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Biomimetic Syntheses of Indole Alkaloids. 11. Syntheses of β-Carboline and Indoloazepine Intermediates

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The preparation and rearrangement of α-carbomethoxy-α-(chloromethyl)tetrahydro-β-carbolines (**9a,b**) provided methyl 1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylates (**10a,b**) and derivatives, which serve as intermediates in a series of alkaloid syntheses.

In a series of biomimetic alkaloid syntheses, based on the generation and reactions of secodines, the indoloazepine ester **1a** served as a key synthetic precursor.[1-7] Because of the recurring use of compound **1a** this paper details an alternative advantageous route to this versatile intermediate and to related compounds.

Initially,[1,2] the indoloazepine ester **1a** was obtained by a reaction sequence that was derived from considerations of biogenetic oxidative alkylation reactions of indole alkaloids. Thus chlorination of tetrahydro-β- or tetrahydro-γ-carbolines **2** or **3** and reactions of the resultant chloroindolenines **4** or **5** with thallium dialkyl malonates led to the 3,3-spiro-substituted 2-alkylidene indolines **6**. The latter compounds quantitatively rearranged to indoloazepine diesters **7** on warming.[3] A final decarbomethoxylation and debenzylation provided the desired monoester **1a** (Scheme I).

An advantage in the use of the tetrahydro-γ-carboline **3**, which is derived from *N*-benzyl-4-piperidone by a Fischer indole synthesis, is lack of dependence on a tryptamine precursor. While this feature is still of great value for syntheses of aryl-substituted indoloazepines,[3] it has become less significant for generation of the parent compound **1a**, because of the improved access to tryptamine through new economical methods of decarboxylation of tryptophan.[8,9]

Table I. Reactions of the Cloroindolenine 5 with Dialkyl Malonate Salts

solvent	time/temp	metal cation	yield prod 6	yield prod 7
THF	14 h/20 °C	Tl^+	80%	
THF	11 h/67 °C	Tl^+		78%
t-BuOH	8 h/83 °C	Tl^+		59%
DMF	2 h/80 °C	Tl^+		37%
THF	6 h/67 °C	Na^+ (with or without trace of Tl^+		12%
THF	6 h/67 °C	$^2Li^+$, K^+, or Mg^+		≈0%

The reaction sequence starting with the tetrahydro-γ-carboline **3** provided practical quantities of the indoloazepine ester **1a**, but it should be noted that the intermediate chloroindolenine **5** used here is subject to acid-catalyzed and thermal rearrangement. Thus attempted chromatography of the chloroindolenine **5** on silica resulted in its quantitative conversion to the chloroindole **8**.[10]

Although useful laboratory syntheses of the indoloazepine ester **1a** were achieved (66% yields) by passing from tryptamine through the tetrahydro-β-carboline **2** or from *N*-benzyl-4-piperidone through the γ-carboline **3**, their dependence on toxic thallium dimethyl malonate was of concern for frequent large-scale preparations. A study of reactions with alternative metal dimethyl malonates did not furnish the desired products **6** or **7** in useful yields (Table I). For speculative explanations of the superior yields obtained with thallium dimethyl malonate one may

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(3) Kuehne, M. E.; Kirkemo, C. L.; Matsko, T. H.; Bohnert, J. C. *J. Org. Chem.* **1980**, *45*, 3259.
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(5) Kuehne, M. E.; Bohnert, J. C. *J. Org. Chem.* **1981**, *46*, 3443.
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(7) Kuehne, M. E.; Earley, W. G. *Tetrahedron* **1983**, *39*, 3707, 3715.
(8) Takano, S.; Nishimura, T.; Ogasawara, K. *Heterocycles* **1977**, *6*, 1167.
(9) Kametani, T.; Suzuki, T.; Otsuka, C.; Takahashi, K.; Fukumoto, K. *Yakugaku Zasshi* **1975**, *95*, 363.
(10) The principle of such rearrangements was studied by: (a) Ebnother, A.; Niklaus, P.; Suess, S. *Helv. Chim. Acta* **1969**, *52*, 629. (b) Sniekus, V.; Bhandari, K. S. *Synthesis* **1971**, 327 (reported the analogous bromination and rearrangement of an *N*-methyltetrahydro-γ-carboline. (c) Nagai, Y.; Irie, A.; Uno, H.; Minami, S. *Chem. Pharm. Bull. (Jpn.)* **1979**, *27*, 1922. (d) Rearrangement of the *N*-methylchloroindolenine has since been reported by: Hershenson, F. M.; Swenton, L.; Prodan, K. A. *Tetrahedron Lett.* **1980**, 2617. A confirmatory 300-MHz NMR spectrum of **8** was kindly provided Dr. B. H. Arison of Merck, Sharp and Dohme.

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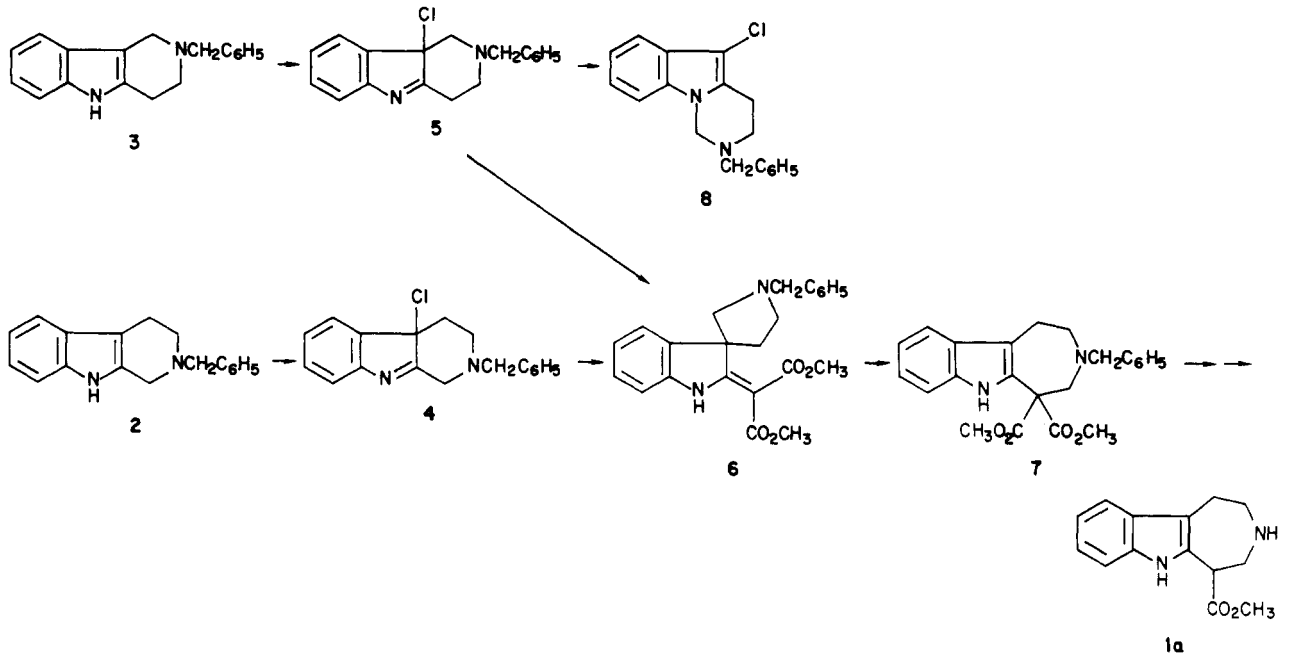
Scheme I



recall the preferential abstraction of the halogen substituent by sodium malonates from chloroindolenines,[11] which may be suppressed in favor of addition to the imine by the relatively soft character of Tl^+,[12a] and/or invoke consideration of the crystal structure of thallium dimethyl malonate in this heterogeneous reaction.[12b,c]

In order to circumvent these problems, an alternative synthesis of the indoloazepine **1a** was developed (Scheme II). Condensation of methyl chloropyruvate with tryptamine gave the chloromethyl tetrahydro-β-carboline **9a** in 74% yield. On heating in pyridine this compound was converted to the olefinic indoloazepine **10a** in 69% yield.

An analogous skeletal rearrangement was obtained by treatment of the (chloromethyl)tetrahydro-β-carboline **9a** with sodium acetate in acetic acid. However, in this case the product was the α-hydroxy ester acetamide **11**.

These rearrangement reactions presumably proceed by intramolecular N-alkylation and opening of an aziridine intermediate **12**.[13] While proton abstraction in pyridine gives the olefin **10a**, nucleophile attack by acetate leads to an amino acetate intermediate, which can undergo O to N acyl migration, to furnish the hydroxy amide **11**. Dehydration of this compound with *p*-toluenesulfonic acid in toluene provided the unsaturated amide **13**.

The structure of the acetamide **13** could be confirmed by an alternative synthesis, which utilized an acetylation of the indoloazepine **1a**, initially available through the sequence of Scheme I, and reaction of the resultant amide **14** with *tert*-butyl hypochlorite and base.

On reaction with acetic anhydride and triethylamine the (chloromethyl)carboline **9a** was converted to the acetoxy amide **15**. This product was doubly deacylated with methanolic HCl at room temperature, thus furnishing only the amino alcohol **16a** and showing no evidence of any monoacyl intermediates in the reaction. The facile halide displacement on acylation of the chlorocarboline **9a** and the ease of double deacylation of the acetoxy amide **15** suggest an anchimeric assistance in the reactions of these dual funtionalities.

The hydroxyl group of **16a** could be selectively masked (**16b** or **16c**) by silylations with trimethyl- or *tert*-butyldimethylsilyl chloride.

Reduction of the olefinic amino ester **10a** with sodium cyanoborohydride in acetic acid provided the saturated amino ester **1a**.[13] While good yields (85%) could generally be obtained in this step on a reaction scale below 30 g, caution must be exercised in the acidic workup and concentration of the product in order to avoid its facile decarbomethoxylation to the indoloazepine **17**.

A more economical reduction of the vinylogous urethane **10a** could be obtained with pyridine–borane complex in formic acid, giving at least 75% yields of **1a**. Reductions with zinc and sulfuric acid, or with sodium in liquid ammonia, gave good yields of the indoloazepine in small-scale reactions but they were not preparatively useful.

Since our synthetic studies directed at vindoline also required the N^a-methylated azepine **1b**, we examined several modifications of the new synthesis leading to the azepine **1a**. Starting with N^a-methyltryptamine,[14] the pertinent preceding reactions of Scheme II (i.e., **9b** → **10b** → **1b**) could be duplicated with analogous results. An alternative methylation of the unsaturated azepine **10a** with methyl iodide and sodium hydride did not show the desired regioselectivity but led primarily to the N^b-methylated product **18** and substantial formation of N^a,N^b-dimethylated product **19**. Attempted N^a-monomethylation of an N^b urethane derivative of **1a** resulted in much methylation α to the carbomethoxy function, as well as on N^a (**20**). In this context it may be noted that N^b may be masked (**21**) by mono N^b-benzylation of **1a** with benzyl bromide without competing quaternization.

The foregoing indoleazepines and tetrahydrocarbolines served as intermediates in several syntheses of indole al-

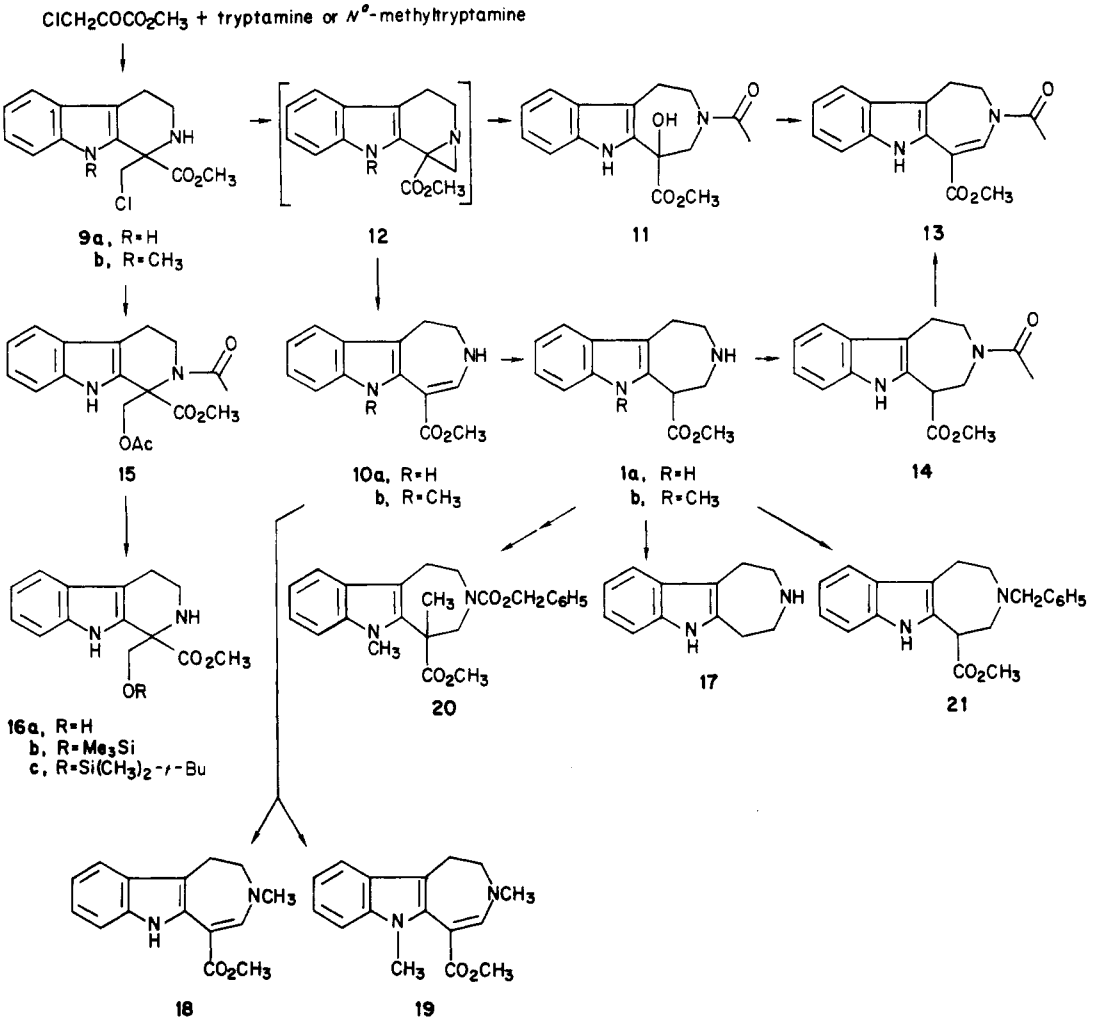
(11) Kuehne, M. E.; Hafter, R. *J. Org. Chem.* **1978**, *43*, 3702.

(12) (a) Pearson, R. G.; Songstad, J. *J. Am. Chem. Soc.* **1967**, *89*, 1827. (b) Taylor, E. C.; McKillop, A. *Acc. Chem. Res.* **1970**, *3*, 338. (c) The referee of this paper suggested preferential coordination of thallium with the indolenine nitrogen or promotion of ionization of the chloroindolenine malonate adduct as alternative explanations.

(13) A condensation of tryptamine and chloroacetaldehyde, followed by reduction with sodium borohydride, has been reported to furnish the corresponding indoloazepine **17** (Julia, M.; Bagot, J.; Siffert, O. *Bull. Soc. Chim. Fr.* **1973**, 1424, but Dr. R. Davis could not duplicate those results in our laboratory.

(14) Potts, K. T.; Saxton, J. E. *J. Chem. Soc.* **1954**, 2641.

Scheme II



kaloids, which are the subject of previous[1-7] and forthcoming papers in this series. Their collective description should provide a central reference and clarify those presentations.

Experimental Section

General Methods. All reactions were carried out under nitrogen or argon. Melting points were obtained in a heated oil bath, or on a Kofler microhotstage, with thermometers calibrated against a National Bureau of Standards certified set. NMR spectra were recorded on a Bruker 250-MHz or a JEOL 100-MHz instrument. Mass spectra were obtained with a Finnegan 4610 quadrupole instrument at 70 eV, calibrated with perfluorotributylamine and hexafluorotriphenylphosphine for compounds below MW 600 and with tris(perfluorononyl)-*s*-triazine for higher molecular weight compounds. IR spectra were obtained with a Nicolet 6000 FT or a Perkin-Elmer 267 grating instrument. UV spectra were recorded on Perkin-Elmer 202 or 402 instruments. TLC data were obtained with E. Merck 60F-254 precoated silica on aluminum sheets. For visualization (10%) cerric ammonium sulfate (CAS) in phosphoric acid was employed as spray reagent. For centrifugal chromatography a Harrison Chromatotron was used with E. Merck 60 PF 254 silica with gypsum. For column chromatography 60–200 mesh Baker R3405 silica was used. Microanalyses were provided by George Robertson, Robertson Laboratories, Florham Park, NJ.

Chlorination and Rearrangement of *N*-Benzyltetrahydro-γ-carboline (3). To a solution of 0.50 g (1.9 mmol) of the tetrahydrocarboline 3[2] and 0.232 g (2.3 mmol) of triethylamine in 7 mL of dichloromethane, cooled to −78 °C, was added dropwise 0.245 g (2.3 mmol) of *tert*-butyl hypochlorite. After 30 min at 18 °C the reaction mixture was concentrated under vacuum and the residual chloroindolenine 5,[2] dissolved in dichloromethane, was column chromatographed on silica. The eluate 8 (480 mg, 85%) could be crystallized from heptane, mp 82–83 °C. The compound was recovered unchanged from treatment with ethanolic potassium hydroxide at 18 °C for 15 h or from lithium aluminum hydride in refluxing tetrahydrofuran for 18 h. The compound formed a crystalline hydrochloride in ether, mp 157–158 °C: UV (ethanol) λ_{max} 228, 285, 292 (sh) nm; IR (KBr) ν_{max} 3040, 3010, 2930, 2875, 2840, 1598, 748, 700, 652 cm^{-1}; 300-MHz NMR ($CDCl_3$) δ 3.02 (t, 2 H), 3.18 (t, 2 H) 3.86 (s, 2 H), 4.81 (s, 2 H), 7.16–7.40 (m, 4 H), 7.36 (s, 5 H); MS, *m/z* (relative abundance) 296 (M^+, 85), 261 (4), 177 (100), 156 (1), 142 (2), 118 (1), 91 (2). Anal. Calcd for $C_{18}H_{17}N_2Cl$: C, 72.84; H, 5.77; N, 9.44; Cl, 11.94. Found: C, 72.99; H, 5.82; N, 9.18; Cl, 11.69.[10,15]

Formation of Dimethyl 3-Benzyl-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-5,5-dicarboxylate (7) (from Table I). The chloroindolenine 5 was prepared in dichloromethane as described above, on a 1.24-g scale for the reaction in *tert*-butyl alcohol and on a 1.60-g scale for the reaction in dimethylformamide. Evaporation of the dichloromethane under vacuum, replacement with the respective reaction solvent, addition of 1.2 equiv of thallium dimethyl malonate, and stirring at 20 °C for 1 h in *tert*-butyl alcohol and 8 h in DMF were follwed by the respective periods (8 h, 2 h) at elevated temperature. The reactions in tetrahydrofuran were carried out as described in ref 2 with the modifications indicated in Table I. The cooled reaction mixtures were concentrated under vacuum and diluted with 75 mL of dichloromethane and 50 mL of saturated aqueous sodium chloride. Concentration of the organic phase and chromatography

(15) We thank Dr. Lawrence F. Mullen of our group for preparation of an analytical sample and spectroscopic data.

on silica, eluting with ethyl ether/hexane (2:3) afforded the indoloazepine 7.

1-Carbomethoxy-1-(chloromethyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (9a). A mixture of 100 g (0.51 mol) of tryptamine hydrochloride, 80 g (0.58 mol) of methyl chloropyruvate,[16,17] and 5.5 g of decolorizing charcoal was heated in 2 L of anhydrous methanol, at reflux, under nitrogen, for 18 h. The cooled reaction mixture was filtered and concentrated under vacuum to about 200 mL and then diluted with about 1.5 L of water. Slow addition of concentrated ammonium hydroxide, until the aqueous phase became strongly basic, and filtration gave a crude crystalline product, which was rinsed with 40 mL of ether. Recrystallization from 1150 mL of acetone, by addition of 1 L of water, provided 93.5 g of colorless crystalline product. On concentration under vacuum at 20 °C, further 11.5 g of product was obtained, yield 74%. A sample recrystallized from acetone and water had mp 137–139 °C dec: 100-MHz NMR ($CDCl_3$) δ 2.80 (t, 2 H), 3.02 (s, 1 H), 3.24 (t, 2 H), 3.81 (d, J = 11 Hz, 1 H) 3.87 (s, 3 H), 4.26 (d, J = 11 Hz, 1 H), 7.08–7.68 (m, 4 H), 8.44 (s, 1 H); IR ($CHCl_3$) ν_{max} 3460, 3010, 2950, 2820, 1735, 1450, 1430, 1300 cm^{-1}; MS, m/z (relative abundance) 278 (M^+, 15), 242 (66), 229 (66), 219 (100). Anal. Calcd for $C_{14}H_{15}N_2O_2Cl$: C, 60.33; H, 5.42; N, 10.05; Cl, 12.77. Found: C, 59.91; H, 5.70; N, 9.70; Cl, 12.63.

Methyl 1,2,3,6-Tetrahydroazepino[4,5-*b*]indole-5-carboxylate (10a). A solution of 93.5 g (0.33 mol) of the (chloromethyl)carboline **9a** in 500 mL of pyridine was heated under nitrogen. After 12 min required to attain reflux and 15 min at reflux, the solution was concentrated under vacuum. The residue was dissolved in dichloromethane and washed 3 times with 100 mL of water. Concentration and trituration with 100 mL of ethyl acetate gave 62 g of crude crystalline product, which was recrystallized from 140 mL of acetone by addition of 100 mL of water, to give 56 g of product. This was treated with 5 g of decolorizing carbon in acetone, filtered, and crystallized by addition of water to give 55 g (69%) of the pale yellow product, mp 138–139 °C: 100-MHz NMR ($CDCl_3$) δ 1.30 (br s, 1 H), 3.00 (t, J = 6 Hz, 2 H), 3.34 (dt, J = 9, 6 Hz, 2 H), 3.72 (s, 3 H), 6.96–7.48 (m, 4 H), 7.54 (d, J = 9 Hz, 1 H), 10.40 (s, 1 H); UV (MeOH) λ_{max} 220, 242, 264, 291, 310, 343 nm; IR ν_{max} 1600 cm^{-1}; MS, m/z (relative abundance) 243 (M + 1, 18), 242 (M^+, 100) 241 (9), 211 (9), 210 (38), 209 (18), 183 (9), 182 (18), 181 (18), 155 (15), 154 (60), 153 (15), 149 (9). Anal. Calcd for $C_{14}H_{13}H_2O_2$: C, 69.40; H, 5.81; N, 11.56. Found: C, 69.18; H, 5.86; N, 11.33.

Methyl 1,2,3,4,5,6-Hexahydroazepino[4,5-*b*]indole-5-carboxylate (1a). (a) To a stirred slurry of 5.00 g (20.5 mmol) of the unsaturated azepine (**10a**) in 50 mL of glacial acetic acid was added 3.40 g (53.2 mmol) of sodium cyanoborohydride in small portions over 2 h. TLC (SiO_2, EtOAC, and 25% methanol in dichloromethane) then showed completion of the reaction. In a fume hood ca. 12 mL of concentrated hydrochloric acid was slowly added, with cooling, until gas evolution ceased. The reaction mixture was then concentrated under vacuum at 50 °C and the syrupy residue added to ice and basified with ammonium hydroxide. Three extractions with 30-mL portions of dichloromethane, concentration of the dried (Na_2SO_4) extracts under vacuum, and trituration of the residue with ether gave 4.9 g (98%) of crude product. On scaling up this reaction to 30 and 50 g it was found that 80–85% yields were obtained and that increasing amounts of decarbomethoxylated product were formed. Rapid concentration and minimal heating of the hydrochloric acid–acetic acid solution are imperative. The product can be recrystallized from ethyl acetate and hexane, mp 138–139 °C.[1] (b) To a clear solution of 2.40 g (1.0 mmol) of the unsaturated azepine **10a** in 6 mL of formic acid, cooled in an ice bath, was added 1.20 mL (1.16 mmol) of pyridine–borane complex over 5 min. After 10 min the ice bath was removed and the reaction mixture stirred at 20 °C for 30 min. With cooling in ice 5 mL of 10% HCl was then added, followed after 30 min by 15 mL of concentrated NH_4OH. Extraction with 3 × 25 mL of dichloromethane, washing of the combined extracts with 3 × 25 mL of water and 1 × 25 mL of brine, and concentration gave a gummy residue, which was dissolved in 20 mL of methanol (foaming). Concentration and trituration with 15 mL of ether gave 2.40 g of crystalline product showing the expected TLC behavior (below). Recrystallization from 5 mL of methanol gave 1.45 g (60%) of product 1, mp 138–139 °C; TLC (SiO_2, 25% methanol in dichloromethane) R_f 0.3 (CAS, blue-gray).

Methyl 3-Benzyl-1,2,3,6-Tetrahydroazepino[4,5-*b*]indole-5-carboxylate (21). A solution of 1.00 g (4.10 mmol) of the indoloazepine **1a** and 1.05 g (6.15 mmol) of benzyl bromide in 10 mL of dichloromethane was stirred at 20 °C for 10 h. The heterogeneous mixture was diluted with dichloromethane, washed with dilute sodium hydroxide solution, and concentrated under vacuum. The residue was recrystallized from ethanol, providing 0.76 g (56% yield) of product, mp 138–139 °C.[1]

α-(Acetoxymethyl)-α-carbomethoxy-*N*-acetyltetrahydro-β-carboline (15). The chlorocarboline **9a** (2.0 g) was stirred in acetic anhydride (5 mL) and triethylamine (1 mL) for 16 h at 20 °C. The mixture was then poured onto ice, basified with 10% NH_4OH(aq), and extracted 3 times with 20-mL aliquots of CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and concentrated to a dark residue. This was dissolved in hot methanol and treated with decolorizing carbon, filtered, and concentrated by heating. Crystallization on cooling gave 1.4 g (54%) of the amide acetate, mp 181–183 °C: TLC (SiO_2, 7.5% methanol in CH_2Cl_2) R_f 0.60 (CAS, gray); NMR ($CDCl_3$) δ 8.85 (s, 1 H), 7.53 (d, 1 H, J = 7.7 Hz), 7.37 (d, 1 H, J = 7.3 Hz), 7.12–7.22 (m, 2 H), 5.22 (1 H, J = 12.0 Hz), 5.00 (d, 1 H, J = 11.6 Hz), 4.10 (m, 1 H), 3.60–3.73 (m, 1 H), 3.59 (s, 3 H), 2.90–3.00 (m, 2 H), 2.29 (s, 3 H), 1.87 (s, 3 H); IR (KBr) ν_{max} 3270, 2960, 1737, 1617 cm^{-1}; MS, m/e (relative abundance) 344 (M^+, 23), 285 (27), 243 (63), 229 (100). Anal. Calcd for methanolate $C_{19}H_{24}N_2O_6$: C, 60.63; H, 6.42; N, 7.44. Found: C, 60.39; H, 6.30; N, 7.39.

Methyl 3-Acetyl-5-hydroxyhexahydroazepino[4,5-*b*]-indole-5-carboxylate (11). The carboline **9a** (2.0 g, 7.2 mmol) and sodium acetate (0.60 g, 7.3 mmol) were refluxed in 16 mL of a 1:1 solution of acetic acid and THF for 4 h. After cooling, the mixture was added to ice and basified with 10% NH_4OH(aq). The aqueous phase was extracted 3 times (20-mL aliquots) with CH_2Cl_2. The combined extracts were dried (Na_2SO_4), reduced to about one-half volume and then permitted to crystallize with cooling. An analytical sample was recrystallized from methanol, yield 1.13 g (52%), mp 193–195 °C: TLC (SiO_2, 3:7 EtOAc:CH_2Cl_2) R_f 2.3 (CAS, gray); NMR ($CDCl_3$) δ 8.53 (s, 1 H), 7.54, (d, 1 H, J = 6.8 Hz), 7.33 (d, 1 H), 7.10–7.26 (m, 2 H), 4.57 (d, 1 H, J = 14.0 Hz), 4.01–4.09 (m, 1 H), 3.72 (d, 1 H, J = 14.0 Hz), 3.71 (s, 3 H), 3.50–3.65 (m, 1 H), 3.08–3.22 (m, 2 H), 2.15 (s, 3 H); IR (KBr) ν_{max} 3388, 3283, 1747, 1624, 1613 cm^{-1}; MS, m/e (relative abundance) 302 (M^+, 78), 243 (44), 170 (39), 156 (57), 144 (100). Anal. Calcd for $C_{16}H_{18}N_2O_4$: C, 63.57; H, 6.00; N, 9.27. Found: C, 63.28; H, 6.07; N, 9.23.

***N*-Acetyl Tetrahydroindoloazepine (14).** The azepine **1a** (1.0 g) was dissolved in a minimum amount of acetic anhydride (ca. 3 mL). After 15 h at 20 °C the resulting crystals were collected and washed with 10 mL of dry ether to yield 0.94 g (80%) of product. An analytical sample was recrystallized from methanol, mp 189–191 °C: NMR ($CDCl_3$) δ 8.55 (s, 1 H), 7.49 (m, 1 H), 7.32 (m, 1 H), 7.08–7.21 (m, 2 H), 3.94–4.40 (m, 3 H), 3.77 (s, 3 H), 3.65–3.79 (m, 2 H), 3.02–3.28 (m, 2 H), 2.23 (s, 0.70 H), 2.13 (s, 2.3 H); IR (KBr) ν_{max} 3281, 1736, 1635, 1617, 1438, 735 cm^{-1}; MS, m/e (relative abundance) 286 (M^+, 50), 254 (87), 211 (58), 154 (100). Anal. Calcd for $C_{16}H_{18}N_2O_3$: C, 67.12; H, 6.34; N, 9.78. Found: C, 66.95; H, 6.51; N, 9.67.

Methyl 3-Acetyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate (13). Method A: The hydroxyazepine **11** (2.0 g) and a catalytic amount of *p*-toluenesulfonic acid were heated in toluene (15 mL) at reflux for 2.5 h. After cooling the toluene was evaporated under vacuum and the residue column chromatographed (SiO_2, 5% methanol/CH_2Cl_2) and the eluate crystallized by trituration with ether to yield 0.94 g (77%) of product. An analytical sample was recrystallized from methanol, mp 126–128 °C: TLC (SiO_2, 2% methanol/CH_2Cl_2) R_f 0.66 (CAS, green); NMR ($CDCl_3$) δ 10.51 (s, 1 H), 8.12 (br s, 1 H), 7.49 (d, 1 H, J = 7.7 Hz), 7.37 (d, 1 H, J = 7.0 Hz), 7.06–7.25 (m, 2 H), 3.99 (t, 2 H, J = 4.6 Hz), 3.91 (s, 3 H), 3.14 (t, 2 H, J = 4.9 Hz), 2.37 (s, 3 H); IR

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(KBr) ν_{max} 3388, 1677, 1591, 1343, 1221 cm^{-1}; UV (ethanol) λ_{max} 219, 232, 253, 270, 330 nm; MS, *m/e* (relative abundance) 284 (M^+, 100) 242 (19), 225 (19), 154 (62). Anal. Calcd for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.80; H, 5.91; N, 9.69. **Method B**: A solution of *N*-acetylazepine **14** (0.20 g, 0.70 mmol) and triethylamine (0.10 mL, 0.70 mmol) in 5 mL of CH_2Cl_2 was cooled in an ice bath at 0 °C under N_2. A cold solution of *tert*-butyl hypochlorite (0.085 mL, 0.70 mmol) in 5 mL of CH_2Cl_2 was added rapidly via a chilled syringe and the mixture was allowed to stir for 1.5 h at 0 °C. The solution was washed with ice water and extracted with dichloromethane and the concentrated extract triturated with ether to yield 0.12 g (60%) of **13**.

α-Carbomethoxy-α-(hydroxymethyl)tetrahydro-β-carboline (16a). The carboline **15** (0.50 g) was dissolved in methanol (5 mL) saturated with HCl and allowed to stir at 20 °C for 24 h. The solution was then added to ice, basified with 10% NH_4OH(aq), and extracted with CH_2Cl_2. The extracts were dried (Na_2SO_4) and concentrated to dryness. The residue was triturated with ether to yield 0.27 g (71%) of **16a**. An analytical sample was crystallized from benzene, mp 163–164 °C dec: TLC (SiO_2, 7.5% methanol/CH_2Cl_2) R_f 0.38 (CAS, gray); NMR ($CDCl_3$) δ 8.32 (s, 1 H), 7.07–7.52 (m, 4 H), 4.02 (d, 1 H, J = 10.7 Hz), 3.84 (s, 3 H), 3.82 (d, 1 H, J = 10.5 Hz), 3.05–3.32 (m, 2 H), 2.70–2.77 (m, 2 H), 1.75 (s, 2 H); IR (KBr) ν_{max} 3415, 3276, 1738, 1460 cm^{-1}; MS, *m/e* (relative abundance) 260 (M^+, 9) 229 (100), 201 (43), 169 (41), 115 (26). Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.88; H, 66.01; N, 10.51.

α-Carbomethoxy-α-([(trimethylsilyl)oxy]methyl)tetrahydro-β-carboline (16b). To a CH_2Cl_2 (50 mL) solution of hydroxycarboline **16a** (1.0 g, 3.8 mmol) and triethylamine (1.3 mL, 9.6 mmol), stirring in an ice bath, was added trimethylsilyl chloride (1.3 mL, 9.6 mmol). The mixture was allowed to warm and stir overnight at 20 °C. The solution was washed with ice water and the organic layer dried ($MgSO_4$) and concentrated to dryness. A solution of the residue was passed through a short plug of silica (5% methanol/CH_2Cl_2) and the concentrated eluate was triturated with ether/hexane to yield 0.75 g of crystalline **16b** (59%). An analytical sample was recrystallized from petroleum ether (mp 125–127 °C): TLC (SiO_2, 7.5% methanol/CH_2Cl_2) R_f 0.70 (CAS, gray); NMR ($CDCl_3$) δ 8.46 (s, 1 H), 7.05–7.52 (m, 4 H), 4.06 (d, 1 H, J = 10.7 Hz), 3.92 (d, 1 H, J = 10.6 Hz), 3.83 (s, 3 H), 3.06–3.29 (m, 2 H), 2.74–2.86 (m, 2 H), 2.74 (br s, 1 H); IR (KBr) ν_{max} 3380, 1710, 1430, 1250, 872, 845 cm^{-1}; MS, *m/e* (relative abundance) 332 (M^+, 5), 273 (8), 229 (100), 169 (15); UV (ethanol) λ_{max} 232, 276, 282, 290 nm. Anal. Calcd for $C_{17}H_{24}N_2O_3Si$: C, 61.41; H, 7.28; N, 8.43. Found: C, 61.14; H, 7.41; N, 8.43.

α-Carbomethoxy-α-([(*tert*-butyldimethylsilyl)oxy]methyl)tetrahydro-β-carboline (16c). To carboline **16a** (1.0 g, 3.8 mmol) and imidazole (0.31 g, 4.6 mmol), stirring in THF (8 mL) at 0 °C in an ice bath, was added *tert*-butyldimethylsilyl chloride (0.68 g, 4.5 mmol). The solution was allowed to come to 20 °C and stir overnight and then partitioned between THF and water. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated to dryness. The residue was triturated with hexane to yield 0.99 g of product (69%). An analytical sample was crystallized from petroleum ether, mp 93–94 °C: TLC (SiO_2, 7.5% methanol/CH_2Cl_2) R_f 0.58 (CAS, gray); NMR ($CDCl_3$) δ 8.47 (s, 1 H), 7.06–7.52 (m, 4 H), 4.06 (d, 1 H, J = 9.1 Hz), 3.82 (d, 1 H, J = 9.1 Hz), 3.76 (s, 3 H), 3.03–3.30 (m, 2 H), 2.73–2.81 (m, 2 H), 0.91 (s, 9 H), 0.07 (s, 6 H); IR (KBr) ν_{max} 3480, 1705, 1455, 1430, 1245 cm^{-1}; UV (ethanol) λ_{max} 236, 276, 282, 291 nm; MS, *m/e* (relative abundance) 374 (M^+, 6), 315 (6), 229 (100). Anal. Calcd for $C_{20}H_{30}N_2O_3Si$: C, 64.13; H, 8.07; N, 7.48. Found: C, 64.13; H, 8.33; N, 7.48.

1-Carbomethoxy-1-(chloromethyl)-9-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (9b). A solution of 6.3 g (29.9 mmol) of N^a-methyltryptamine hydrochloride and 6.0 g (44.0 mmol) of methyl chloropyruvate in 50 mL of anhydrous methanol was refluxed under N_2 for 20 h, when a white precipitate had formed. After cooling, filtration of the reaction mixture and recrystallization of the solid from $CHCl_3$ afforded 6.75 g of the N^a-methyl(chloromethyl)carboline hydrochloride as white crystals, mp 193–200 °C: NMR ($CDCl_3$ + 3 drops of Me_2SO-d_6 to solubilize) δ 7.56–7.14 (m 4 H), 4.83 (d, 2 H, J = 12 H), 4.68 (d, J = 12 Hz) 3.95 (s, 3 H), 3.94 (s, 3 H), 3.83–3.92 (m, 2 H), 3.41–3.50 (m, 1 H), 3.10–3.39 (m, 1 H), 2.59 (t, 2 H, J = 2 Hz); IR (KBr) ν_{max} 2986, 2572, 2430, 1739, 1437, 1238, 754 cm^{-1}; UV (EtOH) λ_{max} 237, 287 nm. Anal. Calcd for $C_{15}H_{18}Cl_2N_2O_2$: C, 54.72; H, 5.51; N, 8.51. Found: C, 54.75; H, 5.80; N, 8.67.

The free base was obtained as a pale yellow oil by neutralization of the hydrochloride salt with saturated $NaHCO_3$, extraction with 3 × 20 mL of CH_2Cl_2, drying (anhydrous $MgSO_4$), and concentration under reduced pressure. MS, *m/z* (relative abundance) 292 (26) 235 (29) 233 (100) 219 (13) 199 (44) 197 (30) 183 (18) 168 (21).

Methyl 6-Methyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate (10b). A solution of 3.5 g of the N^a-methyl (chloromethyl)carboline **9b** hydrochloride in 50 mL of pyridine was heated at reflux for 30 min; TLC (SiO_2, CH_2Cl_2) R_f 0.1 (CAS, pale yellow) then showed no starting material with R_f 0.0. After concentration under reduced pressure, 50 mL of 10% aqueous HCl was added to the residue and the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were dried (anhydrous $MgSO_4$) and concentrated under reduced pressure. Chromatography on silica (3 × 30 cm column) with CH_2Cl_2 elution gave 2.54 g (83%) of white needles after recrystallization from $CHCl_3$, mp 226–228 °C: NMR ($CDCl_3$) δ 7.02–7.72 (5 H, m); 6.13 (1 H brd s) 3.78 (3 H, s), 5.54 (3 H, s) 3.49–3.53 (2 H, m), 2.09–2.14 (2 H, m); UV (ethanol) ν_{max} 251, 268, 296, 309, 328 nm; IR (KBr) ν_{max} 3337, 2950, 1663, 1594, 1540, 1278 cm^{-1}; MS, *m/z* (relative abundance) 256 (100) 241 (19) 209 (28) 168 (32). Anal. Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.00; H, 6.53; N, 10.67.

Methyl 3-Methyl- and 3,6-Dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate (19, 20). Addition of 0.12 g (5.0 mmol) of sodium hydride to a solution of unsaturated indoloazepine **1a** (1.00 g, 4.13 mM) in DMF (50 mL) at 0 °C was followed after 30 min by dropwise addition of methyl iodide (0.074 g, 5.00 mM). The mixture was stirred under N_2 at 0 °C for 30 min. TLC (SiO_2, CH_2Cl_2) showed only two products: major R_f 0.62 (CAS, bright yellow) and minor R_f 0.26 (CAS, light yellow). Water (300 mL) was then added and the mixture extracted with ether (3 × 100 mL). The combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The two products were isolated by chromatography on silica (3 × 30 cm column). The major product **19** was obtained first by CH_2Cl_2 elution. Concentration of the fractions gave 577 mg (55%) of a yellow oil, which crystallized from $CHCl_3$, mp 97–99 °C: NMR ($CDCl_3$) δ 10.48 (s, 1 H), 7.75 (s, 1 H), 7.39–6.98 (m, 4 H), 3.79 (s, 3 H), 3.44 (m, 2 H), 3.14 (s, 3 H), 3.08 (m, 2 H); IR (KBr) ν_{max} 3476, 2898, 1659, 1601, 1255, 743 cm^{-1}; UV (EtOH) λ_{max} 249, 270, 296, 315, 356 nm; MS, *m/z* (relative abundance) 256 (M + 100), 224 (15), 154 (18). Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.40; H, 6.28; N, 10.84.

Continued elution with CH_2Cl_2 gave 381 mg (34%) of **20** as a yellow oil, which crystallized from $CHCl_3$, mp 126–128 °C: 250 MHz NMR ($CDCl_3$) δ 7.71 (s, 1 H) .740–7.02 (m, 4 H), 3.78 (s, 3 H), 3.47 (s, 3 H) 3.42–3.48 (m, 2 H), 3.14 (s, 3 H), 3.05–3.12 (m, 2 H); IR (KBr) ν_{max} 2941, 1692, 1594, 1256, 1255, 1148, 741 cm^{-1}; UV (EtOH) λ_{max} 249, 261, 300, 309, 338 nm; mass spectrum, *m/z* (relative intensity) 270 (100) 255 (30), 222 (28), 168 (26). Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 71.09; H, 6.71; N; 10.36. Found: C, 71.00; H, 6.85; N; 10.21.

Methyl 6-Methyl-1,2,3,4,5,6-hexahydro[4,5-*b*]indole-5-carboxylate (1b). Sodium cyanoborohydride (0.31 g, 5.0 mmol) was added in several portions to a suspension of the N^a-methyl unsaturated indoloazepine **10b** (1.00 g, 3.9 mmol) in acetic acid (20 mL). After addition, the solution cleared and TLC (SiO_2–ether) showed that all of the starting material had reacted, forming a single product with R_f 0.1 (CAS, purple-gray). Concentrated HCl (2.0 mL) was then added dropwise to the reaction mixture. The mixture was cooled in ice, neutralized by dropwise addition of concentrated NH_4OH and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated to give 0.95 g (94%) of a pale yellow oil: NMR ($CDCl_3$) δ 7.51–7.06 (m, 4 H), 3.95 (t, 1 H, J = 3.0 Hz), 3.80 (dd, 1 H, J = 3.5, 14.0 Hz), 3.69 (s, 3 H), 3.68 (s, 3 H), 3.42 (dd, 1 H, J = 3.0, 7.0 Hz), 3.11 (dd 1 H, J = 2.6, 13.9 Hz), 2.90–3.03 (m, 1 H), 2.85 (dd, 1 H, J = 2.6, 10.6 Hz), 2.82–2.89 (m, 1 H), 2.17 (br s, 1 H).

The hydrochloride salt was obtained by adding HCl saturated ether to an ether solution of the azepine. Filtration and recrystallization (ethanol) afforded the hydrochloride salt as pale yellow crystals, mp 195–197 °C dec: NMR (Me_2SO-d_6) δ 7.00–7.54 (m, 4 H), 4.78 (br s, 1 H), 3.92 (dd, 1 H), 3.73 (s, 3 H), 3.70 (s, 3 H), 3.38–3.48 (m, 2 H), 2.94–3.24 (m, 3 H); IR (KBr) ν_{max} 2953, 2642, 2623, 2527, 1740, 1462, 1207, 762 cm^{-1}; UV (ethanol) λ_{max} 235, 279 nm. Anal. Calcd for $C_{13}H_{19}N_2O_2Cl$: C, 61.12; H, 6.50; N, 9.50; Cl, 12.03. Found: C, 61.02; H, 6.37; N, 9.26; Cl, 11.92.

Methyl 3-[(Benzyloxy)carbonyl]-5,6-dimethyl-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-5-carboxylate (20). Benzyl chloroformate (0.77 g, 4.51 mmol) was added to a solution of the indoloazepine **1a** (1.0 g, 4.1 mmol) in CH_2Cl_2 (100 mL), containing solid Na_2CO_3. After 5 min, TLC (SiO_2, ether) showed that the starting material had reacted completely and the presence of a single product with R_f 0.69 (CAS, green). The reaction mixture was washed with saturated $NaHCO_3$ (50 mL) and the organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (SiO_2, 3 × 30 cm column, ether) gave 1.2 g (83%) of the benzylurethane derivative of **1a** after recrystallization from ether, mp 158–159 °C: NMR ($CDCl_3$) δ 8.40, 8.49 (2 br s, 3:2, 1 H), 7.20–7.45 (m, 9 H), 5.13–5.29 (m, 2 H), 4.06–4.23 (m, 3 H), 3.83–3.65 (m, 2 H), 3.72, 3.66 (2 s, 3:2, 3 H), 3.01–3.13 (m, 2 H); IR (KBr) ν_{max} 3311, 2908, 1743, 1671, 1297, 1199 cm^{-1}; UV (ethanol) λ_{max} 233, 284, 292 nm; MS, *m/z* (relative intensity) 378 (16), 346 (44), 255 (41), 214 (25), 91 (100). Anal. Calcd for $C_{22}H_{22}N_2O_4$: C, 69.83; H, 5.85; N, 7.40. Found: C, 69.67; H, 6.14; N, 7.11.

Sodium hydride (1.2 equiv) was added to the benzylurethane derivative of **1a** (700 mg, 1.85 mmol) in 50 mL of dimethylformamide and the mixture was stirred at 0 °C for 30 min under N_2. Methyl iodide (0.32 g, 2.2 mmol) was added dropwise and the mixture was stirred at 0 °C under N_2 for an additional 30 min. TLC (SiO_2, 1:1 ether:pentane) of the reaction mixture showed two major products with R_f 0.81 (CAS, purple) and R_f 0.76 (CAS, blue), at least three minor products, and unreacted starting material. Water (300 mL) was added to the reaction mixture and the suspension was extracted with ether (3 × 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure, and the two major products and unreacted starting material were separated by chromatography (SiO_2, 1:1 ether:pentane, 3 × 30 cm column). The product that eluted first was crystallized from ether and pentane to give 180 mg (25%) of the dimethyl[(benzyloxy)carbonyl]indoloazepine **20**, mp 107–109 °C: NMR ($CDCl_3$) δ 7.12–7.53 (m, 9 H), 5.11–5.20 (m, 2 H), 4.24 (m, 1 H), 3.97–4.05 (m, 1 H), 3.72–3.79 (m, 2 H), 3.55, 3.54 (2 s, 2:1, 3 H), 3.51, 3.52 (2 s, 2:1, 3 H), 3.12–3.18 (m, 2 H), 1.59, 1.53 (2 s, 2:1, 3 H); IR (KBr) ν_{max} 2949, 1731, 1697, 1262, 1131 cm^{-1}; UV (ethanol) λ_{max} 237, 286 nm; MS, *m/z* (relative intensity) 406 (M^+, 23), 347 (12), 283 (10), 230 (49), 182 (13), 168 (12), 91 (100), 65 (14). Anal. Calcd for $C_{24}H_{26}N_2O_4$: C, 70.92; H, 6.21; N, 6.89. Found: C, 70.95; H, 6.43; N, 6.71.

Continued elution gave 116 mg (15%) of the C-5 monomethylation product as a colorless oil: NMR ($CDCl_3$) δ 8.37, 8.31 (2 s, 3:2, 1 H), 7.07–7.52 (m, 9 H), 5.10–5.23 (m, 2 H), 4.07–4.15 (m, 2 H), 3.71–3.85 (m, 2 H), 3.67, 3.68 (2s, 3:2, 3 H), 3.03–3.16 (m, 2 H), 1.61, 1.54 (2 s, 3:2, 3 H); IR (KBr) ν_{max} 3354, 2948, 1731, 1698, 1683, 1423, 1215 cm^{-1}; UV (ethanol) λ_{max} 237, 286 nm; MS, *m/z* (relative intensity) 392 (M^+, 17), 301 (11), 269 (10), 257 (5), 242 (7), 230 (10), 168 (14), 91 (100).

Studies in Biomimetic Alkaloid Syntheses. 12. Enantioselective Total Syntheses of (-)- and (+)-Vincadifformine and of (-)-Tabersonine

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The (-) and (+) enantiomers of vincadifformine (**1**) were obtained with ≥98% ee and ≥97% ee, respectively (before purification), from the two enantiomers of epichlorohydrin. This synthetic scheme is based on generation and cyclization of the enantiomeric (hydroxymethyl)norsecodine intermediates **3a,b**. By an alternative synthetic route, passing through (14*S*)-14-hydroxy-$\Delta^{20,21}$-secodine (**14**), (-)-tabersonine (**18b**) was obtained with ≥99% ee.

Aspidosperma alkaloids are found naturally in either of the two possible enantiomeric senses (i.e., as antipodes of the spiro center C7), and their prime representative, vincadifformine (**1**), occurs separately in both enantiomeric forms,[1,2] as well as in form of the racemic natural product.[3] This chiral diversity is of interest in view of a probable proximate achiral precursor, which is responsible for formation of the aspidosperma alkaloid skeleton.

According to the Wenkert–Scott biogenetic hypotheses, a $\Delta^{20,21}$-secodine (**2**) was postulated as the key intermediate in the formation of these pentacyclic alkaloids.[4] Incorporation of isotopically, specifically labeled precursors and establishment of isotopic label distribution in the final alkaloid products supported a secologanin pathway,[4] plausibly passing through an undetected $\Delta^{20,21}$-secodine (**2**) intermediate. This biogenetic proposal was strengthened further by synthetic generation of the transient secodine intermediate **2** through two alternative independent routes and consequent biomimetic cyclization of the secondine **2** in high yield to racemic vincadifformine (**1**).[5,6]

Lack of chirality in the $\Delta^{20,21}$-secodine (**2**) and its instantaneous cyclization to racemic vincadifformine (**1**) pose a challenge, if one hopes to utilize the efficacious secodine

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