7.8, 1.7 Hz, 1 H, 8-H); CIMS, m/z (rel intensity) 355 ($M + H^+$, 100), 297 (9); EIMS, m/z (rel intensity) 354 (M^+, 100), 323 (85); exact mass calcd for $C_{20}H_{18}O_6$ (M^+) 354.1103, found 354.1099.

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Supplementary Material Available: Tables of the atomic positions, temperature factors, bond lengths, and bond angles (2 pages). Ordering information is given on any current masthead page.

Biomimetic Alkaloid Syntheses. 15. Enantioselective Syntheses with Epichlorohydrin: Total Syntheses of (+)-, (-)-, and (±)-Vindoline and a Synthesis of (-)-Vindorosine

Martin E. Kuehne,* David E. Podhorez, Tshilundu Mulamba, and William G. Bornmann

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

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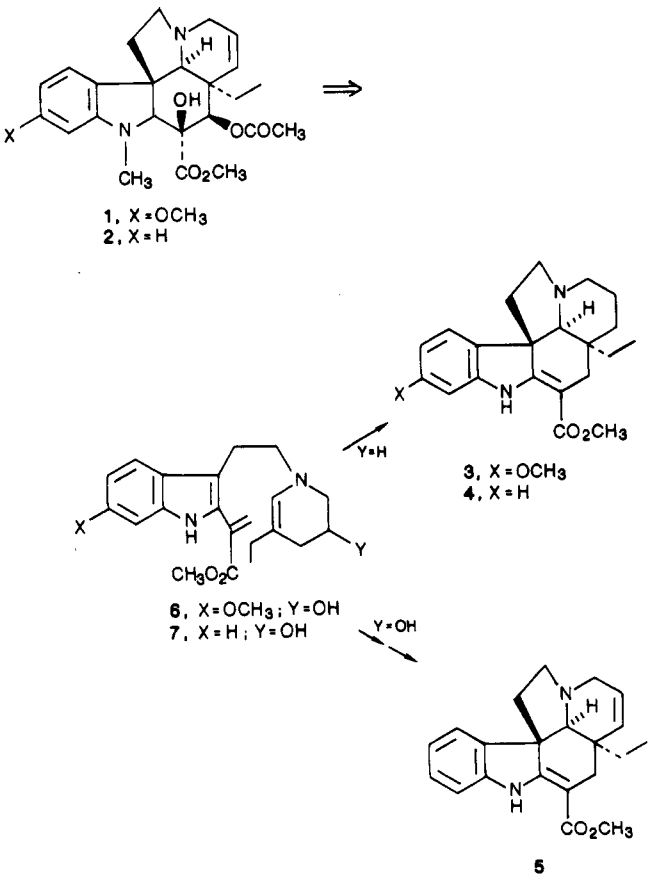
Total syntheses of vindoline (1) in racemic as well as in each enantiomeric form and of (-)-vindorosine (2) are described. They were achieved by generation and diastereoselective cyclizations of 14-hydroxysecodine intermediates **6** and **7**. The subsequent oxidative elaboration of ring E was also studied with 3-oxotabersonine (**24**), 3-oxovincadifformine (**26**), and 14β-hydroxyvincadifformine (**15**). N^a-Methyltabersonine (**22**) was oxidized to a ring-D-contracted α-keto lactam, **23**.

Vindoline (1), the major alkaloid obtained from *Vinca rosea* Linn, is of particular interest because of its biosynthetic[1] and synthetic[2-7] role as a precursor of the carcinostatic alkaloid drugs vinblastine and vincristine. In this report we describe some of our results leading to the first enantioselective total syntheses of vindoline (1) as well as reactions of related compounds. The compounds and structures in this paper are designated as **a** when racemic, as **b** when in the natural (-)-vindoline series, and as **c** when they are in the corresponding (+) enantiomeric series.

Previous studies, utilizing different synthetic strategies, had provided vindoline (1) and vindorosine (2) as racemates.[8-14] Our alternative approach was governed by a desire to utilize the biomimetic principles of secodine cyclizations, which had already provided us with syntheses of ervinceine (3), vincadifformine (4), and tabersonine (5), the latter two in an enantioselective as well as in a racemic

Scheme I



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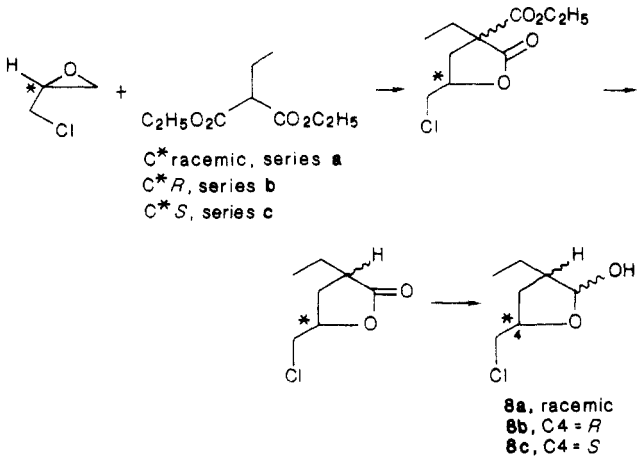
Scheme II



mode[15-20] (Scheme I). Subsequent generation of the ring E oxygenation pattern of vindoline (1) would then provide an expeditious route to the target compounds.[21]

Our earlier enantioselective generation of (−)-tabersonine (**5**), while giving this compound in good enantiomeric purity (99+% ee), had really been only an offshoot of a vincadifformine (**4**) synthesis, and it had resulted in a relatively low yield (10% or 28% by two alternative methods) in the last two steps of the synthesis.[20] It became clear that a better reaction sequence was required for a more effective generation of the key chiral 14-hydroxysecodine intermediates **6** and **7**. Such a route was found in condensation of the C-4 enantiomerically defined 5-chloro-2-ethyl-4-hydroxypentanal lactol (**8**) with the indoloazepines **9** or **10** (Scheme III). The required lactol (also prepared as a racemate (**8a**) was generated in two C-4 enantiomeric series (**8b,c**) from the two chiral epichlorohydrins by alkylation of diethyl 2-ethylmalonate, decarboethoxylation, and reduction of the resultant lactones (Scheme II).

On condensation of the aldehyde equivalent lactols **8** with the indoloazepines **9** and **10**,[16,17,22] the anticipated bridged indoloazepines (**11** and **12**) were detected but not isolated.[23] They were allowed to undergo in situ N-alkylation and fragmentation, to generate the transient 14-hydroxysecodines **6a–c** and **7b**. Intramolecular cycloaddition of these reactive intermediates then provided pairs of 14-hydroxyervinceine (**13a–c** and **14a–c**) and 14-hydroxyvincadifformine (**15b** and **16c**) in the two reaction series. In methanol the 14-axial hydroxy compounds, **13a–c** and **15b**, were obtained as major products from the secodines **6a–c** and **7b**, accompanied by the minor 14-equatorial hydroxy diastereomers **14a–c** and **16c**. This critical diastereoselectivity may be understood as a consequence of the 14-hydroxysecodine's (**6a–c** and **7b**) cyclization proceeding by a stereoelectronically favored addition of the acrylate moiety to the secodine's hydroxypiperideine segment, with the latter in a preferred (OH solvated and bulky) 14-hydroxy equatorial conformation (**6^Xa–c** and **7^Xb**). It may be noted that in the resultant major products **13a–c** and **15b**, the conformation of the 14-hydroxy group is, however, inverted relative to that in the major hydroxysecodine conformers **6^Xa–c** and **7^Xab**.

The diastereomeric alcohols **13a–c** and **15b** vs. **14a–c** and **16c** were readily separated in the course of chromatographic purification of the reaction products. Only the major 14-axial hydroxy products **13a–c** and **15b** undergo facile dehydration with formation, respectively, of 11-methoxytabersonine (**17a–c**) or tabersonine (**5b**) on heating with triphenylphosphine and carbon tetrachloride in acetonitrile. The minor equatorial 14-hydroxy products **14a–c** and **16c** undergo intramolecular N-alkylation and rearrangements.[18] The consequent difference in reaction product types is of potential interest for the preparative purification of the major diastereomeric product series.

For the following oxidative elaboration of ring E of 11-methoxytabersonine (**17a–c**) and of tabersonine (**5b**) we turned to phenylselenoylation, based on a speculative vinylogy of an oxidation of these NH enamines to previous oxidations of NH amines to imines by such a process.[24,25] The oxidation of 11-methoxytabersonine (**17a–c**) and of tabersonine (**5b**) to transient $\Delta^{16,17}$-unsaturated imines **18a–c** and **19b** by phenylseleninic anhydride and their hydration thus furnished the desired 17β-hydroxy products **20a–c** and **21b** in high yield, in agreement with parallel results obtained by Danieli.[21] The vinylogous analogy to other NH amine oxidations was sustained by the observation that a reaction of N^a-methyltabersonine (**22b**) under slightly more vigorous conditions did not result in oxidation of ring E but gave instead the 3-nor keto lactam **23b** in 67% yield. (A similar oxidative ring D contraction of 17-deacetoxyvindorosine, on reaction with iodine in aqueous acid, has previously been observed by Lévy.[26]) N^a-Methyl-3-oxotabersonine and N^a-methylvincadifformine (minovine) were not oxidized on heating with phenylseleninic anhydride, but 3-oxotabersonine (**24a,b**) readily gave the 17-hydroxy derivative **25a,b**, and 3-oxovincadifformine (**26a,b**) was also oxidized (Scheme IV).

The secondary hydroxylation step of this sequence was found to be very structure dependent. While an isolable $\Delta^{16,17}$-unsaturated imine, **27b**, derived from vincadifformine (**4b**) could be substantially (4:1) hydrated at equilibrium,[21] it was found that the corresponding 3-oxo lactams **28a,b** provided only a 1:1 equilibrium mixture with their hydration products **29a,b**. Oxidation of 14β-hydroxyvincadifformines (**15a,b**)[18,27] with phenylseleninic anhydride led only to the C14–C17 ethers **30a,b**.

These ethers differ from all other amines described in this study in that they have a conformationally inverted N^b, which places its lone-pair cis periplanar to the C-21 methine H. As a consequence, these compounds show no Wenkert–Bohlmann bands[28] in their IR spectra and in NMR spectra the hydrogen at C-21 is shifted downfield from its usual position at δ 2.8 to 4.0.[29,30]

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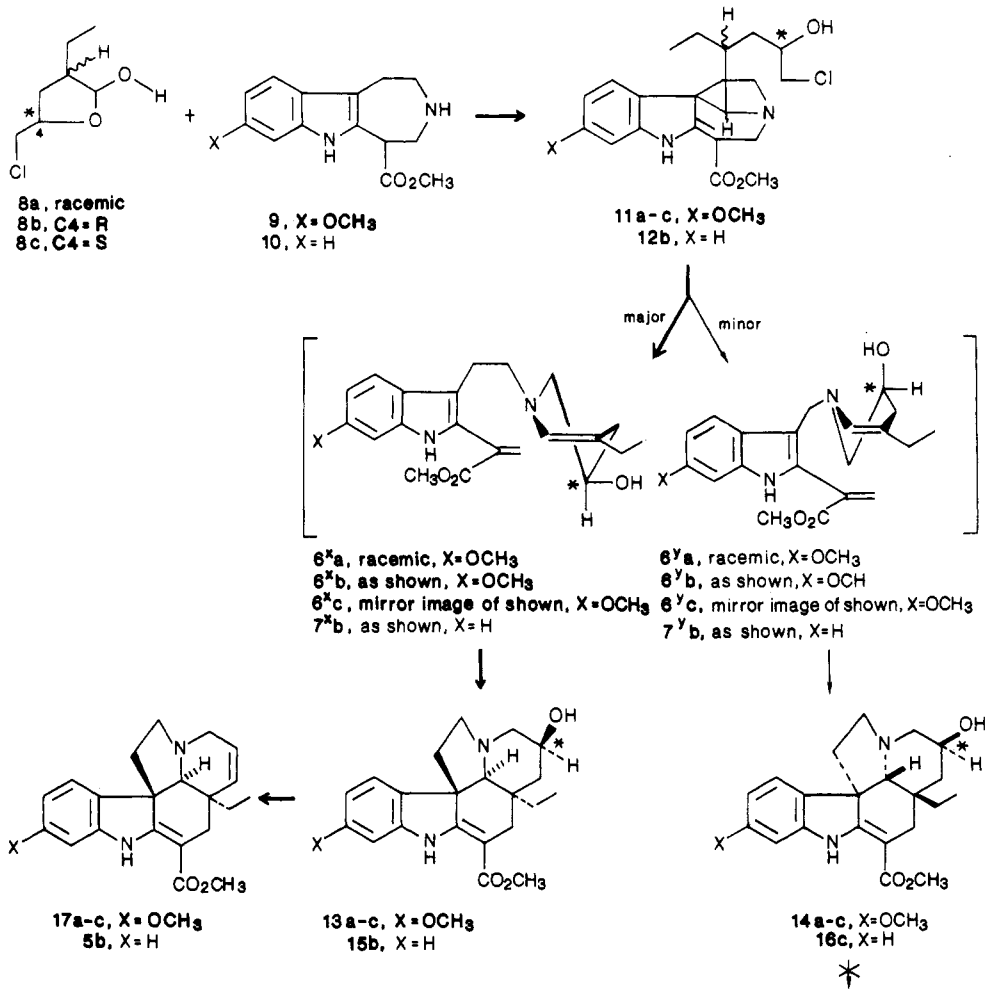
Scheme III



Oxidation of the corresponding 14-carbobenzyloxy alcohol derivative **31b** provided only the unsaturated imine **32b**, which resisted hydration. Thus, the stereospecific, axial introduction of a hydroxyl function at C-17, with a basic or neutral N^b, and lack of formation of an epimeric hydration product, when the axial approach is blocked, suggests that this hydration may be subject to steric and stereoelectronic control factors.[31]

Further elaboration of our intermediates **20a–c** and **21b** to vindoline (**1a–c**) and vindorosine (**2b**) met initially with great difficulty.[32] It was achieved by an oxidation of these vinylogous urethanes (**20a–c** and **21b**) with *m*-chloroperoxybenzoic acid, followed directly by reduction of the resulting imines with sodium cyanoborohydride and an in situ reductive N^a-methylation with formaldehyde. One may note here that while the analogous oxidation step with *m*-chloroperoxybenzoic acid is known to proceed well with vincadifformine (**4b**, 75%),[26] this oxidation was less satisfactory with tabersonine (**5b**, 38–40%).[26,33] In the oxidation of the 17-hydroxy compounds **20a–c** and **21b** a short reaction time gave little or no N^b-oxide product, even with 1.9 equiv of the peroxy acid (Attempts to push the oxidation to the N^b-oxide stage, followed by reduction later in the sequence, affected the final product yields adversely). The resultant 16-hydroxy imine products **33a–c** and **34b** were particularly unstable under acidic conditions. Consequently, the imine reduction and reductive alkylation steps could only be achieved by solution of the hydroxy imines **33a–c** and **34b** in a mixture of 40% aqueous formaldehyde and sodium cyanoborohydride, followed by the addition of acetic acid. In general, yields of the 16,17β-diols **35a–c** and **36b** were around 35%. A final acylation with acetyl chloride provided vindoline (**1a–c**) and vindorosine (**2b**).

Since this total synthesis of vindoline was carried through with each enantiomeric series as well as with racemic compounds, the antipode **1c** of natural vindoline (**1b**) has now become available for the synthesis and biological evaluation of the antipode of vinblastine class compounds.

Experimental Section

General Methods. All reactions were carried out under nitrogen or argon. Melting points were obtained in a heated oil bath or on a Kofler micro hotstage with thermometers calibrated against a National Bureau of Standards certified set. NMR spectra were recorded on Bruker 250-MHz or 270-MHz instruments. Mass spectra were obtained with a Finegan 4610 quadrupole instrument at 70 eV, calibrated with perfluorotributylamine and bis(pentafluorophenyl)phenylphosphine for compounds below M_r 600 and with tris(perfluorononyl)-*s*-triazine for higher molecular weight

(30) In the C15–C16 ether desacetylcathovaline, the C21 methine hydrogen is found at δ 3.68; Diatta, L.; Langlois, Y.; Langlois, N.; Potier, P. *Bull. Soc. Chim. Fr.* **1975**, 671.

(31) Addition at C17 to the unsaturated imine double bond can be expected to progress along an axis bisecting the H–C17–C20 angle and at about 110° to the double bond, with repulsion by the axial ethyl substituent at C20 on the side of its location. Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 738.

(32) The timely publication from the Danieli group,[21] which claimed this sequence in 55% yield, and procedural alterations kindly provided by Prof. Danieli, unfortunately resulted only in very complex reaction mixtures and no isolable product in our laboratories.

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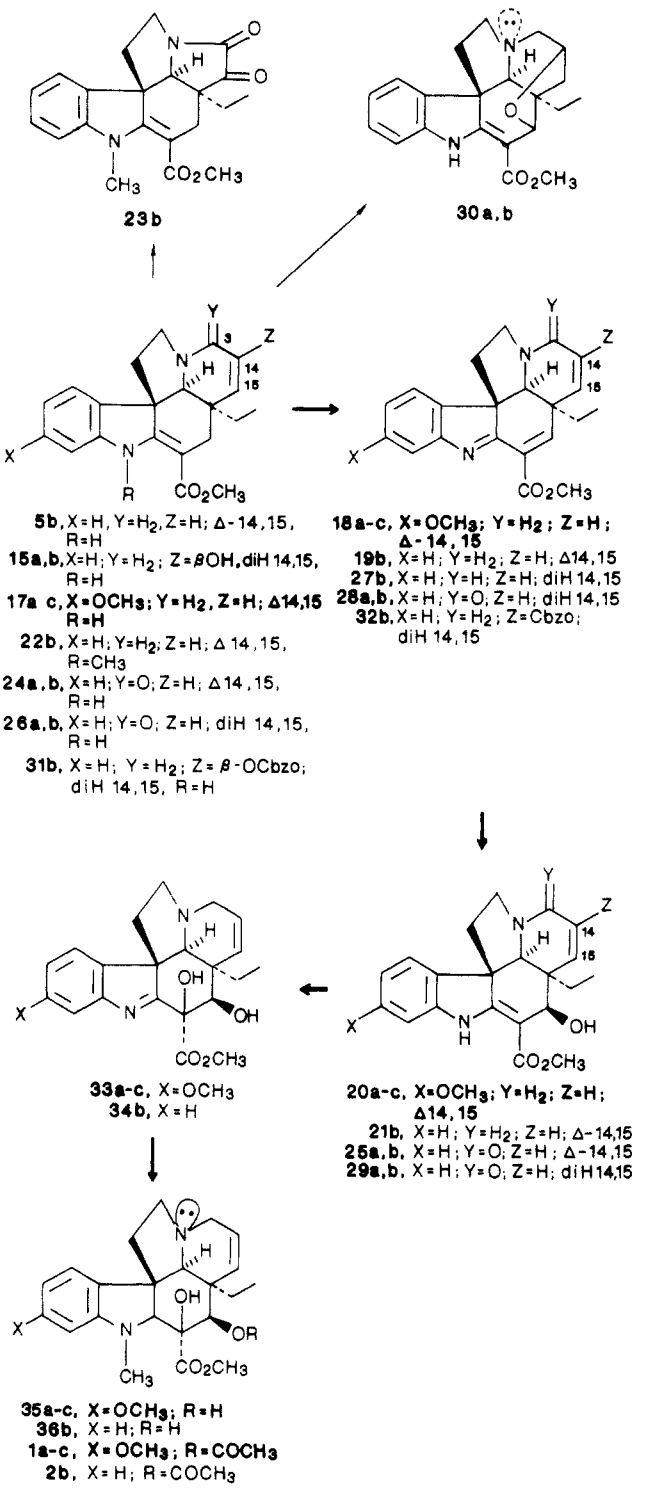
Scheme IV



compounds. IR spectra were obtained with a Nicolet 6000 FT or a Perkin-Elmer 267 grating instrument. UV spectra were recorded on Perkin-Elmer 202 or 402 instruments. TLC data were obtained with E. Merck 60F-254 precoated silica on alumina sheets. For centrifugal chromatography a Harrison Chromatotron was used with E. Merck 60 PF 254 silica with gypsum. For column chromatography 60–200 mesh Baker R3405 silica was used. Microanalyses were provided by George Robertson, Robertson Laboratories, Florham Park, NJ. Optical rotations were measured with a Perkin-Elmer 141 polarimeter.

2-Benzyl-7-methoxy-1,2,3,4-tetrahydro-5*H*-pyrido[4,3-*b*]indole. This compound was prepared by an improved procedure relative to that reported previously.[16] To a slurry of 3.2 g (18 mmol) of (*m*-methoxyphenyl)hydrazine hydrochloride in 40 mL of absolute ethanol was added 3.5 mL (19 mmol) of *N*-benzyl-4-piperidone. After stirring for 1 h at 20 °C, 40 mL of a saturated solution of HCl in ethanol was added, and the slurry was heated at reflux for 2 h. The resultant solution was cooled and concentrated under vacuum, water and chloroform were added, and the mixture was then basified with sodium carbonate. Separation and reextraction of the aqueous phase with chloroform, washing of the combined extracts with saturated brine, and concentration of the Na_2SO_4 dried solution produced a residue which was heated at reflux for 10 min in 20 mL of 95% ethanol. On cooling 3.0 g (57%) of product crystallized: mp 170–172 °C (reported,[16] 172–173 °C).

14(a)-Hydroxyervinceine [13a (Racemic), 13b (14*S*), 13c (14*R*)] and 14(e)-Hydroxyervinceine [14a (Racemic), 14b (14*S*), 14c (14*R*)]. For **13a** and **14a**: A slurry of 840 mg (3.06 mmol) of the 8-methoxyindoloazepine **9** prepared from the above methoxy-γ-carboline,[16,17] 30 mg of boric acid and 655 mg (3.98 mmol) of the racemic lactol **8a**,[18] in 25 mL of anhydrous methanol was heated at reflux for 24 h. Addition of 860 μL (6 mmol) of triethylamine was followed by 12 h at reflux, concentration, and partitioning between water and dichloromethane. The organic extracts were washed with saturated brine, dried (Na_2SO_4), and concentrated. Chromatography on 50 g of silica gel, eluting with 1% ethanol in chloroform, gave 897 mg (75%) of a first eluted, amorphous 14-axial hydroxy product **13a** and 213 mg (18%) of the amorphous 14-equatorial hydroxy product **14a**. In some experiments **13a** was contaminated by recovered lactol **8a**, which could be separated by use of 2× the above amount of silica gel. Its presence did not significantly affect the subsequent dehydration step to **17a**.

For **14a**: TLC (silica gel, 10% ethanol in $CHCl_3$) R_f 0.47; IR (film) ν_{max} 3370, 2960, 2935, 2860, 2835, 2780, 1670, 1610, 1495, 1455, 1435, 1255, 1220, 1190, 1165, 1145, 1120, 1100, 1045, 1025, 945, 790, 730 cm^{-1}; 250-MHz NMR ($CDCl_3$) δ 0.62 (t, 3 H), 0.80–2.70 (m, 12 H), 2.88 (t, 1 H), 3.36 (m, 1 H), 3.75 (2 s, 6 H), 4.06 (m, 1 H), 6.37 (m, 2 H), 7.06 (d, 1 H), 8.86 (br s, 1 H); 70-eV direct insertion probe mass spectrum, *m/z* (relative intensity) 385 (25), 384 (M^+, 100), 268 (3), 155 (8), 141 (8), 140 (89); UV-(methanol) λ_{max} 230, 245, 325 nm.

Starting with 466 mg (1.70 mmol) of the 8-methoxyindoloazepine **9** and the 4*S* lactol **8b**,[18,20] the same procedure gave 460 mg of the crude amorphous 14*S*,21*S* product **13b**, $[\alpha]^{24}_D$ −250° (*c* 0.12, methanol) which contained about 25% of lactol **8b** (about 345 mg, 52% yield of **13b**) and 105 mg of the crude amorphous 14*S*,21*R* product **14c**, $[\alpha]^{24}_D$ +275° (*c* 0.12, methanol). Product **13b** was of adequate purity for the subsequent dehydration step.

From 274 mg (1.0 mmol) of the 8-methoxyindoloazepine **9** and the (4*R*)-lactol **8c**[18,20] but by use of 2× the amount of silica gel for chromatography, this method gave 204 mg (52%) of the amorphous 14*R*,21*R* product **13c**, $[\alpha]^{24}_D$ +336° (*c* 0.14, methanol) and 44 mg (12%) of the amorphous 14*R*,21*S* product **14b**, $[\alpha]^{24}_D$ −350° (*c* 0.12, methanol).

For **13c**: TLC (silica gel, 10% ethanol in $CHCl_3$) R_f 0.53; IR (film) ν_{max} 3370, 2965, 2935, 2880, 2835, 2785, 1670, 1610, 1495, 1455, 1435, 1260, 1225, 1190, 1145, 1110, 1075, 1045, 1025, 945, 805 cm^{-1}; 250-MHz NMR ($CDCl_3$) δ 0.60 (t, 3 H), 0.80–2.80 (m, 12 H), 2.93 (t, 1 H), 3.16 (d, 1 H), 3.72 (2 s, 6 H), 3.93 (br s, 1 H), 6.39 (d, 2 H), 7.07 (d, 1 H), 8.91 (br s, 1 H); 70-eV direct insertion probe mass spectrum, *m/z* (relative intensity) 385 (13), 384 (M^+, 42), 149 (8), 147 (26), 141 (10), 140 (100), 129 (11), 117 (12), 115 (11); UV (methanol) λ max 225, 250, 330 nm.

11-Methoxytabersonine [17a (Racemic), 17b (21*S*), 17c (21*R*)]. A solution of 897 mg (2.30 mmol) of racemic 14(a)-hydroxyervinceine (**13a**) and 1.21 g (4.62 mmol) of triphenylphosphine in 8 mL of dry acetonitrile and 8 mL of dry CCl_4 was heated at 70 °C for 30 min. The cooled reaction mixture was diluted with dichloromethane and washed with dilute ammonium hydroxide and with saturated brine. The organic solution was dried (Na_2SO_4) and concentrated, and the residue was chromatographed on 50 g of silica gel, eluting with 5% ethyl acetate in hexanes, to provide 598 mg (71%) of amorphous 11-methoxytabersonine.[34] For **17a**: TLC (silica gel, ethyl acetate) R_f 0.64; IR (film) ν_{max} 3370, 3025, 2960, 2940, 2880, 2860, 2840, 2780, 2710,

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1675, 1610, 1495, 1455, 1435, 1375, 1355, 1330, 1255, 1185, 1150, 1110, 1025, 945, 800, 760, 735 cm^{-1}; 250-MHz NMR ($CDCl_3$) δ 0.64 (t, 3 H), 0.80–1.10 (m, 2 H), 1.75 (dd, 1 H), 2.03 (m, 1 H), 2.35–2.75 (m, 4 H), 3.02 (t, 1 H), 3.17 (d, 1 H), 3.45 (dd, 1 H), 3.78 (2s, 6 H), 5.74 (m, 2 H), 6.39 (m, 2 H), 7.11 (d, 1 H), 8.95 (br s, 1 H); direct insertion probe 70-eV mass spectrum, m/z (relative intensity) 368 (6), 367 (33), 366 (M^+, 95), 260 (5), 259 (35), 244 (7), 226 (4), 200 (12), 198 (7), 184 (5), 158 (4), 135 (100), 122 (29), 121 (39), 108 (9), 107 (42); UV (methanol) λ_{max} 219, 248, 328 nm. These data matched those obtained with a sample of natural (-)-11-methoxytabersonine.

A perchlorate salt of **17a** had mp 220–222 °C. Anal. Calcd for $C_{22}H_{27}N_2O_7Cl$: C, 56.59; H, 5.83; N, 6.00. Found: C, 56.23; H, 5.86; N, 5.86.

From 136 mg of crude (75%, 104 mg) (-)-14β-hydroxyervinceine (**13b**) this procedure gave 80 mg (81%) of amorphous (-)-11-methoxytabersonine (**17b**), $[\alpha]^{24}_D$ -213° (*c* 0.096, $CHCl_3$). A sample of natural 11-methoxytabersonine had $[\alpha]^{24}_D$ -211° (*c* 0.114, $CHCl_3$). The enantiomeric excess of the synthetic reaction product (**17b**) was determined to be >99% ee by the chiral shift method using 0.3 M $Eu(hfc)_3$.[20] This method resulted in a shift of the uncomplexed methoxy ester signal at δ 3.78 to 5.09 for the complexed (-) enantiomer and to δ 5.59 for the complexed (+) enantiomer.

Dehydration of 80 mg of (+)-14α-hydroxyervinceine (**13c**) by the same procedure gave 51 mg (68%) of amorphous (+)-11-methoxytabersonine (**17c**), $[\alpha]^{23}_D$ +218° (*c* 0.110, $CHCl_3$) in >99% ee.[20]

(-)-Tabersonine (5b). A reaction of 640 mg (2.60 mmol) of the indoloazepine **10**[22] with the chlorolactol **8b**, according to procedure given for the preparation of **13a** and **14a**, provided 760 mg of crude 14β-hydroxyvincadifformine (**15b**), contaminated by <40% of recovered lactol **8b** (NMR) (about 49% corrected), $[\alpha]^{24}_D$ -235° (*c* 0.26, methanol), and 112 mg (12%) of amorphous 14α-hydroxyvincadifformine (**16c**), $[\alpha]^{24}_D$ +367° (*c* 0.90, methanol). Dehydration of 354 mg of the crude alcohol **15b** according to the procedure given for **13a** provided 143 mg (71%, corrected) of amorphous tabersonine (**5b**); $[\alpha]^{24}_D$ -255° (*c* 0.11, ethanol), reported[20] $[\alpha]^{27}_D$ -240° (*c* 0.15, ethanol). TLC (silica gel, ethyl acetate) R_f 0.60; UV (ethanol) λ_{max} 230, 302, 333 nm; IR (film) ν_{max} 3380, 3060, 3025, 2975, 2920, 2880, 2860, 2790, 2715, 1675, 1605, 1480, 1465, 1435, 1380, 1330, 1295, 1275, 1255, 1235, 1205, 1165, 1115, 1040, 1015, 945, 920, 815, 800, 740, 700 cm^{-1}; 250 MHz NMR ($CDCl_3$) δ 9.00 (br s, 1 H), 7.11–7.25 (m, 2 H), 6.80–6.91 (m, 2 H), 5.69–5.82 (m, 2 H), 3.77 (s, 3 H), 3.46 (dd, 1 H), 3.18 (d, 1 H), 3.05 (t, 1 H), 2.68 (m, 2 H), 2.40–2.60 (m, 2 H), 2.07 (m, 1 H), 1.79 (dd, 1 H), 0.80–1.10 (m, 2 H), 0.64 (t, 3 H); direct insertion probe mass spectrum, m/z (relative intensity) 337 (9), 336 (M^+, 35), 229 (11), 214 (7), 168 (20), 167 (14), 158 (16), 154 (15), 136 (10), 135 (100), 134 (15), 122 (37), 121 (38), 115 (13), 108 (22), 107 (62), 106 (12).

17-Hydroxy-11-methoxytabersonine [20a (Racemic), 20b (21*S*), 20c (21*R*)]. To a solution of 485 mg (1.32 mmol) of (±)-11-methoxytabersonine (**17a**) in 15 mL of dry benzene was added 523 mg (1.45 mmol) of benzeneseleninic anhydride. The slurry was heated at reflux for 30 min, 5 mL of water was added, and the mixture was allowed to cool to room temperature. After concentration under vacuum, the residue was taken up in dichloromethane and washed with saturated sodium bicarbonate solution and brine. The dried (Na_2SO_4) solution was concentrated and chromatographed on 50 g of silica gel. Elution with dichloromethane followed by 3% methanol in dichloromethane provided 470 mg (93%) of product. Alternatively, 343 mg (68%) of amorphous product without minor impurities could be obtained by elution with 3:2 ethyl acetate/hexanes, following elution of initial diphenyldiselenide.

For **20a**: TLC (silica gel, ethyl acetate) R_f 0.32; IR (film) ν_{max} 3355, 3030, 2965, 2940, 2880, 2795, 1675, 1605, 1495, 1450, 1435, 1375, 1330, 1250, 1235, 1215, 1185, 1160, 1145, 1110, 1040, 1020, 965, 910, 790 cm^{-1}; 250-MHz NMR ($CDCl_3$) δ 0.64 (t, 3 H), 0.96 (m, 2 H), 1.79 (dd, 1 H), 2.47 (m, 1 H), 2.63 (m, 1 H), 2.88 (d, 1 H), 3.14 (m, 2 H), 3.56 (dd, 1 H), 3.82 (2s, 6 H), 4.69 (d, 1 H), 5.83 (d, 1 H), 6.04 (m, 1 H), 6.43 (m, 2 H), 6.65 (br s, 1 H), 7.08 (d, 1 H), 9.16 (br s, 1 H); direct insertion probe 70-eV mass spectrum, m/z (relative intensity) 382 (M^+, 25), 365 (14), 364 (54), 335 (37), 306 (8), 275 (8), 257 (16), 224 (9), 198 (19), 136 (11), 135 (100), 134 (30), 122 (23), 121 (68), 108 (21), 107 (38); UV (methanol) λ_{max} 225, 253, 330 nm.

17-Hydroxylation of 245 mg of (-)-11-methoxytabersonine (**17b**) and chromatography of the product with ethyl acetate/hexane gave 198 mg (77%) of amorphous alcohol **20b** $[\alpha]^{25}_D$ -196° (*c* 0.074, methanol). From 660 mg of (+)-11-methoxytabersonine (**17c**) 360 mg (52%) of the purified, amorphous product **20c**, with $[\alpha]^{25}_D$ +200° (*c* 0.07, methanol) was obtained.

(-)-17-Hydroxytabersonine (21b). By use of the procedure described for the 11-methoxy analogue **17a,c**, 1 g of (-)-tabersonine furnished, after chromatography, 980 mg (93%) of the amorphous 17-hydroxylation product **21b**. TLC (silica gel, 3% methanol in dichloromethane) R_f 0.33 (CAS blue); UV (ethanol) λ_{max} 220, 295, 328 nm; IR (film) ν_{max} 3380, 3340, 3080, 2860, 2770, 1665, 1630, 1608, 1470, 1457, 1280, 1255, 1180, 720 cm^{-1}; 250-MHz NMR ($CDCl_3$) δ 9.20 (s, 1 H^{NH}), 7.15 (t, 2 $H^{10,11}$) 6.92 (d, 1 H^9), 6.88 (d, 1 H^{12}), 6.65 (s, 1 H^{OH}), 6.08 (dd, 1 H^{14}), 5.83 (d, 1 H^{15}), 4.69 (d, 1 H^{17}), 3.80 (s, 3 H^{OCH_3}), 3.55 (dd, 1 H^3), 3.16 (dd, 1 H^5), 3.10 (d, 1 H^3), 2.81 (d, 1 H^{21}), 2.70 (m, 1 H^5), 2.46 (m, 1 H^6), 1.81 (dd, 1 H^6), 0.92 (m, 2 H^{19}), 0.60 (t, 3 H^{18}); direct insertion probe 70-eV mass spectrum, m/z (relative intensity) 352 (M^+, 6), 334 (30), 305 (19), 218 (10), 168 (15), 167 (11), 135 (100), 134 (27), 122 (27), 121 (66), 107 (42); $[\alpha]^{23}_D$ -256° (*c* 0.09, methanol).

Vincadifformine 14,17-Oxide (30a,b). A slurry of 216 mg (0.60 mmol) of benzeneseleninic anhydride and 194 mg (0.55 mmol) of (±)-14β-hydroxyvincadifformine (**15a**)[18] in 8 mL of dry benzene was heated near 60 °C for 30 min. The cooled reaction mixture was concentrated under vacuum and the residue dissolved in dichloromethane. After the solution had been washed with saturated sodium bicarbonate and brine and concentrated, the organic extracts were chromatographed on silica gel, eluting with 5% ethanol in chloroform. After initial diphenyldiselenide fractions, 93 mg (49%) of the amorphous product was collected. TLC (silica, 40% ethanol in chloroform) R_f 0.44; IR (film) ν_{max} 3460, 3055, 2965, 2960, 2880, 2855, 1675, 1605, 1475, 1465, 1435, 1390, 1280, 1245, 1195, 1125, 1105, 1045, 1030, 930, 865, 785, 745, 730 cm^{-1}; 250-MHz NMR ($CDCl_3$) δ 0.73 (t, 3 H), 1.01 (m, 2 H), 1.75–2.15 (m, 4 H), 2.75 (d, 1 H), 3.04 (m, 1 H), 3.17 (m, 1 H), 3.32 (d, 1 H), 3.79 (s, 3 H), 4.04 (br s, 1 H^{21}), 4.43 (br d, 1 H^{14}), 4.62 (d, 1 H^{17}), 6.93 (m, 2 H), 7.26 (m, 2 H), 9.29 (br s, 1 H); direct insertion probe 70-eV mass spectrum, m/z (relative intensity) 353 (26), 352 (M^+, 58), 323 (13), 293 (12), 253 (14), 238 (13), 227 (17), 206 (11), 194 (10), 180 (11), 167 (12), 154 (13), 123 (47), 122 (100), 115 (11), 110 (17), 108 (79); UV (methanol) λ_{max} 212, 250, 325 nm; UV (ethanol) λ_{max} 232, 297, 324 nm.

By the same procedure, starting from 180 mg of the crude (-)-14β-hydroxyvincadifformine, obtained above, 86 mg (81% corrected) of the amorphous ether **30b** was obtained; $[\alpha]^{24}_D$ -328° (*c* 0.64, ethanol).

N^a-Methyl-14,15-dioxo-D-norvincadifformine (23b). A mixture of 230 mg (0.657 mmol) of N^a-methyltabersonine, 316 mg (0.877 mmol) of benzeneseleninic anhydride and 10 mL of dry benzene was heated at reflux for 2 h. The reaction mixture was concentrated under vacuum and the residue dissolved in dichloromethane. After being washed with 10% sodium bicarbonate and water, the dried ($MgSO_4$) solution was concentrated and the residue chromatographed on silica gel, eluting with 1:2 ethyl acetate/pentane, to provide 160 mg (67%) of the amorphous lactam **23**. TLC (silica gel, ethyl acetate) R_f 0.61 (CAS blue); UV (ethanol) λ_{max} 220, 302, 325 nm; IR (film) ν_{max} 3040, 3000, 2960, 2900, 2850, 1760, 1730, 1690, 1600, 1490, 1230, 750 cm^{-1}; 250-MHz ^1H NMR ($CDCl_3$) δ 7.30 (m, 2 $H^{9,10}$), 7.03 (t, 1 H^{11}), 6.90 (d, 1 H^{12}), 4.45 (dd, 1 H^5), 4.20 (s, 1 H^{21}), 3.75 (s, 3 H^{OCH_3}), 3.60 (ddd, 1 H^5), 3.36 (s, 3 H^{NCH_3}), 2.78 (d, 1 H^{17}), 2.20 (d, 1 H^{17}), 1.97 (m, 2 H^6), 1.70 (m, 1 H^{19}), 1.55 (m, 1 H^{19}), 0.83 (t, 3 H^{18}); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 202.86, 166.53, 161.27, 159.60, 147.06, 135.49, 129.11, 121.67, 120.90, 108.81, 91.52, 65.99, 55.51, 54.00, 51.30, 45.12, 42.30, 35.48, 35.44, 22.69, 8.92; direct insertion probe 70-eV mass spectrum, m/z (relative intensity) 366 (M^+, 34), 355 (1), 241 (7), 229 (13), 228 (100), 194 (6), 168 (13).

17β-Hydroxy-3-oxotabersonine [25a (Racemic), 25b (-)]. A mixture of 0.200 g (0.571 mmol) of 3-oxotabersonine (**24a**) or **24b**,[35,36] 0.226 g (0.628 mmol) of benzeneseleninic anhydride and

(35) Racemic 3-oxotabersonine (**25a**) was prepared by a total synthesis by W. G. Bornmann, manuscript in preparation.

7 mL of dry benzene was heated at 70 °C for 3 h. The cooled mixture was concentrated under vacuum and the residue dissolved in 25 mL of dichloromethane. After being washed with 50 mL of cold saturated sodium bicarbonate and brine, the dried ($MgSO_4$) solution was concentrated under vacuum and the residue subjected to centrifugal chromatography on a 2-mm silica gel disc, by eluting with ethyl acetate. After removal of yellow selenium compounds in initial fractions, the 17-hydroxy compound was collected. Racemic **25a** crystallized from ether to give 0.115 g (55%); mp 156–157 °C. A sample recrystallized from aqueous methanol and then from benzene/dichloromethane had mp 191–193 °C. TLC (silica gel, ethyl acetate) R_f 0.3 (CAS blue); UV (ethanol) λ_{max} 220, 295, 326 nm; IR (KBr) ν_{max} 3353, 3220, 3022, 2972, 2947, 1665, 1626, 1608, 1466, 1245, 1201, 1110, 804, 742 cm^{-1}; 250-MHz NMR ($CDCl_3$) δ 9.33 (s, 1 H^{NH}) 7.25 (m, 2 $H^{9,10}$), 6.95 (m, 2 $H^{11,12}$), 6.39 (d, 1 H^{15}), 6.23 (d, 1 H^{14}), 4.70 (dd, 1 H^{17}), 4.35 (dd, 1 H^5), 4.20 (br s, 1 H^{21}), 3.80 (s, 3 H^{OCH_3}), 3.40 (m, 1 H^5), 2.71 (m, 1 H^6), 1.95 (dd, 1 H^6), 1.12 (m, 2 H^{19}), 0.80 (t, 3 H^{18}); direct insertion probe 70-eV mass spectrum, m/z (relative intensity) 348 (M^+ – 18, 98), 319 (81), 280 (22), 261 (13), 260 (37), 205 (12), 204 (24), 140 (12), 130 (12), 124 (7), 116 (22), 115 (81), 113 (11), 108 (14), 103 (13), 102 (26). Anal. Calcd for $C_{21}H_{22}N_2O_4$: C, 68.83; H, 6.05; N, 7.65. Found: C, 68.48; H, 6.24; N, 7.15.

(±)-3-Oxo-1,17-didehydrovincadifformine (28a) and (±)-17β-Hydroxy-3-oxovincadifformine (29b). Following the above procedure given for the oxidation of 3-oxotabersonine, 0.500 g of (±)-3-oxovincadifformine[23] was oxidized with phenylseleninic anhydride to give 0.266 g (≃ 52%) of a product which was initially a 3:1 mixture of the imine **28a** and the alcohol **29a**, according to its NMR spectrum. Heating this product at 80 °C in benzene with 2% aqueous HCl for 48 h resulted in a 1:1 mixture of these products, which did not change on further heating: TLC (silica gel, ethyl acetate) R_f 0.25 (imine?); UV (ethanol) λ_{max} 218, 230, 292, 323 nm; 270 MHz NMR ($CDCl_3$) 1:1 equilibrium mixture **28a**/**29a**. Characteristic isolated signals for **28a**: δ 4.40 (dd, 1 H^5), 3.90 (s, 3 H^{OCH_3}), 3.82 (br s, 1 H^{21}), 1 H^{17} in the aromatic region. For **29a**: δ 9.28 (s, 1 H^{NH}), 4.77 (d, J = 1.8 Hz, 1 H^{17}), 4.12 (dd, 1 H^5), 3.80 (s, 3 H^{OCH_3}), 2.58 (d, 1 H^{21}). All other proton signals of **28a** and **29a** were found to overlap.

(–)-14β-Carbobenzyloxy-1,17-didehydrovincadifformine (32b). To a solution of 400 mg (1.13 mmol) of (–)-14β-hydroxyvincadifformine (**15b**) in 8 mL of dichloromethane at 0 °C was added 166 mg (1.36 mmol) of 4-(dimethylamino)pyridine in 1 mL of dichloromethane, followed after 2 min by dropwise addition of 205 μL (1.36 mmol) of benzyl chloroformate. After stirring for 2 h at 0 °C and 10 h at 20 °C the reaction mixture was partitioned between water and dichloromethane. The dried ($MgSO_4$) and concentrated organic extract was chromatographed on silica gel. Elution with 0.5% methanol in dichloromethane furnished 336 mg (54%) of product **31b** and 170 mg of recovered starting alcohol **15b**. TLC (silica gel, 4% methanol/chloroform) R_f 0.60; UV (ethanol) λ_{max} 220, 300, 330 nm; IR (film) ν_{max} 3360, 3060, 3040, 2960, 2900, 2780, 1750, 1680, 1610, 1460, 1250, 1110, 950, 910, 740 cm^{-1}; 250-MHz NMR ($CDCl_3$) δ 8.90 (s, 1 H^{NH}), 7.40 (m, 5 H^{phenyl}), 7.15–6.82 (m, 4 H^{indole}), 5.20 (s, 2 H^{benzyl}), 4.92 (m, 1 H^{14}), 3.76 (s, 3 H^{OCH_3}), 3.32 (br d, 1 H^3), 2.93 (br dd, 1 H^5), 2.85 (d, 1 H^{17}), 2.79 (dd, 1 H^3), 2.61 (m, 1 H^5), 2.50 (br s, 1 H^{21}), 2.40 (d, 1 H^{17}), 2.12 (m, 1 H^6), 2.05 (br d, 1 H^{15}), 1.71 (dd, 1 H^{15}), 1.58 (dd, 1 H^6), 1.30 (m, 1 H^{19}), 0.90 (m, 1 H^{19}), 0.65 (t, 3 H^{18}); direct insertion probe 70-eV mass spectrum, m/z (relative intensity) 488 (M^+, 48), 343 (3), 275 (10), 274 (50), 180 (10), 168 (4), 151 (8), 149 (4), 122 (5), 107 (21), 92 (15), 91 (100).

A mixture of 330 mg (0.670 mmol) of the above product **31b**, 360 mg (1.00 mmol) of benzeneseleninic anhydride, and 10 mL of dry benzene was heated at reflux for 1 h. After addition of 1 mL of water and continued heating for 10 min, the mixture was concentrated under vacuum and dissolved in 50 mL of dichloromethane and the solution washed with 10% sodium bicarbonate. The dried ($MgSO_4$) solution was concentrated and the residue chromatographed on silica gel. Elution with dichloromethane, followed by 2% methanol in dichloromethane provided 200 mg (61%) of the unsaturated imine **32b**. No 17-hydroxy product was found. TLC (silica gel, 2% methanol/CH_2Cl_2) R_f 0.41 (CAS brown); UV (ethanol) λ_{max} 228, 300 nm; IR (film) ν_{max} 3030, 2980, 2800, 2740, 1750, 1730, 1610, 1550, 1450, 1390, 1260, 750 cm^{-1}; 250-MHz NMR ($CDCl_3$) δ 7.65 (d, 1 H^9), 7.50 (d, 1 H^{17}), 7.48–7.20 (m, 8 H), 5.26 (d, 1 H^{benzyl}), 5.16 (d, 1 H^{benzyl}), 4.96 (m, 1 H^{14}), 3.89 (s, 3 H^{OCH_3}), 3.45 (br d, 1 H^3), 3.08 (t, 1 H^5), 2.75–2.55 (m, 1 H^5), 2.70 (d, 1 H^{21}), 2.49 (br d, 1 H^3), 2.31 (m, 1 H^6), 1.76 (m, 2 H^{15}), 1.55 (dd, 1 H^6), 0.91–0.70 (m, 2 H^{19}), 0.65 (t, 3 H^{18}); direct insertion probe 70-eV mass spectrum, m/z (relative intensity) 486 (M^+, 15), 334 (8), 266 (12), 108 (11), 91 (100).

Deacetylvindoline [35a (Racemic), 35b (–), 35c (+)]. A solution of 300 mg (0.784 mmol) of racemic 17-hydroxy-11-methoxytabersonine (**20a**) in 10 mL of dry dichloromethane was cooled to –16 °C. Addition of 8 mL of saturated aqueous bicarbonate was followed by dropwise addition, over 2 min, of a solution of 264 mg (1.53 mmol) of *m*-chloroperoxybenzoic acid in 2 mL of dichloromethane. After 2 min more, the layers were separated, and the aqueous layer was extracted twice with dichloromethane. Concentration of the combined organic solutions under vacuum was followed by addition, in rapid succession, of 2 mL of 40% aqueous formaldehyde, 100 mg of sodium cyanoborohydride, 20 mL of a buffer (18 mL of methanol, 2 mL of acetic acid, 800 mg of sodium acetate) and an additional 200 mg of sodium cyanoborohydride, added in small portions over 2 min. After stirring for 10 min, the mixture was concentrated under vacuum, poured onto ice, basified with ammonium hydroxide, and extracted with dichloromethane. The dried (Na_2SO_4) extracts were concentrated under vacuum. In some runs this crude product was subjected to 4 h of stirring with 3 g of activated zinc and 50% aqueous acetic acid to reduce any *N*-oxide product. Those reduction mixtures were then filtered through Celite, made alkaline with ammonium hydroxide, and extracted with dichloromethane. The brine-washed extracts were dried ($MgSO_4$) and concentrated.

The crude concentrated product, obtained with or without the zinc reduction step, was then chromatographed on 10 g of silica gel, by eluting with 70:30 ethyl acetate/hexanes. After five uncharacterized minor products, the major product **35a**, 113-200 mg (34–59%) was obtained as an amorphous solid. For **35a**: TLC (silica gel, ethyl acetate) R_f 0.13 UV (methanol) λ_{max} 227, 253, 305 nm; IR (film) ν_{max} 3840, 3460, 2960, 2945, 2880, 2835, 1735, 1615, 1595, 1500, 1460, 1435, 1330, 1240, 1160, 1120, 1080, 1040, 1030, 975, 935, 815, 730 cm^{-1}; 250-MHz NMR ($CDCl_3$) δ 9.45 (br s, 1 H^{OH16}), 6.87 (d, 1 H^9), 6.28 (dd, 1 H^{10}), 6.06 (d, 1 H^{12}), 5.87 (m, 1 H^{14}), 5.73 (d, 1 H^{15}), 4.09 (m, 1 H^{17}), 3.84 (s, 3 H^{OCH_3}), 3.78 (s, 3 H^{OCH_3}), 3.73 (s, 1 H^2), 3.43 (m, 2 $H^{3,5}$), 2.85 (d, 1 H^3), 2.72 (s, 3$H^{N\text{-}CH_3}$), 2.65 (s, 1 H^{21}), 2.50 (m, 2 $H^{5,6}$), 2.24 (m, 2 $H^{6,OH17}$), 1.45 (m, 1 H^{19}), 1.08 (m, 1 H^{19}), 0.67 (t, 3 H^{18}); direct insertion probe 70-eV mass spectrum, m/z (relative intensity) 415 (21), 414 (M^+, 100), 325 (18), 298 (30), 241 (11), 240 (94), 216 (23), 198 (18), 189 (28), 188 (52), 175 (10), 174 (36), 173 (10), 162 (17), 161 (22), 135 (80), 124 (13), 123 (12), 122 (41), 121 (59), 108 (15), 107 (30).

Starting with 185 mg of (–)-**20b**, 40 mg (20%) of (–)-**35b** $[\alpha]^{23}_D$ –26° (*c* 0.046, methanol), and from 340 mg of (+)-**20c**, 90 mg (24%) of (+)-**35c** $[\alpha]^{25}_D$ +30° (*c* 0.060, methanol) was obtained.

(–)-Deacetylvindorosine (36b). Following the above procedure used for the 11-methoxy analogue **20a–c**, 2.0 g of (–)-17-hydroxytabersonine (**21b**) was converted to 825 mg (37%) of the amorphous diol **36b**: TLC (silica gel, ethyl acetate) R_f 0.23; UV (ethanol) λ_{max} 218, 253, 305 nm; IR (film) ν_{max} 3400 (br), 3040, 2960, 2860, 2800, 2720, 1730, 1610, 1480, 1450, 1425, 1230, 720 cm^{-1}; 270-MHz NMR ($CDCl_3$) δ 9.36 (s, 1 H^{OH16}), 7.19 (t, 1 H^{10}), 7.05 (d, 1 H^9), 6.79 (t, 1 H^{11}), 6.55 (d, 1 H^{12}), 5.90 (dd, 1 H^{14}), 5.79 (d, 1 H^{15}), 4.14 (s, 1 H^{12}), 3.82 (s, 3 H^{OCH_3}), 3.72 (s, 1 H^2), 3.46 (m, 2 $H^{3,5}$), 2.90 (d, 1 H^3), 2.71 (s, 3 H^{NCH_3}), 2.70 (s, 1 H^{21}), 2.60 (m, 2 $H^{5,OH17}$), 2.30 (m, 2 H^6), 1.44 (m, 1 H^{19}), 1.00 (m, 1 H^{19}), 0.66 (t, 3 H^{18}), direct insertion probe 70-eV mass spectrum, m/z (relative intensity) 384 (M^+, 36), 325 (4), 268 (12), 240 (62), 186 (25), 159 (13), 158 (57), 144 (21), 143 (15), 140 (14), 135 (100), 132 (16), 131 (15), 126 (15), 124 (10), 122 (36), 121 (39), 108 (20), 107 (38); $[\alpha]^{24}_D$ –28° (*c* 0.072, methanol).

Vindoline [1a (Racemic), 1b (–), 1c (+)]. For **1a**: To a solution of 100 mg (0.24 mmol) of (±)-deacetylvindoline **34a** and 5 mg of 4-(dimethylamino)pyridine in 30 mL of dichloromethane and 50 μL (0.36 mmol) of triethylamine, cooled to 0 °C, was added

(36) (–)-3-Oxotabersonine (**25b**) was prepared by oxidation of (–)-tabersonine: Aimi, N.; Asada, Y.; Sakai, S.; Haginiwa *Chem. Pharm. Bull.* **1978**, *26*, 1182.

26 μL (0.36 mmol) of acetyl chloride. After 6 h at room temperature, the mixture was partitioned between water and dichloromethane. Concentration of the organic extracts and chromatography of the residue on 10 g of silica gel, eluting with 1:1 ethyl acetate/hexanes gave 38 mg (35%) of material which crystallized from ether with mp 203–205 °C (reported[8] 203–205 °C).[37] TLC (silica gel, ethyl acetate) R_f 0.24; UV (methanol) λ_{max} 220, 253, 303 nm; IR (film) ν_{max} 3680, 3035, 2960, 2880, 2835, 2805, 2715, 1740, 1610, 1595, 1500, 1430, 1370, 1240, 1220, 1170, 1140, 1120, 1085, 1030, 970, 940, 735 cm^{-1}; 250-MHz NMR ($CDCl_3$) δ 0.49 (t, 3 H^{18}), 1.13 (m, 1 H^{19}), 1.62 (m, 1 H^{19}), 2.08 (s, 3 H^{COCH_3}), 2.33 (m, 2 H^6), 2.51 (m, 1 H^5), 2.67 (s, 3 H^{NCH_3}), 2.82 (d, 1 H^3), 3.46 (m, 2 $H^{3,5}$), 3.75 (s, 1 H^2), 3.79 (2s, 6 $H^{2\,OCH_3}$), 5.23 (d, 1 H^{15}), 5.46 (s, 1 H^{17}), 5.84 (m, 1 H^{14}), 6.08 (d, 1 H^{12}), 6.30 (dd, 1 H^{10}), 6.89 (d, 1 H^9), 9.58 (br s, 1 H^{OH16}); direct insertion probe 70-eV mass spectrum, m/z (relative intensity) 456 (M^+, 10), 296 (13), 282 (21), 189 (34), 188 (50), 174 (36), 173 (10), 162 (16), 161 (22), 136 (13), 135 (100), 122 (37), 121 (60), 108 (14), 107 (31). Anal. Calcd for $C_{25}H_{32}N_2O_6$: C, 65.77; H, 7.07; N, 6.14. Found: C, 66.01; H, 7.36; N, 6.02.

By the same procedure 30 mg of synthetic (-)-deacetylvindoline **35b**, prepared above, was acylated to give 17 mg (52%) of (-)-vindoline (**1b**). Alternatively, acetylation of 20 mg of **35b** with acetic anhydride in pyridine[14] gave 12 mg (55%) of (**1b**), mp 171–172 °C, crystallized from ether (reported[38,39] 174–175 °C, 164–165 °C); $[\alpha]^{25}_D$ –62° (*c* 0.26, methanol); reported[38] $[\alpha]_{600}$ –48°, $[\alpha]_{500}$ –69° (methanol), $[\alpha]^{20}_D$ –18° (chloroform). A sample of natural vindoline gave $[\alpha]^{23}_D$ –60° (*c* 0.10, methanol) and $[\alpha]^{23}_D$ –28° (*c* 0.10, chloroform). Acylation of 75 mg of (+)-deacetyl vindoline (**35c**) from above, gave 55 mg (67%) of (+)-vindoline (**1c**), $[\alpha]^{23}_D$ +57° (*c* 0.088, methanol); mp 170–172 °C, crystallized from ether.

(-)-Vindorosine (2). Acylation of 50 mg of the diol **36** according to the above generation of vindoline (**1a–c**) provided 59 mg (99%) of unchromatographed vindorosine **2**, mp 165–167 °C from ether (reported[33] 165 °C). TLC (silica gel, ethyl acetate) R_f 0.39 (CAS red); UV (ethanol) λ_{max} 218, 255, 305 nm; IR (film) ν_{max} 3020, 2960, 2860, 2800, 2720, 1732, 1600, 1465, 1230, 1040, 730 cm^{-1}; 270 MHz NMR ($CDCl_3$) δ 9.55 (s, 1 H^{OH16}), 7.19 (t, 1 H^{10}), 7.05 (d, 1 H^9), 6.83 (t, 1 H^{11}), 6.56 (d, 1 H^{12}), 5.90 (dd, 1 H^{14}), 5.50 (s, 1 H^{17}), 5.28 (d, 1 H^{15}), 3.82 (s, 3 H^{OCH_3}), 3.72 (s, 1 H^2), 3.48 (m, 2 $H^{3,5}$), 2.90 (d, 1 H^3), 2.70 (s, 3 H^{NCH_3}), 2.55 (m, 1 H^5), 2.45 (m, 2 H^6), 2.15 (s, 3 H^{COCH_3}), 1.70 (m, 1 H^{19}), 1.10 (m, 1 H^{19}), 0.44 (t, 3 H^{18}); direct insertion probe 70-eV mass spectrum, m/z (relative intensity) 426 (M^+, 16), 282 (12), 267 (13), 266 (42), 159 (10), 158 (45), 144 (12), 135 (100), 132 (8), 131 (8), 122 (17), 121 (22), 107 (15); $[\alpha]^{24}_D$ –31° (*c* 0.096 $CHCl_3$); reported[38] $[\alpha]^{16}_D$ –31° ($CHCl_3$). Anal. Calcd for $C_{24}H_{30}N_2O_5$: C, 66.97; H, 6.84; N, 6.79. Found: C, 66.65; H, 7.05; N, 6.39.

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A Short Stereoselective Synthesis of the Alkaloid Vincamine

Denis Gênin, Ratremaniaina Zo Andriamialisoa, Nicole Langlois, and Yves Langlois*

Institut de Chimie des Substances Naturelles du CNRS, 91190 Gif-sur-Yvette, France

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The indole alkaloid vincamine (1) has been prepared from 3,4-dihydro-β-carboline (3) in a six-step sequence. An imino Diels–Alder between 3 and methyl pentadienoate led to a mixture of indoloquinolizidines **4a** and **4b** which were directly deprotonated and alkylated affording indoloquinolizidine **5** as a single diastereoisomer. After a reduction–oxidation sequence compound **5** led to aldehyde **9**. This compound was directly transformed into vincamine (1) by treatment with methyl isocyanoacetate anion followed by an acidic and basic workup.

Vincamine (**1**),[1] a major alkaloid of Vinca minor used in the treatment of vascular diseases, has been the subject of a number of synthetic studies.[2] This Eburna alkaloid is biogenetically related to the Aspidosperma alkaloids,[3,4] and these two families show the same configurations at C_{20} and C_{21}.[5] Our strategy was first directed toward the synthesis of indolo[2,3-*a*]quinolizidines, bearing the appropriate configurations at these two centers. We anticipated that these compounds could be versatile synthons in the syntheses of both the above families of alkaloids.

Our recent work has demonstrated the synthetic usefulness of the imino Diels–Alder reaction in the preparation of octahydroindolo[2,3-*a*]quinolizidine derivatives,[6] which have been transformed into the Aspidosperma alkaloids vindorosine (**2a**) and vindoline (**2b**).[7] In this report we have applied the same reaction to a highly stereoselective synthesis of the Eburna alkaloid vincamine (1).

Thus, 3,4-dihydro-β-carboline (**3**)[8] was treated with methyl pentadienoate at 120 °C in chlorobenzene to afford two isomeric indoloquinolizidines **4a** and **4b** (total yield 69%) (Scheme I). The two compounds as a mixture were deprotonated at –70 °C with LDA–HMPA complex[9] (2.2 equiv) and alkylated at the same temperature with ethyl iodide (1 equiv). This led to the anticipated indolo-

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