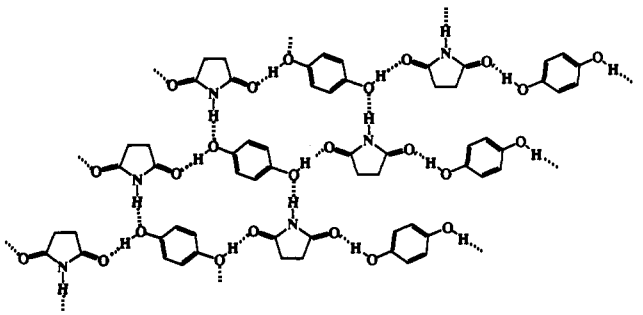

1:1 Cocrystal of a Cyclic Imide and Hydroquinone

hydroquinone. Thus, the hydrogen bond patterns of the cyclic or acyclic imide–hydroquinone complexes are completely different. We are currently studying the relationships between cyclic and acyclic imide cocrystal patterns and plan in the future to relate these systems to uracils.

Conclusions

The use of hydrogen bond interactions to direct selective molecular recognition processes of acyclic imides has been demonstrated by studying their cocrystallization properties. Acyclic imides retain their native conformation (as found in homomeric crystals) when interacting with guest molecules during the cocrystallization process. Host–guest pairs self-assemble in the absence of preorganized cavities according to relative hydrogen bond donating and accepting abilities of the functional groups that are present as well as according to the number and orientation of such groups. These results show that cocrystallization experiments provide a useful way to map out the molecular recognition properties of a class of molecules and to test for hydrogen bond selectivity in weakly associated, multifunctional systems.

Acknowledgment. We gratefully acknowledge Prof. Doyle Britton, Department of Chemistry, University of Minnesota, for his crystallographic assistance and the NIH (GM 42148-01) for financial support.

Supplementary Material Available: Positional parameters, anisotropic thermal parameters, intra- and intermolecular bond lengths and angles, and unit cell drawings for seven crystal structures (149 pages); tables of observed and calculated structure factors (147 pages). Ordering information is given on any current masthead page.

Use of Aza-Cope Rearrangement–Mannich Cyclization Reactions To Achieve a General Entry to *Melodinus* and *Aspidosperma* Alkaloids. Stereocontrolled Total Syntheses of (±)-Deoxoapodine, (±)-Meloscine, and (±)-Epimeloscine and a Formal Synthesis of (±)-1-Acetylaspidoalbidine

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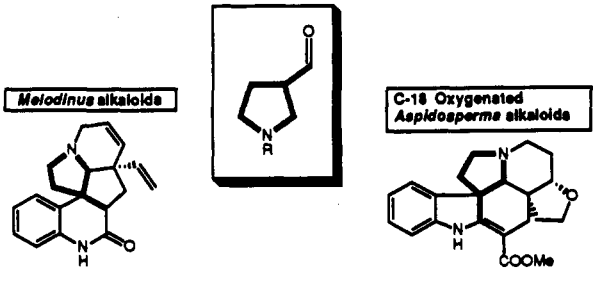
Abstract: The first total syntheses of the structurally unusual pentacyclic *Melodinus* alkaloids (±)-meloscine (**1**) and (±)-epimeloscine (**2**) and the hexacyclic *Aspidosperma* alkaloid (±)-deoxoapodine (**4**) are reported. The syntheses proceed via a highly functionalized common tetracyclic intermediate **7**, which is accessed (with complete stereocontrol) by the title rearrangement of pyrindinol **10**. These syntheses provide excellent examples of the power of tandem aza-Cope rearrangement–Mannich cyclization reactions as the key element of stereocontrolled alkaloid synthesis design.

In recent years we have developed a fundamentally new approach to alkaloid synthesis in which the facile [3,3]-sigmatropic rearrangement of iminium cations is combined with an intramolecular Mannich cyclization.[1] In the simplest case, a homoallylic amine with alkoxyl or hydroxyl substitution at the allylic site is allowed to react with an aldehyde or ketone in the presence of an equivalent or less of acid to yield a substituted 3-acylpyrrolidine product (eq 1).[2] If the starting amino alcohol is cyclic, the aza-Cope rearrangement–Mannich cyclization reaction affords a pyrrolidine annulated product in which the initial ring is expanded by one carbon. This latter transformation has been employed to provide a variety of cis fused hydroindoles, cyclopenta[*b*]pyrrolidines, and cyclohepta[*b*]pyrrolidines (eq 2)[3] as well as complex alkaloids of the *Dendrobatid*,[4] *Amaryllidaceae*,[5] and *Aspidosperma*[6] families.

Chart I



(1) Part 21 in the series *Synthesis Applications of Cationic Aza-Cope Rearrangements*. For a brief review, see: Overman, L. E.; Ricca, D. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon: Oxford, in press.

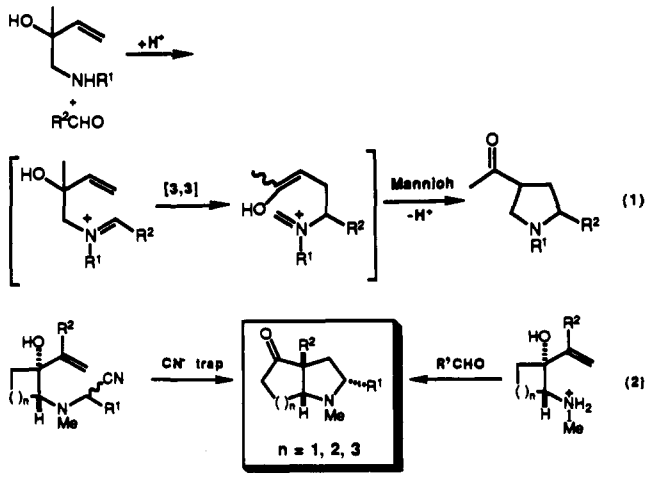
(2) See, inter alia: (a) Overman, L. E.; Mendelson, L.; Jacobsen, E. J. *J. Am. Chem. Soc.* **1983**, *105*, 6629. (b) Overman, L. E.; Jacobsen, E. J.; Doedens, R. J. *J. Org. Chem.* **1983**, *48*, 3393. (c) Overman, L. E.; Okazaki, M. E.; Jacobsen, E. J. *J. Org. Chem.* **1985**, *50*, 2403.

(3) Overman, L. E.; Kakimoto, M.-a.; Okazaki, M. E.; Meier, G. *J. Am. Chem. Soc.* **1983**, *105*, 6622. Overman, L. E.; Kakimoto, M.-a. *J. Am. Chem. Soc.* **1979**, *101*, 1310.

(4) Overman, L. E.; Fukaya, C. *J. Am. Chem. Soc.* **1980**, *102*, 1454.

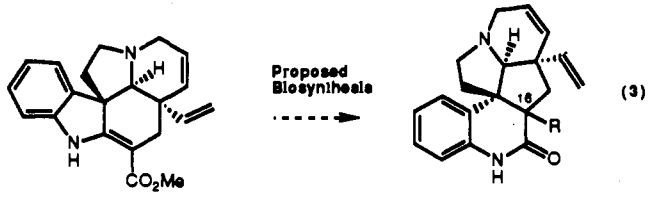
(5) Overman, L. E.; Sugai, S. *Helv. Chim. Acta* **1985**, *68*, 745.

0002-7863/91/1513-2598$02.50/0



The core functionality accessible by the "aza-Cope–Mannich" transformation is a 3-acylpyrrolidine. Herein we detail the use of aza-Cope–Mannich chemistry to achieve the first total syntheses of members of the *Melodinus* alkaloid group as well as syntheses of rare *Aspidosperma* alkaloids containing oxidation of C-18. Chart I illustrates the transcription of the 3-acylpyrrolidine unit onto these target alkaloid skeleta.

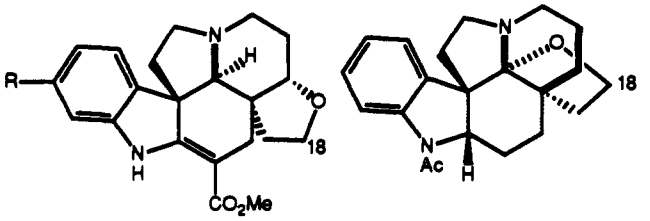
The *Melodinus* alkaloids, isolated from the New Caledonian plant *Melodinus scandens* Forst., are structurally unique by virtue of incorporating a quinoline moiety within an *Aspidosperma* alkaloid skeleton.[7] These alkaloids, e.g., meloscine (**1**), epimeloscine (**2**), and scandine (**3**), are believed to arise by oxidative rearrangement of 18,19-dehydrotabersonine (eq 3).[7-10] Recent efforts at delineating the chemical relationship between the *Aspidosperma* and *Melodinus* alkaloid families lend credence to this hypothesis.[10,11] Notably, Hugel and Lévy[10] have achieved the conversion, albeit in low (ca. 2%) overall yield, of 18,19-dehydrotabersonine to (+)-meloscine (**1**) and (+)-scandine (**3**), effectively emulating the proposed biotransformation.



18,19-Dehydrotabersonine

1 Meloscine C-16 β-H
2 Epimeloscine C-16 α-H
3 Scandine C-16 β-CO_2Me

Deoxoapodine (**4**), first isolated[12a] from *T. armeniaca*, is one of the few *Aspidosperma* alkaloids that contain oxygenation at C-18. Subsequently isolated[12b] from *Hazunta modesta* it was shown to be similar in structure to vandrikine (**5**).[13] 1-Acetylaspidoalbidine (**6**), an example of the aspidoalbine class of C-18 oxidized *Aspidosperma* alkaloids, was first isolated[14a] from *vallesia dichotoma* Ruiz et Pan. The structure, proposed originally by Djerassi,[14b] was later confirmed by the total synthesis efforts of Ban and co-workers.[15,16]



4 R = H Deoxoapodine
5 R = OMe Vandrikine

6 1-Acetylaspidoalbidine

In this paper we report, with full experimental detail, use of the aza-Cope–Mannich reaction to achieve the first total syntheses of (±)-meloscine (**1**), (±)-epimeloscine (**2**), and (±)-deoxoapodine (**4**).[17] These syntheses evolve from a highly functionalized common intermediate, which is also employed to complete a formal total synthesis of (±)-1-acetylaspidoalbidine (**6**).

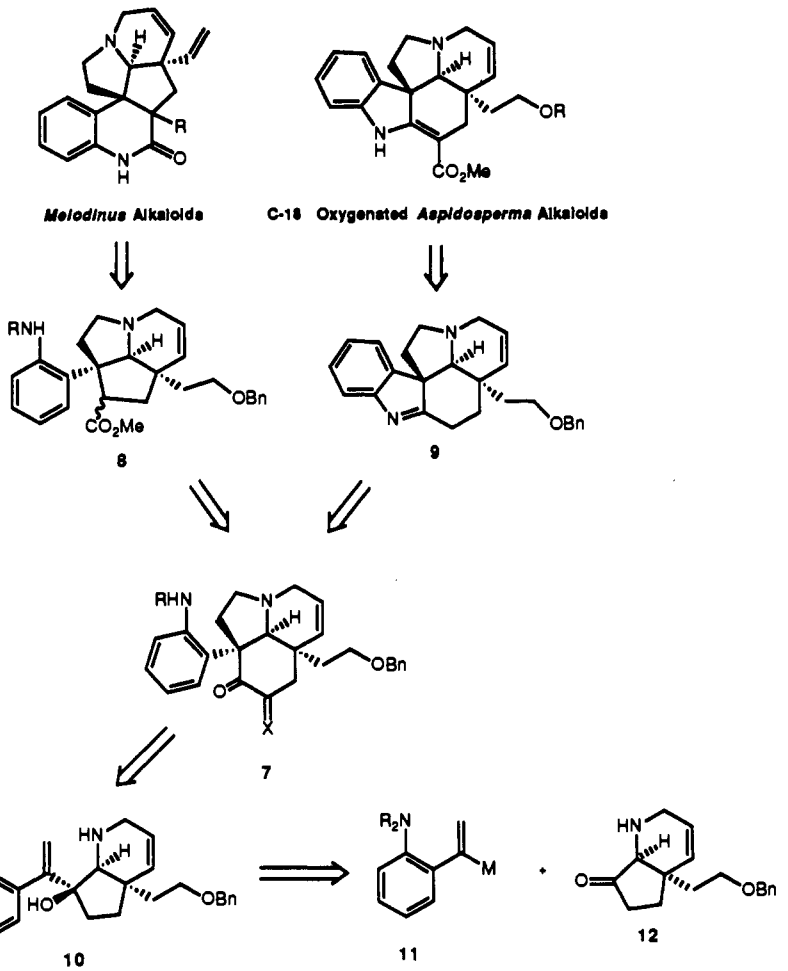
Results and Discussion

1. Synthesis Plan. The basic strategy is presented in retrosynthetic format in Scheme I. We envisaged Wolff ring contraction of **7** (X = N_2) followed by cyclization of the resulting amino ester **8** to provide access to the *Melodinus* alkaloid skeleton. The *Aspidosperma* skeleton would also evolve from **7** (X = H, H) by simple imine formation to provide pentacycle **9**. The heart of our plan is the stereocontrolled assembly of the 9a-arylhydrololidine intermediate **7** (X = H, H) by aza-Cope–Mannich rearrangement of pyrindinol **10**. The trans orientation of the amine and vinyl functionality on the cyclopentane ring of this latter intermediate ensures that the aza-Cope–Mannich rearrangement will proceed to develop the tricyclic core of **7** with the desired all-cis relationship of the three angular substituents.[1a,6,21] Pyrindinol **10** would derive from convex face addition of a styrenyl nucleophile **11** to the *cis*-hexahydro-7*H*-pyrindin-7-one **12**. The preparation of this ketone and its coupling to **10** were anticipated to follow lines outlined in our earlier synthesis of *Aspidosperma* alkaloids lacking oxidation at C-18.[6]

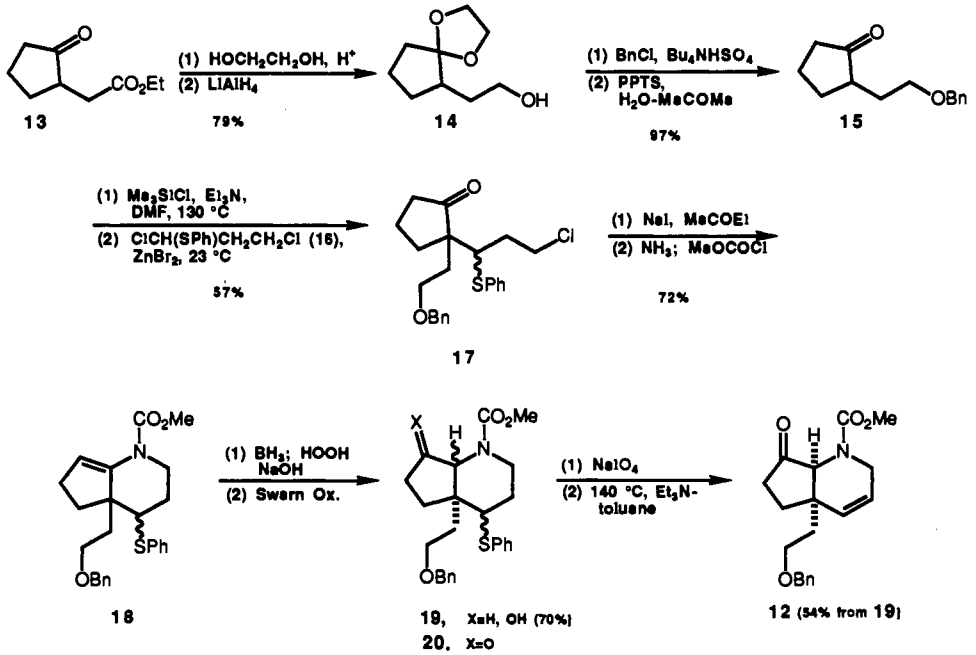
2. Preparation of *cis*-Pyrindinone 12. Readily available[18] 2-oxocyclopentaneacetate **13** was the starting point. Standard operations (Scheme II) provided 2-[2-(benzyloxy)ethyl]cyclopentanone (**15**) in 77% yield. Thermodynamic enol silylation[19] of **15** yielded the fully substituted enoxysilane with high (>20:1) regiochemical fidelity when the conversion was conducted in *N,N*-dimethylformamide (DMF) at 130 °C. Zinc bromide-promoted alkylation of this intermediate with the dichlorosulfide **16** appended the three carbons of the piperidine ring in 58% overall yield from **15**.[20] By using conditions we had defined earlier[6] in a deoxy series, **17** was then converted in good yield to the bicyclic enecarbamate **18**. In preliminary investigations we discovered

(6) Overman, L. E.; Sworin, M.; Burk, R. M. *J. Org. Chem.* **1983**, *48*, 2685.
(7) (a) Bernauer, K.; Englert, G.; Vetter, W.; Weiss, E. *Helv. Chim. Acta* **1969**, *52*, 1886. (b) Oberhansli, W. E. *Helv. Chim. Acta* **1969**, *52*, 1905. (c) Plat, M.; Hachem-Mehri, M.; Koch, M.; Scheidegger, U.; Potier, P. *Tetrahedron Lett.* **1970**, 3395.
(8) Scandine[7a] was originally suggested to have the α configuration at C-16. However, ^{13}C NMR data by Wenkert[9a] indicated that the correct configuration at C-16 is β. A subsequent crystal structure[9b] confirmed Wenkert's assignment. Unfortunately, the incorrect configuration still appears in recent discussions of these alkaloids.[10]
(9) (a) Daudon, M.; Hachem-Mehri, M.; Plat, M.; Hagaman, E. W.; Schell, F. M.; Wenkert, E. *J. Org. Chem.* **1975**, *40*, 2838. (b) Cannon, J. R.; Croft, K. D.; Matsuki, Y.; Patrick, V. A.; Toia, R. F.; White, A. H. *Aust. J. Chem.* **1982**, *35*, 1655.
(10) Hugel, G.; Lévy, J. *J. Org. Chem.* **1986**, *51*, 1594. Hugel, G.; Lévy, J. *J. Org. Chem.* **1984**, *49*, 3275.
(11) Palmisano, G.; Danieli, B.; Lesma, G.; Riva, R.; Riva, S.; Demartin, F.; Masciocchi, N. *J. Org. Chem.* **1984**, *49*, 4138.
(12) (a) Iglesias, R.; Diatta, L. *Rev. CENIC, Cienc. Fis.* **1975**, *6(1)*, 135. (b) Bui, A.; Das, B. C.; Potier, P. *Phytochem.* **1980**, *19*, 1473.
(13) (a) Lounasmaa, M.; Kan, S.-K. *Acta Chem. Scand. B* **1980**, *34*, 397. (b) Wenkert, E.; Cochran, D. W.; Hagaman, E. W.; Schell, F. M.; Neuss, N.; Katner, A. S.; Potier, P.; Kan, C.; Plat, M.; Koch, M.; Hachem-Mehri, M.; Poisson, J.; Kunesh, N.; Rolland, Y. *J. Am. Chem. Soc.* **1973**, *95*, 4990.
(14) (a) Brown, K. S.; Budzikiewski, H.; Djerassi, C. *Tetrahedron Lett.* **1963**, 1731. (b) Walser, A.; Djerassi, C. *Helv. Chim. Acta* **1965**, *48*, 391.
(15) Ban, Y.; Ohnuma, T.; Seki, K.; Oishi, T. *Tetrahedron Lett.* **1975**, 727.
(16) (a) For a recent review of *Aspidosperma* alkaloids total synthesis, see: Overman, L. E.; Sworin, M. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; John Wiley: New York, 1985; Vol. 3, chapter 7. (b) The biogenetic numbering system will be employed for *Aspidosperma* alkaloids in the narrative of this paper. The IUPAC names and numbering system is employed in the Experimental Section.
(17) The syntheses of **1** and **2** have been described in a preliminary communication: Overman, L. E.; Robertson, G. M.; Robichaud, A. J. *J. Org. Chem.* **1989**, *54*, 1236.
(18) Peet, N. P.; Cargill, R. L. *J. Org. Chem.* **1973**, *38*, 1215.
(19) Fleming, I.; Paterson, I. *Synthesis* **1979**, 736.
(20) Truce, W. E.; Hollister, K. R.; Lindy, L. B.; Parr, J. E. *J. Org. Chem.* **1968**, *33*, 43. Paterson, I.; Fleming, I. *Tetrahedron Lett.* **1979**, 2179.

Scheme I



Scheme II

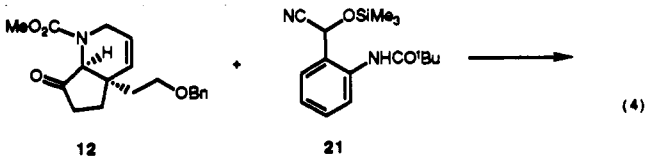


that the double bond of the methoxy analogue of **18** was remarkably resistant to epoxidation with *m*-chloroperoxybenzoic acid. Thus, the two-step sequence we employed earlier[6] for accessing the related pyrindinone containing an angular ethyl group could not be employed. We reverted to a sequence defined in our very first model studies in this area.[21] Hydroboration[22] of **18** followed by Swern oxidation[23] provided **20** as a complex mixture of stereoisomers. Oxidation to the corresponding sulfoxides

(21) Overman, L. E.; Sworin, M.; Bass, L. S.; Clardy, J. *Tetrahedron* **1981**, *37*, 4041.
(22) Borowitz, I. J.; Williams, G. L. *J. Org. Chem.* **1967**, *32*, 4157.

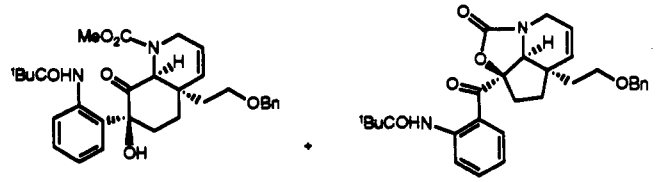
followed by pyrolysis at 140 °C in toluene containing Et_3N provided a single *cis*-pyrindinone **12** in 38% overall yield from **18**. The sequence summarized in Scheme II allowed reproducible access to **12** on a multigram scale and 12% overall yield from the γ-keto ester **13**.

3. Conversion to Aza-Cope–Mannich Rearrangement Precursors. The next conversion required was the addition of a suitably protected *o*-aminostyrenyl nucleophile to pyrindinone **12** (see Scheme I). We initially examined the sequence employed in our earlier synthesis of 16-methoxytabersonine in which the dianion of a *o*-(pivaloylamino)benzaldehyde silyl cyanohydrin is the key nucleophilic component.[6] In the case at hand, **21** was deprotonated with 2 equiv of *n*-BuLi at −70 °C and pyrindinone **12** was added (eq 4). Following our earlier protocol exactly, the reaction was then allowed to warm to 0 °C prior to sequential quenching with dilute HCl and LiOH/MeOH.[6] To our initial surprise, the major product obtained in this way was hydroquinolone **22**; only trace amounts of the desired tetracyclic adduct **23** were isolated.



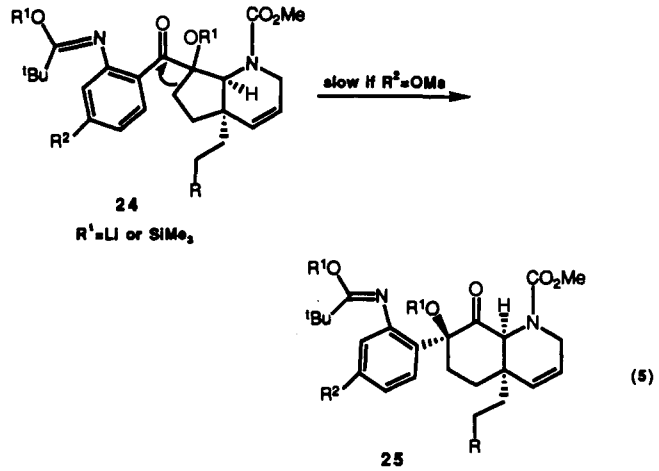
(4)

12 **21**



22 **23**

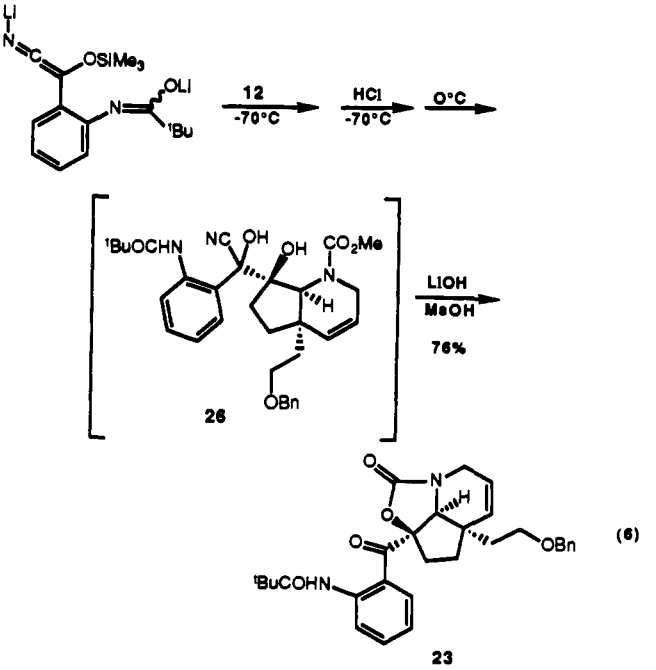
Quinolone **22** must derive from α-ketol rearrangement of an intermediate such as **24** (R^2 = H) (eq 5). That quinolone products were not observed in our earlier endeavors in the related methoxy series presumably results from the lower electrophilicity of the carbonyl carbon of **24** when R^2 = OMe.



24 **25**

(5)

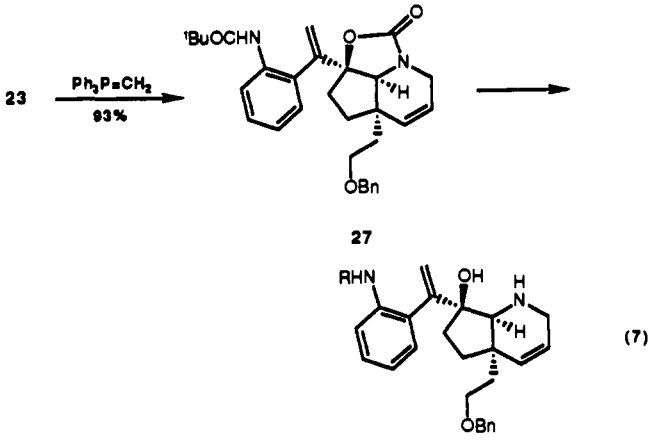
Reasoning that α-ketol rearrangement would be prevented if loss of cyanide from the initial adduct produced from **12** and **21** was suppressed, we developed a successful experimental procedure for obtaining **23** (eq 6). Thus, the reaction of the dianion of **21** and **12** was quenched at −70 °C with acid to bring the pH to ca. 6.5 prior to allowing the reaction to warm to room temperature. This treatment provided an intermediate, presumably cyanohydrin **26**, which did not show diagnostic ^1H NMR signals at 8.8 ppm for the ortho hydrogen of an aryl ketone. Treatment of this intermediate at 0 °C with LiOH/MeOH affected the desired intramolecular acylation, without α-ketol rearrangement, to deliver **23** in 76% yield on a gram scale.[24]



26 **23**

(6)

Elaboration of intermediate **23** to appropriate aza-Cope rearrangement precursors is summarized in eq 7. Reaction of **23** with excess methylenetriphenylphosphorane at room temperature afforded styrene **27** in 93% yield. It is at this juncture that the synthetic pathways to the *Melodinus* and *Aspidosperma* alkaloids diverge. Selective hydrolysis of the five-membered cyclic carbamate of **27** with excess KOH in $EtOH/H_2O$ at 130 °C gave the *Melodinus* alkaloid precursor **28** in 78% overall yield from **23**. More vigorous hydrolysis of **27** with an even larger excess of KOH in $EtOH/H_2O$ at ca. 210 °C effected hydrolysis of both the cyclic carbamate and pivalamide groups to afford the diamino alcohol **29**. This intermediate, obtained in 58% overall yield from **23**, is employed in our syntheses of the *Aspidosperma* alkaloids deoxoapodine and 1-acetylaspidoalbidine.



27

(7)

28 R = CO^{t}Bu (84%)
29 R = H (62%)

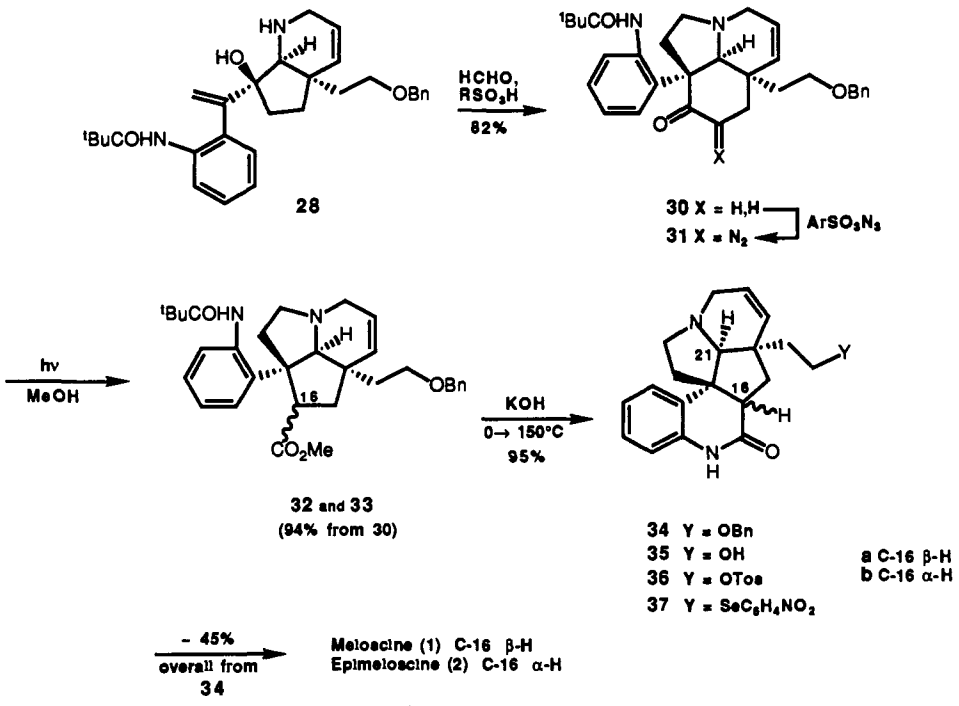
4. Rearrangement of Pyrindinol 28 and Elaboration of the Aza-Cope–Mannich Product to (±)-Meloscine and (±)-Epimeloscine. Aza-Cope rearrangement–Mannich cyclization of pyrindinol **28** was effected by treatment with excess paraformaldehyde and 0.9 equiv of camphorsulfonic acid in refluxing benzene to afford the *all-cis* hydrololidine **30** as a beautifully crystalline solid in 82% yield (Scheme III).

Attempted formylation of **30** (as a prelude to forming the α-diazoketone **31**) was not successful, since treatment of **30** with

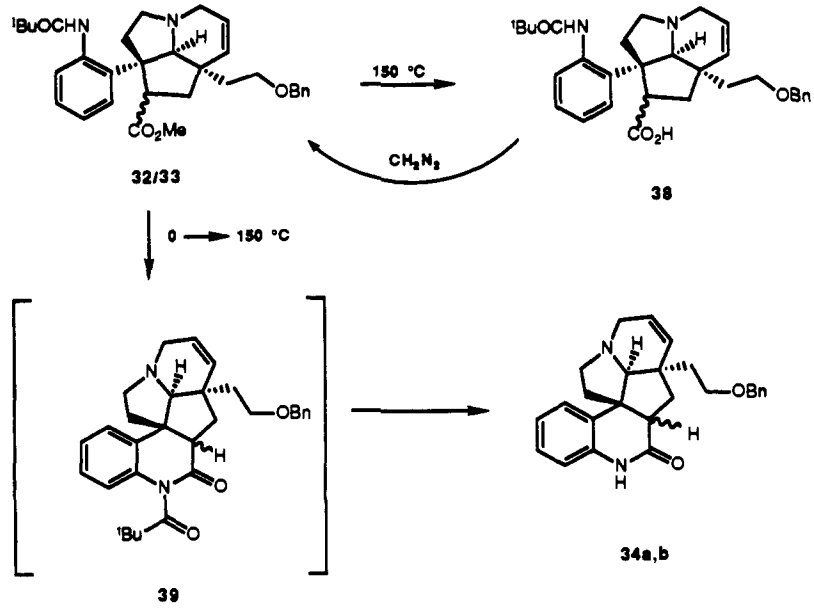
(23) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(24) The successful workup was designed to favor cyclization of the vicinal hydroxy carbamate grouping prior to cleavage of the cyanohydrin moiety.

Scheme III



Scheme IV



strong bases led to either decomposition or cyclization[6] to form the pentacyclic *Aspidosperma* skeleton. Nor were we successful in engendering ring contraction from the reaction of the enoxysilane of **30** with *p*-bromophenylsulfonyl azide.[25] Fortunately, diazo transfer to **30** from 2,4,6-triisopropylbenzenesulfonyl azide could be accomplished in nearly quantitative yield when carried out under phase-transfer catalysis as described by Lombardo and Mander.[26] Salient spectral features of the α-diazoketone **31** include a strong IR absorption at 2096 cm^{-1} and two doublets (J = 13.7 Hz) at 3.09 and 2.67 ppm in the ^1H NMR spectrum for hydrogens α to the diazo group.

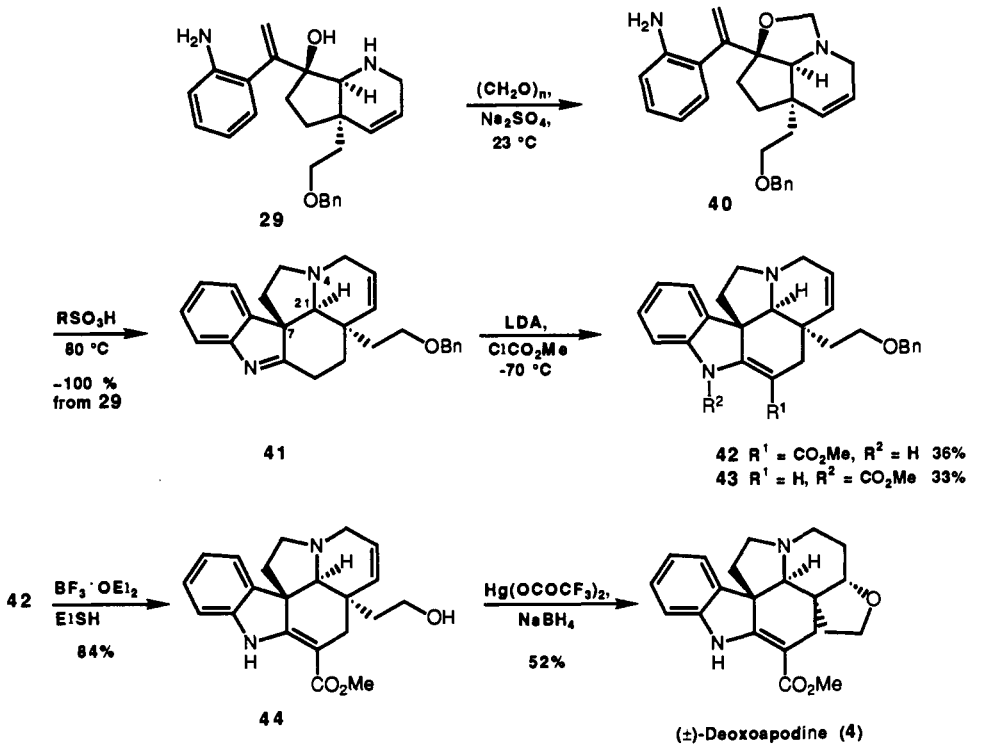
Conventional irradiation of diazoketone **31** in Et_2O–MeOH at room temperature with a Vycor-filtered Hanovia lamp produced the epimeric ring-contracted esters **32** (major diastereomer) and **33** (minor diastereomer) in a ratio of 4:1 and in excellent overall yield (94% from ketone **30**). ^1H NMR decoupling and 2D COESY clearly defined the gross structures of these epimers, but the relative stereochemistry at C-16 was not rigorously determined. However, this is of no consequence, since treatment of *either* diastereomer with a large excess of KOH in EtOH/H_2O at 0 °C followed by slow warming to 150 °C over a 24-h period gave the desired pentacyclic amides **34a** and **34b** in 95% yield and in a thermodynamic ratio of 10:1, respectively. In addition, a small amount (0–4%) of acid **38** (see Scheme IV) was obtained under these conditions. It is worthy of note that simple ester hydrolysis to afford **38** predominates when the basic reaction mixture is rapidly heated to 150 °C. We believe that the successful conversion of **32**/**33** to **34a,b** proceeds by way of the pentacyclic imide **39**[27] and that it is this intermediate which suffers deacylation at higher temperatures. For reasons which remain unclear, warming

(25) Wohl, R. *Helv. Chim. Acta* **1973**, *56*, 1826. Goldsmith, D. J.; Soria, J. J. *Tetrahedron Lett.* **1986**, *27*, 4701.

(26) Lombardo, L.; Mander, L. N. *Synthesis* **1980**, 368.

(27) Attempts to isolate this intermediate were unsuccessful.

Scheme V



the reaction mixture too quickly results in ester hydrolysis at the expense of deacylation.[28] The structure of **38** was confirmed by methylation with ethereal diazomethane to return **32** and **33**.

The pentacyclic lactam epimers **34a** and **34b** were readily separated by silica gel chromatography, and their ^1H NMR spectra exhibited diagnostic singlets at 3.58 and 3.91 ppm for the C-21 methine hydrogens. Meloscine and epimeloscine exhibit singlets for the C-21 hydrogens at 3.54 and at 3.94 ppm, respectively.[7] Bernauer has shown that equilibration of epimeloscine to meloscine is readily accomplished[7a] under basic conditions. Thus, not surprisingly, treatment of **34b** with KO*t*-Bu in *t*-BuOH at 75 °C afforded epimer **34a** almost exclusively. This epimerization coupled with ^1H NMR spectral data was the basis for the stereochemical assignments for the epimer pair **34**. These assignments were subsequently confirmed (vide infra) by conversion of these intermediates to (±)-meloscine (**1**) and (±)-epimeloscine (**2**).

Elaboration of the pentacyclic amide **34a** to (±)-meloscine (**1**) was reasonably straightforward. Treatment of **34a** with sodium in liquid NH_3 at −70 °C effected debenzylation to afford the primary alcohol **35a** in essentially quantitative yield (Scheme III). To prevent reduction of the dihydroquinolone moiety, this procedure had to be carried out at temperatures below −60 °C and the reaction quenched *immediately* with solid NH_4Cl once the persistence of the dark blue color was observed. Tosylation[29] of **35a** followed by displacement of the tosylate with excess *o*-nitrophenylselenide anion afforded selenide **37a** in 58% yield (>90% efficiency based on consumed starting tosylate). Finally, oxidation of **37a** with *m*-chloroperoxybenzoic acid and subsequent selenoxide elimination provided (±)-meloscine (**1**) in 81% yield as a colorless solid, mp 220–222 °C (Et_2O). Spectral (500 MHz ^1H NMR, ^{13}C NMR) properties of this material were consistent with those reported,[7,9a] and synthetic (±)-(**1**) was indistinguishable by TLC comparisons from an authentic sample of (+)-meloscine kindly provided by Prof. J. Lévy.

Repetition of this sequence with the minor pentacyclic diastereomer **34b** afforded (±)-epimeloscine (**2**) in 43% overall yield. It is noteworthy that this epimer, known to be unstable under basic conditions (vide supra),[7a] was not epimerized to any significant extent during this reaction sequence. Spectral properties of synthetic (±)-epimeloscine were in accord with authentic characterization data provided by Professor K. Bernauer.[7,9a]

5. Elaboration of Pyrindinol 29 to (±)-Deoxoapodine and (±)-1-Acetylaspidoalbidine. Entry to the class of C-18 oxygenated *Aspidosperma* alkaloids was readily accomplished from diamino alcohol **29** (Scheme V). Treatment of **29** with paraformaldehyde and Na_2SO_4 in benzene at room temperature provided the oxazoline **40** in quantitative yield. Best results for the aza-Cope–Mannich rearrangement were obtained when this intermediate was isolated and then subsequently subjected to acidic rearrangement conditions. Thus treatment of **40** with an excess of camphorsulfonic acid and Na_2SO_4 in refluxing benzene afforded the crude pentacyclic imine **41** in excellent crude yield. The proclivity of pentacyclic imines of this type to undergo retro-Mannich cleavage of the C-7/C-21 bond (cleavamine fragmentation) is well precedented.[31] Therefore, use of excess acid in the rearrangement step, which presumably deactivates N-4 toward retro-Mannich fragmentation by protonation, was necessary to obtain optimum yields of the pentacyclic imine **41**. Not unexpectedly, silica gel chromatography of **41** led to considerable decomposition.

The remaining carbomethoxy substituent of the cyclohexane C-ring was most conveniently introduced by directed acylation of imine **41**. By using a procedure developed earlier,[6] this crude imine was treated with a large excess of LDA at −70 °C, and the resulting enamine anion was acylated with methyl chloroformate to provide the tabersonine derivative **42** (36% from **40**) and nearly equal amounts of the N-acylated product **43** (33% from **40**). Although this latter product should be readily converted to **42** by using protocols developed by Magnus,[32] this transformation was not investigated.

Assembly of the tetrahydrofuran ring remained as the last obstacle to the total synthesis of (±)-deoxoapodine. Attempts to

(28) The carboxylic acids **38** are not converted to **34a/34b** under the reactions/conditions employed to prepare these products from **32/33**.

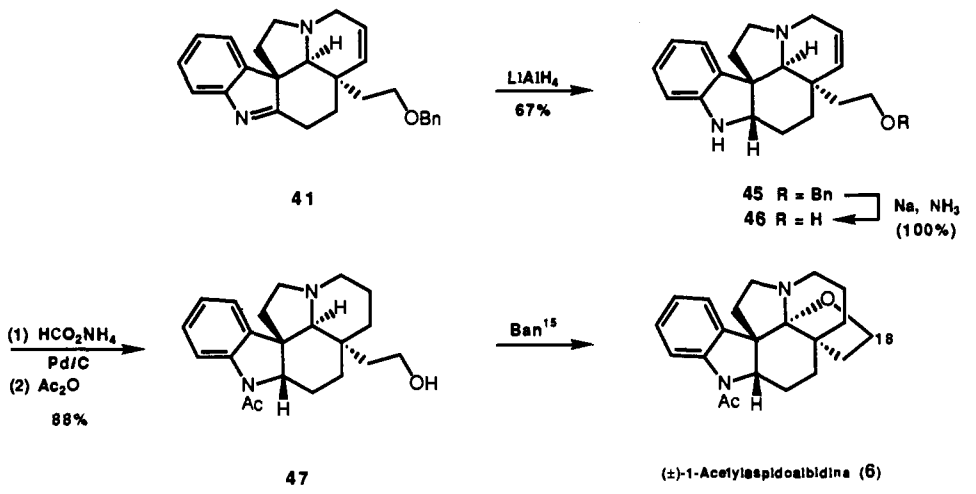
(29) Kabalka, G. W.; Varma, M.; Varma, R. S.; Srivastava, P. C.; Knapp, F. F., Jr. *J. Org. Chem.* **1986**, *51*, 2386.

(30) Sharpless, K. B.; Young, M. W. *J. Org. Chem.* **1975**, *40*, 947.

(31) Stork, G.; Dolfini, J. E. *J. Am. Chem. Soc.* **1963**, *85*, 2872 and references cited therein.

(32) Cardwell, K.; Hewitt, B.; Ladlow, M.; Magnus, P. *J. Am. Chem. Soc.* **1988**, *110*, 2242.

Scheme VI



remove the benzyl ether protecting group of **42** employing catalytic transfer hydrogenolysis or dissolving metal reduction resulted in partial reduction of one or both alkene moieties. However, deprotection was successfully achieved upon treatment of **42** with an excess of BF_3·OEt_2 in refluxing ethanethiol[33] which gave alcohol **44** in 90% yield after chromatographic purification. Treatment of **44** in THF with an excess of mercuric trifluoroacetate at −70 °C followed by warming the reaction to room temperature and subsequent reductive workup[34] afforded (±)-deoxoapodine (**4**) in 52% yield (74% based on consumed **44**).

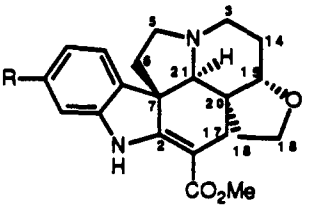
An authentic sample of deoxoapodine was not available from the Gif group. However, the spectral data of synthetic (±)-deoxoapodine correlated well with scarce data reported by Potier and co-workers for natural deoxoapodine.[35] In addition, a comparison of the spectral data (^{1}H NMR, ^{13}C NMR) of synthetic (±)-deoxoapodine with the reported high field ^{13}C NMR data[11] for the 11-methoxy derivative, vandrikine (**5**), left little doubt that deoxoapodine had been successfully accessed (Table I).

The conversion of the 1,2-dehydroaspidospermidine intermediate **41** to the penultimate precursor **47** of (±)-1-acetylaspidoalbidine (**6**) is outlined in Scheme VI. Hydride reduction of the imine functionality of **41** followed by debenzylation of this product (Na/NH_3) afforded **46** in 67% yield. Convincing precedent indicates that hydride addition to **41** would occur from the β face.[16,31,36] Saturation of the D ring of **46** followed by acetylation provided (±)-1-acetyl-18-hydroxyaspidospermidine (**47**). This intermediate showed ^{1}H NMR spectral properties in accord with authentic spectra provided by Professor Y. Ban. *N*-Acetyl-18-hydroxyaspidospermidine (**47**) has been converted to 1-acetylaspidoalbidine (**6**), albeit in modest yield, by Ban and co-workers.[15]

Conclusion

The first total syntheses of the structurally unusual *Melodinus* alkaloids (±)-meloscine and (±)-epimeloscine were accomplished in ca. 24 steps and 3–4% overall yield from ethyl 2-oxocyclopentaneacetate. The quaternary stereocenter and the cis fusion of the C and D rings of these targets were *predictably* established with *complete* stereocontrol by the chair topographic aza-Cope–Mannich rearrangement of pyrindinol **28**. The related rearrangement of oxazolidine **40** takes place in essentially quantitative yield and with complete stereocontrol to form three of the six rings of the C-18 oxygenated *Aspidosperma* alkaloids (±)-deoxoapodine and (±)-1-acetylaspidoalbidine. These concise total syntheses provide further demonstrations of the power of aza-Cope rearrangement–Mannich cyclization synthesis strategies for assembling stereochemically complex alkaloid skeleta.

Table I. ^{13}C NMR Data for Synthetic (±)-Deoxoapodine (**4**) and Natural Vandrikine (**5**)[13]



R = H DEOXOAPODINE 4
R = OMe VANDRIKINE 5

	4	5		4	5
2	167.3	167.4	17	26.9	26.6
3	46.0	45.7	18	65.0	64.7
5	51.5	51.2	19	34.9	34.6
6	45.2	45.1	20	46.6	46.4
7	55.1	54.2	21	68.8	68.7
14	27.6	27.4	C=O	168.8	168.5
15	80.0	79.8	OMe	51.1	50.8
16	93.9	93.9			

Experimental Section[37]

9-(2-Hydroxyethyl)-1,4-dioxaspiro[4.4]nonane (14). A solution of keto ester **13**[18] (26 g, 0.16 mmol), dry toluene (200 mL), ethylene glycol (30 mL, 0.54 mmol), and pyridine *p*-toluenesulfonate (PPTS, 100 mg) was heated at gentle reflux for 12 h with azeotropic removal of water. After cooling to 23 °C, the reaction was diluted with ether (150 mL) and washed with saturated aqueous $NaHCO_3$ solution (100 mL) and brine (100 mL). Evaporation of the dried ($MgSO_4$) organic phase and distillation of the resulting residue gave 28.6 g (86%) of the dioxolane ester as a colorless liquid: bp 165–169 °C/22 mm; ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.26 (q, J = 6.7 Hz, OCH_2CH_3), 3.90 (m, 4 H, OCH_2), 2.55–1.33 (m, 9 H), 1.27 (t, J = 6.7 Hz, CH_3) ppm; IR (film) 1735 cm^{-1}.

A solution of this dioxolane ester (28.6 g, 0.13 mmol) and dry Et_2O (200 mL) was added dropwise at 0 °C to a well-stirred suspension of $LiAlH_4$ (6.8 g, 0.18 mmol) in dry Et_2O (1.3 L). The reaction was stirred at 0 °C for 1 h and then at 23 °C for 1 h. The reaction mixture was then cooled to ca. 10 °C and quenched by cautious addition of water (6.7 mL), followed by 2 M aqueous NaOH (6.7 mL) and additional water (13.4 mL). The precipitated salts were removed by suction filtration and were

(33) Fuji, K.; Ichikawa, K.; Node, M.; Fujita, E. *J. Org. Chem.* **1979**, *44*, 1661.

(34) Brown, H. C.; Rei, M.-H. *J. Am. Chem. Soc.* **1969**, *91*, 5646. Brown, H.-C.; Geoghegan, P. J., Jr.; Lynch, G. L.; Kurek, J. T. *J. Org. Chem.* **1972**, *37*, 1941.

(35) Bui, A.; Das, B. C.; Potier, P. *Phytochem.* **1980**, *19*, 1473.

(36) Ban, Y.; Sato, Y.; Inoue, I.; Nagai, M.; Oishi, T.; Terashima, M.; Yonemitsu, Y.; Kanaoka, Y. *Tetrahedron Lett.* **1965**, 2261.

(37) Most general experimental details have been described: Fisher, M. J.; Overman, L. E. *J. Org. Chem.* **1988**, *53*, 2630. All reactions were conducted under an inert atmosphere of N_2 or argon. Room temperature is specified as 23 °C.

(38) Freedman, H. H.; Dubois, R. A. *Tetrahedron Lett.* **1975**, 3251.

(39) Some NMR signals of this intermediate are broadened or made more complex by the presence of amide and/or carbamate geometrical isomers.

washed with Et_2O. Evaporation by the dried ($MgSO_4$) filtrate and distillation of the residue gave 21.2 g (92%) of **14** as a colorless liquid: bp 110–112 °C/1.5 mm; ^1H NMR (300 MHz, $CDCl_3$) δ 3.8–4.1 (m, 4 H, HCO), 3.55–3.77 (m, 3 H, HCO), 1.4–2.3 (m, 9 H), ppm; IR (film) 3406 cm^{-1}; MS (EI) 172.1103 (60, 172.1099 calcd for $C_9H_{16}O_3$, M).

2-[2-(Benzyloxy)ethyl]cyclopentanone (15). Following the general procedure of Freedman and Dubois,[38] 50% aqueous NaOH (32 mL, 0.40 mmol) was added to a well-stirred solution of alcohol **14** (13.5 g, 78.6 mmol) and benzyl chloride (60 mL, 0.5 mmol). A catalytic amount of $(n\text{-}Bu)_4NHSO_4$ (1.3 g, 5%) was then added, and the reaction was stirred at 23 °C for 45 min. The reaction mixture was then diluted with water (200 mL) and extracted with Et_2O (3 × 100 mL). The combined organic extracts were washed with 10% HCl (100 mL), saturated aqueous $NaHCO_3$ solution (100 mL), and brine (100 mL). Evaporation of the dried ($MgSO_4$) organic phase followed by distillation of the residue gave 20.5 g (99%) of the benzyl ether as a colorless liquid: bp 148–150 °C/0.5 mm Hg; ^1H NMR (250 MHz, $CDCl_3$) δ 7.23–7.37 (m, 5 H, PhH), 5.55–5.61 (m, 1 H, HCO), 4.50 (ABq, 15.1 Hz, OCH_2Ph), 3.82–3.94 (m, 4 H, CH_2O), 3.42–3.62 (m, OCH_2), 1.30–2.10 (m, 8 H) ppm; IR (film) 3030, 1435, 1103 cm^{-1}; MS (EI) 262.1557 (20, 262.1569 calcd for $C_{16}H_{22}O_3$, M).

A solution of this ketal (20.5 g), acetone (800 mL), water (8 mL), and PPTS (2 g, 8 mmol) was heated under gentle reflux for 16 h. After cooling to 23 °C, the solvent was evaporated, and the resulting residue was taken up in Et_2O (300 mL). The Et_2O solution was washed with saturated aqueous $NaHCO_3$ solution (100 mL) and brine (100 mL). Evaporation of the dried ($MgSO_4$) organic phase gave 16.6 g of the ketone **15** (97% for the two steps) as a white crystalline solid: mp 38–41 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25–7.36 (m, 5 H, PhH), 4.49 (ABq, J = 13.6 Hz, OCH_2Ph), 3.50–3.65 (m, OCH_2), 1.45–2.34 (m, 9 H) ppm; IR (film) 1736 cm^{-1}; MS (EI) 218.1305 (1, 218.1307 calcd for $C_{14}H_{18}O_2$, M), 111 (30), 110 (36), 105 (100), 91 (54).

2-[2-(Benzyloxy)ethyl]-2-[3-chloro-1-(phenylthio)propyl]cyclopentanone (17). Following the general procedure of Fleming,[19] Me_3SiCl (15 mL, 0.12 mmol) was added dropwise to a stirred solution of ketone **15** (24.6 g, 0.11 mmol), dry Et_3N (27 mL, 0.20 mmol), and dry DMF (140 mL), and the reaction mixture was maintained at 130 °C for 96 h. After cooling to 23 °C, the mixture was diluted with Et_2O (400 mL) and washed with ice-cold saturated aqueous $NaHCO_3$ solution (400 mL). The aqueous phase was back-extracted with Et_2O (150 mL), and the combined organic extracts were washed rapidly with ice-cold 10% HCl (200 mL), saturated $NaHCO_3$ solution (200 mL), and brine (200 mL). Evaporation of the dried ($MgSO_4$) organic extracts gave 32.4 g of the crude silyl enol ether as a pale yellow liquid, which was used directly for the next step: ^1H NMR (250 MHz, $CDCl_3$) δ 7.24–7.89 (m, 5 H, PhH), 4.52 (s, OCH_2Ph), 3.50 (t, J = 7.3 Hz, OCH_2), 2.01–2.40 (m, 6 H), 1.75–1.86 (m, 2 H), 0.17 (s, $(CH_3)_3Si$); MS (EI) 290.1690 (290.1702 calcd for $C_{17}H_{26}O_2Si$).

A stirred solution of the crude silyl enol ether (32.4 g), freshly prepared[6] 1,3-dichloro-1-(phenylthio)propane **16** (26 g, 0.12 mmol) and dry CH_2Cl_2 (600 mL) was cooled to 0 °C and a catalytic amount (500 mg, 2.2 mmol) of freshly sublimed $ZnBr_2$ was added.[6,20] The reaction mixture was allowed to warm to 23 °C and after 1 h was filtered and concentrated. The residue was purified by flash chromatography (silica HF_{254}, 1:1 Et_2O/hexane) to give 25.4 g (57%) of ketone **17**, a mixture of diastereomers, as a viscous yellow oil: ^1H NMR (250 MHz, $CDCl_3$) δ 7.20–7.48 (m, 10 H, PhH), 4.29 and 4.43 (ABq, J = 11.6 Hz, OCH_2Ph), 3.38–3.80 (m, 5 H, CH_2O, CHSPh, and CH_2Cl), 1.87–2.35 (m, 10 H) ppm; IR (film) 1734 cm^{-1}; MS (CI) 403 (MH); MS (EI) 402.1415 (402.1420 calcd for $C_{23}H_{27}ClO_2S$, 40), 185 (15), 159 (15), 91 (100).

4a-[2-(Benzyloxy)ethyl]-1-(methoxycarbonyl)-4-(phenylthio)-2,3,4,4a,5,6-hexahydro-1*H*-1-pyrindine (18). A solution of chloride **17** (27.5 g, 68.2 mmol) and dry 2-butanone (ca. 75 mL) was deoxygenated by passing argon through the solution. To this stirred solution was added $NaHCO_3$ (7.0 g, 84 mmol) and NaI (20.5 g, 136 mmol), and deoxygenation was continued for 1 h. The reaction mixture was then stirred at 23 °C for 22 h and at gentle reflux for 20 h. After cooling to 23 °C, 10% aqueous $Na_2S_2O_3$ solution (300 mL) was added, and the resulting mixture was extracted with $CHCl_3$ (3 × 300 mL). The combined organic extracts were washed with brine (300 mL), dried ($MgSO_4$), and concentrated to give the crude iodide as a yellow oil, which was used immediately for the next step.

A solution of this crude iodide in $CHCl_3$ (120 mL) was added to freshly distilled liquid NH_3 (80 mL) at −70 °C in a Fischer–Porter pressure bottle. The resulting solution was stirred at room temperature (ca. 100 psi) for 72 h. Excess NH_3 was carefully vented, and the reaction mixture was concentrated to ~60 mL and then diluted with $CHCl_3$ (100 mL). The precipitated salts were removed by filtration, and the residue was diluted with $CHCl_3$ (250 mL). The resulting solution was purged for 1 h with argon while rapidly stirred, and then $KHCO_3$ (9 g, 100 mmol) and MeOCOCl (9.8 mL, 150 mmol) were added. The resulting mixture was stirred at 23 °C for 14 h and then filtered. The filtrate was washed with 10% HCl (100 mL), saturated aqueous $NaHCO_3$ solution (100 mL), and brine (100 mL). Concentration of the dried ($MgSO_4$) organic phase and purification of the residue by flash chromatography (silica, 1:1 Et_2O/hexane) gave 20.7 g (72%) of enecarbamate **18**, a mixture of diastereomers, as a pale yellow oil: ^1H NMR (250 MHz, $CDCl_3$)[39] δ 7.21–7.46 (m, 10 H, CH_2Ph and SPh), 5.51 and 5.61 (m, 1 H, =CH), 4.49 (ABq, J = 9.9 Hz, OCH_2Ph), 4.20 (ddd, J = 1.7, 4.9, 12.9 Hz, C-2 H_β), 3.66 and 3.72 (s, CO_2Me), 3.56 (t, J = 7.6 Hz, OCH_2), 3.04 (dd, J = 4.1, 12.4 Hz, C-2 H_α), 1.7–2.4 (m, 10 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$)[39] δ 155.4, 140.0, 138.5, 135.1, 132.6, 129.0, 128.7, 128.5, 128.4, 128.3, 127.6, 127.4, 127.2, 119.4, 112.5, 73.0, 60.4, 52.7, 50.6, 45.6, 35.5, 32.1, 28.7, 28.5 ppm; IR (film) 1706, 1656 cm^{-1}; MS (CI) 424.1926 (424.1946 calcd for $C_{25}H_{30}NO_3S$, MH), 181, 180, 178, 166, 91.

***cis*-4aα-[2-(Benzyloxy)ethyl]-1-(methoxycarbonyl)-4-(phenylthio)-1,2,3,4,5,6,7,7a-octahydro-7*H*-1-pyrindin-7-ol (19).** A 1 M solution of BH_3 in THf (4.0 mL, 4.0 mmol) was added dropwise at 23 °C to a well-stirred solution of enecarbamate **18** (680 mg, 1.6 mmol) and dry THF (50 mL). The resulting solution was maintained at 23 °C for 45 min, and then 3 M NaOH (5.3 mL) was added, followed by 30% aqueous HOOH (1.4 mL), and the resulting mixture was stirred at 23 °C for 2 h. The reaction mixture was then diluted with H_2O (80 mL) and extracted with Et_2O (3 × 100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated, and the residue was purified by flash chromatography (silica HF_{254}, Et_2O) to give 500 mg (70%) of alcohol **19**, a mixture of diastereomers, as a viscous, nearly colorless oil: IR (film) 3489, 1690, 1667 cm^{-1}; MS (CI) 442.2040 (442.2052, calcd for $C_{25}H_{32}NO_4S$, MH), 350, 180, 91.

4aα-[2-(Benzyloxy)ethyl]-1-(methoxycarbonyl)-1,2,4a,5,6,7aα-hexahydro-7*H*-1-pyrindin-7-one (12). Following the general procedure of Swern,[23] a solution of oxalyl chloride (3.2 mL, 36 mmol) and dry CH_2Cl_2 (70 mL) was cooled to −60 °C, and a solution of dry DMSO (5 mL, 70 mmol) and dry CH_2Cl_2 (70 mL) was added dropwise. After 50 min at −60 °C, a solution of alcohol **19** (10.6 g, 24 mmol, freshly azeotroped with toluene) and dry CH_2Cl_2 (70 mL) was added dropwise and the resulting mixture was maintained at −60 °C for 3 hours. Dry Et_3N (20 mL) was then added, and the reaction was allowed to warm to 23 °C. The mixture was then diluted with H_2O (200 mL), the aqueous phase separated and extracted with $CHCl_3$ (2 × 200 mL). The combined organic extracts were washed with brine (200 mL), dried ($MgSO_4$), and concentrated. The residue was filtered through silica gel (Et_2O) to give 10.6 g of ketone **20**, a mixture of at least three diastereomers, which was used directly for the next step: MS (EI) 439.1802 (30, 439.1817 calcd for $C_{25}H_{29}NO_4S$, M).

A solution of $NaIO_4$ (6.7 g, 31 mmol) and H_2O (75 mL) was added to a stirred solution of this sample of sulfide ketones **20** (10.6 g) and MeOH (150 mL). The reaction mixture was maintained at 23 °C for 72 h and subsequently filtered, washed with $CHCl_3$ (30 mL), and concentrated. The residue was extracted with $CHCl_3$ (3 × 70 mL), and the combined organic extracts were washed with brine (150 mL), dried ($MgSO_4$), and concentrated to give the crude sulfoxides (11 g) as a yellow oil, which was used directly in the next step.

A solution of this sample of crude sulfoxide ketones (11 g) and dry toluene (400 mL) containing Et_3N (10% by volume) was deoxygenated with argon and then heated to reflux for 72 h. After cooling to 23 °C, the mixture was diluted with Et_2O (200 mL), washed with 10% HCl (200 mL), saturated aqueous $NaHCO_3$ solution (200 mL), brine (200 mL), dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography (silica, Et_2O) to give 4.27 g (54%) of pyrindinone **12** as an orange oil: ^1H NMR (500 MHz, $CDCl_3$)[39] δ 7.26–7.36 (m, 5 H, ArH), 5.66–5.76 (m, 1 H, 4-H), 5.54–5.61 (m, 1 H, C-3 H), 4.64 and 4.47 (s, 1 H, C-7a H), 4.45–4.55 (m, 2 H, OCH_2Ph), 4.00–4.16 (m, 1 H, C-2 H_β), 3.75 and 3.66 (s, 3 H, CO_2Me), 3.46–3.60 (m, 3 H, OCH_2 and C-2 H_α), 1.90–2.30 (m, 6 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$)[39] δ 213.4, 213.3, 157.1, 156.5, 138.3, 130.3, 129.7, 128.4, 128.3,m 127.6, 127.5, 126.5, 126.0, 73.1, 73.0, 66.9, 66.8, 66.3, 65.9, 53.0, 52.9, 42.0, 41.9, 40.8, 32.5, 31.0, 30.9 ppm, two carbamate isomers; IR (film) 1753, 1700 cm^{-1}; MS (CI) 330 (MH); MS (EI) 329.1629 (329.1627 calcd for $C_{19}H_{23}NO_4$, M).

2-(Trimethylacetamido)benzaldehyde. Methyllithium (106 mL of 1.4 M solution in Et_2O) was added dropwise at 23 °C to a solution of 2-bromoaniline (12.7 g, 74.1 mmol) and dry THF (450 mL). After 2 h, the resulting solution was cooled to −78 °C, and freshly distilled trimethylacetyl chloride (9.2 mL, 75 mmol) was added dropwise. After 15 min at −78 °C, *tert*-butyllithium (87 mL of a 1.7 M solution in pentane) was added dropwise, and the resulting solution was maintained at −78 °C for 1 h and warmed to −10 °C whereupon dry DMF (30 mL, 380 mmol) was added. After 30 min at −10 °C, the reaction mixture was

allowed to warm to 23 °C and after 2 h was quenched by pouring into a stirred mixture of 1 M HCl and Et_2O (1:1, 800 mL). The aqueous phase was extracted with Et_2O (2 × 100 mL), and the combined organic extracts were washed with brine (300 mL). Evaporation of the dried ($MgSO_4$) organic extracts and flash chromatography (silica, 3:1, hexane/Et_2O) gave 11.5 g (66%) of *o*-(pivaloylamino)benzaldehyde as a yellow liquid: ^1H NMR (300 MHz, $CDCl_3$) δ 11.4 (br s, NH), 9.93 (s, CHO), 8.80 (d, J = 8.5 Hz, 1 H, ArH), 7.67 (dd, J = 1.5, 7.6 Hz, 1 H, ArH), 7.60 (dt, J = 1.6, 8.7 Hz, 1 H, ArH), 7.21 (dt, J = 0.8, 7.5 Hz, 1 H, ArH), 1.36 (s, *t*-Bu) ppm; ^{13}C NMR ($CDCl_3$) δ 195.5, 178.4, 141.4, 136.1, 136.0, 122.6, 122.1, 119.9, 40.4, 27.6 ppm; IR (film) 3299, 1671, 1587, 1479, 1446, 1401, 1318 cm^{-1}; MS (CI) 206.1184 (206.1181 calcd for $C_{12}H_{16}NO_5$, MH), 205, 149, 148, 121, 93, 85.

2-[2-(Trimethylacetamido)phenyl]-2-[(trimethylsilyl)oxy]acetonitrile (21). To a solution of *o*-(pivaloylamino)benzaldehyde (7.8 g, 38 mmol) and dry THF (50 mL) was added a catalytic amount of KCN–18-crown-6 complex (10 mg), followed by freshly distilled Me_3SiCN (15 mL, 110 mmol). The reaction mixture was maintained at 23 °C for 1 h and then was concentrated to afford the crude silyl cyanohydrin as a yellow oil. Crystallization from cold pentane (30 mL) gave 8.9 g (77%) of **21** as white crystals: mp 66.5–68 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 8.75 (s, 1 H, NH), 8.28 (d, J = 8.1 Hz, 1 H, ArH), 7.43 (dt, J = 1.7, 7.9 Hz, 1 H, ArH), 7.06–7.20 (m, 2 H, ArH), 5.42 (s, 1 H, CHCN), 1.28 (s, CO^{t}Bu), 0.23 (s, $(CH_3)_3Si$); MS (CI) 304.1592 (304.1607 calcd for $C_{16}H_{25}N_2O_2Si$, MH), 289, 278, 220, 219, 215, 178, 176, 157, 132, 130. Anal. Calcd for $C_{16}H_{24}N_2O_2Si$: C, 63.12; H, 7.95; N, 9.20. Found: C, 63.02; H, 7.94; N, 9.27.

4aα-[2-(Benzyloxy)ethyl]-7β-hydroxy-1-(methoxycarbonyl)-7α-[2-(trimethylacetamido)benzoyl]-1,2,4a,5,6,7,8a-octahydro-8*H*-quinolin-8-one (22). Following the procedure described for the preparation of **23**, a solution of cyanohydrin **21** (80 mg, 0.26 mmol) and dry THF (4 mL) was converted to the dianion, and pyrindinone **12** (43 mg, 0.13 mmol) was added. The resulting solution was maintained at −70 °C for 1 h and then allowed to warm to 0 °C. After 1 h the reaction was quenched by adding 3 M HCl/Et_2O (1:1, 20 mL). After 1 h at 23 °C the mixture was basified with solid potassium hydroxide, and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic extracts were concentrated and then diluted with methanol (10 mL). Lithium hydroxide (500 mg) was added, and the resulting suspension was maintained at 23 °C for 14 h. The methanolic solution was diluted with water (20 mL) and extracted with Et_2O (3 × 30 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), and concentrated. The residue was purified by column chromatography (silica HF_{254}, Et_2O) to give 27 mg (39%) of quinolone **22** as a pale yellow oil: ^1H NMR (250 MHz, $CDCl_3$)[39] δ 7.85–7.93 (m, 1 H, ArH), 7.47–7.27 (m, 7 H, PhH and ArH), 7.18 (app t, J = 7.6 Hz, 1 H, ArH), 5.6–5.77 (m, 1 H, =CH), 5.45–5.55 (m, 1 H, =CH), 4.91 and 4.74 (s, 1 H, NCHC=O), 4.49 (m, OCH_2Ph), 4.05–4.35 (m, 1 H, α CH_2N), 3.79 and 3.71 (s, 3 H, CO_2Me), 3.67–3.53 (m, 3 H), 2.85–3.0 (m, 2 H), 2.0–2.1 (m, 2 H), 1.32 and 1.31 (s, *t*-Bu), 1.2–1.4 (m, 2 H) ppm; IR (film) 3326, 1725, 1717, 1706, 1700 cm^{-1}; MS (CI) 517.2681 (517.2691 calcd for $C_{31}H_{37}N_2O_5$, MH − H_2O), 107, 92.

6aα-[2-(Benzyloxy)ethyl]-8aα-[2-(trimethylacetamido)benzyl]-1,2,4,6a,7,8,8a,8bα-octahydro-1-oxacyclopent[*hi*]indolizin-2-one (23). To a solution of the trimethylsilyl cyanohydrin **21** (1.68 g, 5.53 mmol) and dry THF (40 mL) at −70 °C under argon was added *n*-BuLi (5.1 mL of a 2.3 M solution in cyclohexane). The resultant red solution was maintained at −70 °C for 45 min whereupon a solution of the ketone **12** (0.91 g, 2.76 mmol) and dry THF (23 mL) was slowly added. After 4 h, HCl (4.3 mL of a 2.96 M solution in MeOH) was added at −70 °C (equivalent to the total base concentration of the *n*-BuLi solution), and the mixture was allowed to warm to 0 °C. After dilution with brine the aqueous phase was extracted with Et_2O (3 × 100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. The residue was taken up in MeOH (22 mL) and treated with $LiOH·H_2O$ (0.70 g, 16.7 mmol) at 0 °C. The mixture was allowed to warm to 23 °C where it was maintained for 16 h. The aqueous mixture was then diluted with H_2O and brine and extracted with Et_2O (3 × 100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by flash chromatography (HF_{254} silica, 3:1 Et_2O/hexane) yielded 1.06 g (76%) of **23** as a colorless oil: ^1H NMR (500 MHz, $CDCl_3$)[39] δ 11.4 (br s, N*H*), 8.77 (dd, J = 8.5, 0.8 Hz, 1 H, ArH), 8.26 (dd, J = 8.1, 1.4 Hz, 1 H, ArH), 7.58 (dt, J = 7.9, 1.3 Hz, 1 H, ArH), 7.26–7.37 (m, 5 H, ArH), 7.13 (dt, J = 7.7, 1.1 Hz, 1 H, ArH), 5.89 (dt, J = 10.5, 2.1 Hz, C*H*=CHCH$_2$), 5.71 (ddd, J = 10.4, 4.2, 1.7 Hz, CH=C*H*CH$_2$), 4.52 (s, C*H*N bridgehead), 4.51 (q, J = 15.5 Hz, OCH_2Ph), 4.19 (ddd, J = 18.1, 4.1, 2.0 Hz, CH_2N), 3.40–3.71 (m, CH_2OBn and CH_2N), 2.46 (dd, J = 14.7, 6.8 Hz, 1 H), 2.32 (dt, J = 14.6, 6.9 Hz, 1 H), 2.02 (dd, J = 12.9, 6.9 Hz, 1 H), 1.88–1.96 (m, 2 H), 1.75 (dt, J = 14.4, 6.3 Hz, 1 H), 1.34 (s, CO-*t*-Bu) ppm; ^{13}C NMR (125 MHz, $CDCl_3$)[39] δ 199.9, 177.9, 154.9, 142.3, 138.1, 135.6, 132.8, 131.1, 128.4, 128.3, 128.2, 127.6, 127.5, 122.2, 121.7, 121.0, 119.2, 94.1, 73.1, 66.6, 65.0, 45.5, 40.4, 40.3, 38.9, 36.7, 34.5, 27.6 ppm; IR (KBr) 3311, 1768, 1764, 1692 cm^{-1}; MS (CI) 503 (MH), 459, 204, 107; MS (EI) 502.2461 (<1, 502.2467 calcd for $C_{30}H_{34}N_2O_5$, M), 401 (7), 204 (100), 120 (18), 91 (47). Anal. Calcd for $C_{30}H_{34}N_2O_5$: C, 71.69; H, 6.82; N, 5.57. Found: C, 71.58; H, 6.83; N, 5.52.

6aα-[2-(Benzyloxy)ethyl]-8aα-[1-[2-(trimethylacetamido)phenyl]-ethenyl]-1,2,4,6a,7,8,8a,8bα-octahydro-1-oxacyclopent[*hi*]indolizin-2-one (27). To a suspension of methyltriphenylphosphonium bromide (26.9 g, 75.3 mmol) in dry THF (200 mL) at −70 °C was added *n*-BuLi (19.6 mL of a 2.86 M solution in hexanes, 56.1 mmol). The reaction mixture was maintained at −70 °C for 30 min and then allowed to warm to 23 °C where it was maintained for 40 min before recooling to −70 °C. A solution of ketone **23** (1.91 g, 3.80 mmol) and dry THF (50 mL) was then added dropwise, and the resultant mixture was maintained at −70 °C for 1 h. Finally the reaction mixture was allowed to warm to 23 °C where it was maintained for 48 h. Addition of 1 M aqueous HCl (200 mL) was followed by extraction of the separated aqueous phase with Et_2O (3 × 70 mL). The combined organic extracts were washed with brine (200 mL), dried ($MgSO_4$), and concentrated. Purification of the residue by flash chromatography (HF_{254} silica, 10:1 Et_2O/hexane) afforded 1.77 g (93%) of alkene **27** as a colorless oil: ^1H NMR (500 MHz, $CDCl_3$) δ 8.27 (app d, J = 8.2 Hz, 1 H, ArH), 7.90 (br s, N*H*), 7.25–7.39 (m, 6 H, ArH), 7.11 (dd, J = 7.6, 1.4 Hz, 1 H, ArH), 7.02 (dt, J = 7.5, 1.1 Hz, 1 H, ArH), 5.95 (d, J = 0.5 Hz, 1 H, =CH_2), 5.63–5.69 (m, 2 H, C*H*=C*H*), 5.32 (d, J = 0.8 Hz, 1 H, =CH_2), 4.38 (q, J = 11.8 Hz, OCH_2Ph), 4.13 (app d, 1 H, J = 18.3 Hz, CHCH_2N), 3.94 (br s, 1 H), 3.21–3.41 (m, 3 H), 1.90–2.35 (m, 2 H), 1.63–1.78 (m, 3 H), 1.33–1.43 (m, 1 H), 1.26 (s, CO-*t*-Bu) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.6, 156.2, 145.7, 138.1, 135.9, 131.3, 129.6, 129.0, 128.9, 128.4, 127.7, 127.6, 123.5, 122.2, 121.7, 119.4, 91.4, 73.1, 66.6, 45.6, 40.5, 40.0, 36.0, 35.8, 35.1, 27.6 ppm; IR (film) 3425, 1756, 1685, 1519, 1479 cm^{-1}; MS (CI) 501 (MH), 457, 107, 89; MS (EI) 500.2690 (<1, 500.2675 calcd for $C_{31}H_{36}N_2O_4$, M), 456 (40), 321 (100), 91 (75).

4aα-[2-(Benzyloxy)ethyl]-7a-[1-[2-(trimethylacetamido)phenyl]-ethenyl]-2,4a,5,6,7,7aα-hexahydro-1*H*-1-pyridin-7-ol (28). Solid KOH (4 g, 70 mmol) was added at 0 °C to a deoxygenated solution of alkene **27** (1.77 g, 3.55 mmol), H_2O (5 mL), and EtOH (20 mL). The reaction mixture was then heated to 130 °C (bath temperature) under an argon atmosphere for 20 h. After cooling to 23 °C, the reaction mixture was diluted with H_2O (70 mL) and extracted with Et_2O (3 × 50 mL). The combined organic extracts were then extracted with 1 M aqueous HCl (3 × 50 mL). The ice-cold acidic extracts were then basified with KOH, extracted with Et_2O (3 × 50 mL), dried ($MgSO_4$), and concentrated. Purification of the residue by flash chromatography (HF_{254} silica gel, 9:1:0.1 $CHCl_3$, MeOH, NH_4OH) gave 1.41 g (84%) of **28** as a pale yellow viscous oil: ^1H NMR (500 MHz, $CDCl_3$) δ 9.32 (br s, N*H*CO), 8.06 (m, 1 H, ArH), 7.24–7.38 (m, 6 H), 6.99 (m, 2 H), 5.80 (dt, J = 10.2, 3.7 Hz, CH_2CH=CH), 5.57 (m, CH_2CH=C*H*), 5.51 (s, CH_2=C), 5.28 (br s, NH), 4.42 (q, J = 11.8 Hz, OCH_2Ph), 3.47–3.56 (m, 2 H), 3.37 (br s, 1 H), 3.01–3.14 (m, 2 H), 2.18 (m, OH), 1.59–1.66 (m, 4 H), 1.26–1.37 (m, 2 H), 1.25 (s, CO-*t*-Bu) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.1, 151.1, 138.2, 133.2, 129.5, 128.4, 127.9, 127.6, 127.4, 125.1, 123.5, 115.7, 82.0, 73.1, 67.8, 64.1, 41.8, 41.1, 40.7, 39.7, 36.7, 27.6 ppm; IR (film) 3028, 1677, 1580, 1525, 1522, 1498, 1477, 1445 cm^{-1}; MS (CI) 475 (MH), 214, 107, 89; MS (EI) 474.2850 (22, 474.2882 calcd for $C_{30}H_{38}N_2O_3$, M), 415 (26), 383 (23), 214 (95), 91 (87), 57 (100).

4aα-[2-(Benzyloxy)ethyl]-7a-[1-(2-aminophenyl)ethenyl]-2,4a,5,6,7,7aα-hexahydro-1*H*-pyridin-7-ol (29). Solid KOH (50 g, 900 mmol) was added at 0 °C to a deoxygenated solution of the carbamate **27** (614 mg, 1.20 mmol), H_2O (130 mL), and EtOH (80 mL). The resulting mixture was deoxygenated and then heated to 210 °C (sand bath temperature) under an argon atmosphere for 16 h. After cooling to 23 °C, the reaction mixture was diluted with H_2O (100 mL) and extracted with Et_2O (3 × 100 mL). The combined organic extracts were then extracted with 1 M aqueous HCl (2 × 50 mL), and these aqueous acidic extracts were combined, cooled in an ice bath, and made basic by addition of solid KOH. Extraction of the basic mixture was done with Et_2O (3 × 80 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by flash chromatography (HF_{254} silica gel, 5–8% MeOH, 0.3% Et_3N, CH_2Cl_2) gave 296 mg (62%) of the diamino alcohol **29** as a colorless oil: ^1H NMR (500 MHz, $CDCl_3$) δ 7.32–7.37 (m, 2 H, ArH), 7.22–7.30 (m, 3 H, ArH), 7.07 (dt, J = 7.7, 1.5 Hz, 1 H, ArH), 6.92 (dd, J = 7.5, 1.4 Hz, 1 H, ArH), 6.68 (dt, J = 7.4, 1.1 Hz, 1 H, ArH), 6.63 (dd, J = 8.0, 0.8 Hz, 1 H, ArH), 5.82 (ddd, J = 10.2, 4.6, 3.1 Hz, CH=C*H*CH$_2$), 5.64 (d, J = 1.9 Hz, 1 H, =CH_2), 5.61 (br d, J = 10.0 Hz, C*H*=CHCH$_2$), 5.06 (d, J = 1.9 Hz, 1 H, =CH_2), 4.38 (q, J = 11.8 Hz, OCH_2Ph), 3.94 (br

s, bridgehead C*H*), 3.39–3.49 (m, 3 H), 3.28 (br s, 1 H), 3.23 (dd, *J* = 4.6, 1.1 Hz, 1 H), 3.17 (dt, *J* = 16.1, 2.6 Hz, 1 H), 1.99–2.03 (m, 1 H), 1.69–1.84 (m, 2 H), 1.52–1.57 (m, 3 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.2, 144.7, 138.3, 133.8, 130.1, 128.4, 128.2, 127.6, 127.3, 125.0, 117.7, 115.6, 115.4, 82.8, 73.0, 67.8, 64.4, 41.3, 41.1, 41.0, 36.6, 35.0 ppm; IR (film) 3450, 3352, 3027, 2906, 1616, 1494, 1452, 1100 cm^{-1}; MS (CI) 391 (MH); MS (EI) 390.2331 (3.1, 390.2315 calcd for $C_{25}H_{30}N_2O_2$, M), 214 (53), 94 (71), 91 (100).

6aα-[2-(Benzyloxy)ethyl]-9aα-[2-(trimethylacetamido)phenyl]-1,2,4,6a,7,8,9,9bα-octahydro-9*H*-pyrrolo[3,2,1-*ij*]quinolin-9-one (30). To a deoxygenated solution of the amino alcohol **28** (360 mg, 0.76 mmol) and dry benzene (28 mL) was added paraformaldehyde (68 mg, 2.3 mmol) and camphorsulfonic acid (88 mg, 0.38 mmol). The reaction mixture was heated to reflux for 3 h, then cooled to 23 °C, and treated with 1:1 Et_2O/NH_4OH (10 mL). The aqueous phase was separated and extracted with Et_2O (3 × 30 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$), and concentrated. Purification of the residue by flash chromatography (HF_{254} silica, 3:1 Et_2O/hexane) afforded 305 mg (83%) of **30** as a white solid: mp 120–120.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (br s, NH), 7.60 (app d, *J* = 13.1, Hz, 1 H, ArH), 7.52 (d, *J* = 7.8 Hz, 1 H, ArH), 7.36–7.23 (m, 6 H, ArH), 7.11 (app dt, *J* = 7.7, 1.2 Hz, 1 H, ArH), 5.70 (ddd, *J* = 9.9, 4.4, 3.2 Hz, CH_2CH=CH), 5.51 (m, CH_2CH=C*H*), 4.46 (q, *J* = 13.8 Hz, OCH_2Ph), 3.56–3.66 (m, 2 H), 3.45 (s, bridgehead C*H*N), 3.31–3.39 (m, 1 H), 3.14–3.20 (m, 1 H), 3.09–3.13 (m, 1 H), 2.81 (dt, *J* = 16.5, 2.2 Hz, 2 H, =CHCH_2N), 2.55–2.59 (m, 1 H), 2.28–2.35 (m, 1 H), 1.98–2.04 (m, 2 H), 1.85–1.88 (m, 1 H), 1.73–1.78 (m, 1 H), 1.66–1.71 (m, 1 H), 1.32 (s, CO-*t*-Bu) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.0, 177.2, 138.3, 135.8, 134.3, 132.5, 128.4, 128.1, 128.0, 127.7, 127.6, 125.4, 123.9, 73.1, 72.5, 66.8, 62.1, 52.3, 51.9, 39.7, 38.9, 37.0, 36.0, 35.7, 33.0, 27.4 ppm; IR (film) 1711, 1683, 1676 cm^{-1}; MS (CI) 487 (MH), 107; MS (EI) 486.2854 (<1, 486.2882 calcd for $C_{31}H_{38}N_2O_3$, M), 91 (42), 69 (100).

8-Diazo-6aα-[2-(benzyloxy)ethyl]-9aα-[2-(trimethylacetamido)-phenyl]-1,2,4,6a,7,8,9,9bα-octahydro-9*H*-pyrrolo[3,2,1-*ij*]quinolin-9-one (31). The general procedure of Lombardo and Mander[26] was followed. To a solution of ketone **30** (390 mg, 0.80 mmol) and freshly distilled benzene (14 mL) was added 2,4,6-triisopropylphenylsulfonyl azide (298 mg, 0.96 mmol), (*n*-Bu)$_4$NBr (77 mg, 0.24 mmol), and 18-crown-6 (11 mg, 0.040 mmol). To this mixture was added warm 66% aqueous KOH (14 mL). The biphasic mixture was stirred vigorously at 35 °C for 1 h whereupon it was cooled to 23 °C. The reaction mixture was diluted with Et_2O (60 mL) and H_2O (20 mL). The aqueous layer was extracted with Et_2O (30 mL), and the combined organic extracts were washed with H_2O (50 mL) and brine (50 mL), dried ($MgSO_4$), and concentrated. Flash chromatography of the residue (HF_{254} silica, Et_2O) gave 402 mg (98%) of **31** as an orange foam: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.56 (s, 1 H, NH), 7.66 (dd, *J* = 1.4, 8.1 Hz, 1 H, ArH), 7.2–7.32 (m, 7 H, ArH), 7.07 (dt, *J* = 1.5, 7.7 Hz, 1 H, ArH), 5.78 (s, 2 H, vinylic), 4.40 (dd, *J* = 11.8, 31.8 Hz, OCH_2Ph), 3.45–3.52 (m, 2 H), 3.42 (dd, *J* = 2.2, 16.6 Hz, 1 H), 3.15 (app dd, *J* = 7.1, 8.4 Hz, 1 H), 3.13 (s, 1 H), 3.09 (d, *J* = 14.7 Hz, 1 H), 2.91 (d, *J* = 16.6 Hz, 1 H), 2.68 (dd, *J* = 0.83, 13.7 Hz, 1 H), 2.45–2.60 (m, 2 H), 2.37–2.45 (m, 1 H), 1.95 (app ddd, *J* = 6.2, 7.8, 14.2 Hz, 1 H), 1.79 (dt, *J* = 5.4, 14.5 Hz, 1 H), 1.31 (s, CO-*t*-Bu) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.6, 163.4, 138.8, 137.6, 137.5, 132.5, 129.8, 129.0, 128.7, 128.5, 128.3, 128.1, 126.3, 125.3, 74.6, 74.0, 67.0, 65.0, 59.6, 54.8, 53.0, 40.2, 39.9, 39.3, 36.3, 31.6, 28.2 ppm; IR ($CHCl_3$) 2096, 1671, 1502, 1441 cm^{-1}; MS (CI) 485 (MH – N_2), 401, 107, 103, 92, 85.

Methyl (6aα,8aα,8bα)-6a-[2-(Benzyloxy)ethyl]-8a-[2-(trimethylacetamido)phenyl]-1,2,3,6a,7,8,8b-heptahydro-4*H*-cyclopent[*hi*]indolizine-8-carboxylate (32) and (33). The crude α-diazoketone **31** (402 mg, 0.78 mmol) was dissolved in dry Et_2O (40 mL) and placed in a 60-mL quartz photolysis vessel. Dry MeOH (2.2 mL) was added, and the sealed reaction vessel was irradiated (mercury arc lamp, Vycor filter) for 15 min (until TLC analysis indicated consumption of starting material). The reaction mixture was then concentrated, and the residue was purified by flash chromatography, (HF_{254} silica, 3:1 Et_2O/hexane) to give 320 mg (77%) of **32** as a pale yellow oil. Elution with 8% MeOH/92% CH_2Cl_2 provided 75 mg (18%) of **33** also as a pale yellow oil. **Major Diastereomer 32**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.9 (br s, 1 H, N*H*), 8.15 (dd, *J* = 1.0, 8.2 Hz, 1 H, ArH), 7.57 (d, *J* = 7.8 Hz, 1 H, ArH), 7.18–7.35 (m, 6 H, ArH), 7.01 (d, *J* = 7.1 Hz, 1 H, ArH), 5.81 (dd, *J* = 2.2, 10.4 Hz, CC*H*=CH), 5.67 (dd, *J* = 3.6, 10.3 Hz, CH_2CH=CH), 4.36 (d, *J* = 2.2 Hz, OCH_2Ph), 3.91 (dd, *J* = 6.6, 13.3 Hz, C*H*CO_2Me), 3.69 (s, OCH_3), 3.52 (s, C*H*N, bridgehead), 3.37–3.48 (m, 1 H, CH=CHCH_2N and 2 H, CH_2OBn), 3.10–3.22 (m, 2 H, CH_2CH_2N), 3.09 (m, 1 H, CH=CHCH_2N), 2.38–2.46 (m, 1 H, CH_2CH_2N), 2.24 (dd, *J* = 7.2, 14.4 Hz, CH_2CH_2N), 2.14 (dd, *J* = 6.5, 13.0 Hz, 1 H, CH_2CHCO$_2$Me cis to C*H*CO$_2$Me), 1.98 (app dd, *J* = 13.1 Hz, 1 H, CH_2CHCO$_2$Me trans to C*H*CO$_2$Me), 1.83–1.93 (m, 1 H, CH_2CH_2OBn), 1.68–1.79 (m, 1 H, CH_2CH_2OBn), 1.26 (s, CO-*t*-Bu) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.9, 173.8, 138.1, 137.8, 135.9, 131.5, 128.4, 128.3, 127.5, 127.4, 126.5, 125.1, 123.1, 120.7, 76.6, 72.9, 66.9, 59.8, 53.6, 51.9, 48.5, 45.6, 42.1, 40.3, 39.9, 39.2, 33.4, 27.5 ppm; IR ($CHCl_3$) 2955, 1733, 1686, 1586, 1541, 1476, 1445, 1163, 1121 cm^{-1}; MS (CI) 517 (MH), 518, 108, 107, 103, 102, 91, 87; MS (EI) 516.2962 (1.2, 516.2988, calcd for $C_{32}H_{40}N_2O_4$, M), 459 (21), 425 (15), 91 (89), 57 (100).

Minor Diastereomer 33: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (s, NH), 7.73–7.82 (br s, 1 H, ArH), 7.25–7.36 (m, 7 H, ArH), 7.04 (dt, *J* = 1.2, 7.6 Hz, 1 H, ArH), 6.01 (dt, *J* = 4.3, 10.0 Hz, CH=C*H*CH_2N), 5.83 (d, *J* = 10.0 Hz, C*H*=CHCH_2N), 4.44 (s, OCH_2Ph), 3.84 (s, C*H*N, bridgehead), 3.48–3.60 (m, C*H*CO_2Me), 3.45 (s, OCH_3), 3.35–3.45 (m, CH_2O), 3.20 (dd, *J* = 0.85, 4.1 Hz, 1 H), 3.06 (dt, *J* = 6.6, 9.2 Hz, 1 H), 2.94 (dd, *J* = 6.9, 10.5 Hz, 1 H), 2.84 (bt, *J* = 6.8 Hz, 1 H), 2.43 (ddd, *J* = 3.0, 6.2, 12.6 Hz, 1 H), 2.29 (ddd, *J* = 7.4, 9.2, 12.7 Hz, 1 H), 2.22 (dd, *J* = 10.6, 13.2 Hz, 1 H), 2.09 (dd, *J* = 6.9, 13.2 Hz, 1 H), 1.94–2.04 (m, 1 H), 1.83–1.92 (m, 1 H), 1.33 (s, CO-*t*-Bu) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.8, 174.8, 138.3, 136.2, 135.5, 128.3, 127.7, 127.6, 127.5, 127.4, 127.0, 124.5, 79.3, 73.0, 67.8, 61.9, 53.4, 51.8, 51.6, 45.5, 41.9, 41.4, 41.1, 39.6, 37.9, 37.8, 27.4 ppm; IR (film) 3373, 2956, 1726, 1677, 1507, 1444, 750 cm^{-1}; MS (CI) 517 (MH), 518, 107, 87; MS (EI) 516.3005 (9, 516.2988 calcd for $C_{32}H_{40}N_2O_4$), 459 (100), 425 (40), 393 (30), 371 (33), 270 (34).

(6aβ,7aα,11aα,13a*R*)-7a-[2-(Benzyloxy)ethyl]-6a,7,7a,11a,12,13-hexahydro-10*H*-indolizino[1′,8′:2,3,4]cyclpenta[1,2-*c*]quinolin-6(5*H*)-one (34a) and (6aα)-Epimer (34b).** To a solution of the methyl ester **32** (89 mg, 0.17 mmol) in EtOH (11 mL) and H_2O (2 mL) was added powdered KOH (6.9 g, 124 mmol) at 0 °C. The mixture was stirred vigorously at room temperature for 1 h and then at 50 °C for 0.5 h (oil bath temperature). Heating was slowly increased to 80 °C where it was maintained for 4 h. Again heating was slowly increased to 120 °C where it was maintained for 11 h. Finally heating was increased to 150 °C where the reaction mixture was maintained for 3 h. Concentration of the reaction mixture to half its original volume at 150 °C followed by continued heating at this temperature for 6 h led to complete reaction. The cooled reaction mixture was quenched with H_2O (50 mL) and saturated aqueous NH_4Cl (50 mL), followed by extraction with EtOAc (3 × 40 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Radial chromatography of the residue (GF_{254} silica, 5–10% $MeOH/CH_2Cl_2$) yielded 59.7 mg (87%) of pentacycle **34a** as a colorless glass, 5.9 mg (8%) of pentacycle **34b** as a colorless glass, and 4.4 mg (4%) of tetracyclic carboxylic acid **38** as a white crystalline solid: **34a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.91 (s, NH), 7.40 (d, *J* = 7.4 Hz, 1 H, ArH), 7.18–7.38 (m, 5 H, ArH), 7.15 (dt, *J* = 0.9, 7.6 Hz, 1 H, ArH), 7.05 (t, *J* = 7.1 Hz, 1 H, ArH), 6.78 (dd, *J* = 0.8, 7.8 Hz, 1 H, ArH), 5.95 (ddd, *J* = 2.1, 5.5, 9.9 Hz, CH=C*H*CH_2N), 5.76 (dd, *J* = 2.0, 9.8 Hz, C*H*=CHCH_2N), 4.33 (s, OCH_2Ph), 3.58 (br s, C*H*N, bridgehead), 3.30–3.42 (m, 2 H, CH_2CH_2OBn), 3.26 (dd, *J* = 5.4, 16.2 Hz, 1 H, CH=CHCH_2N), 3.08–3.19 (m, C*H*CO_2Me and 1 H, CH=CHCH_2N), 2.89 (dd, *J* = 8.0, 10.6 Hz, 2 H, CH_2CH_2N), 2.28 (dd, *J* = 7.9, 12.7 Hz, 1 H, CH_2CH_2N), 2.04–2.14 (m, 1 H, CH_2CHCO$_2$Me), 1.83–1.95 (m, 1 H, CH_2CHCO$_2$Me and 1 H, CH_2CH_2N), 1.59–1.68 (m, 1 H, CH_2CH_2OBn), 1.47–1.55 (m, 1 H, CH_2CH_2OBn) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1, 138.2, 135.0, 133.9, 128.2, 127.7, 127.6, 127.5, 127.4, 127.3, 126.8, 124.0, 115.5, 80.5, 72.8, 67.4, 57.1, 52.8, 50.2, 46.4, 44.9, 43.6, 41.1, 40.7 ppm; IR ($CHCl_3$) 2969, 2929, 1694, 1593, 1492, 1389, 1114 cm^{-1}; MS (CI), 401 (MH), 266, 107; MS (EI) 400.2130 (2, 400.21406 calcd for $C_{26}H_{28}N_2O_2$, M), 309 (50), 266 (35), 108 (20), 91 (100), 79 (16). **34b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (s, NH), 7.25–7.48 (m, 6 H, ArH), 7.15 (dt, *J* = 1.4, 7.7 Hz, 1 H, ArH), 7.02 (dt, *J* = 1.0, 7.5 Hz, 1 H, ArH), 6.83 (dd, *J* = 0.85, 7.8 Hz, 1 H, ArH), 5.86 (dd, *J* = 2.4, 10.4 Hz, C*H*=CHCH_2N), 5.70 (ddd, *J* = 1.7, 5.3, 10.3 Hz, CH=C*H*CH_2N), 4.45 (s, OCH_2Ph), 3.91 (s, C*H*N, bridgehead), 3.48–3.61 (m, 2 H, CH_2CH_2OBn and 1 H, NCH_2CH=CH), 3.20 (dd, *J* = 5.3, 17.3 Hz, 1 H, NCH_2CH=CH), 3.02 (dd, *J* = 5.6, 13.1 Hz, C*H*CONH), 2.96 (dd, *J* = 8.8, 18.7 Hz, 1 H, CH_2CH_2N), 2.89 (dd, 7.8, 8.9 Hz, 1 H, CH_2CH_2N), 2.12 (ddd, *J* = 1.6, 8.2, 13.4 Hz, 1 H, CH_2CH_2N), 1.98 (dd, *J* = 5.6, 12.6 Hz, 1 H, CH_2CHCONH), 1.74–1.83 (m, 1 H, CH_2CH_2OBn and 1 H, CH_2CH_2N), 1.61–1.72 (m, 1 H, CH_2CH_2OBn and 1 H, CH_2CHCONH) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.6, 138.2, 136.5, 136.4, 132.2, 128.3, 127.6, 127.5, 127.0, 123.6, 122.8, 121.9, 116.0, 73.1, 70.6, 67.1, 55.6, 51.8, 48.0, 46.1, 41.1, 40.0, 35.9, 35.4 ppm; MS (CI) 401 (MH), 309, 107, 91; MS (EI) 400.2151 (7, 400.21506 calcd for $C_{26}H_{28}N_2O_2$, M), 309 (17), 136 (20), 91 (100), 83 (17), 79 (22). **Acid 38**: IR (film) 3426, 3207, 3030, 2966, 1670, 1526, 1478, 753 cm^{-1}; MS (CI) 503 (MH), 401, 107, 103; MS (EI) 502.2867 (27, 502.28313 calcd for $C_{31}H_{38}N_2O_4$, M), 484 (59), 445 (48), 91 (100).

(6aβ,7aα,11aα,13aR*)-7a-(2-Hydroxyethyl)-6a,7,7a,11a,12,13-hexahydro-10H-indolizino[1′,8′:2,3,4]cyclopenta[1,2-c]quinolin-6(5H)-one (35a). A solution of the pentacyclic benzyl ether **34a** (59 mg, 0.148 mmol) and freshly distilled THF (2 mL) was added to a two-necked flask (equipped with a dry ice condenser) containing distilled liquid NH_3 (~8 mL) at −70 °C. To this solution was added very small chunks of Na metal at −70 °C until a dark blue color persisted for 5–10 s. The reaction was then immediately quenched by addition of solid NH_4Cl. The NH_3 was then allowed to evaporate whereupon the residue was partitioned between H_2O (20 mL), and $CHCl_3$ (20 mL). The aqueous layer was separated and extracted with $CHCl_3$ (2 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), and concentrated. Flash chromatography of the residue (230–400 mesh silica, 8–10% $MeOH/CH_2Cl_2$) afforded 46 mg (100%) of **35a** as a white solid: mp 107–110 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.19 (s, NH), 7.44 (d, J = 7.6 Hz, 1 H, ArH), 7.17 (t, J = 7.6 Hz, 1 H, ArH), 7.07 (t, J = 7.5 Hz, 1 H, ArH), 6.73 (d, J = 7.8 Hz, 1 H, ArH), 5.98 (ddd, J = 2.3, 5.3, 9.9 Hz, CH=CHCH$_2$N), 5.79 (dd, J = 1.9, 10.0 Hz, CH=CHCH$_2$N), 3.51–3.63 (m, CHN bridgehead and 2 H, CH$_2$OH), 3.28 (dd, J = 5.3, 16.2 Hz, 1 H, NCH$_2$C=CH), 3.22 (br s, CHCONH), 3.16 (dd, J = 7.2, 16.1 Hz, 1 H, NCH$_2$CH=CH), 2.91 (bt, J = 9 Hz, 2 H, CH$_2$CH$_2$N), 2.29 (dd, J = 8.1, 12.7 Hz, 1 H, CH$_2$CH$_2$N), 2.12 (ddd, J = 4.6, 6.4, 12.7 Hz, 1 H, CH$_2$CH$_2$N), 1.88–1.95 (m, 2 H, CH$_2$CHCONH), 1.47–1.58 (m, 2 H, CH$_2$CH$_2$OH) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5, 135.7, 134.3, 128.4, 128.3, 127.6, 124.8, 116.1, 81.3, 60.7, 57.7, 53.8, 51.0, 47.4, 45.8, 44.4, 44.3, 42.1, 31.6 ppm; IR ($CHCl_3$) 2960, 1670 cm^{-1}; MS (CI) 311 (MH), 85, 83, 81, 79, 71; MS (EI) 310.1677 (21, 310.16811 calcd for $C_{19}H_{22}N_2O_2$, M), 152 (77), 108 (63), 91 (51), 77 (98), 55 (100).

(6aα,7aα,11aα,13aR*)-7a-(2-Hydroxyethyl)-6a,7,7a,11a,12,13-hexahydro-10H-indolizino[1′,8′:2,3,4]cyclopenta[1,2-c]quinolin-6(5H)-one (35b). Following the procedure used for the preparation of pentacycle **35a**, the pentacyclic benzyl ether **34b** (14.2 mg, 0.035 mmol) was debenzylated. Purification of the residue by flash chromatography (230–400 mesh silica, 1:1 $MeOH/CH_2Cl_2$) afforded 9.2 mg (85%) of **35b** as an opaque glass: ^1H NMR (500 MHz, $CDCl_3$) δ 7.42 (s, NH), 7.35 (d, J = 7.4 Hz, 1 H, ArH), 7.16 (dt, J = 1.3, 7.6 Hz, 1 H, ArH), 7.04 (dt, J = 0.9, 7.5 Hz, 1 H, ArH), 6.80 (d, J = 7.8 Hz, 1 H, ArH), 5.93 (dd, J = 2.5, 10.4 Hz, CH=CHCH$_2$N), 5.75 (ddd, J = 1.6, 5.3, 10.3 Hz, CH=CHCH$_2$N), 3.84 (s, CHN bridgehead), 3.70–3.80 (m, CH$_2$CH$_2$OH), 3.56 (bd, J = 17.3 Hz, NCH$_2$CH=CH), 3.24 (dd, 5.4, 17.3 Hz, NCH$_2$=CH), 3.00 (dd, J = 5.6, 13.2 Hz, CHCONH), 2.96 (d, J = 9.5 Hz, CH$_2$CH$_2$N), 2.87–2.93 (m, CH$_2$CH$_2$N), 2.12 (ddd, J = 1.7, 8.1, 13.4 Hz, CH$_2$CH$_2$N), 1.98 (dd, J = 5.5, 12.6 Hz, CH$_2$CHCONH), 1.75–1.83 (m, CH$_2$CH$_2$N), 1.60–1.73 (m, CH$_2$CHCONH and CH$_2$CH$_2$OH) ppm; MS (CI) 311 (MH), 310; MS (EI) 310.1666 (34, 310.16811 calcd for $C_{19}H_{22}N_2O_2$, M), 199 (24), 172 (46), 159 (47), 152 (100), 130 (33), 77 (40).

(6aβ,7aα,11aα,13aR*)-7a-(2-Tosylethyl)-6a,7,7a,11a,12,13-hexahydro-10H-indolizino[1′,8′:2,3,4]cyclopenta[1,2-c]quinolin-6(5H)-one (36a). To a mixture of alcohol **35a** (17.0 mg, 0.055 mmol) and dry $CHCl_3$ (200 mL) was added freshly distilled pyridine (18 mL, 0.22 mmol) and recrystallized *p*-toluenesulfonyl chloride (20.9 mg, 0.11 mmol).[29] After stirring vigorously in a microvial for 16 h, additional pyridine (10 mL) and *p*-toluenesulfonyl chloride (10 mg) were added to drive the reaction to completion. After 4 h the reaction mixture was quenched by adding 1 M aqueous NaOH (5 mL), and the resulting mixture was diluted with $CHCl_3$ (5 mL) and H_2O (5 mL). The aqueous layer was separated and extracted with $CHCl_3$ (2 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), and concentrated. Flash chromatography of the residue (230–400 mesh silica, 5% $MeOH/CH_2Cl_2$) afforded 24.3 mg (96%) of **36a** as a colorless glass: ^1H NMR (500 MHz, $CDCl_3$) δ 9.11 (s, NH), 7.68 (d, J = 8.3 Hz, 2 H, aromatic), 7.33 (d, J = 7.8 Hz, 1 H, ArH), 7.30 (d, J = 8.2 Hz, 2 H, ArH), 7.16 (dt, J = 1.1, 7.6 Hz, 1 H, ArH), 7.03 (dt, J = 0.7, 7.5 Hz, 1 H, ArH), 6.79 (d, J = 7.9 Hz, 1 H, ArH), 5.94 (ddd, J = 1.9, 5.6, 9.8 Hz, CH=CHCH$_2$N), 5.61 (dd, J = 1.9, 9.9 Hz, CH=CHCH$_2$N), 3.86–3.96 (m, CH$_2$OTs), 3.37 (br s, CHN bridgehead), 3.24 (dd, J = 5.6, 16.4 Hz, 1 H), 3.12 (dd, 6.9, 15.8 Hz, CHCONH), 3.03 (bd, J = 16.3 Hz, 1 H), 2.93 (dd, J = 8.7, 10.1 Hz, 1 H), 2.83 (bdd, J = 8.1, 12.4 Hz, 1 H), 2.43 (s, PhCH$_3$), 2.28 (dd, J = 8.4, 12.9 Hz, 1 H), 2.08–2.15 (m, 1 H), 1.85 (dt, J = 7.3, 12.8 Hz, 1 H), 1.79 (dd, J = 10.5, 12.8 Hz, 1 H), 1.57–1.63 (m, 1 H), 1.47–1.56 (m, 1 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1, 144.7, 135.1, 132.9, 132.3, 129.8, 127.5, 127.4, 124.1, 115.7, 80.1, 67.6, 56.9, 52.8, 50.2, 46.7, 44.9, 43.4, 41.0, 39.3, 21.6 ppm; IR ($CHCl_3$) 2959, 2928, 2855, 1674, 1465, 1356 cm^{-1}; MS (CI) 465 (MH), 329, 309, 293, 157, 141, 92; MS (EI) 464.1752 (3, 464.17695 calcd for $C_{26}H_{28}N_2O_4S$, M), 309 (100), 134 (60), 91 (87), 77 (49).

(6aα,7aα,11aα,13aR*)-7a-(2-Tosylethyl)-6a,7,7a,11a,12,13-hexahydro-10H-indolizino[1′,8′:2,3,4]cyclopenta[1,2-c]quinolin-6(5H)-one (36b). Following the procedure used for the preparation of **36a**, alcohol **35b** (5.8 mg, 0.018 mmol) was treated with pyridine, recrystallized *p*-toluenesulfonyl chloride,[29] and dry $CHCl_3$. Purification of the residue by flash chromatography (230–400 mesh silica, 1:20 $MeOH/CH_2Cl_2$) afforded 6.7 mg (81%) of **36b** as a colorless glass: ^1H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, J = 8.3 Hz, 2 H, ArH), 7.64 (s, NH), 7.28–7.34 (m, 3 H, ArH), 7.18 (dt, J = 1.3, 7.7 Hz, 1 H, ArH), 7.05 (dt, J = 1.0, 7.5 Hz, 1 H, ArH), 6.82 (dd, J = 0.62, 7.7 Hz, 1 H, ArH), 5.68–5.78 (m, CH=CHCH$_2$N), 4.08–4.20 (m, CH$_2$OTs), 3.71 (s, CHN bridgehead), 3.55 (t, J = 8.2 Hz, 1 H), 3.45 (d, J = 17.6 Hz, 1 H), 3.19 (dd, J = 4.5, 17.5 Hz, 1 H), 2.87–2.93 (m, 2 H), 2.84 (dd, J = 5.6, 13.1 Hz, 1 H), 2.42 (s, PhCH$_3$), 2.05–2.12 (m, 1 H), 1.86 (dd, J = 5.6, 12.7 Hz), 1.60–1.83 (m, 3 H) ppm; MS (CI) 465 (MH), 293, 173, 157, 93; MS (EI) 464.1770 (38, 464.17695 calcd for $C_{26}H_{28}N_2O_4S$, M), 309 (100), 265 (22), 199 (20), 134 (45).

(6aβ,7aα,11aα,13aR*)-7a-[2-[(o-Nitrophenyl)seleno]ethyl]-6a,7,7a,11a,12,13-hexahydro-10H-indolizino[1′,8′:2,3,4]cyclopenta[1,2-c]quinolin-6(5H)-one (37a). To a deoxygenated solution of freshly sublimed (*o*-nitrophenyl)selenocyanate (98 mg, 0.43 mmol) and dry EtOH (1 mL) at 0 °C was added $NaBH_4$ (16.2 mg, 0.43 mmol).[30] After the mixture turned dark red (~10 min), a deoxygenated solution of the tosylate **36a** (20 mg, 0.043 mmol) and dry EtOH (2 mL) was added. The resulting mixture was maintained at 23 °C for 14 h, whereupon additional (*o*-nitrophenyl)selenocyanate (50 mg, 0.21 mmol) and $NaBH_4$ (8 mg, 0.21 mmol) were added. After 5 h the mixture was partioned between H_2O (20 mL) and $CHCl_3$ (20 mL). The aqueous layer was separated and extracted with $CHCl_3$ (2 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Flash chromatography of the residue (230–400 mesh silica, 3–5% $MeOH/CH_2Cl_2$) gave 12.3 mg (58%) of **37a** as a bright yellow glass: ^1H NMR (500 MHz, $CDCl_3$) δ 8.61 (s, NH), 8.24 (dd, J = 1.0, 8.4 Hz, 1 H, ArH), 7.38–7.48 (m, 2 H, ArH), 7.27–7.33 (m, 2 H, ArH), 7.17 (t, J = 7.3 Hz, 1 H, ArH), 7.06 (t, J = 7.6 Hz, 1 H, ArH), 6.76 (d, J = 7.7 Hz, 1 H, ArH), 6.08 (ddd, J = 1.8, 5.5, 9.8 Hz, CH=CHCH$_2$N), 5.82 (d, J = 9.7 Hz, CH=CHCH$_2$N), 3.5 (br s, CHN bridgehead), 3.32 (dd, J = 5.0, 16.4 Hz, 1 H), 3.19 (dd, J = 6.9, 15.7 Hz, 2 H), 2.98 (t, J = 9.2 Hz, 1 H), 2.92 (br s, 1 H), 2.74 (app dd, J = 8.4 Hz, 2 H), 2.35 (dd, J = 8.3, 12.9 Hz, 1 H), 2.11–2.18 (m, 1 H), 1.88–1.99 (m, 2 H), 1.57–1.70 (m, 2 H) ppm; MS (CI) 496 (MH), 494, 492, 466, 94 71; MS (EI) 495.1049 (21, 495.10609 calcd for $C_{25}H_{25}N_3O_3Se$, M), 478 (60), 373 (33), 309 (100), 264 (41).

(6aα,7aα,11aα,13aR*)-7a-[2-[(o-Nitrophenyl)seleno]ethyl]-6a,7,7a,11a,12,13-hexahydro-10H-indolizino[1′,8′:2,3,4]cyclopenta[1,2-c]quinolin-6(5H)-one (37b). Following the procedure used for the preparation of selenide **37a**, tosylate **36b** (6.0 mg, 0.013 mmol) was transformed into the selenide derivative. Purification of the residue by flash chromatography (230–400 mesh silica, 1:30 $MeOH/CH_2Cl_2$) gave 6.6 mg (~100%) of **37b** as a bright yellow glass. This material was suitable for use in the next step: ^1H NMR (500 MHz, $CDCl_3$) δ 8.27 (d, J = 8 Hz, 1 H, ArH), 7.51 (s, NH), 5.89 (ddd, CH=CHCH$_2$), 5.97 (dd, C$_H$=CHCH$_2$), 3.81 (br s, CHN).

(±)-Meloscine (1). To a solution of the selenide **37a** (11 mg, 0.022 mmol) and dry CH_2Cl_2 (2 mL) at −70 °C was added a solution of ~80% *m*-chloroperoxybenzoic acid (5.8 mg, 0.026 mmol) and CH_2Cl_2 (0.10 mL). The resulting mixture was maintained at −70 °C for 1.5 h whereupon Me_2S (81 μL, 1.1 mmol) and freshly distilled Et_3N (80 μL, 0.57 mmol) were added. The resultant solution was allowed to warm to 23 °C where it was maintained for 4.5 h. Saturated aqueous $NaHCO_3$ solution (10 mL) was added, and the aqueous layer was extracted with $CHCl_3$ (3 × 15 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Flash chromatography of the residue (230–400 mesh silica, 2–5% $MeOH/CH_2Cl_2$) afforded 5.2 mg (81%) of (±)-meloscine (**1**) as a white solid. An analytically pure sample was obtained by recrystallization from Et_2O: mp 183–185 °C. Spectral (500 MHz ^1H NMR, ^{13}C NMR) properties of this material were indistinguishable from those reported,[7,9] and synthetic (±)-meloscine (**1**) was also indistinguishable by TLC comparison (in three solvent systems) with an authentic sample of meloscine provided by Professor J. Lévy.

(±)-16-Epimeloscine (2). Following the procedure used for the preparation of (±)-meloscine (**1**), selenide **37b** (6.4 mg, 0.013 mmol) was oxidized and allowed to warm to 23 °C. Flash chromatography of the residue (230–400 mesh silica, 2–5% $MeOH/CH_2Cl_2$) afforded 2.6 mg (69%) of (±)-epimeloscine (**2**) as an opaque glass. Spectral (500-MHz ^1H NMR, ^{13}C NMR) properties of this material were indistinguishable from those reported.[7a]

6aα-[2-(Benzyloxy)ethyl]-8aα-[1-(2-aminophenyl)ethenyl]-1,2,4,6a,7,8,8a,8bα-octahydro-1-oxacyclopent[hi]indolizine (40). To a deoxygenated solution of the diamino alcohol **29** (150 mg, 0.38 mmol)

and dry toluene (8 mL) was added paraformaldehyde (14 mg, 0.46 mmol) and anhydrous Na_2SO_4 (120 mg, 0.85 mmol). The reaction mixture was stirred at 23 °C for 24 h and then filtered through a bed of Celite. The filtrate was concentrated to dryness, and the residue was purified by flash chromatography (230–400 mesh silica, 2% MeOH/0.2% Et_3N/CH_2Cl_2) to give 155 mg (100%) of **40** as a colorless oil: ^1H NMR (500 MHz, $CDCl_3$) δ 7.33–7.37 (m, 2 H, ArH), 7.27–7.30 (m, 3 H, ArH), 7.06 (dt, J = 7.7, 1.4 Hz, 1 H, ArH), 6.97 (dd, J = 7.5, 1.5 Hz, 1 H, ArH), 6.67 (dt, J = 7.4, 0.9 Hz, 1 H, ArH), 6.63 (d, J = 8.0 Hz, 1 H, ArH), 5.73–5.77 (d, J = 2.1 Hz, 1 H, =CH_2), 5.75 (m, 1 H, CH=CHCH$_2$), 5.64 (ddd, J = 10.3, 4.6, 2.3 Hz, CH=CHCH$_2$), 5.15 (d, J = 2.1 Hz, 1 H, =CH_2), 4.70 (s, 1 H, OCH_2N), 4.45–4.47 (m, 1 H, OCH_2N), 4.34 (q, J = 11.9 Hz, OCH_2Ph), 3.87 (br s, 1 H, bridgehead CH), 3.69 (s, 1 H), 3.42 (dt, J = 17.5, 2.2 Hz, 1 H), 3.33–3.39 (m, 3 H), 3.12 (dd, J = 17.6, 4.6 Hz, 1 H), 1.99–2.05 (m, 2 H), 1.86 (dt, J = 13.7, 3.9 Hz, 1 H), 1.60–1.63 (m, 2 H), 1.45–1.51 (m, 1 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.1, 144.5, 138.4, 132.8, 130.1, 128.3, 127.6, 127.5, 126.6, 121.7, 117.5, 116.2, 115.2, 96.9, 86.8, 72.9, 69.8, 67.3, 42.8, 40.8, 38.9, 38.3, 34.9 ppm; IR (film) 3025, 2927, 2903, 1616, 1494, 1452 cm^{-1}.

(6aβ,13bα,13aα)-13a-[2-(Benzyloxy)ethyl]-5,6,12,13,13a,13b-hexahydro-3*H*-cyclopent[*ij*]indolo[2,3-*a*]quinolizine (42) and Methyl (6aβ,13bα,13aα)-13a-[2-(Benzyloxy)ethyl]-5,6,11,13,13a,13b-hexahydro-3*H*-cyclopent[*ij*]indolo[2,3-*a*]quinolizine-12-carboxylate (43). To a deoxygenated solution of the oxazoline **40** (104 mg, 0.26 mmol) and dry benzene (14 mL) was added anhydrous Na_2SO_4 (73 mg, 0.52 mmol) and camphorsulfonic acid (180 mg, 0.78 mmol). This mixture was heated at reflux for 2.5 h, cooled to 23 °C, and then treated with 4 M aqueous NaOH (5 mL) and $CHCl_3$ (10 mL). The aqueous layer was separated and extracted with $CHCl_3$ (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried (K_2CO_3), and concentrated to yield 100 mg of a pale yellow semisolid. This crude sample of imine **41** was suitable for use in the next step: ^1H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, J = 7.5 Hz, 1 H, ArH), 7.12–7.53 (m, 8 H, ArH), 5.67 (ddd, J = 14.0, 9.9, 4.5 Hz, C-14 H), 5.61 (dt, J = 9.9, 1.8 Hz, C-15 H), 4.15 (q, J = 22.4 Hz, OCH_2Ph), 3.51 (ddd, J = 15.9, 4.5, 1.4 Hz, C-3 H), 3.24–3.31 (m, 2 H), 3.14–3.18 (m, 1 H), 3.09 (d, J = 16.0 Hz, 1 H), 2.96–3.02 (m, 1 H), 2.86–2.93 (m, 1 H), 2.79–2.84 (m, 1 H), 2.73 (s, C-21 H), 2.64–2.79 (m, 1 H), 2.27 (dt, J = 11.8, 6.4 Hz, 1 H), 1.72–1.79 (m, 1 H), 1.69 (dd, J = 12.0, 4.8 Hz, 1 H), 1.22–1.31 (m, 1 H), 1.16–1.22 (m, 1 H) ppm; ^{13}C NMR (500 MHz, $CDCl_3$) δ 189.7, 154.3, 147.3, 138.4, 134.6, 128.2, 127.7, 127.5, 125.3, 124.5, 121.2, 120.1, 73.2, 72.4, 66.5, 60.9, 53.3, 51.4, 39.5, 35.6, 34.4, 30.7, 24.6 ppm; IR (film) 2933, 2885, 1574, 1495 cm^{-1}; MS (EI) 384.2222 (100, 384.2201 calcd for $C_{26}H_{28}N_2O$, M).

A portion of this sample of crude imine **41** (48 mg, 0.12 mmol) and dry THF (2.0 mL) was added to a solution of LDA (0.80 mL of a 2.0 M solution in cyclohexane) and dry THF (3.0 mL) at −70 °C. After maintaining the reaction at −70 °C for 1.5 h, methyl chloroformate (117 mg, 1.24 mmol) was added dropwise, and the resulting mixture was maintained at −70 °C for 2 h. The reaction was then quenched with 1 N NaOH/MeOH (5 mL) and allowed to warm to 23 °C, where it was diluted with H_2O (10 mL) and extracted with Et_2O (3 × 20 mL). The organic phase was extracted with 1 M aqueous HCl (3 × 50 mL), and the aqueous acidic extracts were then combined and made basic by addition of solid KOH. This aqueous mixture was then extracted with Et_2O (3 × 50 mL), and the combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4), and concentrated. Purification of the residue by flash chromatography (230–400 mesh silica, 5–10% EtOAc/$CHCl_3$) afforded 18.4 mg (36%) of the C-acylated pentacycle **42** as a colorless oil. In addition, 18.1 mg (33%) of the N-acylated product **43** was isolated also as a pale yellow oil. **42**: ^1H NMR (500 MHz, $CDCl_3$), δ 8.97 (br s, indole NH), 7.15–7.30 (m, 6 H, ArH), 7.14 (t, J = 7.6 Hz, 1 H, ArH), 6.85 (t, J = 7.6 Hz, 1 H, ArH), 6.82 (d, J = 7.7 Hz, 1 H, ArH), 5.75–5.82 (m, C-15 H and C-14 H), 4.31 (br s, OCH_2Ph), 3.71 (s, OCH_3), 3.47 (dd, J = 15.2, 2.8 Hz, C-3 H), 3.34–3.43 (m, C-18 H), 3.26–3.33 (m, C-18 H), 3.19 (d, J = 15.9 Hz, C-3 H), 3.03 (app dd, J = 7.1, 7.1 Hz, C-5 H), 2.74 (s, C-21 H), 2.65–2.72 (m, C-5 H), 2.50 (s, 2 H, C-17 H), 2.02–2.19 (m, C-6 H), 1.79 (dd, J = 11.5, 4.2 Hz, C-6 H), 1.32–1.42 (m, 2 H, C-19 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.7, 166.6, 143.1, 138.3, 137.8, 133.4, 128.3, 127.7, 127.5, 127.4, 125.1, 121.4, 120.7, 109.4, 92.1, 72.9, 69.7, 66.4, 55.1, 51.0, 50.9, 50.5, 44.5, 40.4, 33.9, 29.3 ppm; IR (film) 3372, 2932, 2861, 1675, 1609, 1465, 1437, 1294, 1253, 1160 cm^{-1}; MS (CI) 443 (MH), 107; MS (EI) 442.2222 (28, 442.2256 calcd for $C_{28}H_{30}N_2O_3$, M), 241 (38), 229 (37), 168 (29), 135 (34), 91 (100). **43**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.80 (bd, J = 7.0 Hz, 1 H), 7.13–7.33 (m, 7 H, ArH), 6.99 (dt, J = 7.5, 1.0 Hz, 1 H, ArH), 5.97 (bd, J = 6.9 Hz, 1 H), 5.71–5.82 (m, 2 H, CH=CHCH$_2$), 4.32 (d, J = 2.0 Hz, OCH_2Ph), 3.93 (s, CO_2CH_3), 3.48 (dd, J = 16.0, 4.5 Hz, 1 H), 3.31–3.41 (m, 2 H), 3.10 (d, J = 15.8 Hz, 1 H), 3.00 (dd, J = 8.6, 6.6 Hz, 1 H), 2.66 (d, J = 1.5 Hz, 1 H), 2.54 (dd, J = 15.4, 3.1 Hz, 1 H), 2.47–2.52 (m, 1 H), 1.93–2.07 (m, 2 H), 1.74 (dd, J = 12.0, 4.9 Hz, 1 H), 1.31–1.49 (m, 2 H) ppm; MS (CI) 443 (MH), 107, 91; MS (EI) 442.2245 (4, 442.2256 calcd for $C_{28}H_{30}N_2O_3$, M), 227 (28), 91 (100).

Methyl (6aβ,13bα,13aα)-13a-[2-(Benzyloxy)ethyl]-5,6,11,13,13a,13b-hexahydro-3*H*-cyclopent[*ij*]indolo[2,3-*a*]quinolizine-12-carboxylate (44). To a solution of the pentacycle **42** (16.0 mg, 0.036 mmol) and freshly distilled EtSH (2 mL) at 0 °C was added dry $BF_3 \cdot OEt_2$ (102 mg, 0.72 mmol).[34] The resulting mixture was heated at reflux for 17 h and then, after cooling to 23 °C, was quenched with H_2O (5 mL) and saturated aqueous $NaHCO_3$ solution (5 mL). The aqueous mixture was extracted with $CHCl_3$ (3 × 15 mL), and the combined organic extracts were dried (K_2CO_3) and concentrated. Purification of the residue by flash chromatography (230–400 mesh silica, 2–5% MeOH/CH_2Cl_2) gave 10.7 mg (84%) of the alcohol **44** as a white solid: ^1H NMR (500 MHz, $CDCl_3$) δ 8.97 (br s, indole NH), 7.23 (d, J = 7.4 Hz, 1 H, ArH), 7.15 (dt, J = 7.7, 1.1 Hz, 1 H, ArH), 6.88 (dt, J = 7.5, 0.8 Hz, 1 H, ArH), 6.82 (d, J = 7.7 Hz, 1 H, ArH), 5.78–5.83 (m, C-14 H), 5.72–5.77 (m, C-15 H), 3.77 (s, OCH_3), 3.50–3.53 (m, CH_2OH), 3.47 (ddd, J = 16.0, 4.7, 1.1 Hz, C-3 H), 3.20 (bd, J = 16.0 Hz, C-3 H), 3.04 (app dd, J = 7.3, 7.3 Hz, C-5 H), 2.76 (s, C-21 H), 2.71 (ddd, J = 11.1, 8.4, 4.7 Hz, C-5 H), 2.52 (d, J = 15.1 Hz, C-17 H), 2.49 (dd, J = 15.2, 1.3 Hz, C-17 H), 2.06 (app ddd, J = 11.4, 11.4, 6.4 Hz, C-6 H), 1.80 (ddd, J = 11.7, 7.0, 0.8 Hz, C-6 H), 1.31 (app ddd, J = 13.9, 8.7, 6.4 Hz, C-19 H), 1.20 (app ddd, J = 14.0, 8.4, 6.1 Hz, C-19 H), 1.03–1.12 (m, CH_2OH) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.8, 166.5, 143.1, 137.7, 133.3, 127.8, 125.4, 121.4, 120.7, 109.4, 92.1, 69.5, 58.8, 55.1, 51.1, 50.8, 50.5, 44.6, 40.4, 37.3, 29.5 ppm; IR ($CHCl_3$) 3388, 2988, 1674, 1610, 1439, 1296, 1253, 1229 cm^{-1}; MS (CI) 353 (MH), 169, 124, 103, 99; MS (EI) 352.1796 (57, 352.1787 calcd for $C_{21}H_{24}N_2O_3$, M), 168 (47), 151 (100), 137 (40), 123 (45).

(±)-Deoxoapodine (4). To a solution of the pentacyclic alcohol **44** (2.9 mg, 0.0082 mmol) and dry THF (0.5 mL) at −70 °C was added a solution of $Hg(OCOCF_3)_2$ (4.2 mg, 0.01 mmol) and dry THF (0.5 mL).[35] The resulting mixture was allowed to warm to 23 °C where it was maintained for 2 h. The reaction mixture was then treated with a mixture of 1 M aqueous NaOH (1 mL) and $NaBH_4$ (~5 mg) and vigorously stirred at 23 °C for 2.5 h. The biphasic mixture was then diluted with H_2O (5 mL) and saturated aqueous $NaHCO_3$ solution (10 mL), and the aqueous layer was extracted with $CHCl_3$ (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by flash chromatography (230–400 mesh silica, 1–5% MeOH/CH_2Cl_2) yielded 1.5 mg (52%) of (±)-deoxoapodine (**4**) as a clear colorless glass and 0.9 mg of recovered **44**. **4**: ^1H NMR (500 MHz, $CDCl_3$) δ 8.90 (br s, indole NH), 7.24 (d, J = 7.3 Hz, 1 H, ArH), 7.15 (dt, J = 7.7, 1.1 Hz, 1 H, ArH), 6.89 (dt, J = 7.6, 0.9 Hz, 1 H, ArH), 6.81 (d, J = 7.7 Hz, 1 H, ArH), 3.78 (s, OCH_3), 3.72–3.81 (m, C-15 H), 3.65–3.73 (m, 2 H, C-18 H), 2.92–2.98 (m, C-3 H and C-5 H), 2.83 (s, C-21 H), 2.75 (d, J = 14.5 Hz, C-17 H), 2.65–2.77 (m, C-3 H and C-5 H), 2.30 (dd, J = 14.6, 1.7 Hz, C-17 H), 2.03 (app ddd, J = 11.3, 11.3, 6.3 Hz, C-6 H), 1.93–2.00 (m, 2 H, C-14 H), 1.76 (dd, J = 11.5, 4.5 Hz, C-6 H), 1.45 (ddd, J = 12.8, 10.0, 7.4 Hz, C-19 H), 1.29 (app ddd, J = 12.8, 8.3, 4.6 Hz, C-19 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.8, 167.3, 143.1, 137.9, 127.7, 121.3, 120.7, 109.3, 93.9, 80.0, 68.8, 65.0, 55.1, 51.5, 46.6, 46.0, 45.2, 34.9, 27.6, 26.9 ppm.

(6aβ,11aβ,13bα,13aα)-13a-[2-(Benzyloxy)ethyl]-5,6,11,11a,12,13,13a,13b-octahydro-3*H*-cyclopent[*ij*]indolo[2,3-*a*]quinolizine (45). A solution of the imine **41** (0.20 mmol) and dry THF (15 mL) was cooled to 0 °C, and excess $LiAlH_4$ (30 mg) was added. The reaction mixture was maintained at 0 °C for 2 h, and then was quenched by adding H_2O, 15% aqueous NaOH, and H_2O. The resulting mixture was filtered thru a bed of Celite, dried ($MgSO_4$), and concentrated. Flash chromatography of the residue (230–400 mesh silica, 2–5% MeOH/CH_2Cl_2) gave 52 mg (67%) of **45** as a pale yellow glass: ^1H NMR (500 MHz, $CDCl_3$) δ 7.33–7.38 (m, 2 H, ArH), 7.27–7.30 (m, 3 H, ArH), 7.07 (d, J = 7.3 Hz, 1 H, ArH), 7.04 (dt, J = 1.2, 7.6 Hz, 1 H, ArH), 6.73 (dt, J = 0.9, 7.4 Hz, 1 H, ArH), 6.66 (d, J = 7.7 Hz, 1 H, ArH), 5.68 (ddd, J = 1.6, 4.8, 10.0 Hz, CH=CHCH$_2$), 5.60 (bdd, J = 0.8, 9.9 Hz, CH=CHCH$_2$), 4.40 (dd, J = 12.0, 33.0 Hz, OCH_2Ph), 3.49–3.57 (m, 2 H), 3.38–3.48 (m, 2 H), 3.29 (br s, 1 H), 2.78 (d, J = 16.1 Hz, 1 H), 2.66 (br s, 1 H), 2.28–2.40 (m, 2 H), 1.65–1.78 (m, 2 H), 1.53–1.64 (m, 2 H), 1.23–1.52 (m, 4 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.2, 138.5, 134.5, 128.3, 127.6, 127.5, 127.4, 122.8, 122.3, 119.2, 110.3, 72.8, 66.8, 66.4, 53.3, 53.2, 52.9, 39.2, 38.1, 34.7, 30.2, 27.0 ppm; IR (film) 3355, 2927, 2863, 2790, 1607, 1481, 1463, 1453, 1095 cm^{-1}; MS (CI) 387 (MH), 107, 92, 70; MS (EI) 386.2359 (1, 386,23580 calcd for $C_{26}H_{30}N_2O$, M), 144 (36), 91 (100).

(6aβ,11aβ,13bα,13aα)-13a-(2-Hydroxyethyl)-5,6,11,11a,12,13,13a,13b-octahydro-3*H*-cyclopent[*ij*]indolo[2,3-*a*]quinolizine (46). Following

the procedure used for the debenzylation of the pentacyclic amide **34a**, dihydroindole **45** (11.0 mg, 0.029 mmol) was similarly debenzylated with Na/NH_3. Purification of the crude product by flash chromatography (230–400 mesh silica, 2–8% $MeOH/CH_2Cl_2$) afforded 8.6 mg (100%) of alcohol **46** as a colorless glass: ^1H NMR (500 MHz, $CDCl_3$) δ 7.11 (dd, J = 0.5, 7.4 Hz, 1 H, ArH), 7.04 (dt, J = 1.1, 7.6 Hz, 1 H, ArH), 6.75 (dt, J = 0.8, 7.4 Hz, 1 H, ArH), 6.66 (d, J = 7.7 Hz, 1 H, ArH), 5.70 (ddd, J = 1.6, 4.9, 9.9 Hz, CH=C*H*CH_2), 5.59 (dd, J = 0.8, 10.0 Hz, C*H*=$CHCH_2$), 3.61–3.72 (m, 2 H), 3.53 (dd, J = 5.8, 10.9 Hz, 1 H), 3.46 (dd, J = 4.1, 16.2 Hz, 1 H), 3.25–3.33 (m, 1 H), 2.80 (d, J = 16.1 Hz, 1 H), 2.69 (s, 1 H), 2.30–2.40 (m, 2 H), 1.55–1.78 (m, 4 H), 1.35–1.48 (m, 2 H), 1.20–1.32 (m, 2 H) ppm; MS (CI) 297 (MH); MS (EI) 296.1905 (7, 296.18885 calcd for $C_{19}H_{24}N_2O$, M), 151 (98), 144 (68), 138 (48), 137 (100), 130 (40).

(6aβ,11aβ,13bα,13aα)-11-Acetyl-13a-(2-hydroxyethyl)-2,3,5,6,11,11a,12,13,13a,13b-decahydro-1*H*-cyclopent[*ij*]indolo[2,3-*a*]quinolizine (47). A solution of the alcohol **46** (7.0 mg, 0.024 mmol) and EtOH (1 mL) containing catalytic Pd/C (7 mg) and ammonium formate (15 mg, 0.24 mmol) was heated at reflux for 1 h. The reaction mixture was then cooled to 23 °C, filtered through a bed of Celite, washed with $CHCl_3$, and concentrated. Flash chromatography of the residue (230–400 mesh silica, 2–8% $MeOH/CH_2Cl_2$) yielded 6.9 mg (98%) of the dihydro product as a pale yellow solid: ^1H NMR (500 MHz, $CDCl_3$) δ 7.08 (d, J = 7.4 Hz, 1 H, ArH), 7.00 (dt, J = 1.1, 7.6 Hz, 1 H, ArH), 6.73 (dt, J = 0.8, 7.4 Hz, 1 H, ArH), 6.63 (d, J = 7.7 Hz, 1 H, ArH), 3.61 (td, J = 5.5, 10.4 Hz, 1 H), 3.45–3.52 (m, 2 H), 3.11 (bdd, J = 7.0, 10.3 Hz, 1 H), 3.04 (bd, J = 10.8 Hz, 1 H), 2.20–2.32 (m, 3 H), 2.04 (dt, J = 3.1, 13.8 Hz, 1 H), 1.98 (app dt, J = 2.5, 11.7 Hz, 1 H), 1.60–1.83 (m, 4 H), 1.45–1.52 (m, 3 H), 1.13–1.33 (m, 4 H), 1.00–1.16 (m, 1 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.4, 135.2, 127.3, 122.7, 119.2, 110.5, 70.7, 65.3, 58.6, 53.7, 53.4, 52.8, 40.5, 38.5, 35.4, 29.7, 28.2, 24.2, 21.7 ppm; IR (KBr) 3312, 3189, 2940, 2911, 2813, 1608, 1463, 1043, 743 cm^{-1}; MS (CI) 299 (MH); MS (EI) 298.2056 (3, 298.20450 calcd for $C_{19}H_{20}N_2O$, M), 141 (10), 140 (100).

This intermediate (6.9, mg, 0.023 mmol) was acetylated as described by Ban[15] to provide, after purification by flash chromatography (230–400 mesh silica, 2%–8% $MeOH/CH_2Cl_2$), 7.0 mg (89%) of **47** as a colorless solid: ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4, 140.6, 138.0, 127.6, 124.3, 122.3, 118.3, 70.3, 67.9, 53.6, 52.8, 52.4, 40.3, 39.5, 35.2, 35.0, 25.8, 24.1, 23.2, 21.5 ppm; MS (CI) 341 (MH); MS (EI) 340.2148 (9, 340.21506 calcd for $C_{21}H_{28}N_2O_2$, M), 312 (9), 168 (6), 140 (100). The ^1H NMR spectra of this intermediate agreed with an authentic spectrum provided by Professor Y. Ban.

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Supplementary Material Available: Experimental preparations and spectroscopic data (^1H NMR and MS) for **35b**, **36b**, and **37b** (2 pages). Ordering information is given on any current masthead page.

Synthetic Studies on Basmane Diterpenes. Enantiospecific Total Synthesis of (+)-7,8-Epoxy-2-basmen-6-one by Claisen Ring Expansion

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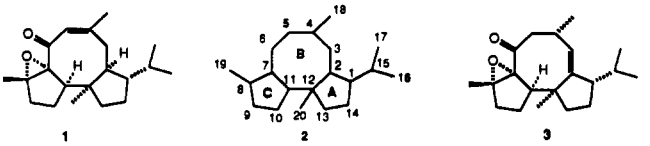
Abstract: The first synthesis of an epoxybasmenone is described. The enantiospecific pathway begins by transforming optically pure aldehyde **10** into bicyclic lactone **39**. Methylenation of **39** by means of the Tebbe reaction allows for operation of a Claisen rearrangement that proceeds almost completely by way of chair transition state **44** to give the cyclooctadienone **42**. Regiospecific cyclopentannulation with installation of four additional stereogenic centers rested upon successful introduction of a functionalized four-carbon chain as in **48**, facially controlled hydrogenation of the conjugated double bond, cyclization, and hydroxyl-directed epoxidation. Finally, Swern oxidation led to the target molecule **3**, whose three-dimensional structural features were confirmed by X-ray crystallography.

Introductory Remarks

The discovery of (+)-**1** in the sun-cured leaves of Greek tobacco (Serres) by Wahlberg et al.[1] has been important in identifying a new class of carbotricyclic diterpenes and in confirming that intramolecular proton-induced cyclization of cembranoids need not give hydrophenanthrenes exclusively.[2] The studies described herein not only were formulated to develop concise routes to basmanes, the generic name assigned to this class (see **2** for atomic numbering),[1] but were seen to have the potential for broad application toward other biologically significant targets. In this paper, we detail an enantiospecific route to (+)-7,8-epoxy-2-basmen-6-one (**3**), the first member of this group to yield to total synthesis.[3]



1 2 3

A third inducement to undertake this work centered about the unusual structural features of the basmenones. The 1*S* configuration is a characteristic of all known tobacco cembranoids.[4]

(1) Wahlberg, I.; Eklund, A.-M.; Nishida, T.; Enzell, C. R.; Berg, J.-E. *Tetrahedron Lett.* **1983**, *24*, 843.
(2) Dauben, W. G.; Hubbell, J. P.; Oberhausli, P.; Thiessen, W. E. *J. Org. Chem.* **1979**, *44*, 669.
(3) Preliminary communication: Kang, H.-J.; Paquette, L. A. *J. Am. Chem. Soc.* **1990**, *112*, 3252.
(4) (a) Colledge, A.; Reid, W. W.; Russell, R. *Chem. Ind. (London)* **1975**, 570. (b) Enzell, C. R.; Wahlberg, I. *Recent Adv. Tobacco Sci.* **1980**, *6*, 64.

0002-7863/91/1513-2610$02.50/0