MS (70 eV), m/e (relative intensity) 570 (M^+, 62), 70 (100); ^1H NMR ($CDCl_3$, Me_4Si) δ 0.96 (m, 6 H), 1.00–2.60 (m, 9 H), 1.45 (s, 9 H), 2.75–4.00 (m, 4 H), 3.80 (s, 3 H), 4.00–4.70 (m, 3 H), 5.00–5.50 (m, 2 H), 5.90 (d, J = 8.5 Hz, 1 H), 6.50–7.05 (m, 4 H), 8.35 (d, J = 11 Hz, 1 H); high-resolution MS, calcd for $C_{30}H_{42}N_4O_7$ m/e 570.3054, found m/e 570.3052.

Zizyphine A (3). A solution of 60 mg (0.105 mmol) of **27a** and 0.1 mL of *m*-dimethoxybenzene in 5 mL of trifluoroacetic acid was stirred for 0.5 h at room temperature and then evaporated in vacuo. The solution of the residue in CH_2Cl_2 was washed with 1 N $KHCO_3$, dried, filtered, and evaporated. Recrystallization of the residue from ethyl acetate/petroleum ether afforded 50 mg (100%) of cyclo[*N*-[3-[[3-[2-(*Z*)-aminovinyl]-4-methoxyphenyl]oxy]-*N*-isoleucyl-(2*S*,3*S*)-prolyl]-(*S*)-prolyl]. This product was added to a solution of 25 mg of 4-(dimethylamino)pyridine and 100 mg (0.3 mmol) of the pentafluorophenyl ester of *N*-(dimethylamino)-L-isoleucine in 3 mL of absolute dioxane. The reaction mixture was kept at 80 °C for 7 h and then evaporated, and the residue was chromatographed on silica gel with CH_2Cl_2/*i*-PrOH (92.5:7.5) to yield zizyphine A (**3**): 35 mg (54%); $[\alpha]^{20}_D$ −430° (*c* 0.093, $CHCl_3$) (lit.[18a] $[\alpha]^{24}_D$ −464° (*c* 1, $CHCl_3$); lit.[18c] $[\alpha]^{20}_D$ −411° (*c* 0.086, $CHCl_3$)). The CD of the synthetic product was identical with the CD of the natural product (Ciba-Geigy): CD Δ_{emax} (λ_{max},nm) −32.7 (258), −15.7 (318); ^1H NMR ($CDCl_3$, Me_4Si) δ 0.9 (m, 12 H), 1.19 (m, 3 H), 1.6 (m, 2 H), 1.8 (m, 3 H), 1.97 (m, 2 H), 2.25 (s, 6 H), 2.42 (m, 4 H), 3.33 (m, 1 H), 3.67 (m, 1 H), 3.8 (s, 3 H), 4.32 (m, 3 H), 4.55 (m, 2 H), 5.26 (m, 1 H), 5.96 (d, 1 H, J = 9.0 Hz), 6.89 (m, 4 H), 8.34 (d, 1 H, J = 11.7 Hz); MS (20 eV) m/e (relative intensity) 611 (M^+, 2), 114 (100); high-resolution MS, calcd for $C_{33}H_{49}N_5O_6$ m/e 611.3683, found m/e 611.3677.

The synthetic product and the natural compound were identical by HPLC [ethanol/H_2O (7:3), LiChroprep Si 60 (15–25 μm) treated with $C_{18}H_{37}SiCl_3$].

Acknowledgment. We thank the Fonds der Chemischen Industrie, the BASF AG, and the Deutsche Forschungsgemeinschaft for their generous support of this research, Dr. W. Rozdzinski for recording numerous mass spectra, and Degussa AG for the gift of amino acids and noble-metal catalysts.

Registry No. **3**, 51059-42-8; **10**, 86272-64-2; **11**, 86272-65-3; **11**-Na, 86288-21-3; (±)-*trans*-**12**, 79816-21-0; (±)-*cis*-**12**, 79816-22-1; (±)-*trans*-**13**, 86272-66-4; (±)-*trans*-**14**, 79816-23-2; **15a**, 86272-67-5; **15b**, 86272-68-6; **16a**, 86272-69-7; **17a**, 86272-70-0; **18a**, 86272-71-1; **19a**, 86272-72-2; **20a**, 86272-73-3; **21a**, 86272-74-4; **21c**, 86333-64-4; **22a**, 86333-89-3; **22c**, 86272-75-5; **23a**, 86272-76-6; **23c**, 86333-65-5; **24a**, 79816-29-8; **24a** *p*-nitrophenyl selenide, 86272-77-7; **24c**, 79854-70-9; **24c** *p*-nitrophenyl selenide, 86333-66-6; **25a**, 79816-31-2; **26a**, 79816-32-3; **27a**, 86288-22-4; *N*,*N*-dimethyl-L-isoleucine pentafluorophenyl ester, 86272-78-8; 5-(benzyloxy)-2-methoxybenzoic acid, 84923-68-2; *tert*-butyl 5-(benzyloxy)-2-methoxybenzoate, 86272-63-1; methyl 3-bromo-1-pyrrolin-2-carboxylate, 72978-15-5; proline benzylic ester hydrochloride, 16652-71-4; benzyl malonate magnesium salt, 79816-35-6; pentafluorophenol, 771-61-9.

A New Approach for the Total Synthesis of Pentacyclic *Aspidosperma* Alkaloids. Total Synthesis of *dl*-16-Methoxytabersonine[1]

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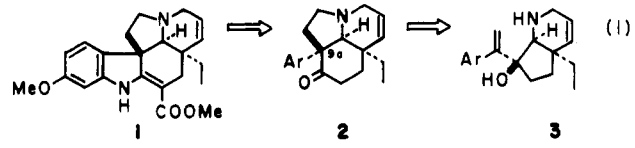
The pentacyclic *Aspidosperma* alkaloid *dl*-16-methoxytabersonine (**1**) has been synthesized by an efficient convergent sequence. The key step in the synthesis is the "ring-enlarging pyrrolidine annulation" reaction of 7-styrylhydropyridin-7-ols **17** and **18** to give 9a-arylhydrolilolidine **19** and 16-methoxy-1,2,6,7-tetradehydroaspidospermidine (**20**), respectively.

Continuing intense interest in the synthesis of pentacyclic *Aspidosperma* alkaloids[2,3] stems in part from the occurrence of the highly functionalized indoline vindoline in the clinically used antineoplastic agents vincaleukoblastine and leurocristine.[4]

We recently outlined[5] a fundamentally new approach to the pentacyclic *Aspidosperma* skeleton in which tricyclic hydrolilolidines, which incorporate the synthetically demanding quaternary aryl function, are key intermediates (eq 1).[6] The central feature of this scheme is the "ring-



1 2 3 (1)

enlarging pyrrolidine annulation" reaction[7] of the formaldehyde iminium ion derived from pyridinol **3**. If the

(1) Part 10 in the series "Synthesis Applications of Aza-Cope Rearrangements". For part 9 see: Overman, L. E.; Jacobsen, E. J. *Tetrahedron Lett.* **1982**, *23*, 2741–2744.

(2) For a recent review, see: Cordell, G. A. "The Alkaloids"; Manske, R. H. F., Rodrigo, R., Eds.; Academic Press: New York, 1979; Vol. XVII, Chapter 3.

(3) Recent examples include: (a) Kuehne, M. E.; Okuniewicz, F. J.; Kirkemo, C. L.; Bohnert, J. C. *J. Org. Chem.* **1982**, *47*, 1335–1343. (b) Gallagher, T.; Magnus, P.; Huffman, J. C. *J. Am. Chem. Soc.* **1982**, *104*, 1140–1141. Pearson, A. J.; Rees, D. C. *Ibid.* **1982**, *104*, 1118–1119. Ban, Y.; Yoshida, K.; Goto, J.; Oishi, T. *Ibid.* **1981**, *103*, 6990–6992. Speckamp, W. N.; Veenstra, S. J. *Ibid.* **1981**, *103*, 4645–4646. Kuehne, M. E.; Bohnert, J. C. *J. Org. Chem.* **1981**, *46*, 3443–3447.

(4) Cf.: Neuss, N. In "Indole and Biogenetically Related Alkaloids"; Phillipson, J. D., Zenk, M. H., Ed; Academic Press: New York, 1980; Chapter 17.

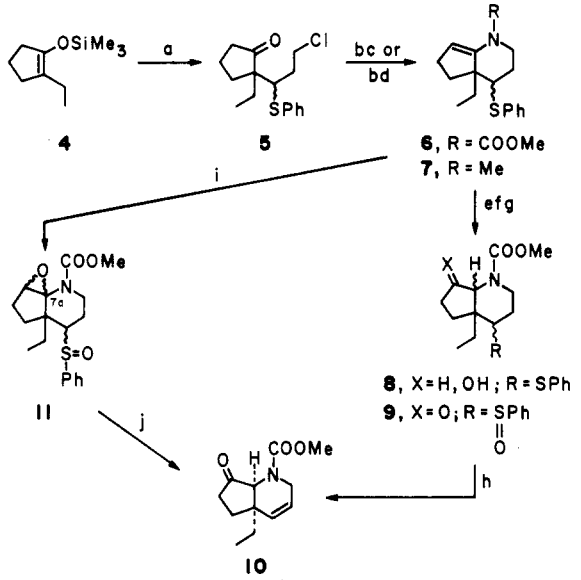
(5) Overman, L. E.; Sworin, M.; Bass, L. S.; Clardy, J. *Tetrahedron* **1981**, *37*, 4041–4045.

(6) Hydrolilolidines with 9a-hydrogen substituents were intermediates in the original Stork and Ban syntheses of the *Aspidosperma* skeleton; see: Nakanishi, K.; Goto, T.; Ito, S.; Natori, S.; Nozoe, S. "Natural Products Chemistry"; Academic Press: New York, 1975; Vol. 2, pp 400–405.

(7) (a) Cf.: Overman, L. E.; Mendelson, L. T. *J. Am. Chem. Soc.* **1981**, *103*, 5579–5581. (b) We wish to stress that, although we have chosen for simplicity to discuss this reaction[1,5,7a] as a [3,3]-sigmatropic rearrangement followed by a Mannich cyclization, alternate mechanisms with similar topological constraints are not excluded by data currently available. For example, with electron-rich styrenyl substrates, cyclization to a benzylic cation followed by pinacolic rearrangement is a conceivable alternative.

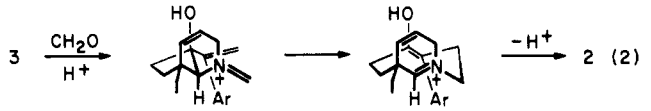
0022-3263/83/1948-2685$01.50/0

Scheme I[a]



[a] (a) $PhSCHClCH_2CH_2Cl$, $ZnBr_2$, CH_2Cl_2, 25 °C; (b) NaI, 2-butanone, reflux; (c) NH_3, $CHCl_3$, 25 °C; MeOCOCl, diethylaniline, $PhCH_3$, 25 °C; (d) $MeNH_2$, $MgSO_4$, $PhCH_3$, 25 °C; (e) BH_3, THF, 25 °C; NaOH, HOOH; (f) Ac_2O, NaOAc; PhOCOCl, $KHCO_3$, $CHCl_3$, reflux; NaOMe, MeOH, reflux; (g) $NaIO_4$, MeOH, 25 °C; Me_2SO, $(ClCO)_2$; (h) Et_3N, $PhCH_3$, reflux; (i) *m*-chloroperbenzoic acid (2.10 equiv), $CHCl_3$, −40–0 °C; (j) *o*-dichlorobenzene, $CaCO_3$, 165 °C.

vinyl and amine groups of **3** have a trans relationship, this sequence should stereospecifically afford 9a-arylhydrolilolidine **2**, since reaction via only a single "chairlike" conformation is possible (eq 2).[5,7] We now report the short



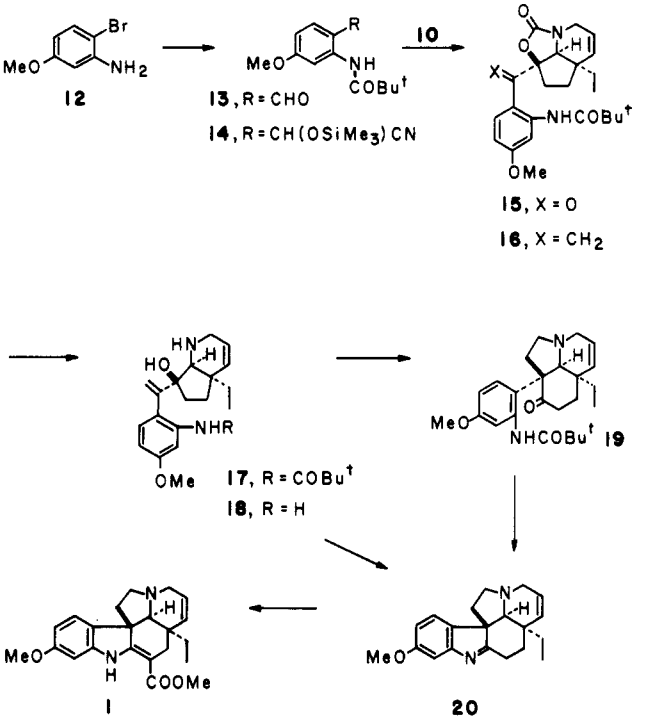
and completely stereocontrolled total synthesis of *dl*-16-methoxytabersonine (**1**)[8-10] by this approach.

Results and Discussion

We anticipated that the 1-arylvinyl group of **3** could be attached stereoselectively to a ketone precursor from the convex α face, and thus the *cis*-hexahydro-7*H*-1-pyrindin-7-one **10** became our initial target. Two routes to this ketone, which start with the thermodynamic silyl enol ether **4** of 2-ethylcyclopentanone,[5] are outlined in Scheme I.

Zinc bromide catalyzed reaction[11] of **4** with 1,3-dichloro-1-(phenylthio)propane provided the chloro ketone **5** in 84% yield. Conversion to the iodide was followed by treatment with excess NH_3 and reaction of the resulting

Scheme II



bicyclic imine with methyl chloroformate.[12] The bicyclic enecarbamate **6** was isolated in 68% yield after chromatographic purification. We initially attempted to convert **6** to ketone **9** by a modification of the hydroboration–oxidation sequence we had utilized[5] in an earlier model study. However, the carbamate group of **6** was reduced[13] with borane–tetrahydrofuran (THF) at a rate comparable with alkene hydroboration.[14,15] We were able to prepare alcohol **8** (in 64% yield from **5**) in an indirect fashion via the *N*-methyl enamine **7**, and this sequence is detailed in Scheme I. Sulfide alcohol **8** was a mixture of at least three stereoisomers. Oxidation of **8** with periodate and then the Swern reagent[16] gave keto sulfoxide **9**, which yielded a *single* bicyclic ketone, **10** (38% from **8**), when heated in refluxing toluene containing triethylamine. The formation of only one bicyclic ketone derives from a strong thermodynamic preference[17] for a cis ring fusion in this series.

A much more direct synthesis of **10** followed from the realization that epoxide sulfoxide **11** incorporated appropriate functionality for direct transformation to ketone **10**.[18] Although enecarbamates[19] (and enamides)[18] are quite reactive toward peracids, the issue in the direct preparation

(8) Isolation of **1**: (a) Pyuskyulev, B.; Kompis, I.; Ognyanov, I.; Spiteller, G. *Collect. Czech. Chem. Commun.* **1967**, *32*, 1289–1294. (b) KanFan, C.; Das, B. C.; Husson, H.-P.; Potier, P. *Bull. Soc. Chim. Fr.* **1974**, 2839–2841. Baassou, S.; Mehri, H.; Plat, M. *Phytochemistry* **1978**, *17*, 1449–1450.

(9) Although this alkaloid has not been previously prepared by total synthesis, racemic tabersonine has been prepared several times[3a,10b] since the pioneering efforts of Ziegler.[10a]

(10) (a) Ziegler, F. E.; Bennett, G. B. *J. Am. Chem. Soc.* **1973**, *95*, 7458–7464. (b) Levy, J.; Laronze, J.-Y.; Laronze, J.; MeMen, J. *Tetrahedron Lett.* **1978**, 1579–1580. Takano, S.; Hatakeyama, S.; Ogasawara, K. *J. Am. Chem. Soc.* **1979**, *101*, 6414–6420. Imanishi, T.; Shin, H.; Yagi, N.; Hanaoka, M. *Tetrahedron Lett.* **1980**, *21*, 3285.

(11) Truce, W. E.; Hollister, K. R.; Lindy, L. B.; Parr, J. E. *J. Org. Chem.* **1968**, *33*, 43–47. Paterson, I.; Fleming, I. *Tetrahedron Lett.* **1979**, 2179–2182.

(12) Oppolzer, W.; Bieber, L.; Francotte, E. *Tetrahedron Lett.* **1979**, *981*–984.

(13) Cf.: Brown, H. C.; Heim, P. *J. Org. Chem.* **1973**, *38*, 912–916.

(14) Previous work in our laboratory had shown that benzyl *trans*-1,3-butadiene-1-carbamate could be cleanly hydroborated (with BH_3–THF) at the terminal double bond without competing reduction of the carbamate group. See also: Imanishi, T.; Shin, H.; Yagi, N.; Hanaoka, M. *Tetrahedron Lett.* **1980**, *21*, 3285–3288. Undoubtably, hydroboration of the hindered double bond of **6** is much slower, and, thus, competitive carbamate reduction results.

(15) For examples of enamine hydroboration, see: Borowitz, I. J.; Williams, G. J. *J. Org. Chem.* **1967**, *32*, 4157–4160.

(16) Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480–2482.

(17) Cf.: Cicero, B. L.; Weisbuch, F.; Dana, G. *J. Org. Chem.* **1982**, *46*, 914–919 and references cited therein.

(18) The synthesis of α-(acylamino) ketones by this general strategy has precedent. See: Masamune, T.; Takasugi, M.; Murai, A.; Kobayashi, K. *J. Am. Chem. Soc.* **1967**, *89*, 4521–4523.

(19) (a) Back, T. G.; Edwards, O. E.; MacAlpine, G. A. *Tetrahedron Lett.* **1977**, 2651–2654. (b) Mahajan, J. R.; Ferreira, G. A. L.; Araujo, H. C.; Nunes, B. J. *Synthesis* **1976**, 112–113.

of 11 from 6 was whether this oxidation would be more rapid than conversion of a sulfoxide to a sulfone. The desired selectivity was obtained when 6 was oxidized (−40–0 °C) in $CHCl_3$ with 2.10 equiv of *m*-chloroperbenzoic acid. The product of this treatment was a complex mixture of stereoisomers, which showed no vinylic hydrogen absorption in the ^1H NMR spectrum and a molecular ion at *m/e* 350 in the chemical-ionization mass spectrum. Careful control of experimental conditions (temperature, peracid purity, and thus reaction medium acidity) was critical, or else a significant amount of an aldehyde impurity was produced.[20] When crude 11 was heated at 165 °C in the presence of $CaCO_3$, ketone 10 was obtained in 44% overall yield from 6. This convenient sequence provides access to key intermediate 10 on a multigram scale in *six steps* (two isolated and purified intermediates) and 25% overall yield from 4.

The preparation of the elements of the A and B rings began with arene 12 (see Scheme II), which is readily available[21] from inexpensive 4-methoxy-2-nitroaniline. By use of a procedure similar to one reported,[22] 12 was treated sequentially in THF with 2 equiv of MeLi (25 °C), 1 equiv of pivaloyl chloride (−78 °C), and 2 equiv of *tert*-butyllithium (−78 °C). Addition of excess *N,N*-dimethylformamide at −10 °C was followed by acidic hydrolysis at room temperature to give the crystalline aldehyde 13 in 63% yield after purification.

The critical coupling of the aromatic and hydropyrindinone pieces was accomplished in excellent yield by reaction of the dianion of silyl cyanohydrin[23] 14 (1.1 equiv) with 10 at −78–0 °C. Quenching at 0 °C with HCl and ether afforded a mixture of tetracyclic carbamate 15 and the corresponding tricyclic hydroxy and silyloxy carbamates. Brief treatment of this mixture with methanolic LiOH was followed by chromatographic purification on silica gel to give crystalline 15: mp 164–165 °C; 80% yield. To achieve good yields in this addition reaction, it was essential that crystalline samples of silyl cyanohydrin 14 were employed. The excellent yield thus obtained in uniting the highly functionalized components 10 and 14 is particularly notable in light of the difficulties often encountered in the addition of basic nucleophiles to cyclopentanones.[24] Methylenation of 15 was cleanly accomplished by reaction with excess methylenetriphenylphosphorane at room temperature to give crystalline styrene 16 in 97% yield. The rearrangement substrates 17 and 18 were readily obtained from 16. Thus, treatment of 16 with 40% methanolic KOH at reflux gave aniline 18 in 96% yield, while similar treatment of 16 with 20% methanolic KOH gave a 7:3 mixture of 17 and 18, from which pure 17 could be isolated in 50% yield after chromatography.

Rearrangement of 17 was cleanly effected[5,7a] by treatment with excess paraformaldehyde and a catalytic amount of camphorsulfonic acid in refluxing benzene for 2 h to give hydrolilolidine 19 in 96% yield after purification. Conversion to the desired pentacyclic ring system was accomplished by treatment of 19 with 25% NaOMe in refluxing methanol to afford 16-methoxy-1,2,6,7-tetradehydroaspidospermidine (20) in 67% yield. This material was indistinguishable (250-MHz ^1H NMR, solution IR, and TLC analysis) from an authentic sample prepared from natural 16-methoxytabersonine by treatment with hot 5 N HCl.[25]

More concise entry to the *Aspidosperma* skeleton was accomplished by reaction of aniline 18 with paraformaldehyde (1.1 equiv) and anhydrous Na_2SO_4 (2 equiv) in toluene at room temperature to form the corresponding oxazolidine. This intermediate was not isolated but was rearranged in situ in refluxing toluene for 6 h (without added acid)[26] to give 20 directly in yields which ranged from 70% to 90%. The ability to accomplish the ring-enlarging pyrrolidine annulation reaction in the presence of an *unprotected* ortho amino group was most pleasing and provides a further example of the "mildness" of this reaction.

Carbon acylation of 20 was successfully accomplished by sequential treatment with lithium diisopropylamide and methyl chloroformate to afford 16-methoxytabersonine (1) as the major product. Contaminating amounts of N-acylated material were removed by chromatography on silica gel to give pure racemic 16-methoxytabersonine in 31% yield from 18. The 250-MHz ^1H NMR and 63-MHz ^{13}C NMR spectra, solution infrared spectra, mass spectra, and TLC mobility (in three solvent systems) of synthetic 1 were indistinguishable from those of an authentic sample of the natural product kindly furnished by Dr. A. J. Hannart of Omnichem.

The total synthesis of *dl*-16-methoxytabersonine was thus accomplished in 11 steps and 6% overall yield from enol silyl ether 4.

Conclusion

A conceptually new, completely stereocontrolled, and efficient approach for the total synthesis of pentacyclic *Aspidosperma* alkaloids has been developed. The synthetic sequence provides an excellent illustration of the utility of "directed" cationic aza–Cope rearrangements for assembling complex polycyclic systems. Of particular note is the conversion of 18 to 20 which proceeded in high yield to elaborate three rings of the pentacyclic target in a single step with complete stereocontrol. The preparation of the oxidized aromatic A ring from the convenient aniline precursor 12 and the mode of B ring construction are also noteworthy features of this new entry to the *Aspidosperma* skeleton.

Experimental Section[27]

2-Ethyl-2-[3-chloro-1-(phenylthio)propyl]cyclopentanone (5). A solution of 1-chloro-3-(phenylthio)propane[28] (30.2 g, 162 mmol) and CCl_4 (150 mL) was treated with *N*-chlorosuccinimide,

(20) The aldehyde presumably results from acid-catalyzed addition of RCO_3H to 11 (at C-7a), followed by oxidative fragmentation. Related oxidative fragmentations have been reported.[19]

(21) Samant, B. V. *Chem. Ber.* **1942**, *75*, 1008–1015. Frank, H. R.; Fanta, P. E.; Tarbell, D. S. *J. Am. Chem. Soc.* **1948**, *70*, 2314–2320.

(22) Wender, P. A.; White, A. W. *Tetrahedron Lett.* **1981**, *22*, 1475–1478.

(23) Hünig, S.; Wehner, G. *Chem. Ber.* **1979**, *112*, 2062–2067. Deuchert, K.; Hertenstein, U.; Hünig, S.; Wehner, G. *Ibid.* **1979**, *112*, 2045–2061.

(24) Enolization in the addition of basic nucleophiles and cyclopentanones is, of course, well-known. For a recent example of leading references, see: Dauben, W. G.; Walker, D. M. *J. Org. Chem.* **1981**, *46*, 1103–1108.

(25) See: Henriques, A.; Kan, C.; Chiaroni, A.; Riche, C.; Husson, H.-P.; Kan, S.-K.; Lounasmaa, M. *J. Org. Chem.* **1982**, *47*, 803–811.

(26) It is likely that the rearrangement is catalyzed by traces of formic acid in the paraformaldehyde.

(27) General experimental details have been described. See: Overman, L. E.; Freerks, R. L.; Petty, C. B.; Clizbe, L. A.; Ono, R. K.; Taylor, G. F.; Jessup, P. J. *J. Am. Chem. Soc.* **1981**, *103*, 2816–2822. Electron-impact high-resolution mass spectra were determined at 70 eV with a Kratos MS-50 at the Midwest Center for Mass Spectroscopy, University of Nebraska. All NMR spectra were determined with a Bruker WM 250 spectrometer (^1H at 250 MHz, ^{13}C at 63 MHz) and are reported in parts per million from tetramethylsilane. All reactions were run under an argon atmosphere, and concentrations were done with a rotary evaporator under reduced pressure.

(28) Truce, W. E.; Lindy, B. L. *J. Org. Chem.* **1961**, *26*, 1463–1467.

and the resulting mixture was stirred at room temperature for 8 h. Filtration and concentration gave 35.8 g of crude 1,3-dichloro-1-(phenylthio)propane, which was used immediately in the next step.

A stirred solution of 2-ethyl-1-(trimethylsiloxy)cyclopentene (**4**, 27.6 g, 150 mmol),[5] 1,3-dichloro-1-(phenylthio)propane (35.8 g), and dry CH_2Cl_2 (250 mL) was cooled to 0 °C, and a catalytic amount (~0.8 g, ~3 mmol) of anhydrous $ZnBr_2$ was added. The reaction mixture was allowed to warm to room temperature, stirred for 1 h, and concentrated, and the residue was purified by chromatography on silica gel (7:1 hexane–ethyl acetate) to give 37.4 g (84%) of **5** as a light yellow oil, which was a 3:2 mixture of stereoisomers: ^{1}H NMR ($CDCl_3$) δ 7.2–7.5 (m, PhH), 3.66–3.82 (m, CH_2Cl), 3.60 (dd, J = 2.4, 11.6 Hz, CHSPh of major isomer), 3.48 (dd, J = 2.5, 11.5 Hz, CHSPh of minor isomer), 1.5–2.4 (m, 10 H), 0.90 (t, J = 7.5 Hz, CH_3 of major isomer), 0.75 (t, J = 7.5 Hz, CH_3 of minor isomer); IR (film) 1730, 741, 687, 640 cm^{-1}; MS(CI), m/e 299 (MH^+), 298, 297 (MH^+), 296, 189, 187, 185.

Vacuum distillation resulted in partial cyclization to a bicyclic enol ether.

4a-Ethyl-1-(methoxycarbonyl)-4-(phenylthio)-2,3,4,4a,5,6-hexahydro-1*H*-1-pyrindine (6). A rapidly stirring solution of **5** (9.14 g, 30.8 mmol), NaI (6.9 g, 46 mmol), and dry 2-butanone (250 mL) was evacuated and refilled with Ar (5×). The resulting solution was heated at reflux for 22 h. After cooling to room temperature, 300 mL of 5% aqueous $Na_2S_2O_3$ was added. The resulting mixture was extracted with $CHCl_3$ (3×, 100 mL), and the organic extracts were washed with $Na_2S_2O_3$ (5% aqueous) and brine, dried ($MgSO_4$), and concentrated to give the corresponding iodide [^{1}H NMR ($CDCl_3$) δ 3.1–3.5 (m, CH_2I and CHSPh)], which was used immediately in the next reaction.

The crude iodide and $CHCl_3$ (80 mL) were added under an Ar atmosphere to NH_3 (50 mL) at −78 °C in a Fischer–Porter pressure bottle. The resulting solution was allowed to stand at room temperature for 2 days behind a safety shield. **CAUTION: the bottle pressure is 114 psig.** Excess NH_3 was carefully vented, and the reaction mixture was concentrated. The resulting residue was diluted with $CHCl_3$ (100 mL), the precipitated ammonium salts were removed by filtration, and the filtrate was concentrated to give the bicyclic imine [MS(CI), m/e 260 (MH^+), 170, 150], which was immediately acylated.[12]

A solution of the crude bicyclic imine, *N*,*N*-diethylaniline (4.6 g, 31 mmol), methyl chloroformate (4.4 g, 46 mmol), and dry toluene (100 mL) was stirred at room temperature for 14 h and filtered. The filtrate was washed with 10% HCl (3 × 10 mL), saturated aqueous $NaHCO_3$ (10 mL), and brine and dried ($MgSO_4$). Concentration and purification of the residue by flash chromatography (silica gel, 10:1 hexane–ethyl acetate) gave 6.61 g (68%) of **6** as a yellow oil, which was a ~1:1 mixture of stereoisomers. An analytical sample was prepared by bulb-to-bulb distillation: ^{1}H NMR ($CDCl_3$) δ 7.2–7.5 (m, PhH), 5.4–5.6 (m, =CH), 4.20 (ddd, J = 2.1, 5.2, 12.8 Hz, NCH of one diastereomer), 3.4–4.0 (m, 1 H of one diastereomer, 2 H of one diastereomer), 3.72 and 3.71 (s, OMe), 3.10 (dd, J = 4.1, 10.0 Hz, CHSPh of one diastereomer), 2.76 (apparent dt, J = 3.7, 12.9 Hz, NCH of one diastereomer), 1.5–2.4 (m, 8 H), 0.91 and 0.88 (t, J = 7.4 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$) 155.98 (s), 155.81 (s), 140.2 (s), 139.4 (s), 136.2, 135.7, 132.6, 131.6, 129.29, 129.20, 127.3 (d), 126.9 (d), 119.6 (d), 118.1 (d), 60.7 (d), 52.98, 52.87, 52.42, 45.9 (q), 41.4 (t), 35.2, 30.4, 30.1, 29.2, 29.0, 28.6, 26.0, 25.2, 8.9 (q), 8.5 ppm (q); IR (film) 3065, 1715, 1588, 735, 695 cm^{-1}; MS(CI), m/e 318 (MH^+), 208; MS(EI), m/e 317.145 (317.145 calcd for $C_{18}H_{23}NO_2S$). Anal. Calcd for $C_{18}H_{23}NO_2S$: C, 68.10; H, 7.30; N, 4.41; S, 10.10. Found: C, 67.94; H, 7.32; N, 4.50; S, 9.80.

4aα-Ethyl-1-(methoxycarbonyl)-1,2,4a,5,6,7aα-hexahydro-7*H*-1-pyrindin-7-one (10). A solution of **6** (1.44 g, 4.54 mmol) and $CHCl_3$ (20 mL) was cooled to −40 °C, and *m*-chloroperbenzoic acid (34.1 mL of a 0.28 M solution in $CHCl_3$, 9.5 mmol) was added dropwise. After 1.5 h, the reaction was allowed to warm to 0 °C and 1 N NaOH (20 mL) was added. The organic layer was separated, washed with saturated $NaHCO_3$ solution (10 mL), dried ($MgSO_4$), and concentrated to give crude epoxide sulfoxide **11** [^{1}H NMR ($CDCl_3$) δ 7.4–7.8 (m, OSPhH), no vinylic hydrogens; MS(CI), m/e 350 (MH^+, 100), 224 (50)]. This sample changed upon storage at room temperature and was therefore immediately dissolved in dry *o*-dichlorobenzene (25 mL) and heated at 165 °C in the presence of $CaCO_3$ (0.56 g, 5.6 mmol) for 12 h. After cooling to room temperature, $CHCl_3$ (50 mL) was added, and the resulting solution was washed with 1 N NaOH (2 × 10 mL) and brine. Concentration, followed by purification of the residue by flash chromatography (silica gel, 4:1 hexane–ethyl acetate) and bulb-to-bulb distillation (oven temperature 150–185 °C (1 mm)) gave 442 mg (44%) of pure **10** as a light yellow liquid: ^{1}H NMR ($CDCl_3$, two carbamate conformational isomers, absorptions for the major isomer are in italics) δ 5.45–5.85 (m, CH=CH), *4.62* and 4.41 (s, CHN), 3.84 (ABq, J = 18.8 Hz, $\Delta\nu$ = 161 Hz) and *3.81* (ABq, J = 18.4 Hz, $\Delta\nu$ = 123 Hz, A part dd, J = 3.7, 2.6 Hz, B part t, J = 2.2 Hz, CH_2N), *3.77* and 3.74 (s, MeO), 0.93 (t, J = 7.7 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$, two carbamate conformational isomers) 213.5 (s), 213.4 (s), 157.1 (s), 156.4 (s), 130.6 (d), 130.1 (d), 126.2 (d), 125.9 (d), 65.9 (d), 65.4 (d), 52.8 (q), 52.7 (q), 43.3 (s), 43.1 (s), 40.8 (t), 32.6 (t), 32.2 (t), 32.1 (t), 30.0 (t), 29.9 (t), 8.6 ppm (q); IR ($CHCl_3$) 1760, 1694 cm^{-1}; MS(CI), m/e 224 (MH^+), 223; MS(EI), m/e 223.121 (223.121 calcd for $C_{12}H_{17}NO_3$).

4-Methoxy-2-(trimethylacetamido)benzaldehyde (13). MeLi (41 mL of a 1.45 M solution in ether, 59 mmol) was added dropwise at room temperature to a solution of 2-bromo-4-methoxyaniline[21] (6.00 g, 29.7 mmol) and dry THF (200 mL). The resulting solution was stirred for 2 h and cooled to −78 °C, and freshly distilled trimethylacetyl chloride (3.7 mL, 29.7 mmol) was added dropwise. After 15 min at −78 °C, *t*-BuLi (25.8 mL of a 2.3 M solution in pentane, 59 mmol) was added over ~15 min. The resulting solution was stirred at −78 °C for 1 h, warmed to −10 °C, and dry *N*,*N*-dimethylformamide (12 mL, 0.15 mol) added. After 30 min at −10 °C, the reaction mixture was allowed to warm to room temperature and after 2 h was quenched by pouring into a mixture of excess 1 M HCl and ether. The aqueous portion was extracted with ether, and the combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated. Flash chromatography (silica gel, 9:1 hexane–ethyl acetate) gave 4.95 g (71%) of chromatographically pure **13** as a yellow oil. Crystallization from cold pentane gave 4.42 g (63%) of pure **13** (mp 43–44 °C) as white fluffy crystals. An analytical sample was prepared by recrystallization from cold pentane: mp 43–44 °C; ^{1}H NMR ($CDCl_3$) δ 11.69 (br s, NH), 9.76 (s, CHO), 8.46 (d, J = 2.4 Hz, H-3), 7.54 (d, J = 8.6 Hz, H-6), 6.69 (dd, J = 8.6, 2.4 Hz, H-5), 3.90 (s, MeO), 1.36 (s, CMe_3); ^{13}C NMR ($CDCl_3$) 193.6 (d), 179.1 (s), 166.1 (s), 144.0 (s), 137.9 (d), 116.2 (s), 110.5 (d), 103.5 (d), 55.9 (q), 40.6 (s), 27.7 ppm (q); IR (KBr) 3261, 1701, 1655, 1618 cm^{-1}; MS(CI), m/e 236 (MH^+). Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N. 5.95. Found: C, 66.56; H, 6.97; N, 5.96.

6aα-Ethyl-8aα-[4-methoxy-2-(trimethylacetamido)benzoyl]-1,2,4,6a,7,8,8a,8bα-octahydro-1-oxacyclopent[*hi*]indolizin-2-one (15). To a solution of aldehyde **13** (760 mg, 3.23 mmol) and $CHCl_3$ (3 mL) was added a catalytic amount of a KCN–18-crown-6 complex, followed by trimethylsilyl cyanide (960 mg, 9.7 mmol). The reaction was stirred at room temperature for 30 min and concentrated. Crystallization from cold pentane gave 950 mg (88%) of silyl cyanohydrin **14** as a white solid: mp 69–72 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.8 (br s, NH), 8.02 (d, J = 2.4 Hz, ArH-3), 7.04 (d, J = 8.5 Hz, ArH-6), 6.59 (dd, J = 8.4, 2.4 Hz, ArH-5), 5.36 (s, CHCN), 3.82 (s, OMe), 1.35 (s, Me_3C), 0.21 (s, Me_3Si). This material could not be recrystallized but was sufficiently pure for the next step.

A solution of **14** (452 mg, 1.35 mmol) and dry THF (13 mL) was cooled to −78 °C, and *n*-BuLi (1.20 mL of a 2.3 M solution in hexane, 2.8 mmol) was added over ~5 min. After 30 min at −78 °C, a solution of **10** (275 mg, 1.23 mmol) and THF (4 mL) was added over ~5 min, and the resulting solution was stirred at −78 °C for 1 h. The reaction mixture was allowed to warm to 0 °C, stirred at 0 °C for 1 h, and quenched by pouring into a 1:1 mixture (50 mL) of 3 N HCl and ether. After 1 h of stirring, the mixture was basified with solid KOH, the ether layer was separated, and the aqueous layer was extracted with ether (3 × 50 mL). The combined organic extracts were concentrated and MeOH (20 mL) and LiOH (1 g) were added, and the resulting solution was kept at room temperature for 12 h. After partitioning between H_2O (10 mL) and ether (50 mL), the aqueous layer was extracted with ether (3 × 50 mL) and the combined organic extracts were dried ($MgSO_4$). Concentration to ~2 mL and

filtration gave 410 mg of **15** as a white solid. Purification of the filtrate by flash chromatography (silica gel, 3:1 hexane–ethyl acetate) gave an additional 68 mg of crystalline **15**. The combined product (478 mg, 91%) was recrystallized from cold hexane to give 420 mg (80%) of **15**, mp 162–164 °C. An analytical sample was prepared by recrystallization from ether and then hexane: mp 164–165 °C; ^{1}H NMR ($CDCl_3$) δ 11.97 (br s, NH), 8.53 (d, J = 2.7 Hz, ArH-3), 8.26 (d, J = 9.2 Hz, ArH-6), 6.64 (dd, J = 9.2, 2.6 Hz, ArH-5), 5.7–5.85 (m, CH=CH), 4.48 (s, CHN), 3.91 (ABq, CH_2N), 3.90 (s, MeO), 1.36 (s, CMe_3), 0.98 (t, J = 7.4 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$) 197.9 (s), 178.6 (s), 165.5 (s), 155.2 (s), 145.8 (s), 135.2 (d), 131.5 (d), 122.1 (d), 112.3 (s), 109.9 (d), 104.1 (d), 94.3 (s), 64.0 (d), 55.7 (q), 46.8 (s), 40.6 (t), 40.5 (s), 39.0 (t), 36.3 (t), 27.8 (t), 27.6 (q), 8.4 (q); IR (KBr) 3260, 1769, 1697, 1625, 1591 cm^{-1}; MS(CI), m/e 427 (MH^+), 385, 383, 234. Anal. Calcd for $C_{24}H_{30}N_2O_5$: C, 67.58; H, 7.09; N, 6.57. Found: C, 67.48; H, 7.21; N, 6.48.

6aα-Ethyl-8aα-[1-[4-methoxy-2-(trimethylacetamido)-phenyl]ethenyl]-1,2,4,6a,7,8,8a,8bα-octahydro-1-oxacyclopent[*hi*]indolizin-2-one (16). To a suspension of methyltriphenylphosphonium bromide (4.12 g, 11.5 mmol) in dry THF (100 mL) at −78 °C was slowly added *n*-BuLi (4.8 mL of a 1.8 M solution in hexane, 8.6 mmol). The yellow reaction mixture was warmed to room temperature and stirred for 15 min, and the now orange solution was recooled to −78 °C. A solution of **15** (248 mg, 0.582 mmol) and dry THF (20 mL) was added, and the reaction mixture mixture was allowed to warm to room temperature. After 36 h, the reaction was quenched by pouring into excess 1 N HCl–ether, and the aqueous portion was extracted with ether. The combined organic extracts were dried ($CaSO_4$) and concentrated. The residue was purified by flash chromatography (silica gel, 20:1 $CHCl_3$–ethyl acetate) to give a colorless oil, which crystallized to afford 240 mg (97%) of **16** as a while solid: mp 163–164 °C; ^{1}H NMR ($CDCl_3$) δ 8.09 (d, J = 2.6 Hz, ArH-3), 7.91 (br s, NH), 6.99 (d, J = 8.5 Hz, ArH-6), 6.64 (dd, J = 8.5, 2.6 Hz, ArH-5), 6.00 (d, J = 1.4 Hz, =C*H*H), 5.7–5.6 (m, CH=CH), 5.32 (d, J = 1.3 Hz, =CH*H*), 3.83 (s, MeO), 3.62 (s, CHN), 1.26 (s, CMe_3), 0.64 (t, J = 7.2 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$) 176.6 (s), 160.0 (s), 156.3 (s), 145.7 (s), 137.1 (s), 131.4 (d), 130.0 (d), 122.3 (d), 120.3 (s), 119.7 (t), 110.1 (d), 105.6 (d), 91.5 (s), 64.5 (d), 55.4 (q), 46.7 (s), 40.6 (t), 40.1 (s), 35.7 (t), 35.0 (t), 28.0 (t), 27.5 (q), 8.2 ppm (q); IR (KBr) 3444, 1760, 1677, 1617, 1588 cm^{-1}; MS(CI), m/e 425 (MH^+), 381; MS(EI), m/e 424.238 (424.236 calcd for $C_{25}H_{32}N_2O_4$).

4aα-Ethyl-7α-[1-[4-methoxy-2-(trimethylacetamido)-phenyl]ethenyl]-2,4a,5,6,7,7aα-hexahydro-1*H*-1-pyrindin-7-ol (17). A degassed solution of **16** (64.0 mg, 0.151 mmol), KOH (5.5 g, 98 mmol), MeOH (20 mL), and H_2O (2 mL) was heated at reflux for 36 h. The reaction mixture was diluted with H_2O and extracted with ether, and the combined organic extracts were extracted with 1 N HCl. The acidic extract was basified with solid KOH, extracted with ether, dried ($CaSO_4$), and concentrated. The residue was purified by preparative TLC (silica gel, 5:1 $CHCl_3$–MeOH) to give 29.8 mg (50%) of chromatographically pure **17** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 9.22 (br s, NH), 7.86 (d, J = 2.3 Hz, ArH-3), 6.93 (d, J = 8.4 Hz, ArH-6), 6.62 (dd, J = 8.4, 2.6 Hz, ArH-5), 5.8–5.6 (m, CH=CH), 5.53 (d, J = 1.1 Hz, =C*H*H), 4.98 (d, J = 1.2 Hz, =CH*H*), 3.83 (s, MeO), 3.12 (s, CHN), 1.26 (s, CMe_3), 0.84 (t, J = 7.3 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$) 177.4 (s), 159.5 (s), 151.3 (s), 138.1 (s), 134.1 (d), 130.0 (d), 124.8 (s), 124.2 (d), 116.5 (t), 110.6 (d), 107.0 (d), 82.3 (s), 64.5 (d), 55.6 (q), 43.9 (s), 41.2 (t), 40.1 (s), 35.6 (t), 34.5 (t), 34.3 (t), 27.8 (q), 9.3 ppm (q); IR ($CHCl_3$) 3422, 1671, 1618, 1584 cm^{-1}; MS(CI), m/e 399 (MH^+), 398, 108; MS(EI), m/e 398.257 (398.257 calcd for $C_{24}H_{34}N_2O_3$).

6aα-Ethyl-9aα-[4-methoxy-2-(trimethylacetamido)-phenyl]-1,2,4,6a,7,8,9a,9bα-octahydro-9*H*-pyrrolo[3,2,1-*ij*]-quinolin-9-one (19). To a solution of **17** (29.8 mg, 0.0748 mmol) and benzene (10 mL) was added paraformaldehyde (30 mg, 1.0 mmol) followed by a catalytic amount of camphorsulfonic acid. The reaction mixture was heated to reflux for 2 h, quenched with 1 N NaOH, and extracted with ether, and the combined organic extracts were extracted with 1 N HCl. The acidic extract was basified with solid KOH, extracted with ether, dried ($CaSO_4$), and concentrated. The residue was purified by preparative TLC (silica gel, 1:1 $CHCl_3$–ethyl acetate) to give 29.5 mg (96%) of chromatographically pure **19** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.89 (br s, NH), 7.45 (d, J = 2.8 Hz, ArH-3), 7.41 (d, J = 9.1 Hz, ArH-6), 6.69 (dd, J = 9.0, 2.8 Hz, ArH-5), 5.4–5.8 (m, CH=CH), 3.80 (s, MeO), 3.30 (s, CHN), 1.34 (s, CMe_3), 0.95 (t, J = 7.4 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$) 214.8 (s), 177.4 (s), 158.9 (s), 137.5 (s), 132.8 (d), 128.9 (d), 125.2 (s), 123.9 (d), 111.5 (d), 111.2 (d), 72.5 (d), 61.9 (s), 55.6 (q), 52.6 (t), 52.3 (t), 40.1 (s), 40.0 (s), 36.0 (t), 35.1 (t), 33.2 (t), 30.1 (t), 27.6 (q), 8.5 (q); IR ($CHCl_3$) 3454, 1705, 1683, 1616, 1582 cm^{-1}; MS(CI), m/e 411 (MH^+), 95; MS(EI), m/e 410.257 (410.257 calcd for $C_{25}H_{34}N_2O_3$).

4aα-Ethyl-7α-[1-(4-methoxy-2-aminophenyl)ethenyl]-2,4a,5,6,7,7aα-hexahydro-1*H*-1-pyrindin-7-ol (18). A degassed solution of **16** (110 mg, 0.259 mmol), KOH (10 g, 180 mmol), MeOH (18 mL), and H_2O (3 mL) was heated at reflux for 8 h. After being cooled to room temperature, the reaction mixture was diluted with H_2O (10 mL) and extracted with ether (2 × 25 mL), and the combined organic extracts were extracted with 1 N HCl (25 mL). The acidic extract was basified with solid KOH, extracted with ether, dried ($CaSO_4$), and concentrated. Purification of the residue by flash chromatography (silica gel, 9:1:0.1 $CHCl_3$–MeOH–concentrated NH_4OH) gave 78 mg (96%) of pure **18**: ^{1}H NMR ($CDCl_3$) δ 6.85 (d, J = 8.2 Hz, ArH-6), 6.30–6.24 (m, ArH-3 and H-5), 5.9–5.6 (m, CH=CH), 5.64 (d, J = 2.1 Hz, =C*H*H), 5.04 (d, J = 2.1 Hz, =CH*H*), 4.2–3.2 (br, NH_2), 3.76 (s, MeO), 3.12 (s, CHN), 0.76 (t, J = 7.3 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$) 159.9 (s), 152.3 (s), 146.1 (s), 134.5 (d), 130.8 (d), 124.4 (d), 120.5 (s), 116.0 (t), 103.3 (d), 101.0 (d), 82.9 (s), 64.4 (d), 55.2 (q), 43.3 (s), 41.4 (t), 35.8 (t), 34.9 (t), 34.4 (t), 9.2 ppm (q); IR ($CHCl_3$) 3458, 3370, 3335, 3270, 1618, 1579 cm^{-1}; MS(CI), m/e 315 (MH^+), 314; MS(EI), m/e 314.200 (314.199 calcd for $C_{19}H_{26}N_2O_2$). This sample was used directly in the next experiment.

***dl*-16-Methoxy-1,2,6,7-tetradehydroaspidospermidine (20) from 18.** To a degassed solution of **18** (36.0 mg, 0.115 mmol) and dry toluene (4 mL) was added paraformaldehyde (38 mg, 0.13 mmol) and Na_2SO_4 (33 mg, 0.23 mmol). This mixture was vigorously stirred at room temperature for 1 h to give the corresponding oxazolidine [^{1}H NMR ($CDCl_3$) δ 4.72 and 4.49 (doublets, $J \sim 1$ Hz, NCH_2O]. The mixture was then heated at reflux for 6 h and allowed to cool to room temperature. Filtration, concentration of the filtrate, and purification of the residue by flash chromatography (silica gel, 198:2:2 $CHCl_3$–MeOH–concentrated NH_4OH) gave 25.2 mg (71%) of chromatographically pure **20** as a light yellow oil:[26] ^{1}H NMR ($CDCl_3$) δ 7.22 (d, J = 8.2 Hz, H-14), 7.11 (d, J = 2.3 Hz, H-17), 6.71 (dd, J = 8.2, 2.4 Hz, H-15), 5.45–5.75 (m, CH=CH), 3.84 (s, MeO), 2.69 (d, J = 1.3 Hz, CHN), 0.58 (t, J = 7.2 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$) 191.8 (s), 160.1 (s), 155.8 (s), 139.7 (s), 134.4 (d), 124.7 (d), 121.5 (d), 111.1 (d), 106.2 (d), 73.4 (d), 60.6 (s), 55.7 (q), 53.5 (t), 51.7 (t), 40.5 (s), 36.1 (t), 30.1 (t), 27.6 (t), 24.9 (t), 8.4 ppm (q); IR ($CHCl_3$) 1622 cm^{-1}; MS(CI), m/e 309 (MH^+), 308; MS(EI), m/e 308.189 (308.189 calcd for $C_{20}H_{24}N_2O$). Typically this material was not chromatographed, and the crude product was used directly in the next step.

In other reactions, crude **20** was isolated in yields up to 90% by filtration of a pentane solution of crude material, followed by concentration.

Preparation of *dl*-16-Methoxy-1,2,6,7-tetradehydroaspidospermidine (20) from 19. A degassed solution of **19** (21.4 mg, 0.0521 mmol) and 25% NaOMe–MeOH (5 mL) was heated at reflux for 3 h, cooled, diluted with H_2O, and extracted with ether. The combined organic extracts were dried ($CaSO_4$) and concentrated to give 10.8 mg (67%) of **20**. The spectral and chromatographic characteristics of this sample were identical with **20** prepared directly from **18**.

***dl*-16-Methoxytabersonine (1).** A solution of crude imine **20** (prepared from 24 mg, 0.076 mmol of **18**) and dry THF (5 mL) was added dropwise at 0 °C to a large excess of LDA [prepared from dry diisopropylamine (1.0 mL, 7.1 mmol), *n*-BuLi (1.0 mL of a 1.8 M solution in hexane, 1.8 mmol), and dry THF (15 mL) at 0 °C for 30 min]. The resulting solution was maintained at room temperature for 8 h and cooled to −78 °C, and methyl chloroformate (0.5 mL, 6.5 mmol) was added dropwise. After 1 h at −78 °C, the reaction mixture was quenched at −78 °C with 1 N NaOH–MeOH solution and partitioned between ether and 1 N NaOH. The aqueous phase was extracted with ether, and the combined organic extracts were extracted with 1 N HCl. The

acidic solution was basified with solid KOH, extracted with ether, dried ($CaSO_4$), and concentrated. The residue was purified by preparative TLC (silica gel, 10:1 $CHCl_3$–ethyl acetate) to give 8.8 mg of 1 (32% from 18) as a colorless oil and 6.3 mg (22%) of N-acylated product. 1: ^1H NMR ($CDCl_3$)[29] δ 8.96 (br s, NH), 7.10 (d, J = 7.8 Hz, H-14), 6.42–6.37 (m, H-15 and H-17), 5.82–5.68 (m, CH=CH), 3.78 (s, MeO), 3.76 (s, MeO), 2.63 (d, J = 1.5 Hz, CHN), 0.64 (t, J = 7.4 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$) 169.2 (s), 167.4 (s), 160.3 (s), 144.7 (s), 133.4 (d), 130.8 (s), 125.1 (d), 122.0 (d), 105.3 (d), 96.9 (d), 92.7 (s), 70.4 (d), 55.7 (q), 54.8 (s), 51.2 (2C, q and t), 50.8 (t), 44.8 (t), 41.7 (s), 28.8 (t), 27.2 (t), 7.7 ppm (q); IR ($CHCl_3$) 3397, 2795, 1675, 1618 cm^{-1}; MS(CI), m/e 367 (MH^+), 366. All spectral (250-MHz ^1H NMR, 63-MHz ^{13}C NMR, solution IR, and mass) and chromatographic data (TLC in three solvent systems) of synthetic 1 were indistinguishable from those of an authentic sample of 16-methoxytabersonine.

***dl*-16-Methoxy-1-(methoxycarbonyl)-2,3,6,7-tetradehydroaspidospermidine:** ^1H NMR ($CDCl_3$) δ 7.49 (d, J = 2.2 Hz, H-17), 7.09 (d, J = 8.2 Hz, H-14), 6.56 (dd, J = 8.2, 2.3 Hz, H-15), 5.92 (dd, J = 8.5, 3.1 Hz, H-3), 5.6–5.85 (m, HC=CH), 3.93 (s, MeO), 3.82 (s, MeO), 2.58 (d, J = 1.6 Hz, CHN), 0.65 (t, J = 7.5 Hz, CH_2CH_3).

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Registry No. (±)-1, 86116-70-3; 4, 81903-99-3; (±)-5 (isomer 1), 86045-65-0; (±)-5 (isomer 2), 86045-79-6; 5 iodide derivative, 86045-77-4; (±)-6 (isomer 1), 86045-66-1; (±)-6 (isomer 2), 86045-80-9; 6 (R = H), 86045-78-5; (±)-10, 86045-67-2; 11, 86045-68-3; 13, 86045-69-4; (±)-14, 86045-70-7; (±)-15, 86064-56-4; (±)-16, 86045-71-8; (±)-17, 86064-57-5; (±)-18, 86045-73-0; (±)-18 oxazolidine derivative, 86045-75-2; (±)-19, 86045-72-9; (±)-20, 86045-74-1; 1-chloro-3-(phenylthio)propane, 4911-65-3; (±)-1,3-chloro-1-(phenylthio)propane, 86045-76-3; 2-bromo-4-methoxyaniline, 32338-02-6; trimethylacetyl chloride, 3282-30-2; trimethylsilyl cyanide, 7677-24-9; methyltriphenylphosphonium bromide, 1779-49-3; methyl chloroformate, 79-22-1.

Supplementary Material Available: Experimental and spectral data for the preparation of 10 via intermediates 7–9 (3 pages). Ordering information is given on any current masthead.

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Efficient Construction of the 10*H*-Pyrido[3,4-*b*]carbazole Ring System. Syntheses of Isoellipticine and 7-Methoxyisoellipticine

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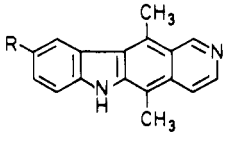
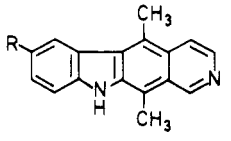
Practical syntheses of isoellipticine (**2a**) (5,11-dimethyl-10*H*-pyrido[3,4-*b*]carbazole) and 7-methoxyisoellipticine (**2b**) are described in which the key steps are regioselective acylation of a 3-lithio-1-(phenylsulfonyl)indole (**12** or **25**) with 3,4-pyridinedicarboxylic anhydride (**7**) and strong-base-mediated cyclization to the corresponding quinone (**5** or **28**). Further manipulation affords **2a** and **2b** in 20% and 21% overall yield from indole (**10**) and 5-methoxyindole (**23**), respectively. Keto acid **20** was also converted to isoellipticine (**2a**) in 85% yield.

The Ochrosia and Aspidosperma plant alkaloids ellipticine (**1a**) (5,11-dimethyl-6*H*-pyrido[4,3-*b*]carbazole) and, particularly, 9-methoxyellipticine (**1b**) are potent anticancer agents, and a derivative of **1b** is currently in clinical use in France.[2] Since the isolation of these two alkaloids[3] and the discovery of their anticancer activity,[4] many synthetic approaches to the pyrido[4,3-*b*]carbazole ring system have been reported.[5-7] Our own work in this area has recently culminated in a highly efficient synthesis of ellipticine (**1a**), proceeding in ca. 55% overall yield from indole (six steps).[7]

In contrast to the intense activity directed toward the synthesis of pyrido[4,3-*b*]carbazoles, very little attention has been focused on the isomeric pyridocarbazoles, such as 5,11-dimethyl-10*H*-pyrido[3,4-*b*]carbazole (**2a**) (hereafter referred to as "isoellipticine"). In fact, only one total synthesis of isoellipticine (**2a**)[8] and the preparation of isoellipticine quinone **5**[6a] have been described. Herein we delineate a new approach for the construction of the pyrido[3,4-*b*]carbazole ring system, resulting in syntheses of isoellipticine (**2a**) and the previously unknown 7-methoxyisoellipticine (**2b**).



1a (R = H)
1b (R = OCH_3)



2a (R = H)
2b (R = OCH_3)

Our synthetic approach to isoellipticine (**2a**) parallels that which we devised to fashion ellipticine (**1a**),[7] and both strategies are outlined in Scheme I. One obvious attractive

(1) Work done in partial fulfillment of the requirements for the Ph.D., Dartmouth College, 1982.

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