absorbing at 246 and 306 nm.

Experimental Section

Mass spectra were recorded at 70 eV on a VG MM 7070F instrument; precise mass measurements were obtained by the peak-matching method. UV spectra were recorded on a Unicam SP 18 instrument and IR spectra on a Perkin-Elmer 580 spectrometer. ^{13}C NMR spectra were recorded at 67.889 MHz and ^1H NMR spectra at 270 MHz on a Bruker HX-270 FT instrument. In the case of the NOE difference measurements, the method described in ref 1 was used on argon-flushed and dust-free samples. All NMR spectra were recorded in $CDCl_3$, and chemical shifts are reported in parts per million downfield from internal Me_4Si.

Isolation of Flustramine C and Flustraminol A and B. *Flustra foliacea* (L.) (2.5 kg, dry weight) was extracted with 70% ethanol and 96% ethanol, respectively. The combined ethanolic extracts were separated into an ether- and a water-soluble part. After evaporation, the ether soluble part was extracted with pentane. Evaporation left 30 g of crude oil with a bromine content of 6%. A separation between basic and nonbasic parts gave 400 mg of basic black oil. On the basis of UV absorption (254 and 280 nm), this oil was separated into several fractions by column chromatography (silica gel, A 60 Lobar size C, Merck) with ethyl acetate as the eluant. Three of these fractions were purified further and are given in the order of increasing polarity as follows.

Flustraminol A was rechromatographed on silica gel RP-8 (Merck) and silica gel A60 (Merck), respectively, by using ethyl acetate as the eluant. This gave 16 mg of flustraminol A as a brown oil (6×10^{-4}% of dry weight).

Flustramine C was rechromatographed on silica gel A60 (Merck) with ethyl acetate as the eluant. This gave 8 mg of flustramine C as a colorless oil (3×10^{-4}% of dry weight).

Flustraminol B was rechromatographed on silica gel A60 (Merck) by using ethyl acetate and ethyl acetate/methanol (9:1) as eluents, respectively. This gave 2 mg of impure flustraminol B as a brown oil (8×10^{-5}% of dry weight).

Spectroscopic Data. Flustraminol A: $C_{16}H_{21}BrN_2O$; mass spectrum (100 °C), m/e (relative intensity) 338/336 (0.8), 269/267 (100), 212/210 (10); metastable ions at m/e 167.1/165.2 indicate the fragmentations m/e 269/267 → 212/210; high-resolution measurements, m/e 336.083 (calcd for $C_{16}H_{21}BrN_2O$ m/e 336.083), 269.0111 (calcd for $C_{11}H_{12}BrN_2O$ 269.0113); UV (EtOH) λ_{max} 215 nm (ϵ 1.7×10^4), 256 (6.5×10^3), 318 (2.3×10^3); UV (0.5 N ethanolic HCl) 215 nm (ϵ 1.8×10^4) 234 (sh, 8.6×10^3), 246 (5.4×10^3), 306 (23×10^3); IR ($CHCl_3$) 3540 (w, br), 3450 (w, br), 3010 (m), 2970 (s), 2940 (s), 1715 (m), 1675 (w), 1600 (s), 1570 (s), 1490 cm^{-1} (s).

Flustramine C: $C_{16}H_{19}BrN_2$; mass spectrum (100 °C), m/e (relative intensity) 320/318 (34), 251/249 (100), 210/208 (6), 170 (49), 129 (16), 69 (9); metastable ions at m/e 116.1/115.1 indicate the fragmentations m/e 251/249 → 170 (loss of bromine); high-resolution measurements, m/e 318.073 (calcd for $C_{16}H_{19}BrN_2$ m/e 318.073); UV (EtOH) λ_{max} 210 nm (sh, ϵ 1.0×10^4), 232 (2.7×10^4), 290 (9.4×10^3), 307 (4.3×10^3); UV (0.5 N ethanolic HCl): 210 nm (sh, ϵ 1.3×10^4), 230 (2.3×10^4), 280 (4.6×10^3); IR ($CHCl_3$) 2970 (s), 1635 (s), 1585 (s), 1565 (s), 1435 (s), 1415 cm^{-1} (s).

Debromo-8,8a-dihydroflustramine C. A solution of 4 mg (0.013 mmol) of flustramine C in 1 mL of dry ether was added to a stirred suspension of 2 mg (0.053 mmol) of LAH in 1 mL of dry ether at room temperature. The stirring was continued for 1 h at room temperature. The reaction mixture was diluted with water and extracted with ether. The dried etheral extract gave upon evaporation debromo-8,8a-dihydroflustramine C as a colorless oil: 3.5 mg (87.5%); mass spectrum (70 °C), m/e (relative intensity) 242 (24), 173 (100), 130 (44); metastable ion at m/e 97.7 indicates the fragmentation m/e 173 → 130; ^1H NMR (270 MHz, $CDCl_3$) δ 1.01, 1.08 (s, 3, H-10, H-11), 2.42 (s, 3, H-14), 4.42 (s, 1, H-8a), 5.04 (m, 2, H-13), 6.59, 7.13 (d, 1, H-4, H-7), 6.70, 7.05 (t, 1, H-5, H-6); ^{13}C NMR (69.89 MHz, $CDCl_3$) δ 53.2 (C-2), 34.5[§] (C-3), 64.5 (C-3a), 125.1[†] (C-4), 118.5 (C-5), 127.8[†] (C-6), 109.1 (C-7), 84.4(C-8a), 41.4 (C-9), 23.2* (C-10), 22.5* (C-11), 144.8 (C-12), 113.0 (C-13), 36.8[§] (C-14). Assignments for values marked with the same symbols may be interchanged.

Flustraminol B: $C_{16}H_{21}BrN_2O$; mass spectrum (130 °C), m/e (relative intensity) 338/336 (57), 320/218 (20), 305/303 (6), 281/279 (29), 266/264 (27), 226/224 (21), 210/208 (21), 69 (100); metastable ions at m/e 302.9/300.9 indicate the fragmentations m/e 338/336 → 320/318 (loss of H_2O); high-resolution measurements, m/e 336.087 (calcd for $C_{16}H_{21}BrN_2O$ m/e 336.084); UV (EtOH) λ_{max} 220 nm (ϵ 1.7×10^4), 256 (6.3×10^3), 310 (2.3×10^3); UV (0.5 N ethanolic HCl) 220 nm (ϵ 1.7×10^4), 240 (sh, 6.3×10^3), 298 (2.3×10^3); IR ($CHCl_3$) 3590 (w), 3360 (wb), 3020 (m), 2980 (s), 2940 (s), 1670 (s), 1600 (s), 1485 cm^{-1} (s).

Acknowledgment. The chromatographic equipment (Grant J.nr. 511-6810) and the Bruker HX-270 NMR spectrometer were purchased by the Danish Natural Science Council, to whom we are also grateful for a fellowship (J.nr. 511-100166) to J.S.C. A grant from Carlsberg Foundation is likewise acknowledged. Finally we thank Dr. Ole Manscher for the ^1H NMR simulation and Dr. K. Schaumburg for obtaining the NOE difference data.

Registry No. 1, 78127-86-3; 1 debromo-8,8a-dihydro, 78127-87-4; 2, 78127-88-5; 3, 78127-89-6.

Studies in Biomimetic Alkaloid Syntheses. 7. Stereospecific Total Syntheses of Ibophyllidine and 20-Epiibophyllidine

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Received March 20, 1981

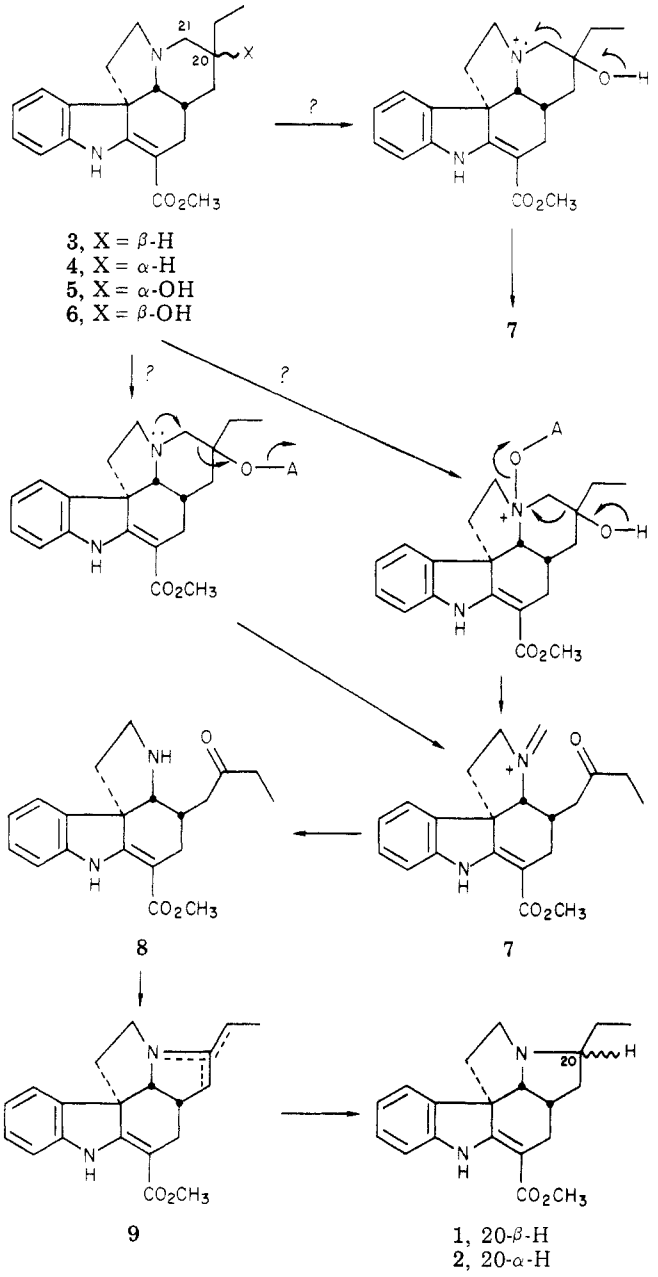
The alkaloids ibophyllidine (1) and 20-epiibophyllidine (2) were selectively synthesized by utilizing reaction pathways which pass respectively either through a biomimetic ring D–seco intermediate, 8, or through a norsecodine intermediate, 13.

While the indole and dihydroindole alkaloids, which are biosynthetically derived from tryptamine and secologanine, exhibit a rich diversity of structural variations based on skeletal rearrangements, they generally maintain all carbons of their biosynthetic precursors. An exception is found in the recently isolated and characterized alkaloids ibophyllidine (1) and 20-epiibophyllidine (2).[1,2] The structural similarity of these compounds to the C-20 epimeric Ψ-vincadifformines (3, 4) and pandolines (5, 6)

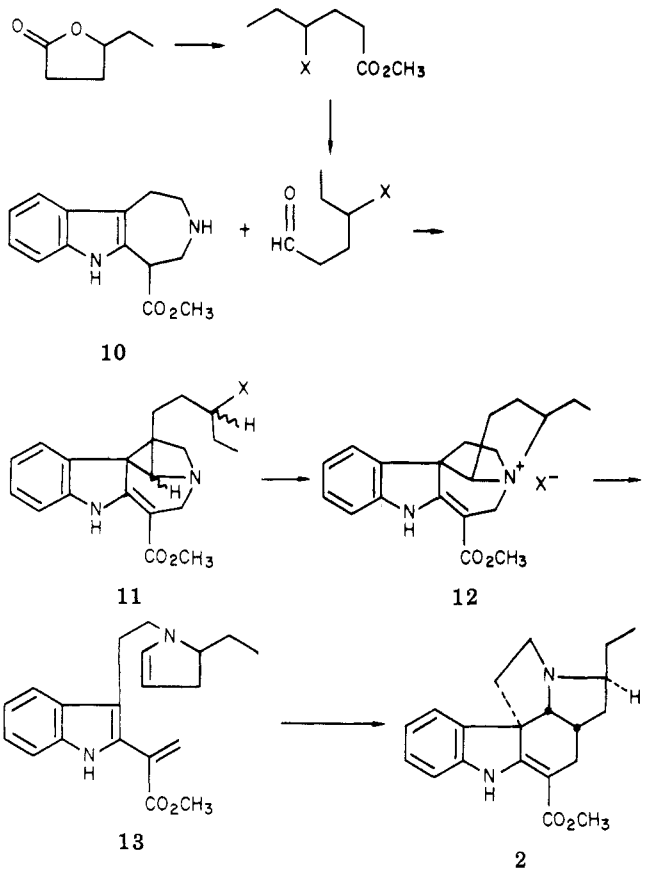
(1) F. Khuong-Huu, M. Cesario, J. Guilhem, and R. Goutarel, *Tetrahedron*, 32, 2539 (1976).
(2) C. Kan, H.-P. Husson, J. Jacquemin, S.-K. Kan, and M. Lounasmaa, *Tetrahedron Lett.*, 55, (1980).

0022-3263/81/1946-3443$01.25/0

Scheme I



Scheme II



suggests derivation of the ibophyllidines (1, 2) from the latter by loss of the C-21 carbon.[1,3] Such a biogenetic degradation may, in principle, be considered to be based on several alternative oxidative pathways which could lead to fragmentation of ring D of pandoline (Scheme I). The resultant keto immonium intermediate 7 would provide an amino ketone, 8, on hydrolysis. Intramolecular condensation of the latter, followed by reduction of consequent immonium or enamine intermediates 9, would then result in formation of the C-20 epimeric ibophyllidines (1, 2). While our attempts at a biomimetic oxidative fragmentation of ring D of the pandolines by a variety of oxidative and hydrolytic conditions have not yet led to a satisfactory generation of the amino ketone 8, this key intermediate could be synthesized and biomimetically converted to ibophyllidine (1).

A first synthesis directed at the ibophyllidines (1, 2) was based on the strategy of our other vincadifformine class alkaloid syntheses (Scheme II).[4-7] Thus the indoloazepine ester 10 was condensed with 4-bromo- or 4-chlorohexanal at room temperature. (The halo aldehydes required for these transformations were readily obtained from 4-ethylbutyrolactone on reaction with HCl or HBr and esterification, followed by reduction of the halo esters with diisobutylaluminum hydride). Chromatographic separation of the chloro aldehyde derived condensation products 11 showed a mixture of bridged azepines, with the predominant epimers having the proximate acrylate and alkylhalide chain.[7] The epimeric products had UV and IR absorptions characteristic of analogous vinylogous urethanes and gave the expected mass spectroscopic parent ions.[7]

When warmed at 60 °C in tetrahydrofuran for 96 h, the mixture of epimeric condensation products 11 slowly generated a quaternary salt, 12, in 84% yield. This product was converted to 20-epiibophyllidine (2) in 98% yield on heating with triethylamine in methanol. No ibophyllidine (1) was detected by high-pressure liquid chromatography of the reaction product.

The complete stereospecificity obtained in this rearrangement of the bridged indoloazepine 12 to 20-epiibophyllidine (2) can be ascribed to selective addition of the indoloacrylate unit of a norsecodine, 13, to the relatively planar pyrrolideine ring on the side which is not shielded by the ethyl substituent. This reaction course may be contrasted with the formation of a 5:1 mixture, *with pre-*

(3) C. Kan, H.-P. Husson, S.-K. Kan, and M. Lounasmaa, *Tetrahedron Lett.*, 3363 (1980). This corresponds to scheme presented by M.E.K. at University of Reims, Nov 1979.

(4) M. E. Kuehne, D. M. Roland, and R. Hafter, *J. Org. Chem.*, **43**, 3705 (1978).

(5) M. E. Kuehne, T. H. Matsko, J. C. Bohnert, and C. L. Kirkemo, *J. Org. Chem.*, **44**, 1063 (1979).

(6) M. E. Kuehne, C. L. Kirkemo, T. H. Matsko, and J. C. Bohnert, *J. Org. Chem.*, **45**, 3259 (1980).

(7) M. E. Kuehne, T. H. Matsko, J. C. Bohnert, L. Motyka, and D. Oliver-Smith, *J. Org. Chem.*, **46**, 2002 (1981).

dominant opposite relative stereochemistry of the ethyl group and the C/D ring juncture protons, formed in the homologous reaction leading to Ψ-vincadifformine (**3**) and 20-epi-Ψ-vincadifformine (**4**).[6] In contrast to the present reaction, the higher homologue reaction is governed by a stereoelectronically controlled addition of the indoloacrylate to a nonplanar piperideine with a predominantly Ψ-equatorial ethyl substituent, thus leading to preferential introduction of the indoloacrylate cis to the ethyl substituent and to predominant formation of Ψ-vincadifformine (**3**).

A comparison of synthetic 20-epiibophyllidine (**2**) with natural ibophyllidine (**1**)[8] showed a small difference in high-pressure liquid chromatography retention times, while spectroscopic data indicated a close structural relationship. In order to reach a correlation between these two compounds, 20-epiibophyllidine (**2**) was converted to its *N*-oxide and the latter then treated with trifluoroacetic anhydride. The resulting mixture of Polonovsky–Potier reaction[9] products gave, on hydrogenation, predominantly 20-epiibophyllidine (**2**) and yielded little ibophyllidine (**1**). Thus little of the desired *O*-acyl *N*-oxide elimination with formation of the immonium/enamine products **9** had taken place.

In an alternative approach to these alkaloids, a stereospecific synthesis of ibophyllidine (**1**) could be derived from our most recently developed synthetic strategy for *D*-secoaspidosperma alkaloids.[7] This reaction pathway (Scheme III) provided a direct route to the biogenetic amino ketone intermediate **8**.

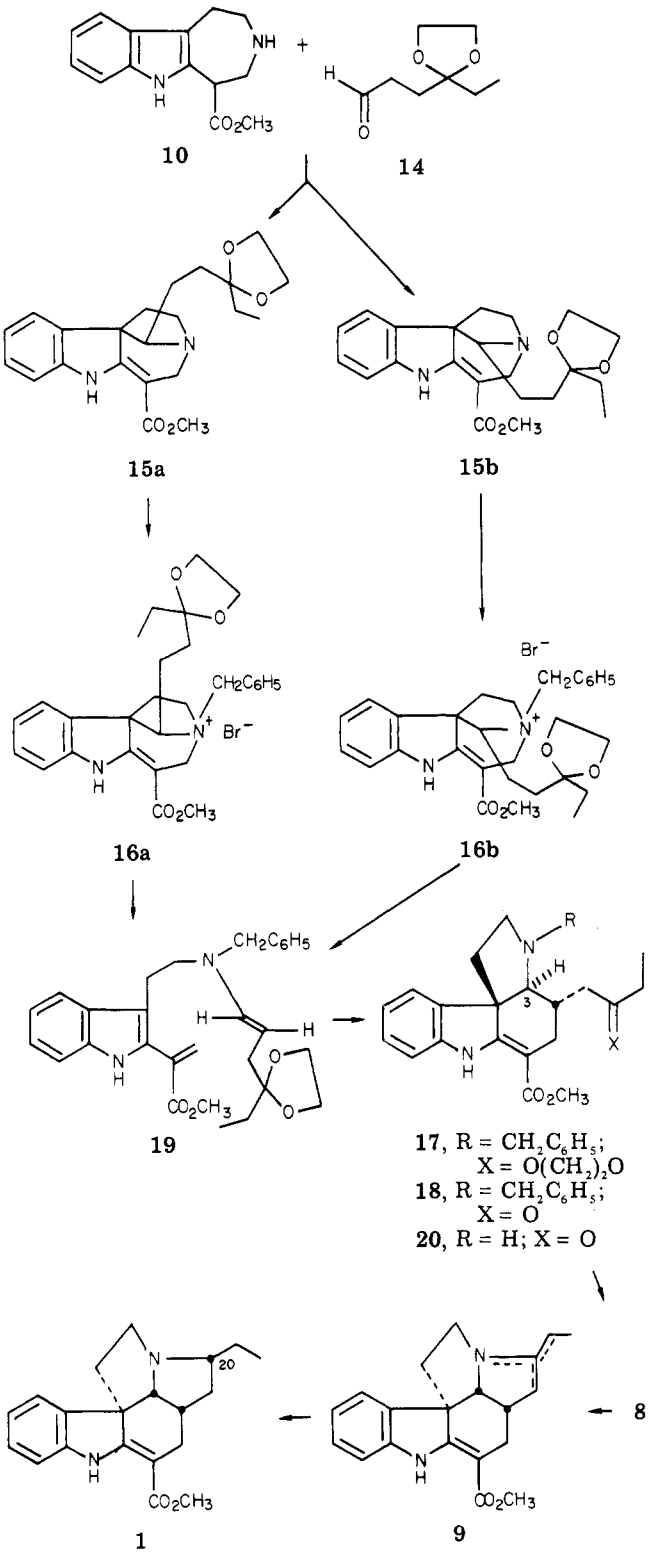
Condensation of the indoloazepine **10** with the ethylene ketal of 4-oxohexanal (**14**; obtained from the corresponding ketal ester by reduction with diisobutylaluminum hydride) gave the bridged azepines **15a,b**, in a 2:3 ratio in 97% yield after 2 h at 20 °C in methanol. Alkylation of each epimer with benzyl bromide provided the respective quaternary salts **16a,b**. The less hindered amine **15b** (lower R_f) reacted more rapidly at lower temperature with benzyl bromide in accord with other analogous quaternizations.[7] For full characterization of the bridged azepines, the ketal function was hydrolyzed to furnish crystalline ketones corresponding to **15a,b** and **16a,b**.

On reaction with triethylamine in methanol, the quaternary salts **16a,b** rearranged to a single amino ketal **17** in 85% and 82% yields, respectively. Hydrolysis of this product provided the corresponding amino ketone **18**.

Transformation of the quaternary salts **16a,b** to the rearranged skeleton **17** is based on the intermediacy of an open-chain secodine analogue, **19**. We have previously found that such intermediates are generated as *E* enamines, with consequent stereospecific formation of ring C trans-substituted tetracyclic products.[7] This result could again be seen in the amino ketone **18**, which showed the NMR characteristics of a C-3 proton of such products.[7]

Hydrogenolysis of the *N*-benzyl substituent of the amino ketone **18** and epimerization and cyclization in acetic acid, followed by hydrogenation, gave ibophyllidine (**1**) in one operation in 79% yield. The observed epimerization at C-3 is obtained by protonation of the aminoacrylate function of the trans-substituted ring C intermediate **20**. Consequently, reversible opening of ring C to an indolic immonium salt leads to a cis-substituted ring C in **8**, which is required for a facile cyclization. The cyclization in turn siphons epimerization in the direction of the natural C/D ring juncture stereochemistry of ibophyllidine (**1**). Catalytic hydrogenation of the cyclization product **9** from the less hindered side of ring D finally accounts for the correct generation of the C-20 stereochemistry found in ibophyllidine (**1**).

Scheme III



The two synthetic sequences presented here demonstrate the option of stereoselection of products based on a complete stereospecificity inherent in reactions of norsecodine **13** or acyclic secodine **19** intermediates and their transformation products. The operational simplicity and efficiency of these syntheses also show how their underlying strategy can be used as a practical tool for rapid

(8) We thank Professor R. Goutarel and Dr. J. Hannart for providing natural ibophyllidine for comparison.

(9) A. Ahond, A. Cavé, C. Kan-Fan, H.-P. Husson, J. de Rostolan, and P. Potier, *J. Am. Chem. Soc.*, **90**, 5622 (1968).

structure confirmations of new variations of this large class of alkaloids.

Experimental Section

NMR data obtained with 100-MHz JEOL instruments unless specified as obtained with 250-MHz Bruker instrument.

4-Chloro- and 4-Bromohexanal.[10] A solution of 20 g of γ-ethylbutyrolactone in 200 mL of methanol at 0 °C was saturated with HCl gas and sealed in a Parr bottle. After 4 days at 35 °C the pressure was released, the solvent was removed under vacuum, and the residue was poured into 150 mL of water and 150 mL of dichloromethane. Neutralization with sodium bicarbonate, extraction with dichloromethane, concentration, and distillation at 84 °C (20 mm) gave 14 g (48%) of methyl 4-chlorohexanoate: IR (neat) ν_{max} 1740 cm^{-1}; NMR ($CDCl_3$) δ 3.86 (1 H, m), 3.62 (3 H, s), 2.50 (2 H, t), 2.20–1.64 (4 H, m), 1.02 (3 H, t).

The corresponding bromo ester was prepared by passing HBr gas through 33 g of the lactone held at 70 ± 5 °C for 3 h. The resulting bromo acid was then poured into 450 mL of methanol, and HBr gas was passed into the solution for 15 min. After being heated at reflux for 2 h, the solution was cooled and concentrated under vacuum, and the workup was continued as described above to give 42 g (70%) of methyl 4-bromobutyrate: bp 36–40 °C (0.05 mm); IR 1735 cm^{-1}; NMR ($CDCl_3$) δ 4.00–3.70 (1 H, m), 3.66 (3 H, s), 2.50 (2 H, t), 2.10–1.50 (4 H, m), 1.00 (3 H, t). The product was contaminated by about 7% of starting lactone and 1.5% of methyl 4-methoxyhexanoate as seen in the IR and NMR spectra.

Over 15 min was added 125 mL (0.12 mol) of 1 M diisobutylaluminum hydride in hexane to 17.9 g (0.11 mol) of methyl 4-chlorohexanoate in 100 mL of dichloromethane at −78 °C. After being stirred for 1 h at −78 °C, the mixture was poured onto 125 g of crushed ice and 25 mL of concentrated HCl. The mixture was stirred until it reached 18 °C, and the organic phase was separated, dried over magnesium sulfate, concentrated under vacuum, and distilled at 64–80 °C (13 mm) to give 8.62 g (59%) of aldehyde of 95% purity, as judged by the NMR aldehyde proton signal: IR (neat) ν_{max} 2970, 2840, 2730, 1725 cm^{-1}; NMR ($CDCl_3$) δ 9.84 (1 H, s), 4.00–3.72 (1 H, m), 2.72 (2 H, t), 2.18–1.78 (4 H, m), 1.04 (3 H, t).

Methyl 4-bromohexanoate was reduced by the procedure given for the chloro analogue, thus furnishing the bromo aldehyde: bp 34–35 °C (0.05 mm); 60% yield; IR (neat) ν_{max} 1725 cm^{-1}; NMR ($CDCl_3$) δ 9.70 (1 H, s), 4.00–3.80 (1 H, m), 2.60 (2 H, t), 2.10–1.60 (4 H, m), 0.96 (3 H, t). A 2,4-dinitrophenylhydrazone derivative, recrystallized from ethanol, had a melting point of 85–87 °C. Anal. Calcd for $C_{12}H_{15}N_4O_4Br$: C, 40.13; H, 4.20; N, 15.59. Found: C, 40.29; H, 4.44; N, 15.41.

20-Epiibophyllidine (2). A solution of 0.50 g (2.0 mmol) of the indoloazepine **10** and 0.33 g (2.5 mmol) of 4-chlorohexanal in 50 mL of tetrahydrofuran was stirred under nitrogen at 20 °C. After 14 h the indoloazepine had been consumed completely, and the bridged azepines **11** had formed, as seen by TLC [silica, ethyl acetate/ethanol (4:1), blue stain with 10% cerric ammonium sulfate in 85% phosphoric acid (CAS)] R_f 0.85 and 0.57. Concentration of the reaction mixture under reduced pressure and chromatography of the residue on silica, eluting with hexane, 1:1 ethyl acetate–hexane, and ethyl acetate, gave 0.22 g (30%) of the higher R_f isomers and 0.41 g (57%) of the lower R_f isomers of **11**; the latter were contaminated by some epiibophyllidine (**2**). The two sets of isomers showed identical UV and IR spectra and molecular ions: UV λ_{max} (ethanol) 227, 298, 327 nm; IR (KBr) ν_{max} 1680, 1610 cm^{-1}; mass spectrum (molecular ions), *m/e* 360, 362 (3:1); NMR ($CDCl_3$) for lower R_f isomers δ 9.00 (1 H, br s), 7.63–6.80 (4 H, m), 4.20–3.70 (2 H, m), 3.80 (3 H, s), 3.50–3.20 (3 H, m), 3.10–2.70 (1 H, m), 2.40–2.10 (2 H, m), 1.90–1.20 (6 H, m), 0.96 (3 H, t); NMR ($CDCl_3$) for higher R_f isomers δ 9.16 (1 H, br s), 7.50–6.90 (4 H, m), 4.30–3.80 (2 H, m), 3.80 (3 H, s), 3.60–3.24 (3 H, m), 3.08–2.70 (1 H, m), 2.40–2.10 (2 H, m), 2.04–1.60 (6 H, m), 1.04 (3 H, t). The isomers with higher R_f gave an intramolecular quaternization product on standing in $CDCl_3$.

In an alternative experiment the initial tetrahydrofuran solution of condensation products **11** was heated at 60 °C for 96 h, cooled, and filtered to give 0.62 (84%) of quaternary salts **12**: UV (ethanol) λ_{max} 227, 295, 326 nm. A tetraphenylborate salt, recrystallized from acetone, had a melting point of 187–189 °C dec. Anal. Calcd for $C_{44}H_{45}BN_2O_4$: C, 81.98; H, 7.03; N, 4.13. Found: C, 81.94; H, 7.04; N, 4.13.

A solution of 0.26 g (0.63 mmol) of the quaternary chlorides **12** and 0.3 mL (2 mmol) of triethyl amine in 20 mL of methanol, heated at reflux for 24 h, showed only one product with R_f 0.35 by TLC (silica, ethyl acetate–ethanol (4:1), blue stain with CAS). Concentration and chromatography of the residue on silica, eluting with ethyl acetate–ethanol (9:1), gave 0.23 g (98%) of epiibophyllidine (**2**), recrystallized from methanol to a melting point of 142–143 °C: UV (ethanol) λ_{max} 224 nm (log ε 4.06), 298 (4.14), 328 (4.2); IR (KBr) ν_{max} 3360, 2930, 2860, 2800, 1675, 1610, 1465, 1435, 1380, 1300, 1275, 1250, 1200 cm^{-1}; 250-MHz NMR ($CDCl_3$) δ 9.08 (1 H, br s), 7.40–6.82 (4 H, m), 3.89 (1 H, d), 3.76 (3 H, s), 3.37 (1 H, dt), 2.97 (1 H, dd), 2.77 (2 H, dd), 2.11–1.86 (4 H, m), 1.78–1.60 (3 H, m), 1.50–1.39 (1 H, m), 0.95 (3 H, t); mass spectrum (80 eV), *m/e* (relative intensity) 325 (60), 324 (100), 295 (48) 293 (29), 180 (31), 167 (39), 132 (30), 131.5 (62), 111 (56), 110 (90). Anal. Calcd for $C_{20}H_{24}N_2O_2$: C, 74.02; H, 7.46; N, 8.64. Found: C, 73.89; H, 7.39; H, 8.45. The overall yield of 20-epiibophyllidine was only 45% when the bromo aldehyde was used, and intermediates were not isolated.

4-Oxohexanal Ethylene Ketal (14). Acetone was distilled from a mixture of 14 g (0.14 mol) of 1,1-dimethyl dioxalane, 10 g (0.069 mol) of methyl 4-oxohexanoate,[11] and 200 mg of *p*-toluenesulfonic acid held at 140 °C. Distillation of the residue gave 1.8 g of recovered ketone and 9.8 g (75%) of ketal ester: bp 42 °C (0.02 mm); NMR (CDCl) δ 4.00 (4 H, s), 3.74 (3 H, s), 2.42 (2 H, t), 1.98 (2 H, t), 1.64 (2 H, q), 0.92 (3 H, t); IR (neat) ν_{max} 2980, 2950, 1740 cm^{-1}.

Addition of 44 mL of 1 M diisobutylaluminmum hydride in hexane (44 mmol) to 7.0 g (37 mmol) of the ketal ester in 20 mL of dichloromethane, at −78 °C, was followed by rapid stirring for 1 h at −78 °C. The mixture was then poured into 500 mL of ether and 5 mL of water, stirred at 20 °C for 30 min, and filtered. The residual salts were washed with 100 mL of ether, the combined ether solutions were dried over magnesium sulfate and concentrated, and the residue was distilled at 28–30 °C (0.02 mm), giving 4.21 (64%) of ketal aldehyde **14** of 90% purity (based on NMR aldehyde proton signal): NMR ($CDCl_3$) δ 9.72 (1 H, s), 3.94 (4 H, s), 2.44 (2 H, t), 2.02 (2 H, t), 1.64 (2 H, q), 0.90 (3 H, t); IR (neat) ν_{max} 2980, 2880, 2740, 1725 cm^{-1}.

Ibophyllidine (1). A solution of 1.85 g (7.58 mmol) of the indoloazepine **10** and 1.50 g (9.50 mmol) of the ketal aldehyde **14** in 50 mL of methanol was stirred under nitrogen for 2 h at 20 °C. TLC then showed formation of two products **15a,b** with R_f 0.67 and 0.37 (silica, ethyl acetate–ethanol (4:1), blue stain with CAS). The mixture was concentrated under vacuum, and the residue was chromatographed on neutral alumina (activity II–III), eluting with ethyl acetate–hexane (1:9) for collection of 1.11 g (38%) of the bridged azepine **15a** and with ethyl acetate for collection of 1.73 g (60%) of its epimer **15b**. The two products were contaminated by some corresponding ketonic products. For characterization, these ketones were prepared by hydrolysis of the ketals. A parallel reaction mixture was stirred with 10 mL of 10% aqueous HCl for 2 h, diluted with water, and extracted with dichloromethane. Column chromatography, as described for the ketal mixture, provided 0.26 g (10%) of the more rapidly eluted ketone epimer corresponding to **15a** and 1.85 g (72%) of the less rapidly eluted ketone epimer corresponding to **15b**. Hydrolyses of the separated ketals **15a** or **15b** (above) resulted in epimerization and formation of mixtures of the two ketones. The major ketone (corresponding to **15b**) was recrystallized from ether–hexane: mp 109–111 °C; UV (ethanol) λ_{max} 2.44 nm (log ε 4.02), 301 (4.13), 3.28 (4.19); IR (KBr) ν_{max} 3330, 2950, 2850, 1720, 1680, 1615, 1485, 1470, 1440, 1415, 1405, 1385, 1370, 1320, 1295, 1240, 1190 cm^{-1}; 250-MHz NMR ($CDCl_3$) δ 8.80 (1 H, br s), 7.12–6.81 (4 H, m), 3.81 (1 H, d), 3.72 (3 H, s), 3.46–3.27 (3 H, m), 3.34 (1 H, d), 2.98–2.86 (1 H, m), 2.59–2.45 (2 H, m), 2.40–2.15

(10) M. Ota, K. Fujiwara, and N. Takahashi, Japanese Patent 4060 (1963); *Chem Abstr.* **59**, 11265 (1963).

(11) Prepared according to the method for the corresponding ethyl ester: P. A. Wehili and V. Chu, *Org. Synth.*, **58**, 79, (1978); J. Cason and F. S. Prout, "Organic Syntheses", Collect. Vol. III, Wiley, New York, 1955, p 601.

(2 H, m), 2.33 (2 H, q), 1.60–1.49 (1 H, m), 0.89 (3 H, t); mass spectrum (80 eV), *m/e* (relative intensity) 341 (83), 340 (100), 283 (86), 215 (71), 214 (95), 154 (76). Anal. Calcd for $C_{20}H_{24}N_2O_3$: C, 70.56; H, 7.11; N, 8.23. Found: C, 70.35; H, 7.37; N, 8.05.

Quaternization of 1.62 g (4.23 mmol) of the amino ketal **15b** with 0.870 g (5.10 mmol) of benzyl bromide, stirred in 50 mL of toluene at 20 °C for 15 h followed by 12 h at 50 °C, provided 1.80 g (77%) of the quaternary bromide **16b**. For quaternization of 0.850 g (2.2 mmol) of the less reactive amino ketal **15a** heating for 48 h at 60 °C was required, giving 0.650 g (53%) of the quaternary bromide **16a**.

The ketones corresponding to **15a,b** were quaternized analogously and the products converted to their tetraphenylboron salts for characterization: For the ketone corresponding to **16a**: mp 172–175 °C dec (recrystallized from acetone–methanol); 250 MHz NMR (acetone-d_6) δ 9.83 (1 H, br s), 7.80–6.74 (29 H, m), 5.09 (1 H, d), 4.83 (1 H, d), 4.83 (1 H, d), 4.69 (1 H, dd), 4.43 (1 H, dt), 4.07 (1 H, d), 3.78–3.68 (1 H, m), 3.71 (3 H, t), 2.74–2.54 (2 H, m), 2.48–2.37 (3 H, m), 2.19 (2 H, q), 1.97–1.82 (1 H, m), 0.86 (3 H, t). For the ketone corresponding to **16b**: mp 190–192 °C (recrystallized from acetone–methanol); 250 MHz NMR (acetone-d_6) δ 9.83 (1 H, s), 7.78–6.75 (29 H, m), 5.04 (1 H, d), 4.75 (1 H, d), 4.60 (1 H, d), 4.54 (1 H, dd), 4.42–4.26 (1 H, m), 4.04 (1 H, d), 3.70 (3 H, s), 3.72–3.61 (1 H, m), 2.66–2.51 (2 H, m), 2.48–2.36 (3 H, m), 2.16 (2 H, dq), 1.93–1.80 (1 H, m), 0.86 (3 H, t); UV (ethanol) λ_{max} 226, 298, 328 nm. Anal. Calcd for $C_{51}H_{51}N_2O_3B$: C, 81.58; H, 6.79; N, 3.73. Found: C, 81.82; H, 7.08; N, 3.74.

A solution of 1.60 g (2.88 mmol) of the bromide **16b** and 0.50 mL (3.6 mmol) of triethylamine in 40 mL of methanol was heated at reflux for 2 h. TLC (silica; ether–hexane, 1:1) then showed only one compound (**17**) with R_f 0.44 (CAS, blue). The cooled reaction mixture was concentrated under vacuum, and the residue was partitioned between 50 mL of dichloromethane and 50 mL of water which was made basic with dilute NaOH. Concentration of the organic extract and chromatography on basic alumina (activity II–III), eluting with ether–hexane (1:1), gave 1.13 g (82%) of the amino ketal **17**. An analogous reaction of 0.140 g of the epimeric bromide **16a** produced 0.101 g (85%) of the same product **17**.

Hydrolysis of the ketal function was achieved by stirring 0.340 g (0.70 mmol) of the amino ketal **17** in 10 mL of methanol and 5 mL of 10% aqueous HCl for 2 h at 20 °C. Addition of 50 mL of water, basification with dilute NaOH, extraction with dichloromethane, concentration of the extract, and chromatography on basic alumina (activity II–III), eluting with ether–hexane (1:1), gave 0.270 g (87%) of the amino ketone **18**: mp 110–111 °C (after recrystallization from methanol); UV (ethanol) λ_{max} 216 nm (log ϵ 4.08), 2.27 (4.02), 299 (4.02), 329 (4.16); IR (KBr) ν_{max} 3390, 2930, 2810, 1710, 1680, 1610, 1485, 1470, 1440, 1305, 1280, 1255 cm^{-1}; 250-MHz NMR ($CDCl_3$) δ 8.99 (1 H, br s), 7.42–6.78 (9 H, m), 4.37 (1 H, d, J = 13.7 Hz), 3.77 (3 H, s), 3.75 (1 H, d, J = 13.7 Hz), 2.94 (1 H, s, for C-3 proton), 2.89 (1 H, dd), 2.67–2.57 (4 H, m), 2.40–1.90 (5 H, m), 1.65 (1 H, dd), 0.93 (3 H, t); mass spectrum (80 eV), *m/e* (relative intensity) 431 (39), 430 (100), 374 (50), 373 (98), 298 (42), 297 (92), 228 (52), 217 (38), 216 (83), 91 (71). Anal. Calcd for $C_{27}H_{30}N_2O_3$: C, 75.32; H, 7.02; N, 6.51. Found: C, 75.24; H, 7.19; N, 6.67.

A mixture of 1.60 g of the amino ketone **18** and 0.40 g of 10% Pd/C catalyst in 20 mL of acetic acid was stirred for 4 days under hydrogen at atmospheric pressure. The reaction mixture was filtered, the catalyst was washed with 50 mL of hot methanol, and the filtrates were concentrated under vacuum. Partitioning of the residue between dichloromethane and dilute NaOH, concentration of the organic extract, and chromatography of the residue on basic alumina (activity II–III), eluting with ether–hexane (1:1), provided 0.95 g (79%) of ibophyllidine (**1**): mp 106–108 °C (recrystallized from ether–hexane); UV (ethanol) λ_{max} 230 nm (log ϵ 3.18), 300 (3.96), 328 (4.08); IR (KBr) ν_{max} 3400, 2970, 2940, 2870, 1675, 1615, 1470, 1440, 1385, 1290, 1250, 1200, 1180 cm^{-1}; 250-MHz NMR ($CDCl_3$) δ 9.13 (1 H, br s), 7.50–6.80 (4 H, m), 3.76 (3 H, t), 3.49 (1 H, d), 3.18–3.07 (3 H, m), 2.77 (1 H, q), 2.26–1.75 (6 H, m), 1.60–1.51 (1 H, m), 1.35–1.25 (1 H, m), 1.03 (3 H, t); mass spectrum (80 eV), *m/e* (relative intensity) 325 (80), 324 (100), 295 (74), 293 (50), 180 (60), 168 (50), 167 (56), 131.5 (58), 132 (54), 111 (60), 110 (89). Anal. Calcd for $C_{20}H_{24}N_2O_2$: C, 74.02; H, 7.46; N, 8.64. Found: C, 73.76; H, 7.67; N, 8.36.

A hydrochloride salt, recrystallized from methanol, had a melting point of 212 °C dec. Anal. Calcd for $C_{20}H_{25}N_2O_2Cl$: C, 66.56; H, 6.98; N, 7.76: Cl 9.55. Found: C, 66.42; H, 7.05; N, 7.78; Cl, 9.78.

Ibophyllidine (**1**) and 20-epiibophyllidine had the same TLC values (silica, 4:1 ethylacetate–ethanol; CAS, blue), R_f 0.35. Separation was, however, possible by HPLC (μ-Porasil column, 3:1 ethyl acetate–ethanol), where 20-epiibophyllidine showed a slightly greater retention time.

Hydrogenolysis of the *N*-benzylamino ketal **17** in methanol provided a secondary amino ketal which could be hydrolyzed to a secondary amino ketone, **20**: IR (KBr) ν_{max} 3400, 2950, 1710, 1675, 1610, 1465, 1440 cm^{-1}; NMR ($CDCl_3$) δ 9.16 (1 H, br s), 7.40–6.80 (4 H, m), 3.90 (3 H, s), 3.50 (1 H, br s), 3.34 (1 H, d), 3.24 (1 H, d), 2.80–1.80 (10 H, m), 1.02 (3 H, t). The *N*-benzyl ketal **17** and *N*-benzyl ketone **18** did not epimerize on being heated in toluene with *p*-toluenesulfonic acid,[7] but partial epimerization was found under these conditions for the corresponding debenzylation products. While the debenzylated ketone **20** did not undergo cyclization and dehydration, its epimerization product could not be isolated because of spontaneous cyclization with enamine **9** generation, which in turn allowed hydrogenation to ibophyllidine (**1**).

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Registry No. (±)-**1**, 78019-50-8; (±)-**1**·HCl, 78019-51-9; (±)-**2**, 78019-52-0; (±)-**10**, 66859-22-1; **11** (X = Cl), 78019-53-1; **12** (X = Cl^-), 78019-54-2; **12** (X = BPh_4^-), 78019-56-4; **14**, 78019-57-5; (±)-**15a**, 78019-58-6; (±)-**15b**, 78087-05-5; (±)-**16a**, 78019-59-7; (±)-**16b**, 78087-95-3; (±)-**17**, 78019-60-0; (±)-**18**, 78019-61-1; (±)-**20**, 78019-62-2; (±)-4-chlorohexanal, 78019-63-3; (±)-4-bromohexanal, 78019-64-4; (±)-γ-ethylbutyrolactone, 57129-70-1; (±)-methyl 4-chlorohexanoate, 78019-65-5; methyl 4-bromobutyrate, 4897-84-1; (±)-methyl 4-bromohexanoate, 78019-66-6; (±)-4-bromohexenal DNP, 78019-67-7.