Syntheses of 5a′-*homo*-Vinblastine and Congeners Designed to Establish Structural Determinants for Isolation of Atropisomers

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

The syntheses of 5a′-*homo*-vinblastine (**3a**) and its C-20′ methyl congener **62a** were achieved. In contrast to vinblastine, these compounds did not allow isolation of atropisomers because of their lower conformational inversion barrier. However, annelation of a six-membered ring to the conformationally mobile D′-piperidine ring provided an isolated atropisomer **81a**, which could be converted to its lower energy conformation **65a** on heating. The 5a′-*homo*-vinblastine congeners **3a**, **62a**, and **65a** showed vinblastine-like inhibition of tubulin polymerization and cytotoxicity to L1210 leukemia cells, albeit at lower potency for the latter activity, than that found with the corresponding compounds in the vinblastine series.

Introduction

In 1991, we reported a practical synthesis of vinblastine (VLB, **1**).[1] In its course it was possible to generate and to isolate a vinblastine atropisomer **2** in which the piperidine ring D′ of the cleavamine moiety is in a conformationally inverted chair form relative to that found in natural vinblastine (Figure 1). This atropisomer **2** lacks the cytotoxicity and inhibition of tubulin polymerization that is the basis of vinblastine's anti-cancer activity. Since the atropisomer **2** could be converted to vinblastine (**1**) on heating, it might be considered, in principle, as a noncytotoxic vinblastine pro-drug that could be thermally activated. However, the thermal barrier for this conformational inversion (100 °C) precludes a practical in vivo thermal activation. While variations of the piperidine ring D′ substitution did have some influence on the conformational inversion barrier of this ring,[2,3] a more pronounced attenuation of the thermal barrier was required. Interestingly, this thermal barrier is lowered considerably (by 40 °C) for the piperidine inversion in the cleavamine lacking vindoline as a C-16′ substituent,[4] but such a compound does not have any anti-cancer potential.

Consequently, we decided to see if a 5a′-*homo*-vinblastine (**3a**), in which the nine-membered ring C′ of the VLB cleavamine moiety is expanded by one methylene unit, could be synthesized. Would a 10-membered ring C′, with an expected lower conformational inversion barrier for the piperidine ring D′, still allow isolation of an atropisomer that might be used as a noncytotoxic pro-drug? Of course, the requisite tubulin activity and cytotoxicity of the final *homo*-vinblastine would also have to be attained. In this context, one might note that 5a′-*nor*-anhydrovinblastine (Navalbine) is in clinical use as an anti-cancer agent.

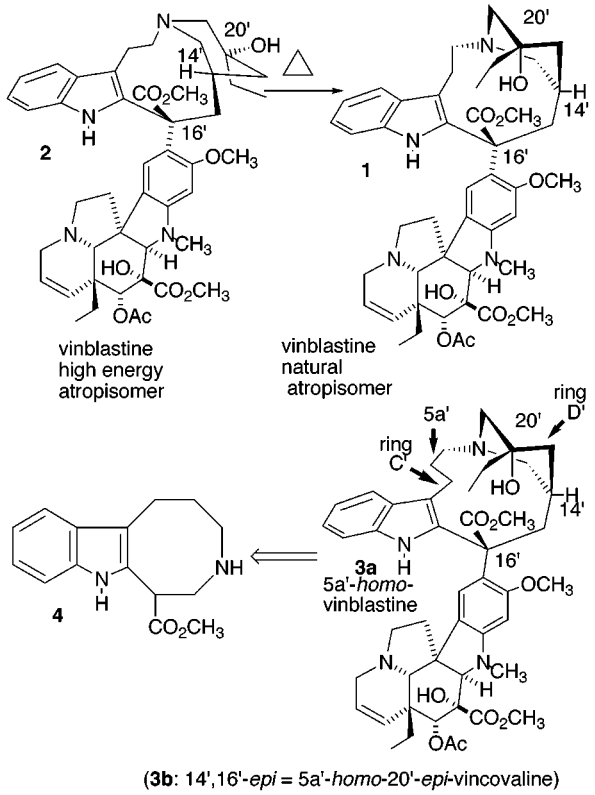

Figure 1. Established thermal conformational inversion of vinblastine atropisomer **2** to natural atropisomer **1** and projected syntheses of 5a′-*homo*-vinblastine (**3a**) and 5a′-*homo*-20′-*epi*-vincovaline (**3b**).

Results and Discussion

Potential Routes to Indoloazocines 4, 22. To see if our previous vinblastine synthesis could be extended to 5a′-*homo*-vinblastine (**3a**), a synthesis of the indoloazocine **4** was required. While the corresponding in-

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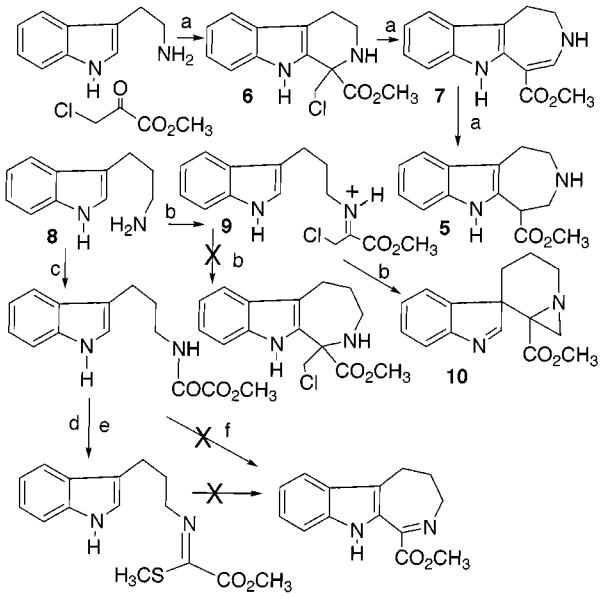
10.1021/jo000249z CCC: $20.00
Published on Web 07/07/2001

Scheme 1[a]



[a] Key: (a) ref 5; (b) Me Cl-pyruvate, MeOH, HCl or tol. TsOH, reflux; (c) $MeO(CO)_2Cl$, Et_3N, CH_2Cl_2; (d) Lawesson's reagent, THF, rt, 80%; (e) MeI, THF, 48 h reflux; $POCl_3$, tol. reflux 3 h.

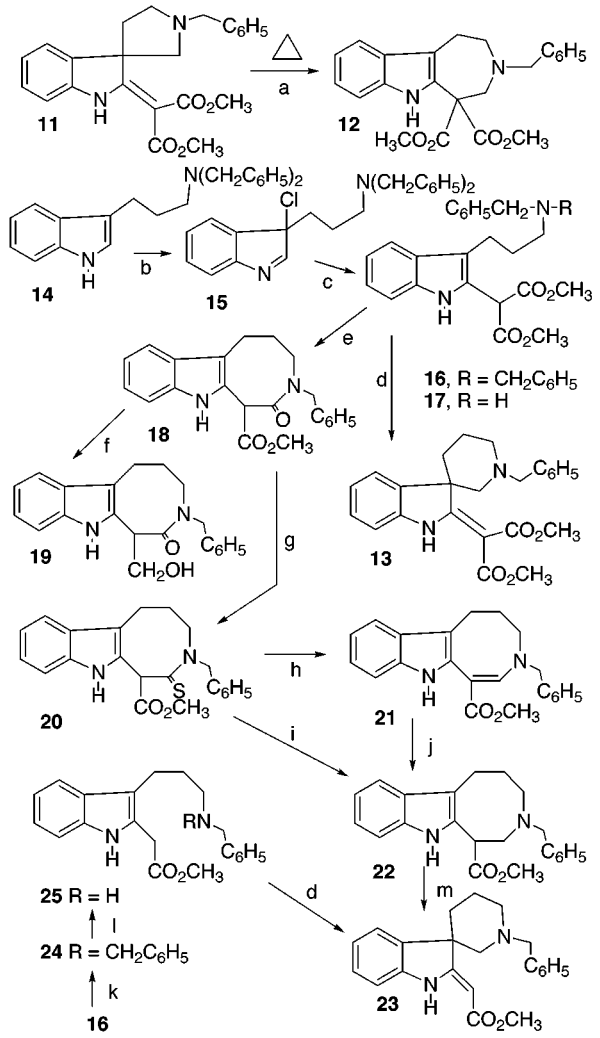
doloazepine **5** is readily made by condensation of tryptamine with methyl chloropyruvate, followed by rearrangement of the chloromethyltetrahydrocarboline **6**, and reduction of the unsaturated azepine **7** (Scheme 1),[5] this sequence failed with *homo*-tryptamine (**8**), prepared from indole and acrylonitrile, followed by reduction.[6] Under a variety of Pictet−Spengler condensation conditions, this process did not proceed past the initial formation of an iminium salt **9**, or else it resulted in as many as eight products, of which the tetracyclic product **10** could be identified. These results support previous observations that closure to form a seven-membered ring on condensation of *homo*-tryptamine (**8**) with aldehydes is problematic (0.4%, ref 7).[7]

Attempted alternative Bischler−Napieralski cyclization of an oxalamide ester, for subsequent methylene addition,[8] and of its thioimonium derivative,[9] also did not give an indole annelation product (Bischler−Napieralski cyclizations are known to fail with amides bearing an adjacent electron-withdrawing function).[10] Therefore, construction of the indoloazocine **4** was explored through a Mannich cyclization.

We had previously found that the spiropyrrolidine indoline alkene **11** rearranged quantitatively, at 60 °C in THF, to form the indoloazepine **12** (Scheme 2).[5] To attempt the homologous rearrangement, the spiropiperidine indoline **13** was synthesized.

Chlorination of *N*,*N*-dibenzyl-*homo*-tryptamine **14** with *tert*-butyl hypochlorite and reaction of the resulting

Scheme 2[a]



[a] Key: (a) ref 5; (b) *t*-BUOCl, THF, −20 °C; (c) Tl Me_2 malonate, THF/Et_2O, −10 °C to rt, 76% **16**; or *N*-BOC analogue of **15**, 1 M $ZnCl_2$, THF, Li Me_2 malonate, −60 °C to rt; MeOH/HCl, 88% **17**; (d) MeOH, CH_2O, 93%; (e) tol. reflux 71%; (f) $POCl_3$, $NaBH_4$, 91%; (g) Lawesson's reagent, tol., reflux, 76%; (h) R/Ni, EtOH, refl. 81%; (i) $NaBH_4$, $NiCl_2$; (j) $NaCNBH_4$, HOAc, 90%; (k) LiCl, DMA, Et_3N−HCl, 120−130 °C, 82%; (l) Pd/C, H_2, HOAc; (m) chromatography SiO_2.

chloroindolenine **15** with thallium dimethylmalonate gave the 2-indolylmalonate **16**. A significant improvement to this earlier methodology for formation of 2-indolylmalonates[5] was found in the reaction of the *N*-BOC-*N*-benzyl compound corresponding to **15** with lithium dimethylmalonate and $ZnCl_2$. Hydrolysis of the BOC derivative, or hydrogenolysis of the dibenzyl compound **16**, and condensation of the resulting secondary amine **17** with formaldehyde readily provided the spiroindoline alkene **13**; but in contrast to the lower homologue **11**, its rearrangement for formation of an indoloazocine could not be accomplished.

Formation of the azocine ring was, however, achieved by thermal cyclization of the malonate **17** to the lactam ester **18**. An attempt to selectively reduce the lactam function by its reaction with $POCl_3$, followed by reduction with sodium borohydride, yielded only the lactam alcohol **19** (this method was developed for the selective reduction

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(6) (a) Misztal, S.; Boska, J.; Chojnacka-Wojcik, E.; Tatarczynska, E. *Pol. J. Pharmacol. Pharm.* **1979**, *31*, 149; (b) Murphy, H. W. *J. Pharm. Sci.* **1964**, *53*, 272.

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(10) Whately, W. M.; Govindachari, T. R. *Org. React. VI* **1951**, 74.

of amides in the presence of ester functions,[11] though not for malonamide esters). Conversion of the lactam ester **18** to a thiolactam **20** with Lawesson's reagent and its treatment with Raney nickel provided the 1,2,3,4-tetrahydroazocine **21**, which could be further reduced to the saturated indoloazocine **22** with cyanoborohydride in acetic acid. A mixture of indoloazocines **21** and **22** was obtained by reduction of the thiolactam **20** with nickel boride, generated in situ from sodium borohydride and nickel chloride.

The indoloazocine **22** is not stable to chromatography on silica gel, and it readily undergoes acid-catalyzed rearrangement to the spirocyclic isomer **23**, which was independently synthesized by condensation of formaldehyde with the amino ester **25** (obtained from the diester **16**, through its mono-decarbomethoxylation with LiCl/DMF to *N*,*N*-dibenzyl ester **24** and mono-debenzylation of the monoester **24** by hydrogenolysis).

Generation of Tetracyclic Intermediates 27a,b and Their Coupling to Vindoline. Condensation of the indoloazocine **22** with the aldehyde **26**,[1] in refluxing toluene, provided an anticipated diastereomeric mixture of tetracyclic products **27a**,**b** in 97% isolated yield, after chromatography (Scheme 3). Thus, the higher homologue **22** of our N^b-benzyl indoloazepine underwent fragmentation and the intramolecular Diels−Alder-type reaction as readily as the earlier fragmentation and biogenetic secodine analogue reaction.[1]

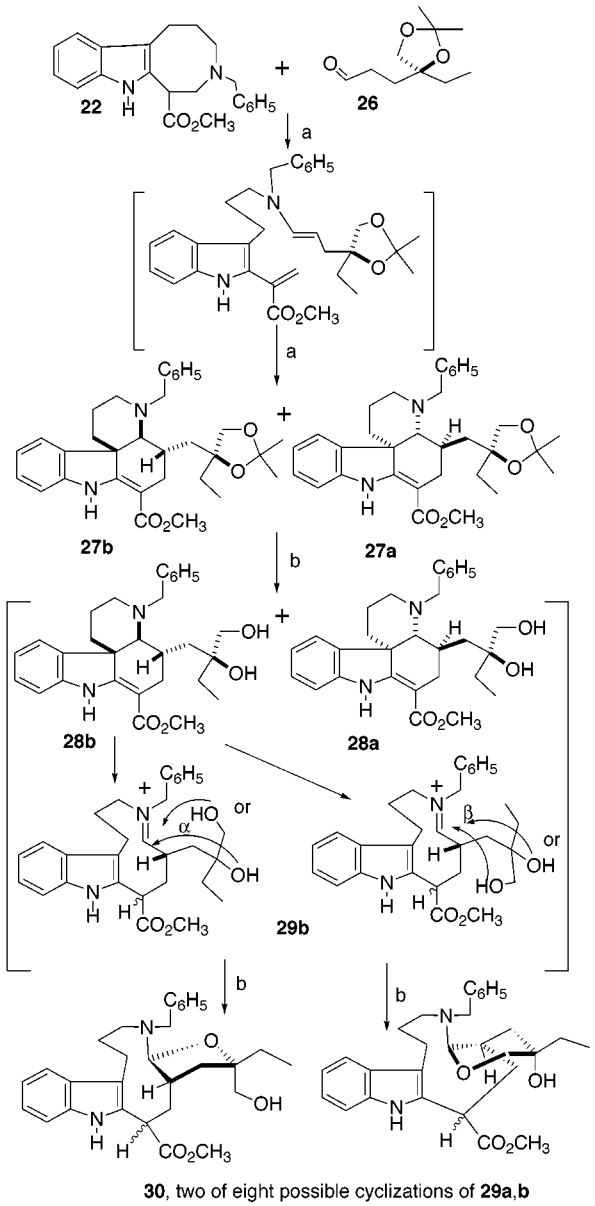
For chromatographic separation of diastereomers, we had hydrolyzed the acetonides corresponding to acetonides **27a**,**b** to diols in the VLB synthesis.[1] When this was attempted in the present sequence, a new structural product type was formed. It was isomeric with the target diols **28a,b** but it lacked UV and IR spectroscopic characteristics of an aminoacrylate, and it was instead indolic.

We had previously found that the pentacyclic aminoacrylate alcohol alkaloid ibophyllidine, under acidic conditions, gave an indolic hemiaminal cyclic ether.[12] Therefore, in the present case, liberation of two hydroxyl functions on acid hydrolysis of the acetonides **27a**,**b**, and intramolecular formation of hemiaminal ethers by alterfacial attack of the hydroxyl groups on an intermediate iminium function **29** could possibly lead to eight potential stereoisomeric hemiaminal ethers **30** (16 diastereomers if epimeric esters are considered). This complexity did not bode well for a separation of diastereomers arising from hydrolysis of the pair of acetonides **27a**,**b**.

Since an indoline vinylogous urethane structure, as in the diols **28a**,**b**, is key to stereoselectivity in the anticipated coupling reaction with vindoline,[1] and since the hemiaminal ether products **30** did not show any tendency to revert to that ring system, a coupling reaction had to be performed directly on the diastereomeric mixture of acetonides **27a**,**b**.

Chlorination of the mixture of acetonides **27a**,**b** with *tert*-butyl hypochlorite, followed by reaction of the resulting chloroalkyl indoline imine with silver tetrafluoroborate and vindoline, provided the indoline imines **31a**,**b** (Scheme 4). Reductive cleavage of the C-3′−C-7′ bond with potassium borohydride in acetic acid then afforded the indoles **32a**,**b**, showing four NMR methyl singlets for these acetonides. Hydrolysis of the acetonides **32a**,**b** with

Scheme 3[a]



[a] Key: (a) tol. reflux 12 h, 96%; (b) MeOH, aqueous HCl, reflux 30 min.

HCl in aqueous methanol gave primarily two diols **33a** and **33b**, which were separated by chromatography and derivatized with *p*-toluenesulfonic anhydride to furnish the primary tosylates **34a** and **34b**.

Formation of 5a′-*homo*-Vinblastine (3a) and Its C-14′*epi*,C-16′*epi*-Diastereomer 3b. Heating of each of the tosylates **34a** and **34b** might allow cyclization to two diastereomeric quaternary salts **35a**, **36a**, and **35b**, **36b**, respectively, while cyclization of the tosylate- derived epoxides **37a** and **37b** should be stereoelectronically directed to the unique quaternary salts **35a** and **35b**.[1−4] On debenzylation by hydrogenolysis, these compounds would give the (high energy) atropisomers **38a** of 5a′-*homo*-vinblastine and **38b** of 20′-*epi*-5a′-*homo*-vincovaline, in analogy to the corresponding compounds in the VLB series.[1]

To achieve selective epoxide formation, the tosylate **34a** was treated with sodium hydride and the resulting product **37a** was heated in methanol to provide a

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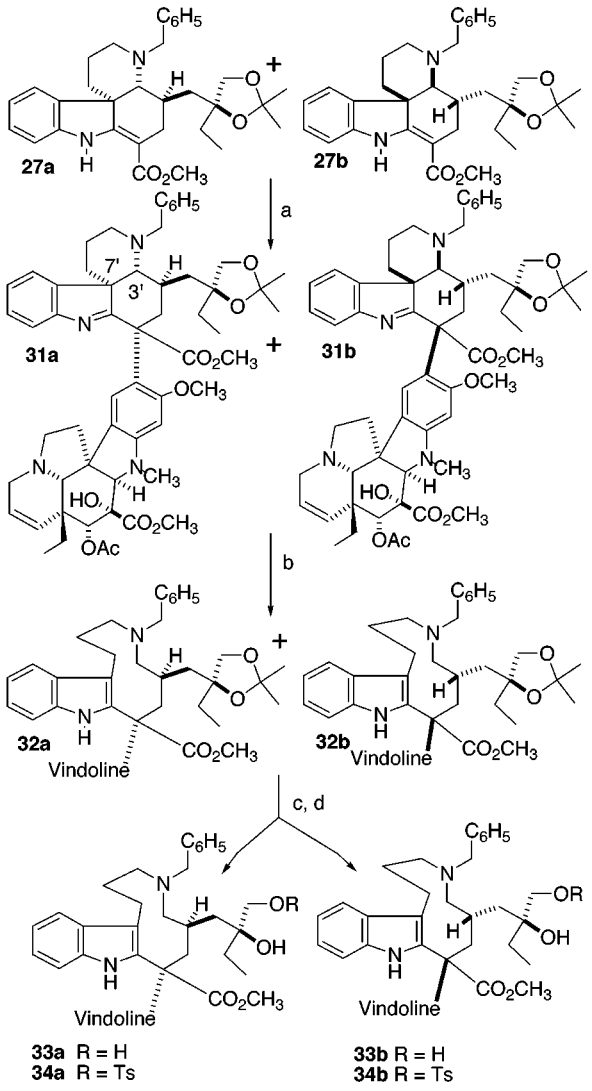
Scheme 4[a]

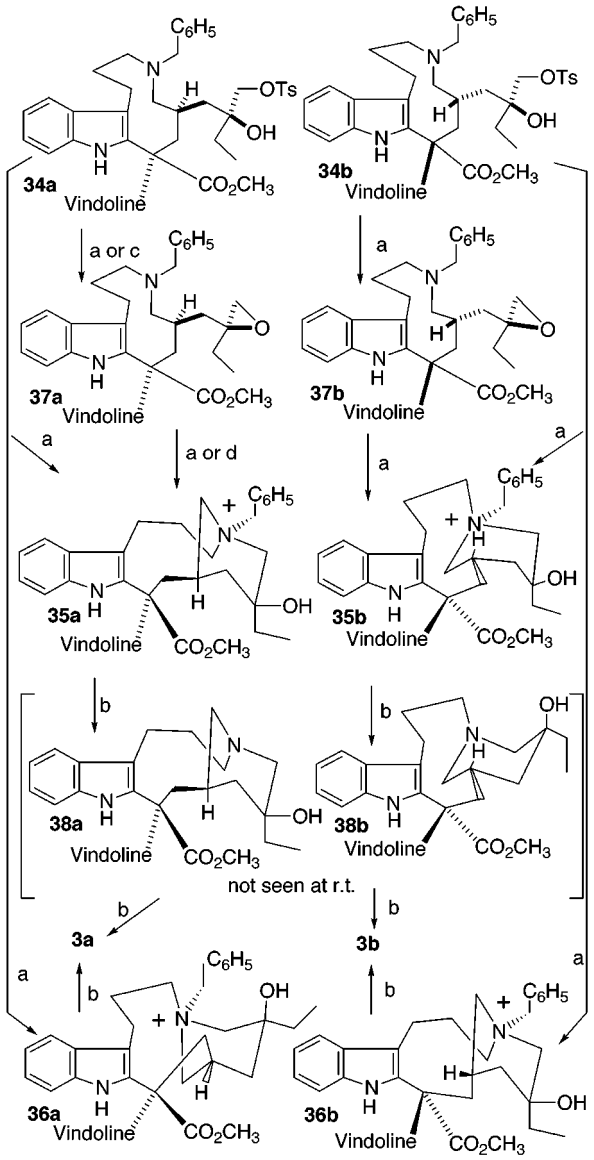


[a] Key: (a) *t*-BUOCl, CH_2Cl_2, 0 °C; vindoline, HBF_4-Et_2O, $AgBF_4$, acetone; (b) KBH_4, HOAc; (c) 1 N HCl, reflux 1 h; (d) Ts_2O, CH_2Cl_2, 0 °C, 63−66%.

quaternary salt **35a** (Scheme 5). Its hydrogenolysis gave a compound, albeit in low yield, which fit the expected NMR and TLC characteristics of a 5a′-*homo*-vinblastine low energy atropisomer **3a**, rather than the pronounced characteristics expected for the corresponding high energy atropisomer **38a**.[1] The same product was also obtained by direct cyclization of the tosylate **34a** in refluxing toluene (that is expected to pass primarily through the epoxide **37a)**,[1] followed by debenzylation.

Alternative Sequences Providing Tetracyclic Diols 28a,b or 45a,b and Epoxides 37a,b. To improve access to the epoxides **37a**,**b**, two reaction sequences were examined. In the first, the acetonide protecting group of aldehyde **26** was replaced by a carbonate function **39** (Scheme 6), since that would allow eventual deprotection of the diol under nonacidic conditions and avoid ring fragmentation to the hemiaminal derivatives **30**. Derivatization of the diol **40** with phosgene and pyridine, followed by ozonolysis, provided the aldehyde **39** for condensation with the indoloazocine **22**. Analogously, the lower homologue (see below) methyl diol **41** and its aldehyde carbonate derivative **42** were also prepared. On

Scheme 5[a]

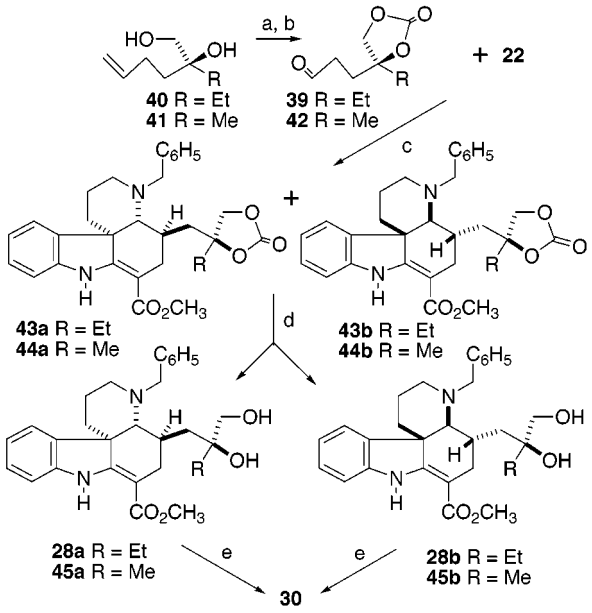


[a] Key: (a) tol. reflux 8 h; (b) Pd/C, H_2, MeOH, 3 h; 68−73% overall; (c) NaH, THF; (d) MeOH, reflux.

condensation of the indoloazocine **22** with the aldehydes **39** and **42**, formation of two diastereomeric pairs of tetracyclic carbonate derivatives **43a**,**b** and **44a**,**b** was achieved in high yields. Their hydrolysis with 1 N sodium hydroxide gave the separable diols **28a**,**b** and **45a**,**b**. While these diols underwent the aforementioned rearrangement on silica gel chromatography, this could be suppressed by column pretreatment with triethylamine. But, the desired monotosylation of these diols proved to be impossible and resulted in rearrangement to the hemiaminal cyclic ethers (i.e., **30**), found before.

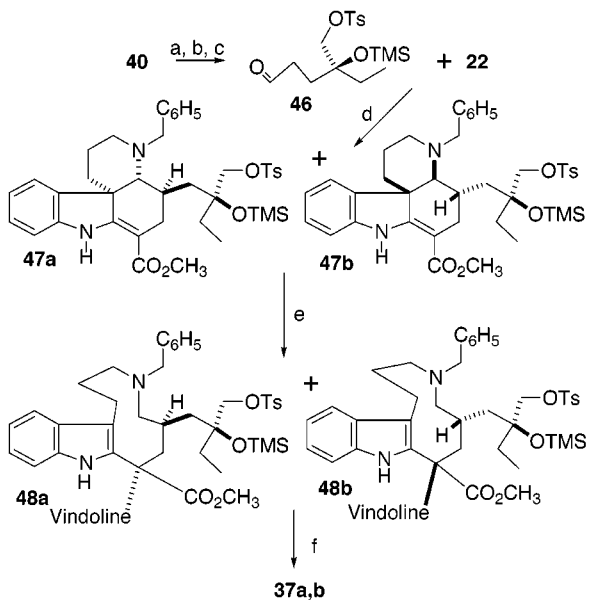
The second alternative sequence to the epoxides **37a**,**b** was based on an initial functionalization of the starting aldehyde by synthesis of the trimethylsilyl ether tosylate **46** from the olefinic diol **40** by its reaction with tosyl anhydride and triethylamine, followed by TMS triflate, and ozonolysis (Scheme 7). While we were concerned that there could be an undesired *N*-alkylation on formation of the tetracyclic intermediates **47a**,**b** in refluxing toluene, this was not problematic and a 93% yield of these products was obtained. Chromatographic separation of

Scheme 6[a]



[a] Key: (a) pyd, C_6H_6, $COCl_2$, 84%, 96%; (b) O_3, 73%, 75%; (c) tol. reflux 79%, 88%; (d) 0.5 N NaOH, 1 h, rt; (e) $CDCl_3$ rt.

Scheme 7[a]

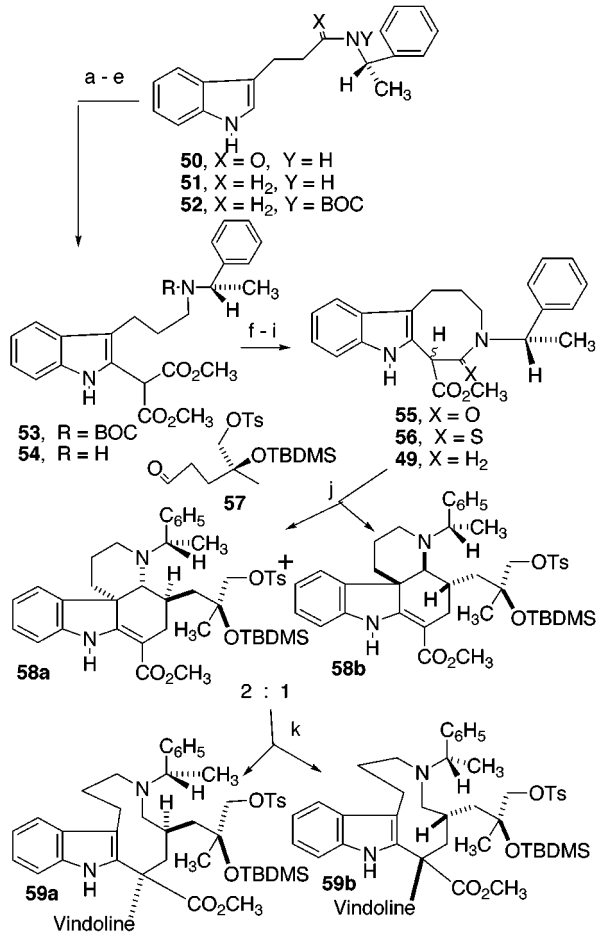


[a] Key: (a) Ts_2O, Et_3N, 83%; (b) TMSOTf, DMAP, Et_3N, 91%; (c) O_3, 93%; (d) tol. reflux, 97%; (e) *t*-BUOCl, CH_2Cl_2, 0 °C; vindoline, HBF_4-Et_2O, $AgBF_4$, acetone; KBH_4, HOAc, 51% overall; (f) TBAF, THF, 25 °C, 90%.

the diastereomers was, however, not possible at this stage, or even after the coupling reaction with vindoline and imine reduction to tosylates **48a**,**b**. Thus, a diastereomeric mixture of epoxides **37a**,**b** was made by treatment of the silyl ethers **48a**,**b** with fluoride. Their cyclization and hydrogenolysis gave the separable 5a′-*homo*-vinblastine (**3a**) and 20′-*epi*-5a′-*homo*-vincovaline (**3b**) shown in Scheme 5. Again, no atropisomer of these products (**38a** or **38b**) was detected.

Diastereoselective Formation of Tetracyclic Intermediates 58a,b, Their Coupling to Vindoline, and Conversion of the Major Diastereomer Product 59a to 18′-*nor*-5a′-*homo*-vinblastine (62a). With the

Scheme 8[a]



[a] Key: (a) BH_3-Me_2S, 91%; (b) (*t*-BUO)$_2$CO, NaOH, 96%; (c) *t*-BUOCl, Et_3N; (d) Tl Me_2 malonate, c + d 87%; or $ZnCl_2$, Li Me_2 malonate, c + d 91%; (e) MeOH, HCl, reflux, 98%; (f) tol. reflux 85%; (g) Lawesson's reagent, tol. reflux 64%; (h) R/Ni, MeOH, 81%; (i) $NaCNBH_4$, HOAc, 62%; (j) tol. reflux 89%; (k) *t*-BUOCl, CH_2Cl_2, 0 °C; vindoline, HBF_4-Et_2O, $AgBF_4$, acetone; KBH_4, HOAc, 62% overall.

objective of introducing diastereoselectivity in generation of our key tetracyclic intermediates (e.g., **47a**,**b**) and in order to have a better chance of separation of subsequent diastereomeric intermediates, the indoloazocines **49** with a chiral α-phenethyl N^b-substituent were chosen for condensation with an aldehyde (Scheme 8). They were prepared by formation of the indole 3-propionic acid amide **50** of *S*-(−)-α-methylbenzylamine and its reduction with lithium aluminum hydride to the corresponding amine **51**. In a better alternative, this compound was obtained from indole-3-propionitrile, its reduction with DIBALH to the corresponding aldehyde, a subsequent condensation with *S*-(−)-α-methylbenzylamine, and final reduction with sodium borohydride. Installation of a *t*-BOC amide **52** allowed conversion to a chloroindolenine with *tert*-butylhypochlorite and its reaction with thallium dimethyl malonate to form the malonylindole **53**. Removal of the BOC protecting group and cyclization of the resulting amine **54** afforded the lactams **55**. Their conversion to thiolactams **56** with Lawesson's reagent**,** desulfurization with R/Ni, and reduction with $NaBH_4/NiCl_2$, gave the indoloazocines **49** (mixture of ester epimers).

For formation of tetracyclic intermediates to be used in the following reaction sequence, the lower homologue

aldehyde **57** rather than aldehyde **46** was chosen for two reasons: We had previously found that the anti-leukemic cytotoxicity (L1210 cells) of VLB congeners with C-20 modified substituents follows the order of $CH_3 > C_2H_5 > H$, C_3H_7 and we hoped to maximize this activity in the *homo*-VLB case. Also, a C-20′ methyl substituent would simplify NMR spectra and thus facilitate analysis of atropisomeric products, if they were obtained. Finally, a TBDMS substituent in aldehyde **57**, rather than the TMS substituent in aldehyde **46**, was selected to ensure better hydrolytic stability during the C-3′−C-7′ reductive cleavage reaction of the vindoline coupling product in acetic acid.

Condensation of the chiral indoloazocines **49** with the aldehyde **57** produced a 2:1 mixture of diastereomers, analogous to that found in the VLB synthesis.[1,13] Coupling of the tetracyclic condensation products **58a**,**b** to vindoline, followed by reductive cleavage of the C-3′−C-7′ bond proceeded, as described above, to give the *seco*-products **59a**,**b**. Here, the chiral N^b-substituent allowed chromatographic separation of diastereomers.

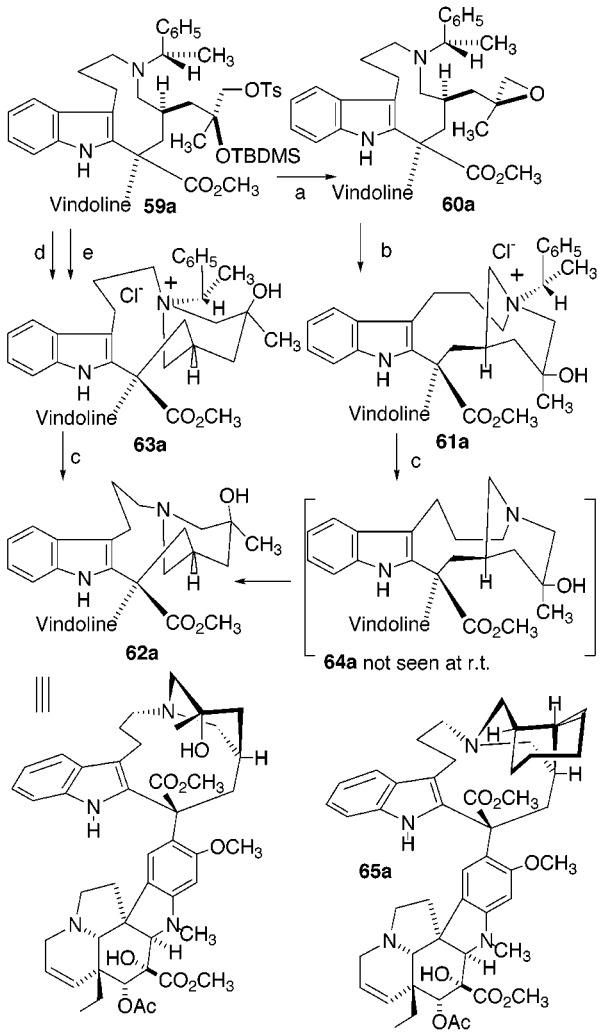
The major diastereomer **59a** was directed along two pathways (Scheme 9). Its conversion to a unique epoxide **60a** on treatment with fluoride was followed by cyclization of the epoxide in refluxing methanol. A quaternary salt, which was expected to have the configuration leading to the higher energy atropisomeric conformation of 18′-*nor*-5a′-*homo*-vinblastine, was obtained and converted to its chloride **61a** on an ion-exchange resin. On hydrogenolysis of this salt, 18′-*nor*-5a′-*homo*-vinblastine **62a** with the lower energy atropisomeric conformation was obtained.

Alternatively, the tosylate **59a** was subjected to cyclization by direct N^b-alkylation in benzene at 150 °C, and the quaternary product, after cleavage of the silyl ether, was converted to its chloride **63a** by ion exchange. On the basis of the analogous reaction sequence in the VLB synthesis, a quaternary salt with a configuration leading to the lower energy atropisomer of the amine is expected here.[1]

Unfortunately, a definitive NMR comparison of the two quaternary salts **61a** and **63a** (i.e., NOE signals for the C-20′ methyl substituent) was not possible due to intense signal broadening.[14] However, a comparison of the CD spectra of the quaternary salts **61a** and **63a**, and their comparison with CD spectra of the VLB atropisomers,[1] clearly showed that the expected two configurations **61a** and **63a** had been obtained by the two cyclization routes. Yet, both salts **61a** and **63a** gave rise to the same product **62a** on hydrogenolysis. Therefore, it must be concluded that a higher energy atropisomer of 18′-*nor*-5a′-*homo*-vinblastine (**64a**) is converted to its lower energy atropisomer **62a** at ambient temperatures by inversion of the bridged piperidine ring (in contrast to the conformational stability of the corresponding VLB atropisomer).[1]

Syntheses of Perhydroisoquinoline Congeners 65a,b of 5a′-*homo*-Vinblastine (3a), Their Isolable Atropisomers 81a,b, and Thermal Conformational Inversion to 65a,b. Our goal of lowering the atropisomeric inversion barrier of vinblastine (100 °C) had been achieved, but exceeded. Some conformational restraint was required to bring this barrier back up and into a range where it might be clinically exploited. Therefore, we set out to synthesize a 5a′-*homo*-vinblastine congener **65a** with a cis-fused bridged perhydroisoquinoline (Scheme 9) in place of the bridged piperidine ring.

Scheme 9[a]



[a] Key: (a) TBAF, THF, 74%; (b) MeOH, reflux; Amberlite IRA 400; (c) Pd/C, H_2, b + c 81%; (d) C_6H_6, 150 °C; (e) TBAF, THF; Amberlite IRA 400.

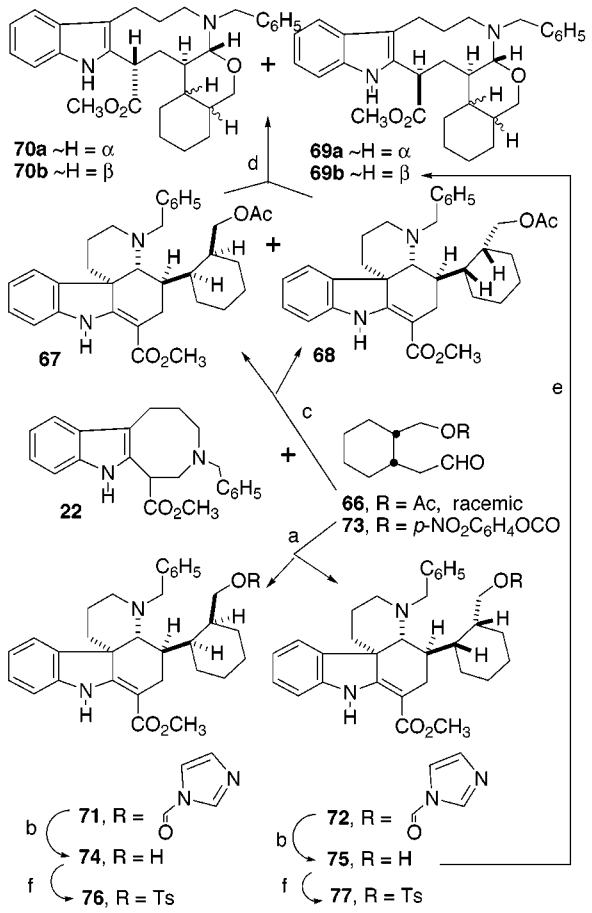
Condensation of the racemic aldehyde acetate **66**[15] with the indoloazocine **22** led to a 1:1 diastereomeric mixture of cyclohexyl-substituted tetracyclic vinylogous urethanes **67** and **68** (Scheme 10) Their relative stereochemistry is consistent with the later cyclization results (below). Methanolysis of their primary acetate function did not give the corresponding primary alcohols but, instead, the now expected hemi-aminal cyclic ethers derived from C-3−C-7 cleavage of the tetracyclic ring moiety. A mixture of two C-16 epimeric ester pairs, **69a**,**b** and **70a**,**b**, was formed with sodium methoxide over 4 h. The esters **70a**,**b**, which in molecular modeling showed their C-16 *H* directed toward the N^b lone pair, were distin-

(13) Use of a chiral 2-ferrocenyl auxiliary N-substituent, which gives complete diastereoselectivity in the vinblastine synthesis, was developed later: Kuehne, M. E.; Bandarage, U. K. *J. Org. Chem.* **1996**, *61*, 1175.

(14) We had already seen that in contrast to vinblastine in its normal lower energy atropisomeric conformation, the higher energy atropisomer of VLB gives a very poorly defined ^1H NMR spectrum.[1]

(15) Prepared and used by Dr. I. Marko in syntheses of the corresponding VLB congeners with two distereomeric cis-fused perhydroisoquinoline moieties; manuscript in preparation.

Scheme 10[a]



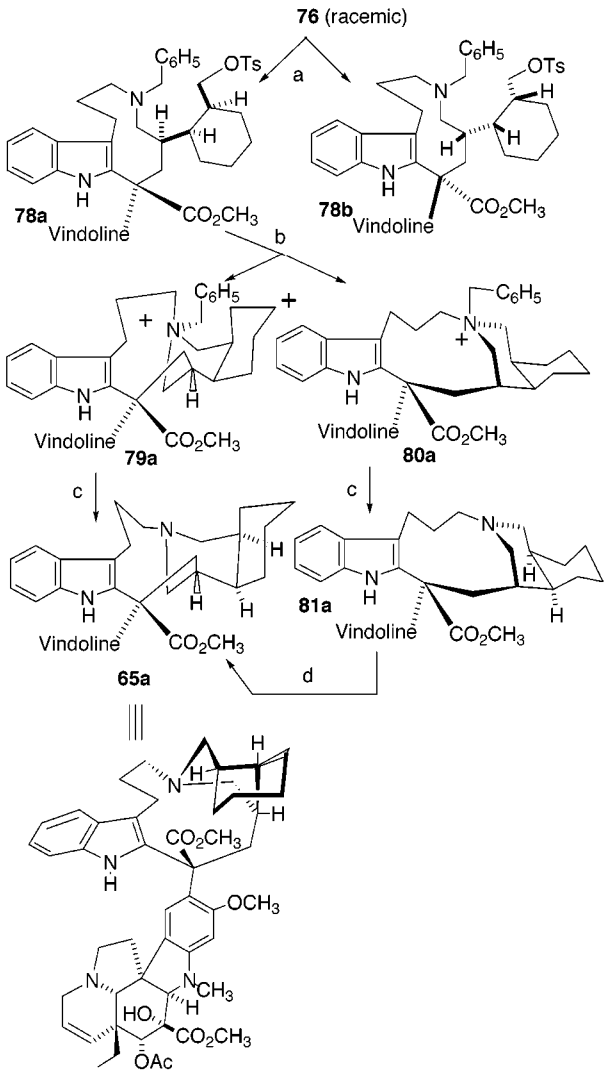
[a] Key: (a) tol. reflux 69%; (b) 2 N NaOH, rt, 40 min, 98%; (c) tol. reflux 91%; (d) NaOMe, rt, 4 h, 71%; (e) $CHCl_3$, rt, 10 h, 94%; (f) Ts_2O, DMAP, Et_3N, 71%.

guished by a strong downfield ^{1}H NMR shift for C-16 *H* (to δ 5.07−5.13), in analogy to corresponding C-16 epimeric carbomethoxycleavamine spectra.[16]

Separation of the tetracyclic diastereomeric series (**67** and **68)** was achieved through the corresponding 18-imidazolyl urethanes **71** and **72**, which were obtained by condensation of the indoloazocine **22** with the *p*-nitrophenyl carbonate aldehyde **73** and subsequent displacement of the *p*-nitrophenol substituent with imidazole. Careful hydrolysis of the separated urethanes **71** and **72** provided the alcohols **74** and **75**. These sensitive compounds underwent rearrangement to the cyclic ethers **69a**,**b** (without epimerization at C-16) in $CDCl_3$ at room temperature during their NMR characterization, or on storage at 0 °C. However, they could be trapped as their tosylate derivatives **76** (71%) and **77** (68%).

Coupling of the racemic tosylate **76** with vindoline, and reduction according to the above protocol, provided the chromatographically separated diastereomeric tosylates **78a** and **78b** (Scheme 11). Cyclization of the former tosylate to the corresponding quaternary salts **79a** and **80a** and debenzylation of these salts by hydrogenolysis, furnished the binary indole-indoline compound with C-14′, C-16′ VLB-type stereochemistry in two atropisomeric forms **65a** (49%) and **81a** (39%). On heating in toluene, the latter atropisomer was converted to the former (with natural VLB-type conformation), with 50% conversion in 4 h at 91 °C.

Scheme 11[a]



[a] Key: (a) *t*-BUOCl, CH_2Cl_2, 0 °C; vindoline, HBF_4−Et_2O, $AgBF_4$, acetone; KBH_4, HOAc, 66% overall; (b) tol. reflux; (c) Pd/C, H_2, MeOH, b + c 49% **65a**, 39% **81a**; (d) 91 °C.

A kinetic study of this atropisomerism at 110, 100, and 91 °C gave $\Delta G^{\ddagger} = 29$ kcal/mol, $\Delta H^{\ddagger} = 25$ kcal/mol, $\Delta S^{\ddagger} = 11 \pm 2$ eu.

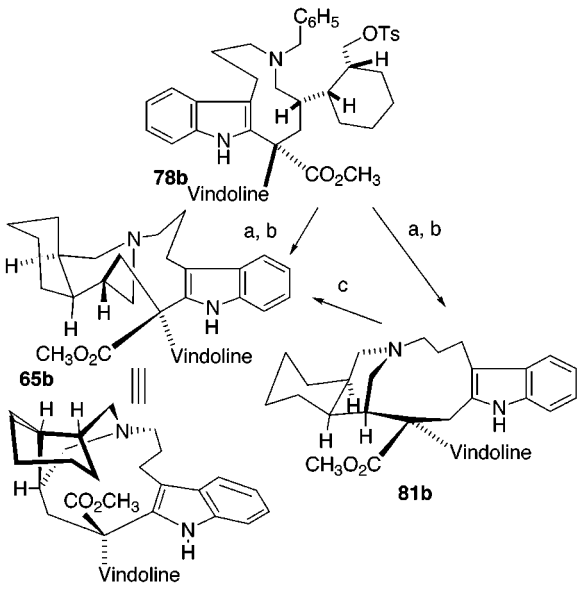
Analogously, the diastereomeric tosylate **78b** furnished the atropisomeric indole-indolines **81b** (37%) and **65b** (52%, Scheme 12). Here, the thermal energy barrier, determined in toluene at 101, 90, and 75 °C, was found to have $\Delta G^{\ddagger} = 28$ kcal/mol, $\Delta H^{\ddagger} = 20$ kcal/mol, $\Delta S^{\ddagger} = 20 \pm 5$ eu, with 50% conversion of **81b** to **65b** in 5 h at 75 °C.

As in vinblastine and related examples,[1] the higher energy atropisomers **81a** and **81b** gave characteristic very diffuse, poorly resolved ^{1}H NMR spectra.

The coupling products **82a**,**b**, which were obtained from the other racemic cyclohexyl cis-substituted tosylate **77** on coupling to vindoline (Scheme 13), could not be separated. However, their cyclization and debenzylation allowed chromatographic isolation of two binary indoline-indole products **83a** (27%) and **83b** (24%), to which the lower (natural VLB-type) atropisomer conformation could

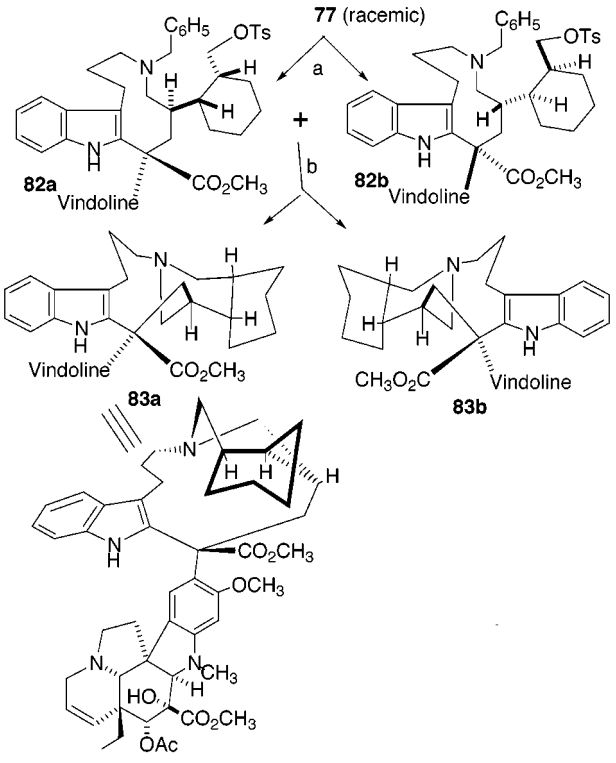
(16) Kuehne, M. E.; Kirkemo, C. L.; Matsko, T. H.; Bohnert, J. C. *J. Org. Chem.* **1980**, *45*, 3259.

Scheme 12[a]



[a] Key: (a) tol. reflux; (b) Pd/C, H_2, MeOH, a + b 52% **65b**, 37% **81b**; (c) 75 °C.

Scheme 13[a]



[a] Key: (a) *t*-BUOCl, CH_2Cl_2, 0 °C; vindoline, HBF_4−Et_2O, $AgBF_4$, acetone; KBH_4, HOAc; (b) tol. 50 °C, 4 h; Pd/H_2, MeOH, 3 h, a + b overall 27% **83a**, 24% **83b**.

be assigned on the basis of their well-defined ^{1}H NMR spectra. The corresponding more polar, higher energy atropisomers were not found in this more complex reaction mixture.[17]

Biological evaluation of 5a′-*homo*-vinblastine (**3a**) showed that, like vinblastine, it inhibits tubulin polymerization at the same concentration characteristic for very active VLB congeners ($ED_{50} = 1 \times 10^{-7}$ M). With L1210 leukemia cells, and with Sarcoma 180 cells, however, the cytotoxicity ED_{50} for 5a′-*homo*-vinblastine (**3a**) was only 5×10^{-8} and 2×10^{-7} M, respectively, compared to a 1×10^{-9} M L1210 cytotoxicity for vinblastine.

We had discovered that in the vinblastine series (in contrast to the present 5a′-*homo*-vinblastine congeners) the cis-fusion of a six-membered ring to the D′-piperidine ring resulted in an L1210 leukemia cell cytotoxic potency 500−1000 times greater than that of natural vinblastine ($ED_{50} = 8 \times 10^{-13}$ M for the lower homologue corresponding to **65a** and 3×10^{-13} M for lower homologue corresponding to **83a**). Therefore, we hoped that this structural element would also lead to a greatly increased activity in the higher homologues **65a** and **83a**, but this was not found (L1210 $ED_{50} > 1 \times 10^{-7}$M, Sarcoma 180 $ED_{50} = 1 \times 10^{-7}$ M for **65a**). As expected, the diastereomeric 5a′-*homovinblastine*- congeners **3b** and **62b** did not inhibit tubulin polymerization, nor did they show L1210 cytotoxicity in a measured significant range.

Conclusion. The syntheses of 5a′-*homo*-vinblastine (**3a**) and its 18′-*nor*-congener **62a** demonstrated that, in contrast to vinblastine, separate atropisomers derived from a ring D′-piperidine chair-chair conformational inversion, cannot be isolated here. However, cis-fusion of the D′-piperidine ring to a cyclohexane ring raises the energy barrier sufficiently to allow isolation of two atropisomers, and permits a conformational inversion at 75−90 °C. Thus, introduction of an additional conformational barrier (compare 13.0 kcal/mol for cis-decalin vs 10.8 kcal/mol for cyclohexane inversions) has provided a yardstick for the design of other ring D′-substituted 5a′-*homo*-vinblastine congeners that will fall into a potentially practical range for clinical, thermal pro-drug activation.

Experimental Section

A complete Experimental Section containing full NMR, IR, UV, mass spectrometry, and elementary analyses/HRMS data, as well as original NMR spectra, is provided in the Supporting Information. Procedures for preparation of compounds **8**, **19**, **27a,b**, **28a**,**b**, **30**, **39**, **42**, **43a**,**b**, **44a**,**b**, **45a**,**b**, **69a**,**b**, **70a**,**b**, and good alternative preparations for **14**, **17**, **53**, are given there.

3-[3-[(*N*^{b},*N*^{b}-Dibenzyl)amino]propyl]indole (14). Method B. Indole-3-propionic acid (10.25 g, 54.2 mmol) and dibenzylamine (10.69 g, 54.2 mmol) in 250 mL of CH_2Cl_2 were stirred at 0 °C, and 11.8 g (54.2 mmol) of dicyclohexyl carbodiimide in 50 mL of CH_2Cl_2 was added in a stream. The mixture was allowed to warm to 25 °C and stirred for 4 h. The solvent was evaporated and 50 mL of Et_2O added, causing dicyclohexylurea to crystallize. Filtration and concentration afforded a yellow oil, which was purified by chromatography, eluting with 1% MeOH−CH_2Cl_2. Trituration with hexane induced crystallization of the product indole-3-(*N*,*N*-dibenzyl)propanamide. Recrystallization from methanol provided 12.8 g (34.7 mmol, 64%) of product, which was free of both DCU and *N*-acyl urea rearrangement product: mp 89 °C; TLC (Et_2O) $R_f = 0.40$ (CAS, tan).

$LiAlH_4$ (10.4 mL, 1.0 M in THF) in 10 mL of THF was cooled to 0 °C, and indole-3-(*N*,*N*-dibenzyl)propanamide (3.83 g, 10.4 mmol) in 20 mL of THF was added to the stirred solution. After

(17) In contrast to the cyclization of tosylate **78a** leading to **79a** (with three 1,3 diaxial C/C repulsions relieved by a twist boat conformation) and formation of **80a** (no 1,3 diaxial C/C repulsions), the cyclization of tosylate **82a** to the quaternary salt precursor of amine **83a** generates no 1,3-diaxial C/C interactions. The same difference is found for cyclization of tosylate **78b** vs **82b**. Thus, lack of these 1,3-diaxial interactions on cyclization of **82a**,**b** would not promote cyclization to a quaternary salt precusor of a higher energy atropisomer corresponding to **81a**,**b**.

the addition was complete, the reaction mixture was heated at reflux for 2−3 h and then cooled in ice. The reaction was quenched by slow addition of 5 mL of water, followed by 20 mL of 2 N NaOH. Extraction with 5 × 30 mL of Et_2O, washing of the combined organic phases with brine, drying ($MgSO_4$), filtration, and concentration furnished a yellow oil, which was purified by flash chromatography (SiO_2, CH_2Cl_2). The amine was triturated with hexane to afford 3.28 g (89%) of the title compound as a white powder. An analytical sample was recrystallized from methanol: mp 80 °C; TLC (ethyl acetate−hexane) R_f = 0.58 (CAS, yellow-orange).

Dimethyl 3-[3-[(*N*^{b},*N*^{b}-Dibenzyl)amino]propyl]indole-2-propanedioate (16). *N*,*N*-Dibenzyl-*homo*-tryptamine (**14**, 17.1 g, 48.4 mmol), in 250 mL of dry Et_2O, under argon, was cooled to −20 °C, and then 8.1 mL (58.1 mmol) of triethylamine and 6.58 mL (58.1 mmol) of *tert*-butyl hypochlorite in 20 mL of THF were added sequentially. The mixture was stirred for 1 h at −15 to −10 °C and then filtered through a plug of Celite into a stirred suspension of thallium dimethyl malonate in 100 mL of 1:1 THF/Et_2O, maintained at −10 °C. After 5 h at −10 °C, the reaction mixture was warmed to room temperature, filtered to remove thallium chloride, then washed with brine, dried ($MgSO_4$), concentrated, and then triturated with 50 mL of 1:1 ether−hexane to give 17.8 g (76%) of the title compound as a white powder: mp 95−96 °C; TLC (1:1 ether−hexane) R_f = 0.36 (CAS blue).

Dimethyl 3-[3-[(*N*^{b}-Benzyl)amino]propyl]-indole-2-propanedioate (17). Method B. Dimethyl 3-[3-(*N*,*N*-dibenzylamino)propyl]-indole-2-propanedioate (**16**, 11.68 g, 24.13 mmol) and 3.5 g of 10% palladium on carbon, in 80 mL of wet acetic acid, was vigorously stirred under a hydrogen atmosphere for 3 h, purged with nitrogen, and filtered through Celite. The filtrate was poured over crushed ice, basified with concentrated NH_4OH, and then extracted with methylene chloride (3 × 50 mL). The organic layers were dried ($MgSO_4$), and the solvent was removed to yield 7.1 g (75%) of the monobenzyl product **17** as a yellow oil: TLC (5% MeOH−$CHCl_3$) R_f = 0.14 (CAS, blue).

Dimethyl 1′-Benzyl[spiro(3*H*-indole-3,3′-piperidino)]-2-methylenedicarboxylate (13). A 100 mL, two-necked round-bottom flask, containing 866 mg (2.19 mmol) of mono-*N*-benzyl diester homotryptamine **17** in 20 mL of methanol, was fitted with a reflux condenser and an adapter, connecting it, via a glass tube, to a second flask, containing about 500 mg of paraformaldehyde. The paraformaldehyde container was immersed in a 140 °C oil bath for 1−2 min; an aspirator vacuum was then applied to the first vessel. The gaseous formaldehyde was bubbled into the stirred amine solution until the solid paraformaldehyde was used up. Then the aspiration was discontinued, and the solution was heated at reflux for 4 h. The solution was condensed to ∼3 mL, diluted with 20 mL of diethyl ether, and washed with water to remove excess paraformaldehyde. Concentration of the organic layers furnished a white foam, which was purified by flash chromatography (SiO_2, 3:2 Et_2O−hexane) to give 827 mg (93%) of the title compound: TLC (3:2 Et_2O−hexane) R_f = 0.46 (CAS, blue).

Methyl 3-Benzyl-2-oxo-2,3,4,5,6,11-hexahydro-1*H*-azocino[4,5-*b*]indole-1-carboxylate (18). *N*-Benzyl diester homotryptamine **17** (7.1 g, 18.0 mmol) in 50 mL of toluene was heated under a Dean−Stark trap at reflux for 5 h.The toluene was removed in *vacuo*, and the resulting oil was chromatographed (silica gel, 7:3 ether−hexane), to furnish a yellow oil, which crystallized on trituration with petroleum ether. The product lactam was recrystallized from methanol (4.64 g, 12.8 mmol, 71%): mp 112−115 °C; TLC (5% MeOH−CH_2Cl_2) R_f = 0.75 (CAS, blue).

Methyl 2-Thioxo-2,3,4,5,6,11-hexahydro-1*H*-azocino[4,5-*b*]indole-1-carboxylate (20). A solution of 4.47 g (12.3 mmol) of methyl 3-benzyl-1-hydroxymethyl-2-oxo-2,3,4,5,6,11-hexahydro-1*H*-azocino[4,5-*b*]indole-1-carboxylate (**18**) and 6.49 g (16.0 mmol, 1.3 equiv) of Lawesson's reagent in toluene was heated for 12 h. Cooling to 25 °C, filtration through a plug of silica gel, and concentration gave a yellow oil, which crystallized on cooling in 10 mL of anhydrous methanol to give 3.54 g (76%) of the title compound: mp 197−198 °C; TLC (CH_2Cl_2) R_f = 0.29 (CAS, yellow).

Methyl 3-Benzyl-4,5,6,11-tetrahydro-3*H*-azocino[4,5-*b*]-indole-1-carboxylate (21). Raney nickel (500 mg) was washed repeatedly with anhydrous ethanol and added to a stirred solution of 3.19 g (8.44 mmol) of methyl 2-thioxo-2,3,4,5,6,11-hexahydro-1*H*-azocino[4,5-*b*]indole-1-carboxylate (**20**). The mixture was heated at reflux for 3.5 h, cooled, filtered and condensed to give a yellow solid, which was purified by flash chromatography on a 3 × 12 cm silica gel column, eluting with 1% MeOH−CH_2Cl_2, to give 2.36 g (81%) of the title compound. An analytically pure sample was obtained by recrystallization from methanol: mp 177−178 °C; TLC (7:3 ether−hexane) R_f = 0.35 (CAS, yellow).

Methyl 3-Benzyl-2,3,4,5,6,11-hexahydro-1*H*-azocino-[4,5-*b*]indole-1-carboxylate (22). Unsaturated *N*-benzyl azocine (**21**, 1.62 g, 4.68 mmol), was dissolved in a minimum of glacial acetic acid (∼ 3 mL) and, with stirring, 2 eq. of sodium cyanoborohydride was added over 10 min.The reaction mixture was stirred for an additional 15 min, then cooled to 0 °C and basified with 10 mL of ice-cold concentrated ammonium hydroxide. The mixture was extracted with Et_2O and the extract washed with brine, dried, and filtered. The solvent was removed in vacuo and the resulting yellow gum purified by flash chromatography, eluting with 7:3 Et_2O−hexane, to give 1.48 g (90%) of the title compound as a white foam. Addition of HCl to the reaction mixture prior to workup resulted in significantly reduced yields: TLC (7:3 ether−hexane) R_f = 0.50 (CAS, blue).

1′-Benzyl-2-methoxycarbonylmethylen[spiro(3*H*-indole-3,3′-piperidine)] (23). Dibenzyl diester *homo*-tryptamine **16** (905 mg, 1.87 mmol) was combined with 103 mg (2.43 mmol, 1.3 equiv) of lithium chloride and 77 mg (506 mmol, 0.3 equiv) of triethylamine hydrochloride in 10 mL of DMA. The stirred solution was then heated at 120−130 °C for 2 h. After cooling, the contents of the reaction vessel were diluted with 20 mL of Et_2O and were washed repeatedly with water. Chromatography of the crude product provided 650 mg (82%) of dibenzyl monoester *homo*-tryptamine **24**. A 330 mg sample of this monoester was subjected to the monodebenzylation and condensation of the product **25** with formaldehyde, under the same conditions described for the preparation of the spiro product **13** from the diester **17**, above. The product was filtered through a plug of silica gel and crystallized upon trituration with 1:1 Et_2O−hexane: TLC (5% MeOH−$CHCl_3$) R_f = 0.74 (CAS, blue).

(6*R*,8*S*)- and (6*S*,8*R*)-Methyl 4-Benzyl-2,3,4,4a,5,6,8,9-octahydo-6-[(2*S*)-2-ethyl-2,3-(isopropylidenedioxy)propyl]-8-(15-vindolinyl)-1*H*-azecino-[5,4-*b*]indole-8-carboxylate (32a and 32b). A solution of 858 mg (1.66 mmol) of acetonide tetracycles **27a**,**b** and 254 μL (1.83 mmol, 1.1 equiv) of triethylamine in 30 mL of CH_2Cl_2, under argon, was cooled to 0 °C. Dropwise addition of 220 μL (1.83 mmol) of *tert*-butyl hypochlorite and stirring for 5 min gave a solution that by TLC was free of starting material (CAS, blue) and contained a more polar compound (CAS, green). The solution was washed with water, dried ($MgSO_4$), and concentrated under reduced pressure to give a white foam that was used in the next step.

The chloroindolenine was taken up in 30 mL of dry acetone, and 756 mg (1.66 mmol) of vindoline was added, followed by 640 μL (3.32 mmol) of tetrafluoroboric acid−diethyl ether complex. After 5 min, 646 mg (3.32 mmol) of silver tetrafluoroborate in acetone was added, causing the mixture to become heterogeneous. After being stirred for an additional 5 min, this mixture was basified by addition of 20 mL of 10% aqueous ammonium hydroxide and then extracted with CH_2Cl_2. Drying and solvent removal gave the coupling product **31a**,**b** as a white foam.

This material was dissolved in 10 mL of acetic acid and reduced by slow addition of 432 mg (8.3 mmol) of potassuim borohydride. The solution was stirred for 10 min and then poured into crushed ice and made basic with concentrated ammonium hydroxide. The mixture was then extracted with CH_2Cl_2. The organic phases were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Chromatography, eluting

with ethyl acetate, gave the title compounds as an inseparable mixture of diastereomers. The diols **33a**,**b**, resulting from acid hydrolysis of the acetonide functionality, were also isolated.

For **32a**, **32b**: TLC (ethyl acetate) $R_f = 0.28$ (CAS, purple-tan).

(6*R*,8*S*)- and (6*S*,8*R*)-Methyl 4-Benzyl-2,3,4,4a,5,6,8,9-octahydro-6-[(2*S*)-2-ethyl-2,3-dihydroxypropyl]-8-(15-vindolinyl)-1*H*-azecino[5,4-*b*]indole-8-carboxylate (33a and 33b). A mixture of 1.48 g (1.52 mmol) of the acetonide dimers **32a** and **32b** was dissolved in 50 mL of THF, and 30 mL of 1 N HCl was added. The solution was heated at reflux for 1 h, cooled to 0 °C, and basified by addition of concentrated ammonium hydroxide. The mixture was then extracted with 1:1 ethyl acetate−Et_2O, and the organic extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude diols were purified by successive chromatography, eluting first with ethyl acetate, and then with 5% MeOH−CH_2Cl_2.

Data for the higher R_f isomer **33b**: TLC (5% MeOH−CH_2Cl_2) $R_f = 0.34$ (CAS, purple). Data for lower R_f isomer **33a**: TLC (5% MeOH−CH_2Cl_2) $R_f = 0.16$ (CAS, tan).

(6*R*,8*S*)-Methyl 4-Benzyl-2,3,4,4a,5,6,8,9-octahydo-6-[(2*S*)-2-ethyl-3-(*p*-tolylsulfonyl)oxy-2-hydroxypropyl]-8-(15-vindolinyl)-1*H*-azecino[5,4-*b*]indole-8-carboxylate (34a). A solution of 150 mg (0.161 mmol) of the more polar diol **33a** and 42 mL (1.5 equiv) of diisopropylethylamine in 15 mL of $CH_2Cl_2$was cooled to 0 °C, and then 80 mg (0.241 mmol, 1.5 equiv) of *p*-toluenesulfonic anhydride was added to the stirred solution. After 24 h, TLC indicated that the starting material had been consumed and a new, less polar, product was present. Additionally, a small amount of a very polar material (4° salt?) was evident. The mixture was washed with 10 mL of water and 10 mL of brine, dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by radial chromatography on a 2 mm plate to give 110 mg (63%) of the tosylate as a white foam: TLC (5% MeOH−CH_2Cl_2) $R_f = 0.33$ (CAS, purple).

(6*S*,8*R*)-Methyl 4-Benzyl-2,3,4,4a,5,6,8,9-octahydo-6-[(2*S*)-2-ethyl-3-(*p*-tolylsulfonyl)oxy-2-hydroxypropyl]-8-(15-vindolinyl)-1*H*-azecino[5,4-*b*]indole (34b). A solution of 328 mg (0.0.351 mmol) of the less polar diol dimer **33b** was subjected to the same conditions as described for the preparation of **34a**. After chromatography, 250 mg (66%) of the tosylate was obtained as a white foam: TLC (5% MeOH−CH_2Cl_2) $R_f = 0.53$ (CAS, purple).

5a′-Homovinblastine (3a). Tosylate **34a** (25 mg, 0.023 mmol) was heated in toluene for 8 h, after which time TLC indicated complete conversion to a new, very polar compound (**36a**), with $R_f = 0.02$ (10%MeOH−CH_2Cl_2). The solvent was removed by rotary evaporation, and the resulting white residue was dissolved in 5 mL of MeOH and hydrogenated in the presence of 5 mg of 10% palladium on carbon. After 3 h, a new product $R_f = 0.72$ (10%MeOH−CH_2Cl_2) had been formed. Chromatography (SiO_2, 5% MeOH−CH_2Cl_2), afforded 19 mg (68%) of the title compound as the sole product: TLC (5% MeOH−CH_2Cl_2) $R_f = 0.44$ (CAS, light purple).

20′-*epi*-5a′-Homovincovaline (3b). When a 40 mg sample of tosylate **34b** was subjected to the same procedure that was applied to product **34a**, above, 33 mg (73%) of 20′-*epi*-5a′-homovincovaline **3b** was obtained: TLC (10% MeOH−CH_2Cl_2) $R_f = 0.29$ (CAS, purple).

(4*S*)-4-Ethyl-5-(*p*-tolylsulfonyloxy)-4-(trimethylsilyloxy)-pentanal (46). A solution of 0.835 g (5.76 mmol) of (2*S*)-2-ethyl-2-hydroxyhex-5-enol (**40**) and 0.965 mL of triethylamine (6.92 mmol) was cooled to 0 °C, and 2.26 g (6.92 mmol, 1.2 equiv) of toluenesulfonic anhydride in 1 mL of dichloromethane was added. After being stirred at room temperature for 12 h, the solution was washed with water and brine, dried ($MgSO_4$), and concentrated to furnish a yellow oil. The crude product was purified by column chromatography, eluting with 1:1 Et_2O−hexane, to furnish 1.50 g (83%) of the tosylate as a clear colorless oil.

To a solution of 1.50 g (5.4 mmol) of the above alcohol tosylate in 100 mL of dry THF, stirring at 0 °C under nitrogen, was added 1.42 mL (1.5 equiv) of triethylamine, 1.79 g (1.5 equiv) of trimethylsilyl trifluoromethanesulfonate, and about 10 mg of DMAP. After 30 min, the mixture was poured into 75 mL of saturated sodium bicarbonate. Extraction with ether, washing of the extract with saturated sodium bicarbonate and brine, drying over magnesium sulfate, and concentration gave 1.86 g (91% yield) of the TMS ether.

A solution of 1.86 g (4.91 mmol) of (2*S*)-2-ethyl-1-(*p*-tolylsulfonyloxy)-2-(trimethylsiloxy)hex-5-ene in CH_2Cl_2 was cooled to −78 °C and ozone was bubbled through the stirred solution until a blue tint persisted (∼15 min). Excess ozone was removed by purging the reaction vessel with argon for 5 min. Then 1.14 g (5.4 mmol, 1.1 equiv) of triphenylphosphine was introduced as a solution in CH_2Cl_2, and the mixture was allowed to warm to 25 °C. After being stirred for 6 h, the solution was concentrated and the residue was disolved in 1:1 Et_2O−hexane. The triphenylphosphine oxide, which precipitated, was filtered off and the filtrate was purified by flash chromatography, eluting with 1:1 Et_2O−hexane. The aldehyde was obtained as 1.71 g (93%) of a colorless oil: TLC (1:1 Et_2O−hexane) $R_f = 0.35$ (DNP).

(4a*R*,5*R*,12b*S*)- and (4a*S*,5*S*,12b*R*)-Methyl 4-Benzyl-1,2,3,4,4a,5,6,8-octahydro-5-[(2*S*)-2-ethyl-2-[(trimethylsilyl)oxy]-3-[(*p*-tolylsulfonyl)oxy]propyl]pyrido[2,3-*d*]carbazole-7-carboxylate (47a and 47b). In a reaction vessel fitted with a Dean−Stark trap, 1.25 g (3.58 mmol) of *N*-benzyl indoloazocine **22** and 1.42 g (3.83 mmol, 1.1 equiv) of TMS-tosyl aldehyde **46** in 50 mL of toluene were heated at reflux for 18 h. The solvent was removed in vacuo, and the resulting foam was purified by flash chromatography, eluting with 2:1 Et_2O−hexane, to give 2.46 g (97%) of the title compound as an inseparable mixture: TLC (1:1 Et_2O−hexane) $R_f = 0.29$ (CAS, blue-green).

(6*R*,8*S*)- and (6*S*,8*R*)-Methyl 4-Benzyl-2,3,4,4a,5,6,8,9-octahydo-6-[(2*S*)-2-ethyl-2-[(trimethylsilyl)oxy]-3-[(*p*-tolylsulfonyl)oxy]propyl]-8-(15-vindolinyl)-1*H*-azecino-[5,4-*b*]indole-8-carboxylate (48a and 48b). Following the procedure for formation of the binary compounds **32a**,**b**, 437 mg (0.622 mmol) of TMS-tosyl tetracycles **47a**,**b** was coupled to 269 mg (0.591 mmol) of vindoline. Chromatography, eluting with ethyl acetate, gave 361 mg (51%) of the title compounds as an inseparable mixture of diastereomers, along with another very polar material resulting from hydrolysis of the TMS group: TLC (ethyl acetate) $R_f = 0.54$ (CAS, purple).

(6*R*,8*S*)- and (6*S*,8*R*)-Methyl 4-Benzyl-2,3,4,4a,5,6,8,9-octahydo-6-[(2*S*)-2-ethyl-2,3-epoxypropyl]-8-(15-vindolinyl)-1*H*-azecino[5,4-*b*]indole-8-carboxylate (37a and 37b). A solution of 57 mg (0.0492 mmol) of the TMS-tosyl products **48a** and **48b** in 20 mL of THF was stirred at 25 °C, and 0.147 mL of TBAF (3 equiv, 1 M in THF) was added dropwise. After 25 min, TLC indicated complete conversion to a new, more polar product. The reaction mixture was diluted with 20 mL of Et_2O and then washed with aqueous saturated sodium bicarbonate, followed by brine. Drying and concentration gave a yellow foam, which was purified by radial chromatography on a 2 mm plate, eluting with ethyl acetate. The products were obtained as 40 mg (90%) of the title epoxides as a mixture of diastereomers: TLC (ethyl acetate) $R_f = 0.28$ (CAS, purple).

[N^b-(*S*)-α-Methlybenzyl](3-indolyl)-3-propanamide (50) A stirred solution of 9.1 g (48.1 mmol) of indole-3-propionic acid and 6.41 g (52.9 mmol, 1.1 equiv) of *S*-(−)-α-methylbenzylamine in 250 mL of 5:1 CH_3CN−CH_2Cl_2 was cooled to 0 °C. A solution of 10.9 g (52.9 mmol, 1.1 equiv) of dicyclohexylcarbodiimide in 40 mL of $CH_2Cl_2$was added via addition funnel. After the addition was complete, the reaction was stirred at 25 °C for 3 h. The solution was filtered to remove dicyclohexylurea and was then transferred to a separatory funnel and washed successively with 50 mL portions of 1 N HCl, water, 1 N NaOH, and brine. The product mixture was dried ($MgSO_4$) and concentrated by rotary evaporation. The residue was then taken up in Et_2O. The product crystallized from solution as 8.5 g of white prisms. The mother liquor was concentrated and chromatographed, eluting with 1:1:1 ethyl acetate-Et_2O−hexane to furnish an additional 1.3 g of product (70% overall yield): mp 121−122 °C; TLC (3% MeOH−CH_2Cl_2) $R_f = 0.20$ (CAS, yellow orange); $[\alpha]^{25}_D$ −33.4 (*c* 10, MeOH).

3-(3-Indolyl)propanal. A solution of 14.1 g (82.7 mmol) of 3-(2-cyanoethyl)indole in 100 mL of CH_2Cl_2 was stirred vigorously at −60 °C. Then 91 mL of DIBALH (1.0 M in CH_2Cl_2) was added by addition funnel. After being stirred for 30 min at −60 °C, the mixture was stirred an for an additional 1 h at 25 °C, cooled to 0 °C, and quenched by very slow addition of 20 mL of methanol, followed by 25 mL of saturated aqueous sodium potassium tartrate. Vigorous stirring was continued for 40 min (a gelatinous material may form which can be dissolved by addition of 1:1 MeOH−CH_2Cl_2). The product mixture was washed with water and brine, then dried and concentrated. The resulting yellow oil was filtered through a plug of silica gel, rinsing with Et_2O, to give 10.45 g (73%) of the aldehyde, which was used directly in the next step. Note: the R_f of the product matches that of the starting material: TLC (CH_2Cl_2) $R_f = 0.55$ (CAS, orange).

3-[3-[(*N*^{b}-(*S*)-α-Methylbenzyl)amino]propyl]indole (51). Method A. From 10.45 g (60.4 mmol) of indole-3-propionaldehyde, 60 mL of benzene, and 7.8 mL (60.4 mmol) of *S*-(−)-α-methylbenzylamine the solvent was distilled until the volume was reduced by half and the distillate was clear (20 min). The reaction mixture was cooled, and the remaining solvent was removed in vacuo. The residue was taken up in 40 mL of anhydrous methanol and cooled to 0 °C, and sodium borohydride (4.0 g, 110 mmol) was added in several portions with vigorous stirring. After 30 min, 5 mL of concentrated HCl was added dropwise. Concentration to ∼10 mL gave 8.93 g of the amine hydrochloride as a white crystalline solid, which was collected by suction filtration. The filtrate was basified with 10% aqueous ammonium hydroxide and extracted with CH_2Cl_2. Solvent removal provided an additional 2.3 g of the title compound as the free amine. An analytical sample was obtained by flash chromatography (SiO_2, 5% MeOH in CH_2Cl_2), followed by trituration of the concentrated eluate with hexane.

Method B. A solution of 9.47 g (32.4 mmol) of chiral indole-3-propanamide **50** in 100 mL of dry THF was heated to reflux, and 48.6 mL of borane−methyl sulfide solution (2.0 M in THF) was added dropwise. After the addition was complete, the reaction mixture was allowed to stir at reflux for 1 h. The solvent and dimethyl sulfide were distilled until the volume had been reduced by half. The reaction mixture was then cooled to 0 °C, and 60 mL of HCl-saturated methanol was slowly added with vigorous stirring. The acidified solution was then heated to reflux for 30 min to decompose the boron−amine complex. The solvent was removed in vacuo, and the residue was dissolved in a minimum amount of methanol, basified with concentrated ammonium hydroxide, and extracted with CH_2Cl_2. The combined organic extracts were dried, concentrated, and chromatographed, eluting with 5% MeOH−CH_2Cl_2. The product was obtained as 8.22 g (91%) of a yellow oil, which solidified on standing, or on trituration with hexane: mp 83 °C; TLC (5% MeOH−CH_2Cl_2) $R_f = 0.26$ (CAS, yellow).

3-[3-[(*N*^{b}-(*S*)-α-Methylbenzyl-*N*^{b}-*tert*-butoxycarbonyl)-amino]propyl]indole (52). (*S*)-α-Methlybenzyl-*homo*-tryptamine **51** (8.6 g, 27 mmol) was stirred in 100 mL of THF at 0 °C, and 80 mL of 1.0 N NaOH was added, followed by 7.2 g (1.1 equiv) of di-*tert*-butyl dicarbonate. The mixture was stirred for 1 h and then allowed to warm to 25 °C. Diethyl ether (50 mL) was added, and the organic phase was separated, washed twice with 30 mL portions of brine, dried over $MgSO_4$, and concentrated in vacuo. The product was chromatographed (1:1 Et_2O−hexane) to furnish 9.9 g (96%) of the title compound as a colorless oil: TLC (CH_2Cl_2) $R_f = 0.56$ (CAS, yellow); $[\alpha]^{25}_D$ −60.6 (*c* 10, MeOH).

Dimethyl 3-[3-[*N*-(*S*)-α-Methylbenzyl-*N*-*tert*-butoxycarbonylamino]propyl]indole-2-propanedioate (53). Method B. A solution of 2.37 g (5.75 mmol) of chiral benzyl BOC homotryptamine **52** and 0.882 mL (6.33 mmol) of triethylamine in 30 mL of THF was cooled to −60 °C. Dropwise addition of 0.717 mL (6.33 mmol) of *tert*-butyl hypochlorite and stirring for 20 min resulted in complete conversion to the more polar chloroindolenine (CAS, colorless). A solution of 1.3 mL of zinc chloride (1.0 M in Et_2O, 0.2 equiv) was added, and after an additional 5 min, 1.22 g of lithium dimethyl malonate was added as a solution in THF. The reaction mixture was allowed to warm to room temperature and stirring was continued for 6 h. Methanol (2 mL) was added, followed by 20 mL of water, and then the mixture was extracted with Et_2O and the combined organic extracts were washed with 50 mL of brine. Solvent removal, followed by flash chromatography, eluting with CH_2Cl_2, furnished 2.89 g (91%) of **53** as a colorless gum, which was free of *tert*-butyl alcohol: TLC (1:1 Et_2O−hexane) $R_f = 0.28$ (CAS, blue); $[\alpha]^{25}_D$ −50.6 (*c* 10, MeOH).

Dimethyl 3-[3-[*N*^{b}-(*S*)-α-Methylbenzylamino]propyl]indole-2-propanedioate (54). Anhydrous methanol, saturated with HCl, was added to a stirred solution of *t*-BOC derivative **53** (2.85 g, 5.6 mmol) in 10 mL of THF. The clear, colorless solution was heated to near reflux for 3 h, cooled to 23 °C and concentrated by rotary evaporation to ∼3 mL. The residue was basified (10% NH_4OH) and extracted with Et_2O, (3 × 30 mL). The organic extracts were washed with brine and dried ($MgSO_4$). Concentration, followed by flash chromatography (5% MeOH−$CHCl_3$), gave 2.24 g (5.5 mmol, 98%) of the title compound as a colorless oil: TLC (5% MeOH−$CHCl_3$) $R_f = 0.19$ (CAS, blue).

(1*R* and 1*S*)-Methyl 3-[(*S*)-α-Methylbenzyl]-2-oxo-2,3,4,-5,6,11-hexahydro-1*H*-azocino[4,5-*b*]indole-1-carboxylates (55). A solution of dimethyl 3-[3-[(*N*-(*S*)-α-methylbenzyl)-amino]propyl]indole-2-propanedioate (**54**, 2.3 g, 5.6 mmol) in 50 mL of toluene was heated at reflux for 12 h using a Dean−Stark apparatus filled with 4 Å molecular sieves. The solvent was removed in vacuo, and the crude products were chromatographed on a 3 × 15 cm flash silica column, eluting with 1:1 ethyl acetate−hexane. The isolated yield of the products was 85% (1.78 g): TLC (1:1 ethyl acetate−hexane) $R_f = 0.33$, 0.41-(CAS, blue).

(1*R* and 1*S*)-Methyl 3-[(*S*)-α-Methylbenzyl]-2-thioxo-2,3,4,5,6,11-hexahydro-1*H*-azocino[4,5-*b*]indole-1-carboxylate (56). A solution of 1.70 g (4.51 mmol) of chiral lactams **55** and 0.6 equiv of Lawesson's reagent was heated in toluene at 110 °C for 6 h. The cooled reaction mixture was diluted with Et_2O, washed with 10 mL of dilute acetic acid and 10 mL of brine, and then dried and concentrated. The resulting yellow/brown oil was chromatographed, eluting with 3:2 ether−hexane ($CHCl_3$ was used to facilitate solution) to furnish 1.13 g (64%) of the title compound as a mixture of C-1 epimers: TLC (3:2 ether−hexane) $R_f = 0.40$, 0.47 (CAS, yellow).

(1*R* and 1*S*)-Methyl 3-[(*S*)-α-Methylbenzyl]-2,3,4,5,6,-11-hexahydro-1*H*-azocino-[4,5*b*]-indole-1-carboxylates (49). Raney nickel (200 mg) was washed repeatedly with anhydrous methanol and added to a stirred solution of 800 mg (2.22 mmol) of chiral thiolactam **56** in methanol. The mixture was warmed for 3.5 h, cooled, filtered and concentrated to give a yellow solid, which was purified by flash chromatography on a 3 × 12 cm silica gel column, eluting with 1% MeOH−$CHCl_3$, to give 2.36 g (81%) of methyl 3-[(*S*)-α-methylbenzyl]-4,5,6,11-tetrahydro-3*H*-azocino[4,5*b*]indole-1-carboxylate. TLC (7:3 Et_2O−hexane) $R_f = 0.49$ (CAS, yellow).

To a stirred solution of 616 mg (1.32 mmol) of methyl 3-[(*S*)-α-methylbenzyl]-4,5,6,11-tetrahydro-3*H*-azocino-[4,5*b*]-indole-1-carboxylate in 5 mL of glacial acetic acid was added 200 mg (3.31 mmol, 2.5 equiv) of sodium cyanoborohydride in several portions over 10 min. The reaction mixture was allowed to stir for an additional 15 min, then cooled to 0 °C, and basified with 10 mL of ice-cold concentrated ammonium hydroxide. The mixture was extracted with Et_2O, and then the extract was washed with brine, dried ($MgSO_4$), and filtered. The solvent was removed in vacuo, and the resulting foam was purified by flash chromatography, eluting with 7:3 Et_2O−hexane, to give 382 mg (62%) of the title compound as a white foam. Addition of HCl to the reaction mixture prior to workup resulted in significantly reduced yields: TLC (7:3 Et_2O−hexane) $R_f = 0.49$, 0.40 (CAS, blue).

(4*S*)-4-Methyl-5-(*p*-tolylsulfonyloxy)-4-(*tert*-butyldimethylsilyloxy)pentanal (57). A solution of 8.14 g (62.6

mmol) of distilled (2*S*)-2-methyl-2-hydroxyhex-5-enol (**41**)[18] and 14 mL (10.0 mmol) of triethylamine in 50 mL of CH_2Cl_2 was cooled to 0 °C, and 19.1 g (10.0 mmol) of *p*-toluenesulfonyl chloride, as a solution in 15 mL of CH_2Cl_2, was added from an addition funnel. After being stirred at 25 °C for 12 h, the solution was washed with water and was then dried and concentrated. Flash chromatography, eluting with Et_2O, furnished 7.35 g (86%) of 5-(*S*)-5-methyl-5-hydroxy-6-[(*p*-tolylsulfonyl)oxy]hexene: TLC (1:1 Et_2O−hexane) $R_f = 0.3$ (PMA).

A solution of 2.10 g (7.38 mmol) of the tosylate and 1.6 mL (11.4 mmol) of triethylamine in 30 mL of CH_2Cl_2 was stirred at 25 °C, and 2.54 mL (11.1 mmol) of *tert*-butyldimethylsilyl triflate was added dropwise. After the addition was complete, 45 mg (0.37 mmol) of DMAP was added. The reaction was allowed to proceed for 12 h, and the mixture was then washed with saturated sodium bicarbonate (2 × 30 mL), followed by brine. The organic solution was then dried over $MgSO_4$ and concentrated. The orange residue was purified by flash chromatography, eluting with 1:1 Et_2O−hexane, to furnish 2.49 g (87%) of the TBDMS tosylate: TLC (1:2 Et_2O−hexane) $R_f = 0.8$ (PMA).

All of the preceding alkene was taken up in 30 mL of dry CH_2Cl_2 and the solution cooled to −78 °C. Ozone was bubbled through the stirred solution until a blue color was present. The ozone flow was discontinued, and the solution was purged with argon until the blue color faded. A solution of 2.0 g (7.53 mmol) of triphenylphosphine was added as a solution in 5 mL of CH_2Cl_2, and the stirred reaction mixture was allowed to warm to 25 °C. After 8 h the solution was then concentrated to a yellow oil, from which triphenylphosphine oxide solidified. The residue was triturated with hexane and the solid oxide was filtered off. The filtrate was concentrated and purified by flash chromatography to give 2.46 g (98%) of aldehyde: TLC (1:1 Et_2O−hexane) $R_f = 0.58$ (PMA).

(4a*R*,5*R*,12b*S*)- and (4a*S*,5*S*,12b*R*)-Methyl 4-[(*S*)-α-Methylbenzyl]-1,2,3,4,4a,5,6,8-octahydro-5-[(2*S*)-2-methyl-2-[(*tert*-butyldimethylsilyl)oxy]-3-[(*p*-tolylsulfonyl)oxy]-propyl]pyrido[2,3-*d*]carbazole-7-carboxylate (58a and 58b). Under a Dean−Stark trap, 511 mg (1.41 mmol) of chiral *N*-benzyl azocine **49** and 657 mg (1.64 mmol) of (4*S*)-4-methyl-5-(*p*-tolylsulfonyloxy)-4-(*tert*-butyldimethylsilyloxy)pentanal (**57**) in 40 mL of toluene were heated at reflux for 20 h. The solvent was removed in vacuo and the resulting yellow foam was purified by flash chromatography, eluting with 1:1 ethyl acetate−hexane, to give 931 mg (89%) of tosyl TBDMS tetracycles **58a** and **58b**: TLC (1:1 Et_2O−hexane) $R_f = 0.29$ (CAS, blue-green).

(6*R*,8*S* and 6*S*,8*R*)-Methyl 4-[(*S*)-α-Methylbenzyl]-2,3,4,-4a,5,6,8,9-octahydro-6-[(2*S*)-2-methyl-2-[(*tert*-butyldimethylsilyl)oxy]-3-[(*p*-tolylsulfonyl)oxy]propyl]-8-(15-vindolinyl)-1*H*-azecino[5,4-*b*]indole-8-carboxylate (59a and 59b). Following the above procedure for formation of compounds **32a**,**b**, 803 mg (1.08 mmol) of tetracycles **58a**,**b** was coupled to 467 mg (1.03 mmol) of vindoline to provide 301 mg (23%) of the higher R_f (minor) isomer **59b** and 505 mg (39%) of the lower R_f isomer **59a**.

Lower R_f isomer **59a**: TLC (3% MeOH−$CHCl_3$) $R_f = 0.23$ (CAS, purple).

Higher R_f isomer: **59a**: TLC (3% MeOH−$CHCl_3$) $R_f = 0.43$ (CAS).

(6*R*,8*S*)-Methyl 4-[(*S*)-α-Methylbenzyl]-2,3,4,4a,5,6,8,9-octahydro-6-[(2*S*)-2-methyl-2,3-epoxypropyl]-8-(15-vindolinyl)-1*H*-azecino[5,4-*b*]indole-8-carboxylate (60a). A solution of 185 mg (0.154 mmol) of tosyl TBDMS dimer **59a** in 10 mL of THF was stirred at 25 °C and 478 mL of TBAF (1.0 M in THF), was added dropwise. The reaction was allowed to proceed for 4 h and was then diluted with 10 mL of Et_2O and washed with 10 mL of saturated sodium bicarbonate. The organic phase was dried and concentrated to give a white solid that was purified by radial chromatography, eluting with ethyl acetate. The product was obtained as 103 mg (74%) of a white foam: TLC (ethyl acetate) $R_f = 0.25$ (CAS, brown).

(18) Leboulluec, K. L. Ph.D. Thesis, University of Vermont, 1990. Manuscript in preparation.

(6*S*,8*R*)-Methyl 4-[(*S*)-α-Methylbenzyl]-2,3,4,4a,5,6,8,9-octahydro-6-[(2*S*)-2-methyl-2,3-epoxypropyl]-8-(15-vindolinyl)-1*H*-azecino[5,4-*b*]indole-8-carboxylate (60b). A solution of 80 mg (0.0667 mmol) of TBDMS toslyate **59b** was subjected to the conditions described for the epoxidation of **59a**. The product was purified by flash chromatography, eluting with ethyl acetate, to give 54 mg (89%) of epoxide **60b**: TLC (ethyl acetate) $R_f = 0.27$ (CAS, purple).

20′-Desethyl-20-methyl-5a′-homovinblastine (62a). A solution of 25 mg (0.027 mmol) of epoxide **60a** was heated in 5 mL of methanol for 24 h. The solution was cooled to 25 °C and ∼5 mg of 10% palladium on carbon was added, then the stirred mixture was purged with hydrogen. After 2 h, TLC indicated complete debenzylation of the quaternary salt. The solution was filtered, concentrated and purified by flash chromatography to give 17 mg (81%) of **62a**: TLC (ethyl acetate) $R_f = 0.32$ (CAS, purple-tan).

Quarternary Salt (63a). A 50 mg portion of (6*R*,8*S*)-methyl 4-[(*S*)-α-methylbenzyl]-2,3,4,4a,5,6,8,9-octahydro-6-[(2*S*)-2-methyl-2-[(*tert*-butyldimethylsilyl)oxy]-3-[(*p*-tolylsulfonyl)oxy]-propyl]-8-(15-vindolinyl)-1*H*-azecino[5,4-*b*]indole-8-carboxylate (**59a**) was dissolved in 10 mL of benzene and heated at 150 °C in a sealed tube, under an argon atmosphere, for 24 h. After cooling to 25 °C, the solvent was removed by rotary evaporation. The crude product was taken up in THF and treated with 125 mL (0.042 mmol, 3 equiv) of TBAF. The reaction mixture was stirred at 25 °C for 4 h and then concentrated. This material was disolved in ∼2 mL of methanol and applied to a 8 × 1 cm column of Amberlite IRA 400 (chloride) ion-exchange resin, and eluted with methanol. CD data: λ_{max} 256, 316 nm, $q = +31, 18$.

Quaternary Salt (61a). A 45 mg (0.049 mmol) sample of (6*R*,8*S*)-methyl 4-[(*S*)-α-methylbenzyl]-2,3,4,4a,5,6,8,9-octahydro-6-[(2*S*)-2-methyl-2,3-epoxypropyl]-8-(15-vindolinyl)-1*H*-azecino[5,4-*b*]indole-8-carboxylate (**60a**) was heated at reflux in 10 mL of methanol for 18 h. The solution was concentrated to ∼2 mL and passed through an 8 × 1 cm column of Amberlite IRA 400 (chloride) ion-exchange resin. Solvent removal afforded the "unnatural" quaternary salt as a white film. CD data: λ_{max} 261, 300 nm, $q = +39, -8$.

***cis*-(2-(2,5-Dithiolanylmethyl)cyclohexyl)methyl (*p*-Nitrophenoxy)formate.** A solution of *cis*-(2-(2,5-dithiolanylmethyl)cyclohexyl)methan-1-ol (1.0 g, 4.3 mmol)[15] and *p*-nitrophenyl chlorocarbonate (984 mg, 4.73 mmol) in 20 mL of pyridine was stirred at room temperature for 24 h. The solvent was evaporated under reduced pressure. The residue was dissolved in ether and washed with water and brine. The residue, obtained on concentration, was purified on a silica gel column, eluting with ether−hexane (3:7), to afford 1.7 g of product as a colorless oil (99% yield): TLC $R_f = 0.29$ (Et_2O/Hex, 3:7).

***cis*-2-(2-Oxoethyl)cyclohexyl)methyl (*p*-Nitrophenoxy)-formate (73).** To a solution of HgO (217 mg, 1.0 mmol) and HBF_4 (48%, 393 μL, 2.15 mmol) in 4 mL of THF and 1 mL of water, at room temperature, was added dropwise *cis*-(2-(2,5-dithiolanylmethyl)cyclohexyl)methyl (*p*-nitrophenoxy)formate (200 mg, 0.5 mmol) in 2 mL of THF. The solution was stirred for an additional 5 min, dichloromethane was added, and the mixture was filtered through a Celite pad. The filtrate was washed with 10% NaI and saturated $NaHCO_3$. Chromatography on a silica gel column, eluting with ether−hexane (2:3), gave 140 mg of product as an oil (87% yield): TLC $R_f = 0.31$ (Et_2O/Hex, 2:3).

(4a*R*,*S*,5*R*,*S*,12b*S*,*R*)-Methyl 4-Benzyl-1,2,3,4,4a,5,6,8-octahydro-5-((1′*S*,*R*, 2′*S*,*R*, and 1′*R*,*S*,2′*R*,*S*)-2-((1-imidazole)carbonyloxymethyl)cyclohexyl)pyrido[2,3-*d*]carbazole-7-carboxylate (71, 72). A solution of indoloazocine **22** (100 mg, 0.287 mmol) and *cis*-(2-(2-oxoethyl)cyclohexyl)methyl (*p*-nitrophenoxy)formate (**73**, 111 mg, 0.344 mmol) in 5 mL of dry toluene was heated at reflux for 5 h. The solvent was removed under reduced pressure and the residue taken into 4 mL of THF and 1 mL of water. Imidazole (40 mg, 0.574 mmol) was added at room temperature, and the solution was stirred for an additional 2 h. The product was extracted with dichloromethane. The combined organic phase was washed

with saturated sodium bicarbonate and brine. The residue was chromatographed on a silica gel column, eluting with EtOAc−Hex (3:7), to give 55 mg of tetracycle **72** (33% yield) and 60 mg of tetracycle **71** (36% yield) as a white foam.

For **72**: TLC $R_f = 0.14$ (EtOAc/Hex, 3:7; CAS, green).

For **71**: TLC $R_f = 0.08$ (EtOAc/Hex, 3:7; CAS, green).

(4a*R*,*S*,5*R*,*S*,12b*S*,*R*)-Methyl 4-Benzyl-1,2,3,4,4a,5,6,8-octahydro-5-((1′*S*,*R*,2′*S*,*R*, and 1′*R*,*S*,2′*R*,*S*)-2-(hydroxymethyl)cyclohexyl)pyrido[2,3-*d*]carbazole-7-carboxylate (74, 75). Method a. A solution of indoloazocine **22** (500 mg, 1.435 mmol) and *cis*-(2-(2-oxoethyl)cyclohexyl)methyl (*p*-nitrophenoxy)formate (**73**, 553 mg, 1.72 mmol) in 20 mL of dry toluene was heated at reflux for 5 h. The solvent was removed under reduced pressure, and the residue was taken into 20 mL of THF and 5 mL of 2 N NaOH. The solution was stirred at room temperature for 40 min and then extracted with dichloromethane. The residue, obtained on concentration, was chromatographed on a silica gel column (EtOAc−Hex, 35:65) to afford 210 mg of tetracycle **75** (30% yield) and 220 mg of tetracycle **74** (32% yield) as a white foam.

For **75**: TLC $R_f = 0.33$ (EtOAc/Hex, 35:65; CAS, green).

For **74**: TLC $R_f = 0.21$ (EtOAc/Hex, 35:65; CAS, green).

Method b. A solution of imidazole derivative **72** (60 mg, 0.103 mmol) in 3 mL of THF and 0.5 mL of 2 N NaOH was stirred at room temperature for 40 min. The product was extracted with dichloromethane. The residue, obtained on concentration, was chromatographed on a silica gel column (EtOAc−Hex, 1:1) to afford 49 mg of product **75** as a white foam (98% yield).

(4a*R*,*S*,5*R*,*S*,12b*S*,*R*)-Methyl 4-Benzyl-1,2,3,4,4a,5,6,8-octahydro-5-((1′*S*,*R*,2′*S*,*R*)-2-(tosyloxymethyl)cyclohexyl)pyrido[2,3-*d*]carbazole-7-carboxylate (76). To a solution of the tetracyclic alcohol **74** (160 mg, 0.329 mmol), DMAP (4 mg, 0.033 mmol), and Et_3N (91 μL, 0.658 mmol) in 15 mL of dichloromethane, at 0 °C, was added Ts_2O (172 mg, 0.526 mmol) in one portion. The solution was stirred at 0 °C for 1.5 h, and then the solvent was evaporated in a vacuum at 15 °C. The residue was chromatographed on a silica gel column (Et_2O−Hex, 2:3) to afford 150 mg of the title product as a white foam (71% yield): TLC $R_f = 0.20$ (Et_2O/Hex, 2:3; CAS, blue/green).

(6*R*,8*S*)-Methyl 4-Benzyl-2,3,4,4a,5,6,8,9-octahydro-6-(1′*S*,2′*S*)-2-(tosyloxymethyl)cyclohexyl]-8-(15-vindolinyl)-1*H*-azecino[5,4-*b*]indole-8-carboxylate (78a) and Its (6*S*,8*R*,1′*R*,2′*R*)-Diastereomer (78b). To a solution of tetracyclic tosylate **76** (70 mg, 0.11 mmol) and Et_3N (19 μL, 0.132 mmol) in 6 mL of dichloromethane, at 0 °C, was added dropwise *t*-BuOCl (16 μL, 0.132 mmol). After being stirred for 5 min at 0 °C, the mixture was partioned between water and dichloromethane. The dried organic phase was concentrated under vacuum at 20 °C. The residue was dissolved in 6 mL of dry acetone and cooled to 0 °C. Vindoline free base (48 mg, 0.104 mmol) was added, followed by dropwise addition of HBF_4·Et_2O complex (42 μL, 0.219 mmol). The solution was stirred for 5 min. $AgBF_4$ (43 mg, 0.219 mmol) was added in one portion. After the solution was stirred in the dark for 15 min, 10% NH_4OH in saturated brine was added and the solution was extracted several times with dichloromethane. The dried organic phase was concentrated under vacuum. The residue was dissolved in 4.5 mL of HOAc, and KBH_4 (59 mg, 1.1 mmol) was added at 20 °C in several portions. After 10 min of further stirring, the reaction was quenched by adding water−ice and then basified to pH ∼10 with concentrated NH_4OH, while the flask was well cooled in an ice bath. The aqueous phase was extracted with dichloromethane. The residue, obtained on concentration, was chromatographed on a silica gel column, eluting with EtOAc−Hex (4:1), to obtain 40 mg of **74a** ($R_f = 0.5$, EtOAc/Hex, 4:1; CAS blue/green; 35% yield) and 35 mg of **74b** ($R_f = 0.3$, EtOAc/Hex, 4:1; CAS, blue/green; 31% yield) as a white solid.

(3*S*,18*S*,23*R*)-Methyl 5,16-Diazapentacyclo[14.7.1.0^{4,12}.0^{6,11}.0^{18,23}]tetracosa-4(12),6(11),7,9-tetraene-3-vindolinyl-3-carboxylate (65a) and Its Higher Energy Atropisomer (81a). A solution of 80 mg of the tosylate **78a** (0.073 mmol) in 20 mL of dry toluene was heated at reflux for 4 h. The solvent was removed under reduced pressure, and the residue (**79a**, **80a**) was hydrogenolyzed in 10 mL of MeOH in the presence of 7.7 mg of 10% Pd−C for 3 h. Filtration through Celite and concentration gave the crude products, which were dissolved in dichloromethane and shaken with 10% Na_2CO_3. The aqueous layer was extracted with dichloromethane. The residue was chromatographed on a silica gel column, eluting with EtOAc−MeOH−Et_3N (90:10:1), followed by MeOH−Et_3N (9:1), to give 30 mg of "natural" conformation product **65a** (49% yield) and 25 mg of its atropisomer **81a** (39% yield) as a white solid.

For **65a**: TLC $R_f = 0.95$ (CH_2Cl_2/MeOH, 98:2, SiO_2 plate deactivated with Et_3N; CAS, light blue/gray).

For **81a**: TLC $R_f = 0.5$ (CH_2Cl_2/MeOH, 9:1, SiO_2 plate deactivated with Et_3N; CAS, light blue/gray).

(3*R*,18*R*,23*S*)-Methyl 5,16-Diazapentacyclo[14.7.1.0^{4,12}.0^{6,11}.0^{18,23}]tetracosa-4(12),6(11),7,9-tetraene-3-vindolinyl-3-carboxylate (65b) and Its Higher Energy Atropisomer (81b). A solution of 70 mg of tosylate **78b** (0.064 mmol) in 20 mL of dry toluene was heated at reflux for 4 h. The solvent was removed under reduced pressure, and the residual quaternary salts were hyrogenolyzed for 3 h in 10 mL of MeOH in the presence of 6.8 mg of 10% Pd−C. Filtration through Celite and concentration gave the crude ammonium salts, which were dissolved in dichloromethane and shaken with 10% Na_2CO_3. The aqueous layer was extracted with dichloromethane. The residue was chromatographed on a silica gel column, eluting with EtOAc−MeOH−Et_3N (90:10:1), followed by MeOH−Et_3N (9:1), to give 30 mg of the lower energy conformer **65b** (52% yield) and 18 mg of its higher energy atropisomer **81b** (37% yield) as white solids.

For **65b**: TLC $R_f = 0.96$ (CH_2Cl_2/MeOH, 9:1, SiO_2 plate deactivated with Et_3N; CAS light blue/grey).

For **81b**: TLC $R_f = 0.34$ (CH_2Cl_2/MeOH, 9:1, SiO_2 plate deactivated with Et_3N; CAS, light blue/gray).

(4a*R*,*S*,5*R*,*S*,12b*S*,*R*)-Methyl 4-Benzyl-1,2,3,4,4a,5,6,8-octahydro-5-((1′*R*,*S*,2′*R*,*S*)-2-(tosyloxymethyl)cyclohexyl)pyrido[2,3-*d*]carbazole-7-carboxylate (77). To a solution of alcohol **75** (190 mg, 0.39 mmol), DMAP (5 mg, 0.041 mmol), and Et_3N (108 μL, 0.78 mmol) in 15 mL of dichloromethane at 0 °C was added Ts_2O (204 mg, 0.62 mmol) in one portion. The solution was stirred at 0 °C for 1.5 h. The solvent was evaporated in a vacuum at 15 °C, and the residue was chromatographed on a silica gel column (CH_2Cl_2-EtOAc−Hex, 1:1:8) to afford 180 mg of the tosylate **77** as a white foam (72% yield): TLC $R_f = 0.19$ (EtOAc/CH_2Cl_2/Hex, 1:1:8, CAS, blue/green).

(3*R*,18*S*,23*R*)-Methyl 5,16-Diazapentacyclo[14.7.1.0^{4,12}.0^{6,11}.0^{18,23}]tetracosa-4(12),6(11),7,9-tetraene-3-vindolinyl-3-carboxylate (83a) and Its (3*S*,18*R*,23*S*)-Diastereomer (83b). To a solution of tosylate **77** (65 mg, 0.086 mmol) and Et_3N (15 μL, 0.103 mmol) in 5 mL of dichloromethane, at 0 °C, was added *t*-BuOCl (13 μL, 0.103 mmol) dropwise. After being stirred for 5 min at 0 °C, the mixture was partioned between water and dichloromethane. The dried organic phase was concentrated under vacuum at 20 °C and the residue was dissolved in 6 mL of dry acetone, and cooled to 0 °C. Vindoline free base (37 mg, 0.081 mmol) was added, followed by dropwise addition of HBF_4·Et_2O complex (30 μL, 0.081 mmol). The solution was stirred for 5 min, and $AgBF_4$ (39 mg, 0.172 mmol) was added in one portion. After stirring in the dark for 15 min, 10% NH_4OH in saturated brine was added, and the solution was extracted with dichloromethane several times.The dried organic phase was concentrated under vacuum. The residue was dissolved in 4 mL of HOAc, and KBH_4 (47 mg, 0.86 mmol) was added at 20 °C in several portions. After 10 min of further stirring, the reaction was quenched by adding water−ice, and the mixture was basified to pH ∼10 with concentrated NH_4OH, while the flask was well cooled in an ice bath. The aqueous phase was extracted with dichloromethane. The residue (**82a**, **82b**), obtained on concentration, was dissolved in 40 mL of dry toluene and the solution was heated at 50 °C for 4 h. Concentration and chromatography (CH_2Cl_2−MeOH, 9:1) gave 55 mg of the white, solid quaternary salts, which were hyrogenolysed in 20 mL of MeOH, in the presences of 4

mg of 10% Pd−C, for 3 h. Filtration through Celite and concentration gave the crude products, which were dissolved in dichloromethane and shaken with 10% Na_2CO_3. The aqueous layer was extracted with dichloromethane. The residue was chromatographed on a silica gel column, eluting with CH_2Cl_2−Hex-Et_3N (100:100:1), to give 18 mg of natural conformation product **83a** (27% yield) and 16 mg of its diasteromer **83b** (24% yield) as white solids.

For **83a**: TLC R_f = 0.19 (CH_2Cl_2/Hex, 1:1, SiO_2 plate deactivated with Et_3N; CAS, light blue/grey).

For **83b**: TLC R_f = 0.12 (CH_2Cl_2/Hex, 1:1, SiO_2 plate deactivated with Et_3N; CAS, light blue/grey).

Atropisomeric Inversions. Rates of conformational inversions of the atropisomers **81a** and **81b** to the corresponding binary indole-indolines **65a** and **65b** were measured by heating 1 mg samples in 2.5 mL of toluene at 110 °C ($k = 2.73 \times 10^{-4}s^{-1}$), 100 °C ($k = 9.82 \times 10^{-5}s^{-1}$), 91 °C ($k = 4.62 \times 10^{-5}s^{-1}$) and at 101 °C ($k = 4.88 \times 10^{-4}s^{-1}$), 90 °C ($k = 1.52 \times 10^{-4}s^{-1}$) and 75 °C ($k = 4.18 \times 10^{-5}s^{-1}$), respectively, taking 10−18 conversion points. The progress of the conformational inversion was followed by HPLC on a Rainin Rabbit-HP instrument with an Si column, eluted with CH_2Cl_2/MeOH/Et_3N, 85:15:3, at 580 psi and 300 mL/min (refill 8, comp rate 4 settings). The relative retention times were **65a**: 2.27 min, **81a**: 8.44 min, **65b**: 2.29 min, **81b**: 11.11 min. Thermodynamic constants were calculated from $\Delta G^{\ddagger} = RT(23.76 + \ln T - \ln k)/1000$; $\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$.

Biological Data. Tubulin polymerization inhibition and L-1210 or S-180 cytotoxicities were determined according to protocols previously used in our laboratories with vinblastine congeners.[19,20]

Acknowledgment. We thank Mr. Robert Bennett of our group for low-resolution mass spectra and the Emory University Mass Spectrometry Center and Dr. Michael Gross of the Washington University Mass Spectrometry Research Resource for high-resolution mass spectra. These studies were supported by the National Cancer Institute through NIH Grant No. CA RO1 12010.

Supporting Information Available: A complete Experimental Section containing UV, IR, ^1H and ^{13}C NMR, MS data, and elemental analyses/HRMS molecular ion values is provided. Also, full NMR spectra, ^1H and ^{13}C, except where marked by (), for compounds **3a**,**b**, **8**, **13**, **14**, **16**−**23**, **27a**,**b**, (**28b**), (**30**), (**33a**), (**33b**), (**34b**), (**37a** and **37b**), (**39**), **42**, **44a**,**b**, (**46**), (**47a** + **b**), (**48a** + **b**), **49**, **50**−**55**, **56 upper**, **56 lower**, (**57**), (**58a** + **b**), **59a**,**b**, **60a**, (**60b**), **62a**, (**69a** + **b**), **69b**, (**70a** + **b**), **71**, (**72**), **73**, **74**, (**75**), (**76**), **77**, **83a**,**b**, and NMR spectra for unnumbered intermediates indicated in the Experimental Section, are reproduced. This material is available free of charge via the Internet at http://pubs.acs.org.

JO000249Z

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