Total Synthesis of (±)-Aspidofractinine and (±)-Aspidospermidine

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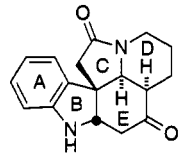
Functional group manipulations on a previously constructed, easily accessible deethylaspidospermidine derivative have transformed the latter in few steps into a ring E diene, whose Diels–Alder reaction with phenyl vinyl sulfone and subsequent reductions has led to (±)-aspidofractinine. One-bond unraveling of a (phenylsulfonyl)aspidofractinine intermediate, followed by reductions, provided a second-generation pathway to (±)-aspidospermidine.

The ready, two-step access to the pentacyclic nucleus (**1**) of the Aspidosperma alkaloids (N-alkylation of 3-acetyl-1,4,5,6-tetrahydropyridine by indoleacetic anhydride, followed by acid-induced cyclization)[1] has made available a versatile intermediate for the construction of Aspidosperma and related bases. A recent synthesis of (±)-aspidospermidine (**3**)[2] (via pentacycle **2b**) illustrated one possible use of the intermediate in alkaloid synthesis and the present paper portrays its utilization in a synthesis of (±)-aspidofractinine (**4**)[3] and in a second-generation synthesis of (±)-aspidospermidine (**3**).[4]



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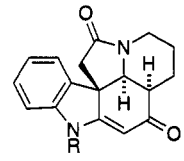
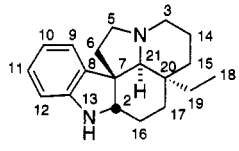


2a, R = H
b, R = $SO_2C_6H_4Me(p)$
c, R = $CH_2O(CH_2)_2SiMe_3$
d, R = CO_2Me



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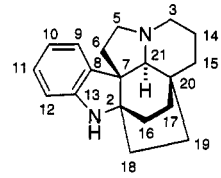

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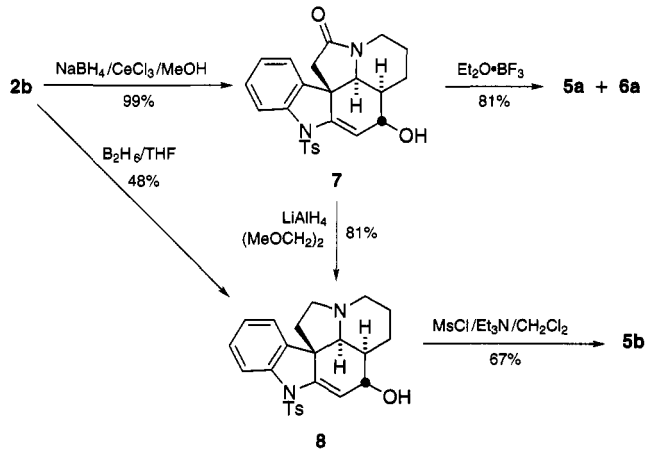
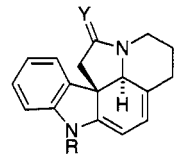
Aspidofractinine (4). For the buildup of the aspidofractinine-like, hexacyclic nucleus it was decided to start with easily prepared pentacycle **2b**,[2] convert its ring E into a 1,3-cyclohexadiene, and expose the resultant product to a Diels–Alder reaction with an appropriate dienophile (i.e., follow a reaction route introduced conceptually by Ban in the mid-1970s[3]). Furthermore, it was hoped that intermediate **2b** could be transformed into four dienes (**5a–d**), thus lending a certain amount of flexibility to the cycloaddition process. Dienes **5c** and **5d** were expected to exist as tautomers **6a** and **6b**,

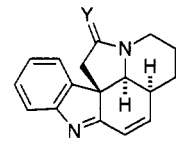
Scheme 1



respectively, but be formed in situ during the Diels–Alder reactions.



5a, R = Ts, Y = O
b, R = Ts, Y = H_2
c, R = H, Y = O
d, R = H, Y = H_2
e, R = CO_2Me, Y = O



6a, Y = O
b, Y = H_2

As Scheme 1 indicates, borohydride reduction of keto lactam **2b** yielded quantitatively hydroxy lactam **7**, whose treatment with boron trifluoride etherate produced a 5:1 mixture of diene **5a** and α,β-unsaturated imine **6a** (i.e., the tautomer of diene **5c**) in 81% yield. Thus two of the four desired compounds were in hand.

Reduction of keto lactam **2b** with diborane gave alcohol **8** (48%), whose dehydration with methanesulfonyl chloride and triethylamine furnished the third of the four needed compounds—diene **5b** (67%). The alcohol intermediates could be obtained also from lithium aluminum hydride reduction of keto lactam **2b**, albeit in the form of product mixtures. Thus in refluxing tetrahydrofuran the reaction led to a 2.3:1 mixture (97%) of olefin **9a** and alcohol **8** and at 0 °C to a 2.5:1.4:1 **8/9a/7** mixture (78%). Reduction of hydroxy lactam **7** with lithium aluminum hydride in 1,2-dimethoxyethane afforded alcohol **8** (81%).

The last of the four dienes, **5d** (but in the form of **6b**), unfortunately escaped isolation. The formation of olefin

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(1) (a) Wenkert, E.; Bindra, J. S.; Chauncy, B. *Synth. Commun.* **1972**, *2*, 285. (b) Wenkert, E.; Orito, K.; Simmons, D. P.; Kunesch, N.; Ardisson, J.; Poisson, J. *Tetrahedron* **1983**, *39*, 3719.

(2) Le Ménez, P.; Kunesch, N.; Liu, S.; Wenkert, E. *J. Org. Chem.* **1991**, *56*, 2915.

(3) For previous syntheses of this alkaloid, see: Ban, Y.; Honma, Y.; Oishi, T. *Tetrahedron Lett.* **1976**, 111. Kinoshita, H.; Ohnuma, T.; Oishi, T.; Ban, Y. *Chem. Lett.* **1986**, 927. Cartier, C.; Oahrani, M.; Levy, J. *Tetrahedron Lett.* **1989**, 1951. Dufour, M.; Gramain, J.-C.; Husson, H.-P.; Sinibaldi, M. E.; Troin, Y. *Tetrahedron Lett.* **1989**, 3429; *J. Org. Chem.* **1990**, *55*, 5483.

(4) For previous syntheses of this alkaloid, see ref 2. Wenkert, E.; Hudlicky, T. *J. Org. Chem.* **1988**, *53*, 1953 and references therein.

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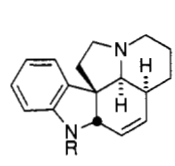
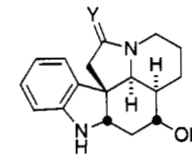
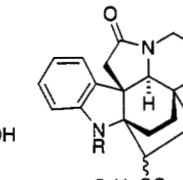
9a in the lithium aluminum hydride reduction of keto lactam **2b** showed indolenine **6b** to have been an all too easily reducible intermediate in the multistep process. An attempted **9a** → **6b** conversion by lead tetraacetate oxidation failed, as did a boron trifluoride-promoted **8** → **6b** detosylation–dehydration (tested by analogy with the above **7** → **6a** transformation). Finally, reductive detosylation of sulfonamide **8** was tried with the hope that the resultant β-hydroxy imine subsequently would undergo ready dehydration. But interaction of compound **8** with sodium amalgam in methanol led to alcohol **10a** (56%), unfortunately a product of overreduction.[5]



9a, R = H
b, R = $CH_2O(CH_2)_2SiMe_3$



10a, Y = H_2
b, Y = O



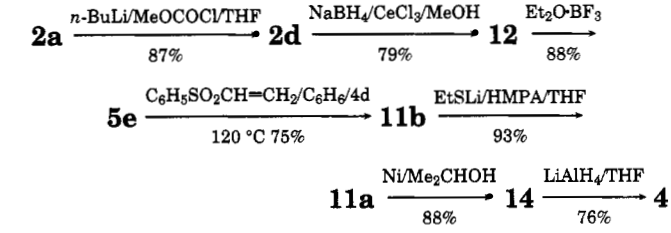
11a, R = H
b, R = CO_2Me

Phenyl vinyl sulfone was chosen as the dienophile for the Diels–Alder reaction[6] and yielded adduct **11a** (87%) as a single stereoisomer of undetermined C(18) configuration on exposure of conjugated indolenine **6a** (reacting presumably via its dienamine tautomer **5c**) to a benzene solution of the sulfone at 80 °C. Contrastingly, the *N*-tosyl dienamines **5a** and **5b** proved inert toward (phenylsulfonyl)ethylene in benzene solution at up to 140 °C for up to 6 days of reaction time. This lack of diene reactivity could not be overcome by the utilization of commercially available 1,2- and 1,1-bis(phenylsulfonyl)-ethylenes and cyclic 1,2-disulfonylethylenes.[7] Whereas the ease of cycloaddition of electron-rich dienes such as **5c** with (phenylsulfonyl)ethylene was precedented,[6a–c] the inertness of the electron-poorer sulfonamido dienes (**5a–b**) was surprising, especially in the face of the successful Diels–Alder reactions of 17-ethoxy-**5b** with (phenylsulfonyl)ethylene[6d] and of a sulfonamido diene of type **5a** with nitroethylene.[3] Thus compared with previous examples, the present unsuccessful cycloaddition cases revolved around the use of both an electron-poor dienophile and electron-deficient dienes.

In view of the facile **6a** → **11a** cycloaddition, indolenine **6a** should have been chosen as the proper intermediate for the further pursuit of the aspidofractinine synthesis. However its production as only a minor constituent of a two-component reaction mixture (see Scheme 1) and its fragility blocked its use.[8]

As Scheme 2 illustrates, the reaction route emanating from N^a-methoxycarbonyl keto lactam **2d** led ultimately to aspidofractinine (**4**). Treatment of keto lactam **2a** with

Scheme 2



n-butyllithium and methyl chlorocarbonate yielded derivative **2d**[1b] (96%), whose reduction with sodium borohydride and ceric chloride gave alcohol **12** (75%). Interaction of the latter with boron trifluoride etherate afforded diene **5e** (88%) and a trace of alcohol **13** (a single stereoisomer of undetermined C-2 configuration), the heating of whose benzene solution liberated quantitatively more diene **5e**. Cycloaddition of the latter with phenyl vinyl sulfone in benzene solution at 125 °C for 4 days furnished adduct **11b** (75%), whose exposure to

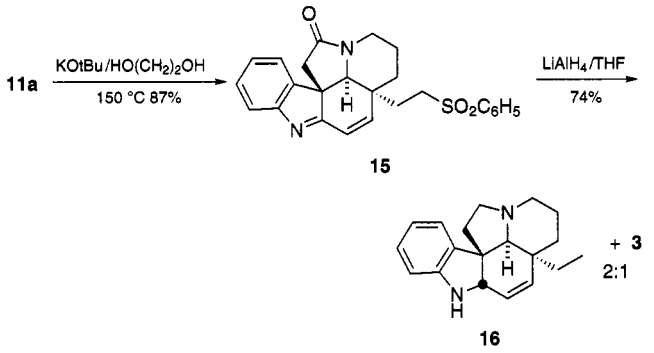
(5) The C(17) stereochemistry of alcohols **7** and **8** was reflected by the coupling characteristics of H(17) in the ^1H NMR spectra. It was confirmed by the full ^1H NMR spectral analyses of alcohol **10a** and its 17-epimer[1b] [IR ($CHCl_3$) OH 3380 (br m), NH 3350 (br m), C=C 1605 (m) cm^{-1}; ^1H NMR δ 1.27 (t, 1, *J* = 12, 11 Hz, H-16), 1.58–1.68 (m, 3, H-20, C-14 Hs), 1.90–1.94 (m, 1, H-5), 2.02–2.06 (m, 1, H-16), 2.08–2.16 (m, 2, C-6 Hs), 2.19–2.36 (m, 3, H-3, C-15 Hs), 2.74 (br s, 1, H-21), 3.14–3.20 (m, 2, H-3, H-5), 3.73 (dd, 1, *J* = 11, 6 Hz, H-2), 3.91 (br s, 1, H-17), 6.68 (d, 1, *J* = 8 Hz, H-12), 6.73 (t, 1, *J* = 8 Hz, H-10), 7.01 (t, 1, *J* = 8 Hz, H-11), 7.09 (d, 1, *J* = 8 Hz, H-9); ^{13}C NMR δ 23.3 (C-4), 28.9 (C-15), 35.4 (C-20), 38.7 (C-16), 39.3 (C-6), 53.9 (C-5), 54.0 (C-7), 54.9 (C-3), 63.0 (C-2), 69.1 (C-21), 73.3 (C-17), 111.9 (C-12), 120.3 (C-10), 122.9 (C-9), 128.7 (C-11), 134.0 (C-8), 150.9 (C-13)].

(6) For previous example of cycloadditions of dienes of structure type **5** with (phenylsulfonyl)ethylene, see: (a) Kuehne, M.; Seaton, P. J. *J. Org. Chem.* **1985**, *50*, 4790. (b) Ogawa, M.; Kitagawa, Y.; Natsume, M. *Tetrahedron Lett.* **1987**, 3985. (c) Wenkert, E.; Pestchanker, M. *J. Org. Chem.* **1988**, *53*, 4875. (d) LeMénez, P.; Sápi, J.; Kunesch, N.; Angell, E. C.; Wenkert, E. *J. Org. Chem.* **1989**, *54*, 3216.

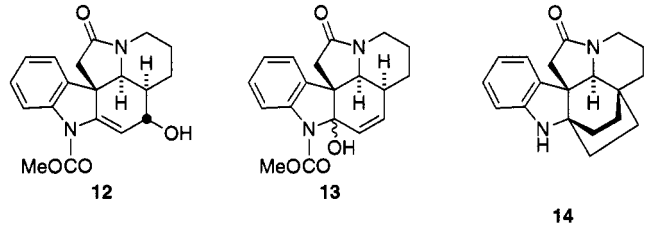
(7) Wenkert, E.; Broka, C. A. *Finn. Chem. Lett.* **1984**, *126*.

(8) As a consequence N^a-unsubstituted Diels–Alder dienes or compounds N^a-substituted by groups other than sulfonyl moieties had to be investigated. Unfortunately reduction of vinylogous amide **2a** with lithium aluminum hydride gave over-reduced olefin **9a** (22%) (see Experimental Section) and with sodium borohydride and ceric chloride over-reduced alcohol **10b** (63%) [mp 189–192 °C; ^1H NMR δ 1.24–1.53 (m, 2, H-14, H-20), 1.58–1.68 (m, 2, H-14, H-16), 1.98–2.00 (m, 1, H-16), 2.26 (d, 1, *J* = 17 Hz, H-6), 2.31–2.36 (m, 1, H-15), 2.68–2.74 (m, 1, H-15), 2.75 (d, 1, *J* = 17 H, H-6), 2.81–2.87 (m, 1, H-3), 3.59 (dd, 1, *J* = 11, 5, Hz, H-2), 3.76 (ddd, 1, *J* = 10, 10, 2 Hz, H-17), 3.99 (d, 1, *J* = 4 Hz, H-21), 4.11–4.17 (m, 1, H-3), 6.68 (d, 1, *J* = 7 Hz, H-12), 6.80 (t, 1, *J* = 7 Hz, H-10), 7.08–7.13 (m, 2, H-9, H-11); ^{13}C NMR δ 18.4 (C-14), 23.9 (C-15), 38.6 (C-16), 39.5 (C-20), 40.8 (C-6), 44.6 (C-3), 48.7 (C-7), 61.8 (C-2), 63.2 (C-21), 64.7 (C-17), 110.6 (C-12), 119.5 (C-10), 122.4 (C-9), 128.7 (C-11), 129.9 (C-8), 149.8 (C-13), 173.0 (C-5)]. N^a-Alkylation of vinylogous amide **2a** with [β-(trimethylsilyl)-ethoxy]methyl chloride and sodium hydroxide in toluene under phase-transfer conditions produced a 3:1 mixture (46%) of isomers **2c** [liquid; UV λ_{max} 238 nm (ε 12 000), 295 (5900), 341 (8500); IR C=O 1685 (s), 1635 (s), C=C 1595 (s) cm^{-1}; ^1H NMR δ −0.06 (s, 9, methyls), 0.89 (t, 2, *J* = 8 Hz, $SiCH_2$), 1.58–1.62 (m, 3, H-15, C-14 Hs), 2.46–2.52 (m, 1, H-15), 2.54–2.56 (m, 1, H-20), 2.60 (d, 1, *J* = 18 Hz, H-6), 2.77 (d, 1, *J* = 18 Hz, H-6), 2.80–2.85 (m, 1, H-3), 3.65 (t, 2, *J* = 8 Hz, OCH_2), 4.21–4.26 (m, 1, H-3), 4.39 (d, 1, *J* = 6 Hz, H-21), 5.02 (q, 2, *J* = 11 Hz, NCH_2O), 5.63 (s, 1, H-16), 6.97 (d, 1, *J* = 8 Hz, H-12), 7.04 (t, 1, *J* = 8 Hz, H-10), 7.24–7.28 (m, 2, H-9, H-11); ^{13}C NMR δ −1.5 (Me), 17.7 ($SiCH_2$), 20.8 (C-14), 22.3 (C-15), 40.1 (C-6), 42.9 (C-20), 47.6 (C-7), 51.8 (C-3), 55.6 (C-21), 66.5 (OCH_2), 73.1 (NCH_2O), 97.2 (C-16), 109.2 (C-12), 120.9 (C-10), 122.9 (C-9), 128.7 (C-11), 134.3 (C-8), 143.5 (C-13), 168.7 (C-5), 169.3 (C-2), 194.3 (C-17); MS *m/e* 410 (M^+, 5), 75 (base)] and 20-*epi*-**2c** [liquid; ^1H NMR δ −0.11 (s, 9, (methyls), 0.94 (t, 2, *J* = 8 Hz, $SiCH_2$), 1.47 (m, 1, H-15), 1.58–1.76 (m, 1, H-14), 1.86 (br dd, 1, *J* = 13, 3 Hz, H-14), 2.33 (ddd, 1, *J* = 11, 11, 2 Hz, H-20), 2.48 (br s, 1, H-15), 2.48 (d, 1, *J* = 17 Hz, H-6), 3.04 (ddd, 1, *J* = 14, 13, 4 Hz, H-3), 3.18 (d, 1, *J* = 17 Hz, H-6), 3.61 (dt, 2, *J* = 8, 1 Hz, OCH_2), 3.81 (d, 1, *J* = 11 Hz, H-21), 4.26 (dd, 1, *J* = 14, 3 Hz, H-3), 5.03 (q, 2, *J* = 11 Hz, NCH_2O), 5.66 (s, 1, H-16), 6.94–6.99 (m, 2, H-10, H-12), 7.27 (t, 1, *J* = 7 Hz, H-11), 7.35 (d, 1, *J* = 7 Hz, H-9); ^{13}C NMR δ −1.4 (Me), 17.8 ($SiCH_2$), 23.2 (C-14), 25.2 (C-15), 41.4 (C-6), 45.4 (C-3), 48.0 (C-7), 48.1 (C-20), 66.5 (OCH_2), 67.9 (C-21), 72.9 (NCH_2O), 101.3 (C-16), 109.0 (C-12), 121.6 (C-10), 122.6 (C-9), 129.1 (C-11), 134.3 (C-8), 143.5 (C-13), 167.7 (C-2), 172.3 (C-5), 193.2 (C-5)]. Reduction of N^a-alkylated vinylogous amide **2c** with lithium aluminum hydride in the presence of potassium *tert*-butoxide (conditions designed for interception of the expected α,β-unsaturated indolenium cation intermediate by C-20 deprotonation) furnished unfortunately over-reduction product **9b** [liquid; IR C=O 1685 (s), C=C 1600 (m) cm^{-1}; ^1H NMR δ −0.4 (s, 9, methyls), 0.92–0.99 (m, 2, $SiCH_2$), 1.61–1.70 (m, 3, H-15, C-14 Hs), 2.49–2.54 (m, 1, H-15), 2.58–2.65 (m, 1, H-20), 2.71 (d, 1, *J* = 3 Hz, H-21), 2.85 (d, 1, *J* = 17 Hz, H-6), 3.06 (ddd, 1, *J* = 13, 13, 4 Hz, H-3), 3.21 (d, 1, *J* = 17 Hz, H-6), 3.40–3.65 (m, 2, OCH_2), 3.83 (d, 1, *J* = 1 Hz, H-2), 4.27–4.33 (m, 1, H-3), 5.04–5.08 (m, 2, NCH_2O), 5.11–5.14 (m, 2, H-16, H-17), 6.97 (d, 1, *J* = 8 Hz, H-12), 7.01 (t, 1, *J* = 8 Hz, H-10), 7.23–7.33 (m, 2, H-9, H-11)]. These results indicated the necessity for N^a to be substituted by an electron-withdrawing group, albeit weaker than sulfonyl function.

Scheme 3



lithium ethanethiolate in hexamethylphosphoramide–tetrahydrofuran produced indoline **11a** (93%). Reduction of hexacycle **11a** with Raney nickel in an isopropyl alcohol solution and the resultant 5-oxoaspidofractinine (**14**) (88%) with lithium aluminum hydride created (±)-aspidofractinine (**4**) (76%).[3]



Aspidospermidine (3). A recent synthesis of aspidospermidine (**3**)[2] included as crucial reaction the angular ethylation of keto lactam **2b**, a sterically exceedingly difficult process in view of the establishment of a quaternary carbon site in a 1,3-relationship to another quaternary carbon center. Whereas under the circumstances the formation of 20-α-ethyl-**2b** in 44% yield was an admirable feat, an alternate route for the C(20) introduction of a two-carbon unit remained a desirable goal of synthesis. Since the above **6a** → **11a** and **5e** → **11b** Diels–Alder reactions were high-yielding C(20)-ethylation equivalents, only a C(2)–C(18) bond fragmentation of an appropriate hexacyclic precursor of aspidofractinine (**4**) stood in the way of achieving the goal.

Heating of an ethylene glycol solution of potassium *tert*-butoxide and hexacycle **11a** at 150 °C produced pentacyclic indolenine **15** (87%), whose lithium aluminum hydride reduction led to a 2:1 mixture (74%) of 16,17-didehydroaspidospermidine (**16**) and (±)-aspidospermidine (**3**) (Scheme 3). Conversion of the olefin **16** into the racemic alkaloid (**3**) has been reported.[2] This completes the transformation of an aspidofractinine-bound hexacyclic intermediate into (±)-aspidospermidine (**3**).

Experimental Section

Melting points were observed on a Reichert micro hotstage and are uncorrected. Ultraviolet spectra of ethanol solutions and infrared spectra of $CHCl_3$ solutions were recorded on IBM 9400 and Perkin-Elmer 1320 spectrophotometers, respectively. ^1H and ^{13}C NMR spectra of $CDCl_3$ solutions were taken on a GE QE-300 spectrometer operating in the Fourier transform mode at 300 and 75.5 MHz, respectively. The carbon shifts are downfield from Me_4Si; $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm. Complete hydrogen and carbon signal assignments are based on COSY and CSCM4 spectroscopies and APT experiments. On use of dry solvents the reactions were performed under argon and in glassware dried at 120 °C for 1 h prior to usage. On workup, CH_2Cl_2 was the extracting solvent and the extracts were washed with water and brine and dried over anhydrous Na_2SO_4. Chromatographic separations were executed on 60–200 mesh E. M. Laboratories SiO_2. Low-resolution mass spectra were recorded on a HP-5890 GC-MS spectrometer.

20-Deethyl-2,16-didehydro-17α-hydroxy-5-oxo-1-(*p*-tolylsulfonyl)aspidospermidine (7). A suspension of 102 mg (0.24 mmol) of keto lactam **2b** and 179 mg (0.48 mmol) of $CeCl_3 \cdot 7H_2O$ in 2 mL of THF and 5 mL of methanol was stirred at room temperature for 10 min. Sodium borohydride (18 mg, 0.48 mmol) was added and the stirring continued for 40 min. The solvents were evaporated to dryness, and the residue was dissolved in a 1:1 H_2O/CH_2Cl_2 mixture. The aqueous layer was extracted with CH_2Cl_2, and the combined organic solutions were washed, dried, and evaporated. Crystallization of the residue from acetone afforded 104 mg (99%) of colorless, crystalline hydroxy lactam **7**: mp 196–197 °C; UV λ_{max} 247 nm (ϵ 7500), $\lambda_{shoulder}$ 267 (5900); IR OH 3605 (m), C=O 1675 (s), C=C 1600 (m), SO_2 1360 (m), 1165 (m) cm^{-1}; ^1H NMR δ 1.46–1.62 (m, 3), 1.69 (d, 1, J = 18 Hz), 1.85 (d, 1, J = 18 Hz), 2.36 (s, 3), 2.39–2.45 (m, 1), 2.76–2.84 (m, 2), 4.01 (d, 1, J = 5 Hz), 4.22 (br s, 1), 4.25 (br s, 1), 6.35 (d, 1, J = 1 Hz), 7.10 (d, 1, J = 8 Hz), 7.14 (t, 1, J = 8 Hz), 7.20 (d, 1, J = 8 Hz), 7.31 (dt, 1, J = 7, 1 Hz), 7.62 (d, 1, J = 8 Hz), 7.82 (d, 1, J = 8 Hz); ^{13}C NMR δ 19.6, 21.5, 23.1, 40.5, 41.6, 45.4, 48.7, 61.4, 63.8, 115.9, 121.1, 121.4, 125.6, 126.9, 128.7, 129.6, 134.1, 136.7, 139.9, 142.0, 145.0, 169.7; MS *m/e* 436 (M^+, 14), 265 (14), 264 (base), 235 (15), 91 (18), 82 (24); exact mass *m/e* 436.1451 (calcd for $C_{24}O_4N_2S$ 436.1458). Anal. Calcd for $C_{24}H_{24}O_4N_2S$: C, 66.04; H, 5.54; N, 6.42. Found: C, 66.52; H, 5.69; N, 6.22.

20-Deethyl-2,16,17,20-tetradehydro-5-oxo-1-(*p*-tolylsulfonyl)aspidospermidine (5a) and 20-Deethyl-1,2,16,17-tetrahydro-5-oxoaspidospermidine (6a). A solution of 417 mg (0.96 mmol) of hydroxy lactam **7** in 4 mL of $Et_2O \cdot BF_3$ was heated at 60 °C for 0.5 h and then poured into 20 mL of ice water. The mixture was neutralized with ammonium hydroxide and extracted with CH_2Cl_2. The extract was washed with saturated NH_4Cl and 5% $NaHCO_3$ solutions and with water, dried, and evaporated. Crystallization of the residue from acetone furnished 273 mg (68%) of colorless, crystalline diene **5a**: mp 212 °C; UV λ_{max} 223 nm (ϵ 17 000), 279 (8800), 317 (5600); IR C=O 1680 (s), C=C 1600 (m), SO_2 1360 (s), 1170 (s) cm^{-1}; ^1H NMR δ 1.33 (d, J = 17 Hz), 1.45–1.61 (m, 1), 1.74–1.79 (m, 1, 2.13–2.20 (m, 1), 2.17 (d, 1, J = 17 Hz), 2.36 (s, 3), 2.52 (br d, 1, J = 14 Hz), 2.89 (ddd, 1, J = 13, 13, 3 Hz), 4.23 (dd, 1, J = 13, 4 Hz), 4.34 (s, 1), 5.74 (d, 1, J = 6 Hz), 6.23 (d, 1, J = 6 Hz), 7.07 (t, 1, J = 8 Hz), 7.19 (m, 3, H-9), 7.31 (dt, 1, J = 8, 1 Hz), 7.69 (d, 2, J = 8 Hz), 7.83 (d, 1, J = 8 Hz); ^{13}C NMR δ 21.6, 25.9, 31.0, 41.4, 45.9, 46.8, 64.8, 108.2, 116.3, 116.8, 121.0, 125.5, 126.9, 128.9, 129.6, 130.3, 134.4, 136.1, 140.4, 141.7, 144.9, 172.9. Anal. Calcd for $C_{24}H_{22}O_3N_2S$: C, 68.88; H, 5.30; N, 6.69. Found: C, 68.36; H, 5.25; N, 6.64.

Chromatography of the mother liquor and elution with 10:1 to 5:1 CH_2Cl_2/Me_2CO led to 33.7 mg (13%) of colorless, crystalline imino lactam **6a**: mp 145–147 °C; UV $\lambda_{shoulder}$ 226 nm (ϵ 4500), 284 (1400); IR C=O 1670 (s), C=C 1610 (w), 1590 (w) cm^{-1}; ^1H NMR δ 1.25–1.61 (m, 1), 1.65–1.70 (m, 1), 1.76–1.88 (m, 1), 1.98–2.20 (m, 1), 2.45 (br s, 1), 2.61 (d, 1, J = 18 Hz), 2.74 (d, 1, J = 18 Hz), 2.88 (ddd, 1, J = 13, 13, 3 Hz), 4.12 (d, 1, J = 5 Hz), 4.33 (br dd, 1, J = 13, 2 Hz), 6.20 (dd, 1, J = 10, 1 Hz), 6.88 (dd, 1, J = 10, 3 Hz), 7.23–7.38 (m, 3), 7.56 (d, 1, J = 7 Hz); ^{13}C NMR δ 20.7, 27.7, 35.0, 40.6, 41.1, 55.5, 57.2, 121.0, 121.4, 126.0, 126.5, 128.6, 142.4, 143.8, 155.2, 170.3, 180.1; MS *m/e* 264 (M^+, base), 180 (15); exact mass *m/e* 264.1253 (calcd for $C_{17}H_{16}ON_2$ 264.1264).

When the dehydration was carried out by heating a solution of 164 mg (0.38 mmol) of hydroxy lactam **7** in 4 mL of $Et_2O \cdot BF_3$ at 115 °C for 5 min, it led to 37 mg (24%) of crystalline diene **5a** and 63 mg (64%) of crystalline imine **6a**.

20-Deethyl-2,16-didehydro-17α-hydroxy-1-(*p*-tolylsulfonyl)aspidospermidine (8). A 1M THF solution of diborane (20.7 mL, 20.0 mmol) was added dropwise over a 5-h period to a stirring mixture of 1.80 g (4.1 mmol) of keto lactam **2b** in 50 mL of anhydrous THF and the stirring then continued for another 1 h. For the decomposition of excess diborane, a 1:1

HOAc/MeOH mixture was added dropwise and then 30 mL of a methanolic NaOAc solution added and the mixture refluxed for 40 min. It was neutralized with 5% aqueous Na_2CO_3 solution and extracted with $CHCl_3$. The extract was washed with brine, dried, and evaporated. Chromatography of the residue and elution with 2:1 to 1:1 hexane/EtOAc provided 822 mg (48%) of colorless, crystalline alcohol **8**: mp 180–181 °C; UV λ_{max} 226 nm (ϵ 18 000), 243 (17 000), 267 (12 700): IR OH 3580 (w), C=C 1677 (w), SO_2 1360 (m), 1165 (m) cm^{-1}; ^1H NMR δ 0.79–0.84 (m, 1), 0.99–1.08 (m, 1), 1.28–1.39 (m, 1), 1.40–1.45 (m, 1), 1.50–1.55 (m, 1), 1.77–1.85 (m, 2), 2.16–2.23 (m, 1), 2.26–2.30 (m, 1), 2.33 (s, 3), 2.59 (dd, 1, J = 8, 7 Hz), 2.64 (d, 1, J = 3 Hz), 3.05–3.08 (m, 1), 4.60 (dd, 1, J = 10, 1 Hz), 6.19 (d, 1, J = 1 Hz), 7.07–7.12 (m, 1), 7.18 (d, 2, J = 8 Hz), 7.22–7.27 (m, 2), 7.66 (d, 2, J = 8 Hz), 7.80 (d, 1, J = 7 Hz); ^{13}C NMR δ 21.4, 21.4, 23.4, 42.9, 44.6, 51.5, 51.7, 52.4, 65.8, 65.9, 115.7, 121.2, 121.6, 124.6, 127.1, 127.6, 129.4, 135.3, 138.0, 140.2, 143.5, 144.1; MS *m/e* 422 (M^+, 1), 268 (22), 267 (base), 96 (45); exact mass *m/e* 422.1640 (calcd for $C_{24}H_{26}O_3N_2S$ 422.1666).

A mixture of 20 mg (0.046 mmol) of hydroxy lactam **7** and 3 mg (0.08 mmol) of lithium aluminum hydride in 1.5 mL of 1,2-dimethoxyethane was refluxed for 3.5 h. Workup as above afforded 15.5 mg (81%) of crystalline alcohol **8**.

20-Deethyl-16,17-didehydroaspidospermidine (9a). A mixture of 1.43 g (3.3 mmol) of keto lactam **2b** and 760 mg (20 mmol) of lithium aluminum hydride in 270 mL of dry THF was refluxed for 20 h and then cooled. Ethyl acetate (5 mL) and then 1 M hydrochloric acid were added cautiously, and the mixture was concentrated to a low volume. Potassium sodium tartrate solution (20 mL of 5%) was added, and the mixture was neutralized with ammonium hydroxide solution and extracted with $CHCl_3$. The extract was washed with water, dried, and evaporated. Chromatography of the residue and elution with 1:2 to 5:1 EtOAc/hexane yielded 229 mg (29%) of crystalline alcohol **8** (vide supra) and 602 mg (68%) of colorless, crystalline amine **9a**: mp 54–55 °C; UV λ_{max} 242 nm (ϵ 6000), 296 (2800); IR (CH_2Cl_2) NH 3380 (w), C=C 1600 (m) cm^{-1}; ^1H NMR δ 1.44–1.61 (m, 3), 1.73 (br d, 1, J = 12 Hz), 1.81–1.90 (m, 1, H-6), 2.00–2.07 (m, 1), 2.17–2.26 (m, 1), 2.31–2.40 (m, 2), 2.44 (d, 1, J = 4 Hz), 3.07 (d, 1, J = 11 Hz), 3.21 (ddd, 1, J = 9, 9, 4 Hz), 3.98 (br s, 1), 5.54 (d, 1, J = 10 Hz), 5.61–5.66 (m, 1), 6.56 (d, 1, J = 8 Hz), 6.70 (t, 1, J = 8 Hz), 6.96–7.03 (m, 2); ^{13}C NMR δ 21.7, 28.7, 31.0, 39.2, 52.2, 52.7, 52.8, 63.4, 68.0, 109.5, 118.5, 122.6, 127.6, 128.0, 131.1, 132.2, 150.6; MS *m/e* 252 (M^+, base), 251 (34), 130 (34), 122 (92), 92 (22); exact mass *m/e* 252.1624 (calcd for $C_{17}H_{20}N_2$ 252.1628).

A mixture of 152 mg (0.35 mmol) of keto lactam **2b** and 53.3 mg (1.4 mmol) of lithium aluminum hydride in 13 mL of dry THF was stirred at 0 °C for 2 h and then worked up as above. Chromatography of the crude residue and elution with 1:2 to 2:1 EtOAc/hexane gave 59 mg (40%) of crystalline amino alcohol **8**, 24.4 mg (16%) of crystalline hydroxy lactam **7**, and 19 mg (22%) of crystalline amine **9a**.

Finally, a mixture of 500 mg (1.8 mmol) of keto lactam **2a** and 271 mg (7.2 mmol) of lithium aluminum hydride in 50 mL of dry THF was refluxed for 18 h. Cautious addition of EtOAc destroyed the excess hydride. The mixture was poured onto ice, permitted to warm, and filtered. The filtrate was extracted with EtOAc. The extract was washed with water, dried, and evaporated. Chromatography of the residue and gradient elution with 5:1 to 2:1 CH_2Cl_2/EtOAc furnished 97.4 mg (22%) of crystalline amine **9a**.

20-Deethyl-2,16,17,20-tetrahydro-1-(*p*-tolylsulfonyl)-aspidospermidine (5b). Methanesulfonyl chloride (0.21 mL, 2.70 mmol) was added dropwise to a stirring solution of 757 mg (1.79 mmol) of alcohol **8** and 0.40 mL (2.70 mmol) of triethylamine in 80 mL of dry CH_2Cl_2 at 0 °C and stirring continued at this temperature for 1 h and then at room temperature for 17 h. The mixture was diluted with CH_2Cl_2, washed with 5% $NaHCO_3$ solution, saturated NH_4Cl solution, and water, dried ($MgSO_4$), and evaporated. Chromatography of the residue and elution with 3:1 to 2:1 hexane/EtOAc yielded a product whose crystallization from acetone gave 343 mg of crystalline product. Rechromatography of the residue of the mother liquor led to 144.6 mg of pure product, i.e. a total of 487.6 mg (67%) of colorless crystalline diene **5b**: mp 163–165 °C; UV λ_{max} 233 nm (ϵ 9000), 279 (9100), 324 (5200); IR C=C 1600 (w), SO_2 1362 (m), 1170 (m) cm^{-1}; ^1H NMR δ 0.93–0.98 (m, 1), 1.42–1.48 (m, 1), 1.70–1.80 (m, 1), 1.78–1.80 (m, 1), 2.13 (d, 1, J = 9 Hz), 2.35 (s, 3), 2.40 (d, 1, J = 9 Hz), 2.67 (ddd, 1, J = 16, 16, 2 Hz), 2.87 (dd, 1, J = 16, 7 Hz), 3.14 (d, 2, J = 9 Hz), 3.74 (br s, 1), 5.70 (dd, 1, J = 6, 2 Hz), 6.20 (d, 1, J = 6 Hz), 7.08 (t, 1, J = 7 Hz), 7.23 (d, 1, J = 8 Hz), 7.26 (t, 1, J = 7 Hz), 7.49 (d, 1, J = 7 Hz), 7.64 (d, 2, J = 8 Hz), 7.82 (d, 1, J = 7 Hz); ^{13}C NMR δ 20.4, 21.5, 32.0, 41.6, 46.8, 47.5, 52.9, 66.8, 105.7, 115.6, 117.0, 123.0, 125.0, 127.1, 127.9, 129.3, 133.4, 134.7, 138.3, 140.6, 144.0, 144.2; MS *m/e* 404 (M^+, 12), 249 (base); exact mass *m/e* 404.1587 (calcd for $C_{24}H_{24}O_2N_2S$ 404.1560). Anal. Calcd for $C_{24}H_{24}O_2N_2S$: C, 71.35; H, 5.98; N, 6.93. Found: C, 70.86; H, 6.18; N, 6.47.

20-Deethyl-17α-hydroxyaspidospermidine (10a). Sodium amalgam (366 mg of 6%) was added to a stirring mixture of 95 mg (0.22 mmol) of alcohol **8** and 135 mg (0.95 mmol) of Na_2HPO_4 in 0.5 mL of DME and 5 mL of dry MeOH at −5 °C and vigorous stirring continued at room temperature for 50 min. Another portion of the same amount of sodium amalgam was added and stirring continued for 2 h. The mixture was poured onto ice and extracted with $CHCl_3$. The extract was washed with water, dried, and evaporated. Chromatography of the residue and gradient elution with 60:1 to 12:1 $CHCl_3$/MeOH led to the recovery of 10 mg of starting alcohol (**8**) and 30 mg (56% yield, based consumed starting material) of amino alcohol **10a**: mp 198–200 °C; UV λ_{max} 244 nm (ϵ 6700), 296 (3000); IR OH 3380 (w), NH 3360 (w), C=C 1604 (w) cm^{-1}; ^1H NMR δ 1.25–1.37 (m, 1), 1.41–1.56 (m, 3), 1.62–1.82 (m, 3), 2.00 (dd, 1, J = 12, 11 Hz), 2.12–2.26 (m 3), 2.46 (br s, 1), 3.11–3.13 (m, 2), 3.70 (dd, 1, J = 10, 5 Hz), 4.04 (ddd, 1, J = 9, 9, 4 Hz), 6.67 (d, 1, J = 8 Hz), 6.78 (t, 1, J = 8 Hz), 7.03–7.09 (m, 2); ^{13}C NMR δ 20.8, 24.5, 37.3, 39.2, 40.0, 53.1, 53.7, 54.0, 64.8, 66.1, 69.7, 110.6, 119.4, 122.4, 127.8, 134.0, 150.0; MS *m/e* 270 (M^+, 88), 178 (35), 144 (35), 130 (87), 96 (base).

16,17-Didehydro-5-oxo-18-(phenylsulfonyl)aspidofractinine (11a). A mixture of 70 mg (0.27 mmol) of indolenine **6a** and 106 mg (0.63 mmol) of phenyl vinyl sulfone in 1 mL of dry benzene was heated at 90 °C in a sealed tube for 24 h. Chromatography of the solution and elution with 20:1 to 5:1 CH_2Cl_2/Me_2CO afforded 101 mg (87%) of colorless, crystalline sulfone **11a**: mp 119–120 °C; UV $\lambda_{shoulder}$ 220 nm (ϵ 8400), 292 (1100); IR NH 3370 (w), C=O 1675 (s), C=C 1610 (m), SO_2 1310 (m), 1152 (m) cm^{-1}; ^1H NMR δ 1.38–1.45 (m, 1), 1.45–1.51 (m, 1), 1.59–1.75 (m, 3), 2.00 (d, 1, J = 18 Hz), 2.08 (br s, 1), 2.74 (ddd, 1, J = 14, 14, 5 Hz), 3.12 (d, 1, J = 18 Hz), 3.44 (s, 1), 3.58 (dd, 1, J = 10, 6 Hz), 4.20 (dd, 1, J = 14, 3 Hz), 5.95 (d, 1, J = 9 Hz), 6.61 (d, 1, J = 9 Hz), 6.80 (d, 1, J = 8 Hz), 6.84 (t, 1, J = 8 Hz), 7.05 (d, 1, J = 8 Hz), 7.14 (t, 1, J = 8 Hz), 7.52 (t, 2, J = 7 Hz), 7.62 (t, 1, J = 7 Hz), 7.67 (d, 2, J = 7 Hz); ^{13}C NMR δ 22.2, 32.7, 34.7, 39.8, 40.0, 42.2, 55.6, 60.8, 64.9, 73.3, 112.1, 120.7, 121.6, 128.2, 128.6, 129.3, 132.6, 133.2, 133.8, 139.3, 149.3, 171.2; Ms *m/e* 432 (M^+, 5), 264 (base), 125 (24), 113 (28); exact mass *m/e* 432.1508 (calcd for $C_{25}H_{24}O_3N_2S$ 432.1509).

A 1.6 M hexane solution of *n*-butyllithium (0.6 mL) was added to a solution of 0.5 mL of ethyl mercaptan and 1 mL of HMPA at 0 °C and stirred for 3 min. A solution of 158 mg (0.32 mmol) of carbamate **11b** in 2 mL of THF was added dropwise to the stirring mixture and the stirring was continued at 0 °C for 1 h and at room temperature for 60 h. The mixture then was poured into water and extracted with chloroform. The extract was washed with water, dried, and evaporated. Chromatography of the residue and elution with 1:1 to 2:1 ethyl acetate–hexane yielded 128 mg of lactam **11a**: mp 119–120 °C (MeOH); spectrally identical with the above sample.

20-Deethyl-2,16-didehydro-1-(methoxycarbonyl)-5,17-dioxoaspidospermidine (2d). A 1.6 M hexane solution of *n*-butyllithium (1.9 mL, 3.0 mmol) was added dropwise to a stirring solution of 683 mg (2.4 mmol) of keto lactam **2a** in 150 mL of dry THF at −78 °C and the stirring continued for 40 min. Methyl chlorocarbonate (0.068 mL, 3.1 mmol) was

added and the mixture stirred for another 15 min and then allowed to warm to room temperature. Wet EtOAc (2 mL) was added dropwise for the decomposition of excess base and the mixture poured into water and extracted with CH_2Cl_2. Standard workup of the extract and crystallization of the product from methanol gave 776 mg (96%) of carbamate **2d**:[1b] mp 240–242 °C; UV, IR, and ^1H NMR spectrally identical with recorded data;[1b] ^{13}C NMR δ 20.6, 22.2, 40.3, 43.1, 51.2, 53.8, 56.3, 109.9, 115.9, 120.7, 125.4, 129.0, 134.0, 139.8, 152.3, 160.9, 168.2, 196.4.

20-Deethyl-2,16-didehydro-17α-hydroxy-1-(methoxycarbonyl)-5-oxoaspidospermidine (12). A mixture of 1.52 g (4.5 mmol) of carbamate **2d**, 3.4 g (9.0 mmol) of $CeCl_3 \cdot 7H_2O$, and 342 mg (9.0 mmol) of sodium borohydride in 150 mL of methanol was stirred at room temperature for 24 h. Another portion of sodium borohydride of like size was added and the stirring continued for 24 h more. The mixture was evaporated and the residue taken up in 2:1 CH_2Cl_2/H_2O. The organic solution was filtered through Celite and the aqueous layer extracted with CH_2Cl_2. The combined extract and organic solution were washed with brine, dried, and evaporated. Crystallization of the residue from acetone gave 1.15 (75%) of colorless, crystalline alcohol **12**: mp 215 °C; UV λ_{max} 247 nm (ϵ 14 000), $\lambda_{shoulder}$ 274 (1800), 288 (1500); IR OH 3670 (w), C=O 1720 (s), 1678 (s), C=C 1603 (m) cm^{-1}; ^1H NMR δ 1.52–1.56 (m, 1), 1.56–1.66 (m, 2), 1.68–1.74 (m, 1), 2.42 (br d, 1, J = 14 Hz), 2.55 (d, 1, J = 18 Hz), 2.70 (d, 1, J = 18 Hz), 2.82–2.91 (m, 1), 3.95 (s, 3), 4.15 (d, 1, J = 5 Hz), 4.31–4.36 (m, 2), 6.28 (s, 1), 7.12 (t, 1, J = 8 Hz), 7.20 (d, 1, J = 8 Hz), 7.27 (t, 1, J = 8 Hz), 7.81 (d, 1, J = 8 Hz); ^{13}C NMR δ 19.7, 23.2, 40.6, 41.6, 45.2, 49.4, 53.1, 61.6, 63.9, 115.5, 116.7, 121.0, 124.5, 128.5, 136.0, 142.7, 152.8, 170.2; MS *m/e* 340 (M$^+$, 36), 202 (base), 83 (28); exact mass *m/e* 340.1422 (cald for $C_{19}H_{20}O_4N_2$ 340.1424).

20-Deethyl-2,16,17,20-tetradehydro-1-(methoxycarbonyl)-5-oxoaspidospermidine (5e) and 20-Deethyl-17,20-didehydro-2ξ-hydroxy-1-(methoxycarbonyl)-5-oxoaspidospermidine (13). A mixture of 840.7 mg (2.47 mmol) of alcohol **12** and 10 mL of $Et_2O \cdot BF_3$ was stirred at room temperature for 5 min, at 45 °C for 15 min, and at 60 °C for 10 min. The solution was poured onto ice, brought to pH 8 with ammonium hydroxide, and extracted with chloroform. The extract was washed with water, dried, and evaporated. Chromatography of the residue and elution with 20:1 to 4:1 CH_2Cl_2/Me_2CO provided 700 mg (88%) of colorless, crystalline diene **5e**: mp 125–126 °C (EtOAc); UV λ_{max} 261 nm (ϵ 10 400), 280 (9980), 317 (6670); IR C=O 1715 (s), 1685 (s), C=C 1615 (w), 1602 (w) cm^{-1}; ^1H NMR δ 1.57–1.68 (m, 1), 1.75–1.83 (m, 2), 2.41 (d, 1, J = 17 Hz), 2.54 (br d, 1, J = 14 Hz), 2.92 (d, 1, J = 17 Hz), 2.96 (ddd, 1, J = 13, 13, 3 Hz), 3.97 (s, 3), 4.30–4.36 (m, 1), 4.45 (s, 1), 5.75 (d, 1, J = 6 Hz), 6.19 (d, 1, J = 6 Hz), 7.06 (t, 1, J = 7 Hz), 7.28 (t, 1, J = 7 Hz), 7.33 (d, 1, J = 7 Hz), 7.83 (d, 1, J = 7 Hz); ^{13}C NMR δ 26.1, 31.0, 41.5, 45.3, 47.9, 53.1, 65.2, 103.2, 115.5, 117.4, 120.8, 124.2, 128.3, 128.7, 135.4, 140.4, 142.6, 152.6, 173.5; MS *m/e* 322 (M$^+$, base), 280 (24); exact mass *m/e* 322.1311 (calcd for $C_{19}H_{18}O_3N_2$ 322.1318). Anal. Calcd for $C_{19}H_{18}O_3N_2$: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.22; H, 5.65; N, 8.69.

Further elution gave colorless liquid hydroxy lactam **13** (<3%): UV λ_{max} 242 nm (ϵ 11 000), 282 (3100); IR OH 3560 (w), 3420 (br w), C=O 1690 (s), 1670 (s), C=C 1600 (w) cm^{-1}; ^1H NMR δ 1.47–1.59 (m, 1), 1.75–1.79 (m, 1), 2.14 (d, 1, J = 18 Hz), 2.25 (dd, 1, J = 14, 13 Hz), 2.36 (d, 1, J = 17 Hz), 2.47 (d, 1, J = 14 Hz), 2.80 (dd, 1, J = 17, 7 Hz), 2.88 (dd, 1, J = 14, 11 Hz), 3.53 (d, 1, J = 18 Hz), 3.92 (s, 3), 4.22 (s, 1), 4.29 (dd, 1, J = 14, 4 Hz), 5.49–5.51 (m, 1), 7.08 (t, 1, J = 8 Hz), 7.20–7.26 (m, 2), 7.54 (d, 1, J = 8 Hz); ^{13}C NMR δ 25.2, 31.9, 32.4, 39.6, 40.1, 49.1, 52.7, 61.4, 93.7, 115.0, 117.0, 121.8, 124.1, 128.4, 133.6, 135.2, 138.3, 154.2, 170.2; MS *m/e* 340 (M$^+$, 18), 109 (base); exact mass *m/e* 340.1391 (calcd for $C_{19}H_{20}O_4N_2$ 340.1424).

When a benzene solution of alcohol **13** was refluxed for 4 h, total dehydration took place and diene **5e** was formed in quantitative yield.

16,17-Didehydro-1-(methoxycarbonyl)-5-oxo-18ξ-(phenylsulfonyl)aspidofractinine (11b). A mixture of 759 mg (2.48 mmol) of diene **5e** and 834 mg (4.96 mmol) of phenyl vinyl sulfone in 5 mL of dry benzene was heated in a sealed tube at 125 °C for 96 h. Chromatography of the mixture and elution with 16:1 CH_2Cl_2/Me_2CO yield 908 mg (75%) of colorless, crystalline sulfone **11b**: mp 235–236 °C (EtOAc); UV λ_{max} 245 nm (ϵ 11 000), 273 (2600), 284 (1800), $\lambda_{shoulder}$ 264 (3000); IR C=O 1710 (s), 1680 (s), C=C 1605 (w), SO_2 1309 (m), 1145 (m) cm^{-1}; ^1H NMR δ 1.43–1.53 (m, 1), 1.61–1.73 (m, 4), 2.03 (d, 1, J = 18 Hz), 2.11 (br s, 1), 2.70–2.79 (m, 1), 2.96 (d, 1, J = 18 Hz), 3.47 (s, 1), 3.59 (t, 1, J = 8 Hz), 3.88 (s, 3), 4.21 (br d, 1, J = 11 Hz), 6.05 (br d, 2, J = 4 Hz), 7.06–7.14 (m, 4), 7.45–7.50 (m, 2), 7.55–7.63 (m, 3); ^{13}C NMR δ 22.0, 32.3, 34.3 (br), 39.4, 42.5, 52.4, 55.9, 59.5 (br), 63.6, 73.6, 118.5 (br), 121.1, 124.3, 128.0, 128.4, 128.8, 131.2 (br), 132.3, 133.3, 135.5 (br), 139.1, 141.0 (br), 153.2 (br), 169.8; MS *m/e* 490 (M$^+$, 4), 322 (base); exact mass *m/e* 490.1567 (calcd for $C_{27}H_{26}O_5N$ 490.1564).

5-Oxoaspidofractinine (14). A stirring suspension of 12.3 mg (0.029 mmol) of sulfone **11a** and an excess of W-2 Raney nickel (Aldrich Chemical Co.) in 2 mL of isopropyl alcohol was refluxed under argon for 2 h. The mixture was passed through a pad of silica gel and washed exhaustively with CH_2Cl_2. The combined filtrate and washings were evaporated. Chromatography of the residue and elution with 3:1 CH_2Cl_2/Me_2CO gave a solid, whose crystallization from ethanol afforded 7.4 mg (88%) of colorless, crystalline lactam **14**: mp 180–183 °C; UV λ_{max} 244 nm (ϵ 2700), 292 (1400); IR C=O 1670 (s), C=C 1610 (w) cm^{-1}; ^1H NMR δ 1.18 (t, 1, J = 11 Hz), 1.24–1.43 (m, 4), 1.45–1.54 (m, 1), 1.57–1.68 (m, 3), 1.77–1.93 (m, 2), 2.03–2.18 (m, 1), 2.11 (d, 1, J = 18 Hz), 2.76 (ddd, 1, J = 4, 13, 13 Hz), 3.18 (d, 1, J = 18 Hz), 3.62 (s, 1), 4.26 (dd, 1, J = 5, 13 Hz), 6.67 (d, 1, J = 7 Hz), 6.79 (t, 1, J = 7 Hz), 7.04 (d, 1, J = 7 Hz), 7.08 (t, 1, J = 7 Hz); ^{13}C NMR δ 20.5, 24.8, 26.8, 30.2, 32.2, 32.4, 35.3, 40.2, 40.9, 48.8, 64.0, 66.6, 111.1, 120.0, 121.4, 127.7, 137.1, 149.9, 172.6; MS *m/e* 294 (M$^+$, base), 156 (75), 143 (21), 90 (20); exact mass *m/e* 294.1720 (calcd for $C_{19}H_{22}ON_2$ 294.1734).

(±)-Aspidofractinine (4). A solution of 10.0 mg (0.034 mmol) of lactam **14** in 1 mL of THF was added dropwise to a stirring suspension of 5.2 mg (0.136 mmol) of lithium aluminum hydride in 1.5 mL of dry THF, and the mixture was refluxed for 1 h. Solvent removal and the usual workup led to a residue, whose chromatography and elution with 15:1 to 8:1 CH_2Cl_2/Me_2CO led to 7.2 mg (76%) of colorless, amorphous amine **4**: IR and mass spectra identical with comparison spectra;[9] ^1H NMR spectrally identical with recorded spectra; ^{13}C NMR δ 17.2, 26.5, 29.2, 31.4, 31.5, 34.8, 35.1, 36.1, 47.8, 50.7, 56.9, 64.6, 69.0, 110.8, 119.7, 122.0, 126.6, 140.3, 150.0.

1,2,16,17-Tetradehydro-5-oxo-18-(phenylsulfonyl)aspidospermidine (15). A mixture of 307 mg (0.71 mmol) of sulfone **11a** and 162 mg (1.44 mmol) of potassium *tert*-butoxide in 3 mL of dry ethylene glycol was heated at 150 °C for 5 h and then poured into 5 mL of water. The mixture was extracted with $CHCl_3$, and the extract washed with water, dried, and evaporated. Chromatography of the residue and elution with 16:1 to 8:1 CH_2Cl_2/Me_2CO provided 260 mg (85%) of colorless, crystalline sulfone **15**: mp 96–98 °C; UV λ_{max} 236 nm (ϵ 9400), 265 (3200), 272 (3600), 299 (4300); IR C=O 1680 (s), 1610 (w), 1595 (w), 1580 (w), SO_2 1305 (m), 1145 (m) cm^{-1}; ^1H NMR δ 0.89 (ddd, 1, J = 5, 13, 13 Hz), 1.41 (ddd, 1, J = 4, 13, 13 Hz), 1.47–1.56 (m, 2), 1.72–1.76 (m, 1), 2.04–2.13 (m, 1), 2.56 (s, 2), 2.75–2.85 (m, 2), 2.96 (ddd, 1, J = 4, 13, 13 Hz), 3.84 (d, 1, J = 1 Hz), 4.30 (dd, 1, J = 2, 15 Hz), 6.02 (dd, 1, J = 1, 10 H), 6.87 (d, 1, J = 10 Hz), 7.24–7.44 (m, 4), 7.41 (t, 2, J = 8 Hz), 7.54 (d, 2, J = 8 Hz), 7.62 (t, 1, J = 8 Hz); ^{13}C NMR δ 21.2, 33.4, 34.0, 40.2, 40.3, 41.0, 50.6, 55.5, 61.8, 121.2, 121.7, 126.9, 127.0, 127.5, 128.6, 129.2, 133.7, 137.6, 142.2, 145.1, 154.1, 169.4, 179.5; MS *m/e* 432 (M$^+$, 87), 291 (28), 290 (31), 277 (33), 263 (base), 235 (50), 221 (41), 206 (23), 143 (28); exact mass *m/e* 432.1506 (calcd for $C_{25}H_{24}O_3N_2S$ 432.1509).

(±)-16,17-Didehydroaspidospermidine (16) and (±)-Aspidospermidine (3). A solution of 14.3 mg (0.033 mmol) of lactam **15** in 1.5 mL of dry THF was added to a stirring

(9) The authors are indebted to Professor Ban for copies of the spectra.

suspension of 12.5 mg (0.33 mmol) of lithium aluminum hydride in 0.8 mL of dry THF, and the mixture was refluxed for 18 h. It then was worked up in the usual manner, and the crude product was chromatographed. Elution with 6:1 to 2:1 CH_2Cl_2/Me_2CO afforded sequentially 4.5 mg (49%) of colorless, crystalline amine **16** (mp 102–105 °C; spectrally identical with an authentic sample[2]) and 2.3 mg (25%) of colorless, amorphous amine **3** (spectrally identical with an authentic sample[2]).

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Supplementary Material Available: ^1H and ^{13}C NMR spectra of **6a**, **8**, **10a**, **11a**, **11b**, **12**, **13**, **14**, and **15** (27 pages). This material contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.