Three Routes to the Critical C16′–C14′ Parf Relative Stereochemistry of Vinblastine. Syntheses of 20′-Desethyl-20′-deoxyvinblastine and 20′-Desethyl-20′-deoxyvincovaline

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Coupling reactions of vindoline (**2**) with the racemic chloro imine derivative **8** of 14-epi-*D*-secodesethylvincadifformine (**7**) resulted in a selective high yield formation of the C16′–C14′ parf (vinblastine type) relative configuration of the coupling products. Coupling of vindoline (**2**) with the racemic chloroindoline–alkene derivative **28** of the *D*-secodesethylcleavamine **27** proceeds through an intermediate subject to less rigid stereochemical control. The two coupling routes and subsequent cyclization steps gave syntheses of 20′-desethyl-20′-deoxyvinblastine (**17**) and 20′-desethyl-20′-deoxyvincovaline (**18**). The same products were also formed, but only in 1.2% and 2.4% yields, respectively, from the chlorinated cleavamine **22** by an analogous procedure. Alternatively, corresponding C16′–C14′ pref products could also be formed selectively from **22** and from the chlorinated desethylvincadifformine (**21**) under conditions previously used for such coupling reactions.

Starting from consideration of the notorious failures to obtain the pharmacologically essential natural C16′–C14′ parf relative stereochemistry of vinblastine (VLB, **1a**, R^1 = OH, R = C_2H_5)[1] by coupling of vindoline (**2**) to derivatives of carbomethoxycleavamine (**3**) or of *D/E-cis*-Ψ-vincadifformine (**4**),[2-4] from which only the C16′–C14′ pref stereochemistry (**1b**) was formed, we had been led to the synthesis of *D/E-trans*-desethyl-Ψ-vincadifformine (**5**) as an alternative precursor for the coupling reaction (Scheme I). There we had found, however, that cleavage of the C3–C7 bond and entry into the cleavamine class of structures could not be obtained, thus also blocking this approach to vinblastine-type indole–indoline alkaloids.[5] An inviting access to such indole–indoline alkaloids then seemed to lie in the D-seco precursors **6** of our *D/E-trans*-Ψ-vincadifformine type compounds. All of the relevant stereochemical centers of a *D/E-trans*-Ψ-vincadifformine were incorporated here, but these compounds, or their vindoline coupling products, were not expected to suffer from the stereochemical restraints to reductive cleavage of the C3–C7 bond.[5a] Stereoelectronic considerations (see below) allowed the prediction that while coupling of *D/E-cis*-Ψ-vincadifformine (**4**) must lead to the C16′-C14′ pref stereochemistry, the D-seco trans precursor **6** could favor formation of the desired C16′–C14′ parf stereochemistry.

Our synthesis of indole–indoline dimers thus started from the key amino tosylate **7**,[5a] which was activated for coupling to vindoline (**2**) by chlorination with *tert*-butyl hypochlorite, to provide the chloro imines **8** as a 1:1.7 mixture of C16 epimers (Scheme II).

Table I. Key Circular Dichroism Data for the C14′–C16′ Pref and Parf Indole–Indoline Dimers

	molecular ellipticities × 10^{-3}					
λ_{max}, nm	**17**	**18**	**19**	**20**	**23**	**24**
211–213	−307	+114	−135	+44	+163	−198
223–226	+158	−218	+106	−102	−183	+160
257–260	+90	+25	+38	+18	−74	+125
304–310	+27	−37	−11	+8	+32	−39

When this racemic derivative mixture **8** was combined with *l*-vindoline (**2**) and silver tetrafluoroborate, in the presence of a protic acid, two diastereomeric imines, **9** and **10**, with the desired C16′–C14′ parf stereochemistry were produced in high yield. In addition, minor amounts of the C16′–C14′ pref diastereomers of **9** and **10** were formed. The amount of those minor isomers and the ratio of the major products **9**/**10** was found to depend on the pH of the coupling medium, the reaction temperature, and the concentration of reactants. The isomeric product composition was best determined by HPLC product analysis after conversion of the total coupling products to 20′-desethyl-20′-deoxyvinblastine (**17**) and its stereoisomers **18**, **23**, and **24** (see Table III).

In this reaction sequence a reductive cleavage of the C3′–C7′ bond of the coupling products **9** and **10** with sodium borohydride in acetic acid gave the chromatographically separable D′-seco vinblastine analogue **11** and its corresponding diastereomer **12**. These amino tosylates cyclized on brief heating in toluene to provide quaternary salts **13a**/**15a** and **14a**/**16a**. ^1H and ^{13}C NMR analysis of the separately obtained cyclization products showed about a 90% conformational isomeric purity for the former product while the latter was found to be a 1.3:1 mixture.

Hydrogenolysis of the quaternary tosylates **13a**/**15a** and **14a**/**16a** on Pd/C catalyst, at 0 °C, basification, and heating of the amine products in toluene provided desethyldeoxyvinblastine **17** and its C14′–C16′ diastereomer desethyldeoxyvincovaline **18**. A piperidine ring conformational isomer (**19**), expected as precursor of **17**, in analogy to the isolation and characterization of such compounds from the same reaction sequence with intermediates lacking the C16′ vindolinyl substituent,[5a] was here found in variable amounts but generally as a minor product (15% of **19**/**17** mixture). In the diastereomeric sequence, the expected higher energy piperidine conformer **20** was obtained in larger amounts (50%). Interestingly, this compound (**20**) exists in two conformational forms (1:1) of the nine-membered ring, which can be seen in NMR spectra (below). On heating in toluene at reflux, the higher

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(4) Royer, D. Doctoral Dissertation, Reims, 1980, and de Moraes Britto Filho, N. Doctoral Dissertation, Reims, 1981. We thank Prof. J. Levy for providing us with copies of these theses.

(5) (a) Kuehne, M. E.; Zebovitz, T. C. *J. Org. Chem.*, preceding paper in this issue. (b) The present syntheses of 20′-desethyl-20′-deoxyvinblastine (**17**) and 20′-desethyl-20′-deoxyvincovaline (**18**) and syntheses of vinblastine and deoxyvinblastine were presented at the XXI Rencontres de Chimie Therapeutique, Reims, September 11–13, 1985, and at the IUPAC Congress on Medicinal Natural Products, Shanghai, November 1985. They were communicated in *Actual. Chim. Ther.* **1986**, *13*, 211. A different route to products **17** and **18** has since appeared in preliminary form from Schill, G.; Priester, C. U.; Windhövel, U. F.; Fritz, H. *Helv. Chim. Acta* **1986**, *69*, 438.

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Scheme I

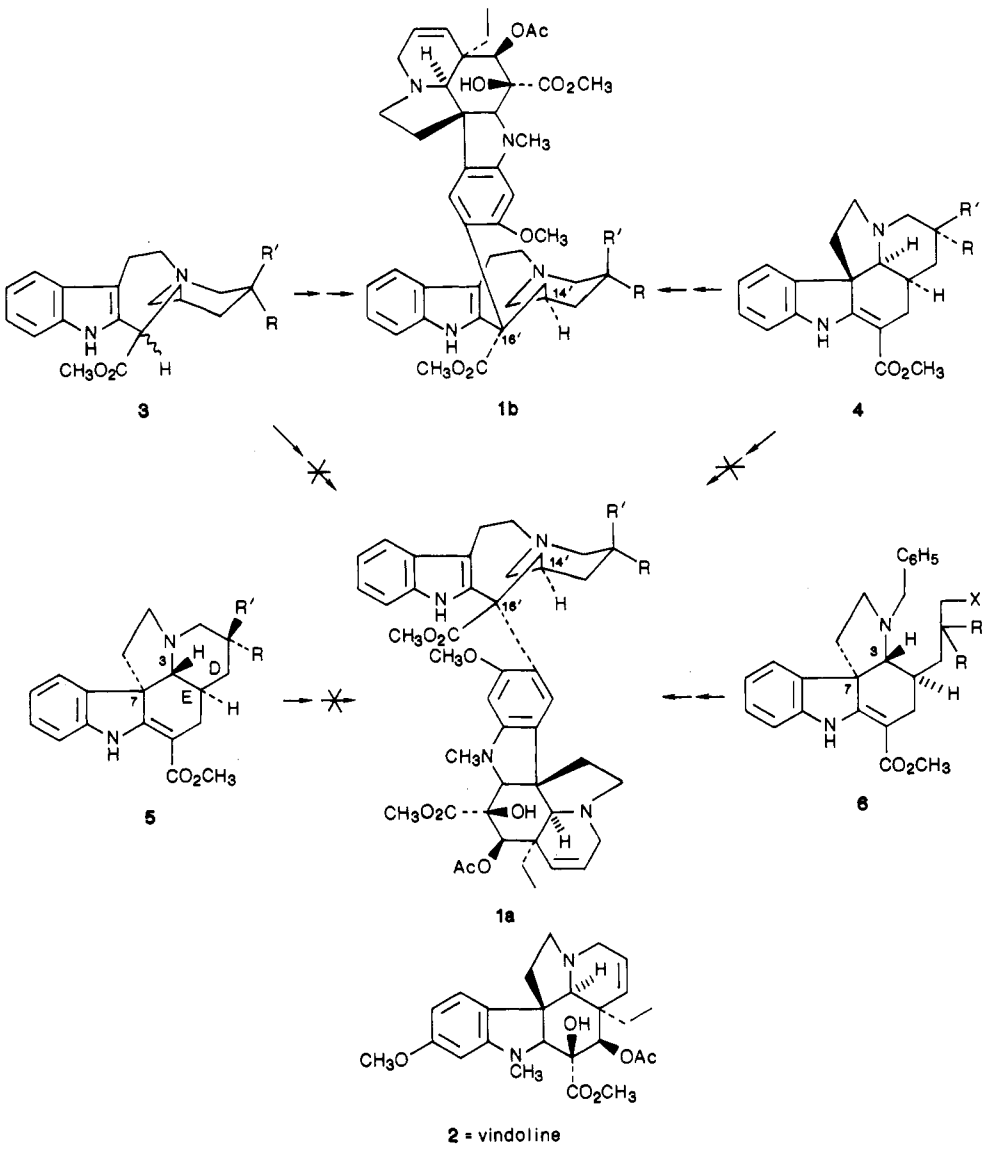


Table II. Chromatographic Comparison of the Stereoisomeric Desethyldeoxyvinblastine Compounds 17, 18, 23, and 24 and Their Precursors 13a,b, 14a,b, 19, and 20

TLC[a]	13a/15a	13b/15b	14a/16a	14b/16b	19	20	17	18	23	24
R_f	0.41	0.41	0.42	0.42	0.17	0.17	0.56	0.62	0.54	0.45

HPLC[b]	17	18	23	24	19	20
t_R, min	15	13	14	12	37	39

HPLC[c]	13a	13b	14a	14b	15a	15b	16a	16b	19	20	17	18
t_R, min	19.5	19.3	16.5	16.4	15.8	15.3	12.3	12.4	4.7	4.2	1.1	1.9

[a] SiO_2, CH_2Cl_2, 15% methanol, 0.5% triethylamine; detection cerric ammonium sulfate (CAS). [b] C-18 Microsorb-R, 4.6 mm × 25 cm reverse phase column; methanol–water–triethylamine (70:30:1); flow rate 0.85 mL/min; detection 260 nm. [c] C-18 Microsorb-R, 4.6 mm × 10 cm reverse phase column; methanol–water–triethylamine (90:10:1); flow rate 2.0 mL/min at 2550 psi; detection 260 nm.

energy conformer **19** was converted to product **17** in 1.5 h while the diastereomer **20** required 3.5 h for a conformational inversion to its product **18**.

In a more detailed study of the kinetics of these conformational inversions, it was found that for the transformation of **19** to **17**, the activation energy $\Delta G^{\ddagger} = 28.2$ kcal/mol with an insignificant entropy factor, $\Delta S^{\ddagger} = 0$. For conversion of the diastereomer **20** to **18**, an activation energy $\Delta G^{\ddagger} = 29.0$ kcal/mol was obtained at 111 °C, with $\Delta S^{\ddagger} = 26 \pm 3$ eu.

The final products **17** and **18** could also be prepared by reversing the last two reaction steps. Catalytic debenzylation of the amino tosylates **11** and **12**, followed by cyclization, provided the final products directly by a route which would not be expected to pass through the higher energy conformation intermediates.[5a]

In pursuit of the higher energy conformers **19** and **20**, it was found that the quaternary hydroxides **13b/15b** and **14b/16b** derived from the quaternary tosylates sometimes contaminated the respective hydrogenolysis products **19/17** and **20/18**. These ammonium hydroxides (but not the tosylates from which they could also be readily generated with ammonium hydroxide) were debenzylated (without the hydrogenation step) by heating at 60 °C (for **15b**), or at 110 °C (for **14b/16b**), with formation of the corresponding final products **17** and **18**.

Scheme II

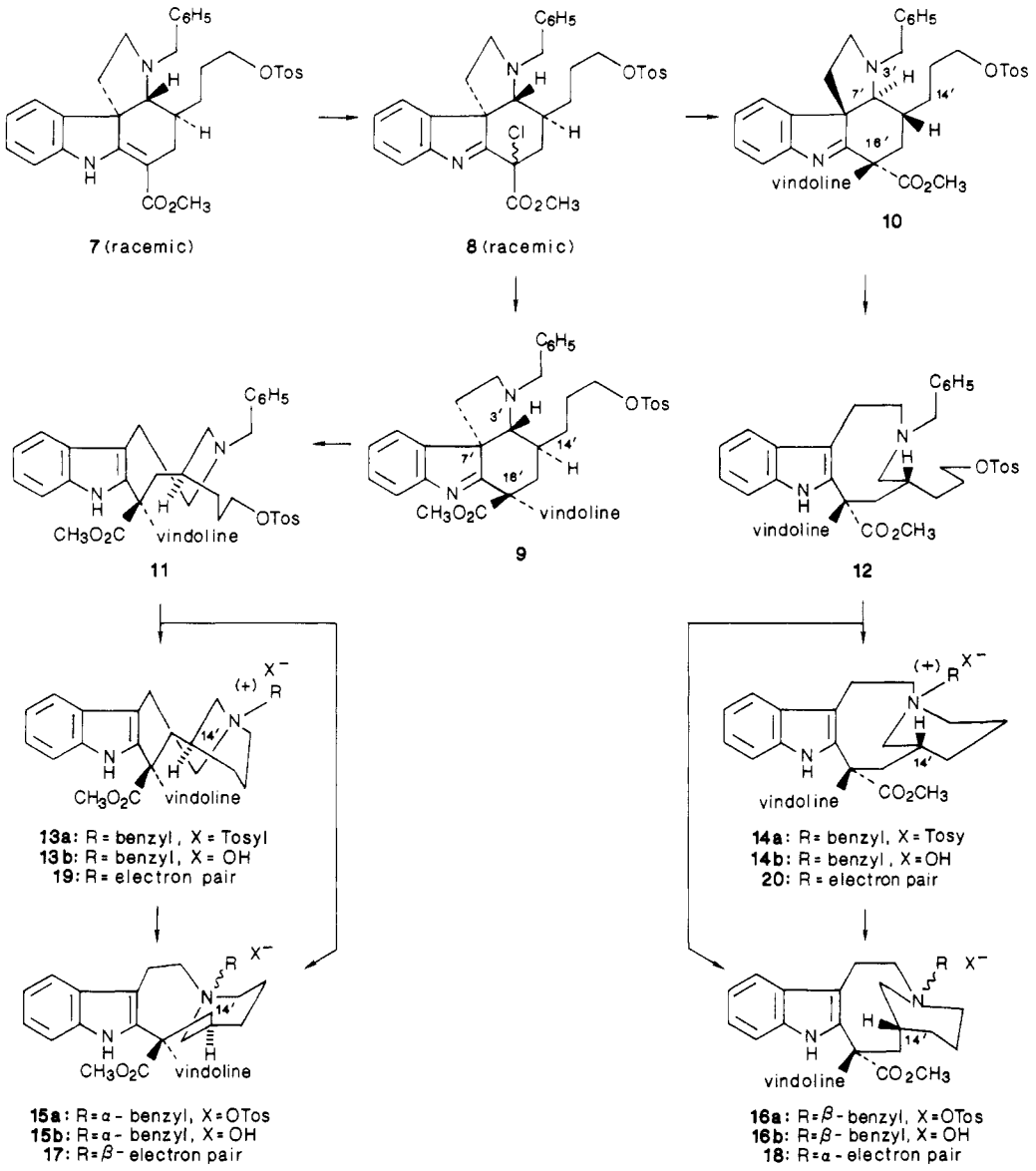


Table III. Coupling Reaction of the Chloro Imines 8 with Vindoline (2)[a]

no.	conditions	% composition of HPLC eluate[b] 17	18	23	24	% composition of dimers[c] 17	18	23	24	% parf:pref	ratio 17/18
1	−78 °C	44	27	2	3	58	35	3	4	93:7	1.7
2	0 °C	48	33	2	2	57	39	2	2	96:4	1.5
3	26 °C	37	30	3	3	52	38	5	5	90:10	1.4
4	56 °C	22	22	18	15	28	28	24	19	57:43	1.0
5	100 mL of solvent	26	29	9	7	37	41	13	9	78:22	0.9
6	1 mL of solvent	33	29	7	6	44	38	10	8	82:18	1.2
7	0.77 equiv of HCl,[e] 3 equiv of $AgBF_4$, 6 mL[d] of solvent	33	32	8	6	41	40	10	8	82:18	1.0
8	no HBF_4 or HCl	10	23	16	12	16	37	26	20	53:47	0.4
9	2.0 equiv of HBF_4	34	30	4	4	47	41	6	5	89:11	1.2
10	3.0 equiv of HBF_4	32	23	6	6	48	34	9	9	82:18	1.4
11	0.77 equiv of HCl,[e] 3 equiv of $AgBF_4$	32	24	7	5	46	35	10	8	82:18	1.3
12	1 equiv of vindoline, 1 equiv of HCl,[e] 3 equiv of $AgBF_4$	36	25	5	3	52	36	7	5	88:12	1.4
13	0.43 equiv of vindoline, 1.5 equiv of HBF_4	31	21	10	7	45	30	15	11	75:25	1.5
14	0.43 equiv of vindoline, 0.43 equiv of HCl,[e] 1.5 equiv of $AgBF_4$	29	18	7	5	50	31	11	8	81:19	1.6
15	2 equiv of vindoline, 3.5 equiv of HBF_4	19	17	1	3	48	42	3	6	91:9	1.1
16	no $AgBF_4$, 26 °C	traces									
17	no $AgBF_4$, 56 °C	24	33	13	10	30	41	16	13	71:29	0.7

[a] General conditions: 1 equiv of 8, 0.77 equiv of vindoline (2), 1.5 equiv of HBF_4, 1.1 equiv of $AgBF_4$ added in acetone, 10 mL total acetone, 26 °C (example 3). Other examples with changes as indicated. Optimum conditions, example 2. Actual yields higher than under group *b* and lower than under group *c*. [d] In run 7, $AgBF_4$ was added as a solid. [e] HCl introduced as vindoline hydrochloride.

To verify previous reports of exclusive formation of C14′-C16′ pref products from coupling of vindoline with chloro derivatives of the vincadifformine- or cleavamine-type structures[2-4] and to obtain such comparison products

Table IV. Conformational Inversion of Compounds 19 and 20[a]

	for 19					
	108.5 °C		98.5 °C		88.5 °C	
time, 10^{-2} s	% 17	% 19	% 17	% 19	% 17	% 19
0	0	100	0	100	0	100
9	35.7	64.3	18.3	81.7		
18	59.9	40.1	34.4	65.6	10.9	89.1
27	75.6	24.4	48.2	51.8		
36	83.7	16.3	56.5	43.5	26.4	76.6
45	90.5	9.5	63.8	36.2		
54	94.8	8.2	68.8	31.2	34.4	65.6
63	96.9	3.1	73.1	26.9		
72	98.3	1.7	77.0	23.0	44.0	56.0
90					53.0	47.0
108	100	0	86.5	13.5	58.6	41.4
126					62.7	37.3
144			93.0	7.0	66.2	33.8
162					69.7	30.2
180			97.0	3.0	74.0	26.0
216			98.0	2.0	79.0	21.0
252					81.6	18.4

k^b = 5.36 × 10^{-4} s^{-1} (108.5 °C)
2.19 × 10^{-4} s^{-1} (98.5 °C)
7.61 × 10^{-5} s^{-1} (85.5 °C)

$\Delta G^{\ddagger c}$ = 28.2 kcal/mol (108.5 °C)
28.1 kcal/mol (98.5 °C)
28.1 kcal/mol (88.5 °C)

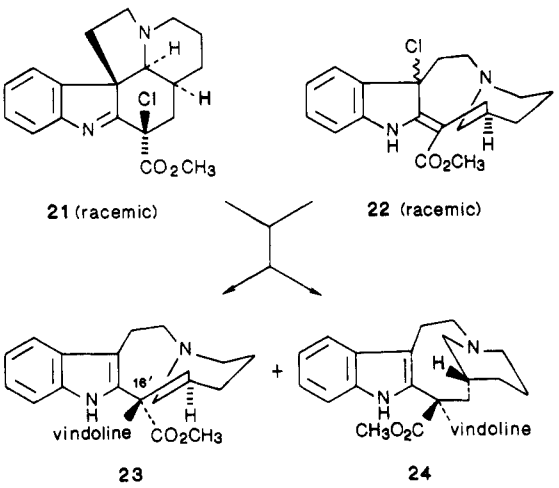
	for 20					
	111 °C		91 °C		81 °C	
time, 10^{-2} s	% 18	% 20	% 18	% 20	% 18	% 20
0	0	100	0	100	0	100
9	18.0	82.0				
18	36.2	63.8	5.0	95.0		
27	49.8	50.2				
36	60.5	39.5	9.4	90.6		
45	68.9	31.1				
54	73.3	26.7	16.9	83.1		
63	77.5	22.5				
72	82.1	17.9	21.6	78.4	9.1	90.9
81	86.1	13.9				
90	88.2	11.8	25.9	74.1		
99	90.4	9.6				
108	91.6	8.4	30.3	69.7		
126	94.1	5.9	35.2	64.8		
144	97.1	2.9	39.5	60.5	15.9	84.1
162			43.4	56.6		
180	100		47.2	52.7		
198			49.2	50.8		
216			52.2	47.8	25.4	74.6
234			55.8	44.2		
252			58.2	41.8		
288			62.5	37.5	29.7	70.3
360					34.6	65.4
432					40.2	59.8
504					44.6	55.4
576					47.6	52.4
648					52.0	48.0
720					55.7	44.3
1152					72.6	27.4

k^b = 2.41 × 10^{-4} s^{-1}
3.36 × 10^{-5} s^{-1}
1.18 × 10^{-5} s^{-1}
from $\Delta G^{\ddagger c} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$
$\Delta H^{\ddagger}$ = 19.3 kcal/mol
$\Delta S^{\ddagger}$ = 26 ± 3 eu

$\Delta G^{\ddagger c}$ = 29.0 (111 °C)
28.9 (91 °C)
28.6 (81 °C)

[a] The inversion rates were obtained at three temperatures by HPLC determination of relative concentrations of 19 and 17, using conditions specified in Table IIa. [b] k = (ln % 19 or 20)/t. [c] $\Delta G^{\ddagger}$ = $RT(23.76 + \ln T - \ln k)/1000$. R = 1.986, T = temperature, K.

Scheme III



for our study, vindoline (2) was coupled with the chloro imine derivative 21 of racemic desethylvincadifformine[5a,6,7] and with the chloroindoline–alkene derivative 22 of racemic 16-carbomethoxy desethyldihydrocleavamine.[5] The resulting two diastereomeric C14′-C16′ pref products 23 and 24 (Scheme III) were readily distinguished by chromatography (Table II) and spectroscopy (below) from the C14′-C16′ parf products 17 and 18.

Spectroscopic Comparison of the Four Diastereomeric Indole–Indoline Dimers 17, 18, 23, and 24.[4,8–12] For diagnosis, the NMR chemical shift of the vindolinyl ethyl CH_3 group is most noteworthy. It is found at δ −0.11 for the 16′*S*, C14′–C16′ pref compound 24 and at δ 0.81 for the 16′*S*, C14′–C16′ parf compound 17. The 16′*R* compounds have this signal at intermediate values of δ 0.66 for the pref compound 23 and at δ 0.41 for the parf compound 18. Both pref compounds 23 and 24 display a broad one-proton triplet at δ 4.04, which is shifted in the parf series to δ 3.55 for 17 and to δ 3.65 for 18. It should be noted here that this signal is, however, not universally characteristic of the C14′–C16′ pref vs. parf series in related compounds which have variations of piperidine ring substitution and conformation.[13] The C14′–C16′ pref series is also distinguished by having two overlapping methoxy signals upfield from the third methoxy signal for 23 and 24, while in the parf compounds 17 and 18 the overlapping methoxy signals are found downfield from the third one. In the aromatic region, the C9 proton singlet of the C14′–C16′ parf compounds 17 and 18 falls at δ 6.6 and 6.7, respectively, whereas the pref compounds 23 and 24 have this signal at δ 7.0.

The compounds 19 and 20 with the higher energy piperidine conformation both have their vindolinyl ethyl signal as a broad, poorly defined triplet at δ 0.5. The 1:1 mixture of nine-membered ring conformers for compound 20, at room temperature, results in distinct signal pairs at

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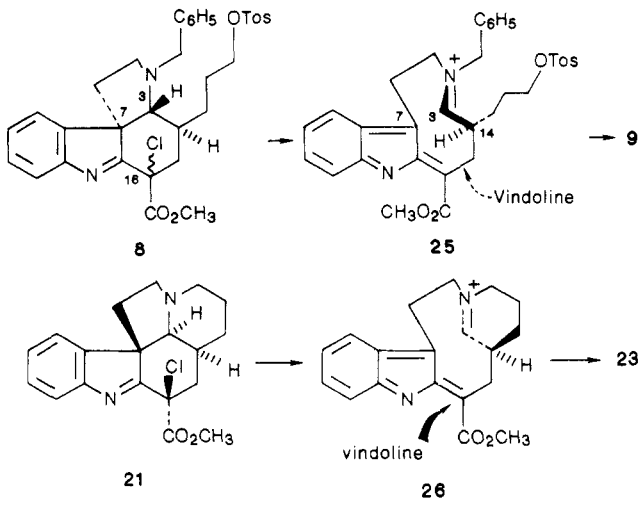
(13) To be presented in a subsequent publication.

Scheme IV



δ 10.8 and 7.6 (NH) and δ 9.5 and 9.7 (OH). These signal pairs coalesce to corresponding signals at δ 7.3 and δ 9.2 on heating of compound **20** to 70 °C. The original spectrum was regenerated on cooling. For the diastereomer **19** there is also considerable broadening of NMR signals at room temperature but no definitive separation into signal pairs. A spectrum at −30 °C resulted in pronounced sharpening of the broad methoxy signal at δ 3.55 and definition of the methyl triplet at δ 0.51.

Compounds **19** and **20**, with an equatorial $N^{b'}$ electron pair, show diminished Wenkert–Bohlmann IR bands (now only due to the vindoline moiety) relative to their piperidine conformational isomers **17** and **18**.

In mass fragmentation spectra, the C14′–C16′ parf compounds **17** and **18**, in contrast to the C14′–C16′ pref compounds **23** and **24**, gave an m/z 736 ($M + 1 - OCH_3$) peak, suggesting of a facilitated methoxyl loss from the C20′ ester group when the latter is in proximity to $N^{b'}$.

A correlation of circular dichroism spectra of the four diastereomers **17**, **18**, **23**, and **24** (Table I) with corresponding data for other indole–indoline compounds,[4,8-12] with C16′ *S* or *R*, also allowed unambiguous assignments to these compounds. This spectroscopic correlation was buttressed by the unique vinblastine-like biological activity (below) found only in compound **17**,[13] which has the C14′–C16′ absolute configuration of vinblastine.

An understanding of the discovery that 14-epi-*D*-seco-(Ψ)vincadifformine type compounds **7** and **8** undergo coupling to vindoline with high stereoselectivity in the desired sense of establishing a C16′–C14′ parf relative stereochemistry, whereas the usual D/E cis-fused (Ψ-)-vincadifformine type structures give only the corresponding C16′–C14′ pref products, may be obtained from the following considerations: The Ag^+-promoted conversion of initial chloro imine **8** to a cationic intermediate suggests that such an intermediate is not likely to have the skeletal structure of the tetracyclic precursor **8**, with localization of a positively charged center at C16 between the positive imine and ester functions. Instead, the cationic intermediate is better represented as the result of rupture of the C3 to C7 bond, with formation of a nine-membered ring imonium salt (**25**) (Scheme IV). Starting from *D/E-cis*-(Ψ-)vincadifformine type chloro imine derivative **21**, the corresponding imonium salt **26** would be expected. One can now anticipate that the ease of formation of such imonium salts should correlate with the lability of the C3–C7 bond, so that an imonium salt should form most readily from the D-seco precursor **8**, somewhat less readily from the chloro imine derivative (**21**) of *D/E-cis*-desethylvincadifformine and not at all from a D/E trans desethylvincadifformine (**5**) derived chloro imine.[5] These expectations were borne out by corresponding yields of vindoline-based coupling products, which were best for the D-seco compound **7**, modest for the *D/E-cis*-desethylvincadifformine (**4**), and nil for attempted coupling of the *D/E-trans*-desethylvincadifformine (**5**) series. We also found that coupling of the *D/E-cis*-desethylvincadifformine derivative **21** with vindoline was strongly influenced by the reaction temperature (i.e., by the energetic requirement for cleavage of the C3 to C7 bond).[5] Thus C14′–C16′ pref indole–indoline product yields of 6% (0 °C), 21% (22 °C), and 51% (50 °C) resulted from **21** by temperature variation, while the D-seco compound **8** gave good yields of coupling products even at −78 °C. No traces of C14′–C16′ parf products were obtained from the pentacyclic chloro compound **21**.

At the stage of bond formation of C16′ to vindoline, one-sided interaction of the extended polyene including the reaction site C16′, with the imonium function will then differ in the reactants **25** and **26** as a consequence of the respective geometries of the chloro imines **8** and **21** and result in stereospecific control (electronic and steric) of attack by the nucleophile vindoline to give only the respective C16′–C14′ parf or pref products.

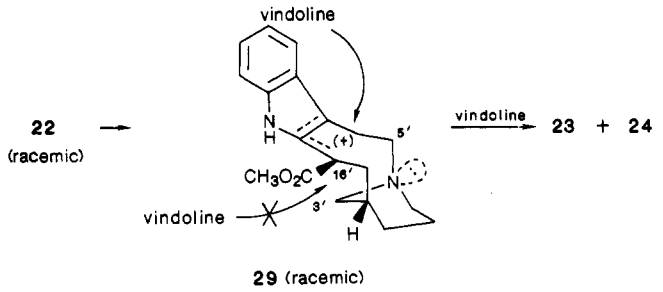
A fundamental requirement for achievement of the C14′–C16′ parf relative stereochemistry in the coupling products is therefore the maintenance of the initial geometry of the imonium intermediate **25**, which is derived from the geometry of the tetracyclic precursor **8**. We speculated that loss of this geometry, which defines the spatial relationship of C3 to C7, relative to C14, might arise from thermal activation and/or from reversible generation of a transient C3–C14 enamine. In accord with this expectation it was found that formation of the very minor C14′–C16′ pref products **23** and **24** could be increased substantially by initiating the coupling reaction of the tetracyclic chloro compound **8** with protonated vindoline at elevated temperatures or by conducting the reaction under more basic reaction conditions, which would favor generation of a transient C3–C14 enamine (entries 1–4, 8, Table III).

That formation of a 1:1 ratio of C14′–C16′ pref:parf products under basic conditions was not due to an epimerization of the chloro imine skeleton **8**, and coupling of a C14–C3 cis H precursor, followed from the stability of precursors **8** (unchanged NMR spectrum) in the absence of silver ion and with replacement of vindoline by triethylamine. In the absence of silver ion the chloro imine **8** did not react significantly with vindoline in acetone at room temperature but at reflux the C14′–C16′ pref and parf coupling products were again obtained.

The small increase in C16′–C14′ pref products **23** and **24**, found on increasing the acidity of the reaction mixture beyond 2 equiv (entries 3 vs. 9 and 10, Table III), may reflect a competing reaction pathway, where vindoline adds to an N^a protonated (dicationic) species derived from protonation of the initial intermediate **25**. In such a pathway the N^b imonium function of **25** could not exert its previous stereoelectronic control (concerted trans addition) on the coupling process. Consequently, this second reaction path should result in a C16′–C14′ stereochemistry which approaches the one obtained when the imonium function of **25** is replaced by a protonated 3° N^b (see below).

In order to accept the variations of C16′–C14′ relative stereochemistry with variations of reaction conditions as a consequence of the behavior of an initial imonium in-

Scheme V



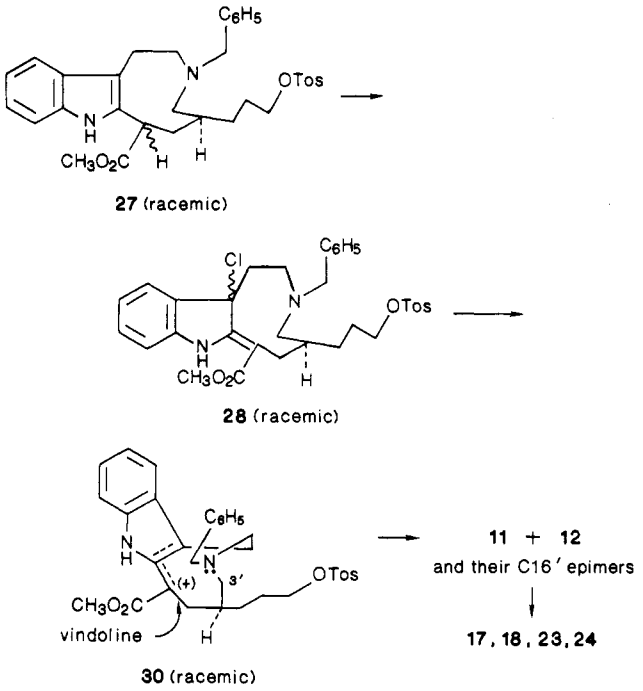
termediate **25**, it was necessary to establish that the imine products **9** and **10** did not undergo epimerization at C14′ under the reaction conditions. While some reversible C3′–C7′ bond cleavage, with C3′–C14′ enamine formation may take place with these imines **9** and **10**, their relative stereochemistry hardly changed even on prolonged treatment with acid, base, or on heating.

Of interest is also the observation that with an excess of the racemic chloro imines **8** over vindoline, under acidic conditions, a diastereomeric excess (3:2) of the desired coupling product **9** over its isomer **10** was obtained, thus providing some enantioselectivity to the overall synthesis of 20′-desethyl-20′-deoxyvinblastine (**17**). This selectivity decreased with increasing temperature of the coupling reaction (entries 1–4, Table III), and it was reversed when vindoline base, rather than a protic salt of vindoline, was used.

Having obtained the desired stereochemical reversal of the wrong coupling sequence of a *D/E-cis*-(Ψ-)vincadifformine structure (**4** → **23** + **24**) by use of D seco compound **6**, we could ask if an analogous reversal of the cleavamine coupling sequence (**3** → **23** + **24**) could also be achieved by use of a corresponding D seco cleavamine compound (**27**). While the preceding discussion indicates that in either sequence one is actually considering nine-membered ring systems as the reactive intermediates for arylation by vindoline, these reactants differ fundamentally. In the first cases (**21** → **23** + **24** or **8** → **9** + **10**) electronic interaction of the C3–N^b imonium function with the indolic C7 carbon restricts the conformational options of the nine-membered ring, which results in concerted formation of a C3′–C7′ bond while generating the C16′ to vindoline bond in the coupling process. This same stereoelectronic control is not available to the vindoline coupling reaction of a chloroalkene derivative of a cleavamine **3**, nor to its D-seco analogue **28**, yet complete C16′–C14′ pref stereoselectivity had been found for all examples of cleavamine coupling reactions (**3** → **1b**[2,3] and **22** → **23** + **24**), typically conducted in methanol or dimethylformamide in the presence of excess acid. As a molecular model, which might explain that stereochemical result, one may consider a preferential stacked nine-membered ring–piperidine conformation **29** (with C5 axial?) and N^b protonated equatorially, resulting in one-sided steric shielding of a C16 cationic center by the C3 methylene group (Scheme V).

For coupling of vindoline to the chloro derivative of a *D*-secocleavamine (**27**), a cationic intermediate with a conformationally more flexible nine-membered ring can be expected (Scheme VI). In order to direct the reaction of such a *D*-secocleavamine chloroindoline–alkene derivative (**28**) toward the formation of a C16′–C14′ parf product, one would like nine-membered ring conformation **30** in which N^b and C3 are folded over the allylic cation function, thus shielding it from nucleophilic attack on one side. For this purpose N^b should not be protonated in

Scheme VI



order to avoid repulsion by the cationic center at C16. Under strongly acidic conditions protonation of N^b can be expected to result in an alternative conformation with maximum separation of C16 and N^b and consequent loss of the desired steric shielding at C16.

While initial coupling reactions of the chloroalkene indoline **28** with vindoline suggested that the desired parf stereochemistry may be obtained selectively,[14] reactions under acidic conditions (which were also used above for coupling of the chlorinated cleavamine **22**) showed that the expected undesired C16′–C14′ pref products predominated. Conversion of such a product mixture to 20′-desethyl-20′-deoxyvinblastine (**17**) and its stereoisomers **18**, **23**, and **24** by the above-described cyclization and debenzylation sequence provided a mixture of C16′–C14′ parf and pref products **17** (11%), **18** (5%), **21** (15%), and **22** (26%).

A modification of the coupling procedure, which corresponds to reaction conditions used in coupling of the chloro imines **8** (i.e. a reaction of the chloroindoline–alkene **28** with silver tetrafluoroborate, vindoline and 1.5 equiv of HBF_4 in acetone) produced, in low overall yields, a more equal ratio of C16′–C14′ parf to pref products: **17** (2.4%), **18** (3.6%), **23** (2.4%), **24** (4.6%).

Previous extensive searches for conditions which would generate vinblastine-type C16′–C14′ parf coupling products from reactions of chlorinated cleavamines with vindoline had failed.[2,3] However, we have now found that even this result can be obtained, albeit in very low yield, by alternative reaction conditions. Coupling of the racemic chloroindoline–alkene **22** with vindoline, when initiated by silver tetrafluoroborate in acetone produced the C16′–C14′ parf products **17** (1.2%) and **18** (2.4%) together with the pref products **23** (1.1%) and **24** (1.0%). While the desired vinblastine analogue **17** was thus formed under these reaction conditions in slight excess over the corre-

(14) Results obtained in our laboratory by Dr. J. Tagat. A detailed study of this coupling reaction with variations of conditions and substrates will be reported later.

(15) Full details of the biological evaluation of this and related compounds will be presented elsewhere with Profs. L. Borman, M. Hacker, and J. McCormack of the University of Vermont Pharmacology Department.

sponding pref diastereomer **24**, its minute yield from this reaction is obviously not of practical value. The results show, however, that an alternative to the reaction pathway in HCl–methanol, represented by intermediate **29**, is attainable.

Biological evaluation of 20′-desethyl-20′-deoxyvinblastine (**17**) showed that this compound has pronounced cell culture cytotoxicity for L1210 leukemia cells, with an $ID_{50} = 1.5 \times 10^{-7}$ M, which corresponds to a 300 times lower potency than that of vinblastine (**1a**). Both compounds **17** and **1a** arrest mitosis at metaphase. Compound **17** also shows at 2×10^{-6} M concentration the inhibition of microtubule formation found on reaction of calf brain tubulin with vinblastine at a 3×10^{-7} M concentration. These results indicate an analogous mechanism of action for the two compounds. In vivo tests of the vinblastine analogue **17** with P388 leukemia in mice demonstrated a therapeutic index superior to that of vinblastine (**1a**).[15] The other diastereomeric product **18** (C16′*R*) of the C16′–C14′ parf coupling reaction and the C16′–C14′ pref isomers **23** and **24** (C16′*R* and *S*) did not show cytotoxicity at 1×10^{-5} M concentration, nor was it found with the quaternary salts **13a,b/15a,b** or the initial debenzylation product with the higher energy conformational structure **19**. This piperidine atropisomer **19** of 20′-deoxyvinblastine **17** also did not inhibit the generation of microtubules from tubulin.

Establishment of vinblastine-like biological activity for 20′-desethyl-20′-deoxyvinblastine (**17**) and lack of such activity in its precursors **13a,b/15a,b** and **19** is of particular interest in view of the facile thermal conversion of **13b,15b** and **19** to the active compound. These results allow one to propose that with optimization of such conversions and better cytotoxicity in corresponding analogues, an *in tumor site energetic activation* of noncytotoxic pro-drugs may become of value in cancer chemotherapy. Application of such *site activation chemotherapy* (*SAC*) to localized tumors is the subject of our continuing research.

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 Finnegan 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 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 gel on alumina sheets. For centrifugal chromatography a Harrison Chromatotron was used with E. Merck 60 PF 254 silica gel with gypsum. For column chromatography 60–200-mesh Baker R3405 silica gel was used. Microanalyses were provided by Mr. George Robertson, Robertson Laboratories, Florham Park, NJ.

N^b-Benzyl-20-[3-(*p*-toluenesulfonyloxy)propyl]-20-desethyl-*D*-norvincadifformine (7). A solution of N^b-benzyl-20-(3-hydroxypropyl)-*D*-nordesethylvincadifformine (11.53 g, 27.5 mmol)[5] in 200 mL of dry dichloromethane and 5.37 mL (1.4 equiv) of triethylamine was cooled to 0 °C and a solution of 12.58 g (38.5 mmol) of *p*-toluenesulfonic anhydride in 50 mL of dichloromethane added over 2 h. After 6 h at 0 °C, the mixture was extracted with 200 mL of 10% ammonium hydroxide in saturated brine, dried over anhydrous magnesium sulfate, and concentrated under vacuum. The residue was column chromatographed on silica gel, eluting with 1:1 ether/hexane, to provide 14.5 g (92%) of the product **7** which matched the previously characterized sample, prepared by an alternative procedure,[5] in mp and spectroscopic data.

16-Carbomethoxy-16-vindolinyl-N^b-benzyl-20-[3-(*p*-toluenesulfonyloxy)propyl]-*D*-norcleavamines (11 and 12). A solution of the tosylate **7** (0.740 g, 1.30 mmol) in 10 mL of dichloromethane and 0.18 mL (1.3 mmol) of triethylamine was cooled to 0 °C. Dropwise addition of 0.200 mL (1.69 mmol) of *tert*-butyl hypochlorite and stirring for 10 min gave a solution which by TLC was free of starting compound **7** (CAS, blue) and which contained a new less polar compound (CAS, brown). The reaction mixture was washed with 2 × 10 mL of water and 10 mL of brine and dried (Na_2SO_4). Concentration under vacuum gave 0.800 g (1.30 mmol) of chloro imine product **8** as a white foam. NMR spectra of this product indicated a 1:1.7 ratio of two compounds (C16 epimers) by the presence of respective methyl ester signals at δ 4.13 (s) and 3.95 (s) and tosylaromatic protons at δ 7.65 (d) and 7.72 (d). These NMR spectra did not change after stirring the product **8** in acetone and triethylamine for 30 min.

To a solution of these chloro imines **8** and vindoline × 1.5 HCl (**2**, 0.456 g, 0.90 mmol) in 15 mL of dry acetone was added a solution of 0.80 g (4.0 mmol) of $AgBF_4$ in 15 mL of dry acetone at room temperature. After 5 min the heterogeneous gray reaction mixture contained neither starting material **8** nor **2**. Addition of 10 mL of concentrated ammonium hydroxide, 10 mL of water, and 10 mL of brine, extraction with 3 × 20 mL of dichloromethane, washing of the extracts with brine, drying (Na_2SO_4), and concentration gave 1.20 g of crude imines **9** and **10**.

This crude imine product (**9**, **10**) was dissolved in 15 mL of acetic acid and, with stirring at room temperature, 0.54 g (10 mmol) of sodium borohydride was added in six portions. After the final addition the reaction mixture was stirred for 10 min and then poured onto ice. Adjustment of the pH to 9–10 with concentrated ammonium hydroxide was followed by extraction with 60 mL of dichloromethane. The extract was washed with water (3 × 25 mL) and brine (25 mL), dried (Na_2SO_4), and concentrated to 1.10 g of a yellow solid. Column chromatography on silica gel, eluting with ethyl acetate, gave 0.83 g (90% based on 0.9 mmol of vindoline) of the tosylates **11** and **12** as a white solid, R_f 0.25 (SiO_2, ethyl acetate, CAS brown). The diastereomers **11** and **12** showed slight separation on TLC using methanol–dichloromethane as solvent.

Preparative isolation of the separated isomers **11** and **12** was achieved by medium pressure liquid chromatography using, in series, one 25 × 500 mm and two 25 × 1,000 mm Altex columns packed with silica gel 60 (E. Merck, 230–400 mesh) for the coupling product derived from 1.0 g of the tosylate **7**. Elution with anhydrous ether/acetone/triethylamine (100/20/2) at 40 psi and 11 mL/min and collection of 20-mL fractions gave isomer **11** 0.57 g (41%) in fractions 16–52, followed by the precursor of **23**, 0.021 g (1.5%) (NMR vindolinyl ethyl triplet δ 0.58), then isomer **12**, 0.46 g (33%) in fractions 106–156, followed by the precursor of **24**, 0.028 g (2%) (NMR vindolinyl ethyl triplet δ 0.15). Cyclization of each of these products and hydrogenolytic debenzylation by the following procedures then gave the respective products **17**, **18**, **23**, and **24** in quantitative yields from these separated indole–indoline tosylates.

Physical data for less polar isomer 11: TLC (SiO_2, 7.5% methanol/CH_2Cl_2) R_f 0.63 (CAS, brown); UV (ethanol) λ_{max} 228, 262, 290, 297 nm; IR (KBr) ν_{max} 3470, 3057, 3026, 2948, 2877, 2860, 2839, 2793, 2740, 2720, 2713, 1739, 1615, 1597, 1501, 1460, 1432, 1362, 1337, 1293, 1244, 1226, 1188, 1175, 1142, 1120, 1097, 1040, 1012, 961, 929, 918, 815, 734, 700, 680, 663, 646, 554 cm^{-1}; 250-MHz NMR ($CDCl_3$) δ 0.84 (t, 3 H), 0.96–1.82 (m, 10 H), 2.03–2.15 (m, 2 H), 2.09 (s, 3 H), 2.25–2.76 (m, 8 H), 2.41 (s, 3 H), 2.70 (s, 3 H), 3.06–3.32 (m, 6 H), 3.60–3.65 (m, 1 H), 3.62 (s, 3 H), 3.73 (s, 1 H), 3.78 (s, 6 H), 5.29 (d, 1 H), 5.44 (s, 1 H), 5.81 (dd, 1 H), 6.09 (s, 1 H), 6.76–6.87 (m, 4 H), 6.98 (dt, 2 H), 7.09–7.16 (m, 2 H), 7.26 (d, 2 H), 7.36 (d, 1 H), 7.68 (d, 2 H), 8.03 (br s, 1 H), 9.87 (br s, 1 H); MS, *m/z* (relative intensity) 856 (M^+ – *p*-toluenesulfonic acid, 0.78), 825 (0.40), 767 (1.0), 766 (0.81), 737 (1.2), 735 (4.1), 708 (3.8), 608 (1.6), 606 (1.4), 499 (1.1), 470 (1.1), 468 (1.1), 283 (1.1), 262 (1.1) 186 (5.4), 182 (2.0), 167 (2.5), 156 (1.7), 155 (4.3), 135 (4.0), 126 (3.2), 124 (1.4), 122 (2.1), 121 (2.0), 110 (8.7), 108 (4.8), 107 (31), 106 (5.0), 105 (5.0), 96 (4.1), 93 (4.1), 92 (31), 91 (100), 89 (6.8), 86 (13), 84 (14), 77 (15), 65 (30), 63 (12), 51 (32), 50 (20).

Physical data for more polar isomer 12: TLC (SiO_2, 7.5% methanol/CH_2Cl_2) R_f 0.62 (CAS, brown); UV (ethanol) λ_{max} 228, 260, 295 nm; IR (KBr) ν_{max} 3444–3415, 3055, 3027, 2949, 2939,

2876, 2853, 2840, 2804, 2742, 2716, 1738, 1615, 1597, 1498, 1460, 1432, 1361, 1338, 1297, 1245, 1224, 1189, 1175, 1121, 1109, 1096, 1038, 1012, 960, 914, 816, 735, 701, 681, 664, 644, 570, 554; 250-MHz NMR ($CDCl_3$) δ 0.35 (t, 3 H), 0.98–1.02 (m, 4 H), 1.25–1.75 (m, 6 H), 2.02–2.83 (m, 14 H), 2.06 (s, 3 H), 2.39 (s, 3 H), 2.71 (s, 3 H), 2.99–3.05 (m, 1 H), 3.21–3.45 (m, 4 H), 3.52–3.60 (m, 1 H, 3.56 (s, 3 H), 3.67–3.85 (m, 1 H), 3.77 (s, 3 H), 3.80 (s, 3 H), 5.16 (d, 1 H), 5.46 (s, 1 H), 5.75 (dd, 1 H), 6.12 (s, 1 H), 6.89 (s, 1 H), 6.95–7.26 (m, 9 H), 7.39 (d, 1 H), 7.71 (d, 2 H), 8.08 (br s, 2 H), 9.67 (br s, 1 H); MS, m/z (relative intensity) 856 (M^+ – *p*-toluenesulfonic acid, 0.4) 766 (1.9), (735 (1.1), 707 (1.8), 636 (0.5), 608 (0.7), 469 (2.1), 310 (1.2), 282 (1.5), 262 (2.3), 221 (1.8), 220 (7.8), 206 (1.6), 205 (12), 189 (1.1), 187 (1.0), 186 (6.0), 182 (2.0), 177 (1.2), 172 (1.4), 167 (2.8), 165 (1.7), 157 (1.0), 156 (2.3), 155 (5.6), 149 (7.7), 135 (4.3), 128 (1.8), 126 (5.6), 124 (1.3) 122 (2.1), 121 (3.4), 111 (2.1), 110 (6.91), 109 (2.3), 108 (5.8), 107 (44), 105 (5.8), 97 (3.8), 96 (4.3), 95 (3.1), 93 (3.8), 92 (2.9), 91 (100), 89 (7.1), 86 (8.0), 85 (5.3), 84 (17), 83 (4.0), 82 (3.6), 79 (8.0), 77 (12), 65 (32), 63 (11), 57 (20), 55 (11), 51 (22), 50 (15).

20′-Desethyl-20′-desoxyvinblastine and Its C-14′–C-16′ Diastereomer (17, 18). a. The mixture of diastereomers **11,12** (0.258 g, 0.250 mmol) was dissolved in 2.5 mL of dry toluene and heated at reflux, with stirring for 1.5 h. At that point the quaternary salts **13a–16a** had precipitated as a brown gum and TLC indicated complete reaction of the two diasteromeric tosylates **11,12**. The solvent was removed under vacuum and the residual solid (0.258 g, 100%) with R_f (SiO_2, 95:5 CH_2Cl_2/methanol, CAS pink) 0.05 was used directly in the following debenzylation.

A solution of 0.206 g (0.200 mmol) of the quaternary salts in 5 mL of dry methanol was stirred with 20 mg of 10% palladium on charcoal under a hydrogen atmosphere at −5 to 0 °C for 1–2 h, when 4.5 mL (0.20 mmol) of hydrogen had been consumed. Filtration through Celite, concentration at 20 °C, and partitioning of the residue between 30 mL of dichloromethane and 10% aqueous ammonium hydroxide, followed by washing of the organic extracts with water and brine gave, on concentration, 150 mg (99%) of products with TLC R_f (SiO_2, CH_2Cl_2/methanol 9:1, CAS brown) 0.10. The product mixture (0.150 g, 0.195 mmol) was dissolved in 5 mL of toluene and heated at reflux for 2 h. TLC then showed formation of the two diasteromeric products **17,18** with the 14′ axially substituted piperidine conformation. TLC (SiO_2, 10% methanol in CH_2Cl_2, CAS brown) R_f 0.35 and 0.16. Concentration and centrifugal chromatography on a 2-mm SiO_2 plate, eluting with 5% methanol in CH_2Cl_2, gave 32 mg of 20′-desethyl-20′-deoxyvinblastine (**17**) (R_f 0.16) and 35 mg of its 14′,16′ enantiomeric diasteromer **18** (R_f 0.35). Yield, 47% for each diastereomer.

b. Using the separated tosylates **11** and **12** and the same procedure on a 0.5-g scale gave the chromotographed products **17** and **18** in quantitative yields.

c. Alternatively, the quaternary salts **13a–16a** were dissolved in methanol (5 mL) and the solution was purged with nitrogen. Palladium catalyst (10% Pd/C, 0.10 g) was added, and the flask fitted with a reflux condenser and heated in a 90 °C oil bath. An excess of sodium borohydride (ca. 0.3 g) was added through the top of the condenser as rapidly as possible, so that the vigorous reaction could be contained. TLC's were taken throughout this procedure to qualitatively determine if any starting material remained. The addition of the borohydride reagent took about 5 min. A short reaction time was necessary because a less polar side product seemed to form on longer reaction times. The hot solution was filtered and washed with hot methanol (ca. 50 mL) followed by CH_2Cl_2 (ca. 10 mL). The solution was partially concentrated and NH_4OH (10% aqueous) was added. The aqueous solution was extracted with CH_2Cl_2, and the organic extracts were dried (Na_2SO_4) and concentrated to a residue, which was identified as a mixture of diastereomeres **17,18**. Yield, 0.13 g (70%).

Analytical samples of products **17** or **18** prepared by chromatography of 100 mg of the respective compound on a 1.0 cm × 6.0 cm silica gel column (which had been prepared as a slurry with methanol and eluted with 25 mL of methanol prior to application). The compounds were added in 2 mL of methanol and eluted with methanol until all of the compound had been recovered. The methanol was then concentrated to 5 mL and passed through a HPLC filter (3-mm Nylon syringe filter, 0.2 μm pore size) followed by 5 mL of methanol. Concentration under reduced pressure at 42 °C, followed by heating in a drying pistol (CCl_4, 77 °C) at 0.05 mm gave samples for elemental analyses. The 1 equiv of water of hydration seen in NMR spectra and in elemental analyses persisted in these, as well as in analytical samples prepared by alternative precipitations from mixed solvents. Analogously, a sample of natural vinblastine retained water of hydration.

Physical data for less polar isomer 18: TLC (SiO_2, 15% methanol/CH_2Cl_2) R_f 0.62 (CAS, brown); UV (ethanol) λ_{max} 230, 260, 290, 297 nm; IR 3465, 2946, 2927, 2877, 2843, 2805, 2748, 1742, 1615, 1502, 1459, 1431, 1370, 1332, 1295, 1243, 1224, 1175, 1144, 1121, 1102, 1064, 1039, 1003, 734; 250-MHz ^1H NMR (hydrate, $CDCl_3$) δ 0.41 (t, 3 H), 1.09 (q, 2 H), 1.33 (t, 2 H), 1.48–1.64 (m, 1 H), 1.52 (s, 2 H, H_2O), 1.81–1.88 (m, 1 H), 2.07 (s, 3 H), 2.16–2.47 (m, 4 H), 2.42 (s, 1 H), 2.64–2.79 (m, 1 H), 2.72 (s, 3 H), 2.88–3.45 (m, 11 H), 3.57 (s, 3 H), 3.61 (t, 1 H), 3.79 (s, 1 H), 3.80 (s, 6 H), 5.24 (d, 1 H), 5.48 (s, 1 H), 5.79 (dd, 1 H), 6.14 (s, 1 H), 6.73 (s, 1 H), 7.07–7.26 (m, 3 H), 7.50 (d, 1 H), 8.07 (s, 1 H), 9.68 (s, 1 H); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 174.8, 171.9, 170.6, 158.2, 153.2, 135.2, 131.0, 130.1, 129.1, 124.0, 123.8, 123.7, 122.3, 121.2, 118.9, 118.4, 110.2, 94.2, 83.6, 79.6, 76.1, 67.3, 59.0, 56.1 (2 × 55.7), 53.4, 53.0, 52.2, 52.1, 51.2, 50.6, 48.3, 44.6, 43.0, 38.4, 34.3, 31.5, 31.0, 29.6, 28.5, 22.0, 21.0, 8.3; MS, m/z (relative intensity) 766 (M^+, 8), 735 (3), 707 (9), 607 (3), 527 (4), 499 (2), 469 (19), 311 (9), 310 (10), 309 (5), 297 (7), 283 (7), 282 (20), 273 (5), 272 (7), 251 (5), 240 (5), 239 (7), 237 (7), 224 (9), 222 (9), 214 (5), 202 (6), 200 (6), 188 (9), 185 (7), 174 (5), 170 (5), 156 (5), 144 (11), 136 (10), 135 (10), 134 (5), 130 (6), 124 (16), 122 (26), 121 (24), 112 (7), 111 (15), 110 (100), 109 (12), 108 (18), 107 (31), 106 (11), 97 (24), 96 (41), 94 (8), 92 (12), 91 (13), 86 (7), 84 (11), 83 (12), 82 (23), 81 (12), 79 (7), 73 (7), 72 (7), 71 (7), 70 (8), 69 (17), 68 (7), 67 (9), 65 (8), 60 (11), 58 (29), 57 (26), 56 (12), 55 (20).

Anal. Calcd for $C_{44}H_{54}N_4O_8 \cdot H_2O$: C, 67.33; H, 7.18; N, 7.14. Found: C, 67.14; H, 7.18; N, 6.73.

Physical data for more polar isomer 17: TLC (SiO_2, 15% methanol/CH_2Cl_2) R_f 0.42 (CAS, brown); UV (ethanol) λ max 230, 263, 289, 296 nm; IR (KBr) 3459, 2936, 2925, 2877, 2836, 2809, 2748, 2740, 1740, 1614, 1501, 1432, 1370, 1333, 1297, 1244, 1224, 1174, 1145, 1121, 1103, 1065, 1038, 1004, 734; 250-MHz ^1H NMR (hydrate, $CDCl_3$) δ 0.75–0.82 (m, 1 H), 0.81 (t, 3 H), 1.34 (q, 2 H), 1.52 (br s, 2 H, H_2O), 1.73–1.67 (m, 3 H), 2.11 (s, 3 H), 2.10–2.46 (m, 4 H), 2.62–2.97 (m, 5 H), 2.68 (s, 1 H), 2.72 (s, 3 H), 3.13–3.53 (m, 8 H), 3.63 (s, 3 H), 3.73 (s, 1 H), 3.79 (s, 6 H), 5.30 (d, 1 H), 5.46 (s, 1 H), 5.85 (dd, 1 H), 6.10 (s, 1 H), 6.60 (s, 1 H), 7.07–7.16 (m, 3 H), 7.50 (d, 1 H), 8.00 (s, 1 H), 9.88 (s, 1 H); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 174.9, 171.7, 170.8, 158.2, 152.8, 135.2, 130.6, 130.1, 129.3, 124.4, 123.6, 123.0, 122.3, 121.5, 118.9, 118.4, 117.3, 110.4, 94.2, 83.5, 79.7, 77.2, 65.9, 56.8, 55.8, 55.6, 53.4, 53.3, 52.3, 52.1, 50.5, 50.4, 47.6, 44.5, 42.8, 38.3, 33.9, 31.5, 30.9, 29.6, 28.3, 21.9, 21.0, 8.3; MS, m/z (relative intensity) 766 (M^+, 7), 736 (5), 735 (13), 708 (6), 607 (6), 527 (5), 499 (4), 469 (7), 468 (5), 350 (4), 311 (5), 310 (9), 309 (5), 297 (5), 283 (4), 282 (18), 272 (4), 254 (5), 239 (7), 237 (5), 226 (8), 224 (6), 222 (7), 188 (5), 149 (5), 144 (8), 141 (10), 136 (8), 135 (45), 124 (13), 122 (23), 121 (17), 112 (9), 111 (13), 110 (100), 109 (10), 108 (11), 107 (21), 106 (8), 98 (8), 97 (21), 96 (49), 95 (9), 93 (16), 92 (14), 91 (6), 85 (7), 84 (12), 83 (15), 82 (20), 81 (13), 79 (7), 74 (8), 71 (10), 70 (7), 69 (20), 68 (6), 67 (8), 65 (5), 60 (22), 58 (13), 57 (28), 56 (11), 55 (23).

Anal. Calcd for $C_{44}H_{54}N_4O_8 \cdot H_2O$: C, 67.33; H, 7.18; N, 7.14. Found: C, 67.02; H, 6.98; N, 7.00.

Physical Data for the Quaternary Salts. 15a: UV (ethanol) λ_{max} 225, 270, 290, 310 nm; IR (KBr) ν_{max} 3448, 3026, 2950, 2877, 2840, 2813, 2737, 1738, 1616, 1501, 1460, 1433, 1371, 1337, 1322, 1296, 1226, 1196, 1144, 1120, 1033, 1011, 979, 817, 743, 706, 681, 568; 250-MHz ^1H NMR ($CDCl_3$) δ 0.73 (t, 3 H), 1.22–2.44 (m, 18 H), 2.10 (s, 3 H), 2.31 (s, 3 H), 2.56–2.76 (m, 3 H), 2.76 (s, 3 H), 3.19–4.12 (m, 14 H), 3.64 (s, 3 H), 3.79 (s, 3 H), 4.67 (d, 1 H), 4.95 (d, 1 H), 5.25 (d, 1 H), 5.42 (s, 1 H), 5.83 (dd, 1 H), 6.09 (s, 1 H), 6.41 (s, 1 H), 7.06–7.59 (m, 15 H), 7.67 (d, 2 H), 8.17 (s, 1 H), 9.88 (s, 1 H); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 173.8, 171.6, 170.9, 157.9, 153.5, 144.2, 138.8, 134.8, 133.4, 131.4, 130.4, 129.9 129.7, 129.0, 128.6, 128.4, 127.3, 125.9, 124.6, 124.0, 123.4, 122.9, 120.1, 119.0, 117.8, 110.8, 94.1, 83.0, 79.7, 70.4, 65.7, 59.3, 58.3, 56.8, 55.8, 55.1, 53.2, 52.6, 52.0, 50.4, 50.2, 44.6, 42.7, 37.9, 36.6, 30.8, 28.5, 26.4, 21.2, 21.0, 20.9, 17.6, 8.3; MS, m/z (relative intensity) CI (methane) 857 (1.7), 768 (15), 766 (12), 187 (34), 107 (18), 93 (11), 92 (13),

91 (100); EI 736 (1), 735 (1.0), 707 (1), 186 (5), 155 (3), 135 (2), 122 (1), 110 (8), 108 (4), 107 (33), 93 (3), 92 (34), 91 (100), 86 (18), 84 (34), 79 (8), 77 (16), 65 (33), 63 (10), 57 (91), 55 (6), 51 (43), 50 (12).

14a/16a: UV (ethanol) λ_{max} 229, 270, 293, 312 nm; IR (KBr) ν_{max} 3441, 3029, 2947, 2875, 2838, 2817, 1737, 1616, 1500, 1459, 1432, 1371, 1337, 1320, 1302, 1226, 1194, 1120, 1086, 1033, 1011, 977, 961, 817, 744, 708, 680, 657; 250-MHz ^{1}H NMR ($CDCl_3$) δ 0.33/0.51 (2 t, 3 H, 1.7:1.3), 1.00–2.13 (m, 18 H), 2.10/2.07 (2 s, 3 H), 2.32 (s, 3 H), 2.37–2.45 (m, 3 H), 2.75 (s, 3 H), 3.12–4.21 (m, 14 H), 3.61 (s, 3 H), 3.82 (s, 3 H), 3.80 (s, 3 H), 4.59 (d, 1 H), 4.92 (d, 1 H), 5.25 (d, 1 H), 5.47/5.42 (2 s, 1 H, 0.56:0.44), 5.88 (m, 1 H), 6.06/6.14 (2 s, 1 H), 6.64 (s, 1 H), 7.06–7.77 (m, 15 H), 7.75 (d, 2 H), 8.23 (s, 1 H), 9.74 (s, 1 H); 67.9-MHz ^{13}C NMR (CD_2Cl_2) δ 173.7, 172.5 (172.4), 170.9 (170.8), 158.7, 154.4, 145.6, 139.2, 135.4, 134.2, 133.8 (133.6), 131.0 (130.8), 130.7 (130.3), 129.7, 129.5 (109.3), 128.8, 128.5, 127.5, 126.3, 124.8, 123.2, 122.3, 120.4, 120.1, 118.4, 118.0, 111.1, 94.7, 83.9, 79.7 (79.6), 69.4, 67.4, 58.2, 56.2, 56.1, 54.6, 54.0, 53.6, 52.6, 52.4, 52.3, 51.5, 45.0, 43.6 (43.4), 38.6, 38.3, 31.5 (31.6), 29.1, 27.3, 21.3, 21.1, 20.6, 17.3, 8.8 (8.0); MS, m/z (relative intensity) CI (methane) 857 (0.8), 768 (0.7), 766 (2), 201 (14), 187 (31), 186 (28), 155 (10), 108 (7), 107 (25), 93 (7), 92 (22), 91 (100); EI 766 (0.8), 707 (0.8), 469 (1), 262 (2), 220 (2), 205 (9), 186 (7), 155 (6), 149 (5), 138 (7), 135 (2), 128 (2), 126 (7), 122 (2), 121 (2), 110 (3), 108 (4), 107 (31), 105 (3), 101 (2), 93 (3), 92 (22), 91 (100), 85 (24), 84 (15), 83 (8), 82 (3), 81 (3), 79 (12), 77 (10), 71 (4), 70 (3), 69 (7), 65 (32), 63 (13), 62 (4), 60 (6), 59 (5), 58 (12), 57 (15), 56 (33), 55 (29), 51 (17), 50 (12).

d. Isolation of the Higher Energy Conformation Products 19 and 20. The hydrogenolysis products, after the workup described above (**a**), prior to heating in toluene, were dissolved in 2 mL of dichloromethane and subjected to centrifugal chromatography on a 1-mm SiO_2 disk, eluting with methanol/triethylamine, 95:5, at 1 mL/min. The separated diastereomeric series fractions 5–12 gave 114 mg (77%) of **17** and fraction 16–36 gave 17 mg (11%) of **19**; alternatively fractions 3–9 gave 60 mg (41%) of **18** and fractions 12–38 gave 58 mg (39%) of **20**. Purification of **19** and **20** by HPLC on a 25 × 2.5 cm Dynamax SiO_2 column, eluting with methanol/triethylamine, 98:2, at 10 mL/min gave **19** (27 min) and **20** (20 min).

For **19**: TLC (SiO_2, 15% methanol, 0.5% triethylamine/CH_2Cl_2) R_f 0.17; 250-MHz ^{1}H NMR ($CDCl_3$) δ 9.70 (br s, 1 H), 7.50 (m, 2 H), 7.14 (m, 5 H), 6.10 (br, 1 H), 5.87 (dd, J = 4, 9 Hz, 1 H), 5.50 (br s, 1 H), 5.24 (d, J = 9 Hz, 1 H), 3.85 (s, 1 H), 3.82 (s, 3 H), 3.72 (s, 3 H), 3.55 (br s, 3 H), 3.55–3.26 (m, 6 H), 3.03–2.40 (m, 9 H), 2.74 (s, 3 H), 2.11 (s, 3 H), 1.89–1.11 (m, 8 H), 0.51 (br t, 3 H); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 171.9, 170.8, 170.6, 159.8, 153.7, 134.0, 130.2, 124.4, 124.3, 121.6, 119.3, 118.4, 110.5, 94.7, 83.4, 79.5, 77.2, 65.8, 55.8, 55.7, 53.1, 52.6, 52.2, 51.8, 51.5, 51.0, 50.8, 49.3, 43.7, 43.1, 37.8, 31.1, 31.0, 30.9, 29.0, 28.9, 22.6, 20.9, 8.1; MS, m/z (relative intensity) 767 (M^+ + 1, 6), 766 (M^+, 5), 736 (6), 735 (15), 708 (8), 707 (12), 607 (7), 527 (6), 499 (5), 469 (7), 468 (5), 389 (4), 381 (4), 325 (4), 311 (8), 310 (10), 309 (4), 297 (8), 296 (4), 295 (4), 283 (5), 282 (16), 273 (4), 272 (5), 251 (5), 240 (4), 239 (8), 237 (6), 224 (10), 222 (7), 188 (7), 181 (5), 149 (8), 144 (8), 138 (27), 136 (8), 135 (38), 130 (5), 127 (5), 125 (5), 124 (18), 122 (18), 121 (16), 115 (10), 113 (6), 112 (19), 110 (100), 109 (12), 108 (10), 107 (15), 100 (22), 99 (6), 98 (18), 97 (25), 96 (39), 95 (9), 94 (7), 93 (13), 91 (9), 87 (11), 86 (13), 85 (11), 84 (25), 83 (20), 82 (26), 81 (13), 73 (9), 72 (12), 71 (19), 70 (18), 69 (26), 68 (9), 67 (10), 60 (19), 59 (7), 58 (44), 57 (46), 56 (34), 55 (46); IR (KBr) ν_{max} 3452, 3405, 3330, 2957, 2924, 2873, 2852, 2814, 2748, 1740, 1616, 1498, 1458, 1433, 1371, 1248, 1235, 1199, 1171, 1142, 1107, 1093, 1041 cm^{-1}.

For 20: TLC (SiO_2, 15% methanol, 0.5% triethylamine/CH_2Cl_2) R_f 0.17; 250-MHz ^{1}H NMR ($CDCl_3$, 30 °C) δ 10.81 (br s, 0.5 H), 9.68/9.47 (br s, 0.5/0.5 H), 7.49 (br s, 0.5 H), 7.45–7.30 (m, 1 H), 7.14–6.99 (m, 4 H), 6.08/5.97 (2 br s, 1 H), 5.90 (dd, J = 10, 4 Hz, 1 H), 5.50 (br s, 1 H), 5.25 (dd, J = 10 Hz, 1 H), 3.86 (s, 1 H), 3.81 (s, 3 H), 3.58 (s, 6 H), 2.69 (s, 3 H), 2.10 (s, 3 H), 0.53 (br t, 3 H), remaining H's poorly defined broadened multiplet; ($CDCl_3$, 70 °C) δ 9.14 (br s, 1 H), 7.29 (m, 2 H), 6.99 (m, 3 H), 5.92 (s, 1 H), 5.78 (dd, J = 10, 3 Hz, 1 H), 5.40 (s, 1 H), 5.17 (d, J = 10 Hz, 1 H), 3.75 (s, 1 H), 3.71 (s, 3 H), 3.51 (s, 6 H), 3.12–2.75 (m, 9 H), 2.62 (s, 3 H), 2.44–2.25 (m, 8 H), 1.99 (s, 3 H), 1.63–1.43 (m, 7 H), 0.81 (m, 1 H), 0.45 (t, J = 7 Hz, 3 H); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 177.4, 171.8, 170.7, 159.9, 152.9, 133.9, 130.8, 128.2, 124.1, 121.6, 120.3, 119.3, 118.8, 118.1, 110.6, 95.6, 83.4, 79.4, 76.3, 67.3, 58.8, 55.9, 53.4, 53.0, 52.4, 52.1, 51.1, 50.9, 46.0, 44.8, 42.9, 38.0, 34.8, 30.8, 29.4, 29.0, 21.0, 20.9, 7.5; MS, m/z (relative intensity) 767 (M^+ + 1, 4), 766 (M^+, 8), 735 (4), 708 (4), 707 (8), 607 (4), 527 (4), 469 (9), 311 (8), 310 (8), 297 (6), 283 (5), 282 (13), 239 (6), 224 (7), 222 (6), 202 (5), 188 (6), 144 (7), 138 (14), 136 (7), 135 (32), 124 (13), 122 (17), 121 (15), 115 (8), 112 (7), 111 (14), 110 (100), 109 (9), 108 (9), 107 (13), 100 (10), 98 (8), 97 (24), 96 (36), 95 (5), 94 (5), 93 (11), 87 (6), 86 (13), 85 (6), 84 (13), 83 (13), 82 (21), 81 (8), 74 (9), 72 (9), 71 (9), 70 (12), 69 (18), 68 (6), 67 (6), 61 (17), 60 (19), 59 (8), 58 (51), 57 (27), 56 (22), 55 (24); IR (KBr) ν_{max} 3451, 3414, 3393, 3352, 2923, 2877, 2853, 2810, 1741, 1616, 1499, 1459, 1432, 1370, 1249, 1196, 1176, 1149, 1110, 1041 cm^{-1}.

e. General Conditions for Data in Table III, Entry 2. The chloroindolenines **8** prepared from 0.317 g (0.552 mmol) of the tosylate **7** were dissolved in 10 mL of acetone (distilled from boron oxide). After addition of 0.195 g (0.428 mmol) of vindoline base the solution was cooled to 0 °C and 0.122 mL (0.883 mmol) of tetrafluoroboric acid diethyl ether complex was added. After 2 min 0.107 g (0.552 mmol) of silver tetrafluoroborate in 1 mL of acetone was added at 0 °C and the reaction mixture stirred for 10 min. The reaction mixture was then poured into 10% ammonium hydroxide in saturated brine and extracted with 3 × 25 mL of dichloromethane. Variations of these conditions are indicated in Table III.

For a test of the stereochemical stability of the imines **9** and **10**, the above product mixture was dissolved in 2.5 mL of acetone and then stirred as such or with addition of 2.79 g (27.6 mmol) of triethylamine or with 4.47 g (27.6 mmol) of tetrafluoroboric acid diethyl ether complex for 5 h. The reaction mixtures were concentrated at 42 °C under vacuum and the resulting solid foams were then subjected to the subsequent reduction step.

Reduction of the imines **9** and **10** from the above coupling reaction was achieved by solution of the crude product mixture in 2 mL of acetic acid and, with rapid stirring, addition of 60 mg (1.1 mmol) of potassium borohydride in small portions. The reaction mixture was then poured into 10 mL of ammonium hydroxide and 10 g of crushed ice and extracted 3× with 10-mL portions of dichloromethane. The dried extracts ($MgSO_4$) were concentrated to a foam under vacuum. The resultant mixture of tosylates **11** and **12** and 25 mL of dry toluene was heated at reflux for 100 min, when TLC indicated complete quaternization. The reaction mixture was then concentrated under vacuum and the solid residue dissolved in 10 mL of methanol. Addition of 5 mg of 10% Pd/C and hydrogenation for 5 h at atmospheric pressure, filtration through Celite 545, with a subsequent 10-mL methanol wash, and concentration gave a mixture of amine tosylate salts. The mixture was dissolved in 15 mL of dichloromethane and washed with 20 mL of 10% ammonium hydroxide in saturated brine, and the dried ($MgSO_4$) extract was concentrated at 42 °C under vacuum. The residue and 25 mL of dry toluene were then heated at reflux for 5 h. Concentration under vacuum provided a product mixture which was subjected to HPLC analysis under conditions indicated in Table III.

f. Hydrogenation of a solution of the tosylates 11 and 12, obtained from the *D*-secovincadifformine route (Table III, entry 3), in acetic acid for 3 h with 10% Pd/C. Concentration under vacuum and partitioning of the residue between dichloromethane and 10% ammonium hydroxide in saturated brine provided the indole–indoline dimers **17** (27%), **18** (27%), and 29% of unidentified coupling products. HPLC retentions and NMR spectra of **17** and **18** matched those of the products obtained from the alternative reaction sequence above.

Coupling of the *D*-Secocleavamines 27 with Vindoline (2). a. A solution of 0.315 g (0.547 mmol) of the indolic tosylates **27**[5] and 0.114 mL (0.083 g, 0.82 mmol) of triethylamine in 215 mL of dichloromethane was cooled to 0 °C. With rapid stirring 0.095 mL (0.82 mmol) of *tert*-butyl hypochlorite was added in one portion. After 20 min TLC showed complete conversion of the tosylate to the slightly less polar chloroalkene–indoline(s) **28** (R_f 0.8, 5% methanol in dichloromethane, CAS orange). The reaction mixture was poured into 50 mL of water and extracted with 3 × 20 mL of dichloromethane, and the combined extracts were dried ($MgSO_4$) and concentrated at 42 °C under vacuum. The residual chloride(s) **28** were dissolved in 4 mL of 1.5% HCl in

methanol which contained 0.162 g (0.356 mmol) of vindoline. After 24 h the green solution was poured into 50 mL of 10% ammonium hydroxide in brine and extracted with 3 × 25 mL of dichloromethane. The dried ($MgSO_4$) extracts were concentrated under vacuum at 42 °C and the residue of tosylates **11,12** and their C16′ epimers was heated in 50 mL of toluene at reflux for 2 h. Concentration under vacuum and solution of the resultant quaternary salts in 10 mL of methanol was followed by hydrogenation with 50 mg of 10% Pd/C at 25 °C and atmospheric pressure for 5 h. Filtration through a 1 × 3 cm pad of Celite 545, concentration, and partitioning between 20 mL of 10% ammonium hydroxide and 25 mL of dichloromethane was followed by concentration. The residue was heated in 50 mL of dry toluene at reflux for 5 h. Concentration under high vacuum provided a mixture of indole–indoline dimers. HPLC analysis according to the conditions (Table II) used for the reactions of Table III showed the relative amounts of the products **17** (11%), **18** (5%), **21** (15%), and **22** (26%).

b. Alternatively, the chloroalkene–indoline(s) **28** were dissolved in 10 mL of dry acetone and 0.193 g (0.424 mmol) of vindoline and 0.161 mL (1.09 mmol) of tetrafluoroboric acid diethyl ether complex were added, resulting in a red solution. Addition of 0.106 g (0.548 mmol) of silver tetrafluoroborate, in 1 mL of acetone, with rapid stirring, resulted in a pale green solution and precipitation of silver chloride. After 15 min the reaction mixture was partitioned between 50 mL of 10% ammonium hydroxide in saturated brine and 3 × 25 mL of dichloromethane. Concentration provided a mixture of tosylates **11** and **12** and their C16′ epimers. Cyclization in toluene at reflux and debenzylation as described under **a** provided the indole–indoline dimer mixture for HPLC analysis: **17** (2.4%), **18** (3.6%), **23** (2.4%), **24** (4.6%).

Diastereomeric 16′-Epi-20′-desethyl-20′-deoxyvinblastines (23, 24). a. The procedure given is one adapted from Kutney et al.[2] Epimeric **3** (R = R^1 = H)[5] (0.10 g, 0.32 mmol) was dissolved in CH_2Cl_2 (2 mL) to which triethylamine (0.045 mL, 0.32 mmol) was added. The mixture was placed under a nitrogen atmosphere and cooled in an ice bath. A cold solution of *tert*-butyl hypochlorite (0.038 mL, 0.32 mmol) in CH_2Cl_2 (2 mL) was added via a chilled syringe. TLC showed the immediate formation of the less polar chloroindoline–alkene(s) **22** (CAS, violet). The solution was washed with ice water, dried (Na_2SO_4), and concentrated at 20 °C. To the residue was added vindoline (0.11 g, 0.25 mmol), and the system was purged with nitrogen. A methanolic solution of HCl (2 mL, formed by adding 0.060 mL of acetyl chloride to 2 mL of methanol) was added and the deep green mixture was allowed to stir at 20 °C overnight. The reaction was quenched by addition to ice water and basification (NH_4OH 10% aqueous) followed by extraction with CH_2Cl_2. The organic extracts were dried (Na_2SO_4) and concentrated to a residue, which was chromatographed to yield two diastereomers, the less polar, 0.063 g (33%), and the more polar, 0.050 g (26%). HPLC analysis under the standard conditions indicated in Table III showed a 1:1 mixture of the diastereomers **23** and **24** and neither of the compounds **17** or **18** in the total reaction products.

Physical data for less polar isomer 23: TLC (SiO_2, 15% methanol/CH_2Cl_2) R_f 0.54 (CAS, brown); UV (ethanol) λ_{max} 230, 264, 290, 297, shld 310 nm; IR (KBr) ν_{max} 3457, 3031, 2937, 2928, 2877, 2840, 2804, 1741, 1617, 1500, 1461, 1432, 1371, 1335, 1300, 1248, 1225, 1193, 1167, 1144, 1122, 1101, 1083, 1038, 1007, 955, 910, 737, 703; 250-MHz ^1H NMR (hydrate (?) $CDCl_3$) δ 0.65 (t, 3 H), 1.23 (q, 2 H), 1.36 (m, 1 H), 1.52–2.20 (m, 10 H), 2.08 (s, 3 H), 2.56–2.74 (m, 2 H), 2.85 (s, 1 H), 2.93–3.20 (m, 8 H), 3.37–3.54 (m, 2 H), 3.68 (s, 1 H), 2.74 (s, 3 H), 3.76 (s, 3 H), 3.89 (s, 3 H), 4.08 (t, 1 H), 5.32 (d, 1 H), 5.36 (s, 1 H), 5.92 (dd, 1 H), 6.01 (s, 1 H), 6.98 (t, 1 H), 7.02 (s, 1 H), 7.09 (t, 1 H), 7.24 (d, 1 H), 7.35 (d, 1 H), 9.08 (s, 1 H), 9.64 (s, 1 H); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 175.4, 171.5, 170.7, 156.4, 151.9, 134.7, 134.3, 130.5, 128.2, 126.5, 124.3, 124.2, 121.3, 119.6, 118.3, 117.9, 111.2, 110.4, 94.5, 83.0, 79.9, 77.5, 77.0, 76.5, 66.1, 56.0, 55.8, 53.8, 53.2, 52.6, 52.0, 51.9, 51.1, 50.8, 48.8, 43.8, 42.8, 38.3, 32.2, 31.2, 30.7, 28.8, 22.5, 21.0, 7.5; MS, *m/z* (relative intensity) 767 (M^+ + 1, 6), 766 (M^+, 3), 379 (4), 311 (9), 310 (9), 309 (8), 297 (5), 283 (5), 282 (20), 273 (4), 272 (5), 240 (3), 239 (4), 308 (8), 224 (4), 222 (6), 188 (6), 144 (9), 136 (9), 135 (61), 124 (3), 123 (3), 122 (22), 121 (20), 112 (5), 111 (13), 110 (100), 109 (11), 108 (15), 107 (27), 106 (8), 97 (16), 96 (24), 95 (6), 94 (6), 93 (15), 92 (12), 91 (10), 86 (10), 84 (17), 83 (11), 82 (18), 81 (10), 79 (6), 70 (6), 73 (14), 72 (17), 71 (14), 69 (14), 68 (5), 67 (5), 60 (13), 58 (26), 57 (25), 56 (12), 55 (20).

Physical data for more polar isomer 24: TLC (SiO_2, 15% methanol/CH_2Cl_2) R_f 0.45 (CAS, brown); UV (ethanol) λ_{max} 230, 263, 290, 296, shld 310 nm; IR (KBr) ν_{max} 3455, 2936, 2928, 2877, 2848, 2809, 2799, 2729, 1740, 1616, 1597, 1500, 1460, 1432, 1370, 1334, 1300, 1247, 1225, 1193, 1166, 1143, 1120, 1101, 1084, 1039, 1007, 737; 250-MHz ^1H NMR (hydrate (?) $CDCl_3$) δ −0.10 (t, 3 H), 0.56 (dq, 1 H), 1.28 (dq, 1 H), 1.36–1.42 (m, 1 H), 1.56–2.11 (m, 7 H), 2.25–2.47 (m, 2 H), 2.53 (s, 1 H), 2.57–3.23 (m, 12 H), 3.40–3.53 (m, 2 H), 3.73 (s, 1 H), 3.76 (s, 6 H), 3.91 (s, 3 H), 4.06 (t, 1 H), 5.06 (d, 1 H), 5.28 (s, 1 H), 5.79 (dd, 1 H), 6.06 (s, 1 H), 6.93 (t, 1 H), 7.04 (s, 1 H), 7.06 (t, 1 H), 7.20 (d, 1 H), 7.27 (d, 1 H), 8.89 (s, 1 H), 9.68 (s, 1 H); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 175.2, 171.8, 170.4, 156.2, 152.1, 134.8, 134.0, 130.4, 128.2, 126.4, 125.2, 123.8, 121.4, 119.5, 118.2, 117.7, 111.0, 110.4, 94.5, 83.5, 79.4, 76.3, 67.1, 56.0, 55.8, 53.6, 53.1, 52.8, 52.1, 51.9, 51.0, 48.4, 44.0, 42.7, 38.3, 37.8, 31.9, 31.0, 30.7, 29.1, 22.3, 20.8, 6.9; MS, *m/z* (relative intensity) 766 (M^+ + 1, 3), 707 (2), 607 (3), 605 (3), 379 (9), 311 (8), 310 (12), 309 (9), 308 (9), 297 (7), 283 (7), 282 (22), 273 (5), 272 (7), 240 (4), 239 (5), 237 (5), 224 (6), 222 (8), 214 (6), 202 (5), 200 (5), 188 (9), 174 (5), 144 (14), 136 (15), 135 (100), 134 (6), 130 (6), 124 (8), 123 (6), 122 (34), 121 (34), 113 (5), 112 (8), 111 (19), 110 (81), 109 (17), 108 (27), 107 (41), 106 (16), 98 (7), 97 (40), 96 (42), 95 (14), 94 (10), 93 (37), 92 (19), 91 (20), 87 (8), 86 (16), 85 (12), 84 (24), 83 (23), 82 (24), 81 (21), 79 (11), 72 (21), 71 (22), 77 (7), 73 (18), 70 (14), 69 (10), 68 (10), 67 (16), 65 (11), 60 (33), 59 (10), 58 (48), 57 (52), 56 (19), 55 (40).

b. Alternatively, the chloro derivative **22**, derived from 0.20 g (0.64 mmol) of the cleavamine **3** (R = R^1 = H), was dissolved in 10 mL of dry acetone followed by solution of 0.226 g (0.496 mmol) of vindoline and 0.188 mL (1.28 mmol) of tetrafluoroboric acid diethyl ether complex. To the resultant red solution was added 0.124 g (0.64 mmol) of silver tetrafluoroborate in 1 mL of acetone, in one portion with rapid stirring, resulting in immediate precipitation of silver chloride and formation of a pale green solution. After 15 min the reaction mixture was poured into 50 mL of 10% ammonium hydroxide in saturated brine and the mixture extracted with 3 × 25 mL of dichloromethane. The dried ($MgSO_4$) solution was concentrated at 42 °C under vacuum and the residue subjected to HPLC analysis under conditions listed in Table III. A composition of **17** (1.2%), **18** (2.4%), **23** (1.1%), and **24** (1.0%) was found.

c. Chlorination of desethylvincadifformine **4** (R = R^1 = H)[5] by a procedure described for chlorination of the tosylate **7**, and subsequent coupling of an excess of the chloro imine(s) **21** with vindoline and reduction with potassium borohydride, according to that procedure, provided a mixture of indoline–indole dimers, which was analyzed by HPLC using conditions specified in Table III. The coupling reaction was also conducted at 56 °C, 23 °C, and 0 °C, giving in each case a 1:2 ratio of **24**:**23**. The total amount of dimeric products **24** + **23** was 51% at 56 °C, 21% at 23 °C, and 8% at 0 °C. Centrifugal chromatography provided samples of **23** and **24**. Their NMR spectra matched those given in section **a**.

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