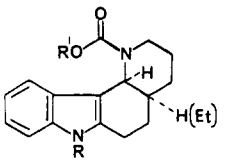
Pentacyclic Systems for Indole Alkaloids. Formation of the C_{11}–C_{12} Bond. Two Syntheses of (±)-Aspidospermidine

Timothy Gallagher,† Philip Magnus,*† and John C. Huffman‡

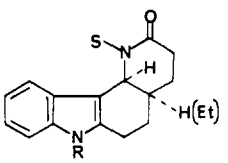
Contribution from the Department of Chemistry and the Molecular Structure Center, Indiana University, Bloomington, Indiana 47405. *Received December 6, 1982*

Abstract: The tetracyclic amide **10** [E = $COCH_2S(O)Ph$] was converted through an intramolecular Pummerer reaction into the pentacyclic amide **11**, having the basic framework of the Aspidosperma alkaloids. Application of this methodology to the synthesis of (±)-aspidospermidine, **3**, proceeded through a route described as an exocyclic carbamate, where the tetracyclic amide **14** [E = $COCH_2S(O)Ph$] is converted into the pentacyclic amide **15** by an intramolecular Pummerer reaction. Desulfurization of **15** to **16** and lithium aluminum hydride reduction gave (±)-aspidospermidine, **3**. A second, alternative strategy for the synthesis of aspidospermidine is described; it has the amide carbonyl in ring D, instead of ring E. This endocyclic amide route proceeds via the tetracyclic amide **27**, which on oxidation to the sulfoxide **28**, followed by intramolecular Pummerer reaction, gave the pentacyclic amide **29**. The structures of **27** and **29** were confirmed by single-crystal X-ray analysis. Desulfurization of **29** gave **30**, which was converted into (±)-aspidospermidine, **3**, by reduction with lithium aluminum hydride.

In the preceding paper[1] we described the synthesis of a number of tetracyclic indole alkaloid precursors of two types, *exocyclic carbamates* **1** and *endocyclic amides* **2**. To complete the investigation of this strategy to assemble indole alkaloids of the Aspidosperma type, it is essential to develop efficient ways of forming the C_{11}–C_{12} bond. Here we describe two syntheses of (±)-aspidospermidine, **3**,[2] that illustrate the overall strategy that has been developed to date.[3]



1



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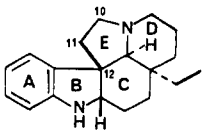
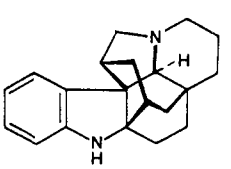


3

The C_{11}–C_{12} bond is a sterically hindered bond, quaternary at C_{12}, and part of a relatively strained five-membered heterocycle ring E. Both molecular models and the literature[4] demonstrate that an intramolecular-S_N2[5] displacement process, using the indole 2,3-double bond as the nucleophile toward a leaving group attached to C_{11}, would be difficult since the pseudopentacoordinate transition state required is severely sterically impeded by the overall steric congestion in this part of the molecule. Interestingly, as seen later, the C_{11}–C_{12} bond, once formed, is a long bond: 1.563 Å. Consequently, it would be expected that a substantial activation energy barrier exists to prevent the formation of the C_{11}–C_{12} bond via a displacement process. Previous experience with this particular situation has been documented by Ziegler,[6] Wenkert and Potier,[7] and most recently by Natsume.[8] Their joint findings are summarized in Scheme I, which shows that while it is possible to make the C_{11}–C_{12} bond in the manner described, it is not a high-yielding process. Furthermore, we were especially interested in the possibility of having a functional group handle at C_{11} to enable the more highly condensed members of the *Aspidosperma* alkaloids such as the kopsanes **4** or fruticosanes **5** to be made.[9]

Changing the hybridization of C_{11} from sp^3 to sp^2 means that intramolecular participation of the indole 2,3-double bond leads directly to the establishment of the C_{11}–C_{12} bond, Scheme II. The intermediate trigonally hybridized intermediate **6** has no steric requirements for its formation since the indole 2,3-double bond is not involved in its formation. The stereoelectronics of the interaction of $C = X^+$ with the indole 2,3-double bond predicts an explicit stereochemistry for the X group, as shown. This prognosis turns out to be a viable working hypothesis for making suitable substrates that can be subsequently converted into *Aspidosperma* alkaloids.



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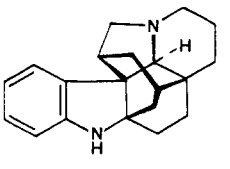

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Results

The tetracyclic diamine **7**[1] was converted into the *N*-acyl derivatives listed as **8** [X = Cl, Br, SPh, S(O)Ph] and exposed to

† Department of Chemistry.
‡ Molecular Structure Center.

(1) Exon, C.; Gallagher, T.; Magnus, P. *J. Am. Chem. Soc.* **1983**, *105*, preceding paper in this issue.
(2) Mills, J. F. D.; Nyburg, S. C. *J. Chem. Soc.* **1960**, 1458. Camerman, A.; Camerman, N.; Trotter, J. *Acta Crystallogr.* **1965**, *19*, 314. Kennard, O.; Kerr, K. A.; Watson, D. G.; Fawcett, J. K.; Riva di Sanseverino, L. *Chem. Commun.* **1967**, 1286. Biemann, K.; Friedmann-Spiteller, M.; Spiteller, G. *Tetrahedron Lett.* **1961**, 485. Smith, G. F.; Wahid, M. A. *J. Chem. Soc.* **1963**, 4002. For a comprehensive list of references describing the synthetic endeavors in the *Aspidosperma* alkaloid area see ref 1–7 in the preceding paper.
(3) Gallagher, T.; Magnus, P. *Tetrahedron* **1981**, *37*, 3889. Gallagher, T.; Magnus, P. *J. Am. Chem. Soc.* **1982**, *104*, 1140.
(4) For a review describing the construction of quaternary carbon centers, see: Martin, S. F. *Tetrahedron* **1980**, *36*, 419.
(5) Tenud, L.; Faroog, S.; Seible, J.; Eschenmoser, A. *Helv. Chim. Acta* **1970**, *53*, 2059. The closure of the ring between the β-position of the indole and C_{11} is formally a 5-*exo*-tet process, and as such is favored (Baldwin, J. E.; *J. Chem. Soc., Chem. Commun.* **1976**, 734). It is amusing to note that the terminology S_N2 is a kinetic definition that strictly speaking cannot apply to an intramolecular situation since both nucleophile and electrophile are contained within the same molecule at the same relative concentration that cannot be varied; only the pseudopentacoordinate transition-state description applies.
(6) Ziegler, F. E.; Spitzner, E. B. *J. Am. Chem. Soc.* **1973** *95*, 7146. Ziegler, F. E.; Bennett, G. B. *ibid.* **1973**, *95*, 7458.
(7) Husson, H.-P.; Thal, C.; Potier, P.; Wenkert, E. *J. Chem. Soc., Chem. Commun.* **1970**, 480. Wenkert, E. *Pure Appl. Chem.* **1981**, *53*, 1271.
(8) Natsume, M.; Utsunomiya, I *Heterocycles* **1982**, 111.
(9) Bycroft, B. W.; Schumann, D.; Patel, M. B.; Schmid, H. *Helv. Chim. Acta* **1964**, *47*, 1147. Schumann, D.; Bycroft, B. W.; Schmid, H. *Experientia* **1964**, *20*, 202. Kump, C.; Dugan, J. J.; Schmid, H. *Helv. Chim. Acta* **1966**, *49*, 1237. Kump, C.; Schmid, H. *Ibid.* **1962**, *45*, 1090. Battersby, A. R.; Gregory, H. *J. Chem. Soc.* **1963**, 22. Achenbach, H.; Biemann, K. *J. Am. Chem. Soc.* **1965**, *87*, 4944. Djerassi, C.; Budzikiewicz, H.; Owellen, R. J.; Wilson, J. M.; Kump, W. G.; LeCount, D. J.; Battersby, A. R.; Schmid, H. *Helv. Chim. Acta* **1963**, *46*, 742. Craven, B. M.; Gilbert, B.; Paes Leme, L. A. *Chem. Commun.* **1968**, 955. See also: *J. Chem. Soc. C* **1966**, 1260.

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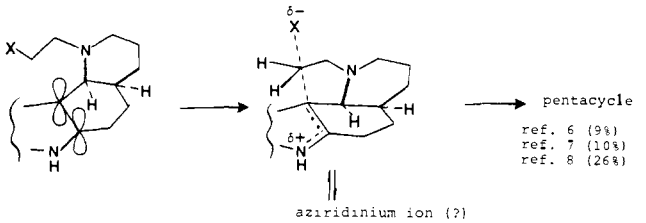
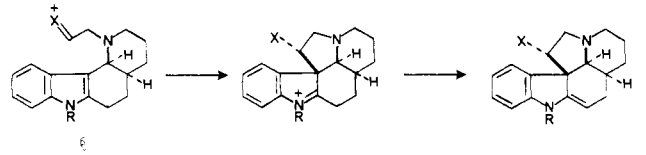
Scheme I

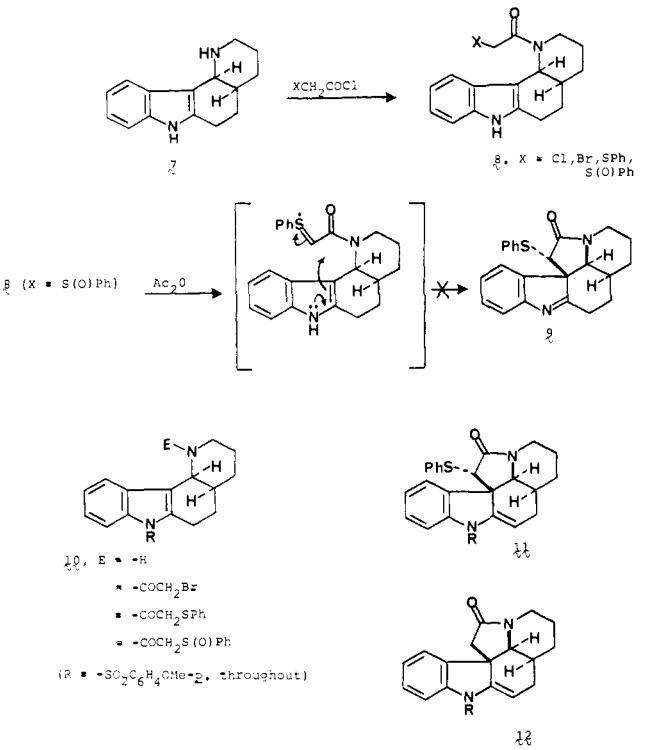


Scheme II



a variety of conditions: **8**, X = Cl (i) K_2CO_3/DMF/110 °C, (ii) Ag_2O/CH_3CN, (iii) NaH/glyme, (iv) NaI/K_2CO_3/THF reflux, (v) pyridine reflux, (vi) $MeOH/NaHCO_3/h\nu$; **8**, X = Br (i) n-Bu_3SnH/PhH/AIBN, (ii) $AgBF_4/CH_2Cl_2$ and conditions given above; **7** (i) $BrCH_2CH_2Br$/DMF/K_2CO_3, (ii) MeMgBr/$BrCH_2CH_2Br$. In no case was any evidence obtained for the formation of the pentacyclic systems.

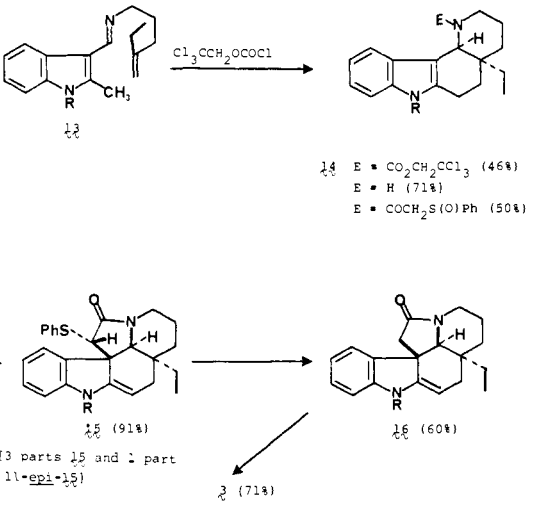
Treatment of the sulfoxide **8** [X = S(O)Ph] with acetic anhydride did not produce the expected pentacyclic amide **9** via the



Pummerer reaction. A complex mixture was formed, and we suspected that if the product **9** were formed, it would be unstable to the Pummerer conditions.[10] Consequently, we turned our attention to tetracyclic amides with the indole nitrogen deactivated by the (*p*-methoxyphenyl)sulfonyl group.

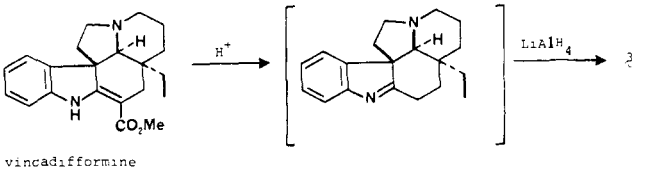
Treatment of **10** (E = H) with (phenylthio)acetyl chloride/CH_2Cl_2/NaOH gave **10** (E = $COCH_2SPh$), which was directly oxidized with MCPBA/CH_2Cl_2/10% aqueous $NaHCO_3$ to give the sulfoxide **10** [E $COCH_2S(O)Ph$] (60%), as a mixture of diastereoisomers. Exposure of the above diastereomeric sulfoxides to trifluoroacetic anhydride (2 equiv) in CH_2Cl_2 at 0 °C for 10 min and then addition of chlorobenzene, followed by heating to 140 °C, gave the pentacyclic system **11** (55%). Most indicative of the structure were ^1H NMR signals at δ 6.36 (1 H, dd, J_s = 9 and 4 Hz) for H-3, 4.02 (1 H, d, J = 5 Hz) for H-19, and 3.75 (1 H, s) for H-11, clearly showing a single stereoisomer at C_{11}. The relative configuration at C_{11} is β as shown in **11** on the basis of mechanism (see later) and, for the endocyclic amide series, a single-crystal X-ray analysis. Desulfurization of **11** with W-2 Raney nickel gave the amide **12** (100%). The α-bromoacetamide **10** (E = $COCH_2Br$) on treatment with Na_2CO_3/DMF/110 °C gave a complex mixture containing none of the pentacycle **12**.

Scheme III. Exocyclic Carbamate Route to (±)-Aspidospermidine[a]



[a] The number of steps from 1-[(*p*-methoxyphenyl)sulfonyl]-2-methyl-3-formylindole to (±)-aspidospermidine is eight, proceeding in an overall yield of 6.3%.

Scheme IV



Exocyclic Carbamate Route to (±)-Aspidospermidine. With a convenient method for making the C_{11}–C_{12} bond, it was applied to the synthesis of (±)-aspidospermidine **3** (Scheme III). The conversion of **13** into **14** (E = $CO_2CH_2CCl_3$) (46%) was found to be more practical than the route proceeding via the monochloro system **14** (E = $CO_2CH_2CH_2Cl$) (70%), followed by samarium diiodide reductive cleavage of the 2-chlorocarbamate to give **14** (E = H), since **14** (E = $CO_2CH_2CCl_3$) was readily cleaved with Zn/AcOH to give **14** (E = H) (71%). This latter sequence is more convenient on a large scale. The tetracyclic amine **14** (E = H) was converted by sequential treatment with $PhSCH_2COCl/CH_2Cl_2$, followed by MCPBA/CH_2Cl_2/$NaHCO_3$, to give the sulfoxide **14** [E = $COCH_2S(O)Ph$] (50%) as a 1:1 mixture of diastereomers. Treatment of **14** [E = $COCH_2S(O)Ph$] with trifluoroacetic anhydride (3 equiv) in CH_2Cl_2 at 0 °C, followed by addition of chlorobenzene and heating to 135 °C for 2.25 h, gave after purification (PLC) **15** (91%), as a mixture (1:3) of epimers at C_{11} (they both give **16** on desulfurization). ^1H NMR signals at δ 6.29 and 6.02 (1 H, two dd, J_s = 9, 4 Hz, in the ratio 1:3) for H-3 and at δ 3.84 and 3.57 two singlets for epimers at C_{11} support the assignments.

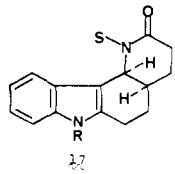
Desulfurization of **15** in ethanol/DMF using W-2 Raney nickel gave **16** (60%): ^1H NMR δ 6.18 (1 H, dd, J_s = 9 and 4 Hz) for H-3 and 3.61 (1 H, s) for H-19. Treatment of **16** with $LiAlH_4$/THF at 20 °C for 20 h gave (±)-aspidospermidine **3** (71%) (identical with an authentic sample made from vincadifformine by hydrolytic decarboxylation and $LiAlH_4$ reduction, Scheme IV).[11] The exceptionally high yield in forming the

(10) Pummerer reaction applied to indoles: Oikawa, Y.; Yonemitsu, O. *J. Org. Chem.* **1976**, *41*, 1118.

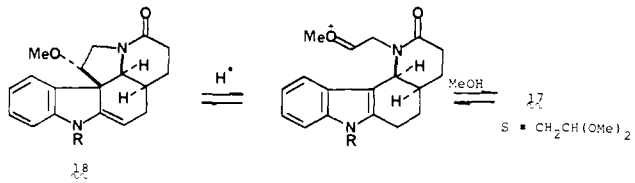
C_{11}–C_{12} bond for this sequence is noteworthy.

While Scheme III illustrates the overall strategy for the synthesis of (±)-aspidospermidine, the methodology in a broader context provides access to *Aspidosperma* alkaloids functionalized at C_{11}, such as **4** or **5**. We have successfully pursued this possibility.[12]

Tetracyclic Endocyclic Amides to Pentacyclic Amides. The tetracyclic amide **17** [S = $CH_2CH(OMe)_2$] is particularly well suited for forming the C_{11}–C_{12} bond, since it should be possible to generate an oxonium ion at C_{11} by acid-catalyzed elimination of methanol. Treatment of **17** [S = $CH_2CH(OMe)_2$] with *p*-toluenesulfonic acid (catalyst) in benzene, heated at reflux for 24 h, gave the 11β-methoxypentacyclic amide **18** (59%): mp



17



18

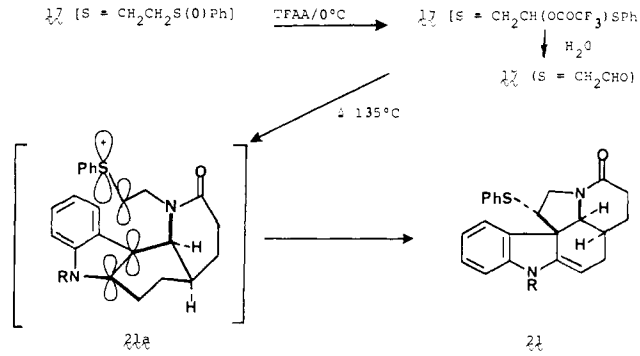
104–108 °C. Diagnostic ^1H NMR signals at δ 6.41 (1 H, dd, J_s = 8 and 3 Hz), 4.4 (1 H, d, J = 4 Hz), and most interestingly the 11β-methoxy group at 2.72 (cf. 3.24 as a reasonable standard) confirm the structure. The striking upfield shift can readily be attributed to the MeO group being rigidly held over the aromatic ring, thus enforcing the assignment of stereochemistry as shown in **18**.

In principle the conversion of **17** [S = $CH_2CH(OMe)_2$] should be reversible, and indeed chloroform solutions of **18**, in moist air, were hydrolyzed to the tetracyclic aldehyde **17** (S = CH_2CHO).

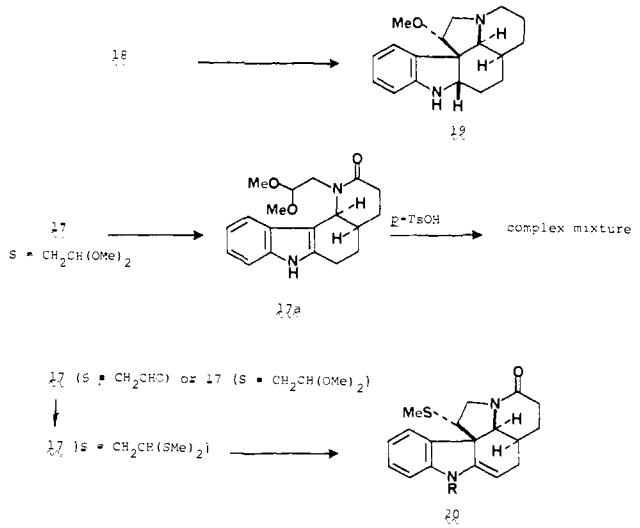
Some years ago it was reported that the *Aspidosperma* alkaloid vincoline had a hydroxyl group at C_{11}, but this was subsequently revised,[13] and to date there are no examples of *Aspidosperma* alkaloids with an oxygen substituent at C_{11}. Recently Kunesch, Poisson, and Wenkert have isolated *Aspidosperma* alkaloids lacking the usual tryptamine C_{10}–C_{11} bridge, which may well have arisen through oxidation at C_{11} and cleavage of the C_{11}–C_{12} bond by the process shown for **18**.[14]

Reduction of **18** with $LiAlH_4$/THF at 20 °C for 12 h gave 11β-methoxy-20,21-dinoraspidospermidine **19** (32%). It is important to emphasize the need to have the indole nitrogen atom protected by the (*p*-methoxyphenyl)sulfonyl group for the conversion of **17** [S = $CH_2CH(OMe)_2$] into **18**. Hydrolysis of **17** [S = $CH_2CH(OMe)_2$] using MeONa/MeOH gave the desulfonylated indole **17a**, which when exposed to the same conditions, namely, *p*-toluenesulfonic acid (catalyst) in benzene at reflux, that cleanly converted **17** [S = $CH_2CH(OMe)_2$] into **18** gave a complex mixture that did not appear (by ^1H NMR) to contain any discernible pentacyclic material. Treatment of the aldehyde **17** (S = CH_2CHO) with *p*-toluenesulfonic acid (catalyst) in benzene at reflux did not lead to any pentacyclic products, presumably because of the easy reversibility of this cyclization for a 11-hydroxy system. A simple way to prevent such facile reversibility is to replace the 11-oxo system by an 11-thio system. When the aldehyde **17** (S = CH_2CHO) was treated with $BF_3{\cdot}OEt_2$/MeSH/CH_2Cl_2 the dithioacetal **17** [S = $CH_2CH(SMe)_2$] (59%)

Scheme V



was formed. Similarly, exposure of **18** to the above conditions gave **17** [S = $CH_2CH(SMe)_2$]. Continued exposure (35 h) of either **17** (S = CH_2CHO), **17** [S = $CH_2CH(OMe)_2$], **17** [S = $CH_2CH(SMe)_2$], or **18** to the thioacetal exchange conditions gave the pentacyclic 11β-thiomethyl amide **20** (84%).



Attempts to make the C_{11}–C_{12} bond by a displacement process (pseudopentacoordinate transition state), as in the endocyclic carbamate series, were unsuccessful (see last paragraph of this section).

The tetracyclic phenylsulfide **17** (S = CH_2CH_2SPh) was oxidized with MCPBA/CH_2Cl_2/$NaHCO_3$ to give the sulfoxide **17** [S = $CH_2CH_2S(O)Ph$] (98%) as a mixture of diastereoisomers. Treatment of **17** [S = $CH_2CH_2S(O)Ph$] with trifluoroacetic anhydride (2.2 equiv) in CH_2Cl_2 at 0 °C for 1 h followed by addition of chlorobenzene and heating at 135 °C for 1.5 h gave the required pentacyclic amide **21** (84%). Scheme V outlines the course of events from **17** [S = $CH_2CH_2S(O)Ph$] to **21**.

The assignment of stereochemistry at C_{11} is based upon mechanistic considerations that align the sulfonium ion trans coplanar to the indole 2,3-double bond—**21a**. The stereochemical assignment at C_{11} is confirmed later in the ethyl series.

Desulfurization of **21** using freshly deactivated Raney nickel (W-2) in ethanol/acetone gave, somewhat surprisingly,[15] the 10,11-dehydropentacycle **22**: ^1H NMR δ 6.68 (1 H, d, J = 5 Hz) for H-11 and 3.50 (1 H, d, J = 5 Hz) for H-10. The structure of **22** was confirmed by oxidation of **21** using MCPBA/CH_2Cl_2/$NaHCO_3$ to give the sulfoxide **23** (apparently a single diastereomer), which on heating in toluene at reflux (15 h) gave **22** (40%). Further exposure of **21** to Raney nickel (W-2) slowly gave the required pentacycle **24**. Desulfurization of **21** using nondeactivated Raney nickel (W-2) in DMF gave **24** (54%), mp 237–238 °C, along with desethylaspidospermid-8-one **25** (26%),

(11) Djerassi, C.; Budzikiewicz, H.; Wilson, J. M.; Gosset, J.; LeMen, J.; Janot, M.-M. *Tetrahedron Lett.* **1962**, 235. See also ref 1.

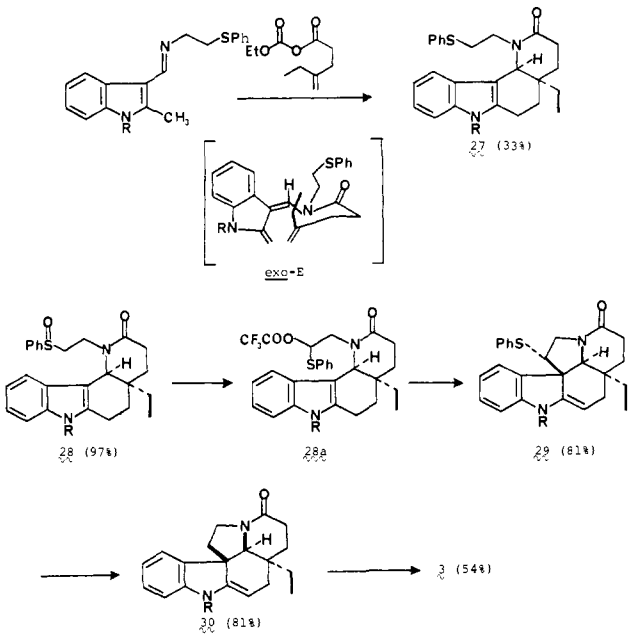
(12) Gallagher, T.; Magnus, P. *J. Am. Chem. Soc.* **1983**, *105*, 2086.

(13) For a discussion of the revised structure of vincoline see: Cordell, G. A. In "The Alkaloids"; Manske, R. H. F., Rodrigo, R., Eds.; Academic Press: New York, 1979, Vol. XVII, p 224.

(14) Kunesch, N.; Ardisson, J.; Poisson, J.; Halls, T. D. J.; Wenkert, E. *Tetrahedron Lett.* **1982**, 1981.

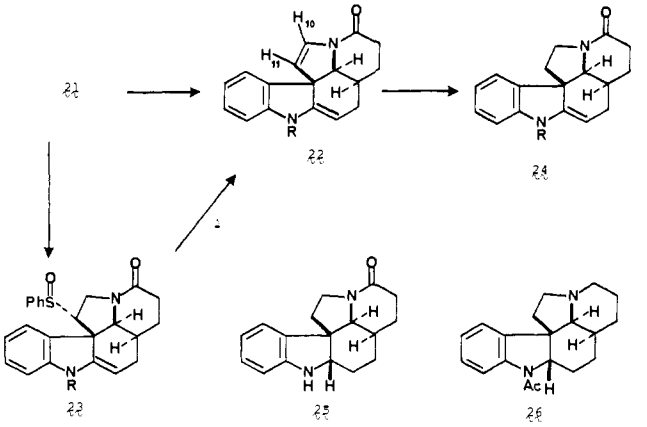
(15) Fishman, J.; Torigoe, M.; Guzik, H. *J. Org. Chem.* **1963**, *28*, 1443. Djerassi, C.; Williams, D. H. *J. Chem. Soc.* **1963**, 4046.

Scheme VI. Endocyclic Amide Route to (±)-Aspidospermidine[a]



[a] The number of steps from 1-[(*p*-methoxyphenyl)sulfonyl]-2-methyl-3-formylindole to (±)-aspidospermidine is six, proceeding in an overall yield of 11.7%.

mp 214–215 °C. Reduction of **24** with $LiAlH_4$, followed by Ac_2O/pyridine gave *N*-acetyldeethylaspidospermidine (**26**).[16]



The application of this sequence to the synthesis of aspidospermidine (**3**) itself was straightforward and is outlined in Scheme VI.

The structure of the first key intermediate **27** was demonstrated by single-crystal X-ray crystallography[17] (Figure 1). The required cis fusion at C_5–C_{19} is confirmed, and most interestingly, the planar

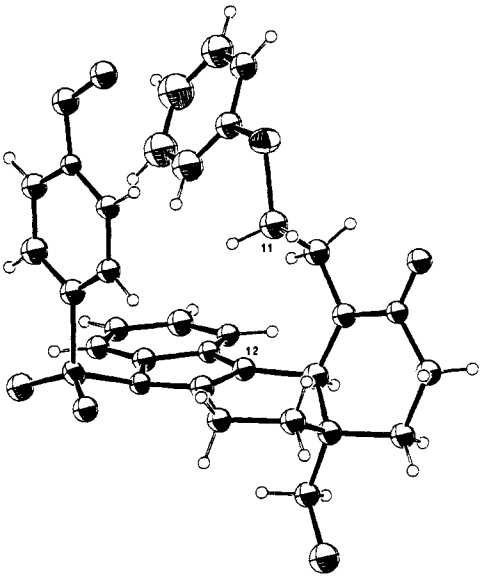


Figure 1.

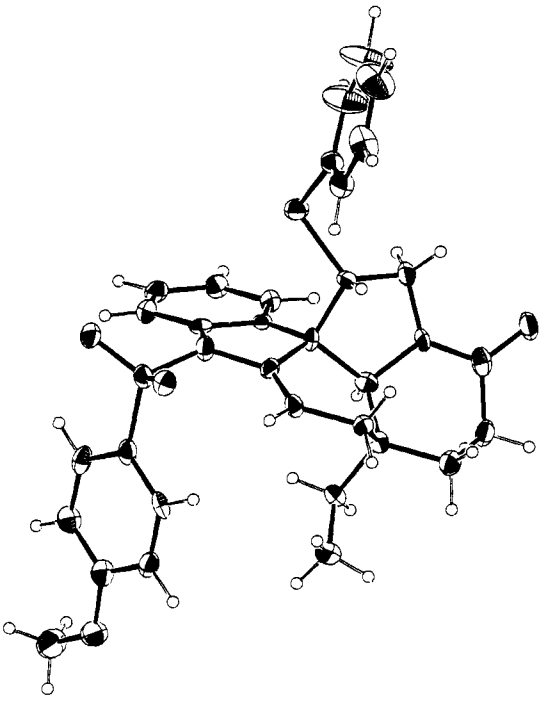


Figure 2.

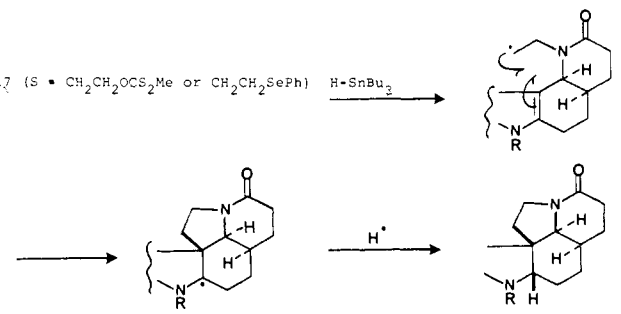
nature of the amide group at C_8–C_9 holds the CH_2CH_2SPh appendage over the indole ring. Indeed, the C_{11} carbon atom is sitting directly above the C_3 position. The (*p*-methoxyphenyl)sulfonyl group and the phenylthio group are lined up on the same side of the indole system and are almost in the same plane. While this only applies to the crystalline state, it would appear that **27** is in an ideal conformation to form the C_{11}–C_{12} bond.

Oxidation of **27** with MCPBA/CH_2Cl_2/$NaHCO_3$ at 0 °C gave the sulfoxide **28** (97%) as a mixture of diastereomers. Treatment of the sulfoxide **28** with TFAA/CH_2Cl_2/0 °C and then warming the mixture to 20 °C, followed by addition of chlorobenzene and heating at 130 °C for 2.5 h, gave the pentacyclic amide **29** (81%): ^1H NMR δ 6.18 (1 H, dd, J_s = 9, 4 Hz) for H-3 and 4.27 (1 H, dd, J_s = 15, 19 Hz) for H-11. The intermediacy of the trifluoroacetate **28a** is inferred from the fact that after TFAA treatment of **28**, but prior to heating at 130 °C, only hydrolysis to the derived aldehyde could be seen by TLC. The complete structure and stereochemistry of **29** was demonstrated by single-crystal X-ray crystallography[18] (Figure 2).

(16) Ban, Y.; Ohnuma, T.; Nagai, M.; Sendo, Y.; Oishi, T. *Tetrahedron Lett.* **1972**, 5023. See also ref 8. Professor Natsume is thanked for NMR data on **26**.

(17) Compound **27** crystallizes in space group $P\bar{1}$ with a = 20.992 (13), b = 15.246 (8), and c = 10.010 (5) Å, α = 118.83 (2), β = 92.29 (2), and δ = 95.22 (2)°, and D_{calcd} = 1.372 g cm^{-3} for Z = 4 at −160 °C. All data were collected at low temperature. The Picker goniostat, experimental details, and data handling techniques have been described in detail previously (Huffman, J. C.; Lewis, L. N.; Caulton, K. G. *Inorg. Chem.* **1980**, *19*, 2755). The structure was solved by direct methods using the 4104 nonzero data (out of 7312) and refined by full-matrix least squares to final residuals of R(F) = 0.097 and R_w(F) = 0.083. The two independent molecules located in the asymmetric unit adopt nearly identical conformations. Complete crystallographic details, including distances and angles, are available from the Chemistry Library, Indiana University, Bloomington, IN. Request Molecular Structure Center Report No. 81064.

Scheme VII



The stereochemistry at C_{11} is confirmed, and substantiates the mechanistic picture given in Scheme V. It is particularly interesting to note that the newly formed C_{11}–C_{12} bond is exceptionally long, 1.563 Å [$\angle C_{11}C_{12}C_{19}$ 103.0°, $\angle C_2C_{12}C_{19}$ 114.6°, and $\angle C_2C_{12}C_{11}$ 109.6°], reflecting the strain in the E ring.

Desulfurization of **29** with Raney nickel (W-2, not deactivated) in ethanol at 20 °C for 1 h gave **30** (81%): mp 195–196 °C. Reduction of **30** with $LiAlH_4$/THF at 20 °C for 48 h cleanly gave (±)-aspidospermidine **3** (54%): mp 99–103 °C (from acetone).[11] Comparison with an authentic sample of aspidospermidine made from (+)-vincadifformine by decarboxylation to dehydroaspidospermidine followed by reduction with $LiAlH_4$ confirmed its identity.

Reduction of the aldehyde **17** (S = CH_2CHO) with $NaBH_4$/MeOH gave the alcohol **17** (S = CH_2CH_2OH) (95%): mp 187–189 °C. Molecular models of **17** (S = CH_2CH_2OH) indicate that the C_{11} position is severely sterically encumbered toward intermolecular S_N2 reactions. Indeed conversion of **17** (S = CH_2CH_2OH) into **17** (S = CH_2CH_2Br) was unsuccessful; neither could we make the *p*-toluenesulfonate ester of **17** (S = CH_2CH_2OH). Mesylation of **17** (S = CH_2CH_2OH) MsCl/pyridine/DMAP gave the mesylate **17** (S = CH_2CH_2OMs), which proved to be unreactive toward a variety of bases. Conversion of **17** (S = CH_2CH_2OH) into the xanthate **17** (S = $CH_2CH_2OCS_2Me$) to attempt to generate the C_{11} radical for a radical cyclization method for making the C_{11}–C_{12} bond failed. In this regard, we treated the tetracyclic phenyl selenide **17** (S = CH_2CH_2SePh) with tri-*n*-butyltin hydride to form the C_{11} radical (Scheme VII) but only observed slow decomposition to intractable material.

Summary. The two separate syntheses of (±)-aspidospermidine illustrate the general utility of the indole-2,3-quinodimethane methodology. Both syntheses are short and convergent and completely stereospecific. We consider these initial studies, reported here, to serve as model systems, and a prelude to the more complicated highly functionalized indole alkaloids. In particular the exocyclic carbamate route, Scheme III, allows C_{11} to be manipulated, with the possibility of constructing the kopsane **4** or fruticosane **5** alkaloids. The endocyclic amide route, Scheme VI, introduces the possibility of functionalizing at C_7 and C_3.

These, and other extensions, are currently being investigated.

Experimental Section

The general comments concerning spectral data, solvents, chromatographic techniques, and product yields are described in detail in the preceding paper in this issue.[1]

2-Chloroacetyl-*cis*-2,3,4,4a,5,6,7,11c-octahydro-7*H*-pyrido[3,2-*c*]-carbazole (8, X = Cl). To an ice-cold, rapidly stirred solution of the diamine **7** (452 mg, 2 mmol) in chloroform (15 mL) was added, simultaneously, a solution of chloroacetyl chloride (350 mg, 3.1 mmol) in chloroform (3 mL) and 1 N NaOH (5 mL). After the solution was stirred for 30 min, chloroacetyl chloride (100 mg) was added. After an additional 1 h the chloroform layer was separated and the aqueous phase extracted once with chloroform (10 mL). The combined extracts were washed with water and dried (Na_2SO_4). Removal of the solvent and chromatography gave, on elution with $CHCl_3$/petroleum ether (2:3), the amide **8** (X = Cl) (280 mg, 46%) as a colorless foam: IR ($CHCl_3$) 3465, 1632, 1455 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.55 and 8.27 (1 H, NH, 2 br s), 7.37–7.25 (2 H, m), 7.23–6.98 (2 H, m), 6.14 and 5.29 (1 H, 2 m), 4.45 and 4.32 (2 d, *J* = 12.5 Hz), 4.32 (s), 4.61 and 3.64 (1 H, 2 m), 3.05–2.36 (3 H, m), 2.32–1.86 (3 H, m), 1.70–1.52 (4 H, m); MS, *m/e* calcd for $C_{17}H_{19}N_2O^{35}Cl$ 302.119, found 302.119.

2-Bromoacetyl-*cis*-2,3,4,4a,5,6,7,11c-octahydro-7*H*-pyrido[3,2-*c*]carbazole (8, X = Br). To an ice-cold stirred solution of the diamine **7**, (340 mg, 1.5 mmol) in chloroform (15 mL) was added, simultaneously, a solution of bromoacetyl chloride (500 mg, 3.2 mmol) in chloroform (5 mL) and 1 N NaOH (5 mL). After the solution was stirred for 1 h, the chloroform layer was separated and the aqueous phase extracted once with chloroform (10 mL). The combined extracts were washed with brine and dried (Na_2SO_4). Removal of solvent and chromatography gave on elution with chloroform/petroleum ether (3:7) **8** (X = Br) (175 mg, 34%) as a colorless foam: IR ($CHCl_3$) 3460, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.34 and 8.18 (1 H, 2 br s, NH), 7.43–7.27 (2 H, m), 7.23–7.00 (2 H, m), 6.16 and 5.34 (1 H, 2 m), 4.45 and 3.66 (1 H, 2 m), 4.27, 4.06 (2 d, *J* = 12 Hz), and 4.09 (s) (comprising 2 H), 3.02–2.57 (3 H, m), 2.52–1.86 (3 H, m), 1.73–1.45 (4 H, m). No satisfactory MS or microanalytical data could be obtained for this compound due to decomposition.

2-(Phenylthio)acetyl-*cis*-2,3,4,4a,5,6,7,11c-octahydro-7*H*-pyrido[3,2-*c*]carbazole (8, X = SPh). To an ice-cold, rapidly stirred solution of the diamine **7** (200 mg, 0.88 mmol) in methylene chloride (20 mL) was added, simultaneously, a solution of (phenylthio)acetyl chloride (280 mg, 1.66 mmol) in methylene chloride (2 mL) and 1 N NaOH (3 mL). After the mixture was stirred for 10 min, the dichloromethane layer was separated and the aqueous phase extracted once with methylene chloride (10 mL). The combined extracts were washed with brine and dried ($MgSO_4$). Removal of solvent and chromatography gave, on elution with $CHCl_3$/petroleum ether (1:1) **8** (X = SPh) (207 mg, 67%) as a colorless foam: IR ($CHCl_3$) 3450, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.70 and 8.43 (1 H, 2 br s, NH), 7.57–6.70 (9 H, m), 6.05 and 5.20 (1 H, 2 m), 4.44 and 3.54 (1 H, 2 m), 4.10, 3.86 (2 d, *J* = 12 Hz), and 3.90 (s) (comprising 2 H), 2.95–1.70 (6 H, m), 1.63–1.30 (4 H, m).

The above product was directly oxidized to the sulfoxide **8** [X = PhS(O)] as follows: A solution of sodium periodate (177 mg, 0.82 mmol) and **8** (X = SPh) (200 mg, 0.55 mmol) in water (2 mL), tetrahydrofuran (4 mL), and methanol (6 mL) was stirred at 20 °C for 36 h. Additional periodate (≃90 mg) was added to complete the reaction. When none of the sulfide could be detected by TLC the solution was filtered, concentrated in vacuo, and diluted with water, and the product was extracted with ethyl acetate. The extracts were washed with water and brine and dried ($MgSO_4$). The product was purified by chromatography to give on elution with chloroform/petroleum ether (4:1) **8** [X = PhS(O)] (77 mg, 34%) as a yellow foam: ^1H NMR ($CDCl_3$) δ 8.85 and 8.65 (1 H, 2 br s, NH), 7.93–7.67 (2 H, m), 7.60–7.39 (3 H, m), 7.34–6.70 (4 H, m), 6.01 and 5.20 (1 H, 2 br s), 4.46 and 3.45 (1 H, 2 m), 4.42, 3.91 (2 d, *J* = 12.5 Hz), and 4.17 (s) (comprising 2 H), 2.82–1.70 (5 H, m), 1.73–1.21 (5 H, m).

Alternatively, a rapidly stirred solution of **10** (E = $COCH_2SPh$) (160 mg) (containing a small quantity of $PhSCH_2CO_2H$) in methylene chloride (10 mL) and 10% aqueous sodium bicarbonate (8 mL) was cooled to 0 °C, and a solution of *m*-chloroperoxybenzoic acid (55 mg, 80–90% pure) in methylene chloride (3 mL) was added over 1 h. The organic phase was separated and the aqueous layer was extracted once with methylene chloride (10 mL). The combined extracts were washed with 10% sodium bicarbonate solution and dried (Na_2SO_4). Removal of the solvent gave **10** [E = $COCH_2S(O)Ph$] (112 mg, 60% from the amine **10**, E = H) free of (phenylthio)acetic acid contamination. Both TLC and ^1H NMR indicated the sulfoxide was a 1:1 mixture of diastereoisomers. These derivatives of **7** all show strong amide resonance giving rise to broad and in some cases doubling of NMR signals. No satisfactory MS or microanalytical data could be obtained due to decomposition.

2-Bromoacetyl-*cis*-2,3,4,4a,5,6,7,11c-octahydro-7-[(*p*-methoxyphenyl)sulfonyl]-1*H*-pyrido[3,2-*c*]carbazole (10, E = $COCH_2Br$). A solution of **10** (E = H) (90 mg, 0.23 mmol) in methylene chloride (10 mL) and 1 N NaOH (8 mL) was cooled to 0 °C, and while the mixture was stirred rapidly, a solution of bromoacetyl chloride (200 mg, 1.27 mmol) in methylene chloride (2 mL) was slowly added. After 30 min the organic layer was separated and the aqueous phase extracted once with methylene chloride (10 mL). The combined extracts were dried (Na_2SO_4), and removal of solvent followed by chromatography gave, on elu-

(18) Compound **29** crystallizes in space group $P\bar{1}$ with a = 11.162 (3), b = 15.860 (5), and c = 8.321 (2) Å, α = 81.25 (1), β = 103.63 (1), and δ = 107.89 (1)°, and D_{calcd} = 1.336 g cm^{-3} for Z = 2 at −160 °C. The structure was solved by direct methods using the 3429 nonzero data (out of 3946) and refined by full-matrix least squares to final residuals of $R(F)$ = 0.066 and $R_w(F)$ = 0.061. Complete crystallographic details are available from the Chemistry Library, Indiana University, Bloomington, IN. Request Molecular Structure Center Report No. 81065.

tion with chloroform/petroleum ether (2:3), **10** (E = $COCH_2Br$) (87 mg, 74%) as a colorless foam: IR ($CHCl_3$) 1635, 1595 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.22 (1 H, m), 7.82–7.68 (2 H, m), 7.39–7.14 (3 H, m), 6.95 (2 H, m), 6.00 and 5.18 (1 H, 2 br s in a ratio of 2:1), 4.43 and 3.61 (1 H, m, in a ratio of 1:2), 4.27–3.91 (2 H, m), 3.79 (3 H, s), 3.16–2.95 (2 H, m), 2.66 (1 H, m), 2.34–1.34 (7 H, m); MS, *m/e* calcd for $C_{24}H_{25}Br^{81}N^2O_4S$ 518.070, found 518.066.

2-(Phenylsulfinyl)acetyl-*cis*-2,3,4,4a,5,6,7,11c-octahydro-7-[(*p*-methoxyphenyl)sulfonyl]-1*H*-pyrido[3,2-*c*]carbazole [10, E = $COCH_2S(O)Ph$]. A solution of **10** (E = H) (130 mg, 0.33 mmol) in methylene chloride (8 mL) was cooled to 0 °C and a solution of (phenylthio)acetyl chloride (300 mg, 1.6 mmol) in methylene chloride (2 mL) and 1 N NaOH (4 mL) were added simultaneously with rapid stirring. After 1 h the organic phase was separated and the aqueous phase extracted with methylene chloride (10 mL). The combined extracts were dried (Na_2SO_4) and concentrated in vacuo, and chromatography gave **10** (E = $COCH_2SPh$) (160 mg) as a colorless foam; this product was used without further purification: IR ($CHCl_3$) 1625, 1590, 1162 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.18 (1 H, m), 7.77–7.66 (2 H, m), 7.59–7.43 (2 H, m), 7.39–7.00 (6 H, m), 6.93–6.82 (2 H, m), 6.00 and 5.16 (1 H, 2 br s in a ratio of 2:1), 4.45 and 3.61 (1 H, m, in a ratio of 1:2), 4.09–3.86 (2 H, m), 3.77 (3 H, s), 3.11–2.93 (2 H, m), 2.66 (1 H, m), 2.11 (1 H, m), 1.95–1.84 (2 H, m), 1.61–1.32 (4 H, m); MS, *m/e* calcd for $C_{30}H_{30}N_2O_4S_2$ 546.165, found 546.166.

A rapidly stirred solution of **10** [E = $COCH_2SPh$] (160 mg) (containing a small quantity of $PhSCH_2CO_2H$) in methylene chloride (10 mL) and 10% aqueous sodium bicarbonate (8 mL) was cooled to 0 °C and a solution of *m*-chloroperoxybenzoic acid (55 mg, 80–90% pure) in methylene chloride (3 mL) was added over 1 h.

The organic phase was separated, and the aqueous layer was extracted once with methylene chloride (10 mL). The combined extracts were washed with 10% sodium bicarbonate solution and dried (Na_2SO_4). Removal of the solvent gave **10** [E = $COCH_2S(O)Ph$] (112 mg, 60% from the amine **10**, E = H) free of (phenylthio)acetic acid contamination. Both TLC and ^1H NMR indicated the sulfoxide was a 1:1 mixture of diastereoisomers.

2,3-Didehydro-1-[(*p*-methoxyphenyl)sulfonyl]-11β-(phenylthio)-20,20-dinoraspidospermidin-9-one (11). A solution of **10** [E = $COCH_2S(O)Ph$] (56 mg, 0.1 mmol) in methylene chloride (5 mL) at 0 °C was treated with trifluoroacetic anhydride (40 μL). After 10 min at 0 °C no trace of the sulfoxides was detected by TLC. Chlorobenzene (8 mL) was added and the solution heated to 140 °C over 40 min, during which time the dichloromethane was allowed to boil out in a stream of argon, and the solution was held at this temperature for 30 min. Removal of solvent gave a tan solid. Recrystallization from benzene/petroleum ether gave **11** (30 mg, 55%): mp 207–209 °C dec; IR ($CHCl_3$) 1685, 1594, 1162 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.91–7.75 (3 H, m), 7.43–4.07 (8 H, m), 6.77 (2 H, d, *J* = 10 Hz), 6.36 (1 H, dd, *J* = 9, 4 Hz), 4.34 (1 H, m), 4.02 (1 H, d, *J* = 5 Hz), 3.75 (1 H, s), 3.68 (3 H, s), 2.86 (1 H, m), 2.18 (1 H, m), 2.02 (1 H, m), 1.87–1.77 (2 H, m), 1.70–1.48 (2 H, m); MS, *m/e* calcd for $C_{30}H_{28}N_2O_4S_2$.

2,3-Didehydro-1-[(*p*-methoxyphenyl)sulfonyl]-20,21-dinoraspidospermidin-9-one (12). A solution of **1** (10 mg, 0.02 mmol) in DMF (1 mL) and ethanol (1 mL) was treated with an excess of W-2 Raney nickel. After it was stirred for 10 min, the mixture was filtered through a Celite pad and the solids washed well with dichloromethane. Removal of the solvent in vacuo gave a quantitative yield of **12**. Recrystallization from methanol gave **12** as colorless crystals: mp 225–226 °C; IR ($CHCl_3$) 1674, 1595 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.87 (1 H, m), 7.68 (2 H, d, *J* = 10 Hz), 7.41–7.09 (3 H, m), 6.87 (1 H, d, *J* = 10 Hz), 6.43 (1 H, m), 4.29 (1 H, m), 4.00 (1 H, d, *J* = 5 Hz), 3.82 (3 H, s), 2.87–2.68 (2 H, m), 2.25–1.23 (8 H, m).

***cis*-4a-Ethyl-2,3,4,4a,5,6,7,11c-octahydro-7-[(*p*-methoxyphenyl)-sulfonyl]-1*H*-pyrido[3,2-*c*]carbazole (14, E = H).** A solution of **14** (E = $CO_2CH_2CCl_3$) (500 mg, 0.83 mmol) in 1:1 acetic acid/water (10 mL) was treated with zinc dust (700 mg) in portions over 4 h. The mixture was then filtered, concentrated to approximately 1 mL, diluted with water (30 mL), and made basic with 2 N sodium hydroxide. The product was extracted with methylene chloride (3 × 10 mL). The combined extracts were washed with brine and dried (Na_2SO_4). Removal of solvent gave **14** (E = H) (250 mg, 71%) as a pale yellow foam, pure by TLC; this material was used without further purification: IR ($CHCl_3$) 3100–2450 (br, NH), 1595, 1162 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.18 (1 H, m), 7.75 (2 H, d, *J* = 10 Hz), 7.37 (1 H, m), 7.41–7.18 (2 H, m), 6.82 (2 H, d, *J* = 10 Hz), 3.79 (3 H, s), 3.57 (1 H, s), 3.20–2.86 (2 H, m), 2.68 (1 H, m), 2.25 (1 H, m), 1.79 (1 H, m), 1.59–0.91 (8 H, m), 0.86 (3 H, t, *J* = 7 Hz); MS, *m/e* calcd for $C_{24}H_{28}N_2O_3S$ 424.182, found 424.178.

2-(Phenylsulfinyl)acetyl-*cis*-4a-ethyl-2,3,4,4a,5,6,7,11c-octahydro-7-[(*p*-methoxyphenyl)sulfonyl]-1*H*-pyrido[3,2-*c*]carbazole [14, E = $COCH_2S(O)Ph$]. A solution of **14** (E = H) (250 mg, 0.59 mmol) in methylene chloride (12 mL) and 1 N NaOH (5 mL) was cooled to 0 °C, and a solution of (phenylthio)acetyl chloride (150 mg, 0.82 mmol) in methylene chloride (2 mL) was added with rapid stirring. After 15 min the dichloromethane solution was separated and dried (Na_2SO_4). Chromatography of the residue after removal of the solvent gave, on elution with chloroform/petroleum ether (1:3) **14** (E = $COCH_2SPh$) (170 mg, 50%) as a pale yellow foam: IR ($CHCl_3$) 1630, 1595, 1162 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.16 (1 H, m), 7.70 (2 H, d, *J* = 10 Hz), 7.57 (1 H, m), 7.43–7.00 (7 H, m), 6.87 (2 H, d, *J* = 10 Hz), 5.70 (1 H, br s), 4.07–3.68 (2 H, m), 3.82 (3 H, s), 3.61 (1 H, m), 3.16–2.91 (2 H, m), 2.59 (1 H, m), 1.95–1.23 (8 H, m), 0.86 (3 H, t, *J* = 7 Hz); MS, *m/e* calcd for $C_{32}H_{34}N_2O_4S$ 574.196, found 574.200.

A rapidly stirred solution of **14** (E = $COCH_2SPh$) (170 mg, 0.29 mmol) in methylene chloride (10 mL) and 10% aqueous sodium bicarbonate (5 mL) was cooled to 0 °C. A solution of *m*-chloroperoxybenzoic acid (75 mg, 80–90% pure) in methylene chloride (8 mL) was added over the course of 1.25 h. The mixture was quenched with 5% aqueous sodium bisulfite (5 mL), the organic layer was separated and the aqueous phase extracted once with methylene chloride (10 mL). The combined extracts were dried (Na_2SO_4) and removal of the solvent gave a quantitative yield of **14** [E = $COCH_2S(O)Ph$] as a pale yellow foam. Both TLC and ^1H NMR analysis indicated that **14** [E = $COCH_2S(O)Ph$] was a 1:1 mixture of diastereoisomers. It was used directly in the next stage to give **15**.

(±)-2,3-Didehydro-1-[(*p*-methoxyphenyl)sulfonyl]-11β-(phenylthio)-aspidospermidin-10-one (15). To an ice-cold solution of **14** [E = $COCH_2S(O)Ph$] (150 mg, 0.25 mmol) in methylene chloride (10 mL) was added trifluoroacetic anhydride (100 μL, 149 mg, 0.71 mmol). After 15 min at 0 °C no trace of the sulfoxides was detected by TLC. Chlorobenzene (12 mL) was added and the mixture was heated to 135 °C over 1 h during which time the methylene chloride was allowed to boil off under a stream of argon. Heating was maintained for a further 1.25 h. Removal of solvent and purification by PLC eluting with ethyl acetate/petroleum ether (3:7), gave **15** (133 mg, 91%) as a pale yellow foam: ^1H NMR indicated that **15** consisted of a 1:3 mixture of epimers at C_{11}; IR ($CHCl_3$) 1685, 1593, 1160 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.93–7.77 (3 H, m), 7.41–7.11 (8 H, m), 6.87–6.82 (2 H, m), 6.29 and 6.02 (1 H, two dd, *J* = 9, 4 Hz, in a ratio of 1:3), 4.27 (1 H, m), 3.84 (1 H, s), 3.70 (3 H, s), 3.57 (1 H, br s), 2.86 (1 H, m), 2.18 (1 H, m), 1.95–1.45 (5 H, m), 0.91 (1 H, m), 0.70 (1 H, m), 0.57 (3 H, t, *J* = 7 Hz); MS, *m/e* calcd for $C_{32}H_{32}N_2O_4S_2$ 572.178, found 572.180.

(±)-2,3-Didehydro-1-[(*p*-methoxyphenyl)sulfonyl]aspidospermidin-10-one (16). A solution of **15** (130 mg, 0.23 mmol) in absolute ethanol (20 mL) and dimethylformamide (3 mL) (warmed to dissolve and then cooled to 20 °C) was treated with W-2 Raney Ni (2 spatulas), and allowed to stir for 20 min. The mixture was filtered through a Celite pad and the solids washed well with ethanol followed by methylene chloride. Removal of the solvent and purification by PLC, eluting with ethyl acetate/chloroform (1:9), gave **16** (70 mg, 60%) as a colorless foam: IR ($CHCl_3$) 1678, 1596, 1162 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.91 (1 H, d, *J* = 8 Hz), 7.73 (2 H, d, *J* = 10 Hz), 7.36 (1 H, m), 7.23–7.09 (2 H, m), 6.93 (2 H, d, *J* = 10 Hz), 6.18 (1 H, dd, *J* = 9, 4 Hz), 4.27 (1 H, m), 3.82 (3 H, s), 3.61 (1 H, s), 2.75 (1 H, m), 2.23 (1 H, m), 1.95–1.77 (4 H, m), 1.66–1.48 (3 H, m), 1.16 (1 H, m), 0.75 (1 H, m), 0.66 (3 H, t, J = 7 Hz); MS, *m/e* calcd for $C_{26}H_{28}N_2O_4S$ 464.177, found 464.181.

(±)-Aspidospermidine (3). To an ice-cold stirred slurry of lithium aluminum hydride (300 mg, 8.1 mmol) in THF (8 mL) was added a solution of **16** (60 mg, 0.13 mmol) in THF (1 mL). The solution was allowed to warm to 20 °C and stirred for 20 h. The mixture was cooled to 0 °C and treated with (i) H_2O (30 μL), (ii) 15% NaOH (300 μL), and (iii) H_2O (900 μL). The solids were removed by filtration and washed well with THF. Chromatography over Florisil gave, on elution with chloroform, (±)-aspidospermidine (**3**) (26 mg, 71%) as a colorless oil that crystallized upon standing: mp 99–103 °C (acetone). TLC behavior and IR and ^1H NMR spectra of this product were identical to with that of (+)-aspidospermidine prepared, as described above, by degradation of (+)-vincadifformine (see later).

(±)-2,3-Didehydro-1-[(*p*-methoxyphenyl)sulfonyl]-11β-methoxy-20,21-dinoraspidospermidin-8-one (18). A solution of **17** [S = $CH_2CH(OMe)_2$] (200 mg, 0.4 mmol) in benzene (10 μL) containing a catalytic amount of *p*-TsOH·H_2O was heated at reflux with a Dean-Stark condenser for 24 h. The volume of the reaction mixture was maintained by addition of benzene. Purification by chromatography gave **18** (110 mg, 59%) as a colorless foam. The product contained a trace amount of aldehyde **17** (S = CH_2CHO). Further purification by recrystallization of **18** from benzene/petroleum ether gave colorless crystals: mp 104–108 °C, ^1H NMR spectrum indicated that these crystals had occluded benzene; IR ($CHCl_3$) 1650, 1592, 1162 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.77 (1 H, d, *J* = 8 Hz), 7.68 (2 H, d, *J* = 10 Hz), 7.34–7.00 (3 H, m), 6.93 (2 H, d, *J* = 10 Hz), 6.41 (1 H, dd, *J* = 8, 3 Hz), 4.20 (1 H, dd, *J* =

9, 5 Hz), 4.4 (1 H, d, J = 4 Hz), 3.82 (3 H, s), 3.23–3.07 (2 H, m), 2.72 (3 H, s), 2.37 (2 H, t, J = 7 Hz), 2.25–2.11 (2 H, m), 2.00–1.70 (2 H, m), 1.59 (1 H, m); MS, m/e calcd for $C_{25}H_{26}N_2O_5S$ 446.156, found 466.156.

11β-Methoxy-20,21-dinoraspidospermidine (19). A solution of **18** (113 mg, 0.24 mmol) in THF (3 mL) was added to a stirred, ice-cold slurry of lithium aluminum hydride (100 mg, 2.6 mmol) in THF (2 mL). The mixture was heated at reflux for 2 h and allowed to stir at 20 °C for 12 h. The mixture was cooled to 0 °C and quenched by dropwise addition of 2 N sodium hydroxide. The product was extracted with chloroform and purified by chromatography. Elution with ethyl acetate/chloroform (7:3) gave **19** (22 mg, 32%) as a pale yellow solid: IR ($CHCl_3$) 3600–3100 (NH, br), 1603 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.18 (1 H, d, J = 7 Hz), 7.04 (1 H, t, J = 7 Hz), 6.77 (1 H, t, J = 7 Hz), 6.64 (1 H, d, J = 7 Hz), 3.73 (1 H, t, J = 7 Hz), 3.64 (1 H, t, J = 8 Hz), 3.39 (1 H, dd, J = 12, 5 Hz), 3.09 (1 H, m), 2.64 (3 H, s), 2.61 (1 H, d, J = 4 Hz), 2.14 (1 H, m), 2.02 (1 H, m), 1.91–1.07 (10 H, m). This substance did not give satisfactory MS or microanalytical data due to its ready oxidation.

Hydrolysis of 17 [S = $CH_2CH(OMe)_2$] to 17 (S = CH_2CHO). A solution of **17** [S : $CH_2CH(OMe)_2$] (300 mg, 0.60 mmol) in 2 N hydrochloric acid (5 mL) and THF (5 mL) was stirred at 20 °C for 14 h. The solution was concentrated in vacuo, water (15 mL) was added, and the product was extracted with chloroform (3 × 10 mL). The combined extracts were washed with brine and dried (Na_2SO_4). Removal of solvent gave a quantitative yield of the aldehyde **17** (S = CH_2CHO) as a colorless foam. Recrystallization from benzene/petroleum ether gave colorless crystals: mp 173–175 °C; IR ($CHCl_3$) 1730, 1630, 1595, 1258, 1160 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.29 (1 H, s), 8.23 (1 H, d, J = 8 Hz), 7.75 (2 H, d, J = 9 Hz), 7.41–7.25 (3 H, m), 6.93 (2 H, d, J = 10 Hz), 4.82 (1 H, d, J = 2 Hz), 4.11 (1 H, d, J = 17 Hz), 3.98 (1 H, d, J = 17 Hz), 3.79 (3 H, s), 3.48–2.93 (3 H, m), 2.64–1.73 (6 H, m); MS m/e calcd for $C_{24}H_{24}N_2O_5S$ 452.141, found 452.142.

***cis*-1,3,4,4a,5,6,7,11c-Octahydro-7-[(*p*-methoxyphenyl)sulfonyl]-1-[2,2-bis(methylthio)ethyl]-2*H*-pyrido[3,2-*c*]carbazol-2-one [17, S = $CH_2CH(SMe)_2$].** A solution of the aldehyde **17** (S = CH_2CHO) (100 mg, 0.22 mmol) in methylene chloride (10 mL) was treated with boron trifluoride etherate (400 μL), and methanethiol was bubbled slowly through the solution for 20 min. The solution was then poured into 10% aqueous sodium carbonate and shaken until no more CO_2 was evolved. The dichloromethane solution was then dried (Na_2SO_4); chromatography of the residue, after removal of solvent, gave on elution with chloroform/petroleum ether (3:2) **17** [S = $CH_2CH(SMe)_2$] (69 mg, 59%) as a colorless foam: IR ($CHCl_3$) 1640, 1594, 1165 cm^{-1}; ^1H NMR ($CDCl)_3$ δ 8.20 (1 H, m), 7.73 (2 H, d, J = 10 Hz), 7.53–7.17 (3 H, m), 6.88 (2 H, d, J = 10 Hz), 4.61 (1 H, d, J = 4 Hz), 3.78 (3 H, s), 3.66 (2 H, s), 3.20–2.93 (2 H, m), 2.46–1.43 (8 H, m), 1.83 (3 H, s), 1.62 (3 H, s); MS, m/e calcd for $C_{26}H_{30}N_2O_4S_3$ 530.137, found 530.136.

The thioacetal **17** [S = $CH_2CH(SMe)_2$] was also obtained by treating a solution of a 1:1 mixture of aldehyde **17** (S = CH_2CHO) and pentacyclic methyl ether **18** in methylene chloride with $BF_3{\cdot}Et_2O$ and methanethiol.

(±)-2,3-Didehydro-1-[(*p*-methoxyphenyl)sulfonyl]-11β-(methylthio)-20,21-dinoraspidospermidine-8-one (20). A 1:1 (as judged by NMR) mixture of **18** and **17** (S = CH_2CHO) (100 mg) in methylene chloride (10 mL) was treated with boron trifluoride etherate (400 μl), and methanethiol was slowly bubbled through this solution for 30 min. After the mixture was stirred for 15 h at 20 °C the only product observed by TLC and ^1H NMR was thioacetal **17** [S = $CH_2CH(SMe)_2$]. Stirring was continued for a further 20 h after which no trace of thioacetal was observed. Following aqueous sodium bicarbonate workup, purification of the residue by chromatography gave on elution with chloroform/petroleum ether (3:2) **20** (88 mg, 84%) as a colorless foam: IR ($CHCl_3$) 1670, 1595, 1160 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.15 (1 H, m), 7.70–7.60 (3 H, m), 7.38–7.19 (2 H, m), 6.84 (2 H, d, J = 10 Hz), 6.07 (1 H, m), 3.76 (1 H, m), 3.74 (3 H, s), 3.55 (2 H, m), 3.03 (1 H, m), 2.41–2.23 (3 H, m), 2.64–2.18 (4 H, m), 1.86 (3 H, s).

***cis*-1,3,4,4a,5,6,7,11c-Octahydro-7-[(*p*-methoxyphenyl)sulfonyl]-1-(2-hydroxyethyl)-2*H*-pyrido[3,2-*c*]carbazol-2-one (17, S = CH_2CH_2OH).** A solution of **17** (S = CH_2CHO) (900 mg, 2 mmol) in methanol (60 mL) was cooled to 0 °C and treated with sodium borohydride (150 mg, 3.9 mmol). After 10 min at 0 °C the solution was filtered to remove some insoluble material and concentrated in vacuo, and the residue crystallized from methanol to give **17** (S = CH_2CH_2OH) (760 mg, 84%) as colorless crystals: mp 187–189 °C. Purification by chromatography of the mother liquors increased the yield of **17** (S = CH_2CH_2OH) to 95%: IR ($CHCl_3$) 3380, 1630, 1590, 1260, 1161 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.27 (1 H, d, J = 8 Hz), 7.73 (2 H, d, J = 10 Hz), 7.45–7.25 (3 H, m), 6.91 (2 H, d, J = 10 Hz), 4.77 (1 H, br s), 3.82 (3 H, s), 3.61 (1 H, m), 3.50–3.27 (3 H, m), 3.23–2.93 (2 H, m), 2.50 (2 H, t, J = 7 Hz), 2.27–1.62 (6 H, m); MS, m/e calcd for $C_{24}H_{26}N_2O_5S$ 454.156, found 454.158.

***cis*-1,3,4,4a,5,6,7,11c-Octahydro-7-[(*p*-methoxyphenyl)sulfonyl]-1-[2-(phenylsulfinyl)ethyl]-2*H*-pyrido[3,2-*c*]carbazol-2-one [17, S = $CH_2CH_2S(O)Ph$].** To a rapidly stirred solution of **17** (S = CH_2CH_2SPh) (1.6 g, 2.93 mmol) in methylene chloride (60 mL) and 10% aqueous sodium bicarbonate (45 mL) at 0 °C was added, over 3 h, a solution of *m*-chloroperoxybenzoic acid (720 mg, 80–90% pure) in dichloromethane (20 mL). The dichloromethane layer was then separated and dried ($MgSO_4$), and removal of the solvent gave a quantitative yield of **17** [S = $CH_2CH_2S(O)Ph$] as a colorless foam. Both TLC and ^1H NMR indicated that the sulfoxide was a 1:1 mixture of diastereoisomers.

(±)-2,3-Didehydro-1-[(*p*-methoxyphenyl)sulfonyl]-11β-(phenylthio)-20,21-dinoraspidospermidin-8-one (21). A solution of **17** [S = $CH_2CH_2S(O)Ph$] (1.65 g, 2.93 mmol) in methylene chloride (40 mL) was cooled to 0 °C and treated with trifluoroacetic anhydride (900 μL, 1.34 g, 6.4 mmol) and allowed to warm to 20 °C over 1 h, after which time no trace of the sulfoxides was observed by TLC. The only material detected corresponded by TLC to aldehyde **17** (S = CH_2CHO). In a separate experiment the aldehyde was isolated after base hydrolysis of the reaction mixture at this stage. Chlorobenzene (40 mL) was added and the mixture heated to 135 °C over 1.5 h, during which time the methylene chloride was allowed to boil out in a stream of argon. After this time complete reaction was observed by TLC, and the solution was concentrated to approximately 10 mL. Hot methanol (30 mL) was then added and the mixture heated rapidly to boiling at which point the product began to crystallize to give **21** (1.3 g, 81%) as colorless crystals. An additional quantity (40 mg) of **21** was obtained by chromatography of the mother liquors to give a total of 1.34 g (84%). An analytical sample was crystallized from acetonitrile: mp 243–243.5 °C dec; IR ($CHCl_3$) 1650, 1595, 1165 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.98 (1 H, d, J = 8 Hz), 7.86 (2 H, d, J = 10 Hz), 7.43 (1 H, t, J = 7 Hz), 7.27–7.11 (5 H, m), 7.05–6.95 (2 H, m), 6.79 (2 H, d, J = 10 Hz), 6.45 (1 H, dd, J = 9, 4 Hz), 4.36 (1 H, dd, J = 14, 7 Hz), 4.14 (1 Hd, d, J = 5 Hz), 3.61 (3 H, s), 3.29–3.09 (2 H, m), 2.36 (2 H, t, J = 7 Hz), 2.25–1.68 (4 H, m), 1.52 (1 H, m); MS, m/e calcd for $C_{30}H_{28}N_2O_4S_2$ 544.149, found 544.146. Anal. Calcd for $C_{30}H_{28}N_2O_4S_2$: C, 66.15; H, 5.18; N, 5.14. Found: C, 65.78; H, 4.75; N, 5.02.

(±)-2,3,10,11-Tetrahydro-1-[(*p*-methoxyphenyl)sulfonyl]-20,21-dinoraspidospermidin-8-one (22). Raney Ni (W-2, 2 spatulas) was deactivated by heating in acetone (10 mL) at reflux for 1 h. The sulfide **21** (20 mg, 0.04 mmol) in ethanol/acetone (1:1) (10 mL) was added and heating at reflux continued for 1.5 h. The mixture was filtered through a Celite pad. Removal of solvent and purification by PLC gave on elution with methanol/ethyl acetate (1:19) **22** (7 mg, 44%) as a colorless glass: IR ($CHCl_3$) 1655, 1610, 1593, 1160 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.88 (1 H, d, J = 8 Hz), 7.68 (2 H, d, J = 10 Hz), 7.36 (1 H, m), 7.23–7.09 (2 H, m), 6.91 (2 H, d, J = 10 Hz), 6.68 (1 H, d, J = 5 Hz), 6.45 (1 H, dd, J = 8, 3 Hz), 4.36 (1 H, m), 3.82 (3 H, s), 3.50 (1 H, d, J = 5 Hz), 2.45–2.11 (3 H, m), 2.07–1.82 (2 H, m), 1.68 (1 H, m), 1.50 (1 H, m). A small quantity of **24** (2 mg, 13%) was also isolated.

A rapidly stirred solution of **21** (108 mg, 0.2 mmol) in methylene chloride (6 mL) and 10% aqueous sodium bicarbonate (5 mL) was cooled to 0 °C, and a solution of *m*-chloroperoxybenzoic acid (46 mg, 80–90% pure) in methylene chloride (2 mL) was added over 30 min. The dichloromethane layer was separated and the aqueous phase extracted with dichloromethane (5 mL). The combined extracts were dried (Na_2SO_4), and removal of solvent gave **23** (90 mg, 80%) as a pale yellow foam, pure by TLC and judging by TLC and ^1H NMR a single diastereoisomer: ^1H NMR ($CDCl_3$) δ 7.98 (1 H, m), 7.86–7.50 (5 H, m), 7.34 (1 H, m), 7.23–7.07 (2 H, m), 6.93 (2 H, d, J = 10 Hz), 6.34 (1 H, m), 4.27 (1 H, d, J = 4 Hz), 3.79 (1 H, s), 3.77 (1 H, m), 3.68 (3 H, s), 2.57 (1 H, t, J = 7 Hz), 2.45–2.31 (2 H, m), 2.18–2.02 (2 H, m), 1.93–1.75 (2 H, m), 1.54 (1 H, m).

The sulfoxide **23** (90 mg, 0.15 mmol) in toluene (10 mL) was heated at reflux for 15 h. Removal of solvent and chromatographic purification gave **22** (28 mg, 40%) as a light yellow glass, whose TLC and NMR spectrum were identical with **22** prepared by reduction of **21** with deactivated Raney Ni (W-2).

(±)-2,3-Didehydro-1-[(*p*-methoxyphenyl)sulfonyl]-20,21-dinoraspidospermid-8-one (24) and Deethylaspidospermid-8-one (25). A solution of **21** (300 mg, 0.55 mmol) in DMF (25 mL) (warmed to dissolve) was treated with Raney Ni (W-2) (~4 spatulas). After the mixture was stirred at 20 °C for 2 h no trace of either **21** or **22** was detected by TLC; the mixture was filtered through a Celite pad, and the solids were best washed by suspending them briefly in methylene chloride. Removal of the solvent and recrystallization of the residue from chloroform/petroleum ether gave **24** (130 mg, 54%) as colorless crystals: mp 237–238 °C; IR ($CHCl_3$) 1648, 1622, 1594, 1162 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.93 (1 H, d, J = 9 Hz), 7.70 (2 H, d, J = 10 Hz), 7.39 (1 H, m), 7.20–7.11 (2 H, m), 6.91 (2 H, d, J = 10 Hz), 6.43 (1 H, dd, J = 8, 4 Hz), 4.02 (1

H, dd, J = 12, 7 Hz), 3.91 (1 H, d, J = 5 Hz), 3.82 (3 H, s), 3.11 (1 H, td, J = 11, 6 Hz), 2.36 (2 H, t, J = 6 Hz), 2.27–2.04 (2 H, m), 1.95–1.79 (2 H, m), 1.52 (1 H, m), 1.14 (1 H, m), 1.82 (1 H, m); MS, m/e calcd for $C_{24}H_{24}N_2O_4S$ 436.144, found 436.146.

The major byproduct of this reaction was identified as **25**, which was isolated by extraction of the reaction mixture with 2 N hydrochloric acid, followed by addition of aqueous sodium hydroxide until basic and back-extraction with ethyl acetate. The amine **25** was isolated in typically 26% yield as colorless crystals from chloroform/petroleum ether: mp 214–215 °C; IR ($CHCl_3$) 3380 (br), 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.18–7.02 (2 H, m), 6.79 (1 H, t, J = 7 Hz), 6.70 (1 H, d, J = 7 Hz), 4.09 (1 H, d, J = 4 Hz), 3.77–3.48 (3 H, m), 3.25 (1 H, q, J = 7.5 Hz), 2.43–2.23 (3 H, m), 2.02–1.68 (4 H, m), 1.57 (1 H, m), 1.18 (3 H, m); MS, m/e calcd for $C_{17}H_2ON_2O$ 268.157, found 268.157.

(±)-*N*-Acetyldeethylaspidospermidine (26).[16] A solution of **24** (116 mg, 0.27 mmol) in THF (10 mL) was added dropwise to a stirred slurry of lithium aluminum hydride (400 mg, 10.5 mmol) in THF (10 mL). The mixture was stirred for 24 h, cooled to 0 °C, and quenched with water (1.9 mL) and 2 N sodium hydroxide (0.5 mL). The solids were removed by filtration and washed well with THF. The filtrate was dried (Na_2SO_4) and purified by chromatography over Florisil, eluting with methanol/ethyl acetate (1:9) to give (±)-deethylaspidospermidine (52 mg, 77%) as a colorless glass: IR ($CHCl_3$) 3370 (br, NH), 1605, 1479, 1460 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.18–7.00 (2 H, m)8 6.82–6.64 (2 H, m), 3.75–3.64 (2 H, m), 3.50 (1 H, dd, J = 11, 6 Hz), 3.41–3.02 (3 H, m br, NH), 2.48 (1 H, d, J = 3.5 Hz), 2.36–2.18 (2 H, m), 2.09–1.14 (9 H, m).

A solution of (±)-deethylaspidospermidine (50 mg, 0.2 mmol) in dry pyridine (2 mL) was treated with acetic anhydride (1.2 mL) and allowed to stir at 25 °C for 14 h. The mixture was concentrated in vacuo; 10% aqueous sodium bicarbonate (10 mL) was added and the mixture extracted with dichloromethane (3 × 5 mL). The combined extracts were washed with water and dried (Na_2SO_4). Purification by PLC eluting with ethyl acetate/methanol (9:1) gave (±)-*N*-acetyldeethylaspidospermidine **26** (30 mg, 51%) as a colorless glass: IR ($CHCl_3$) 1648, 1595 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.16 (1 H, d, J = 8 Hz), 7.34–7.05 (3 H, m), 4.14 (1 H, dd, J = 11, 6 Hz), 3.32–3.11 (2 H, m), 2.61 (1 H, br s), 2.41–1.20 (13 H, m), 2.27 (3 H, s).[16]

(±)-2,3-Didehydro-1-[(*p*-methoxyphenyl)sulfonyl]-11β-(phenylthio)-aspidospermidin-8-one (29). A rapidly stirred solution of **27**[1] (402 mg, 0.7 mmol) in methylene chloride (20 mL) and 10% aqueous sodium bicarbonate (10 mL) was cooled to 0 °C, and a solution of *m*-chloroperoxybenzoic acid (170 mg, 80–90% pure) in methylene chloride (8 mL) was added dropwise over 50 min. The methylene chloride layer was separated and the aqueous phase was extracted once with methylene chloride (10 mL). The combined extracts were washed with brine and dried (Na_2SO_4). Removal of solvent gave a quantitative yield of the sulfoxides **28** as a colorless foam. This product was clearly a mixture of diastereosiomers as judged by NMR and TLC analysis.

A solution of the sulfoxides **28** (280 mg, 0.47 mmol) in anhydrous methylene chloride (10 mL) was cooled to 0 °C and trifluoroacetic anhydride (200 μL, 297 mg, 1.42 mmol) added. After it was stirred for 10 min the solution was allowed to warm to 20 °C and stirring continued for a further 30 min. Chlorobenzene (10 mL) was added, and the mixture was heated to 135 °C over 1.5 h during which time the methylene chloride was allowed to boil out in a slow stream of argon. Heating was maintained for a further 2.5 h. Removal of solvent in vacuo and chromatographic purification gave on elution with chloroform/petroleum ether (1:1) **29** (220 mg, 81%) as a colorless foam. The product was crystallized from benzene/petroleum ether to give **29** as colorless crystals: mp 135–137 °C; NMR analysis indicated that benzene (0.5 equiv) was present in the crystalline material; IR ($CHCl_3$) 1650, 1597, 1260, 1159 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.02 (1 H, d, J = 8 Hz), 7.84 (2 H, d, J = 9 Hz), 7.45 (1 H, m), 7.27–7.04 (7 H, m), 6.78 (2 H, d, J = 9 Hz), 6.18 (1 H, dd, J = 9, 4 Hz), 4.27 (1 H, dd, J = 15, 19 Hz), 3.61 (3 H, s), 3.52 (1 H, s), 3.34–3.18 (2 H, m), 2.41–2.07 (3 H, m), 1.98–1.77 (2 H, m), 1.29 (1 H, m), 0.84 (2 H, q, J = 7 Hz), 0.61 (3 H, t, J = 7 Hz); MS, m/e 572 (M^+, 2.8%), 463 (M–PhS, 10%), 401 ($M^+ - p$-$MeOC_6H_4SO_2$, 40%), 208 (100%). Anal. Calcd for $C_{32}H_{32}N_2O_4S_2 \cdot 0.5C_6H_6$: C, 68.71; H, 5.76; N, 4.68. Found: C, 69.28; H, 5.68; N, 4.84. (The presence of benzene was confirmed in the X-ray crystallographic work.)

(±)-2,3-Didehydro-1-[(*p*-methoxyphenyl)sulfonyl]aspidospermidin-8-one 30. A solution of **29** (120 mg, 0.21 mmol) in absolute ethanol (5 mL) was treated with Raney Ni W-2 (~3 spatulas). After it was stirred at 20 °C for 1 h the mixture was filtered through a Celite pad, and the solids were washed well with ethanol followed by methylene chloride. Removal of solvent in vacuo gave **30** (79 mg, 81%) as a colorless oil that crystallized on standing. Recrystallization from benzene/petroleum ether gave colorless crystals: mp 195–196 °C; IR ($CHCl_3$) 1648, 1595, 1260, 1160 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.91 (1 H, d, J = 8 Hz), 7.70 (2 H, d, J = 9 Hz), 7.35 (1 H, m), 7.18–7.04 (2 H, m), 6.86 (2 H, d, J = 9 Hz), 6.16 (1 H, dd, J = 9, 4 Hz), 3.85 (1 H, m), 3.80 (3 H, s), 3.34 (1 H, s), 3.11 (1 H, td, J = 12, 6 Hz), 2.38–2.04 (3 H, m), 1.97–1.79 (2 H, m), 1.41–1.18 (2 H, m), 1.05–0.82 (3 H, m), 0.66 (3 H, t, J = 7 Hz); MS, m/e 464 (M^+, 5%), 339 (43%), 293 ($M^+ - p$-$MeOC_6H_4SO_2$, 100%). Anal. Calcd for $C_{26}H_{28}N_2O_4S$: C, 67.22, H, 6.07; N, 6.03. Found: C, 66.98; H, 5.81; N, 6.13.

(±)-Aspidospermidine (3). A solution of **30** (79 mg, 0.17 mmol) in THF (5 mL) was added dropwise to a stirred slurry of lithium aluminum hydride (300 mg, 7.9 mmol) in THF (10 mL) at 0 °C. The mixture was allowed to warm to 20 °C and stirred for 48 h.

The mixture was cooled to 0 °C and treated with (i) H_2O (300 μL), (ii) 15% NaOH (300 μL), and (iii) H_2O (900 μL). The mixture was filtered and washed well with dichloromethane. The organic layer was washed with 2 N NaOH (10 mL) and dried (Na_2SO_4), and the product was purified by PLC eluting with methanol/ethyl acetate (1:19) to give (±)-aspidospermidine **3** (26 mg, 54%) as a colorless oil that crystallized on standing. The product was recrystallized from acetone to give colorless crystals: mp 99–103 °C; IR ($CHCl_3$) 3360 (br, NH), 1600, 1475, 1455, 1325, 1158, 1124, 1013 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.18–6.98 (2 H, m), 6.72 (1 H, t, J = 7.5 Hz), 6.66 (1 H, d, J = 7.5 Hz), 3.50 (1 H, dd, J = 7.5, 11 Hz), 3.18–3.00 (2, H, m), 2.95 (1 H, br, NH), 2.38–2.18 (3 H, m), 2.04–1.86 (2 H, m), 1.84–1.25 (7 H, m), 1.20–1.00 (2 H, m), 0.89 (1 H, m), 0.64 (3 H, t, J = 7 Hz).

This material had superimposable IR and ^1H NMR spectra and identical R_f values in MeOH/EtOAc (1:4) (R_f 0.42), $CHCl_3/Me_2CO$ (3:7) (R_f 0.56), EtOAc/EtOH (3:2) (R_f 0.50), and MeOH/MeCN (1:19) (R_f 0.20) with a sample of (+)-aspidospermidine prepared as described below.

A solution of (+)-vincadifformine (40 mg) in 2 N hydrochloric acid (3 mL) was heated in a sealed tube at 100 °C for 6 h. The mixture was cooled and made basic with 0.88 ammonia solution, and the product was extracted with ether (4 × 10 mL). The combined extracts were dried (Na_2SO_4), and removal of the solvent gave (+)-dehydroaspidospermidine as a pale yellow oil. This material was immediately dissolved in ether (3 mL) and added dropwise to a stirred slurry of lithium aluminum hydride (40 mg) in ether (3 mL). The mixture was heated at reflux for 10 min, cooled to 0 °C, and quenched with 2 N sodium hydroxide. The solids were filtered off and washed well with ether. The filtrate was dried (Na_2SO_4). Purification by PLC (95% EtOAc/5% MeOH) gave (+)-aspidospermidine (18 mg) as colorless crystals from acetone:[11] mp 116–118 °C (lit. mp 119–120 °C).

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Registry No. (±)-**3**, 7689-02-3; (±)-**7**, 81816-22-0; (±)-**8** (X = Cl), 85924-05-6; (±)-**8** (X = Br), 85924-06-7; (±)-**8** (X = SPh), 85924-07-8; (±)-**8** (X = PhS(O)), 85924-08-9; (±)-**10** (E = $COCH_2S(O)Ph$) isomer 1, 85924-09-0; (±)-**10** (E = $COCH_2S(O)Ph$) isomer 2, 85955-82-4; (±)-**10** (E = $COCH_2SPh$), 85924-10-3; (±)-**10** (E = H), 81816-22-0; (±)-**10** (E = $COCH_2Br$), 85924-11-4; (±)-**11**, 85924-12-5; (±)-**12**, 85924-13-6; (±)-**14** (E = H), 85924-14-7; (±)-**14** (E = $CO_2CH_2CCl_3$), 85923-70-2; (±)-**14** (R = $COCH_2S(O)Ph$), 85924-15-8; (±)-**14** (R = $COCH_2SPh$), 85924-16-9; (±)-**15**, 85924-17-0; (±)-**16**, 85924-18-1; (±)-**17** (S = $CH_2CH(OMe)_2$), 85923-59-7; (±)-**17** (S = CH_2CHO), 85924-19-2; (±)-**17** (S = CH_2CH_2OH), 85924-20-5; (±)-**17** (S = $CH_2CH_2S(O)Ph$), 85924-21-6; (±)-**17** (S = $CH_2CH(SMe)_2$), 85924-22-7; (±)-**18**, 85924-23-8; (±)-**19**, 85924-24-9; (±)-**20**, 85924-25-0; (±)-**21**, 85924-26-1; (±)-**22**, 85924-27-2; (±)-**23**, 85924-28-3; (±)-**24**, 85924-29-4; (±)-**25**, 85924-30-7; (±)-**26**, 40360-65-4; (±)-**27**, 80664-29-5; (±)-**28**, 85993-33-5; (±)-**29**, 80664-34-2; (±)-**30**, 80664-35-3; (±)-deethylaspidospermidine, 61848-78-0; chloroacetyl chloride, 79-04-9; bromoacetyl chloride, 22118-09-8; (phenylthio)acetyl chloride, 7031-27-8; methanethiol, 74-93-1.