Studies in Biomimetic Alkaloid Syntheses. 2. Synthesis of Vincadifformine from Tetrahydro-β-carboline through a Secodine Intermediate

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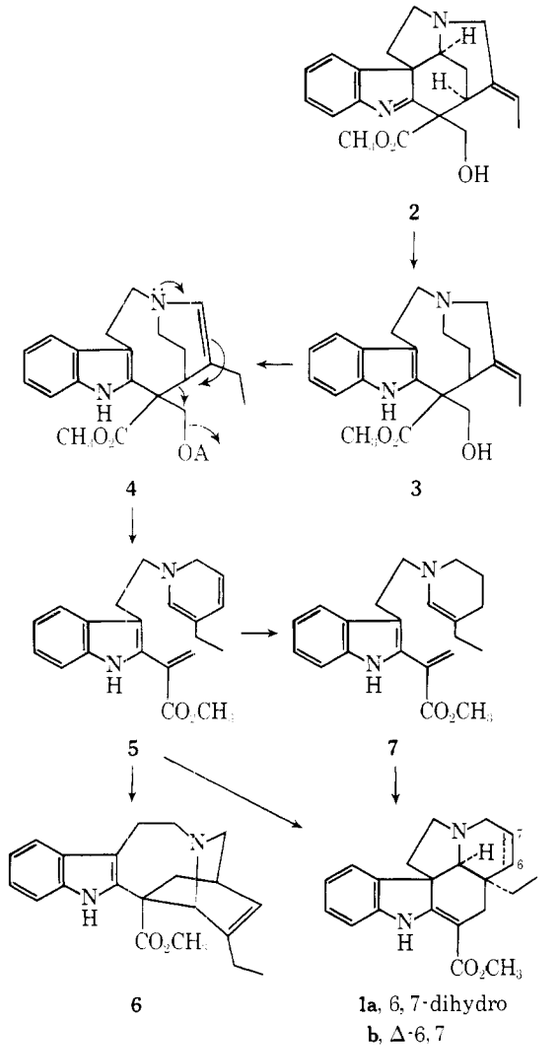
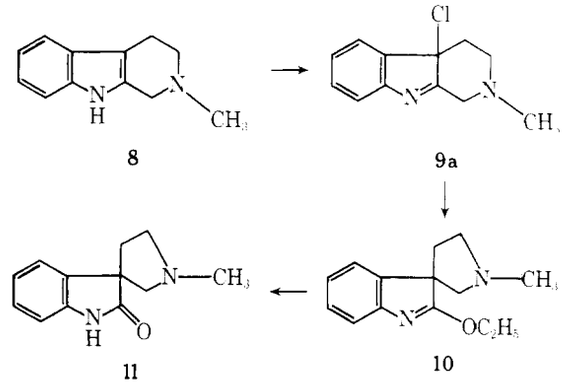
N-Methyl- and *N*-benzyltetrahydro-β-carbolines (**8** and **17**) on reaction with *tert*-butyl hypochlorite gave the corresponding chloroindolenines **9a,b**. The *N*-methyl compound **9a** was converted to the rearranged 2-alkoxy-3-spiropyrrolidylindolenine (**10**) and the oxindole (**11**) on treatment with thallium ethoxide, followed by hydrolysis. Reactions of the chloroindolenines **9a,b** with thallium dialkylmalonates led to the respective indoleazepines **14** and **16**. Monodecarboxylation and debenzylation of the latter provided the amino ester **20**, which was converted to vincadifformine (**1a**) by reaction with 5-bromo-2-ethylpentanal (**23**). The overall synthetic reaction sequence, which proceeded in high yields at each step, passed through the biogenetically postulated secodine **7**. This intermediate underwent a biomimetic cyclization with stereospecific generation of vincadifformine in greater than 67% yield.

Among indole and dihydroindole alkaloids, which comprise one of the largest classes of natural products with a common structural element, alkaloids with the aspidosperma skeleton, exemplified in vincadifformine (**1a**), are prominently represented. Their biosynthetic origin has been traced to tryptophan and loganin precursors with subsequent secoyohimbine (i.e., geissoschizine) and strychnos (i.e., preakuammicinal) biosynthetic stages.[1] (See corresponding structures **1**, **2**, and **3** in the preceeding paper.[2]) Cleavage of ring C in preakuammicine (**2**) and reduction of the resultant immonium function leads to stemmadenine (**3**). Isomerization of the ethylidene double bond in stemmadenine (**3**) can then give rise to a tetrahydropyridine alcohol intermediate **4**, which may undergo fragmentation (as its pyrophosphate?) to a dehydrosecodine (**5**). This structure occupies a key pivotal position in alkaloid biogenesis in that it has been postulated[1,3] to serve as a precursor for generation of aspidosperma (i.e., tabersonine, **1b**) or iboga (i.e., catharanthine, **6**) alkaloid structures by alternative reactions of the acrylic ester and dienamine moieties. Furthermore, reduction to a tetrahydropyridine (perhaps by disproportionation of the dihydropyridine) will furnish a secodine intermediate **7**. The latter can undergo only one of the two fundamental cyclization pathways outlined above, thus leading to vincadifformine (**1a**). The following report describes the synthesis of vincadifformine by generation and reaction of the biogenetically proposed secodine intermediate **7**.



Chlorination of tetrahydrocarbazole and reaction of the resultant chloroindolenine with thallium diethyl malonate had resulted in a 3-spirocyclopentyl-2-alkylideneindoline.[2] Extension of this biomimetic oxidative alkylation reaction sequence to *N*-β-alkyltetrahydrocarbolines **8** and **17** could be expected to proceed in an analogous fashion to give corresponding 3-spiropyrrolidylindoline structures, which would be of potential value for indole alkaloid syntheses. Thus 4a-chloro-2-methyl-1,2,3,4-tetrahydro-4a*H*-pyrido[3,4-*b*]indolenine (**9a**) was prepared in a pilot study by reaction of the tetrahydro-β-carboline **8** with *tert*-butyl hypochlorite. In contrast to the chloroimine derived from tetrahydrocarbazole, the chloroimine **9a** is an isolable crystalline compound, stable on storage at 0 °C in the absence of acids. When treated with thallium ethoxide in refluxing benzene it gave the imido ether **10**, which in turn was hydrolyzed to the 3-spiropyrrolidyl-2-oxindole **11**.



A reaction of the chloroimine **9a** with thallium diethyl malonate, however, furnished an alkylation product which did not show the spectroscopic characteristics of the 3-spiro-2-alkylideneindoline **12**, but instead those of an indole [UV λ_{max}

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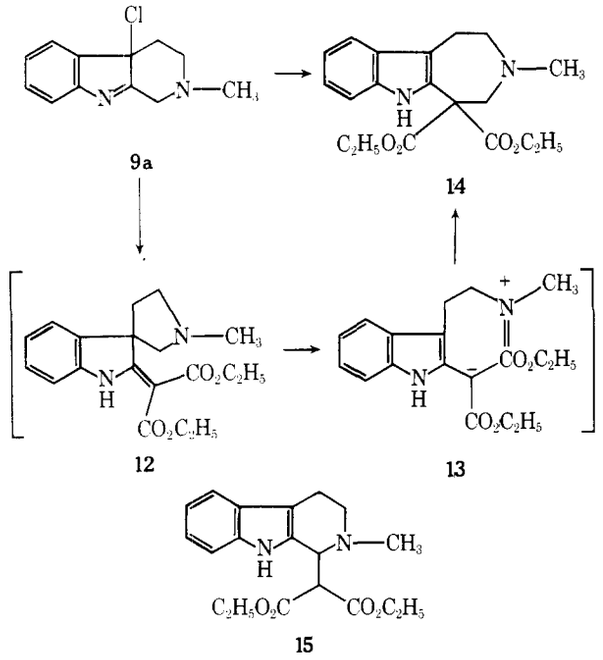
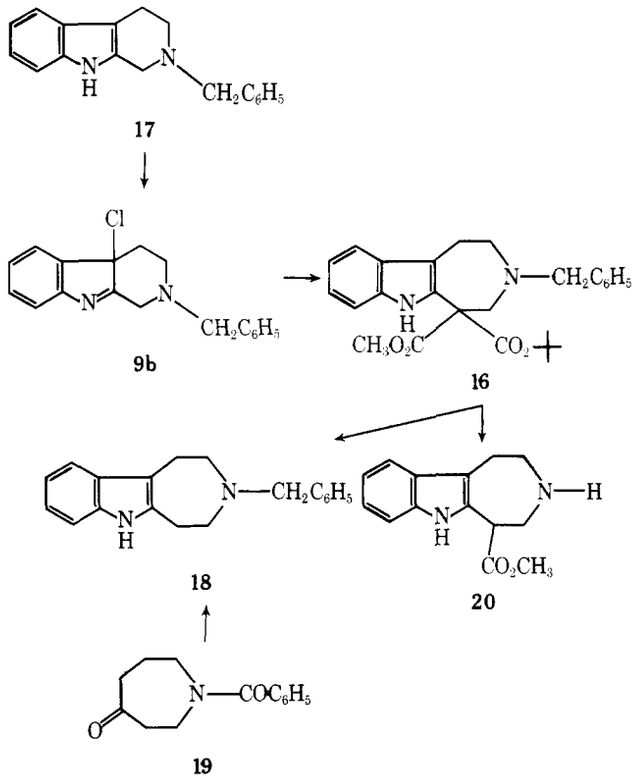
285, 293 nm; ϵ 7950, 6900; IR ν_{max} 3465 cm^{-1} (sharp NH); NMR δ 8.2 (indolic NH)]. It thus appeared that the 3-spiro-2-alkylideneindoline **12** had rearranged through a zwitterionic immonium malonate **13** to the indoloazepine **14.** An alternative malonyl tetrahydro-β-carboline structure (**15**) was considered for this product, based on an imine to enamine tautomerization in **9a** and subsequent vinylogous displacement of chloride by malonate, in analogy to such known reactions of chloroindolenines. However, the alkyl malonic ester structure **15** could be excluded by the NMR spectrum, which did not show an AB pattern for two adjacent methine protons, but instead showed a two-proton singlet at δ 3.4 for a methylene group on nitrogen.



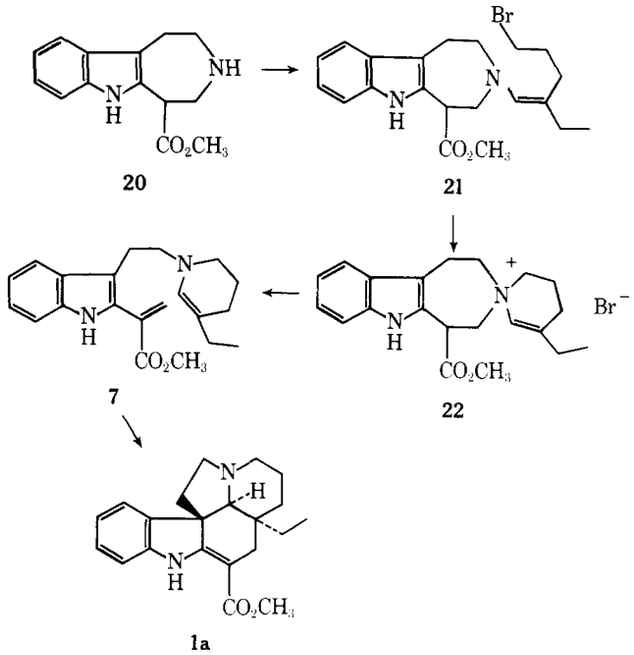
Formation of the indoloazepine **14** provided a conceptual base for syntheses of secodines and aspidosperma alkaloids. To this end it seemed advantageous to promote decarboxylation of one of the ester functions and to remove the N-b alkyl substituent. These two objectives were readily achieved through synthesis of the *tert*-butyl methyl-3-benzyl-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-5,5-dicarboxylate (**16**). The starting material, *N*-benzyltetrahydro-β-carboline **17,** was most readily prepared through benzoylation of tetrahydro-β-carboline and reduction with lithium aluminum hydride, rather than through the reported Leuckart benzylation.[4,5] Conversion of this compound to the chloroindolenine **9b** with *tert*-butyl hypochlorite and triethylamine and subsequent reaction with thallium *tert*-butyl methyl malonate in refluxing benzene gave the desired azepinoindole **16** in 63–85% yield.

Vigorous acid hydrolysis resulted in double decarboxylation of the diester **16** and thus led to the azepinoindole **18.** This compound could alternatively be obtained from *N*-benzoylazepin-4-one (**19**) by a Fischer indole synthesis and reduction with lithium aluminum hydride, thus substantiating the foregoing structure assignments.[6]

While heating of the diester **16** for 1 h with aqueous methanolic hydrochloric acid resulted in double decarboxylation, only the *tert*-butyl ester function was lost in anhydrous methanol or, for optimum yield, on heating with anhydrous trifluoroacetic acid in 1,2-dichlorethane (90% yield). The benzyl group could then be quantitatively removed from the monomethylamino ester by hydrogenolysis in acetic acid over a 5% Pd/C catalyst (or analogously from the *tert*-butyl methyl diester **16**) with generation of the required azepinoindole ester **20.**

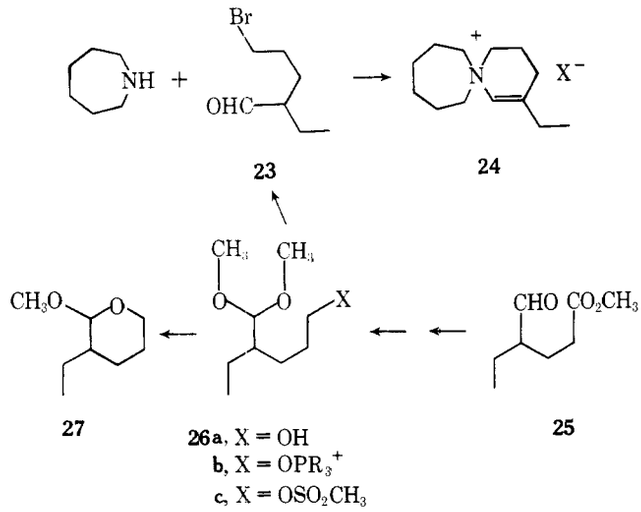


A synthesis of the key secodine intermediate **7** could now be projected through transformation of the azepine **20** into a 5-haloenamine intermediate **21,** its cyclization to a spiroenammonium salt **22,** and fragmentation of this β-ammonium ester. While spiroammonium salts have been made previously,[7,8,9] no intramolecular enamine N-alkylation reaction, needed for transformation of the indole azepine **20** to the spiroammonium salt **22,** has been reported. Thus a model reaction of hexamethyleneimine with 5-bromo-2-ethylpentanal (**23**) was studied and found to give the spiroenammonium salt **24** in 77% yield by heating the reactants in benzene.[10]



The bromo aldehyde **23** used in this reaction was made from methyl 4-formylhexanoate (**25**), which in turn is readily obtained from reaction of butyraldehyde enamines with methyl acrylate.[11] Conversion of the aldehyde **25** to its dimethyl (or

diethyl) acetal (93, 90%) and reduction with lithium aluminum hydride (90%) afforded the acetal alcohol **26a.** Initial attempts at transformation of this alcohol into a corresponding halide were complicated by the intrinsic lability of the acetal function. While trioctylphosphine and carbon tetrachloride[12] have been used with sugar hemiacetals,[13] this reagent appeared to yield primarily the tetrahydropyran **27** as a result of intramolecular methoxy O-alkylation, with displacement of trioctylphosphine oxide in intermediate **26b.** Thionyl chloride or phosphorus tribromide and pyridine also led to the tetrahydropyran **27** as major product. The reaction of the alcohol **26a** with triphenylphosphine and carbon tetrabromide was more successful (65% yield of **23**), but the most satisfactory synthesis of the bromo aldehyde **23** was obtained by quantitative transformation of the acetal alcohol **26a** to its mesylate derivative **26c** and reaction of the latter with lithium bromide in dimethylformamide. On aqueous extractive workup the bromoaldehyde was obtained in 78% yield.[14]



For continuation of the synthetic sequence the bromo aldehyde **23** was combined with the indoloazepine **20.** Under conditions which had produced the model spiroenammonium salt **24,** vincadifformine (**1a**) was generated directly. Following this reaction by high-pressure liquid chromatography it could be seen that an equimolar solution of the reactants in benzene led to formation of the intermediate bromo enamine **21** (isolated and identified by mass spectrum) with its concentration maximized after 22 h and its complete disappearance after 72 h at room temperature, or at 20 min and 3 h, respectively, at reflux. Vincadifformine was slowly generated at room temperature, but it appeared after 7 min at reflux and its concentration in refluxing benzene was maximized after 27 h. The formation of precipitates (presumably in part the spiroenammonium intermediate **22**) could be seen during the course of the reaction. Vincadifformine (**1a**) was isolated in about 23% yield from such reaction mixtures. However, when dimethylformamide at room temperature or methanol at 40 °C were used as solvent, to facilitate solution of the spiro salt **22,** and auxiliary bases such as potassium carbonate or triethylamine were added to promote the fragmentation reaction of the ammonium salt **22,** the yield of vincadifformine (**1a**) could be increased to 70%.

This last step of the synthetic sequence thus demonstrates that the previously postulated biogenetic secodine intermediate **7** can be generated and that it indeed undergoes the biogenetically proposed stereospecific cyclization to vincadifformine (**1a**) in good yield. With an overall yield of vincadifformine from the tetrahydrocarboline **17** above 50%, the synthetic reaction sequence compares quite favorably with the previously reported vincadifformine syntheses[15,16] and the biomimetically relevant synthesis of minovine.[17]

Experimental Section

4a-Chloro-2-methyl-1,2,3,4-tetrahydro-4a*H*-pyrido[3,4-*b*]indolenine (9a). *N*-Methyltetrahydro-β-carboline (2-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole)[18] **8** was alternatively prepared in 33% overall yield by methylation of β-carboline[19] and sodium borohydride reduction[20] of the resultant carbolinium salt. To a solution of 0.930 g (5 mmol) of **8** in 170 mL of dichloromethane containing triethylamine (550 μL), *tert*-butyl hypochlorite (550 μL) was added. The mixture was stirred at room temperature for 1 h, then it was washed with ice water, passed through phase separating paper (Whatman No. 1PS), and concentrated under reduced pressure to a volume of about 10 mL. A precipitate of unreacted starting indole separated and was filtered off (213 mg). The filtrate was evaporated to dryness to give the chloroindolenine **9a** (862 mg, 99%) as a dark oil which solidified on standing in the freezer. Further purification was not attempted: IR (CCl_4) ν 3055, 2935, 2835, 2785, 1600, 1451, 1345, 1250, 1135, 1120, 1060, 1045, 1000, 955, 870, 810 cm^{-1}. NMR ($CDCl_3$) δ 7.3–6.9 (4 H, aromatic), 3.31 (AB q, J_{AB} = 11 Hz, protons at C_1, 2 H), 7.65–7.55 (2 H), 2.26 (s, 3 H), 2.45–1.45 (2 H); UV (EtOH) λ (ε) 226 (8800), 286 (1100).

Reaction of 4a-Chloro-2-methyl-1,2,3,4-tetrahydro-4a*H*-pyrido[3,4-*b*]indolenine (9a) with Thallium(I) Ethoxide. Compound **9a** (300 mg) was dissolved in anhydrous benzene (20 mL). Thallium(I) ethoxide (340 mg, 125 μL) was added and the mixture was stirred and refluxed for 18 h. The mixture was then cooled and filtered (Whatman GF/A) to remove precipitated thallium salts. Concentration under reduced pressure gave an oil (180 mg) which was mainly 2-ethoxy-1′-methylspiro(3*H*-indole-3,3′-pyrollidine) (**10**) together with a little **11.** This oil was dissolved in methanol (10 mL) and 2 N hydrochloric acid was added dropwise to turbidity. After adding sufficient further methanol to disperse the turbidity, the mixture was allowed to stand overnight, diluted with brine, made basic with sodium hydroxide, and extracted with chloroform. The combined extracts were washed with water, dried, and concentrated to an oil (89 mg, 32%) which crystallized on standing. Recrystallization from *n*-heptane gave 1′-methylspiro(3*H*-indole-3,3′-pyrollidine)-2(1H)-one (**11**): mp 113–115 °C; IR (CCl_4) ν 3450, 3200, 3150, 3075, 2970, 2950, 2840, 2770, 1710, 1615, 1470, 915, 790, 640 cm^{-1}; NMR ($CDCl_3$) δ 8.44 (1 H), 7.32–6.70 (aromatic, 4 H), 2.8 (br s, 2 H), 2.40 (s, methyl, 3 H), 3.0–2.0 (complex absorption, 4 H); MS *m/e* 202 (M^+). Anal. Calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.44; H, 7.20; N, 13.84.

Reaction of 4a-Chloro-2-methyl-1,2,3,4-tetrahydro-4a*H*-pyrido[3,4-*b*]indolenine (9a) with Thallium(I) Diethyl Malonate Salt. A solution of **9a** (220 mg, 1 mmol) in dry benzene (20 mL) was added to thallium(I) diethyl malonate salt (364 mg, 1 mmol). The mixture was stirred vigorously and heated under reflux for 20 h, cooled, and filtered (Whatman GF/A) and the solvent was removed in vacuo to leave a dark sticky gum which was adsorbed onto silica gel. Elution with ethyl acetate–dichloromethane (40:60) furnished diethyl 3-methyl-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-5,5-dicarboxylate (**14;** 75 mg, 22%). Recrystallization from *n*-heptane gave colorless prisms: mp 84–86 °C; IR (CCl_4) ν 3465, 3450, 3050, 2985, 2935, 2850, 2803, 1740, 1650, 1525, 1455, 1235, 800 cm^{-1}; NMR ($CDCl_3$) δ 8.2 (indole NH, 1 H), 7.4–6.8 (aromatic 4 H), 4.18 (q, 4 H), 3.36 (s, protons at C_4, 2 H), 2.84 (apparent nine-line system, AA′BB′ for protons at C_1 and C_2, 4 H), 2.24 (s, 3 H) 1.25 (t, 6 H); in benzene the signal for the C_4 protons is considerably broadened, and the protons at C_1 and C_2 are a more usual AA′BB′ system; UV (EtOH) λ (ε) 235 (34 000), 285 (7950), 293 (6900), 340 nm (550); MS *m/e* (%) 344 (90), 288 (58), 227 (100), 208 (66), 184 (41), 153 (61). Anal. Calcd for $C_{19}H_{24}N_2O_4$: C, 66.26; H, 7.02; N, 8.13. Found: C, 66.11; H, 7.30; N, 7.96.

2-Benzoyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole. Tetrahydro-β-carboline[21] (7 g) was dissolved in dry pyridine (35 mL) and a solution of benzoyl chloride (7 mL) in dry benzene (30 mL) was added over 30 min to the stirred mixture. After heating at reflux for 30 min the reaction mixture was poured into water and extracted with chloroform. The combined chloroform extracts were washed with ice cold 2 N hydrochloric acid, water, 3 N potassium carbonate solution, and brine, and then dried over potassium carbonate. Removal of the solvent gave an oil which was triturated with toluene. Once crystallization had begun, *n*-heptane was added. Filtration gave the amide (10.55 g, 94%) as a pale yellow solid. The analytical sample was recrystallized from aqueous ethanol with the aid of charcoal: mp 155–156 °C; IR ($CHCl_3$) ν 3470, 3060, 3020, 2925, 2860, 1625, 1620, 1575, 1490, 1460, 1435, 1305, 1205, 1150, 1045, 1025, 980 cm^{-1}; NMR ($CDCl_3$) δ 8.6 (indole NH, 1 H), 7.6–6.9 (aromatic, 9 H), 4.8 (br s, C_1 protons, 2 H), 3.7 (br s, C protons, 2 H), 2.8 (br s, C_4 protons, 2 H); MS (80 eV) *m/e* 276 (8), 262 (16), 168 (15) 143 (100), 105 (15), 91 (21), 77

(16), 44 (44), 40 (71). Anal. Calcd for $C_{18}H_{16}N_2O$: C, 78.24; H, 5.84; N, 10.14. Found: C, 78.24; H, 5.92; N, 10.18.

2-Benzyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (17). 2-Benzoyl-1,2,3,4-tetrahydro-9H-pyrido[3,4-*b*]indole (10.5 g, 38.5 mmol) dissolved in tetrahydrofuran (150 mL) was added over 1 h to a stirred mixture of tetrahydrofuran (300 mL) and lithium aluminum hydride (1 M solution in ether, 42.5 mL) under a blanket of dry nitrogen. When addition was complete, the mixture was heated to reflux for 6 h. After 12 h at room temperature magnesium sulfate heptahydrate (50 g) was added, with stirring, to destroy excess hydride. After stirring for 12 h the solids were filtered off and the solvent was evaporated to give the product, mp 140–142 °C (reported[4] mp 142 °C), as a white solid (9.15 g, 91.5%).

4a-Chloro-2-benzyl-1,2,3,4-tetrahydro-1*H*-pyrido[3,4-*b*]-indolenine (9b). This compound was prepared from the tetrahydro-β-carboline **17** (1.3 g, 5 mmol) in dry benzene (100 mL) with triethylamine (550 μL) and *tert*-butyl hypochlorite (550 μL) as described above. The resultant solution of **9b** was normally used directly for the next step; however, the compound could be isolated, though it appeared to be less stable than the 2-methyl compound. Removal of the solvent from the reaction mixture in vacuo gave the chloroindolenine **9b** (1.45 g, 98%) as a dark oil: NMR (CCl_4) δ 7.5–7.0 (aromatic, 9 H), 3.58 (s, benzyl CH_2, 2 H), 3.53 (AB q, J_{AB} = 11 Hz, protons at C_1, 2 H), 2.8–2.6 (2 H), 2.55–2.48 (1 H), 2.0–1.6 (1 H).

***tert*-Butyl Methyl 3-Benzyl-1,2,3,4,5,6-hexahydroazepino-[4,5-*b*]indole-5,5-dicarboxylate (16).** The chloroindolenine **9b** was prepared by dissolving *N*-benzyltetrahydrocarboline **17** (3.522 g, 13.44 mmol) in 100 mL of dry benzene and cooling to 5 °C. To the cold stirring solution was added dry triethylamine (1.16 g, 10 mmol, 1.6 mL) followed by dropwise addition of *tert*-butyl hypochlorite (1.458 g, 13.44 mmol, 1.6 mL). The reaction was kept in an ice bath for 1.5 h, then poured into water at 0 °C (20 mL). The benzene layer was separated and dried over sodium sulfate. The solution was filtered and the volume reduce to one half by vacuum evaporation. Dry benzene was added to a total volume of ~100 mL, then thallium *tert*-butyl methyl malonate (5.28 g, 14 mmol) was added and the stirred solution refluxed for 36 h. The reaction was cooled to room temperature and filtered through glass fiber paper. The solvent was removed and the residue adsorbed onto silica gel (20 g, Woelm Activity III for dry column chromatography). The adsorbed material was placed on top of a 6 in × 1.5 in. column of the dry column silica gel and eluted with dichloromethane. The first 20 mL was discarded and the product was collected in the next 150 mL (3.69 g, 63.3%): maximum yield on a larger scale, 85%; recrystallized from aqueous methanol; mp 118–120 °C; IR ($CHCl_3$) ν 3460, 3440, 3080, 3050, 3020, 2995, 2975, 2940, 2820, 1730, 1610, 1445, 1365, 1250, 1150, 1025, 840, 695 cm^{-1}; NMR ($CDCl_3$) δ 1.44 (s, 9 H), 2.82 (br s, 4 H), 3.60 (s, 2 H), 3.66 (s, 3 H), 3.76 (s, 2 H), 6.84–7.4 (m, 9 H), 8.36 (br s, 1 H); mass spectrum (80 eV) *m/e* (rel intensity) 434 (7), 334 (30), 216 (57), 156 (57), 91 (68), 59 (78), 56 (76), 44 (81), 41 (78), 40 (100). Anal Calcd for $C_{26}H_{30}N_2O_4$: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.97; H, 7.03; N, 6.16.

Methyl 3-Benzyl-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-5-carboxylate. The *tert*-butyl ester **16** (1.890 g, 4.35 mmol) was dissolved in 80 mL of 1,2-dichloroethane and the system flushed with nitrogen. Anhydrous trifluoroacetic acid (1.6 mL) was added via syringe through a rubber septum. The solution was stirred at reflux for 3.5 h. The hot reaction mixture was poured into 100 mL of cold (saturated) aqueous sodium carbonate. The layers were separated and the aqueous phase was extracted with 50 mL of dichloroethane. The combined organic phases were washed with (saturated) sodium carbonate solution and filtered through phase separating paper onto anhydrous potassium carbonate. Filtration and evaporation of the solvent produced a brown oil which was triturated with ethyl acetate–heptane to induce crystallization. The off-white solid was collected in two crops to yield 1.219 g (84%) of decarboxylated amine. The compound was recrystallized twice from aqueous ethanol for analysis: mp 135–135.5 °C; IR ($CHCl_3$) ν 3480, 3075, 3045, 2940, 2840, 1740, 1600, 1500, 1460, 1435, 1350, 1275, 1230, 1220, 1200, 1163, 1026 cm^{-1}; NMR ($CDCl_3$) δ 2.94 (br s, 4 H), 3.24 (m, 2 H), 3.76 (s, 3 H), 3.88 (s, 2 H), 4.16 (m, 1 H), 6.96–7.7 (m, 9 H), 8.68 (br s, 1 H); mass spectrum (80 eV) *m/e* (rel intensity) 334 (M^+, 37), 216 (100), 156 (61), 91 (49), 42 (32). Anal Calcd for $C_{21}H_{22}N_2O_2$: C, 75.42; H, 6.63; N, 8.38. Found: C, 75.63; H, 6.90; N, 8.41.

Methyl *tert*-Butyl 1,2,3,4,5,6-Hexahydroazepino[4,5-*b*]indole-5,5-dicarboxylate. A solution of *N*-benzylamine **16** (202 mg, 0.465 mmol) in dry acetic acid (7.5 mL) was hydrogenated under 1 atm pressure of hydrogen with 5% Pd/C catalyst (22 mg) for 1.5 h. The catalyst was filtered and washed with hot methanol. The solvent was removed from the filtrate by evaporation, leaving a light yellow oil which was dissolved in dichloromethane (50 mL). The solution was cooled to 0 °C, 10% aqueous NaOH (25 mL) was added, and the solution was stirred vigorously for 10 min. The organic phase was separated and dried over anhydrous potassium carbonate. The solution was filtered and the solvent evaporated to a light yellow oil which resisted all attempts at crystallization, but was pure debenzylated diester amine (155 mg, 97%): IR ($CDCl_3$) ν 3445, 3435, 3035, 2975, 2915, 1730, 1615, 1455, 1430, 1365, 1250, 1140, 1020, 840, 800 cm^{-1}; NMR ($CDCl_3$) δ 1.48 (s, 9 H), 2.24 (s, 1 H), 2.96 (m, 2 H), 3.16 (m, 2 H), 3.72 (m, 2 H), 3.78 (s, 3 H), 7.04–7.60 (m, 4 H), 3.88 (br s, 1 H); mass spectrum (80 eV) *m/e* (rel intensity) 344 (M^+, 100%), 245 (82), 229 (56), 216 (96), 215 (87), 203 (87), 171 (67), 155 (74).

Methyl 1,2,3,4,5,6-Hexahydroazepino[4,5-*b*]indole-5-carboxylate (20). The monoester benzylamine (915 mg, 2.74 mmol) was dissolved in 50 mL of glacial acetic acid and 100 mg of 5% Pd/C catalyst was added. The mixture was hydrogenated under 1 atm pressure for 18 h, then filtered through glass fiber paper. The catalyst was washed with 50 mL of hot methanol and the combined filtrates were evaporated to an oily residue. The residue was dissolved in 75 mL of chloroform and 100 mL of (saturated) aqueous sodium carbonate was added. The two-phase system was stirred vigorously for 15 min and the layers were then separated. The aqueous phase was washed with chloroform and the combined chloroform phases were washed with brine, and then filtered through phase separating paper onto anhydrous potassium carbonate. The material was filtered and the solvent evaporated, leaving a thick oily residue which was solidified by trituration with ethyl acetate–heptane. The material was filtered yielding 532 mg (80%) of debenzylated amine. The mother liquor was chromatographed on silica gel with dichloromethane as eluent, producing another 87 mg of material for a combined yield of 93%. The compound can be recrystallized from ethyl acetate–heptane; mp 138–139 °C; IR ($CHCl_3$) ν 3465, 2950, 2925, 1735, 1630, 1460, 1435, 1220, 1160, 1015 cm^{-1}; NMR ($CDCl_3$) δ 2.20 (br s, 4 H), 8.48 (br s, 1 H); mass spectrum (80 eV) *m/e* (rel intensity) 244 (M^+, 58), 215 (29), 202 (100), 170 (31), 156 (26), 142 (35), 43 (80), 42 (30).

(±)-Vincadifformine (1a). Method 1. The bromo aldehyde **23** (194.5 mg, 1 mmol) was dissolved in 6 mL of dry methanol under a nitrogen atmosphere and 123 mg (0.50 mmol) of amine **20** was added in 6 mL of methanol. The mixture was stirred at room temperature for 1 h, then dry triethylamine (0.5 mL) was added and the solution was warmed to 40 °C for 12 h. The reaction was cooled to room temperature and the solvent was evaporated. The residue was taken up in CH_2Cl_2 (40 mL) and extracted with (saturated) aqueous sodium carbonate (10 mL). The organic layer was dried over anhydrous potassium carbonate and filtered. The solvent was evaporated and the residue was spotted on a preparative TLC plate (2 mm, Merck alumina) and developed with dichloromethane. The band at R_f 0.4–0.6 was eluted, resulting in 71 mg of pure (±)-vincadifformine as a white solid.[22] The alkaloid was recrystallized from 95% ethanol: mp 124–125 °C (lit.[15] 124–125 °C); IR ($CHCl_3$) ν 3420, 3360, 2930, 2850, 2775, 1665, 1605, 1470, 1460, 1432, 1290, 1275, 1250, 1235, 1155, 1110, 1045 cm^{-1}; NMR ($CDCl_3$) δ 1.6–3.6 (complex m, 18 H), 3.76 (s, 3 H), 6.74–7.5 (m, 4 H), 8.96 (br s, 1 H); UV (EtOH) λ (log ε) 225 (4.12), 297 (3.15), 327 nm (4.06); mass spectrum (80 eV) *m/e* (rel intensity) 338 (M^+, 67), 124 (100); yield on a larger scale, 70%.

Method 2. The amine **20** (125.8 mg, 0.515 mmol) was dissolved in dry benzene (3 mL) and aldehyde **23** (97.5 mg, 0.505 mmol) was added. The mixture was stirred at 45 °C for 51 h then dissolved in ether–dichloromethane (1:4). The solution was extracted with 1.0 N HCl and the aqueous phase was washed with benzene. The aqueous layer was adjusted to pH 11–12 with 10% aqueous sodium hydroxide and extracted with chloroform. After drying and concentration, a light yellow oil remained (90 mg) which was separated by PTLC (Merck alumina, 5% methanol–95% dichloromethane). The band at R_f 0.5–0.7 was isolated and eluted, yielding (±)-vincadifformine (45 mg, 26%) as an oil which crystallized upon seeding.

High-pressure liquid chromatography analysis of vincadifformine formation is given in Table I.

Methyl 4-Dimethoxymethylhexanoate. To a solution containing anhydrous methanol (70 mL) and concentrated sulfuric acid (3 drops) was added methyl 4-formylhexanoate (**25**;[11] 10.2 g, 64.5 mmol). The solution was stirred at room temperature for 24 h and then solid potassium carbonate was added to neutralize the acid. Most of the solvent was evaporated under vacuum, water (100 mL) was added, and the solution was extracted twice with hexane (50 mL) and twice with ether. The organic phases were combined and dried over anhydrous magnesium sulfate. The solvent was evaporated under vacuum, yielding the desired acetal with no aldehyde contamination (12.27 g, 93.2%): bp 60–70 °C (Kugelrohr, 0.1 mm); IR (neat) ν 2950, 2820, 1730, 1430, 1170, 1105, 1070, 960, 885 cm^{-1}; NMR ($CDCl_3$) δ 0.88 (t, 3 H), 1.24–1.96 (m, 5 H), 2.34 (t, 2 H), 3.32 (s, 6 H), 3.82 (s, 3 H), 4.10 (d, 1 H); mass spectrum (80 eV) *m/e* (rel intensity) 204 (M^+, 1), 203 (6), 173 (100), 141 (99), 109 (73), 99 (90), 75 (97).

Table I. High Pressure Liquid Chromatography Analysis[a] of Vincadifformine Formation

trial	reactants[b]	solvent (mL)	temp, °C	time, h	comments
1	1 equiv amine **20** 1 equiv aldehyde **23**	benzene (1)	80	24	buff ppt occurs; LC of filtrate indicates only vincadifformine; ppt used in run 5
2	1 equiv amine **20** 1 equiv aldehyde **23**	benzene (1)	room temp	36	ppt occurs; IR 1735, 1700, 1615 cm^{-1}; LC (t = 24 h) indicated two components: 1[c] (ret time 6 min), presumably uncyclized enamine, MS m/e 418, 420; 2 (ret time 8 min), identified as vincadifformine
3	1 equiv amine **20** 1 equiv aldehyde **23**	benzene (1)	room temp	48	slight ppt; peak 1 reaches max in 20–24 h, disappears within 72 h; peak 2 reaches max in 24–36 h, does not change afterwards
4	1 equiv amine **20** 1 equiv aldehyde **23**	benzene (1)	80	48	ppt occurs; LC indicates vincadifformine appears within 7 min; increases for 24–30 h; peak 1 max in 20 min then disappears in 3 h
5	ppt from run 1	benzene (1) NEt_3 (0.1)	80	24	LC indicates increase in vincadifformine concentration over 24 h; some ppt remains
6	reaction mixture from run 4	benzene (1) NEt_3 (0.1)	room temp 80	1 30	room temp does not change vincadifformine concentration; reflux does not cause any change
7	reaction mixture from run 3	benzene (1) NEt_3 (0.1) DMF (0.1)	room temp	72	LC indicates slow formation of vincadifformine, but reaction is complicated by new reaction products
8	1 equiv amine **20** 1 equiv aldehyde **23**	CH_3CN, then add NEt_3 (0.1)	room temp room temp reflux	24 3 2	LC indicates slower formation of 1 and 2 components; addition of base has no effect; peak 1 disappears with heating; workup yields mixture
9	1 equiv amine **20** 1 equiv aldehyde **23**	dioxane, then add K_2CO_3 (20 mg)	room temp room temp	1 24	reaction turns dark color; LC indicates much slower formation of components 1 and 2; workup yields mixture
10	0.5 equiv amine **20** 1 equiv aldehyde **23**	benzene (0.9) DMF (0.1) K_2CO_3 (20 mg)	room temp	24	ppt still forms; same components as run 3; workup gave 65% yield of vincadifformine as an oil
11	1 equiv amine **20** 1 equiv aldehyde **23**	benzene p-TsOH (cat)	room temp	14	LC indicates slow formation of vincadifformine; reaction complicated by additional components; workup yielded a mixture
12	1 equiv amine **20** 1 equiv aldehyde **23**	MeOH (1) add NEt_3 (0.1)	room temp room temp 40	3 2 12	no ppt; no discoloration; peak 1 (6 min) max in 3 h; addition of base (t = 3 h) causes rapid formation of vincadifformine; workup produced 67% yield of vincadifformine as an oil

[a] Column, C_{18}-Bondapack (Waters), 4 mm × 30 cm; solvent, 60% acetonitrile–40% 0.01 M aqueous ammonium carbonate; flow rate, 1.5 mL/min. [b] 1 equiv of amine *20* equals 20 mg; 1 equiv of aldehyde **23** equals 15.8 mg (12 μL). [c] While rapid volatilization of component 1 in the mass spectrometer produced the parent ion for the bromo enamine **21**, prior heating in the inlet chamber resulted in loss of this mass peak and generation of peaks corresponding to vincadifformine.

Ethyl 4-Diethoxymethylhexanoate. The ethyl acetal was prepared from the aldehyde in 84% yield in the same manner as the methyl acetal. The ester group exchanges under these conditions: bp 90–100 °C (Kugelrohr, 0.1 mm); NMR ($CDCl_3$) δ 0.95 (t, 3 H), 1.23 (t, 6 H), 1.33 (t, 3 H), 1.25–2.06 (m, 5 H), 2.43 (t, 2 H), 3.63 (q, 4 H), 4.23 (q, 2 H), 4.40 (d, 1 H).

4-Dimethoxymethyl-1-hexanol (26a). The methyl acetal ester (9.8 g, 48 mmol) was dissolved in THF (20 mL) and added dropwise at 0 °C to an ether solution of $LiAlH_4$ (50 mL of a 1 M solution). After addition was completed (~30 min) the reaction was allowed to warm to room temperature and water (1 mL) was added slowly. Enough 20% aqueous KOH was added to dissolve the solid and the solution was extracted five times with ether (25 mL). The ether extracts were washed with brine and dried over anhydrous sodium sulfate. Evaporation of the solvent yielded the desired alcohol **26a** (7.86 g, 93%) as a clear colorless liquid: IR (neat) ν 3400, 2940, 2830, 1460, 1380, 1190, 1110, 1060, 960 cm^{-1}; NMR ($CDCl_3$) δ 0.9 (t, 3 H), 1.4 (m, 7 H), 2.9 (br s, 1 H), 3.2 (s, 6 H), 3.42 (t, 2 H), 4.15 (d, 1 H).

4-Diethoxymethyl-1-hexanol. A solution of the ethyl acetal ester (9.367 g, 38 mmol) in THF (40 mL) was added at 0 °C to a solution of $LiAlH_4$ in ether (40 mL of a 1 M solution) over 0.5 h. The reaction was refluxed for 1 h and then allowed to cool to room temperature. Magnesium sulfate heptahydrate (9.86 g, 40 mmol) was added and the reaction was stirred vigorously 12 h. The solid was filtered and washed with ether several times. The combined filtrate and washings were washed with 10% aqueous KOH (10 mL) and brine (10 mL) and dried over anhydrous sodium sulfate. Evaporation of the solvent followed by Kugelrohr distillation (bp 90–100 °C, 0.1 mm) produced the hydroxy acetal (7.0 g, 90.3%): IR (neat) ν 3400, 2985, 2940, 1880, 1460, 1380, 1115, 1065, 730 cm^{-1}; NMR ($CDCl_3$) δ 0.93 (t, 3 H), 1.23 (t, 6 H), 1.16–1.83 (m, 7 H), 2.16 (br s, 1 H), 3.66 (m, 6 H), 4.40 (d, 1 H).

1-Bromo-4-dimethoxymethylhexane. Carbon tetrabromide (1.824 g, 5.5 mmol) and triphenylphosphine (1.443 g, 5.5 mmol) in ether (15 mL) were refluxed 0.5 h, and then cooled to room temperature. Hydroxy acetal **26a** in ether (6 mL) was added dropwise, resulting in rapid decolorization of the yellow slurry and precipitation of a buff-colored solid. The mixture was filtered through Celite and the solvent was removed under vacuum. The residue was placed under high vacuum (~10^{-3} mm) to remove the excess carbon tetrabromide and the bromoform byproduct. The distillation pot was heated to 50–60 °C and the distillate was collected with the aid of a dry ice trap. The distillate was the desired bromo acetal (700 mg, 66%) contaminated with a trace of carbon tetrabromide and bromoform. This compound was used without further purification for hydrolysis.

Hydrolysis to **23** was achieved by stirring the bromo acetal in THF–1 N HCl (10:1, 6 mL) at room temperature for 24 h (94% yield).

For comparison, the bromo acetal was prepared from the bromo aldehyde **23.** The bromo aldehyde (52.4 mg, 0.27 mmol) was dissolved in dry methanol (1 mL) and one crystal of p-toluenesulfonic acid was added. The solution was stirred at room temperature for 48 h and then poured into dichloromethane (15 mL). The solution was washed with saturated aqueous sodium carbonate (5 mL) and dried over anhydrous sodium sulfate. Concentration yielded the acetal (60.4 mg, 93.2%) as a colorless oil; IR (neat) ν 2960, 1460, 1110, 1070 cm^{-1}; NMR ($CDCl_3$) δ 0.92 (t, 3 H), 1.20–2.04 (m, 7 H), 3.38 (s, 6 H), 3.40 (t, 2 H), 4.16 (d, 1 H); mass spectrum (80 eV) m/e (rel intensity) 238, 240 (M^+, 0.01), 207, 209 (38, 37), 75 (100).

2-Methoxy-3-ethyltetrahydropyran (27). A solution of alcohol

26a (285 mg, 1.62 mmol) in ether (2 mL) was cooled to 0 °C. Phosphorous tribromide (161 mg, 0.6 mmol) was added dropwise and the mixture was stirred at 0 °C for 3 h. The reaction mixture was warmed to room temperature and stirred for another 12 h. Pentane (2 mL) was added and the liquid phase was decanted. A colorless oily residue was left after evaporation of the solvent at room temperature and 1 atm pressure. Spectral data for the product indicated the tetrahydropyran structure (**27**) as a mixture of cis and trans isomers (172 mg, 74%); IR (neat) ν 2960, 2940, 2875, 1470, 1060, 1045, 950 cm^{-1}; NMR ($CDCl_3$) δ 0.94 (m, 3 H), 1.0–2.0 (m, 7 H), 3.38, 3.46 (s, 3 H), 3.30–4.14 (m, 2 H), 4.52 (br s, 1 H); mass spectrum (80 eV) *m/e* (rel intensity) 144 (M^+, 6), 113 (25), 97 (19), 84 (27), 71 (22), 61 (56), 56 (100), 55 (39), 41 (53).

1-(Methanesulfonyl)-4-(diethoxymethyl)hexane. The mesylate of the ethyl acetal alcohol was prepared (100% yield) in the same manner as the methyl acetal mesylate **26c**: IR (neat) ν 2965, 2940, 2875, 1460, 1360, 1180, 1070, 975 cm^{-1}; NMR ($CDCl_3$) δ 0.90 (t, 3 H), 1.20 (t, 6 H), 1.0–2.0 (m, 7 H), 3.02 (s, 3 H), 3.28–3.84 (m, 4 H), 4.16–4.26 (m, 3 H).

The product was hydrolyzed to the aldehyde by refluxing it in ether (30 mL) and 1.0 N HCl (6 mL) for 12 h. The aldehyde was converted to a DNP derivative for analysis, mp 99–100 °C. Anal Calcd for $C_{14}H_{20}N_4O_7S$: C, 43.29; H, 5.19; N, 14.43. Found: C, 43.28; H, 5.34; N, 14.48.

1-(Methanesulfonyl)-4-(dimethoxymethyl)hexane (26c). The acetal alcohol **26a** (13.55 g, 77 mmol) was dissolved in dry dichloromethane (0.2 M, 385 mL) and dry triethylamine (11.66 g, 115 mmol, 1.5 equiv) was added. The solution was cooled to −20 °C in an ice–salt bath and methanesulfonyl chloride (12.35 g, 108 mmol, 1.4 equiv) was added dropwise with stirring over 15 min. The solution was stirred an additional 0.5 h at −15 °C and then poured into a separatory funnel. The solution was washed with ice water (2 × 25 mL), cold 1.0 N HCl (2 × 25 mL), saturated sodium bicarbonate (2 × 25 mL), and finally brine (25 mL). The organic phase was dried over anhydrous magnesium sulfate and then filtered. Evaporation of the solvent yielded pure mesylate **26c** (19.43 g, 99.3%): IR (neat) ν 2970, 2945, 1465, 1360, 1180, 925, 815 cm^{-1}; NMR ($CDCl_3$) δ 0.92 (t, 3 H), 1.20–1.92 (m, 7 H), 3.06 (s, 3 H), 3.44 (s, 6 H), 4.22–4.36 (m, 3 H).

2-Ethyl-5-bromopentanal (23). Anhydrous lithium bromide (11.39 g, 131 mmol) was dissolved in dry DMF (100 mL) and the solution was allowed to cool to room temperature. The LiBr/DMF solution was then siphoned into a flask (via double-tipped needle) containing mesylate **26c** (7.39 g, 29.1 mmol) and a magnetic stir bar. The mixture was heated to 40 °C for 6 h and cooled to room temperature. The reaction mixture was then poured into ice water (750 mL) and extracted with distilled pentane (4 × 100 mL). The pentane phase was washed with 1.0 N HCl (20 mL), water (25 mL), and saturated sodium bicarbonate (30 mL), and then dried over anhydrous sodium sulfate. Evaporation of the solvent and distillation of the residue gave bromo aldehyde **23** (4.72 g, 84%): bp 46–48 °C (0.01 nm); IR (neat) ν 2955, 2930, 2870, 2710, 1715, 1455, 1375, 1240 cm^{-1}; NMR ($CDCl_3$) δ 0.96 (t, 3 H), 1.28–2.12 (m, 7 H), 2.28 (m, 1 H), 3.46 (t, 2 H), 9.70 (d, 1 H, J = 2 Hz); mass spectrum (80 eV) *m/e* (rel intensity) 194 (M^+, 3.6), 192 (M^+, 3.9), 166 (48), 164 (57), 123 (29), 121 (32), 113 (100).

The 2,4-DNP was prepared for analysis and recrystallized from 95% ethanol, mp 105–105.5 °C. Anal. Calcd for $C_{13}H_{17}N_4O_4Br$: C, 41.84; H, 4.59; N, 15.01; Br, 21.47. Found: C, 41.91; H, 4.82; N, 15.06; Br, 21.67.

2-Ethyl-6-azoniaspiro[5.6]dodec-1-ene Bromide (24a). A solution of bromo aldehyde **23** (1.37 g, 7.1 mmol) and hexamethyleneimine (694 mg, 7 mmol) in dry benzene (30 mL) was refluxed for 12 h using a Dean–Stark trap to remove the water. A white crystalline solid precipitated and was filtered after cooling the reaction to room temperature. The solid was dried under vacuum, resulting in 1.5 g (77.3%) of spiro salt **24a**: mp 128–130 °C; NMR ($CDCl_3$) δ 1.10 (t, 3 H), 1.86–2.22 (m, 14 H), 3.82 (m, 6 H), 6.38 (br s, 1 H).

2-Ethyl-6-azoniaspiro[5.6]dodec-1-ene Tetraphenylborate (24b). To a solution of spiroamine salt **24a** (100 mg, 0.364 mmol) in 5 mL of water was added a solution of sodium tetraphenylborate (125 mg, 0.364 mmol) in 20 mL of water with vigorous stirring. The mixture was allowed to stand for 15 min, then the precipitated tetraphenylborate salt was filtered and washed with ether. The dried salt (167 mg, 89.4%) was recrystallized from acetone: mp 215–216 °C dec; NMR (acetone-d_6) δ 1.10 (t, 3 H), 1.86–2.22 (m, 14 H), 3.82 (m, 6 H), 6.38 (br s, 1 H), 6.80–7.56 (m, 20 H). Anal. Calcd for $C_{37}H_{44}NB$: C, 86.53; H, 8.63; N, 2.72. Found: C, 86.42; H, 8.57; N, 2.57.

3-Benzyl-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole (18). The *tert*-butyl methyl diester **16** (72.5 mg) was dissolved in methanol (1.5 mL) and 36% hydrochloric acid (1.5 mL) was added. The mixture was refluxed for 1 h, and then cooled in ice and made basic with ice cold potassium hydroxide. The product was extracted with ether and the organic extracts, after drying, were concentrated to leave a brown solid (35 mg, 73%) which was recrystallized from aqueous ethanol, mp and mmp 115—117 °C.[6] The solid was identical in all respects with authentic 3-benzyl-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole.[6]

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Registry No.—(±)-**1a**, 18374-17-9; **8**, 13100-00-0; **9a**, 66859-15-2; **9b**, 66859-16-3; **10**, 66859-17-4; **11**, 66859-18-5; **14**, 66859-19-6; **16**, 66859-20-9; **16** debenzyl derivative, 66859-21-0; **7**, 47064-53-9; **17** debenzyl derivative, 16502-01-5; **18**, 7546-77-2; **20**, 66859-22-1; hexamethylenemine, 111-49-9; **20** 3-benzyl derivative, 66859-30-1; **23**, 64395-11-5; **23** DNP derivative, 66859-23-2; **24a**, 66859-24-3; **24b**, 66859-26-5; **25**, 66757-48-0; **26a**, 66859-27-6; **26c**, 66859-28-7; **27**, 66859-29-8; thallium(I) diethyl malenate salt 66859-38-9; benzoyl chloride, 98-88-4; thallium *tert*-butyl methyl malonate, 66859-39-0; methyl 4-dimethoxymethylhexanoate, 66859-31-2; ethyl 4-diethoxymethylhexanoate, 66859-32-3; 4-diethoxymethyl-1-bromo-4-(dimethoxymethyl)hexane, 66859-34-5; 1-(methanesulfonoyl)-4-(diethoxymethyl)hexane, 66859-35-6; 1-(methanesulfonyl)-4-(diethoxymethyl)hexane DNP derivative, 66859-08-3; methanesulfonyl chloride 124-63-0; 2-benzoyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole, 66859-09-4; 1-(methanesulfonyl)-4-formylhexane, 66859-10-7.

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