The Syntheses of 16a′-*homo*-Leurosidine and 16a′-*homo*-Vinblastine. Generation of Atropisomers

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Received February 22, 2000 (Revised Manuscript Received May 11, 2001)

The synthesis of 16a′-*homo*-leurosidine was achieved through enantioselective generation of a ring D′-*seco*-precursor **33 (**without requirement of a chiral auxiliary). Its cyclization provided the $N^{b'}$-quaternary salt **35** with a configuration corresponding to the atropisomeric form **8a** rather than **8b** of the target product. On debenzylation, the amine **8a** was obtained and found not to isomerize thermally to the anticipated atropisomer **8b** (in contrast to its lower homologue, with its formation of natural leurosidine). However, on protonation, a 1:1 mixture of atropisomers of 16a′-*homo*-leurosidine was obtained. A synthesis of 16a′-*homo*-vinblastine provided two atropisomers **5a** and **5b** for the free base at equilibrium (1:2.3 at room temperature in $CDCl_3$), with a shift to the major conformer **5b** with increasing solvent acidity or decreasing temperature. The synthesis was achieved through a stereoselective inversion of the tertiary hydroxyl function in the enantioselectively generated C-20′ progenitor **39**.

Introduction

In the course of our syntheses of vinblastine (**1b**)[1] and congeners for evaluation as anti-cancer agents, we had been able to generate and isolate corresponding atropisomers that were noncytotoxic and that did not inhibit tubulin polymerization. These compounds could be considered as potential pro-drugs for thermal activation to the corresponding cytotoxic agents. With the determination that the conformational inversion barrier of isolable atropisomers **1a**, **2a**, and **3a** of the cleavamine congeners **1b**, **2b**, and **3b** depends on C-16 substitution of the azonine ring,[1−3] as well as on substitution of the piperidine moiety,[3,4] and finding that with the C′-azocine ring of 5a′-*homo*-vinblastine (**4b**) this energy barrier is lowered so much that it prevents isolation of an atropisomer **4a**,[5] it was of interest to see if a ring C′-azocine of 16a′-*homo*-vinblastine (**5b**) would allow isolation of an atropisomer **5a**.[6] Generation of this structure seemed accessible by ring expansion of an appropriately C-17 substituted tetracyclic intermediate **6** to the corresponding C-16a homologue **7** (Figure 1).

In this paper, we describe first an enantioselective synthesis of 16a′-*homo*-leurosidine (**8b**) and then its extension to a synthesis of its C-20′ epimer 16a′-*homo*-vinblastine (**5b**). Generation of the expanded ring C′ of these objectives revealed interesting divergence in reactions of intermediates, relative to the general methodology developed for the vinblastine synthesis,[1] that now offered opportunities, but also required solutions to new synthetic hurdles.

Enantioselective Synthesis of the Tetracyclic Intermediates 6. For an effective generation of tetracyclic intermediates **6**, which might allow a ring expansion, the racemic tetrahydrocarboline diester **9** was prepared by reaction of *N*-benzyltryptamine and dimethyl acetylenedicarboxylate.[7] When this tetrahydrocarboline **9** was heated with the (4*R*)-ethyl-4,5-dihydroxypentanal acetonide (**10**),[1] a mixture of four diastereomeric diesters **11a**−**d** was obtained (Scheme 1). In this mixture, the diastereomers **11a**,**b**, derived from an *E*-fumarate intermediate **12**, predominated over the diastereomers **11c**,**d**, derived from a *Z*-maleate intermediate **13** (Table 1). Since the difference in diester product ratios **11a**,**b**/**11c**,**d** was found to be sensitive to reaction conditions, it seemed likely that it did not reflect a kinetic ratio of intermediates **12** and **13**. Indeed, prolonged heating of the separated mixture of diastereomers **11c**,**d** resulted in equilibration into the predominant products **11a**,**b**, as well as some decomposition products.

The ratio of products **11c**/**11d**, derived from the *Z*-diester intermediate **13**, is essentially the same as that found without the C-17 ester substituent;[1] i.e., as in the vinblastine synthesis, there was little chiral induction from the C-20 acetonide substituent in the intramolecular Diels−Alder step. However, the chiral induction increased significantly in the reaction of the *E*-diester **12**,

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(1) Kuehne, M. E.; Matson, P. A.; Bornmann, W. G. *J. Org. Chem.* **1991**, *56*, 513.

(2) Kuehne, M. E.; Zebovitz, T. C. *J. Org. Chem.* **1987**, *52*, 4331.

(3) Kuehne, M. E.; Zebovitz, T. C.; Bornmann, W. G.; Marko, I. *J. Org. Chem.* **1987**, *52*, 4340.

(4) Kuehne, M. E.; Bornmann, W. G. *J. Org. Chem.* **1989**, *54*, 3407.

(5) Kuehne, M. E.; Cowen, S. D.; Xu, F.; Borman, L. S. *J. Org. Chem.* **2001**, *66*, 5303.

(6) Position numbering is that of: Le Men, J.; Taylor, W. I. *Experientia* **1965**, *21*, 501.

(7) Vercauteren, J.; Massiot, G.; Bideau, A. *Tetrahedron Lett.* **1987**, *28*, 1267.

10.1021/jo000250y CCC: $20.00
Published on Web 07/07/2001

Table 1. Condensation of Tetrahydrocarboline 9 with Aldehyde 10[a]

solvent	additive	*T* (°C)	time (h)	yield (%)	ratio of isomers **11**[b,c] **a** + **b**/**c** + **d**(**a**/**b**, **c**/**d**)
PhMe		110	5 days	41.6	1.4:1 (3.6:1, 1.2:1)
PhMe (sealed)	4 A MS	150	48	30.0	1.4:1 (3.6:1, 1.2:1)
neat		130	15	64.5	2.5:1 (2.3:1, 1.1:1)
neat	SiO_2 (100 wt %)	130	5	79.5	3.4:1 (5.0:1, 1.4:1)
neat	SiO_2 (20 wt %)	130	3	81.1	3.4:1 (5.0:1, 1.4:1)

[a] 1.2 equiv of **10** was used. [b] The mixture of **11a** and **11b** can be separated from the mixture of **11c** and **11d** by chromatography; **11a** can be effectively separated from **11b** by recrystallization from petroleum (60−90 °C). [c] The ratios of **11a** to **11b** and **11c** to **11d** were determined by ^{1}H NMR with integration of the doublets at δ 4.29 (**a**), 4.21 (**b**), 4.35 (**c**), and 4.25 (**d**).

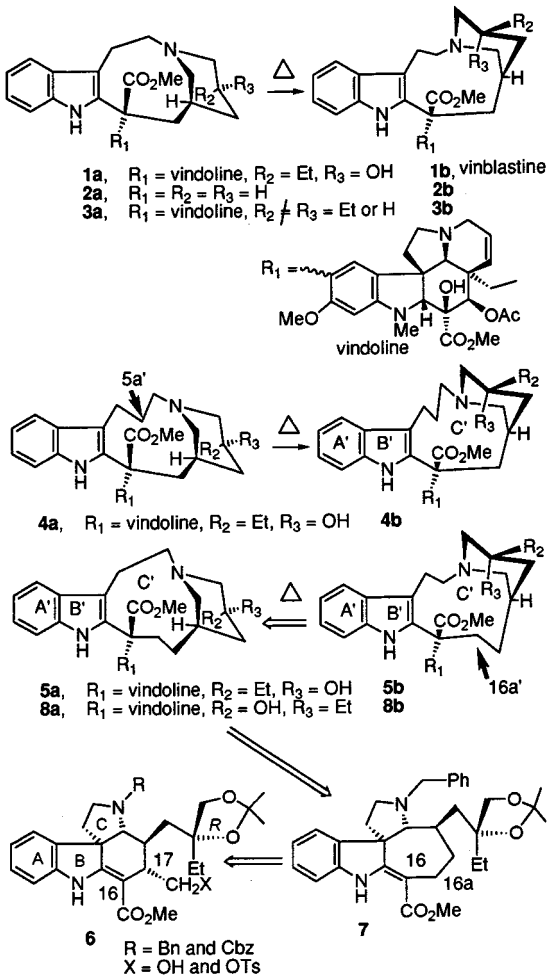
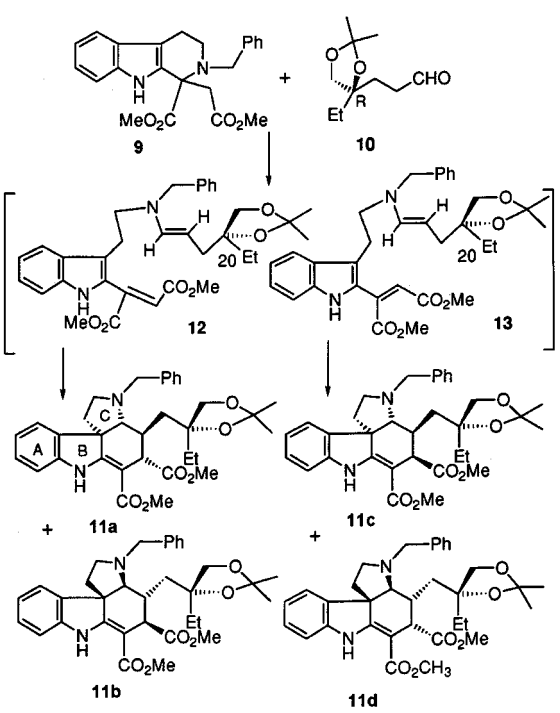


Figure 1. Atropisomers of vinblastine (**1a**,**b**), 5a′-*homo*-vinblastine (**4a**,**b**), and 16a′-*homo*-vinblastine (**5a**,**b**) and their congeners. Synthetic strategy for generation of the 16a′-*homo*-compounds.

to the point where a 5:1 ratio of diastereomeric products **11a/11b** eliminated the necessity of a chiral N^b-substituent to guide the reaction.[8,9] This chiral induction may be ascribed to a six-membered ring interaction of the incipient C-17 ester carbonyl function with the C-20 ether oxygen in the IMDA reaction.

It should be noted, however, that the chirality of the tetracyclic ring system in **11a**, required for synthesis of a vinblastine congener, becomes the result of a pre-

Scheme 1



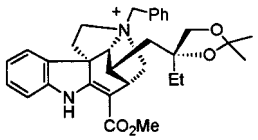
leurosidine (C-20 *R*) acetonide, while a pre-vinblastine (C-20 *S*) acetonide would favor the wrong, epimeric (**11b**), substitution of the tetracycle. (The solution to this problem for a 16a′-homo-vinblastine synthesis is described below.)

Formation of the Ring Expansion Product 7. A reduction of the saturated ester function of the chromatographically separated and fractionally crystallized major tetracyclic product **11a** with DIBALH provided the corresponding alcohol **14**, without affecting the vinylogous urethane function (Scheme 2). To avoid an intramolecular quaternization in the following ring expansion sequence,[10] the *N*^{b}-benzyl substituent of intermediate **14** now had to be temporarily exchanged for a urethane derivative. Hydrogenolysis of the *N*^{b}-benzyl compound **14**, and reaction of the secondary amine **15** with benzyloxycarbonyl chloride, provided the *N*-Cbz derivative **16** (95%), as well as some N,O-double derivative **17** (4%). A reaction of the major Cbz-derivative **16** with tosyl anhydride, DMAP, and triethylamine then furnished the

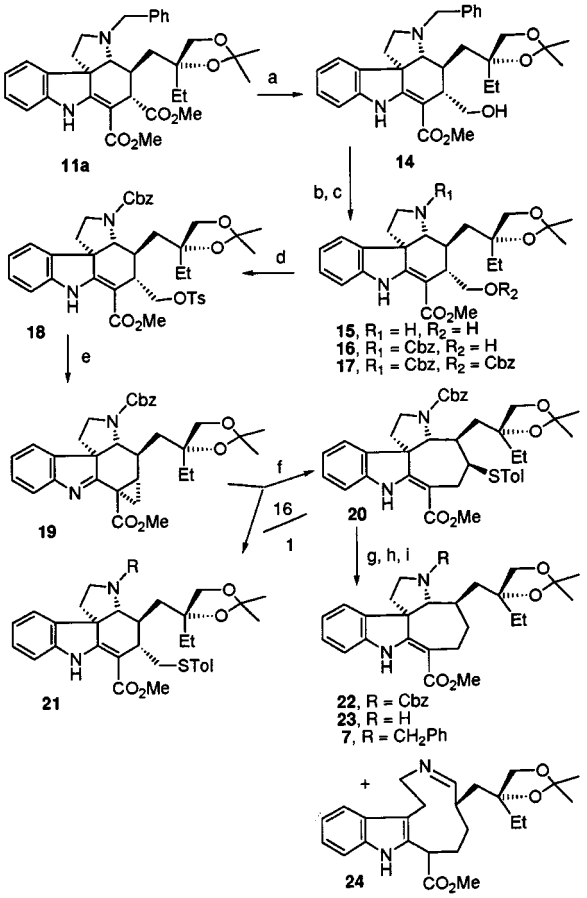
(8) Vercauteren, J.; Massiot, G.; Henin, J.; Legseir, B. *Tetrahedron Lett.* **1987**, *28*, 3573.

(9) While simple molecular modeling (MM-2) of the transition state, with incremental stretching of the two s-bonds formed in the Diels−Alder reaction step, indicated optimal formation of the favored product **11a**, the ratio of calculated transition-state energies for formation of **11a**/**11b** was similar to that going to **11c**/**11d**.

(10) The *N*^{b}-benzyl-4-benzyl congener **14**, on reaction with tosyl anhydride, DMAP, and triethylamine, was found to cyclize to a quaternary ammonium salt:Cowen, S. D. Ph.D. Thesis, University of Vermont, 1994.

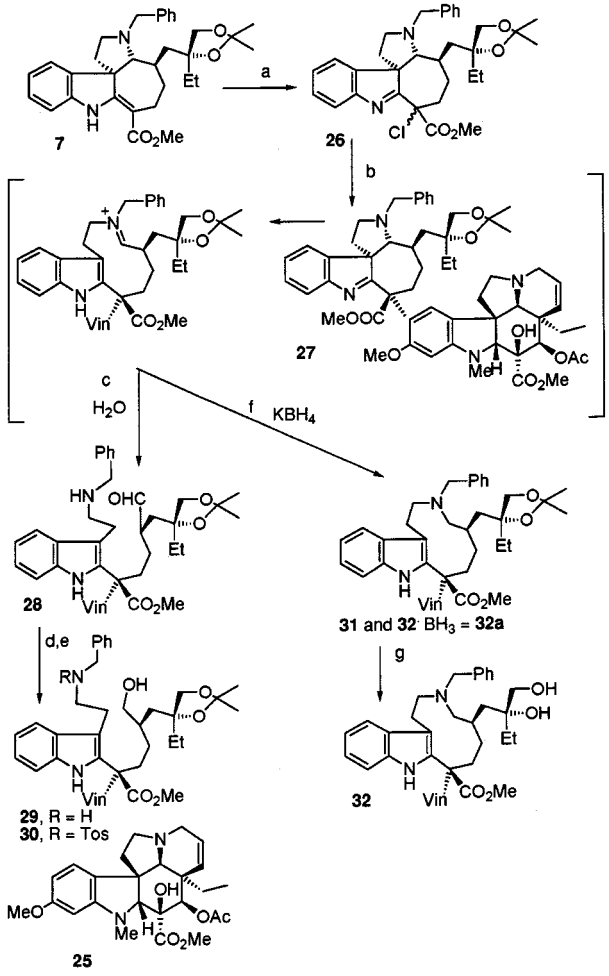


Scheme 2[a]



[a] Key: (a) DIBALH, 0 °C, 85%; (b) Pd/C, H_2, MeOH−EtOAc, NH_4OCHO, reflux, 89%; (c) CbzCl, $NaHCO_3$, aqueous acetone, 95% **16**, 4% **17**; (d) Ts_2O, Et_3N, DMAP; (e) DBU, 91%; (f) thiocresol, 110 °C, 98%; (g) Bu_3SnH, AIBN, tol. reflux, 75%; (h) Pd/H_2, Et_3N, EtOAc,72% **23**, 14% **24**; (i) BzBr, K_2CO_3, 70%.

Scheme 3[a]



[a] Key: (a) ButOCl, Et_3N, 0 °C; (b) **25**, $AgBF_4$, HBF_4; (c) NH_4OH; (d) KBH_4, HOAc, 0 °C, 74% overall; (e) Ts_2O, Et_3N, 77%; (f) KBH_4, HOAc, 0 °C; (g) 10% aqueous HCl, 26% overall.

tosylate **18**, together with the cyclopropane **19**. Treatment with additional base (DBU) completed the cyclization to the cyclopropane **19** (91% overall yield from alcohol **16**).

In analogy to the homo-Michael addition strategy of Danishefsky,[11] nucleophilic opening of the activated cyclopropane **19** with thiocresol occurred primarily with attack at the more substituted position of the activated cyclopropane ring to provide the ring expansion product **20**, together with some thiomethyl ether **21** (98% yield, **20**/**21** = 16:1).[12] Reductive removal of the thioether substituent from the major product **20** with BUT_3SnH then gave the tetracyclic product **22,** containing the target seven-membered ring.

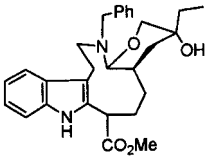
The Cbz protecting group could now be exchanged back for an N^b-benzyl substituent by hydrogenolysis of the urethane **22** to furnish the secondary amine **23**, followed by its benzylation. In this sequence to the tertiary amine **7**, required for a coupling reaction to vindoline, it was necessary to avoid a previously encountered acid-catalyzed cleavage of the tetracyclic skeleton.[13] With 10% Pd/C−H_2, in ethyl acetate, a 73% yield of the tetracyclic amine **23** was obtained, together with 14% of the tricyclic imine **24**. Using transfer hydrogenolysis with ammonium formate and 10% Pd/C, the ratio of products **23**/**24** dropped to 46:32%.

Formation of 16a′-*homo*-Leurosidine in Two Atropisomeric Conformations 8a and 8b. Coupling of the tetracyclic 16a′-homo congener **7** to vindoline (**25**) was modeled on the reaction of its lower homologue in the vinblastine synthesis,[1] but once again, the ring-expanded sequence required reaction modifications (Scheme 3). Chlorination of the vinylogous urethane **7** and reaction of the chloroimine **26** with $AgBF_4$ and vindoline (**25**) was expected to provide a substituted tetracyclic imine **27**. While such an intermediate could be isolated and char-

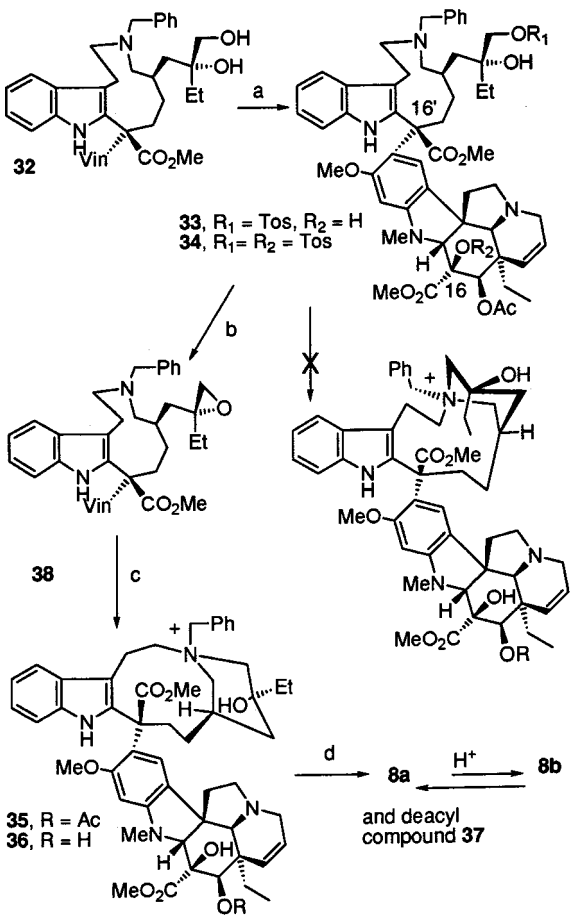
(11) Danishefsky, S. *Acc. Chem. Res.* **1979**, *12*, 66.

(12) In model reactions, the N^b-Boc-4-benzyl congener of this cyclopropano imine ester **19**, in acetic acid at 25 °C, furnished a 55:1 ratio of ring expanded acetate/acetoxymethyl-substituted tetracyclic products (66% yield). With *p*-thiocresol, neat at 110 °C, a 23:1 ratio of the corresponding products was formed in 1.5 h, in 96% yield; and in THF at reflux for 5 h, an 87% yield was obtained. No reaction was found with alkanethiols.

(13) Analogous to the rearrangements of similar vinylogous urethane alcohols to indolic hemiaminal ethers encountered in the synthesis of 5a′-*homo*-vinblastine,[5] and in the synthesis of ibophyllidine[14] hydrolysis of the acetonide **7** resulted in rearrangement to a cyclic hemiaminal ether:



Scheme 4[a]



[a] Key: (a) Ts_2O, Et_3N, 55% **33**, 27% **34**; (b) DBU, THF, rt, 94%; (c) MeOH, reflux, 15 h; b + c: MeOH, reflux, 25 h; (d) Pd/C, H_2, 0 °C, 68% **8a**, 24% **37** overall.

acterized in the vinblastine series,[1] it was now found that an analogous workup of the reaction mixture led to the formation of an amino aldehyde **28**. Reduction of this crude product with potassium borohydride in acetic acid then gave an amino alcohol **29** (74% overall yield from **7**). On reaction of this β-aminoethylindole with tosyl anhydride, a sulfonamide **30** was formed, in 77% yield, in support of the ring C′ cleavage.

Direct reduction of the unisolated tetracyclic imine **27** with potassium borohydride in acetic acid provided the desired vindoline coupling product **31** without rupture of the 10-membered ring. In this sequence, a borane adduct of the corresponding diol **32** was also formed as a minor product. It could be chromatographically separated, and on hydrolysis, it and the acetonide **31** provided the diol **32** for a 26% overall combined yield from the tetracyclic intermediate **7**. The exclusively formed C-16′ absolute stereochemistry could be subsequently verified by the characteristic short wavelength Cotton effect in CD spectra of the final product **8a**.[3,15]

On reaction with tosyl anhydride, the diol **32** provided the primary C-21′ *O*-tosylate **33** (53%), but formation of a C-21′,C-16 di-*O*-tosylate **34** (27%) was difficult to suppress (Scheme 4). In refluxing methanol, the monotosylate **33** slowly cyclized to a quaternary salt **35** containing some deacylated product **36**. Hydrogenolysis of the N^b-benzyl substituent in methanol, at 0 °C, then provided 16a′-*homo*-leurosidine (**8a**), accompanied by its deacylated congener **37**, with the corresponding "unnatural" leurosidine piperidine ring D′ conformation (below). The cyclization most likely proceeded through initial formation of an epoxide **38**.

To unambiguously generate the quaternary salt **35** with a configuration in which the piperidine ring D′ is conformationally inverted relative to leurosidine, the tosylate **33** was treated with DBU in dichloromethane at room temperature for formation of an epoxide **38**. In analogy to the cyclization leading to the precursor of leurosidine,[1] its cyclization in methanol, through a pre-piperidine boat conformation that avoids a tri-1,3-diaxial congestion, was stereoelectronically controlled to provide the quaternary salt **35**. A CD (−)-absorption at λ 304−310 nm confirmed this conformation.[1,3] On debenzylation at 0 °C, the 16a′-*homo*-leurosidine atropisomer **8a** was obtained. Its NMR and CD (strong negative absorbance at 306 nm) spectra matched those of the product obtained by the preceding tosylate cyclization in methanol. Even on prolonged heating in toluene, no formation of an atropisomer **8b** could be detected, contrary to the conformational inversion found in the synthesis of leurosidine.[1] However, on incremental addition of trifluoroacetic acid, NMR spectra in CD_3OD clearly showed the formation of an isomer, with an eventual maximal ratio of 1:1 of the two atropisomers **8a** and **8b** (Figure 2).

It is of interest to contrast these findings with those for the relatively close congeners 16a′-*homo*-vinblastine (below) and 5a′-*homo*-vinblastine (preceding paper). In contrast to those examples, the C-20′ stereochemistry of atropisomer **8a,** with axial hydroxyl and equatorial ethyl substituents, would favor that piperidine ring conformation, particularly with hydrogen bonding to the tertiary amine nitrogen, that can now be allowed by the 10-membered ring bridge, in contrast to the corresponding atropisomer of leurosidine.[1]

Generation of the 16a′-*homo*-Vinblastine Stereochemistry: Inversion of the Quaternary Hydroxyl at C-20. Having attained a synthesis of 16a′-*homo*-leurosidine and our goal of generating its isolatable leurosidine-"unnatural" atropisomer **8a**, we could proceed to a synthesis of 16a′-*homo*-vinblastine (**5b**) and its atropisomer **5a**. To that end, we hoped to utilize the enantioselection found in the formation of the tetracyclic 16a′-*homo*-leurosidine precursor **11a**. As this was based on a C-20 *R* absolute stereochemistry of intermediates, but now a C-20′ *S* absolute stereochemistry was required for 16a′-*homo*-vinblastine, it now became necessary to invert this eventual C-20 center. However, since stereoselective inversion of a tertiary alcohol function, in general, still falls into the realm of unsolved synthetic challenges, our synthetic sequence had to be examined for a suitable intermediate that might allow the desired selective inversion.

Recently, it was reported that a trisubstituted epoxide could be opened with concentrated sulfuric acid to provide a diol with inversion at the tertiary center (95% yield, 98%ee).[16] Hydrolysis of our acetonide intermediate **11a** with 10% HCl/MeOH gave the corresponding diol **39** in 99% yield (Scheme 5). Its monotosylation (98%) and

(14) Kuehne, M. E.; Pitner, J. B. *J. Org. Chem.* **1989**, *54*, 4553.
(15) Kutney, J. P.; Gregonis, D. E.; Imhof, R.; Itoh, I.; Jahngen, E.; Scott, A. I.; Chan, W. K. *J. Am. Chem. Soc.* **1976**, *97*, 5014.
(16) Orru, A. V. A.; Mayer, S. F.; Kroutil, W.; Faber, K. *Tetrahedron* **1998**, 859.

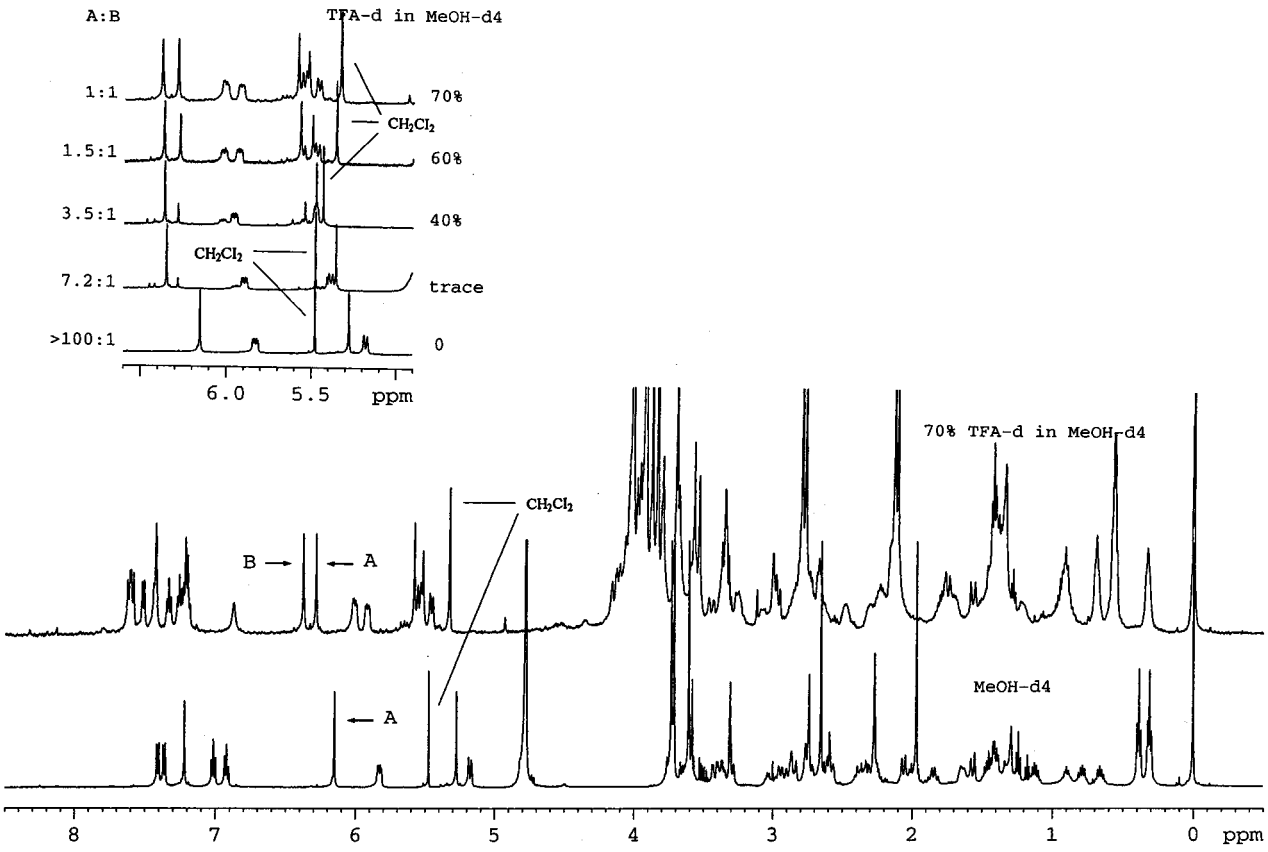


Figure 2. NMR spectra with increasing amounts of TFA of 16a′-*homo*-leurosidine atropisomers **8a** in MeOH-d_4 and 1:1 **8a** and **8b** in 70% TFA in MeOH-d_4.

treatment of the tosylate **40** with DBU provided the requisite epoxide **41** (96%). However, a diastereoselective opening of this epoxide, under the reported conditions, gave only an 86% de and a 42% yield of diol products.

Further exploration of this epoxide opening eventually led to the discovery that sulfuric acid (3 wt %) adsorbed on silica gel suspended in acetone, drying of the adsorbent, and a 10 min contact time with the epoxide **41**, provided the desired C-20 inverted diol **42** and its epimer **39** in a ratio of 31:1 (94% de) and 64% yield, together with 14% of the C-20 inverted acetonide **43** corresponding to the diol **42**.

The diol **42** was protected as its acetonide **43**, and this tetracyclic diester, after selective reduction to the alcohol ester **44**, could then be subjected to a ring expansion sequence (**44**−**48**) analogous to the one used above in the synthesis of 16a′-*homo*-leurosidine. In contrast to that sequence, only a 5:1 (by NMR, rather than 16:1) ratio of ring-expanded product **48** to thiomethyl isomer **49** was obtained on nucleophilic opening of the cyclopropane intermediate **47**. In retrospect, this suggests that the preceding inversion of the oxygen function at C-20 should have been postponed until after the ring expansion had been performed.

It may be noted that in a model tetracyclic compound **50** with a phenyl rather than the acetonide substituent, a 23:1 ratio of ring expanded product **51** to nonexpanded thioether product **52** was obtained (Scheme 6).

The thioether products **48** and **49** were not readily separated by chromatography and, consequently, separation of the isomeric series was best achieved after the following desulfurization. Treatment with tributyltin hydride and removal of the Cbz protecting group from the products **53** and **54** provided the secondary amines **55** and **56.**

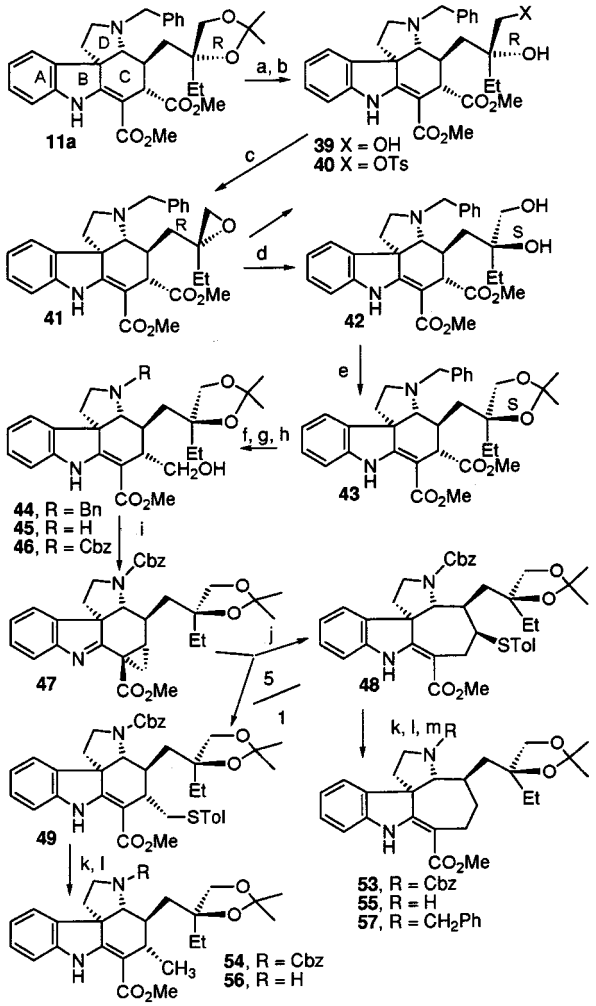
N^b-Benzylation of the major secondary amine **55** resulted in an overall slight improvement of yield in the reaction sequence **48** to **57 (**41% vs 38%) compared to the corresponding one leading to 16a′-*homo*-leurosidine, and the coupling reaction sequence with vindoline (Scheme 7), followed by acetonide hydrolysis (**57** to **59**, 37% vs 26% overall), could also be improved over the earlier sequence.

Formation of a primary tosylate **60** (54%) and its cyclization gave the epoxide **61** (94%). On heating of this epoxide in methanol, a quaternary salt **62** was formed. Its CD spectrum with a negative ellipticity at 299 nm (−21) was consistent with formation of a diastereomer with the piperidine ring D′ configuration corresponding to the unnatural VLB-type atropisomeric conformation.[3]

The same CD spectrum was obtained with the quaternary salt **62** obtained by heating the tosylate **60** in methanol, aparently again through the intermediate formation of epoxide **61**, since direct cyclization of the tosylate should have given the piperidine ring D′ inverted configuration.[3]

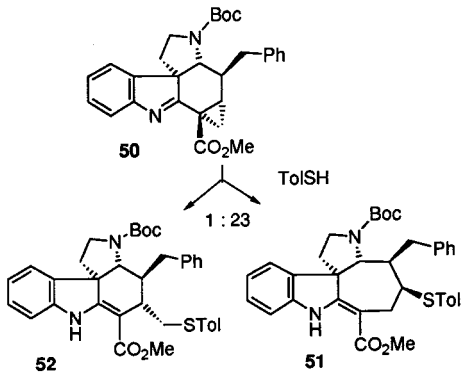
Debenzylation of either quaternary amonium product by hydrogenolysis gave the same tertiary amine product. Only one product could be seen by TLC or on a variety of HPLC columns but, remarkably, its NMR spectrum in $CDCl_3$ indicated a 2.3:1.0 mixture of two components at room temperature. That a mixture of two atropisomers **5b** and **5a** had been generated was supported by a CD spectrum, which displayed a weak positive ellipticity at 299 nm, in agreement with a preponderance of a natural

Scheme 5[a]



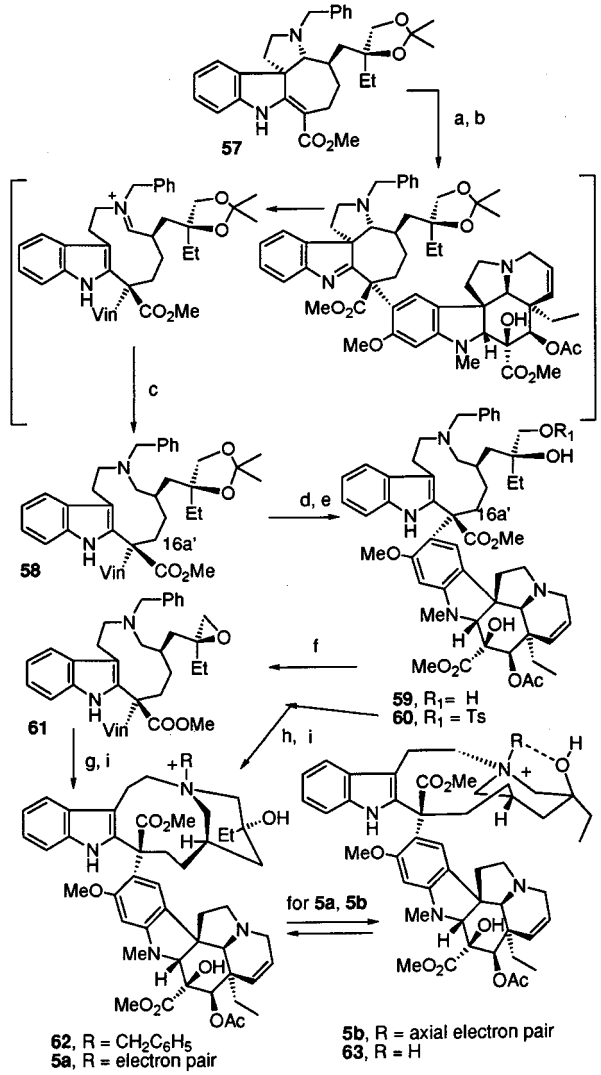
[a] Key: (a) MeOH/10% HCl, 15 min reflux, 99%; (b) Ts_2O, Et_3N, DMAP, CH_2Cl_2, 5 h, 99%; (c) DBU, THF, 6 h, 96%; (d) 3% H_2SO_4 on SiO_2, dioxane−H_2O, 10 min, 94% de, 64% yield, and 14% **43**; (e) 2,2-dimethoxypropane, C_6H_6, cat. TsOH, 2 h refl., 96%; (f) DIBALH, THF, 0 °C, 1 h, 82%; (g) 10% Pd/C, NH_4CHO_2, MeOH, 2 h reflux; (h) CbzCl, $NaHCO_3$, aqueous acetone, 0 °C, 20 min, 85% from **44**; (i) Ts_2O, Et_3N, DMAP, CH_2Cl_2, 5 h, DBU, 24 h, 92%; (j) thiocresol, 110 °C, 2 h, 99% **48** and **49**; (k) BUT_3SnH, AIBN, C_7H_8, 24 h reflux, 75%; (l) PdOH/C, H_2, Et_3N, EtOAc, 1 h; (m) BnBr, K_2CO_3, acetone, 15 h, 55% from **53**.

Scheme 6



VLB-like atropisomer.[3] The relative abundance of the atropisomers showed a small change in going from solvent $CDCl_3$ to CD_3OD (2.3:1 to 3.0:1.0) and a marked decrease of the minor conformer **5a** with decreasing temperature over a temperature range of +25 to −30 °C (3.0:1.0 to 8.8:1.0). On incremental addition of trifluoroacetic acid (Figure 3), the mixture of atropisomers **5a** and **5b** was converted to a single salt **63**. For comparison, analogous spectra with addition of TFA to vinblastine are shown in Figure 4. The CD spectrum of the salt **63** was consistent with an atropisomer analogous to that of natural vinblastine.[3] However, its NMR spectrum showed the C-18 and C-18′ methyl triplets upfield (in the region found with vindoline and numerous D′-*seco*-compounds) rather than corresponding to VLB (δ 0.82, 0.89), suggesting a different environment for the ethyl substituents.

Scheme 7[a]



[a] Key: (a) *t*-ButOCl, Et_3N, 0 °C; (b) vindoline, −10 °C, $AgBF_4$; (c) KBH_4, dry HOAc, 0 °C; (d) 10% HCl, 15 min reflux overall 37% **59** from **57**; (e) Ts_2O, Et_3N, 54%; (f) DBU, 16 h, 94%; (g) MeOH, 16 h reflux; (h) MeOH, 23 h reflux; (i) Pd/C, H_2, MeOH, 0 °C, 83% overall.

Biological Results. Vinblastine-like biological activity, i.e., inhibition of tubulin polymerization and cytotoxicity, was found to depend critically on the nature of C-20′ substitution in VLB congeners.[17] Thus, leurosidine, the C-20′ epimer of VLB, is inactive while 20′-deoxy VLB retains most of the potency and 20′-deoxyleurosidine is

(17) Borman, L. S.; Kuehne, M. E. *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1990; Vol. 37, p 133.

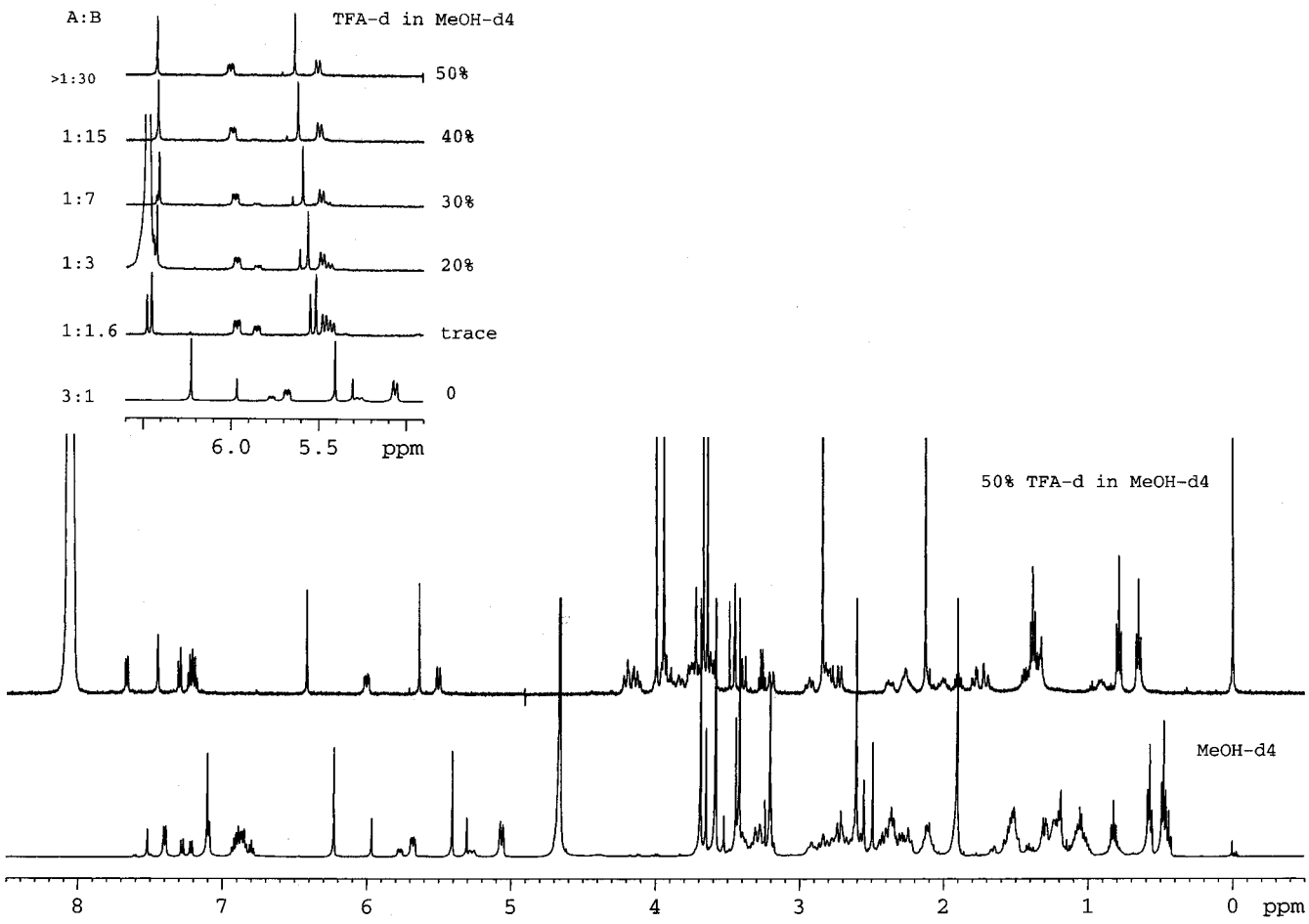


Figure 3. NMR spectra of 16a′-*homo*-vinblastine **5a** and **5b** with increasing amounts of TFA.

only somewhat less active than its epimer, but the C-20′ unsubstituted congener is much less potent. Since NMR spectra indicated (above) that the C-20′ environment was altered in 16a′-*homo*-vinblastine relative to VLB, it was of interest to test its biological activity. No inhibition of tubulin polymerization nor L1210 cytotoxicity were found with **5a**/**5b**.

Since leurosidine (20′-*epi*-vinblastine) does not inhibit tubulin polymerization at concentrations below 1×10^{-5} M,[17] and since the ring D′ inverted atropisomers of vinblastine-type compounds do not show such VLB-like activity[3] or cytotoxicity with L1210 leukemia cells,[3] it was not surprising that the methanesulfonate salt of 16a′-*homo*-leurosidine (**8a**) also lacked these biological activities below 1×10^{-5} M concentrations.

Experimental Section

A corresponding section containing full ^{1}H and ^{13}C NMR, IR, UV, MS, and HRMS data for all compounds is provided with the Supporting Information.

(3a*R*,4*S*,5*S*,11b*S*)-Dimethyl 3-Benzyl-2,3,3a,4,5,7-hexahydro-4-[(2*R*)-2-ethyl-2,3-(isopropylidenedioxy)propyl]-1*H*-pyrrolo[2,3-*d*]carbazole-5,6-dicarboxylate (11a) and Its Epimers (3a*S*,4*R*,5*R*,11b*R*)-11b, (3a*R*,4*S*,5*R*,11b*S*)-11c, and (3a*S*,4*R*,5*S*,11b*R*)-11d. The tetrahydro-β-carboline **9**[7] (24.090 g, 63.4 mmol), 14.150 g (76.08 mmol) of (4*R*)-ethyl-4,5-dihydroxypentanal acetonide (**10**),[1] and 7.560 g of silica gel, in a 250 mL beaker, were brought to 130 °C and vigorously stirred for 3 h. The cooled mixture was taken up in 250 mL of dichloromethane and 50 mL of methanol, and the silica gel was removed by filtration. After addition of 0.950 g (25.00 mmol) of sodium borohydride to reduce the excess aldehyde, and stirring for 10 min at 0 °C, the solution was poured into 300 mL of water. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (3 × 200 mL). The combined organic extracts were dried over magnesium sulfate. Concentration and chromatography (ethyl acetate/hexane 1:3) gave 22.240 g (62.6%) of an inseparable mixture of two isomers **11a** and **11b** in a 5.0:1 ratio ($[\alpha]^{25}_D$ +98.5 (*c* 0.41, CH_2Cl_2)) and 6.550 g (18.5%) of an inseparable mixture of two isomers **11c** and **11d** in a 1.4:1 ratio ($[\alpha]^{25}_D$ −44.6 (*c* 0.37, CH_2Cl_2)). The ratios of **11a** to **11b** and **11c** to **11d** were determined by ^{1}H NMR by integration of the doublet at δ 4.29 (**a**), 4.21 (**b**), 4.35 (**c**), and 4.25 (**d**), respectively. The pure isomer **11a** (18.060 g, 50.9%) was effectively separated from **11b** by repeating the following procedure several times: the mixture of **11a** and **11b** was heated at reflux for 20 min in 20 times of petroleum (60−90 °C), cooled to room temperature, filtered, and washed with hot petroleum to give isomer **11a**. For isomer **11a**: TLC R_f 0.55 (silica gel, ethyl acetate−hexane 1:3, CAS, blue); mp 195−196 °C; $[\alpha]^{25}_D$ +194.7 (*c* 1.20, CH_2Cl_2).

For isomer **11b**: TLC R_f 0.55 (silica gel, ethyl acetate−hexane 1:3, CAS, blue).

Heating a sample of isomers **11c** and **11d** at 150 °C for 24 h resulted in a conversion to predominant isomers **11a** and **11b**, as well as decomposition products.

(3a*R*,4*S*,5*S*,11b*S*)-Methyl 3-Benzyl-2,3,3a,4,5,7-hexahydro-4-[(2*R*)-2-ethyl-2,3-(isopropylidenedioxy)propyl]-1*H*-pyrrolo[2,3-*d*]carbazole-5-hydroxymethyl-6-carboxylate (14). To a solution of 10.00 g (17.86 mmol) of the ester **11a** in 200 mL of dry THF, under argon, was added dropwise 89 mL of 1 M diisobutylaluminum hydride in hexane, at 0 °C, over 45 min. The reaction mixture was allowed to warm to room temperature and stirred for another 3 h. After being

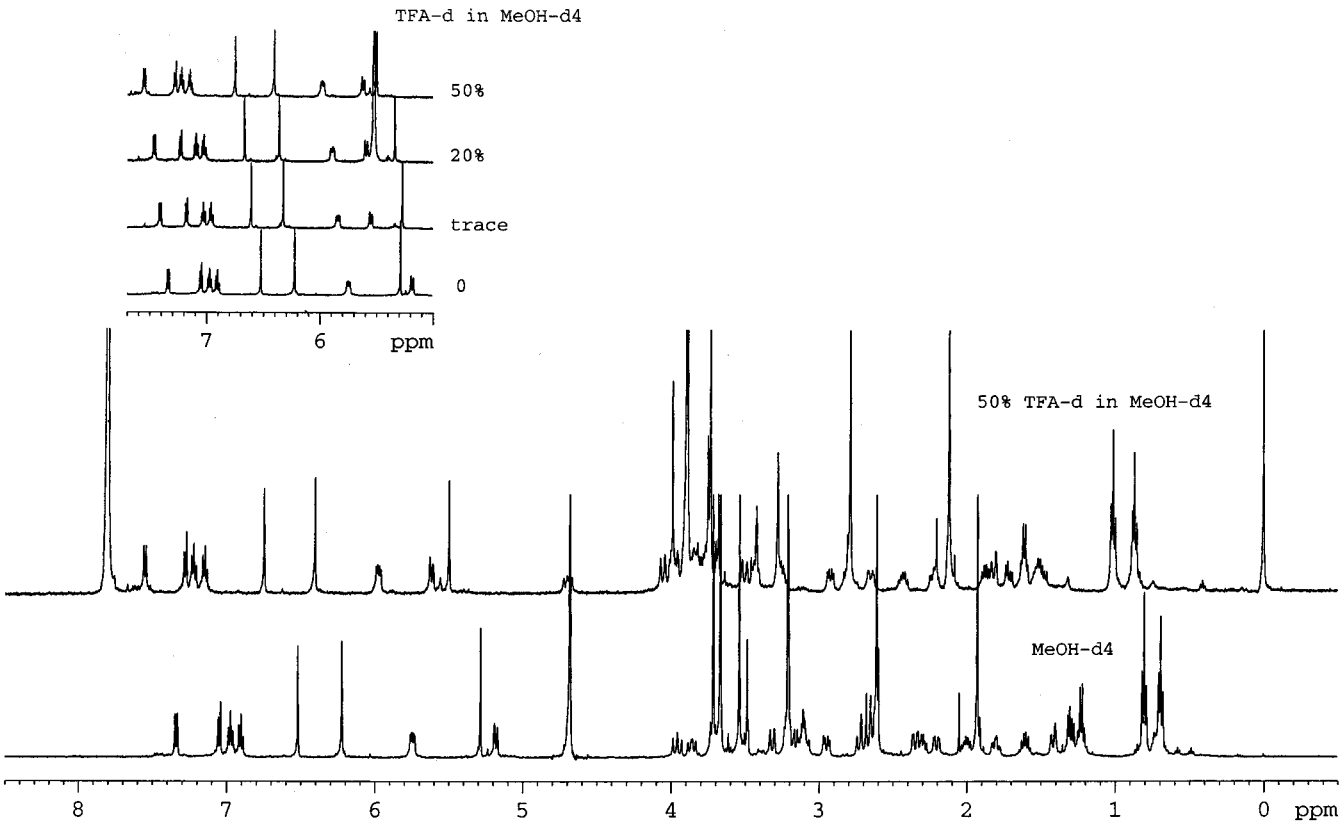


Figure 4. NMR spectra of vinblastine (**1b**) with increasing amounts of TFA.

quenched with methanol at 0 °C, the reaction mixture was added to 200 mL of 1 M NaOH solution and shaken. The organic layer was separated, and the aqueous layer was extracted with ethyl ether (3 × 100 mL). The combined organic extracts were washed with brine (2 × 50 mL), dried with powdered anhydrous $MgSO_4$ for 5 h, and then filtered through Celite 545. Concentration and chromatography (1:2 ethyl acetate−hexanes) gave 8.042 g (84.9%) of the title alcohol: TLC R_f 0.43 (silica gel, 1:2 ethyl acetate−hexanes, CAS, blue); $[\alpha]^{25}_D$ +279.2 (*c* 0.92, CH_2Cl_2).

(3a*R*,4*S*,5*S*,11b*S*)-Methyl 2,3,3a,4,5,7-Hexahydro-4-[(2*R*)-2-ethyl-2,3-(isopropylidenedioxy)propyl]-1*H*-pyrrolo[2,3-*d*]carbazole-5-hydroxymethyl-6-carboxylate (15). A solution of 7.103 g (13.35 mmol) of tertiary amino alcohol **14**, 1.412 g of 10% palladium on carbon, and 4.195 g (66.59 mmol) of ammonium formate in 60 mL of methanol and 30 mL of ethyl acetate was heated at reflux for 2 h. The reaction mixture was filtered through Celite 545 and concentrated to afford crude product, which was purified by chromatography (5:1 ethyl acetate−hexanes) to give 5.223 g (88.5%) of secondary amine **15**: TLC R_f 0.36 (silica gel, 5:1 ethyl acetate−hexanes, CAS, blue); $[\alpha]^{25}_D$ +364.2 (*c* 1.83, CH_2Cl_2).

(3a*R*,4*S*,5*S*,11b*S*)-Methyl 3-Benzyloxycarbonyl-2,3,-3a,4,5,7-hexahydro-4-[(2*R*)-2-ethyl-2,3-(isopropylidene dioxy)propyl]-1*H*-pyrrolo[2,3-*d*]carbazole-5-hydroxymethyl-6-carboxylate (16) and (3a*R*,4*S*,5*S*,11b*S*)-Methyl 3-Benzyloxycarbonyl-2,3,3a,4,5,7-hexahydro-4-[(2*R*)-2-ethyl-2,3-(isopropylidenedioxy)propyl]-1*H*-pyrrolo[2,3-*d*]carbazole-5-benzyloxycarbonyloxymethyl-6-carboxylate (17). To a solution of 6.249 g (14.14 mmol) of amine **15** and 0.363 g (42.42 mmol) of sodium hydrogencarbonate in 50 mL of 95% aqueous acetone was added a solution of 0.883 g (15.55 mmol) of benzyl chloroformate in 5 mL of acetone at 0 °C over 10 min. After addition, the reaction mixture was stirred for another 10 min and concentrated. The residue was dissolved in 50 mL of dichloromethane, the solution was washed with water (2 × 20 mL), dried and concentrated. Chromatography (eluted with 1:2 ethyl acetate−hexanes, then with 1:1 ethyl acetate−hexanes) gave 7.696 g (94.5%) of N^b-Cbz derivative **16** and 0.334 g (4.1%) of N^b,*O*-di-Cbz derivative **17**. For **16**: TLC R_f 0.62 (silica gel, 1:1 ethyl acetate−hexanes); $[\alpha]^{25}_D$ +170.4 (1.88, CH_2Cl_2).

For **17**: TLC R_f 0.62 (silica gel, 1:2 ethyl acetate−hexanes); $[\alpha]^{25}_D$ +102.4 (*c* 0.17, CH_2Cl_2).

(3a*R*,4*S*,5*S*,6*R*,11bS)-Methyl 3-Benzyloxycarbonyl-2,3,-3a,4,5,7-hexahydro-4-[(2*R*)-2-ethyl-2,3-(isopropylidenedioxy)propyl]-1*H*-pyrrolo[2,3-*d*]carbazole-5,6-cyclopropano-6-carboxylate (19). *p*-Toluenesulfonic anhydride (6.692 g, 20.53 mmol) was added to a solution of alcohol **16** (11.838 g, 20.53 mmol), triethylamine (4.150 g, 41.10 mmol), and 4-(dimethylamino)pyridine (0.122 g, 1.00 mmol) in 40 mL of dry dichloromethane. After being stirred for 1 h, another portion of *p*-toluenesulfonic anhydride (3.350 g, 10.28 mmol) was added, and the mixture was stirred for 2 h. At this stage, all of alcohol **16** had been converted to its tosylated derivative **18** and to a small portion of cyclopropane compound **19**. Isolation and purification of the tosylate **18** was not attempted because compound **18** was not stable on storage.

1,8-Diazabicyclo[5,4,0]undec-7-ene (6.247 g, 41.10 mmol) was added to the above reaction mixture, and the reaction mixture was stirred for 12 h. Concentration and chromatography (1:1 ethyl acetate−hexanes) gave 10.441 g (91.2%) of the cyclopropane **19**: TLC R_f 0.45 (silica gel, 1:1 ethyl acetate−hexanes, CAS, blue); $[\alpha]^{25}_D$ +189.0 (*c* 0.92, CH_2Cl_2).

(1*S*,5*R*,6*R*,7*S*)-4-Benzyloxycarbonyl-4,11-diaza-6-((1(*R*)-ethyl-3,3-dimethyl(2,4-dioxalanyl))methyl)-9-(methoxycarbonyl)-7-(methylphenylthio)tetracyclo[8.7.0.0^{1,5}.0^{12,17}]-heptadeca-9,12(13),14,16-tetraene-4-carboxylate (20) and (3a*R*,4*S*,5*S*,11b*S*)-Methyl 3-Benzyloxycarbonyl-2,3,3a,4,5,7-hexahydro-4-[(2*R*)-2-ethyl-2,3-(isopropylidenedioxy)-propyl]-1*H*-pyrrolo[2,3-*d*]carbazole-5-[(4-methylphenylthio)-methyl]-6-carboxylate (21). Under argon, a mixture of cyclopropane **19** (2.683 g, 4.81 mmol) and thiocresol (1.789 g, 14.43 mmol) was heated to 110 °C for 1.5 h. TLC then showed that no starting material remained. The mixture was subjected to flash chromatography (silica gel, 1:3 ethyl acetate−hexanes)

to afford 3.211 g (97.9%) of a mixture of thioethers **20** and **21** in a 16:1 ratio. Analytical samples of **20** and **21** were obtained by preparative layer chromatography. For **20**: TLC R_f 0.31 (silica gel, 1:3 ethyl acetate−hexanes, CAS, blue); $[\alpha]^{25}_D$ +271.4 (*c* 0.52, CH_2Cl_2).

For **21**: TLC R_f 0.34 (silica gel, 1:3 ethyl acetate−hexanes, CAS, blue); $[\alpha]^{25}_D$ +206.7 (*c* 0.44, CH_2Cl_2).

(1*S*,5*R*,6*R*)-Phenylmethyl 4,11-Diaza-6-((1(*R*)-ethyl-3,3-dimethyl(2,4-dioxalanyl))methyl)-9-(methoxycarbonyl)-tetracyclo[8.7.0.0^{1,5}.0^{12,17}]heptadeca-9,12(13),14,16-tetraene-4-carboxylate (22). A solution of thioether **20** (3.358 g, 4.92 mmol), tributyltin hydride (4.291 g, 14.75 mmol), and 2,2′-azobisisobutyronitrile (0.889 g, 5.42 mmol) in 60 mL of toluene was heated at reflux, under argon, for 28 h. Concentration, chromatography (1:3 ethyl acetate−hexanes), and recrystallization from hexanes gave 2.071 g (75.1%) of tetracyclic ester **22**: TLC R_f 0.38 (silica gel, 1:3 ethyl acetate−hexanes, CAS, blue); mp 131−132 °C; $[\alpha]^{25}_D$ +47.2 (*c* 0.53, CH_2Cl_2).

(1*S*,5*R*,6*R*)-Methyl 4,11-Diaza-6-((1(*R*)-ethyl-3,3-dimethyl(2,4-dioxalanyl))methyl)tetracyclo[8.7.0.0^{1,5}.0^{12,17}]-heptadeca-9,12(13),14,16-tetraene-9-carboxylate (23) and (5*R*)-Methyl 7,17-Diaza-5-((1-ethyl-3,3-dimethyl(2,4-dioxalanyl))methyl)tricyclo[8.7.0.0^{11,16}]heptadeca-1(10),6,11(16),12,14-pentaene-2-carboxylate (24). A solution of 1.120 g (2.00 mmol) of Cbz-amide **22**, 0.303 g (3.00 mmol) of triethylamine in 20 mL of ethyl acetate, and 0.121 g (0.20 mmol) of 10% palladium on carbon was stirred under a hydrogen atmosphere for 1 h. Filtration through Celite 545, concentration, and chromatography (10:1 ethyl acetate−hexanes) gave 0.621 g (72.5%) of amine **23** and 0.121 g (14.1%) of *seco*-imine **24**. For **23**: TLC R_f 0.38 (silica gel, 10:1 ethyl acetate−hexanes, CAS, blue).

(1*S*,5*R*,6*R*)-Methyl 4-Benzyl-4,11-diaza-6-((1(*R*)-ethyl-3,3-dimethyl(2,4-dioxalanyl))methyl)tetracyclo-[8.7.0.0^{1,5}.0^{12,17}]heptadeca-9,12(13),14,16-tetraene-9-carboxylate (7). To a suspended solution of 0.821 g (1.93 mmol) of the amine **23**, 0.404 g (4.00 mmol) of triethylamine, and 1.104 g (8.00 mmol) of potassium carbonate in 20 mL of dry acetone was added 0.376 g (2.21 mmol) of benzyl bromide. After 10 h, the reaction mixture was partitioned between 30 mL of water and 30 mL of dichloromethane. The organic layer was separated, and the aqueous layer was washed with dichloromethane (2 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. The residue was applied to a silica gel column and eluted with 1:5 ethyl acetate−hexanes to afford 0.719 g (70.2%) of N^b-benzylamine **7**: TLC R_f 0.38 (silica gel, 1:3 ethyl acetate−hexanes, CAS, blue); $[\alpha]^{25}_D$ +324.5 (*c* 0.87, CH_2Cl_2).

(2*S*,5*R*)-Methyl 7,17-Diaza-5-(2(*R*)-ethyl-2,3-dihydroxypropyl)-7-benzyltricyclo[8.7.0.0^{11,16}]heptadeca-1(10),6,-11(16),12,14-pentaene-2-(10-vindolinyl)-2-carboxylate (31). To an ice-cooled solution of 0.685 g (1.33 mmol) of tetracyclic amine **7** and 0.163 g (1.61 mmol) of triethylamine in 10 mL of dry dichloromethane, under argon, was added dropwise 0.158 g (1.45 mmol) of *tert*-butylhypochlorite, over 5 min. The reaction mixture was stirred for another 10 min at 0 °C, diluted with 60 mL of dichloromethane, and washed with brine (2 × 20 mL). The organic phase was dried and concentrated under vacuum to afford chlorinated product **26**, which was pure enough for the next step.

To the above chlorinated product **26**, under argon, in an ice-cooled three-neck round-bottom flask equipped with a dropping funnel, distillation head, and septa, was added 0.544 g (1.19 mmol) of vindoline (**25**) in 50 mL of dry acetone by syringe, followed by addition of 0.356 g (2.66 mmol) of tetrafluoroboric acid−dimethyl ether complex in one portion. After 5 min, a solution of 0.519 g (2.66 mmol) of silver tetrafluoroborate in 5 mL of dry acetone was added dropwise to the ice-cooled solution, over 10 min. The reaction mixture was shielded from light and allowed to warm to room temperature. After being stirred for 20 min, the reaction mixture was connected to a high vacuum line to remove acetone, with a dry ice trap, to give, as a dark-brown foam, the imine **27**.

The above brown foam (**27**) was dissolved in 10 mL of acetic acid (dried with triacetyl borate), and 0.718 g (13.30 mmol) of potassium borohydride was added in portions over 30 min at 0 °C. The reaction mixture was poured into crushed ice, and the resulting solution was made strongly basic with concentrated ammonium hydroxide. Extraction with dichloromethane (3 × 40 mL), drying ($MgSO_4$), and concentration gave a white foam. Chromatography (silica gel, ethyl acetate) afforded the crude acetonide product **31** (0.406 g) and a borane adduct **32a** (0.102 g) of the corresponding diol, contaminated by vindoline and some impurity, which could not be removed at this step. For **31**: TLC R_f 0.52 (silica gel, ethyl acetate, CAS, brown). For **32a**: TLC R_f 0.45 (silica gel, ethyl acetate, CAS, brown).

The crude acetonide compound **31**, containing some borane complex **32a**, in 15 mL of methanol and 8 mL of 10% aqueous hydrochloric acid, was heated at reflux for 15 min. After removing most of the methanol under reduced pressure, the solution was basified with concentrated ammonium hydroxide and then extracted with dichloromethane (3 × 30 mL). The organic phase was dried and concentrated. Chromatography (silica gel, 10:1 ethyl acetate−methanol) gave 0.259 g (22% yield based on vindoline) of diol **32**. For **32**: TLC R_f 0.42 (silica gel, 10:1 ethyl acetate−methanol, CAS, brown); $[\alpha]^{25}_D$ −17.3 (*c* 0.42, CH_2Cl_2).

Hydrolysis of the crude borane complex **32a** with 10 mL of methanol and 4 mL of 10% hydrochloric acid afforded 0.045 g (4% yield based on vindoline) of diol **32**. Spectra for this sample matched those obtained above.

(2*S*,5*R*)-Methyl 5-((1(*R*)-Ethyl-3,3-dimethyl(2,4-dioxalanyl))methyl)-6-hydroxy-2-(3-(2-(benzylamino)ethyl)indol-2yl)-2-(10-vindolinyl)hexanoate (29) and Its *p*-Toluenesulfonamide 30. To a solution of the chlorinated product **26** (0.226 g, 0.41 mmol) and 0.178 g (0.39 mmol) of vindoline in 30 mL of dry acetone, under argon, and stirred in an ice bath, was added 0.110 g (0.82 mmol) of tetrafluoroboric acid−dimethyl ether complex in one portion. After 5 min, a solution of 0.519 g (2.66 mmol) of silver tetrafluoroborate in 5 mL of dry acetone was added dropwise, over 10 min. The reaction mixture was shielded from light and stirred for another 20 min. After addition of 20 mL of 10% ammonium hydroxide, the solution was extracted with CH_2Cl_2 (2 × 20 mL). The extracts were dried ($MgSO_4$) and concentrated to give a binary indole-indoline product as a white foam (**28**).

To the above coupling product (**28**), in 5 mL of acetic acid, was added 0.221 g (4.10 mmol) of potassium borohydride, in portions over 10 min, at 0 °C. The reaction mixture was poured into crushed ice and the resulting solution was made strongly basic with concentrated ammonium hydroxide. Extraction with dichloromethane (3 × 20 mL), drying ($MgSO_4$), and concentration gave a white foam. Chromatography (silica gel, 10:2 ethyl acetate−methanol) afforded 0.284 g (73.6% yield based on vindoline) of amino alcohol **29**. For **29**: TLC R_f 0.27 (silica gel, 10:2 ethyl acetate−methanol, CAS, brown); $[\alpha]^{25}_D$ −28.5 (*c* 0.90, CH_2Cl_2).

To a stirred solution of 0.087 g (0.09 mmol) of amino alcohol **29** and 0.018 g (0.18 mmol) of triethylamine in 8 mL of dry dichloromethane was added 0.035 g (0.11 mmol) of *p*-toluenesulfonic anhydride. The reaction mixture was stirred for 1 h. Concentration and chromatography (10:1 ethyl acetate−methanol) gave 0.079 g (76.9%) of tosyl amide **30**: TLC R_f 0.35 (silica gel, 10:1 ethyl acetate−methanol, CAS brown); $[\alpha]^{25}_D$ −24.6 (*c* 0.11, CH_2Cl_2).

(2*S*,5*R*)-Methyl 7,17-Diaza-5-(2(*R*)-ethyl-2-hydroxy-3-tosyloxypropyl)-7-benzyltricyclo[8.7.0.0^{11,16}]heptadeca-1(10),6,11(16),12,14-pentaene-2-(10-vindolinyl)-2-carboxylate (33) and Its Vindolinyl 16-*O*-Tosylate (34). To a stirred solution of 0.187 g (0.20 mmol) of diol **32** and 0.040 g (0.40 mmol) of triethylamine in 10 mL of dry dichloromethane was added 0.078 g (0.24 mmol) of *p*-toluenesulfonic anhydride. The reaction mixture was kept at 0 °C for 12 h. Concentration and chromatography (silica gel, ethyl acetate) gave 0.092 g (55.4% yield based on the diol **32** used) of monotosylate compound **33**, 0.052 g (27.4% yield based on the diol **32** used) of ditosylate compound **34**, and recovered 0.044 g of diol **32**. For **33**: TLC R_f 0.35 (silica gel, ethyl acetate, CAS, brown); $[\alpha]^{25}_D$ −6.0 (*c* 0.24, CH_2Cl_2).

16a′-*homo*-Leurosidine (8a) and Its Vindolinyl (C-16) Deacylation Product 37. A solution of 0.090 g (0.08 mmol) of tosylate **33** in 10 mL of dry methanol was heated at reflux under argon for 23 h, during which time the tosylate **33** gradually changed to the quaternary salt **35** and its deacylation product **36**: TLC R_f 0 (ethyl acetate) or 0.25 (1:2 methanol−dichloromethane). The reaction mixture was cooled to 0 °C and stirred with 20 mg of 10% palladium on carbon under a hydrogen atmosphere for 10 min. The reaction mixture was filtered through a pad of Celite 545 and concentrated. Chromatography (10:2 ethyl acetate−methanol) gave 0.045 g (68.2%) of compound **8a** and 0.015 g (24.0%) of the corresponding deacylated compound **37**. For **8a**: TLC R_f 0.44 (silica gel, 10:2 ethyl acetate−methanol, CAS, blue); $[\alpha]^{25}_D$ +6.52 (*c* 0.27, CH_2Cl_2).

For **37**: TLC R_f 0.32 (silica gel, 10:2 ethyl acetate−methanol, CAS, brown); $[\alpha]^{25}_D$ +46.3 (*c* 0.27, CH_2Cl_2).

(2*S*,5*R*)-Methyl 7,17-Diaza-5-(2(*R*)-ethyl-2,3-epoxypropyl)-7-benzyltricyclo[8.7.0.0^{11,16}]heptadeca-1(10),6,-11(16),12,14-pentaene-2-(10-vindolinyl)-2-carboxylate (38) and Its Cyclization. A solution of tosylate **33** (8.2 mg, 0.0075 mmol) and 1,8-diazabicyclo[5,4,0]undec-7-ene (2.2 uL, 0.015 mmol) in 0.5 mL of dry tetrahydrofuran was stirred overnight. Concentration and chromatography (ethyl acetate) gave 6.4 mg (92%) of epoxide **38**: TLC R_f 0.39 (silica gel, ethyl acetate, CAS, brown).

Under argon, a solution of epoxide **38** (6.4 mg, 0.007 mmol) in 5 mL of dry MeOH was heated at reflux for 15 h. The epoxide gradually changed to the quaternary salt **35**: TLC R_f 0 (ethyl acetate), 0.25 (1:2 methanol−dichloromethane); CD data (7.0×10^{-4}M in methanol) λ (ellipticity) 224 (+45), 252 (+31), 275 (−14), 311 (−2). The reaction mixture was cooled to 0 °C and hydrogenated with 2 mg of 10% palladium on carbon under a hydrogen atmosphere for 20 min. Filtration through Celite 545 and chromatography (10:2 ethyl acetate−methanol) gave 4.5 mg (78%) of 16a′-homoleurosidine **8a** and trace of deacylated 16a′-homoleurosidine **37**.

(3a*R*,4*S*,5*S*,11b*S*)-Dimethyl 3-Benzyl-2,3,3a,4,5,7-hexahydro-4-[(2*R*)-2-ethyl-2,3-(dihydroxy)propyl]-1*H*-pyrrolo-[2,3-*d*]carbazole-5,6-dicarboxylate (39). A solution of acetonide **11a** (3.300 g, 5.89 mmol) in 90 mL of methanol and 40 mL of 10% hydrochloric acid was heated at reflux for 15 min. After removal of most of the methanol, the mixture was basified to pH 9 with ammonium hydroxide and extracted with dichloromethane (3 × 70 mL). The combined organic layers were washed with brine (40 mL) and dried over magnesium sulfate. Concentration gave 3.065 g (99%) of diol **39**, which was pure enough (TLC) for spectroscopic characterization and for the next step: TLC R_f 0.50 (silica gel, ethyl acetate, CAS, blue); $[\alpha]^{25}_D$ +181.0 (*c* 0.68, CH_2Cl_2).

(3a*R*,4*S*,5*S*,11b*S*)-Dimethyl 3-Benzyl-2,3,3a,4,5,7-hexahydro-4-[(2*R*)-2-ethyl-2-hydroxy-3-tosyloxypropyl]-1*H*-pyrrolo[2,3-*d*]carbazole-5,6-dicarboxylate (40). To a stirred solution of diol **39** (2.510 g, 4.82 mmol), triethylamine (0.869 g, 8.69 mmol), and 4-(dimethylamino)pyridine (0.058 g, 0.48 mmol) in 20 mL of dichloromethane was added *p*-toluensulfonic anhydride (0.944 g, 2.90 mmol) in one portion. Two hours later, another portion of *p*-toluenesulfonic anhydride (0.944 g, 2.90 mmol) was added again and the reaction was continued for another 3 h. Concentration and flash chromatography (ethyl acetate−hexane 1:1) gave 3.206 g (98.7%) of the tosylate **40**: TLC R_f 0.47 (silica gel, ethyl acetate−hexane 1:1, CAS, blue); $[\alpha]^{25}_D$ +155.2 (*c* 0.52, CH_2Cl_2).

(3a*R*,4*S*,5*S*,11b*S*)-Dimethyl 3-Benzyl-2,3,3a,4,5,7-hexahydro-4-[(2*R*)-2-ethyl-2,3-epoxypropyl]-1*H*-pyrrolo[2,3-*d*]-carbazole-5,6-dicarboxylate (41). A solution of tosylate **40** (0.750 g, 1.13 mmol) in 15 mL of dry tetrahydrofuran was stirred with 1,8-diazabicyclo[5.4.0]undec-7-ene (0.257 g, 1.69 mmol) for 8 h. The solvent was evaporated under reduced pressure, and the residue was purified by flash chromatography (ethyl acetate−hexanes 1:2) to afford 0.546 g (96.3%) of epoxide **41**: TLC R_f 0.55 (silica gel, ethyl acetate−hexanes 1:2, CAS blue); $[\alpha]^{25}_D$ +183.9 (*c* 0.27, CH_2Cl_2).

(3a*R*,4*S*,5*S*,11b*S*)-Dimethyl 3-Benzyl-2,3,3a,4,5,7-hexahydro-4-[(2*S*)-2-ethyl-2,3-dihydroxypropyl]-1*H*-pyrrolo[2,3-*d*]carbazole-5,6-dicarboxylate (42) and (3a*R*,4*S*,5*S*,11b*S*)-Dimethyl 3-Benzyl-2,3,3a,4,5,7-hexahydro-4-[(2*S*)-2-ethyl-2,3-(isopropylidenedioxy)propyl]-1*H*-pyrrolo[2,3-*d*]-carbazole-5,6-dicarboxylate (43). (**a**) For the following procedure, concentrated sulfuric acid was employed directly: To a stirred solution of epoxide **41** (0.334 g, 0.67 mmol) in 67 mL of dry dioxane containing 60 μL of water (3.33 mmol) was added concentrated sulfuric acid (0.782 g, 7.98 mmol). The mixture was stirred for 10 min and neutralized with triethylamine (4.030 g, 39.90 mmol). Concentration and flash chromatography (ethyl acetate) gave 0.145 g (41.6%) of a mixture of diols **39** and **42** in a 1:13 ratio (85.7% de), analyzed by ^{1}H NMR with integration of the singlet at δ 3.17 (**39**) and 3.12 (**42**).

(b) For the following procedure, 3 wt % of the concentrated sulfuric acid on silica gel was employed: To a vigorously stirred suspension of silica gel (78.4 g) in acetone was added 3 wt % of concentrated sulfuric acid (24 mmol). The solvent was evaporated, and the silica gel was dried at aspirator vacuum at 40 °C for 2 h. To this silica gel was added 200 mL of dry dioxane containing 180 μL of water (10 mmol). With vigorous stirring, a solution of epoxide **41** (1.004 g, 2.00 mmol) in 5 mL of dioxane was added. The mixture was stirred for 10 min and neutralized with triethylamine (12.120 g, 120 mmol). The silica gel was removed by filtration and was washed with methanol and dichloromethane. Concentration and flash chromatography (first eluting with 1:3 ethyl acetate−hexanes, then eluting with 4:1 ethyl acetate−hexanes) gave 0.670 g (64.4%) of a mixture of diols **39** and **42** in a 1:31 ratio (93.7% de) and 0.152 g (13.6%) of acetonide **43**. Diols **39** and **42** could be separated by preparative thin-layer chromatography.

By employing 6 wt % of concentrated sulfuric acid on silica gel, hydrolysis of epoxide **41** gave 61.7% of a mixture of diols **39** and **42** in a 1:22 ratio (91.3% de) and 12.2% of acetonide **43**.

For the diol **42**: TLC R_f 0.47 (silica gel, ethyl acetate, CAS, blue); $[\alpha]^{25}_D$ +199.1 (*c* 0.22, CH_2Cl_2).

Preparation of Acetonide 43 from Diol 42. A solution of diol **42** (1.200 g, 2.31 mmol) and 2 mL of 2,2-dimethoxypropane in 20 mL of dry benzene was heated at reflux with a catalytic amount of *p*-toluenesulfonic acid for 2 h. The mixture was basified with 0.5 mL of ammonium hydroxide. The solvent was removed under reduced pressure, and the crude product was purified by chromatography (ethyl acetate−hexanes, 1:3) to give 1.244 g (96.1%) of acetonide **43**.

For acetonide **43**: TLC R_f 0.55 (silica gel, ethyl acetate−hexane 1:3, CAS, blue); $[\alpha]^{25}_D$ +150.7 (*c* 1.52, CH_2Cl_2).

(3a*R*,4*S*,5*S*,11b*S*)-Methyl 3-Benzyl-2,3,3a,4,5,7-hexahydro-4-[(2*S*)-2-ethyl-2,3-(isopropylidenedioxy)propyl]-1*H*-pyrrolo[2,3-*d*]carbazole-5-hydroxymethyl-6-carboxylate (44). To a solution of 11.200 g (20.00 mmol) of acetonide **43** in 200 mL of dry THF, under argon, was added dropwise 120 mL of 1 M diisobutylaluminum hydride in hexanes, at 0 °C, over 1 h. The reaction mixture was allowed to warm to room temperature and stirred for another 3 h. After quenching with methanol at 0 °C, the reaction mixture was added to 150 mL of a 1 M NaOH solution, and shaken. The organic layer was separated, and the aqueous layer was extracted with ethyl ether (3 × 100 mL). The combined organic extracts were washed with brine (2 × 50 mL), dried with powdered anhydrous $MgSO_4$ overnight, and then filtered through Celite 545. Concentration and chromatography (ethyl acetate−hexanes 1:2) gave 8.692 g (81.7%) of the title alcohol: TLC R_f 0.40 (silica gel, ethyl acetate−hexanes 1:2, CAS, blue); $[\alpha]^{25}_D$ +195.4 (*c* 0.49, CH_2Cl_2).

(3a*R*,4*S*,5*S*,11b*S*)-Methyl 2,3,3a,4,5,7-Hexahydro-4-[(2*S*)-2-ethyl-2,3-(isopropylidenedioxy)propyl]-1*H*-pyrrolo[2,3-*d*]carbazole-5-hydroxymethyl-6-carboxylate (45) and (3a*R*,4*S*,5*S*,11b*S*)-Methyl 3-(Benzyloxycarbonyl)-2,3,3a,4,-5,7-hexahydro-4-[(2*S*)-2-ethyl-2,3-(isopropylidenedioxy)-propyl]-1*H*-pyrrolo[2,3-*d*]carbazole-5-hydroxymethyl-6-carboxylate (46). A solution of alcohol **44** (7.586 g, 14.26 mmol), 1.520 g of 10% palladium on carbon, and 4.947 g (78.43 mmol) of ammonium formate in 120 mL of methanol and 60 mL of ethyl acetate was heated at reflux for 2 h. The reaction

mixture was filtered through Celite 545 and concentrated to afford crude amine **45**. An analytic sample was obtained by chromatography (ethyl acetate−hexanes 5:1): TLC R_f 0.36 (silica gel, ethyl acetate−hexanes 5:1, CAS, blue); $[\alpha]^{25}_D$ +350.3 (*c* 0.92, CH_2Cl_2).

The above crude amine **45** was dissolved in 90 mL of 90% aqueous acetone. To the solution was added sodium hydrogencarbonate (2.396 g, 28.52 mmol) in one portion, followed by dropwise addition of a solution of benzyl chloroformate (4.121 g, 28.52 mmol) in 5 mL of acetone, at 0 °C over 10 min. After the addition, the reaction mixture was stirred for another 10 min and then concentrated. The residue was dissolved in 50 mL of dichloromethane, and the solution was washed with water (2 × 20 mL), dried, and concentrated. Chromatography (ethyl acetate−hexanes 1:1) gave 6.940 g (84.5% for two steps from alcohol **44**) of Cbz derivative **46**: TLC R_f 0.45 (silica gel, ethyl acetate−hexane 1:1); $[\alpha]^{25}_D$ +170.4 (0.72, CH_2Cl_2).

(3a*R*,4*S*,5*S*,11b*S*)-Methyl 3-Benzyloxycarbonyl-2,3,-3a,4,5,7-hexahydro-4-[(2*S*)-2-ethyl-2,3-(isopropylidenedioxy)propyl]-1*H*-pyrrolo[2,3-*d*]carbazole-5,6-cyclopropano-6-carboxylate (47). *p*-Toluenesulfonic anhydride (4.177 g, 12.81 mmol) was added to a solution of alcohol **46** (6.150 g, 10.67 mmol), triethylamine (2.155 g, 21.34 mmol), and 4-(dimethylamino)pyridine (0.130 g, 1.07 mmol) in 80 mL of dry dichloromethane. After the mixture was stirred for 5 h, 1,8-diazabicyclo[5.4.0]undec-7-ene (3.201 g, 21.34 mmol) was added and the reaction mixture stirred for 24 h. Concentration and chromatography (ethyl acetate−hexanes 1:1) gave 5.495 g (92.3%) of cyclopropane **47**: TLC R_f 0.50 (silica gel, ethyl acetate−hexanes 1:1, CAS, blue); $[\alpha]^{25}_D$ +195.8 (*c* 1.10, CH_2Cl_2).

(1*S*,5*R*,6*R*,7*S*)-4-Benzyloxycarbonyl-4,11-diaza-6-((1(*S*)-ethyl-3,3-dimethyl(2,4-dioxalanyl))methyl)-9-(methoxycarbonyl)-7-(methylphenylthio)tetracyclo[8.7.0.0^{1,5}.0^{12,17}]-heptadeca-9,12(13),14,16-tetraene-4-carboxylate (48) and (3a*R*,4*S*,5*S*,11b*S*)-Methyl 3-Benzyloxycarbonyl-2,3,3a,4,5,7-hexahydro-4-[(2*S*)-2-ethyl-2,3-(isopropylidenedioxy)-propyl]-1*H*-pyrrolo[2,3-*d*]carbazole-5-[(4-methylphenylthio)-methyl]-6-carboxylate (49). Under argon, a mixture of cyclopropane compound **47** (5.197 g, 9.31 mmol) and thiocresol (3.465 g, 27.94 mmol) was heated to 110 °C for 2 h. The mixture was applied to flash chromatography (ethyl acetate−hexanes 1:3) to afford 6.279 g (98.8%) of an inseparable mixture of thioethers **48** and **49** in a 4.7:1 ratio. For **48** (contaminated by **49**): TLC R_f 0.31 (silica gel, ethyl acetate−hexanes 1:3, CAS, blue).

4-*tert*-Butoxycarbonyl-4,11-diaza-6-phenyl-9-(methoxycarbonyl)-7-(methylphenylthio)tetracyclo[8.7.0.0^{1,5}.0^{12,17}]-heptadeca-9,12(13),14,16-tetraene-4-carboxylate (51). Under argon, a mixture of methyl 3-*tert*-butoxycarbonyl-2,3,3a,-4,5,7-hexahydro-4-benzyl-1*H*-pyrrolo[2,3-*d*]carbazole-5,6-cyclopropano-6-carboxylate (**50**), prepared by the methodology used for formation of compound **47**, and thiocresol (0.077 g, 0.60 mmol) was heated to 110 °C for 1.5 h. ^{1}H NMR analysis of the unpurified product showed a 1:23 ratio of thiomethyl ether **52** to ring-expanded product **51** by integration of the indole *N*-H proton at δ 9.25 (**52**) and δ 10.05 (**51**). The reaction mixture was purified by chromatography (ethyl acetate−hexanes, 1:4, on silica gel) to give 0.081 g of pure compound **51** and 0.033 g of a mixture of the two products (total yield 96%). For compound **51**: TLC R_f 0.42 (silica gel, ethyl acetate−hexanes 1:4, CAS, blue).

(1*S*,5*R*,6*R*)-4-Benzyloxycarbonyl-4,11-diaza-6-((1(*S*)-ethyl-3,3-dimethyl(2,4-dioxalanyl))methyl)-9-(methoxycarbonyl)tetracyclo[8.7.0.0^{1,5}.0^{12,17}]heptadeca-9,12(13),14,16-tetraene-4-carboxylate (53) and (3a*R*,4*S*,5*S*,11b*S*)-Methyl 3-Benzyloxycarbonyl-2,3,3a,4,5,7-hexahydro-4-[(2*S*)-2-ethyl-2,3-(isopropylidenedioxy)propyl]-5-methyl-1*H*-pyrrolo[2,3-*d*]carbazole]-6-carboxylate (54). A solution of a mixture of thioethers **48** and **49** in a 4.7:1 ratio (5.523 g, 8.10 mmol containing 1.42 mmol of compound **49** and 6.68 mmol of compound **48**), tributyltin hydride (7.071 g, 24.30 mmol), and 2,2′-azobisisobutyronitrile (1.463 g, 8.91 mmol) in 150 mL of toluene was heated at reflux under argon for 24 h. Concentration and chromatography (ethyl acetate−hexanes 1:3) gave 2.458 g (65.7%) of ring expansion product **53**, 0.538 g of a mixture of **53** and methyl product **54** in a 1.8:1 ratio (containing 0.342 g (9.1%) of compound **53**), and 0.196 g (24.6%) of compound **54**, and recovered 0.654 g of unreacted thioether **49**.

For thioether **49** (contaminated by its desulfurization product **54**): TLC R_f 0.34 (silica gel, ethyl acetate−hexanes 1:3, CAS, blue).

For ring-expansion product **53**: TLC R_f 0.38 (silica gel, ethyl acetate−hexanes 1:3, CAS, blue); mp 131−132 °C; $[\alpha]^{25}_D$ +27.1 (*c* 0.24, CH_2Cl_2).

(1*S*,5*R*,6*R*)-4,11-Diaza-6-((1(*S*)-ethyl-3,3-dimethyl(2,4-dioxalanyl))methyl)-9-(methoxycarbonyl)tetracyclo-[8.7.0.0^{1,5}.0^{12,17}]heptadeca-9,12(13),14,16-tetraene-4-carboxylate (55) and (1*S*,5*R*,6*R*)-4-Phenylmethyl-4,11-diaza-6-((1(*S*)-ethyl-3,3-dimethyl(2,4-dioxalanyl))methyl)-9-(methoxycarbonyl)tetracyclo[8.7.0.0^{1,5}.0^{12,17}]heptadeca-9,12(13),14,16-tetraene-4-carboxylate (57), and (3a*R*,4*S*,5*S*,-11b*S*)-Methyl 2,3,3a,4,5,7-Hexahydro-4-[(2*S*)-2-ethyl-2,3-(isopropylidenedioxy)propyl]-5-methyl-1*H*-pyrrolo[2,3-*d*]carbazole]-6-carboxylate (56). A solution of 2.450 g (4.38 mmol) of Cbz compound **53**, 0.664 g (6.57 mmol) of triethylamine, and 0.470 g (0.34 mmol) of 10% palladium hydroxide on carbon in 40 mL of ethyl acetate was stirred under a hydrogen atmosphere for 1 h. Filtration through Celite 545 and concentration gave crude amine **55**. An analytical sample of **55** was obtained by chromatography (ethyl acetate−triethylamine 10:1). For compound **55**: TLC R_f 0.40 (silica gel, ethyl acetate−triethylamine 10:1, CAS, blue); $[\alpha]^{25}_D$ +361.2 (*c* 0.95, CH_2Cl_2).

To a suspended solution of the above crude amine **55**, 0.885 g (8.76 mmol) of triethylamine, and 1.813 g (13.14 mmol) of potassium carbonate in 40 mL of dry acetone was added 0.794 g (4.64 mmol) of benzyl bromide. After 15 h, the reaction mixture was partitioned between 50 mL of water and 60 mL of dichloromethane. The organic phase was separated, and the aqueous layer was washed with dichloromethane (2 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography (ethyl acetate−hexanes 1:3) to afford 1.231 g (54.5% for two steps from **53**) of N^b-benzylamine **57**: TLC R_f 0.38 (silica gel, ethyl acetate−hexanes 1:3, CAS, blue); $[\alpha]^{25}_D$ +322.5 (*c* 1.00, CH_2Cl_2).

The 5-methyl secondary amine **56** was generated and separated from amine **55** in 88.6% yield (counted from compound **54**) by hydrogenation of a 1.8:1 mixture of compounds **53** and **54**, followed by chromatography (ethyl acetate−triethylamine 10:1).

For 5-methyl secondary amine **56**: TLC R_f 0.50 (silica gel, ethyl acetate−hexanes 10:1, CAS, blue); $[\alpha]^{25}_D$ +347.0 (*c* 1.33, CH_2Cl_2).

(2*S*,5*R*)-Methyl 7,17-Diaza-5-(2(*S*)-ethyl-2,3-dihydroxypropyl)-7-benzyltricyclo[8.7.0.0^{11,16}]heptadeca-1(10),6,-11(16),12,14-pentaene-2-(10-vindolinyl)-2-carboxylate (59). To an ice-cooled solution of 1.595 g (3.09 mmol) of tetracyclic *N*-benzylamine **57**, under argon, and 0.406 g (4.02 mmol) of triethylamine in 10 mL of dry dichloromethane, at 0 °C, was added dropwise 0.371 g (3.71 mmol) of *tert*-butyl hypochlorite over 10 min. The reaction mixture was stirred for another 10 min at 0 °C, diluted with 60 mL of dichloromethane, and washed with brine (2 × 20 mL). The organic phase was dried and concentrated under vacuum to afford chlorinated product, which was pure enough for the next step.

Under argon, a solution of the above chlorinated product and 1.717 g (3.76 mmol) of vindoline, in 70 mL of dry acetone, was added by syringe to a cooled (−10 °C) three-neck round-bottom flask equipped with dropping funnel, distillation head, and septa. Then 1.040 g (7.73 mmol) of tetrafluoroboric acid−dimethyl ether complex was added in one portion. After 5 min, a solution of 1.507 g (7.73 mmol) of silver tetrafluoroborate in 15 mL of dry acetone was added dropwise over 20 min. After being stirred for 1 h at −10 °C and shielded from light, the reaction mixture was connected to a high vacuum line to remove acetone with a dry ice trap to give a dark-brown foam.

The above dark-brown foam was dissolved in 40 mL of dry acetic acid, and 1.672 g (30.90 mmol) of potassium borohydride was added in portions over 30 min at 0 °C. The reaction mixture was poured into crushed ice, and the resulting solution was made strongly basic with concentrated ammonium hydroxide. Extraction with dichloromethane (3 × 40 mL), drying ($MgSO_4$), and concentration gave a white foam. Chromatography (ethyl acetate−methanol 10:1) afforded 2.052 g of crude acetonide **58** contaminated by vindoline and some impurity, which could not be removed at this step, and 0.125 g (4.2%) of the borane adduct of the diol **59**. For compound **58**: TLC R_f 0.65 (silica gel, ethyl acetate−methanol 10:1, CAS, brown); For the borane adduct of **59**: TLC R_f 0.40 (silica gel, ethyl acetate−methanol 10:1, CAS, brown).

The crude acetonide **58** in 80 mL of methanol and 30 mL of 10% aqueous hydrochloric acid was heated at reflux for 15 min. After removal of most of the methanol under reduced pressure, the solution was basified with concentrated ammonium hydroxide and then extracted with dichloromethane (3 × 30 mL). The organic phase was dried and concentrated. Chromatography (ethyl acetate−methanol 10:1) gave 1.183 g (36.8%) of diol **59**.

For **59** (contaminated by inseparable impurity): TLC R_f 0.40 (silica gel, ethyl acetate−methanol 10:1, CAS, brown).

For the borane adduct of **59**: TLC R_f 0.50 (silica gel, ethyl acetate−methanol 10:1, CAS brown); $[\alpha]^{25}_D$ −88.8 (*c* 1.09), CH_2Cl_2).

(2*S*,5*R*)-Methyl 7,17-Diaza-5-(2(*S*)-ethyl-2-hydroxy-3-tosyloxypropyl)-7-benzyltricyclo[8.7.0.0^{11,16}]heptadeca-1(10),6,11(16),12,14-pentaene-2-(10-vindolinyl)-2-carboxylate (60). To a stirred solution of 1.142 g (1.22 mmol) of diol **59** and 0.185 g (1.83 mmol) of triethylamine in 8 mL of dry dichloromethane was added 0.479 g (1.47 mmol) of *p*-toluenesulfonic anhydride. The reaction was stirred for 2 h. Concentration and chromatography (10:10:1 ethyl acetate−dichloromethane−methanol) gave 0.513 g (54.3%) of tosylate **60** and 0.328 g of recovered diol **59**: TLC R_f 0.55 (silica gel, ethyl acetate−dichloromethane−methanol 10:10:1, CAS, brown); $[\alpha]^{25}_D$ −68.2 (*c* 0.17, CH_2Cl_2).

(2*S*,5*R*)-Methyl 7,17-Diaza-5-(2(*S*)-ethyl-2,3-epoxypropyl)-7-benzyltricyclo[8.7.0.0^{11,16}]heptadeca-1(10),6,-11(16),12,14-pentaene-2-(10-vindolinyl)-2-carboxylate (61). A solution of tosylate **60** (0.162 g, 0.15 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.045 g, 0.03 mmol) in 3 mL of dry tetrhydrofuran was stirred for 16 h. Concentration and chromatography (ethyl acetate−dichloromethane−methanol 10:10:1) gave 0.128 g (93.6%) of epoxide **61**: TLC R_f 0.60 (silica gel, ethyl acetate−dichloromethane−methanol 10:10:1, CAS, brown); $[\alpha]^{25}_D$ −91.6 (*c* 0.12, CH_2Cl_2).

Two Atropisomers of 16a′-*homo*-Vinblastine (5a and 5b). A solution of 0.048 g (0.044 mmol) of tosylate **60** in 10 mL of dry methanol was heated at reflux under argon for 23 h, during which time the compound gradually formed a quaternary salt **62**: TLC R_f 0 (ethyl acetate) or 0.15 (1:2 methanol−dichloromethane), CD data (2.2×10^{-3} M in methanol) λ (ellipticity) 231 (−21), 252 (+25), 299 (−21). The reaction mixture was cooled to 0 °C and stirred with 10 mg of 10% palladium on carbon under a hydrogen atmosphere for 20 min. The reaction mixture was filtered through Celite 545 and concentrated. Chromatography (ethyl acetate-methanol 10:1) gave 0.030 g (83.3%) of an inseparable mixture of amine atropisomers **5a** and **5b** in a 1:2.3 ratio (in $CDCl_3$, determined by integration of the triplets of two isomers' methyl groups at 0.46 and 0.57 ppm respectively; a 1.0:3.0 ratio was determined in MeOH-d_4 at room temperature by integration of the singlets of the two isomers' aromatic proton at 5.97 and 6.23 ppm respectively; the ratio of the two isomers was 1.0:4.7 at −10 °C; the ratio of the two isomers was 1.0:8.8 at −30 °C).

An inseparable mixture of atropisomers **5a** and **5b** in a 1.0:2.3 ratio (in $CDCl_3$, but a 1.0:3.0 ratio in MeOH-d_4) was prepared in 83.7% yield from epoxide **61** by heating at reflux in methanol for 13 h to form a quaternary salt **62** (CD data of the salt (1.7×10^{-3} M in methanol) λ (ellipticity) 229 (−35), 254 (+24), 302 (−21)), followed by hydrogenation at 0 °C for 20 min.

For atropisomers **5a** (minor) and **5b** (major): TLC R_f 0.35 (silica gel, ethyl acetate-methanol 10:1, CAS, blue); $[\alpha]^{25}_D$ −50.5 (*c* 0.15, CH_2Cl_2); CD (1.7×10^{-3} M in methanol) λ (ellipticity) 224 (−39), 252 (+8), 313 (+5).

Acknowledgment. This work was supported by the Cancer Institute of the National Institutes of Health through Grant No. R01 CA 12010. We are indebted to Robert Bennett, Patrick Jokiel, and Wenning Dai of our group for low-resolution mass spectra and to Dr. Michael Gross of the Washington University Mass Spectroscopy Resource for high-resolution mass spectra. We thank Mr. Timothy Hefferman for assistance in the cytotoxicity determination, and we are particularly grateful to Dr. Jean Hannart of OMNI CHEM for the gift of vindoline that was used in this study.

Supporting Information Available: A complete Experimental Section containing full ^{1}H and ^{13}C NMR, IR, UV, MS, and HRMS data. Also ^{1}H and ^{13}C NMR spectra, except where marked by parentheses (^{1}H only), for compounds **5a** and **5b** in $CDCl_3$ and in MeOH-d_4 at variable temperature to −50 °C, **7**, **8a**, (**8a** and **8b**), **11a**, (**11a** and **11b**), (**11c** and **11d**), **14**−**16**, (**17**), **19**−**22**, **24**, **29**, **30**, **32**−**34**, **37**, (**38**), **39**−**42**, (**39** + **42**), **43**−**47**, **48** + **49**, **49**, (**51**), **53**, **55**−**57**, and **59**−**61**. CD spectra for **8a** and 1:1 **8a**/**8b, 35**, **62**, **63**, and **5a**,**b**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO000250Y