(s, 3), 3.80–3.62 (m, 1), 3.37–1.70 (multiplets, 10), 1.10 (t, 3).

11: methyl iodide (1.2 equiv); yield 92% (GLC); ^{1}H NMR ($CDCl_3$) δ 6.89 and 6.81 (AB, 2), 3.84 (s, 3), 3.83 (s, 3), 3.85–3.73 (m, 1), 3.40–1.74 (multiplets, 10), 2.27 (s, 3), 1.11 (t, 3).

12: hexachloroethane (1.1 equiv);[21] yield 93% (GLC); ^{1}H NMR ($CDCl_3$) δ 7.08 and 6.85 (AB, 2), 3.87 (s, 3), 3.86 (s, 3), 3.88–3.75 (m, 1), 3.35–1.83 (multiplets, 10), 1.11 (t, 3).

2,3-[(Diphenylmethylene)dioxy]benzene (13). Catechol (7.15 g, 65 mmol) and dichlorodiphenylmethane (17.10 g, 70 mmol) was heated at 170 °C for 5 min.[22] The reaction mixture was recrystallized from EtOH to give 10.5 g (59%) of **13**, mp 87–89 °C (lit.[23] mp 94–95 °C).

2,3-[(Diphenylmethylene)dioxy]benzoic Acid (14). 2,3-[(Diphenylmethylene)dioxy]benzene (**13**, 10.0 g, 36.5 mmol) in anhydrous THF under N_2 was treated with *n*-butyllithium (27.5 mL of 1.6 M in hexane, 44 mmol) at −5 °C followed by 2 h at room temperature. The reaction mixture was poured into solid carbon dioxide in Et_2O. After reaching room temperature the reaction mixture was partitioned between water and Et_2O. The alkaline aqueous layer was repeatedly extracted with Et_2O while the pH was continuously adjusted with HCl to 8.0–8.5. Drying and evaporation of the solvent gave 8.86 g (76%) of acid **14** (one spot on TLC). An analytical sample was prepared by recrystallization from *i*-Pr_2O/MeOH (6:1): mp 188–189 °C (lit.[24] mp 188–190 °C); IR (KBr) 1680 cm^{-1}. Anal. Calcd for $C_{20}H_{14}O_4$: C, 75.46; H, 4.43; O, 20.10. Found: C, 75.44; H, 4.55; O, 19.88.

(*S*)-2,3-[(Diphenylmethylene)dioxy]-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]benzamide (15) was prepared from the acid **14** in analogy with the amide **5** (method A). Recrystallization of the solid residue from *i*-Pr_2O/MeOH gave the title compound in 66% yield: mp 142–144 °C; ^{1}H NMR ($CDCl_3$) δ 7.64–6.87 (multiplets, 13), 3.90–3.78 (m, 1), 3.40–1.62 (multiplets, 10), 1.02 (t, 3). Anal. Calcd for $C_{27}H_{28}N_2O_3$: C, 75.68; H, 6.59; N, 6.53. Found: C, 75.75; H, 6.73; N, 6.52.

(*S*)-2,3-[(Diphenylmethylene)dioxy]-6-methyl-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]benzamide (16). Preparation from compound **15**, by the procedure used for compound **9**, gave the desired product in 57% yield after recrystallization from *i*-Pr_2O: mp 143–145 °C; ^{1}H NMR ($CDCl_3$, 22 °C) δ 7.80–6.89 (multiplets, 12), 3.86–3.76 (m, 1), 3.34–1.70 (multiplets, 10), 2.23 and 2.24 (2 s, atropisomers, 3), 1.04 and 0.88 (2 t, atropisomers, 3). Anal. Calcd for $C_{28}H_{30}N_2O_3$: C, 75.99; H, 6.83; N, 6.33; O, 10.85. Found: C, 76.03; H, 6.60; N, 6.26; O, 10.81.

2,3-Dimethoxy-*N*-[2-(dimethylamino)ethyl]benzamide (17) was obtained as an oil in 71% yield by preparation from 2,3-dimethoxybenzoic acid and 2-(dimethylamino)ethylamine in analogy with compound **5** (method A): ^{1}H NMR ($CDCl_3$) δ 7.69, 7.15 and 7.03 (ABX, 3), 3.90 (s, 3), 3.89 (s, 3), 3.55 (dt, 2), 2.51 (t, 2), 2.28 (s, 6). An analytical sample of the oxalate hydrate was recrystallized from EtOH/Et_2O, mp 127–128 °C. Anal. Calcd for $C_{13}H_{20}N_2O_3 \cdot C_2H_2O_4 \cdot H_2O$: C, 50.00; H, 6.72; N, 7.77; O, 35.52. Found: C, 50.07; H, 6.84; N, 7.73; O, 35.24.

2,3-Dimethoxy-6-(trimethylsilyl)-*N*-[2-(dimethylamino)-ethyl]benzamide (18) was prepared from compound **17** in analogy with compound **9**: yield 93% (GLC), 71% (isolated); ^{1}H NMR ($CDCl_3$) δ 7.30 and 6.93 (AB, 2), 3.87 (s, 3), 3.84 (s, 3), 3.51 (q, 2), 2.49 (t, 2), 2.23 (s, 6), 0.28 (s, 9). An analytical sample of the HCl salt was prepared, mp 126–128 °C. Anal. Calcd for $C_{16}H_{30}N_2O_4Si \cdot HCl$: C, 50.71; H, 8.25; N, 7.39; Cl, 9.35. Found: C, 50.72; H, 8.03; N, 7.47; Cl, 9.23.

2,3-Dimethoxy-6-(trimethylsilyl)-*N*-methylbenzamide (20) was prepared from 2,3-dimethoxy-*N*-methylbenzamide[25] (**19**) in analogy with compound **9**. An analytical sample of **20** was crystallized from *i*-Pr_2O: mp 151–152 °C; yield 76% of **20** and 9% of the 4-trimethylsilyl isomer (GLC–MS); ^{1}H NMR ($CDCl_3$) δ 7.30 and 6.93 (AB, 2), 3.87 (s, 3), 3.82 (s, 3), 2.99 (d, 3), 0.27 (s, 9). Anal. Calcd for $C_{13}H_{21}NO_3Si$: C, 58.39; H, 7.92; N, 5.24. Found: C, 58.34; H, 7.84; N, 5.29.

(21) Gay, R. L.; Crimmins, T. F.; Hauser, C. R. *Chem. Ind. (London)* **1966**, 1635.
(22) Jurd, L. *J. Am. Chem. Soc.* **1959**, *81*, 4606–4610.
(23) Mason, H. S. *J. Am. Chem. Soc.* **1944**, *66*, 1156–1158.
(24) Bachi, M. D.; Klein, J. *J. Chem. Soc., Perkin Trans. 1* **1983**, *8*, 1925–1928.
(25) Vekemans, J.; Hoornaert, G. *Tetrahedron* **1980**, *36*, 943–950.

Studies in Biomimetic Alkaloid Syntheses. 17. Syntheses of Iboxyphylline and Related Alkaloids

Martin E. Kuehne* and J. Bruce Pitner

Department of Chemistry, University of Vermont, Burlington, Vermont 05405

Received February 8, 1989

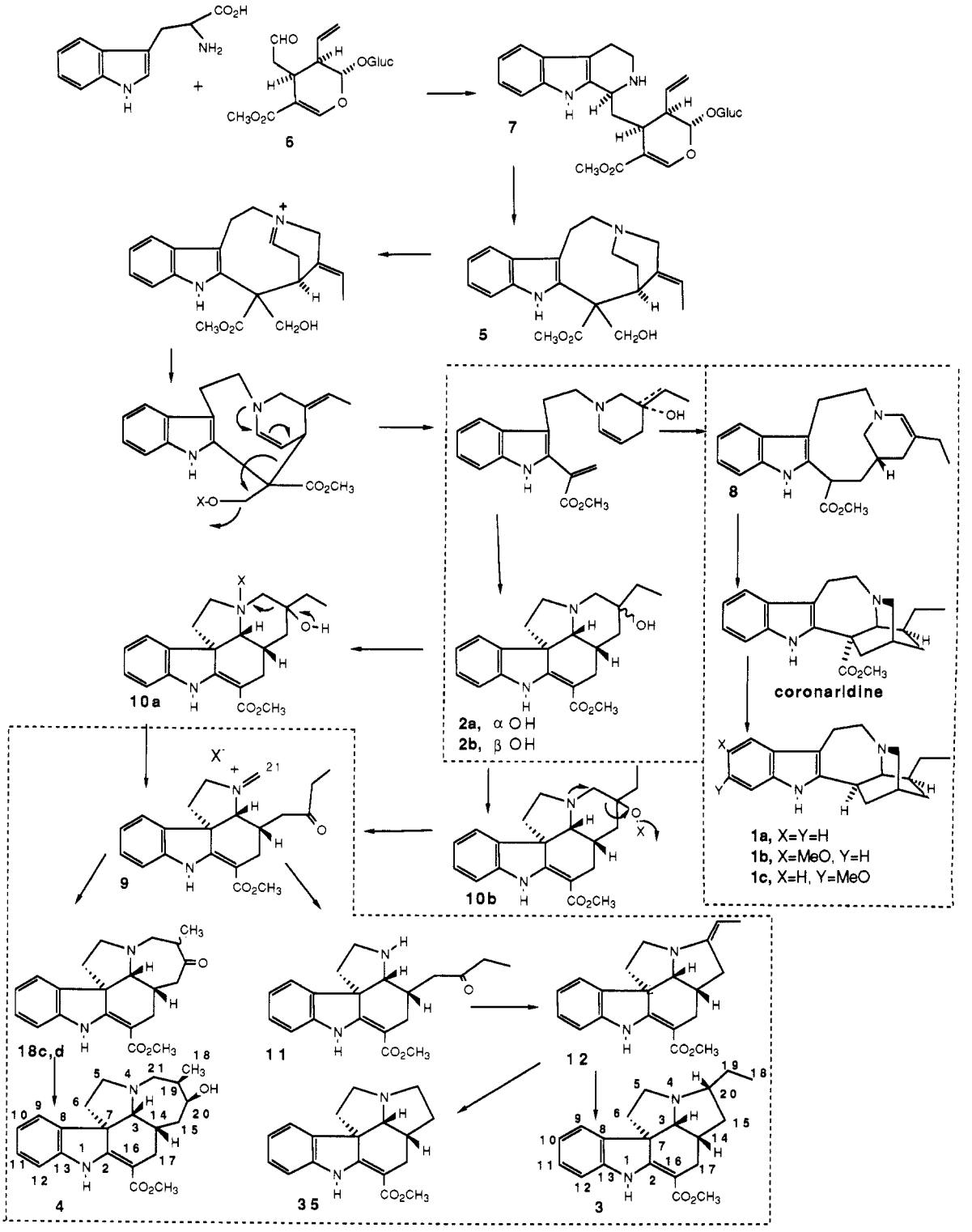
A synthesis of the amino ketal **16** and its condensation with formaldehyde provided, after hydrolysis, a biomimetic formation of the iboxyphylline ketones **18c,d**. The major methyl epimer, **18d**, obtained on equilibration, was reduced to iboxyphylline (**4**). The condensation also provided D/E trans products **18a,b** and the five-membered ring D ketones **19a,b**. For alternative syntheses of the iboxyphylline skeleton, a *D-homo*-secodine intermediate **40a** was generated, leading specifically to the *D/E-cis*-demethyliboxyphylline ketone **50**. Attempts to extend this approach to an iboxyphylline synthesis provided, instead, the spirocyclopentanones **53a–d**. Generation of dehydroibophyllidine (**12**) and its autoxidation gave 20-oxodeethylibophyllidine (**34**). Alternative syntheses of that lactam and its reduction to the alkaloid deethylibophyllidine (**35**) and a synthesis of the corresponding D/E trans epimer **37** are described.

The powdered root of *Tabernanthe iboga* has been used in West Africa, in small doses, as a stimulant to keep hunters alert for days and, in larger doses, as a ceremonial hallucinogen.[1] Its alkaloidal components (Scheme I) include the isoquinuclidines ibogaine (**1b**, with established analogous uses in Western drug culture), ibogamine (**1a**), and tabernanthine (**1c**),[2–5] as well as the ψ-vincadifformine

(1) (a) Pope, H. G. *Econ. Bot.* **1968**, *23*, 174. (b) Dybowski, J.; Landrin, E. *Compt. Rend.* **1901**, *133*, 748. (c) Haller, A.; Heckel, E. H. *Ibid.* **1901**, *133*, 850. (d) Lambert, M.; Heckel, E. *Ibid.* **1901**, *133*, 1236.
(2) Vincent, D.; Sero, J. *Compt. Rend. Soc. Biol.* **1942**, *136*, 612.
(3) (a) Dickel, D. F.; Holden, C. L.; Maxfield, R. C.; Paszek, L. E.; Taylor, W. I. *J. Am. Chem. Soc.* **1958**, *80*, 123. (b) Bartlett, M. F.; Dickel, D. F.; Taylor, W. I. *Ibid.* **1958**, *80*, 126.

0022-3263/89/1954-4553$01.50/0

Scheme I



alkaloid pandoline (**2a**),[6,7] the related 21-nor alkaloid ibophyllidine (**3**),[8,9] and the D-homo alkaloid iboxyphylline (**4**).[8] A biogenetic interrelation of these alkaloids can be derived from a stemmadenine (**5**) type precursor (Scheme I),[10] which arises from tryptophan and *seco*-loganin (**6**)

(4) van Beek, T. A.; van Gessel, M. A. J. T. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley Interscience: New York, 1988; Vol. 6, Chapter 2.

(5) Danieli, B.; Palmisano, G. In *The Alkaloids: Chemistry and Pharmacology*; Brossi, A., Ed.; Academic Press: New York, 1986; Vol. 27, Chapter 1.

(6) (a) Hoizey, M. J.; Debray, M. M.; LeMen-Olivier, W. L.; LeMen, J. *Phytochemistry* **1974**, *13*, 1995. (b) LeMen, J.; Lucacs, G.; LeMen-Olivier, L.; Levy, J.; Hoizey, M. J. *Tetrahedron Lett.* **1974**, 483. (c) Hoizey, J.; Sigault, C.; Jacquier, M. J.; LeMen-Oliver, L.; Levy, J.; LeMen, J. *Ibid.* **1974**, 1601.

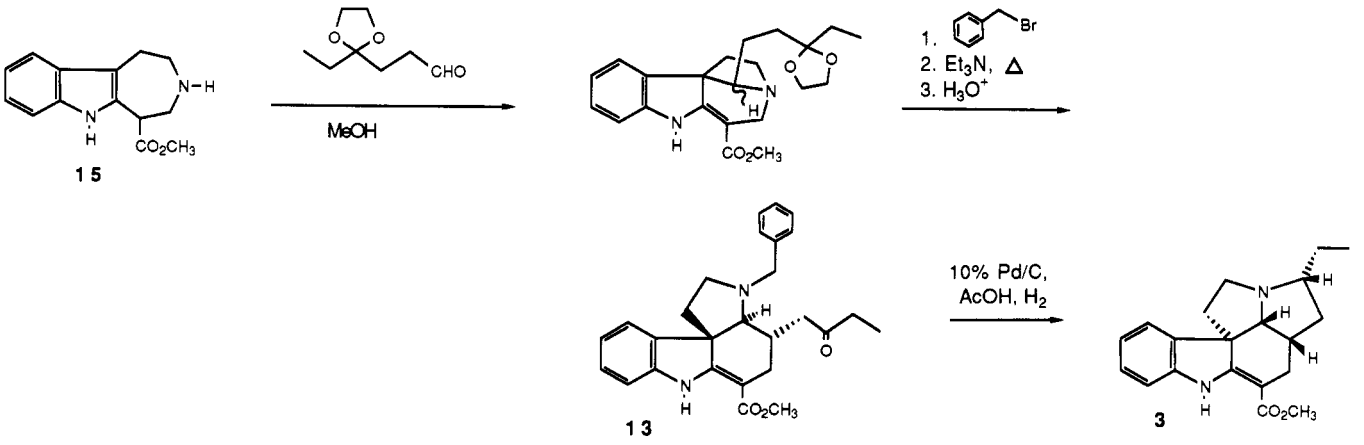
(7) (a) Kuehne, M. E.; Kirkemo, C. L.; Matsko, T. H.; Bohnert, J. C. *J. Org. Chem.* **1980**, *45*, 3259. (b) Kuehne, M. E.; Okuniewicz, F. I.; Kirkemo, C. L.; Bohnert, J. C. *Ibid.* **1982**, *45*, 1335.

(8) Khuong-Huu, F.; Cesario, F.; Guilhem, J.; Goutarel, R. *Tetrahedron* **1976**, *32*, 2539.

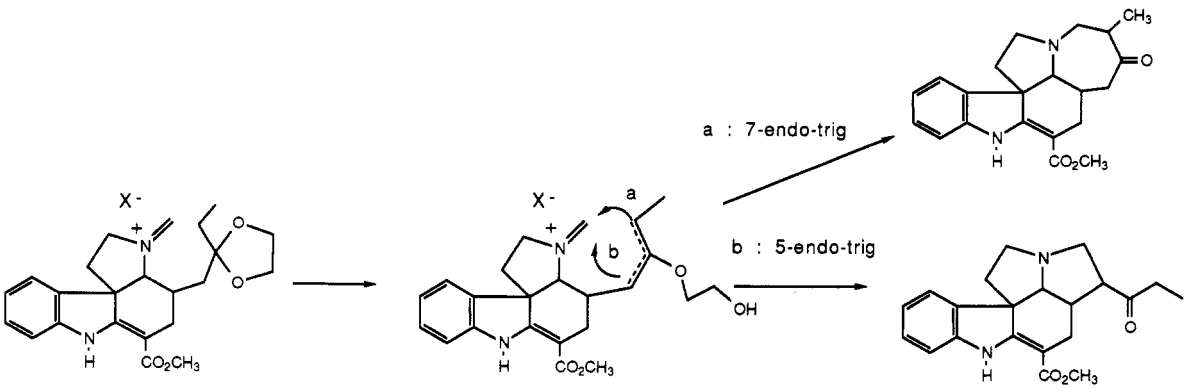
(9) Kuehne, M. E.; Bohnert, J. C. *J. Org. Chem.* **1981**, *46*, 3443.

(10) Stemmadenine has been isolated from the closely related Tabernaemontanae tribe stemadenia Donnell-Smithii (Rose) Woodsön: (a) Walls, F.; Collera, O.; Sandoval, A. *Tetrahedron* **1958**, *2*, 173. (b) Kutney, J. P.; Fuller, G. B. *Heterocycles* **1975**, *3*, 197.

Scheme II



Scheme III



through strictosidine (isovincoside, **7**).[11] Cleavage of pandoline (**2a**) and of 20-*epi*-pandoline (**2b**) by oxidative attack on N^b (i.e. **10a**) or on the hydroxyl group (i.e. **10b**),[8,9] could be envisioned to generate an imonium ketone **9**, which should undergo cyclization to furnish 20-keto precursors **18c,d** of iboxyphylline (**4**) or, alternatively, would by hydrolysis lead to a secondary amino ketone **11**.[12] Its cyclization to an enamine **12** and reduction would provide ibophyllidine (**3**).[8,9]

Indeed, a synthesis of the racemic amino ketone **13** and its in situ debenzylation, epimerization, cyclization, and reduction, leading to ibophyllidine (**3**), could already be reported (Scheme II).[9] The facility of cyclization of the unisolated amino ketone intermediate **11** of this sequence, however, did not make it attractive as a synthetic substrate for generation of the imonium ketone **9**, which is required for an intramolecular Mannich reaction directed at a synthesis of iboxyphylline (**4**). To achieve such a synthetic strategy, we took advantage of the known cyclization reactions of imonium ketals (Scheme III).[13-17] In our case there were, however, two alternative cyclization paths that had to be considered. It was hoped that the biomimetic seven-membered ring formation would compete favorably with formation of a five-membered ring, since the latter would involve a 5-*endo-trig* cyclization.[18] While 5-*endo-trig* cyclizations are obtained in instances where cationic intermediates are stabilized (i.e. through tertiary carbocations,[19] and particularly with imonium functions, i.e. in Pictet–Spengler type cyclizations[20]), it was hoped that their increased energy barrier would compensate for an otherwise slower formation of a seven-membered ring.

Another problematic consideration in our synthetic strategy was the likely need for epimerization of a *D-seco-D/E-trans*-iboxyphylline intermediate to a D/E-cis compound prior to cyclization. Such epimerization had been obtained completely in cyclizations of amino ketones and amino esters, leading, respectively, to five-[9] and six-membered ring cyclization products,[20] but with an amino tosylate as substrate for the latter class, *D/E-trans*-deethylvincadifformine could be obtained.[21] Speculation about the relative rates of epimerization vs cyclizations to

(11) For a general review of biogenetic and biosynthetic routes to such indole and indoline alkaloids, see: Scott, A. I. *Biorg. Chem.* **1974**, *3*, 398.

(12) It may be noted that while a dehydrosecodine has been postulated as precursor of the isoquinuclidine alkaloids, notably of catharanthine (which has an absolute stereochemistry opposite to that of the iboga alkaloids!), such a transformation could only be accomplished experimentally with more highly oxidized substrates: Kuehne, M. E.; Bornmann, W. G.; Earley, W. G.; Marko, I. *J. Org. Chem.* **1986**, *51*, 2913. On the other hand we have found that coronaridine is generated quantitatively and spontaneously from the enamine precursor **8**, as shown in Scheme 1: results obtained with Bornmann, W. G. See also: Kutney, J. P.; Brown, R. T.; Piers, E. *J. Am. Chem. Soc.* **1964**, *86*, 2287. A different route to the amino ketone **11**, consistent with a high-yield autoxidation observed in a number of related Δ^{20}-enamines (results obtained with Bornmann, W. G.) would be an autoxidative cleavage of a Δ^{20}-dehydropandoline to a keto formamide, and its hydrolysis.

(13) (a) Wenkert, E. *Acc. Chem. Res.* **1968**, *1*, 78. (b) Wenkert, E.; Dave, K. G.; Stevens, R. V. *J. Am. Chem. Soc.* **1968**, *90*, 6177.

(14) (a) Bosch, J.; Rubiralta, M.; Moral, M.; Valls, M. *J. Heterocycl. Chem.* **1983**, *20*, 595. (b) Bosch, J.; Rubiralta, M. *Ibid.* **1981**, *18*, 485. (c) Bosch, J.; Rubiralta, M.; Moral, M. *Heterocycles* **1982**, *19*, 473.

(15) Carruthers, W.; Moses, R. C. *J. Chem. Soc., Chem. Commun.* **1987**, 509.

(16) Gnecco Medina, D. H.; Grierson, D. S.; Husson, H.-P. *Tetrahedron Lett.* **1983**, *24*, 2099.

(17) Jacobsen, E. J.; Levin, J.; Overman, L. E. *J. Am. Chem. Soc.* **1988**, *110*, 4329 (and references therein).

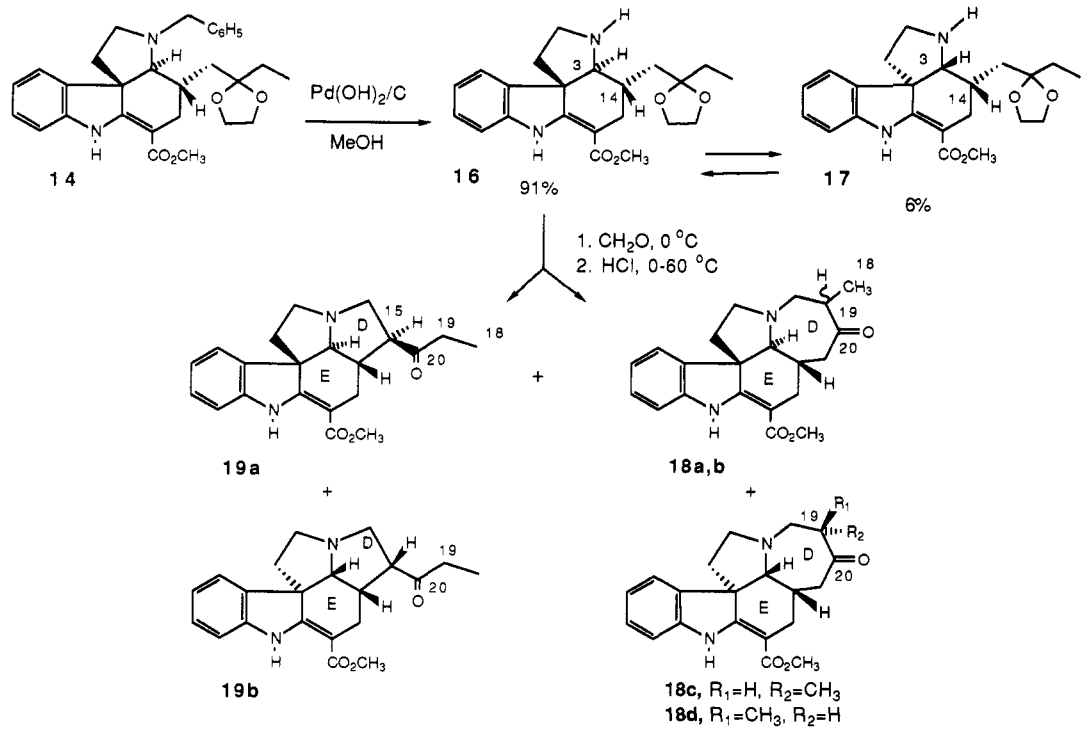
(18) (a) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734. (b) Baldwin, J.; Cutting, J.; Dupont, W.; Kruse, L.; Silberman, L.; Thomas, R. C. *Ibid.* **1976**, 736.

(19) Klein, H.; Mayr, H. *Angew. Chem.* **1982**, *93*, 1069.

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

(21) Kuehne, M. E.; Zebovitz, T. C. *J. Org. Chem.* **1987**, *52*, 4331.

Scheme IV



D/E cis or trans products heightened our anticipation of the reaction results.

Debenzylation of the amino ketal **14** (Scheme IV), obtained by condensation of the indoloazepine **15** with 4-oxohexanal ethylene ketal and alkylation with benzyl bromide (Scheme II),[9] provided the 3,14-trans-substituted secondary amine **16** (91%) and its C14 epimer **17** (6%). Epimerization of the pure trans amine **16** produced a similar mixture on standing in dichloromethane. The two compounds could be readily distinguished by the ^{1}H NMR signal for the C3 proton, which appears as a singlet at δ 3.8 (in the ketal signal envelope in chloroform) or at δ 3.66 (in benzene) for the trans compound **16** and as a doublet ($J_{3,14}$ = 5 Hz) at δ 3.81 (in chloroform) for the cis epimer **17**.[20]

A reaction with gaseous formaldehyde, bubbled into a methanol solution of the amino ketal **16** at 0 °C, resulted in rapid formation of an unstable product (carbinolamine and/or dimeric aminal) which, after addition of ethereal HCl and heating at reflux for 4 h, resulted in a mixture (71% total yield) of nearly equal amounts of seven-membered to five-membered ring ring ketones **18** and **19**. Alternative protocols for these Mannich reactions, using formaldehyde in toluene, formalin, dimethoxymethane in methanol or toluene, all under acidic conditions, or alkylations with dibromo- or diiodomethane in THF or methanol containing base, followed by acid, were not successful.

Four seven-membered ring products **18a–d** (6:3:6:5) and two five-membered ring products **19a,b** (3:1) were obtained and separated by chromatography. The same proportion of products was obtained starting from either the C3/C14 trans or cis substituted amino ketals **16** or **17**, suggesting equilibration prior to cyclization. Equilibration of the products by a reverse Mannich reaction[22] seems less likely, since it could not be achieved with the separated products. That all of these products **18**, **19** had incorporated a new

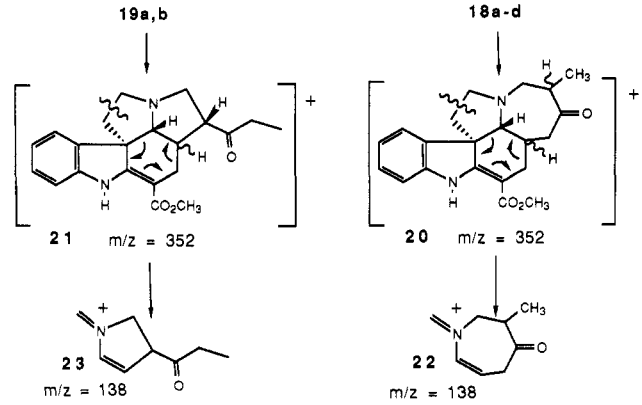


Figure 1.

methylene unit into their D ring, and had therefore been formed by a Mannich reaction, was obvious from their mass spectra. All showed peaks for a molecular ion **20** and **21** at m/z 352 and major D ring fragment peaks **22**, **23** at m/z 138 (Figure 1).

The two five-membered ring D products **19a,b** were easily distinguished from the four seven-membered ring D products **18a–d** by typical ^{1}H NMR signals for the C18–19 ethyl ketone chain, whereas the four seven-membered ring products each showed a C18 methyl doublet. These latter compounds were assigned D/E trans (**18a,b**) vs D/E cis (**18c,d**) structures on the basis of the ^{1}H NMR coupling constant for the hydrogen at C3, which was greater for the trans compounds **18a,b** ($J_{3,14}$ = 9, 10 Hz) than for the cis compounds **18c,d** ($J_{3,14}$ = 5, 6 Hz). The relative stereochemistry of the methyl substituent in the D/E cis series became clear from the reduction of one of these isomers (**18d**) to iboxyphylline (**4**), for which an X-ray crystallographic structure analysis had been obtained.[8] This reduction, when carried out with lithium tri-*sec*-butylborohydride at −78 °C, gave racemic iboxyphylline in 68% yield as the only isolable product (7% overall from the indoloazepine **15**). Equilibration of the D/E cis ketones with sodium methoxide in methanol produced a 1:3

(22) Oppolzer, W.; Hauth, H.; Pfaffli, P.; Wenger, R. *Helv. Chim. Acta* **1977**, *60*, 1801.

Scheme V

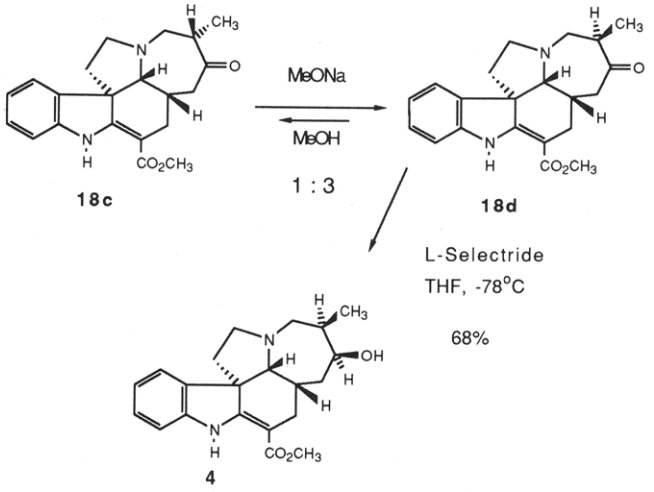


Table I. ^{1}H NMR Values of Cis and Trans D/E Compounds

compd	H-3, ppm	$J_{3,14}$, Hz	solvent	acid
18a	3.26	9	$CDCl_3$	none
18b	3.05	10	$CDCl_3$	none
18c	3.15	5	$CDCl_3$	none
18d	2.86	6	$CDCl_3$	none
4	3.41	5	$CDCl_3$	none
19a	2.95	11	$CDCl_3$	none
19a	2.68	10	C_6D_6	none
19a	4.03	11	$CDCl_3$	CF_3CO_2H
19b	3.79	8	$CDCl_3$	none
19b	4.32	7	$CDCl_3$	CF_3CO_2H
34	4.32	6	$CDCl_3$	none
35[20]	3.77	6	$CDCl_3$	none
35[20]	4.66	7	$CDCl_3$	CF_3CO_2H
3[9]	3.51	8	$CDCl_3$	none
37	2.77	11	$CDCl_3$	none
37	3.43	11	$CDCl_3$	CF_3CO_2H
24[21]	2.87	3	$CDCl_3$	none
25[21]	2.82	10	$CDCl_3$	none
25[21]	3.91	11	$CDCl_3$	CF_3CO_2H

ratio of methyl epimers **18c**:**18d** (Scheme V). Under the same conditions the D/E trans compounds **18a,b** suffered decarbomethoxylation. The relative stereochemistry of the methyl substituent in those compounds could not be established with certainty from the available data.

The two five-membered ring D products **19a,b** could also be assigned D/E trans vs cis structures on the basis of ^{1}H NMR data. However, here it was necessary to isolate the C3 proton signal by incremental additions of trifluoroacetic acid in deuteriochloroform (Figure 2).[23] The coupling constant ($J_{3,14}$ = 11 Hz for the D/E trans compound **19a** vs $J_{3,14}$ = 8 Hz for the D/E cis compound **19b**) was found to vary only very slightly with protonation of these and analogous compounds (see Table I). For comparison, *D/E-trans*-deethylibophyllidine **37** was synthesized (see below, Scheme IX) and contrasted with deethylibophyllidine **35** with established D/E cis stereochemistry.[20] An analogous and, as anticipated, more pronounced difference in the C3 hydrogen coupling constant is found in the *D/E-cis*- and *-trans*-deethylvincadifformines **24** and **25**[21] (Table I).

A common C15 vs C3 and C7 relative stereochemistry is tentatively assigned to the five-membered ring D Mannich products **19** on the basis of a complex ^{1}H NMR multiplet for the C19 methylene group in the D/E cis compound **19b** (hindered rotation of the ketone side chain)

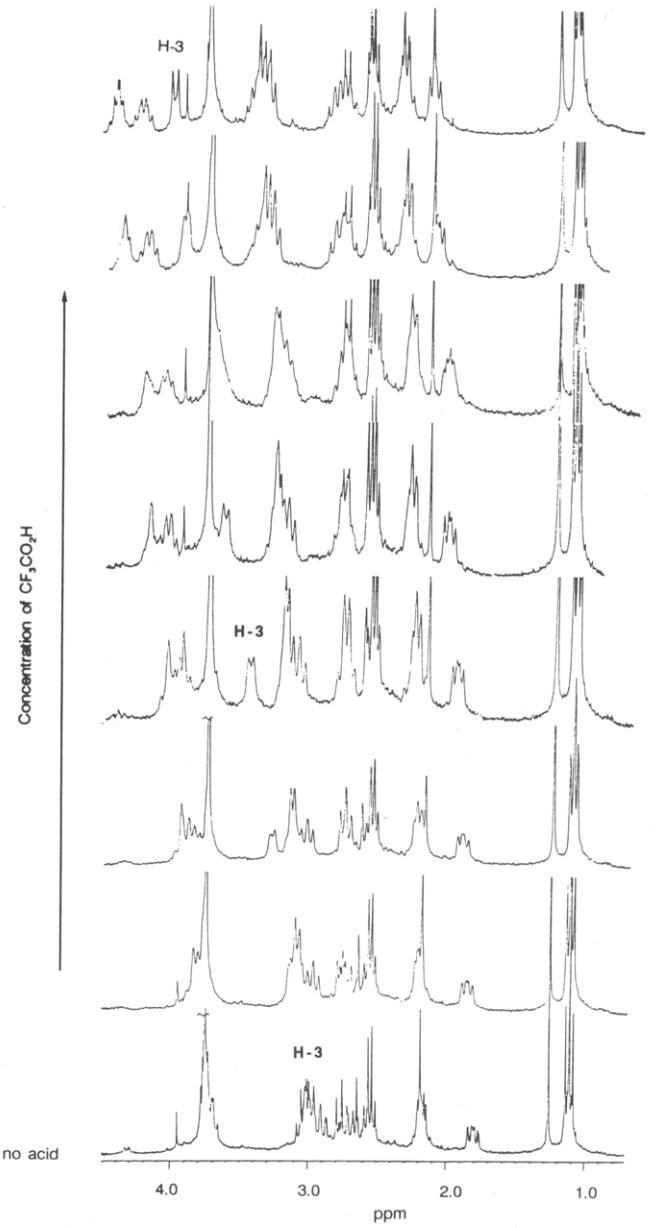


Figure 2. Isolation of H-3 NMR signals of **19a** with increasing acid concentration.

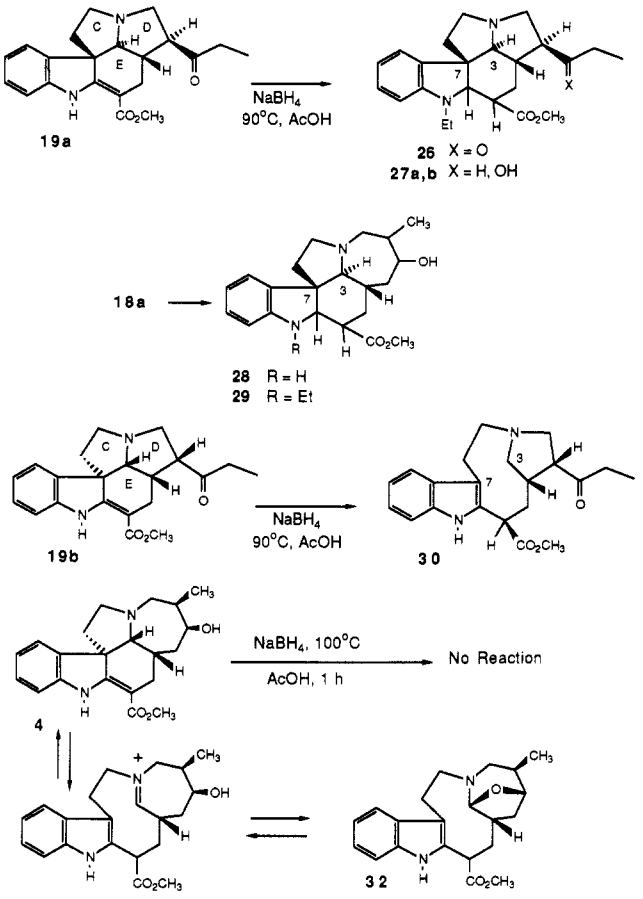
vs a clean quartet found in the D/E trans compound **19a**. (The alternative stereochemical assignments would be inconsistent with this difference in encumbrance of the side chain.) Neither ketone could be epimerized with sodium methoxide in methanol under conditions of equilibration of the methyl ketones **18c,d**.

The D/E trans vs cis compounds **18a,b**, **19a** vs **18c,d**, **19b** could also be distinguished chemically by their reactions with sodium borohydride in hot acetic acid, in analogy to the reactions of the corresponding *D/E-trans*- and *-cis*-deethylvincadifformines.[21] Thus the D/E trans compounds underwent reduction of the vinylogous urethane function and N^a-ethylation, to produce the indolines **26**, **27a,b**, **28**, **29** (Scheme VI). The five-membered D/E cis compound **19b**, on the other hand, gave instead an indoloazonine **30**, arising from more favorable trans-periplanar orientation of the C3–C7 bond with the nitrogen lone pair,[24] and its consequent rupture with formation of an imonium intermediate **31**, which was reduced (Scheme

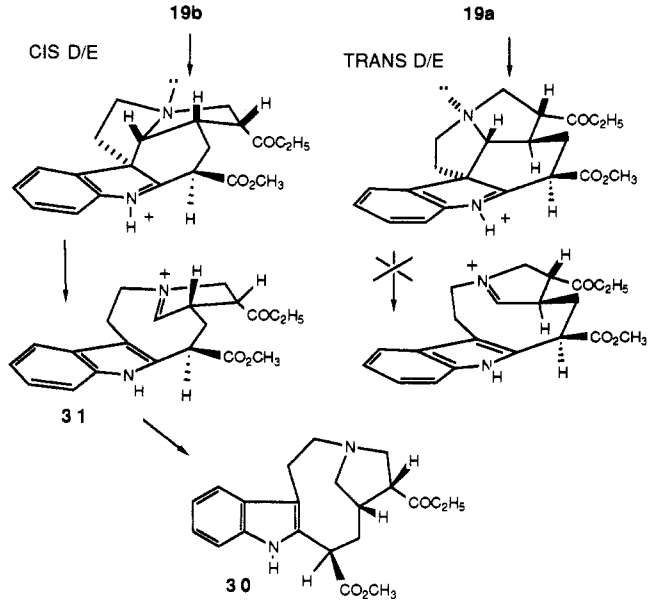
(23) (a) Schripsema, J.; Verpoorte, R.; Baerheim Svendsen, A. *Tetrahedron Lett.* **1986**, *22*, 2523. (b) Verpoorte, R. *J. Nat. Prod.* **1986**, *49*, 1.

(24) Kuehne, M. E.; Bornmann, W. G. *J. Org. Chem.* **1989**, *54*, 3407.

Scheme VI

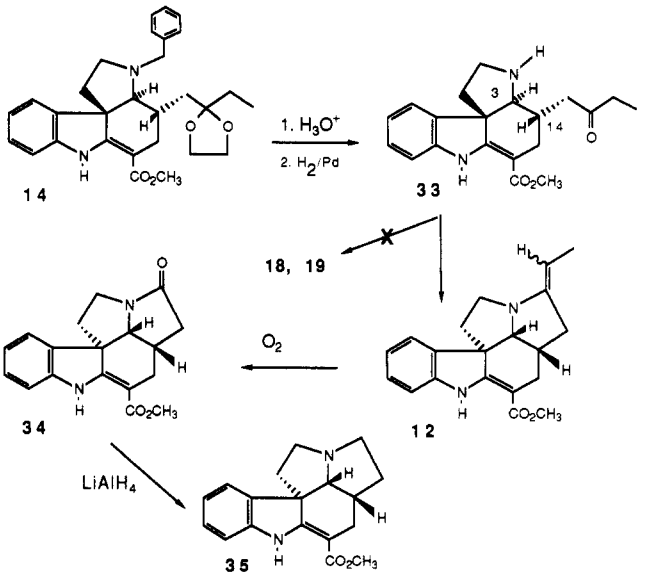


Scheme VII



VII). Remarkably, the seven-membered D/E cis isomer **18d** did not follow either of these reaction courses and gave instead iboxyphylline (**4**) as the only reduction product, obtained even under much more vigorous conditions (20 equiv of sodium borohydride in acetic acid at 100 °C, added over 1 h vs 7 min for reduction of the D/E trans compound **18a**, or the D/E trans or cis compounds **19a,b**). The failure of iboxyphylline (**4**) to undergo reduction may be due to intramolecular trapping of an imonium function, with reversible formation of the cyclic carbinolamine ether **32** (Scheme VI).[25-27]

Scheme VIII

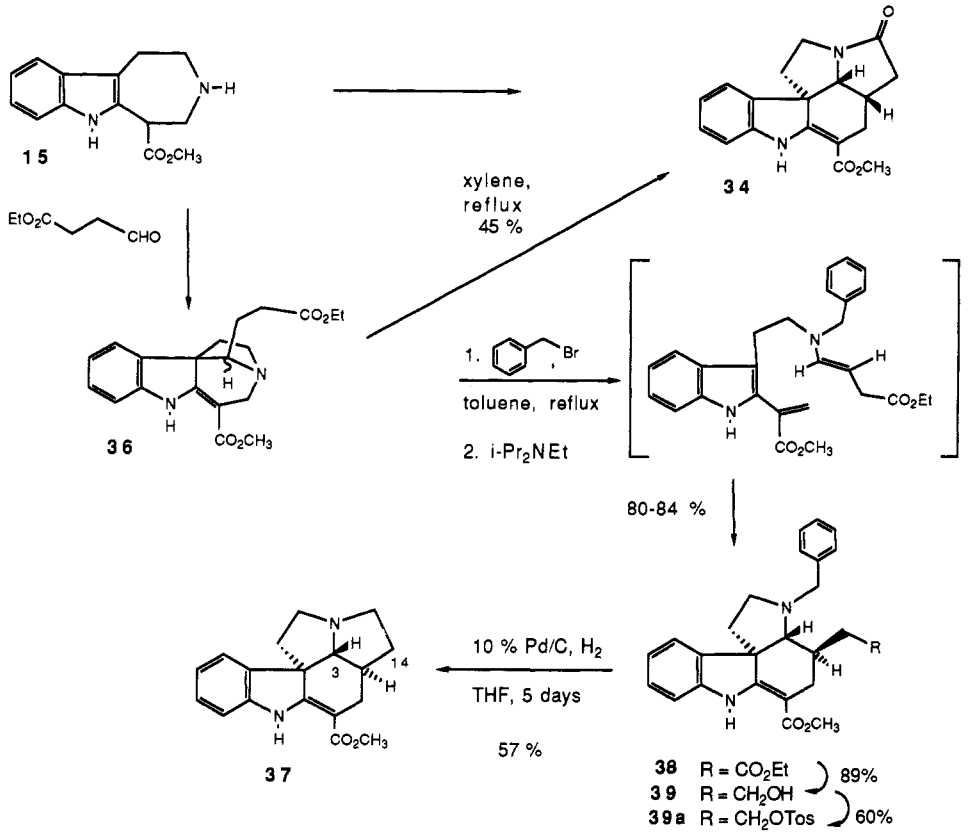


For diagnostic purposes, it is noteworthy that the D/E trans pentacyclic compounds can be differentiated from their D/E cis isomers by a difference in color reactions with ceric ammonium sulfate spray on TLC. While the D/E cis compounds gave the usual intense blue coloration commonly expected for vincadifformine-type vinylogous urethanes, the five-membered D/E trans compound **19a** gave a purple color and the seven-membered ring isomers **18a,b** gave a blue coloration, which quickly faded to green, similar to the color reactions of the bridged indoloazepines.[20]

Attempts were also made to use the 3,14-trans-substituted secondary amino ketone **33** in the Mannich cyclization reaction. This compound could be obtained from the ketal **14** by hydrolysis with HCl in aqueous methanol, followed by hydrogenolysis of the benzyl substituent in methanol (Scheme VIII). Its C3,14 trans-substitution could be substantiated by a ^{1}H NMR broad singlet at δ 3.45 for the C3 hydrogen, consistent with a nearly 90° dihedral angle between C3H and C14H, found here and in analogous tetracyclic compounds.[20] Retention of this geometry in this hydrogenolysis reaction without acid prevents a spontaneous cyclization of the amino ketone **33**. On treatment with formaldehyde under the various conditions studied with the corresponding ketal (see above), the desired cyclization products were, however, not obtained. Instead, the lactam **34** was consistently isolated (30%). It could be demonstrated that this product arose, in the absence of formaldehyde, by autoxidation of an intermediate enamine **12**.[28] Accordingly, its formation was enhanced to 67% by UV irradiation of the enamine **12**, while a stream of oxygen was bubbled through its solution in dichloromethane. Reduction of the lactam function with lithium aluminum hydride provided deethylibophyllidine (**35**), a compound previously synthesized through a deethyl-*nor*-secodine, thus establishing its D/E cis stereochemistry.[20] The facility of spontaneous autoxidation of the enamine **12** provides an alternative hypothetical pathway to the biogenetic route to deethylibophyllidine (**35**), previously formulated as a fragmentation and re-

(25) Pierron, C.; Garnier, J.; Levy, J.; Le Men, J. *Tetrahedron Lett.* **1971**, 1007.
(26) Cava, M. P. *Can. J. Chem.* **1973**, *51*, 3102.
(27) Brennan, J. P.; Saxton, J. E. *Tetrahedron* **1986**, *42*, 6719.
(28) (a) Foot, C. S.; Wei-Ping Lin, J. *Tetrahedron Lett.* **1968**, 3267. (b) Huber, J. E. *Ibid.* **1968**, 3270.

Scheme IX



duction product of 19-hydroxyibophyllidine.[29]

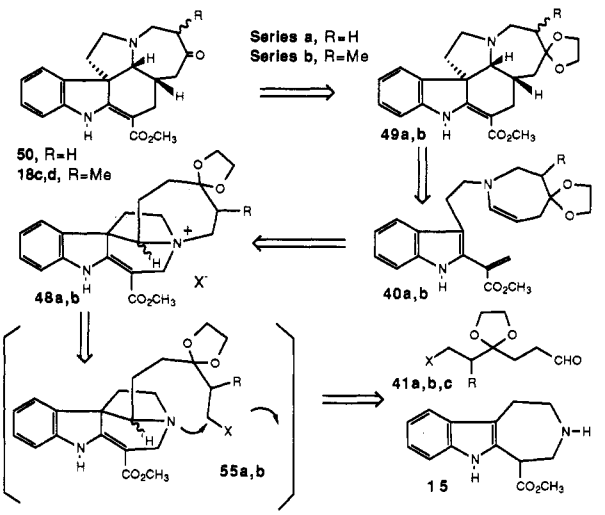
For a more rapid, unambiguous synthesis of the lactam **34** (Scheme IX), the indoloazepine **15** was heated with ethyl 4-oxobutanoate in xylene at reflux for 3 days (45% yield). The conditions required for rearrangement and cyclization of the isolable intermediate bridged indoloazepines **36** are more drastic in this instance (no reaction in refluxing toluene) than those for formation of the homologous six-membered ring D lactam of 3-oxovincadifformine, which was formed in 18 h in toluene at reflux (85% yield).[20]

D/E-trans-Deethylibophyllidine (**37**), required for the NMR structure correlations of Table I and for the structure assignments to the Mannich cyclization products **19a,b**, could be obtained through benzylation of the bridged indoloazepines **36** and treatment of the resulting quaternary salts with *N,N*-diisopropylethylamine. The resulting C3/C14 trans-substituted tetracyclic ester **38** (80–84%) was reduced to an alcohol **39**, and its tosylate derivative **39a** was then subjected to debenzylation and cyclization at room temperature. The product **37** gave UV and mass fragmentation spectra and showed TLC behavior essentially identical with those of the D/E cis isomer **35**, but its C3H signal at δ 2.77 ($J_{3,14}$ = 11 Hz) established its D/E trans stereochemistry.

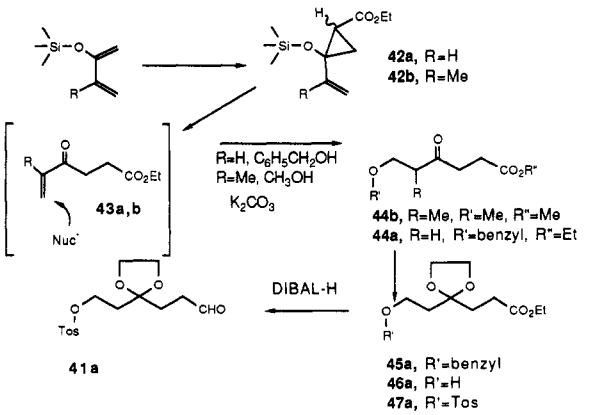
As an alternative to the biomimetic Mannich cyclization reaction leading to the *D-homo*-aspidosperma alkaloid skeleton, we also pursued approaches passing through *homo*-secodine intermediates **40a,b**. Here, it was anticipated that only the desired D/E cis-fused pentacyclic alkaloid skeleton would form (Scheme X).

A synthesis of the hexanal **41a** (R = H, X = Tos), required for condensation with the indoloazepine **15**, was

Scheme X

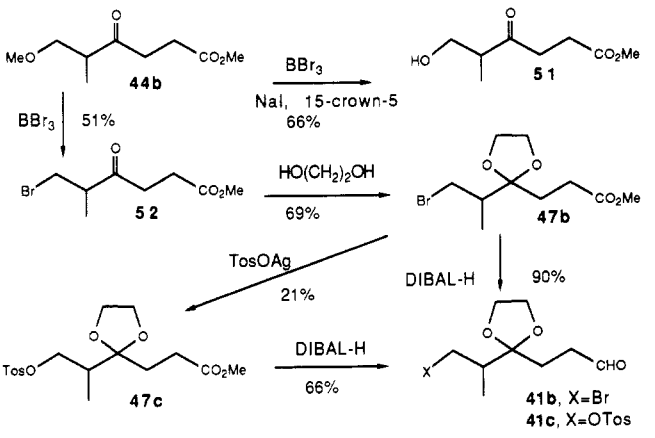


Scheme XI



(29) Kan, C.; Husson, H.-P.; Jacquemin, H.; Kan, S.-E.; Lounasmaa, M. *Tetrahedron Lett.* **1980**, *21*, 55; **1980**, *21*, 3363.

Scheme XII



based on the elegant generation of β-substituted ketones from vinyl(silyloxy)cyclopropanes (Scheme XI).[30] Thus addition of ethyl diazoacetate to 2-(trimethylsilyloxy)butadiene, in the presence of cupric acetylacetonate, provided a substrate **42a** (78% yield) for formation of a corresponding vinyl ketone **43a** and its nucleophilic addition by benzyl alcohol. The resulting ketone **44a** (83%) was masked as its ethylene ketal **45a**, the benzyl group was removed by hydrogenolysis (88%), and the resulting alcohol **46a** was converted to a tosylate **47a** (85%). A final DIBAL-H reduction of the ester function then provided the aldehyde **41a** (87%).

When the aldehyde **41a** was heated at 50 °C with the indoloazepine **15** in toluene, the bridged indoloazepine quaternary salts **48a** were formed. Without isolation, these ammonium salts were subjected to cleavage with triethylamine. Cycloaddition of the resulting intermediate *homo*-secodine **40a** provided the pentacyclic vinylogous urethane **49a** (63%), and hydrolysis of its ketal function gave the ketone **50**. Demethyliboxyphylline ketone (**50**) was thus produced in 52% overall yield from condensation of the indoloazepine **15** and the aldehyde **41a**.

Attempts to extend this methodology to a synthesis of iboxyphylline encountered several obstacles. While the isopropenylcyclopropane **42b** was readily prepared, its desilylation product, enone **43b**, could not be induced to add benzyl alcohol. However, with methanol, a 2:1 mixture of the methoxy ether **44b** with the enone **43b** could be obtained, along with an ester exchange. Cleavage of the methyl ether with sodium iodide and 15-crown-5 ether (Scheme XII), in the presence of boron tribromide, at −40 to 0 °C,[31] provided the alcohol **51** (66%), whereas a reaction with boron tribromide alone, at −78 °C, reversed the direction of ether cleavage and gave the bromide **52** (51%). The bromo ketone **52** was masked as its ethylene ketal **47b** (69%), and the ester function was reduced with DIBAL-H to the bromo aldehyde **41b**. Alternatively, the bromo ester **47b** could be converted with silver tosylate to the corresponding tosylate **47c** and the latter reduced to the aldehyde tosylate **41c**. Attempted transformations of the hydroxy keto ester **51** to the aldehyde tosylate **41c** failed.

When the bromo aldehyde **41b** was subjected to reaction with the indoloazepine **15** and a following hydrolysis, under the conditions used in the sequence with the demethyl tosylate **41a**, only 1% of the expected C19 epimeric iboxyphylline ketones **18c,d** was obtained. Instead, a mixture of isomeric ketones **53a–d** was produced (Scheme XIII). One of these could be separated chromatographically (26%) while the others (22%), consisting mostly of two compounds, remained as a mixture. All of these products have essentially identical mass spectroscopic fragmentation patterns, indicating that they are diastereomers. While the UV absorption at 329 nm, characteristic of the indolinoacrylate function, and a molecular ion at m/z 352 correspond to expectations for the compounds **18a–d**, the mass spectra lacked the intense retro-Diels–Alder fragment at m/z 138. In ^{1}H NMR spectra, the C18 methyl group appears as a doublet for these compounds, and the C3H signal is now a sharp singlet, rather than the doublet found in the seven-membered ring compounds **18a–d**, suggesting disubstitution on C14. Thus the cyclopentanone structures **53a–d** could be proposed. Accordingly, a ^{13}C NMR spectrum of **53a** showed a quaternary carbon signal at δ 56.6 for C14 and a cyclopentanone carbonyl carbon at δ 219.5. The IR absorption at 1736 cm^{-1} confirmed a five-membered ring ketone function. Monoformylation of amino ketal precursors **54a–d** with formic acid and dicyclohexylcarbodiimide substantiated the presence of a secondary amine group.

An explanation of the divergence from the reaction route followed by the demethyl analogue **41a** may be derived from hindrance to N-alkylation at the bridged indoloazepine stage **55b** (Scheme X), with resulting failure to generate a quaternary salt **48b** and a subsequent *homo*-secodine **40b**. If, instead, an imonium salt **56** and an enamine **57** (Scheme XIV) are generated and intramolecular enamine alkylation results in a new imonium salt **58** and in formation of bridged indoloazepines **59a,b**, one can understand a cleavage to the secodine analogue **60** and final cyclization to the spirocyclopentane products **54a–d**. These products thus revealed yet another variation and structure constraint to the *seco*-secodine chemistry, which we have developed in the preceding papers in this series.[20,21]

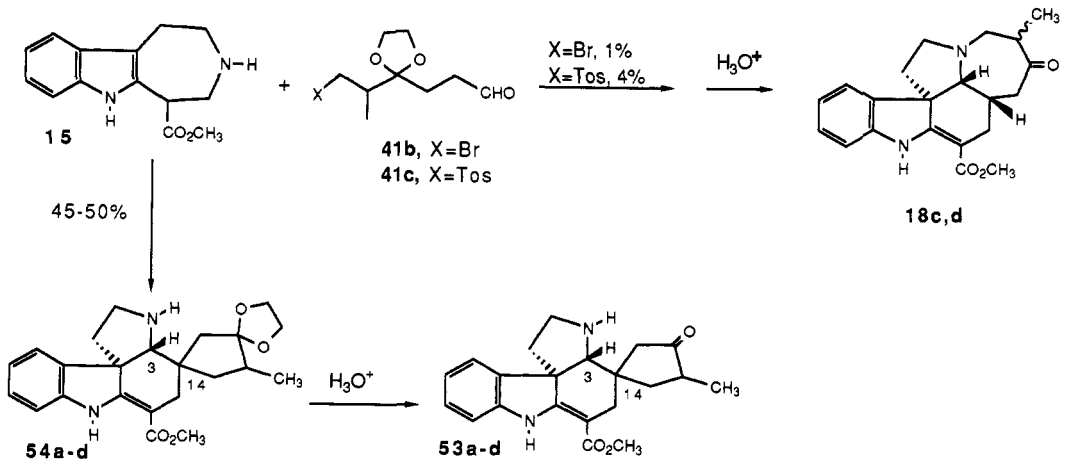
With the consideration of providing a harder leaving group for the required N-alkylation of the bridged indoloazepine **55b**, the tosyl aldehyde **41c** was subjected the same condensation with the indoloazepine **15**. Now, a 4% yield of the iboxyphylline ketones **18c,d** could be obtained, but the major reaction course was still toward the spirocyclopentane products **54a–d**. The competitive enamine alkylation therefore had to be suppressed by another strategy.

To avoid the intramolecular enamine alkylation leading to the spirocyclopentane products **54a–d**, we hoped to take advantage of an alternative alkylation process, which we had found to give access to the demethyliboxyphylline ketone **50**. Condensation of the ketal aldehyde **41d** with the indoloazepine **15** provided a mixture of epimerizable bridged indoloazepines **61a,b** (Scheme XV). Treatment of the major isomer **61a** (where the ketal chain is α) with HCl in acetic acid resulted in formation of the corresponding vinyl ketone **62a** (42%) and its epimer **62b** (13%). When the major vinyl ketone **62a** was heated in toluene at reflux for 24 h, a 27% yield of the demethyliboxyphylline ketone **50** was obtained. This product was also obtained from reactions in dimethyl acetamide or in *tert*-butyl alcohol.

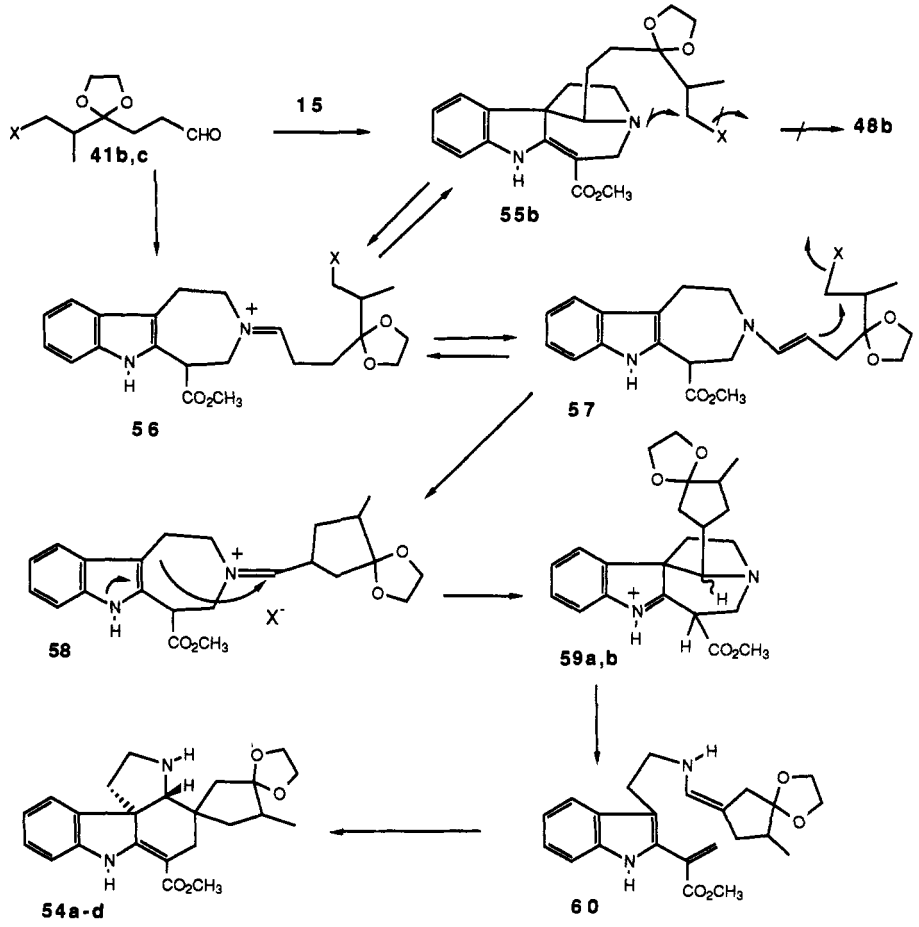
Synthesis of the corresponding methyl-substituted bridged indoloazepine enones **62c,d** then promised to provide alkylation substrates, which would not allow the intramolecular enamine addition to the vinyl ketone function, since such an alkylation would entail cyclization by an unlikely 5-*endo*-*trig* Michael addition reaction.[18]

(30) (a) Grimm, E. L.; Zschiesche, R.; Reissig, H.-U. *J. Org. Chem.* **1985**, *50*, 5543. (b) Kunkel, E.; Reichelt, I.; Reissig, H.-U. *Justus Liebigs Ann. Chem.* **1984**, *512*, 531 (synthesis of the corresponding methyl ester).
(31) Niwa, H.; Hida, T.; Yamada, K. *Tetrahedron Lett.* **1981**, *22*, 4239.

Scheme XIII



Scheme XIV



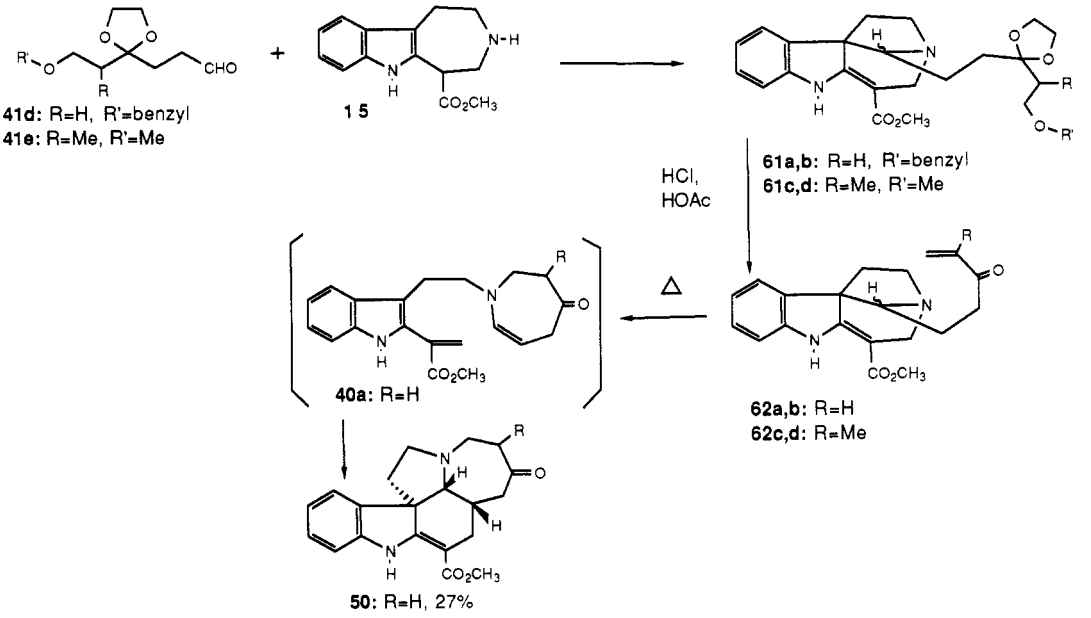
However, when these compounds were heated in toluene or in *tert*-butyl alcohol, neither the iboxyphylline ketone products **18c,d** nor the spirocyclopentanones **53a–d** were produced, and prolonged heating led only to decomposition products.

With the results described in this report, we have completed experimental synthetic transformations in support of the blocked-in areas of the hypothetical biogenetic alkaloid derivations shown in Scheme I. The biomimetic cyclization reactions leading to the iboxyphylline ketones **18c,d**, as well as to the cyclopentane product **19b**, suggest that compounds of the latter skeletal type may be anticipated as natural products. Also, the facile autoxidation of dehydroibophyllidine (**12**), which is an assumed intermediate in the biosynthesis of ibophyllidine (**3**), suggests that the lactam **34** may be found in plant extracts.

Experimental Section

General Methods. All reactions were run under a nitrogen atmosphere unless otherwise stated. Melting points were obtained on a Kofler micro hotstage with thermometers calibrated against a National Bureau of Standards certified set. NMR spectra were obtained with Bruker 250 or 270-MHz instruments, and chemical shifts are expressed as parts per million (δ) downfield from tetramethylsilane. Mass spectra were obtained with a Finnigan 4610 quadrupole instrument at 70 eV, calibrated with perfluorotributylamine and hexafluorotriphenyl-*s*-triazine for higher molecular weight compounds. Chemical ionization spectra employed methane as the reagent gas. IR spectra were obtained with either

Scheme XV



a Nicolet 6000 FT or a Perkin-Elmer 1430 grating instrument. Perkin-Elmer 402 and Lambda instruments were used for recording UV spectra. TLC data were obtained with E. Merck 60 PF 254 precoated silica gel on aluminum sheets. Indole derivatives were characterized with a 10% solution of ceric ammonium sulfate (CAS) in phosphoric acid as a spray reagent, and other compounds were visualized by either UV, iodine vapor, or treatment with an acid and heating. Flash chromatography[32] employed Baker 7024-R 40 μm diameter silica gel. Microanalyses were provided by George Robertson, Robertson Laboratories, Florham Park, NJ.

N^b-Benzyl-14-(2-oxobutyl)-(15,18-21)-nor-ψ-vincadifformine Ethylene Ketal (14). This compound was synthesized from indoloazepine **15** and 4-oxohexanal ethylene ketal by the previously described procedure,[9] without isolation of intermediates, in 62–70% yield. An analytical sample was recrystallized from methanol, mp 118–119 °C: UV (ethanol) λ_{max} 229, 299, 329 nm; IR (KBr) ν_{max} 3378, 2970, 2941, 2778, 1672, 1615, 1464, 1440, 1299, 1278, 1248, 1205, 1132, 1100, 1044, 1034, 747 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.96 (br s, 1 H), 7.22–7.44 (m, 5 H), 7.12 (t, 1 H, J = 8 Hz), 6.97 (d, 1 H, J = 7 Hz), 6.82 (t, 1 H, J = 8 Hz), 6.79 (d, 1 H, J = 8 Hz), 4.20 (d, 1 H, J = 14 Hz), 3.67–3.85 (m, 5 H), 3.77 (s, 3 H), 3.19 (br s, 1 H), 2.88 (dd, 1 H, J = 9, 6 Hz), 2.56–2.74 (m, 3 H), 2.12 (m, 1 H), 2.01 (m, 1 H), 1.65 (dd, 1 H), 1.58 (q, 2 H, J = 7 Hz), 1.32 (dd, 1 H, J = 15, 5 Hz), 1.07 (dd, 1 H, J = 15, 6 Hz), 0.80 (t, 3 H, J = 7 Hz); EIMS m/z (relative intensity) 474 (M^+, 8), 373 (22), 341 (10), 260 (15), 228 (12), 101 (100), 91 (78). Anal. Calcd for $C_{29}H_{34}N_2O_4$: C, 73.39; H, 7.22; N, 5.90. Found: C, 73.34; H, 7.29; N, 5.84.

N^b-H-14-(2-oxobutyl)-(15,18-21)-nor-ψ-vincadifformine Ethylene Ketal (16). The benzyl ketal **14** (1.37 g, 2.89 mmol) was dissolved in 50 mL of dry methanol and Pearlman's catalyst (20% $Pd(OH)_2/C$, 0.15 g) was added under a stream of nitrogen. This mixture was stirred under a hydrogen atmosphere for 3 h and then filtered through Celite. The residue was rinsed with two further 25-mL portions of methanol and then one warm 25-mL portion. The solvent was evaporated, and the resulting oil was separated by flash chromatography (silica, 7.5% methanol in CH_2Cl_2) to yield the cis amino ketal **17** (65 mg, 6%) as a foam, ibophyllidine (**3**, 12 mg, 1.3%) as an oil, and the trans amino ketal **16** (1.01 g, 91%), which crystallized as a white solid when concentrated in methanol. An analytical sample was recrystallized from methanol, mp 164–166 °C: TLC (silica, 10% methanol in CH_2Cl_2) R_f 0.32 (blue, fades rapidly to green, CAS); UV (ethanol) λ_{max} 231, 302, 333 nm; IR (KBr) 3307, 2965, 2940, 2880, 2866, 1682, 1600, 1482, 1468, 1436, 1334, 1303, 1273, 1246, 1207, 1121, 1104, 1057, 946, 854, 844, 756 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.05 (s, 1 H), 7.24 (d, 1 H, J = 8 Hz), 7.15 (t, 1 H, J = 8 Hz), 6.88 (t, 1 H, J = 8 Hz), 6.83 (d, 1 H, J = 8 Hz), 3.70–3.88 (m, 5 H), 3.77 (s, 3 H), 3.10–3.17 (m, 2 H), 2.83 (br s, 1 H), 2.71 (dd, 1 H, J = 15, 2 Hz), 2.37 (dd, 1 H, J = 15, 4 Hz), 1.79–1.99 (m, 3 H), 1.59 (q, 2 H, J = 7 Hz), 1.31 (dd, 1 H, J = 15, 7 Hz), 1.16 (dd, 1 H, J = 15, 7 Hz), 0.80 (t, 3 H, J = 7 Hz); ^1H NMR (benzene-d_6) 9.38 (s, 1 H), 7.05 (d, 1 H, J = 7 Hz), 6.92 (t, 1 H, J = 8 Hz), 6.75 (t, 1 H, J = 8 Hz), 6.24 (d, 1 H, J = 8 Hz), 3.66 (s, 1 H, H-3), 3.57 (s, 3 H), 3.38–3.46 (m, 4 H, ketal), 2.97 (m, 1 H), 2.66–2.79 (m, 2 H), 2.56 (dd, 1 H, J = 3, 15 Hz), 2.03 (br s, 1 H, N-H), 1.67–1.79 (m, 1 H), 1.50–1.58 (m, 4 H, includes q at 1.55), 1.35 (dd, 1 H, J = 7, 14 Hz), 1.01–1.12 (m, 1 H), 0.83 (t, 3 H); EIMS m/z (relative intensity) 384 (M^+, 5), 284 (2), 283 (11), 214 (4), 154 (5), 101 (100); ^{13}C NMR ($CDCl_3$) δ 168.9, 165.6, 143.2, 137.8, 127.7, 121.8, 120.6, 112.0, 109.1, 91.2, 67.4, 64.7, 64.5, 55.5, 50.6, 45.2, 44.7, 38.4, 36.7, 30.1, 24.3, 7.8. Anal. Calcd for $C_{22}H_{28}N_2O_4$: C, 68.73; H, 7.34; N, 7.29. Found: C, 68.56; H, 7.39; N, 7.16.

Physical data for cis amino ketal **17**: TLC (silica, 10% methanol in CH_2Cl_2) R_f 0.38 (blue, CAS); UV (ethanol) λ_{max} 231, 301, 329 nm; IR (KBr) 3380, 2972, 2944, 2882, 1679, 1608, 1480, 1468, 1438, 1283, 1245, 1202, 1105, 1070, 1048, 755 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.94 (s, 1 H), 7.25 (d, 1 H, J = 8 Hz), 7.17 (t, 1 H, J = 8 Hz), 6.89 (t, 1 H, J = 8 Hz), 6.83 (d, 1 H, J = 8 Hz), 3.86–3.96 (m, 4 H, ketal), 3.81 (d, 1 H, J = 5 Hz, H-3), 3.77 (s, 3 H, OMe), 3.10–3.19 (m, 2 H), 2.30–2.48 (m, 2 H), 2.01–2.15 (m, 2 H), 1.68–2.02 (m, 3 H), 1.58 (q, 2 H, J = 8 Hz), 1.40–1.52 (m, 1 H), 0.88 (t, 3 H, J = 8 Hz); EIMS m/z (relative intensity) 384 (M^+, 9), 284 (3), 283 (19), 215 (2), 154 (4), 101 (100); ^{13}C NMR ($CDCl_3$) δ 168.4, 165.6, 143.6, 137.8, 127.8, 121.8, 120.5, 112.2, 109.1, 95.6, 64.9, 64.5, 61.9, 56.7, 50.8, 44.9, 44.4, 37.9, 36.9, 30.4, 25.1, 8.2.

Mannich Reaction of the Trans Amino Ketal 16. Method A. The NH trans ketal **16** (825 mg, 2.15 mmol) was dissolved in 50 mL of methanol in a three-neck flask equipped with a condenser, a rubber septum, and an inlet with a pipette extending into the solution. This flask was cooled to 0 °C with stirring in a salt–ice bath. A second flask with paraformaldehyde (644 mg) was heated in an oil bath, and when the temperature of the bath reached 150 °C a vacuum of approximately 15 mm was used to draw gaseous formaldehyde from the second flask through a short length of tubing through the pipette into the methanol solution. When all the paraformaldehyde had been consumed (10 min), the vacuum was removed. TLC (silica, 4:1 ethyl acetate–ethanol) indicated that no **16** remained in the methanol solution and a product at R_f 0.60 (blue, fading quickly to green, CAS) had formed.

A saturated solution of HCl in ether (3.0 mL) was added to the mixture, and it was allowed to warm slowly over 15 min to ambient temperature. The reaction vessel was purged with nitrogen, and the mixture was heated at reflux for 4 h. At this time 1.0 mL of water was added, and the mixture was stirred for 20

(32) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

min before cooling. The mixture was concentrated to 5 mL and poured onto 25 mL of ice water. This was made basic to litmus with NaOH and extracted exhaustively with CH_2Cl_2 (200 mL total). Removal of the solvent by rotary evaporation and flash chromatography (silica) of the resulting residue, eluting with 3% methanol in CH_2Cl_2, gave 260 mg (34%) of a crude mixture of the seven-membered ring epimers **18a–d**. Further elution with 7.5% methanol in CH_2Cl_2 provided the trans five-membered ring ketone **19a** as an oil (212 mg, 28%) and the cis ketone **19b** as an oil (66 mg, 9%).

The mixture of seven-membered ring compounds was then separated by a second flash column (silica, 1:1 ether–pentane) to give **18a** (48 mg, 6%), **18b** (21 mg, 3%), **18c** (45 mg, 6%), and iboxyphylline ketone (**18d**, 36 mg, 5%) as oils.

Reaction of the cis ketal **17** under the same conditions gave essentially the same product distribution but with a lower combined yield.

Method B. An improved yield of iboxyphylline ketone **18d** was achieved by taking the crude Mannich product mixture (after aqueous workup and extraction of the free base into CH_2Cl_2) and stirring it in methanol at room temperature for 6 h with a slight excess of sodium methoxide. This mixture was neutralized with dilute HCl, concentrated, and extracted from a saturated sodium bicarbonate solution with CH_2Cl_2. By this procedure, 190 mg of the trans NH ketal **16** (0.495 mmol) provided an isolated yield of 28 mg of iboxyphylline ketone **18d** (16%) as an oil after flash chromatography (silica, 1:1 ether–pentane). By stirring pure **18c** or **18d** in methanol at room temperature, an equilibrium ratio of approximately 3:1 (**18d**:**18c**) formed, as determined by integration of the C-18 methyl signals in the ^1H NMR spectrum.

Physical data for **19-ξ-3,7-*epi*-20-oxoiboxyphylline (18a)**: TLC (silica, 1:1 ether–pentane) R_f 0.35 (blue, fades to brown, CAS); UV (ethanol) λ_{max} 221, 293, 325 nm; IR (KBr) ν_{max} 3435, 2925, 2854, 1710, 1686, 1626, 1609, 1466, 1248, 1128, 1082, 1197, 748 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.98 (s, 1 H), 7.08–7.18 (m, 2 H), 6.85 (t, 1 H, J = 8 Hz), 6.79 (d, 1 H, J = 8 Hz), 3.75 (s, 3 H), 3.32 (dd, 1 H, J = 7, 11 Hz), 3.26 (d, 1 H, J = 9 Hz, H-3), 2.95–3.12 (m, 3 H), 2.04–2.39 (m, 4 H), 1.74 (dd, 1 H, J = 6, 12 Hz), 1.13 (d, 3 H, J = 7 Hz); EIMS m/z (relative intensity) 352 (M^+, 50), 296 (12), 295 (14), 214 (20), 194 (13), 180 (20), 167 (18), 154 (13), 139 (12), 138 (100).

Physical data for **19-*epi*-ξ-3,7-*epi*-20-oxoiboxyphylline (18b)**: TLC (silica, 1:1 ether–pentane) R_f 0.26 (blue, fades to brown, CAS); UV (ethanol) λ_{max} 222, 295, 327 nm; IR (KBr) ν_{max} 3368, 2926, 2849, 1698, 1688, 1609, 1466, 1437, 1379, 1352, 1287, 1240, 1209, 1127, 1082, 754 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.97 (s, 1 H), 7.48 (d, 1 H, J = 7 Hz), 7.11 (t, 1 H, J = 8 Hz), 6.84 (t, 1 H, J = 7 Hz), 6.77 (d, 1 H, J = 8 Hz), 3.74 (s, 3 H), 3.01–3.32 (m, 6 H, includes d, J = 10 Hz at 3.05, H-3), 2.55–2.78 (m, 3 H), 2.28–2.51 (m, 2 H), 1.85–2.12 (m, 2 H), 1.05 (d, 3 H, J = 6 Hz); EIMS m/z (relative intensity) 352 (M^+, 42), 295 (6), 214 (22), 180 (16), 167 (13), 154 (11), 139 (15), 138 (100).

Physical data for **19-*epi*-20-oxoiboxyphylline (18c)**: TLC (silica, ether) R_f 0.55 (blue, CAS); UV (ethanol) λ_{max} 226, 297, 326 nm; IR (KBr) ν_{max} 3384, 2932, 2850, 1701, 1681, 1610, 1480, 1466, 1436, 1281, 1248, 1202, 1151, 1118, 1051, 749 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.91 (s, 1 H), 7.11–7.20 (m, 2 H), 6.89 (dt, 1 H, J = 1, 8 Hz), 6.81 (d, 1 H, J = 8 Hz), 3.75 (s, 3 H), 3.24 (dd, 1 H, J = 5, 13 Hz), 3.15 (d, 1 H, J = 5 Hz, H-3), 2.91–3.08 (m, 3 H), 2.73 (dd, 1 H, J = 5, 11 Hz), 2.62 (dd, 1 H, J = 7, 11 Hz), 2.50–2.59 (m, 2 H), 1.95–2.13 (m, 2 H), 1.72 (dd, 1 H, J = 4, 12 Hz), 1.56–1.68 (m, 1 H, H-14), 1.25 (d, 3 H, J = 7 Hz); EIMS m/z (relative intensity) 352 (M^+, 48), 295 (13), 214 (19), 182 (18), 180 (10), 167 (10), 154 (10), 139 (12), 138 (100).

Physical data for **20-oxoiboxyphylline (18d)**: TLC (silica, ether) R_f 0.47 (blue, CAS); UV (ethanol) λ_{max} 225, 297, 326 nm; IR (KBr) ν_{max} 3346, 2973, 2937, 2847, 2796, 1700, 1680, 1608, 1480, 1466, 1454, 1436, 1278, 1244, 1212, 1196, 1159, 1112, 1090, 1046, 746 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.93 (s, 1 H), 7.16 (dt, 1 H, J = 1, 8 Hz), 7.08 (d, 1 H, J = 7 Hz), 6.87 (t, 1 H), 6.81 (d, 1 H, J = 8 Hz), 3.77 (s, 3 H), 3.37 (dd, 1 H, J = 8, 12 Hz), 3.14 (dd, 1 H, J = 6, 9 Hz), 2.86–3.09 (m, 2 H), 2.86 (d, 1 H, J = 6 Hz, H-3), 2.74 (dd, 1 H, J = 10, 10 Hz), 2.51–2.60 (m, 2 H), 2.33 (dd, 1 H, J = 12, 12 Hz), 1.99–2.12 (m, 2 H), 1.72 (dd, 1 H, J = 5, 12 Hz), 1.46–1.59 (m, 1 H, H-14), 1.00 (d, 3 H, J = 7 Hz, H-18); EIMS (m/z (relative intensity) 352 (M^+, 31), 295 (10), 214 (19), 182 (11), 180 (14), 167 (11), 154 (11), 139 (12), 138 (100). An analytical sample was crystallized from ether–pentane: mp 208 °C dec. Anal. Calcd for $C_{21}H_{24}N_2O_3$: C, 71.57; H, 6.86; N, 7.95. Found: C, 71.12; H, 6.73; N, 7.80.

Physical data for **3,7-*epi*-15β-(1-oxopropyl)deethylibophyllidine (19a)**: TLC (silica, 15% methanol in CH_2Cl_2) R_f 0.56 (purple, CAS); UV (ethanol) λ_{max} 225, 293, 326 nm; IR (KBr) ν_{max} 3356, 2970, 2944, 2879, 1710, 1678, 1605, 1466, 1438, 1280, 1244, 1202, 1166, 1098, 748 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.20 (s, 1 H), 7.29 (d, 1 H, J = 8 Hz), 7.13 (t, 1 H, J = 8 Hz), 6.85 (t, 1 H, J = 8 Hz), 6.79 (d, 1 H, J = 8 Hz), 3.63–3.79 (m, 2 H), 3.74 (s, 3 H), 2.64–3.05 (m, 6 H, includes d, J = 11 Hz at 2.95, H-3), 2.54 (q, 2 H, J = 7 Hz), 2.12–2.19 (m, 2 H), 1.79–1.86 (m, 1 H), 1.11 (t, 3 H, J = 7 Hz); EIMS m/z (relative intensity) 353 (23), 352 (M^+, 100), 295 (28), 263 (68), 235 (47), 228 (17), 214 (29), 206 (23), 180 (25), 168 (26), 167 (30), 154 (23), 138 (43). An analytical sample was crystallized from cyclohexane: mp 93–96 °C dec. Anal. Calcd for $C_{21}H_{24}N_2O_3$: C, 71.57; H, 6.86; N, 7.95. Found: C, 72.33; H, 7.42; N, 7.15. The sample was seen to lose solvent (cyclohexane) at its melting point even after drying at 55 °C for 2 days under vacuum.

Physical data for **15α-(1-oxopropyl)deethylibophyllidine (19b)**: TLC (silica, 15% methanol in CH_2Cl_2) R_f 0.49 (blue, CAS); UV (ethanol) λ_{max} 224, 297, 326 nm; IR (KBr) ν_{max} 3382, 2925, 2854, 1710, 1679, 1609, 1468, 1246, 1203, 1112, 748 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.10 (s, 1 H), 7.37 (d, 1 H), 7.17 (t, 1 H), 6.90 (t, 1 H), 6.84 (d, 1 H), 3.79 (d, 1 H, J = 8 Hz, H-3), 3.77 (s, 3 H), 3.41–3.55 (m, 2 H), 3.09–3.16 (dd, 1 H), 2.96–3.04 (m, 2 H), 2.82–2.91 (m, 1 H), 2.50–2.63 (m, 2 H, H-19), 2.35–2.45 (m, 1 H), 2.10–2.21 (m, 1 H), 1.88–1.98 (dd, 1 H), 1.77–1.85 (ddd, 1 H), 1.08 (t, 3 H, J = 7 Hz); EIMS m/z (relative intensity) 353 (22), 352 (M^+, 60), 295 (87), 263 (100), 235 (45), 228 (21), 209 (13), 168 (33), 167 (23), 138 (55). An analytical sample was recrystallized from hexane: mp 93–95 °C. Anal. Calcd for $C_{21}H_{24}N_2O_3$: C, 71.57; H, 6.86; N, 7.95. Found: C, 71.23; H, 6.62; N, 7.60.

Iboxyphylline (4). A solution of 25 mg of iboxyphylline ketone **18d** (0.071 mmol) in 2.5 mL of tetrahydrofuran was cooled to −78 °C with stirring. A solution of L-Selectride (Aldrich, lithium tri-*sec*-butylborohydride, 0.11 mL of a 1.0 M solution in tetrahydrofuran) was added dropwise and the reaction mixture was stirred for 2 h. The reaction was quenched with 0.1 mL of water and warmed to room temperature. Excess solvent was removed under reduced pressure, and the residue was partitioned between CH_2Cl_2 and an aqueous layer made basic with NaOH. After two further extractions with CH_2Cl_2 the combined organic layers were concentrated and chromatographed (flash silica, 5% methanol in CH_2Cl_2) to yield 17 mg of iboxyphylline (**4**) (68%), identical by ^1H NMR, ^{13}C NMR, mass spectrum, TLC, and IR (in CH_2Cl_2 solution) with an authentic sample:[8] TLC (silica, 10% methanol in CH_2Cl_2) R_f 0.46 (blue, CAS); IR (CH_2Cl_2) ν_{max} 3614, 3390, 2956, 2932, 1680, 1612, 1480, 1468, 1438 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.90 (s, 1 H), 7.12–7.23 (m, 2 H), 6.88 (t, 1 H, J = 8 Hz), 6.80 (d, 1 H, J = 8 Hz), 4.01 (d, 1 H, J = 8 Hz, H-20), 3.76 (s, 3 H, OMe), 3.41 (d, 1 H, J = 5 Hz, H-3), 2.95–3.07 (m, 2 H), 2.82–2.89 (m, 1 H), 2.59 (dd, 1 H), 2.46 (dd, 1 H), 2.14–2.25 (m, 1 H), 1.97–2.08 (m, 2 H), 1.86–1.94 (m, 1 H), 1.53–1.72 (m, 3 H), 1.40–1.47 (m, 1 H), 0.98 (d, 3 H, J = 7 Hz, H-18); EIMS m/z (relative intensity) 354 (M^+, 38), 297 (3), 278 (8), 140 (100).

Reduction of 19a. The trans D/E ketone **19a** (34 mg, 0.097 mmol) was added to 1.5 mL of acetic acid and heated with stirring to 90 °C. Sodium borohydride (50 mg, 1.3 mmol) was added slowly to the solution, and stirring was continued for 7 min at 90 °C. The reaction mixture was poured onto ice, basified with NH_4OH, and extracted with three 15-mL portions of CH_2Cl_2. The solvent was removed, and flash chromatography of the residue (silica, 10% methanol in CH_2Cl_2) yielded the N^a-ethyl-2,16-dihydro ketone **26** (8.5 mg, 23%) as an amorphous oil: TLC (silica, 15% methanol in CH_2Cl_2) R_f 0.52 (red-orange, CAS); UV (methanol) λ_{max} 218, 257, 304 nm; IR (KBr) ν_{max} 2976, 2933, 2875, 1738, 1720, 1605, 1485, 1460, 1260, 1205, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.13 (d, 1 H, J = 7 Hz), 7.08 (t, 1 H, J = 8 Hz), 6.69 (t, 1 H, J = 7 Hz), 6.43 (d, 1 H, J = 8 Hz), 4.03 (d, 1 H, J = 5 Hz), 3.62–3.72 (m, 2 H), 3.46 (s, 3 H), 3.24–3.40 (m, 1 H), 2.83–3.11 (m, 5 H), 2.47 (q, 2 H, J = 7 Hz), 1.72–2.36 (m, 6 H), 1.08 (t, 3 H, J = 7 Hz), 1.06 (t, 3 H, J = 7 Hz); EIMS m/z (relative intensity) 382 (M^+, 19), 296 (5), 240 (18), 239 (100), 172 (69), 158 (14), 138 (14).

Further elution with methanol–CH_2Cl_2 (1:2) provided the two diastereomeric N^a-ethylindoline alcohols, **27a** and **27b** (in a 1:1 ratio by ^1H NMR), as an oil (22 mg, 59%). Further attempts to separate them were unsuccessful.

Physical data for the diastereomeric mixture of **27a** and **27b**: TLC (silica, 15% methanol in CH_2Cl_2) R_f 0.12 and 0.20 (red-orange, CAS); UV (methanol) λ_{max} 221, 260, 307 nm; ^1H NMR ($CDCl_3$) δ partial spectrum 7.02–7.19 (m), 6.62–6.71 (m), 6.38–6.75 (m), 4.03 (2 d's) 3.48 (s, OMe), 3.45 (s, OMe), 1.09 (t, J = 7 Hz), 1.08 (t, J = 7 Hz), 0.97 (t, J = 7 Hz), 0.96 (t, J = 7 Hz); EIMS m/z (relative intensity) 384 (M^+, 19), 298 (12), 240 (17), 239 (100), 172 (30), 158 (11), 140 (49).

Reduction of 18a. The trans D/E ketone **18a** (12 mg, 0.034 mmol) was reduced by the same procedure as the ketone **19a**, using 15 mg of sodium borohydride. After workup, TLC (silica, 10% methanol in CH_2Cl_2) indicated two major products, with R_f 0.42 (yellow-orange, CAS) and with R_f 0.36 (red-orange, CAS). Flash chromatography (silica, 5% methanol in CH_2Cl_2) provided 2.5 mg (21%) of a first-eluted yellow-orange compound, tentatively identified as N^a-H alcohol **28**, and 7.5 mg (57%) of a second-eluted N^a-ethyl compound **29**.

Physical data for **28**: UV (ethanol) λ_{max} 207, 242, 295 nm; ^1H NMR ($CDCl_3$) δ partial spectrum 7.01–7.16 (m, 2 H), 6.73 (t, 1 H), 6.65 (d, 1 H, J = 8 Hz), 4.14 (br s, 1 H), 3.75 (s, 3 H), 0.99 (d, 3 H, J = 6 Hz); EIMS m/z (relative intensity) 357 (10), 356 (M^+, 43), 355 (10), 264 (41), 182 (11), 144 (12), 143 (11), 141 (12), 140 (100).

Physical data for **29**: UV (ethanol) λ_{max} 208, 252, 301 nm: ^1H NMR ($CDCl_3$) δ 7.01–7.16 (m, 2 H), 6.68 (t, 1 H, J = 7 Hz), 6.47 (d, 1 H, J = 8 Hz), 3.96 (d, 1 H, J = 3 Hz), 3.75 (m, 2 H), 3.58 (s, 3 H), 2.82–3.32 (m, 5 H), 2.51–2.70 (m, 3 H), 1.55–2.20 (m, 12 H), 0.98–1.12 (m, 6 H); EIMS m/z (relative intensity) 384 (M^+, 18), 298 (13), 158 (11), 141 (11), 140 (100), 57 (39).

Reduction of 19b. The cis D/E ketone **19b** (34 mg, 0.097 mmol) was reduced by an identical procedure employing 50 mg of sodium borohydride (1.3 mmol). TLC analysis (silica, 15% methanol in CH_2Cl_2) of the crude reaction mixture after workup indicated that all of the starting ketone had reacted to form a major product having an R_f of 0.51 (gray, CAS) along with numerous minor products. Flash chromatography (silica, 10% to 15% methanol in CH_2Cl_2) yielded 12 mg (35%) of the cleavamine ketone **30** as an oil: UV (ethanol) λ_{max} 226, 284, 292 nm; IR (KBr) ν_{max} 3420, 2923, 2845, 1736–1710 (broad, both C=O), 1460, 1438, 1246, 1168, 744 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.70 (s, 1 H), 7.51 (d, 1 H, J = 7 Hz), 7.34 (d, 1 H, J = 8 Hz), 7.10–7.22 (m, 2 H)), 4.19 (d, 1 H, J = 12 Hz), 3.74 (s, 3 H), 3.54–3.65 (m, 1 H), 2.75–3.20 (m, 7 H), 2.50–2.62 (m, 1 H), 2.51 (q, 2 H, J = 7 Hz), 2.25–2.42 (m, 2 H), 1.92–2.00 (m, 1 H), 1.08 (t, 3 H, J = 7 Hz); EIMS m/z (relative intensity) 355 (16), 354 (M^+, 67), 297 (56), 211 (20), 152 (100), 138 (24), 96 (37), 94 (61), 82 (49).

N^b-H-14-(2-oxobutyl)-(15,18–21)-nor-ψ-vincadifformine (33). The benzyl ketal **14** (820 mg, 1.73 mmol) was stirred in methanol (30 mL) with 15 mL of 10% HCl for 20 h. The solution was made basic with aqueous NaOH and extracted with several portions of CH_2Cl_2. The combined organic extracts were dried with sodium sulfate and concentrated to yield the crude benzyl ketone as a foam. This was dissolved in 45 mL of methanol, and 10% Pd/C (75 mg) was added cautiously under a stream of nitrogen. The mixture was stirred for 18 h under an atmosphere of hydrogen. After filtering through Celite and concentration, the resulting oil was chromatographed (silica, 5% methanol in CH_2Cl_2) to give 320 mg of the amorphous amino ketone **33** (54% for both steps): TLC (silica, 10% methanol in CH_2Cl_2) R_f 0.41 (blue-green, CAS); UV (ethanol) λ_{max} 231, 299, 332 nm; IR (KBr) ν_{max} 3375, 2972, 2945, 1713, 1678, 1609, 1467, 1438, 1286, 1246, 1204, 1107, 749 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.08 (s, 1 H), 7.23 (d, 1 H, J = 8 Hz), 7.18 (dt, 1 H, J = 1, 8 Hz), 6.84–6.93 (m, 2 H), 3.76 (s, 3 H), 3.45 (br s, 1 H, H-3), 3.13–3.18 (m, 2 H), 2.38–2.63 (m, 4 H), 2.22 (q, 2 H, J = 7 Hz), 1.85–2.16 (m, 4 H), 0.94 (t, 3 H, J = 7 Hz); EIMS m/z (relative intensity) 341 (11), 340 (M^+, 47), 297 (16), 283 (100), 228 (51), 215 (43), 168 (39), 154 (44), 126 (59).

Reaction of the Trans Amino Ketone 33 with Formalin. The trans ketone **33** (25 mg, 0.065 mmol) was stirred with 0.1 mL of 40% aqueous formaldehyde (formalin) and 0.1 mL of 10% HCl in 3 mL of methanol, and the mixture was then heated at reflux for 6 h. The solvent was removed in vacuo, and the resulting residue was partitioned between CH_2Cl_2 and an aqueous layer, made basic with NH_4OH. After two further extractions with CH_2Cl_2, the combined solvent fractions were dried with sodium sulfate, concentrated to an oil by rotary evaporation, and purified by flash chromatography (silica, 6% methanol in CH_2Cl_2), to yield 6 mg of 20-oxodesethylibophyllidine **34** (30%) as the major product. The freshly prepared crude reaction mixture in CH_2Cl_2 containing **12** (after neutralization with NH_4OH) gave the following mass spectrum: EIMS m/z (relative intensity) 322 (M^+, 31), 263 (14), 215 (18), 214 (39), 167 (14), 154 (24), 109 (11), 108 (100).

An improved yield of the autoxidation product **34** was obtained by stirring 70 mg (0.18 mmol) of the amino ketone **33** overnight in 2 mL of methanol with 2 mL of 20% HCl. TLC analysis (silica, 10% methanol in CH_2Cl_2) of a neutralized sample showed one component at R_f 0.18 (blue, CAS), presumed to be the enamine **12**. The reaction mixture was concentrated to approximately 1 mL and partitioned between a basic (NH_4OH) aqueous layer and CH_2Cl_2. The aqueous layer was extracted further with three 5-mL portions of CH_2Cl_2, keeping the total volume to a minimum, and the extracts were dried briefly with sodium sulfate. The solution, in a 25-mL flask, was quickly transfered to an ice bath and irradiated with a Sylvania 275-W sun lamp for 30 min, with a steady stream of oxygen bubbling through the stirred solution. Concentration, and chromatography as above, gave 38 mg (67%) of 20-oxodesethylibophyllidine **34**.

Deethylibophyllidine (35). To a solution of the lactam **34** (28 mg, 0.090 mmol) in dry tetrahydrofuran (4 mL), at 0 °C, was added dropwise 0.4 mL of a 1.0 M solution of LAH in tetrahydrofuran. The mixture was slowly warmed to room temperature and stirred for 5 h. At this point some of the unreacted lactam **34** was still observable by TLC, but longer reaction times led to decreased yields of desethylibophyllidine **35** (R_f 0.18 on silica with 15% methanol in CH_2Cl_2, blue with CAS). To quench the reaction, 1.0 mL of water was added, and after stirring for an additional 15 min, the organic solvent was removed under reduced pressure to give a foamy residue. This was partitioned between a basic (NaOH) aqueous layer (5 mL) and CH_2Cl_2. The aqueous layer was extracted exhaustively with CH_2Cl_2, and the combined organic extracts were concentrated and chromatographed (silica, 10–20% methanol in CH_2Cl_2) to yield unreacted lactam **34** (6 mg, 22%) and desethylibophyllidine **35** as an oil (12 mg, 45%, 57% based on recovered **34**), which was identical with a sample prepared by an alternative route.[20]

Ethyl 4-Oxobutanoate.[33] A solution of ethyl pent-4-enoate (4.25 g, 33.2 mmol) in dry CH_2Cl_2 (50 mL) was cooled to −78 °C, and ozone was bubbled through the solution via pipette until the solution turned blue (30 min). The flask was swept with nitrogen and stirred for 60 min at −78 °C. Triphenylphosphine (4.0 g, 15 mmol) was added, and stirring was continued for 15 min as the solution was warmed to room temperature. Hexane (100 mL) was added, and the resulting white crystalline precipitate was filtered and washed with CH_2Cl_2 (50 mL). The combined filtrates were then washed with 50 mL of aqueous saturated NaCl, followed by 50 mL of water, and dried with $MgSO_4$. After removal of the solvents, vacuum distillation yielded 2.80 g of ethyl 4-oxobutanoate as a clear oil: bp 78–82 °C (20 mm); IR (film, NaCl) ν_{max} 2986, 2944, 2909, 2842, 2732, 1720–1750 (broad, both C=O), 1373, 1349, 1165, 1102, 1049, 1010 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.82 (s, 1 H), 4.15 (q, 2 H, J = 7 Hz), 2.81 (t, 2 H, J = 7 Hz), 2.63 (t, 2 H, J = 7 Hz), 1.27 (t, 3 H, J = 7 Hz); EIMS m/z (relative intensity) 131 (M^+ + 1, 38), 102 (25), 85 (100).

20-Oxodeethylibophyllidine (34). A solution of ethyl 4-oxobutanoate (110 mg, 0.846 mmol) and indoloazepine **15** (180 mg, 0.738 mmol) in toluene (25 mL) was heated at reflux and stirred with 3-Å molecular sieves for 18 h. TLC analysis of the reaction mixture showed the formation of two products. **36a** and **36b**, with R_f values of 0.58 and 0.32 (silica, 4:1 ethyl acetate–ethanol, blue with CAS). Concentration under reduced pressure and flash chromatography of the residue (silica, 5:1 ethyl acetate–ethanol) gave 149 mg (56%) of the bridged azepine ester **36a** and 68 mg (26%) of its more polar isomer **36b** as gummy oils.

(33) Taylor, W. G. *J. Org. Chem.* **1981**, *46*, 4290 (synthesis of corresponding methyl ester).

Physical data for the less polar ester **36a**: UV (ethanol) λ_{max} 229, 304, 333 nm; IR (film, NaCl) ν_{max} 3380, 2980, 2950, 2865, 1734, 1685, 1610, 1468, 1436, 1371, 1288, 1240, 1191, 746 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.95 (s, 1 H), 7.27 (d, 1 H, J = 8 Hz), 7.17 (t, 1 H, J = 8 Hz), 6.89 (t, 1 H, J = 8 Hz), 6.83 (d, 1 H, J = 8 Hz), 4.13 (q, 2 H, J = 7 Hz), 3.88 (d, 1 H, J = 16 Hz), 3.71 (s, 3 H), 3.45 (d, 1 H, J = 16 Hz), 3.27–3.39 (m, 1 H), 2.90 (dd, 1 H, J = 4, 12 Hz), 2.73–2.86 (m, 1 H), 2.53–2.66 (m, 1 H), 1.87–2.47 (m, 5 H), 1.26 (t, 3 H, J = 7 Hz); EIMS m/z (relative intensity) 357 (14), 356 (M^+, 65), 215 (23), 214 (100), 154 (43).

Physical data for the more polar ester **36b**: UV (ethanol) λ_{max} 230, 301, 332; IR (NaCl, film) ν_{max} 3376, 2980, 2948, 2870, 1735, 1685, 1612, 1468, 1436, 1372, 1296, 1236, 1187, 736 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.82 (s, 1 H), 7.14–7.21 (m, 2 H), 6.92 (t, 1 H, J = 8 Hz), 6.84 (d, 1 H, J = 8 Hz), 4.06 (q, 2 H, J = 7 Hz), 3.82 (d, 1 H, J = 16 Hz), 3.74 (s, 3 H), 3.35 (d, 1 H, J = 16 Hz), 3.29–3.43 (m, 2 H), 2.87–2.98 (m, 1 H), 2.19–2.48 (m, 4 H), 1.48–1.75 (m, 2 H), 1.21 (t, 3 H, J = 7 Hz); EIMS m/z (relative intensity) 357 (12), 356 (M^+, 56), 215 (19), 214 (100), 154 (44).

The indoloazepine **15** (60 mg, 0.46 mmol) and ethyl 4-oxobutanoate (100 mg, 0.41 mmol) were heated at reflux in xylene with 3-Å molecular sieves. Formation of the bridged azepine esters **36a** and **36b** was indicated by TLC after 8 h. After 3 days rearrangement of the bridged esters had occurred, forming a new product which gave a blue stain with CAS at R_f 0.60 (silica, 4:1 ethyl acetate–ethanol). The solvent was removed under vacuum and flash chromatography (silica, 5:1 ether–acetone) of the residue provided 57 mg (45%) of the lactam **34** as a white solid. An analytical sample was recrystallized from methanol: mp 234 °C dec; UV (ethanol) λ_{max} 228, 299, 330 nm; IR (KBr) ν_{max} 3382, 2945, 2837, 1694, 1675, 1608, 1484, 1440, 1278, 1251, 1204, 1113, 752 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.05 (s, 1 H), 7.21–7.29 (m, 2 H), 6.95 (t, 1 H, J = 8 Hz), 6.88 (d, 1 H, J = 8 Hz), 4.32 (d, 1 H, J = 6 Hz, H-3), 4.13–4.21 (m, 1 H, H-5β), 3.78 (s, 3 H), 3.21–3.32 (m, 1 H, H-5α), 2.86 (dd, 1 H, J = 6, 16 Hz, H-15), 2.78 (dd, 1 H, J = 5, 15 Hz, H-17β), 2.12–2.26 (m, 1 H, H-14), 2.15 (d, 1 H, J = 16 Hz, H-15), 1.83–1.92 (m, 2 H, H-6α and β), 1.79 (dd, 1 H, J = 12, 15 Hz, H-17α); EIMS m/z (relative intensity) 311 (17), 310 (M^+, 94), 228 (10), 227 (58), 215 (15), 214 (100), 195 (37), 180 (15), 167 (25), 154 (58), 96 (10); HRMS[34] for fragment at 227 m/z, required for $C_{14}H_{13}NO_2$ 227.0946, found 227.0957. Anal. Calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.40; H, 6.01; N, 9.06.

N^b-Benzyl-14-(carbethoxymethyl)-(15,18–21)-nor-ψ-vincadifformine (38). The less polar bridged azepine ester **36a** (53 mg, 0.15 mmol) and benzyl bromide (0.030 mL, 0.25 mmol) were heated at reflux in 10 mL of toluene for 18 h. At this point, TLC (silica, 4:1 ethyl acetate–ethanol) indicated that the quaternary salt had formed (R_f 0.0, blue with CAS) and some rearrangement to N-benzyl ester **38** (R_f 0.69, blue with CAS) had already occurred. Diisopropylethylamine (0.035 mL, 0.20 mmol) was added, and the mixture was heated at reflux for a further 12 h. The reaction vessel was cooled, and the solution was partitioned between an aqueous layer made basic to litmus with NaOH and 20 mL of CH_2Cl_2. The aqueous layer was extracted twice with CH_2Cl_2, and the combined organic extracts were concentrated under reduced pressure. Flash chromatography (silica, 4–8% methanol in CH_2Cl_2) provided the N-benzyl ester **38** (56 mg, 84%) as a white foam, after solvent removal. An analytical sample was recrystallized from methanol: mp 138–140 °C; UV (ethanol) λ_{max} 232, 294, 327 nm; IR (KBr) ν_{max} 3363, 2968, 2943, 2798, 1720, 1685, 1608, 1478, 1466, 1438, 1301, 1280, 1248, 1202, 1185, 1125, 744 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.96 (s, 1 H), 7.26–7.42 (m, 6 H), 7.14 (t, 1 H, J = 8 Hz), 6.91 (d, 1 H, J = 8 Hz), 6.82 (t, 1 H, J = 8 Hz), 4.30 (d, 1 H, J = 14 Hz), 4.05 (q, 2 H, J = 7 Hz), 3.76 (s, 3 H), 3.75 (d, 1 H, J = 14 Hz), 3.04 (s, 3 H), 2.86–2.93 (m, 1 H), 2.48–2.65 (m, 4 H, includes d at 2.64 with J = 3 Hz), 1.84–2.09 (m, 3 H), 1.66 (dd, 1 H, J = 5, 12 Hz), 1.18 (t, 3 H, J = 7 Hz); EIMS m/z (relative intensity) 447 (8), 446 (M^+, 36), 401 (8), 314 (15), 313 (74), 233 (10), 232 (66), 91 (100). Anal. Calcd for $C_{27}H_{30}N_2O_4$: C, 72.62; H, 6.77; N, 6.27. Found: C, 72.56; H, 6.99; N, 6.27.

(34) We would like to thank Dr. Eric Block of the MIT Mass Spectrometry Laboratory, Cambridge, MA, for the high-resolution mass spectrum.

A similar procedure using the more polar bridged azepine ester **36b** (139 mg, 0.39 mmol), benzyl bromide (0.060 mL, 0.51 mmol), and diisopropylethylamine (0.10 mL, 0.57 mmol) yielded 139 mg (80%) of the N-benzyl ester **38** after chromatography.

N^b-Benzyl-14-(2-hydroxyethyl)-(15,18–21)-nor-ψ-vincadifformine (39). The N-benzyl ester **38** (187 mg, 0.419 mmol) was dissolved in 20 mL of dry tetrahydrofuran and cooled to 0 °C in an ice bath with stirring. A 1.0 M solution of LAH in tetrahydrofuran (0.45 mL) was added dropwise, and stirring was continued for 20 min at 0–5 °C after the addition was complete. The reaction was quenched with 1.0 mL of water, the mixture was stirred for 10 min at 15 °C, and the solvent then removed by rotary evaporation. The residue was partitioned between an aqueous layer made basic with NaOH and 20 mL of CH_2Cl_2. The aqueous layer was washed with two further 20-mL portions of CH_2Cl_2, the combined organic extracts were concentrated to a residue and separated by flash chromatography (silica, 5% methanol in CH_2Cl_2) to give the alcohol **39** (151 mg, 89%) as an oil: TLC (silica, 5% methanol in CH_2Cl_2) R_f 0.33 (blue, CAS); UV (methanol) λ_{max} 232, 301, 333 nm; IR (KBr) ν_{max} 3388 (broad), 2925, 2854, 2793, 1679, 1610, 1467, 1438, 1281, 1249, 1201, 1128, 745 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.94 (s, 1 H), 7.28–7.41 (m, 5 H), 7.13 (dt, 1 H, J = 1, 8 Hz), 6.97 (d, 1 H, J = 7 Hz), 6.78–6.86 (m, 2 H), 4.11 (d, 1 H, J = 13 Hz), 3.76 (s, 3 H), 3.75 (d, 1 H, J = 13 Hz), 3.49 (t, 2 H, J = 7 Hz), 2.95 (s, 1 H), 2.88–2.94 (m, 1 H), 2.50–2.71 (m, 3 H), 1.95–2.11 (m, 2 H), 1.66 (dd, 1 H, J = 12, 5 Hz), 1.07–1.49 (m, 3 H); EIMS m/z (relative intensity) 404 (M^+, 36), 279 (15), 273 (13), 271 (71), 205 (21), 191 (11), 190 (75), 167 (35), 149 (56), 91 (100).

14-*epi*-Deethylibophyllidine (37). The N-benzyl alcohol **39** (130 mg, 0.322 mmol) and triethylamine (0.10 mL, 0.72 mmol) were dissolved in 5 mL of freshly distilled CH_2Cl_2 and stirred in a round-bottom flask, cooled to 0 °C in an ice bath. p-Toluenesulfonic acid anhydride (157 mg, 0.483 mmol) was added dropwise, as a solution in 2.0 mL of dry CH_2Cl_2. The mixture was stirred at 0–5 °C for 30 min after the addition was complete and warmed to 25 °C over 5 min. It was then poured onto a cold saturated aqueous solution of sodium bicarbonate and extracted with three 20-mL portions of CH_2Cl_2. After concentration under reduced pressure, the residue was subjected to flash chromatography (silica, 2% methanol in CH_2Cl_2) to give the tosylate **39a** (108 mg, 60%) as an oil: TLC (3% methanol in CH_2Cl_2) R_f 0.73 (blue, CAS); UV (methanol) λ_{max} 233, 298, 329 nm; IR (film, NaCl) ν_{max} 3384, 2958, 2832, 1678, 1609, 1466, 1357, 1280, 1250, 1175 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.95 (s, 1 H), 7.72 (d, 2 H, J = 8 Hz), 6.75–7.51 (m, 11 H), 4.01 (d, 1 H, J = 13 Hz), 3.92 (t, 2 H, J = 7 Hz), 3.75 (s, 3 H), 3.64 (d, 1 H, J = 13 Hz), 2.88 (br s, 1 H), 2.55–2.68 (m, 1 H), 2.29–2.48 (m, 2 H), 2.39 (s, 3 H), 1.88–2.05 (m, 2 H), 1.62 (m, 1 H), 1.13–1.45 (m, 3 H); CIMS m/z (relative intensity) 559 (M^+ + 1, 0.5), 387 (23), 228 (57), 187 (32), 91 (100).

The tosylate **39a** (138 mg, 0.247 mmol) was dissolved in 12 mL of freshly distilled tetrahydrofuran in a round-bottom flask. After the flask was swept with nitrogen, 50 mg of 10% Pd/C was added, and the resulting mixture was stirred under a hydrogen atmosphere. Every 24 h the hydrogen was replaced and 10 mg more catalyst was added. After 5 days the reaction mixture was filtered through Celite. The remaining catalyst was rinsed with two 30-mL portions of methanol followed by 30 mL of hot methanol. The solvents were removed under reduced pressure, and the residue was extracted from an aqueous layer (made basic with NaOH) by three 15-mL portions of CH_2Cl_2. Concentration and flash chromatography (10–15% methanol in CH_2Cl_2) gave the tosylate **39a** (18 mg) as an oil and *D/E-trans*-deethylibophyllidine **37** (36 mg, 49%, 57% based on recovered **39a**) as an oil: UV (ethanol) λ_{max} 224, 293, 327 nm; IR (KBr) ν_{max} 3440, 2924, 2854, 1678, 1603, 1466, 1436, 1241, 1202, 1150, 1096, 746 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.20 (s, 1 H), 7.32 (d, 1 H, J = 8 Hz), 7.12 (t, 1 H, J = 8 Hz), 6.84 (t, 1 H, J = 8 Hz), 6.79 (d, 1 H, J = 8 Hz), 3.75 (s, 3 H), 3.55–3.75 (m, 2 H), 2.55–2.89 (m, 3 H), 2.77 (d, 1 H, J = 11 Hz, H-3), 2.03–2.19 (m, 2 H) 1.69–1.86 (m, 3 H), 1.45–1.55 (m, 1 H); EIMS m/z (relative intensity) 296 (M^+, 32), 180 (5), 167 (4), 154 (3), 83 (8), 82 (100); CIMS 297 (M^+ + 1, 100).

Ethyl 2-[(Trimethylsilyl)oxy]-2-vinylcyclopropane-1-carboxylate (42a).[30b] A mixture of 3.50 g (0.0246 mol) of 3-[(trimethylsilyl)oxy]-1,3-butadiene and 109 mg (0.418 mmol) of cupric acetylacetonate was stirred in a round-bottom flask,

equipped with a condenser, in an oil bath heated to 90 °C. A solution of 3.10 mL (0.0296 mol) of ethyl diazoacetate in 50 mL of dry benzene was added dropwise to this mixture, through the condenser, over 3.5 h. When addition was complete, the mixture was cooled to 20 °C and filtered. The benzene was removed by rotary evaporation, and the residue was vacuum distilled, giving 4.35 g of a clear oil (78%) bp 72–78 °C (2 mm). Integration of the vinyl signals in the ^{1}H NMR spectrum showed this to be a 2:1 mixture of diastereomeric cyclopropyl esters **42a**: IR (neat, NaCl) ν_{max} 2962, 2905, 1734, 1377, 1354, 1292, 1254, 1165, 1065 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.88 (dd, 0.67 H, J = 11, 17 Hz), 5.58 (dd, 0.33 H, J = 10, 17 Hz), 5.36 (dd, 0.67 H, J = 2, 17 Hz), 5.26 (dd, 0.33 H, J = 1, 17 Hz), 5.18 (dd, 0.67 H, J = 2, 11 Hz), 5.10 (dd, 0.33 H, J = 1, 10 Hz), 4.08–4.19 (m, 2 H, ester CH_2), 2.17 (dd, 0.67 H, J = 1, 10 Hz), 1.78–1.86 (m, 0.67 H), 1.42–1.58 (m, 1.67 H), 1.18–1.32 (m, 3 H, ester CH_3), 0.15 (s, 9 H, Me_3Si); EIMS m/z (relative intensity) 229 (1), 228 (M^+, 2), 213 (6), 155 (73), 73 (100); CIMS 301 ($M^+ + Me_3Si$, 40), 229 ($M^+ + 1$, 100), 213 (82), 155 (96). Anal. Calcd for $C_{11}H_{20}O_3Si$: C, 57.86; H, 8.83. Found: C, 57.59; H, 8.77.

Ethyl 6-(Benzyloxy)-4-oxohexanoate (44a). A mixture of 3.00 g of the silyl esters **42a** (0.0132 mol), 8.00 g of benzyl alcohol, and 100 mg of potassium carbonate was stirred for 8 h at 20 °C, followed by 8 h at 45 °C. After filtering, the excess benzyl alcohol was removed by vacuum distillation, and the remaining oil was purified by flash chromatography (silica, 2:1 pentane–ether) to yield 2.89 g (83%) of benzyl ester **44a** as a clear oil: IR (neat, NaCl) ν_{max} 3032, 2984, 2906, 2870, 1718–1740 (both C=O), 1456, 1371, 1201, 1102, 1029, 741, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.21–7.41 (m, 5 H), 4.51 (s, 2 H), 4.13 (q, 2 H, J = 7 Hz), 3.75 (t, 2 H), 2.71–2.82 (m, 4 H), 2.58 (t, 2 H), 1.25 (t, 3 H, J = 7 Hz); EIMS m/z (relative intensity) 265 ($M^+ + 1$, 13), 246 ($M^+ - H_2O$, 18), 158 (18), 157 (16), 112 (83), 91 (100); CIMS 265 ($M^+ + 1$, 100).

Ethyl 6-Hydroxy-4-oxohexanoate Ethylene Ketal (46a). The benzyl ketal ester **45a** (see under preparation of **41d**) (2.86 g, 9.29 mmol) was dissolved in 25 mL of dry ethanol in a round-bottom flask. After sweeping the flask with nitrogen, 0.25 g of 10% Pd/C was added, and the mixture was stirred under a hydrogen atmosphere for 16 h. The mixture was filtered through Celite, and the solids were washed with two further portions of ethanol. The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography to give 1.78 g (88%) of the alcohol **46a** as a clear oil: TLC (silica, ether) R_f 0.24; IR (neat, NaCl) ν_{max} 3100–3600 (broad, O–H), 2967, 2892, 1734, 1568, 1446, 1369, 1304, 1184, 1128, 1043 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.17 (q, 2 H, J = 7 Hz), 4.03 (br s, 4 H), 3.80 (t, 2 H, J = 6 Hz), 3.20 (br s, 1 H), 2.41 (t, 2 H, J = 8 Hz), 2.05 (t, 2 H, J = 8 Hz), 1.92 (t, 2 H, J = 6 Hz), 1.26 (t, 3 H, J = 7 Hz); EIMS m/z (relative intensity) 219 ($M^+ + 1$, 14), 201 ($M^+ - H_2O$, 20), 173 (79), 155 (14), 145 (20), 117 (100), 101 (17), 99 (84); CIMS 219 ($M^+ + 1$, 100), 201 (47).

Ethyl 6-[(*p*-Tolylsulfonyl)oxy]-4-oxohexanoate Ethylene Ketal (47a). The ketal alcohol **46a** (1.00 g, 4.59 mmol) was dissolved in 10 mL of distilled CH_2Cl_2 and cooled to 0 °C with stirring. Triethylamine (0.96 mL, 6.9 mmol) was added via syringe, followed by dropwise addition of a CH_2Cl_2 solution (ca. 8 mL) containing 2.25 g of *p*-toluenesulfonic anhydride (6.9 mmol). The resulting mixture was stirred for 30 min at 0 °C and warmed to 20 °C over 30 min, turning yellow in the process. The reaction was quenched by addition of 3 mL of H_2O, poured onto a cold aqueous solution of sodium bicarbonate, and extracted with CH_2Cl_2. The solvent was removed at reduced pressure, and the residue was subjected to flash chromatography (1:1 ether–pentane) to yield 1.45 g (85%) of tosylate **47a** as a clear oil: TLC (1:1 ether–pentane) R_f 0.16; IR (neat, NaCl) ν_{max} 3064, 2984, 2892, 1732, 1597, 1446, 1360, 1306, 1180, 1098, 1035, 972, 912, 734, 665 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.79 (d, 2 H, J = 8 Hz), 7.35 (d, 2 H, J = 8 Hz), 4.11 (q, 2 H, J = 7 Hz), 3.84–3.92 (m, 4 H), 2.45 (s, 3 H), 2.31 (t, 2 H, J = 8 Hz), 2.00 (t, 2 H, J = 7 Hz), 1.92 (t, 2 H, J = 8 Hz), 1.25 (t, 3 H, J = 7 Hz); CIMS m/z (relative intensity) 373 ($M^+ + 1$, 68), 271 (13), 202 (12), 201 ($M^+ - OTos$, 100), 173 (27), 157 (14), 155 (38).

6-[(*p*-Tolylsulfonyl)oxy]-4-oxohexanal Ethylene Ketal (41a). To a stirred solution of 1.40 g of ethyl ester **47a** (3.76 mmol) in 10 mL of dry CH_2Cl_2 at −78 °C was added 4.52 mL of a 1.0 M solution of diisobutylaluminum hydride in CH_2Cl_2. The mixture was stirred for 1 h at −78 °C and allowed to warm to 0 °C. Aqueous sodium bicarbonate (1.5 mL) and ether (25 mL) were added, and the resulting slurry was stirred for 25 min at room temperature. The solvent was decanted from the white salts, which were rinsed with three more portions of ether. The organic fractions were combined and dried with sodium sulfate. Removal of the solvent by rotary evaporation gave 1.19 g (87%) of the crude aldehyde **41a** as a clear oil of 90% purity (determined by ^{1}H NMR): IR (neat, NaCl) ν_{max} 2964, 2892, 2728, 1723, 1599, 1448, 1358, 1178, 1096, 1062, 952, 817, 770, 734, 664 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.66 (br s, 1 H), 7.79 (d, 2 H, J = 8 Hz), 7.36 (d, 2 H, J = 8 Hz), 4.12 (t, 2 H, J = 7 Hz), 3.86 (br s, 4 H), 2.45 (s, 3 H), 2.41 (t, 2 H, J = 7 Hz), 1.94–2.03 (m, 4 H); CIMS m/z (relative intensity) 329 ($M^+ + 1$, 23), 271 (8), 269 (15), 267 (9), 157 ($M^+ - OTos$, 89), 129 (21), 113 (26), 73 (42), 57 (100).

19-Demethyl-20-oxoiboxyphylline Ethylene Ketal (49a). A mixture of 200 mg of aldehyde **41a** (0.610 mmol) and 125 mg of indoloazepine **15** (0.512 mmol) was stirred in 5 mL of toluene with 3-Å molecular sieves at room temperature. After 1.5 h a TLC was taken (10% methanol in CH_2Cl_2, silica). This indicated that all of the indoloazepine **15** had reacted and two new products (bridged indoloazepines **55a**) at R_f 0.39 and 0.56, respectively (both blue, CAS), were present. The mixture was then warmed to 50–55 °C for 12 h, at which point a TLC indicated that a very polar compound (quaternary salt **48a** R_f 0.0, blue with CAS) had formed. Triethylamine (15 mL) was added, and the reaction mixture was heated at reflux for 6 h. A TLC indicated that all of the polar compound had reacted and a single major product (**49a**) had formed. The mixture was partitioned between CH_2Cl_2 and 5% aqueous NH_4OH. The aqueous layer was washed with two further portions of CH_2Cl_2, and the combined organic layers were dried and reduced to a residue by rotary evaporation. Flash chromatography of the residue (silica, 4% methanol in CH_2Cl_2) provided 123 mg (63%) of the ketal **49a** as a white foam: TLC (silica, 5% methanol in CH_2Cl_2) R_f 0.45 (blue-green with CAS); UV (ethanol) λ_{max} 223, 297, 328 nm; IR (KBr) ν_{max} 3358, 2946, 2886, 2843, 2808, 1679, 1606, 1480, 1467, 1434, 1304, 1277, 1248, 1210, 1198, 1171, 1123, 1066, 1043, 892, 752 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.92 (s, 1 H), 7.13–7.21 (m, 2 H), 6.89 (t, 1 H, J = 8 Hz), 6.81 (d, 1 H, J = 8 Hz), 3.83–3.92 (m, 4 H, ketal), 3.76 (s, 3 H), 3.34 (d, 1 H, J = 5 Hz, H-3), 3.03–3.16 (m, 2 H), 2.81–2.91 (m, 1 H), 2.73 (dt, 1 H, J = 4, 13 Hz), 2.44 (ddd, 1 H, J = 1, 2, 15 Hz, H-17β), 1.71–2.10 (m, 6 H), 1.66 (dd, 1 H, J = 4, 12 Hz), 1.37–1.52 (m, 1 H, H-14); ^{13}C NMR ($CDCl_3$) δ 168.3, 164.6, 143.5, 137.9, 127.9, 122.8, 120.4, 110.6, 109.1, 94.8, 70.5, 65.1, 63.5, 58.0, 53.3, 52.0, 50.7, 41.5, 40.3, 40.0, 36.5, 26.1; EIMS m/z (relative intensity) 382 (M^+, 29), 325 (7), 180 (5), 169 (11), 168 (100), 154 (5); CIMS 383 ($M^+ + 1$, 100).

An analytical sample was recrystallized from methanol as a 1:0.75 methanol complex (methanol, d at 3.49 in the ^{1}H NMR): mp 182–4 °C. Anal. Calcd for $C_{22}H_{26}N_2O_4 \cdot 0.75CH_3OH$: C, 67.22; H, 7.19; N, 6.89. Found: C, 67.46; H, 6.83; N, 6.97.

Hydrolysis of 49a to 19-Demethyl-20-oxoiboxyphylline (50). To a stirred solution of ketal **49a** (93 mg, 0.24 mmol) in 10 mL of methanol at 20 °C was added 1 mL of concentrated HCl and 10 mL of water. After the solution was stirred for 16 h, the total volume was reduced in vacuo to 5 mL, and the resulting residue was poured onto ice. A solution of 20% NH_4OH was added until the mixture was basic to litmus, and it was extracted with several portions of CH_2Cl_2. The combined organic fractions were concentrated to an oil and purified by flash chromatography (silica, ether) to give 68 mg (84%) of **50** as a white foam: TLC (silica, ether) R_f 0.32 (blue, CAS); UV (ethanol) λ_{max} 221, 298, 327 nm; IR (NaCl) ν_{max} 3376, 2947, 2848, 2814, 1704, 1680, 1610, 1479, 1466, 1437, 1384, 1355, 1323, 1307, 1280, 1247, 1206, 1155, 1116, 1085, 1040, 746 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.93 (s, 1 H), 7.08–7.20 (m, 2 H), 6.87 (dt, J = 1, 8 Hz), 6.81 (d, 1 H, J = 8 Hz), 3.76 (s, 3 H), 3.28–3.37 (m, 1 H), 3.11 (dd, 1 H, J = 7, 9 Hz), 2.99 (d, 1 H, J = 5 Hz, H-3), 2.39–2.95 (m, 7 H), 1.97–2.15 (m, 2 H), 1.72 (dd, J = 5, 12 Hz), 1.48–1.60 (m, 1 H, H-14); ^{13}C NMR ($CDCl_3$) δ 210.3, 168.1, 164.4, 143.4, 136.9, 128.1, 122.2, 120.6, 109.3, 95.1, 71.4, 57.8, 53.0, 50.9, 50.8, 46.3, 45.4, 42.2, 37.5, 25.5; EIMS m/z (relative intensity) 338 (M^+, 22), 281 (11), 214 (25), 180 (13), 168 (6), 167 (15), 154 (18), 125 (7), 124 (100). An analytical sample was prepared by crystallization from ether–hexane: mp 146–8 °C. Anal. Calcd for $C_{20}H_{22}N_2O$: C, 70.99; H, 6.55; N, 8.28. Found: C, 70.82; H, 6.48; N, 8.30.

2-Methyl-3-[(trimethylsilyl)oxy]-1,3-butadiene.[35] To a stirred solution of lithium diisopropylamide at −78 °C (prepared from 15.7 mL of diisopropylamine (0.111 mol) and 45.3 mL of 2.5 M *n*-butyllithium in hexanes (0.113 mol), in 60 mL of dry tetrahydrofuran) was added dropwise 10.0 mL of 3-methyl-3-buten-2-one (0.102 mol, purchased from CTC Organics/Tokyo Kasei, Inc.). After 10 min, a solution of 15.0 mL of freshly distilled trimethylsilyl chloride (0.118 mol) in 20 mL of tetrahydrofuran was added slowly. The solution was stirred at −78 °C for 1 h, allowed to warm to room temperature over 20 min, and quenched with 10 mL of ice water. The mixture was poured into a separatory funnel, rinsing with ether, and washed with two portions of cold 5% HCl, two portions of saturated sodium bicarbonate, and one portion of water. After drying over sodium sulfate, the solvent was removed in vacuo, and the resulting oil was vacuum distilled to give 11.0 g (69%) of the diene as a clear oil: bp 39–44 °C (18 mm) [lit.[36] bp 35–37 °C (12 mm)]; IR (neat, NaCl) ν_{max} 3124, 3101, 2961, 2901, 1590, 1354, 1338, 1253, 1188, 1021, 852 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.37 (br s, 1 H), 4.95 (br s, 1 H), 4.50 (br s, 1 H), 4.34 (br s, 1 H), 1.87 (s, 3 H), 0.22 (s, 9 H).

Ethyl 2-[(Trimethylsilyl)oxy]-2-isopropenylcyclopropane-1-carboxylate (42b). This compound was prepared by the same procedure as silyl ester **42a**, from 2-methyl-3-[(trimethylsilyl)oxy]-1,3-butadiene (11.0 g, 0.0705 mol), ethyl diazoacetate (7.62 mL, 0.0725 mol), and 350 mg of cupric acetylacetonate (1.34 mmol), yielding 11.55 g of **42b** (68%) as a diastereomeric mixture: bp 68–78 °C (1.5 mm); IR (neat, NaCl) ν_{max} 2979, 2960, 1733 (broad), 1447, 1397, 1377, 1328, 1301, 1253, 1233, 1165, 1060, 1013, 927, 846 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.95–5.03 (m, 1.5 H), 4.85 (m, 0.5 H), 4.05–4.26 (m, 2 H), 2.02 (dd, 0.5 H), 1.79 (br s, 3 H), 1.64–1.75 (m, 1.5 H), 1.18–1.45 (m, 4 H); CIMS *m/z* (relative intensity) 315 ($M^+ + Me_3Si$, 5), 243 ($M^+ + 1$, 56), 227 (51), 197 (21), 173 (59), 169 (100), 141 (14), 125 (20), 73 (27). Anal. Calcd for $C_{12}H_{22}O_3Si$: C, 59.46; H, 9.16. Found: C, 59.25; H, 9.16.

Methyl 6-Methoxy-5-methyl-4-oxohexanoate (44b). The isopropenylcyclopropane ester **42b** (10.0 g, 0.0413 mol) was stirred in a round-bottom flask for 24 h at room temperature with 0.50 g of potassium carbonate in 50 mL of distilled methanol. The reaction mixture's volume was reduced to ca. 15 mL by rotary evaporation, and the syrupy residue was partitioned between CH_2Cl_2 and saturated aqueous NaCl. The CH_2Cl_2 fraction was separated, washed twice with water, and dried over sodium sulfate. Evaporation of the solvent and flash chromatography of the residue (silica, gradient elution from 2:1 pentane–ether to ether) provided 1.92 g of the isopropenyl ester **43b** and 4.50 g of the methoxy ester **44b**. The isopropenyl ester **43b** was "recycled" by using identical reaction conditions and provided a further 1.39 g of methoxy compound **44b** for a total yield of 5.89 g (76%). Analysis of the crude reaction mixture by ^{1}H NMR spectroscopy indicated an equilibrium with a 2:1 ratio of **44b** to **43b**.

Physical data for **methyl 5-methyl-4-oxohex-5-enoate (43b)**: TLC (silica, 2:1 pentane–ether) R_f 0.35 (H_3PO_4): IR (neat, NaCl) ν_{max} 2957, 2930, 1735, 1680, 1438, 1360, 1265, 1205, 1175, 1090 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.03 (d, 1 H, J = 1 Hz), 5.81 (d, 1 H, J = 1 Hz), 3.69 (s, 3 H), 3.05 (t, 2 H, J = 7 Hz), 2.64 (t, 2 H, J = 7 Hz), 1.89 (s, 3 H); CIMS *m/z* (relative intensity) 157 ($M^+ + 1$, 69), 125 (M^+ − OMe, 100).

Physical data for methoxy ester **44b**: TLC (silica, 1:1 pentane–ether) R_f 0.32 (H_3PO_4); IR (neat, NaCl) ν_{max} 2935, 2880, 1740, 1715, 1435, 1360, 1205, 1170, 1105, 1022 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.68 (s, 3 H), 3.55 (dd, 1 H, J = 8, 9 Hz), 3.40 (dd, 1 H, J = 5, 9 Hz),3.32 (s, 3 H), 2.78–2.91 (m, 3 H), 2.54–2.64 (m, 2 H), 1.10 (d, 3 H, J = 7 Hz); CIMS *m/z* (relative intensity) 189 (M^+, 100), 157 (M^+ − OMe, 78); ^{13}C NMR ($CDCl_3$) δ 210.4, 173.0, 74.6, 58.8, 51.4, 46.5, 36.5, 27.7, 13.2. An analytical sample was prepared by distillation: bp 48–50 °C (0.05 mm). Anal. Calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.33; H, 8.29.

Methyl 6-Hydroxy-5-methyl-4-oxohexanoate (51). This was prepared by modifications to a procedure by Niwa et al.[31] The methoxy ester **44b** (1.55 g, 8.24 mmol) was dissolved in 15 mL of dry CH_2Cl_2 and cooled to −40 °C, with stirring. A saturated solution of sodium iodide (5.56 g, 4.5 equivalents) and 15-crown-5 ether (7.36 mL, 4.5 equiv) in CH_2Cl_2 (ca. 60 mL) was added slowly by syringe. After 10 min, 24.7 mL of a 1.0 M solution of BBr_3 in CH_2Cl_2 (Aldrich) was added, turning the solution a dark brown color. The reaction mixture was stirred for 3 h, allowed to warm to 0 °C, and quenched by the addition of 20 mL of saturated aqueous sodium bicarbonate. The CH_2Cl_2 layer was separated, dried with sodium sulfate, and reduced under vacuum to a brown oil. Flash chromatography (silica, gradient elution from 2:1 pentane–ether to ether) provided 0.95 g (66%) of **51** as a clear oil: TLC (silica, ether) R_f 0.32; IR (film, NaCl) ν_{max} 3200–3600 (O–H, broad), 2925, 2878, 1737, 1711, 1457, 1439, 1410, 1356, 1212, 1171, 1117, 1099, 1041 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.69–3.75 (m, 2 H), 3.68 (s, 3 H), 3.54–3.94 (m, 6 H), 1.14 (d, 3 H, J = 7 Hz); CIMS *m/z* (relative intensity) 175 ($M^+ + 1$, 100), 157 (49), 143 (36), 125 (21), 115 (19).

Methyl 6-Bromo-5-methyl-4-oxohexanoate (52). The methoxy ester **44b** (800 mg, 4.25 mmol) was dissolved in 12 mL of freshly distilled CH_2Cl_2 and cooled to −78 °C, with stirring, in a round-bottom flask. Via syringe, 1.70 mL of a 1.0 M solution of boron tribromide in CH_2Cl_2 (Aldrich) was slowly added, and the solution was stirred for 30 min at −78 °C and allowed to warm to 10 °C over 30 min. Saturated aqueous sodium bicarbonate (5 mL) was added, and the organic layer was separated, dried over sodium sulfate, and reduced to an oil by rotary evaporation. Flash chromatography of the oil (silica, gradient elution from 2:1 pentane–ether to ether) gave 516 mg (51%) of the bromo ester **52** as a clear oil. Varying amounts of the isopropenyl ketone **43b** and the alcohol **51** were also present, but their formation was minimized by the initial boron tribromide addition at −78 °C and by a rapid workup. Physical data for **52**: TLC (silica, 1:1 pentane–ether) R_f 0.38 (H_3PO_4); IR (neat, NaCl) ν_{max} 2977, 2954, 2939, 1736, 1718, 1437, 1361, 1262, 1231, 1211, 1172, 1089, 1020 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.68 (s, 3 H), 3.61 (dd, 1 H, J = 7, 10 Hz), 3.38 (dd, 1 H, J = 6, 10 Hz), 2.58–3.06 (m, 5 H), 1.25 (d, 3 H, J = 7 Hz); CIMS *m/z* (relative intensity) 239/237 ($M^+ + 1$, 20/19), 207 (47), 205 (45), 157 (11), 125 (100); ^{13}C NMR ($CDCl_3$) δ 208.9, 172.9, 51.7, 48.4, 36.3, 33.2, 27.6, 16.1.

Methyl 6-Bromo-5-methyl-4-oxohexanoate Ethylene Ketal (47b). The bromo ketone **52** (0.450 g, 1.89 mmol) was heated for 24 h at reflux with 3.0 mL of ethylene glycol, 50 mg of *p*-toluenesulfonic acid, and 75 mL of benzene in a flask equipped with a condenser and a trap with 3-Å molecular sieves. The flask was cooled, and the mixture was washed twice with saturated aqueous sodium bicarbonate, once with saturated NaCl, and once with water. After drying over sodium sulfate and removal of benzene in vacuo, the crude product was purified by flash chromatography to give 320 mg (69%) of bromo ketal **47b** as a clear oil, plus 50 mg of unreacted ketone **52**. Physical data for bromo ketal **47b**: TLC (silica, 1:1 ether–pentane) R_f 0.50 (H_3PO_4); IR (neat, NaCl) ν_{max} 2979, 2972, 2954, 1738, 1437, 1312, 1243, 1201, 1170, 1122, 1052 cm^{-1}; ^{1}H NMR δ 3.91–4.00 (m, 4 H, ketal), 3.68 (s, 3 H), 3.64–3.69 (m, 1 H), 3.12 (dd, 1 H, J = 10, 11 Hz), 2.36 (t, 2 H, J = 8 Hz), 2.08–2.16 (m, 1 H), 1.91–2.08 (m, 2 H), 1.14 (d, 3 H, J = 7 Hz); CIMS *m/z* (relative intensity) 283/281 ($M^+ + 1$, 17/16), 251 (12), 249 (11), 207 (10), 205 (10), 201 (M^+ − Br, 68), 195 (5), 193 (6), 159 ($M^+ - C_3H_6Br$, 100).

6-Bromo-5-methyl-4-oxohexanal Ethylene Ketal (41b). The bromo ketal ester **47b** (150 mg, 0.53 mmol) was dissolved in 3 mL of freshly distilled CH_2Cl_2 and cooled to −78 °C, with stirring. Diisobutylaluminum hydride (0.64 mL of a 1.0 M solution in CH_2Cl_2) was added slowly by syringe, and the mixture was stirred for 45 min at −78 °C. The reaction mixture was allowed to warm to 0 °C, 10 mL of ether and 0.5 mL of saturated aqueous sodium bicarbonate were added, and the flask was stirred at room temperature for 20 min. After filtering, rinsing the precipitate with 50 mL of ether, and drying the combined filtrate with sodium sulfate, rotary evaporation provided (135 mg) of the crude aldehyde **41b** as a clear oil (>90% pure by ^{1}H NMR): ^{1}H NMR ($CDCl_3$) δ 9.69 (t, 1 H, J = 2 Hz), 3.93 (s, 4 H), 3.67 (dd, 1 H, J = 3, 10 Hz), 3.14 (t, 1 H, J = 10 Hz), 2.43 (dt, 2 H, J = 2, 7 Hz), 1.88–2.19 (m, 3 H), 1.15 (d, 3 H, J = 7 Hz); CIMS *m/z* (relative intensity) 253/251 ($M^+ + 1$, 43/40), 235 (18), 233 (14), 209 (16), 207 (15), 193 (17), 191 (25), 189 (17), 171 (M^+ − Br, 44), 129 ($M^+ - C_3H_6Br$, 100), 127 (33).

Reaction of Aldehyde 41b with Indoloazepine 15. The freshly prepared aldehyde **41b** (120 mg, 0.476 mmol) was slowly

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added to a stirred solution of 115 mg of indoloazepine **15** (0.471 mmol) in 8 mL of dry toluene at room temperature. The mixture was stirred for 2 h at 40 °C, at which time TLC (silica, 10% methanol in CH_2Cl_2) indicated that all of the indoloazepine **15** had reacted and that two pairs of racemic compounds (**55b**) with R_f values from 0.45 to 0.60 were present (blue, CAS). After stirring for 4 h longer, a TLC showed the more polar pair of compounds had become the major component. Triethylamine (0.5 mL) was added, and the mixture was heated at reflux for 8 h. After cooling, the reaction mixture was partitioned between CH_2Cl_2 and 10% aqueous NH_4OH. The aqueous layer was extracted with CH_2Cl_2 twice, and the combined extracts were dried and reduced to a residue by solvent removal in vacuo. Flash chromatography provided a 22-mg fraction consisting of several less polar products and 112 mg of a diastereomeric mixture of the spiro ketals **54a–d** (EIMS m/z (relative intensity) 397 (28), 396 (M^+, 100), 242 (32), 216 (18), 215 (94), 214 (38), 182 (98), 149 (53)). Hydrolysis of the less polar fraction with 10% HCl in methanol provided 2 mg of **18d** (1%) after chromatography. A similar hydrolysis of the spiro ketal fraction provided 36 mg (22%) of a 1:1 mixture of diastereomers **53b,c** (with a trace amount, ca. 10%, of a third compound, presumed to be **53d**) and 43 mg (26%) of the spiro ketone **53a**: TLC (silica, 10% methanol in CH_2Cl_2) R_f 0.33 (blue, CAS); UV (ethanol) λ_{max} 227, 296, 329 nm; IR (NaCl) ν_{max} 3360, 2928, 2871, 2852, 1736, 1677, 1609, 1479, 1466, 1436, 1285, 1249, 1204, 1110, 1049, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.03 (s, 1 H), 7.15–7.25 (m, 2 H), 6.85–6.94 (m, 2 H), 3.77 (s, 3 H), 3.52 (s, 1 H), 3.09–3.17 (m, 2 H), 2.15–2.80 (m, 6 H, includes NH), 1.85–2.09 (m, 3 H), 0.97 (d, 3 H, J = 7 Hz), 0.82 (t, 1 H, J = 12 Hz); EIMS m/z (relative intensity) 353 (11), 352 (M^+, 53), 242 (12), 216 (20), 215 (100), 214 (44), 182 (8), 154 (25), 138 (40), 111 (9), 110 (30); CIMS 353 (M^+ + 1, 100); ^{13}C NMR ($CDCl_3$) δ 219.5, 168.6, 165.7, 143.2, 137.1, 128.1, 121.6, 120.9, 109.4, 92.0, 70.9, 56.6, 53.3, 51.0, 47.7, 45.4, 45.3, 41.8, 40.0, 27.6, 14.6.

Physical data for the diastereomeric mixture of ketones **53b,c**: TLC (silica, 10% methanol in CH_2Cl_2) R_f 0.39 (blue, CAS); ^1H NMR ($CDCl_3$), partial spectrum, δ 9.03 (s, 0.5 H), 8.98 (s, 0.5 H), 7.13–7.20 (m, 2 H), 6.82–6.95 (m, 2 H), 3.78 (s, 1.5 H), 3.74 (s, 1.5 H), 3.55 (s, 0.5 H), 3.51 (s, 0.5 H), 1.09 (d, 1.5 H, J = 7 Hz), 0.96 (d, 1.5 H, J = 7 Hz); EIMS m/z (relative intensity) 353 (8), 352 (M^+, 37), 242 (12), 216 (20), 215 (100), 214 (53), 182 (11), 168 (14), 167 (16), 155 (12), 154 (31), 138 (46), 111 (56), 110 (46). A trace (ca. 10%) of a third diastereomer (**53d**) was indicated by ^1H NMR signals at 3.76 (s, ester) and 9.01 ppm (br s, NH).

N^b-Formylation of Spiro Ketal 54. Dicyclohexylcarbodiimide (DCC, 39 mg, 0.19 mmol) was dissolved in 1.0 mL of CH_2Cl_2 and cooled to 0 °C in a round-bottom flask with stirring. Freshly distilled formic acid (0.020 mL, 0.38 mmol) was added, and the solution was stirred for 5 min, a white precipitate forming in the process. A solution of the spiro ketals **54a–d** (25 mg, 0.063 mmol) in 1.0 mL of CH_2Cl_2 was added, and the solution was stirred at −78 °C for 20 min and warmed to room temperature over 20 min. After filtering, the solution was added to 10% aqueous NH_4OH and extracted with CH_2Cl_2 three times. Concentration and flash chromatography (silica, ether) of the residue provided 8 mg (30%) of one spiro ketal as a mixture of *N*-formamide rotamers: TLC (silica, ether) R_f 0.29 (one spot, blue, CAS); UV (ethanol) λ_{max} 226, 297, 329 nm; IR (film, NaCl) ν_{max} 3325, 2924, 2851, 1675–1650 (broad), 1607, 1479, 1467, 1435, 1383, 1288, 1242, 1185, 1105, 1045 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.53 (s, major rotamer NCHO); EIMS 425 (13), 424 (M^+, 65), 310 (28), 309 (30), 270 (10), 227 (100), 214 (44), 195 (41), 182 (13), 168 (16), 154 (26); CIMS m/z (relative intensity) 425 (M^+ + 1, 100).

Methyl 6-[(*p*-Tolylsulfonyl)oxy]-5-methyl-4-oxohexanoate Ethylene Ketal (47c). The bromo ketal ester **47b** (200 mg, 0.709 mmol) was stirred with 297 mg (1.06 mmol) of silver *p*-toluenesulfonate for 36 h in 5 mL of acetonitrile at reflux. The solution was cooled, filtered, and reduced to a residue, which was then subjected to flash chromatography (silica, 3:1 ether gradient to 100% ether) to yield 56 mg (21%) of the ester **47c** as a clear oil: TLC (silica, 1:1 ether–pentane) R_f 0.17; ^1H NMR ($CDCl_3$) δ 7.79 (dd, 2 H), 7.35 (d, 2 H), 4.14–4.23 (m, 1 H), 3.75–4.05 (m, 3 H), 3.66 (2 s, 3 H), 2.49–3.05 (3 H), 2.45 (s, 3 H), 2.30 (t, 2 H, J = 7 Hz), 1.70–2.17 (m, 2 H), 1.13 (d, 1.5 H, J = 7 Hz), 0.98 (d, 1.5 H, J = 7 Hz); CIMS m/z (relative intensity) 373 (M^+ + 1, 58), 271 (13), 201 (M^+ − OTos, 100), 173 (28), 155 (39), 111 (23).

Methyl 6-[(*p*-Tolylsulfonyl)oxy]-5-methyl-4-oxohexanal Ethylene Ketal (41c). The ester **47c** (75 mg, 0.20 mmol) was dissolved in 5 mL of CH_2Cl_2 and cooled to −78 °C. A solution of 1.0 M diisobutylaluminum hydride in CH_2Cl_2 (0.26 mL) was added dropwise, and the resulting solution was stirred at −78 °C for 1 h, at which time 0.8 mL of water and 5 mL of ether were added, and the solution was allowed to warm to room temperature. After stirring for 30 min the white precipitate was filtered, the solvent was removed from the filtrate by concentration under vacuum, and the residue was purified by flash chromatography to yield 45 mg (66%) of aldehyde **41c**, which decomposed at room temperature and was used immediately in the next reaction: TLC (silica, ether) R_f 0.4; CIMS m/z (relative intensity) 343 (M^+ + 1, 28), 285 (9), 284 (9), 283 (55), 281 (11), 172 (11), 171 (100), 129 (55), 127 (16), 111 (30), 109 (22).

Reaction of Aldehyde 41c with Indoloazepine 15. The aldehyde tosylate **41c** (45 mg, 0.13 mmol) and 32 mg of indoloazepine **15** (0.13 mmol) were stirred for 12 h at 45–50 °C in toluene. Triethylamine (0.1 mL) was added, and the mixture was stirred for 8 h at reflux. The cooled mixture was then partitioned between CH_2Cl_2 and 10% aqueous NH_4OH, the aqueous layer was washed with two further portions of CH_2Cl_2, and the combined portions were dried and concentrated. Flash chromatography (silica, 4% to 15% gradient of methanol in CH_2Cl_2) provided an 8-mg mixture of less polar compounds (blue, CAS) and 23 mg (45%) of a mixture of the spiro ketals **54a–d**. The less polar fraction was hydrolyzed with aqueous HCl, and the residue was chromatographed using similar conditions to yield a 2 mg (4%) mixture of **18c,d**.

6-(Benzyloxy)-4-oxohexanal Ethylene Ketal (41d). A mixture of 3.10 g of ketone **44a** (0.0117 mol), 55 mg of *p*-toluenesulfonic acid monohydrate, 5.0 mL of ethylene glycol, and 100 mL of benzene was heated at reflux for 5 h in a round-bottom flask equipped with a condenser and a Dean–Stark trap. The mixture was then cooled, and the volume was reduced to 50 mL by distillation of benzene. The mixture was washed twice with 25 mL of 10% NaOH, twice with H_2O, and dried with sodium sulfate. The solvent was removed under reduced pressure to yield 3.33 g (92%) of the crude ketal ester **45a**: ^1H NMR ($CDCl_3$) δ 7.23–7.38 (m, 5 H), 4.49 (s, 2 H), 4.11 (q, 2 H), 3.91 (br s, 4 H), 3.57 (t, 2 H), 2.37 (t, 2 H), 1.91–2.05 (m, 4 H), 1.24 (t, 3 H).

The crude ester **45a** was dissolved in 20 mL of dry THF and added slowly to a stirred solution of 1.40 g of LAH in THF at 0 °C. The mixture was allowed to warm to 20 °C and was stirred for 4 h. The flask was set in an ice bath, and 2 mL of H_2O was added slowly to quench the reaction. After stirring for 30 min, filtration, and solvent removal in vacuo, the residue was purified by flash chromatography (silica, ether) to yield 2.01 g (65% from **44a**) of 6-(benzyloxy)-4-oxohexanol ethylene ketal as a clear oil. An analytical sample was prepared by microdistillation (oil bath temperature 183–187 °C/0.01 mm): IR (neat, NaCl) ν_{max} 3200–3600 (broad, O–H), 3032, 2957, 2878, 1498, 1481, 1455, 1367, 1312, 1207, 1100, 1066, 948, 740, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.24–7.35 (m, 5 H), 4.49 (s, 2 H), 3.93 (br s, 4 H), 3.60 (t, 2 H, J = 6 Hz), 3.59 (t, 2 H, J = 7 Hz), 2.12 (br s, 1 H, OH), 2.00 (t, 2 H, J = 7 Hz), 1.61–1.75 (m, 4 H); EIMS m/z (relative intensity) 267 (M^+ + 1, 6), 249 (6), 207 (26), 206 (14), 205 (100), 131 (36), 99 (35), 98 (10), 97 (18), 91 (16). Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33. Found: C, 67.37; H, 8.51.

This (benzyloxy)hexanol (1.53 g, 5.75 mmol) was dissolved in 30 mL of dry CH_2Cl_2 and added to a vigorously stirred slurry of 1.86 g of PCC (8.63 mmol) and 40 mg of sodium acetate in 30 mL of CH_2Cl_2. The dark brown mixture was stirred for 1.25 h at 20 °C. Ether (150 mL) and silica gel (2.0 g) were added, and the resulting brown solids were removed by filtering through Celite, rinsing with 100 mL of ether. The filtrate was reduced to 10 mL, more ether was added, and the residual solids were removed by filtration. This yielded 1.49 g (98%) of the crude aldehyde **41d** as a clear oil after removal of solvents in vacuo: ^1H NMR ($CDCl_3$) δ 9.68 (t, 1 H, J = 2 Hz), 7.25–7.36 (m, 5 H), 4.49 (s, 2 H), 3.89 (br s, 4 H), 3.58 (t, 2 H, J = 7 Hz), 2.45 (dt, 2 H, J = 2, 7 Hz), 2.08 (t, 2 H, J = 7 Hz), 1.97 (t, 2 H, J = 7 Hz). This compound was used directly in the next reaction without further purification.

Preparation of the Benzyloxy Bridged Indoloazepines (61a,b). The aldehyde **41d** was dissolved in methanol (5 mL) and slowly added to a stirred solution of 1.20 g (4.92 mmol) of indoloazepine **15** in 75 mL of methanol, and the mixture was stirred

for 4 h at room temperature. TLC analysis showed that all indoloazepine **15** had reacted and two major products had formed, with R_f values of 0.52 and 0.31, respectively (5% methanol in CH_2Cl_2, both blue with CAS). The solvent was removed in vacuo, and the residue was subjected to flash chromatography (silica, 4% methanol in CH_2Cl_2) to yield 735 mg (30%, based on indoloazepine **15**) of the less polar bridged isomer **61b** and 1.147 g (48%) of the more polar isomer **61a**, both as oils.

Physical data for the less polar isomer **61b**: UV (ethanol) λ_{max} 227, 301, 329 nm: IR (film, NaCl) ν_{max} 3884, 3056, 3030, 2953, 2872, 1680, 1610, 1480, 1467, 1436, 1368, 1288, 1240, 1190, 1104, 1074, 744, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.84 (s, 1 H), 7.19–7.35 (m, 5 H), 7.10–7.17 (m, 2 H), 6.88 (t, 1 H, J = 8 Hz), 6.80 (d, 1 H, J = 8 Hz), 4.42 (s, 2 H), 3.69–3.88 (m, 5 H), 3.71 (s, 3 H), 3.46 (t, 2 H, J = 7 Hz), 3.21–3.36 (m, 2 H), 2.86–2.93 (m, 2 H), 2.17–2.35 (m, 2 H), 1.86 (t, 2 H, J = 7 Hz), 1.77–1.86 (m, 1 H), 1.45–1.59 (m, 2 H), 1.25–1.35 (m, 1 H); EIMS m/z (relative intensity) 491 (19), 490 (M^+, 60), 335 (16), 283 (20), 244 (17), 215 (30), 214 (100), 208 (11), 207 (92), 202 (17), 168 (14), 154 (46), 99 (12), 91 (83).

Physical data for the more polar compound **61a**: UV (ethanol) λ_{max} 224, 299, 327 nm; IR (film, NaCl) ν_{max} 3388, 3054, 3032, 2952, 2872, 1682, 1611, 1480, 1466, 1436, 1367, 1294, 1233, 1187, 1101, 736, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.89 (s, 1 H), 7.20–7.35 (m, 5 H), 7.09–7.17 (m, 2 H), 6.88 (t, 1 H, J = 7 Hz), 6.80 (d, 1 H, J = 8 Hz) 4.48 (m, 1 H), 4.41 (s, 2 H), 3.71 (s, 3 H), 3.28–3.95 (m, 8 H, includes t, J = 7 Hz, at 3.45), 2.84–2.97 (m, 1 H), 1.70–2.43 (m, 6 H, includes t, J = 7 Hz, at 1.85), 1.22–1.62 (m, 3 H); EIMS m/z (relative intensity) 491 (8), 490 (M^+, 26), 355 (10), 283 (21), 228 (9), 215 (21), 214 (96), 208 (14), 207 (100), 168 (12), 154 (29), 91 (32).

Preparation of the Bridged Indoloazepine Vinyl Ketones (62a,b). A solution of 80 mg (0.16 mmol) of bridged benzyl ketal **61a**, 2.0 mL of glacial acetic acid, and 1.0 mL of concentrated HCl was stirred at room temperature for 20 h. The mixture was poured onto ice and made basic to litmus by addition of aqueous NaOH. The resulting suspension was extracted three times with CH_2Cl_2, and the combined organic extracts were reduced to an oil by rotary evaporation. Flash chromatography of the oil (silica, 10% to 25% gradient of methanol in CH_2Cl_2) yielded 7 mg (13%) of the less polar vinyl ketone **62b** and 23 mg (42%) of its very polar isomer **62a**.

Physical data for the less polar vinyl ketone **62b**: TLC (silica, 10% methanol in CH_2Cl_2) R_f 0.42 (blue, fades to gray, CAS); UV (ethanol) λ_{max} 224, 298, 327 nm; ^1H NMR ($CDCl_3$) δ partial spectrum 8.95 (br s, 1 H), 7.12–7.32 (m, 2 H), 6.81–6.99 (m, 2 H), 6.21–6.44 (m, 2 H), 5.84 (dd, 1 H, J = 2, 10 Hz), 3.75 (s, 3 H); EIMS m/z (relative intensity) 338 (M^+, 18), 283 (12), 214 (100), 182 (9), 154 (36).

Physical data for the more polar diastereomer **62a**: TLC (silica, 10% methanol in CH_2Cl_2) R_f 0.07 (blue, fades to gray, CAS); UV (ethanol) λ_{max} 225, 298, 327 nm; IR (film, NaCl) ν_{max} 3365, 2947, 2925, 2873, 1681 (broad, both C=O), 1611, 1481, 1466, 1437, 1388, 1295, 1245, 1189, 1128, 1102, 735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.85 (s, 1 H), 7.15–7.23 (m, 2 H), 6.93 (t, 1 H, J = 8 Hz), 6.84 (d, 1 H, 8 Hz), 6.27 (dd, 1 H, J = 10, 18 Hz), 6.15 (dd, 1 H, J = 2, 18 Hz), 5.89 (dd, 1 H, J = 2, 10 Hz), 3.85 (d, 1 H, J = 16 Hz), 3.74 (s, 3 H), 3.36–3.52 (m, 2 H, includes d, J = 16 Hz, at 3.39), 2.61–3.05 (m, 4 H), 2.19–2.46 (m, 2 H), 1.55–1.78 (m, 2 H); EIMS m/z (relative intensity) 338 (M^+, 28), 283 (28), 215 (19), 214 (100), 182 (9), 167 (7), 154 (33); CIMS 339 (M^+ + 1, 100).

19-Demethyl-20-oxoiboxyphylline (50). The more polar vinyl bridged indoloazepine **62a** (22 mg, 0.065 mmol) was dissolved in 3 mL of anhydrous toluene and heated at reflux under nitrogen for 24 h. Some initial equilibration of **62a** with **62b** was observed by TLC. The solvent was removed under reduced pressure, and the resulting oil was purified by flash chromatography (silica, ether) to yield 6 mg (27%) of ketone **50** as an oil. The product was spectroscopically identical with the product characterized above.

Preparation of Bridged Indoloazepines 62c,d. Via the procedures given for the preparation of the corresponding demethyl compounds **45a**, the keto ester **44b** was converted to its ethylene ketal derivative: ^1H NMR ($CDCl_3$) δ 3.94, (broad, s, 4 H), 3.67 (s, 3 H), 3.50 (dd, 1 H, J = 4, 9 Hz), 3.32 (s, 3 H, methyl ether), 3.19 (dd, 1 H, J = 8, 9 Hz), 2.35 (t, 2 H, J = 8 Hz), 1.89–2.09 (m, 3 H), 1.01 (d, 3 H, J = 7 Hz); CIMS m/z (relative intensity) 233 (M^+ + 1, 76), 201 (100), 169 (19), 159 (80), 145 (32), 99 (24).

Reduction of this ester, according to the DIBAL-H procedure given for reduction of the ester **47c** provided the aldehyde **41e**: ^1H NMR ($CDCl_3$) δ 9.68 (t, 1 H, J = 2 Hz), 3.92 (br s, 4 H, ketal), 3.49 (dd, 1 H, J = 5, 9 Hz), 3.33 (s, 3 H), 3.23 (t, 1 H, J = 8 Hz), 2.42 (dt, 2 H, J = 2, 7 Hz), 1.94–2.17 (m, 3 H), 1.01 (d, 3 H, J = 7 Hz); CIMS m/z (relative intensity) 203 (M^+ + 1, 58), 185 (13), 171 (M^+ – MeO, 51), 159 (14), 145 (15), 141 (100), 129 (58), 109 (63).

Condensation of the aldehyde **41e** with the indoloazepine **15** according to the procedure given for the preparation of the bridged indoloazepines **61a,b** and subsequent treatment with 2:1 acetic acid–HCl, according to the procedure for generation of the vinyl ketones **62a,b**, gave the corresponding methyl-substituted analogues **62c,d**. For the less polar isomer **62d**: TLC (silica gel, 5% methanol in CH_2Cl_2) R_f 0.28 (blue CAS); UV (ethanol) λ_{max} 224, 299, 327 nm; IR (film, NaCl) ν_{max} 3370, 2927, 2881, 2857, 1678, 1609, 1466, 1436, 1287, 1246, 1236, 1192, 1105, 1069, 1039, 746 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.93 (br s, 1 H), 7.30 (d, 1 H, J = 7 Hz), 7.18 (t, 1 H, J = 8 Hz), 6.91 (t, 1 H, J = 8 Hz), 6.83 (d, 1 H, J = 8 Hz), 6.01 (br s, 1 H), 5.75 (br s, 1 H), 3.88 (d, 1 H, J = 15 Hz), 3.72 (s, 3 H), 3.25–3.57 (m, 3 H), 2.71–3.07 (m, 4 H), 1.73–2.35 (m, 3 H), 1.82 (br s, 3 H); EIMS m/z (relative intensity) 352 (M^+, 37), 283 (31), 228 (15), 215 (17), 214 (100), 195 (11), 168 (27), 167 (17), 166 (16), 154 (37). For the more polar isomer **62c**: TLC (silica gel, 5% methanol in CH_2Cl_2) R_f 0.15 (blue, CAS) UV (ethanol) λ_{max} 221, 298, 327 nm; IR (film, NaCl) 3375, 2950, 2927, 2896, 2877, 1681, 1611, 1481, 1466, 1436, 1373, 1295, 1234, 1189, 1126, 1102, 1055, 746 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.83 (br s, 1 H), 7.12–7.23 (m, 2 H), 6.92 (t, 1 H, J = 8 Hz), 6.84 (d, 1 H, J = 8 Hz), 5.86 (br s, 1 H), 5.68 (br s, 1 H), 3.84 (d, 1 H, J = 16 Hz), 3.73 (s, 3 H), 3.23–3.49 (m, 3 H), 2.72–3.05 (m, 3 H), 2.21–2.45 (m, 2 H), 1.80 (br s, 3 H), 1.56–1.68 (m, 2 H); EIMS m/z (relative intensity) 352 (M^+, 38), 283 (29), 228 (8), 215 (15), 214 (100), 182 (13), 168 (13), 167 (16), 154 (57). Attempts at cyclization of **62c,d** according to the procedure for conversion of **62a** to **50**, or at higher temperature, in toluene or in *tert*-butyl alcohol gave no analogous products **18c,d**.

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