before until only the resonances due to the stereoisomeric bis adducts and the unreacted *N*-methylmaleimide could be observed. ^{1}H NMR spectral data for the mono adduct **9** and bis adducts **4a,b** are given below.

9: 8.89 (s), 8.00 (s), 7.8 (d, J = 9 Hz), 7.95 (d, J = 8.7 Hz), 7.60 (d with J = 9 Hz assumed), 7.59 (d with J = 9 Hz assumed), 4.19 (s), 2.44 (s), 1.41 (s), 1.39 (s).

Major bis adduct **4a:** = 7.88 (d, J = 8.5 Hz), 7.82 (s), 7.56 (d, J 8.5 Hz), 4.15 (s), 2.32 (s), 1.39 (s).

Minor bis adduct **4b:** 7.87 (d, J = 8.4 Hz), 7.81 (s), 7.55 (d, J = 8.4 Hz), 4.17 (s), 2.44 (s), 1.37 (s). Stereoisomeric ratio = 1.3:1

In a second experiment, an estimate for k_1/k_2 was obtained. Solutions of the bisisobenzofuran and *N*-methylmaleimide were mixed and the ^{1}H NMR spectrum was recorded as a function of time. Concentrations of the two reactants immediately after mixing were 1.5 mM **3** and 4.2 mM *N*-methylmaleimide. The ratio k_1/k_2 is given by the ratio of the maximum mono adduct concentration to the bisisobenzofuran concentration at the time corresponding to the maximum mono adduct concentration.

Bis *N*-(4-*tert*-Butylphenyl)maleimide Derivative 11. A freshly prepared sample of **3** (56 mg, 0.069 mmol) was stirred in chloroform (15 mL) with *N*-(4-*tert*-butylphenyl)maleimide (53.7 mg, 0.234 mmol) for 18 h under nitrogen and in the absence of light. The reaction mixture was filtered to give **10** as a white solid (43 mg, 49%) which was essentially pure by ^{1}H NMR and TLC. The solvent was removed from the filtrate, and the resulting product was purified by flash chromatography (silica gel, chloroform) to give more of the previously obtained white solid (11 mg, 13%): mp, some decomposition evident at 135 °C; ^{1}H NMR ($CDCl_3$) 7.95 (d, J = 8.4 Hz, 8 H), 7.93 (s, 4 H), 7,58 (d, J = 8.4 Hz, 8 H), 7.10 (d, J = 8.6 Hz, 4 H), 6.35 (d, J = 8.6 Hz, 4 H), 4.28 (s, 4 H), 1.39 (s, 36 H), 1.15 (s, 18 H); IR cm^{-1} (KBr disk) 2963, 1779, 1716, 1678, 1517, 1366, 1176, 832.

The adduct **10** (21 mg, 0.016 mmol) was stirred with concentrated sulfuric acid (8 mL) for 5 h. The reaction mixture was then poured onto crushed ice and then extracted with chloroform (3 × 40 cm^3). The solvent was removed to give **11** as a bright golden-yellow solid (20 mg, 98%) which was pure by TLC: mp >360 °C, slight darkening observed: ^{1}H NMR 8.99 (s, 4 H), 7.58 (d, J = 8.4 Hz, 8 H), 7.41 (d, J = 8.4 Hz, 8 H), 7.40 (d, J = 8.6 Hz, 4 H), 7.24 (d, J = 8.6 Hz), 1.42 (s, 36 H), 1.26 (s, 18 H); ^{13}C NMR 182.0 (no H), 165.6 (no H), 152.1 (no H), 151.5 (no H), 142.0 (no H), 138.4 (no H), 131.7 (no H), 130.4 (no H), 130.1 (no H), 129.8 (1 H), 128.6 (no H), 126.48 (no H), 126.45 (1 H), 125.9 (1 H), 125.4 (1 H), 34.9 (no H), 34.7 (no H), 31.4 (3 H), 31.2 (3 H); IR cm^{-1} (KBr disk) 2963, 1772, 1724, 1688, 1365, 1265, 806; high resolution mass spectrum (FAB), 1239.6277 corresponding to protonated molecular ion, calcd for $C_{86}H_{83}N_2O_6$ 1239.6251.

Cyclophane 13. A 15-mL $CHCl_3$ solution containing approximately 0.1 mmol of **3** (unpurified) was added dropwise over a 30-min period to a refluxing solution of dimaleimidobenzene (**12**) (268 mg, 1.0 mmol) in 30 mL of dry $CHCl_3$. The purple color disappeared rapidly, but the refluxing and stirring were continued for 17 h.

The reaction mixture was allowed to cool, upon which the filtrate was concentrated to 7 mL. The resulting insoluble mass was removed again by filtration, and the product was collected from the filtrate and purified by column chromatography (silica gel, CH_2Cl_2). A white solid was obtained (56 mg, 52%): ^{1}H NMR ($CDCl_3$) 1.41 (s, 36 H), 4.14 (s, 4 H), 7.18 (s, 4 H), 7.60 (d, J = 8 Hz, 4 H), 7.66 (s, 4 H), 7.95 (d, J = 8 Hz, 4 H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) carbons with 0 or 2 protons attached 34.9, 92.0, 131.0, 131.5, 135.3, 148.8, 152.6, 172.7, 183.7; carbons with 1 or 3 protons attached 31.4, 52.9, 119.8, 121.0, 126.0, 127.1; IR (KBr) 2967, 1780, 1718, 1679, 1605 cm^{-1}; mass spectrum (FAB), m/e 1085.4 (protonated parent ion), 817.3 (base); absorption spectrum (CH_3CN) λ_{max} 253 nm (ϵ 68 650), 322 (6050). Anal calcd for $C_{72}H_{64}O_8N_2$: C, 79.68; H, 5.94; N, 2.58. Found: C, 79.55; H, 6.05; N, 2.47.

Acknowledgment. This work was supported by the Office of Naval Research and by the University of Minnesota Microelectronics and Information Science Center. Helpful comments from W. Christopfel are acknowledged. UV spectra on **13** were provided by Mr. Stan Rak.

Studies in Biomimetic Alkaloid Syntheses. 16. Syntheses of D/E Trans and Cis Desethylvincadifformines[1] and of the C16 Epimeric Carbomethoxydesethyldihydrocleavamines and Their Isolable Piperidine Ring Conformational Isomers[†]

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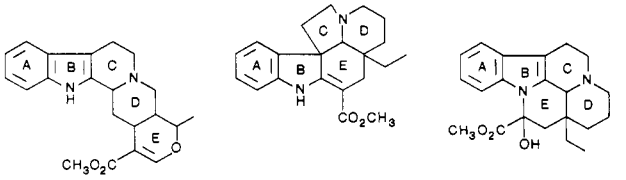
Generation of *D*-secodesethylvincadifformine intermediate **18** allowed its conversion to D/E trans and D/E cis desethylvincadifformine (**10** and **19**) as well as to two C-16 epimeric carbomethoxydesethyldihydrocleavamines, each of the latter selectively obtained in two isolable conformational forms: **26** vs. **20** and **28** vs. **21**. Corresponding conformation inversion energies were determined to be about $\Delta G^{\ddagger}$ = 28 kcal/mol and 23 kcal/mol, respectively.

Confronted with a quarter century challenge of providing syntheses of the clinically used "dimeric" indole–indoline alkaloids of the vinblastine class, the chemical community had, until completion of the present sudies (see following paper and its ref 5b), furnished only one method of coupling of monomeric precursor units,[6-8] which provides the crucial C10 to C16′ linkage of the two halves in the stereochemical sense essential for antineoplastic activity,[9] i.e., with a C16′ to C14′ priority antireflective (parf) relative stereochemistry.[10] This biomimetic[11,12] coupling of catharanthine *N*-oxide (**1**) and vindoline (**2**), followed

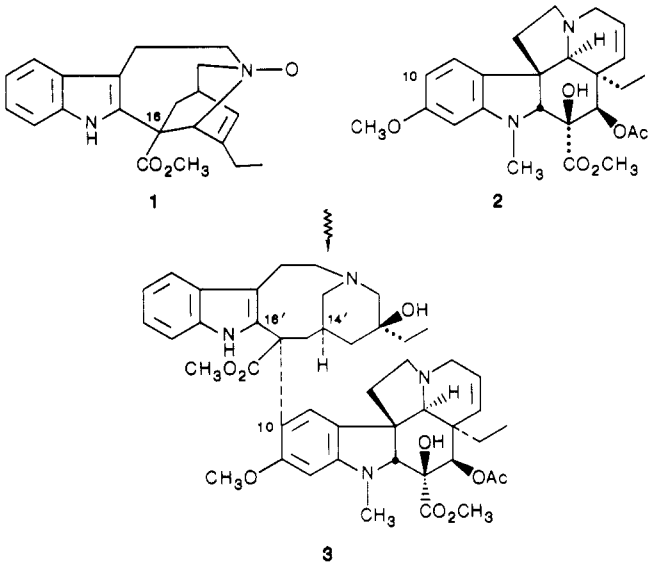
[†]Dedicated to Professor Gibert Stork on occasion of his 65th birthday by representatives of two chemical generations, who benefited from his wise tutelage.

(1) For ring labeling (ABCDE) of the vincadifformine type compounds we adopt a pattern that parallels the commonly used biogenetic numbering system[2] and that differs from one we and others used previously,[3,4] but which has also been used elsewhere.[5]



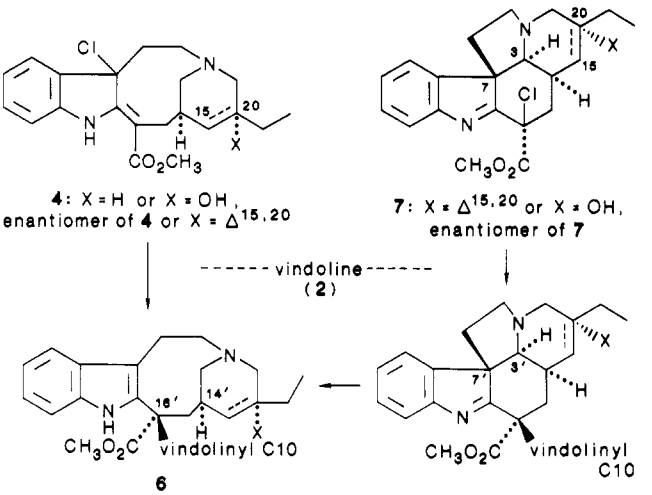
0022-3263/87/1952-4331$01.50/0

by a reduction step, constituted a major breakthrough on the road to vinblastine (**3**)[13] and to potential analogues with anticancer activity. Unfortunately, its practical extension encountered severe limitations.[13,14]



1 **2** **3**

In searches for alternative coupling methods, intensive studies of the coupling of vindoline (**2**) to chlorinated derivatives **4** of cleavamines invariably led only to the wrong C16′ epimeric products **6**,[15] which are devoid of antineoplastic activity.[9] The same wrong products were obtained by coupling of vindoline (**2**) to the chloroimine derivative **7** of the Ψ-vincadifformine skeleton, i.e., racemic apopandoline (**8a**),[16] with subsequent reductive cleavage of the central C3′ to C7′ bond. Either route led only to the C16′–C14′ priority reflective (pref) relative stereochemistry,[10] while a C16′–C14′ parf relationship, as well as a C16′ *S* absolute configuration, can be shown to be required for binding of the dimeric alkaloids to tubulin for arrest of cell division at metaphase and vinblastine type antineoplastic activity.[9,15d,17]



4: X = H or X = OH, enantiomer of **4** or X = $\Delta^{15,20}$

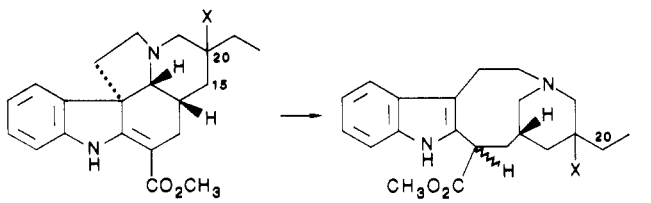
7: X = $\Delta^{15,20}$ or X = OH, enantiomer of **7**

vindoline (**2**)

vindolinyl C10

6

Although we had been able to provide practical syntheses of the racemic pandolines (**8b,c**) and the racemic carbomethoxyvelbanamines (**9b,c**),[18] their direct use in coupling to vindoline (**2**) could thus lead only to products that are worthless for chemotherapy. In order to avoid this impass, we directed our attention to the generation of related alternative precursors, which might provide a more valuable stereochemical outcome of the coupling reaction with vindoline (**2**). Our next paper will detail the gratifying coupling reaction results that were derived from concepts developed in the present report. The approach is based on further exploitation of our biomimetic secodine chemistry.



8a, X = $\Delta^{15,20}$
8b, X = 20α OH
8c, X = 20β OH

9b, X = 20α OH
9c, X = 20β OH

Since coupling of vindoline (**2**) to the natural *D/E-cis*-Ψ-vincadifformine type alkaloids and analogues had given only the undesired C16′–C14′ pref stereochemistry, we considered coupling of vindoline (**2**) to precursors in which C14 is inverted relative to the centers at C3 and C7. To this end, we desired a synthesis of *D/E-trans*-desethylvincadifformine (**10**) as a first goal.[19] Assuming availability of such a substrate, it would then have to be established if, in analogy to the D/E cis series (i.e., **7**), a chloro imine derivative could be formed from this compound and if that derivative could be coupled to vindoline (**2**). It was rec-

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(5) Wenkert, E.; Porter, B.; Simmons, D. P.; Ardisson, J.; Kunesch, N.; Poisson, J. *J. Org. Chem.* **1984**, *49*, 7377.
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(7) (a) Kutney, J. P.; Ratcliffe, A. H.; Treasurywala, A. M.; Wunderly, S. *Heterocycles* **1975**, *3*, 639. (b) Kutney, J. P.; Hibino, T.; Jahngen, E.; Okutani, T.; Ratcliffe, A. H.; Treasurywala, A. M.; Wunderly, S. *Helv. Chim. Acta* **1976**, *59*, 2858.
(8) (a) Atta-ur-Rahman; Basha, A.; Ghazala, M. *Tetrahedron Lett.* **1976**, 2651. (b) Atta-ur-Rahman. *J. Chem. Soc. Pak.* **1979**, *1*, 81.
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(10) Carey, F. A.; Kuehne, M. E. *J. Org. Chem.* **1982**, *47*, 3811.
(11) (a) Scott, A. I.; Gueritte, F.; Lee, S. L. *J. Am. Chem. Soc.* **1978**, *100*, 6253. (b) Baxter, R. L.; Dorschel, C. A.; Lee, S. L.; Scott, A. I. *J. Chem. Soc., Chem. Commun.* **1979**, 257.
(12) Stuart, K. L.; Kutney, J. P.; Honda, T.; Worth, R. B. *Heterocycles* **1978**, *9*, 1391, 1419.
(13) Mungeney, P.; Andriamialisoa, R. Z.; Langlois, N.; Langlois, Y.; Potier, P. *J. Am. Chem. Soc.* **1979**, *101*, 2243.
(14) (a) Kutney, J. P.; Joshua, A. V.; Liao, P. H.; Worth, B. R. *Can. J. Chem.* **1977**, *55*, 3235. (b) Kutney, J. P.; Joshua, A. V.; Liao, P. H. *Heterocycles* **1977**, *6*, 297. (c) Mangeney, P.; Costa, R.; Langlois, Y.; Potier, P. *C.R. Hebd. Seances Acad. Sci., Ser. C* **1977**, *284*, 701. (d) Honma, Y.; Ban, Y. *Heterocycles* **1977**, *6*, 291. (e) Kutney, J. P.; Honda, T.; Joshua, A. V.; Lewis, N. G.; Worth, B. R. *Helv. Chim. Acta* **1978**, *61*, 690.
(15) (a) Harley-Mason, J.; Atta-ur-Rahman *J. Chem. Soc., Chem. Commun.* **1967**, 1048. (b) Neuss, N.; Gorman, M.; Cone, N. J.; Huckstep, L. L. *Tetrahedron Lett.* **1968**, 783. (c) Kutney, J. P.; Beck, J.; Bylsma, F.; Cook, J.; Cretney, W. J.; Fuji, K.; Imhof, R.; Treasurywala, A. M. *Helv. Chim. Acta* **1975**, *58*, 1690. (d) Kunesch, N.; Vancamps, P. L.; Cave, A.; Poisson, J.; Wenkert, E. *Tetrahedron Lett.* **1979**, 5073.
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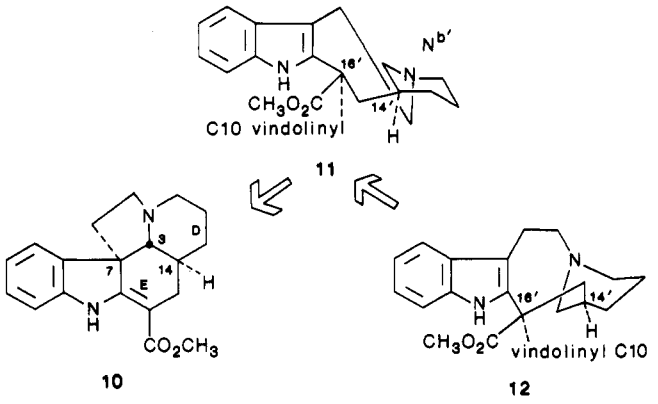
(17) Studies on our compounds by Dr. Linda Borman, Department of Pharmacology, University of Vermont, in association with our research group in the Vermont Regional Cancer Center.
(18) Kuehne, M. E.; Kirkemo, C. L.; Matsko, T. H.; Bohnert, J. C. *J. Org. Chem* **1980**, *45*, 3259.
(19) Alternative syntheses of D/E trans and cis desethylvincadifformine have since been reported: (a) Wenkert, E.; Orito, K.; Simmons, D.; Kunesch, N.; Ardisson, J.; Poisson, J. *Tetrahedron* **1983**, *39*, 3719. (b) Wenkert, E.; Orito, K.; Simmons, D. *J. Org. Chem.* **1983**, *48*, 5006.

ognized, however, that even if the desired C16′–C14′ parf stereochemistry would be obtained by this sequence and if a reductive cleavage of the C7′ to C3′ bond would be obtained, in analogy to results found in the D/E cis series, one might still anticipate a possible problem in that the D/E trans-fused intermediates would lead eventually to "unnatural" piperidine conformation **11**, in which the $N^{b'}$–$C_{14'}$ bridge (a nine-membered ring) might prevent final passage to a molecular structure **12** with the "natural" vinblastine conformation. A piperidine chair to chair flip of **11** to **12** through a strained transition state might be required in order to obtain a product, which has not only the required relative and absolute stereochemistry at all centers but also the correct conformational shape of the VLB class alkaloids.



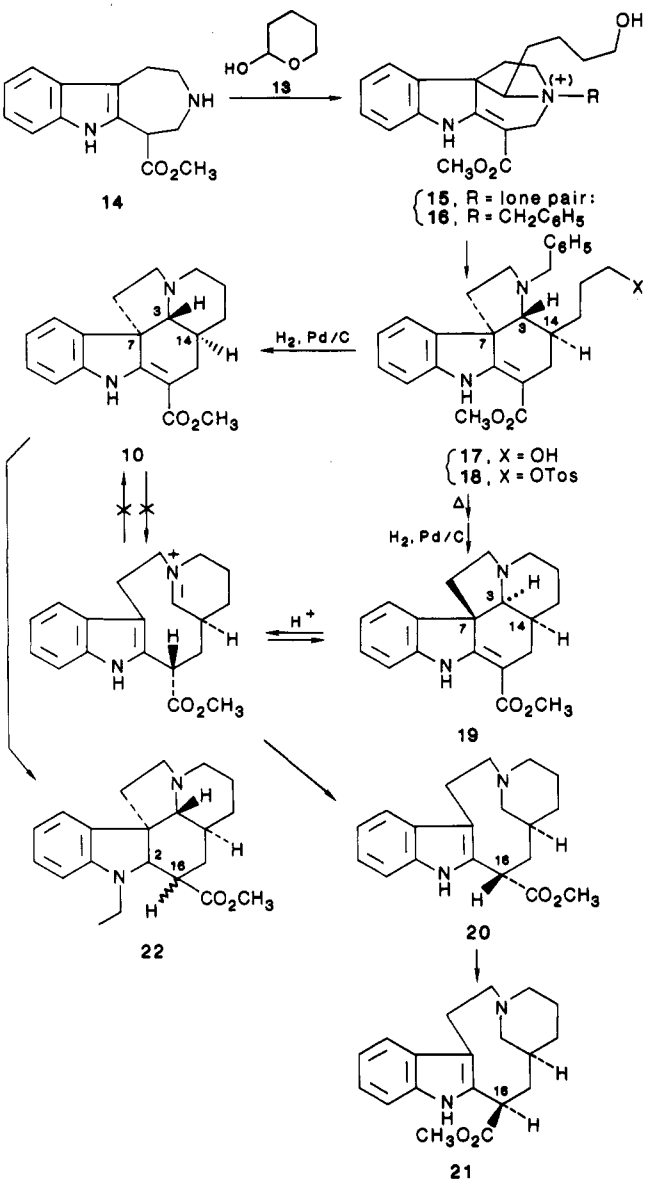
Access to the requisite C14 vs. C3 and C7 stereochemistry had been opened by our earlier seco secodine chemistry,[20] where it had been shown that, in contrast to the piperideine secodine intermediates, which always gave a D/E cis-fused vincadifformine type skeleton, acyclic enamine analogues led to products with a C14 inverted center. Thus, a synthesis of *D/E-trans*-desethylvincadifformine could be started by condensation of dihydropyran, as its hydration product **13**, with the indoloazepine **14** (Scheme I). N^b-Benzylation of the condensation product **15** and reaction of the resultant quaternary salt **16** with base produced the expected rearrangement to a *D*-seco-14-epidesethylvincadifformine (**17**). For closure of ring D the hydroxyl group was converted to a tosylate derivative **18**. Catalytic hydrogenolysis of the N^b-benzyl substituent of the latter, at room temperature, resulted in cyclization to desethyl-14-epivincadifformine (**10**). This crystalline product could be readily assigned the expected D/E trans ring juncture from its C3 proton NMR coupling constant (d, J = 10.2 Hz).[19]

When, on the other hand, the tosylate **18** was heated in toluene and the resultant quaternary salt was subjected to hydrogenolysis, *D/E-cis*-desethylvincadifformine (**19**) was obtained. The product **19** obtained here matched the one obtained previously from the desethylsecodine reaction sequence.[19,20]

Closure of ring D by quaternization of the 3° amine function is thus facilitated by an initial epimerization, through reversible rupture of the C3 to C7 bond. An inspection of molecular models of the amino tosylate **18** suggests a preferential ground-state orientation of the N^b-benzyl substituent facing the alkyl tosyl chain, with the nitrogen lone pair directed at the aromatic ring. Hydrogenolysis of the benzyl substituent eliminates this energetic barrier to cyclization.

(20) Kuehne, M. E.; Matsko, T. H.; Bohnert, J. C.; Motyko, L.; Oliver-Smith, D. *J. Org. Chem.* **1981**, *46*, 2002.

Scheme I



With the readily prepared C14 epimeric desethylvincadifformines **10** and **19** in hand, one could now consider reductive cleavage of the C3 to C7 bond. A reaction of the *D/E-cis*-desethylvincadifformine (**19**) with sodium borohydride in acetic acid at 90 °C provided the C16 epimeric carbomethoxydesethyldihydrocleavamines **20** and **21** as a 2:1 mixture.

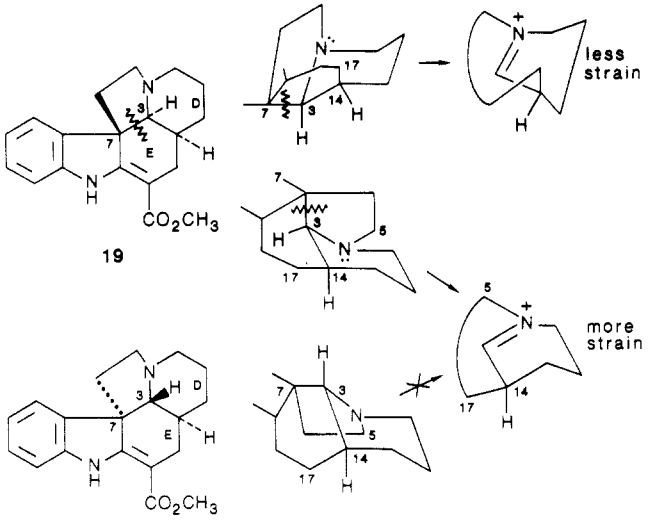
The C16–C14 pref compound **20** was completely isomerized to its C16 epimer **21** by heating in acetic acid at 90 °C for 4.5 h. In this transformation of **20** to **21**, an ester epimerization, through enolization, was indicated by complete exchange of the C16 proton for deuterium in deuterioacetic acid. A thermal conformation inversion relationship of compounds **20** to **21** (see below) could be excluded by the observation that the isomer **20** was recovered unchanged from heating in toluene.

On the other hand, a reaction of the *D/E-trans*-desethylvincadifformine (**10**) with sodium borohydride in hot acetic acid gave N^a-ethylated 2,16-dihydro product **22** in high yield. Other studies have shown that 2,16-dihydro products are obtained also from *D/E-cis*-vincadifformine type compounds when the reduction is carried out at low temperature and that hot acetic acid is required for rupture of the C3 to C7 bond and reductive formation of a cleavamine.[21] Analogous N-ethylations, under these conditions,

were reported for the related reduction of indoles.[22] Reduction of the 2,16 double bond in the D/E trans compound **10** was also found at higher temperature with sodium borohydride in refluxing propionic acid or when the stronger acid trifluoroacetic acid was used.

Failure of *D/E-trans*-desethylvincadifformine (**10**) to undergo reduction to a cleavamine product thus showed a higher energy requirement for cleavage of the C3 to C7 bond, relative to the D/E cis case, and a relatively more rapid reduction at 90 °C of the N^a imonium salt derived from the D/E trans compound **10**.

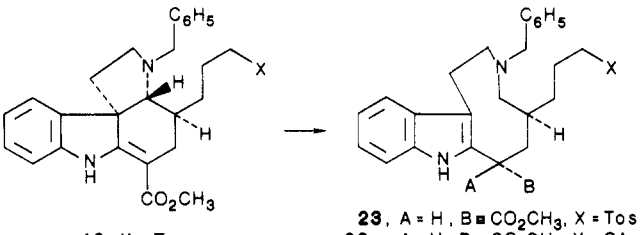
No isomerization of *D/E-trans*-desethylvincadifformine (**10**) to the D/E cis isomer **19** could be seen in acetic acid at 90 °C nor when the temperature was raised to 230 °C. While this result again suggests failure of the C3 to C7 bond to rupture even under these drastic conditions, this lack of isomerization could also derive from an inability of the anticipated N^b imonium carbon, or its more bulky acetate adducts, to achieve the required passage through the inside of the nine-membered ring containing two indole sp^2 centers (impossible with Dreiding models of the imonium system and unlikely with its acetate adducts).



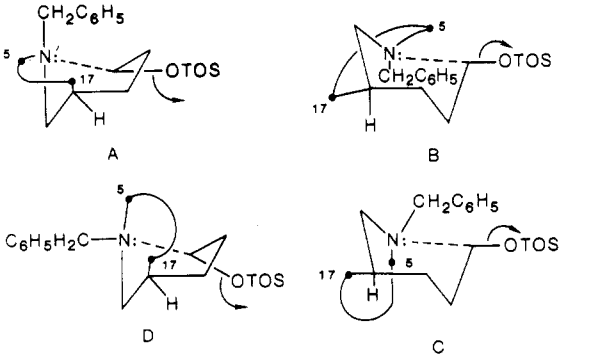
The higher energy barrier for rupture of the C3 to C7 bond in the D/E trans (**10**) vs. the D/E cis (**19**) system can be ascribed to two factors. While it is possible to invoke a 1,2-diaxial periplanar orbital overlap of the N^b lone pair and the C3–C7 bond in the D/E cis series **19**, and a Dreiding model can be persuaded to assume this conformation, such a relationship is impossible in the D/E trans series **10**. Moreover, in the latter case (but not with **19**), the developing imonium intermediate would require initial coplanarity of the now equatorial C14 to C17 and N^b to C5 bonds and thus a strain, which is not found when starting with the axial C14 to C17 bond in **19**.

Lack of reductive cleavage of the central C3 to C7 bond in the D/E trans pentacyclic ring system **10** had now established that such intermediates would not be directly useful for the synthesis of vinblastine type alkaloids. Consequently, as an alternative, the D-seco precursor **17** or its derivatives, with the requisite C14 vs. C3 trans stereochemistry, had to be considered for coupling to vindoline. In a subsequent formation of the bridged piperidine ring system, some likely synthetic strategies then allowed one to foresee, again, a possible problem due to reaching a wrong conformational isomer of the desired ring skeleton and perhaps a prohibitive energy barrier for a piperidine chair to chair inversion. We thus set out to establish if bridged piperidines, in the present context, could indeed be formed and isolated in two distinct conformational forms and if the latter could be interconverted under reasonable conditions.

Reductive cleavage of the C3 to C7 bond with sodium borohydride in acetic acid readily converted the tetracyclic tosylate **18** to an epimeric mixture of pref and parf indoloazonine esters **23** and **24**, in a ratio of 4:1. For a study of the equilibrium ratio of the pref and parf isomers, the corresponding acetate **18a** was reduced to the pref and parf acetates **23a** and **24a**. On equilibration in hot acetic acid, a 2:1 ratio of these compounds was obtained. Parallel H/D exchange indicated loss of the C16 methinyl protons. The relative stereochemistry of the carbomethoxy and (tosyloxy)propyl substituents in the epimers **23** and **24** was established by their conversion to the cyclization products **20** and **21** (below).



For a subsequent cyclization of the amino tosylates **23** and **24**, one could consider alternative conformational possibilities and anticipate exclusion of transition state conformers (**A** and **B**) with an axial N-benzyl substituent in the piperidine ring formation, due to the respective 1,3-diaxial repulsion with C17, or strain in the bridged nine-membered ring system, with C17 and C5 as equatorial piperidine substituents. Based on studied (and disputed) conformations of vinblastine and dihydrocleavamines,[23,24] one could also expect that 1,3-axial–equatorial arrangement **C** of the bridging piperidine substituents might be favored over 1,3-diaxial bridge D. [However, this expectation was tempered by recognition of the 1,3-diaxial interaction effect of C20′ substituents, which also enhances stability of a 1,3-axial–equatorial bridge similar to C (with C17 and C5 conformationally reversed) over a 1,3-diaxial bridge similar to D in those model cases.]



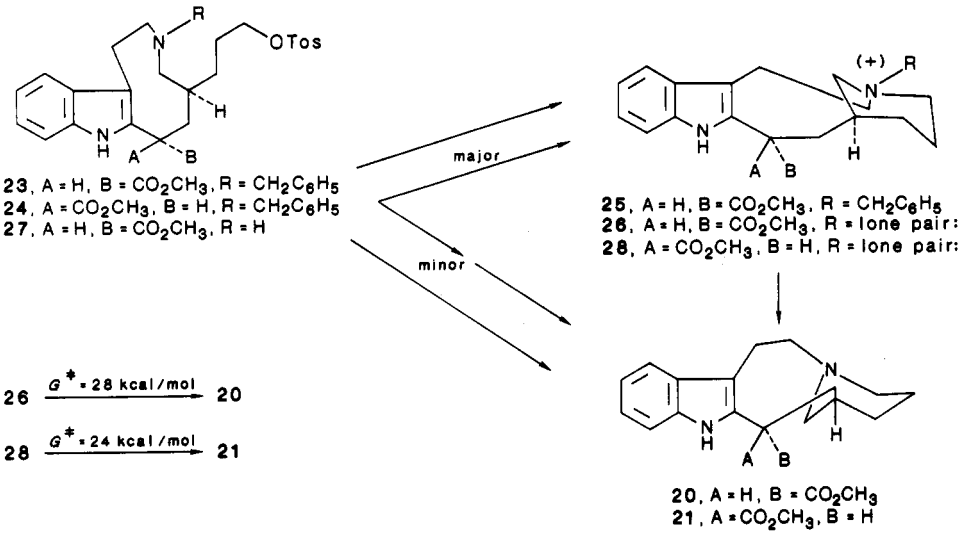
(21) (a) Kunesch, N.; Miet, C.; Poisson, J. *Bull. Soc. Chim. Fr.* **1982**, *II*, 285. (b) Bruneton, J.; Dave, A.; Hagaman, E. W.; Kunesch, N.; Wenkert, E. *Tetrahedron Lett.* **1976**, 3567.

(22) Gribble, G. W.; Lord, P. D.; Skotnicki, J.; Dietz, S. E.; Eaton, J. T.; Johnson, J. L. *J. Am. Chem. Soc.* **1974**, *96*, 7812.

(23) (a) de Bruyn, A.; De Taeye, L.; Anteunis, M. J. O. *Bull. Soc. Chim. Belg.* **1980**, *89*, 629. (b) Hunter, B. K.; Hall, L. D.; Sanders, J. K. M. *J. Chem. Soc., Perkin Trans. 1* **1983** *Perk. I*, 657, however, suggest a pseudoaxial 5′ substituent.

(24) Wenkert, E.; Hagaman, E. W.; Kunesch, N.; Wang, Nai-yi; Zsadon, B. *Helv. Chim. Acta* **1976**, *59*, 2711.

Scheme II



On heating in toluene, the amino tosylate **23** underwent cyclization to give the quaternary salt **25** (Scheme II). Initial attempts of debenzylation of this product by catalytic hydrogenolysis seemed to fail, until it was discovered that the resultant 3° amine **26** is less mobile (!) on TLC (R_f 0, SiO_2, 7.5% methanol in CH_2Cl_2) than the quaternary salt **25**. It differs in this respect markedly from the conformationally alternative 3° amine **20** (TLC R_f 0.91, SiO_2, 1.5% methanol in CH_2Cl_2), which has the same relative stereochemistry. That the formation of the "unnatural" piperidine conformation in **25** and **26** is due to exclusion of the cyclization transition state A could be seen by reversing the cyclization and debenzylation steps. Thus, the 2° amino tosylate **27** cyclized to give only the "natural" conformational isomer **20**.

While cyclization of the amino tosylate **23** proceeded through transition state C to the quaternary salt **25**, cyclization of the epimer **24** also involved, to a minor extent, the transition state D. On debenzylation this route then furnished the cleavamine **28** and its conformationally isomer **21** as a minor product. Concurrently with the catalytic debenzylation of the quaternary salt **25**, we also studied a debenzylation with sodium borohydride in the presence of Pd/C. From these reductions a BH_3 complex of **26** (TLC R_f 0.86, SiO_2, 7.5% methanol in CH_2Cl_2) was isolated. This complex was recovered unchanged after 12 h in refluxing toluene. The alternative piperidine conformational isomer **20**, on the other hand, formed a labile BH_3 complex (TLC R_f 0.82, SiO_2, 2% methanol in CH_2Cl_2) which decomposed even at 20 °C and reverted to the amine **20** on warming in toluene.

The dramatic difference in chemical reactivity of N^b in the two sets of conformational isomers **26** and **28** vs. **20** and **21**, expressed in their relative TLC mobilities and BH_3 complex stabilities, was clearly reflected in their respective IR spectra. Thus initially formed conformers **26** and **28**, with an equatorial N^b lone pair show no Wenkert-Bohlmann bands below 2860 cm^{-1}, while the N^b axial lone pair conformers **20** and **21** each displayed such peaks (2743, 2748 cm^{-1}) prominently.

When the amine **26** and its C16 epimer **28** were heated in toluene, the corresponding conformational isomers **20** and **21** were formed respectively. For complete conversion C_{16}–C_{14} pref epimer **26** required about 2.5 h at 100 °C while for the C_{16}–C_{14} parf epimer **28** the piperidine chair–chair flip was completed in about 2.5 h at 42 °C.

Corresponding rough thermodynamic values are $\Delta G^{\ddagger}$ = 28 kcal/mol, $\Delta H^{\ddagger}$ = 23 kcal/mol, and $\Delta S^{\ddagger}$ = 10 eu for conformational inversion of the C_{16}–C_{14} pref isomer **26** and $\Delta G^{\ddagger}$ = 24 kcal/mol for the C_{16}–C_{14} parf isomer **28**. The conformational inversion rates were not affected by addition of a protic acid or a base.

A controlled flip of isolated piperidine chair conformers has, to our knowledge, limited precedent. Such a conformational inversion, apparently promoted by an enolization step, was described for an eight-membered ring bridged piperidine ring and, more analogously, a thermal inversion has been reported for the very similar piperidine with a nine-membered lactam bridge.[25] While isolation and thermal inversion of the present conformers **26** and **28** is thus of intrinsic chemical interest, it will be seen in the following paper that these findings also have a practical significance, which may be synthetically exploited, and that they open for exploration a new approach to cancer chemotherapy.

Experimental Section

General Methods. All reactions were carried out under nitrogen or argon. Melting points were obtained in a heated oil bath with thermometers calibrated against a National Bureau of Standards certified set. NMR spectra were recorded on a Bruker 250-MHz or a JEOL 100-MHz instrument. Mass spectra were obtained with a Finnegan 4610 quadrupole instrument at 70 eV, calibrated with perfluorotributylamine and hexafluorotriphenylphosphine 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-hydroxypropyl)-*D*-nordesethylvincadifformine (17).** To the azepine 14[26] (5.0 g, 20 mmol) stirring in methanol (25 mL) was added enough methanol saturated with HCl to turn moist universal pH paper red. The methanol was evaporated at reduced pressure, to the residue were added H_2O (50 mL) and 2-hydroxytetrahydropyran (13, 2.2 g, 22 mmol), and the mixture was allowed to stir at 20 °C overnight. TLC (SiO_2,

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(26) Kuehne, M. E.; Bohnert, J. C.; Bornmann, W. G.; Kirkemo, C. L.; Kuehne, S. E.; Seaton, P. J.; Zebovitz, T. C. *J. Org. Chem.* **1985**, *50*, 919.

7.5% methanol/CH_2Cl_2) of the mixture showed the formation of two products, **15**, (R_f 0.68 and 0.76, CAS, blue). The reaction mixture was basified (NH_4OH, 10% aqueous) and extracted three times with CH_2Cl_2. The organic extracts were dried (Na_2SO_4) and concentrated to a residue, which was immediately dissolved in THF (100 mL). To the THF solution was added benzyl bromide (2.5 mL, 21 mmol) and then the solution was heated to reflux and monitored by TLC until conversion to the base-line material, salt **16** (about 2 h), was completed. At this point the THF was evaporated and replaced with methanol (100 mL) and diisopropylethyl amine (5.3 mL). Reflux was restarted until TLC showed complete disappearance of the salt **16**. The methanol was evaporated and the residue chromatographed (SiO_2, 5% methanol/CH_2Cl_2) to yield 5.7 g (67%) of **17** as a gum: TLC (SiO_2, 7.5% methanol/CH_2Cl_2) R_f 0.86 (CAS, blue); NMR ($CDCl_3$) δ 8.94 (s, 1 H), 7.25–7.41 (m, 5 H), 6.78–7.13 (m, 4 H), 4.08 (d, 1 H, J = 13.4 Hz), 3.76 (s, 3 H), 3.75 (d, 1 H, J = 13.2 Hz), 3.45 (t, 2 H, J = 6.6 Hz), 2.92 (s, 1 H), 2.90 (d, 1 H), 2.34–2.64 (m, 3 H), 1.38–2.15 (m, 7 H), 0.89–0.91 (m, 2 H); IR (KBr) ν_{max} 3365, 2937, 2879, 2853, 2793, 2731 (W), 1728, 1677, 1608, 1479, 1465, 1435, 1280, 1249, 1202, 1127, 1101, 744 cm^{-1}; UV (ethanol) λ_{max} 227, 299, 329 nm; MS, m/e (relative intensity) 419 (1), 418 (M^+, 5), 285 (16), 204 (44), 91 (100).

N^b-Benzyl-20-[3-(*p*-toluenesulfonyloxy)propyl]-20-desethyl-*D*-norvincadifformine (18). Compound **17** (1.0 g, 2.4 mmol) and *p*-toluenesulfonyl chloride (0.55 g, 2.9 mmol) were stirred in pyridine (4 mL) under a nitrogen atmosphere at 20 °C overnight. The mixture, which had developed a precipitate, was diluted with CH_2Cl_2, washed with 10% NH_4OH and brine, dried (Na_2SO_4), and taken to dryness first at aspirator pressure and then high vacuum in order to avoid excess heating of the product. The residue was dissolved in methanol and allowed to crystallize overnight in the freezer; yield 0.59 g (40%). An analytical sample was recrystallized from methanol, mp 158–159 °C: TLC (SiO_2, 7.5% methanol/CH_2Cl_2) R_f 0.91 (CAS, blue); NMR ($CDCl_3$) δ 8,92 (s, 1 H), 7.70 (d, 2 H, J = 8.3 Hz), 7.24–7.36 (m, 7 H), 6.80–7.18 (m, 4 H), 4.03 (d, 1 H, J = 13.4 Hz), 3.84 (t, 2 H, J = 6.5 Hz), 3.76 (s, 3 H), 3.71 (d, 1 H, J = 13.4 Hz), 2.89 (dd, 1 H, J = 8.9, 6.2 Hz), 2.84 (s, 1 H), 2.35–2.69 (m, 4 H), 2.39 (s, 3 H), 1.95–2.08 (m, 1 H), 1.25–1.78 (m, 3 H), 0.79–0.89 (m, 2 H); IR (KBr) ν_{max} 3380, 1726, 1675, 1609, 1249, 1189 cm^{-1}; UV (ethanol) λ_{max} 229, 303, 332 nm; MS, m/e (relative intensity) 572 (M^+, 1), 400 (70), 310 (11), 106 (24), 91 (100). Anal. Calcd for $C_{33}H_{36}N_2O_5S$: C, 69.21; H, 6.16; N, 4.89; S, 5.60. Found: C, 68.93; H, 6.16; N, 4.76; S, 5.51.

N^b-Benzyl-20-(3-acetoxypropyl)-20-desethyl-*D*-norvincadifformine (18a). Compound **17** (2 g, 4.8 mmol) was dissolved in acetic anhydride (5 mL) to which a trace of 4-(dimethylamino)pyridine was added. The mixture was placed under a nitrogen atmosphere and stirred overnight at 20 °C. The mixture was then poured into a saturated sodium bicarbonate solution and stirred for 15 min. The aqueous phase was extracted with CH_2Cl_2, and the extracts were dried (Na_2SO_4) and concentrated to a residue, which was chromatographed (SiO_2, 5% methanol/CH_2Cl_2). The product **18a** (1.5 g, 67%) was isolated as a gum: TLC (SiO_2, 7.5% methanol/CH_2Cl_2) R_f 0.76 (CAS, blue); NMR ($CDCl_3$) δ 8.95 (s, 1 H), 7.28–7.42 (m, 5 H), 7.14 (td, 1 H, J = 1.2 Hz, 7.7), 6.99 (d, 1 H, J = 7.2 Hz), 6.80–6.88 (m, 2 H), 4.10 (d, 1 H, J = 13.3 Hz), 3.89 (t, 2 H, J = 6.7 Hz), 3.78 (s, 3 H), 3.73 (d, 1 H, J = 13.3 Hz), 2.91 (s, 1 H), 2.90 (d, 1 H, J = 15.1 Hz), 2.65–2.70 (m, 2 H), 2.48–2.54 (m, 1 H), 1.98–2.11 (m, 1 H), 1.95 (s, 3 H), 1.91–1.95 (m, 1 H), 1.82–1.88 (m, 1 H), 1.45–1.69 (m, 2 H), 0.85–1.23 (m, 2 H); IR (film) ν_{max} 3379, 2948, 2800, 1738, 1677, 1610, 1478, 1466, 1454, 1437, 1384, 1367, 1345, 1278, 1252, 1206, 1132, 1104, 1078, 1050, 748, 701, 517 cm^{-1}; UV (ethanol) λ_{max} 227, 300, 329, nm; MS, m/e (relative intensity) 461 (13), 460 (M^+, 27), 429 (4), 327 (49), 246 (41), 91 (100). The hydrochloride was precipitated from ether, mp 209–210 °C dec. Anal. Calcd for $C_{28}H_{33}N_2O_4Cl$: C, 67.66; H, 6.69; N, 5.64; Cl, 7.13. Found: C, 67.60; H, 6.86; N, 5.40; Cl, 7.32.

***D*/*E*-*trans*-20-Desethylvincadifformine (10).** The *N*-benzyl tosylate **18** (4.0 g, 7.0 mmol) was dissolved in THF (75 mL) and the mixture was deoxygenated by purging several times with nitrogen gas. To this was added 10% Pd/C (0.60 g) and the mixture was stirred under a hydrogen atmosphere for 5 days. The THF solution was evaporated and the residue chromatographed (SiO_2, 5% methanol/CH_2Cl_2) to yield 1.5 g (69%) of crude **10**: TLC (SiO_2, 7.5% methanol/CH_2Cl_2) R_f 0.80 (CAS, blue). An analytical sample was recrystallized from methanol (mp 132–134 °C): NMR ($CDCl_3$) δ 9.04 (s, 1 H), 7.56 (d, 1 H, J = 7.4 Hz), 6.74–7.26 (m, 3 H), 3.74 (s, 3 H), 3.08–3.22 (m, 4 H), 2.85 (d, 1 H, J = 10.2 Hz), 2.45–2.54 (m, 2 H), 1.80–2.02 (m, 5 H), 1.25–1.45 (m, 2 H); IR (KBr) ν_{max} 3334, 2948, 2917, 2893, 2871, 2846, 1674, 1607, 1474, 1439, 1234, 750 cm^{-1}; UV (ethanol) λ_{max} 228, 298, 327 nm; MS, m/e (relative intensity) 310 (M^+, 46), 251 (4), 167 (8), 96 (100). Anal. Calcd for $C_{19}H_{22}N_2O_2$: C, 73.52; H, 7.14; N, 9.02. Found: C, 73.59; H, 6.95; N, 9.03.

20-Desethylvincadifformine (19). *N*-Benzyl tosylate **18** (0.030 g) was refluxed in toluene (2 mL) overnight under a nitrogen atmosphere. On cooling a quaternary salt precipitated and was collected. The hygroscopic solid was dissolved in methanol (1 mL), the methanol solution was purged with nitrogen, and 10% Pd/C (0.0030 g) was added. The solution was stirred under a hydrogen atmosphere for 1.5 h and filtered. The liquor was dissolved in CH_2Cl_2 and washed with 10% NH_4OH, dried, and concentrated to dryness. Analysis of the residue showed it to be identical (TLC, R_f, NMR, IR, UV) with an authentic sample of 20-desethylvincadifformine.[20]

16-Carbomethoxydihydrodesethylcleavamines (20 and 21). Method A. Desethylvincadifformine (**19**, 2.0 g, 6.5 mmol) was dissolved in acetic acid (20 mL) and heated to 90 °C in an oil bath. Sodium borohydride (1.5 g, 39 mmol) was added in portions, but as quickly as possible to keep the ethylation reaction to a minimum. After the last of the borohydride reagent was added, the mixture was added to ice and shaken. The solution was made basic by addition of NH_4OH (10%) and extracted with CH_2Cl_2. The organic phase was dried (Na_2SO_4) and concentrated to a residue, which was chromatographed (SiO_2, 2% methanol/CH_2Cl_2) to yield two major fractions, **20** (0.26 g, 13%) and **21** (0.14 g, 7.0%). In addition a minor (CAS, red) compound showed up, wich was determined to be an N-ethylated product. **Physical data for 20**: TLC (SiO_2, 1.5% methanol/CH_2Cl_2) R_f 0.91 (CAS, violet); NMR ($CDCl_3$) δ 8.60 (s, 1 H), 7.49 (d, 1 H, J = 7.6 Hz), 7.34 (d, 1 H, J = 7.4 Hz), 7.04–7.17 (m, 2 H), 5.57 (d, 1 H, J = 11.7 Hz), 3.69 (s, 3 H), 2.96–2.98 (m, 1 H), 2.84–2.89 (m, 2 H), 2.44–2.61 (m, 3 H), 2.25–2.32 (m, 1 H), 2.21 (s, 2 H), 1.94 (d, 1 H, J = 14.4 Hz), 1.76–1.77 (m, 1 H), 1.45–1.57 (m, 4 H); IR (KBr) ν_{max} 3371, 2947, 2925, 2900, 2841, 2804, 2778, 2743, 1719, 1460, 1428, 1334, 1307, 1293, 1279, 1252, 1186, 1159, 997, 737 cm^{-1}; UV (ethanol) λ_{max} 235, 286, 294 nm; MS, m/e (relative intensity) 313 (19), 312 (M^+, 68), 253 (7), 215 (27), 182 (36), 156 (13), 110 (100), 96 (35), 82 (22). An analytical sample was recrystallized from methanol (mp 176–178 °C). Anal. Calcd for $C_{19}H_{24}N_2O_2$: C, 73.05; H, 7.74; N, 8.97. Found: C, 73.16; H, 7.80; N, 8.91. **Physical data for 21**: TLC (SiO_2, 1.5% methanol/CH_2Cl_2) R_f 0.49 (CAS, violet); NMR ($CDCl_3$) δ 8.99 (s, 1 H), 7.48 (d, 1 H, J = 7.3 Hz), 7.32 (d, 1 H, J = 7.5 Hz), 7.02–7.15 (m, 2 H), 3.93 (d, 1 H, J = 6.0 Hz), 3.74 (s, 3 H), 3.50 (d, 1 H, J = 12.2 Hz), 2.89–2.94 (m, 2 H), 2.47–2.51 (m, 1 H), 2.21–2.36 (m, 4 H), 1.92–2.02 (m, 3 H), 1.17–1.55 (m, 4 H), IR (film) ν_{max} 3432, 2930, 2883, 2855, 2789, 2748, 1724, 1462, 1435, 1335, 1301, 1289, 1261, 1192, 1166, 1008, 742 cm^{-1}; UV (ethanol) λ_{max} 236, 285, 294 nm; MS, m/e (relative intensity) 313 (6), 312 (32), 253 (5), 215 (5), 182 (42), 156 (11), 110 (100), 96 (29), 82 (16). Compound **21** was not crystalline; the hydrochloride was prepared by precipitation from ether (mp 156–160 °C dec). Anal. Calcd for the monohydrate $C_{19}H_{27}N_2O_3Cl$: C, 62.20; H, 7.41; N, 7.63; Cl, 9.66. Found: C, 62.09; H, 7.25; N, 7.29; Cl, 9.55.

Method B. Compound **27** (0.042 g, 0.087 mmol), freshly formed from compound **23** by hydrogenolysis with 10% Pd/C in methanol, was dissolved in toluene (5 mL) and diisopropylethylamine (1 drop), placed under a nitrogen atmosphere, and heated at reflux overnight. The toluene was removed and the residue chromatographed (SiO_2, 5% methanol/CH_2Cl_2) to yield crystalline compound **20** (0.0056 g, 21%) as confirmed by NMR, IR, and TLC.

Isomerization Studies of Carbomethoxycleavamine 20. Carbomethoxycleavamine **20** (0.020 g) was dissolved in acetic acid (2 mL), placed under a nitrogen atmosphere, and heated in a 90 °C oil bath. TLC (SiO_2, 7.5% methanol/CH_2Cl_2) showed complete conversion to the more polar epimer **21** after 4.5 h.

Deuteriation Study of Carbomethoxycleavamine 20. Carbomethoxycleavamine **20** (0.020 g) was dissolved in deuter-

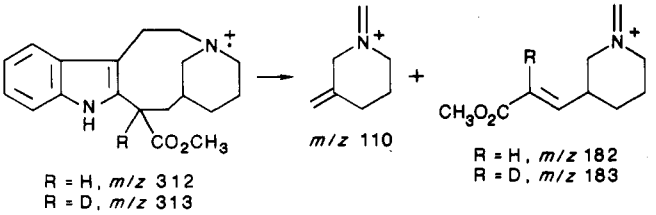

Figure 1. Fragmentation patterns of deuteriated cleavamines.

ioacetic acid (2 mL) and heated in a 90 °C oil bath for 4.5 h. TLC (SiO_2, 7.5% methanol/CH_2Cl_2) showed complete conversion to the more polar isomer **21**. The solvent was evaporated and the residue, without further workup, was analyzed by NMR and mass spectroscopy. The NMR spectra of the reaction product and authentic **21** were found to be identical with the following exceptions: The indole NH from the deuteriation study integrated for less than 1 H and the doublet at 3.93 ppm was absent. The MS was found to be consistent with deuteriation α to the ester. The major m/e fragments of **21** (R = H) are 312, 182, and 110. The major m/e fragments of **21** (R = D) are 313, 183, and 110. The fragmentation patterns depicted in Figure 1 are consistent with the expected placement of deuterium.

***N*^{a}-Ethyldihydro-*D*/*E*-*trans*-20-desethylvincadifformine (22).** *D*/*E*-*trans*-20-Desethylvincadifformine (**10**) (0.25 g, 0.81 mmol) was dissolved in acetic acid (2 mL) and heated to 90 °C in an oil bath. Sodium borohydride (0.18 g, 4.8 mmol) was added in portions. After addition of the reducing agent, the mixture was poured onto ice and basified with 10% NH_4OH (aq). The aqueous phase was extracted with CH_2Cl_2, and the extracts were dried (Na_2SO_4) and concentrated to a residue, which was chromatographed (SiO_2, 5% methanol/CH_2Cl_2) to yield **22** as the major product (0.17 g, 67%): TLC (SiO_2, 10% methanol/CH_2Cl_2) R_f 0.57 (CAS, orange); NMR ($CDCl_3$) δ 7.04–7.18 (m, 2 H), 6.73 (td, 1 H, J = 0.8, 7.4 Hz), 6.50 (d, 1 H, J = 7.8 Hz), 3.96 (d, 1 H, J = 3.3 Hz), 3.73 (s, 3 H), 3.21–3.33 (m, 1 H), 2.83–3.27 (m, 5 H), 2.65–2.72 (m, 1 H), 2.17–2.26 (m, 1 H), 2.17 (d, 1 H, J = 10.4 Hz), 1.97–2.09 (m, 1 H), 1.53–1.80 (m, 4 H), 1.06–1.30 (m, 3 H), 0.99 (t, 3 H, J = 7.0 Hz); IR (KBr) ν_{max} 2921, 2893, 2852, 2840, 2821, 1727, 1607, 1481, 1451, 1268, 1214, 1179, 1134, 756, 741 cm^{-1}; UV (ethanol) λ_{max} 252, 297 nm; MS, m/e (relative intensity) 341 (3), 340 (M^+, 16), 254 (18), 158 (7), 96 (100).

16-Carbomethoxy-*N*^{b}-benzyl-20-(3-(*p*-toluenesulfonyloxy)propyl)-*D*-nordesethylcleavamines (23 and 24). N^b-Benzyl tosylate **18** (0.10 g, 0.17 mmol) was dissolved in acetic acid (1 mL) and heated in a 90 °C oil bath. Sodium borohydride (0.040 g, 1.1 mmol) was added quickly in portions and the reaction was quenched by being poured onto ice. The aqueous phase was basified with NH_4OH (10% aqueous) and extracted with CH_2Cl_2. The organic extracts were dried (Na_2SO_4) and concentrated to a residue, which was chromatographed (SiO_2, 2% methanol/CH_2Cl_2) to yield **23** (0.055 g, 55%) and **24** (0.015 g, 15%) as amorphous solids. These compounds tended to undergo, on standing, cyclization to the internal quaternary salt. Efforts to form crystalline derivatives for elemental analysis were fruitless.

Physical data for 23: TLC (SiO_2, 1.5% methanol/CH_2Cl_2) R_f 0.74 (CAS, violet); NMR ($CDCl_3$) δ 8.69 (s, 1 H), 7.65 (d, 2 H, J = 8.3 Hz), 7.46 (d, 1 H, J = 7.4 Hz), 7.23–7.39 (m, 8 H), 7.03–7.17 (m, 2 H), 5.60 (dd, 1 H, J = 12.0, 4.7 Hz) 3.83 (d, 1 H, J = 13.0 Hz), 3.78 (t, 2 H, J = 4.0 Hz), 3.76 (s, 3 H), 3.60 (d, 1 H, J = 13.0 Hz), 2.81–2.82 (m, 2 H), 2.56–2.61 (m, 1 H), 2.41 (s, 3 H), 2.27–2.41 (m, 3 H), 1.90 (t, 1 H, J = 12.2 Hz), 1.25–1.48 (m, 4 H), 0.95–1.02 (m, 2 H); IR (film) ν_{max} 3414, 2962, 1726, 1618, 1598, 1494, 1462, 1358, 1189, 1175, 918, 740, 701 cm^{-1}; UV (ethanol) λ_{max} 235, 284, 293 nm; MS, m/e (relative intensity) 574 (M^+, 9), 503 (5), 438 (12), 429 (26), 401 (7), 369 (12), 355 (18), 281 (23), 221 (25), 202 (15), 147 (25), 133 (14), 91 (58), 73 (100).

Physical data for 24: TLC (SiO_2, 1.5% methanol/CH_2Cl_2) R_f 0.47 (CAS, violet); NMR ($CDCl_3$) δ 8.59 (s, 1 H), 7.72 (d, 2 H, J = 8.3 Hz), 7.24–7.42 (m, 9 H), 7.05–7.14 (m, 2 H), 5.03 (d, 1 H, J = 8.7 Hz), 3.93 (t, 2 H, J = 6.3 Hz), 3.77–3.83 (m, 1 H), 3.77 (s, 3 H), 3.32 (d, 1 H, J = 12.9 Hz), 2.58–2.92 (m, 3 H), 2.40 (s, 3 H), 2.15–2.39 (m, 3 H), 1.71–2.02 (m, 2 H), 1.50–1.62 (m, 2 H), 0.95–1.16 (m, 3 H); IR (Film) ν_{max} 3418, 2963, 1727, 1678, 1609, 1599, 1494, 1462, 1357, 1189, 1175, 923, 739, 700; UV (ethanol) λ_{max} 232, 284, 294 nm; MS, m/e (relative intensity) 574 (M^+, 6), 438 (13), 358 (8), 281 (4), 261 (19), 222 (13), 202 (24), 149 (49), 133 (18), 105 (24), 91 (100), 84 (35).

Table I. NMR Ratios of Equilibration Studies of 23a:24a

compounds heated in acetic acid	NH signals 8.80:8.59 ratio	C16 H signals 5.63:5.06 ratio
23a	2.2	2.1
24a	2.3	2.4

16-Carbomethoxy-20-[3-(*p*-toluenesulfonyloxy)propyl]-*D*-nordesethylcleavamine (27). Compound **23** (0.17 g, 0.30 mmol) was dissolved in methanol (2 mL) to which a drop of perchloric acid was added. The mixture was purged with nitrogen and 10% palladium on carbon (0.050 g) was added. The mixture was then purged with hydrogen and allowed to stir overnight under an atmosphere of hydrogen at 20 °C. The mixture was then filtered and the filtrate was washed with hot methanol. The liquor and washings were combined and concentrated to a residue, which was chromatographed (SiO_2, 5% methanol/CH_2Cl_2) to yield 0.063 g (47%) of **27** as a glassy solid, which decomposed on standing to base-line material, which was unchanged when heated in toluene: TLC (SiO_2, 7.5% methanol/CH_2Cl_2) R_f 0.46 (CAS, gray); NMR ($CDCl_3$) δ 8.68 (s, 1 H), 7.68 (d, 2 H, J = 8.3 Hz), 7.47 (d, 1 H, J = 7.3 Hz), 7.21–7.36 (m, 2 H), 7.05–7.19 (m, 3 H), 5.16–5.22 (m, 1 H), 3.75–3.87 (m 2 H), 3.71 (s, 3 H), 3.40–3.46 (m, 1 H), 2.99–3.07 (m, 1 H), 2.68–2.78 (m, 1 H), 2.57–2.65 (m, 1 H), 2.43 (s, 3 H), 2.01–2.13 (m, 1 H), 1.75–1.85 (m, 1 H), 1.23–1.57 (m, 4 H), 0.94–1.13 (m, 4 H); IR (film) ν_{max} 3386, 2950, 2922, 2851, 1726, 1461, 1356, 1262, 1244, 1189, 1174, 1098, 1010, 912, 735, 664 cm^{-1}; UV (ethanol) λ_{max} 237, 286, 294 nm; MS, m/e (relative intensity) 312 (M^+–*p*-toluenesulfonic acid, 31), 280 (9), 253 (5), 215 (17), 182 (26), 169 (7), 156 (9), 127 (14), 110 (199), 96 (68), 91 (22).

16-Carbomethoxy-*N*^{b}-benzyl-20-(3-acetoxypropyl)-*D*-nordesethylcleavamines (23a and 24a). N^b-Benzyl-20-(3-acetoxypropyl)-*D*-nordesethylvincadifformine (**18a**) (0.50 g, 1.0 mmol) was dissolved in acetic acid (3 mL) and heated to 90 °C in an oil bath. Sodium borohydride (0.25 g, 6.5 mmol) was added as quickly as possible in portions and then the mixture was poured onto ice. The aqueous phase was basified with NH_4OH (10% aqueous) and extracted with CH_2Cl_2. The organic extracts were dried (Na_2SO_4) and concentrated to a residue, which was chromatographed (SiO_2, 2% methanol/CH_2Cl_2) to yield **23a** (0.27 g, 54%) and **24a** (0.10 g, 20%) as gums.

Physical data for 23a: TLC (SiO_2, 5% methanol/CH_2Cl_2) R_f 0.72 (CAS, gray); NMR ($CDCl_3$) δ 8.80 (s, 1 H), 7.45 (d, 1 H, J = 7.4 Hz), 7.21–7.40 (m, 6 H), 7.02–7.16 (m, 2 H), 5.63 (dd, 1 H, J = 12.0, 4.7 Hz), 3.77–3.86 (m, 3 H), 3.74 (s, 3 H), 3.60 (d, 1 H, J = 13.0 Hz), 2.81–2.91 (m, 2 H), 2.62–2.68 (m, 1 H), 2.31–2.45 (m, 3 H), 1.98–2.02 (m, 1 H), 1.92 (s, 3 H), 1.28–1.59 (m, 4 H), 0.96–1.08 (m, 2 H); IR (film) ν_{max} 3397, 2927, 1729, 1462, 1434, 1365, 1246, 1163, 1026, 737, 701 cm^{-1}; UV (ethanol) λ_{max} 237, 285, 292 nm; MS, m/e (relative intensity) 463 (16), 462 (M^+, 64), 334 (22), 246 (10), 215 (27), 202 (36), 133 (27), 91 (100). The hydrochloride was precipitated from ether for an analytical sample (mp 210–212 °C dec). Anal. Calcd for $C_{28}H_{35}N_2O_4Cl$: C, 67.39; H, 7.07; N, 5.61; Cl, 7.10. Found: C, 67.10; H, 7.03; N, 5.53; Cl, 7.33.

Physical data for 24a: TLC (SiO_2, 5% methanol/CH_2Cl_2) R_f 0.72 (CAS, gray); NMR ($CDCl_3$) δ 8.59 (s, 1 H), 7.26–7.43 (m, 7 H), 7.02–7.18 (m, 2 H), 5.06 (d, 1 H, J = 8.3 Hz), 3.97 (t, 2 H, J = 6.6 Hz), 3.77 (d, 1 H, J = 13.7 Hz), 3.75 (s, 3 H), 3.36 (d, 1 H, J = 13.9 Hz), 2.69–2.83 (m, 3 H), 2.26–2.38 (m, 4 H), 2.06 (s, 3 H), 1.86–1.99 (m, 2 H), 1.54–1.62 (m, 2 H), 1.07–1.16 (m, 2 H); IR (film) ν_{max} 3388, 2949, 1729, 1462, 1434, 1365, 1244, 1163, 1028, 737, 701 cm^{-1}; UV (ethanol) λ_{max} 238, 286, 294 nm; MS, m/e (relative intensity) 463 (5), 462 (M^+, 21), 334 (9), 246 (9), 215 (21), 202 (24), 133 (24), 91 (100). The hydrochloride was precipitated from ether for an analytical sample (mp 125–130 °C dec). Anal. Calcd for $C_{28}H_{35}N_2O_4Cl$: C, 67.39; H, 7.07; N, 5.61; Cl, 7.10. Found: C, 67.11; H, 7.28; N, 5.83; Cl, 7.34.

Equilibrium Studies of 23a and 24a in Hot Acetic Acid. Compound **23a** (0.060 g, 0.13 mmol) was dissolved in acetic acid and heated in a 90 °C oil bath under a nitrogen atmosphere overnight. The mixture was examined by TLC (SiO_2, 5%

Table II. Thermal Ring Flipping Experiment of Unnatural Conformer 26 to Natural Conformer 20

	indole NH			C16-methinyl H				
time (min)	unnat	nat	[A] (UN/total)	unnat	nat	[A] (UN/total)	average [A]	ln [A]
			Temperature 103.5 °C (376.7 K)					
0	1	0	1	1	0	1	1	0
30.0	35.0	71.0	0.330	36.0	79.0	0.313	0.322	−1.14
64.0	6.0	79.0	0.076	8.0	83.0	0.0879	0.0793	−2.54
80.0	2.5	71.0	0.0340	3.0	75.0	0.0400	0.0370	−3.30
			Temperature 90.5 °C (363.7 K)					
0	1.0	0	1	1	0	1	1	0.00
30.0	42.0	12.0	0.778	46.0	14.0	0.767	0.773	−0.258
58.0	23.0	21.0	0.523	25.0	23.0	0.521	0.522	−0.650
85.0	27.5	52.0	0.346	32.0	57.0	0.360	0.353	−1.04
123.0	22.0	71.0	0.237	24.0	74.0	0.245	0.241	−1.42
			Temperature 75.0 °C (352.2 K)					
0	1	0	1	1	0	1	1	0
60	68.0	14.0	0.829	70.0	15.0	0.824	0.827	−0.191
88	70.0	55.0	0.560	72.0	53.0	0.576	0.568	−0.566
353	10.0	39.0	0.204	10.5	40.0	0.208	0.206	−1.58

Table III. Determination of Rate Constant k (s^{-1}) and $\Delta G^{\ddagger}$ at Each Temperature for the Reaction

$$\Delta G^{\ddagger} = \frac{RT(23.76 + \ln T - \ln k)}{1000}$$

temperature			
°C	K	k (s^{-1})	$G^{\ddagger}$ (kcal/mol)
103.5	376.7	6.85×10^{-4}	27.7
90.5	363.7	2.00×10^{-4}	27.6
79.0	352.2	0.743×10^{-4}	27.4
		$\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$	
		$\Delta H^{\ddagger} = 23.3$ kcal/mol	
		$\Delta S^{\ddagger} = -10 \pm 6$ eu	

methanol/CH_2Cl_2) periodically until there appeared to be no changes in the ratios of **23a** and **24a**. The total reaction time was 23.5 h. The acetic acid was removed under high vacuum and the residue subjected to analysis by NMR. The identical procedure was performed with **24a**. Examination of the NMR spectra allowed the determination of the **23a:24a** ratio by integration of the indole NH signals at 8.80 and 8.59 ppm, respectively, and of the C-16 methinyl proton signal at 5.63 and 5.06 ppm, respectively. The results are summarized in Table I. Thus the equilibrium ratio of **23a** to **24a** is slightly greater than 2:1.

Deuteriation Studies of 23a and 24a in Hot Deuterioacetic Acid. Each of **23a** and **24a** (0.060 g, 0.13 mmol) was dissolved in deuterioacetic acid, placed under a nitrogen atmosphere, and heated in a 90 °C oil bath overnight. The acid was removed under high vacuum and the residues were examined by NMR and mass spectroscopy. NMR showed the absence of the absorptions at 5.63 and 5.06 ppm corresponding to the C-16 methinyl protons of **23a** and **24a**, respectively. Comparison of the mass spectra of the deuteriated vs. undeuteriated compounds showed m/e 463 and 203 vs. 462 and 202.

16-Carbomethoxy-20-desethyldihydrocleavamine *N*-Benzyl Ammonium Salt (25). Compound **23** (0.30 g) was dissolved in toluene (20 mL) and heated at reflux overnight under a nitrogen atmosphere. The cooled mixture was transferred to a larger flask, using CH_2Cl_2 as a rinse solvent and to assure that the mixture was homogeneous. The mixture was concentrated to a mass which was triturated with ether to yield 0.29 g (97%) of an amorphous salt identified as quaternary salt **25**: TLC (SiO_2, 7.5% methanol/CH_2Cl_2) R_f 0.05 (CAS, faint green); NMR ($CDCl_3$) δ 9.37 (s, 1 H), 7.86 (d, 2 H, J = 8.1 Hz), 7.68–7.74 (m, 2 H), 7.06–7.43 (m, 9 H), 5.10 (d, 1 H, J = 12.9 Hz), 4.95 (d, 1 H, J = 12.9 Hz), 4.27–4.38 (m, 2 H), 3.92–4.08 (m, 2 H), 3.76 (s, 3 H), 3.73–3.74 (m, 1 H), 2.94–3.61 (m, 4 H), 2.29 (s, 3 H), 1.31–1.86 (m, 7 H); ^{13}C NMR 174.5, 144.2, 139.1, 135.0, 133.6, 130.3, 129.3, 129.2, 128.6, 127.7, 127.6, 126.1, 122.4, 119.9, 117.7, 112.1, 111.2, 69.0, 60.2, 58.0, 57.8, 52.6, 40.2, 32.1, 30.4, 27.9, 22.8, 21.2, 17.6, 15.3. IR (KBr) ν_{max} 3433, 3229, 3055, 1731, 1494, 1460, 1193, 1121, 1034, 1011, 755, 681, 566 cm^{-1}; UV (ethanol) λ_{max} 228, 283, 291 nm.

Table IV. Conformational Inversion of 26 to 20 in *tert*-Butyl Alcohol (Neutral, Acidic, and Basic) (All Experiments Performed at 82.5 °C (355.7 K))

	indole NH			C16-methinyl H				
time (min)	unnat	nat	[A] (UN/total)	unnat	nat	[A] (UN/total)	average [A]	ln [A]
				Neutral				
0	1	0	1	1	0	1	1	0
40.0	40.0	18.0	0.690	43	18	0.705	0.698	−0.360
75.0	62.0	69.0	0.473	33	34	0.492	0.483	−0.729
194.0	8.0	52.0	0.133				0.133	−2.017
				Acidic				
0	1	0	1	1	0	1	1	0
40.0	50.0	23.0	0.685	53.0	23.0	0.697	0.691	−0.370
75.0	23.0	27.0	0.540	30.0	25.0	0.545	0.543	−0.611
194.0	8.0	47.0	0.145	11.0	48.0	0.186	0.166	−1.799
				Basic				
0	1	0	1	1	0	1	1	0
40.0	91.0	35.0	0.722	54.0	18.0	0.750	0.736	−0.307
75.0	29.0	30.0	0.491	31.0	31.0	0.500	0.496	−0.702
194.0	4.5	41.0	0.100	5.0	42.0	0.106	0.103	−2.27

Kinetic Values

experiment	k (s^{-1})	$\Delta G^{\ddagger}$ (kcal/mol)
neutral	1.75×10^{-4}	27.1
acidic	1.55×10^{-4}	27.1
basic	2.00×10^{-4}	27.0

Table V. Conformational Flip Studies of 28 to 21

time (min)	indole NH unnat	indole NH nat	[A]	ln [A]
0	1	0	1	0
30.0	35.2	7.0	0.834	−0.182
81.0	45.3	26.0	0.635	−0.454
123.0	25.2	25.0	0.501	−0.691

$$k = 9.28 \times 10^{-5}\ s^{-1}$$

$$\Delta G^{\ddagger} = \frac{RT(23.76 + \ln T - \ln k)}{1000} = 24.3\ \text{kcal/mol}$$

Catalytic Debenzylation of Compound 25 To Form the Unnatural Conformer of C16–C14 Pref 20-Desethyldihydrocleavamine (26). Compound **25** (0.40 g, 0.70 mmol) was dissolved in methanol (10 mL) and the mixture was purged with nitrogen. The catalyst (20% Pd/C, Pearlman's catalyst, 0.10 g) was added and the stirring mixture was placed under a hydrogen atmosphere and allowed to stir for 5 h. The catalyst was filtered and washed with hot methanol (ca. 50 mL) and then CH_2Cl_2 (ca. 10 mL). All of the liquid phases were combined and partially concentrated to approximately a 10-mL volume. This was basified with NH_4OH (10% aqueous) and extracted three times with CH_2Cl_2. The extracts were dried (Na_2SO_4) and concentrated to a residue, which was identified as structure **26**, yield 0.21 g (97%). The conformational flip to compound **20** was observed in refluxing toluene within 10 min: TLC (SiO_2, 7.5% methanol/CH_2Cl_2) R_f 0.00 (CAS, gray, turns yellow); NMR ($CDCl_3$) δ 9.27 (s, 1 H), 7.50 (d, 1 H, J = 7.7 Hz), 7.35 (d, 1 H, J = 7.5 Hz), 7.09–7.22 (m, 2 H), 4.31 (dd, 1 H, J = 12.0, 4.6 Hz), 3.88 (d, 1 H, J = 13.7 Hz), 3.81 (s, 3 H), 3.21–3.34 (m, 2 H), 3.05 (td, 1 H, J = 13.7, 4.0 Hz), 2.67–2.96 (m, 3 H), 2.32–2.41 (m, 1 H), 1.18–1.77 (m, 7 H); IR (KBr) ν_{max} 3417, 2962, 2922, 2860, 1727, 1461, 1434, 1337, 1283, 1262, 1200, 1169, 1118, 1023, 742 cm^{-1}; UV (ethanol) λ_{max} 232, 285, 292 nm.

Debenzylation of Compound 25 To Form the Amine–Borane Complex of the Unnatural Conformer 26. Compound **25** (0.20 g) was dissolved in methanol (5 mL) and the mixture was purged with nitrogen by alternately exposing it to aspirator pressure and a positive pressure of nitrogen. This served to deoxygenate the system so that the palladium catalyst (10% Pd/C, 0.10 g) may be added safely. The flask was fitted with a reflux condenser and placed in an oil bath at 90 °C. When the methanol was boiling a large excess of sodium borohydride (ca. 0.3 g) was added in portions at a rate such that the frothing reaction mixture did not overflow through the condenser. During the process TLC's were taken to determine qualitatively if the base-line material was consumed. The hot solution was immediately filtered and the filtrate was washed with hot methanol (ca. 50 mL) followed by dichloromethane (ca. 10 mL). The solutions were partially concentrated under vacuum and then an aqueous solution of NH_4OH (10%) was added. The aqueous layer was extracted with CH_2Cl_2, and the organic extracts were dried (Na_2SO_4) and concentrated to a residue which was purified by passing it through a plug of silica gel (5% methanol/CH_2Cl_2) to yield 0.11 g (95%) of a boron complex. This product was recovered unchanged after refluxing in toluene overnight: TLC (SiO_2, 7.5% methanol/CH_2Cl_2) R_f 0.86 (CAS, gray, rapidly turns yellow); NMR ($CDCl_3$) δ 9.30 (s, 1 H), 7.06–7.49 (m, 4 H), 4.27 (d, 1 H, J = 14.3 Hz), 3.83 (s, 3 H), 3.72–3.83 (m, 1 H), 3.23–3.49 (m, 2 H), 2.99–3.18 (m, 3 H), 2.83–2.97 (m, 1 H), 2.33–2.45 (m, 1 H), 1.27–1.73 (m, 10 H); IR (KBr) ν_{max} 3413, 2962, 2927, 2367, 2317, 2271, 1728, 1488, 1460, 1262, 1206, 1173, 1100, 1059, 804, 744 cm^{-1}; UV (ethanol) λ_{max} 233, 285, 292 nm; MS, m/e (relative intensity) 313 (7), 312 ($M^+ - BH_3$, 23), 295 (9), 215 (21), 182 (29), 156 (11), 149 (20), 110 (100), 96 (36), 82 (19).

Treatment of Compound 20 with BH_3·THF To Form an Amine–Borane Complex. Compound **20** (0.050 g, 0.16 mmol) was dissolved in THF (1 mL) and a solution of BH_3 in THF (ca. 0.2 mL of a 1 M solution in THF) was added. TLC showed that the reaction occurred instantly. Water was added and the mixture was extracted with CH_2Cl_2. The extracts were dried (Na_2SO_4) and concentrated to a residue, which was identified as a boron complex (0.047 g, 90%). This product is unstable in solution at 20 °C and on heating in toluene it reverted to the starting material **20**: TLC (SiO_2, 2% methanol/CH_2Cl_2) R_f 0.82 (CAS, gray, rapidly turns yellow); NMR ($CDCl_3$) δ 8.36 (s, 1 H), 7.54–7.58 (m, 1 H), 7.09–7.32 (m, 3 H), 4.26 (d, 1 H, J = 10.1 Hz), 3.77 (s, 3 H), 3.71–3.75 (m, 1 H), 3.41–3.52 (m, 2 H), 2.85–3.28 (m, 6 H), 2.28–2.40 (m, 2 H), 2.07–2.18 (m, 1 H), 1.53–1.96 (m, 6 H); IR (KBr) ν_{max} 3376, 2950, 2373, 2319, 2275, 1735, 1462, 1434, 1292, 1232, 1167, 1012, 744 cm^{-1}; UV (ethanol) λ_{max} 235, 281, 292 nm; MS, m/e (relative intensity) 326 (M^+, 6), 325 (7), 312 (48), 215 (21), 169 (8), 154 (10), 144 (5), 110 (100), 96 (18), 82 (17); MS, m/e (relative intensity) 312 (M^+, 29), 182 (30), 110 (100), 96 (45), 82 (22).

"Unnatural" Conformer of C16–C14 Parf 20-Desethyldihydrocleavamine (28). The *N*-benzyl tosylate **24** (0.40 g) was dissolved in dry toluene, placed under a nitrogen atmosphere, and heated at reflux for 12 h. After cooling, the solution was concentrated to a residue, which was triturated with ether. A crude solid quaternary salt (0.29 g, 75%) obtained on filtration was not homogeneous. A contaminant is believed to be a different N-benzyl conformer. This crude quaternary salt (0.21 g, 0.37 mmol) was dissolved in methanol (2 mL), and the mixture purged with nitrogen and then Pearlman's catalyst (20% $Pd(OH)_2$ on carbon, 0.10 g) was added. The mixture was allowed to stir under a hydrogen atmosphere for 3.5 h. The catalyst was then filtered off and washed with methanol, followed by CH_2Cl_2. The combined solutions were concentrated to $^1/_4$ volume at room temperature and made basic with NH_4OH (10% aqueous). The aqueous layer was separated, and the organic layer was dried (Na_2SO_4) and concentrated. TLC of the residue (SiO_2, 7.5% methanol/CH_2Cl_2) showed it to contain a small amount of the natural conformer (**21**). Chromatography (activity I alumina, 5% methanol/CH_2Cl_2) served to completely remove this minor product and gave 0.100 g of **28** (86%): TLC (SiO_2, 7.5% methanol/CH_2Cl_2) R_f 0.00 (CAS, grey); NMR ($CDCl_3$) δ 9.26 (br s, 1 H), 7.46–7.55 (m, 1 H), 7.33 (d, J = 7.7 Hz, 1 H), 7.09–7.22 (m, 2 H), 3.91–4.09 (m, 1 H), 3.78 (s, 3 H), 3.70–3.75 (m, 1 H), 3.21–3.56 (m, 2 H), 2.67–3.05 (m, 3 H), 2.22–2.57 (m, 2 H), 2.03–2.16 (m, 1 H), 1.23–2.06 (m, 6 H); IR (KBr) ν_{max} 3395, 2962, 2951, 2927, 2887, 2852, 1730, 1460, 1430, 1341, 1261, 1229, 1204, 1167, 1157, 1103, 1089, 1060, 1019, 801 cm^{-1}; UV (ethanol) λ_{max} 232, 285, 292 nm; MS, m/e (relative intensity) 312 (M^+, 52), 215 (25), 182 (30), 110 (100), 96 (31), 82 (24).

General Procedure for Conformational Flip Studies. The unnatural conformer (**26** or **28**) (0.020 g, 0.064 mmol) was placed in a three-neck round-bottom flask equipped with a thermometer, a rubber septum, and a nitrogen purge line. The solvent, toluene or *tert*-butyl alcohol (4 mL), was added and the mixture was purged with nitrogen. In the acidic *tert*-butyl alcohol study a crystal of *p*-toluenesulfonic acid was added. In the basic *tert*-butyl alcohol study a small sliver of potassium was dissolved in the solvent before the compound was added. The apparatus was placed in an oil bath that had been allowed to equilibrate to the desired temperature. The temperature value used in the calculations was that obtained directly from the reaction mixture. Aliquots (1 mL) were removed via syringe at intervals and the solvent was removed first at aspirator pressure (room temperature) and then high vacuum. The residues were then immediately examined by NMR spectroscopy and the indole NH and C16 methinyl protons used to evaluate the extent of conformational inversion.

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