Synthesis of 20-Epipseudoaspidospermidine, 20-Epidehydropseudoaspidospermidine, and 20-Epipseudovincadifformine

Ernest Wenkert,*[1a,b] Barry Porter,[1b] and Dana P. Simmons[1a]

Departments of Chemistry, Rice University, Houston, Texas 77001, and University of California—San Diego, La Jolla, California 92093

Janick Ardisson, Nicole Kunesch, and Jacques Poisson

C.N.R.S., ERA 317, Centre d'Etudes Pharmaceutiques, 92290 Châtenay-Malabry, France

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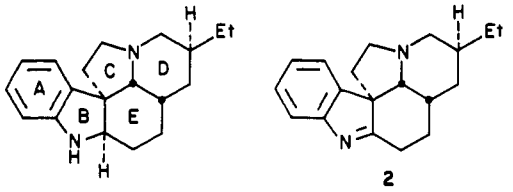
A short synthesis of 3-acetyl-5-ethylpyridine and its three-step conversion into pentacycles of the Aspidosperma alkaloid type by the β-acylpyridine reduction–cyclization route are described. The reductive transformations of the resultant pentacycles into racemic 20-epipseudoaspidospermidine and its oxidative conversion into racemic 20-epidehydropseudoaspidospermidine are portrayed. N-Carbomethoxylation of the latter and photorearrangement of the product into racemic 20-epipseudovincadifformine are illustrated. The ^{13}C NMR spectral analysis of a large number of Aspidosperma-like pentacycles is presented.

As recent syntheses of the deethyl derivatives of aspidospermidine and vincadifformine illustrated (Scheme I),[2] the facile conversion of β-acylpyridines into tetrahydro compounds on hydrogenation and the electrophilic properties of the latter have opened a simple route for the construction of the Aspidosperma alkaloids by a short reaction sequence. The reaction scheme now has been utilized for the synthesis of the alkaloids 20-epipseudoaspidospermidine (**1**),[3,4] 20-epidehydropseudoaspidospermidine (**2**),[3,4b] and 20-epipseudovincadifformine (**3**).[4a,5,6]



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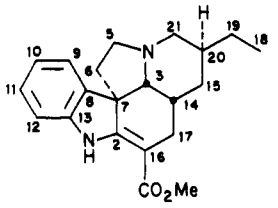

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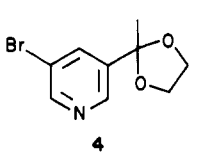
The starting compound (**5a**) was prepared by metal–halogen exchange between *n*-butyllithium and 3-acetyl-5-bromopyridine ethylene ketal (**4**),[7] treatment of the resultant pyridyllithium derivative with ethyl iodide, and subsequent acid-catalyzed hydrolysis. Hydrogenation of the product over palladium yielded the tetrahydropyridine



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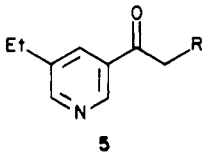

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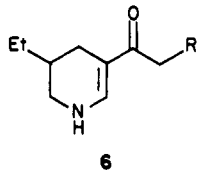

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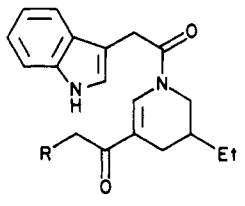

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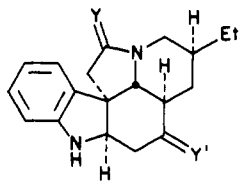
a, R = H; **b**, R = CO_2Me

6a, whose exposure to indoleacetic anhydride[8] gave the *N*-acyl derivative **7a**. Treatment of the latter with boron trifluoride etherate led to the stereoisomeric, pentacyclic keto lactams **8a**, **9a**, and **10a** in a ca. 4:4:1 ratio.[9,10]



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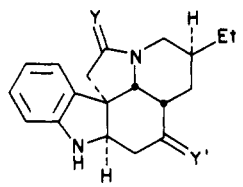

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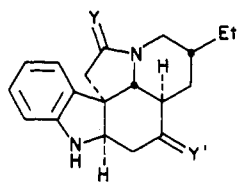

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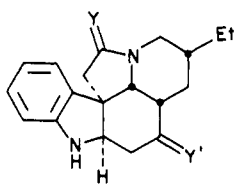

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a, Y = Y' = O; **b**, Y = O, Y' = $NNHSO_2C_7H_7$; **c**, Y = H_2, Y' = $NNHSO_2C_7H_7$; **d**, Y = H_2, Y' = O; **e**, Y = Y' = H_2; **f**, Y = O, Y' = H_2

The stereochemistry of the keto lactams was clarified by the observation of a facile acid-catalyzed transformation of lactam **9a** into a mixture of pentacycles **8a** and **9a** and by NMR spectral analyses of compounds **8a**, **9a**, and **10a**

(1) (a) Rice University. (b) University of California.

(2) (a) Wenkert, E.; Bindra, J. S.; Chauncy, B. *Synth. Commun.* **1972**, *2*, 285. (b) Wenkert, E. *Pure Appl. Chem.* **1981**, *53*, 1271. (c) Wenkert, E.; Orito, K.; Simmons, D. P.; Kunesch, N.; Ardisson, J.; Poisson, J. *Tetrahedron* **1983**, *39*, 3719. (d) Wenkert, E.; Orito, K.; Simmons, D. P.; Ardisson, J.; Kunesch, N.; Poisson, J. *J. Org. Chem.* **1983**, *48*, 5006.

(3) Andriantsiferana, M.; Picot, F.; Boiteau, P.; Husson, H.-P. *Phytochemistry* **1979**, *18*, 911.

(4) (a) Kutney, J. P.; Brown, R. T.; Piers, E.; Hadfield, J. R. *J. Am. Chem. Soc.* **1970**, *92*, 1708. (b) Quirin, F.; Debray, M.-M.; Sigaut, C.; Thepenier, P.; LeMen-Olivier, L.; LeMen, J. *Phytochemistry* **1975**, *14*, 812.

(5) (a) Gorman, M.; Neuss, N.; Cone, N. J. *J. Am. Chem. Soc.* **1965**, *87*, 93. (b) Brown, R. T.; Hill, J. S.; Smith, G. F.; Stapleford, K. S. J. *Tetrahedron* **1971**, *27*, 5217. (c) LeMen, J.; Caron-Sigaut, C.; Hugel, G.; LeMen-Olivier, L.; Lévy, J. *Helv. Chim. Acta* **1978**, *61*, 566.

(6) For a total synthesis of (±)-**3** see: Kuehne, M. E.; Kirkemo, C. L.; Matsko, T. H.; Bohnert, J. C. *J. Org. Chem.* **1980**, *45*, 3259.

(7) McLean, S.; Murray, D. G. *Can. J. Chem.* **1972**, *50*, 1478.

(8) Hart, J. C.; Matheson, E. M.; Hutzinger, O. *Can. J. Chem.* **1970**, *48*, 177.

(9) Paralleling the work in the deethyl series[2d] keto esters were prepared also. For the synthesis of compounds **5b**, **6b**, and **7b** see the Experimental Section.

(10) Treatment of ester **7b** with polyphosphoric acid at ca. 100 °C for 3 h yielded pentacycles **30b** and **30c** and their enols.

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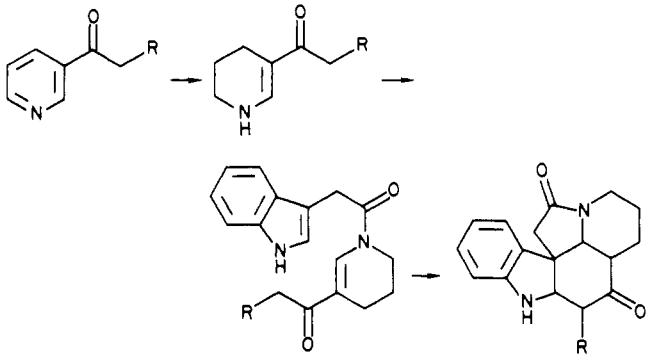
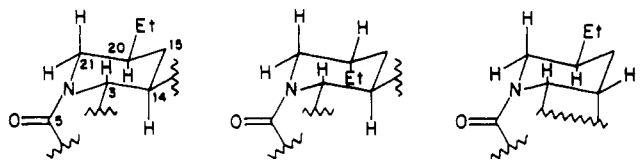
Scheme I[a]



[a] R = H or CO_2Me.

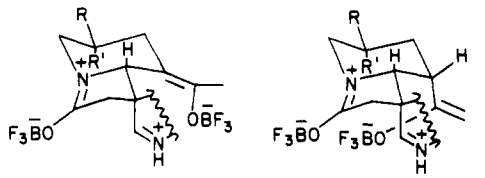
and comparison with the NMR data obtained previously[2c] for the deethyl equivalents of substances **8a** and **9a**. The 12-Hz H(3)–H(14) coupling constant for compounds **8a** and **10a** and the J value of only 4 Hz for pentacycle **9a** revealed the former compounds to be *trans*-perhydroquinolines and the latter substance to contain a *cis*-perhydroquinoline unit. Furthermore, the D–E trans compound **8a** exhibited H(21β)–H(20) and H(21α)–H(20) coupling characteristics of 12 and 4 Hz, respectively, indicative of the presence of an axial C(20) hydrogen, while the other D–E trans compound (**10a**) exhibited H(21) J values of 3 and 2 Hz, respectively, characteristic of an equatorial C(20) hydrogen. These facts supported conformations **12** and **13** for keto lactams **8a** and **10a**, re-



12 **13** **14**

spectively, and thus the relative configurations depicted in the latter two formulas. The axial orientation of the ethyl group in keto lactam **10a** was confirmed by the strong shielding of C(14) in this compound's ^{13}C NMR spectrum (vide infra) vs. the C(14) field position in the spectra of pentacycle **8a** and its deethyl derivative.[2a-c] Finally, the H(21β)–H(20) and H(21α)–H(20) coupling of 13 and 3 Hz, respectively, in the ^1H NMR spectrum of the D–E cis compound **9a** showed it to possess the same steric environment around C(20) as its isomer **8a** and the ring D conformation as portrayed in formula **14**. The axial orientation of C(17) with respect to ring D was confirmed by the strong shielding of C(20) vs. that of compound **8a** in the ^{13}C NMR spectra (vide infra).

Since C(20) is too far removed from the initial carbon–carbon bond-forming sites, i.e., C(3) and C(7), involved in the keto lactam construction, the strong preference for the β-ethyl orientation must be stereoelectronic in nature, i.e., a preponderant equatorial side chain conformation in the transition state of the indolizidone formation. Maximum π-bond overlap between the indole enamine unit and the 1:1 or 2:1 boron trifluoride complex of the 1,3-diacyltetrahydropyridine unit of compound **7a** leads to an indolizidone intermediate (**15**) in which the C(3) and C(7) configuration of the final keto lactams has been fixed.[11] If it be assumed that the kinetic protonation of the enol borate proceeds from its less hindered side, the resultant intermediate (**16**) possesses a cis H(3)–H(14) configuration.

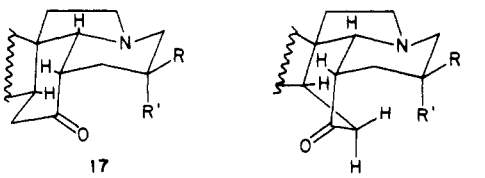


15 **16**

a, R = Et, R' = H; **b**, R = H, R' = Et

This stereochemical feature makes keto lactams **9a** and **11a** the major and minor primary products, respectively. Under the reaction conditions keto lactam **9a** is converted in part into isomer **8a**, a substance with trans H(3)–H(14) stereochemistry, while keto lactam **11a**, a compound with strong 1,3-diaxial repulsion between C(17) and C(19) (already apparent in the precursor **16b**) undergoes total transformation into isomer **10a**. An alternate rationale for the high stereospecificity of pentacycle construction is the assumption of the C(3)–C(7) and C(14)–H(14) bond formations being reversible processes and the C(20) substituent showing preference for an equatorial orientation in the C(2)–C(16) bond-producing step.

With the synthesis of amine **1** as the initial goal it became important to deoxygenate keto lactams **8a**, **9a**, and **10a**. Since it seemed reasonable to remove one carbonyl group at a time, the deoxygenation study was initiated by the reduction of the lactam carbonyl group in compounds whose ketone unit had been masked as a *p*-toluenesulfonylhydrazone (**8b** and **9b**) or an ethylene ketal. Thus as in the deethyl series[2c] the lactams were exposed to lithium aluminum hydride reduction. The reaction with lactam **8b** yielded hydrazone **8c** and a minor amount of amine **8e**, while that with isomer **9b** gave hydrazone **9c**. Acid-catalyzed hydrolysis of hydrazones **8c** and **9c** afforded ketone **9d**. Lithium aluminum hydride reduction of the ketals and lactams **8a** and **9a**, followed by acid-induced hydrolysis of the ketal products, led to ketone **9d** and the same reaction sequence on the ketal of lactam **10a** produced ketone **11d** (albeit in low yield). Both ketones **9d** and **11d** possess *cis*-perhydroquinoline and *trans*-indolizidine units, the latter of which was revealed by characteristic absorption bands in the infrared spectra.[12] The ^1H NMR spectrum of ketone **9d** exhibited H(21β)–H(20) and H(21α)–H(20) coupling constants of 12 and 2 Hz, respectively, and its ^{13}C NMR spectrum (vide infra) depicted carbon signals normal for ring D in chair form and the ethyl group in equatorial orientation. The H(2) coupling behavior (J = 3 Hz) of the ketone as well as of all 17-ketones or hydrazones of D–E cis configuration was incompatible with a ring E chair conformation, as depicted in formula **17**, and indicated part structure **18a** as the one



17 **18**

a, R = Et, R' = H; **b**, R = H, R' = Et

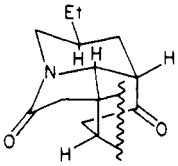
encompassing all facts known about ketone **9d**. Whereas this conformational structure is unusual and not demanded from cursory inspection of models, its unanticipated ring E boat form may relieve some nonbonded repulsion be-

(11) See also: Wenkert, E.; Bindra, J. S.; Chang, C.-J.; Cochran, D. W.; Rearick, D. E. *J. Org. Chem.* **1974**, *39*, 1662.

(12) Wenkert, E.; Roychaudhuri, D. K. *J. Am. Chem. Soc.* **1956**, *78*, 6417. Crabb, I. A.; Newton, R. F.; Jackson, D. *Chem. Rev.* **1971**, *71*, 121.

tween H(20α) and the oxygen and introduce only minimally unfavorable interactions of which one, the nonbonded stem-to-stern interaction between H(16α) and N_b, may be one of attraction of an acidic hydrogen by a basic site.[13]

All the spectral properties of ketone **9d** were duplicated by ketone **11d** except for the *J* values of the C(21) hydrogens. The 3 and <2 Hz coupling of H(21β) and H(21α), respectively, with H(20) was compatible with structure **18b**. Surprisingly, the keto lactams of both *cis*-**9a** and *trans*-perhydroquinoline (**8a** and **10a**) types revealed H(2)–H(16) coupling information characteristic of ring E boat conformations (**19** and **20**, respectively).



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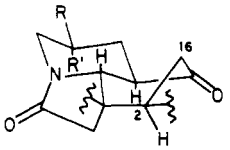

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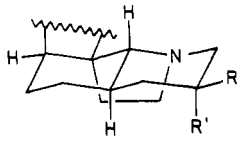
Reduction of ketone **9d** with hydrazine and sodium diethyleneglycolate in diethylene glycol yielded a ca. 1:1 mixture of amines **8a** and **1** (**9e**), while a similar Wolff–Kishner reduction of ketone **11d** gave amine **10e**. The absence of *trans*-indolizidine bands[12] in the infrared spectra of the *trans*-perhydroquinolinic amines **8e** and **10e** and the *J* (H-2) value of 3 Hz observed in the ^{1}H NMR spectra of these substances showed them to be represented by conformational part structures **21a** and **21b**, respectively. The presence of infrared bands[12] in the spectrum

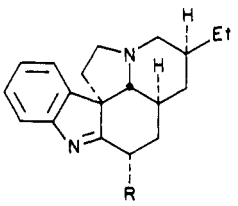


21a, R = Et; R' = H
b, R = H; R' = Et

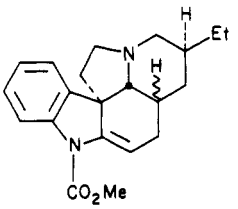
of *cis*-perhydroquinolinic amine **1** (**9e**) and its H(2) NMR coupling constants of 13 and 5 Hz revealed this pentacyclic amine to be conformationally most probably deoxo-**17a**, i.e., a system with ring E in chair form. These observations are in agreement with the physical data and, hence, the conformational structures of pentacyclic amines in the deethyl series, i.e., amines deethyl-**8e** and deethyl-**9e**.[2a,c]

Wolff–Kishner reduction of keto lactam **8a** produced a ca. 12:1 mixture of lactams **8f** and **9f**, respectively. Lithium aluminum hydride reduction of each of the products led to amines **8e** and **1** (**9e**), respectively. One-step removal of both oxygens of keto lactam **9a** by way of a diborane reduction of its *p*-toluenesulfonylhydrazone (**9b**) yielded amine **1** (**9e**), accompanied by small quantities of ketone **9d** and lactam **9f**. Finally, Wolff–Kishner reduction of keto lactam **10a** gave lactam **10f**, whose diborane reduction afforded amine **10e**.

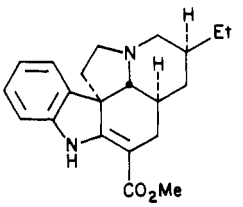
In the absence of sufficient quantity of the latter amine only pentacycles **8e** and **1** (**9e**) could be used for further transformations. Oxidation of these substances with potassium permanganate in benzene solution in the presence of 18-crown-6 ether converted them into indolenines **22a** and **2**, respectively. Their infrared spectra[12] showed the former to be a *cis*-indolizidine (cf. **21**) and the latter a *trans*-indolizidine (cf. **17**–**18**). The syntheses thus far had produced the alkaloids 20-epipseudoaspidospermidine (**1**) and 20-epidehydropseudoaspidospermidine (**2**) in racemic forms, leaving only the alkaloids of the pseudovincadifformine type to be constructed.



22a, R = H
b, R = CO_2Me



23a, 14α-H
b, 14β-H



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In analogy with the chemistry of the deethyl series[2a-c] indolenines **22a** and **2** were transformed into their enamides **23a** and **23b**, respectively, by treatment with sodium hydride and methyl chlorocarbonate. Photolysis of urethane **23a** in methanol solution yielded imino ester **22b** and its tautomer **24**. Treatment of the imino ester, whose structure **22b** is based on the weak coupling of its H(16) with the C(17) hydrogens in the ^{1}H NMR spectrum, with acid caused its quantitative conversion into the tautomer. Photolysis of urethane **23b** gave (±)-20-epipseudovincadifformine (**3**).[6,14,15] It is noteworthy that, as in the deethyl series,[2c] the photolysis of the *trans*-perhydroquinolinic enamide led to a mixture of imino ester and enamino ester, while the *cis*-perhydroquinolinic derivatives was transformed solely into the enamino ester tautomer. This unusual fact can be explained readily on the assumption of the primary photolysis products in all cases being ca. 1:1 mixtures of 16α- and 16β-carbomethoxyindolenines and a facile isomerization of an imine into an enamine requiring coplanarity of the imine π orbital with an α carbon–hydrogen bond. In view of the conformational flexibility of pentacycles containing *cis*-perhydroquinoline units the tautomerism of the C(16) epimers of their imino esters would be expected to have no barriers. The rigidity of the pentacycles with *trans*-perhydroquinoline moieties, however, constrains one imino ester epimer (16-*epi*-**22b**) to a ring E conformation conducive to spontaneous tautomerization and another (**22b**) to an orientation requiring serious ring E deformation for enamine formation.

^{13}C NMR Spectral Analysis. ^{13}C NMR spectroscopy played an important role in the structure analysis of synthetic intermediates en route to the pseudovincadifformine system and, in earlier studies,[2] to the deethyl equivalent. Table I and the numbers of formula **28** show carbon shift data aquired for the D/E trans pentacyclic compounds.

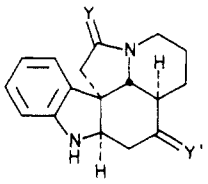
As a comparison of the carbon shifts of five pairs of compounds—**8a**/**25a**, **8f**/**25c**, **8e**/**25b**, **22a**/**27**, and **24**/

(13) For the first presentation of pentacyclic 17-ketones with ring E boat conformation see: Ban, Y.; Sendo, Y.; Nagai, M.; Oishi, T. *Tetrahedron Lett.* **1972**, 5027.

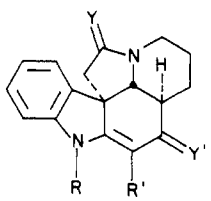
(14) For an example of a direct carbomethoxylation of the **2** → **3** conversion type (31% yield) see the synthesis of 16-methoxytabersonine: Overman, L. E.; Sworin, M.; Burk, R. M. *J. Org. Chem.* **1983**, *48*, 2685.

(15) Whereas a one-step C(16) carbomethoxylation would be preferred to the present two-step reaction scheme, the Overman procedure[14] perhaps may not be universally applicable. Thus even though the C(14)-substituted dehydroaspidospermidine can be acylated at N_a and C(16) under the reported reaction conditions (J. Ardisson, unpublished observations), attempted direct carbomethoxylation of indolenine **22a** led to decomposition of the starting material.

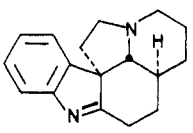
(16) Wenkert, E.; Simmons, D. P., unpublished observations.



25a, Y = Y' = O
b, Y = Y' = H_2
c, Y = O, Y' = H_2



26a, R = R' = H; Y = Y' = O
b, R = $CH_2C_6H_5$; R' = H; Y = Y' = O
c, R = H; R' = CO_2Me; Y = Y' = H_2



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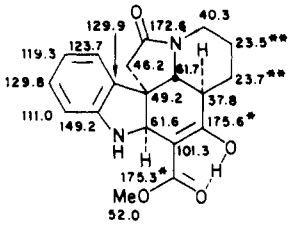

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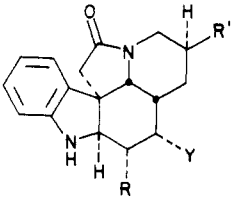
26c—indicates, the introduction of a β-ethyl group at C(20) of the pentacyclic nucleus leads to a 11–14 ppm α-shift at C(20) and 5–6 and 5–8 ppm β-shifts at C(15) and C(21), respectively, in consonance with the side chain being equatorial. Whereas the magnitude of the α- and β-effects at the three carbon sites differs with the presence of carbonyl or imino groups in the ring system, the chemical shifts of the carbons of the ethyl groups are impervious to the changes in the nucleus. A comparison of the carbon shifts of keto lactam **10a** with those of its deethyl counterpart **25a** show the α- and β-effects to be diminished, as expected for the presence of an axial 20-ethyl group in compound **10a**. More importantly, the side chain of the latter exerts a 4.7 ppm γ-effect on C(14), which is reciprocated at C(19), albeit to a low extent (2.7 ppm). Besides these stereochemically diagnostic facts it is noteworthy also that the methyl group of the axially ethylated compound (**10a**) is deshielded by 1.1 ppm vs. all 20β-ethyl compounds. The ca. 4.5 ppm shielding of C(14) of imino ester **22b**, compared with this carbon site in imines **22a** or **27**, shows the carbomethoxy group to be oriented axially in ring E of ester **22b**.

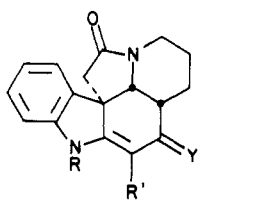
Table II incorporates the carbon shift data for D/E cis pentacyclic compounds of the keto lactam, enol lactam, and ketone types. Comparison of the C(20), C(15), and C(21) shifts of pentacycles **29a**, **29c**, **30a**, **30d**, and **31c** with those of compounds **9a**, **9d**, **30b**, **30e**, and **31d**, respectively, showed that the introduction of an equatorial (i.e., β) ethyl group at C(20) yields an α-effect of 12.4 ± 0.7 ppm at C(20) and β-effects of 6.8 ± 0.1 and 5.2 ± 0.3 ppm at C(15) and C(21), respectively. Similar shift inspection of the **29c**/**11d**, **30a**/**30c**, and **30d**/**30f** pairs of substances reveals deshielding of C(20), C(15), and C(21) by 13.5 ± 0.6, 4.2 ± 0.2, and 3.7 ± 0.4 ppm on introduction of a 20α-ethyl group into ring D. Whereas these effects are diagnostic of the relative C(20) configuration, the lack of shift variation of C(19) throughout the D/E cis as well as D/E trans (vide supra) series of compounds make the δ value of C(19) useless for the determination of stereochemistry. On the other hand, as in the D/E trans compounds (vide supra), a ca. 1 ppm difference of the methyl shift between 20β- and 20α-ethyl compounds distinguishes these substances.

A comparison of C(14) isomers, e.g., the D/E trans compounds **25a**, **8a**, and **28** with their D/E cis counterparts **29a**, **9a**, and **31c**, respectively, yields some interesting shift changes. For example, in the cis series C(16) is shielded and the 1,3-diaxial interaction of C(8) and C(14) induces an upfield shift of the signals of these centers. Most importantly, C(17) being axially disposed toward ring D in the cis compounds causes a γ-effect on C(20). Hence the latter carbon center is shielded (3.7 ± 0.4 ppm) in the cis substances.

Table III presents the carbon shifts of D/E cis lactams not discussed heretofore. The hydroxy group of lactam **33b** is axially disposed toward ring E, as shown by its 6.9 ppm γ-effect on C(2) and the 1.7 ppm δ-effect on C(20). Similar analyses of lactams **33d** and **33e** reveal their hydroxy groups to possess the same configuration. The absence of any γ-shift at C(14) on introduction of a 16-carbomethoxy group indicates the equatoriality of this function in esters **33c–e**.

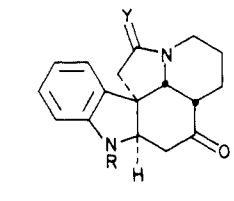


33a, R = R' = Y = H
b, R = R' = H; Y = OH
c, R = CO_2Me; R' = Y = H
d, R = CO_2Me; R' = H; Y = OH
e, R = CO_2Me; R' = Et; Y = OH

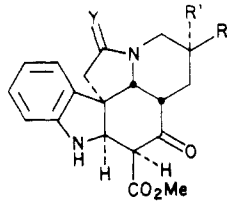


34a, R = R' = H; Y = O
b, R = $CH_2C_6H_5$; R' = H; Y = O
c, R = H; R' = CO_2Me; Y = O
d, R = H; R' = CO_2Me; Y = H_2

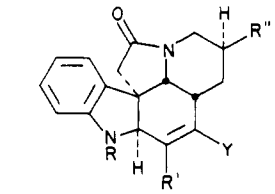
The carbon shifts of pseudoaspidospermidine-like (**9e** and **35**) and pseudovincadifformine-like (**3** and **36**) compounds are recorded in Table IV. The orientation of the 17-hydroxy group of the amino alcohols **35b** and **35e** can be obtained from the C(2) and C(20) shift differences in the **35a**/**35b** and **35d**/**35e** pairs of compounds. The distinct γ- and δ-effects on C(2) and C(20), respectively, point to an axial disposition of the hydroxy group to ring E in the oxygenated substances and hence to an 17α-hydroxy configuration. Comparison of the δ values of amines **35a** and **35b** with those of esters **35d** and **35e**, respectively, reveals the absence of any γ-effect on C(14) and δ-effects on C(8) and C(13), as expected for axial carbomethoxy



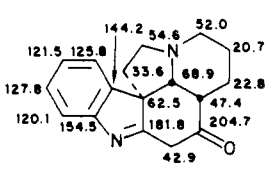
29a, R = H; Y = O
b, R = Et; Y = O
c, R = H; Y = H_2



30a, R = R' = H; Y = O
b, R = Et; R' = H; Y = O
c, R = H; R' = Et; Y = O
d, R = R' = H; Y = H_2
e, R = Et; R' = H; Y = H_2
f, R = H; R' = Et; Y = H_2



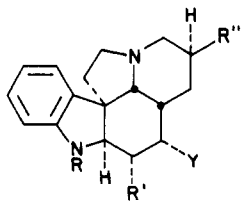
31a, R = Ac; R' = R'' = H; Y = OMe
b, R = R'' = Y = H; R' = CO_2Me
c, R = R'' = H; R' = CO_2Me; Y = OH
d, R = H; R' = CO_2Me; R'' = Et; Y = OH



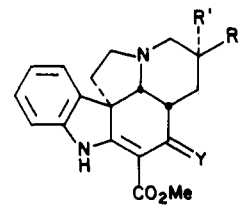
32

(17) High-resolution ^1H NMR: δ 1.1–2.4 (m, 9, methylenes, methines), 2.35 (dd, 1, J = 15, 3 Hz, H-17β), 2.58 (dd, 1, J = 15, 12 Hz, H-17α), 2.87 (s, 1 H-3), 2.92 (dd, 1, J = 10, 7 Hz, H-5), 3.18 (dd, 1, J = 11, 4 Hz, H-21), 3.75 (s, 3, OMe), 6.7–7.3 (m, 4, aromatic Hs).

(18) Pseudovincadifformine (**36b**), prepared from catharanthine by a reduction–oxidation process, gave the following high-resolution ^1H NMR spectrum: δ 0.91 (t, 3, J = 7 Hz, Me), 1.3–1.5 (m, 2, CH_2), 1.6–2.1 (m, 7, methylenes, methines), 2.28 (dd, 1, J = 15, 12 Hz, H-17α), 2.53 (dd, 1, J = 15, 3 Hz, H-17β), 2.7–3.0 (m, 4, methylenes), 3.76 (s, 3, OMe), 6.8–7.2 (m, 4, aromatic Hs).



35a, R = R' = R'' = Y = H
b, R = R' = R'' = H; Y = OH
c, R = $CH_2C_6H_5$; R' = R'' = H; Y = OH
d, R = R'' = Y = H; R' = CO_2Me
e, R = R'' = H; R' = CO_2Me; Y = OH



36a, R + R' = Y = H_2
b, R = H; R' = Et; Y = H_2
c, R = R' = H; Y = O
d, R = Et; R' = H; Y = O

groups. Hence the ester side chains are equatorial, i.e., 16α-carbomethoxy functions. The $\Delta\delta$(C-20), $\Delta\delta$(C-15), and $\Delta\delta$(C-21) values for the **35a**/**9e** pair of amines are the same as those of the **29c**/**9d** pair of keto amines and different from those of the **29c**/**11d** pair of substances, indicating the equatorial conformation of the 20-ethyl group of amine **9e**.

With the ^{13}C NMR data on the amines **9e** and **35** in hand, it is now possible to analyze the ring E conformation of their 17-ketones, whose ^1H NMR spectral analysis had indicated the presence of a boat conformation (vide supra). Comparison of the C(15) shifts of the D/E trans pentacycles **8f** and **25c** with those compounds **8a** and **25a**, respectively, shows that the introduction of a keto group at C(17), i.e., the introduction of a peri interaction between the keto oxygen and the 15-hydrogens, shields strongly C(15) (ca. 7 ppm).[19] Inspection of models of 17-ketones of D/E cis pentacycles with ring D and E chair conformations reveals the keto oxygen to be oriented away from the 15-hydrogens and toward H-20α. This steric interaction would impose a δ-effect on C(20) and no γ-effect at C(15). However, a comparison of the C(20) and C(15) δ values of amines **9e** and **35a** with those of their 17-ketones **9d** and **29c**, respectively, shows the introduction of the keto function to cause shielding of C(15) (ca. 5.5 ppm) and minimal change at C(20). This observation can be justified by a ring E boat conformation for the ketones, in which models reveal a peri interaction between the oxygen and H-15α and lack of proximity of the oxygen to H-20α.

The ^{13}C NMR spectral data can be used for easy differentiation of pentacycles of the *trans*-hydroquinoline type from those of the D/E cis mode. Inspection of conformational structures **21** (R = R' = H or **21a**) and 17-deoxo-**17** (R = R' = H or **17a**) shows different carbons exposed to 1,3-diaxial interactions with hydrogens or lone electron pairs and hence expected to exhibit γ-effects. The resonances of carbons 3, 5, 6, 8, and 9 are most diagnostic for distinguishing the two stereochemical series. As a comparison of the shift data for the amine pairs **8e**/**9e** and **25b**/**35a** illustrates, C(5) and C(6) are shielded in the D/E trans vs. cis series in view of their axial disposition toward the *trans*-hydroquinoline system and equatorial orientation in the cis isomers. The close proximity of H(3) to H(9) in the D/E cis system causes shielding of C(3) and C(9) in the latter vs. the trans compounds. The axiality of C(8) in ring E of the D/E cis substances makes the resonance of this center upfield of that of their trans counterparts. Whereas several other carbon centers might have been expected to exhibit shift changes in the two stereochemical series, balancing γ-effects appear to maintain the shifts. Thus, for example, C(20) feels a γ-effect from C(5) in the trans compounds and from C(17) in the cis substances. Removal of the C(5) interaction, as in D/E trans lactam **25c**, causes deshielding of C(20) vs. this center in D/E cis lactam **33a**.

As the ^{13}C NMR spectral data for deethylvincadifformine (**36a**), 20-epipseudovincadifformine (**3**), and pseudovincadifformine (**36d**) indicate, the introduction of a 20β-ethyl group produces α- and β-effects at C(20), C(15), and C(21) similar to those observed earlier for the entry of an equatorial C(20) side chain in a chair ring D of either D/E cis or trans pentacycles. The 20α-ethyl compound exhibits ethyl-induced α- and β-effects and a C(18) shift found earlier for an axial C(20) side chain within a chair ring D. Furthermore, C(17) and C(19) are deshielded, as expected for a δ-effect emanating from their 1,3-diaxial interaction. These data favor the formulation of a ring D chair conformation for the three substances in solution.[20,21]

Experimental Section

Melting points were determined on a Kofler micro hotstage and are uncorrected. Infrared spectra were recorded on Perkin-Elmer 137 and 257 spectrophotometers and ultraviolet spectra of 95% ethanol solutions on Cary 14, Cary 17, and Unicam SP 1800 spectrophotometers. Mass spectra were obtained on Finnigan 3300, CEC 21-110B and AEI MS902 spectrometers. ^1H NMR spectra of $CDCl_3$ solutions with Me_4Si as internal standard (δ = 0 ppm) were taken on a Varian EM-390 spectrometer and on an experimental 400 MHz instrument built at the Institut d'Electronique Fondamentale (91405 Orsay, France).[22] ^{13}C NMR spectra of $CDCl_3$ solutions were obtained on Varian CFT-20, JEOL JNM-PS-100, Nicolet NT-200 (wide-bore, broad-band, with Oxford magnet), and Bruker WH400 spectrometers, operating in the Fourier transform mode. The δ values on compounds **28**[2d] and **32**[16] are in ppm downfield from Me_4Si, signals with asterisks being interchangeable; δ (Me_4Si) = δ ($CDCl_3$) + 76.9 ppm. Column chromatography was carried out with Merck silica gel (70–230 mesh) and high-pressure chromatography with Merck silica or alumina (325 mesh) under 10 bar pressure on a Jobin-Yvon Miniprep apparatus. Photochemical experiments were executed in a quartz reactor under argon with immersion high-pressure mercury Hanau TQ 150 and low-pressure mercury Hanau TNN 15/32 lamp assemblies. All reactions were run under nitrogen, the crude products were extracted with methylene chloride, and the extracts were dried (Na_2SO_4) and evaporated.

3-Acetyl-5-ethylpyridine (5a). A solution of 970 mg (4 mmol) of 3-acetyl-5-bromopyridine ethylene ketal (**4**)[7] in 15 mL of anhydrous tetrahydrofuran (THF), cooled to −78 °C, was added dropwise to a 0.78 M *n*-butyllithium solution and 30 mL of 1:1 hexane–THF, and the mixture stirred at −78 °C for 0.5 h. Thereafter a solution of 1.5 mL (18 mmol) of ethyl iodide in 15 mL of anhydrous THF was added at such a rate as to keep the temperature below −60 °C and the mixture stirred at −78 °C for 2 h. After the mixture had warmed to 0 °C, 20 mL of water and 40 mL of hexane were added and the mixture was extracted with 1 N hydrochloric acid. Saturated sodium bicarbonate solution was added to the extract and the organic material worked up normally.

A solution of the crude ketal in 30 mL of 0.5 N hydrochloric acid was refluxed for 3 h. Saturated sodium bicarbonate solution was added to the cooled mixture and the organic product worked up normally. Elution of the column chromatogram with 1.5:1 hexane–ether yielded 345 mg (58%) of liquid ketone **5a**: IR ($CHCl_3$) C=O 1695 (s), C=C 1595 (s) cm^{-1}; ^1H NMR δ 1.25 (t,

(19) This γ-effect has been observed in *trans*-decalin upon introduction of a 1-keto group; see inter alia: Fringuelli, F.; Pizzo, F.; Taticchi, A.; Halls, T. D. J.; Wenkert, E. *J. Org. Chem.* **1982**, *47*, 5056.

(20) In an earlier description of pseudovincadifformine (**36b**) its ring D was suggested to be in a boat conformation.[6] The analysis included $\Delta\delta$ values for various carbons of the **3**/**36b** C(20) epimer pairs of which the $\Delta\delta$(C-15) was reported incorrectly.

(21) One feature of the ^1H NMR spectra of the three substances also favors this conformation. Whereas the H(17α) signal of pentacycles **36a** and **3** appears at 2.58 ppm,[17] that of pseudovincadifformine (**36b**) is moved upfield to 2.28 ppm.[18] This shielding effect on H(17α) in the 20α-ethyl case is explained readily by the anisotropy of the ethyl group 1,3-diaxial to C(17) within a ring D chair conformation.

(22) Gonord, P.; Kan, S. K.; Sauzade, M. *J. Magn. Res.* **1976**, *24*, 457. Kan, S. K.; Gonord, P.; Fan, M.; Sauzade, M.; Courtieu, J. *Rev. Sci. Instrum.* **1978**, *49*, 785.

Table I. ^{13}C Chemical Shifts of D/E Trans Pentacycles 8, 10, and 22–27[a]

	25a[b]	8a	10a	25c[b]	8f	25b[b]	8e	27[b]	22a	22b	26a[b]	26b[c,d]	23a	26c[b]	24
C(2)	63.0	63.2	63.3	61.9	62.0	63.6	63.6	186.0	186.3	189.5	168.6	167.9	140.4[e]	164.1	164.8
C(3)	65.1	65.2	65.6	69.6	69.5	70.4	70.4	75.2	75.5	74.8	68.1	67.8	67.8	66.7	66.7
C(5)	171.2	171.2	172.0	171.7	171.8	47.7	46.9	46.9	47.5	47.3	172.4	172.1	47.0	47.6	46.1
C(6)	43.1	43.4	43.4	39.6	39.6	32.7	32.7	33.0	33.0	33.8	44.9	45.2	32.0	31.8	32.0
C(7)	46.7	46.7	47.3	45.0	44.9	52.8	52.7	63.2	63.3	63.7	48.1	48.0	51.6	54.9	55.2
C(8)	134.0	134.1	134.3	136.0	136.0	139.3	139.2	146.2	146.4	146.1	134.2	134.3	139.5	137.5	137.4
C(9)	121.9	122.0	122.3	121.5	121.6	123.4	123.4	125.0	125.3	125.8	122.4	122.0	123.8	122.9	122.9
C(10)	119.8	119.9	120.3	118.4	118.6	118.5	118.4	122.9	123.1	123.0	121.9	121.3	123.0	120.6	120.6
C(11)	128.8	128.9	129.2	127.7	127.8	126.6	126.4	127.2	127.4	127.4	129.1	127.6	127.1	127.1	127.2
C(12)	110.3	110.4	110.7	108.8	108.9	108.4	108.4	119.4	119.7	120.0	110.2	108.5	110.5	108.9	109.0
C(13)	147.4	147.4	147.6	148.4	148.4	148.5	148.5	153.7	153.9	153.5	142.8	144.1	142.8[e]	143.7	143.2
C(14)	50.1	50.1	45.4	40.1	39.6	32.3	32.2	34.1	34.3	29.7	48.1	48.0	40.2	41.2	41.1
C(15)	22.9	29.1	27.5	30.3	36.7	31.2	37.5	30.1	36.6	36.2	23.3	23.1	37.1	30.5	36.8
C(16)	44.7	44.9	45.1	27.5	27.6	27.6	27.6	30.8[e]	31.0[e]	47.0	101.8	99.9	115.0	98.5	98.4
C(17)	206.1	206.1	207.0	23.3	23.3	25.5	25.4	31.3[e]	31.6[e]	31.2	193.1	192.5	30.8	30.0	29.9
C(18)		11.0	12.3		11.0		11.2		11.4	11.3			11.4		11.3
C(19)		26.4	23.7		26.6		27.0		27.1	26.9			27.3		27.1
C(20)	24.0	36.9	35.3	25.5	38.2	20.5	31.9	20.5	32.5	32.0	25.2	25.1	31.1	20.5	31.8
C(21)	40.1	45.4	43.7	40.6	45.9	46.0	54.0	46.5	53.5	53.3	41.5	41.3	54.1	45.3	53.7
C=O										171.4			153.1	168.8	168.4
OMe										50.9			52.7	50.9	50.9

[a] The δ values are in ppm downfield from Me_4Si; $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm. [b] Reference 2c. [c] Reference 16. [d] Benzyl group: $\delta(CH_2) = 46.9$, $\delta(ipso\text{-}C) = 134.3$, $\delta(o\text{-}C) = 126.3$, $\delta(m\text{-}C) = 128.7$, $\delta(p\text{-}C) = 128.8$ ppm. [e] Signals within a vertical column may be interchanged.

Table II. ^{13}C Chemical Shifts of D/E Cis Pentacycles 9, 11, and 29–31[a]

	29a[b]	29b[c,d]	9a	30a[e]	30b[f]	30c[f]	29c[g]	9d	11d	30d[e]	30e[c]	30f[c]	31a[c,h]	31b[e]	31c[e]	31d[f]
C(2)	66.0[i]	68.6	66.1	67.1	67.2	67.5	66.0	66.0	66.8	67.4	67.4	67.9	66.2	61.6	66.0	66.1
C(3)	66.4[i]	66.1	65.8	65.4	65.5	65.7	75.1	75.2	75.8	73.9	74.0	74.6	60.3	61.6	63.3	63.4
C(5)	172.2	171.8	171.3	173.9	174.0	174.0	54.9	54.7	55.5	54.5	54.5	54.8	171.5	171.8	171.6	172.8
C(6)	43.4	43.2	43.7	42.5	42.9	42.9	37.8	38.1	38.5	37.0	37.3	37.3	47.0	46.8	45.8	45.2
C(7)	46.5	45.8	46.2	47.1	46.2	46.9	51.6	51.3	52.1	52.0	51.7	51.5	47.4	49.1	47.4	47.2
C(8)	131.7	131.5	131.5	130.1	130.7	130.7	135.5	135.5	135.8	133.7	133.8	133.8	131.8	131.9	131.3	130.2
C(9)	122.8	122.1	122.6	122.3	122.4	122.4	123.2	123.2	123.5	122.7	122.8	122.9	122.0	122.3	122.6	122.7
C(10)	119.9	118.4	119.5	119.4	119.7	119.4	119.3	119.3	119.6	119.0	119.1	119.1	123.7	118.3	119.0	119.2
C(11)	128.9	128.7	128.6	129.0	129.1	129.1	127.5	127.9	128.1	128.0	128.1	127.9	128.7	128.3	128.5	128.7
C(12)	110.3	107.8	109.9	109.9	109.9	109.9	109.2	109.2	109.3	109.1	109.2	109.6	117.1	108.8	109.2	109.4
C(13)	150.1	150.8	150.0	149.7	149.8	149.8	150.3	150.2	150.5	149.8	149.9	149.9	141.8	150.1	150.1	150.2
C(14)	43.7	43.4	43.6	43.4	43.6	42.0	44.2	44.1	42.7	43.9	43.8	42.3	31.5	31.6	35.5	35.8
C(15)	24.6	24.5	31.3	25.4	32.1	29.4	24.0	30.9	28.4	24.9	31.7	29.1	23.7	27.9	23.1	29.8
C(16)	41.0	39.0	40.9	55.8	55.7	54.7	39.8	39.8	40.2	54.6	54.3	54.2	93.8	129.0	98.3	98.1
C(17)	209.1	208.6	209.0	203.8	204.0	203.6	211.0	211.2	212.5	203.6	203.6	203.8	154.7	142.1	*j*	*j*
C(18)			10.9		10.8	12.3		11.3	12.8		11.2	12.6				10.9
C(19)			26.5		26.5	25.5		26.9	26.7		26.8	26.4				26.6
C(20)	20.3	20.2	32.8	20.5	32.5	33.6	21.9	34.1	36.0	22.3	34.6	35.5	19.1	19.6	20.1	33.2
C(21)	40.3	40.0	45.2	40.1	45.2	43.6	53.0	58.5	57.1	52.5	58.0	56.1	40.4	39.7	40.0	45.2
C=O				171.6	171.6	171.6				171.0	171.3	171.3		165.8	169.6	169.8
OMe				52.3	52.5	52.5				51.9	52.1	52.1	54.3	51.6	51.7	51.8

[a] The δ values are in ppm downfield from Me_4Si; $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm. [b] References 2a and c. [c] Reference 16. [d] N_a–Et: $\delta(CH_2) = 38.6$, $\delta(Me) = 10.2$ ppm. [e] Reference 2d. [f] Reference 10. [g] Reference 2c. [h] N_a–Ac: $\delta(C{=}O) = 167.7$, $\delta(Me) = 23.8$ ppm. [i] Signals may be interchanged. [j] Signal unrecorded.

3, J = 6 Hz, Me), 2.57 (s, 3, COMe), 2.68 (q, 2, J = 6 Hz, CH_2), 8.05 (t, 1, J = 2 Hz, H-4), 8.60 (d, 1, J = 2 Hz, H-6), 8.95 (d, 1, J = 2 Hz, H-2); m/e 149 (M^+, 47%), 134 (base), 106 (75), 43 (30); exact mass, m/e 149.0842, calcd for $C_9H_{11}ON$, m/e 149.0840.

Methyl (5-Ethylnicotinyl)acetate (5b). A solution of 7.60 g (51 mmol) in 25 mL of dimethyl carbonate was added dropwise to a suspension of 2.60 g of sodium hydride in 200 mL of dimethyl carbonate at 90 °C and the mixture refluxed for 12 h. Ice water was added to the cooled mixture and the latter extracted with ether. The remaining aqueous solution was brought to pH 6–7 with 6 N hydrochloric acid, saturated with brine, and worked up normally. Kugelrohr distillation of the crude product at 125 °C (0.04 torr) gave 9.24 g (82%) of liquid ester **5b**: IR ($CHCl_3$) OH 3360 (m), C=O 1745 (m), 1690 (s), 1655 (m), C=C 1630 (s), 1595 (m), 1575 (m) cm^{-1}; ^1H NMR (ca. 3:1 keto enol mixture) δ 1.25 (t, 3, J = 6 Hz, Me), 2.69 (q, 2, J = 6 Hz, CH_2), 3.80 (s, 2.25, OMe), 3.85 (s, 0.75, enol OMe), 4.03 (s, 1.5, $COCH_2$), 5.69 (s, 0.5, enol CH), 7.84 (t, 0.25, J = 2 Hz, enol H-4), 8.02 (t, 0.75, J = 2 Hz, H-4), 8.49 (d, 0.25, J = 2 Hz, enol H-6), 8.62 (d, 0.75, J = 2 Hz, H-6), 8.78 (d, 0.25, J = 2 Hz, enol H-2), 8.95 (d, 0.75, J = 2 Hz, H-2).

Anal. Calcd for $C_{11}H_{13}O_3N$: C, 63.75; H, 6.32; N, 6.76. Found: C, 63.69; H, 6.44; N, 6.56.

3-Acetyl-5-ethyl-1,4,5,6-tetrahydropyridine (6a). A mixture of 10.0 g (67 mmol) of ketone **5a** and 800 mg of 10% palladium–charcoal in 30 mL of ethanol was hydrogenated at 3 atm. Upon cessation of hydrogen uptake the mixture was filtered through a Whatman GF/A glass microfiber filter and the filtrate evaporated. Chromatography of the residue and elution with ethyl acetate yielded 8.70 g (85%) of solid 2-piperideine **6a**: mp 47–49 °C (from EtOAc); IR (neat) NH 3200 (s), C=O, C=C 1625 (m), 1560 (s), 1510 (s) cm^{-1}; ^1H NMR δ 0.95 (t, 3, J = 6 Hz, Me), 1.2–1.5 (m, 2, CH_2), 1.6–1.9 (m, 1, H-5), 2.10 (s, 3, COMe), 2.5–2.9 (m, 2, γ-CH_2), 3.1–3.4 (m, 2, NCH_2), 7.47 (d, 1, J = 7 Hz, H-2); ^{13}C NMR δ 10.9 (Me), 23.0 (acetyl Me), 25.6 (CH_2), 26.1 (C-4), 32.1 (C-5), 45.2 (C-6), 106.6 (C-3), 146.7 (C-2), 193.2 (C=O); m/e 153 (M^+, 55%), 138 (base), 124 (73), 110 (23), 82 (39), 80 (30), 43 (55); exact mass m/e 153.1107, calcd for $C_9H_{15}ON$, m/e 153.1153.

Methyl (5-Ethyl-1,4,5,6-tetrahydronicotinyl)acetate (6b). A mixture of 3.00 g (14.5 mmol) of ester **5b** and 500 mg of 5% palladium–charcoal in 50 mL of methanol was hydrogenated at 3 atm. Upon cessation of hydrogen uptake the catalyst was filtered through Celite and the filtrate evaporated under vacuum, yielding 3.00 g (97%) of liquid ester **6b**: IR ($CHCl_3$) NH 3300 (m), C=O, C=C 1735 (s), 1580 (m), 1520 (m) cm^{-1}; ^1H NMR δ 0.95 (t, 3, J = 6 Hz, Me), 1.2–1.5 (m, 2, CH_2), 1.6–1.9 (m, 1, H-5), 2.5–2.9 (m,

Table III. ^{13}C Chemical Shifts of D/E Cis Lactams 33 and 34[a]

	33a[b]	33b[c,d]	33c[e]	33d[e]	33e[c]	34a[b]	34b[c,f]	34c[e]	34d[e]
C(2)	64.7	57.8	65.5	61.5	61.6	171.3	168.3	166.1	163.7
C(3)	60.1	60.1	58.9	58.2	58.5	55.2	55.2	54.6	63.2
C(5)	172.9	170.3	172.9	172.1	171.9	169.3	169.3	168.6	170.4
C(6)	45.0	45.0	44.5	44.8	45.2[g]	50.8	51.4	50.3	47.8
C(7)	48.6	47.1	49.0	48.1	47.8	47.9	47.5	49.4	48.9
C(8)	129.8	131.5	128.9	130.1	130.2	134.2	134.3	135.3	135.7
C(9)	121.9	122.3	121.3	121.7	121.7	122.0	122.2	123.9	121.3
C(10)	118.7	117.3	118.4	118.7	118.7	120.7	120.6	121.1	121.3
C(11)	128.2	127.7	128.2	128.5	128.5	128.5	127.4	128.9	128.5
C(12)	110.0	109.2	109.5	109.9	109.9	110.2	108.2	111.4	109.4
C(13)	149.8	150.7	148.7	148.7	148.7	142.9	143.8	141.3	143.3
C(14)	32.1	34.0	31.3	34.5	35.2	42.5	42.6	44.5	35.8
C(15)	28.8	29.5	28.1	27.4	34.7	22.2	22.1	22.4	28.2
C(16)	29.8	36.7	44.9	50.1	50.5	96.8	95.8	98.8	95.7
C(17)	20.7	68.5	23.8	71.4	71.3	194.6	193.5	190.3	23.0
C(18)					11.0				
C(19)					27.5				
C(20)	18.5	20.2	18.0	20.2	31.8	20.6	20.6	20.7	20.0
C(21)	40.5	39.7	40.1	40.3	45.5[g]	40.0	39.8	40.4	40.4
C=O			173.8	173.4	173.5			175.0	167.8
OMe			51.6	52.1	52.0			51.4	51.0

[a] The δ values are in ppm downfield from Me_4Si: $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm. [b] Reference 2c. [c] Reference 16. [d] In Me_2SO-d_6: $\delta(Me_4Si) = \delta(Me_2SO\text{-}d_6) + 39.5$ ppm. [e] Reference 2d. [f] Benzyl group: $\delta(CH_2) = 46.5$, $\delta(ipso\text{-}C) = 134.2$, $\delta(o\text{-}C) = 126.0$, $\delta(m\text{-}C) = 128.5$, $\delta(p\text{-}C) = 128.3$ ppm. [g] Signals may be interchanged.

Table IV. ^{13}C Chemical Shifts of D/E Cis Pentacycles 35 and 36[a]

	35a[b]	9e	35b[b]	35c[c,d]	35d[e]	35e[e]	36a[e,f]	3	36b[g]	36c[b,e]	36d[c]
C(2)	66.0	66.4	62.1	66.5	66.5	63.2	166.8	166.4	167.5	166.4	167.0
C(3)	67.5	68.0	68.0	67.7	67.2	67.4	67.3	67.0	65.5	57.2	57.5
C(5)	53.6[h]	53.7	53.8[h]	54.0[h]	54.0	53.8	51.9	51.7	51.6	48.8[h]	49.3
C(6)	38.1	38.9	37.8	38.0	37.8	37.4	45.6	45.4	43.9	46.8	47.1
C(7)	53.2	53.3	52.7	52.2	53.3	53.1	56.2	55.8	55.3	57.2	57.2
C(8)	133.8	134.3	132.5	133.7	133.2	131.9	137.4	136.6	137.4	136.5	137.0
C(9)	121.9	122.3	121.8	121.2	121.8	121.5	121.5	121.5	121.8	123.0	123.3
C(10)	118.6	119.0	118.5	117.1	118.7	118.4	120.7	120.6	120.4	120.9	121.4
C(11)	127.2	127.6	127.5	127.6	127.7	127.9	127.8	127.6	127.6	127.6	128.0
C(12)	109.9	110.3	110.1	106.7	110.0	109.6	109.3	109.1	109.2	110.6	110.7
C(13)	150.0	150.4	149.7	150.0	149.4	149.0	143.8	143.5	143.4	141.0	141.3
C(14)	32.5	32.8	34.4	34.6	32.2	34.7	36.2	36.0[h]	35.8[h]	43.3	44.1
C(15)	29.2	36.7	27.9	28.0	28.9	27.9	28.4	35.3	32.1	22.7	29.5
C(16)	31.5	31.9	39.0	33.6	47.0	52.5	96.2	96.3	95.2	98.1	98.4
C(17)	22.1	23.1	71.8	71.7	25.1	73.6	24.4	25.2	26.7[i]	192.4	193.0
C(18)		11.6						11.4	12.2		11.1
C(19)		27.5						27.1	28.5[i]		27.0
C(20)	21.1	33.5	22.3	22.5	20.9	22.3	21.4	35.8[h]	35.7[h]	17.8	28.8
C(21)	54.2[h]	60.1	54.0[h]	53.0[h]	54.0	52.7	51.1	56.1	54.7	48.6[h]	54.6
C=O					175.2	173.5	168.9	168.6	168.4	177.1	177.6
OMe					51.8	51.6	50.8	50.9	50.9	50.9	51.2

[a] The δ values are in ppm downfield from Me_4Si; $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm. [b] Reference 2c. [c] Reference 16. [d] Benzyl group: $\delta(CH_2) = 48.3$, $\delta(ipso\text{-}C) = 138.3$, $\delta(o\text{-}C) = 126.9$, $\delta(m\text{-}C) = 128.1$, $\delta(p\text{-}C) = 126.6$ ppm. [e] Reference 2d. [f] Reference 17. [g] Reference 18. [h,i] Signals within any vertical column may be interchanged.

2, γ-CH_2), 3.2–3.4 (m, 2, NCH_2), 3.55 (s, 2, $COCH_2$), 3.70 (s, 3, OMe), 7.65 (d, 1, J = 7 Hz, H-2).

Anal. Calcd for $C_{11}H_{17}O_3N$: C, 62.53; H, 8.11; N, 6.63. Found: C, 62.74; H, 8.06; N, 6.73.

3-Acetyl-5-ethyl-1-(3-indolylacetyl)-1,4,5,6-tetrahydropyridine (7a). A solution of 765 mg (5 mmol) of 2-piperideine **6a** and 2.20 g (6.6 mmol) of indoleacetic anhydride[8] in 100 mL of anhydrous THF was stirred at room temperature for 24 h and then evaporated. A methylene chloride solution of the residue was washed with 10% hydrochloric acid solution and 5% sodium bicarbonate solution and then worked up normally. HPLC chromatography of the crude product on silica and elution with 50:15:1.3:1 dichloromethane/hexane/ethyl acetate/methanol afforded 930 mg (60%) of amorphous imide **7a**: IR (KBr) NH 3265 (m), C=O, C=C 1680 (m), 1650 (m), 1610 (s) cm^{-1}; ^1H NMR δ 0.86 (t, 3, J = 6 Hz, Me), 1.1–1.4 (m, 2, CH_2), 1.6–3.0 (m, 5, methylenes, H-5), 2.10 (s, 3, COMe), 4.00 (s, 2, $COCH_2$), 6.9–7.6 (m, 5, aromatic Hs), 8.93 (s, 1, H-2); m/e 310 (M^+, 13%), 130 (56), 86 (68), 84 (base); exact mass, m/e 310.1675, calcd for $C_{19}H_{22}O_2N_2$, m/e 310.1681.

Methyl [5-Ethyl-1-(3-indolylacetyl)-1,4,5,6-tetrahydronicotinyl]acetate (7b). A solution of 5.10 g (24 mmol) of ester **6b** in 20 mL of anhydrous THF was added dropwise to a suspension of 600 mg (25 mmol) of sodium hydride in 50 mL of anhydrous THF at 0 °C and the mixture stirred at this temperature for 0.5 h. Indoleacetic anhydride,[8] 8.02 g (24 mmol), was added and the mixture stirred at room temperature for 48 h. It then was evaporated under vacuum, and the residue shaken in 200 mL of water and extracted with methylene chloride. The extract was washed with 1 N hydrochloric acid and saturated sodium carbonate solution. Normal, further workup and elution of the column chromatogram with 20:1 dichloromethane–acetone led to 3.17 g (37%) of liquid ester **7b**: IR ($CHCl_3$) NH 3350 (m), C=O, C=C 1740 (s), 1685 (s), 1660 (m) cm^{-1}; ^1H NMR δ 1.0–2.0 (m, 5, methylenes, H-5), 1.78 (t, 3, J = 6 Hz, Me), 3.4–3.6 (m, 4, NCH_2, $COCH_2CO$), 3.62 (s, 3, OMe), 4.00 (s, 2, indolyl CH_2), 6.8–7.6 (m, 5, aromatic Hs), 8.81 (s, 1, H-2); exact mass, m/e 368.1746, calcd for $C_{21}H_{24}O_4N_2$, m/e 368.1736.

14-Iso-5,17-dioxo-20-epipseudoaspidospermidine (8a), 5,17-Dioxo-20-epipseudoaspidospermidine (9a), and 14-Iso-5,17-dioxopseudoaspidospermidine (10a). A solution of 1.24 g (4 mmol) of imide **7a** in 25 mL of freshly distilled boron trifluoride etherate was heated at 90–95 °C for 20–25 min and then poured into ice water and washed with ether. The mixture was

basified with dilute aqueous ammonia and worked up in the usual manner. HPLC of the crude product on silica gel and elution with 8:4:1.5 dichloromethane/ethyl acetate/methanol yielded 410 mg (33%) of crystalline pentacycle **9a**: mp 208–210 °C (from MeOH); IR (KBr) NH 3280 (m), C=O, C=C 1720 (m), 1690 (s), 1610 (m) cm^{-1}; UV λ_{max} 246 nm (log ϵ 3.85), 299 (3.40); ^1H NMR δ 0.92 (t, 3, J = 7 Hz, Me), 0.9–1.3 (m, 5, methylenes, H-20), 2.23 (t, 1, J = 13 Hz, H-21β), 2.5–2.6 (m, 1, H-14), 2.60, 3.25 (d, 1 each, J = 17 Hz, 2 H-6), 2.68, 2.80 (dd, 1 each, J = 17, 3 Hz, 2 H-16), 3.60 (d, 1, J = 4 Hz, H-3), 4.12 (t, 1, J = 3 Hz, H-2), 4.18 (dd, 1, J = 13, 3 Hz, H-21α), 6.6–7.2 (m, 4, aromatic Hs); m/e 310 (M^+, 57%), 130 (base).

Anal. Calcd for $C_{19}H_{22}O_2N_2$: C, 73.52; H, 7.14; N, 9.03. Found: C, 73.76; H, 7.14; N, 8.92.

The second product consisted of 120 mg (10%) of crystalline pentacycle **10a**: mp 159–160 °C (from MeOH); IR (KBr) NH 3300 (m), C=O, C=C 1720 (m), 1675 (s), 1605 (m) cm^{-1}; UV λ_{max} 245 nm (log ϵ 3.87), 300 (3.39); ^1H NMR δ 1.00 (t, 3, J = 7 Hz, Me), 1.2–1.8 (m, 5, methylenes, H-20), 2.2–2.3 (m, 1, H-14), 2.35 (dd, 1, J = 17, 11 Hz, H-16β), 2.58 (dd, 1, J = 17, 3 Hz, H-16α), 2.68, 2.73, 2.92, 2.97 (4-line AB, 2, J = 17 Hz, 2 H-6), 2.98 (dd, 1, J = 15, 3 Hz, H-21β), 3.60 (d, 1, J = 13 Hz, H-3), 4.06 (dd, 1, J = 11, 3 Hz, H-2), 4.18 (dd, 1, J = 15, 2 Hz, H-21α), 6.9–7.5 (m, 4, aromatic Hs); m/e 310 (M^+, 90%), 268 (30), 130 (base); exact mass, m/e 310.1675, calcd for $C_{19}H_{22}O_2N_2$, m/e 310.1681.

The third product consisted of 448 mg (36%) of crystalline pentacycle **8a**: mp 158–161 °C (from MeOH); IR (KBr) NH 3250 (m), C=O, C=C 1715 (m), 1680 (s), 1605 (m) cm^{-1}; UV λ_{max} 242 nm (log ϵ 3.87), 297 (3.45); ^1H NMR δ 0.95 (t, 3, J = 7 Hz, Me), 1.0–1.5 (m, 5, methylenes, H-20), 2.16 (td, 1, J = 12, 3 Hz, H-14), 2.37 (dd, 1, J = 18, 12 Hz, H-16β), 2.46 (t, 1, J = 12 Hz, H-21β), 2.60 (dd, 1, J = 18, 4 Hz, H-16α), 2.67, 2.71, 2.87, 2.91 (4-line AB, 2, J = 17 Hz, 2 H-6), 3.56 (d, 1, J = 12 Hz, H-3), 4.08 (dd, 1, J = 12, 4 Hz, H-2), 4.30 (dd, 1, J = 12, 4 Hz, H-21α), 6.6–7.1 (m, 4, aromatic Hs); m/e 310 (M^+, 55%), 130 (base).

Anal. Calcd for $C_{19}H_{22}O_2N_2$: C, 73.52; H, 7.14; N, 9.03. Found: 73.62; H, 7.13; N, 9.12.

Refluxing a 1 N hydrochloric acid solution of keto lactam **9a** for 15 min and workup as above yielded a ca. 1:1 **8a–9a** mixture.

17-Oxo-20-epipseudoaspidospermidine (9d). A solution of 300 mg (1.6 mmol) of *p*-toluenesulfonylhydrazine, 300 mg (0.96 mmol) of keto lactam **8a**, and 150 mg of *p*-toluenesulfonic acid in 20 mL of 95% ethanol was stirred at room temperature for 24 h and the resultant suspension evaporated. The residue was dissolved in a mixture of methylene chloride and a 10% sodium bicarbonate solution and the organic solution exposed to normal workup. Elution of a column chromatogram of the crude product with 1:1 dichloromethane/ethyl acetate yielded 450 mg (97%) of crystalline hydrazone **8b**: IR (KBr) NH 3310 (m), C=O 1660 (s), C=N, C=C 1605 (w) cm^{-1}; ^1H NMR δ 0.98 (t, 3, J = 7 Hz, Me), 2.41 (s, 3, aryl Me), 1.2–2.5 (m, 9, methylenes, methines), 2.55, 2.60, 2.78, 2.83 (4-line AB, 2, J = 17 Hz, 2 H-6), 3.20 (d, 1, J = 12 Hz, H-3), 3.88 (dd, 1, J = 10, 3 Hz, H-2), 4.30 (dd, 1, J = 10, 3 Hz, H-21α), 6.6–7.8 (m, 8, aromatic Hs).

A mixture of 450 mg (0.93 mmol) of hydrazone **8b** and 300 mg (8 mmol) of lithium aluminum hydride in 100 mL of anhydrous THF was refluxed for 1 h and then acidified with 1 N hydrochloric acid. The organic solvent was evaporated and the remaining aqueous solution treated with a saturated Seignette salt (potassium, sodium tartrate) solution and subsequently with aqueous ammonia. The mixture was extracted with methylene chloride and the extract worked up in the normal manner. HPLC chromatography on alumina and elution with 50:1 cyclohexane/ethyl acetate yielded 40 mg (15%) of crystalline 14-iso-20-epipseudoaspidospermidine (**8e**): mp 114–115 °C (from MeOH); IR (KBr) NH 3350 (m), C=C 1600 (m) cm^{-1}; UV λ_{max} 246 nm (log ϵ 3.82), 297 (3.45); ^1H NMR δ 0.95 (t, 3, J = 7 Hz, Me), 1.0–2.2 (m, 12, methylenes, methines), 1.86 (dd, 1, J = 14, 3 Hz, H-16), 2.20 (d, 1, J = 12 Hz, H-3), 2.44 (t, 1, J = 14 Hz, H-21β), 3.03 (m, 1, H-21α), 3.16 (m, 1, H-5), 3.80 (t, 1, J = 3 Hz, H-2), 6.6–7.2 (m, 4, aromatic Hs); m/e 282 (M^+, 38%), 281 (23), 190 (28), 130 (20), 124 (base); exact mass, m/e 282.2102, calcd for $C_{19}H_{26}N_2$, m/e 282.2096.

The second elution product amounted to 240 mg (55%) of crystalline hydrazone **8c**: IR ($CHCl_3$) NH 3360 (m), 3200 (m), C=N, C=C 1605 (m) cm^{-1}; ^1H NMR δ 0.95 (t, 3, J = 7 Hz, Me), 1.2–3.2 (m, 15, methylenes, methines), 2.41 (s, 3, aryl Me), 3.81 (dd, 1, J = 9, 7 Hz, H-2), 6.1–7.9 (m, 8, aromatic Hs). It was dissolved in 10 mL of 1 N hydrochloric acid and the solution refluxed for 0.5 h. Normal workup led to 150 mg (98%) (52% total yield from **8a**) of crystalline ketone **9d**: mp 110–112 °C (from MeOH); IR (KBr) NH 3310 (s), CH^{12} 2760 (m), 2720 (w), C=O 1710 (s), C=C 1610 (m) cm^{-1}; UV λ_{max} 245 nm (log ϵ 3.82), 297 (3.45); ^1H NMR δ 0.90 (t, 3, J = 7 Hz, Me), 1.1–2.5 (m, 8, methylenes, methines), 1.56 (t, 1, J = 12 Hz, H-21β), 2.12 (d, 1, J = 3 Hz, H-3), 2.58, 3.10 (dd, 1 each, J = 17, 2 Hz, 2 H-16), 3.12 (dd, 1, J = 12, 2 Hz, H-21α), 3.19 (t, 1, J = 8 Hz, H-5), 3.96 (t, 1, J = 2 Hz, H-2), 6.6–7.2 (m, 8, aromatic Hs); m/e 296 (M^+, 11), 124 (base); exact mass, m/e 296.1888, calcd for $C_{19}H_{24}ON_2$, m/e 296.1889.

Conversion of 135 mg (0.43 mmol) of keto lactam **9a** into its *p*-toluenesulfonylhydrazone by the above **8a** → **8b** procedure and elution of the column chromatogram of the crude product with 4:1 dichloromethane/ethyl acetate yielded 200 mg (97%) of crystalline hydrazone **9b**: IR (KBr) NH 3320 (m), C=O 1660 (s), C=N, C=C 1605 (w) cm^{-1}; ^1H NMR δ 0.66 (t, 3, J = 7 Hz, Me), 0.9–2.9 (m, 10, methylenes, methines), 2.42 (s, 3, aryl Me), 2.46, 3.12 (d, 1 each, J = 16 Hz, 2 H-6), 3.75 (d, 1, J = 3 Hz, H-3), 3.97 (t, 1, J = 3 Hz, H-2), 6.5–7.9 (m, 8, aromatic Hs).

Hydride reduction of 200 mg (0.42 mmol) of hydrazone **9b** by the above **8b** → **8c** reduction procedure gave 175 mg (90%) of crystalline hydrazone **9c**: IR ($CHCl_3$) NH 3360 (m), 3220 (m), CH^{12} 2770 (m), 2730 (w), C=N, C=C 1605 (m) cm^{-1}; ^1H NMR δ 0.66 (t, 3, J = 7 Hz, Me), 0.9–3.0 (m, 15, methylenes, methines), 2.41 (s, 3, aryl Me), 3.88 (s, 1, H-2), 6.6–7.9 (m, 8, aromatic Hs). Hydrolysis of **9c** in 1 N hydrochloric acid by the above **8c** → **9d** reaction procedure and elution of the column chromatogram of the crude product with 20:1 cyclohexane/acetone afforded 100 mg (80%) (70% total yield from **9a**) of crystalline ketone **9d**: mp 110–112 °C; spectrally identical with the above sample.

A solution of 300 mg (0.96 mmol) of keto lactam **8a**, 30 mg of *p*-toluenesulfonic acid, and 1 mL of ethylene glycol in 50 mL of benzene was refluxed in a Dean–Stark apparatus until the separation of water had ceased. It was cooled and poured into 10% sodium bicarbonate solution and worked up in the usual manner. A mixture of the crude ketal and 300 mg (8 mmol) of lithium aluminum hydride in 30 mL of anhydrous THF was refluxed for 4 h, then cooled, and added dropwise to a 1 N hydrochloric acid solution, 50 mL. THF was removed under vacuum and the remaining aqueous solution refluxed for 1.5 h. Workup as in the above **8c** → **9d** reaction procedure and elution of the column chromatogram of the crude product with 20:1 cyclohexane/acetone furnished 170 mg (60%) of crystalline **9d**.

The identical treatment of 300 mg (0.96 mmol) of keto lactam **9a** led to 154 mg (54%) of crystalline **9d**.

17-Oxopseudoaspidospermidine (11d). The identical treatment of 150 mg (0.48 mmol) of keto lactam **10a** and elution of the column chromatogram of the crude product with 20:1 cyclohexane/ethyl acetate gave 28 mg (20%) of crystalline ketone **11d**: mp 144–146 °C; IR (KBr) NH 3320 (m), CH^{12} 2750 (m), 2720 (w), C=O 1710 (s), C=C 1610 (m) cm^{-1}; UV λ_{max} 246 nm (log ϵ 3.80), 299 (3.46); ^1H NMR δ 0.84 (t, 3, J = 7 Hz, Me), 1.2–2.5 (m, 9, methylenes, methines), 2.00 (dd, 1, J = 12, 3 Hz, H-21), 2.01 (d, 1, J = 3 Hz, H-3), 2.55, 3.66 (dd, 1 each, J = 16, 3 Hz, 2 H-16), 2.96 (dd, 1, J = 12, 2 Hz, H-21), 3.15 (t, 1, J = 8 Hz, H-5), 3.98 (t, 1, J = 3 Hz, H-2), 6.5–7.1 (m, 4, aromatic Hs); m/e 296 (M^+, 24%), 254 (22), 124 (base); exact mass, m/e 296.1882, calcd for $C_{19}H_{24}ON_2$, m/e 296.1889.

14-Iso-5-oxo-20-epipseudoaspidospermidine (8f) and 5-Oxo-20-epipseudoaspidospermidine (9f). A solution of 1.00 g (3.2 mmol) of keto lactam **8a**, 1.70 mL (35 mmol) of hydrazine hydrate, and sodium ethylene glycolate (from 5.0 g of sodium) in 150 mL of ethylene glycol was heated at 160 °C for 1 h. The water and excess hydrazine were removed by distillation and the remaining solution was heated at 210 °C for 2 h. The mixture was cooled, poured into ice water, and worked up in the usual fashion. Crystallization of the crude product from methanol yielded 300 mg of major product and elution of a column chromatogram of the mother liquor with 9:1 dichloromethane/acetone gave 495 mg (83% total yield) more of crystalline lactam **8f**: mp 184–186 °C (from MeOH); IR (KBr) NH 3305 (m), C=O 1680 (s), C=C 1610 (m) cm^{-1}; UV λ_{max} 245 nm (log ϵ 3.86), 300 (3.41); ^1H NMR δ 0.93 (t, 3, J = 7 Hz, Me), 1.1–1.9 (m, 8, methylenes,

methines), 1.74, 2.00 (m, 1 each, 2 H-16), 2.36 (t, 1, J = 13 Hz, H-21β), 2.64 (s, 2, 2 H-6), 2.76 (d, 1, J = 11 Hz, H-3), 3.95 (t, 1, J = 3 Hz, H-2), 4.20 (dd, 1, J = 13, 5 Hz, H-21α), 6.6–7.1 (m, 4, aromatic Hs); m/e 296 (M^+, 99%), 130 (base); exact mass, m/e 296.1897, calcd for $C_{19}H_{24}ON_2$, m/e 296.1889.

Further elution yielded 67 mg (7%) of crystalline lactam **9f**: mp 194–195 °C (from MeOH); IR (KBr) NH 3300 (m), C=O 1675 (s), C=C 1605 (m) cm^{-1}; UV λ_{max} 245 nm (log ϵ 3.82), 297 (3.45); ^1H NMR δ 0.95 (t, 3, J = 7 Hz, Me), 1.2–1.8 (m, 10, methylenes, methines), 2.21, 2.83 (d, 1 each, J = 16 Hz, 2 H-6), 2.26 (t, 1, J = 13 Hz, H-21β), 3.37 (dd, 1, J = 12, 5 Hz, H-2), 3.93 (d, 1, J = 3 Hz, H-3), 4.25 (dd, 1, J = 13, 5 Hz, H-21α), 6.6–7.1 (m, 4, aromatic Hs); m/e 296 (M^+, base), 204 (37%), 182 (23), 130 (54); exact mass, m/e 296.1895, calcd for $C_{19}H_{24}ON_2$, m/e 296.1889.

14-Iso-5-oxopseudoaspidospermidine (10f). The Wolff–Kishner reduction of 100 mg (0.32 mmol) of keto lactam **10a** and its workup followed the **8a** → **8f** reaction procedure, leading to 76 mg (80%) of crystalline lactam **10f**: mp 185–187 °C; IR (KBr) NH 3310 (m), C=O 1675 (s), C=C 1605 (m) cm^{-1}; UV λ_{max} 242 nm (log ϵ 3.87), 297 (3.45); ^1H NMR δ 0.98 (t, 3, J = 7 Hz, Me), 1.3–1.6 (m, 9, methylenes, methines), 1.9–2.0 (m, 1, H-16), 2.16, 2.66, 2.67, 2.72 (4-line AB, 2, J = 17 Hz, 2 H-6), 2.79 (d, 1, J = 10 Hz, H-3), 2.89 (dd, 1, J = 13, 5 Hz, H-21), 3.95 (t, 1, J = 3 Hz, H-2), 4.06 (dd, 1, J = 13, 2 Hz, H-21), 6.6–7.1 (m, 4, aromatic Hs); m/e 296 (M^+, base), 130 (84%); exact mass, m/e 296.1885, calcd for $C_{19}H_{24}ON_2$, m/e 296.1889.

14-Iso-20-epipseudoaspidospermidine (8e) and (±)-20-Epipseudoaspidospermidine (1, 9e). A solution of 600 mg (2.0 mmol) of ketone **9d** and 1.00 mL (20 mmol) of hydrazine hydrate in 10 mL of ethylene glycol was refluxed for 1.5 h. The water and excess hydrazine were removed by distillation and a solution of sodium ethylene glycolate (from 2.0 g of sodium) in 50 mL of ethylene glycol was added. The mixture was refluxed for 1.5 h, cooled, poured into ice water, and worked up as above. HPLC chromatography of the crude product on alumina and elution with 9:1 hexane/ethyl acetate furnished 143 mg (25%) of amine **8e**: mp 114–115 °C (from MeOH); spectrally identical with above sample.

Further elution gave 200 mg (30%) of amine 1 (**9e**): mp 89–90 °C (from MeOH); IR (KBr) NH 3320 (m), CH^{12} 2750 (m), 2720 (w), 2690 (w), C=C 1610 (m) cm^{-1}; UV λ_{max} 245 nm (log ϵ 3.86), 297 (3.47); ^1H NMR δ 0.94 (t, 3, J = 7 Hz, Me), 1.1–2.4 (m, 12, methylenes, methines), 2.2–2.4, 3.1–3.2 (m, 2 each, 2 H-21, 2 H-5), 2.46 (d, 1, J = 3 Hz, H-3), 3.52 (dd, 1, J = 13, 5 Hz, H-2), 6.6–7.1 (m, 4, aromatic Hs); m/e 282 (M^+, 60%), 281 (32), 190 (29), 124 (base); exact mass, m/e 282.2095, calcd for $C_{19}H_{26}N_2$, m/e 282.2096.

A suspension of 200 mg (0.67 mmol) of lactam **8f** and 200 mg (5.2 mmol) of lithium aluminum hydride in 100 mL of anhydrous THF was refluxed for 4 h, then cooled, and added dropwise to a 0.5 N hydrochloric acid solution. THF was evaporated under vacuum, Seignette salt and dilute ammonia solution added consecutively to the remaining aqueous solution and the latter extracted with methylene chloride. Normal workup led to 140 mg (75%) of amine **8e** (vide supra).

Hydride reduction of 50 mg (1.3 mmol) of lactam **9f** under identical conditions (except for the reaction time being 2 h) and workup yielded 40 mg (83%) of amine 1 (**9e**) (vide supra).

A 1 M borane–THF solution, 3 mL (3.0 mmol), was added dropwise over a 0.5-h period to a suspension of hydrazone **9b**, prepared from 100 mg (0.32 mmol) of keto lactam **9a**, in 10 mL of THF at 0 °C and the mixture then refluxed for 2 h. It was added to 20 mL of methanol saturated with sodium acetate and the mixture refluxed for 0.5 h. Hydrochloric acid, 1 N, was added and THF evaporated under vacuum. After basification with dilute ammonia the solution was worked up in the usual manner. Elution of the column chromatogram of the crude product with 4:1 cyclohexane/ethyl acetate yielded 3 mg (3%) of crystalline ketone **9d**, then 7 mg (8%) of crystalline amine 1 (**9e**), and finally, 3 mg (3%) of lactam **9f**.

14-Isopseudoaspidospermidine (10e). Borane reduction of 50 mg (0.17 mmol) of lactam **10f** under conditions identical with those of the above **9b** → 1 reaction, HPLC of the crude product on alumina, and elution with 12:1 cyclohexane/dichloromethane yielded 31 mg (62%) of amorphous amine **10e**: IR (KBr) NH 3340 (m), C=C 1605 (m) cm^{-1};) UV λ_{max} 245 nm (log ϵ 3.80), 298 (3.50); ^1H NMR δ 0.93 (t, 3, J = 7 Hz, Me), 1.2–3.5 (m, 16, methylenes, methines), 2.11 (d, 1, J = 9 Hz, H-3), 3.83 (t, 1, J = 3 Hz, H-2), 6.6–7.2 (m, 4, aromatic Hs); m/e 282 (M^+, 98%), 281 (57), 190 (97), 152 (25), 130 (22), 125 (26), 124 (base); exact mass, m/e 282.2111, calcd for $C_{19}H_{26}N_2$, m/e 282.2096.

Wolff–Kishner reduction of 20 mg (0.07 mmol) of ketone **11d** under the conditions of the above **9d** → **8e** reaction, HPLC of the crude product on alumina, and elution with 12:1 cyclohexane/dichloromethane led to 10 mg (53%) of amine **10e**.

14-Iso-20-epidehydropseudoaspidospermidine (22a). A mixture of 100 mg (0.63 mmol) of potassium permanganate and 160 mg (0.63 mmol) of 18-crown-6 ether in 2 mL of anhydrous benzene was stirred at room temperature for 15 min. After **8e**, 100 mg (0.35 mmol), was added and the stirring continued for 2 h. The mixture was filtered through a Whatman GF/A glass microfiber filter and the filtrate washed with 10% sodium bicarbonate solution. It was dried (Na_2SO_4) and evaporated. HPLC of the residue on alumina and elution with 20:1 cyclohexane/ethyl acetate yielded 70 mg (71%) of crystalline indolenine **22a**: mp 75–77 °C (from MeOH); IR (KBr) C=C 1605 (w), C=N 1575 (s) cm^{-1}; UV λ_{max} 222 nm (log ϵ 4.19), 227 (shoulder, 4.10), 264 (3.73); ^1H NMR δ 0.91 (t, 3, J = 7 Hz, Me), 1.1–1.3 (m, 2, CH_2), 1.6–2.8 (m, 9, methylenes, methines), 2.31 (d, 1, J = 11 Hz, H-3), 2.61 (t, 1, J = 13 Hz, H-21β), 2.94 (dt, 1, J = 13, 3 Hz, H-16), 3.1–3.2 (m, 1, H-21α), 3.30 (td, 1, J = 11, 5 Hz, H-6), 3.3–3.4 (m, 1, H-5), 7.1–7.6 (m, 4, aromatic Hs); m/e 280 (M^+, base), 279 (22%), 137 (51), 124 (43); exact mass, m/e 280.1938, calcd for $C_{19}H_{24}N_2$, m/e 280.1939.

(±)-20-Epidehydropseudoaspidospermidine (2). Permanganate oxidation of 100 mg (0.35 mmol) of amine 1 (**9e**) under the above conditions and elution of the HPLC column with 12:1 hexane/ethyl acetate produced 45 mg (47%) of amorphous indolenine **2**: IR (KBr) CH^{12} 2740 (m), C=C 1605 (w), C=N 1580 (m) cm^{-1}; UV λ_{max} 222 nm (log ϵ 4.20), 227 (shoulder, 4.12), 265 (3.71); ^1H NMR δ 0.87 (t, 3, J = 7 Hz, Me), 1.1–1.2 (m, 2, CH_2), 1.4–2.8 (m, 11, methylenes, methines), 2.56 (d, 1, J = 3 Hz, H-3), 3.00 (td, 1, J = 13, 5 Hz, H-5), 3.1–3.2 (m, 2, H-21, H-16), 7.2–7.5 (m, 4, aromatic Hs); m/e 280 (M^+, base), 279 (20%), 195 (24), 180 (24), 137 (72), 124 (30); exact mass, m/e 280.1940, calcd for $C_{19}H_{24}N_2$, m/e 280.1939.

1-Carbomethoxy-2,16-dehydro-14-iso-20-epipseudoaspidospermidine (23a). Methyl chlorocarbonate, 0.04 mL (0.51 mmol), was added dropwise to a stirring suspension of 15 mg (0.30 mmol) of sodium hydride (50% in mineral oil) and 70 mg (0.25 mmol) of indolenine **22a** in 3 mL of anhydrous 1,2-dimethoxyethane at 0 °C and the mixture stirred at room temperature for 2.5 h. It then was poured into ice water and worked up in the usual manner. Elution of the column chromatogram of the crude product with 20:1 cyclohexane/ethyl acetate afforded 62 mg (73%) of crystalline urethane **23a**: mp 104–106 °C; IR (KBr) C=O 1720 (s), C=C 1600 (m) cm^{-1}; UV λ_{max} 248 nm (log ϵ 3.96), 281 (3.05); ^1H NMR δ 0.92 (t, 3, J = 7 Hz, Me), 1.1–1.3 (m, 2, CH_2), 1.7–2.4 (m, 8, methylenes, methines), 2.63 (t, 1, J = 12 Hz, H-21β), 2.65 (d, 1, J = 12 Hz, H-3), 2.9–3.1 (m, 2, H-21α, CH), 3.1–3.2 (m, 1, H-5), 3.83 (s, 3, OMe), 5.75 (s, 1, H-16), 6.8–7.5 (m, 3, aromatic Hs), 7.66 (d, 1, J = 8 Hz, H-12); m/e 338 (M^+, 47%), 124 (base); exact mass, m/e 338.1990, calcd for $C_{21}H_{26}O_2N_2$, m/e 338.1994.

1-Carbomethoxy-2,16-dehydro-20-epipseudoaspidospermidine (23b). N_a-Carbomethoxylation of 70 mg (0.25 mmol) of indolenine **2** under the above conditions (except for the reaction mixture being stirred at 0 °C for 45 min), HPLC of the crude product on alumina, and elution with 40:1 cyclohexane/ethyl acetate gave 56 mg (66%) of amorphous urethane **23b**: IR (KBr) CH^{12} 2740 (m), 2720 (w), C=O 1720 (s), C=C 1605 (m) cm^{-1}; UV λ_{max} 250 nm (log ϵ 3.96), 282 (3.08); ^1H NMR δ 0.92 (t, 3, J = 7 Hz, Me), 1.2–1.3 (m, 2, CH_2), 1.5–1.6 (m, 2, H-14, H-15), 1.67 (dd, 1, J = 11, 4 Hz, H-6), 1.7–1.9 (m, 3, H-15, H-17β, H-20), 1.9–2.0 (m, 2, H-6, H-21β), 2.4–2.5 (m, 1, H-5), 2.63 (t, 1, J = 14 Hz, H-17α), 2.71 (s, 1, H-3), 2.90 (t, 1, J = 7 Hz, H-5), 3.21 (dd, 1, J = 10, 2 Hz, H-21α), 3.90 (s, 3, OMe), 6.10 (d, 1, J = 7 Hz, H-16), 7.0–7.2 (m, 3, aromatic Hs), 7.78 (d, 1, J = 8 Hz, H-12); m/e 338 (M^+, 18%), 124 (base); exact mass, m/e 338.1990, calcd for $C_{21}H_{26}O_2N_2$, m/e 338.1994.

16α-Carbomethoxy-14-iso-20-epidehydropseudoaspidospermidine (22b) and 14-Iso-20-epipseudovincadifformine (24). A solution of 50 mg (0.15 mmol) of urethane

23a in 50 mL of methanol was irradiated by a low-pressure mercury lamp for 0.5 h and then evaporated to dryness. HPLC of the residue on silica and elution with 25:1 cyclohexane/ether yielded 8 mg (16%) of crystalline vinylogous urethane **24**: mp 148–150 °C (from MeOH); IR (KBr) NH 3340 (m), C=O, C=C 1650 (s), 1605 (s) cm^{-1}; UV λ_{max} 225 nm (log ϵ 4.10), 297 (4.00), 328 (4.20); ^1H NMR δ 0.95 (t, 3, J = 7 Hz, Me), 1.1–1.3 (m, 2, CH_2), 1.3–2.0 (m, 5, methylenes, methines), 2.00 (dd, 1, J = 16, 13 Hz, H-17β), 2.4–2.6 (m, 2, H-17α, CH), 2.67 (t, 1, J = 13 Hz, H-21β), 2.76 (d, 1, J = 11 Hz, H-3), 3.0–3.1 (m, 2, H-21α, CH), 3.2–3.3 (m, 1, H-5), 3.76 (s, 3, OMe), 6.2–7.5 (m, 4, aromatic Hs); m/e 338 (M^+, base), 180 (20%), 167 (27), 124 (91); exact mass, m/e 338.1992, calcd for $C_{21}H_{26}O_2N_2$, m/e 338.1994.

The second eluate, 6 mg (12%), was starting urethane **23a**. As third eluate there appeared 15 mg (30%) of crystalline imino ester **22b**: mp 135 °C (from MeOH); IR (KBr) C=O 1735 (s), C=C 1605 (w), C=N 1570 (m) cm^{-1}; UV λ_{max} 221 nm (log ϵ 4.15), 266 (3.66); ^1H NMR δ 0.92 (t, 3, J = 7 Hz, Me), 1.1–1.3 (m, 2, CH_2), 1.3–2.0 (m, 6, methylenes, methines), 1.34 (td, 1, J = 13, 6 Hz, H-17β), 2.29 (d, 1, J = 10 Hz, H-3), 2.4–2.5 (m, 1, H-17α), 2.58 (t, 1, J = 14 Hz, H-21β), 3.0–3.1 (m, 1, H-21α), 3.2–3.3 (m, 1, H-6), 3.3–3.4 (m, 1, H-5), 3.75 (s, 3, OMe), 4.11 (dd, 1, J = 6, 2 Hz, H-16), 7.2–7.6 (m, 4, aromatic Hs); m/e 338 (M^+, base), 337 (28%), 194 (20), 180 (25), 124 (78); exact mass, m/e 338.1991, calcd for $C_{21}H_{26}O_2N_2$, m/e 338.1994.

Exposure of the latter compound to glacial acetic acid for 15 min converted it into vinylogous urethane **24**.

(±)-20-Epipseudovincadifformine (3). Photolysis of 50 mg (0.15 mmol) of urethane **23b** under the above conditions (except for the use of a high-pressure lamp and the irradiation lasting 45 min), HPLC of the crude product on alumina, and elution with 9:1 cyclohexane/dichloromethane furnished 12 mg (25%) of crystalline vinylogous urethane **3**: mp 127–128 °C (lit.[6] mp 127–128 °C); spectra identical with those reported[6] [^1H NMR δ 0.91 (t, 3, J = 7 Hz, Me), 1.1–1.3 (m, 2, CH_2), 1.4–2.7 (m, 7, methylenes, methines), 2.14 (t, 1, J = 10 Hz, H-21β), 2.35 (dd, 1, J = 15, 3 Hz, H-17β), 2.58 (dd, 1, J = 15, 12 Hz, H-17α), 2.87 (s, 1, H-3), 2.92 (dd, 1, J = 10, 7 Hz, H-5), 3.18 (dd, 1, J = 11, 4 Hz, H-21α), 3.75 (s, 3, OMe), 6.7–7.3 (m, 4, aromatic Hs)]. As second eluate there was isolated 5 mg (10%) of starting material.

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Registry No. (±)-**2**, 91670-85-8; (±)-**3**, 73836-92-7; **4**, 59936-01-5; **5a**, 42972-47-4; **5a** (ketal), 91670-73-4; **5b**, 91670-74-5; (±)-**6a**, 91670-75-6; (±)-**6b**, 91670-76-7; (±)-**7a**, 91670-77-8; (±)-**7b**, 91670-78-9; (±)-**8a**, 91740-06-6; (±)-**8b**, 91670-80-3; (±)-**8c**, 91670-81-4; (±)-**8e**, 91740-07-7; (±)-**8f**, 91670-83-6; (±)-**9a**, 91670-79-0; (±)-**9b**, 91740-15-7; (±)-**9c**, 91740-08-8; (±)-**9d**, 91686-45-2; (±)-**9e**, 91740-10-2; (±)-**9f**, 91740-09-9; (±)-**10a**, 91740-05-5; (±)-**10d**, 91670-82-5; (±)-**10e**, 91740-11-3; (±)-**10f**, 91670-84-7; (±)-**22a**, 91740-12-4; (±)-**22b**, 91670-87-0; (±)-**23a**, 91670-86-9; (±)-**23b**, 91740-13-5; (±)-**24**, 91740-14-6; (±)-**26a**, 89240-71-1; (±)-**26b**, 91740-18-0; (±)-**26c**, 89300-61-8; (±)-**29a**, 38216-76-1; (±)-**29b**, 89240-70-0; (±)-**29c**, 38216-77-2; (±)-**30a**, 87495-05-4; (±)-**30b**, 91670-96-1; (±)-**30c**, 91670-97-2; (±)-**30d**, 87495-06-5; (±)-**30e**, 91670-93-8; (±)-**30f**, 91670-94-9; (±)-**31a**, 91670-95-0; (±)-**31b**, 87508-89-2; (±)-**31c**, 91740-16-8; (±)-**31d**, 91670-98-3; (±)-**33a**, 89300-59-4; (±)-**33b**, 91670-88-1; (±)-**33c**, 87495-09-8; (±)-**33d**, 91670-88-1; (±)-**33e**, 91670-89-2; (±)-**34a**, 89300-58-3; (±)-**34b**, 91670-90-5; (±)-**34c**, 87508-87-0; (±)-**34d**, 87508-90-5; (±)-**35a**, 61848-78-0; (±)-**35b**, 91740-17-9; (±)-**35c**, 91670-91-6; (±)-**35d**, 87495-10-1; (±)-**35e**, 87495-07-6; (±)-**36a**, 77080-74-1; (±)-**36b**, 73837-57-7; (±)-**36c**, 87508-88-1; (±)-**36d**, 91670-92-7; indoleacetic anhydride, 41547-05-1.

Biosynthetic Studies of Marine Lipids. 4.[1] Mechanism of Side Chain Alkylation in (*E*)-24-Propylidenecholesterol by a Chrysophyte Alga

W. C. M. C. Kokke,[†] James N. Shoolery,[‡] William Fenical,[§] and Carl Djerassi*[,†]

Department of Chemistry, Stanford University, Stanford, California 94305, Varian Associates, Palo Alto, California 94306, and Institute of Marine Resources, Scripps Institution of Oceanography, La Jolla, California 92093

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A photosynthetic marine Chrysophyte (unicellular alga) was cultured in a medium containing labeled methionine (methyl-^{13}C, methyl-d_3). The ^2H and ^{13}C distribution in the alkyl substituents of the sterols was determined by ^2H and ^{13}C NMR. Although two novel cyclopropyl sterols—(24*R*,28*R*)- [or (24*S*,28*S*)-] and (24*S*,28*R*)-24,28-methylene-5-stigmasten-3β-ol—and their ring opening products were found as trace sterols in the alga, the results of ^2H NMR indicate that the substituent in the side chain of the main sterol ((*E*)-24-propylidenecholesterol) is not formed by ring opening of these cyclopropyl sterols. Instead, the main sterol is most likely formed by further alkylation of a 24-vinyl sterol which has so far not been encountered in nature. Other novel sterols encountered in the Chrysophyte belong to the rare classes of Δ^{23}, 14α-methyl, and $\Delta^{8(14),15}$-diene sterols.

More than two decades ago it was discovered that the methyl group of methionine in the form of *S*-adenosylmethionine (SAM) is used as a carbon source in enzymatic transmethylation reactions.[2] Reactions which SAM is known to undergo are aromatic substitution, methyl ester formation, and alkylation at N,[3] O,[4] and at a double bond.[2,5,6] The primary products of the last reaction are usually olefins, but cyclopropanes can also be formed.[6]

Sterols with side chains having more carbon atoms than the cholesterol side chain are found[7] in plants (phyto-

[†] Stanford University.
[‡] Varian Associates.
[§] Scripps Institution of Oceanography.

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