Studies in Biomimetic Alkaloid Syntheses. 6. Alternative Pathways to Secodines and Their Acyclic Enamino Acrylate Analogues. Total Syntheses of Desethylibophyllidine, *D*-Norvincadifformine, Desethylvincadifformine, 20-Methyldesethylvincadifformine, and 3-Oxovincadifformine

Martin E. Kuehne,* Thomas H. Matsko, John C. Bohnert, Linda Motyka, and David Oliver-Smith

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

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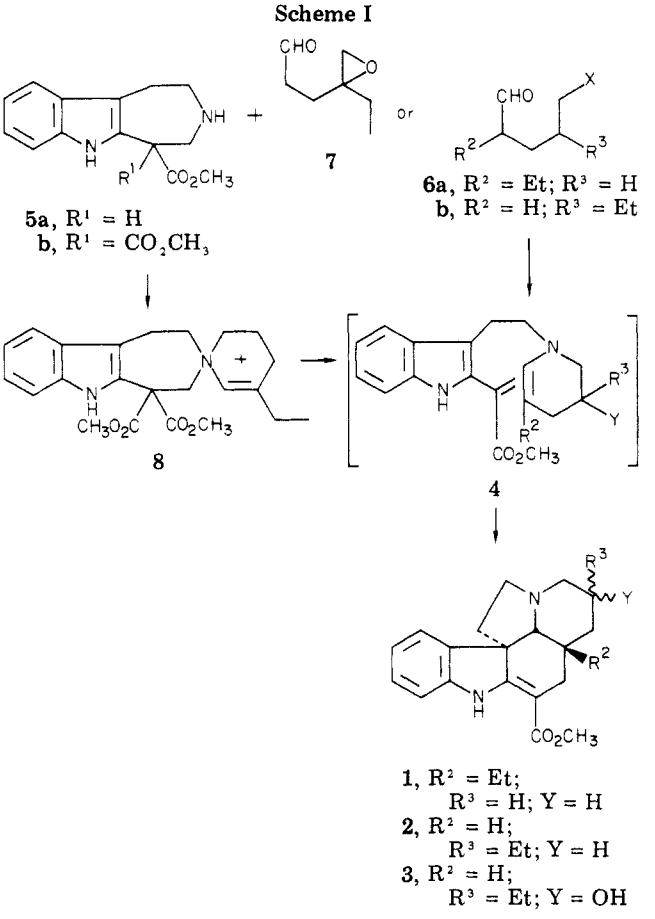
Reactions of methyl 1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-5-carboxylate (**5a**) with aldehydes gave 3,10b-alkano bridged azepines **9–14**, **28**, and **33**. On inter- or intramolecular quaternization and treatment with base the salts **17–20**, **29**, and **34** derived from aldehydes with an α-proton rearranged to the A, B, C, E (and D) ring system of vincadifformine-type alkaloids through initial generation of enamino acrylate analogues **25** of secodines. A corresponding condensation and intramolecular acylation reaction gave 3-oxovincadifformine (**35**) in 85% yield.

In earlier syntheses of vincadifformine (**1**), the ψ-vincadifformines (**2**), and the pandolines (**3**) through secodine (**4**) intermediates,[1-5] we had utilized reactions of the indoloazepine esters **5a,b** with halo aldehydes **6a,b** or the epoxy aldehyde **7** (Scheme I). An interest in the examination of the mechanistic details of these syntheses, with consequent possibilities for extensions to other alkaloids and analogues has now led to more detailed definition of the key condensation and alkylation steps of **5a** and to elucidation of analogous sequential reactions and rearrangements described in this report.

Previously, a spiroenammonium intermediate, **8**, generated by enamine formation and intramolecular N-alkylation, had been isolated in a reaction of the indoloazepine diester **5b** with the bromo aldehyde **6a**.[3] This quaternary salt underwent concerted decarbomethoxylation and fragmentation to a secondine **4**. An analogous reaction sequence, with even more facile base-promoted fragmentation, was assumed for conversion of the indoloazepine monoester **5a** to a secodine, **4**. In order to study this reaction sequence, we condensed the indoloazepine monoester **5a** with a variety of aldehydes. Thus, it was found that aliphatic and aromatic aldehydes rapidly form the bridged indoloazepines **9–14** (Scheme II), as indicated by the characteristic β-anilinoacrylate chromophore (UV λ_{max} 230, 299, 328 nm) in the bridged structures, rather than enamine or aminal products with an indole chromophore (UV λ_{max} 226, 285 nm).

With aldehydes other than formaldehyde two condensation products were produced. While a difference in TLC mobilities and nucleophilic amine reactivities might suggest skeletal isomerism for the products derived from aliphatic aldehydes (see below), their essentially identical mass-fragmentation patterns indicated stereoisomeric structures. The epimers with substituents protruding over the acrylate double bond (**10a–14a**) and having a less encumbered nitrogen lone pair would be expected to show lower R_f values on TLC. This assignment is supported by an upfield shift of δ 0.5 for the methyl substituent of the acetaldehyde derived product with lower R_f, **11a**, and by observation of two methyl doublets at δ 1.13 and 0.43 for the corresponding isobutyraldehyde-derived product **14a**. With increasing substituent bulk these epimers, **10a–14a**, showed increasing predominance over epimers **10b–14b** when generated in methanol. This predominance may be ascribed to absence of steric crowding of a methanol-solvated N_b electron pair in **10a–14a**, in contrast to **10b–14b**. When the condensation was carried out in chloroform, a 1:1 ratio of epimers was formed from aliphatic aldehydes, and the benzaldehyde condensation gave a 2:1 ratio of **10b** to **10a**, contrasted with a 1:2 ratio of **10b** to **10a** in methanol. In the predominant epimer **10b** obtained from benzaldehyde in chloroform, the proximity of the phenyl substituent and an aromatic peri proton could be seen

Scheme I



(1) (a) A. I. Scott, *Acc. Chem. Res.*, **3**, 151 (1970); (b) *Bioorg. Chem.*, **3**, 398 (1974).
(2) M. E. Kuehne, D. M. Roland, and R. Hafter, *J. Org. Chem.*, **43**, 3705 (1978).
(3) M. E. Kuehne, T. H. Matsko, J. C. Bohnert, and C. L. Kirkemo, *J. Org. Chem.*, **44**, 1063 (1979).
(4) M. E. Kuehne, T. H. Matsko, and J. A. Huebner, *J. Org. Chem.*, **44**, 2477 (1979).
(5) M. E. Kuehne, C. L. Kirkemo, J. C. Bohnert, and T. H. Matsko, *J. Org. Chem.*, **45**, 3259 (1980).

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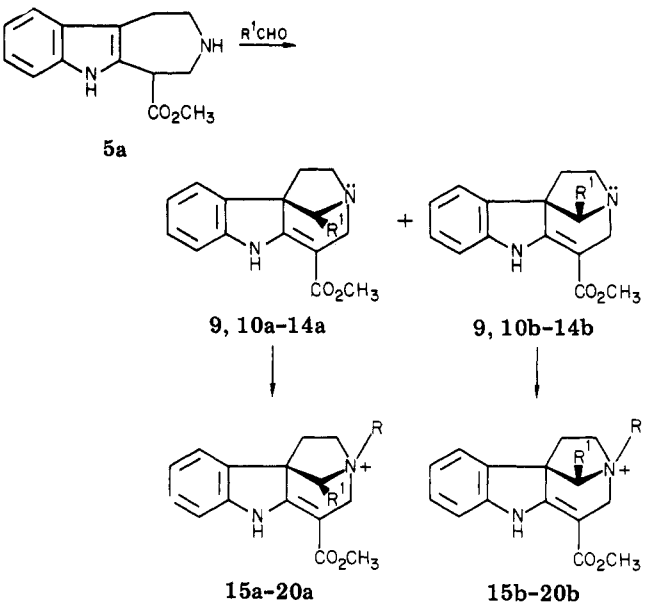
Scheme II[a]



[a] R = CH_3 or $CH_2C_6H_5$; **9**, **15**, R^1 = H; **10**, **16**, R^1 = C_6H_5; **11**, **17**, R^1 = CH_3; **12**, **18**, R^1 = C_2H_5; **13**, **19**, R^1 = n-C_3H_7; **14**, **20**, R^1 = i-C_3H_7.

directly. The strong upfield displacement of this proton to δ 6.33 in the NMR spectrum of the compound thus provided further support for the relative structure assignments of the epimers **10a** and **10b**.

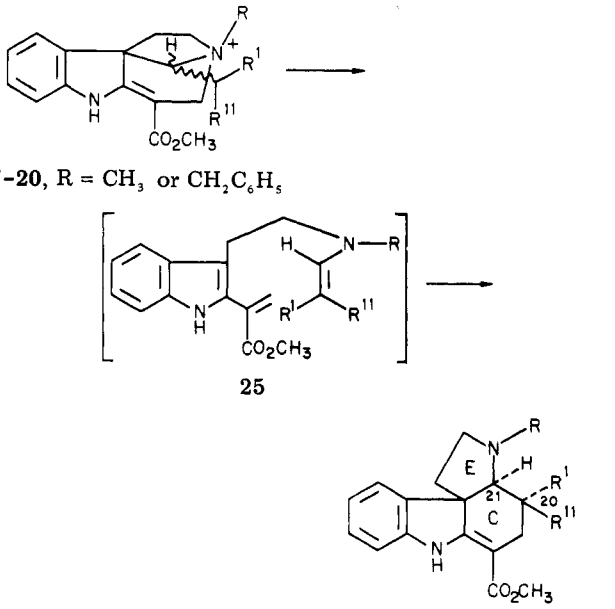
Formation of the bridged indoloazepine products was found to be a readily reversible process. The imonium intermediates required for these reactions also gave rise to facile epimerization at the bridging carbon. While the individual pure isomers could be rapidly chromatographed on silica gel without epimerization, epimeric mixtures, also containing the indoloazepine, were formed on prolonged adsorption.

N_b-Alkylation of the bridged indoloazepines **9–14** with methyl iodide or benzyl bromide resulted in the quaternary salts **15–20**. The bridged indoloazepines **10a–14a** with a less hindered nitrogen lone pair were alkylated more rapidly than their epimers **10b–14b**. The quaternary salts retained the typical UV chromophore of the bridged indoloazepines (λ_{max} 230, 299, 325) but showed a striking change of IR absorption from ν_{max} 1675 and 1600 cm^{-1} for **9–14** to 1685, 1640, and 1600 cm^{-1} for **15–20**. An analogous change was found for the bridged indoloazepine hydrochloride salts (and for vincadifformine hydrochloride vs. its free base).

Addition of tertiary amines to the N-alkylated, bridged indoloazepines **17–20** derived from aldehydes having an α-proton resulted in their rearrangement to tetracyclic products **21–24** with a skeleton of the pentacyclic aspidosperma alkaloids lacking ring D (Scheme III). Thus, the generation and chemical reactivity of the previously achieved biomimetic secodine intermediates[2-5] could also be demonstrated with corresponding seco intermediates **25**, and a versatile path to such intermediates and their cyclization products **21–24** was obtained. Debenzylation of products such as **21** or **24** in turn provided secondary amine synthons, i.e., **26** and **27**, for still further structure modification of the aspidosperma alkaloid skeleton.

While the bridged indoloazepines **11** and **14** derived from acetaldehyde and isobutyraldehyde can only give single products **21** and **24** (assuming a cis C–E ring fusion), C-20 epimeric products might be anticipated from other aldehydes which can give rise to isomeric E or Z enamines

Scheme III



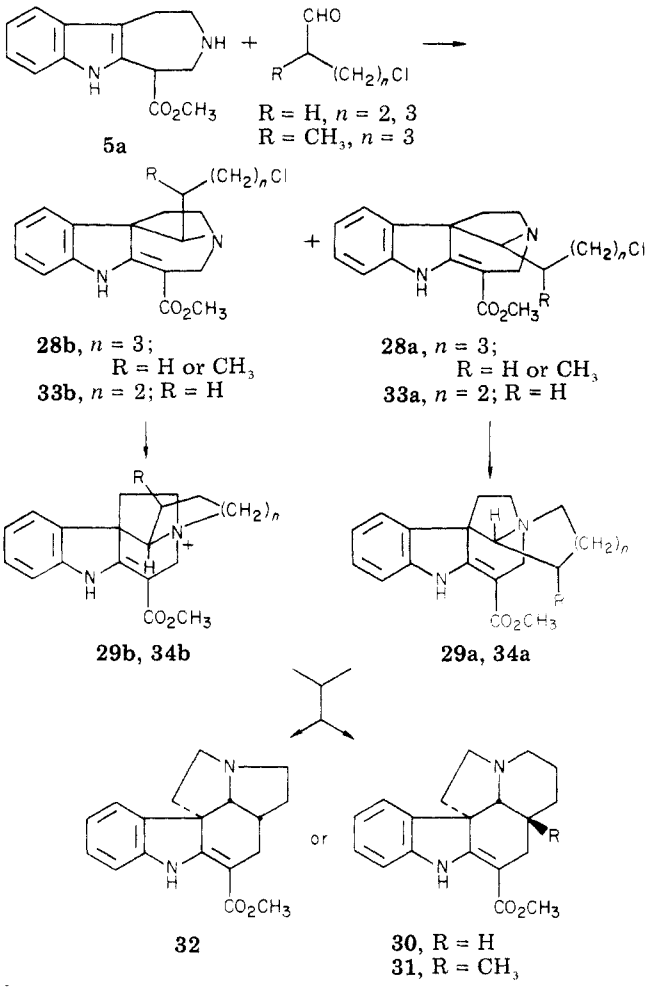
in the fragmentation to **25**.[6] However, only one product was formed in the propionaldehyde- and n-butyraldehyde-derived cases **22** and **23**, suggesting preferential generation and reaction of E enamine intermediates **25** (R^1 = CH_3 or C_2H_5, R^{11} = H). An NMR singlet for the C-21 proton in products **22** and **23**, due to a 90° dihedral angle and lack of coupling between protons at C-21 and C-20, with ring C in a quasi boat conformation, is in agreement with such structure assignments to the stereoselectively formed products **22** and **23**.

A critical question in the proposal of secodine intermediates in syntheses of vincadifformine and related alkaloids by reactions of the indoloazepine monoester **5a** with halo aldehydes had now been opened. Could the bridged indoloazepine intermediates undergo rearrangement to an ABCE tetracyclic moiety of vincadifformine without prior N-alkylation and formation of ring D? If so, a final ring D cyclization would require alternative explanations for the stereoselectivity found in formation of vincadifformine, the ψ-vincadifformines, and the pandolines, which we had previously ascribed to reactions of biomimetic secodine intermediates.[2-5] In order to answer this question, the condensation product **14** of isobutyraldehyde and the indoloazepine **5a** was heated at reflux in toluene, methanol, tetrahydrofuran, or dichloromethane, with or without acids. These are conditions more vigorous or equal to those in our alkaloid syntheses, which already take place at room temperature. Only traces of the secondary amine **27** could be detected by TLC after 20 h at 100 °C. For comparison, this product was obtained by debenzylation of the rearrangement product **24** (R = $CH_2C_6H_5$). An initial N-alkylation, followed by fragmentation (i.e., secodine formation), is therefore indicated in our vincadifformine-type alkaloid syntheses.

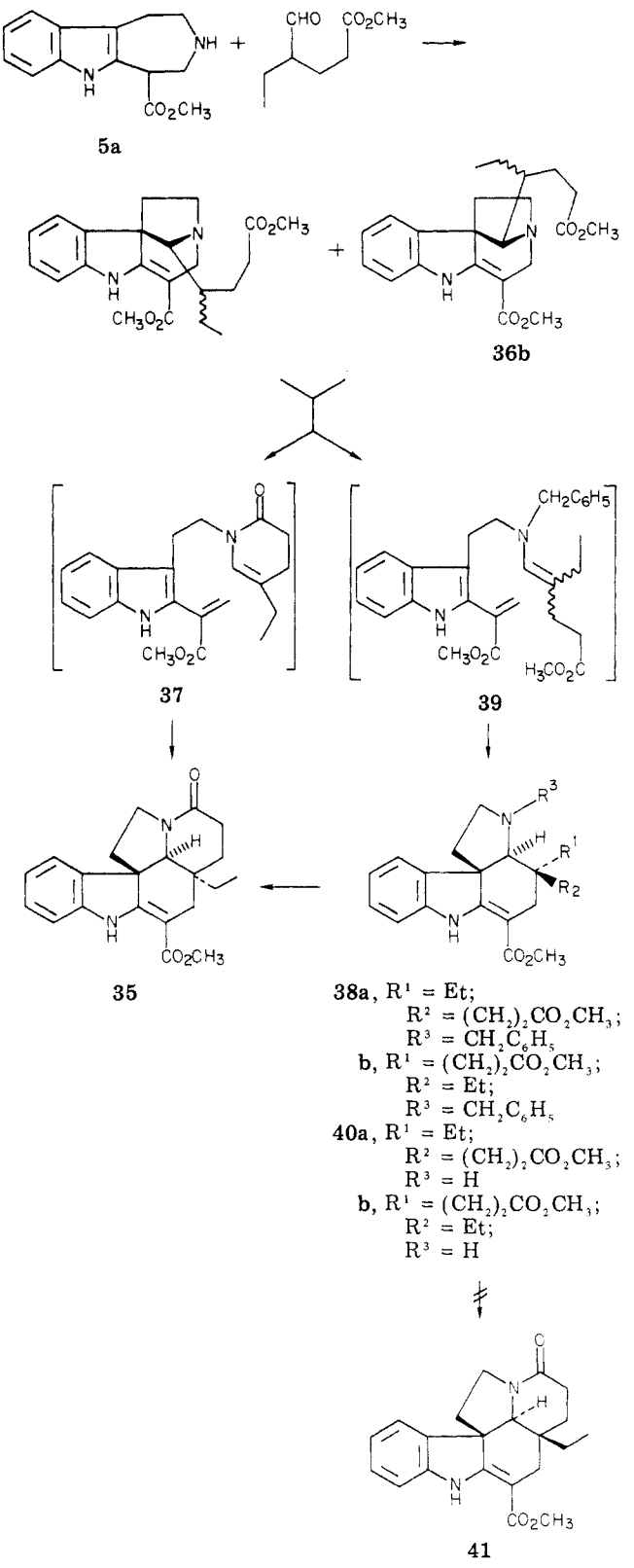
The formation of bridged indoloazepines **11–14** and their

(6) The numbering system used in this publication is one based on a biogenetic interrelationship of indole alkaloids as proposed by J. LeMen and W. I. Taylor, *Experientia*, 21, 508 (1965). All synthetic compounds are racemic, and structures are written in the absolute configurations of the natural products.

Scheme IV



Scheme V



rearrangement on intermolecular N_b-alkylation suggested an analogous pathway for formation of the pentacyclic vincadifformine skeleton from the indoloazepine monoester **5a** on reaction with δ-halo aldehydes.[2-5] When the indoloazepine **5a** was combined with 5-chloropentanal in methanol or tetrahydrofuran, the epimeric anilinoacrylates **28a,b** were generated and transformed into quaternary salts, **29a,b** at 20–40 °C (Scheme IV). Intramolecular quaternization of the less polar intermediate **28b** to form **29b** was more rapid than quaternization of the epimeric more polar intermediate **28a**. On addition of a tertiary amine, the quaternary salts **29a,b** rearranged to desethylvincadifformine (**30**).

Similarly, the stereospecific synthesis of desethyl-20-methylvincadifformine (**31**) was achieved in 72% overall yield from 5-chloro-2-methylpentanal. The observed intermediates were not characterized here because of their stereochemical complexity, an insignificant complication which is lost at the norsecodine stage.

The reaction sequence leading from indoloazepine through its bridged condensation product, intramolecular quaternization and rearrangement, could be very clearly demonstrated in a synthesis of the recently isolated alkaloid desethylibophyllidine (**32**).[7] Thus, condensation of the indoloazepine **5a** with 4-chlorobutyraldehyde in tetrahydrofuran led to rapid generation of the epimeric bridged indoloazepines **33a,b**. In 1 h all of the starting materials had reacted, but after 5 min a quaternary salt already started to precipitate. This salt could be ascribed exclusively to cyclization of the higher R_f bridged intermediate **33b**, which was completely converted to the quaternary salt **34b** in 3 h at room temperature (51%). Separation of the reaction mixture then provided the pure lower R_f bridged intermediate **33a** (49%), which underwent cyclization to the quaternary salt **34a** on being refluxed in tetrahydrofuran for 3 h. On reaction with triethylamine, desethylibophyllidine (**32**) was formed from either of the quaternary salts **34a,b**.

(7) C. Kan, H.-P. Husson, H. Jacquemin, S.-K. Kan, and M. Lounasmaa, *Tetrahedron Lett.*, 55 (1980).

Since rearrangement of bridged indoloazepines **11–14**, **28**, and **33** to the vincadifformine type skeleton (**21–24**, **30–32**) was promoted by N-alkylation, an analogous N-acylation was explored. Thus, it was found that heating of the indoloazepine **5a** with methyl 4-formylhexanoate in toluene gave 3-oxovincadifformine (**35**) in 85% yield (Scheme V).[8] The intermediate bridged indoloazepines **36a,b** were generated at room temperature. Again the product **36b** with higher R_f already rearranged slowly at room temperature. The less reactive isomeric product **36a** could be generated preferentially when the condensation reaction was carried out in presence of an equivalent of HCl, due to greater N_b basicity in **36a**.

In view of the inability of a bridged indoloazepine to rearrange substantially without N_b-alkylation, the present oxovincadifformine synthesis must proceed through an oxosecodine intermediate, **37**. Cyclization of this intermediate to 3-oxovincadifformine then represents the first example where preference for a concerted intramolecular Diels–Alder reaction, rather than a stepwise mechanism, can be expressed for a secodine-type cyclization. In the oxosecodine cyclization a stepwise generated acylimonium intermediate would be of higher energy than the imonium intermediate derived from a basic secodine. The observed stereospecificity in generation of 3-oxovincadifformine is also in accord with a 3-oxosecodine, **37**, intermediate in this reaction.

On N_b-benzylation of the bridged indoloazepine esters **36a,b** and reaction of the resultant quaternary salts with base, a C-20 epimeric mixture of the rearrangement products **38a,b** was obtained. A lack of stereospecificity was anticipated here since less selectivity in *E* vs. *Z* enamine formation would be expected on generation of a disubstituted enamine intermediate **39** than on generation of a monosubstituted enamine **25**. The chromatographically separated tetracyclic amino esters **38a,b** proved to be relatively stable to epimerization. They were not interconverted in refluxing methanol, in toluene at 100 °C, or in acetic acid at 20 °C, but in acetic acid at 100 °C or on hydrochloride formation, epimerization (through reversible C/E ring cleavage) was observed.

Debenzylation of the amino esters **38a,b** by hydrogenolysis in acetic acid led to the corresponding secondary amines **40a,b**. While one of these amino esters, **40a**, already underwent cyclization to 3-oxovincadifformine (**35**) at room temperature during the hydrogenolysis, its epimer **40b** could be isolated and required heating in toluene with acid catalysis for cyclization. The product then was again 3-oxovincadifformine (**35**) rather than a C/D *trans*-3-oxovincadifformine, **41**.

Experimental Section

Condensation of Methyl 1,2,3,4,5,6-Hexahydroazepino[4,5-*b*]indole-5-carboxylate (5a) with Aldehydes. (A) With Formaldehyde To Form 9. A solution of 50 mg (1.67 mmol) of paraformaldehyde and a crystal of KOH in 2 mL of methanol was added to 150 mg (0.614 mmol) of the indoloazepine **5a** in 5 mL of methanol. After the mixture was stirred for 5 h at 22 °C under nitrogen, TLC (SiO_2, 5% methanol in dichloromethane) showed no starting amine but a less polar product with R_f 0.2 which stained blue with cerric ammonium sulfate (CAS) spray. Concentration under vacuum and filtration of an ether solution of the residue through neutral alumina, concentration, and crystallization from ether–hexane gave 0.15 g (95%) of product: mp 147–150 °C; NMR (250 MHz, $CDCl_3$) δ 8.91 (1 H, br s), 7.31–6.82 (4 H, m), 3.98 (1 H, d, J = 16 Hz), 3.86 (3 H, s), 3.41 (2 H, m), 3.20 (1 H, d, J = 12 Hz), 2.92 (2 H, m), 2.44–2.12 (2 H, m); IR (KBr) ν_{max} 3400, 1675, 1605 cm^{-1}; UV (MeOH) λ_{max} 230, 297, 329 nm; mass spectrum (80 eV), *m/e* (relative intensity) 257 (29), 256 (100), 215 (48), 214 (87), 155 (28), 154 (66), 128 (28), 127 (28).

Anal. Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.54; H, 6.38; N, 10.80.

(B) With Benzaldehyde To Form 10a,b. A mixture of 200 mg (0.82 mmol) of the indoloazepine **5a** and 96.7 mg (0.90 mmol) of benzaldehyde in 5 mL of dry methanol was stirred for 8 h. Concentration under vacuum and TLC of the residue (SiO_2, 5% methanol in dichloromethane) then showed two products with R_f 0.5 and 0.7 and a trace of starting amine with R_f 0.1, all staining blue with CAS spray. The two products **10a,b** were present in a ratio of 2:1 (judged by NMR, below). Fractional crystallization from ether or cyclohexane gave the more polar isomer **10a**: mp 148–150 °C; NMR ($CDCl_3$) δ 8.96 (1 H, br s), 7.26–6.89 (9 H, m), 4.60 (1 H, s), 3.65–3.54 (5 H, m, includes OCH_3, 3 H, s at 3.60), 3.27 (1 H, d, J = 16 Hz), 3.12–3.01 (1 H, m), 2.54 (2 H, m); IR (KBr) ν_{max} 3380, 3310, 2890, 2850, 1675, 1600, 1460, 1425, 1380, 1290, 1245, 1225, 1180, 1045, 800, 770, 750, 735, 730, 690 cm^{-1}; UV (MeOH) λ_{max} 210, 225 (sh), 300, 330; mass spectrum (80 eV), *m/e* (relative intensity) 333 (29), 332 (96), 215 (51), 214 (100), 182 (21), 155 (22), 154 (73), 91 (37).

Anal. Calcd for $C_{21}H_{20}N_2O_2$: C, 75.88; H, 6.07; N, 8.43. Found: C, 75.93; H, 6.28; N, 8.26.

Separation of 164 mg (60%) of the isomeric products, obtained by filtrations of a 1:3 dichloromethane/ether solution of the reaction concentrate (generated above) through alumina, by chromatography on alumina (neutral, activity I) and elution with ethyl acetate/hexane (1:1) gave the less polar isomer **10b**: mp 156–158 °C; NMR ($CDCl_3$) δ 9.14 (1 H, s), 7.22–6.27 (8 H, m), 6.33 (1 H, d, J = 8 Hz), 4.19 (1 H, s), 4.09 (1 H, d, J = 16 Hz), 3.82–3.67 (5 H, m, contains 3.74, 3 H, s, and 3.64, 2 H, d, J = 16 Hz), 3.10–2.95 (1 H, m), 2.42–2.11 (2 H, m); IR (KBr) ν_{max} 3380, 2960, 2900, 2855, 1670, 1605, 1460, 1435, 1285, 1235, 1190, 1050, 1025, 780, 755, 740, 725, 705 cm^{-1}; UV (MeOH) λ_{max} 227, 229, 328 nm; mass spectrum (80 eV), *m/e* (relative intensity) 333 (31), 332 (97), 215 (48), 214 (100), 182 (18), 154 (65), 137 (18), 91 (46).

Anal. Calcd for $C_{21}H_{20}N_2O_2$: C, 75.88; H, 6.07; N, 8.43. Found: C, 75.85; H, 6.23; N, 8.40.

(C) With Acetaldehyde To Form 11a,b. A 3% methanolic HCl solution was added to 500 mg (2.05 mmol) of the indoloazepine monoester **5a** in 5 mL of dry methanol until the solution was strongly acidic. The methanol and excess HCl were removed under vacuum, and the residual amine hydrochloride was dissolved in 5 mL of water. To this solution was added 0.51 mL of methanol containing 113 mg (2.60 mmol) of acetaldehyde. After being stirred for 8 h at 22 °C, the reaction mixture contained a trace of indoloazepine **5a** as seen by TLC (SiO_2, 5% methanol in dichloromethane, R_f 0.1) and two isomeric products (**11a,b**, R_f 0.20–0.25) which all stained blue with cerric ammonium sulfate (CAS) spray. The reaction mixture was diluted with 20 mL of ether, and aqueous ammonia was added dropwise with rapid stirring until the aqueous layer was strongly basic. The phases were separated, and the aqueous layer was extracted with 15 mL of ether. The combined ether solutions were washed with water (2 × 25 mL) and brine (25 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum to yield 0.502 g (91%) of the amorphous condensation products **11a,b** in a ratio of 3:2 as determined by NMR (below). The product mixture crystallized from ether with variable melting points. Separation of the mixture on alumina (neutral, activity II) by elution with ether gave the more polar product **11a**: mp 149–151 °C; NMR ($CDCl_3$) δ 9.33 (1 H, br s), 7.58–7.0 (4 H, m), 4.17–3.3 (7 H, m), 3.2–2.8 (1 H, br m), 2.5–2.05 (2 H, m), 1.05 (3 H, d, J = 5 Hz); IR (KBr) ν_{max} 3400, 2910, 2840, 1675, 1605, 1460, 1430, 1280, 1270, 1240, 1175, 1140, 1030, 760, 725 cm^{-1}; UV (MeOH) λ_{max} 225, 295, 327 nm; mass spectrum (80 eV), *m/e* (relative intensity) 271 (21), 270 (100), 215 (42), 214 (90), 155 (21), 154 (64), 127 (21), 56 (43).

Anal. Calcd for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.37. Found: C, 77.24; H, 6.82; N, 10.22.

The less polar product **11b** was crystallized from cyclohexane: mp 144–145 °C; NMR ($CDCl_3$) δ 9.45 (1 H, br s), 7.78–7.0 (4 H, m), 4.34–3.5 (6 H, m), 3.45–2.81 (2 H, m), 2.49 (2 H, t, J = 8 Hz), 1.52 (3 H, d, J = 5 Hz); IR (KBr) ν_{max} 3400, 2930, 2860, 1675, 1605, 1460, 1435, 1270, 1240, 1230, 1185, 1035, 775, 750, 740, 728 cm^{-1};

(8) We thank Professor J. Lévy for a comparison sample of 3-oxovincadifformine, obtained by oxidation of (-)-vincadifformine.

UV λ_{max} 225, 295, 327 nm; mass spectrum (80 eV), *m/e* (relative intensity) 271 (22), 270 (100), 215 (46), 214 (89), 155 (23), 154 (64), 127 (21), 56 (42).

Anal. Calcd for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.37. Found: C, 71.35; H, 6.88; N, 10.18.

(D) With Propionaldehyde To Form 12a,b. From 200 mg (0.82 mmol) of indoloazepine and 52.4 mg (0.90 mmol) of propionaldehyde in 5 mL of methanol at 22 °C were obtained two products after 8 h, which had R_f 0.26 and 0.48 [SiO_2, 5% methanol in dichloromethane, detected with CAS (blue)]. NMR analysis of the mixure indicated a 2:1 product ratio in favor of the more polar isomer. Fractional crystallization from ether gave the more polar isomer **12a**, mp 157–158 °C. Chromatographic separation of the isomers by preparative TLC on Al_2O_3 with ether gave the less polar isomer **12b** as a noncrystalline solid. For the more polar isomer **12a**: NMR ($CDCl_3$) δ 8.89 (1 H, br s), 7.30–6.75 (4 H, m), 3.96–3.65 (4 H, m includes OCH_3 at 3.73, 3 H, s), 3.45–2.72 (4 H, m), 2.39–2.15 (2 H, m), 1.48–1.16 (2 H, m), 0.88 (3 H, t, J = 7 Hz); IR (KBr) ν_{max} 3360, 2940, 2850, 1680, 1610, 1465, 1435, 1295, 1240, 1180, 1045, 1015, 880, 805, 780, 760, 745, 730 cm^{-1}; UV (MeOH) λ_{max} 230, 300, 327 nm; mass spectrum (80 eV), *m/e* (relative intensity) 285 (54), 284 (99), 215 (71), 214 (100), 182 (46), 154 (79), 127 (43), 70 (54).

Anal. Calcd for $C_{17}H_{20}N_2O_2$: C, 71.80; H, 7.09; N, 9.85. Found: C, 71.71; H, 7.17; N, 9.59.

For the less polar isomer **12b**: NMR ($CDCl_3$) δ 9.02 (1 H, br s), 7.34–6.75 (4 H, m), 4.08–3.85 (1 H, d, J = 16 Hz), 3.74 (3 H, s), 3.60–3.15 (2 H, m), 2.96–2.64 (2 H, m), 2.39–2.15 (2 H, m), 1.95–1.61 (2 H, m), 1.03 (3 H, t, J = 7 Hz); IR (KBr) ν_{max} 3360, 2920, 2860, 1675, 1605, 1465, 1435, 1365, 1285, 1235, 1190, 1040, 780, 745 cm^{-1}; UV (MeOH) λ_{max} 230, 300, 327 nm; mass spectrum (80 eV), *m/e* (relative intensity) 285 (42), 284 (100), 215 (74), 214 (99), 182 (36), 154 (78), 127 (34), 70 (52).

(E) With *n*-Butyraldehyde To Form 13a,b. After 18 h at 22 °C a solution of 250 mg (1.02 mmol) of the indoloazepine **5a** and 77.6 mg (1.08 mmol) of *n*-butyraldehyde in 5 mL of methanol showed two products by TLC [SiO_2, 5% methanol in dichloromethane, R_f 0.58 and 0.38, detected with CAS spray (blue)] as well as some starting amine **5a** [R_f 0.08 (blue)]. The solvent was evaporated under vacuum and a solution of the residue in ether filtered through neutral alumina. On concentration, 240 mg (80%) of the reaction products showed a 2:1 isomer ratio by NMR (below), in favor of the lower R_f product. The isomers were separated by column chromatography (SiO_2, 5% methanol in dichloromethane).

The lower R_f isomer **13a** was crystallized from ether: mp 144–145 °C; NMR ($CDCl_3$) δ 8.99 (1 H, s), 7.33–6.80 (4 H, m), 4.02–3.70 (4 H, m contains OCH_3 3.77, 3 H, s), 3.50–3.19 (3 H, m), 3.09–2.70 (1 H, m), 2.40–2.12 (2 H, m), 1.57–1.02 (4 H, m), 0.96–0.69 (3 H, t); IR (KBr) ν_{max} 3340, 2930, 2860, 1680, 1610, 1460, 1430, 1290, 1240, 1180, 735 cm^{-1}; UV (MeOH) λ_{max} 232, 305 (sh), 332 nm; mass spectrum (80 eV), *m/e* (relative intensity) 299 (34), 298 (97), 215 (64), 214 (100), 182 (24), 155 (24), 154 (72), 84 (47); hydrochloride, mp 183–184 °C dec.

Anal. Calcd for $C_{18}H_{23}N_2O_2Cl$: C, 64.56; H, 6.92; N, 8.37; Cl, 10.59. Found: C, 64.29; H, 7.20; N, 8.22; Cl, 10.29.

For the higher R_f amorphous isomer: NMR ($CDCl_3$) δ 9.01 (1 H, s), 7.35–6.76 (4 H, m), 3.95 (1 H, d, J = 16 Hz), 3.72 (3 H, s), 3.59–3.18 (2 H, m), 3.02–2.59 (2 H, m), 2.37–2.14 (2 H, m), 1.82–1.15 (4 H, m), 1.08–0.82 (3 H, t); IR (KBr) ν_{max} 3380, 2950, 2860, 1675, 1605, 1465, 1435, 1285, 1235, 1185, 1050, 1020, 800, 735 cm^{-1}; UV (MeOH) λ_{max} 232, 305 (sh), 332 nm; mass spectrum (80 eV), *m/e* (relative intensity) 299 (18), 298 (84), 215 (31), 214 (100), 155 (13), 154 (51), 84 (23), 43 (29).

(F) With Isobutyraldehyde To Form 14a,b. A solution of 250 mg (1.02 mmol) of the indoloazepine **5a**, 81.3 mg (1.13 mmol) of isobutyraldehyde, and a crystal of benzoic acid in 10 mL of dry methanol was stirred under nitrogen at 50 °C for 14 h. TLC (SiO_2, 5% methanol in dichloromethane) then showed two products, R_f 0.7 and 0.3, detected with CAS spray (blue), with the more polar component predominating. Concentration under vacuum and recrystallization of the crystalline residue from methanol gave 174 mg of the lower R_f component which was recrystallized from ether–hexane; mp 157–158 °C. Chromatography of the initial methanolic mother liquors on silica gel, elution with 2.5% methanol in dichloromethane, and crystallization from ether–hexane gave an additional 36 mg of the more polar product (total yield 70%): NMR ($CDCl_3$) δ 9.31 (1 H, br s), 7.58–7.02 (4 H, m), 4.02 (1 H, d, J = 17 Hz), 3.88 (3 H, s), 3.8–3.3 (3 H, m), 3.18–2.8 (3 H, m), 2.5–2.6 (2 H, m), 1.98–1.66 (1 H, m), 1.13 (3 H, d, J = 7 Hz), 0.43 (3 H, d, J = 7 Hz); IR (KBr) ν_{max} 3390, 3310, 2900, 2860, 1605, 1460, 1430, 1290, 1245, 1225, 1180, 1050, 775, 750, 740, 730, 695 cm^{-1}; UV (MeOH) λ_{max} 225, 300, 327 nm; mass spectrum (80 eV), *m/e* (relative intensity) 299 (49), 298 (99), 215 (67), 214 (100), 167 (30), 155 (33), 154 (78), 84 (57).

Anal. Calcd for $C_{18}H_{22}N_2O_2$: C, 72.45; H, 7.43; N, 9.39. Found: C, 72.69; H, 7.51; N, 9.37.

N-Alkylation and Rearrangement of Aldehyde Condensation Products. (A) Benzylation of Acetaldehyde Condensation Products 11a,b To Form 21 and Debenzylation to 26. A solution of 150 mg (0.56 mmol) of the bridged indoloazepines **11a,b** derived from acetaldehyde and 105 mg (0.61 mmol) of benzyl bromide in 5 mL of chloroform was refluxed under nitrogen for 20 h. Addition of 150 μL of *N,N*-diisopropylethylamine was followed by continued reflux for 6 days. TLC (SiO_2, 5% methanol in dichlormethane) then showed a major product at R_f 0.85 and a few minor components. Concentration under vacuum and column chromatography of the residue on silica gel gave nonpolar components with 50 mL of dichloromethane followed by 110 mg (54%) of the major product **21**, eluted with 5% ether in dichloromethane. A sample was recrstallized from methanol: mp 58–60 °C; NMR ($CDCl_3$) δ 9.36 (1 H, br s), 7.85–7.03 (9 H, m), 4.25 (1 H, d, J = 12 Hz), 4.08–3.80 (4 H, m, includes OCH_3 at 3.99, 3 H, s), 3.67 (2 H, s), 3.48 (1 H, d, J = 4 Hz), 3.19–1.20 (6 H, br m); IR (KBr) 3390, 2910, 2810, 1670, 1605, 1465, 1435, 1275, 1250, 1235, 1180, 1025, 750 cm^{-1}; UV (MeOH) λ_{max} 220, 292, 329 nm; mass spectrum (80 eV), *m/e* (relative intensity) 361 (46), 360 (98), 228 (74), 227 (100), 167 (62), 154 (51), 146 (83), 91 (79).

Anal. Calcd for $C_{23}H_{24}N_2O_2$: C, 76.64; H, 6.71; N, 7.77. Found: C, 76.42; H, 6.84; N, 7.57.

Hydrogenolysis of 180 mg (0.50 mmol) of **21** in 5 mL of acetic acid with 36 mg of 10% palladium on carbon catalyst at atmospheric pressure was continued until 1.2 equiv of hydrogen was absorbed. The solution was filtered, the flask and filter were rinsed with 5 mL of methanol, and the combined filtrates were poured into 20 mL of water and 10 mL ether. At 0 °C ammonium hydroxide was added with vigorous stirring until the aqueous layer was basic. The organic phase was separated, dried (Na_2SO_4), and concentrated, and the residue was crystallized from ether–hexane to give 123 mg (91%) of **26**: mp 145–148 °C; NMR ($CDCl_3$) δ 9.04 (1 H, br s), 7.29–6.75 (4 H, m), 3.76 (3 H, s), 3.19–2.97 (2 H, m), 2.81–2.90 (1 H, m), 2.28–1.06 (7 H, m); IR (KBr) ν_{max} 3305, 3200 (br), 2925, 2825, 1675, 1595, 1245, 1195, 740 cm^{-1}; UV (MeOH) λ_{max} 230, 300, 329 nm; mass spectrum (80 eV), *m/e* (relative intensity) 270 (100), 227 (63), 215 (99), 214 (91), 182 (33), 167 (34), 154 (51), 56 (55).

A hydrochloride, formed with dry HCl in ether and recrystallized from methanol–acetonitrile, had a melting point of 212–213 °C dec.

Anal. Calcd for $C_{16}H_{19}N_2O_2Cl$: C, 62.54; H, 6.24; N, 9.13; Cl, 11.56. Found: C, 62.64; H, 6.52; N, 9.09; Cl, 11.56.

(B) Methylation of Acetaldehyde Condensation Products 11a,b To Form 21′. A solution of 100 mg (0.37 mmol) of the acetaldehyde derived product mixture **11a,b** and 57.8 mg (0.41 mmol) of methyl iodide in 5 mL of chloroform was stirred under N_2 for 24 h. *N,N*-Diisopropylethylamine (0.5 mL) and additional methyl iodide (6 mg, 0.04 mmol) were added, and the solution was refluxed for 7 days. TLC (SiO_2, 5% dichloromethane in methanol) showed one major product of R_f 0.4, staining blue with CAS reagent. Extractive workup followed by chromatography on silica gel with elution with ether gave 80.7 mg (77%) of product **21′** as an amorphous solid: NMR ($CDCl_3$) δ 9.12 (1 H, br s), 7.36–6.78 (4 H, m), 3.78 (3 H, s), 3.12–1.34 (12 H, m, includes NMe, 2.58, s), 1.28–0.86 (1 H, br m); IR (KBr) ν_{max} 3370, 2940, 2840, 2780, 1670, 1605, 1239, 1200, 1190 cm^{-1}; UV (MeOH) λ_{max} 230, 297, 330 nm; mass spectrum (80 eV), *m/e* (relative intensity) 284 (88), 228 (45), 227 (100), 214 (52), 201 (30), 167 (30), 154 (30), 70 (81).

A hydrochloride, formed with dry HCl in ether and recrystallized from acetonitrile, had a melting point of 238–239 °C dec.

Anal. Calcd for $C_{17}H_{21}N_2O_2Cl$: C, 63.64; H, 6.60; N, 8.73. Found: C, 63.43; H, 6.64; N, 8.59.

Alternatively, rearrangement product **21′** could be formed by methylation of the secondary amine **26**. A mixture of 50 mg (0.185 mmol) of the amine **26** and 1.1 equiv of iodomethane in 2 mL of dichloromethane was stirred in the dark for 48 h. TLC (SiO_2, 4:1 ethyl acetate–methanol) showed two mobile spots staining blue with CAS reagent at R_f 0.85 (product **21′**) and 0.15 (starting material **26**) as well as a blue spot at the origin. A basic workup followed by column chromatography on silica gel with elution with 20–50% methanol in ethyl acetate yielded the *N*-methyl product as a white foam and 13.5 mg of crystalline starting material. Dissolution of the foam in dichloromethane, treatment with a solution of HCl gas in ether, and subsequent crystallization from ether–acetonitrile yielded 33.1 mg of a hydrochloride (56%, 76% based on recovered starting material) which was identical by IR, UV, TLC, melting point and mixture melting point with the hydrochloride of the product **21′** formed above.

(C) Benzylation of Propionaldehyde Condensation Products 12a,b To Form 22. Use of procedure A with 176 mg (0.62 mmol) of the propionaldehyde-bridged indoloazepines **12a,b** and 117 mg (0.68 mmol) of benzyl bromide and heating for 48 h after addition of 120 mg (0.93 mmol) of *N,N*-diisopropylethylamine gave, after chromatography, 194 mg (84%) of the amorphous product **22**: NMR ($CDCl_3$) δ 8.99 (1 H, br s), 7.44–6.76 (4 H, m), 4.12 (1 H, d, J = 13 Hz), 3.81–3.62 (4 H, m, includes 3.77, OCH_3, 3 H, s), 2.96–2.84 (2 H, m), 2.73–2.50 (3 H, m), 2.15–1.94 (2 H, m), 1.72–1.60 (1 H, m), 0.61 (3 H, d, J = 7 Hz); NMR (250 MHz) δ 3.75 (3 H, s, OCH_3), 2.89 (1 H, q, H-5), 2.87 (1 H, s, H-21); IR (KBr) ν_{max} 3360, 2940, 2900, 2895, 1675, 1610, 1250, 1205, 1145, 745, 705 cm^{-1}; mass spectrum (80 eV), m/e (relative intensity) 374 (69), 241 (100), 161 (56), 160 (94), 106 (53), 105 (55), 91 (75), 77 (54). A hydrochloride was recrystallized from acetonitrile–methanol: mp 242–243 °C; UV (MeOH) λ_{max} 230, 300, 327 nm.

Anal. Calcd for $C_{24}H_{27}N_2O_2Cl$: C, 70.14; H, 6.62; N, 6.82; Cl, 8.63. Found: C, 70.00; H, 6.90; N, 6.81; Cl, 8.63.

(D) Benzylation of Butyraldehyde Condensation Product 13a To From 23 and Debenzylation. A solution of the amine **13a** (129 mg, 0.43 mmol) and benzyl bromide (77 mg, 0.45 mmol) in 5 mL of chloroform was refluxed under N_2 for 16 h. Diisopropylethylamine (59 mg, 0.45 mmol) was added and the mixture refluxed for 4 days. TLC (SiO_2, 5% methanol in dichloromethane) then showed one product of R_f 0.85, staining blue with CAS reagent. The solvent was evaporated at reduced pressure and the residue chromatographed (SiO_2 column, 2–3% ether in dichloromethane) to yield 158 mg (94%) of **23** as a white foam which crystallized from a methanol or ether–hexane, giving 150 mg (90%) of white crystals: mp 92–94 °C; NMR ($CDCl_3$) δ 9.10 (1 H, br s), 7.60–6.76 (9 H, m), 4.13 (1 H, d, J = 13 Hz), 3.84–3.60 (4 H, m, includes 3.77, 3 H, s), 2.93–2.42 (5 H, m), 2.14–1.60 (3 H, m), 0.92–0.60 (5 H, m); NMR (250 MHz) δ 3.77 (3 H, s, OCH_3), 2.93 (1 H, s, H-21), 2.90 (1 H, q, H-5); IR (KBr) ν_{max} 3370, 2900, 2800, 1670, 1608, 1260, 1245, 1235, 1195, 740, 695 cm^{-1}; UV (MeOH) λ_{max} 227, 300, 327 nm; mass spectrum, m/e (relative intensity) 388 (95), 256 (54), 255 (100), 175 (65), 174 (99), 167 (46), 154 (34), 91 (81).

Anal. Calcd for $C_{25}H_{28}N_2O_2$: C, 77.29; H, 3.26; N, 7.21. Found: C, 77.27; H, 7.39; N, 7.00.

Hydrogenolysis of 150 mg (0.39 mmol) of **23** in 3 mL of acetic acid with 25 mg of **10** palladium on carbon catalyst at atmospheric pressure was stopped when 1.1 equiv of hydrogen had been absorbed. The solution was filtered, and the flask and catalyst were washed with 5 mL of methanol. The methanol was evaporated under vacuum, and the remaining solution was poured into 15 mL of water and 15 mL of ether and cooled to 0 °C. Concentrated ammonia was added dropwise with vigorous stirring until the aqueous layer was basic. The organic layer was separated, washed with water and brine, dried (Na_2SO_4), and concentrated to 114 mg of white foam which yielded 104 mg (90%) of white crystals from ether. An analytical sample was recrystallized from ether–hexane: mp 127–129 °C; NMR ($CDCl_3$) δ 9.37 (1 H, br s), 7.60–6.94 (4 H, m), 3.86 (3 H, s), 3.54 (1 H, br s), 3.34–3.08 (2 H, m), 2.80–2.30 (3 H, m), 2.06–1.52 (3 H, m), 1.12–0.86 (5 H, m); IR (KBr) ν_{max} 3290, 3220, 2920, 2850, 1665, 1590, 1240, 1195, 730 cm^{-1}; UV (MeOH) λ_{max} 230, 300, 330 nm; mass spectrum (80 eV), m/e (relative intensity) 298 (100), 255 (63), 216 (59), 215 (92), 214 (70), 167 (46), 154 (64), 84 (74).

Anal. Calcd for $C_{18}H_{22}N_2O_2$: C, 72.45; H, 7.43; N, 9.39. Found: C, 72.52; H, 7.36; N, 9.42.

(E) Benzylation of Isobutyraldehyde Condensation Product 14a To Form 24 and Debenzylation to 27. Use of procedure A, 200 mg (0.671 mmol) of the amine **14a**, 126 mg (0.738 mmol) of benzyl bromide, and 200 μL of *N,N*-diisopropylethylamine led to a concentrate which was dissolved in 10 mL of methanol and poured into aqueous K_2CO_3. Extraction with ether (3 × 10 mL), washing of the combined extracts with water and brine, drying over Na_2SO_4, concentration, column chromatography (SiO_2, 2.5% methanol in dichloromethane), and crystallization from methanol gave 0.18 g (69%) of **24**: mp 96–97 °C; NMR ($CDCl_3$) δ 9.08 (1 H, br s), 7.62–6.78 (9 H, m), 4.32 (1 H, d, J = 13 Hz), 3.84–3.64 (4 H, m, contains OCH_3 at 3.90, 3 H, s), 3.08–1.88 (6 H, m), 1.70–1.42 (1 H, m), 1.30 (3 H, s), 0.62 (3 H, s); IR (KBr) ν_{max} 3400, 2950, 2840, 2790, 1675, 1605, 1460, 1435, 1280, 1245, 1205, 1185, 1165, 1110, 1040, 745 cm^{-1}; UV (MeOH) λ_{max} 220, 292, 328 nm; mass spectrum (80 eV), m/e (relative intensity) 388 (63), 175 (50), 174 (100), 144 (49), 131 (65), 130 (50), 102 (69), 91 (72).

Anal. Calcd for $C_{25}H_{28}N_2O_2$: C, 77.29; H, 7.26; N, 7.21. Found: C, 77.08; H, 7.43; N, 7.06.

Hydrogenation of 80 mg (0.21 mmol) of **24** in 3 mL of acetic acid with 8 mg of 10% palladium on carbon catalyst at atmospheric pressure was stopped when 1.1 equiv of hydrogen had been taken up. The solution was filtered, the flask and catalyst were rinsed with 5 mL of methanol, and the combined filtrates were poured into 50 mL of water and 50 mL of ether. At 0 °C ammonium hydroxide was added dropwise with rapid stirring until the aqueous layer was basic. The organic phase was then separated, washed with water and brine, dried (Na_2SO_4), and concentrated to 56 mg (91%) of the amorphous amine **27**. A hydrochloride, formed with dry HCl in ether and recrystallized from methanol, had a decomposition point ≃300 °C: NMR (free base, $CDCl_3$) δ 9.17 (1 H, br s), 7.43–6.97 (4 H, m), 3.85 (3 H, s), 3.33 (1 H, s), 3.16 (2 H, m), 2.26 (3 H, s), 1.85 (2 H, m), 1.13 (3 H, s), 0.57 (3 H, s); IR (HCl salt, KBr) ν_{max} 3400, 3220, 2950, 2860, 1675, 1600, 1460, 1435, 1380, 1305, 1285, 1250, 1225, 1200, 1165, 870, 750, 730, 695 cm^{-1}; UV (HCl salt, MeOH) λ_{max} 225, 295, 325 nm; mass spectrum (of free base, 80 eV), m/e (relative intensity) 299 (56), 298 (100), 216 (48), 215 (87), 214 (37), 154 (43), 84 (85).

Anal. Calcd for $C_{18}H_{23}N_2O_2Cl$: C, 64.56; H, 6.92; N, 8.37; Cl, 10.59. Found: C, 64.46; H, 7.22; N, 8.17; Cl, 10.70.

5-Bromopentanal and 5-Chloropentanal.[9] **Method A.** To 5-chlorovaleronitrile (1.0 g, 8.5 mmol) stirred at −78 °C in 5 mL of dichloromethane was added 10.2 mL of a 1 M solution of diisobutylaluminum hydride in hexane. The reaction mixture was stirred for 1 h, poured into cold 10% aqueous sulfuric acid, and extracted with hexane. The organic layer was washed with saturated brine and dried (Na_2SO_4). Solvent removal and immediate distillation (Kugelrohr) yielded 0.50 g (49%) of a clear colorless oil: bp 60–66 °C (10 mm); IR ν_{max} 2970, 2850, 2740, 1730, 1260 cm^{-1}; NMR ($CDCl_3$) δ 1.88 (4 H, m), 2.52 (2 H, m), 3.59 (2 H, t), 9.88 (1 H, t). The bromo compound prepared analogously: bp 35–40 °C; NMR δ 3.40 (2 H, t).

Method B. In 40 mL of THF was dissolved 7.32 g (59 mmol) of the imine [bp 44–46 °C (10 mm)] derived from acetaldehyde and cyclohexylamine. The solution was stirred under a nitrogen atmosphere in a dry ice/acetone bath, and 60 mL of a 1 M solution of lithium diisopropylamide (generated at −10 °C from *n*-butyllithium and diisopropylamine in THF) was added by syringe. The resulting solution was stirred for 0.5 h followed by the addition of 6.5 mL (66 mmol) of 1-chloro-3-bromopropane over 10 min. The reaction mixture was stirred for 0.5 h and allowed to warm to room temperature and stirred for 24 h. The reaction mixture was poured into 150 mL of water and extracted with dichloromethane. The organic extracts were washed with brine and concentrated. To the residue was added 25 g of oxalic acid and 200 mL of water, and the mixture was subjected to steam distillation. The crude product from the steam distillation was distilled under reduced pressure: yield 3.32 g (47%); bp 60–66 °C (10 mm).

2-Methyl-5-chloropentanal. A preparation analogous to that

(9) A. J. Speziale and L. R. Smith, *J. Org. Chem.*, **27**, 4361 (1962).
(10) R. B. Loftfield, *J. Am. Chem. Soc.*, **73**, 1365 (1951).

of the above aldehyde from 4.87 g (35 mmol) of the imine from propanal and cyclohexylamine yielded the 2-methylpentanal: 2.23 g (47%); bp 72–77 °C (10 mm); NMR ($CDCl_3$) δ 1.12 (3 H, d), 1.84 (4 H, m), 2.34 (1 H, m), 3.54 (2 H, t), 9.66 (1 H, d).

20-Desethylvincadifformine (30). Method A. To a solution of methyl 1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-5-carboxylate (**5a**; 100 mg, 0.41 mmol) and a crystal of benzoic acid in 2 mL of dry methanol stirred under N_2 was added 5-bromopentanal (74 mg, 0.45 mmol). After 1.5 h a white precipitate had started to form, and TLC (SiO_2, 5% methanol in dichloromethane) after 3 h showed mostly one spot (staining blue with cerric ammonium sulfate spray) at the origin, along with minor amounts of starting material (also blue with CAS spray) and another less polar (R_f ~0.6) blue-staining spot. Triethylamine (85 μL) was added, and the reaction was heated to 50 °C (oil bath) and stirred vigorously. After 20 h the precipitate had dissolved, and the solution had taken on a yellowish tint. TLC showed essentially one spot which stained blue and had an R_f of ~0.6. Solvent evaporation and chromatography on silica, with elution first with 75 mL of dichloromethane to remove excess aldehyde and then with 10% ether in dichloromethane to elute the alkaloid, afforded the amorphous product: 89 mg (70%); NMR ($CDCl_3$) δ 8.84 (1 H, br s), 7.36–6.73 (4 H, m), 3.84 (3 H, s), 3.36–2.89 (3 H, m), 2.84–2.48 (4 H, m), 2.25–1.43 (7 H, m); IR (KBr) ν_{max} 3360, 2930, 2850, 2770, 1670, 1600, 1475, 1460, 1430, 1300, 1242, 1200, 1182, 1150, 1112, 1040, 780, 740 cm^{-1}; mass spectrum (80 eV), *m/e* (relative intensity) 310 (100), 96 (95); hydrochloride, mp 244–245 °C.

Anal. Calcd for $C_{19}H_{23}N_2O_2Cl$: C, 65.79; H, 6.68; N, 8.08; Cl, 10.22. Found: C, 65.65; H, 6.64; N, 7.93; Cl, 10.51.

Method B. To 100 mg (0.41 mmol) of azepine **5a**, dissolved in 4 mL of dry methanol, was added 59 mg (0.49 mmol) of 5-chloropentanal. The mixture was stirred under nitrogen at 20 °C. TLC (SiO_2, 5% methanol in dichloromethane) after 30 min showed almost complete conversion of starting material (R_f 0.1) to the less polar products **28a,b** (R_f 0.35 and 0.59) which stained blue with CAS reagent. These two spots almost disappeared gradually, with the blue-staining quaternary salts **29a,b** forming at the origin. Only a trace of the less polar (R_f 0.59) **28b** intermediate remained after 4 h while the more polar (R_f 0.35) intermediate **28a** persisted for 9 h. After 9 h, 66 mg (0.51 mmol) of *N,N*-diisopropylethylamine was added and the reaction mixture was heated to and maintained at 55 °C for 2.5 days. TLC showed a trace of the quaternary salts **29a,b** at the origin and a product **30** with R_f 0.65, both staining blue with CAS reagent. Solvent removal and chromatography on silica, eluting with 30 mL of dichloromethane to remove nonpolar impurities and then with 5–10% ether in dichloromethane, afforded desethylvincadifformine (**30**) as an amorphous solid; yield 92 mg (72%).

20-Desethyl-20-Methylvincadifformine (31). To a solution of methyl 1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-5-carboxylate (**5a**; 100 mg, 0.41 mmol) and a crystal of benzoic acid in 2 mL of dry methanol, under N_2, was added the 5-chloro-2-methylvaleraldehyde (61 mg, 0.45 mmol). The solution was stirred for 2 h, at which time TLC (SiO_2, 5% methanol in dichloromethane) showed a multitude of spots staining blue with cerric ammonium sulfate spray reagent, as well as some unreacted starting material. Triethlyamine (85 μL) was added, the reaction was placed in a 45 °C oil bath, and the disappearance of starting material and intermediates and concomitant formation of product were followed by TLC. After 10 h, TLC showed essentially one product. The reaction was stopped, the solvent was removed under vacuum, and the residue was taken up in dichloromethane. Chromatography on SiO_2 (1 cm × 8 cm column), with elution first with 75 mL of dichloromethane to remove excess aldehyde and then with 10% of ether in dichloromethane to elute the alkaloid, afforded upon solvent removal a colorless glass which gave 95 mg (72%) of white crystals from methanol: mp 116–118 °C; IR (KBr) ν_{max} 3350, 2440, 2790, 1670, 1610, 750 cm^{-1}; mass spectrum *m/e* 324 (M^+), 110 (100%); NMR ($CDCl_3$) δ 8.83 (1 H, br s), 7.30–6.73 (4 H, m), 3.73 (3 H, s), 3.28–1.27 (13 H, m), 0.53 (3 H, s).

Anal. Calcd for $C_{20}H_{24}N_2O_2$: C, 74.04; H, 7.46; N, 8.64. Found: C, 74.02; H, 7.65; N, 8.46.

4-Chlorobutanal.[10] At −78 °C 1.2 equiv of a 1 M solution of diisobutylaluminum hydride in hexane was added over 30 min to 18.5 g of methyl 4-chlorobutyrate in 125 mL of dichloromethane. After being stirred for 45 min, the mixture was poured onto 300 g of ice and 100 mL of concentrated HCl. The mixture was stirred for 30 min and then extracted with 200 mL of ether. The dried ($MgSO_4$) extract was concentrated under vacuum and distilled at 30–32 °C (0.2 mm) to give 6.1 g (50%) of the aldehyde. The 2,4-dinitrophenylhydrazone melting point was 134–135 °C.

Anal. Calcd for $C_{10}H_{11}N_4O_4Cl$: C, 41.89; H, 3.87; N, 19.54; Cl, 12.37. Found: C, 41.88; H, 3.89; N, 19.33; Cl, 12.48.

Desethylibophyllidine (32). A solution of 800 mg (75 mmol) of 4-chlorobutanal and 1.25 g (51 mmol) of the indoloazepine **5a** in 50 mL of tetrahydrofuran was stirred at 20 °C. After 5 min a solid started to precipitate. TLC (silica, 4:1 ethyl acetate/ethanol) then showed the generation of three products: **33a** (R_f 0.53), **33b** (R_f 0.77) (both blue fading to green with CAS spray), and **34b** (R_f 0, blue with CAS). After 1 h all starting indoloazepine had reacted, and after 3 h only **33a** remained in solution. Filtration and washing with tetrahydrofuran gave 872 mg (51%) of **34b**: IR (KBr) ν_{max} 3350, 2960, 1695, 1635, 1608 cm^{-1}; UV (EtOH) λ_{max} 226 nm (log ϵ 4.15), 295 (4.08), 326 (4.44). For the tetraphenylborate salt: mp 198–199 °C dec; NMR (acetone-d_6) δ 9.80 (1 H, br s), 7.50–6.70 (24 H, m), 4.57 (1 H, d), 4.35 (1 H, d), 4.23 (1 H, t), 4.10–3.87 (2 H, m), 3.86–3.76 (1 H, m), 3.75 (3 H, s), 3.75–3.66 (1 H, m), 2.90–2.76 (2 H, m), 2.70–2.30 (4 H, m).

Anal. Calcd for $C_{42}H_{41}N_2O_2B$: C, 81.81; H, 6.70; N, 4.54. Found: C, 81.61; H, 7.05; N, 4.30.

The filtrate was concentrated under vacuum and the residue chromatographed on a 2.5 × 15 cm silica column by eluting with 200 mL of ethyl acetate followed by 200 mL of 9:1 ethyl acetate/ethanol to give 8.45 mg (49%) of **33a**: IR (KBr) ν_{max} 3360, 1675, 1605 cm^{-1}; UV (EtOH) λ_{max} 226 nm (log ϵ 4.06), 299 (4.09), 327 (4.14); NMR ($CDCl_3$) δ 8.85 (1 H, br s), 7.23–8.40 (4 H, m), 3.87 (1 H, d), 3.74 (3 H, s), 3.48 (2 H, t), 3.35 (1 H, d), 3.43–3.25 (2 H, m), 3.00–2.85 (1 H, m), 2.45–1.25 (4 H, m); mass spectrum (80 eV), *m/e* (relative intensity) 334 (23), 332 (69), 296 (24), 215 (50), 214 (100), 154 (60), 82 (60).

A solution of 361 mg of **33a** in 20 mL of tetrahydrofuran was heated at reflux for 6 h, cooled, and filtered to give 350 mg (97%) of **34a**: IR (KBr) ν_{max} 3360, 2960, 1695, 1635, 1610 cm^{-1}; UV (EtOH) λ_{max} 230 nm (log ϵ 4.28), 294 (4.31), 327 (4.45). For the tetraphenylborate salt: mp 160 °C dec; NMR (acetone-d_6) δ 9.80 (1 H, br s), 7.45–6.72 (24 H, m), 4.61 (1 H, d), 4.40 (1 H, d), 4.29 (1 H, t), 4.17–3.96 (2 H, m), 3.95–3.79 (1 H, m), 3.76–3.64 (1 H, m), 3.74 (3 H, s), 2.90–2.78 (2 H, m), 2.69–2.34 (4 H, m).

A solution of 870 mg (2.6 mmol) of salt **34b** and 0.5 mL of triethylamine in 20 mL of methanol was heated for 48 h, cooled, and concentrated under vacuum. The residue was partitioned between 20 mL of dichloromethane and 20 mL of water basified with NaOH. Concentration of the organic solution gave 666 mg of crude desethylibophyllidine which was purified by chromatography on alumina (activity III) eluted with ethyl acetate to give 657 mg (84%) of the alkaloid **32**: mp 110 °C; IR (KBr) ν_{max} 3360, 1675, 1605 cm^{-1}; UV (EtOH) λ_{max} 227 nm (log ϵ 3.91), 297 (4.03), 327 (4.14); NMR ($CDCl_3$) δ 9.10 (1 H, br s), 7.40–6.82 (4 H, m), 3.77 (3 H, s), 3.75 (1 H, d), 3.45–3.25 (2 H, m), 2.98–2.71 (3 H, m), 2.25–1.98 (3 H, m), 1.95–1.63 (3 H, m); mass spectrum (80 eV), *m/e* (relative intensity) 297 (68), 296 (100), 216 (41), 180 (45), 167 (54), 154 (52), 82 (91).

Anal. Calcd for $C_{18}H_{20}N_2O_2$: C, 72.97; H, 6.80; N, 9.45. Found: C, 72.98; H, 6.81; N, 9.45.

3-Oxovincadifformine (35). Method A. To 0.200 g (0.820 mmol) of the monoester amine **5a**, suspended with stirring in 10 mL of anhydrous toluene, was added 0.142 g (0.900 mmol) of methyl 4-formylhexanoate. The mixture, heated to reflux under a nitrogen atmosphere with a 4-Å molecular sieve water trap, became homogeneous. After 18 h all starting amine had been consumed as seen by TLC (SiO_2 with 5% methanol in dichloromethane, R_f 0, blue stain with cerric ammonium sulfate), and one major product (R_f 0.5, blue with CAS) had formed. Cooling to −25 °C and filtration gave 0.181 g of 3-oxovincadifformine, mp 204–205 °C. Concentration of the filtrate and crystallization from methanol provided an additional 0.063 g of the lactam, total yield 85%. A sample recrystallized for analysis from methanol had a melting point of 206–207 °C. It gave IR ($CHCl_3$ solution) and NMR (270 MHz, proton) spectra and TLC and HPLC (25-cm Microporasil column, $CHCl_3$, 1 mL/min, 9.2 min) retention times identical with those of a sample of (−)-3-oxovincadifformine obtained by oxidation of (−)-vincadifformine:[8]

UV (EtOH) λ_{max} 210, 225, 297, 330 nm; IR (KBr) ν_{max} 3300, 2960, 2940, 2890, 1670, 1650, 1600, 1425, 1230, 1180, 740 cm^{-1}; NMR ($CDCl_3$) δ 9.09 (s, 1 H), 7.10 (m, 4 H), 4.16 (m, 1 H), 3.77 (s, 3 H), 3.44 (m, 2 H), 2.82–1.15 (br m, 8 H), 0.93 (t, 2 H), 0.67 (t, 3 H); mass spectrum (80 eV), *m/e* (relative intensity) 352 (M^+, 45), 227 (100), 138 (17).

Anal. Calcd for $C_{21}H_{24}N_2O_3$: C, 71.57; H, 6.86; N, 7.95. Found: C, 71.61; H, 6.88; N, 7.71.

Method B. Condensation. A mixture of 100 mg (0.41 mmol) of the indoloazepine **5a** and 81 mg (0.51 mmol) of methyl 4-formylhexanoate in 5 mL of chloroform was stirred under nitrogen in the presence of Linde 4-Å molecular sieves at 40 °C for 20 h. TLC (SiO_2, 5% methanol in dichloromethane) showed a trace of starting amine at R_f 0.1 and two major spots at R_f 0.34 and 0.62, all of which stained blue with CAS reagent spray. Concentration under vacuum and chromatography of the residue on alumina, with elution with acetonitrile, afforded the bridged azepines as a colorless unstable oil (0.125 g, 80%). NMR spectra of the mixture indicated a ratio of approximately 2:1 in favor of the more polar isomers. The isomers were separated on silica with 5% methanol in dichloromethane by using centrifugal thin-layer chromatography (Harrison Chromatotron). The less polar isomers, **36b**, crystallized as a diastereomeric pair from ether: NMR ($CDCl_3$) δ 9.06 (1 H, br s), 7.33–6.68 (4 H, m), 4.07–3.02 (9 H, m, includes singlets at 3.70, 3.66, and 3.60), 3.00–1.06 (11 H, m), 0.96–0.76 (3 H, m); IR (KBr) ν_{max} 3360, 2945, 2870, 1725, 1670, 1595, 1465, 1280, 1250, 1230, 1180, 1040, 760 cm^{-1}; UV (MeOH) λ_{max} 225, 304, 330 nm; mass spectrum (80 eV), *m/e* (relative intensity) 385 (30), 384 (100), 352 (20), 215 (30), 171 (30), 170 (85), 138 (15).

The more polar isomers, **36a**, resisted crystallization: NMR ($CDCl_3$) δ 8.94 (1 H, br s), 7.50–6.67 (4 H, m), 3.94–3.07 (11 H, m, includes singlets at 3.74 and 3.64), 3.03–2.66 (1 H, m), 2.47–1.40 (6 H, m), 0.99–0.47 (5 H, m); IR (KBr) ν_{max} 3410, 2960, 1739, 1680, 1620, 1475, 1445, 1300, 1240, 1195; UV (MeOH) λ_{max} 228, 300, 329 nm; mass spectrum (80 eV), *m/e* (relative intensity) 385 (31), 384 (100), 352 (19), 215 (32), 171 (28), 170 (80), 138 (20).

Alkylation and Rearrangement. To 146 mg (0.38 mmol) of the methyl 4-formylhexanoate derived product mixture **36a,b** in 3 mL of chloroform, stirred under N_2, was added 72 mg (0.42 mmol) of benzyl bromide. The solution was refluxed for 24 h, *N,N*-diisopropylethylamine (73 mg, 0.57 mmol) was added, and reflux was continued for 6 days. TLC (SiO_2, 5% methanol in dichloromethane) then showed a major product at R_f 0.9 and a few minor components. Concentration under vacuum and column chromatography on silica gel, with elution with 50 mL of dichloromethane to remove nonpolar impurities and then with 5% ether in dichloromethane afforded 0.108 g (60%) of the amino esters **38a,b** as a light yellow oil. TLC of the oil on silica with ether–hexane (1:1) showed it to consist only of two components with R_f 0.33 and 0.46, both staining blue with CAS spray reagent. NMR ($CDCl_3$) showed the ratio to be approximately 1:1. The two compounds were separated by using centrifugal thin-layer chromatography (Harrison Chromatotron).

The more polar compound, **38b**, was crystallized from methanol: mp 131–132 °C; NMR ($CDCl_3$) δ 9.14 (1 H, br s), 7.61–6.76 (9 H, m), 4.28 (1 H, d, J = 14 Hz), 3.90–3.50 (7 H, m, includes OCH_3, 3 H, at 3.75 and 3.56), 3.16–1.50 (11 H, m), 1.41–0.89 (5 H, m, includes CCH_3, 3 H, t centered at 1.03); IR (KBr) ν_{max} 3340, 2955, 2915, 1720, 1675, 1605, 1250, 1210, 755, 715 cm^{-1}; UV (MeOH) λ_{max} 210, 228 (sh), 300, 330 nm; mass spectrum (80 eV), *m/e* (relative intensity) 475 (38), 474 (96), 443 (29), 332 (52), 261 (84), 260 (100), 91 (73).

Anal. Calcd. for $C_{29}H_{34}N_2O_4$: C, 73.39; H, 8.06; N, 5.90. Found: C, 73.58; H, 7.44; N, 5.78.

The less polar compound, **38a**, resisted crsytallization. A picrate was prepared in and recrystallized from aqueous methanol: mp 190–191 °C; NMR ($CDCl_3$) δ 8.85 (1 H, br s), 7.62–6.70 (9 H, m), 4.30 (1 H, d, J = 14 Hz), 4.05–3.59 (7 H, m, includes OCH_3, 3 H, s at 3.85 and 3.71), 3.20–1.52 (11 H, m), 1.13–0.56 (5 H, m, includes CH_3, 3 H, s at 0.71); IR (film) ν_{max} 3370, 2940, 1730, 1675, 1605, 1280, 1250, 1210, 745, 700 cm^{-1}; UV (MeOH) λ_{max} 210, 228 (sh), 300, 330 nm; mass spectrum (80 eV), *m/e* (relative intensity) 475 (39), 474 (92), 443 (25), 332 (52), 261 (87), 260 (100), 91 (68).

Anal. Calcd for $C_{35}H_{37}N_5O_{11}$: C, 59.74; H, 5.30; N, 9.95. Found: C, 59.65; H, 5.57, N, 9.92.

Hydrogenolysis of 62 mg (0.13 mmol) of **38b** in 3 mL of acetic acid with 12 mg of 10% palladium on carbon catalyst at atmospheric pressure was stopped after 4 h when TLC (SiO_2, 5% methanol in dichloromethane) showed the reaction to be complete. The solution was filtered, the flask and catalyst were rinsed with 5 mL of methanol, and the combined filtrates were poured into 20 mL of water with 10 mL of ether. At 0 °C, aqueous potassium carbonate was added slowly with vigorous stirring until the aqueous layer was basic. The organic phase was separated, washed with water and brine, dried (Na_2SO_4), and concentrated to give **40b** as a colorless glass which crystallized and was recrystallized from ether–hexane: mp 132–133 °C; NMR ($CDCl_3$) δ 8.99 (1 H, br s), 7.30–6.78 (4 H, m), 3.78 (3 H, s), 3.56 (3 H, s), 7.32 (1 H, br s), 3.22–3.00 (2 H, m), 2.27–0.76 (14 H, m, includes CH_3, 3 H, t, J = 8 Hz, centered at 0.89); IR (KBr) ν_{max} 3390, 2970, 2890, 1725, 1675, 1610, 1285, 1250, 1210, 750 cm^{-1}; UV (MeOH) λ_{max} 210, 230, 300, 329 nm; mass spectrum, *m/e* (relative intensity) 385 (22), 384 (86), 353 (15), 227 (14), 215 (33), 171 (33), 170 (100), 138 (27).

An analogous hydrogenolysis of **38a** in acetic acid over 10% palladium on carbon catalyst at 1 atm yielded 3-oxovincadifformine, identified by thin-layer chromatographic, IR spectroscopic, and melting and mixture melting point comparisons with the product obtained above.

When a sample of the amino ester **40b** was heated at reflux in toluene with a catalytic amount of *p*-toluenesulfonic acid for 18 h, it was completely converted to 3-oxovincadifformine (**35**), identified by TLC (SiO_2, 5% methanol in dichloromethane, R_f 0.55), IR (KBr and $CHCl_3$ phases), and melting and mixture melting point comparisons with the samples obtained above.

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Registry No. (±)-**5a**, 66859-22-1; (±)-**9**, 77080-57-0; (±)-**10a**, 77080-58-1; (±)-**10b**, 77122-12-4; (±)-**11a**, 77080-59-2; (±)-**11b**, 77122-13-5; (±)-**12a**, 77122-86-2; (±)-**12b**, 77080-60-5; (±)-**13a**, 77080-61-6; (±)-**13a**·HCl, 77122-14-6; (±)-**13b**, 77122-15-7; (±)-**14a**, 77097-71-3; (±)-**14b**, 77122-87-3; (±)-**21** (R = $CH_2C_6H_5$), 77080-62-7; (±)-**21′** (R = CH_3; R^1 = R^{11} = H), 77080-63-8; (±)-**21′**·HCl (R = CH_3; R^1 = R^{11} = H), 77080-64-9; (±)-**22** (R = $CH_2C_6H_5$), 77080-65-0; (±)-**22**·HCl (R = $CH_2C_6H_5$), 77080-66-1; (±)-**23** (R = $CH_2C_6H_5$), 77080-67-2; (±)-**23** (R = H), 77080-68-3; (±)-**24** (R = $CH_2C_6H_5$), 77080-69-4; (±)-**26**, 77080-70-7; (±)-**26**·HCl, 77080-71-8; (±)-**27**, 77080-72-9; (±)-**27**·HCl, 77080-73-0; (±)-**30**, 77080-74-1; (±)-**30**·HCl, 77080-75-2; (±)-**31**, 77080-76-3; (±)-**32**, 77080-77-4; (±)-**33a**, 77080-78-5; (±)-**33b**, 77122-16-8; (±)-**34a**·BPh_4^-, 77097-73-5; (±)-**34b**·BPh_4^-, 77122-89-5; (±)-**35**, 53507-95-2; (±)-**36a** (isomer 1), 77122-90-8; (±)-**36a** (isomer 2), 77122-91-9; (±)-**36b** (isomer 1), 77080-79-6; (±)-**36b** (isomer 2), 77122-92-0; (±)-**38a**, 77080-80-9; (±)-**38a** picrate, 77097-01-9; (±)-**38b**, 77122-17-9; (±)-**40b**, 77080-81-0; formaldehyde, 50-00-0; benzaldehyde, 100-52-7; acetaldehyde, 75-07-0; propionaldehyde, 123-38-6; *n*-butyraldehyde, 123-72-8; isobutyraldehyde, 78-84-2; 5-bromopentanal, 1191-30-6; 5-chloropentanal, 20074-80-0; 5-chloropentanenitrile, 6280-87-1; 5-bromopentanenitrile, 5414-21-1; *N*-ethylidenecyclohexylamine, 1193-93-7; 1-chloro-3-bromopropane, 109-70-6; (±)-2-methyl-5-chloropentanal, 77080-82-1; *N*-propylidenecyclohexylamine, 1195-49-9; 4-chlorobutanal, 6139-84-0; methyl 4-chlorobutyrate, 3153-37-5; 4-chlorobutanal 2,4-dinitrophenylhydrazone, 7405-06-3; methyl (±)-4-formylhexanoate, 66757-48-0.