Total Synthesis of Indole and Dihydroindole Alkaloids. 14.[1] A Total Synthesis of Vindoline

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Abstract: A synthetic route to (±)-vindoline (**1**) is described. A transannular cyclization reaction provided 2,3-anhydro-4-deacetoxy-6,7-dihydrovindoline (**7**), which was also available via a degradation of vindoline. Functional group elaboration of **7**, already bearing the pentacyclic skeleton of the Aspidosperma family, completed the synthesis of the natural product.

The alkaloid vindoline[2] (**1**) is one of the most highly oxygenated members of the Aspidosperma series. It is the major alkaloidal constituent of *Catharanthus roseus* G. Don and the dihydroindole unit of the clinically important antitumor agent vinblastine. The first synthesis of **1** was reported by Buchi and co-workers[3] and we report here an alternative of different strategy.

As part of an overall synthetic program concerning a series of indole and dihydroindole alkaloids, it was of interest to develop a route to vindoline which would also afford intermediates suitable for coupling with catharanthine to yield derivatives of the bisindole alkaloids.[4-7] The unsaturated ester **7**, available from previous investigations, was selected as the appropriate starting material.

Transannular cyclization of *dl*-vincaminoridine and *dl*-epivincaminoridine[8,9] provided the ester **7** with the required pentacyclic skeleton of vindoline. Since this intermediate was crucial to all subsequent studies it was necessary to establish, unambiguously, its structure and stereochemistry at the various chiral centers by direct comparison with a degradation product from vindoline, for which an x-ray analysis was available.[10] The degradation sequence[11] employed is shown in Figure 1.

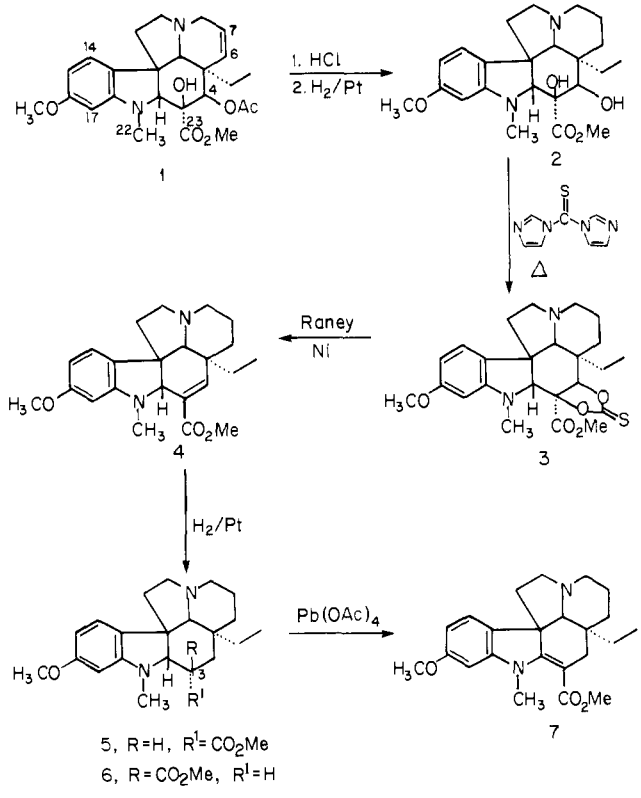
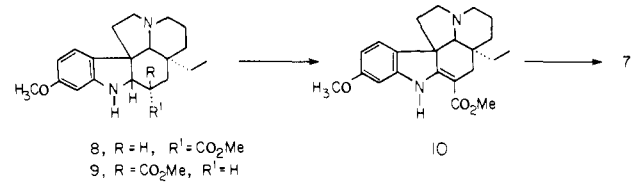


Figure 1.

Deacetyldihydrovindoline (**2**)[2] was reacted with *N,N'*-thiocarbonyldiimidazole[12] in refluxing, anhydrous 2-butanone to give an 88% yield of the crystalline thionocarbonate (**3**), mp 222-223 °C. An efficient conversion (84%) to the α,β-unsaturated ester (**4**) was accomplished by reaction with Raney nickel in tetrahydrofuran. The carbonyl frequency of the ester appeared at 1703 cm^{-1} and a one-proton absorbance at δ 7.23 in the ^1H NMR spectrum was characteristic of the β hydrogen of an α,β-unsaturated ester system. Catalytic hydrogenation of **4** gave a high yield of the 3(*S*) ester **5**. The C_2 hydrogen of this product absorbed at δ 3.60 (d, J = 2 Hz) while that for C_3 H appeared as a multiplet at δ 4.1 ppm. Epimerization of **5** with potassium *tert*-butoxide afforded the more stable equatorial 3(*R*) ester **6**, mp 162-164 °C, for which the C_2 hydrogen resonated as a doublet (J = 10 Hz) at δ 3.85 ppm. Further support for the stereochemical assignments was available from the *N*-methyl absorbances in the ^1H NMR spectra of **5** and **6**. Axial constraint of the ester function in **5** allowed shielding of the proximate methyl group (3 H, s, at δ 2.55 ppm), while in **6** this signal appeared at δ 2.71 ppm. The final step in the degradation to **7** involved lead tetraacetate oxidation of the epimeric esters **5** and **6**. This transformation was particularly sensitive to reaction variables. Under optimum conditions, two major products (**7** and **8**) were isolable. The required ester **7**, $[\alpha]_D$ −377°, from this degradation sequence was identical (except in optical rotation) with the racemic material from the transannular cyclization. The demethyl product **8** could also be transformed to **7** by oxidation to **10** and subsequent methylation. In this manner, the overall conversion to **7** was improved.



In order that the subsequent intermediates could also be used in synthetic studies toward vinblastine derivatives, the optically active material (**7**) from the degradation sequence was employed in the elaborations to vindoline (Figures 2 and 3).

Dissolving metal reduction (zinc, 10% sulfuric acid, methanol) of **7** afforded the esters **6** and **5** in the ratio ca. 8:1, respectively. Hydrogenation of **7** over Adams' catalyst gave the respective epimers in the ratio ca. 5:1. Reduction, with aluminum hydride, of these saturated esters gave the corresponding primary alcohols **11**, $[\alpha]_D$ +63.5°, and **12**, $[\alpha]_D$ +44.7°, in high yield. The acetate **13** showed, in its ^1H NMR spectrum, doublet absorbance at δ 4.18 (J = 8 Hz) for the

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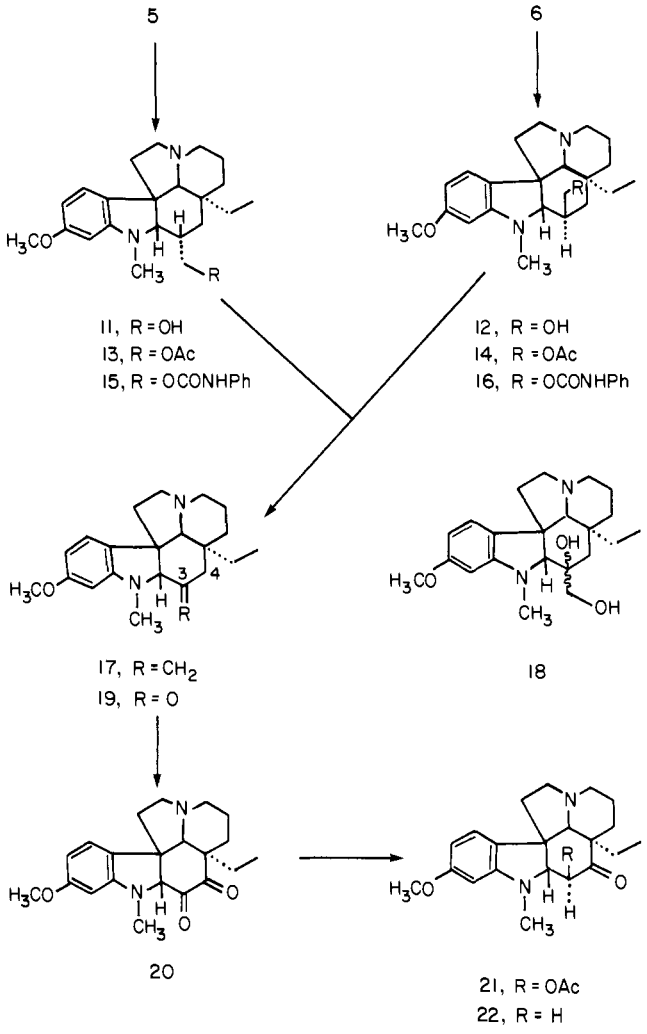


Figure 2.

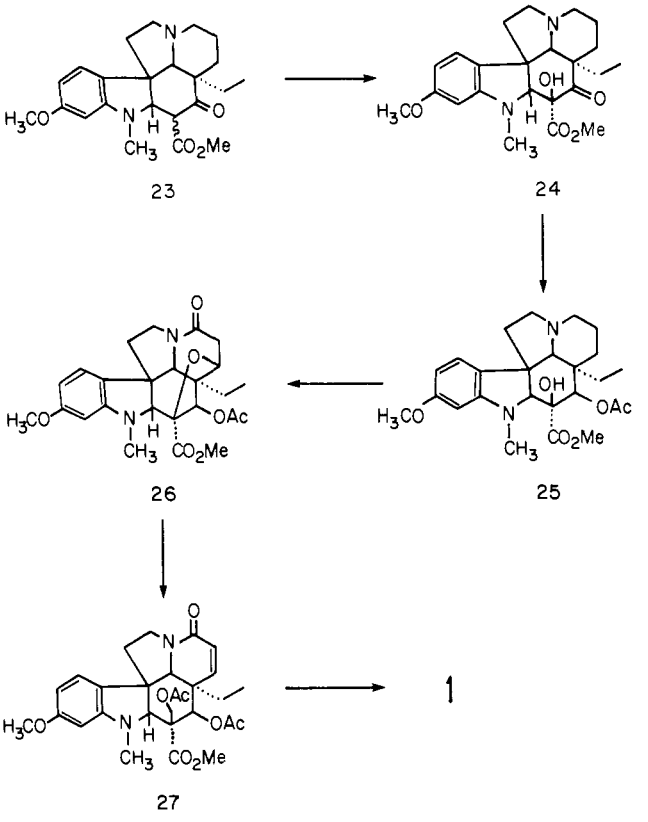


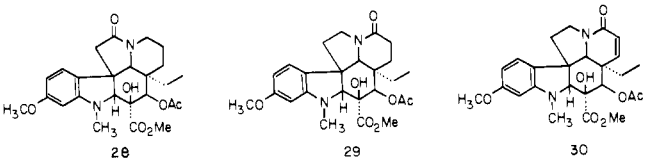
Figure 3.

C_{23}-methylene protons, whereas for **14,** nonequivalence led to signals at δ 4.35 (dd, J = 11, 2.5 Hz) and 4.05 ppm (dd, J = 11, 6 Hz). Each of the primary alcohols, on reaction with phenyl isocyanate,[13] afforded a phenylcarbamate (**15, 16**) in ca. 80% yield. Barbier-Wieland pyrolysis[13] of either **15** or **16** gave the olefin **17** in 70% yield. This product exhibited ^{1}H NMR singlet absorbance at δ 3.46 for C_2H, while a broad singlet at δ 4.93 was assigned to the vinyl protons. Osmylation provided a crystalline mixture of diols **18,** mp 146-150 °C, which on periodate cleavage gave the 3-ketone **19** (Figure 2).

To complete the functionalization of ring C, an oxygenation at C_4 and subsequent carbomethoxylation at C_3 were required. Ketone transposition to the known 4-ketone **22** was pursued; however, standard methods[14] were unsuccessful. Thus base-induced hydroxylation,[15] using a molybdenum peroxide complex,[16] followed by cupric acetate oxidation of the intermediate ketol was utilized to form the bright yellow dione **20** (mp 143-145 °C, ν_{max} 1710 cm^{-1}, δ 3.70, s, C_2 H). Selective 3-keto reduction with titanous chloride in methanol[18] and acetylation gave **21** (ν_{max} 1738 and 1720 cm^{-1}). The ^{1}H NMR spectrum showed doublet signals (J = 8.5 Hz) at δ 5.33 and 3.85 assigned to C_2H and C_3H, respectively. Reduction of **21** with the zinc dust and hydriodic acid provided the 4-ketone **22,** $[\alpha]_D$ +12°, identical with a sample obtained by degradation of vindoline.[2]

Carbomethoxylation using sodium hydride and dimethyl carbonate[3,19] in tetrahydrofuran gave the ester **23,** $[\alpha]_D$ −13.7°, as a mixture of keto and enol forms. Subsequent hydroxylation[3,20] with hydrogen peroxide in the presence of potassium *tert*-butoxide afforded **24** (ν_{max} 3450, 1748, 1712 cm^{-1}). Complexation with aluminum chloride followed by reduction with "Red-Al" in tetrahydrofuran, as described in the earlier work,[3] provided the 4(R) alcohol, which on acetylation gave **25,** identical with an authentic sample of 6,7-dihydrovindoline.

The remaining problem for the completion of the synthesis involved the introduction of Δ^6 unsaturation in ring E of the pentacyclic system. A solution became available from a complementary series of investigations involving novel vindoline derivatives from degradations of the parent alkaloid. During these studies it was found that lactam derivatives within the vindoline series were available via several oxidative procedures. The reagent of choice, mercuric acetate in dioxane as solvent, converted 6,7-dihydrovindoline (**25**) to the three lactam derivatives **26,**[21] **28,** and **29,** presumably via the sequence **25** → **29** → **30** → **26.** Molecular models revealed the hydroxyl group,



in **30,** ideally situated for favored 5-exo-trig.[22] cyclization to C_6 via Michael addition. The required ether lactam **26,** mp 201-202 °C, $[\alpha]_D$ − 13.6°, showed ^{1}H NMR singlet absorbances at δ 5.77, 4.09, and 3.61 attributed to C_4 H, C_2 H, and C_{19} H, respectively. Notably, **26** was also available by mercuric acetate oxidation of vindoline.

Cleavage of the cyclic ether and conversion to the diacetate **27** was accomplished by the action of tritylllithium in tetrahydrofuran and in situ acetylation to prevent recyclization of the intermediate anion. The unsaturated lactam system of **27** exhibited ^{1}H NMR doublet absorbances (J = 10 Hz) at δ 6.01 and 5.90 ppm due to C_6 H and C_7 H, respectively.

Removal of the lactam carbonyl in **27** was achieved by sodium borohydride reduction of the corresponding imino ether, generated from **27** with Meerwein reagent. Subsequent 3-O-deacylation in the presence of moist silica gel afforded vindoline (**1**) identical with an authentic sample.

Experimental Section

Uncorrected melting points were determined on a Reichert micro hot stage. Infrared spectra were recorded on either a Perkin-Elmer 21 or 137 spectrophotometer. Ultraviolet spectra were recorded on a Cary 15 spectrophotometer. Mass spectra were recorded on an Atlas CH-4B or AEI MS-902 spectrometer. ^{1}H NMR spectra were recorded on a Varian HA-100 or XL-100 instrument with Me_4Si as internal standard (δ 0 ppm). Optical rotations (corrected) were measured using a Perkin-Elmer 141 polarimeter at 25 °C.

(±)-2,3-Anhydro-4-deacetoxy-6,7-dihydrovindoline (7). A. Mercuric acetate (96 mg) and *dl*-vincaminoridine (22 mg) were stirred in glacial acetic acid (11 mL) at ambient temperature under a nitrogen atmosphere for 43 h. The mixture was filtered, basified with 7% sodium bicarbonate solution, and extracted with dichloromethane. The extract was dried (Na_2SO_4) and concentrated under vacuum. Chromatography on neutral alumina gave the racemic ester **7** (2 mg, 11%) identical with that prepared via the degradation of vindoline (see below).

B. Similar results were obtained starting from *dl*-epivincaminoridine.

4-*O*-Deacetyl-6,7-dihydrovindoline Thionocarbonate (3). 4-*O*-Deacetyl-6,7-dihydrovindoline (2.1 g) and *N,N'*-thiocarbonyldiimidazole (5.4 g) were stirred in refluxing 2-butanone (125 mL) under a nitrogen atmosphere for 28 h. The solvent was removed under reduced pressure and the residue chromatographed on silica gel to give **3** (2.06 g, 88%): mp (ethyl acetate) 222–223 °C; $[\alpha]_D$ +97.6° (*c* 0.88, $CHCl_3$); IR ($CHCl_3$) 1739, 1304 cm^{-1}; UV (EtOH) 208 nm (log ϵ 4.53), 233 (4.33), 298 (3.69); ^{1}H NMR ($CDCl_3$) δ 6.98 (1 H, d, J = 8 Hz, C_{14} H), 6.37 (1 H, dd, J = 8, 2.3 Hz, C_{15} H), 6.10 (1 H, d, J = 2.3 Hz, C_{17} H), 5.31 (1 H, s, C_4 H), 3.93 (3 H, s, -OCH_3), 3.80 (1 H, s, C_2 H), 3.76 (3 H, s, -OCH_3), 2.63 (3 H, s, -NCH_3), 0.46 (3 H, t, J = 7 Hz, -CH_2CH_3); *m/e* 458 (M^+), 381, 298, 149, 124. Anal. ($C_{24}H_{30}N_2O_5S$) C, H, N.

3,4-Anhydro-4-deacetoxy-6,7-dihydrovindoline (4). The ester **3** (645 mg) and Raney nickel (deactivated with acetone, 10 g) were stirred in refluxing tetrahydrofuran (30 mL) for 24 h. The mixture was filtered and the filtrate concentrated under vacuum. Chromatography on silica gel gave the α,β-unsaturated ester **4** (453 mg, 84%): $[\alpha]_D$ −204.1° (*c* 0.17, $CHCl_3$); IR ($CHCl_3$) 1703 cm^{-1}; UV (EtOH) 212 nm (log ϵ 4.53), 253 (3.82), 307 (3.62); ^{1}H NMR ($CDCl_3$) δ 7.23 (1 H, bs, C_4 H), 6.96 (1 H, d, J = 8 Hz, C_{14} H), 6.22 (1 H, dd, J = 8, 2 Hz, C_{15} H), 5.94 (1 H, d, J = 2 Hz, C_{17} H), 4.27 (1, H, s, C_2 H), 3.78 (3 H, s, -OCH_3), 3.75 (3 H, s, -OCH_3), 2.75 (3 H, s, -NCH_3), 0.59 (3 H, t, J = 7 Hz, -CH_2CH_3); *m/e* 382.222 (M^+, calcd for $C_{23}H_{30}N_2O_3$, 382.225), 263, 208, 174, 149, 124. Anal. ($C_{23}H_{30}N_2O_3$) C, H, N.

4-Deacetoxy-3(*S*)-deoxy-6,7-dihydrovindoline (5). The α,β-unsaturated ester **4** (438 mg) and 10% palladium on carbon catalyst were stirred in 95% ethanol (10 mL) at ambient temperature under 1 atm of hydrogen for 72 h. The catalyst was removed by filtration and the filtrate concentrated under reduced pressure. Chromatography on silica gel afforded the ester **5** (385 mg, 80%) as a colorless oil: $[\alpha]_D$ + 62.5° (*c* 0.29, $CHCl_3$); IR ($CHCl_3$) 1720 cm^{-1}; UV (EtOH) 212 nm (log ϵ 4.35), 253 (3.69), 305 (3.53); ^{1}H NMR ($CDCl_3$) δ 6.92 (1 H, d, J = 8 Hz, C_{14} H), 6.22 (1 H, dd, J = 8, 2 Hz, C_{15} H), 5.99 (1 H, d, J = 2 Hz, C_{17} H), 4.10 (1, H, m, J = 12, 6, 2 Hz, C_3 H), 3.78 (3, H, s, -OCH_3), 3.73 (3 H, s, -OCH_3), 3.60 (1, H, d, J = 2 Hz, C_2 H), 2.55 (3 H, s, -NCH_3), 0.50 (3 H, t, J = 7 Hz, -CH_2CH_3); *m/e* 384 (M^+), 298, 210, 124. Anal. ($C_{23}H_{32}N_2O_3$) C, H, N.

4-Deacetoxy-3(*R*)-deoxy-6,7-dihydrovindoline (6). Potassium *tert*-butoxide (53 mg) and the ester **5** (93 mg) were stirred in 1,2-dimethoxyethane (5 mL) and *tert*-butyl alcohol (1 mL) for 8 h at ambient temperature. The solvent was removed under reduced pressure and the residue partitioned between saturated sodium chloride solution and ethyl acetate. The organic layer was dried (Na_2SO_4) and concentrated. Chromatography on silica gel gave **5** (6 mg) and **6** (68 mg, 70%): mp (methanol) 162–164 °C; $[\alpha]_D$ −77.2° (*c* 0.35, $CHCl_3$); IR ($CHCl_3$) 1725 cm^{-1}; UV (EtOH) 212 nm (log ϵ 4.42), 256 (3.80), 307 (3.65); ^{1}H NMR ($CDCl_3$) δ 6.87 (1 H, d, J = 8 Hz, C_{14} H), 6.16 (1 H, dd, J = 8, 2 Hz, C_{15} H), 5.94 (1 H, d, J = 2 Hz, C_{17} H), 3.85 (1 H, d, J = 10 Hz, C_2 H), 3.76 (3 H, s, -OCH_3), 3.69 (3 H, s, -OCH_3), 2.71 (3 H, s, -NCH_3), 0.67 (3 H, t, J = 7 Hz, -CH_2CH_3); *m/e* 384 (M^+), 298, 188, 124. Anal. ($C_{23}H_{32}N_2O_3$) C, H, N.

2,3-Anhydro-4-deacetoxy-6,7-dihydrovindoline (7) and 4-Deacetoxy-*N*-demethyl-3(*S*)-deoxy-6,7-dihydrovindoline (8). A. The ester **5** (80 mg) and lead tetraacetate (97 mg) were stirred in dry benzene (5 mL) at ca. 5 °C for 30 min. Alumina (grade III) was added and the mixture filtered through Celite. The filtrate was concentrated and chromatographed on silica gel to give the ester **5** (10 mg); the ester **7** (14 mg, 20%) $[[\alpha]_D$ −377.2° (*c* 0.17, $CHCl_3$); IR ($CHCl_3$) 1664, 1583 cm^{-1}; UV (EtOH) 205 nm (log ϵ 4.78), 240 (4.30), 334 (4.22); ^{1}H NMR ($CDCl_3$) δ 7.06 (1 H, d, J = 8 Hz, C_{14} H), 6.40 (1 H, dd, J = 8, 2 Hz, C_{15} H), 6.36 (1 H, d, J = 2 Hz, C_{17} H), 3.78 (3 H, s, -OCH_3), 3.72 (3 H, s, -OCH_3), 3.20 (3 H, s, -NCH_3), 0.62 (3 H, t, J = 7 Hz, -CH_2CH_3); *m/e* 382.2258 (M^+, calcd for $C_{23}H_{30}N_2O_3$, 382.2255), 258, 124, 95, 69, 57]; and the ester **8** (12 mg, 17%) $[[\alpha]_D$ +28.8° (*c* 0.72, $CHCl_3$); IR ($CHCl_3$) 3420, 1722, 1620 cm^{-1}; UV (EtOH) 208 nm (log ϵ 4.54), 245 (3.73), 301 (3.72); ^{1}H NMR ($CDCl_3$) δ 6.89 (1 H, d, J = 8 Hz, C_{14} H), 6.22 (1 H, dd, J = 8, 2 Hz, C_{15} H), 6.10 (1 H, d, J = 2 Hz, C_{17} H), 3.69 (3 H, s, -OCH_3), 3.62 (3 H, s, -OCH_3), 0.50 (3 H, t, J = 7 Hz, -CH_2CH_3); *m/e* 370.2223 (M^+, calcd for $C_{22}H_{30}N_2O_3$, 370.2256), 284, 124, 74, 59].

B. Similar oxidation of **5** (42 mg) with lead tetraacetate (97 mg) in dry pyridine (5 mL) gave the ester **7** (4 mg, 10%) together with **8** (17 mg, 41%).

2,3-Anhydro-4-deacetoxy-6,7-dihydrovindoline (7) and 4-Deacetoxy-*N*-demethyl-3(*R*)-deoxy-6,7-dihydrovindoline (9). Oxidation of **6** (80 mg) with lead tetraacetate (97 mg), as described above, in dry benzene (5 mL) gave the ester **7** (9 mg, 11%) and the demethyl derivative **9** (13 mg, 17%): $[\alpha]_D$ −47.0° (*c* 0.10, $CHCl_3$); IR ($CHCl_3$) 3470, 1720, 1660, 1620 cm^{-1}; UV (MeOH) 245 nm (log ϵ 3.80), 301 (3.75); ^{1}H NMR ($CDCl_3$) δ 6.91 (1 H, d, J = 8 Hz, C_{14} H), 6.27 (1 H, dd, J = 8, 2 Hz, C_{15} H), 6.20 (1 H, d, J = 2 Hz, C_{17} H), 3.72 (3 H, s, -OCH_3), 3.69 (3 H, s, -OCH_3), 0.65 (3 H, t, J = 7 Hz, -CH_2CH_3); *m/e* 370.

2,3-Anhydro-4-deacetoxy-*N*-demethyl-6,7-dihydrovindoline (10). A. Oxidation of **8** (100 mg) with lead tetraacetate (126 mg) in dry benzene (5 mL) at ca. 5 °C, as described above, gave the ester **10** (78 mg, 78%): $[\alpha]_D$ −447.7° (*c* 0.33, $CHCl_3$); IR ($CHCl_3$) 3430, 1670, 1610 cm^{-1}; UV (MeOH) 244 nm (log ϵ 4.13), 324 (4.26); ^{1}H NMR ($CDCl_3$) δ 8.91 (1 H, bs, -NH), 7.09 (1 H, d, J = 8 Hz, C_{14} H), 6.43 (1 H, d, J = 2 Hz, C_{17} H), 6.39 (1 H, dd, J = 8, 2 Hz, C_{15} H), 3.77 (3 H, s, -OCH_3), 3.75 (3 H, s, -OCH_3), 0.59 (3 H, distorted triplet, -CH_2CH_3); *m/e* 368.2110 (M^+, calcd for $C_{22}H_{28}N_2O_3$, 368.2100), 337, 283, 184, 168, 124 (100%).

B. Similar oxidation of **9** gave **10** in 61% yield.

2,3-Anhydro-4-deacetoxy-6,7-dihydrovindoline (7). Sodium hydride (99%, 3 mg) was added to a solution of **10** (10 mg) in dry tetrahydrofuran (2 mL) at ambient temperature. After 20 min, methyl iodide (10 mg) was added and the mixture stirred for 30 min. The solvent was removed under vacuum and the residue extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and concentrated under vacuum. Chromatography on silica gel afforded **7** (4 mg, 40%) identical with a sample prepared earlier.

Esters 5 and 6. A. Hydrogenation of the α,β-unsaturated ester **7** over Adams' catalyst at ambient temperature in ethanol gave the esters **5** (10%) and **6** (46%) identical with respective samples prepared earlier.

B. Zinc powder (150 mg) and the ester **7** (16 mg) were stirred in 10% sulfuric acid in methanol (1 mL) at ambient temperature for 10 min. The mixture was partitioned between saturated sodium bicarbonate solution and ether. The ether layer was dried (Na_2SO_4) and concentrated. Chromatography on silica gel gave **5** (1.5 mg, 9%) and **6** (12 mg, 75%) identical with authentic samples.

Alcohol 11. Aluminum chloride (175 mg) was added to lithium aluminum hydride (165 mg) in dry ether (5 mL) at 0 °C and the suspension stirred for 30 min at ambient temperature. The mixture was chilled to 0 °C and the ester **5** (50 mg) in ether (1 mL) added. Stirring was continued for 30 min at 0 °C and the mixture then partitioned between water and ethyl acetate. The organic layer was dried (Na_2SO_4) and evaporated to give **11** (47 mg, 95%) as a colorless foam: $[\alpha]_D$ +63.5° (*c* 0.26, $CHCl_3$); IR ($CHCl_3$) 3650, 1620–1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.92 (1 H, d, J = 8 Hz, C_{14} H), 6.27 (1 H, dd, J = 8 Hz, C_{15} H), 6.06 (1 H, d, J = 2 Hz, C_{17} H), 3.77 (3 H, s,

$-OCH_3$), 2.81 (3 H, s, $-NCH_3$); *m/e* 356.246 (M^+, calcd for $C_{22}H_{32}N_2O_2$, 356.246), 338, 298, 220, 188, 174, 124.

Alcohol 12. Similarly, reduction of **6** gave the alcohol **12** (95%) as a colorless foam: $[\alpha]_D$ +44.7° (*c* 0.33, $CHCl_3$); IR ($CHCl_3$) 3650, 1620–1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.92 (1 H, d, *J* = 8 Hz, C_{14} H), 6.25 (1 H, dd, *J* = 8, 2 Hz, C_{15} H), 6.07 (1, H, d, *J* = 2 Hz, C_{17} H), 3.77 (3 H, s, $-OCH_3$), 2.98 (3 H, s, $-NCH_3$), 0.63 (3 H, t, *J* = 7 Hz, $-CH_2CH_3$); *m/e* 356.246 (M^+, calcd for $C_{22}H_{30}N_2O_2$, 356.246), 326, 208, 220, 188, 174, 135, 125, 124.

Acetate 13. Acetylation of **11** with acetic anhydride–pyridine at ambient temperature for 1 h gave **13** (87%) as a colorless oil: IR ($CHCl_3$) 1725 cm^{-1}; UV (EtOH) 212 nm (log ϵ 4.54), 252 (3.88), 304 (3.75); ^1H NMR ($CDCl_3$) δ 6.92 (1 H, d, *J* = 8 Hz, C_{14} H), 6.28 (1 H, dd, *J* = 8, 2 Hz, C_{15} H), 6.06 (1 H, d, *J* = 2 Hz, C_{17} H), 4.18 (2 H, d, *J* = 8 Hz, $-CH_2OAc$), 3.78 (3 H, s, $-OCH_3$), 3.17 (1 H, d, *J* = 2 Hz, C_2 H), 2.76 (3 H, s, $-NCH_3$), 2.08 (3 H, s, $-OCOCH_3$), 0.48 (3 H, t, *J* = 7 Hz, $-CH_2CH_3$); *m/e* 398 (M^+), 339, 338, 298, 124.

Acetate 14. Similarly, **12** gave an acetate **14** (82%): IR ($CHCl_3$) 1725 cm^{-1}; UV (EtOH) 212 nm (log ϵ 4.45), 258 (3.83), 309 (3.67); ^1H NMR ($CDCl_3$) δ 6.87 (1 H, d, *J* = 8 Hz, C_{14} H), 6.18 (1 H, dd, *J* = 8, 2 Hz, C_{15} H), 5.99 (1 H, d, *J* = 2 Hz, C_{17} H), 4.35 (1 H, dd, *J* = 11, 2.5 Hz, $-CHOAc$), 4.05 (1 H, dd, *J* = 11, 6 Hz, $-CHOAc$), 3.79 (3 H, s, $-OCH_3$), 3.02 (3 H, s, $-NCH_3$), 2.08 (3 H, s, $-OCOCH_3$), 0.66 (3 H, t, *J* = 7 Hz, $-CH_2CH_3$); *m/e* 398 (M^+), 339, 298, 124.

Phenylcarbamate 15. Phenyl isocyanate (0.15 mL) was added to the alcohol **11** (47 mg) in carbon tetrachloride (1 mL) and stirring continued at ambient temperature for 2 h. The solvent was removed under vacuum and the residue chromatographed on silica gel to give **15** (56 mg, 90%) as a colorless foam: IR ($CHCl_3$) 3440, 1720 cm^{-1}; UV (EtOH) 230 nm (log ϵ 4.39), 255 (sh), 303 (3.73); ^1H NMR ($CDCl_3$) δ 6.92–7.54 (5 H, m, aromatic H), 6.92 (1 H, d, *J* = 8 Hz, C_{14} H), 6.64 (1 H, bs, –NH), 6.28 (1 H, dd, *J* = 8, 2 Hz, C_{15} H), 6.08 (1 H, d, *J* = 2 Hz, C_{17} H), 4.30 (2 H, d, *J* = 8 Hz, $-CH_2O-$), 3,80 (3 H, s, $-OCH_3$), 3.20 (1 H, d, *J* = 3 Hz, C_2 H), 2.81 (3 H, s, $-NCH_3$), 0.49 (3 H, t, *J* = 7 Hz, $-CH_2CH_3$); *m/e* 475 (M^+), 356, 339, 338, 124.

Phenylcarbamate 16. Similarly the alcohol **12** gave **16** (82%): IR ($CHCl_3$) 3445, 1730 cm^{-1}; UV (EtOH) 212 nm (log ϵ 4.45), 230 (4.31), 258 (3.86), 309 (3.64); ^1H NMR ($CDCl_3$) δ 6.92–7.62 (5 H, m, aromatic H), 6.87 (1 H, d, *J* = 8 Hz, C_{14} H), 6.20 (1 H, dd, *J* = 8, 2 Hz, C_{15} H), 6.01 (1 H, d, *J* = 2 Hz, C_{17} H), 4.32 (2 H, bs, $-CH_2O-$), 3.79 (3 H, s, $-OCH_3$), 3.06 (3 H, s, $-NCH_3$), 0.69 (3 H, t, *J* = 7 Hz, $-CH_2CH_3$); *m/e* 475 (M^+), 431, 398, 356, 338, 309, 298, 164, 124.

Olefin 17. A. The carbamate **15** (14 mg) was heated to 180–195 °C under reduced pressure (ca. 10 mmHg) for 1 h. The residue was chromatographed on silica gel to give **17** (7 mg, 70%) as a colorless oil: $[\alpha]_D$ +46.7° (*c* 0.14, $CHCl_3$); IR ($CHCl_3$) 1640, 1610, 1090, 900 cm^{-1}; UV (EtOH) 254 nm (log ϵ 3.90), 307 (3.73); ^1H NMR ($CDCl_3$) δ 6.90 (1 H, d, *J* = 8 Hz, C_{14} H), 6.18 (1 H, dd, *J* = 8, 2 Hz, C_{15} H), 5.97 (1 H, d, *J* = 2 Hz, C_{17} H), 4.93 (2 H, bs, $-C{=}CH_2$), 3.78 (3 H, s, $-OCH_3$), 3.46 (1 H, s, C_2 H), 2.78 (3 H, s, $-NCH_3$), 0.52 (3 H, t, *J* = 7 Hz, $-CH_2CH_3$); *m/e* 338 (M^+), 323, 309, 202, 164, 124.

B. Similarly, **16** gave **17** in 70% yield.

Diols 18. The olefin **17** (354 mg) and osmium tetroxide (500 mg) were stirred in dry tetrahydrofuran (10 mL) at 0 °C for 2 h. Saturated sodium sulfite solution (5 mL) was added and the mixture stirred at 0 °C for 45 min. The mixture was poured into saturated sodium bicarbonate solution and extracted with ether. The ether layer was dried (Na_2SO_4) and evaporated. Chromatography on silica gel gave a mixture of diols **18** (240 mg, 62%): mp 146–150 °C; IR ($CHCl_3$) 3520 cm^{-1}.

3-Ketone 19. The diols **18** (240 mg) and sodium periodate (460 mg) were stirred in a mixture of methanol (10 mL) and water (2 mL) at 0–5 °C for 60 min. The mixture was poured into saturated sodium bicarbonate solution and extracted with ether. The extract was dried (Na_2SO_4) and evaporated. Chromatography on silica gel gave the ketone **19** (117 mg, 54%): IR ($CHCl_3$) 1700 cm^{-1}; UV (EtOH) 212 nm (log ϵ 4.45), 253 (3.72), 304 (3.56); ^1H NMR ($CDCl_3$) δ 6.88 (1 H, d, *J* = 8 Hz, C_{14} H), 6.22 (1 H, dd, *J* = 8, 2 Hz, C_{15} H), 6.03 (1 H, d, *J* = 2 Hz, C_{17} H), 3.79 (3 H, s, $-OCH_3$), 3.50 (1 H, s, C_2 H), 2.90 (3 H, s, $-NCH_3$), 0.62 (3 H, t, *J* = 7 Hz, $-CH_2CH_3$); *m/e* 340 (M^+), 312, 283, 188, 138, 124.

Dione 20. The ketone **19** (52 mg), diisopropylamine (0.1 mL), and *n*-butyllithium (0.62 mL of a 1 N solution) were stirred in dry tetrahydrofuran (2 mL) at ambient temperature for 30 min. Molybdenum peroxide/pyridine/HMPA complex[16] (70 mg) was added at 0 °C and the mixture stirred at ambient temperature for 30 min. A further amount of the complex (30 mg) was added and stirring continued for 2 h. The mixture was partitioned between water and dichloromethane. The organic layer was dried (Na_2SO_4) and evaporated. The residue (48 mg) was stirred with cupric acetate (50 mg) in methanol (1 mL) at ambient temperature for 30 min. The mixture was chromatographed on silica gel to give starting material **19** (4 mg) and the yellow dione **20** (27 mg, 50%): mp 143–145 °C; $[\alpha]_D$ +37.7° (*c* 0.19, $CHCl_3$); IR ($CHCl_3$) 1710 cm^{-1}; UV (EtOH) 248 nm (log ϵ 3.86), 299 (3.73), 320–460 (sh); ^1H NMR ($CDCl_3$) δ 7.03 (1 H, d, *J* = 8 Hz, C_{14} H), 6.38 (1 H, dd, *J* = 8, 2 Hz, C_{15} H), 6.16 (1 H, d, *J* = 2 Hz, C_{17} H), 3.81 (3 H, s, $-OCH_3$), 3.70 (1 H, s, C_2 H), 2.67 (3 H, s, $-NCH_3$), 0.58 (3 H, t, *J* = 7 Hz, $-CH_2CH_3$); *m/e* 354 (M^+), 326, 298, 124.

Acetate 21. The dione **20** (26 mg) in methanol (1 mL) was treated with titanium trichloride (0.5 mL of a 0.4 M solution in methanol) at ambient temperature and stirring continued for 3 h. The solution was partitioned between saturated sodium bicarbonate solution and ether. The ether layer was dried and evaporated. The residue (25 mg) was stirred in acetic anhydride (0.25 mL)/pyridine (0.25 mL) for 30 min. Chromatography on silica gel gave starting material **20** (4 mg) and the acetate **21** (19 mg, 65%): IR ($CHCl_3$) 1738, 1720 cm^{-1}; UV (EtOH) 212 nm (log ϵ 4.44), 247 (3.82), 307 (3.80); ^1H NMR ($CDCl_3$) δ 6.98 (1 H, d, *J* = 8 Hz, C_{14} H), 6.25 (1 H, dd, *J* = 8, 2 Hz, C_{15} H), 6.05 (1 H, d, *J* = 2 Hz, C_{17} H), 5.33 (1 H, d, *J* = 8.5 Hz, C_2H), 3.85 (1 H, d, *J* = 8.5 Hz, C_3H), 3.80 (3 H, s, $-OCH_3$) 2.82 (3 H, s, $-NCH_3$), 2.17 (3 H, s, $-OCOCH_3$) 0.66 (3 H, t, *J* = 7 Hz, $-CH_2CH_3$); *m/e* 398 (M^+), 370, 369, 355, 327, 298, 224, 188, 124.

Ketone 22. The acetate **21** (18 mg) and zinc powder (50 mg) were heated in a mixture of acetic acid (1.5 mL) and hydriodic acid (0.05 mL) under reflux for 3 h. The mixture was partitioned between saturated sodium bicarbonate solution and dichloromethane. The organic layer was dried (Na_2SO_4) and evaporated. Chromatography on silica gel gave starting material **21** (7 mg) and the ketone **22** (7 mg, 45%): mp 130–132 °C (lit.[2] mp 130–132 °C); $[\alpha]_D$ +12° (lit.[2] +12°; *c* 1, $CHCl_3$); IR ($CHCl_3$) 1700 cm^{-1}; UV (EtOH) 213 nm (log ϵ 4.48), 252 (3.81), 305 (3.73); ^1H NMR ($CDCl_3$) δ 7.00 (1 H, d, *J* = 8 Hz, C_{14} H), 6.29 (1 H, dd, *J* = 8, 2 Hz, C_{15} H), 6.04 (1 H, d, *J* = 2 Hz, C_{17} H), 3.78 (3 H, s, $-OCH_3$), 2.68 (3 H, s, $-NCH_3$), 0.46 (3 H, t, *J* = 7 Hz, $-CH_2CH_3$); *m/e* 340 (M^+), 312, 298, 188, 174, 166, 124.

β-Keto Ester 23. A solution of the ketone **22** (400 mg) in anhydrous tetrahydrofuran (5 mL) was added, over a period of 20 min, to a suspension of sodium hydride (300 mg of 56% dispersion in oil) in tetrahydrofuran (20 mL) under an atmosphere of nitrogen. The mixture was stirred at ambient temperature for 2 h, dimethyl carbonate (1.8 mL) was added, and the mixture was heated to reflux. After 38 h, the mixture was cooled and excess sodium hydride destroyed by the addition of glacial acetic acid. The solution was diluted with water (20 mL) and extracted with ether. The ether extract was washed with sodium bicarbonate solution and with sodium chloride solution, dried (Na_2SO_4), and concentrated. Chromatography on silica gel gave **23** (336 mg, 71%): $[\alpha]_D$ −13.7° (*c* 0.73, $CHCl_3$); IR ($CHCl_3$) 1725, 1700, 1610 cm^{-1}; UV (EtOH) 212 nm (log ϵ 4.39), 252 (3.88), 304 (3.59); ^1H NMR ($CDCl_3$) δ 6.38 (1 H, s, –OH enol form) 6.96 and 6.92 (1 H, 2 d, *J* = 8 Hz, C_{14} H), 6.26 and 6.18 (1 H, 2 dd, *J* = 8, 2 Hz, C_{15} H), 6.03 and 5.92 (1 H, 2 d, *J* = 2 Hz, C_{17} H), 4.30 (1 H, s, C_2 H enol form), 4.18 (1 H, d, *J* = 4 Hz), 4.00 (1 H, d, *J* = 6 Hz), 3.78 (3 H, s, $-OCH_3$), 3.76 (3 H, s, $-OCH_3$), 2.70 and 2.68 (3 H, 2 s, $-NCH_3$), 0.60 and 0.50 (3 H, 2 t, *J* = 7 Hz, $-CH_2CH_3$); *m/e* 398.220 (M^+, calcd for $C_{23}H_{30}N_2O_4$, 398.218), 298, 188, 174, 124.

Hydroxy Ester 24. A solution of potassium *tert*-butoxide (7 mL of a solution prepared from 214 mg of potassium metal in 25 mL of anhydrous *tert*-butyl alcohol) was added to the keto ester **23** (70 mg) in 1,2-dimethoxyethane (20 mL) and *tert*-butyl alcohol (1 mL). The mixture was stirred for 15 min at ambient temperature, cooled to −35 °C (dry ice–benzyl chloride), and treated with hydrogen peroxide (0.08 mL of a 98% solution). Oxygen was then passed through the reaction mixture (−35 °C) for a period of 21 h. The mixture was allowed to attain room temperature and concentrated under vacuum. The residue was partitioned between brine and ethyl acetate, and the organic layer was dried (Na_2SO_4) and concentrated. Chromatography

on silica gel gave starting material **23** (15 mg) and the hydroxy ester **24** (35 mg, 59%): $[\alpha]_D$ +4.9° (*c* 0.08, $CHCl_3$); IR ($CHCl_3$) 3450, 1748, 1712 cm^{-1}; (EtOH) 213 nm (log ϵ 4.49), 248 (3.81), 303 (3.67); ^1H NMR ($CDCl_3$) δ 6.96 (1 H, d, *J* = 8 Hz, C_{14} H), 6.36 (1 H, dd, *J* = 8, 2 Hz, C_{15} H), 6.11 (1 H, d, *J* = 2 Hz, C_{17} H), 3.83 (3 H, s, $-OCH_3$), 3.75 (3 H, s, $-OCH_3$), 2.64 (3 H, s, $-NCH_3$), 0.51 (3 H, t, *J* = 7 Hz, $-CH_2CH_3$); *m/e* 414.214 (M^+, calcd for $C_{23}H_{30}N_2O_5$, 414.215), 258, 188, 174, 124.

Deacetyl-6,7-dihydrovindoline (2). Reduction of **24** as described in the literature[3] gave **2**, identical with an authentic sample, in only 5% yield. Similar yields were obtained by reduction with sodium borohydride in tetrahydrofuran.

6,7-Dihydrovindoline (25). Acetylation of **2** with acetic anhydride/sodium acetate at ambient temperature gave **25** identical with an authentic sample.

Lactams 26, 28, and 29. A. Mercuric acetate (398 mg) and dihydrovindoline **25**, (114 mg) were heated in dioxane (2 mL) at 110 °C for 36 h. The mixture was cooled, filtered through Celite, and evaporated. The residue was dissolved in 2 N ammonium hydroxide solution and extracted with dichloromethane. The extract was washed with brine, dried (Na_2SO_4), and concentrated. Chromatography on silica gel gave starting material (14 mg) together with the lactam ether **26**[21] (20 mg, 19%) [mp 201–202 °C (ethyl acetate–ether); $[\alpha]_D$ −13.6° (*c* 0.34, $CHCl_3$); IR (CH_2Cl_2) 1747, 1655, 1649 cm^{-1}; UV (EtOH) 214 nm (log ϵ 4.57), 256 (3.82), 308 (3.70); ^1H NMR ($CDCl_3$) δ 6.91 (1 H, d, *J* = 8 Hz, C_{14} H), 6.30 (1 H, dd, *J* = 8, 2 Hz, C_{15} H), 6.06 (1 H, d, *J* = 2 Hz, C_{17} H), 5.77 (1 H, s, C_4 H), 4.26–4.60 (2 H, m, C_6 H and C_7 H), 4.09 (1 H, s, C_2 H), 3.79 (3 H, s, $-OCH_3$), 3.78 (3 H, s, $-OCH_3$), 3.61 (1 H, s, C_{19} H), 2.80 (3 H, s, $-NCH_3$), 1.96 (3 H, s, $-OCOCH_3$), 0.89 (3 H, t, *J* = 7 Hz, $-CH_2CH_3$); *m/e* 470 (M^+), 411, 188, 187, 174, 173, 172, 159, 157, 145. Anal. ($C_{25}H_{30}N_2O_7$) C, H, N]; the lactam **28** (20 mg, 19%) [mp 225–227 °C (ethyl acetate–ether); IR (CH_2Cl_2) 3530, 1686, 1675, 1616, 1600 cm^{-1}; UV (EtOH) 211 nm (log ϵ 4.65), 249 (3.93), 302 (3.74); ^1H NMR ($CDCl_3$) δ 7.01 (1 H, d, *J* = 8 Hz, C_{14} H), 6.38 (1 H, dd, *J* = 8, 2 Hz, C_{15} H), 6.14 (1 H, d, *J* = 2 Hz, C_{17} H), 5.64 (1 H, s, C_4 H), 4.08 (1 H, bd, *J* = 16 Hz, C_{11} H), 3.82 (3 H, s, $-OCH_3$), 3.78 (3 H, s, $-OCH_3$), 3.68 (1 H, s, -OH), 3.61 (1 H, s, C_2 H), 3.50 (1 H, s, C_{19} H), 2.98 (1 H, dd, *J* = 18,1.5 Hz), 2.63 (1 H, d, *J* = 18 Hz), 2.63 (3 H, s, $-NCH_3$), 2.03 (3 H, s, $-OCOCH_3$), 0.57 (3 H, t, *J* = 7 Hz, $-CH_2CH_3$); *m/e* 472.2167 (M^+, calcd for $C_{25}H_{32}N_2O_7$, 472.2208), 458, 442, 430, 413, 412, 312, 174, 159. Anal. ($C_{25}H_{32}N_2O_7$) C, H, N]; and the lactam **29** (6 mg, 5%) [IR (CH_2Cl_2) 3500, 1747, 1667, 1645, 1617 cm^{-1}; UV (EtOH) 214 nm (log ϵ 4.63), 253 (3.94), 305 (3.73); ^1H NMR ($CDCl_3$) δ 6.86 (1 H, d, *J* = 8 Hz, C_{14} H), 6.27 (1 H, dd, *J* = 8, 2 Hz, C_{15} H), 6.05 (1 H, d, *J* = 2 Hz, C_{17} H), 5.25 (1 H, s, C_4 H), 3.91 (1 H, s, C_2 H), 3.78 (3 H, s, $-OCH_3$), 3.76 (3 H, s, $-OCH_3$), 3.27 (1 H, s, C_{19} H), 2.67 (3 H, s, $-NCH_3$), 1.98 (3 H, s, $-OCOCH_3$), 0.75 (3 H, t, *J* = 7 Hz, $-CH_2CH_3$); *m/e* 472 (M^+), 471, 470, 458, 442, 430, 413, 412, 312, 298, 280, 209, 188, 187, 174, 157, 124, 84, 43].

B. Similar oxidation of vindoline (**1**) gave **26**, in 56% yield, identical with that prepared above.

3-*O*-Acetyl-8-oxovindoline (27). A solution of trityllithium (2 equiv) in tetrahydrofuran was added to the lactam ether **26** (44 mg) in tetrahydrofuran at 0 °C under a nitrogen atmosphere. After 15 min a further 2 equiv of trityllithium solution was added. Stirring was continued for 5 min. Acetic anhydride (153 mg) in tetrahydrofuran (1 mL) was added at 0 °C and the mixture stirred at this temperature for 30 min, then at ambient temperature for 2 h. The mixture was poured into saturated sodium bicarbonate solution and extracted with dichloromethane. The extract was washed with sodium bicarbonate solution and water, dried (Na_2SO_4), and concentrated. Chromatography on silica gel gave the acetate **27** (11.5 mg, 24%): mp >250 °C; $[\alpha]_D$ −141.3° (*c* 0.14, $CHCl_3$); IR (CH_2Cl_2) 1760, 1688 cm^{-1}; UV (EtOH) 214 nm (log ϵ 4.66), 251 (3.95), 302 (3.76); ^1H NMR ($CDCl_3$) δ 6.85 (1 H, d, *J* = 8 Hz, C_{14} H), 6.35 (1 H, dd, *J* = 8, 2 Hz, C_{15} H), 6.18 (1 H, d, *J* = 2 Hz, C_{17} H), 6.01 (1 H, d, *J* = 10 Hz, C_6 H), 5.90 (1 H, d, *J* = 10 Hz, C_7 H), 5.29 (1 H, s, C_4 H), 4.22 (1 H, s, C_2 H), 3.78 (3 H, s, $-OCH_3$), 3.72 (3 H, s, $-OCH_3$), 2.84 (3 H, s, $-NCH_3$), 2.03 (3 H, s, $-OCOCH_3$), 2.01 (3 H, s, $-OCOCH_3$), 0.75 (3 H, t, *J* = 7 Hz, $-CH_2CH_3$); *m/e* 512 (M^+), 188, 187 (100%), 174, 172, 159, 144.

Vindoline (1). Trimethyloxonium tetrafluoroborate (87 mg) and the lactam **27** (20 mg) were stirred in dry dichloromethane (2 mL) for 56 h. The solution was evaporated and the residue dissolved in absolute ethanol (2 mL). Sodium borohydride (23 mg) was added in portions and stirring continued at 0 °C for 20 h. Water (1 mL) was added and the mixture filtered. The filtrate was partitioned between water and dichloromethane. The organic phase was washed with saturated ammonium chloride, dried (Na_2SO_4), and evaporated. Chromatography on silica gel gave starting material **27** (8 mg) together with a mixture of 3-*O*-acetylvindoline and vindoline. This mixture was treated with methanol (1 mL), water (1 drop), and silica gel (9 mg) for 13 h at ambient temperature to give pure vindoline (**1**, 1.3 mg, 10%) identical with an authentic sample.

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