carbon tetrachloride, differs from that previously calculated for the model *trans*-decahydroisoquinolin-4α-ol equilibrium (74:26) in tetrachloroethylene.[8] (This compound reacted with carbon tetrachloride.) Since the solvent difference should presumably not be a factor, this discrepancy may be due to a maximum experimental error that reflects a 3–5 mol % probable error in the experimental values of the various conformer percentages. We favor the present assignments, however, due to the internal consistency of these results. For comparison, values of 53% **9d** and 10% **9c** have been reported by S. Vasickova, A. Vitek, and M. Tichy, *Collect. Czech. Chem. Commun.*, **38**, 1791 (1973), based upon other model systems.

(23) W. Barbieri, L. Bernardi, and P. Maggioni, *Chim. Ind.* (*Milan*), **52**, 240 (1970).

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Application of a Modification of the Polonovski Reaction to the Synthesis of Vinblastine-Type Alkaloids

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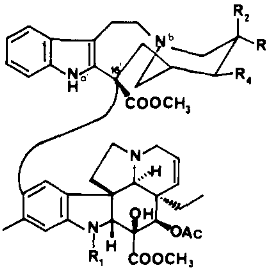
Abstract: A new C(16)–C(21) skeletal fragmentation of ibogane derivatives, induced by the modified Polonovski reaction, leads in the presence of aspidospermane derivatives to vinblastine-type compounds with the natural C(16′) configuration, which seems necessary for significant antitumor activity. This new method of coupling, which could be the same as the biogenetical pathway, has been and will be applied to partial synthesis of naturally occurring antitumor alkaloids of *Catharanthus roseus*. The circular dichroism technique is of high diagnostic value for this series of compounds to distinguish between the natural or unnatural C(16′) configurations. Another type of skeletal fragmentation at C(5)–C(6), also encountered during this study, was minimized under the experimental conditions.

Several antitumor alkaloids have been isolated from *Catharanthus roseus*,[1] including vinblastine[2] (**1a**), vincristine[2] (**1b**), leurosidine[3] (**1c**), and leurosine[3] (**1d**), and two of them, **1a** and **1b**, are widely used in cancer chemotherapy,



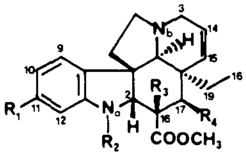
1a: $R_1 = CH_3$; $R_2 = OH$; $R_3 = Et$; $R_4 = H$
1b: $R_1 = CHO$; $R_2 = OH$; $R_3 = Et$; $R_4 = H$
1c: $R_1 = CH_3$; $R_2 = Et$; $R_3 = OH$; $R_4 = H$
1d: $R_1 = CH_3$; $R_2 = Et$; $R_3 + R_4 =$ "O"

Unfortunately these compounds are present at very low concentrations in the plant material and their isolation is long, costly, and fraught with difficulty. For these reasons, their synthesis (partial or total) has been the subject of a considerable amount of work in the past ten years.[4-12]

All these attempts were unsuccessful and led to compounds having "unnatural" configuration at C(16′) and consequently, biologically inactive. Therefore, we recently[13] introduced a new method based on a modification of the Polonovski reaction,[14] which was afterwards[15] adopted by other workers.[16]

The procedures used by our predecessors[7,9,10,12] consisted of condensing vindoline (**2a**) or one of its derivatives with compounds having the *tetracyclic* ibogane skeleton, **4** or **5**, obtained by cleavage[17] of the C(16)–C(21)[18] bond of catharanthine (**3a**) (Scheme I) or by total synthesis.[5b,5c]

However, a plausible biogenetic hypothesis[10] proposes that the vinblastine-type alkaloids could well be formed in nature by direct coupling of vindoline (**2a**) with catharanthine (*pentacyclic* ibogane skeleton) (**3a**), major alkaloidal components of *C. roseus*. This hypothesis has been verified[19] in vivo; coupling of the two "monomeric" units could take place with concomitant breaking of the C(16)–C(21) bond of catharanthine (**3a**).



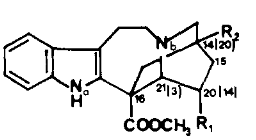
2a: $R_1 = OCH_3$; $R_2 = CH_3$
$R_3 = OH$; $R_4 = OAc$

2b: $R_1 = H$; $R_2 = CH_3$
$R_3 = OH$; $R_4 = OAc$

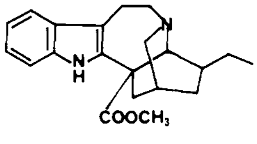
2c: $R_1 = H$; $R_2 = CH_3$
$R_3 = H$; $R_4 = H$

2d: $R_1 = OCH_3$; $R_2 = CH_3$
$R_3 = H$; $R_4 = H$

2e: $R_1 = OCH_3$; $R_2 = CHO$
$R_3 = H$; $R_4 = H$

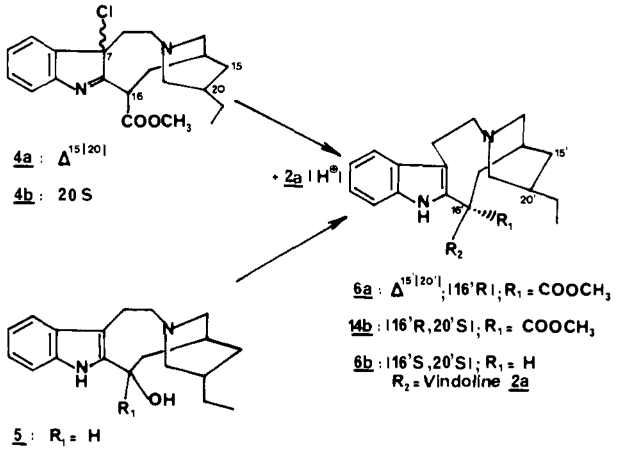


3a: $\Delta^{15(20)}$; $R_1 = Et$; $R_2 = H$
3b: $R_1 = 20S$ Et; $R_2 = H$
3c: $\Delta^{(14)}$; $R_1 = H$; $R_2 = Et$
3d: $R_1 = H$; $R_2 = Et$



3e

Scheme I



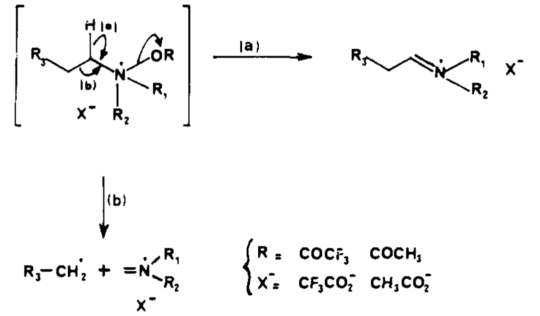
4a: $\Delta^{15(20)}$
4b: 20 S

5: $R_1 = H$

6a: $\Delta^{15'(20')}$; (16′R); $R_1 = COOCH_3$
14b: (16′R,20′S); $R_1 = COOCH_3$
6b: (16′S,20′S); $R_1 = H$
$R_2 =$ Vindoline **2a**

It is known that the Polonovski reaction[20]—action of an acid anhydride on an *N*-oxide—can give rise both to elimination (path a) or fragmentation reactions (path b),[21] as shown in Scheme II.

Scheme II

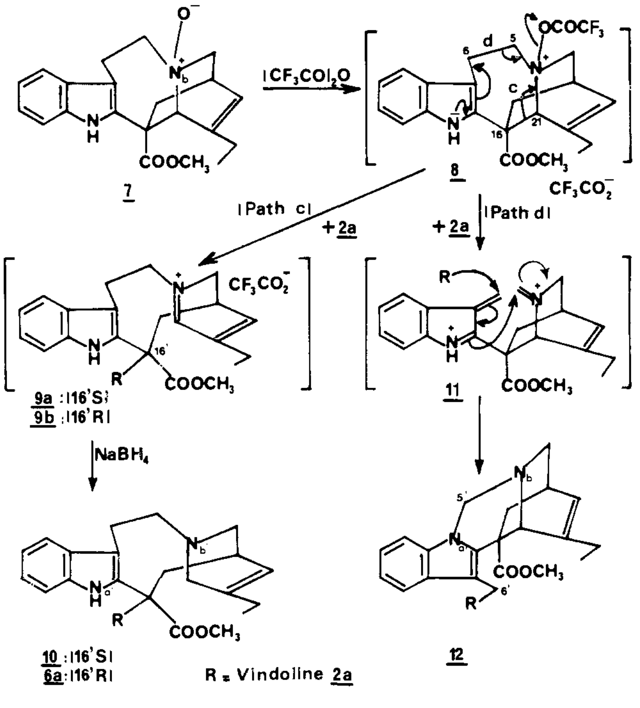


Preference for one or the other pathway is governed by electronic factors (nucleophilicity of X^-, nature of the leaving group RO^-) and steric factors (antiparallelism of C-C and $\geqslant N^+$-O^- bonds).[22]

In the past ten years, we have found many applications for this reaction; for example, in the preparation of a versatile Mannich reagent,[23] the synthesis[24] and partial synthesis[25] of natural products. The partial synthesis of vinblastine-type alkaloids[13] constitutes one of the recent important developments of this reaction.

The rigid conformation of *pentacyclic* ibogane-type alkaloids (i.e., **3a**) lends itself to fragmentation reactions, since the bonds C(16)-C(21) and C(5)-C(6) are antiparallel with respect to the $\geqslant N^+$-O^- bond of the corresponding *N*-oxides of these alkaloids; they are therefore susceptible to cleavage induced by suitable reagents such as trifluoroacetic anhydride.[21] The formation of only one *N*-oxide is observed for catharanthine (**3a**) or its immediate derivatives. After treating the *N*-oxide (**7**) (a compound which is itself not stable and readily undergoes a facile skeletal rearrangement[26]) with trifluoroacetic anhydride in the presence of vindoline (**2a**), two sorts of fragmentation are observed, as shown in Scheme III.

Scheme III

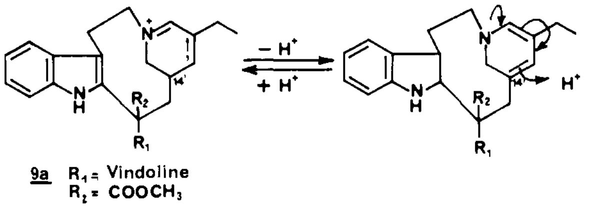


I. **Cleavage of the C(16)-C(21) bond** (path c) leads to the compound **10** (16′*S*) or anhydrovinblastine (yield 50%) and its 16′*R* epimer **6a**, after direct reduction of the corresponding immoniums **9a** and **9b** in the reaction medium. The relative amounts of these two compounds and the total yields vary with the concentrations used (see Experimental Section). This, along with an inspection of the molecular models, leads one to assume that compound **10** ("natural" configuration) would be the result of a concerted reaction and **6a** the result of a stepwise reaction. For the latter case, the assumed intermediate could well be analogous to that obtained from coupling reactions using derivatives such as **4** or **5**.[12]

The nature of the junction between the two monomers was elucidated from ^1H NMR studies (240 MHz):[27] the protons C(12)-H and C(9)-H appear as singlets for **10** and **6a**, showing that the vindoline part is substituted at C(10); also, a comparison of the chemical shifts of C(9)-H, C(12)-H, and C(18)-H of **10**, vinblastine (**1a**), leurosidine (**1c**), and leurosine (**1d**) show that there is a strong similarity between these compounds. Finally, the absence of signals between 4 and 5 ppm eliminates the possibility of a junction α to $N_{b'}$ of the ibogane moiety.

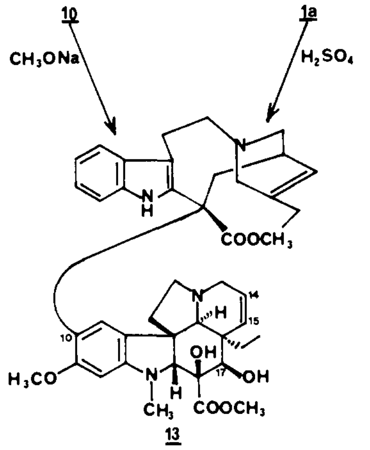
To exclude the possibility of isomerization at C(14′) through an ene-immonium **9a**-dieneamine equilibrium (Scheme IV), a correlation between **10** and vinblastine (**1a**) has been carried out.

Scheme IV



Treatment of vinblastine (**1a**) by H_2SO_4 at 0 °C gives, among other products (see Experimental Section) a dehydrated ($\Delta^{15'(20')}$) and C(17) deacetylated product **13**, which is identical with the product obtained by deacetylation of **10** at C(17) (Scheme V).

Scheme V



Finally, compound **6a** ("unnatural" configuration 16′*R*) proved to be identical with the compound obtained[10-12] by coupling the chloroindolenine (**4a**) with vindoline (**2a**) (Scheme I).

The coupling reaction of 15,20*S*-dihydrocatharanthine (**3b**) (as the Nb oxide) with vindoline (**2a**) gives, through the same type of cleavage reaction (path c, Scheme III) three compounds having the same planar structure. These are **14a** (16′*S*,20′*S*) and the two compounds **14b** (16′*R*,20′*S*) and **14c** (16′R,20′*R*) (Scheme VI).

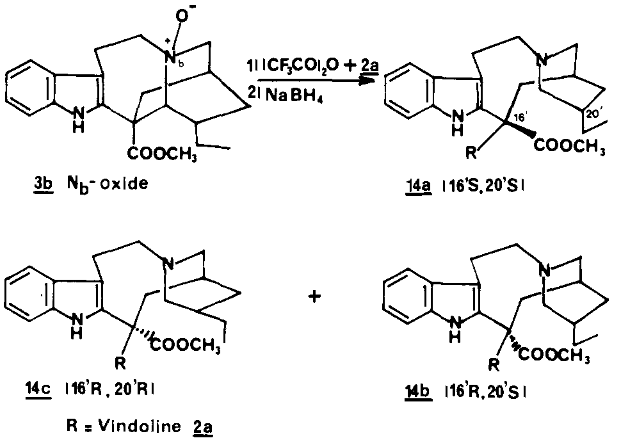
Because of the similarities between the spectral properties of "deoxy vinblastine B" and isoleurosine (20′ epimers),[7] compound **14a** was converted to the corresponding hydrazide, whose optical rotation show it to be a compound of configu-

Table I

	Products			
	Fragmentation C(16)-C(21)			
Substrates	16'*S* configuration (%)	16'*R* configuration (%)	Fragmentation C(5)-C(6) (%)	Other products (%)
2a + **7**^{b}	**10** (50)	**6a** (12)	**12** (4)	
2a + **3b**^{a,b}	**14a** (20'*S*) (10)	**14b** (20'*S*) (19) **14c** (20'*R*) (4)	**20** (9)	
2a + **3c**^{a,c}	**21** (20)			**18a** (3)
2a + **3d**^{a,b}	**22** (11)		**23** (17)	
2a + **3e**^{a,c}	**24a**^{d} (39) **24b**^{d} (10)	**24c**^{e} (4)	**24d** (17)	**18a** (16) **18b** (9)
7 + **2b**^{b}		**25** (18)		
7 + **2c**^{b}	**26** (12)			
7 + **2d**^{b}	**27a** (19)	**27b** (3)	**28** (6)	**19a** + **19b** (48)
7 + **2e**^{b}				**2e** (90)

[a] Previously treated by p-$NO_2C_6H_4CO_3H$. [b] Coupling temperature −78 °C. [c] Coupling temperature 0 °C. [d] Attributed configuration 16'*S*. [e] Attributed configuration 16'*R*.

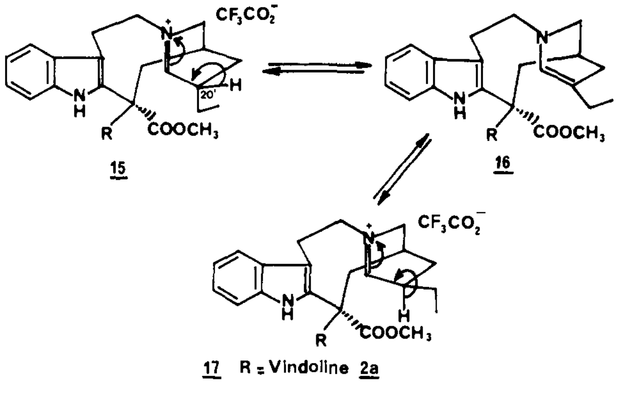
Scheme VI



ration 20'*S*. This result was also confirmed by direct comparison of compound **14a** with an authentic sample of "deoxy vinblastine B".[7]

Also **14b** is identical with the coupling product of the chloroindolenine of 15,20*S*-dihydro-16*S*-carbomethoxycleavamine (**4b**)[28] with vindoline (**2a**) (Scheme I). Configurations of **14b** and **14c** are therefore determined. Isomerization at C(20) of **14b** and **14c** is explained through the equilibrium immoniums **15** (**17**)-enamine **16**; reprotonation, followed by reduction, can lead either to the isomer 20'*S* **14b** or 20'*R* **14c** (Scheme VII).

Scheme VII



The compound having the configurations 16'*S*,20'*R* was not obtained from our experiments.

The ene-immonium **9a** (Scheme III), when treated with sodium cyanoborohydride in an acid medium also gives **14a**, undoubtedly by a 1,4-reduction of the dihydropyridine system, giving an intermediate enamine which reprotonates and undergoes further reduction.

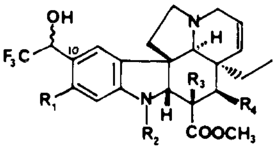
Finally, compound **10** (Scheme III) can be reduced regio- and stereospecifically to **14a**, the Δ^{14} bond of the vindoline moiety being unaffected under the conditions used.

II. Cleavage of the C(5)-C(6) bond (path d, Scheme III) leads to products such as **12**,[29] a minor product in the reaction conditions (CH_2Cl_2, $(CF_3CO)_2O$, −78 °C).

However, this type of fragmentation, the reverse of a previously observed example,[30] becomes predominant as the nucleophilicity of R increased (R = X^- = $CH_3CO_2^-$, OH^-).[29]

Similar compounds **20**, **23**, **24d**, and **28** are obtained from the coupling of various aspidospermane-ibogane alkaloids or derivatives (Table I).

These coupling reactions are accompanied by a side reaction due to the nucleophilic character of C(10) of aspidospermane alkaloids with respect to the CF_3CO^+ ion. For example, in the case of vindoline (**2a**), the two epimeric alcohols **18a** and **18b** are obtained after reduction of the reaction mixture with sodium borohydride.



18a - 18b : R_1 = OCH_3; R_2 = CH_3 ; R_3 = OH ; R_4 = OAc
19a - 19b : R_1 = OCH_3; R_2 = CH_3 ; R_3 = H ; R_4 = H

Use of a "Polonovski-type" cleavage reaction for the partial syntheses of vinblastine-type alkaloids makes many compounds having the "natural" configuration at C(16') readily accessible starting from aspidospermane and ibogane alkaloids or derivatives. Thus, one can vary independently the different functionalities in the alkaloids before coupling them to produce new "dimers" for biological evaluation. This enables studies of the structure-activity relationship for this important group of compounds, in particular the study of their interaction with tubuline. For these reasons, a number of condensations have been carried out starting with various aspidospermane and ibogane alkaloids and derivatives. The results obtained are shown in Table I.

With reference to Table I several comments are in order. For the ibogane alkaloids or derivatives one notices that those

Table II

16′*S*	**1a**	**1b**	**1c**	**10**	**14a**	**21**	**22**	**26**	**27a**
λ, nm	254	254	260	258	255	258	259	264	263
Δϵ	10.5	13.1	+12.8	+14.0	+12.5	+7.9	14.6	+12.8	+13.4
λ, nm	302	302	305	305	302	302	305	304	305
Δϵ	4.8	7.0	5.7	6.5	5.0	0.2	7.3	5.9	5.8

16′*R*	**6a**	**14b**	**14c**	**25**	**24a** (16′*S*)	**24b** (16′*S*)
λ, nm	258	260	259	257	263	257
Δϵ	−13	−13.8	−11.8	−13	31.2	34.0
λ, nm	309	307	310	303	312	310
Δϵ	8.5	8.2	5.9	+8.4	−11.5	−9.9

which contain a double bond in the isoquinuclidine part, i.e., catharanthine (**3a**) and allocatharanthine (**3c**),[41] give better yields of the coupled products than their saturated analogues (dihydrocatharanthine (**3b**) and dihydroallocatharanthine (**3d**)), the cleavage reaction between C(16–C(21) being favored by the presence of the double bond.

Similarly, we have varied the nucleophilic character of the aspidospermane moiety. In every case, vindoline (**2a**) gives the best results in the coupling reaction. The presence of the basic nitrogen N_a seems necessary: N_a-formyl-2,16-dihydro-11-methoxytabersonine (**2e**) does not undergo any coupling reaction. On the other hand, the influence of an oxygen atom on C(11) seems less marked[11] (as in the case of N_a-methyl-2,16-dihydrotabersonine (**2c**) and N_a-methyl-2,16-dihydro-11-methoxytabersonine (**2d**)). It is worthy to note that, rather unexpectedly, vindorosine (**2b**) yielded only one "dimer" **25** having "unnatural" 16′*R* configuration.

As we have already pointed out, for the first time,[13,15b] circular dichroism allows a ready distinction to be made between the 16′*S* compounds and their "unnatural" epimers 16′*R* (Table II). This diagnostic tool was also subsequently used by others.[31] There is a good agreement between the values obtained from vinblastine (**1a**) and the compounds 16′*S* on one hand and the compounds 16′*R* on the other hand. Coronaridine (**3e**) is enantiomeric to dihydrocatharanthine (**3b**);[32] CD curves of coupling compounds **24a** and **24b** (coronaridine (**3e**)-vindoline (**2a**)) imply that the configuration of these compounds may be 16′*S*.

Conclusion

The modified Polonovski reaction, discovered in our laboratory and applied to the *N*-oxides of ibogane alkaloids or derivatives, gives, principally, in the presence of a sufficiently nucleophilic alkaloidal counterpart, coupling products of the vinblastine type, of which one epimer has the "natural" configuration at C(16′). This method allows access to this type of highly active biological compounds by partial synthesis for the first time. Partial synthesis of antitumor alkaloid has been developed in our laboratory.[33]

The results obtained in these studies enable us to reach original structures having interesting pharmacological activities.

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, infrared spectra (ν cm^{-1}, $CHCl_3$) on a Perkin-Elmer 257, ultraviolet spectra [EtOH, λ_{max}, nm (ϵ)] on a Bausch and Lomb Spectronic 505, CD curves [EtOH, λ_{max}, nm ($\Delta\epsilon$)] on a Roussel-Jouan Dichrograph II. ^{1}H NMR spectra were obtained ($CDCl_3$, Me_4Si, δ = 0 ppm) from Varian T 60 or IEF 240[27] spectrometers (coupling constants, *J*, are given in hertz; s, d, t, dd, and m indicate singlet, doublet, triplet, doublet of doublet, and multiplet, respectively). Mass spectra were measured on an AEI MS 9. Preparative layer chromatography (preparative TLC) is performed with Kieselgel HF 254 + 366 Merck.

Catharanthine *N*-Oxide (7). *p*-Nitroperbenzoic acid (490 mg, 2.68 mmol, 98%) in 62 ml of CH_2Cl_2 was added at 0 °C to a stirred solution of 600 mg (1.79 mmol) of catharanthine (**3a**) in 18 ml of CH_2Cl_2. After 5 min, the reaction mixture was poured into 50 ml of a 10% aqueous solution of Na_2CO_3. Usual workup followed by evaporation *below 40 °C* gives catharanthine *N*-oxide in a quantitative yield: uv 277, 284, 293 nm; ^{1}H NMR (60 MHz) δ 8.06 (1 H, N_a–H); 7.6-7.0 (4 H, aromatic); 6.13 (br d, 1 H, $J \sim 7$ Hz, C(15)–H); 4.73 (br s, 1 H, C(21–H), 3.73 (s, 3 H, CO_2CH_3), 1.12 (t, 3 H, J = 7 Hz, C(18)–H); MS *m/e* 352 (100%, M·$^+$), 336, 335, 293, 254, 248, 222, 204, 144, 143. This spectrum is not that expected for catharanthine *N*-oxide, but rather that of its rearranged product.[26]

Coupling of Catharanthine *N*-Oxide (7) with Vindoline (2a). Trifluoroacetic anhydride (0.115 ml, 0.8 mmol) was added to a stirred solution of catharanthine *N*-oxide (**7**) (100 mg, 0.3 mmol) and vindoline[34] (**2a**) (135 mg, 0.3 mmol) in dry CH_2Cl_2 (0.83 ml) under N_2 at −78 °C. After 30 min, excess solvent and trifluoroacetic anhydride were distilled off in vacuo at 20 °C. The residue was dissolved in MeOH (5.7 ml) and excess $NaBH_4$ was added at 0 °C; after 15 min, the reaction mixture was poured into H_2O (100 ml) and extracted with $CHCl_3$. Preparative TLC (AcOEt–MeOH 96:4) of the residue (230 mg) afforded **10** (114 mg, 50%), **6a** (29 mg, 12%), and a mixture of **12** (9 mg, 4%) and vindoline (**2a**), which was separated by a second preparative TLC (AcOEt). This crucial experiment was carried out under various experimental conditions (see Table III).

$\Delta^{15'}$20′-Dehydroxyvinblastine (10) (anhydro VLB): mp 208–210 °C dec from methanol; $[\alpha]^{22}$D 19° (c = 0.70); ir 1740 (esters), 1615 cm^{-1} (indoline); uv 263 (17 500), 290 (14 300), and 297 nm (13 400), superposition of indole and dihydroindole chromophores; CD 258 (14.0), 305 (6.5); ^{1}H NMR δ 9.77 (1 H, C(16)–OH), 7.87 (br s, 1 H, $N_{a'}$–H), 6.52 and 6.03 (s, 1 H, C(9)–H and C(12)–H), 5.76 (dd, $J_{14,15}$ = 9.4 and $J_{3,14} \sim$ 3.8 Hz, C(14)–H), 5.4 (C(15′)–H), 5.37 (s, C(17)–H), 5.22 (br d, 1 H, J = 9.4 Hz, C(15)–H), 3.74 (s, 3 H), 3.70 and 3.55 (s, 3 H, C(11)–OCH_3, C(16)–CO_2CH_3, and C(16′)–CO_2CH_3, 2.65 (s, 3 H, N_a–CH_3), 2.07 (s, 3 H, $OCOCH_3$), 0.96 (t, 3 H, $J_{18',19'}$ = 7.5 Hz, C(18′)–H), 0.81 (t, 3 H, $J_{18,19}$ = 7 Hz, C(18)–H); MS *m/e* 792.4085 (calcd 792.4098, $C_{46}H_{56}N_4O_8$, M·$^+$) 761, 733, 633, 611, 469, 336, 282.1340 (calcd 282.1341, $C_{14}H_{20}NO_5$), 136, 135.1043 (calcd 135.1048, $C_9H_{13}N$), 122, 121, 107.

$\Delta^{15'}$16′-*epi*-20′-Dehydroxyvinblastine (6a) (16′-epi anhydro VLB): mp (hydrobromide) >260 °C (methanol); $[\alpha]^{22}$D −86.4° (c = 0.72); ir 1740 (esters), 1620 cm^{-1} (indoline); uv 217 (44 300), 263 (12 600), 289 (10 700), 297 nm (11 000); CD 258 (−13.0), 282 (3.2), 309 (8.5); ^{1}H NMR δ 8.99 (s, 1 H, $N_{a'}$–H), 6.85 and 5.92 (s, 1 H, C(9)–H and C(12)–H), 5.84 (dd, 1 H, $J_{14,15}$ = 9.4 and $J_{3,14}$ = 4 Hz, C(14)–H), 5.50 (m, 1 H, C(15′)–H), 5.28 (s, 1 H, C(17)–H), 5.24 (d, 1 H, $J_{14,15}$ = 9.4 Hz, C(15)–H), 3.86 (s, 3 H) and 3.74 (br s, 6 H), C(11)–OCH_3, C(16)–CO_2CH_3, and C(16′)–CO_2CH_3), 2.60 (s, 3 H, N_a–CH_3), 2.07 (s, 3 H, $OCOCH_3$), 1.00 (t, 3 H, $J_{18',19'}$ = 7.0 Hz, C(18′)–H), 0.60 (t, 3 H, $J_{18,19}$ = 7.0 Hz, C(18)–H); MS *m/e* 792 (M·$^+$), 733, 669, 633, 610, 525, 510, 469, 336, 282, 135 (100%), 121, 107.

This compound is identical in all respects with that obtained by the coupling of chloroindolenine (**4a**) and vindoline (**2a**).[10-12]

"Dimeric" Compound 12 (violet with ceric ammonium sulfate (CAS[35]) reagent): $[\alpha]$D −55.8° (c = 0.67); ir 1745 (esters), 1620 cm^{-1} (indoline); uv 222 (37 400), 226 (sh, 36 000), 258 (12 300), 288 (9700), 296 nm (9900); in presence of acid 222 (39 000), 224 (sh, 37 400), 255 (12 000), 287 (8900) and 295 nm (9000); CD 250 (11.0),

Table III

Experiment No.	**7**, mmol (mol/l)	**2a**, mmol (mol/l)	$(CF_3CO)_2O$, mmol (mol/l)	CH_2Cl_2, ml	% **10**	% **6a**	% **18**	% **12**
1[a]	0.199 (3.44×10^{-2})	0.209 (3.6×10^{-2})	5.6 (0.96)	5.8	10	20	**18a,** 31 **18b,** 11	1.5
2[a]	1.5 (3.33×10^{-2})	1.58 (3.50×10^{-2})	4.31 (0.96)	45	5.8	8.5	**18a,** 54 **18b,** 13	
3[a]	0.199 (3.44×10^{-2})	0.209 (3.60×10^{-2})	0.56 (0.096)	5.8	15.8	28		
4[a]	0.199 (3.44×10^{-1})	0.209 (3.6×10^{-1})	0.56 (0.96)	0.58	40	10		2.5
5[b]	0.284 (3.44×10^{-1})	0.296 (3.56×10^{-1})	0.825 (0.96)	0.85	50	12		4

[a] 0 °C. [b] −78 °C.

304 (−5.1); ^{1}H NMR δ absence of N$_{a'}$-H, 7.2–6.8 (4 H, aromatic), 6.40 and 5.97 (s, 1 H, C(9)–H and C(12)–H), 5.97 (masked, 1 H, C(15′)–H), 5.70 (dd, 1 H, $J_{14,15}$ = 9.5 and $J_{3,14} \sim$ 3 Hz, C(14)–H), 5.22 (s, 1 H, C(17)-H), 5.10 (br d, 1 H, J = 9.5 Hz, C(15)–H), 5.05 and 4.93 (2 d, 2 H, J_{AB} = 12 Hz, C(5′)–H), 3.80 (s, 3 H), 3.71 and 3.45 (s, 3 H, C(11)–OCH_3, C(16)–CO_2CH_3, and C(16′)–CO_2CH_3), 2.67 (s, 3 H, N$_a$–CH_3), 2.04 (s, 3 H, $OCOCH_3$), 1.03 (t, 3 H, $J_{18',19'}$ = 7 Hz, C(18′)-H), 0.09 (t, 3 H, $J_{18,19} \sim$ 7 Hz, C(18)–H). MS *m/e* 790.3956 (calcd 790.3941, $C_{46}H_{54}N_4O_8$, M·$^+$), 731.3753 (calcd 731.3808, $C_{44}H_{51}N_4O_6$), 682.3106 (calcd 682.3128, $C_{39}H_{44}N_3O_8$), 631.3596 (calcd 631.3648, $C_{40}H_{47}N_4O_3$), 629, 523, 522.2741 (calcd 522.2756, $C_{33}H_{36}N_3O_3$), 509, 508.2595 (calcd 508.2600, $C_{32}H_{34}N_3O_3$), 308, 282.1335 (calcd 282.1341, $C_{14}H_{20}NO_5$), 188.1073 (calcd 188.1075, $C_{12}H_{14}NO$), 135.1044 (calcd 135.1048, $C_9H_{13}N$, 100%), 122, 121.0890 (calcd 121.0891, $C_8H_{11}N$), 107.0731 (calcd 107.0735, C_7H_9N).

Dehydration (and Deacetylation) of Vinblastine (VLB). Vinblastine sulfate (160 mg) was added with stirring under N_2 to 4 ml of concentrated H_2SO_4 at 0 °C; after 130 min, excess concentrated NH_4OH was added at 0 °C and extraction with $CHCl_3$ afforded a mixture which was separated by preparative alkaline TLC (ether–cyclohexane-MeOH 100:8:15) and gave **13** (17 mg) and $\Delta^{19'}$-deacetyl **14a** (22 mg), *E* + *Z* isomers.

Deacetyl anhydro VLB 13 (from VLB): $[\alpha]_D$ 88 ± 4° (c = 1.09); ir 3460 (NH, chelated OH), 1730 (esters), 1620 cm^{-1} (indoline); uv 217 (35 500), 268 (11 700), 290 (9300), 299 nm (8400); CD 260 (12.0), 304 (4.8); ^{1}H NMR 9.41 (1 H, C(16)–OH), 7.89 (1 H, N$_{a'}$–H), 7.41 (1 H, aromatic), 7.2–6.9 (3 H, aromatic), 6.50 and 6.02 (s, 1 H, C(9)–H and C(12)–H), 5.76 (dd, $J_{14,15}$ = 9.5 and $J_{3,14} \sim$ 3.5 Hz, C(14)–H), 5.66 (br d, J = 9.5 Hz, C(15)-H), 5.38 (1 H, C(15′)-H), 4.03 (C(17)–H), 3.80 (s), 3.76 and 3.56 (s, C(11)–OCH_3, C(16)–CO_2CH_3, and C(16′)–CO_2CH_3), 2.72 (s, 3 H, N$_a$–CH_3), absence of acetyl group, 1.90 (C(19′)–H), 1.68 (C(19)–H), 0.97 (t, $J_{18',19'}$ = 7 Hz, C(18′)–H), 0.93 (t, $J_{18,19}$ = 6.8 Hz, C(18)–H); MS *m/e* 750 (M·$^+$), 691, 633, 553, 427, 336, 265, 240, 188, 144, 136, 135, 122, 121 (100%), 108, 107, 106.

$\Delta^{19'}$-Deacetyl 14a (*E* + *Z* isomers) (a = major product, b = minor product: uv 217, 269, 289, 298, sh 318 nm; CD 16′*S* configuration; ^{1}H NMR δ 9.40 (1 H, C(16)–OH), 7.84 (1 H, N$_{a'}$–H), 7.37 (1 H, aromatic), 7.1–6.9 (3 H, aromatic), 6.46 and 6.00 (s, 1 H, C(9)–H and C(12)–H), 5.72 (dd, $J_{14,15}$ = 10 and $J_{3,14}$ = 3 Hz, C(14)–H), 5.64 (d, J = 10 Hz, C(15)–H), 5.38 (q, $J_{18',19'}$ = 6 Hz, C(19′)–H of a), 5.18 (q, $J \sim$ 7 Hz, C(19′)–H of b), 4.01 (C(17)–H), 3.78 (s), 3.74 and 3.53 (s, C(11)–OCH_3, C(16)–CO_2CH_3, and C(16′)–CO_2CH_3), 2.71 (s, N$_a$–CH_3), 1.70 (d, $J \sim$ 7 Hz, C(18′)–H of b), 1.65 (d, J = 6 Hz, C(18′)–H of a), 0.91 (t, $J \sim$ 6.5 Hz, C(18)–H); MS *m/e* 750 (M·$^+$), 692, 691, 633, 427, 265, 240, 136 (100%), 135, 122, 121 (100%), 108, 107.

Deacetyl Anhydro VLB 13 from 10. A solution of **10** (18 mg, 0.02 mmol) in MeOH (2 ml) was added with stirring to a solution of sodium methoxide (Na, 54 mg; MeOH, 2 ml). After 90 min at room temperature, the reaction mixture was poured into brine; usual workup afforded **13,** (14 mg, 80%) identical in all respects with compound **13** obtained from VLB.

15,20*S*-Dihydrocatharanthine *N*-Oxide (3b *N*-Oxide). 15,20*S*-Dihydrocatharanthine (**3b**)[17a] (464 mg, 1.37 mmol) treated by *p*-nitroperbenzoic acid (1.65 mmol) in the same experimental conditions as described for catharanthine (**3a**) (see above) afforded the corresponding *N*-oxide in quantitative yield: uv 277, 284, 293 nm; ^{1}H NMR δ 8.0 (1 H, N$_a$–H), 7.2–7.0 (4 H, aromatic), 4.23 (1 H, C(21)–H), 3.70 (s, 3 H, C(16)–CO_2CH_3); MS *m/e* 354 (M·$^+$), 338 (100%), 277, 214, 169, 144, 124, 120.

Coupling of 15,20*S*-Dihydrocatharanthine *N*-Oxide (3b *N*-Oxide) with Vindoline (2a). Trifluoroacetic anhydride (0.134 ml, 0.97 mmol) was added to a stirred solution of **3b** *N*-oxide (120 mg, 0.34 mmol) and vindoline (**2a**) (162 mg, 0.35 mmol) in 1.0 ml of dichloromethane under argon at −78 °C. After 50 min, usual workup led to a residue which was purified by preparative TLC (AcOEt–EtOH 3:1), yielding **14a** (26 mg, 10%) and 230 mg of a mixture of **14b, 14c, 20,** and vindoline (**2a**), which was again purified by TLC (AcOEt–MeOH 92:8) to give **14b** (55 mg, 19%), **14c** (12 mg, 4%) and 120 mg of a mixture of **20** and vindoline (**2a**). This mixture purified by preparative TLC (Merck HF 254 + 366, AcOEt eluent, two successive elutions) gave **20** (24 mg, 9%) and vindoline (**2a**) (67 mg).

"Dimeric" compound 14a ("deoxy-VLB B"): mp 214 °C (methanol); $[\alpha]_D$ 69° (c = 0.43); ir 1740, 1615 cm^{-1}; uv 216 (42 300), 263 (11 900), 290 (10 800), 297 (10 200); CD 255 (12.5), 302 (5.0); ^{1}H NMR δ 9.77 (1 H, C(16)–OH)), 7.83 (N$_{a'}$–H), 7.0 (aromatic), 6.49 and 6.02 (s, 1 H, C(9)–H and C(12)–H), 5.78 (dd, $J_{14,15}$ = 9 and $J_{3,14}$ $\sim$ 4 Hz, C(14)–H), 5.36 (s, 1 H, C(17)-H), 5.23 (br d, J = 9 Hz, C(15)–H), 3.74 (s, 6 H) and 3.55 (s, 3 H, C(11)–OCH_3, C(16)–CO_2CH_3, and C(16′)–CO_2CH_3), 2.67 (s, 3 H, N$_a$–CH_3), 2.08 (s, 3 H, $OCOCH_3$), 0.86 and 0.82 (2 superposed t, C(18′)-H and C(18) –H); MS *m/e* 794.4234 (calcd 794.4254, $C_{46}H_{58}N_4O_8$), 792, 763, 735, 635, 525, 510.2757 (calcd 510.2756, $C_{32}H_{36}N_3O_3$), 469, 338.1988 (calcd 338.1994, $C_{21}H_{26}N_2O_2$), 282.1332 (calcd 282.1341, $C_{14}H_{20}NO_5$), 138.1291 (calcd 138.1288, $C_9H_{16}N$, 100%), 135, 124, 122, 121, 108, 107.

Hydrazide from **14a** was prepared as described;[7] this decarbomethoxy deacetyl compound was identical in all respects with an authentic sample: $[\alpha]_D$ −10° (c = 0.70).

"Dimeric" compound 14b: $[\alpha]_D$ −26° (c = 0.58); uv 216 (43 600), 264 (11 600), 290 (9900), 297 (10 300); CD 260 (−13.8), 282 (5.0), 307 (8.2); ^{1}H NMR δ 9.62 (1 H, C(16)–OH), 8.95 (N$_{a'}$-H), 7.4–7.0 (aromatic), 6.93 and 6.00 (s, 1 H, C(9)–H and C(12)-H), 5.90 (dd, 1 H, $J_{14,15}$ = 9 and $J_{3,14} \sim$ 4 Hz, C(14)–H), 5.38 (d, 1 H, $J_{14,15}$ = 9 Hz, C(15)–H), 5.37 (s, 1 H, C(17)–H), 3.82 (s, 3 H) and 3.68 (s, 6 H, C(11)–OCH_3, C(16)–CO_2CH_3, and C(16′)–CO_2CH_3), 2.58 (s, 3 H, N$_a$–CH_3), 2.05 (s, 3 H, $OCOCH_3$), 0.91 (t, 3 H, J = 7.5 Hz), and 0.67 (t, 3 H, J = 7 Hz, C(18′)–H and C(18)–H); MS *m/e* 794, 763, 735, 635, 469, 338, 282, 138 (100%), 135, 124, 122, 121.

Compound **14b** is identical with the compound obtained[12] by coupling the chloroindolenine (**4b**) with vindoline (**2a**).

"Dimeric" compound 14c: $[\alpha]_D$ −53° (c = 0.60); uv 216 (42 500), 264 (12 700), 290 (11 250), 298 nm (11 500); CD 259 (−11.8), 280 (3.2), 310 (5.85); ^{1}H NMR δ 8.83 (N$_{a'}$–H), 7.2–6.9 (aromatic), 6.56 and 5.91 (s, 1 H, C(9)–H and C(12)–H), 5.85 (dd, $J_{14,15}$ = 9 and $J_{3,14}$ $\sim$ 4 Hz, C(14)–H), 5.24 (1 H, d, J = 9 Hz, C(15)–H), 5.19 (s, 1 H, C(17)–H), 3.83, 3.68, and 3.66 (s, 3 H, C(11)–OCH_3, C(16)–CO_2CH_3, and C(16′)–CO_2CH_3, 2.60 (s, 3 H, N$_a$–CH_3), 2.04 (s, 3 H, $OCOCH_3$), 0.89 (t, 3 H, J = 7.5 Hz) and 0.63 (t, 3 H, $J \sim$ 7 Hz, C(18′)–H and C(18)–H); MS *m/e* 794 (M·$^+$), 763, 735, 635, 469, 338, 282, 138 (100%), 135, 124, 122, 121.

"Dimeric" compound 20 (violet with CAS reagent): $[\alpha]_D$ −66° (c

= 0.58); ir 1740 (esters), 1620 cm^{-1} (indoline); uv 216 (38 700), 226 (sh, 32 300), 256 (11 300), 288 (8900) and 297 nm (9500); acidic medium 216 (41 000), 257 (11 400), 285 (8200), 295 nm (8150); CD 253 (14.0), 304 (−3.2); ^{1}H NMR δ absence of $N_{a'}$–H, 7.3–6.8 (aromatic), 6.33 and 5.98 (s, 1 H, C(9)–H and C(12)–H), 5.66 (dd, 1 H, $J_{14,15}$ = 9.5 and $J_{3,14} \sim$ 3 Hz, C(14)–H), 5.20 (s, 1 H, C(17)–H), 5.08 (d, 1 H, J = 9.5 Hz, C(15)–H), 4.98 and 4.87 (2 d, 2 H, J_{AB} = 11.5 Hz, C(5′)–H), 3.83, 3.74, and 3.47 (s, C(11)–OCH_3, C(16)–CO_2CH_3, and C(16′)–CO_2CH_3, 2.67 (s, 3 H, N_a–CH_3), 2.03 (s, $OCOCH_3$), 0.88 (t, 3 H, J = 7 Hz) and 0.09 (t, 3 H, $J \sim$ 6 Hz, C(18′)–H and C(18)–H); MS *m/e* 792.4075 (calcd 792.4098, $C_{46}H_{56}N_4O_8$, 100%, M$\cdot^+$), 733.3917 (calcd 733.3965, $C_{44}H_{53}N_4O_6$), 732, 645, 633.3753 (calcd 633.3804, $C_{40}H_{49}N_4O_3$), 631, 552, 525, 511, 510.2747 (calcd 510.2756, $C_{32}H_{36}N_3O_3$), 497, 337, 308, 282, 200, 188, 174, 154, 135, 122, 121, 107.

Coupling of Catharanthine *N*-Oxide (7) with Vindoline (2a) Followed by Sodium Cyanoborohydride Reduction. The coupling reaction is carried out in the same experimental conditions as described above. After 30 min, methanol (0.8 ml) and an excess of sodium cyanoborohydride were added to the dichloromethane solution. After 15 min, usual workup led to a foamy residue purified by preparative TLC (AcOEt–MeOH 95:5), yielding **14a** (23 mg, 10%) and **10** (40 mg, 17%).

Hydrogenation of Anhydro Vinblastine (10). Hydrogenation of 32 mg (0.04 mmol) of **10** in EtOH (PtO_2, 5 mg) for 15 h led to a quantitative yield of **14a; hydrazide:**[7] [α]D −8.6° (c = 0.45).

Allocatharanthine *N*-oxide (3c *N*-oxide) is obtained from allocatharanthine[36] (**3c**) (125 mg, 0.37 mmol) in the usual way: *p*-nitroperbenzoic acid (102 mg, 0.56 mmol) in CH_2Cl_2 (16 ml), 3 min at 0 °C, quantitative yield: uv 275, 283, 292 nm; ^{1}H NMR (60 MHz) δ 7.9 (1 H, N_a–H), 7.7–7.0 (4 H, aromatic), 3.73 (s, 3 H, CO_2CH_3), 0.95 (t, 3 H, J = 7 Hz, C(18)–H); MS *m/e* 352 (M$\cdot^+$), 336, 334, 293, 167 (100%), 143.

Coupling of Allocatharanthine *N*-Oxide (3c *N*-Oxide) with Vindoline (2a). Trifluoroacetic anhydride (0.10 ml, 0.7 mmol) was added to a stirred solution of **3c** *N*-oxide (85 mg, 0.24 mmol) and vindoline (**2a**) (114 mg, 0.25 mmol) in 0.7 ml of dry CH_2Cl_2 at 0 °C under argon. After 30 min the mixture was treated in the usual way. The residue (foam) purified by TLC (eluent $CHCl_3$–MeOH 95:5) yielded **21** (37 mg, 20%) and impure **18a** (10 mg). Additional preparative TLC (AcOEt–MeOH 3:1) led to **18a** (4 mg, 3% see further).

"Dimeric" compound 21: [α]D 0° (c = 0.85); ir 1740, 1620, cm; uv 263 (13 300), 291 (8600), 298 nm (9000); CD 258 (7.9), 302 (0.18); ^{1}H NMR (60 MHz) δ 7.80–7.40 (2 H, C(16)–OH and $N_{a'}$–H); 7.4–7.0 (aromatic); 6.90 (s attributed to C(9)–H), 6.02 (s, 1 H, C(12)–H), 6.10–5.10 (4 H, ethylenic), 5.40 (s, 1 H, C(17)–H), 3.80, 3.58, and 3.50 (s, 3 H, C(11)–OCH_3, C(16)–CO_2CH_3, and C(16′) –CO_2CH_3), 2.68 (s, 3 H, N_a–CH_3), 2.08 (s, 3 H, $OCOCH_3$), 0.75–0.45 (2 t, 3 H, C(18)–H and C(18′)–H); MS *m/e* 792, 763, 733, 631, 539, 469, 394, 379, 282, 135 (100%), 122, 121, 107.

14,15-Dihydroallocatharanthine *N*-Oxide (3d *N*-Oxide). *p*-Nitroperbenzoic acid (138 mg, 0.75 mmol) in CH_2Cl_2 (18.6 ml) was added to a stirred solution of 14,15-dihydroallocatharanthine[36] (**3d**) (210 mg, 0.62 mmol) in CH_2Cl_2 (6.2 ml at 0 °C). After 3 min the CH_2Cl_2 solution was treated as usual. The residue obtained was purified by preparative TLC (eluent $CHCl_3$–MeOH 90:10) and yielded **3d** *N*-oxide (197 mg, 90%): uv 274, 283, 292 nm; ^{1}H NMR (60 MHz) δ 9.15 (1 H, N_a–H), 7.55–6.73 (4 H, aromatic), 3.73 (s, 3 H, CO_2CH_3), 0.81 (t, 3 H, J = 7 Hz, C(18)–H); MS *m/e* 354, 352, 338 (100%), 336, 277, 214, 208, 120.

Coupling of 14,15-Dihydroallocatharanthine *N*-Oxide (3d *N*-Oxide) with Vindoline (2a). Trifluoroacetic anhydride (0.10 ml, 0.7 mmol) was added to a stirred solution of **3d** *N*-oxide (100 mg, 0.3 mmol) and vindoline (**2a**) (135 mg, 0.3 mmol) in 0.8 ml of dry dichloromethane at −78 °C under argon. After 50 min the mixture was treated as above. The residual foam purified by preparative TLC (eluent AcOEt–MeOH 97:3) led to **22** (26 mg, 11%) and a mixture of vindoline (**2a**) and **23,** once again purified by preparative TLC (eluent AcOEt–MeOH 96:4), giving compound **23** (40 mg, 17%).

"Dimeric" compound 22: [α]D 13° (c = 0.53); ir 1745, 1620 cm^{-1}; uv 214 (44 500); 259 (15 300), 288 (12 300), 297 nm (11 200), CD 259 (14.6), 305 (7.3); ^{1}H NMR δ 9.73 (s, 1 H, C(16)–OH), 7.92 (br s, 1 H, $N_{a'}$–H), 7.6–7.0 (aromatic), 6.84 (s, 1 H, C(9)–H), 6.04 (s, 1 H, C(12)–H), 5.88 (dd, 1 H, $J_{14,15}$ = 9.6 and $J_{3,14}$ = 3.5 Hz, C(14)–H), 5.47 (s, 1 H, C(17)–H), 5.34 (d, J = 9.6, C(15)–H), 3.91 (2 s, 6 H) and 3.69 (s, 3 H, C(11)–OCH_3, C(16)–CO_2CH_3, and C(16′)–CO_2CH_3), 2.79 (s, 3 H, N_a–CH_3), 2.25 (s, 3 H, $OCOCH_3$), 0.92 (t, 3 H, J = 7.5) and 0.47 (3 H, attributed to C(18′–H and C(18)–H); MS *m/e* 794 (M$\cdot^+$), 763, 735, 664, 635, 469, 338, 282, 135, 124 (100%), 122.

"Dimeric" compound 23 (violet with CAS reagent): [α]D −84° (c = 0.59); ir 1740, 1620 cm^{-1}; uv 226 (sh, 38 000), 256 (10 200), 288 (7200), 297 nm (8000); CD 250 (12.0), 302 (−2.5); ^{1}H NMR δ absence of $N_{a'}$–H, 7.3–6,9 (4 H, aromatic), 6.51 and 6.10 (s, 1 H, C(9)–H and C(12)–H), 5.73 (dd, 1 H, $J_{14,15}$ = 11 and $J_{3,14}$ = 5.5 Hz, C(14)–H), 5,30 (s, 1 H, C(17)–H), 5.15 (dd, 1 H, J = 11 Hz, C(15)-H), 5.05 and 4.92 (2 d, 2 H, J_{AB} = 12.5 Hz, C(5′)-H), 3.86, 3.76, and 3.58 (s, 3 H, C(11)–OCH_3, C(16)–CO_2CH_3, and C(16′) –CO_2CH_3), 2.67 (s, 3 H, N_a–CH_3), 2.03 (s, 3 H, $OCOCH_3$), 0.73 (t, 3 H, J = 7.2 Hz) and 0.0 (t, 3 H, $J \sim$ 7 Hz, C(18′)–H and C(18)–H; MS fragmentation identical with compound **20,** 792 (M$\cdot^+$), 733, 645, 633, 631, 584, 552, 525, 511, 510, 497, 337, 308, 282, 202, 200, 188, 174, 154, 135 (100%), 122, 121, 107.

Coronaridine *N*-Oxide (3e *N*-Oxide). A solution of *p*-nitroperbenzoic acid (212 mg, 1.16 mmol) in dichloromethane (27 ml) was added to a stirred solution of coronaridine[32,37] (**3e**) (261 mg, 0.77 mmol) in dichloromethane (7.8 ml). After 10 min at room temperature and usual workup, the resulting mixture was purified by preparative TLC: **3e** *N*-oxide (234 mg, 86%) and **3e** 7ζ-hydroxyindolenine *N*-oxide (40 mg, 14%).

3e *N*-oxide: mp 208–210 °C dec; uv 225 (27 900), 285 (6300), 293 nm (5300); ^{1}H NMR (60 MHz) δ 8.05 (N_a–H), 7.6–7.1 (4 H, aromatic), 4.18 (C(21)–H and $\underline{C}H$–N_b), 3.80 (s, 3 H, CO_2CH_3), 0.92 (t, 3 H, J = 7 Hz, C(18)–H); MS *m/e* 354 (M$\cdot^+$), 338 (100%), 323, 309, 277, 253, 214, 169, 154, 136, 124, 122.

3e 7ζ-hydroxyindolenine *N*-oxide: mp 260 °C dec; uv: 226 (17 200), 232 (sh, 13 900), 273 nm (5100); ^{1}H NMR (60 MHz) δ absence of N_a–H, 7.7–7.2 (4 H, aromatic), 4.55 (C(21)–H), 3.74 (s, 3 H, CO_2CH_3), 0.84 (t, 3 H, J = 7 Hz, C(18)–H); MS *m/e* 370 (M$\cdot^+$), 354 (100%), 337, 295, 230, 188, 161, 160, 159, 138, 122.

Coupling of Coronaridine *N*-Oxide (3e *N*-Oxide) with Vindoline (2a). Trifluoroacetic anhydride (2 ml, 14.0 mmol) was added to a stirred solution of **3e** *N*-oxide (177 mg, 0.5 mmol) and vindoline (**2a**) (251 mg, 0.6 mmol) in CH_2Cl_2 (15 ml) at 0 °C under nitrogen. After 60 min at room temperature the mixture was treated as usual and purified by preparative TLC ($CHCl_3$–MeOH 96:4), giving "dimeric" compound **24a** (155 mg), a mixture of three compounds (126 mg), trifluoroalcohol **18a** (50 mg), and impure "dimer" **24d** (90 mg). The mixture purified by preparative TLC (hexane–Et_2O–MeOH 10: 100:8) gave "dimer" **24b** (44 mg), "dimer" **24c** (17 mg), and trifluoroalcohol **18b** (27.5 mg).

"Dimer" 24a: crystallized from acetone; mp 275–280 °C dec; [α]D −92° (c = 0.43); ir 3450, 1740, 1620 cm^{-1}; uv 264 (12 600), 291 (11 900), 297 (11 900) nm; CD 263 (31.2), 284 (−4.6), 296 (−4.6), 312 (−11.5); ^{1}H NMR δ 9.60 (1 H, C(16)–OH), 8.75 (s, 1 H, $N_{a'}$–H), 7.3–6.8 (aromatic), 6.90 and 5.97 (s, 1 H, C(9)–H and C(12)–H), 5.71 (dd, 1 H, $J_{14,15}$ = 9.5 and $J_{3,14}$ = 3 Hz, C(14)–H), 5.20 (s, 1 H, C(17)–H), 5.00 (br d, 1 H, J = 9.5 Hz, C(15)–H), 3.87 (s, 3 H), 3.72 and 3.70 (2 s, 6 H, C(11)–OCH_3, C(16)–CO_2CH_3, and C(16′)–CO_2CH_3, 2.63 (s, 3 H, N_a–CH_3), 1.99 (s, 3 H, $OCOCH_3$), 0.93 (t, 3 H, J = 7 Hz) and −0.12 (t, 3 H, J = 6.8 Hz, C(18′)–H and C(18)–H; MS *m/e* 794.4195 (calcd 794.4254, $C_{46}H_{58}N_4O_8$, M$\cdot^+$), 763, 736, 735.4066 (calcd 735.4121, $C_{44}H_{55}N_4O_6$), 635, 611, 610.2920 (calcd 610.2917, $C_{36}H_{40}N_3O_6$), 469, 338, 282.1330 (calcd 282.1341, $C_{14}H_{20}NO_5$), 222, 188, 138.1284 (calcd 138.1283, $C_9H_{16}N$, 100%), 135, 124, 122, 121, 107.

"Dimer" 24b (20′-epi "dimer" 24a): crystallized from acetone–ether; mp 218–220 °C dec; [α]D −66° (c = 0.93); ir 1740, 1620 cm^{-1}; uv 264 (13 400), 291 (11 200), 298 nm (11 400); CD 257 (34.0), 280 (−2.9), 294 (−2.9), 310 (−9.9); ^{1}H NMR δ 9.64 (1 H, C(16)–OH), 8.78 (s, 1 H, $N_{a'}$–H), 7.5–6.8 (aromatic), 6.85 and 6.02 (s, 1 H, C(9)–H and C(12)–H), 5.72 (dd, 1 H, $J_{14,15}$ = 10 and $J_{3,14}$ = 4 Hz, C(14)–H), 5.23 (s, 1 H, C(17)–H), 5.02 (d, 1 H, J = 10 Hz, C(15) –H), 3.89 (s, 3 H) and 3.74 (br s, 6 H, C(11)–OCH_3, C(16)–CO_2CH_3, and C(16′)–CO_2CH_3), 2.64 (s, 3 H, N_a–CH_3), 2.00 (s, 3 H, $OCOCH_3$), 0.92 (t, 3 H, J = 7 Hz) and −0.12 (t, 3 H, $J \sim$ 7 Hz, C(18′)–H and C(18)–H); MS *m/e* 794.4236 (calcd 794.4254, $C_{46}H_{58}N_4O_8$, M$\cdot^+$), 763, 736, 735.4087 (calcd 735.4121, $C_{44}H_{55}N_4O_6$), 635.3939 (calcd 635.3961, $C_{40}H_{51}N_4O_3$), 611.3014 (calcd 611.2995, $C_{36}H_{41}N_3O_6$), 610.2925 (calcd 610.2917, $C_{36}H_{40}N_3O_6$), 527, 469, 338.1989 (calcd 338.1994, $C_{21}H_{26}N_2O_2$), 282.1334 (calcd 282.1341, $C_{14}H_{20}NO_5$), 222, 188, 144, 138.1281 (calcd 138.1283, $C_9H_{16}N$, 100%), 135, 124, 122, 121, 107.

"Dimer" 24c: $[\alpha]$D −158° (c = 0.5); ir 1740, 1615 cm^{-1}; uv 258 (11 600), 291 (10 700), 298 nm (10 700); CD 260 (3.9), 288 (−2.5), 306 (−7.3); ^{1}H NMR δ 7.96 (N$_{a'}$–H), 7.5–7.0 (aromatic), 6.60 and 6.10 (s, 1 H, C(9)–H and C(12)–H), 5.79 (1 H, C(14)–H), 5.43 (s, 1 H, C(17)–H), 5.20 (d, 1 H, $J_{14,15}$ = 9.5 Hz, C(15)–H), 3.82 (br s, C(11)–OCH_3, C(16)–CO_2CH_3, and C(16′)–CO_2CH_3), 2.75 (s, 3 H, N$_a$–CH_3), 2.08 (s, 3 H, $OCOCH_3$), 0.93 and 0.40 (t, J = 7 Hz, C(18′)–H) and C(18)–H); MS m/e 794.4267 (calcd 794.4254, $C_{46}H_{58}N_4O_8$, M$^{\cdot +}$), 763, 736, 735.4099 (calcd 735.4121, $C_{44}H_{55}N_4O_6$), 635.3925 (calcd 635.3961, $C_{40}H_{51}N_4O_3$), 611.3019 (calcd 611.2995, $C_{36}H_{41}N_3O_6$), 610.2951 (calcd 610.2917, $C_{35}H_{40}N_3O_6$), 469, 338.1962 (calcd 338.1994, $C_{21}H_{26}N_2O_2$), 282.1334 (calcd 282.1341, $C_{14}H_{20}NO_5$), 188, 144, 138.1280 (calcd 138.1283, $C_9H_{16}N$, 100%), 135, 124, 122, 121, 107.

"Dimer" 24d (C(5)–C(6) fragmentation) (violet with CAS reagent): 67.6 mg, 17%, crystallized from cyclohexane; mp 188 °C; $[\alpha]$D −27.2° (c = 0.68); uv 252 (13 900), 258 (sh 13 300), 288 (10 100), 296 (11 200); CD 257 (11.4), 280 (−3.0), 305 (−2.7); ^{1}H NMR δ absence of N$_{a'}$–H, 7.3–6.9 (4 H, aromatic), 6.35 and 6.09 (s, 1 H, C(9)–H and C(12)–H), 5.77 (m, 1 H, $J_{14,15}$ = 9.6 Hz), 5.38 (s, 1 H, C(17)-H), 5.19 (d, 1 H, J =9.6 Hz, C(15)–H), 5.11 and 4.96 (2 d, 2 H, J_{AB} = 11.5 Hz, C(5′)–H), 3.88, 3.78, and 3.22 (s, 3 H, C(11)–OCH_3, C(16)–CO_2CH_3, and C(16′)–CO_2CH_3), 2.67 (s, 3 H, N$_a$–CH_3), 2.04 (s, 3 H, $OCOCH_3$), 0.89 (t, 3 H, $J \sim 7$ Hz) and 0.24 (t, 3 H, $J \sim 6.5$ Hz, C(18′)–H and C(18)–H; MS m/e 792 (M$^{\cdot +}$), 733, 645, 633, 631, 552, 525, 511, 510, 497, 396, 337, 308, 282, 222, 202, 200, 188, 174, 154, 136, 135 (100%), 122, 121, 107.

Trifluoro alcohol 18a: crystallized from acetone; mp 275–280 °C; $[\alpha]$D −15.8° (c = 1.07); ir 3380 (OH), 1740 (esters), 1610 cm^{-1} (indoline); uv 258 (8000) and 307 nm (4700), dihydroindole; ^{1}H NMR (60 MHz) δ 6.72 and 6.00 (s, 1 H, C(9)–H and C(12)–H), 5.8 (dd, 1 H, C(14)–H), 5.34 (s, 1 H, C(17)–H), 5.18 (d, 1 H, $J_{14,15}$ = 9.9 Hz, C(15)–H), 3.82 and 3.76 (s, 3 H, C(11)–OCH_3 and C(16) –CO_2CH_3, 2.67 (s, 3 H, N$_a$–CH_3), 2.01 (s, 3 H, $OCOCH_3$), 0.46 (t, 3 H, $J_{18,19}$ = 7 Hz, C(18)–H); MS m/e 554 (M$^{\cdot +}$), 495, 395, 286, 282, 272, 260, 259, 202, 188, 136, 135 (100%), 122, 121, 107.

Trifluoro alcohol 18b: $[\alpha]$D −35.7° (c = 1.31); ir 1745, 1620 cm^{-1}; uv 258 (7400), 307 nm (4600); ^{1}H NMR (60 MHz) δ 6.99 and 6.06 (s, 1 H, C(9)–H and C(12)–H), 5.80 (dd, 1 H, $J_{14,15} \sim 10$ Hz, C(14)–H), 5.34 (s, 1 H, C(17)–H), 5.18 (d, 1 H, $J \sim 10$ Hz, C(15) –H), 3.82 and 3.76 (s, 3 H, C(11)–OCH_3 and C(16)–CO_2CH_3), 2.76 (s, 3 H, N$_a$–CH_3), 2.01 (s, 3 H, $OCOCH_3$), 0.46 (t, 3 H, $J_{18,19}$ = 7 Hz, C(18)–H); MS, fragmentation pattern similar to that of **18a.**

Coupling of Catharanthine *N*-Oxide (7) with Vindorosine (2b). Trifluoroacetic anhydride (0.05 ml, 0.36 mmol) was added to a stirred solution of catharanthine *N*-oxide (50 mg, 0.14 mmol) and vindorosine[38] (**2b**) (63 mg, 0.15 mmol) in CH_2Cl_2 (0.4 ml) at 0 °C under argon. After 50 min usual workup led to a mixture which was purified by preparative TLC (eluent $CHCl_3$–MeOH 97:3), yielding **25** (20 mg, 18%) and **2b** (51 mg, 81%).

"Dimer" 25: $[\alpha]$D −40° (c = 0.5); ir 1745, 1620 cm^{-1}; uv 262 (14 300), 286 (11 200), 294 nm (10 400); CD 257 (−13.0), 285 (7.1), 303 (8.4); ^{1}H NMR δ 9.12 (1 H, C(16)–OH), 6.83 (br s attributed to C(9)–H), 6.34 (d, 1 H, J = 8.5 Hz, C(12)–H), 5.77 (m, 2 H, C(14)–H and C(15′)–H), 5.34 (s, 1 H, C(17)–H), 5.15 (d, 1 H, $J_{14,15}$ = 10 Hz, C(15)–H), 3.82 and 3.79 (2 s, 6 H, C(16)–CO_2CH_3 and C(16′)–CO_2CH_3), 2.70 (s, 3 H, N$_a$–CH_3), 2.11 (s, 3 H, $OCOCH_3$), 1.07 (t, 3 H, $J \sim 7$ Hz, C(18′)–H), 0.27 (t, 3 H, $J \sim 6.5$ Hz, C(18) –H); MS m/e 762 (M$^{\cdot +}$), 703, 603, 580, 495, 480, 349, 336, 282, 135 (100%), 122, 121, 107.

Coupling of Catharanthine *N*-Oxide (7) with *N*$_a$-Methyl-2,16-dihydrotabersonine (2c). Trifluoroacetic anhydride (0.17 ml, 1.18 mmol) was added to a stirred solution of catharanthine *N*-oxide (**7**) (150 mg, 0.43 mmol) and N_a-methyl-2,16-dihydrotabersonine[39] (**2c**) (157 mg, 0.45 mmol) in dry CH_2Cl_2 (1.2 ml) at −78 °C under argon. After 50 min the mixture is treated in the usual way and purified by preparative TLC (eluent heptane-AcOEt 50:50) to give **26** (36 mg, 12%) and **2c** (80 mg, 51%).

"Dimer" 26: $[\alpha]$D 7.3° (c = 1.19); ir 1745, 1620 cm^{-1}; uv 273 (11 500), 286 (sh, 9700), 295 nm (sh, 7900); CD 264 (12.8), 304 (5.8); ^{1}H NMR δ 7.5–6.8 (6 H, aromatic) 6.33 (d, 1 H, $J_{11,12}$ = 8.5 Hz, C(12)–H), 5.69 (dd, 1 H, $J_{14,15}$ = 9.5 and $J_{3,14}$ = 4.5 Hz, C(14)–H), 5.40 (m, 1 H, C(15′)–H), 5.33 (br d, 1 H, J = 9.5 Hz, C(15)–H), 3.73 and 3.60 (s, 3 H, C(16)–CO_2CH_3 and C(16′)–CO_2CH_3), 2.69 (s, 3 H, N$_a$–CH_3), 1.01 (t, 3 H, J = 7.0 Hz) and 0.60 (t, 3 H, J = 6.5 Hz, C(18′)–H and C(18)–H); MS m/e 688 (M$^{\cdot +}$), 673, 657, 629, 506, 365, 336, 297, 144, 135 (100%), 122, 121, 107.

***N*$_a$-Methyl-2,16-dihydro-11-methoxytabersonine (2d).** A 30% aqueous formaldehyde solution (2.7 ml), 10 drops of pure acetic acid, and sodium cyanoborohydride (132 mg) in four portions were added successively to a stirred solution of 2,16-dihydro-11-methoxytabersonine[40] (210 mg, 0.57 mmol) in THF (4 ml). After 15 min, the mixture was poured into water (40 ml) and extracted three times with $CHCl_3$. Usual workup led to N_a-Methyl-2,16-dihydro-11-methoxytabersonine (**2d**) (200 mg, 91%) crystallized from methanol:mp 105 °C dec; $[\alpha]$D 30° (c = 0.48); ir no N–H, 1740, 1625 cm^{-1}; uv 256 (7270), 308 (5120) nm; ^{1}H NMR (60 MHz) δ 6.86 (d, 1 H, $J_{9,10}$ = 8 Hz, C(9)–H), 6.19 (dd, 1 H, $J_{10,12}$ = 2 and $J_{9,10}$ = 8 Hz C(10)–H), 6.00 (s, 1 H, C(12)–H), 5.72 (dd, 1 H, $J_{14,15}$ = 10 and $J_{3,14}$ = 4.7 Hz, C(14)–H), 5.33 (d, 1 H, $J_{14,15}$ = 10 Hz, C(15)–H), 3.74 and 3.70 (s, 3 H, C(11)–OCH_3 and C(16)–CO_2CH_3), 2.68 (s, 3 H, N$_a$–CH_3), 0.53 (t, 3 H, $J_{18,19}$ = 6.6 Hz, C(18)–H); MS m/e 382 (M$^{\cdot +}$), 351, 296, 189, 188, 174, 136, 135 (100%), 122, 121.

Coupling of Catharanthine *N*-Oxide (7) with *N*$_a$-methyl-2,16-dihydro-11-methoxytabersonine (2d). Trifluoroacetic anhydride (0.110 ml, 0.78 mmol) was added to a stirred solution of catharanthine *N*-oxide (**7**) (100 mg, 0.29 mmol) and N_a-methyl-2,16-dihydro-11-methoxytabersonine (**2d**) (114 mg, 0.30 mmol) in 0.82 ml of dry CH_2Cl_2 at −78 °C under argon. After 60 min, the mixture was treated in usual way and the residue obtained was purified by preparative TLC ($CHCl_3$–MeOH 97:3), giving **27a** (40 mg, 19%), **27b** (6 mg, 3%), **19a** (trifluoro alcohol, 40 mg, 27%), and a mixture of "dimer" **28** and trifluoro alcohol **19b.** This mixture was purified by preparative TLC ($CHCl_3$–MeOH 99:1) and yielded **28** (12 mg, 6%) and **19b** (30 mg, 21%).

"Dimer" 27a: $[\alpha]$D 87° (c = 0.42); ir 1740, 1625 cm^{-1}; uv 218 (44 600), 268 (14 000), 290 (11 600), 294 (11 200) nm; CD 263 (13.4), 305 (5.8); ^{1}H NMR δ 7.96 (s, 1 H, N$_{a'}$–H), 7.5–7.0 (4 H, aromatic), 6.54 and 6.08 (s, 1 H, C(9)–H and C(12)–H), 5.70 (dd, 1 H, $J_{14,15}$ = 11 and $J_{3,14}$ = 4.5 Hz, C(14)–H), 5.55 (m, 1 H, C(15′) –H), 5.32 (d, 1 H, J = 11 Hz C(15)–H), 3.85, 3.78, and 3.65 (s, 3 H, C(11)–OCH_3, C(16)–CO_2CH_3, and C(16′)–CO_2CH_3), 2.80 (s, 3 H, N_a–CH_3), 1.12 (t, 3 H, $J_{18',19'}$ = 7 Hz, C(18′)–H), 0.97 (t, 3 H, $J_{18,19}$ = 6.5, C(18)–H); MS m/e 718 (M$^{\cdot +}$), 687, 659, 595, 536, 395, 336 (100%), 295, 293, 135, 122, 121, 107.

"Dimer" 27b: uv 267 (13 500), 287 (10 800), 294 (11 050) nm; CD 263 (−9.0), 287 (3.6), 310 (6.5); ^{1}H NMR δ 9.00 (br s, 1 H, N$_{a'}$–H), 7.4–6.9 (4 H, aromatic and C(9)–H), 5.95 (s, 1 H, C(12)–H), 5.76 (C(14)–H), 5.65 (C(15′)–H) and 5.35 (br d, 1 H, $J_{14,15}$ = 10 Hz, C(15)–H), 3.94, 3.84, and 3.77 (s, 3 H, C(11)–OCH_3, C(16)–CO_2CH_3, and C(16′)–CO_2CH_3), 2.71 (s, 3 H, N$_a$–CH_3), 1.13 (t, 3 H, $J_{18',19'} \sim 7$ Hz, C(18′)–H), 0.76 (t, 3 H, C(18)–H); MS m/e 718 (M$^{\cdot +}$, 100%), 687, 659, 595, 536, 395, 336, 180, 136, 135 (100%), 122, 121, 107.

"Dimer" 28 (violet with CAS reagent): $[\alpha]$D 0° (c = 0.53); uv 226 (39 600), 262 (13 500), 288 (9250), 297 (9700) nm; CD 257 (14.5), 302 (−2.1); ^{1}H NMR δ 6.54 and 6.00 (s, 1 H, C(9)–H and C(12)–H), 5.13 (2 H, C(5′)–H), 3.80, 3.70, and 3.56 (s, 3 H, C(11)–OCH_3, C(16)–CO_2CH_3, and C(16′)–CO_2CH_3), 2.68 (s, 3 H, N$_a$–CH_3), 1.06 (t, 3 H, J = 7 Hz), 0.34 (3 H, C(18′)–H and C(18)-H); MS m/e 716 (M$^{\cdot +}$, 100%), 685, 657, 629, 608, 594, 523, 415, 395, 387, 135, 122, 121, 107.

Trifluoro alcohol 19a: $[\alpha]$D 35° (c = 0.51); ir 1740, 1625 cm^{-1}; uv 262 (12 600), 309 nm (7100), dihydroindole; ^{1}H NMR (60 MHz) δ 6.91 and 5.98 (s, 1 H, C(9)–H and C(12)–H), 5.71 (dd, 1 H, $J_{14,15}$ = 10 Hz, C(14)–H), 5.36 (1 H, C(15)–H), 3.82 and 3.68 (s, 3 H, C(11)–OCH_3 and C(16)–CO_2CH_3), 2.66 (s, 3 H, N$_a$–CH_3), 0.53 (3 H, $J_{18,19}$ = 7 Hz, C(18)–H); MS m/e 480 (M$^{\cdot +}$), 449, 393, 287, 286, 259, 135 (100%), 122, 121, 107.

Trifluoro alcohol 19b: $[\alpha]$D 7° (c = 0.56); ir 1740, 1625 cm^{-1}; uv 263 (12 000), 311 nm (7200); ^{1}H NMR (60 MHz) δ 7.00 and 6.00 (s, 1 H, C(9)–H and C(12)-H), 5.76 (dd, 1 H, $J_{14,15}$ = 10 and $J_{3,14}$ = 5 Hz, C(14)–H), 5.36 (C(15)–H), 3.86 and 3.76 (s, 3 H, C(11)–OCH_3 and C(16)–CO_2CH_3), 2.73 (s, 3 H, N$_a$–CH_3), 0.55 (3 H, $J_{18,19}$ = 7 Hz, C(18)–H); MS identical with MS of **19a.**

***N*$_a$-Formyl-2,16-dihydro-11-methoxytabersonine (2e).** 2,16-Dihydro-11-methoxytabersonine (260 mg, 0.7 mmol) was dissolved in a mixture of acetic anhydride–formic acid (50:50) preheated at 60 °C for 2 h. After stirring for 60 min at room temperature, the mixture was made alkaline with an aqueous solution fo Na_2CO_3 (10%), extracted with $CHCl_3$, washed with water, dried, and evaporated to yield

N_a-formyl-2,16-dihydro-11-methoxytabersonine (270 mg, 97%), crystallized from chloroform–methanol: mp 180 °C dec; $[\alpha]_D$ −28.6° (c = 1.05); ir no N–H absorption, 1745, 1680 cm^{-1}; uv 252, 300 nm; ^{1}H NMR (60 MHz) δ 6.96 (d, 1 H, $J_{9,10}$ = 8 Hz, C(9)–H), 6.66 (s, 1.5 H, C(12)–H and a masked part of C(10)–H), 6.50 (d, part of dd, 0.5 H, $J_{10,12}$ = 2 and $J_{9,10}$ = 8 Hz, part of C(10)–H), 5.83 (dd, 1 H, $J_{14,15}$ = 10 and $J_{3,14}$ = 4.8 Hz, C(14)–H), 5.20 (d, 1 H, $J_{14,15}$ = 10 Hz, C(15)–H), 3.80 and 3.70 (s 3 H, C(11)–OCH_3 and C(16)–CO_2CH_3), 0.76 (t, 3 H, $J_{18,19} \sim 6$ Hz C(18)–H); MS m/e 396 ($M\cdot^+$), 368, 366, 310, 202, 135 (100%), 122, 121.

Coupling of Catharanthine *N*-Oxide (7) with N_a-formyl-2,16-dihydro-11-methoxytabersonine 2e. Trifluoroacetic anhydride (0.110 ml, 0.78 mmol) was added to a stirred solution of catharanthine *N*-oxide (**7**) (100 mg, 0.29 mmol) and N_a-formyl-2,16-dihydro-11-methoxytabersonine (**2e**) (117 mg, 0.3 mmol) in 0.82 ml of CH_2Cl_2 at −78 °C under argon. After 50 min, the mixture was treated in usual way and the residue obtained was purified by alkaline preparative TLC (eluent $CHCl_3$–MeOH (95:5), yielding **2e** (110 mg, 94%) and unidentified products (37 mg).

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(41) The numbering[18] of allocatharanthine series is given between brackets (Scheme I).

Kinetic Applications of Electron Paramagnetic Resonance Spectroscopy. 27. Isomerization of Cyclopropylcarbinyl to Allylcarbinyl[1]

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Abstract. The rate constant for isomerization of cyclopropylcarbinyl to allylcarbinyl has been measured by EPR spectroscopy. It can be represented by: $\log(k_i/\text{s}^{-1}) = (12.48 \pm 0.85) - (5.94 \pm 0.57)/\theta$, where $\theta = 2.3RT$ kcal/mol. This reaction is compared with other primary alkyl radical isomerizations.

The rapid isomerization of the cyclopropylcarbinyl radical (**1**) to the allylcarbinyl radical (**2**) is well known in free-radical chemistry.[3] The rate of this reaction has not been measured and we are aware of only one analogous reaction for which a rate constant has been estimated. For Cristol and Barbour's[4] data on the reduction of 6β-chloro-3α,5α-cyclocholestane (**3**)