2 H, allylic), 2.70 (m, 1 H, CHOH), 4.8–5.3 (m, 2 H, C=CH_2), 5.8–6.3 (m, 1 H, C=CH).

Anal. Calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found: C, 77.59; H, 11.90.

36c: IR (neat) 3400 cm^{-1}; NMR (CCl_4) δ −0.2–0.8 (m, 3 H, cyclopropyl), 0.93 (t, 3 H, CH_3CH_2), 1.00 (s, 3 H, CH_3C), 1.03 (m, 3 H, CH_3CH), 1.2–1.6 (m, 6 H, methylene), 2.67 (m, 1 H, CHOH).

Anal. Calcd for $C_{10}H_{20}O$: C, 76.86; H, 12.96. Found: C, 76.77; H, 13.24.

Acetolyses of 36a–d. In each case approximately 100 mg of alcohol was dissolved in 4 mL of glacial acetic acid containing a drop of boron trifluoride etherate, and the solution was heated at 85 °C for 1.5 h. The mixtures were cooled, poured into water, and extracted with pentane. Extracts were washed with water, aqueous $NaHCO_3$, and finally water and then dried over Na_2SO_4. Solvent removal gave crude mixtures of **38** and **39** analyzed by ^1H NMR with the aid of $Eu(fod)_3$ (see Table I). Bulb-to-bulb distillation of the mixtures of isomeric acetates gave analytical samples affording the following data.

38a, 39a. Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.36; H, 9.49.

38b, 39b. Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.28; H, 10.49.

38c, 39c. Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.61; H, 11.25.

8-Bromo-6-methyl-(*E*)-5-nonen-1-yne[9] (40a). Thirteen milliliters of a solution prepared by dissolving 7.0 g of $ZnBr_2$ in 5 mL of 48% HBr was cooled with a salt–ice bath, and, with vigorous stirring, 3.25 g (28 mmol) of **37a** was added over 5 min. The mixture was stirred at −15 °C for 15 min and then treated with 30 mL of pentane followed by 130 mL of cold water. The pentane extract was washed well with water, dilute $NaHCO_3$, water, and brine and dried over Na_2SO_4. Solvent removal gave 5.4 g (89%) of crude product. GLC analysis (column A, 125 °C) showed the mixture to contain approximately 92% of **40a** (T_r 6.2 min) and 8% of **41a** (T_r 5.9 min). The mixture was freed of solvent by bulb-to-bulb distillation (125 °C (1 mm)): NMR (CCl_4) δ 1.63 (m, 3 H, CH_3C=), 1.67 (d, 3 H, J = 6.8 Hz, CH_3CHBr), 2.1–2.3 (bm, 4 H, $-CH_2CH_2-$), 2.50 (dd, 2 H, $CBrCH_2$), 4.13 (m, 1 H, >CHBr), 5.25 (bm, 1 H, vinyl).

Anal. Calcd for $C_{10}H_{15}Br$: C, 55.83; H, 7.03. Found: C, 56.26; H, 7.20.

Rearrangement of 37a-d_1 under Johnson–Julia Conditions. 5-(*cis*-1,2-Dimethylcyclopropyl)-1-pentyn-5-ol-*5*-d_1 (**37a**-d_1) was prepared by the reduction of **36a** with $LiAlD_4$ as in the preparation of **37a**. Treatment of this alcohol with HBr–$ZnBr_2$ as described above in the preparation of **40a** gave the corresponding bromide mixture **40a**-d_1 and **41a**-d_1. The ^2H NMR spectrum of this sample contained peaks corresponding to vinyl D, >CDBr, and vinyl CH_2D in a ratio of 93:7:15.

5-Bromo-3-methyl-(*E*)-2-hexene (9). Treatment of **8** with HBr–$ZnBr_2$ as described above in the preparation of **40a** gave homoallylic bromide **9** as the sole product detectable by GLC analysis (column B, 80 °C). The bromide was freed of solvent by bulb-to-bulb distillation (115 °C (40 mm)): NMR (CCl_4) δ 1.50–1.65 (m, 6 H, vinyl CH_3), 1.63 (d, 3 H, J = 6.6 Hz, CH_3CH), 2.3–2.7 (m, 2 H, CH_2), 5.25 (bm, 1 H, vinyl).

Anal. Calcd for $C_7H_{13}Br$: C, 47.48; H, 7.40. Found: C, 47.51; H, 7.49.

Rearrangement of 8-d_1 under Johnson–Julia Conditions. 1-(*cis*-1,2-Dimethylcyclopropyl)ethanol-*1*-d_1 (**8**-d_1) was prepared by the reduction of **16** with $LiAlD_4$ as in the preparation of **37a**. Treatment of this alcohol with HBr–$ZnBr_2$ as in the preparation of **9** gave **9**-d_1. The ^2H NMR spectrum of this bromide contained three peaks corresponding to vinyl D, >CDBr, and vinyl CH_2D in the ratio of 55:45:4.

Acknowledgments. We express our sincere appreciation to Dr. G. B. Staal of Zoecon Corp. for helpful discussions and for verification of our bioassays.

Registry No. **1**, 66521-02-6; **4**, 70130-78-8; **5**, 70130-79-9; **6** isomer 1, 70130-80-2; **6** isomer 2, 70190-94-2; (*Z*)-**7**, 70130-81-3; (*E*)-**7**, 70130-82-4; **8** isomer 1, 70190-95-3; **8** isomer 2, 70190-96-4; **8**-d_1, 70130-83-5; **9**, 70130-84-6; **9**-d_1 isomer 1, 70130-85-7; **9**-d_1 isomer 2, 70130-86-8; **9**-d_1 isomer 3, 70130-87-9; (*E*)-**10**, 70130-88-0; (*Z*)-**10**, 70130-89-1; **16**, 70130-90-4; **16**-d_3, 70130-91-5; **17**, 70130-92-6; **19** isomer 1, 70130-93-7; **19** isomer 2, 70130-94-8; **20**, 70130-95-9; **21**, 70130-96-0; **21** *p*-nitrobenzoate, 70130-97-1; **22**, 70130-98-2; **23**, 70130-99-3; **24**, 70131-00-9; **25**, 70131-01-0; **26**, 70131-02-1; **26** diacetate, 70131-03-2; **27**, 70131-04-3; **27** diacetate, 70131-05-4; **28**, 70130-68-6; **28** diacetate, 70130-69-7; **29**, 70131-06-5; **36a**, 70131-07-6; **36b**, 70131-08-7; **36c**, 70131-09-8; **37a**, 42895-35-2; **37b**, 70131-10-1; **37c**, 70131-11-2; **37d**, 70131-12-3; **37a**-d_1, 70131-13-4; (*E*)-**38a**, 70131-14-5; (*Z*)-**38a**, 70131-15-6; (*E*)-**38b**, 70131-16-7; (*Z*)-**38b**, 70131-17-8; (*E*)-**38c**, 70131-18-9; (*Z*)-**38c**, 70131-19-0; (*E*)-**38d**, 70131-20-3; (*Z*)-**38d**, 70131-21-4; **39a**, 70131-22-5; **39b**, 70131-23-6; **39c**, 70131-24-7; **40a**, 70131-25-8; **40a**-d_1 isomer 1, 70131-26-9; **40a**-d_1 isomer 2, 70131-27-0; **40a**-d_1 isomer 3, 70131-28-1; **41a**, 70131-29-2; **41a**-d_1 isomer 1, 70131-30-5; **41a**-d_1 isomer 2, 70131-31-6; **41a**-d_1 isomer 3, 70131-32-7; diethyl carbonate, 105-58-8; biacetyl hydrazone, 33487-48-8; 3-diazo-2-butanone, 14088-58-5; propargyl bromide, 106-96-7; allyl bromide, 106-95-6; propyl iodide, 107-08-4.

Studies on Vindolinine. 6.† Partial Synthesis of Aspidospermane-Type Alkaloids[1,2]

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19-Iodotabersonines (**2**) can be easily obtained from vindolinine (**1**). These compounds are shown to be useful intermediates especially via 19-oxotabersonine (**6**) in partial synthesis of several aspidospermane-type alkaloids. This procedure now allows the preparation of a number of alkaloids which can be isolated only in minute amounts from natural sources.

Vindolinine (**1**), whose structure has been revised mainly by ^{13}C NMR,[3] is one of the major monomeric alkaloids isolated from the Madagascan *Catharanthus* species and particularly from the most common and thoroughly studied of them *C. roseus*.[4] Fragmentation of **1** with iodine (THF–Na_2CO_3) has already been reported by us[1,5] and led mainly to a mixture of both epimeric 19-iodo-

† The authors wish to dedicate this work to memory of the late Professor J. Le Men.

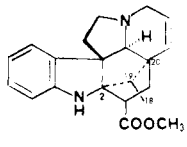
(1) Part V: L. Diatta, R. Z. Andriamialisoa, N. Langlois, and P. Potier, *Tetrahedron*, **32**, 2839 (1976).

(2) Preliminary communications: (a) R. Z. Andriamialisoa and N. Langlois, "Les *Catharanthus*: importance des travaux francais", Tananarive, Sept. 1977; (b) N. Langlois, "Vindolinine, Etudes chimiques et hémi-synthèses", Reims, March 23, 1978.

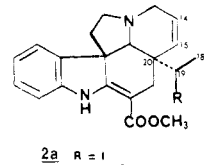
0022-3263/79/1944-2468$01.00/0

tabersonines **2a** and **2b**. Preparation of (−)-tabersonine (**3**) and (−)-vincadifformine (**4**) by hydrogenolysis and hydrogenation (Ni Raney–H_2) of **2** allowed us to determine the absolute configuration of vindolinine (**1**). (−)-Vincadifformine (**4**) was exclusively obtained when PtO_2 was used as catalyst.[5b] Therefore, 19-iodotabersonines (**2**) can be considered as potential vincamine precursors.[6,7] The hemisynthesis from compound **2** (via Δ^{18}-tabersonine (**5**)) of the alkaloid (±)-andranginine has also been reported previously.[8] In the present report, we describe the oxidation of **2** to 19-oxotabersonine (**6**) and the use of this compound for the partial synthesis of some aspidospermane-type alkaloids.

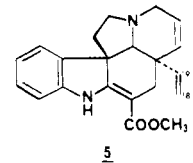
The mixture of 19-iodotabersonines (**2**) readily yields 19-oxotabersonine (**6**) following a modified Kornblum reaction (Me_2SO in the presence of $AgBF_4$ at room temperature).[9] The molecular peak ($M^{+\cdot}$ at m/e 350) and the fragmentation pattern observed in the mass spectrum of **6** are typical of the assigned structure which is confirmed by IR (ν(C=O) 1705 cm^{-1}) and NMR [^1H NMR (CH_3CO) δ 1.95; ^{13}C NMR (C_{19}=O) δ 209.2]. Using strictly anhydrous conditions, 19-oxotabersonine (**6**) is obtained in good yields (75–80%). However, in the presence of water, we also observe a fragmentation of the piperideine part of the molecule with the formation of **7**[10] (previously obtained by heating **2a** in DMF–NaOAc[1]) and substitution of iodide by hydroxyl with the formation of **8b** (see later). The structure of **6** is verified after hydrogenation in neutral



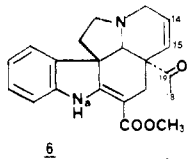
1



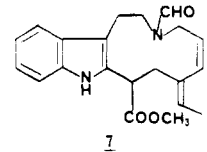
2a R = I
2b 19-epi **2a**
3 R = H
4 R = H 14,15-dihydro



5



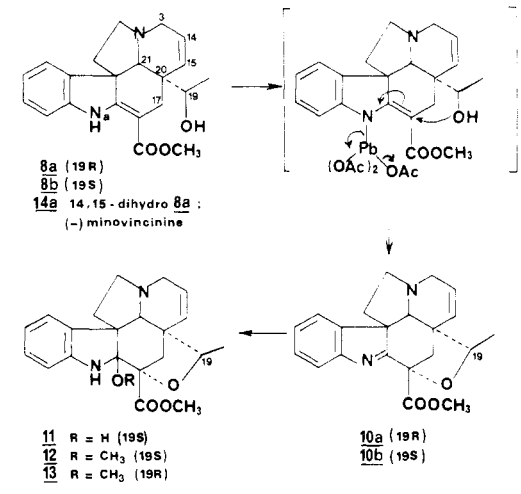
6
9 14,15 dihydro **6**: (−) minovincine



7

medium (H_2–Pd/C–MeOH) which quantitatively leads to (−)-minovincine (**9**), an alkaloid isolated for the first time by Janot, Le Men, et al.[11]

Scheme I



Reduction of **6** (97%) by $NaBH_4$ led to almost equal amounts of the epimeric alcohols **8a** and **8b**, which were identified as two minor alkaloids found in *Catharanthus ovalis* Mgf.[8,12,13] A mixture of these 19-hydroxy tabersonines has already been isolated from *Melodinus celastroides*[14] and more recently, the 19*S* epimer has been identified in the roots of *C. lanceus*.[15,16] However, configurations at C_{19} were not clearly assigned. In the ^1H NMR spectra, the difference in the chemical shifts of the C_{18} protons is too small to be significant by comparison with results obtained in the 14,15-dihydro series by Doepke and Meisel;[17] moreover, reference samples have not been available. Preparation of **8a** and **8b** from 19-iodotabersonines (**2**) allows us to determine unambiguously their respective configurations at this center. For that purpose, we apply Horeau's method[18] to the epimer **8b**. α-Phenylbutyric acid obtained after esterification of **8b** with an excess of racemic α-phenylbutyric anhydride is levorotatory (optical yield 42%), indicating a 19*S* configuration. This result confirms our previous attribution after correlation of **8b** with vincoline (**11**) and kitraline (**12**) via indolenine (**10b**).[10,12] Indolenine (**10b**) is formed (90–100% yield) by treatment of **8b** with lead tetracetate and yields **11** in the presence of water (30%) and **12** in the presence of NaOMe (83%). Likewise, the epimer **8a** gives indolenine **10a** which produces kitramine (**13**),[10,12] and configurations at C_{19} are retained in the mechanism proposed for these cyclizations (Scheme I).

(19*R*)-Hydroxytabersonine (**8a**) is quantitatively hydrogenated to (−)-minovincinine (**14a**), identical with an authentic sample of the alkaloid isolated by Janot, Le Men, et al.,[11] therefore proving the 19*R* configuration of this natural compound and so confirming the conclusions of Doepke and Meisel.[17] Obviously 19-hydroxytabersonines (**8**) are also potential precursors of many natural bases bearing an acyloxyl group at C_{19}.[16,19–21]

(3) A. Ahond, M.-M. Janot, N. Langlois, G. Lukacs, P. Potier, P. Rasoanaivo, M. Sangare, N. Neuss, M. Plat, J. Le Men, E. W. Hagaman, and E. Wenkert, *J. Am. Chem. Soc.*, **96**, 633 (1974). See also: (a) C. Riche and C. Pascard-Billy, *Acta Crystallogr., Sect. B*, **32**, 1975 (1976); (b) L. J. Durham, J. N. Shoolery and C. Djerassi, *Proc. Natl. Acad. Sci. USA*, 71, 3797 (1974).

(4) W. I. Taylor and N. R. Farnsworth, "The *Catharanthus* Alkaloids", Marcel Dekker, New York, 1975, and references therein.

(5) (a) P. Rasoanaivo, N. Langlois, and P. Potier, *Tetrahedron Lett.*, 3669 (1974); (b) P. Rasoanaivo, Thèse de Doctorat es-Sciences, Orsay, France, 1974.

(6) Omnium Chimique S. A. Belgium 811614 (cl C07D), June 17, 1974; Appl. 811614, 27.2. 1974 (*Chem. Abstr.* **82**, 73282 (1975)).

(7) G. Hugel, J. Levy, and J. Le Men, *C. R. Acad. Sci., Ser. C*, **274**, 1350 (1972).

(8) R. Z. Andriamialisoa, L. Diatta, P. Rasoanaivo, N. Langlois, and P. Potier, *Tetrahedron*, **31**, 2347 (1975).

(9) B. Ganem and R. K. Boeckman, *Tetrahedron Lett.*, 917 (1974).

(10) R. Z. Andriamialisoa, Thèse de Doctorat es-Sciences, Orsay, France, 1978.

(11) M. Plat, J. Le Men, M.-M. Janot, H. Budzikiewicz, J. M. Wilson, L. J. Durham, and C. Djerassi, *Bull. Soc. Chim. Fr.*, 2237 (1962).

(12) R. Z. Andriamialisoa, N. Langlois, and P. Potier, *Tetrahedron Lett.*, **163** (1975).

(13) N. Langlois, L. Diatta, and R. Z. Andriamialisoa, *Phytochemistry*, 18, 467 (1979).

(14) (a) A. Rabaron, Thèse de Doctorat es-Sciences, Paris, France, 1974; (b) A. Rabaron, M. H. Mehri, T. Sevenet, and M. M. Plat, *Phytochemistry*, **17**, 1452 (1978).

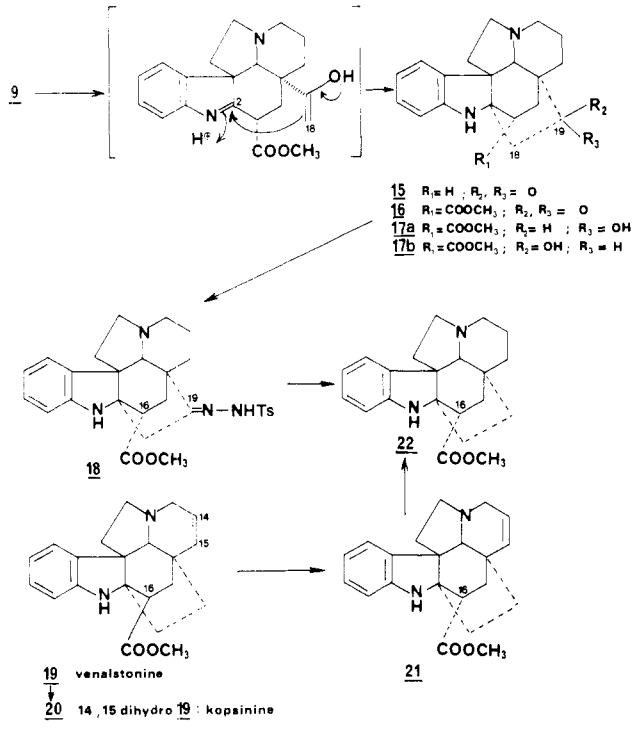
(15) B. Gabetta, E. M. Martinelli, and G. Mustich, *Fitoterapia*, **47**, 6 (1976).

(16) G. A. Cordell, "The Aspidosperma Alkaloids, The Alkaloids", R. H. F. Manske, Ed., Academic Press, New York, 1978.

(17) W. Doepke and H. Meisel, *Tetrahedron Lett.*, 749 (1970).

(18) A. Horeau, "Determination of Configurations by Chemical Methods; Horeau's Method, Stereochemistry Fundamentals and Methods", Ed. H. B. Kagan, Ed., G. Thieme, 1977.

Scheme II



On the other hand, (−)-minovincine (**9**) now being available from 19-iodotabersonine (**2**), we intend to prepare some hexacyclic pleiocarpine-type alkaloids. At least 20 alkaloids belong to this structural type, most of them bearing a methoxycarbonyl group at C_{16}, such as kopsinine (**20**), which exhibits pharmacological activity.[21] 19-Oxooaspidofractinine (**15**) has already been prepared from **9**, but cyclization of $C_{18} \rightarrow C_2$ was accompanied by loss of the methoxycarbonyl group.[22,23] Carrying out cyclization in anhydrous and carefully controlled acidic conditions, we obtain 16-epi-19-oxokopsinine (**16**) in 45–50% yield together with unchanged (−)-minovincine (**9**).

As Djerassi and co-workers have shown in several pleiocarpine-type alkaloids and their derivatives,[24] relative peak intensities at *m/e* 109 and 124 in the mass spectra of kopsinine (**20**) and 16-epikopsinine (**22**) (both obtained from venalstonine (**19**)[20]) are characteristic of the configuration at C_{16}. The comparison of these intensities with those of the peaks at *m/e* 109 and 138 in the mass spectrum of **16** (and at *m/e* 109 and 140 in the mass spectra of the reduction products **17**) is significant and indicates the configuration at C_{16} of the compound **16** as *S*. This assignment is confirmed by deoxygenation of **16** [(a) $TsNH-NH_2 \rightarrow$ **18**; (b) $NaBH_3CN$[25]] which leads to 16-epikopsinine (**22**) (Scheme II).

Starting from vindolinine (**1**), functionalization of the (−)-tabersonine ethyl side chain via 19-iodotabersonines (**2**) allows the preparation by hemisynthesis of many alkaloids which often are present in small quantities in natural sources (*Apocynaceae*) and some derivatives.

Experimental Section

Melting points were taken on a Kofler apparatus, optical rotations measured ($CHCl_3$ solution, g/100 mL) on a Perkin-Elmer 141 MC, IR spectra (ν cm^{-1}; $CHCl_3$) on a Perkin-Elmer 257, UV spectra [EtOH, λ_{max} nm (ϵ)] on a Bausch and Lomb Spectronic 505, and CD curves [EtOH λ_{max} nm] on a Roussel-Jouan Dichrograph II. ^1H NMR spectra were obtained ($CDCl_3$, Me_4Si, δ = 0 ppm) from Varian T60 or IEF 240[26] spectrometers (coupling constants *J* are given in hertz; s, d, dd, and m indicate singlet, doublet, doublet of doublet, and multiplet, respectively). Mass spectra were measured on an AEI MS9. Preparative TLC were performed with Kieselgel HF 254 + 366 Merck.

19-Oxotabersonine (6). (a) 19-Iodotabersonine (**2**) [350 mg, 0.75 mmol prepared as described in ref 1] was added under an inert atmosphere to a stirred solution of $AgBF_4$ (220 mg 1.12 mmole) in 3 mL of dry Me_2SO at room temperature.[9] After 30 min, triethylamine (10 mL) was added and the mixture was stirred for 15 min then poured into H_2O and extracted with ether. After the usual workup, crude 19-oxotabersonine (**6**) (250 mg) was purified by preparative TLC to yield 200 mg of **6** (yield 75%): $[\alpha]^{22}_D$ − 320° (*c* 0.5); IR 3340 (NH), 1705 (C_{19}=O), 1675 and 1610 cm^{-1} (α-methylene indoline ester); UV 225 (14000) 300 (13500) and 330 nm (20000) (α-methylene indoline ester); MS peaks at *m/e* 350 ($M^{+\cdot}$), 319, 307, 229, 214, 168, 149 (100), 121; ^1H NMR (240 MHz) δ 8.83 (s, 1 H, N_aH), 7.4–6.6 (4 H aromatic), 5.95 (dd, 1 H, $J_{14,1,5}$ = 10 Hz and $J_{3,14}$ = 4 Hz, C_{14}–H), 5.78 (d, 1 H, $J_{14,15}$ = 10 Hz, C_{15}–H), 3.75 (s, 3 H, CO_2CH_3), 1.95 (s, 3 H, $C_{18}H$); ^{13}C NMR δ 209.2 (C_{19}), 168.0 (CO_2CH_3), 167.3 (C_2), 142.6 (C_{13}), 138.0 (C_8), 129.3 (C_{15}), 127.6 and 126.8 (C_{11} and C_{14}), 121.1 (C_9 and C_{10}), 109.4 (C_{12}), 90.9 (C_{16}), 66.2 (C_{21}), 57.6 and 55.7 (C_{20} and C_7), 50.5 (OCH_3, C_3 and C_5), 44.3 (C_6), 29.0 (C_{17}), and 25.7 (C_{18}), assignments by comparison with tabersonine signals[27] and literature data.[28]

(b) The same reaction carried out in the presence of traces of water on 19-iodotabersonine (**2a**) (50 mg, 0.11 mmol) yielded, after separation by preparative alkaline TLC ($CHCl_3$), **6** (20 mg, 53%) and a compound identical in all respects with indole **7** previously described[1] (10 mg).

(c) The same reaction carried out in the presence of 0.2 mL of H_2O on 19-iodotabersonine (**2a**) (50 mg) yielded **7** (14 mg) and **8b** (9 mg), identical with (19*S*)-hydroxytabersonine obtained by $NaBH_4$ reduction of **6** (see later).

(−)-Minovincine (9). Hydrogenation of 24 mg (0.07 mmol) of **6** (absolute EtOH (2 mL), Pd/C 10%; 8 mg) for 24 h at room temperature quantitatively led to (−)-minovincine (**9**) (α_D, IR UV, MS and ^1H NMR identical with literature data[11]).

19-Hydroxytabersonines 8. Excess $NaBH_4$ was added to a stirred solution of 19-oxotabersonine (**6**) (740 mg, 2.11 mmol) in MeOH (90 mL) at room temperature. After 10 min, the mixture was poured into H_2O and extracted with $CHCl_3$. After the usual workup, the mixture of epimers (720 mg, 97%) was separated by preparative TLC (AcOEt–hexane–MeOH 1–1–0.1) and yielded: (19*R*)-hydroxytabersonine (**8a**) (223 mg) and (19*S*-hydroxytabersonine (**8b**) (235 mg). **8a**: $[\alpha]^{22}_D$ −365° (*c* 0.53); IR 3500 (sh, OH), 3370 (NH), 1670–1620 cm^{-1} (α-methylene indoline ester); UV 220 (10500), 300 (10500), 330 (13500); MS, *m/e* 352 ($M^{+\cdot}$), 337, 321, 307, 275, 267, 229, 228, 214, 168, 151 (100), 138, 124, 123, 108; ^1H NMR (240 MHz) δ 8.81 (s, 1 H, N_aH), 7.23–6.83 (4 H, aromatic), 5.89 (dd, 1 H, $J_{14,15}$ = 10 Hz and $J_{3,14}$ = 5 Hz, C_{14}–H), 5.68 (d, 1 H, $J_{14,15}$ = 10 Hz, C_{15}–H), 3.76 (s, 3 H, CO_2CH_3), 3.46 (dd, 1 H, $J_{3,3'}$ = 16 Hz and $J_{3,14}$ = 5 Hz, C_3–H), 3.33 (q, 1 H, $J_{18,19}$ = 6 Hz, C_{19}–H), 3.23 (d, 1 H, $J_{3,3'}$ = 16 Hz, C_3–H′), 3.1 (m, 1 H, C_5–H), 2.86 (d, 1 H, $J_{17,17'}$ = 16 Hz, C_{17}–H), 2.76 (s, 1 H, C_{21}–H), 2.70 (m, 1 H, C_6–H), 1.84 (dd, 1 H, $J_{6,6'}$ = 12 Hz and $J_{5',6'}$ = 4 Hz, C_6–H′), 1.57 (s, 1 H disappeared with D_2O, OH), 0.85 (d, 3 H, $J_{18,19}$ = 6 Hz, C_{18}–H). **8b**: $[\alpha]^{22}_D$ −375° (*c* 0.49); IR 3440 (sh, OH), 3370

(19) Tapan Kumar Chanda, Ph.D Thesis, Calcutta, 1973.
(20) (a) M. Hesse, "Indol Alkaloide in Tabellen", Springer, Berlin, 1968, and references therein; (b) B. Gabetta and G. Mustich, "Spectral Data of Indole Alkaloids", Inverni della Beffa, Milan, 1975.
(21) W. I. Taylor and N. R. Farnsworth, "The Vinca Alkaloids", Marcel Dekker, New York, 1973, and references therein.
(22) H. K. Schnoes and K. Biemann, *J. Am. Chem. Soc.*, **86**, 5693 (1964).
(23) A. Guggisberg, A. A. Gorman, J. W. Bycroft, and H. Schmid, *Helv. Chim. Acta*, **52**, 76 (1969).
(24) C. Djerassi, H. Budzikiewicz, R. J. Owellen, J. M. Wilson, W. G. Kump, D. J. Lecount, A. R. Battersby, and H. Schmid, *Helv. Chim. Acta*, **46**, 742 (1963).
(25) R. O. Hutchins, C. A. Milewski, and B. E. Maryanoff, *J. Am. Chem. Soc.*, **95**, 3662 (1973).
(26) S. K. Kan, P. Gonord, C. Duret, J. Salset, and C. Viset, *Rev. Sci. Instrum.*, **44**, 1725 (1973).
(27) E. Wenkert, D. W. Cochran, E. W. Hagaman, M. F. Schell, N. Neuss, A. S. Katner, P. Potier, C. Kan, M. Plat, M. Koch, H. Mehri, J. Poisson, N. Kunesch, and Y. Rolland, *J. Am. Chem. Soc.*, **95**, 4990, 1973.
(28) J. B. Stothers, "Carbon-13 NMR Spectroscopy in Organic Chemistry", A. T. Blomquist and H. H. Wasserman, Eds., Academic Press, New York, 1972.

(NH), 1670–1610 cm^{-1}; UV 220 (13000), 300 (10000), 330 (14000); MS, same fragmentations as **8a**; ^1H NMR (240 MHz) δ 8.93 (s, 1 H, N_aH), 7.28–6.83 (4 H, aromatic), 6.09 (dd, 1 H, $J_{14,15}$ = 10 Hz, and $J_{3,14}$ = 5 Hz, C_{14}–H), 5.73 (d, 1 H, $J_{14,15}$ = 10 Hz, C_{15}–H), 3.76 (s, 3 H, CO_2CH_3), 3.45 (dd, 1 H, $J_{3,3'}$ = 16 Hz and $J_{3,14}$ = 5 Hz, C_3–H), 3.35 (s, 1 H, C_{21}–H), 3.22 (masked q, C_{19}–H), 3.03 (m, 1 H, C_5–H), 2.79 (m, 1 H, C_5–H'), 2.61 (d enlarged by long range coupling, 1 H, $J_{17,17'}$ = 16 Hz, C_{17}–H), 2.48 (d, 1 H, $J_{17,17'}$ = 16 Hz, C_{17}–H'), 2.08 (m, 1 H, C_3–H), 1.87 (dd, 1 H, $J_{6,6'}$ = 14 Hz and $J_{5,6'}$ = 5 Hz, C_6–H'), 1.20 (large d, disappeared with D_2O, OH), 1.02 (d, 3 H, $J_{18,19}$ = 6, C_{18}–H).

Determination of 8b Configuration. A solution of racemic α-phenylbutyric anhydride (124 mg, 0,4 mmol) in 1 mL of dry pyridine was added to **8b** (50 mg, 0.142 mmol). After the solution was stirred for 48 h at room temperature, C_6H_6 and 0.2 mL of H_2O were added. The product was extracted with $CHCl_3$ after addition of 0.1 N NaOH. Integration of the ^1H NMR spectrum indicated that 80% of esterification had occurred.

The aqueous layer was acidified with 0.1 N HCl and the α-phenylbutyric acid was extracted with C_6H_6, $[\alpha]^{22}_D$ –6.7° (optical yield 42%).

(–)-Minovincinine (14a). Hydrogenation of (19*R*)-hydroxytabersonine (**8a**) (24 mg in absolute ethanol (PtO_2)) yielded (–)-minovincinine (**14a**) (20 mg), identical in all respects with the alkaloid isolated from *Vinca minor*:[11] $[\alpha]^{22}_D$ –473° (*c* 0.85, EtOH 95%); ^1H NMR (60 MHz) δ 0.95 (d, 3 H, *J* = 6 Hz, C_{18}–H).

19-Epi-(–)-minovincinine (14b). **8b** was hydrogenated as previously shown, leading to **14b**. The color reaction with ceric ammonium sulfte (CAS) reagent[29] was different from that of **14a**: $[\alpha]^{22}_D$ –530° (*c* 0.78, EtOH 95%); ^1H NMR (60 MHz) δ 0.90 (d, 3 H, *J* = 6 Hz, C_{18}–H).

Indolenine (10a). A solution of $Pb(OAc)_4$ (200 mg) in dry CH_2Cl_2 (5 mL) was added at 0 °C to a stirred solution of **8a** (115 mg, 0.33 mmol) in CH_2Cl_2 (5 mL) under Ar. The mixture was stirred for 15 min at room temperature and poured into H_2O (0 °C). Indolenine (**10a**) (110 mg) was extracted with $CHCl_3$ after alkalinization to pH 8.5 with an aqueous solution of Na_2CO_3: UV 227, 268 nm (acidic medium; 245 and 298 nm); MS 350 (M^+· 100), 335, 321, 305, 291, 180, 170, 169, 121.

Indolenine (10b). (19*S*)-Hydroxytabersonine (8b) (120 mg, 0.34 mmol) was treated with $Pb(OAc)_4$ as was previously described. Indolenine (**10b**) (115 mg) was obtained; MS, same fragmentations as **10a**. *Compounds* **10a** *and* **10b** *were rather unstable and* therefore they were used immediately.

Vincoline (11). Silica gel for TLC (200 mg) was added to a solution of indolenine (**10b**) (45 mg) in Et_2O saturated with H_2O (5 mL). The mixture was stirred at room temperature for 24 h, dried with Na_2SO_4, filtered, and evaporated. Purification by preparative TLC ($CHCl_3$–CH_3OH 94–6) yielded compound (14 mg) identical with an authentic sample of vincoline[30] [F, $[\alpha]_D$, IR, UV, MS, ^1H NMR].

Kitraline (12). A solution of NaOMe in dry MeOH (0, 8 M, 13 mL) was added to **10b** (115 mg) under N_2. After being stirred at room temperature for 35 min, the mixture was concentrated under vacuum at 25 °C, poured into H_2O, and extracted with $CHCl_3$. Usual workup led to a compound (104 mg, 83% yield) identified with kitraline (**12**) isolated from *C. ovalis* Mgf:[10,13] $[\alpha]_D$ –9° (*c* 0.47); IR 3400 (NH), 1740 (ester), 1610 cm^{-1} (indoline); UV 244 (7900) and 300 nm (3400), dihydroindole; MS, high resolution and ^1H NMR (see ref 12).

Kitramine (13). Indolenine (**10a**) (110 mg) was treated as described for **10b** and led to compound **13** (104 mg, 86%) identical with kitramine isolated from *C. ovalis* Mgf:[10,13] $[\alpha]_D$ –46° (*c* 0.45); IR 3390 (NH), 1740 (ester), 1610 cm^{-1} (indoline); UV 245 (6500) and 299 nm (2800), dihydroindole; MS and ^1H NMR (240 MHz), see ref 12.

16-Epi-19-oxokopsinine (16). A solution of (–)-minovincine (**9**) (150 mg, 0.43 mmol) in dry HCl–MeOH (5 M) was heated under reflux for 24 h (oil bath temperature 105 °C). The mixture was made alkaline with an aqueous solution of Na_2CO_3 and extracted with $CHCl_3$. After the usual workup, 16-epi-19-oxokopsinine (**16**) (67 mg, 45%) and (–)-minovincine (**9**) (75 mg) were separated by preparative alkaline TLC ($CHCl_3$): **16** $[\alpha]_D$ +60° (*c* 0.4); IR 3350 (NH), 1740 (sh, ester), 1720 cm^{-1} (C=O); UV 210 (20000), 240 (8200), and 292 (3800), dihydroindole; MS, *m/e* 352 (M^+· 100), 310, 294, 193, 144, 138 (4), 124 (2), 109 (19).

Reduction of 16 with $NaBH_4$ (17a and 17b). $NaBH_4$ in excess was added to a stirred solution of **16** (5 mg 0.014 mmol) in 0.5 mL of MeOH. After the solution sat 5 min at room temperature, workup yielded a mixture (5 mg) separated by preparative alkaline TLC ($CHCl_3$–MeOH 98–2). **Epimer 17a**: IR 3350 (NH), 1720 cm^{-1} (CO_2CH_3); MS, *m/e* 354 (M^+· 100), 321, 310 (M – 44), 152, 140, 122, 109. **Epimer 16b**: IR and MS identical with the spectra of **17a**.

16-Epi-19-oxokopsininetosylhydrazone (18). Tosylhydrazine (11.8 mg) and *p*-toluenesulfonic acid (trace) were added to a solution of 16-epi-19-oxokopsinine (**16**) (17.9 mg, 0.05 mmol) in MeOH (1.5 mL). The mixture was heated at 45 °C for 3 days, diluted with aqueous Na_2CO_3 solution, and extracted as usual. The crude product was purified by preparative alkaline TLC ($CHCl_3$–MeOH 98–2) and yielded unchanged **16** (1.9 mg) and 16-epi-19-oxokopsininetosylhydrazone (**18**) (20 mg, 78%): mp 260–2 °C dec (CH_3OH–Et_2O); IR 3600, 3380, 3200, 1740 and 1650 cm^{-1}; UV 228 (15700) and 292 nm (2700); MS, *m/e* 520, 365, 336, 223, 205, 186 (100), 156, 149, 139, 109, 107; ^1H NMR (60 MHz) δ 7.9–6.7 (8 H aromatic), 3.6 (s, 3 H, CO_2CH_3), 2.5 (CH_3–C_6H_4–).

16-Epikopsinine (22) from Tosylhydrazone (18).[25] $NaBH_3CN$ (5.3 mg) in DMF–sulfolane 1–1 (0.2 mL) was added to tosylhydrazone (**18**) (16.6 mg, 0.03 mmol) under Ar. The mixture was heated at 110 °C with stirring for 24 h. Then the same quantity of reactive was added and heating was maintained for 24 h. After dilution with C_6H_4–Et_2O 1–1, the product was extracted with aqueous HCl (5%). Usual workup and purification by preparative TLC ($CHCl_3$–acetone 1–1) yielded compound (1.5 mg, 15%) identical (R_f, UV, DC, MS) with 16-epikopsinine (**22**) obtained from **19**.

Epimerization of Venalstonine (19):16-Epivenalstonine (21). Venalstonine (**19**) (30 mg, 0.09 mmol) was added to a solution of sodium (30 mg) in MeOH (2 mL) under N_2. The solution was heated for 16 h (oil bath temperature 110 °C) under N_2, then poured into H_2O, and extracted with $CHCl_3$. 16-Epivenalstonine (**21**) (18 mg, 60%) was obtained after the usual workup: IR 3400 (NH), 1740 cm^{-1} (ester); UV 240 and 290 nm; MS, *m/e* 336 (M^+·), 308, 216, 156, 149, 138, 135, 134, 122, 107 (100); ^1H NMR (60 MHz) 7.2–6.6 (4 H aromatic), 4.6 (m, 2 H, C_{14}–H and C_{15}–H), 3.8 (s, 3 H, CO_2CH_3).

16-Epikopsinine (22). Hydrogenation of 21. Hydrogenation of 16-epivenalstonine (**21**) (18 mg, 0.05 mmol) in absolute EtOH (1.5 mL) over PtO_2 yielded after usual workup 16-epikopsinine (**22**) (10 mg, 60%): IR 3400 (NH) and 1740 cm^{-1} (ester); UV 242 and 290 nm; DC 215 (+), 235 (+), and 295 nm (+); MS, *m/e* 338 (23), 310 (18), 149 (28), 136 (9), 124 (21), 109 (100); ^1H NMR (240 MHz) δ 7.4–6.6 (4 H aromatic), 3.85 (s, 3 H, CO_2CH_3).

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Registry No. **2** isomer A, 62960-71-8; **2** isomer B, 70471-41-9; **6**, 70471-42-0; **7**, 62908-27-4; **8a**, 59086-85-0; **8b**, 59086-86-1; **8b** α-phenylbutyrate ester, 70471-43-1; **9**, 6792-12-7; **10a**, 59086-87-2; **10b**, 59086-89-4; **11**, 11034-66-5; **12**, 59086-88-3; **13**, 59129-64-5; **14a**, 6801-25-8; **14b**, 26568-42-3; **16**, 70471-44-2; **17** isomer A, 70560-81-5; **17** isomer B, 26749-18-8; **18**, 70471-45-3; **19**, 5001-20-7; **21**, 70471-46-4; **22**, 28161-78-6.

(29) N. J. Cone, R. Miller, and N. Neuss, *J. Pharm. Sci.*, **52**, 688 (1963).
(30) G. H. Aynilian, S. G. Weiss, G. A. Cordell, D. J. Abraham, F. A. Crane, and N. R. Farnsworth, *J. Pharm. Sci.*, **63**, 536 (1974).