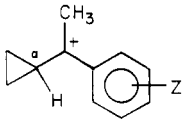
propyl conjugation should give double bond character for the bond between C^+ and C_α carbon atoms. The 2-



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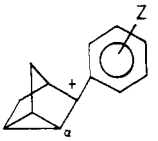

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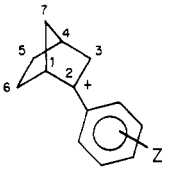
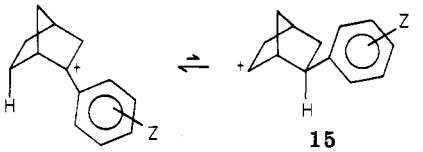


13

aryl-2-norbornyl cations (13) have revealed a deviation in the σ^{C^+}–$\Delta\delta C^+$ plot similar to the deviations observed for systems 1, 4, 11, and 12. The former deviation has been attributed to the "onset of σ-bridging" in the norbornyl system accompanying the introduction of electron-withdrawing substituents.[7,12] However, this explanation will not serve for 1, 4, 11, and 12. Moreover, the behavior of the C_1 and C_6 carbon atoms in 2-aryl-2-norbornyl is not consistent with the σ-bridging proposal.[6] In a σ-bridged ion, the C_6 carbon atom would be pentacoordinated and should exhibit unusual ^{13}C NMR behavior.[6] Instead, the C_6 carbon chemical shifts correlate linearly against the corresponding chemical shifts of the C_β carbon atom in the 1-aryl-1-cyclohexyl cations. Consequently, we must seek some other explanation for the observed deviation in the σ^{C^+}–$\Delta\delta C^+$ plot.

One possibility is the existence of a rapid equilibrium between tertiary and secondary carbocations in the 2-aryl-2-norbornyl system (14 and 15). An alternative



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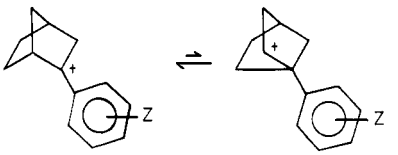
equilibration could involve a Wagner–Meerwein shift (16 and 17). We are subjecting this possible explanation to careful scrutiny.



16 17

However, it should be pointed out that this explanation would not account for systems 1, 4, 11, and 12. Here we are apparently forced to consider either enhanced electron supply from certain organic moieties or inductive π polarization.

Experimental Section

Precursors. The 2- or 3-substituted 9-methylanthracenes 5 were synthesized in five steps from 3- or 4-substituted benzoyl-2′-benzoic acid 6 following a general method reported for the synthesis of 9-methylanthracene derivatives.[11] All of these compounds, except the derivatives Z = 3-OCH_3 and Z = 3-CF_3, are reported in the literature. The previously unknown derivatives, Z = 3-OCH_3 (mp 108–109 °C) and Z = 3-CF_3 (mp 65–66 °C), were also synthesized in the same fashion. Satisfactory analytical data (C, ±0.2; H, ±0.2; F, ±0.1) were obtained for these derivatives. All of these compounds gave ^{13}C NMR data in accordance with their structures.

Carbocations. The substituted 9-methyl-9-anthracenium cations 4 were prepared by slow addition of powdered 9-methylanthracene derivative to a solution of FSO_3H/SO_2ClF cooled to −78 °C with rapid vortex mixing. The acid concentration in the solution was 3 M. The concentration of the ion based on the precursor added was ~0.5 M. Transfer of the solution under nitrogen to an 8-mm NMR tube was achieved via a cooled double-ended syringe, as described previously.[13]

NMR Spectra. ^{13}C NMR spectra were recorded at −80 °C on a Varian CFT-20 spectrometer with 8-mm tubes containing a concentric 3-mm (o.d.) capillary tube of acetone-d_6 and Me_4Si, 8192 data points, a spectral width of 6000 Hz, and a pulse angle of 45°. Chemical shifts are in parts per million downfield from external Me_4Si.

Registry No. 4 (Z = 3-OCH_3), 83220-01-3; 4 (Z = 3-CH_3), 83220-02-4; 4 (Z = 3-Cl), 83220-03-5; 4 (Z = H), 83220-04-6; 4 (Z = 2-Cl), 83220-05-7; 4 (Z = 2-CF_3), 83220-06-8; 4 (Z = 3-CF_3), 83220-07-9; 5 (Z = 3-OCH_3), 83220-08-0; 5 (Z = 3-CF_3), 83231-99-6.

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(13) Kelly, D. P.; Brown, H. C. *Aust. J. Chem.* **1976**, *29*, 957.

Synthesis of Vincamine

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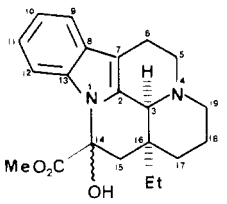
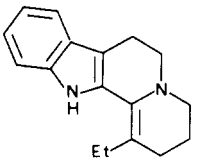
A five-step procedure for the conversion of a well-known indoloquinolizidine into the alkaloid (+)-vincamine is described. The vital step of the synthesis involves the introduction of a side chain, subsequently becoming the functionalized part of the fifth ring of the base, by way of the alkylation of an enamine with methyl bromopyruvate 2,4-dinitrophenylhydrazone.

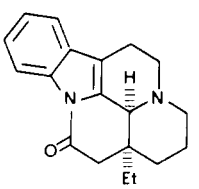
Vincamine (1a), a major alkaloid of the common plant *Vinca minor* L., has gained importance in recent years as a drug in the treatment of cerebral, vascular, and metabolic diseases.[1] Its isolation in crystalline form in 1953[2] led to

0022-3263/82/1947-4745$01.25/0

the determination of its constitution ca. a decade later,[3] since which time several syntheses of the natural base have appeared in the literature.[4] The present paper describes a new synthesis of the alkaloid, in which enamine **2**,[5,6] a crucial intermediate in an early synthesis of the structurally related alkaloid eburnamonine (**3**),[5] serves as starting material.





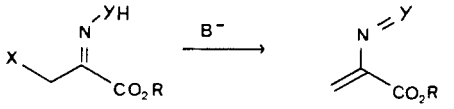


1a, β-OH
b α-OH

2

3

In analogy with the eburnamonine synthesis, tetracycle **2** was to be alkylated at the nucleophilic, ethylated, enamino carbon for the elaboration of the fifth ring of vincamine (**1a**). Since the lacking ring carbons and side chains constituted a masked pyruvic ester moiety, the alkylating agent needed for a rapid introduction of all functional groups was methyl pyruvate substituted by a leaving group α to its keto function. However, such a reagent was considered vulnerable to acid–base interaction with the enamine and thus to destruction by self-condensation. As a consequence, the reagent of choice became the imino equivalent **4**, which as such or as its dehydrohalogenated form **5** could be expected to behave as an electrophile toward enamine **2**.[7]



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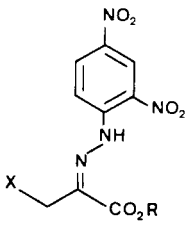
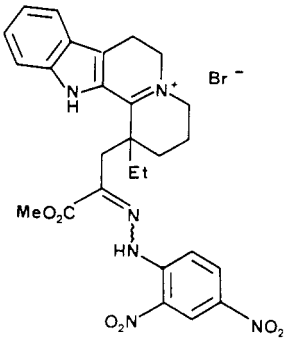
5

After preliminary experiments with various derivatives of bromopyruvic ester the 2,4-dinitrophenylhydrazone **6c**



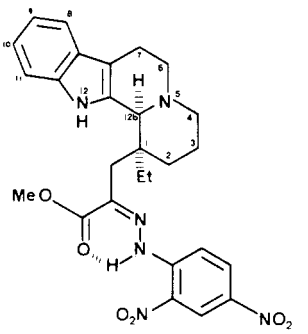
6a, R = X = H
b, R = Me, X = H
c, R = Me, X = Br



7

was adopted as reagent for the first step of the vincamine synthesis. It was prepared by the bromination of methyl pyruvate[8] and subsequent reaction with (2,4-dinitrophenyl)hydrazine in acetic acid or, more efficiently, by the interaction of pyruvic acid 2,4-dinitrophenylhydrazone (**6a**)[9] with thionyl chloride in methanol, followed by bromination of the resultant ester **6b**.

Exposure of hydrazone **6c** to enamine **2**,[5,6] and triethylamine in ethyl acetate solution yielded salt **7**,[10] whose reduction with sodium borohydride produced preponderantly amine **8**. Whereas hydrolysis of the hydrazone



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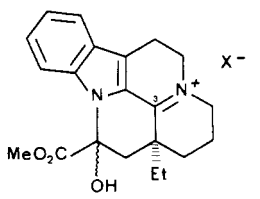
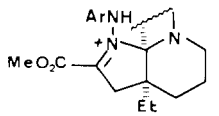


9

moiety of the latter proved exceedingly difficult,[11] aqueous cleavage of the side chain of its precursor (**7**), most efficiently at pH 8, was facile and led to salt **9**. The contrasting behavior of the two hydrazones and the ease of hydrolysis of hydrazone **7** had to be attributed to participation of the nuclear iminium salt unit in the latter reaction. If it be assumed that salt **7** is in equilibrium with isomer **10** in the hydrolysis media and that the latter un-



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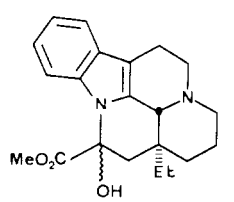


11a, α-OH
b, β-OH

(1) H. Hauth and B. P. Richardson, *Annu. Rep. Med. Chem.*, **12**, 49 (1977); G. Bartholini, E. T. Mackenzie, H. Depoortere, and J. P. Nowicki, in "Etats Déficitaires Cérebraux Liés à l'Age", R. Tissot, Ed., Bel-Air VI Symposium: Geneva, Switzerland, Oct 1980.

(2) E. Schlittler and A. Furlenmeier, *Helv. Chim. Acta*, **36**, 2017 (1953).

(3) J. Trojánek, O. Strouf, J. Holubek, and Z. Cekam, *Tetrahedron Lett.*, 702 (1961); O. Strouf and J. Trojánek, *Chem. Ind. (London)*, 2036 (1962); M. Plat, D. D. Mank, J. Le Men, M.-M. Janot, H. Budzikiewicz, J. M. Wilson, L. J. Durham, and C. Djerassi, *Bull. Soc. Chim. Fr.*, 1082 (1962); J. Mokrý, I. Kompiš, and P. Sefčovič, *Tetrahedron Lett.*, 433 (1962); O. Clauder, K. Gesztes, and K. Szász, *ibid.*, 1147 (1962); J. Mokrý, M. Shamma, and H. E. Soyster, *ibid.*, 999 (1963); J. Mokrý and I. Kompiš, *Lloydia*, **27**, 428 (1964); J. Trojánek, Z. Koblicová, and K. Bláha, *Chem. Ind. (London)*, 1261 (1965); H. P. Weber and T. J. Petcher, *J. Chem. Soc., Perkin Trans. 2*, 2001 (1973).

(4) (a) M. E. Kuehne, *Lloydia*, **27**, 435 (1964); *J. Am. Chem. Soc.*, **86**, 2946 (1964); (b) J. F. D. Barton and J. Harley-Mason, *Chem. Commun.*, 298 (1965); (c) K. H. Gibson and J. E. Saxton, *ibid.*, 799, 1490 (1969); *J. Chem. Soc., Perkin Trans. 1*, 2776 (1972); (d) G. Hugel, J. Levy, and J. Le Men, *C. R. Hebd. Seances Acad. Sci., Ser. C* **274**, 1350 (1972); (e) C. Thal, T. Sevenet, H.-P. Husson, and P. Potier, *ibid.*, **275**, 1295 (1972); C. Thal, T. Imbert, H.-P. Husson, and P. Potier, *Bull. Soc. Chim. Fr.*, 2010, 2013, 1973); (f) Atta-ur-Rahman, *J. Chem. Soc., Perkin Trans. 1*, 731 (1972); (g) Szántay, L. Szabo, and G. Kalaus, *Tetrahedron Lett.*, 191 (1973); *Tetrahedron*, **33**, 1803 (1977); (h) J. L. Herrmann, R. J. Cregge, J. E. Richman, C. L. Semmelhack, and R. H. Schlessinger, *J. Am. Chem. Soc.*, **96**, 3702 (1974); J. L. Herrmann, R. J. Cregge, J. E. Richman, G. R. Kieczykowski, S. N. Normandin, M. L. Quesada, C. L. Semmelhack, A. J. Poss, and R. H. Schlessinger, *ibid.*, **101**, 1540 (1979); (i) D. L. Coffen, D. A. Katonak, and F. Wong, *ibid.*, **96**, 3966 (1974); (j) P. Pfäffli, W. Oppolzer, R. Wenger, and H. Hauth, *Helv. Chim. Acta*, **58**, 1131 (1975); W. Oppolzer, H. Hauth, P. Pfäffli, and R. Wenger, *ibid.*, **60**, 1801 (1977).

(5) E. Wenkert and B. Wickberg, *J. Am. Chem. Soc.*, **87**, 1580 (1965).

(6) B. Danieli, G. Lesma, and G. Palmisano, *J. Chem. Soc., Chem. Commun.*, 109 (1980).

(7) An example of an electrophilic reagent such as **4** is ethyl bromopyruvate oxime, whose chemistry is depicted in the work of T. L. Gilchrist, D. A. Lingham, and T. G. Roberts, *J. Chem. Soc., Chem. Commun.*, 1089 (1979), and previous papers.

(8) S. Archer and M. G. Pratt, *J. Am. Chem. Soc.*, **66**, 1656 (1944).

(9) H. Van Duin, *Recl. Trav. Chim. Pays-Bas*, **73**, 68 (1954).

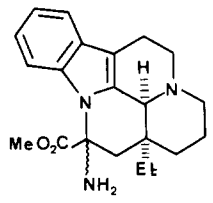
(10) A similar adduct was the consequence of the reaction of the enamine (**2**) with ethyl bromopyruvate oxime.[7]

(11) The acid-catalyzed hydrolyses, in the presence or absence of hydrazone-transfer agents such as acetone or levulinic acid, required long heating and, at best, yielded mixtures of vincamine and apovincamine.

dergoes the hydrazine-extrusion process, a simple rationale for the enhancement of the rate of hydration of the hydrazone imino moiety is on hand.[12]

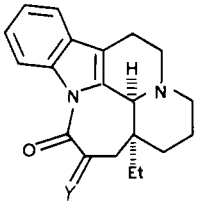
Reduction of salt **9** with sodium borohydride yielded the (±)-3-epivincamines **11**,[4g] in analogy with the stereochemical consequence of the borohydride reduction of 3-dehydroeburnamonine.[5] On the other hand, reduction of the salt with zinc in acetic acid afforded the same isomers as minor components of a mixture containing mostly the (±)-vincamines **1**, from which (±)-vincamine **1a** could be isolated in 12% yield.

In view of the resistance of hydrazone **8** to hydrolysis (vide supra) the ketone derivative was removed by reductive means. Interaction of the hydrazone with titanium trichloride in hydrochloric acid solution[13] gave a mixture of the (±)-vincamines (**1**) and their 14-amino equivalents (**12**). Treatment of these amines with nitrous acid



12a, β-NH_2

b, α-NH_2



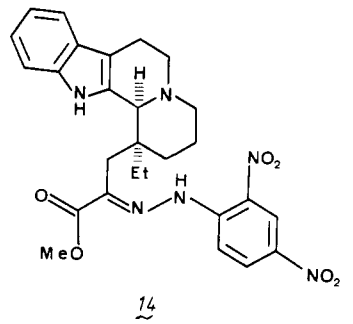
13a, Y = O

b, Y = N-$NHC_6H_3(NO_2)_2$

transformed them into the (±)-vincamines **1**. The yield of the two-step transformation of hydrazone **8** into (±)-vincamine **1a** amounted to 58%.

Upon completion of the synthesis of natural (±)-vincamine **1a**[15] it became of interest to prepare the alkaloid in the dextrorotatory form in view of the importance of this enantiomer as a drug.[1] As a consequence, the precursor amine **8** was exposed to optical resolution. Treatment of the compound with (−)-*O,O*-dibenzoyltartaric acid, separation of the resultant two diastereomeric salts, and reliberation of the amine from the less soluble [(−)-acid–(−)-base] salt led to the optically pure hydrazone (−)-**8**. The desired (+)-**8** enantiomer was obtained optically pure by reliberation of the amine from the more soluble [(−)-acid–(+)-base] salt contained in the mother liquors. This dextrorotatory form could be shown to belong to the (+)-vincamine series by the following correlation study.

Treatment of keto lactam **13a**, the immediate precursor of natural (dextrorotatory) vincamine in a synthesis described in the patent literature,[5] with (2,4-dinitrophenyl)hydrazine produced the derivative **13b**, whose methanolysis permitted the isolation of the tetracyclic anti hydrazone **14**. Acid-induced isomerization of the latter gave hydrazone (+)-**8**, identical in all respects with the product obtained by optical resolution.



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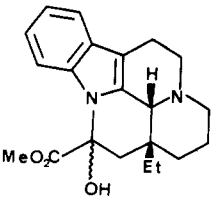


15a, α-OH

b, β-OH

Reduction of hydrazone (+)-**8** with iron in methanolic hydrogen chloride solution[16] led to a mixture of amines **12**, which permitted the isolation of amine **12a**.[14] Treatment of the mixture with nitrous acid converted the amines into the optically active vincamines **1**. The two-step procedure for the conversion of hydrazone (+)-**8** into (+)-vincamine (**1a**) produced the natural base in 54% yield.[17,18]

Experimental Section

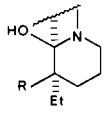
Melting points were determined on a Büchi 510 melting point apparatus and are uncorrected. Thin-layer chromatography was carried out on Merck 60F-254 silica gel plates. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Infrared spectra of the compounds in KBr pellets (indication of shape and intensity of band other than sharp and strong: br = broad, s = shoulder, w = weak) were recorded on a Perkin-Elmer 399 spectrophotometer and are given in reciprocal centimeters; ultraviolet spectra (solvent) were obtained on a Beckman Acta III spectrometer, and maxima are given in nanometers (ε values in parentheses). ^1H NMR and ^{13}C NMR (solvent) spectra were determined on a Bruker WP 80 or WP 200 SY instrument, and ^1H NMR data are given as δ values (multiplicity of signal, coupling constant(s) in hertz, number of protons). Mass spectra were obtained on a VG Micromass 7070F; peaks showing at least 20% of the intensity of the maximum peak are given with the relative intensity in parentheses.

Methyl Bromopyruvate 2,4-Dinitrophenylhydrazone (6c). Bromine (56 mL, 1.09 mol) was added dropwise over a 45-min period under stirring to methyl pyruvate (102 g, 1.00 mol) at 65 °C.[8] The cooled mixture was poured into a stirred suspension of 204 g (1.00 mol) of (2,4-dinitrophenyl)hydrazine in 1.60 L of glacial acetic acid, and the stirring was continued for 15 min. The mixture was filtered, and the precipitate was washed with methanol and dried [70 °C (5 torr)]. Crystallization of the orange powder (180 g, 50%) from ethyl acetate yielded hydrazone **6c**: mp 160–160.5 °C; IR 3200 (w), 1700 (s), 1620 (s); ^1H NMR ($CDCl_3$, 80 MHz) 4.04 (s, 3 H), 4.46 (s, 2 H), 8.15 (d, 9, 1 H), 8.45 (dd, 9, 2, 1 H), 9.17 (d, 2, 1 H) 14.38 (br s, 1 H). Anal. Calcd for $C_{10}H_9O_6N_4Br$: C, 33.26; H, 2.51; N, 15.51. Found: C, 33.19; H, 2.51; N, 15.49.

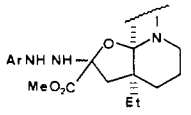
Thionyl chloride (22.18 g, 0.19 mol) was added dropwise to a solution of 50.00 g (0.19 mol) of pyruvic acid 2,4-dinitrophenylhydrazone (**6a**)[9] and 1 mL of dimethylformamide in 500 mL of methanol at 0 °C. The mixture was stirred at room temperature for 16 h and filtered. The precipitate was washed with methanol and dried under vacuum. Crystallization of the solid (44.27 g, 84%) from tetrahydrofuran–methanol yielded hydrazone **6b**, mp 184.5–185 °C (lit.[19] mp 184.5–185 °C).

Bromine (28.3 g, 0.18 mol) was added dropwise over a 1-h period to a stirred solution of 25.0 g (0.09 mol) of hydrazone **6b** in 700 mL of dichloromethane and the stirring continued for 16 h. Nitrogen was bubbled through the solution, and the latter was

(12) An alternative, less likely participation of the nuclear iminium salt in the hydrolysis of hydrazone **7**, albeit operable only at high pH, involves initial formation of the nuclear carbinolamine **i**, intramolecular addition of the latter to the hydrazone imine, and unraveling of the resultant complex **ii**.



i



ii

(13) J. E. McMurry and M. Silvestri, *J. Org. Chem.*, **40**, 1502 (1975).
(14) P. Pfäffly and H. Hauth, *Helv. Chim. Acta*, **61**, 1682 (1978).
(15) M. P. Cava, S. S. Tjoa, Q. A. Ahmed, and A. I. da Rocha, *J. Org. Chem.*, **33**, 1055 (1968).

(16) Whereas the hydrazone could be reduced in the same manner as its racemate had been earlier (vide supra), the titanium trichloride reduction procedure has serious condition constraints. Hence the more convenient iron reduction method was developed.
(17) The same two-step scheme in the enantiomer series converted hydrazone (−)-**8** into unnatural (−)-vincamine (**15a**) and its epimer **15b**.
(18) The entire **6c** → **1a** reaction scheme was paralleled in the ethyl ester series with the use of commercially available ethyl bromopyruvate.
(19) T. Nashima, F. Ishibashi, M. Iwamoto, Y. Aihara, S. Anzai, and G. Yamano, *Bull. Chem. Soc. Jpn.*, **50**, 539 (1977).

washed with water, 5% sodium thiosulfate solution, and again with water, dried (Na_2SO_4), and evaporated. Crystallization of the residue from acetonitrile yielded 25.6 g (82%) of hydrazone **6c**; mp 160 °C.

1-[2-[(2,4-Dinitrophenyl)hydrazono]-2-(methoxycarbonyl)ethyl]-1-ethyl-2,3,4,6,7,12-hexahydro-1*H*-indolo[2,3-*a*]quinolizin-5-ium Bromide (7). A solution of enamine **2** (79.4 g, 0.315 mol) and 31.8 g (0.315 mol) of triethylamine in 700 mL of ethyl acetate was added over a period of 5 min to a stirred suspension of 113.7 g (0.315 M) of hydrazone **6c** in 1.6 L of ethyl acetate. The initially dark red, heterogeneous mixture was stirred for 16 h. The yellow solid formed was collected by filtration and washed consecutively with 200 mL of ethyl acetate and then once with 400 mL, once with 150 mL, and four times with 100 mL of methyl ethyl ketone until colorless washings were obtained. The product was dried at 70 °C (5 torr) to yield 180.2 g (93.3%) of compound **7** as a bright yellow powder (mp 197–199 °C dec), which was used as such for the next step. Crystallization from methanol/acetonitrile yielded an analytically pure sample: mp 207–210 °C dec; TLC (methanol/dichloromethane, 1/3) R_f 0.8; IR 3250, 3090 (br), 1739, 1703 (w), 1615, 1590 (br); UV (methanol) 225 (18 800, sh), 248 (17 200), 267 (10 300, sh), 355 (31 300); ^{1}H NMR (dimethyl-d_6 sulfoxide, 200 MHz) 1.01 (t, 7, 3 H), 1.80–2.15 (m, 4 H), 2.10–2.34 (m, 2 H), 2.70–3.00 (m, 1 H), 3.11–3.22 (m, 2 H), 3.74 (d, 15, 1 H), 3.78 (s, 3 H), 3.96–4.19 (m, 4 H), 7.20 (t, 8.5, 1 H), 7.28 (d, 9.5, 1 H), 7.47 (t, 8.5, 1 H), 7.61 (d, 8.5, 1 H), 7.72 (d, 8.5, 1 H), 8.33 (dd, 2.5, 9.5, 1 H), 8.84 (d, 2.5, 1 H), 11.81 (s, 1 H), 13.79 (s, 1 H); ^{13}C NMR (dimethyl-d_6 sulfoxide, 200 MHz) 7.6, 17.0, 18.0, 26.8, 30.2, 43.4, 52.7, 53.4, 54.2, 113.2, 115.4, 121.0, 122.4, 122.6, 124.4, 125.0, 128.1, 129.6, 130.8, 136.4, 138.7, 140.4, 143.0, 161.4, 170.6. Anal. Calcd for $C_{27}H_{39}N_6O_6Br$: C, 52.86; H, 4.76; N, 13.70; Br, 13.03. Found: C, 52.66; H, 4.82; N, 13.84; Br, 12.86.

(±)-3,4-Didehydro-14,15-dihydro-14-hydroxy-14-(methoxycarbonyl)eburnameninium Perchlorate (9, X = ClO_4). Aqueous sodium borate (0.2 M)/hydrochloric acid (0.4 M) buffer solution (50 mL) was added to a stirred solution of 1.5 g (2.44 mM) of compound **7** in 50 mL of acetonitrile and 150 mL of water at room temperature. After 16 h a slight precipitate was filtered and the filtrate washed two times with 50 mL of toluene. Sodium perchlorate (4 g) was added to the aqueous layer, and the opaque solution was extracted with 50 mL and three times with 10 mL of dichloromethane. The combined organic layers were dried (Na_2SO_4) and evaporated, yielding 0.64 g of a yellow glassy material.

An analytical sample of the mixture of epimers **9** was obtained upon recrystallization from methanol/water followed by a second crystallization from acetonitrile/diisopropyl ether: TLC (methanol/dichloromethane, 2/8) R_f 0.67 (major epimer), 0.5; IR 3440 (br), 2965 (w), 1749, 1647; UV (ethanol) 216 (13 260), 244 (10 720), 357 (19 020); ^{1}H NMR (dimethyl-d_6 sulfoxide, 200 MHz) 0.82 and 0.96 (2 t, 7, 3), 3.70 and 3.78 (2 s), 7.85 and 8.15 (2 s). Anal. Calcd for $C_{21}H_{25}N_2O_7Cl$: C, 55.69; H, 5.56; N, 6.18; Cl, 7.83. Found: C, 55.45; H, 5.55; N, 6.27; Cl, 8.07.

(±)-3-Epivincamines 11a and 11b. Water (300 mL) was added to a suspension of 4.50 g (7.3 mM) of salt **7** in 150 mL of acetonitrile. To the stirred orange solution was added 50 mL of an aqueous solution of sodium borate (0.2 M) and hydrochloric acid (0.4 M). The cherry red mixture was stirred for 16 h at room temperature. A slight precipitate was filtered off and the filtrate washed two times with 100 mL of toluene. Sodium borohydride (280 mg 7.3 mM) was added to the aqueous layer, and the mixture was stirred at room temperature for 15 min and extracted with 200- and 100-mL portions of toluene. The combined organic layers were dried (Na_2SO_4) and evaporated and the residue crystallized from methanol (60 mL treated with charcoal), yielding 950 mg (37%) of an off-white powder. Recrystallization from 55 mL of isopropyl alcohol yielded pure (±)-3-epivincamine (**11a**): 0.258 g; white needles; mp 203–204 °C dec; TLC (methanol/dichloromethane, 1/9) R_f 0.53; IR 3450 (br, w), 2940 (br), 1748, 1632 (w); ^{1}H NMR ($CDCl_3$, 200 MHz) 0.65 (t, 7, 3H), 1.00–1.32 (m, 2 H), 1.50–1.63 (m, 1 H), 1.73–2.03 (m, 4 H), 2.37 (dd, 2, 6, 1 H), 2.41–2.54 (m, 1 H), 2.61–2.74 (m, 2 H), 2.85–2.98 (m, 1 H), 3.00–3.13 (m, 4 H), 3.74 (s, 3 H), 4.36 (s, 1 H), 7.05–7.15 (m, 3 H), 7.41–7.5 (m, 1 H); mass spectrum, *m/e* 354 (85), 353 (100), 336 (24), 308 (27), 307 (44), 306 (28), 293 (33), 252 (67), 237 (23). Anal. Calcd for $C_{21}H_{26}N_2O_3$: C, 71.16; H, 7.39; N, 7.90. Found: C, 71.17; H, 7.36; N, 7.84.

From the mother liquors, cooled to −15 °C, there was obtained 530 mg of (±)-3-epivincamine (**11b**): white crystals; mp 163–163.5 °C; TLC (methanol/dichloromethane, 1/9) R_f 0.64; IR 3510, 2950 (br), 1735, 1638 (w); ^{1}H NMR ($CDCl_3$, 200 MHz) 0.82 (t, 7, 3 H), 1.05 (dt, 2.5, 7, 1 H), 1.30 (dt, 7.0, 7.0, 1 H), 1.5–1.68 (m, 1 H), 1.75–2.08 (m, 3 H), 2.20–2.40 (m, 2 H), 2.53 (dt, 2, 7.5, 1 H), 2.63–2.75 (m, 1 H), 2.85–3.15 (m, 4 H), 3.82 (s, 3 H), 4.60 (s, 1 H), 7.03–7.20 (m, 3 H), 7.40–7.53 (m, 1 H); mass spectrum, *m/e* 355 (20), 354 (100), 353 (89), 339 (35), 295 (43), 294 (20), 293 (38), 252 (76), 237 (34). Anal. Calcd for $C_{21}H_{26}N_2O_3$: C, 71.16; H, 7.39; N, 7.90. Found: C, 71.13; H, 7.42; N, 7.77.

Methyl (±)-(1α,12bα,*Z*)-α-[(2,4-Dinitrophenyl)hydrazono]-1-ethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine-1-propanoate (8). Potassium borohydride (10.5 g, 0.2 M) was added in small portions to a suspension of 80.0 g (0.13 M) of compound **7** in 800 mL of acetonitrile and 800 mL of glacial acetic acid at 4 °C. The mixture was stirred at room temperature for 16 h and filtered. The precipitate was washed with acetonitrile (2 × 50 mL) and dried [70 °C (2 torr)]. The yellow powder (71.1 g) was added to 100 mL of 28% ammonia and 200 mL of water and extracted with 500 mL of dichloromethane. The solvent was distilled off. Crystallization of the residue from 1,2-dichloroethane yielded 50.0 g (72%) of hydrazone **8** as deep red crystals: mp 205.5–206.5 °C; TLC (methanol/dichloromethane, 1/9) R_f 0.65; IR 3470 (s), 3290 (w), 1725 (s); ^{1}H NMR (dichloromethane-d_2, 80 MHz) 1.15 (t, 7, 3 H), 1.4–3.25 (m, 14 H), 3.4 (br s, 1 H), 3.8 (s, 3 H), 6.8–7.55 (m, 4 H), 7.87 (d, 9, 1 H), 7.88 (br s, 1 H), 8.32 (dd, 9, 2, 1 H), 9.09 (d, 2, 1 H), 13.68 (br s, 1 H); mass spectrum *m/e* 534 (M^+), 336 (24), 307 (98), 226 (100), 170 (31). Anal. Calcd for $C_{27}H_{30}N_6O_6$: C, 60.66; H, 5.65; N, 15.72. Found: C, 60.60; H, 5.65; N, 15.75.

Methyl (1α,12bα,*Z*)-α-[(2,4-Dinitrophenyl)hydrazono]-1-ethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine-1-propanoate ((±)-8) and Methyl (1β,12bβ,*Z*)-α-[(2,4-Dinitrophenyl)hydrazono)-1-ethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine-1-propanoate ((−)8). A suspension of racemic hydrazone **8** (26.46 g, 49.5 mM) and 18.63 g (49.5 mM) of dibenzoyl-L-tartaric acid in 800 mL of acetonitrile was refluxed for 30 min and allowed to crystallize at room temperature for 22 h. The crystals were filtered and washed with 50, 30, and 20 mL of acetonitrile. The salt (21.22 g), containing (−)-**8**, was stirred in 200 mL of water and 180 mL of dichloromethane containing 25 mL of 28% ammonia until complete dissolution. The organic layer was separated from the aqueous phase, which was reextracted with 30 mL of dichloromethane. The combined organic layers were washed with 200 mL of water, dried (Na_2SO_4), and evaporated. Crystallization of the residue from 200 mL of methanol yielded 11.82 g (89%) of hydrazone (-)-**8** as yellow fluffy crystals: mp 193–193.5 °C dec; TLC (butyl acetate) R_f 0.5; $[\alpha]^{21}_D$ −77.9° (*c* 0.15, galcial acetic acid). Anal. Calcd for $C_{27}H_{30}N_6O_6$: C, 60.66; H, 5.65; N, 15.72. Found: C, 60.48; H, 5.69; N, 15.78.

The filtrate containing the tartrate salt of (+)-**8** was evaporated, and the residue was treated with aqueous ammonia and extracted with dichloromethane as above. Crystallization from methanol yielded 12.81 g (97%) of hydrazone (+)-**8** as yellow, fluffy crystals: mp 192.5–193 °C dec; TLC (butyl acetate) R_f 0.5; $[\alpha]^{24}_D$ +76° (*c* 0.14, glacial acetic acid); IR 3460 (m), 3200 (w), 1700 (w), 1610 (s); UV (ethanol) 230 (27 000), 269 (13 000), 371 (19 670); ^{1}H NMR ($CDCl_3$, 80 MHz) 1.6 (t, 7, 3 H), 1.37–3.25 (m, 17 H), 3.37 (br s, 1 H), 3.82 (s, 3 H), 6.75–7.50 (m, 4 H), 7.82 (br s, 1 H), 7.83 (d, 9, 1 H), 8.3 (dd, 9, 2, 1 H), 9.05 (d, 2, 1 H), 13.7 (br, s, 1 H); ^{13}C NMR ($CDCl_3$, 200 MHz), 8.2, 21.9, 31.3, 33.6, 35.3, 42.5, 52.6, 54.2, 57.1, 66.9, 110.4, 112.3, 116.4, 117.8, 119.4, 121.6, 123.1, 126.8, 129.6, 130.9, 133.2, 136.2, 139.3, 140.4, 144.2, 162.8; mass spectrum, *m/e* 534 (30), 517 (25), 352 (25), 336 (40), 307 (100), 266 (95), 253 (35), 249 (30), 197 (30), 170 (44). Anal. Calcd for $C_{27}H_{30}N_6O_6$: C, 60.66; H, 5.65; N, 15.72. Found: C, 60.68; H, 5.69; N, 15.73.

Independent Synthesis of Hydrazone (+)-8 from (3α,16α)-D-Homoeburnamonine-14,15-dione (13a). (a) Lactam **13a**[5j] (6 g, 18.6 mM) was added to a solution of 4 g (20 mM) of (2,4-dinitrophenyl)hydrazine in 100 mL of methanol containing 2 mL of concentrated sulfuric acid, and the mixture was placed in an ultrasonic bath for 20 min. The yellow crystals formed were filtered and washed with methanol until colorless washing was

obtained. The powder was dissolved in 100 mL of methylene chloride, and the solution was washed with 5% aqueous sodium bicarbonate (100 mL) and water, dried (Na_2SO_4), and evaporated. The residue was crystallized from acetonitrile, and the crystals were dried [20 °C (2 torr)], yielding lactam **13b** (5 g, 53%) as a mixture of *Z* and *E* isomers of the hydrazone: TLC (methanol/methylene chloride, 5/95) R_f 0.65, 0.7; IR 3315 (w), 1690 (m), 1655 (w), 1620 (w); ^1H NMR ($CDCl_3$, 200 MHz) 1.00–3.35 (m, 17 H), 3.99 and 4.07 (2 br s, 1 H), 7.26–7.49 (m, 3 H), 8.06 and 8.19 (2 d, 9, 1 H), 8.35–8.49 (m, 2 H), 9.15–9.17 (2 d, 2, 1 H), 11.53 and 13.87 (2 br s, 1 H); mass spectrum, *m/e* 502 (80), 485 (82), 411 (38), 320 (33), 306 (42), 292 (42), 277 (90), 263 (80), 251 (50), 237 (40), 223 (30), 169 (50), 129 (55), 124 (36), 115 (26), 84 (100). Anal. Calcd for $C_{26}H_{26}N_6O_5$: C, 62.14; H, 5.21; N, 16.72. Found: C, 62.18; H, 5.35; N, 16.50.

(b) Methyl (1α,12bα,*E*)-α-[(2,4-Dinitrophenyl)hydrazono]-1-ethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine-1-propanoate (14). Sodium methoxide (2 mL, 11 mM, of a 30% solution in methanol) was added to a stirred solution of lactam **13b** (1.9 g, 3.8 mM) in 50 mL of methanol and 30 mL of dichloromethane at room temperature under an argon atmosphere. The dark red mixture was stirred for 4 days. The solid formed was filtered and washed thoroughly with water and with methanol until colorless washing was obtained. Crystallization of the powder from ethyl acetate and drying [60–70 °C (5 torr)] yielded 1.12 g of hydrazone **14**: mp 204.5–205 °C; TLC (acetone/dichloromethane, 1/9) R_f 0.7, TLC (butyl acetate) R_f 0.9; $[\alpha]^{21}_D$ +388.4° (*c* 0.73, glacial acetic acid); IR 3480 (s), 1705 (s), 1615 (s); UV (ethanol) 230 (25 600), 269 (13 730), 366 (18 740); ^1H NMR ($CDCl_3$, 200 MHz) 1.21 (t, 7, 3 H), 1.5–3.37 (m, 17 H), 3.41 (s, 3 H), 6.95–7.3 (m, 4 H), 7.75 (d, 9, 1 H), 7.85 (br s, 1 H), 8.26 (dd, 9, 2, 1 H), 9.1 (d, 2, 1 H), 12.1 (br s, 1 H); ^{13}C NMR ($CDCl_3$) 8.3, 20.9, 21.7, 30.7, 32.4, 35.9, 43.1, 52.2, 54.4, 57.3, 67.5, 110.8, 112.2, 118.8, 119.9, 122.2, 123.1, 126.8, 129.7, 131.9, 132.0, 136.3, 139.6, 144.9, 146.8, 166.4. Anal. Calcd for $C_{27}H_{30}N_6O_6$: C, 60.66; H, 5.65; N, 15.72. Found: C, 60.57; H, 5.69; N, 15.75.

(c) Methyl (1α,12bα,*Z*)-α-[(2,4-Dinitrophenyl)hydrazono]-1-ethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine-1-propanoate ((+)-8). A solution of 0.97 g (1.8 mM) of hydrazone **14** and 5 mL of acetonitrile, containing 1 mL of aqueous hydrogen chloride (*d* 1.19), was stirred at room temperature for 16 h. A solution (50 mL) of 15% aqueous potassium carbonate was added and the aqueous layer extracted twice with 25 mL of methylene chloride. The combined organic layers were dried (Na_2SO_4) and evaporated. The residue was crystallized twice from methylene chloride and methanol, yielding hydrazone **8** as yellow fluffy crystals: mp 192.5–193 °C dec; TLC (butyl acetate) R_f 0.5; $[\alpha]^{23}_D$ +77° (*c* 0.15, glacial acetic acid); IR 3460 (m), 3205 (w), 1700 (w), 1615; ^1H NMR ($CDCl_3$, 80 MHz) 1.16 (t, 7, 3 H), 1.4–3.25 (m, 17 H), 3.4 (br s, 1 H), 3.84 (s, 3 H), 6.75–7.5 (m, 4 H), 7.79 (br s, 1 H), 7.83 (d, 9, 1 H), 8.3 (dd, 9, 2, 1 H), 9.06 (d, 2, 1 H), 13.7 (br s, 1 H).

14-Deoxy-14-aminovincamine (12a).[14] Iron powder (6 g) was added in small portions to a stirred suspension of 1.5 g (2.8 mM) of hydrazone (+)-8 in 50 mL of 6 N methanolic hydrogen chloride. The gently exothermic reaction was stirred at 50 °C for 16 h, filtered, and evaporated. The residue was taken up in 100 mL of dichloromethane and extracted with 100 mL of 5% hydrochloric acid. The aqueous layer was neutralized with 28% aqueous ammonia, extracted twice with 100 mL of dichloromethane, dried (Na_2SO_4), and concentrated. The pale yellow residue, containing mostly **12a** contaminated with some **12b**, was chromatographed (silica gel, elution with 2.5% ethanol in dichloromethane) and crystallized from isopropyl alcohol to yield 270 mg (27%) of **12a**: mp 172.5–173 °C (lit.[14] mp 173–175 °C); TLC (ethanol/dichloromethane, 1/9) R_f 0.4; IR 3410, 3310, 1748; ^1H NMR ($CDCl_3$, 200 MHz) 0.9 (t, 7, 3 H), 1.05–3.42 (m, 16 H), 3.73 (s, 3 H), 3.91 (br s, 1 H), 7.0–7.57 (m, 4 H); mass spectrum, *m/e* 353 (80), 336 (20), 307 (65), 294 (57), 266 (67), 252 (100), 237 (46), 223 (25), 197 (34), 185 (30), 178 (40), 133 (20).

(+)-Vincamine (1a). Iron powder (1.5 g) was added in small portions to a stirred suspension of 0.5 g (0.94 mM) of hydrazone (+)-8 in 12 mL of 6 N methanolic hydrogen chloride at room temperature. The mixture of the initially exothermic reaction was stirred at 50 °C for 16 h, filtered, and poured into 50 mL of ice–water. Concentrated hydrogen chloride (*d* 1.18, 10 mL) was added, and some apovincamine hydrochloride was extracted with 50 mL of methylene chloride. A solution of 4 g of sodium nitrite in 100 mL of water was added slowly to the aqueous layer and the mixture stirred for 30 min at room temperature. Vincamine hydrochloride was extracted from the aqueous layer with methylene chloride (5 × 30 mL) and the combined organic layers were dried (Na_2SO_4). After charcoal treatment and evaporation, a residue was obtained which was taken up in 5 mL of acetic acid and 50 mL of ice–water and neutralized with 28% aqueous ammonia. Filtration and drying [70 °C (5 torr)] of the precipitate yielded 225 mg (68%) of a mixture containing vincamine (**1a**) and 14-epivincamine (**1b**) in a 9:1 ratio (determined by HPLC). Recrystallization from methanol yielded (+)-vincamine (**1a**): 180 mg (54%); mp 227–228 °C; $[\alpha]^{24}_D$ +15.3° (*c* 0.11, glacial acetic acid); IR 3450–3100 (br m), 1745 (s); ^1H NMR ($CDCl_3$, 80 MHz) 0.91 (t, 7, 3 H), 1.16–3.47 (m, 14 H), 3.82 (s, 3 H), 3.92 (br s, 1 H), 4.6 (br, 1 H), 6.95–7.6 (m, 4 H). Anal. Calcd for $C_{21}H_{26}N_2O_3$: C, 71.16; H, 7.39; N. 7.90. Found: C, 71.03; H, 7.38; N, 7.80.

(−)-Vincamine. From hydrazone (−)-8 there was obtained by the same procedure (−)-vincamine (**15a**): mp 227–228.5 °C; $[\alpha]^{20}_D$ −14.6° (*c* 0.5, glacial acetic acid). Anal. Calcd for $C_{21}H_{26}N_2O_3$: C, 71.16; H, 7.39; N, 7.90. Found: C, 71.31; H, 7.45; N, 7.75.

(±)-Vincamine. (a) From racemic hydrazone **8** there was obtained by the above procedure racemic vincamine **1a**, mp 227–228 °C.

(b) In an alternate procedure titanium trichloride was used as a reducing agent. A solution of 2 g (3.74 mM) of hydrazone (±)-8 in a mixture of 88 mL of acetone, 10 mL of aqueous 37% formaldehyde, 20 mL of acetic acid, and 60 mL of 15% titanium trichloride was heated at 60 °C for 15 min. Ice–water (200 mL) was added and the aqueous layer extracted three times with 50 mL and four times with 25 mL of dichloromethane. The residue obtained after evaporation was taken up in 30 mL of ice–water, and 10 mL of 28% aqueous ammonia was added. The precipitate was filtered and dried [60 °C (2 torr)], yielding 574 mg of (±)-vincamine (**1a**) and 14-epivincamine (**1b**). To the aqueous layer there was added 5 g of sodium nitrite in 30 mL of water. Extraction and treatment with ammonia as above yielded another 400 mg of **1a** and **1b**. Crystallization of the off-white powder (0.974 g) from methanol containing a trace of sodium methylate yielded 762 mg (58%) of pure (±)-vincamine (**1a**), mp 228 °C (lit.[4h,14] mp 225–227 °C). Anal. Calcd for $C_{21}H_{26}N_2O_3$: C, 71.16; H, 7.39; N, 7.90. Found: C, 71.03; H, 7.60; N, 7.79.

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Registry No. (±)-**1a**, 2122-39-6; (±)-**1b**, 18210-81-6; **1a**, 1617-90-9; **1b**, 6835-99-0; **2**, 40163-47-1; **6a**, 790-12-5; **6b**, 3618-76-6; **6c**, 78178-96-8; (±)-**7**, 78179-02-9; (±)-**8**, 83289-22-9; (−)-**8**, 83289-23-0; (+)-**8**, 83289-24-1; (±)-**9** (X = ClO_4) (epimer 1), 83289-21-8; (±)-**9** (X = ClO_4) (epimer 2), 78341-00-1; (±)-**11a**, 78341-03-4; (±)-**11b**, 18374-19-1; **12a**, 68353-36-6; **13a**, 35226-43-8; (*E*)-**13b**, 83220-17-1; (*Z*)-**13b**, 83220-18-2; **14**, 83348-67-8; **15a**, 38990-16-8; methyl pyruvate, 600-22-6.