Registry No.—Pregnenolone, 145-13-1.

References and Notes

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Total Synthesis of (±)-6,7-Didehydroaspidospermine

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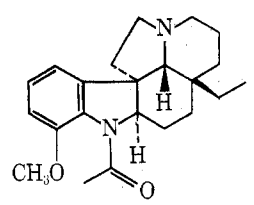
The total synthesis of the indole alkaloid derivative (±)-6,7-didehydroaspidospermine (**5**) by a Fischer indole approach is described. The cyclization precursor **4** was prepared in a stepwise fashion from ethyl 2-formylbutyrate via the key intermediates **10, 14, 16, 21,** and **6**. Upon heating in acetic acid the *o*-methoxyphenylhydrazone of **4** was cyclized to indolenine **27,** which on reduction and acetylation afforded (±)-6,7-didehydroaspidospermine (**5**).

Some years ago a total synthesis of the indole alkaloid aspidospermine (**1**) was developed in these laboratories by Stork and Dolfini.[2,3] This synthesis possessed as its main feature the construction of tricyclic amino ketone **2** and the subsequent Fischer indole cyclization of its *o*-methoxyphenylhydrazone. We became intrigued with the possibility that this approach might be extended to provide a route to 6,7-didehydro indole alkaloids, e.g., the pharmacologically important alkaloids vindoline (**3a**)[4] and vindorosine (**3b**).[5]



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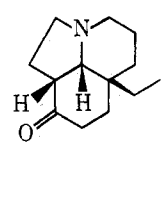

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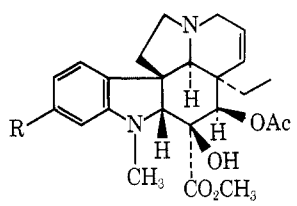
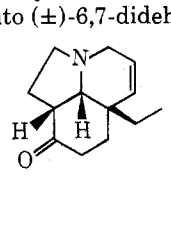


3a, R = OCH_3
b, R = H

We wish to report here a synthesis of the required unsaturated tricyclic amino ketone **4** and its subsequent conversion into (±)-6,7-didehydroaspidospermine (**5**).



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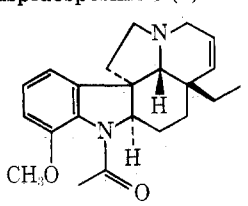

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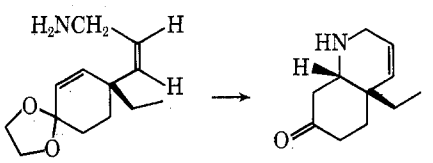
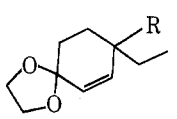
The synthetic plan involved construction of the necessary bicyclic amino ketone **6** by the hydrolysis and subsequent cyclization of ketal cis-allylic amine **7**. The third ring



7 **6**

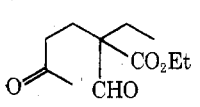
of unsaturated tricyclic amino ketone **4** could then be introduced in the same manner used in the preparation of the saturated analog **2**.[2]

It was decided to build up the cis-allylic amine chain of **7** in a stepwise manner from ketal ester **8**. Michael addition



8, R = CO_2Et
11, R = CH_2OH
12, R = CHO
13, R = CH=CHCl
14, R = C≡CH
15, R = C≡CCH_2OH

of ethyl 2-formylbutyrate[6] to methyl vinyl ketone gave adduct **9**, which was cyclized with piperidine acetate–acetic acid in refluxing benzene[7] to afford cyclohexenone ester **10**



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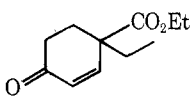


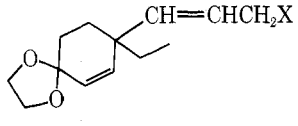
10

in 73% yield. Ketalization gave a quantitative yield of the desired ketal ester **8**.

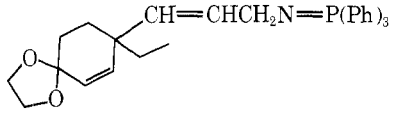
The ketal ester **8** was then reduced with lithium aluminum hydride (ether, 0°, 4 hr) to give ketal alcohol **11** in 57%

yield.[8] Oxidation with pyridine–sulfur trioxide complex in dimethyl sulfoxide–triethylamine[9] afforded ketal aldehyde **12** in 85% yield. The chain was subsequently extended one carbon by condensing ketal aldehyde **12** with chloromethylenetriphenylphosphorane[10] in refluxing tetrahydrofuran to produce ketal chloroolefin **13** in 97% yield. Dehydrohalogenation proceeded smoothly upon treatment of **13** with potassium *tert*-butoxide in 1:1 glyme–hexamethylphosphoramide at 25°, affording a 91% yield of ketal acetylene **14.**

The terminal carbon of the required chain was introduced by treatment of a glyme solution of the lithium acetylide of ketal acetylene **14** with excess monomeric formaldehyde to provide ketal propargyl alcohol **15** in 97% yield. Partial catalytic hydrogenation (PtO_2, ethyl acetate containing triethylamine) afforded a 99% yield of ketal allylic alcohol **16** as an approximately 3:1 mixture of cis to trans isomers.[11] Separation of these isomers was postponed to a later stage in the synthesis.



16, X = OH
17, X = N_3
18, X = OMs, Cl



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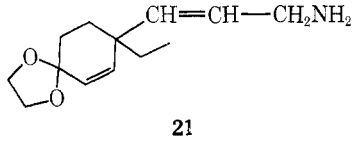
This mixture of allylic alcohols **16** was transformed into ketal allylic azide **17** in 88% yield by conversion into mesylate–chloride mixture **18** (MeLi, benzene, 15°, methanesulfonyl chloride) followed by nucleophilic displacement with sodium azide in aqueous dimethyl sulfoxide. Reduction of ketal allylic azide **17** to the corresponding amine initially caused some difficulty. Treatment of **17** with sodium borohydride both in ethanol at room temperature and 2-propanol at reflux failed to effect any reduction. In an alternative procedure **17** was smoothly converted to ketal phosphinimine **19** by refluxing with triphenylphosphine in benzene.[12] Hydrolysis and cyclization did afford a mixture of bicyclic amino ketone **6** and trans-allylic amine enone **20.** Unfortunately, the large amounts of triphenylphosphine oxide produced during the hydrolysis made separation of amines **6** and **20** very tedious.

This problem was eventually surmounted by reducing azide **17** with aluminum amalgam.[13] Thus stirring **17** with aluminum amalgam in 12:1:1 ether–methanol–water afforded an 81% yield of ketal allylic amine **21** (an approximately 3:1 mixture of ketal cis-allylic amine **7** and its corresponding trans isomer). Hydrolysis and cyclization proceeded in the anticipated manner to give the required bicyclic amino ketone **6** in 29% overall yield from ketal propargyl alcohol **15** after chromatography on activity IV neutral alumina to remove the undesired trans-allylic amine enone **20.**



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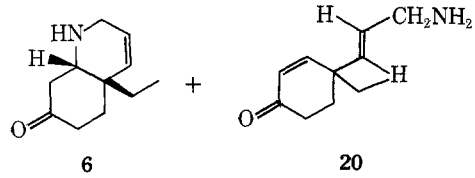
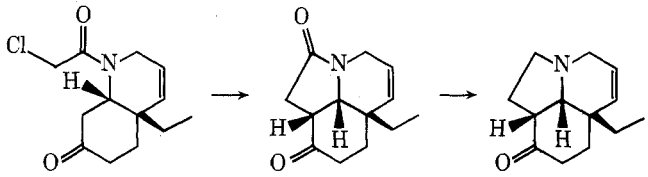
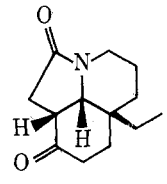


6 **20**

The third ring of **4** was now introduced in a manner identical with that used in the aspidospermine synthesis.[2] Chloroacetylation of **6** afforded chloroacetylamide **22** in 92% yield. Cyclization with potassium *tert*-butoxide in refluxing benzene gave the keto lactam **23** in 28% yield after repeated chromatography on silica gel. The stereochemistry of this intermediate was established as all-cis on the basis of its reduction to the Stork–Dolfini saturated keto lactam **24** (mp and mmp 114–115°) which Ban[14] had determined to possess the all-cis configuration. Ketalization and reduction with lithium aluminum hydride followed by deketalization proceeded in high overall yield to complete the preparation of tricyclic amino ketone **4.**

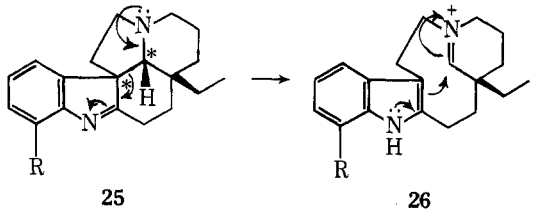


22 **23** **4**



24

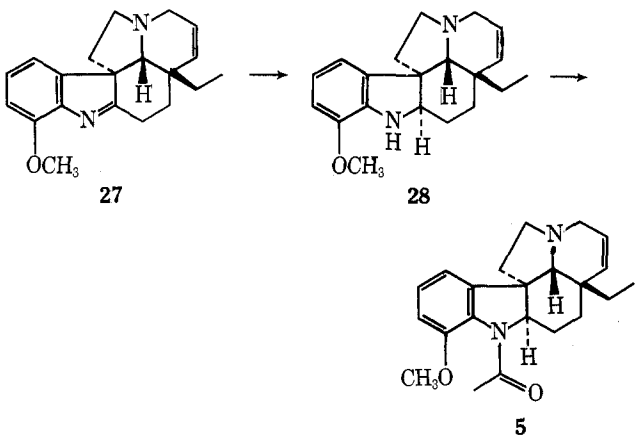
With amino ketone **4** in hand, one was ready to perform the crucial Fischer indole synthesis. It is worthy of note that, although **4** possesses the all-cis configuration necessary to produce a pentacyclic alkaloid precursor having the same relative stereochemical relationships as those present in aspidospermine and related natural products, the three configurational isomers of **4** should also lead to this same final stereochemistry. Stork pointed out that the indolenine **25** formed during the Fischer indole cyclization was generated under conditions which would lead to equilibration at the two centers marked by asterisks via a reverse Mannich reaction.[2] This equilibration proceeds through



25 **26**

the open form **26,** which can conceivably reclose to give any of the possible stereoisomers. However, the reversible nature of this tautomerization dictates that the eventual product possess the thermodynamically most stable arrangement, which in this case turns out to be the natural one.[15]

Fischer indole cyclization of the *o*-methoxyphenylhydrazone of amino ketone **4** was effected in refluxing acetic acid. The resulting indolenine **27** was reduced with lithium aluminum hydride to indoline **28.** Evaporative distillation followed by acetylation with acetic anhydride–sodium acetate gave a crude material from which crystalline (±)-6,7-didehydroaspidospermine (**5,** mp 190–191°) could be readi-



27 28 5

ly obtained. This material afforded (±)-aspidospermine (1), identical in all respects with that prepared by Stork and Dolfini,[2] on catalytic hydrogenation with palladium on charcoal in acetic acid.

It is hoped that a suitable adaptation of this approach will provide a viable route to the more complex, pharmacologically interesting 6,7-didehydro indole alkaloids.

Experimental Section

Melting points were determined on a Büchi capillary melting point apparatus and are uncorrected. Microanalyses were performed by Micro-Tech Laboratories, Inc., Skokie, Ill., or Schwarzkopf Microanalytical Laboratory, Woodside, N.Y. Infrared spectra were recorded on a Perkin-Elmer Model 137 spectrophotometer. Absorptions are in microns using a polystyrene standard. Nuclear magnetic resonance spectra were taken on Varian Model A-60A or T-60 spectrometers using deuteriochloroform as solvent. Signals are reported in parts per million (δ) relative to an internal tetramethylsilane standard. (Notation: s, d, t, etc., refer to singlet, doublet, triplet, etc., and br refers to a broad peak.) Mass spectra were recorded on a Hitachi Perkin-Elmer Model RMU-6D mass spectrometer. Ethereal solvents were distilled from lithium aluminum hydride; dimethyl sulfoxide, *tert*-butyl alcohol, and hexamethylphosphoramide were distilled from calcium hydride. Triethylamine was distilled from barium oxide. Column materials for chromatography were normally 60–100 mesh. The phrase "worked up in the usual manner", as applied to an organic extract, refers to drying over anhydrous sodium sulfate followed by evaporation in vacuo.

Ethyl 2-Formylbutyrate. A. Ethyl 2-formylbutyrate was prepared in 15.6% yield by condensing ethyl butyrate (406 g, 3.50 mol) with ethyl formate (260 g, 3.50 mol) in ether employing sodium hydride as the base, bp 76–80° (25 mm) [lit.[16] bp 64–66° (16 mm)].

B. A solution of 5.06 g (0.05 mol) of diisopropylamine in 50 ml of dry THF was treated with 21.3 ml (0.05 mol) of 2.35 *M* *n*-butyllithium in hexane at room temperature under nitrogen. The resultant pale yellow solution was cooled to −78°, at which time a solution of 5.81 g (0.05 mol) of ethyl butyrate in 15 ml of dry THF was added. Stirring was continued for 0.5 hr at −78°, after which 11.1 g (0.15 mol, 12.2 ml) of ethyl formate was added by syringe. The resultant mixture was allowed to warm to room temperature and stirred for 3 hr under nitrogen. After the addition of 9 g (0.15 mol, 8.55 ml) of acetic acid, the reaction mixture was diluted with 350 ml of ether and washed with water (2 × 100 ml) and saturated aqueous $NaHCO_3$ solution (100 ml). Work-up in the usual manner gave 7.29 g of an orange oil, which was distilled to afford 4.30 g (60%) of ethyl 2-formylbutyrate as a colorless liquid: bp 76–81° (23 mm); ir (film) 2.95, 5.80, 6.00, 6.20 μ; NMR δ 1.04 (t, J = 7 Hz, 3 H), 1.35 (t, J = 7 Hz, 3 H), 1.7–2.5 (m, 2 H), 3.22 (t of d, J_1 = 7, J_2 = 2 Hz, 0.5 H), 4.28 (q, J = 7 Hz, 2 H), 7.02 (d, J = 12 Hz, 0.5 H), 9.76 (d, J = 2 Hz, 0.5 H), 11.41 (d, J = 12 Hz, 0.5 H).

4-Ethyl-4-carboethoxycyclohex-2-enone (10). The cyclohexenone ester **10** was prepared according to the general procedure of Plieninger and coworkers[7]. Treatment of ethyl 2-formylbutyrate with methyl vinyl ketone in *tert*-butyl alcohol containing a catalytic amount of potassium *tert*-butoxide gave Michael adduct **9** as a nearly colorless oil: ir (film) 5.72, 5.80 μ; NMR δ 0.88 (t, J = 7 Hz, 3 H), 1.28 (t, J = 7 Hz, 3 H), 1.5–2.7 (m, 6 H), 2.11 (s, 3 H), 4.25 (q, J = 7 Hz, 2 H), 9.8 (s, 1 H). Cyclization of this material by refluxing in benzene with piperidinium acetate and acetic acid with azeotropic removal of water afforded after distillation a 73% yield of cyclohexenone ester **10:** bp 92–95° (0.25 mm); ir (film) 5.79, 5.91 μ; NMR δ 0.88 (t, J = 7 Hz, 3 H), 1.28 (t, J = 7 Hz, 3 H), 1.5–2.7 (m, 6 H), 4.25 (q, J = 7 Hz, 2 H), 5.98 and 6.95 (AB quartet, J = 10 Hz, 2 H).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.14; H, 8.26.

8-Ethyl-8-carboethoxy-1,4-dioxaspiro[4,5]-6-decene (8). Ketal ester **8** was prepared from cyclohexenone ester **10** using standard ketalization conditions (ethylene glycol, a catalytic amount of *p*-toluenesulfonic acid, and benzene at reflux with a Dean-Stark trap). From 37 g (0.189 mol) of **10** was obtained a nearly quantitative yield of ketal ester **8** as a pale yellow oil, which was used in subsequent experiments without further purification: ir (film) 5.80, 6.03 μ (weak); NMR δ 0.87 (t, J = 7 Hz, 3 H), 1.23 (t, J = 7 Hz, 3 H), 1.45–2.5 (m, 6 H), 3.96 (s, 4 H), 4.15 (q, J = 7 Hz, 2 H), 5.62 and 5.94 (AB quartet, J = 10 Hz, 2 H).

8-Ethyl-8-hydroxymethyl-1,4-dioxaspiro[4,5]-6-decene (11). To a suspension of 4.75 g (0.125 mol) of $LiAlH_4$ in 275 ml of anhydrous ether was added dropwise with stirring at 0° under nitrogen a solution of 34.75 g (0.144 mol) of ketal ester **8** in 75 ml of anhydrous ether. The reaction mixture was then stirred for 4 hr at 0° under nitrogen. Excess $LiAlH_4$ was decomposed by cautious dropwise addition of ethyl acetate and then saturated aqueous sodium sulfate at 0°. The precipitate was filtered off and washed repeatedly with ether. The combined filtrate and washings were evaporated in vacuo and distilled to afford 16.17 g (57%) of ketal alcohol **11** as a viscous, colorless liquid: bp 112–116° (0.25 mm); ir (film) 2.98, 6.05 μ; NMR δ 0.87 (t, J = 7 Hz, 3 H), 1.1–2.0 (m, 6 H), 2.19 (br s, 1 H), 3.41 (slightly broadened s, 2 H), 3.96 (s, 4 H), 5.65 (s, 2 H).

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.54; H, 9.11.

8-Ethyl-8-formyl-1,4-dioxaspiro[4,5]-6-decene (12). The ketal alcohol **11** was oxidized according to the general procedure of Parikh and Doering.[9]

To a solution of 16.10 g (81.3 mmol) of ketal alcohol in 160 ml of dry triethylamine and 160 ml of dry dimethyl sulfoxide (distilled from calcium hydride) was added a solution of 40 g (252 mmole) of pyridine–sulfur trioxide complex[17] in 240 ml of dry dimethyl sulfoxide. The mixture was stirred overnight at room temperature under nitrogen, diluted with 2 l. of ether, and washed with water (4 × 1000 ml). Work-up in the usual manner followed by distillation afforded 13.43 g (85%) of slightly yellow ketal aldehyde **12:** bp 93–97° (0.25 mm); ir (film) 3.40, 3.50, 3.68, 5.79, 6.01 μ; NMR δ 0.87 (t, J = 7 Hz, 3 H), 1.3–2.3 (m, 6 H), 3.98 (s, 4 H), 5.82 (s, 2 H), 9.47 (s, 1 H).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.12; H, 8.36.

Chloromethyltriphenylphosphonium Chloride. Chloromethyltriphenylphosphonium chloride was prepared in 82% yield according to the procedure of Wittig and Schlosser[18] from triphenylphosphine and paraformaldehyde.

8-Ethyl-8-chlorovinyl-1,4-dioxaspiro[4,5]-6-decene (13). The ketal aldehyde **12** was condensed with chloromethylenetriphenylphosphorane according to the general procedure described by Seyferth and coworkers.[10]

To a suspension of 34.7 g (100 mmol) of chloromethyltriphenylphosphonium chloride in 425 ml of dry THF was added 45 ml (100 mmol) of 2.24 *M* phenyllithium in 70:30 benzene–ether in a nitrogen atmosphere. The deep red mixture was allowed to stir at room temperature for 0.5 hr, after which a solution of 10.70 g (54.5 mmol) of ketal aldehyde in 75 ml of dry THF was added dropwise with stirring. The mixture was then refluxed overnight under nitrogen. The cooled reaction mixture was poured into 1.9 l. of 1:1 ether–hexane, washed with water (3 × 850 ml), and worked up in the usual manner. The residue was chromatographed on 80 g of Florisil (60–100 mesh) with 1:5 ether–hexane as eluent. The eluate was evaporated in vacuo and distilled to afford 12.04 g (97%) of colorless ketal chloroolefin **13:** bp 97–102° (0.40 mm); ir (film) 3.38, 3.48, 6.04, 6.14, 6.19, 10.54 μ; NMR δ 0.88 (t, J = 7 Hz, 3 H), 1.2–2.0 (m, 6 H), 3.95 (s, 4 H), 5.4–6.2 (m, 4 H).

8-Ethyl-8-ethynyl-1,4-dioxaspiro[4,5]-6-decene (14). To a solution of 12.0 g (52.5 mmol) of ketal chloroolefin **13** in 135 ml of dry glyme and 135 ml of dry hexamethylphosphoramide was added 30 g (267 mmole) of potassium *tert*-butoxide. The mixture was stirred overnight at room temperature under nitrogen, diluted with 1.8 l. of ether, and washed extensively with water (5 × 900 ml) to remove all the HMPA. Work-up in the usual manner and distil-

lation afforded 9.16 g (91%) of colorless ketal acetylene **14**: bp 75–79° (0.35 mm); ir (film) 3.08, 4.73, 6.03 μ; NMR δ 1.02 (t, J = 7 Hz, 3 H), 1.15–2.05 (m, 6 H), 2.13 (s, 1 H), 3.94 (s, 4 H), 5.50 and 5.78 (AB quartet, J = 10 Hz, 2 H).

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 75.03; H, 8.56.

8-Ethyl-8-hydroxymethylethynyl-1,4-dioxaspiro[4,5]-6-decene (15). Ketal propargyl alcohol **15** was obtained in 97% yield by treating the lithium acetylide prepared from 7.50 g (39 mmol) of ketal acetylene **14** and methyllithium in glyme with excess monomeric formaldehyde: ir (film) 2.97, 4.48, 6.02 μ; NMR δ 1.00 (t, J = 7 Hz, 3 H), 1.15–2.2 (m, 6 H), 2.81 (br s, 1 H), 3.98 (s, 4 H), 4.22 (s, 2 H), 5.50 and 5.77 (AB quartet, J = 10 Hz, 2 H).

Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.10; H, 8.19.

8-Ethyl-8-hydroxymethylvinyl-1,4-dioxaspiro[4,5]-6-decene (16). A solution of 6.669 g (30 mmol) of ketal propargyl alcohol **15** in 125 ml of ethyl acetate containing 9 ml of triethylamine was hydrogenated at atmospheric pressure using 300 mg of 84% platinum oxide as catalyst. After 30 mmol of hydrogen (745 ml plus allowance for catalyst) was absorbed, the reaction was discontinued. The solution was filtered with the aid of filter cel and evaporated in vacuo to afford 6.65 (99%) of ketal allylic alcohol **16** (approximately 3:1, cis/trans) as an orange oil: ir (film) 2.96, 6.04 μ; NMR δ 0.83 (skewed t, 3 H), 1.05–2.0 (m, 6 H), 2.82 (s, 1 H), 3.98 (s, 6 H), 5.1–6.1 (m, 4 H).

Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.88; H, 8.95.

Bicyclic Ether Ketone i. Ketal allylic alcohol **16** (112.2 mg, 0.5 mmol) was hydrolyzed with 5 ml of 1 N hydrochloric acid (30 min). Standard work-up procedures afforded 83 mg of pale yellow oil. Investigation of the ir and NMR spectra of this material indicated that it was an approximately 3:1 mixture of bicyclic ether ketone i and trans-allylic alcohol enone ii, respectively.

8-Ethyl-8-azidomethylvinyl-1,4-dioxaspiro[4,5]-6-decene (17). To a solution of 6.66 g (29.7 mmol) of allylic alcohol **16** in 300 ml of dry benzene at 15° was added 20 ml (32 mmol) of 1.6 M methyllithium in ether. The solution was stirred at 15° under nitrogen for 5 min, after which 3.0 ml (38.4 mmol) of methanesulfonyl chloride was added. This mixture was then stirred overnight at room temperature under nitrogen and poured into 600 ml of 5% aqueous NaOH solution. The mixture was extracted with 1 l. of ether, washed with water (2 × 500 ml), and worked up in the usual manner to give 7.68 g of an approximately 3:1 mixture of ketal allylic mesylate and ketal allylic chloride **18** as a light orange oil: ir (film) no OH, 6.04, 7.37 μ; NMR δ 2.93 (CH_3SO_2–), 3.87 (–CH_2OMs), 3.95 (ketal), 4.80 (–CH_2Cl). Integration indicates that the mesylate:chloride ratio is approximately 3:1.

To a solution of 7.67 g of allylic mesylate–chloride mixture from the previous experiment in 250 ml of dimethyl sulfoxide and 50 ml of water was added 16 g (246 mmol) of sodium azide. The resulting solution was stirred overnight at room temperature under nitrogen, poured into 1200 ml of ether, and washed with water (3 × 500 ml). Work-up in the usual manner gave 6.53 g (88%) of ketal allylic azide **17** as a yellow oil: ir (film) 4.76, 6.04 μ; NMR δ 0.87 (skewed t, J = 7 Hz, 3 H), 1.03–2.10 (m, 6 H), 3.95 (s, 6 H), 5.30–6.00 (m, 4 H).

Ketal Phosphinimine 19. To a solution of 770 mg (3.10 mmol) of ketal allylic azide **17** in 50 ml of dry benzene was added 960 mg (3.66 mmol) of triphenylphosphine. The resulting solution was refluxed overnight under nitrogen, after which the solvent was removed in vacuo to give a quantitative yield of ketal phosphinimine **19** as a viscous yellow oil: ir (film) no azide, 6.30 (weak), 6.80 (strong), 7.00 μ (strong).

8-Ethyl-8-aminomethylvinyl-1,4-dioxaspiro[4,5]-6-decene (21). To aluminum–mercury amalgam prepared from 7.02 g (260 mmol) of aluminum turnings according to the procedure of Wislicenus and Kaufmann[19] under 60 ml of ether was added a solution of 6.52 g (26.2 mmol) of allylic azide **17** in 300 ml of ether. To this suspension was added 30 ml of methanol and 30 ml of water. The resulting mixture was stirred rapidly for 20 hr at room temperature under nitrogen, during which time a cloudy gray precipitate was formed. The mixture was then filtered, the precipitate being washed extensively with ether. The combined ether solutions were washed with 500 ml of water and worked up in the usual manner to afford 4.73 g (81%) of ketal allylic amine **21** as a yellow oil (an approximately 3:1 mixture of ketal cis-allylic amine **7** and its corresponding trans isomer): ir (film) 3.01, 6.07, 6.23 μ; NMR δ 0.87 (skewed t, J = 7 Hz, 3 H), 1.05–2.20 (m, 8 H), 3.95 (s, 6 H), 5.00–6.10 (m, 4 H).

Anal. Calcd for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48. Found: C, 69.76; H, 9.30.

4a-Ethyl-2,4a,5,6,8,8a-hexahydro-7(1*H*)-quinolone (6). A solution of 4.50 g (20.2 mmol) of ketal allylic amine **21** dissolved in 400 ml of 1 N hydrochloric acid and 30 ml of methanol was stirred for 1 hr at room temperature under nitrogen and then made basic with 10% aqueous NaOH. After standing for 10 min, the mixture was extracted with ether (2 × 600 ml). Work-up in the usual manner gave 3.06 g of an orange oil which was shown by ir to be an approximately 3:1 mixture of bicyclic amino ketone **6** and trans-allylic amine enone **20**: ir (film) 3.05, 5.84 (strong), 5.96 μ (medium).

This mixture was chromatographed on 110 g of Woelm neutral alumina (activity IV). Elution with 250 ml of 40% ether–benzene gave first a small amount of a nonbasic enone followed by 1.55 g (29% overall yield from ketal propargyl alcohol **15**) of hexahydroquinolone **6**. If elution was continued with the same solvent transallylic amine enone **20** could be obtained. The chromatography was followed by ir: ir (film) 3.05, 3.45, 5.84, 6.05 μ; NMR δ 0.92 (skewed t, J = 7 Hz, 3 H), 1.05–3.0 (m, 9 H), 3.13 (t, J = 5 Hz, 1 H), 3.38 (br s, 2 H), 5.61 and 5.72 (AB quartet, J = 2.5 Hz, 2 H); MS m/e 179 (M^+), 150, 124, 108.

Anal. Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56. Found: C, 73.91; H, 9.52.

***N*-Chloroacetyl-4a-ethyl-2,4a,5,6,8,8a-hexahydro-7(1*H*)-quinolone (22).** To a solution of 1.07 g (5.97 mmol) of hexahydroquinolone **6** and 605 mg (5.97 mmol) of triethylamine in 80 ml of dry methylene chloride at 0° under nitrogen was added dropwise with stirring a solution of 675 mg (5.97 mmol) of chloroacetyl chloride in 20 ml of dry methylene chloride. After the addition was complete, the reaction mixture was stirred for 1.5 hr at room temperature under nitrogen. The mixture was diluted with 350 ml of methylene chloride and washed with 1 N hydrochloric acid (150 ml), 5% aqueous potassium carbonate solution (150 ml), and water (150 ml). Work-up in the usual manner gave 1.58 g of viscous brown oil. Chromatography on 25 g of silica gel using 1:1 ether–benzene as eluent afforded 1.41 g (92%) of bicyclic chloroacetyl amide **22** as an orange gum: ir (film) 5.82, 6.06 μ; NMR δ 0.9 (skewed t, 3 H), 1.1–2.8 (m, 9 H), 4.10 (br s, 4 H), 5.81 (br s, 2 H).

6a-Ethyl-4,6a,7,8,9a,9b-hexahydro-9*H*-pyrrolo[3,2,1-*ij*]quinoline-2,9(1*H*)-dione (23). A solution of 3.00 g (11.75 mmol) of chloroacetyl amide **22** in 120 ml of dry benzene containing 1.54 g (13.75 mmol) of potassium *tert*-butoxide was refluxed under nitrogen for 26 hr, after which most of the benzene was removed in vacuo. The residue was taken up in 1 l. of methylene chloride, washed with 5% aqueous NaOH (400 ml) and water (500 ml), and worked up in the usual manner to give 2.40 g of an orange foam. This foam was chromatographed on 60 g of silica gel. After elution with 125 ml of 4:1 ether–benzene and 200 ml of ether, to remove any nonpolar by-products and unreacted starting material, a fraction containing the desired tricyclic keto lactam **23** was eluted with 1 l. of 2% methanol–methylene chloride. Evaporation of this fraction in vacuo gave 998 mg of viscous orange gum. As this material was contaminated with a small amount of very polar impurities, it was carefully rechromatographed on 27 g of silica gel using 2% methanol–methylene chloride as eluent. This second chromatography afforded 725 mg (28%) of tricyclic keto lactam **23** as a pale yellow, viscous oil, which was homogeneous on TLC (silica gel G, 2% MeOH–CH_2Cl_2): ir (film) 5.87, 5.93 μ; NMR δ 1.00 (split t, J = 7 Hz, 3 H), 1.30–2.2 (m, 4 H), 2.2–3.3 (m, 4 H), 3.44 (dd, J_1 = 7, J_2 = 2 Hz, 1 H), 3.6–4.07 (m, 2 H), 4.10–4.38 (m, 1 H), 5.72 (s, 2 H); MS m/e 219 (M^+), 190.

High-resolution mass spectrum: Anal. Calcd for $C_{13}H_{17}NO_2$: 219.1259. Found: 219.1259.

6a-Ethyl-1,2,4,6a,7,8,9a,9b-octahydro-9*H*-pyrrolo[3,2,1-*ij*]-quinolin-9-one (4). A solution of 186.8 mg (0.852 mmol) of tricyclic keto lactam **23** and 0.20 ml (3.6 mmol) of ethylene glycol in 30 ml of benzene containing 15 mg of *p*-toluenesulfonic acid monohydrate was refluxed for 19 hr under nitrogen, the water of reaction being removed with a Dean-Stark trap containing molecular sieves. A few drops of triethylamine were added, and the mixture was diluted with 30 ml of benzene and washed with saturated aqueous $NaHCO_3$ solution (2 × 20 ml). Work-up in the usual manner afforded 200 mg (90%) of tricyclic lactam ketal as a viscous orange oil: ir (film) 5.90, 6.03 μ; NMR δ 0.92 (skewed t, 3 H), 1.1–2.0 (m, 4 H), 2.1–2.7 (m, 4 H), 3.0–3.8 (m, 3 H), 3.8–4.2 (m, 1 H), 3.97 (s, 4 H), 5.68 (s, 2 H).

To a suspension of 57 mg (1.5 mmol) of $LiAlH_4$ in 10 ml of dry ether was added dropwise with stirring at room temperature under nitrogen a solution of 197 mg (0.75 mmol) of tricyclic lactam ketal in 5 ml of dry ether. The mixture was then stirred for 3 hr at room

temperature under nitrogen, after which excess $LiAlH_4$ was decomposed by cautious dropwise addition of saturated aqueous sodium sulfate solution at 0°. The precipitate was filtered off and washed with ether. The combined ethereal solutions were evaporated in vacuo to afford 178 mg (95%) of tricyclic amino ketal as a pale yellow gum: ir (film) 3.45, 3.50, Bohlmann bands, 3.61, 3.68 μ; NMR δ 0.90 (skewed t, 3 H), 1.1–2.7 (m, 8 H), 3.0–3.7 (m, 4 H), 3.97 (m, 6 H), 5.60 (br s, 2 H).

To a solution of 177 mg (0.710 mmol) of tricyclic amino ketal in 1.5 ml of methanol was added 3 ml of water and 1.5 ml of concentrated hydrochloric acid. The resulting solution was stirred overnight at room temperature under nitrogen. The mixture was basified with 10% aqueous NaOH and extracted with ether (2 × 60 ml). The combined ether extracts were worked up in the usual manner to afford 142 mg (97%) of crude tricyclic amino ketone **4** as a yellow gum. This gum could be purified by evaporative distillation to give colorless tricyclic amino ketone **4**: bp 120–130° (0.15 mm); ir (film) Bohlmann bands 3.60, 3.68, 5.85 μ; NMR δ 0.90 (skewed t, 3 H), 1.1–3.6 (m, 12 H), 3.95 (br s, 2 H), 5.62 (m, 2 H); MS *m/e* 205 (M^+).

High-resolution mass spectrum: Anal. Calcd for $C_{13}H_{19}NO$: 205.1467. Found: 205.1467.

6a-Ethyl-4,5,6,6a,7,8,9a,9b-octahydro-9*H*-pyrrolo[3,2,1-*ij*]-quinoline-2,9(1*H*)-dione (24). A solution of 355 mg (1.62 mmol) of tricyclic keto lactam **23** in 25 ml of 95% ethanol was hydrogenated at atmospheric pressure using 35 mg of 10% palladium on carbon as catalyst. After 5 hr the theoretical amount of hydrogen (39.6 ml) had been absorbed. The reaction mixture was filtered with the aid of Celite and evaporated in vacuo to afford 346 mg (96%) of saturated tricyclic keto lactam **24** as a viscous yellow oil which had ir and NMR spectra and thin layer properties (silica gel G, 2% MeOH–CH_2Cl_2) identical with those of the Stork–Dolfini saturated tricyclic keto lactam.[2] A small amount of material (53.5 mg) prepared in this manner was chromatographed on 1 g of silica gel with 2% methanol–methylene chloride. When the solvent was removed in vacuo and the residue triturated with ether, 33 mg of white crystalline saturated tricyclic keto lactam **24** was obtained: mp 114–115° (lit.[2] mp 113–116°); mmp 114–115°; ir (film) 5.86, 5.92 μ; NMR δ 0.97 (t, J = 7 Hz, 3 H), 1.10–3.0 (m, 11 H), 3.08 (d, J = 5 Hz, 1 H), 3.45 (dd, J_1 = 2, J_2 = 6 Hz, 2 H), 4.00 (br d, J = 13 Hz, 2 H).

***o*-Methoxyphenylhydrazine.** *o*-Methoxyphenylhydrazine was prepared in 54% yield according to the procedure of Bergmann and Hoffmann[20] by the reduction of diazotized *o*-anisidine with stannous chloride: mp 38–40° (lit.[20] mp 43°); NMR δ 3.78 (s, 3 H), 4.10 (br s, 3 H), 6.6–6.95 (m, 4 H).

(±)-6,7-Didehydroaspidospermine (5). Tricyclic amino ketone **4** (142 mg, 0.69 mmol) was dissolved in 5 ml of ether with 95.5 mg (0.69 mmol) of *o*-methoxyphenylhydrazine. Two drops of acetic acid was added as catalyst and the solution was stirred for 13 hr at room temperature under nitrogen. The solvent was then removed in vacuo to afford the *o*-methoxyphenylhydrazone of amino ketone **4**: viscous orange oil; ir (film) 3.05, 3.64, 3.69, 6.24, 6.63 μ.

The crude tricyclic *o*-methoxyphenylhydrazone was dissolved in 5 ml of glacial acetic acid and heated at reflux for 45 min under nitrogen. The solvent was removed in vacuo to give the crude pentacyclic indolenine **27** as a dark brown oil.

To a suspension of 228 mg (6 mmol) of $LiAlH_4$ in 8 ml of dry ether was added dropwise with stirring at 0° under nitrogen a solution of crude pentacyclic indolenine **27** in 8 ml of 1:1 ether–glyme. This mixture was stirred overnight at room temperature under nitrogen, after which excess $LiAlH_4$ was decomposed by cautious dropwise addition of saturated aqueous sodium sulfate solution at 0°. The precipitate was filtered off and washed repeatedly with ether. The combined ethereal solutions were evaporated in vacuo to afford 197 mg of a brown oil. Evaporative distillation gave two fractions: I, bp 90–150° (0.22 mm), 15 mg; II, bp 140–160° (0.22 mm), 112.4 mg.

The higher boiling fraction, II, was treated with 1 ml of acetic anhydride and 75 mg of anhydrous sodium acetate for 2 hr at room temperature under nitrogen. The acetic anhydride was removed in vacuo and the residue was diluted with 60 ml of benzene and washed with saturated aqueous sodium bicarbonate solution (2 × 25 ml) and water (20 ml). Work-up in the usual manner gave a viscous yellow oil which afforded 21 mg (9%) of crystalline (±)-6,7-didehydroaspidospermine (**5**), mp 190–191°, on trituration with ether. This material had an ir spectrum similar to that of (±)-aspidospermine with some subtle differences in the fingerprint region: ir (KBr) 3.64, 6.09, 6.29, 6.72, 6.90, 7.24 μ; NMR δ 2.20 (s, 3 H), 3.90 (s, 3 H), 5.63 (sharp m, 2 H).

High-resolution mass spectrum: Anal. Calcd for $C_{22}H_{28}N_2O_2$: 352.2151. Found: 352.2150.

Hydrogenation of **5** in the presence of Pd on charcoal in acetic acid afforded (±)-aspidospermine (**1**) identical in all respects with that prepared by Stork and Dolfini.[2]

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Registry No.—i, 54788-77-1; ii, 54788-78-2; **4**, 54788-79-3; **4** *o*-methoxyphenylhydrazone, 54788-80-6; **4** ketal analog, 54788-81-7; **5**, 54788-82-8; **6**, 54788-83-9; **7**, 54788-84-0; **7** trans analog, 54788-85-1; **8**, 54788-86-2; **9**, 54788-87-3; **10**, 54788-88-4; **11**, 54788-89-5; **12**, 54788-90-8; **13**, 54788-91-9; **14**, 54788-92-0; **15**, 54788-93-1; *cis*-**16**, 54788-94-2; *trans*-**16**, 54788-95-3; **17**, 54788-96-4; **18**-Cl, 54788-97-5; **18**-OMe, 54788-98-6; **19**, 54788-99-7; **20**, 54789-00-3; **22**, 54789-01-4; **23**, 54789-02-5; **23** ketal analog, 54789-03-6; **24**, 54831-17-3; **27**, 54789-04-7; **28**, 54789-05-8; ethyl 2-formylbutyrate, 36873-42-4; ethyl butyrate, 105-54-4; ethyl formate, 109-94-4; chloromethyltriphenylphosphonium chloride, 5293-84-5; *o*-methoxyphenylhydrazine, 18312-46-4.

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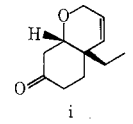
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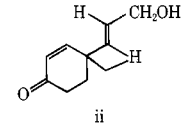
ii

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