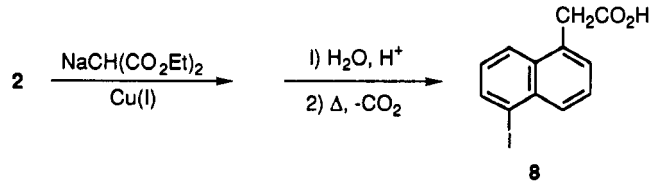

8

Hoover apparatus and are uncorrected. NMR spectra were recorded (δ) by use of a Magnachem-200 or a GN-300 spectrometer with TMS as an internal reference in $CDCl_3$ unless otherwise noted. Mass spectra were obtained on a MAT CH-5-DF(FAB), a FINNIGAN 8230 B(EI), a KRATOS MS-80 (HR EI), and a MAT CH-7(CI) mass spectrometer. Infrared spectra were obtained on a Perkin-Elmer 1420 ratio recording IR spectrophotometer. Dimethylformamide (Fisher), THF (Fisher), ether (Fisher), methylene chloride (Fisher), CuI, ethyl malonate, and *tert*-butyllithium (Aldrich) were all used as received from commercial suppliers.

5-Iodo-1-naphthaldehyde (3). 1,5-Diiodonaphthalene[1,2] (1.14 g, 3.1 mmol) in 15 mL of ether was cooled to −78 °C and treated with 6.3 mmol of *tert*-butyllithium. The resulting pinkish solution was stirred for 6.5 h while being warmed to 5 °C. The now-brown solution was recooled to −78 °C, and 0.45 mL (3.0 mmol) of tetramethylethylenediamine was added. After 10 min, 0.30 mL (3.0 mmol) of dimethylformamide was added and the mixture was stirred for 17 h as it warmed to room temperature. The organic layer was washed with saturated aqueous NH_4Cl, dried ($MgSO_4$), and concentrated to give 0.77 g of crude product. Purification by column chromatography (silica gel, 1:10 ether–hexane, R_f 0.25) yielded 0.47 g (55%) of **3**: mp 115–117 °C; ^1H NMR (200 MHz) δ 7.34 (t, J = 8 Hz, 1 H), 7.68 (t, J = 8 Hz, 1 H), 8.00 (d, J = 8 Hz, 1 H), 8.18 (d, J = 8 Hz, 1 H), 8.40 (d, J = 8 Hz, 1 H), 9.28 (d, J = 8 Hz, 1 H), 10.38 (s, 1 H); IR (KBr) 1685 (C=O) cm^{-1}; HRMS (EI) for $C_{11}H_7IO$ calcd 281.9543, found 281.9547.

5-Iodo-1-naphthoic acid (4). To a solution of 0.61 g (2.17 mmol) of **3** in 30 mL of acetone was added 1.62 mL (4.43 mmol) of Jones reagent. The mixture was stirred for 17 min, filtered, and concentrated in vacuo. The residue was dissolved in 30 mL of 4 N NaOH and filtered. The filtrate was acidified with 2.5 mL of concd H_2SO_4 and cooled to 0 °C. The precipitate was collected by filtration and dried to give 0.73 g (113%) of **4** as a slightly pink solid: mp 250–252 °C (lit.[5] mp 251–252 °C); IR (KBr) 2960–2800, 1615 (C=O) cm^{-1}; HRMS (EI) for $C_{11}H_7IO_2$ calcd 297.9493, found 297.9498.

1,5-Naphthalenediethanol (5). A suspension of 1,5-diiodonaphthalene[1,2] (2.50 g, 6.58 mmol) in 40 mL of ether was cooled to −78 °C, and 16.2 mL of a solution of *tert*-butyllithium (1.7 M in pentane, 26.7 mmol) was added. The light pink suspension was stirred for 1 h, 300 mg (3.30 mmol) of cuprous cyanide was added, and stirring was continued for 45 min at −55 to −65 °C. During this period, the suspension turned yellow. Ethylene oxide (8 mL, 164 mmol) was added all at once, and the mixture was stirred overnight as it gradually warmed to 25 °C. In a good hood the mixture was poured into 100 mL of 10% sulfuric acid (caution: HCN evolved!),[13] filtered, and extracted with CH_2Cl_2 (3 × 50 mL). The extracts were dried (Na_2SO_4) and evaporated to give a crude solid that was triturated with ether to give 0.80 g (56%) of **5** as a white solid: mp 105 °C; ^1H NMR (DMSO-d_6, 200 MHz) δ 3.39 (t, J = 8 Hz, 2 H), 3.86 (t, J = 8 Hz, 2 H), 7.38 (m, 4 H), 7.98 (d, J = 8 Hz, 2 H); IR (KBr) 3350 (br, OH) cm^{-1}; HRMS (EI) for $C_{14}H_{16}O_2$ calcd 216.1150, found 216.1156. Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.67; H, 7.57.

Oxidation of 1,5-Naphthalenediethanol (5). A solution of 335 mg (1.5 mmol) of **5** in 8 mL of acetone was treated with 1.62 mL (4.16 mmol) of Jones reagent for 15 min at 25 °C. The solvent was evaporated, and the residue was dissolved in 25 mL of 4 N sodium hydroxide. The solution was filtered and acidified (H_2SO_4), and the precipitate was collected and dried to give 280 mg (74% on the basis of **6a**) of the diacids **6a**[7] and **7a**. The diacids were esterified ($SOCl_2$, EtOH) under standard conditions to give 392 mg of diesters **6b** and **7b** (ca. 5:1 by ^1H NMR). This mixture was chromatographed on silica gel (1:2 ether–hexane) to give 100 mg of diethyl 1,5-naphthalenediacetate (**6b**) R_f 0.59: mp 82–84 °C; ^1H NMR (200 MHz) δ 1.25 (t, J = 8 Hz, 6 H), 4.10 (s, 4 H), 4.20 (q, J = 8 Hz, 4 H), 7.49 (m, 4 H), 7.99 (d, J = 8 Hz, 2 H); IR (film) 1720 (CO) cm^{-1}; HRMS (EI) for $C_{18}H_{20}O_4$ calcd 300.1361, found 300.1368.

There was also obtained 18 mg of **ethyl 5-carbethoxy-1-naphthylacetate (7b)** (R_f 0.63) as an oil that solidified on standing: mp 45–46 °C; ^1H NMR (200 MHz) δ 1.21 (t, J = 7 Hz, 3 H), 1.46 (t, J = 6 Hz, 3 H), 4.07 (s, 2 H), 4.14 (q, J = 8 Hz, 2 H), 4.58 (q, J = 8 Hz, 2 H), 7.48 (t, J = 8 Hz, 1 H), 7.55 (t, J = 8 Hz, 1 H), 7.53 (d, J = 8 Hz, 1 H), 8.14 (d, J = 8 Hz, 1 H), 8.21 (d, J = 8 Hz, 1 H), 8.82 (d, J = 8 Hz, 1 H); HRMS (EI) for $C_{17}H_{18}O_4$ calcd 286.1205, found 286.1209. Anal. Calcd for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.07; H, 6.55.

5-Iodonaphthylacetic Acid (8). According to Setsune's general procedure,[11] ethyl malonate (1.92 g, 12.0 mmol), sodium hydride (380 mg, 12.5 mmol), CuI (2.29 g, 12.0 mmol), and 1,5-diiodonaphthalene (1.14 g, 3.00 mmol) were combined in 20 mL of dioxane. The mixture was heated at 101 °C for 25 h, cooled to 23 °C, partitioned between chloroform (60 mL) and water (40 mL), and filtered to remove the insoluble solid. The chloroform portion of the filtrate was washed with brine, dried (Na_2SO_4), and concentrated in vacuo to give an oil. The crude product was purified by column chromatography (silica gel, ether–hexane (1:2)) to give 277 mg (24%) of 1,5-diiodonaphthalene (R_f 0.8 in 2:1 $CHCl_3$–ether) and 469 mg of an alkylated product. The malonate-containing portion was heated at reflux in H_2O containing NaOH (771 mg, 19.3 mmol) and NaCl (8.0 g) for 24 h. To the cooled reaction mixture was added concd HCl (3 mL, 30.4 mmol), and the mixture was heated at reflux for 8 h. The crude product was isolated by filtration to give 356 mg (38 or 50% on the basis of recovered **2**) of **8** as a white solid: mp > 290 °C; ^1H NMR (DMSO-d_6) δ 4.10 (s, 2 H), 7.30 (t, J = 8 Hz, 1 H), 7.55 (d, J = 8 Hz, 1 H), 7.65 (t, J = 8 Hz, 1 H), 7.96 (d, J = 8 Hz, 1 H), 8.05 (d, J = 8 Hz, 1 H), 8.20 (d, J = 8 Hz, 1 H); HRMS (EI) for $C_{12}H_9IO_2$ calcd 311.9649, found 311.9672.

Acknowledgment. We thank the Upjohn Co. for support of this research.

Supplementary Material Available: ^1H NMR spectra for compounds **3**, **4**, **6b**, and **8** and ^{13}C NMR spectra for compound **8** (5 pages). Ordering information is given on any current masthead page.

(13) A reviewer suggested that a better workup would use an NH_4Cl–NH_4OH solution as described in: Behling, J. R.; Ng, J. S.; Babiak, K. A.; Campbell, A. L.; Ellsworth, E.; Lipshutz, B. H. *Tetrahedron Lett.* **1989**, *30*, 27.

Synthesis of (±)-Aspidospermidine

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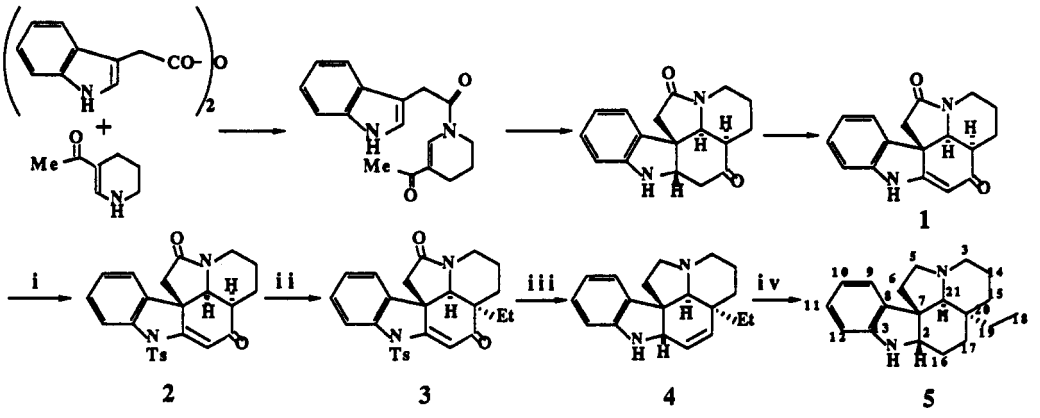
Some time ago there was introduced a short, direct method of construction of the pentacyclic skeleton of the Aspidosperma alkaloids from indoleacetic anhydride[2] and 3-acetyl-1,4,5,6-tetrahydropyridine[3] (i.e., the preparation of lactam **1** in Scheme I).[4] It lacked only the placement

(1) CNRS-URA 1310.
(2) Hart, J. C.; Matheson, E. M.; Hutzinger, O. *Can. J. Chem.* **1970**, *48*, 177.
(3) Wenkert, E.; Dave, K. G.; Haglid, F.; Lewis, R. G. *J. Org. Chem.* **1968**, *33*, 747.
(4) Wenkert, E.; Bindra, J. S.; Chauncy, B. *Synth. Commun.* **1972**, *2*, 285. Wenkert, E.; Orito, K.; Simmons, D. P.; Kunesch, N.; Ardisson, J.; Poisson, J. *Tetrahedron* **1983**, *39*, 3719.

0022-3263/91/1956-2915$02.50/0

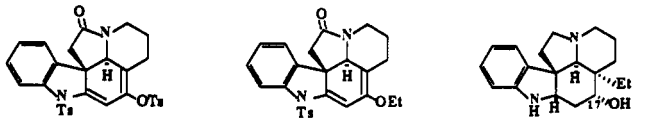
Scheme I[a]



[a] (i) *n*-BuLi, *p*-$MeC_6H_4SO_2Cl$, THF; (ii) KH, LiI, EtI, THF; (iii) $LiAlH_4$, THF, Δ; (iv) H_2, Pt/C, THF, 40 psi.

of a two-carbon residue at the approporiate bridgehead and functional group manipulation to become a procedure for the synthesis of the natural bases themselves. The present paper reports the completion of this task in the form of the total synthesis of (±)-aspidospermidine (**5**; Scheme I).[5]

Treatment of vinylogous amide **1** with *n*-butyllithium and *p*-tolylsulfonyl chloride resulted in the formation of the N_a-tosyl derivative **2** in 92% yield and the O,N_a-ditosyl derivative **6** in 4% yield. Exposure of the former to potassium hydride and lithium iodide and subsequently to ethyl iodide gave in 52% yield a 5.5:1 mixture of angularly ethylated product **3** and *O*-ethyl compound **7**.[6,7] Mild acid

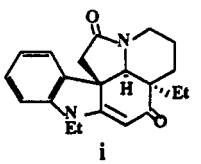


hydrolysis of enol ether **7** led to the recovery (89%) of pentacycle **2**. Exhaustive reduction of the dicarbonyl compound **3** with lithium aluminum hydride produced the diamine **4** (65%) and alcohol **8** (20%). Platinum-assisted hydrogenation of the highly resistant double bond of olefin **4** furnished (±)-aspidospermidine (**5**; 82%).

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

(6) Cf. Le Mênez, P.; Sapi, J.; Kunesch, N.; Angell, E. C.; Wenkert, E. *J. Org. Chem.* **1989**, *54*, 3216.

(7) Maintenance of the reaction conditions described in the Experimental Section was crucial for the optimum yield of the desired product **3**. Variance of the conditions also led to other products. Thus, for example, omission of lithium iodide resulted in the production of a 1:1 mixture (59%) of enol ether **6** and C,N_a-diethyl substance **i**: mp 270–272 °C (Me_2CO); UV (MeOH) λ_{max} 240 nm (ε 16 000), 300 (6600), 347 (17 700); IR C=O 1680 (s), 1620 (s), C=C 1590 (s) cm^{-1}; ^1H NMR δ 0.66 (t, 3, *J* = 7 Hz, Me), 0.90–1.06 (m, 1, H-19), 1.09–1.18 (m, 2, H-14, H-19), 1.24 (t, 3, *J* = 7 Hz, NEt Me), 1.53–1.61 (m, 1, H-14), 1.62–1.68 (m, 1, H-15), 2.59 (d, 1, *J* = 18 Hz, H-6), 2.67–2.74 (m, 1, H-3), 2.77–2.83 (m, 1, H-15), 2.82 (d, 1, *J* = 18 Hz, H-6), 3.72 (q, 2, *J* = 7 Hz, NEt CH_2), 4.04 (s, 1, H-21), 4.25–4.30 (m, 1, H-3), 5.38 (s, 1, H-16), 6.87 (d, 1, *J* = 8 Hz, H-12), 7.06 (t, 1, *J* = 8 Hz, H-10), 7.29 (d, 1, *J* = 8 Hz, H-9), 7.31 (t, 1, *J* = 8 Hz, H-11); ^{13}C NMR δ 7.4 (C-18), 10.6 (NEt Me), 21.2 (C-14), 28.9 (C-15), 35.6 (C-19), 37.8 (NCH_2), 40.2 (C-3), 47.9 (C-7), 49.1 (C-20), 50.6 (C-6), 60.9 (C-21), 93.5 (C-16), 108.5 (C-12), 121.0 (C-10), 122.5 (C-9), 128.5 (C-11), 135.5 (C-8), 143.2 (C-pts13), 168.3 (C-2), 170.1 (C-5), 196.6 (C-17); *m/e* 336 (M^+, 48%), 198 (base); exact mass *m/e* 336.1848 (calcd for $C_{21}H_{24}O_2N_2$ 336.1839).



i

Experimental Section

Melting points were observed on a Reichert micro hostage and are uncorrected. Ultraviolet spectra of ethanol solutions and infrared spectra of $CHCl_3$ solutions were recorded on IBM 9400 and Perkin-Elmer 1320 spectrophotomers, 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; δ(Me_4Si) = δ($CDCl_3$) + 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 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-5,17-dioxo-1-(*p*-tolylsulfonyl)aspidospermidine (2) and 2,16,17,20-Tetradehydro-5-oxo-17-(*p*-tolylsulfonoxy)-1-(*p*-tolylsulfonyl)aspidospermidine (6). A 1.6 M hexane solution of *n*-butyllithium (8.3 mL, 12.7 mmol) was added dropwise over a 20-min period to a stirring solution of 3.40 g (12.1 mmol) of lactam **1** (dried in vacuum at 78 °C for 2 h) in 350 mL of anhydrous THF at −78 °C. The stirring was continued for 20 min, and then a solution of 2.80 g (14.7 mmol) of *p*-tolylsulfonyl chloride in 30 mL of dry THF was added dropwise. The stirring was continued at the low temperature for 10 min and thereafter for 20 min while the suspension was permitted to reach room temperature. Ethyl acetate (500 mL) was added, and the solution was washed with water, dried, and evaporated. Crystallization of the residue from MeOH gave 4.80 g (92%) of colorless, crystalline lactam **2**: mp 120 °C; UV λ_{max} 228 nm (ε 12 000), 272 (7800), 310 (4900); IR C=O 1680 (s), 1630 (s), C=C 1595 (s), SO_2 1370 (s), 1175 (s) cm^{-1}; ^1H NMR δ 1.26–1.62 (m, 3, H-14, H-15), 2.21–2.25 (m, 2, C-6 Hs), 2.40 (s, 3, Me), 2.46–2.55 (m, 2, H-15, H-20), 2.77–2.81 (m, 1, H-3), 4.22 (br dd, 1, *J* = 3, 13 Hz, H-3), 4.38 (d, 1, *J* = 6 Hz, H-21), 6.55 (s, 1, H-16), 7.21–7.25 (m, 2, H-9, H-10), 7.29 (d, 2, *J* = 8 Hz, Ts H-3), 7.36–7.40 (m, 1, H-11), 7.75 (d, 2, *J* = 8 Hz, Ts H-2), 7.89 (d, 1, *J* = 8 Hz, H-12); ^{13}C NMR δ 20.2 (C-14), 21.2 (Me), 21.5 (C-15), 39.6 (C-3), 42.6 (C-20), 46.3 (C-7), 50.5 (C-6), 55.4 (C-21), 108.7 (C-16), 114.1 (C-12), 120.8 (C-10), 125.4 (C-9), 126.5 (Ts C-2), 128.8 (C-11), 129.7 (Ts C-3), 133.1 (C-8), 133.6 (C-13), 139.0 (Ts C-1), 145.6 (Ts C-4), 160.4 (C-2), 167.3 (C-5), 195.4 (C-17); *m/e* 434 (M^+, 11), 324 (30), 169 (55), 91 (base). Anal. Calcd for $C_{24}H_{22}O_4N_2S$·MeOH: C, 64.36; H, 5.61; N, 6.00. Found: C, 63.93; H, 5.61; N, 5.89.

Chromatography of the mother liquor and gradient elution (1:1 to 3:1 EtOAc–C_6H_{14}) afforded 260 mg (4%) of colorless, crystalline lactam **6**: mp 207–209 °C (EtOAc); UV λ_{max} 230 nm (ε 28 000), 276 (13 000), 322 (7700); IR (CH_2Cl_2) C=O 1690 (s), 1625 (w), C=C 1592 (m), SO_2 1370 (s), 1170 (s) cm^{-1}; ^1H NMR δ 0.80–0.95 (m, 1, H-14), 1.41 (d, 1, *J* = 17 Hz, H-6), 1.54 (br d, 1, *J* = 13 Hz, H-15), 1.73 (ddd, 1, *J* = 4, 14, 14 Hz, H-14), 2.13 (d, 1, *J* = 17

Hz, H-6), 2.40 (s, 3, NTs Me), 2.47 (s, 3, OTs Me), 2.69 (br d, 1, J = 15 Hz, H-15), 2.79 (ddd, 1, J = 3, 13, 13, Hz, H-3), 4.08 (dd, 1, J = 4, 13 Hz, H-3), 4.34 (s, 1, H-21), 6.17 (s, 1, H-16), 7.06 (t, 1, J = 7 Hz, H-10), 7.15 (d, 1, J = 7 Hz, H-9), 7.25 (d, 2, J = 8 Hz, NTs H-3), 7.31 (t, 1, J = 7 Hz, H-11), 7.38 (d, 2, J = 8 Hz, OTs H-3), 7.61 (d, 2, J = 8 Hz, NTs H-2), 7.78 (d, 1, J = 7 Hz, H-12), 7.80 (d, 2, J = 8 Hz, OTs H-2); ^{13}C NMR δ 21.6 (NTs Me), 21.6 (OTs Me), 23.9 (C-14), 24.1 (C-15), 41.0 (C-6), 46.0 (C-7), 46.5 (C-3), 64.0 (C-21), 106.4 (C-16), 115.9 (C-12), 118.9 (C-20), 121.0 (C-10), 125.5 (C-9), 127.0 (NTs C-2), 128.2 (OTs C-2), 129.3 (C-11), 129.6 (NTs C-3), 129.0 (OTs C-3), 132.5 (C-17), 134.0 (C-8), 134.6 (NTs C-1), 137.3 (OTs C-1), 140.1 (C-13), 142.6 (C-2), 145.3 (NTs C-4), 145.9 (OTs C-4), 172.2 (C-5); m/e 588 (M^+, 48), 434 (37), 433 (70), 367 (35), 324 (32), 278 (64), 155 (31), 90 (base); exact mass m/e 588.1394 (calcd for $C_{31}H_{28}O_6N_2S_2$ 588.1390). Anal. Calcd for $C_{31}H_{28}O_6N_2S_2$: C, 63.25; H, 4.80; N, 4.76. Found: C, 63.20; H, 4.88; N, 4.68.

2,16-Didehydro-5,17-dioxo-1-(*p*-tolylsulfonyl)aspidospermidine (3) and 2,16,17,20-Tetradehydro-17-ethoxy-5-oxo-1-(*p*-tolylsulfonyl)aspidospermidine (7). A solution of 2.62 g (6.0 mmol) of lactam **2** in 11 mL of anhydrous THF was added dropwise to a stirring suspension of 480 mg (12.0 mmol) of potassium hydride and 802 mg (6.0 mmol) of dry lithium iodide in 7 mL of anhydrous THF at −25 °C. The mixture was evaporated to dryness under high vacuum at the same temperature. Ethyl iodide (10 mL) was added to the dry salts and the vigorously stirring mixture was allowed to warm to room temperature over a 5-h period. It then was diluted with 30 mL of wet EtOAc and poured onto ice. Extraction, washing of the extract, drying and evaporation yielded a residue whose chromatography and gradient elution (1:1 to 3:1 EtOAc–C_6H_{14}) led to 137 mg (8%, based on consumed **2**) of colorless, crystalline diene **7**: mp 176–178 °C (MeOH); UV λ_{max} 231 nm (ϵ 13 000), 281 (9600), 320 (6600); IR (CH_2Cl_2) C=O 1693 (s), 1629 (w), C=C 1600 (m), SO_2 1370 (s), 1175 (s) cm^{-1}; ^{1}H NMR δ 1.29 (t, 3, J = 7 Hz, Me), 1.38 (d, 1, J = 17 Hz, H-6), 1.38–1.48 (m, 1, H-14), 1.69–1.75 (m, 1, H-14), 1.80–1.85 (m, 1, H-15), 2.19 (d, 1, J = 17 Hz, H-6), 2.36 (s, 3, Ts Me), 2.86 (ddd, 1, J = 2, 12, 13 Hz, H-3), 3.04 (br d, 1, J = 14 Hz, H-15), 3.78–3.87 (m, 1, OCH_2 H), 3.91–4.02 (m, 1, OCH_2 H), 4.19 (dd, 1, J = 4, 13 Hz, H-3), 4.41 (s, 1, H-21), 6.31 (s, 1, H-16), 7.07 (t, 1, J = 8 Hz, H-10), 7.20 (m, 3, H-9, Ts C-3 Hs), 7.31 (t, 1, J = 8 Hz, H-11), 7.59 (d, 2, J = 8 Hz, Ts H-2), 7.81 (d, 1, J = 8 Hz, H-12); ^{13}C NMR δ 15.1 (OEt Me), 21.6 (Me), 22.9 (C-14), 24.8 (C-15), 41.5 (C-6), 45.7 (C-7), 46.8 (C-3), 64.9 (C-21), 65.4 (C-19), 106.5 (C-16), 109.7 (C-20), 116.1 (C-12), 121.1 (C-10), 125.5 (C-9), 126.8 (Ts C-2), 129.0 (C-11), 129.6 (Ts C-3), 134.3 (C-8), 135.8 (Ts C-1), 140.3 (C-13), 143.2 (C-2), 143.4 (C-17), 145.1 (Ts C-4), 172.8 (C-5); m/e 462 (M^+, 55), 307 (base), 279 (43); exact mass m/e 462.1620 (calcd for $C_{26}H_{26}O_4N_2S$ 462.1651).

Further elution provided 713 mg (44%, based on consumed **2**) of colorless, crystalline lactam **3**: mp 190 °C (MeOH–CH_2Cl_2); UV λ_{max} 225 nm (ϵ 21 000), 265 (12 000), 312 (7700); IR (film) C=O 1690 (s), 1630 (s), C=C 1587 (s) cm^{-1}; ^{1}H NMR δ 0.39 (t, 3, J = 7 Hz, Me), 0.72, 1.00 (dq, 1 each, J = 7, 14 Hz, C-18 Hs), 1.13 (ddd, 1, J = 4, 13, 13 Hz, H-15), 1.43–1.64 (m, 2, C-14 Hs), 2.32 (d, 1, J = 18 Hz, H-6), 2.38 (s, 3, Ts Me), 2.56 (d, 1, J = 18 Hz, H-6), 2.63–2.81 (m, 2, H-3, H-15), 3.99 (s, 1, H-21), 4.20 (br d, 1, J = 12 Hz, H-3), 6.37 (s, 1, H-16), 7.21–7.30 (m, 4, H-9, H-10, Ts C-3 Hs), 7.33–7.42 (m, 1, H-11), 7.76 (d, 2, J = 8 Hz, Ts C-2 Hs), 7.96 (d, 1, J = 7 Hz, H-12); ^{13}C NMR δ 7.2 (Me), 21.4 (C-14), 21.9 (Ts Me), 28.2 (C-15), 34.7 (C-19), 40.0 (C-3), 46.6 (C-7), 49.1 (C-20), 50.1 (C-6), 61.3 (C-21), 106.0 (C-16), 114.7 (C-12), 120.9 (C-10), 125.7 (C-9), 127.0 (Ts C-3), 129.0 (C-11), 129.9 (Ts C-3), 133.4 (C-8), 134.4 (Ts C-1), 139.4 (C-12), 145.8 (Ts C-4), 161.4 (C-2), 167.2 (C-5), 198.3 (C-17); m/e 462 (M^+, 56), 324 (77), 307 (30), 279 (43), 169 (96), 91 (base). Anal. Calcd for $C_{24}H_{22}O_4N_2S$: C, 66.34; H, 5.10; N, 6.44. Found: C, 66.84; H, 5.49; N, 6.06.

Further elution led to the recovery of 1.02 g (40%) of crystalline starting lactam **2**.

Hydrolysis of Enol Ether 7. A solution of 101 mg (0.22 mmol) of ether **7** in 5 mL of THF and 1 mL of 2 N hydrochloric acid was stirred at room temperature for 40 min. It was neutralized with 5% sodium carbonate solution and concentrated in volume by vacuum evaporation of the THF. The aqueous mixture was extracted and the extract washed, dried and evaporated. Crystallization of the residue from methanol yielded 85 mg (89%) of crystalline, colorless lactam **2**, spectrally idential with the above sample.

16,17-Didehydroaspidospermidine (4) and 17α-Hydroxyaspidospermidine (8). A solution of 208 mg (0.45 mmol) of lactam **3** in 10 mL of anhydrous THF was added to a stirring suspension of 174 mg (4.6 mmol) of lithium aluminum hydride in 35 mL of dry THF and the mixture refluxed for 26 h. It then was stirred at room temperature for 12 h. Slow addition of EtOAc caused the decomposition of excess hydride, and subsequent addition of 1 N hydrochloric acid neutralized the solution. After vacuum evaporation of the THF, solid potassium sodium tartrate was added and the aqueous suspension extracted with $CHCl_3$. The extract was washed, dried, and evaporated. Crystallization of the residue (127 mg) from Me_2CO afforded 26 mg (20%) of colorless, crystalline alcohol **8**: mp 143–145 °C; UV (MeOH) λ_{max} 241 nm (ϵ 7000), 295 (2800); IR (CH_2Cl_2) OH 3620 (m), NH 3370 (w), CH (Wenkert–Bohlmann bands) 2790 (m), 2722 (w), 2672 (w), C=C 1605 (m) cm^{-1}; ^{1}H NMR δ 0.81 (t, 3, J = 7 Hz, Me), 1.13–1.41 (m, 4, C-14 and C-19 Hs), 1.45–1.49 (m, 1, H-5), 1.52–1.58 (m, 1, H-15), 1.70 (ddd, 1, J = 11, 16, 16 Hz, H-16), 1.81–1.92 (m, 2, H-15, H-16), 1.98 (t, 1, J = 11 Hz, H-3), 2.17–2.31 (m, 2, C-6 Hs), 2.56 (s, 1, H-21), 3.05–3.12 (m, 2, H-3, H-5), 3.70 (dd, 1, J = 6, 11 Hz, H-2), 4.45 (dd, 1, J = 4, 16 Hz, H-17), 6.65 (d, 1, J = 7 Hz, H-12), 6.73 (t, 1, J = 7 Hz, H-10), 7.03 (t, 1, J = 7 Hz, H-11), 7.08 (d, 1, J = 7 Hz, H-9); ^{13}C NMR δ (3:1 MeOH-d_4/$CDCl_3$; δ(Me_4Si) = δ(MeOH-d_4) + 29.8 ppm) 8.6 (Me), 21.7 (C-14), 23.1 (C-15), 28.3 (C-19), 37.4 (C-16), 38.6 (C-6), 40.1 (C-20), 52.9 (C-5), 54.2 (C-3), 65.5 (C-2), 66.4 (C-17), 69.8 (C-21), 110.5 (C-12), 118.5 (C-10), 122.5 (C-8), 122.8 (C-9), 127.6 (C-11), 150.9 (C-13); m/e 298 (M^+, 27), 124 (base); exact mass m/e 298.2070 (calcd for $C_{19}H_{26}ON_2$ 298.2083).

Chromatography of the mother liquor and gradient elution (10:1 to 5:1 EtOAc–Me_2CO) gave 82 mg (65%) of colorless, crystalline olefin **4**: mp 102–105 °C (CH_2Cl_2); UV (MeOH) λ_{max} 241 nm (ϵ 4900), 296 (2100); IR (CH_2Cl_2) NH 3380 (w), CH (Wenkert–Bohlmann bands) 2780 (m), 2722 (w), 2685 (w), 2640 (w), C=C 1605 (m) cm^{-1}; ^{1}H NMR δ 0.63 (t, 3, J = 7 Hz, Me), 0.89–1.02 (m, 2, C-19 Hs), 1.12–1.23 (m, 1, H-15), 1.57 (m, 2, C-14 Hs), 1.71 (d, 1, J = 14 Hz, H-15), 1.96 (dd, 1, J = 3, 10 Hz, H-6), 2.00–2.06 (m, 1, H-3), 2.14–2.24 (m, 1, H-6), 2.28 (s, 1, H-21), 2.32–2.41 (m, 1 H-5), 3.07 (d, 1, J = 11 Hz, H-3), 3.20 (ddd, 1, J = 3, 9, 9 Hz, H-5), 4.06 (d, 1, J = 4 Hz, H-2), 5.62 (d, 1, J = 10 Hz, H-17), 5.72 (dd, 1, J = 4, 10 Hz, H-16), 6.56 (d, 1, J = 7 Hz, H-12), 6.70 (t, 1, J = 7 Hz, H-10), 7.00 (t, 1, J = 7 Hz, H-11), 7.08 (d, 1, J = 7 Hz, H-9); ^{13}C NMR δ 7.5 (Me), 23.0 (C-14), 33.9 (C-15), 35.6 (C-19), 38.6 (C-20), 42.5 (C-6), 52.4 (C-5), 52.7 (C-3), 52.9 (C-7), 64.4 (C-2), 72.8 (C-21), 109.6 (C-12), 118.7 (C-10), 123.4 (C-9), 127.5 (C-11), 135.0 (C-8), 149.4 (C-13); m/e 280 (M^+, 55), 150 (base), 124 (40); exact mass m/e 280.1938 (calcd for $C_{19}H_{24}N_2$ 280.1941).

(±)-Aspidospermidine (5). A mixture of 22.4 mg (0.08 mmol) of olefin **4** and 11 mg of 10% platinum on charcoal in 15 mL of dry THF was shaken in a Parr bomb at 40 psi for 72 h. It was filtered and the filtrate evaporated. Chromatography of the residue and elution with 20:1 CH_2Cl_2–MeOH led to 18 mg (82%) of colorless, amorphous alkaloid **5**:[8] UV λ_{max} 243 nm (ϵ 7600), 298 (3400); IR (CH_2Cl_2) NH 3380 (w), CH (Wenkert–Bohlmann bands) 2782 (m), 2722 (w), C=C 1608 (m) cm^{-1}; ^{1}H NMR δ 0.63 (t, 3, J = 7 Hz, Me), 0.83–0.90 (m, 1 H-19), 1.03–1.20 (m, 2, H-15, H-17), 1.25 (m, 1 H-15), 1.39 (d, 1, J = 14 Hz, H-17), 1.43–1.53 (m, 2, H-6, H-19), 1.61–1.67 (m, 2, H-14, H-16), 1.70–1.80 (m, 1, H-14), 1.92–1.99 (m, 2, H-3, H-16), 2.23 (s, 1, H-21), 2.17–2.32 (m, 2, H-5, H-6), 3.07 (br d, 1, J = 14 Hz, H-3), 3.12–3.15 (m, 1, H-5), 3.50 (dd, 1, J = 6, 11 Hz, H-2), 6.64 (d, 1, J = 7 Hz, H-12), 6.73 (t, 1, J = 7 Hz, H-10), 7.01 (t, 1, J = 7 Hz, H-11), 7.08 (d, 1, J = 7 Hz, H-9); ^{13}C NMR δ 6.8 (Me), 21.8 (C-16), 23.0 (C-14), 28.1 (C-17), 30.0 (C-19 or C-15), 34.5 (C-15 or C-19), 35.6 (C-20), 38.8 (C-6), 53.0 (C-5), 53.7 (C-7), 53.9 (C-3), 65.7 (C-2), 71.3 (C-21), 110.3 (C-12), 119.0 (C-10), 122.8 (C-9), 127.1 (C-11), 135.7 (C-8), 149.4 (C-13).

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Stereospecific Reduction and Cross-Coupling of γ-Monosubstituted Allylic Chlorides Using Coordinatively Unsaturated Palladium Catalysts[1]

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A common strategy in the elaboration and transformation of allylic compounds involves transition metal activation of the allylic moiety in an initial step followed by capture of the resultant organometallic intermediates. In this regard, Pd(0)- and Pd(II)-based catalysts have emerged as highly versatile reagents, giving rise to reaction products in excellent yields and of high isomeric purity.

Stereospecific replacement of allylic functional groups by hydrogen remains a challenging problem in organic chemistry. The regio- and stereochemical outcome in these reactions is dependent on steric and electronic factors in the allylic substrate,[2-4] the allylic group being displaced,[5] the nature of the reducing agent,[5-7] and the ligands of the transition-metal catalyst.[8a,c] Excellent selectivity in favor of 1-olefin formation has been achieved in palladium-catalyzed reductions of allylic formates, esters, carbonates, phenyl ethers, chlorides, and vinyl epoxides using formates as the hydride source.[8a-c] Palladium-catalyzed reductions of (*E*)-γ-monosubstituted allylic compounds have been achieved to yield the corresponding 2(*E*)-olefins in high yields (>95%) and with a high degree of stereoselectivity.[2,3,5] Likewise, (*Z*)-γ,γ-disubstituted allylic compounds exhibit excellent regio- and stereoselectivity under similar reaction conditions.[5] However, to our knowledge, palladium-catalyzed reduction of (*Z*)-γ-*mono*substituted allylic compounds such as **3a** to 2(*Z*)-olefins has not been achieved with 100% stereospecificity.

Palladium-catalyzed cross-coupling reactions of allylic substrates with vinylorganometals has been the subject of intense investigation over the past decade.[9] While cross-coupling of γ,γ-*di*substituted allylic compounds generally proceeds with a high degree of stereo- and regioselectivity, similar reactions with γ-*mono*substituted analogues give rise to mixtures of regio- and stereoisomers.[9g-j] Superior selectivity in palladium-catalyzed reactions involving γ,γ-disubstituted allylic compounds is likely due to steric effects in the resultant allylpalladium complex. Presumably, greater steric repulsion at C_3 disfavors formation of a σ-bonded palladium–C_3 intermediate, essential for *E* to *Z* interconversion (i.e. between **7a** and **7b**, Scheme I).[10] In sterically less encumbered allylpalladium complexes therefore, isomerization is expected to be more facile. A rate of isomerization on the order of the ensuing C–H (reduction) or C–C (cross-coupling) bond forming reactions would account for the formation of regio- and stereoisomers.

Based on this line of reasoning, the possibility of capturing allylpalladium complexes prior to σ to π interconversion was investigated. The strategy we have adopted

Scheme I. Palladium-Catalyzed Reduction of γ-Monosubstituted Allylic Compounds

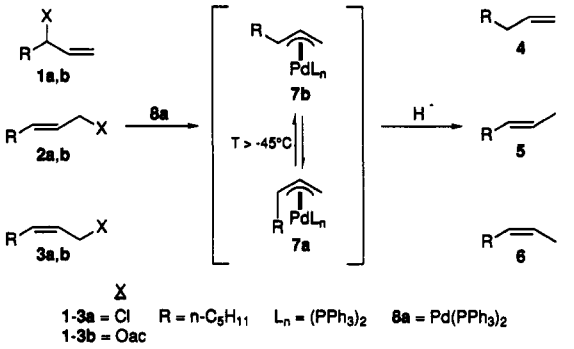

Table I. Diisobutylaluminum Hydride Capture of 3a Derived π-Allylpalladium Complex at Various Temperatures[a]

	product ratios (%)[b]			
temp, °C	4	5	6	yield (%)[b]
−78	–	–	100	100
−45	24	6	70	87
−23	42	21	37	73
0	56	18	26	76
rt	52	14	34	69

[a] Stoichiometric amount of Pd(0) used, 5 equiv of DIBAH added. [b] Product ratios and yields determined by GC.

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