0, 22.0, 21.6, 19.7.

Addition of 3–4 drops of trifluoroacetic acid to the NMR samples in $CDCl_3$ resulted in the following spectra: ^1H NMR δ 3.82 (2 H, 3-line multiplet), 3.00–2.61 (4 H, m), 1.04 (3 H, d, J = 6 Hz); ^{13}C NMR δ 186.9, 60.4, 60.0, 41.3, 36.1, 33.0, 27.7, 25.2, 25.1, 24.2, 20.0, 16.7; two signals apparently overlapped.

The analytical sample was prepared by conversion of the mixture of **8** and **9** to the picrate salt. Recrystallization from 95% EtOH gave yellow needles, mp 141–143 °C.

Anal. Calcd for $C_{19}H_{24}N_4O_7$: C, 54.28; H, 5.75; N, 13.33. Found: C, 54.16; H, 5.76; N, 13.30.

(3aα,6aβ,10β)-(±)-1,2,3,3a,4,5,6,6a,7,8-Decahydro-10-methylpyrido[2,1,6-*de*]quinolizinium Fluorosulfate (39). A solution of 3.75 g (21.2 mmol) of trans enamine **13** in 60 mL of dry ether under N_2 was treated at −78 °C with 1.88 mL (23.3 mmol) of methyl fluorosulfate. After 30 min, the cold bath was removed and the mixture was stirred for another 2 h as a white precipitate gradually formed. The solid was collected by filtration, washed well with dry ether, and dried in vacuo overnight on a vacuum pump to yield 5.27 g (86%) of ene ammonium salt **39** as a white solid: mp 161–162 °C (recrystallization from CH_2Cl_2–hexane); IR 3000, 2960, 2875, 1465, 1450 cm^{-1}; ^1H NMR δ 5.81 (1 H, br d, J = 4 Hz), 3.88 (1 H, br s), 3.77 (1 H, dd, J = 5, 12 Hz), 3.37 (3 H, s).

Anal. Calcd for $C_{13}H_{22}NO_3FS$: C, 53.59; H, 7.61; N, 4.81. Found: C, 53.42; H, 7.58; N, 4.90.

(3aα,6aβ,9aβ)-(±)-1,2,3,3a,4,5,6,6a,7,9a-Decahydropyrido[2,1,6-*de*]quinolizine (41). To a stirred solution of 2.96 g (10.1 mmol) of ene ammonium salt **39** and 2.60 mL (18.3 mmol) of diisopropylamine in 50 mL of dry THF under N_2 and cooled to −78 °C was added 6.20 mL (15.2 mL) of 2.5 M *n*-butyllithium in hexane. After 30 min the resulting yellow suspension was allowed to warm to −30 °C until the solution cleared. The temperature was maintained between −30 and −20 °C for another 30 min and then 2 mL of water was added. All volatile materials were removed in vacuo; the yellow semisolid residue was diluted with 2 mL of water. The aqueous layer was extracted with two 50-mL portions of CH_2Cl_2 and the combined organic extract was dried over Na_2SO_4. The solvent was removed in vacuo to afford 2.7 g (91%) of the ammonium salt **40** as a tan-colored solid. Recrystallization from 2-butanone gave colorless crystals, mp 206–208 °C.

Without purification, the ammonium salt **40** (2.7 g, 9.3 mmol) and 184 mg (23 mmol) LiH were mixed in 7 mL of dry DMF under N_2. Ethanethiol (1.8 mL, 25 mmol) was added and the mixture was heated at 100 °C for 1 h.[59] After the solution had cooled, 10 mL of water was added and the aqueous layer was extracted with five 10-mL portions of hexane. The organic layer was backwashed with six 5-mL portions of water, dried over Na_2SO_4, and concentrated in vacuo. The residue was distilled bulb-to-bulb (50–55 °C (0.3 mmHg)) to give 1.5 g (82% from **39**) of allylic amine **41** as a colorless oil. VPC analysis (OV-101, 130 °C) showed ca. 5% of the starting enamine **13**: IR (film) 3020, 2920, 2850, 2840, 1655, 1460, 1450 cm^{-1}; ^1H NMR δ 5.84 (1 H, m), 5.46 (1 H, dq, J = 10, 2 Hz), 3.68 (1 H, br s), 3.26 (1 H, m), 2.55 (1 H, br t, J = 10 Hz); MS, m/e (relative intensity) 177 (M^+, 61), 176 (100), 162 (56), 149 (18), 148 (36), 136 (16), 135 (26), 134 (49).

The analytical sample was obtained by preparative VPC (OV-101, 130 °C) followed by bulb-to-bulb distillation.

Anal. Calcd for $C_{12}H_{19}N$: C, 81.30; H, 10.80; N, 7.90. Found: C, 81.39; H, 10.68; N, 7.93.

(3aα,6aβ,7aα,8aα,8bβ)-(±)-Dodecahydrooxireno[*a*]pyrido[2,1,6-*de*]quinolizine (47). Trifluoroperoxyacetic acid[77] was prepared by the careful addition of 0.68 mL of 90% H_2O_2 to an ice/water cooled solution of 4.20 mL (30.0 mmol) of trifluoroacetic anhydride in 15 mL of CH_2Cl_2. The mixture was stirred at 0 °C for 45 min, allowed to warm to room temperature, and diluted with 25 mL of CH_2Cl_2. A solution of 760 mg (4.3 mmol) of allylic amine **41** in 6 mL of CH_2Cl_2 was cooled to 0 °C and treated with 0.36 mL (4.7 mmol) of trifluoroacetic acid followed by 7.1 mL (8.6 mmol) of the trifluoroperoxyacetic acid–CH_2Cl_2 solution prepared above.[60] The cold bath was removed immediately and the colorless solution was stirred at room temperature for 30 min. Excess oxidant was destroyed by the addition of saturated aqueous $NaHSO_3$ solution with ice/water cooling. The reaction mixture was made basic with aqueous KOH and the water layer extracted with CH_2Cl_2 (three 20-mL portions). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by bulb-to-bulb distillation (60–65 °C (0.3 mmHg)) to give 601 mg of a colorless oil; VPC analysis (OV-101, 150 °C) indicated a 4:1 mixture of epoxide **47** and unreacted olefin **41**. A pure sample of **47** was obtained by preparative VPC followed by bulb-to-bulb distillation: IR 3000, 2945, 2860, 1445, 875, 805 cm^{-1}; ^1H NMR δ 3.40 (1 H, t, J = 4 Hz), 3.11 (1 H, br s), 2.91 (1 H, dd, J = 2, 4 Hz), 2.86 (1 H, m), 2.43 (1 H, br t, J = 11 Hz); MS, m/e (relative intensity) 193 (M^+, 15), 192 (10), 138 (12), 137 (100), 136 (42), 122 (25), 109 (16), 108 (15).

Anal. Calcd for $C_{12}H_{19}NO$: C, 74.57; H, 9.91; N, 7.25. Found: C, 74.55; H, 9.84; N, 7.21.

(2α,3aα,6aβ,9aα)-Dodecahydropyrido[2,1,6-*de*]quinolizin-2-ol (48). A solution of 601 mg (3.10 mmol) of epoxide **47** in 4 mL of dry ethylenediamine was transferred to a 50-mL flask which had been flame-dried under N_2. To this rapidly stirred (glass-coated magnetic stirring bar) solution was added 65 mg (9.3 mmol) of Li wire, cut into small pieces and washed with hexane. The mixture was heated at 35–40 °C for 30 min as many color changes were observed. When a deep blue color persisted, the solution was cooled to 0 °C and 15 mL of water was added carefully.[61] Extraction with CH_2Cl_2 (give 20-mL portions) followed by drying of the combined extracts over Na_2SO_4 and concentration in vacuo yielded a light yellow oil from which amino alcohol **48** was crystallized by trituration with hexane. Recrystallization from CH_2Cl_2–hexane afforded 352 mg (42% from **41**) of alcohol **48** as colorless crystals: mp 148–150 °C; IR 3605, 3005, 2935, 2865, 1445, 1035 cm^{-1}; ^1H NMR δ 4.32 (1 H, t, J = 3 Hz), 3.46 (2 H, dd, J = 5, 13 Hz), 2.75 (1 H, br t, J = 11 Hz), 2.14 (1 H, td, J = 3, 14 Hz); ^{13}C NMR δ 66.3 (1 C, d), 50.8 (2 C, d), 47.0 (1 C, d), 34.1 (2 C, t), 30.3 (2 C, t), 29.2 (2 C, t), 19.3 (2 C, t); MS, m/e (relative intensity) 195 (M^+, 46), 194 (100), 178 (36), 166 (25), 153 (54), 152 (21), 150 (68), 138 (21), 137 (93), 136 (73).

The analytical sample was prepared by sublimation (105–110 °C (0.5 mmHg)).

Anal. Calcd for $C_{12}H_{21}NO$: C, 73.80; H, 10.84; N, 7.17. Found: C, 73.71; H, 10.81; N, 7.20.

(3aα,6aβ,9aα)-Decahydropyrido[2,1,6-*de*]quinolizin-2-(1*H*)-one (49). A solution of 390 mg (2.0 mmol) of amino alcohol **48** and 0.11 mL (2.0 mmol) of concentrated H_2SO_4 in 4.5 mL of HOAc was treated at 20 °C with 1 mL of Jones reagent.[37] The reaction mixture was stirred for 30 min as a precipitate formed. Excess oxidant was destroyed by the addition of 1 mL of *i*-PrOH, the solution was diluted with 12 mL of water, and 2.5 g (8.5 mmol) of trisodium citrate dihydrate was added. Under N_2, a small piece of freshly amalgamated mossy zinc was added and the mixture was stirred for 15 min. With ice/water cooling, the dark solution was made strongly basic with 20% aqueous NaOH solution.[38] The water layer was extracted with ether (six 10-mL portions). The combined extract was dried (K_2CO_3, Na_2SO_4). Removal of the solvent in vacuo gave a white solid which was recrystallized from hexane to afford 317 mg (81%) of the known[20,21] amino ketone **49**: mp 81–82 °C (lit.[20] mp 82–84 °C); IR 3005, 2940, 2860, 2810, 1700 cm^{-1}; ^1H NMR δ 3.26 (2 H, br d, J = 12 Hz), 2.81 (3 H, br t, J = 13 Hz), 2.00 (4 H, m), 1.26 (2 H, qd, J = 12, 4 Hz); MS, m/e (relative intensity) 193 (M^+, 36), 192 (17), 178 (14), 151 (17), 150 (100), 136 (79), 135 (18), 134 (30), 123 (11), 122 (22).

Anal. Calcd for $C_{12}H_{19}NO$: C, 74.57; H, 9.91; N, 7.25. Found: C, 74.71; H, 9.76; N, 7.06.

(3aα,6aβ,9aα)-Dodecahydro-2-methylenepyrido[2,1,6-*de*]quinolizine (50).[21] To a stirred suspension of 1.38 g (3.80 mmol) of methyltriphenylphosphonium bromide in 10 mL of THF at −78 °C under N_2 was added 1.35 mL (3.30 mmol) of 2.5 M *n*-butyllithium in hexane. When the addition was complete, the cold bath was removed and the yellow mixture stirred for 75 min. A solution of 494 mg (2.60 mmol) of amino ketone **49** in 7 mL

(77) Emmons, W. D.; Pagano, A. S. *J. Am. Chem. Soc.* **1955**, *77*, 89–92.

of THF was added over 5 min. After 5 h, 2 mL of water was added and the solvent removed in vacuo. The aqueous layer was acidified with concentrated HCl and extracted with four 5-mL portions of ether (later discarded). The water layer was made basic with KOH and was extracted with six 10-mL portions of hexane. The combined extract was dried over Na_2SO_4 and concentrated in vacuo. Bulb-to-bulb distillation gave 408 mg (83%) of the known[21] olefin **50** as a colorless oil: IR (film) 3065, 2925, 2860, 1645, 1445, 875 cm^{-1}; ^1H NMR δ 4.65 (2 H, t, J = 2 Hz), 2.96 (2 H, br d, J = 12 Hz), 2.84 (1 H, br t, J = 12 Hz), 2.61 (2 H, br t, J = 13 Hz), 1.72 (2 H, dd, J = 2, 13 Hz); MS, m/e (relative intensity) 191 (M^+, 81), 190 (100), 176 (96), 148 (68), 136 (89), 135 (60), 134 (31).

Anal. Calcd for $C_{13}H_{21}N$: C, 81.62; H, 11.06; N, 7.32. Found: C, 81.50; H, 11.00; N, 7.11.

(3aα,6aβ,9aβ)-(±)-1,2,3,3a,4,5,6,6a,7,9a-Decahydro-8-methylpyrido[2,1,6-*de*]quinolizine (51). A mixture of 365 mg (1.90 mmol) of olefin **50** and 1.1 g (5.7 mmol) of *p*-toluenesulfonic acid monohydrate in 25 mL of xylene was refluxed under a water separator for 6.5 h. When the mixture had cooled, 30 mL of water was added. The aqueous layer was washed with four 5-mL portions of ether (later discarded) and then was made strongly basic with KOH pellets. The aqueous layer was then extracted with six 10-mL portions of hexane. The combined extract was dried (Na_2SO_4) and concentrated in vacuo. Bulb-to-bulb distillation (43–48 °C (0.3 mmHg)) afforded 318 mg (87%) of the known[20] olefin **51** as a colorless oil. Analysis by VPC (OV-101, 160 °C) indicated ca. 5% unisomerized **50** remained: IR (film) 3000, 2925, 2850, 1670, 1445 cm^{-1}; ^1H NMR δ 5.18 (1 H, br s), 3.61 (1 H, br s), 3.20 (1 H, m), 1.68 (3 H, br s); MS, m/e (relative intensity) 191 (M^+, 27), 190 (43), 177 (12), 176 (100), 162 (15), 148 (18).

Precoccinelline (2). Olefin **51** (302 mg) was hydrogenated over 115 mg of 10% Pd on C in 10 mL of MeOH on a Parr apparatus (3 atm).[20] The catalyst was removed by filtration and the filtrate was concentrated in vacuo. The residue was dissolved in 30 mL of hexane and washed with three 5-mL portions of water. The organic layer was dried over Na_2SO_4 and concentrated. The residue was distilled bulb-to-bulb (54–60 °C (0.2 mmHg)) to afford 274 mg (90%) precoccinelline (**2**) as a colorless oil: IR (film) 2925, 2860, 1440 cm^{-1}; ^1H NMR δ 2.94 (2 H, br d, J = 10 Hz), 2.72 (1 H, br t, J = 12 Hz), 0.94 (3 H, d, J = 7 Hz); MS, m/e (relative intensity) 193 (M^+, 36), 192 (100), 164 (31), 151 (51), 150 (57), 137 (41), 136 (40).

The analytical sample was obtained by conversion of **2** to the corresponding picrate. Recrystallization from absolute EtOH gave yellow needles, mp 195–197 °C.

Anal. Calcd for $C_{19}H_{26}N_4O_7$: C, 54.02; H, 6.20; N, 13.26. Found: C, 54.12; H, 6.16; N, 13.34.

The identity of synthetic **2** was established by comparison of its IR, MS, ^1H NMR, and ^{13}C NMR spectra with those of natural material.[51]

Coccinelline (1). A solution of 140 mg (0.80 mmol) of 99+% *m*-chloroperoxybenzoic acid in 5 mL of CH_2Cl_2 was added to 140 mg (0.73 mmol) of precoccinelline (**2**) in 5 mL of CH_2Cl_2 at 0 °C under N_2.[9,20,21] The mixture was stirred at 0 °C for 30 min and then at room temperature for 4 h. The organic layer was washed with 10 mL of 20% aqueous NaOH solution, dried over Na_2SO_4, and concentrated in vacuo to give a quantitative yield of a white solid. Recrystallization from acetone yielded coccinelline (**1**): mp >204 °C dec (lit.[6,20] mp 205–210 °C dec); ^1H NMR δ 3.44 (1 H, br t, J = 12 Hz), 3.29 (2 H, br d, J = 12 Hz), 2.91 (2 H, m), 2.16 (2 H, m), 1.01 (3 H, d, J = 6 Hz); ^{13}C NMR δ 73.4 (2 C, d), 58.2 (1 C, d), 35.5 (2 C, t), 30.3 (1 C, d), 27.1 (2 C, t), 25.2 (2 C, t), 21.1 (1 C, q), 17.8 (2 C, t).

IR, ^1H NMR, and ^{13}C NMR spectra of natural[51] and synthetic material were virtually identical.

Coccinelline (**1**) was treated with anhydrous HCl in CH_2Cl_2 to give the hydrochloride salt, recrystallized from methanol–hexane, mp >215 °C dec (lit.[6,20] mp 215–220 °C, lit.[21] mp >225 °C dec); IR 2965, 2875, 2575, 1510, 1450 cm^{-1}; ^1H NMR δ 4.68 (2 H, br d, J = 12 Hz), 3.73 (1 H, br t, J = 12 Hz), 2.69 (2 H, m), 1.04 (3 H, d, J = 6 Hz).

The synthetic and natural[51] material proved virtually identical by comparison of their IR and ^1H NMR spectra.

(1α,3aα,6aα,9aα)-(±)-Dodecahydropyrido[2,1,6-*de*]quinolizin-1-ol (52). A solution of 1.90 g (10.7 mmol) of cis enamine **14** in 19 mL of dry THF at 0 °C under N_2 was treated with 2.0 mL (21 mmol) of borane–dimethyl sulfide.[42] The cold bath was removed after 2 h and the reaction mixture stirred for 24 h. Excess borane was destroyed by the slow addition of 6 mL of MeOH. The solution was cooled to 0 °C and 20 mL of 7 N aqueous NaOH was added followed by 6 mL of 30% H_2O_2. The cold bath was removed and the mixture stirred for 1 h. Unconsumed peroxide was destroyed by the addition of solid $NaHSO_3$ with ice/water cooling. The solvents were removed in vacuo and the residue was taken up in water and extracted with four 30-mL portions of CH_2Cl_2. The combined extract was dried ($MgSO_4$, Na_2SO_4) and concentrated in vacuo to give a white solid. Recrystallization from CH_2Cl_2–hexane gave pure **52** (1.7 g, 80% yield) as a white crystalline solid: mp 106–108 °C; IR 3620, 3400, 2950, 2875, 2815, 2750, 1045 cm^{-1}; ^1H NMR δ 3.33 (1 H, br t, J = 10 Hz), 2.34 (2 H, m), 1.98–1.23 (17 H, six sets of multiplets); MS, m/e (relative intensity) 195 (M^+, 54), 194 (76), 166 (37), 164 (35), 153 (27), 152 (24), 151 (29), 150 (37), 138 (74), 137 (56), 136 (100).

Anal. Calcd for $C_{12}H_{21}NO$: C, 73.80; H, 10.84; N, 7.17. Found: C, 73.76; H, 10.84; N, 7.16.

(3aα,6aα,9aα)-(±)-Decahydropyrido[2,1,6-*de*]quinolizin-1(2*H*)-one (53). See ref 38. IR (film) 2950, 2875, 2800, 2740, 1720 cm^{-1}; ^1H NMR δ 2.59–2.23 (3 H, m), 2.08–1.21 (16 H, m); MS, m/e (relative intensity) 193 (M^+, 5), 192 (4), 165 (37), 164 (100), 150 (14), 137 (45), 136 (54), 123 (40), 122 (37).

(3aα,6aα,9aα)-(±)-2-[(Dimethylamino)methylene]decahydropyrido[2,1,6-*de*]quinolizin-1(2*H*)-one (54). A mixture of 1.3 g (6.6 mmol) of ketone **53** and 1.74 mL (13.2 mmol) of bis(dimethylamino)methoxymethane[46] was heated under N_2 at 60–65 °C for 12 h. The brown reaction mixture was cooled and 5 mL of dry ether was added. The solution was cooled to −30 °C; within a short time, tan crystals were obtained. These were collected and washed with cold ether to give 1.42 g (87%) of enamino ketone **54**. Recrystallization from acetone–ether gave colorless plates: mp 100–102 °C; IR 2935, 2860, 2800, 2740, 1645, 1530 cm^{-1}; ^1H NMR δ 7.45 (1 H, s), 3.08 (6 H, s).

Anal. Calcd for $C_{15}H_{24}N_2O$: C, 72.54; H, 9.74; N, 11.28. Found: C, 72.60; H, 9.74; N, 11.22.

(3aα,6aα,9aα)-(±)-2-[(*n*-Butylthio)methylene]decahydropyrido[2,1,6-*de*]quinolizin-1(2*H*)-one (56). To a solution of 500 mg (2 mmol) of enamine ketone **54** and 380 mg (2.0 mmol) of *p*-toluenesulfonic acid monohydrate in 20 mL of benzene under N_2 was added 0.24 mL (2.2 mmol) of *n*-butanethiol.[62] The mixture was refluxed under a water separator for 5 h. Benzene (60 mL) was added and the organic layer was washed with three 10-mL portions of 20% aqueous NaOH solution and three 10-mL portions of water. The organic layer was dried ($MgSO_4$, Na_2SO_4) and evaporated in vacuo to give an orange oil. Bulb-to-bulb distillation (145–150 °C (0.01 mmHg)) gave 496 mg (84%) of vinyl sulfide **56** as a straw-colored oil: IR (film) 2930, 2860, 2785, 2720, 1665, 1550, 1320 cm^{-1}; ^1H NMR δ 7.60 (1 H, br s), 2.85 (2 H, t, J = 7 Hz), 0.92 (3 H, t, J = 7 Hz).

(3aα,6aα,9aα)-(±)-1,2,3,3a,4,5,6,6a,7,9a-Decahydropyrido[2,1,6-*de*]quinolizine-8-carboxaldehyde (55). To a stirred suspension of 400 mg (10 mmol) of $LiAlH_4$ in 15 mL of dry ether under N_2 was added a solution of 970 mg (3.3 mmol) of vinylsulfide **56** in 16 mL of dry ether.[63] The mixture was stirred for 6 h and then excess hydride was destroyed by the careful addition of saturated aqueous Na_2SO_4 solution with ice/water cooling. $MgSO_4$ was added and the mixture was filtered. The filtrate was concentrated in vacuo to yield the unstable alcohol resulting from 1,2-reduction as a yellow oil: IR (film) 3400, 3170, 2930, 2860, 2795, 2730, 1610, 1445 cm^{-1}; ^1H NMR δ 5.97 (1 H, br s), 3.83 (1 H, br d, J = 10 Hz), 2.68 (2 H, t, J = 7 Hz), 0.92 (3 H, t, J = 7 Hz).

To a stirred solution of the crude alcohol in 30 mL of ether was added 3 mL of 10% aqueous HCl solution.[63] The two-phase mixture was stirred vigorously for 23 h. Water (50 mL) was added and the aqueous layer was washed with four 15-mL portions of ether (later discarded). KOH pellets were added carefully with ice/water cooling until the water layer was strongly basic. Extraction with five 20-mL portions of ether followed by drying of the extracts over $MgSO_4$, filtration through Na_2SO_4, and concentration in vacuo gave an orange oil. Bulb-to-bulb distillation (75–85 °C (0.12 mmHg)) afforded 380 mg (56% from **56**) of the unsaturated aldehyde **55** as a light yellow oil. VPC analysis

(OV-101, 160 °C and Carbowax, 160 °C) indicated a purity of >95%: IR (film) 2930, 2860, 2790, 2720, 1680, 1630 cm^{-1}; ^1H NMR δ 9.44 (1 H, s), 6.43 (1 H, br s), 2.84 (1 H, br d, J = 10 Hz), 2.40 (1 H, t, J = 3 Hz), 2.34 (1 H, t, J = 3 Hz); MS, m/e (relative intensity) 205 (M^+, 12), 204 (13), 177 (14), 176 (100), 162 (8), 148 (8); calcd for $C_{13}H_{19}NO$, M^+ 205.1466; found, 205.1462.

(2α,3aβ,6aβ,9aβ)-Dodecahydropyrido[2,1,6-*de*]quinolizine-2-carboxaldehyde (57). Ammonia (2 mL) was distilled from Na into a three-necked flask containing 14 mg (2.0 mmol) of Li wire under N_2. The flask was equipped with a mechanical stirrer, dry ice condenser, and an addition funnel. When the reagent had formed, excess ammonia was evaporated and a solution of 198 mg (0.96 mmol) of unsaturated aldehyde **55** in 9 mL of dry THF containing 71 mg (2.0 mmol) of *t*-BuOH was added in a steady stream.[47] The mixture was stirred vigorously for 35 min; then 3 mL of water was added all at once. The solvent was removed in vacuo and several milliliters more water was added. The water layer was extracted with two 30-mL portions of CH_2Cl_2; the combined extract was dried over $MgSO_4$ and filtered through Na_2SO_4. The solvent was evaporated and the residue was distilled bulb-to-bulb (63–68 °C (0.05 mmHg)) to give 143 mg of aldehyde **57** as a colorless oil (72% yield). VPC analysis (Carbowax, 160 °C) and GC–MS showed the presence of two aldehydes, **57** and its C-2 epimer, in a ratio of 85:15.[78] An isomerically pure sample of the desired **57** was obtained by preparative VPC (Carbowax, 140 °C): IR (film) 2920, 2840, 2790, 2725, 1730 cm^{-1}; ^1H NMR δ 9.57 (1 H, br s), 2.35 (1 H, br t, J = 12 Hz), 1.99–1.20 (19 H; three sets of multiplets); MS, m/e (relative intensity) 207 (M^+, 13), 206 (36), 179 (60), 178 (100), 164 (19), 150 (36), 137 (90), 136 (38), 122 (16).

(2α,3aβ,6aβ,9aβ)-Dodecahydro-2-(hydroxymethyl)pyrido[2,1,6-*de*]quinolizine (58). To a rapidly stirred suspension of 61 mg (1.6 mmol) of $LiAlH_4$ in 3 mL of dry ether under N_2 was added a solution of 110 mg (0.53 mmol) of aldehyde **57** (along with its C-2 epimer) in 5 mL of ether. The mixture was stirred for 3 h. Excess hydride was destroyed by the addition of saturated Na_2SO_4 solution with ice/water cooling. $MgSO_4$ was added and the mixture was filtered through Na_2SO_4. Removal of the solvent in vacuo gave 108 mg (97%) of alcohol **58** as a white solid (accompanied by ca. 15% of its C-2 epimer). Recrystallization from ether followed by sublimation (80–90 °C (0.02 mmHg)) afforded an isomerically pure sample of **58**: mp 126–128 °C; IR 3625, 3330, 2935, 2865, 2800, 2740, 1450 cm^{-1}; ^1H NMR δ 3.44 (2 H, br d, J = 6 Hz), 1.07 (2 H, br q, J = 12 Hz); MS, m/e (relative intensity) 209 (M^+, 37), 208 (100), 180 (29), 178 (34), 167 (31), 150 (29), 137 (28), 136 (21).

Anal. Calcd for $C_{13}H_{23}NO$: C, 74.59; H, 11.07; N, 6.69. Found: C, 74.39; H, 11.11; N, 6.64.

(2α,3aβ,6aβ,9aβ)-Dodecahydro-2-(hydroxymethyl)pyrido[2,1,6-*de*]quinolizine, Methanesulfonate Ester (59). A solution of 110 mg (0.52 mmol) of alcohol **58** (along with ca. 15% of the C-2 epimer) and 0.11 mL (0.78 mmol) of Et_3N in 3 mL of dry CH_2Cl_2 under N_2 was cooled to 0 °C and treated with 0.044 mL (0.57 mmol) of MsCl. After 30 min, the cold bath was removed and the mixture was stirred for 2 h. CH_2Cl_2 (40 mL) was added and the organic layer was washed with two 5-mL portions of saturated aqueous $NaHCO_3$ solution. The organic layer was dried ($MgSO_4$, Na_2SO_4) and evaporated to yield a pale yellow oil. Isomerically pure mesylate **59** was obtained (121 mg, 79% yield from aldehyde **57**) as colorless needles after crystallization from ether: mp 81–82.5 °C; IR 2930, 2850, 2800, 2735, 1450, 1365, 1175 cm^{-1}; ^1H NMR δ 4.00 (2 H, d, J = 6 Hz), 3.00 (3 H, s), 1.98–1.25 (18 H, four sets of multiplets), 1.14 (2 H, br q, J = 12 Hz).

Anal. Calcd for $C_{14}H_{25}NO_3S$: C, 58.50; H, 8.77; N, 4.87. Found: C, 58.56; H, 8.74; N, 4.89.

Myrrhine (7). A solution of 110 mg (0.40 mmol) of mesylate **59** in 1 mL of dry THF under N_2 was cooled to 0 °C and treated with 0.76 mL (0.84 mmol) of 1.1 M lithium triethylborohydride in THF.[64] The reaction mixture was allowed to warm to room temperature as a white precipitate formed. After 4 h, the suspension was cooled to 0 °C and 6–8 drops of water was added slowly. To this mixture was added 0.28 mL of 3 N aqueous NaOH solution followed by 0.28 mL of 30% H_2O_2. The solution was warmed to room temperature and stirred for 1 h. Unconsumed peroxide was destroyed by the addition of a small amount of solid $NaHSO_3$. The solution was diluted with water and the aqueous layer extracted with three 10-mL portions of ether. The combined extract was dried ($MgSO_4$, Na_2SO_4) and concentrated in vacuo to afford 73 mg (95%) of myrrhine (**7**) as a colorless oil. Bulb-to-bulb distillation (55–60 °C (0.08 mmHg)) gave 69 mg (90%) of **7** which was shown by VPC analysis to be 98% pure: IR (film) 2930, 2860, 2790, 2730, 1450, 1385, 1325 cm^{-1}; ^1H NMR δ 1.90–1.31 (18 H, four sets of multiplets), 1.04 (2 H, br q, J = 12 Hz), 0.86 (3 H, d, J = 6 Hz); MS, m/e (relative intensity) 193 (M^+, 34), 192 (100), 178 (20), 164 (32), 151 (46), 150 (45), 137 (26), 136 (23).

The analytical sample was obtained by conversion to the picrate salt followed by recrystallization from absolute EtOH to give yellow crystals, mp 195–197 °C.

Anal. Calcd for $C_{19}H_{26}N_4O_7$: C, 54.02; H, 6.20; N, 13.26. Found, C, 53.88; H, 6.22; N, 13.19.

The ^1H NMR, IR, and MS spectra of natural[51] and synthetic myrrhine were virtually identical.

Crystal Structure of (3aα,6aβ,9aβ,10β)-(±)-1,2,3,3a,4,5,6,6a,7,9a-Decahydro-10-methylpyrido[2,1,6-*de*]quinolizinium Chloride (40). The fluorosulfate salt of **40** was converted to the chloride salt by ion exchange chromatography. Crystals were grown from 2-butanone. A crystal 0.25 × 0.30 × 0.40 mm^3 was mounted in a sealed quartz capillary. An orientation matrix was determined from 25 low-angle reflections. Unit cell parameters were determined from least-squares fit to 25 high-angle individually centered reflections distributed uniformly in space. A full data set was collected to 23.5° in Θ on an Enraf-Nonius CAD-4 diffractometer (Mo radiation, graphite monochrometer, λ = 0.71073 Å) and reduced in the usual manner, correcting for Lorentz and polarization effects but not for decay or absorption. Of 2885 measured reflections, 2530 were judged greater than 3σ in intensity based on counting statistics. The structure was solved using MULTAN[79] from an initial phase set with the lowest residual and highest absolute figure of merit. Carbons C2 and C4 were disordered with respect to the position of the double bond (i.e., $—C^2H_2CH{=}C^4H—$ and $—C^2H{=}CHC^4H_2—$). Further refinement gave a final conventional R_{wt} = 0.040 based on unit weights. The structure is shown in Figure 1;[80] tables of bond lengths, bond angles, and atomic positional and thermal parameters have been deposited as Supplementary Data. All calculations were performed using the Enraf-Nonius SDP software package (Jan, 1977). Crystal Data: $C_{26}H_{44}N_2Cl_2$; formula weight, 455.56; monoclinic, $P2_1/n$; a = 16.158 (2) Å; b = 7.484 (2) Å; c = 20.466 (4) Å; β = 95.26 (1); V = 2464.4; ρ_{calcd} = 1.228 for Z = 4. Function minimized in least squares: $\sum w(|F_o| - |F_c|)^2$.

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Registry No. **1**, 34290-97-6; **2**, 38211-56-2; (±)-**3**, 59685-36-8; (±)-**4**, 59685-37-9; (±)-**5**, 75556-13-7; (±)-**6**, 75556-12-6; **7**,

(78) The ratio of aldehydes (as determined by VPC) obtained in the dissolving metal reduction of **55** varied from one reaction to the next. Quite often, the undesired isomer was isolated initially as the major, kinetic product. Treatment of the crude reaction mixture with a small amount of sodium methoxide in methanol (20 °C, 30 min) was sufficient to establish the equilibrium mixture of the two aldehydes.

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58207-39-9; (±)-8, 75420-51-8; (±)-9, 75420-50-7; 10, 2938-53-6; 11, 57194-67-9; 11 (*N*-oxide), 89959-62-6; 12, 57147-57-6; (±)-13, 75509-50-1; (±)-14, 89959-61-5; (±)-14·picrate, 89959-63-7; 15, 57147-55-4; 16, 57147-56-5; 17, 90025-88-0; 18, 57147-60-1; (±)-19, 90025-89-1; (±)-20, 90027-00-2; (±)-22, 90025-90-4; 23, 61714-12-3; 24, 17508-17-7; (±)-26, 75556-10-4; (±)-27, 75556-08-0; (±)-28, 75556-09-1; (±)-31, 75509-51-2; (±)-32, 89959-64-8; (±)-33, 75543-75-8; (±)-33 (thioketal), 89959-65-9; (±)-33 (tosylhydrazone), 75509-49-8; (±)-33 (hydrazone), 89959-66-0; (±)-35, 75375-41-6; (±)-36, 75375-42-7; (±)-39·FSO_3, 90025-92-6; (±)-40·FSO_3, 90025-94-8; (±)-41, 90025-95-9; (±)-47, 90025-96-0; 48, 72362-35-7; 49, 72473-11-1; 50, 72473-13-3; (±)-52, 90025-97-1; (±)-53, 90025-98-2; (±)-54, 90025-99-3; (±)-55, 89959-68-2; (±)-56, 89959-67-1; 57, 89959-69-3; 57 (*C*-2 epimer), 90026-00-9; 58, 89959-70-6; 59, 89959-71-7; 1,5,9-cyclododecatriene, 4904-61-4; ethyl *O*-(2,4-dinitrophenyl)acetohydroxamate, 54322-32-6.

Supplementary Material Available: A description of the treatment of the disorder between C2 and C4, tables of bond lengths, bond angles, and atomic positional and thermal parameters for the chloride salt of **40** (7 pages). Ordering information is given on any current masthead page.

Synthesis of α,β-Epoxyacyl Azides and Their Rearrangement to Epoxy Isocyanates and 3- and 4-Oxazolin-2-ones

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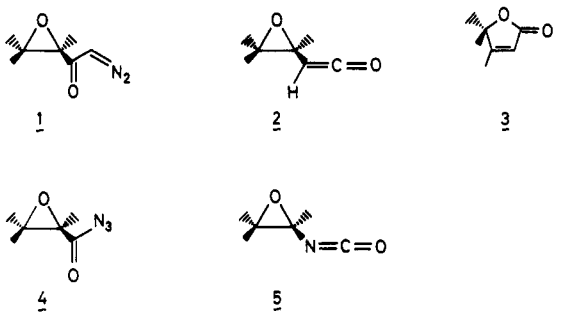
The conversion of α,β-epoxy carboxylates **6** into α,β-epoxyacyl azides **4** proceeds either via reaction of the mixed anhydrides **7** with sodium azide or via reaction of epoxyacyl chlorides **8** with hydrazoic acid–pyridine. The latter method is preferred. The azides **4** undergo a smooth thermal Curtius rearrangement to give 4-oxazolin-2-ones **10** for the substrates **4a–h** having a hydrogen atom at C_β. Monitoring this reaction by means of IR shows that the epoxy isocyanates **5** are intermediates. Intramolecular ring expansion of **5** then leads to 3-oxazolin-2-ones **9** that tautomerize to the 4-isomers **10a–h**. Epoxyacyl azides **4i,n–q**, having no hydrogen atom at C_β, producing 3-oxazolin-2-ones **9i,n–q** by a proton shift is not possible. The products **9i** and **9q** rapidly add water at the imine bond to give oxazolidin-2-ones **11**. Epoxy isocyanate **5k** is reasonably stable in solution; reaction with methanol affords urethane **12**.

In the context of our interest in the selective transformation of functionalized epoxides, we previously investigated the synthesis and chemical behavior of α,β-epoxy diazomethyl ketones[1] **1**. We showed that in these substrates a selective Wolff rearrangement of the diazo ketone moiety can be accomplished upon irradiation in an inert solvent.[1b] The initially formed epoxy ketenes **2** undergo a further intramolecular ring expansion reaction to give the butenolides[1b] **3** (Scheme I). This paper deals with the preparation and reactions of α,β-epoxyacyl azides **4** that are isoelectronic analogues of the diazo ketones **1**. The prime objective of this study is to learn whether a selective Curtius rearrangement of these acyl azides to epoxy isocyanates **5** can be realized. Species of this kind have previously been reported only once during the photochemical rearrangement of 2-oxazolin-4-ones.[2] The epoxides **5** are expected to be reactive compounds that are prone to undergo further reactions, e.g., intramolecular ring expansion reaction similar to that of epoxy ketenes **2**.

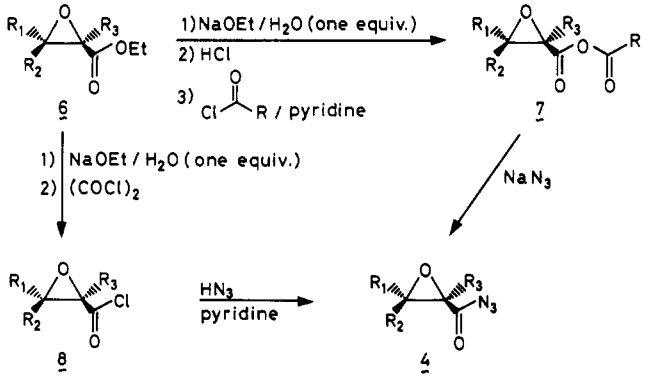
Results and Discussion

The epoxy carboxylic esters **6** serve as starting materials. They can either be prepared[1d] by a Darzens condensation of an appropriate carbonyl compound and an α-halo ester or by epoxidation of α,β-unsaturated carboxylic ester using *m*-chloroperbenzoic acid. The synthesis of the epoxyacyl azides was accomplished by using two related procedures. In the first one, saponification of the epoxy esters using the Claisen method[3] gave, after acidification, the free acids

Scheme I



Scheme II



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