1.57 (s, four CH_3); ^{13}C NMR δ 114.6 (CN), 162.5 (NC). Anal. Calcd for $C_{13}H_{19}O_5N$ (269.29): C, 57.98; H, 7.11; N, 5.20. Found: C, 57.87; H, 7.16; N, 5.19.

Procedure B. Fractions 22-24 from the flash chromatography of **6b/8b** (procedure B) gave a crystalline mass that was recrystallized from THF/petroleum ether to give a mixture of **6a** and **8a**: 0.3 g (2%).

2,3:4,6-Di-*O*-isopropylidene-β-D-mannopyranosyl Cyanide (7b) and 2,3:4,6-Di-*O*-isopropylidene-β-D-mannopyranosyl Isocyanide (9b). Procedure A. The method described for **6b/8b** was applied to **5a** (5.0 g, 19.1 mmol) to give fractions 5-11 containing **7b** and **9b** (a syrup): 2.8 g (54%); $[\alpha]^{20}_D$ -36.3°; TLC R_f 0.73; IR 2950, 3000 (CH), 2125 (CN/NC) cm^{-1}. Anal. Calcd for $C_{13}H_{19}O_5N$ (269.29): C, 57.98; H, 7.11; N, 5.20. Found: C, 57.46; H, 7.03; N, 4.99.

Procedure B. The method described in procedure A was applied to **5b** (5.0 g, 19.1 mmol) and gave a syrup containing **7b** and **9b**: 1.9 g (37%).

Purification of 7b and 9b via Preparative HPLC. The method described for the purification of **6b** and **8b** was applied to **7b** and **9b** (1 g in 2 mL of methanol). Earlier fractions containing **7b** and later fractions containing **9b** were collected, freed from methanol in vacuo, and extracted with CH_2Cl_2. The organic layers were dried (Na_2SO_4) and concentrated in vacuo to give pure **7b** and **9b**. **7b**: 0.2 g; $[\alpha]^{20}_D$ -36.4°; IR (in $CHCl_3$) 2950, 3000 (CH), 2130 (CN) cm^{-1}; ^1H NMR δ 5.53 (d, H^1), 4.38 (d, H^2), 4.27 (m, H^3), 3.77 (m, H^4), 3.60 (m, H^5), 3.71, 3.97 (m, H^6), 1.39, 1.45, 1.52, 1.56 (s, four CH_3); ^{13}C NMR δ 67.36 (C^1), 74.22 (C^2), 74.89 (C^3), 72.13 (C^4), 64.83 (C^5), 61.42 (C^6), 18.79, 26.26, 28.08, 28.89 (four CH_3), 100.01, 110.78 (two $C(CH_3)_2$), 115.53 (CN). **9b**: 0.5 g; $[\alpha]^{20}_D$ -58.7°; IR (in $CHCl_3$) 2945, 3000 (CH), 2125 (NC) cm^{-1}; ^1H NMR δ 5.28 (d, H^1), 4.36 (d, H^2), 4.26 (m, H^3), 3.76 (m, H^4), 3.60 (m, H^5), 3.71, 3.94 (m, H^6), 1.37, 1.43, 1.50, 1.54 (s, four CH_3); ^{13}C NMR δ 65.70 (C^1), 74.67 (C^2), 74.34 (C^3), 72.15 (C^4), 64.84 (C^5), 61.40 (C^6), 18.81, 26.38, 28.12, 28.93 (four CH_3), 100.1, 110.8 (two $C(CH_3)_2$), 163.1 (NC).

2,3:5,6-Di-*O*-isopropylidene-α-D-mannopyranosyl Isocyanide (9a). Procedure A. Fractions 18-19 from the flash chromatography of **7b/9b** (procedure A) gave a crystalline mass that was recrystallized from THF/petroleum ether to give **9a**: 0.4 g (8%); mp 121-122 °C; $[\alpha]^{20}_D$ -55.0°; TLC R_f 0.37; IR 2960, 3000 (CH), 2140 (NC) cm^{-1}; ^1H NMR δ 5.19 (d, H^1), 4.30 (m, H^{2-4}), 3.38 (m, H^5), 3.83, 3.96 (m, H^6), 1.40, 1.43, 1.55, 1.64 (s, four CH_3); ^{13}C NMR δ 78.13 (C^1), 72.82 (C^2), 70.51 (C^3), 75.52 (C^4), 67.50 (C^5), 62.40 (C^6), 18.94, 25.56, 26.97, 28.91 (four CH_3), 100.0, 112.0 (two $C(CH_3)_2$), 163.0 (NC). Anal. Calcd for $C_{13}H_{19}O_5N$ (269.29): C, 57.98; H, 7.11; N, 5.20. Found: C, 57.87; H, 7.16; N, 5.19.

Procedure B. Fractions 18-19 from the flash chromatography of **7b/9b** (procedure B) gave a crystalline mass that was recrystallized from THF/petroleum ether to give a mixture of **7a** and **9a**: 0.5 g (10%). This mixture was subjected to further flash chromatography with THF/methylcyclohexane (2:8) as the solvent. Fractions of 40-50 mL were collected. Fractions 7-8 gave pure **9a**: 0.23 g (4.5%); mp 121-122 °C.

2,3:5,6-Di-*O*-isopropylidene-α-D-mannopyranosyl Cyanide (7a). Procedure A. Fractions 20-23 from the flash chromatography of **7b/9b** (procedure A) gave a mixture of **7a** and **9a** that was saved to be rechromatographed: 0.2 g (4%). Fractions 24-26 of the preceding flash chromatography gave a crystalline mass that was recrystallized from THF/petroleum ether to give **7a**: 0.3 g (6%); mp 148-149 °C; $[\alpha]^{20}_D$ -55.2°; TLC R_f 0.29; IR 2950, 3000 (CH), 2140 (CN) cm^{-1}; ^1H NMR δ 4.70 (d, H^1), 4.50 (d, H^2), 4.13 (q, H^3), 3.76 (t, H^4), 3.19 (m, H^5), 3.89 (m, H^6), 1.39, 1.40, 1.51, 1.60 (s, four CH_3); ^{13}C NMR δ 65.49 (C^1), 73.02 (C^2), 75.50 (C^3), 71.75 (C^4), 69.94 (C^5), 61.54 (C^6), 18.80, 26.25, 28.98, 28.92 (four CH_3), 111.3, 114.8 (two $C(CH_3)_2$), 114.8, (CN). Anal. Calcd for $C_{13}H_{19}O_5N$ (269.29): C, 57.98; H, 7.11; N, 5.20. Found: C, 57.87; H, 7.16; N, 5.19.

Procedure B. Fraction 9 of the second chromatographic purification of **9a** (procedure B) gave a mixture of **7a** and **9a** that was saved to be rechromatographed: 0.1 g (2%). Fractions 10-12 gave pure **7a**: 0.17 g (3.3%); mp 148-149 °C.

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Registry No. **1a**, 89025-46-7; **1b**, 78153-79-4; **2**, 14131-84-1; **3**, 130495-48-6; **4a**, 94898-41-6; **4b**, 96089-62-2; **5a**, 130495-46-4; **5b**, 130495-47-5; **6a**, 130468-51-8; **6b**, 130468-52-9; **7a**, 130495-49-7; **7b**, 130495-50-0; **8a**, 130468-53-0; **8b**, 130468-54-1; **9a**, 130495-51-1; **9b**, 130495-52-2; Et_2AlCN, 5804-85-3; 2-fluoro-1-methylpyridinium tosylate, 58086-67-2; 2,3,4,6-tetra-*O*-benzyl-D-glucose, 38768-81-9; D-mannose, 3458-28-4.

Enantioselective Syntheses of Vinblastine, Leurosidine, Vincovaline, and 20′-*epi*-Vincovaline

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The binary indole-indoline alkaloids vinblastine (**1**), leurosidine (**13**), 20′-*epi*-vincovaline (**14a**), and vincovaline (**14b**) were obtained by coupling of vindoline (**3**) to the tetracyclic intermediates **7a**, **7b** or **22a**, **22b**, followed by reduction and cyclization steps (60% overall yield for these reactions). The intermediates were obtained by enantioselective establishment of C20′ through a first-step Sharpless oxidation (**10a,b**) and followed by a subsequent diastereomeric separation (**20a,b** or **21a,b**). Alternatively, enantioselective control of the key secodine-type cyclization in the reaction sequence provided the tetracyclic intermediates **54** and **60** for coupling to vindoline. Selective generation of the natural (**1**, **13**, **14a,b**) or unnatural (**30**, **34**, **35a,b**) atropisomeric forms of the alkaloids was achieved through alternative closures of ring D′. The natural products were also obtained from the higher energy atropisomers by conformational inversion on heating. For the vinblastine synthesis, the overall yield was 22%.

Efforts directed toward the synthesis of vinblastine (**1**)[1] have a rich history, starting in 1967. Since there are adequate reviews of these studies,[2-4] we summarize here only their culmination for comparison with the results that are

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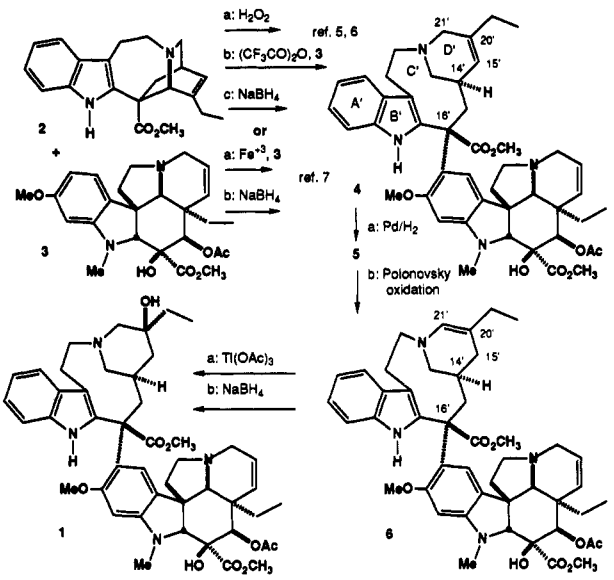
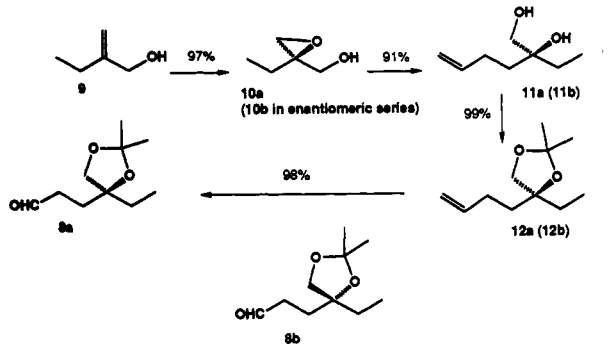
Scheme I



presented below. Starting from the natural products catharanthine (2), a relatively rare alkaloid, and vindoline (3), the major alkaloid of *Catharanthus roseus*, anhydrovinblastine (4) was generated either by coupling of trifluoroacylated catharanthine *N*-oxide (50–60%)[5,6] or by coupling of catharanthine under Fe^{+3}-promoted oxidative conditions (77%),[7] followed in each case by a reduction with sodium borohydride (Scheme I). The starting material catharanthine (2) can be generated synthetically, as a racemate, by two alternative routes in 9%[8] or in 7%[9] overall yield. While we have previously obtained vindoline (3) by an enantiospecific synthesis,[10] natural abundance has generally provided this compound for synthetic studies.

The coupling product anhydrovinblastine (4) was hydrogenated to 20′-deoxyleurosidine (5), and that (natural) product was subjected to a Polonovsky oxidation. A following oxidation of the resultant enamine 6 with thallium triacetate and a final borohydride reduction, with hydrolysis of the 20′-acetate function, then provided vinblastine (1).[11] The reported 30% overall conversion of anhydrovinblastine (4) to vinblastine (which we could confirm only in much lower yield) is surprising in view of the parallel report of Polonovsky oxidation of the amine

Scheme II



5, which gave, instead of the enamine 6, only ring C′ fragmentation products.[12]

An improved oxygenation at C20′ was found in 1,4-reduction of the initial coupling product of catharanthine (2) and vindoline (3) by an NADH analogue, thus directly providing the enamine 6, which was then subjected to $FeCl_3$-promoted oxygenation.[13]

The following report describes the synthesis of an enantiomerically defined substrate **7a** (Scheme IV) for coupling to vindoline (3) and the conversion of this intermediate **7a** to vinblastine (1) in 61% yield. This convergent synthesis provided vinblastine in 22% overall yield.

Four key stereochemical considerations had to be addressed for our synthesis of vinblastine: (1) Achievement of a C16′*S*,C14′*R* configuration was required for the product and for an anticancer activity that is based on interference with cellular microtubule formation. The desired C16′–C14′ *parf* stereochemistry could be expected as a result of coupling of a *D*/*E*-*trans*-*D*-*seco*-ψ-vincadifformine intemediate **7** with vindoline (3), as demonstrated in the synthesis of the model product 20′-deethyl-20′-deoxyvinblastine.[14] (2) Generation of one specific enantiomer (**7a**) of intermediate **7** by a diastereomeric separation was anticipated if precursors of intermediate **7** could be synthesized by a route that would enantioselectively fix the absolute stereochemistry at C20′.[15] (3) A selective formation of the required diastereomer **7a** (vs **22a**) would then entail stereocontrol of the secodine-type cyclization, leading to the tetracyclic intermediate **7**. (4) Finally, better control over the formation of atropisomeric binary alkaloid products was desired.[14,15] All four goals were reached in the studies described below.

For our synthesis of the carbomethoxyvelbanamine moiety of vinblastine (and of 20′-*epi*-vincovaline) we required the 4*S* aldehyde **8a**. This chiral aldehyde was synthesized from 2-ethyl-2-propenol (**9**, Scheme II). A catalytic Sharpless epoxidation[16] of the allylic alcohol **9** with D-(−)-diethyl tartrate, titanium(IV) isopropoxide, and *tert*-butyl hydroperoxide gave 2-ethyl-2,3-epoxypropanol in 97% yield. The enantiomeric purity of this epoxide was determined through ^1H NMR spectra of its Mosher ester,[17] with integration of the doublet signals at δ 4.27 and 4.19, indicating, respectively, formation of 93% of the 2*R* ester diastereomer derived from **10a** and at most 7% of the 2*S* ester diastereomer derived from **10b**. A Grignard reaction

(1) Conformational representations for vinblastine (Scheme V) and other binary alkaloids shown in this paper are approximations of energy-minimized structures obtained by Timothy Spitzer, of our research group, using the Clark Still Macromodel computer program. The position numbering system is that of LeMen, J.; Taylor, W. I. *Experientia* **1965**, *21*, 508.

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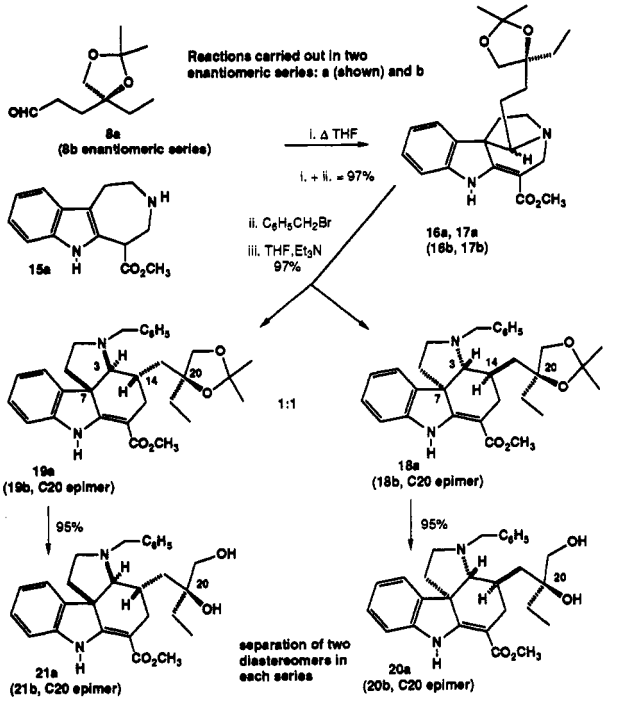
Scheme III



of the epoxide **10a** with allylmagnesium chloride, in the presence of cuprous iodide, then gave the diol **11a** in 91% yield. The hydroxy functions were masked by quantitative formation of an acetonide, using an exchange reaction with 2,2-dimethoxypropane in acetone, and the olefinic ketal **12a** was then subjected to ozonolysis at −78 °C in dichloromethane, to furnish the 4*S* aldehyde **8a** in 98% overall yield from the diol **11a**. Similarly, the 4*R* aldehyde **8b**, which leads to leurosidine (**13**) and to vincovaline (**14b**) was obtained by using L-(+)-diethyl tartrate.

Condensation of the aldehydes **8a** (or **8b**) with the indoloazepine **15a** furnished, respectively, two sets of bridged azepines **16a** and **17a** (or **16b** and **17b**) as diastereomeric mixtures (Scheme III).[18] Without isolation, these products were subjected to N-benzylation and rearrangement by treatment of the initial quaternary salts with triethylamine, to provide the pairs of diastereomeric tetracyclic amines **18a**, **19a** (or **18b**, **19b**) in a 1:1 ratio, in 94% yield in each series.

Alternatively, these tetracyclic amines could be obtained in 89% yield by condensation of the aldehydes **8a** (or **8b**) with the N^b-benzylated indoloazepine **15b** in refluxing toluene. (See further discussion of this reaction below.)

Hydrolysis of the acetonide function with aqueous hydrochloric acid (95% yield) then allowed chromatographic separation of the constituents of each diastereomeric pair of diols (1:1) **20a**, **21a** (or **20b**, **21b**) and the individual processing of each product through the following reactions: The primary hydroxyl function of each diol was converted to a tosylate derivative by reaction with *p*-toluenesulfonic anhydride and triethylamine, and the remaining tertiary hydroxyl group was then protected as a trimethylsilyl ether by reaction with trimethylsilyl trifluoromethanesulfonate and triethylamine. The overall yields of these reactions ranged from 70 to 72%.

Coupling of the resulting tetracyclic amine acrylates **7a** (or **22a**, **7b**, **22b**) to vindoline (**3**) was achieved (Scheme IV) by the methodology previously described for the synthesis of 20′-deethyl-20′-deoxyvinblastine.[14] Thus, chlo-

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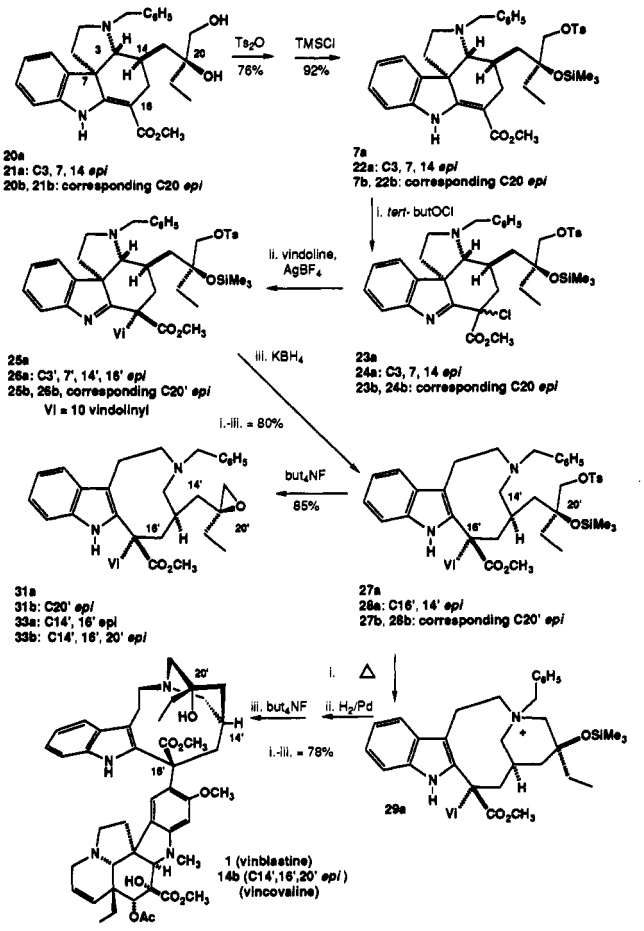
Scheme IV



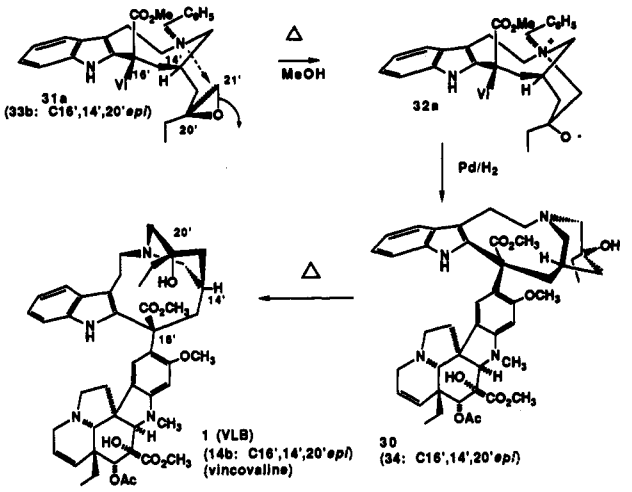
rination with *tert*-butyl hypochlorite and reaction of the resulting chloro imines **23a** (or **24a**, **23b**, **24b**) with silver tetrafluoroborate and vindoline hydrofluoroborate, provided the tetracyclic C16′–C14′ *parf* indolenine **25a** (or **26a**, **25b**, **26b**), from which a reductive opening with potassium borohydride in acetic acid furnished the indoloazonine **27a** (or **28a**, **27b**, **28b**) in 80–85% overall yields. The corresponding (undesired) C16′–C14′ *pref* diastereomers were not detected.

The product structures could be assigned by correlation of the compounds' spectra with those of the 20′-deethyl-20′-deoxy compounds that were characterized earlier,[14] with particular attention to the characteristic chemical shift values of the vindolinyl ethyl CH_3 triplets in the ^1H NMR spectra. Notably, this signal is found in the vinblastine-type C16′–C14′ stereochemical arrangement at δ 0.8, downfield from the signals in the alternative stereochemical arrangements.

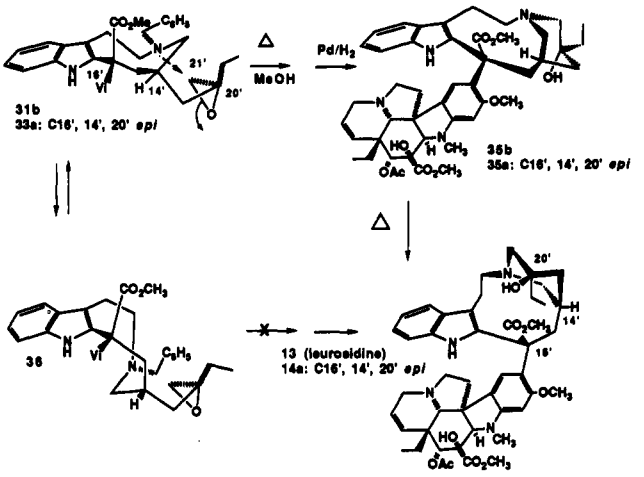
Attempts to obtain cyclization of the vinblastine precursor tosylate **27a** by heating it in toluene, according to the procedure that had given such cyclization in the 20′-deoxy[15] and in the 20′-deethyl-20′-deoxy series,[14] gave only recovered tosylate **27a** after 2 weeks in toluene at reflux. However, in refluxing methanol, the quaternary salt **29a** was formed in 48 h. Hydrogenolysis of its benzyl substituent and cleavage of the silyl ether with fluoride ion then provided vinblastine (**1**) in its natural atropisomeric form in 78% overall yield from the tosylate **27a**.

Indirectly, the silyloxy tosylate **27a** also provided access to a selective synthesis of the higher energy atropisomer **30** of vinblastine (Scheme V). Cleavage of the trimethylsilyl ether function of **27a** with tetrabutylammonium fluoride, in tetrahydrofuran, cleanly produced the epoxide **31a** (Scheme IV). An anti-periplanar opening

Scheme V



Scheme VI



of the epoxide ring on intramolecular alkylation of $N^{b'}$ in this compound (**31a**) requires a transition state with a piperidine chair (Scheme V), which is conformationally isomeric with that found in natural vinblastine. Consequently, formation of only the higher energy atropisomer **30** of vinblastine could be expected after debenzylation of the initially formed quaternary salt **32a**. Not as clear, however, was the feasibility of the initial quaternization reaction, considering that the reverse process, namely, formation of tertiary amine epoxides, is usually observed on treatment of β-hydroxy quaternary salts with base.[19] While the epoxide **31a** indeed remained unchanged after several days in refluxing xylene, and was destroyed in refluxing dimethylacetamide, it was converted to the quaternary salt **32a** in refluxing methanol. Debenzylation by hydrogenolysis then provided the higher energy atropisomer **30** of vinblastine in 89% overall yield from the epoxide **31a**. This product, which shows remarkable chromatographic retention due to its relatively unshielded $N^{b'}$ electron pair and its equatorial C20′ hydroxyl function, was converted to the natural, chromatographically less polar atropisomer of vinblastine (**1**) on heating in toluene (95% yield).

For a synthesis of vincovaline (**14b**), the C14′,16′,20′ epimeric trimethylsilyloxy tosylate **28b** was subjected to the same cyclization, debenzylation, and hydrolysis conditions as the isomer **27a**, to provide the product in its natural atropisomeric form. Passage through an epoxide intermediate (**33b**) again allowed initial isolation of the compound as a higher energy atropisomer (**34**) and its subsequent conversion to the natural conformation **14b** by heating in toluene.

Cyclization of the C20′*R* epoxide **31b** (Scheme VI), obtained from the corresponding trimethylsilyloxy tosylate **27b** with tetrabutylammonium fluoride, might be expected to lead, after debenzylation, directly to the lower energy (natural) atropisomeric form of leurosidine (**13**) on the basis of the same stereoelectronic arguments that predict the cyclization of the C20′*S* epimer **31a** to result in the higher energy (unnatural) atropisomer **30** of vinblastine. However, when the epoxide **31b** was heated for 48 h in methanol and 1.5 equiv of acetic acid and the quaternary salt product was debenzylated, only the higher energy atropisomer **35b** of leurosidine was formed. This result can be understood by consideration of the 1,3,5-triaxial alkyl substitution that would arise on cyclization in the pre-piperidine chair conformation **36**, which would lead to the lower energy atropisomer of leurosidine (**13**). To avoid this steric compression, the alternative pre-piperidine boat conformation **31b**, which leads to the higher energy atropisomer **35b** of leurosidine, thus becomes preferable. Addition of acetic acid to this cyclization reaction was found to minimize deacetylation of the vindoline moiety that occurred by the otherwise generated alkoxide ion.

A higher energy atropisomer was also obtained in the synthesis of 20′-*epi*-vincovaline. Thus desilylation of the TMS tosylate **28a** provided the epoxide **33a** (97% yield), which on cyclization in methanol and acetic acid, followed by debenzylation, then gave the higher energy atropisomer **35a** of 20′-*epi*-vincovaline. Its conformational inversion in refluxing toluene (97%) provided the lower energy atropisomer **14a** in 93% yield from the epoxide **33a**.

Distinction of the binary indole–indolines having the "unnatural" higher energy atropisomeric form (**30**, **34**, **35a,b**) was consistent with an earlier observation on the corresponding 20′-deethyl-20′-deoxy compound.[14] Thus, these compounds, with an equatorial $N^{b'}$ electron pair, were very much more strongly adsorbed on TLC, and their Wenkert–Bohlmann IR peaks (now due only to the vindoline moiety) were diminished relative to the lower energy atropisomers **1**, **13**, and **14a,b**. The "unnatural" atropisomers **30**, **34**, and **35a,b** showed broadening of most NMR signals due to the conformational mobility of the nine-membered ring, and their circular dichroism ellipticities at 304–310 nm had a reverse sign relative to the natural conformers **1**, **13**, and **14a,b**.[14]

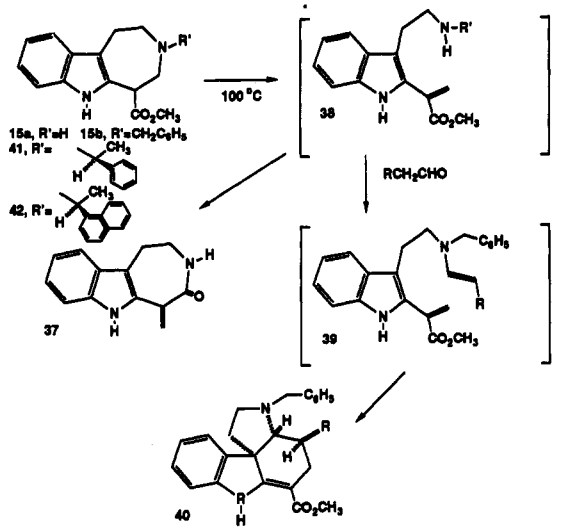
The final problem to be addressed was one of overcoming the intrinsic achirality of the secodine-type cyclization step. While we had observed a small diastereoselectivity in the rearrangement of bridged indoloazepines to *D-seco*-ψ-vincadifformine derivatives in the 20′-deoxy series (compare Scheme III),[15] this was not found in the present work, where the 20′ H is replaced by a 20′ oxygen substituent. However, the generation of tetracyclic intermediates of type **18** or **19** by reactions of N-alkylated indoloazepines (i.e., **15b**) with aldehydes suggested an opportunity for achieving the desired enantioselectivity.[20] This reaction was based on our earlier observation that the N^b-H indoloazepine ester **15a** rearranged to methylene lactam **37** on heating,[21] presumably through fragmentation to primary amine acrylate intermediate **38** (R′ = H), and its cyclization (Scheme VII). Trapping of the corre-

(19) Cope, A. *Org. React.* **1960**, *11*, 317 (see pages 352, 390, 391).

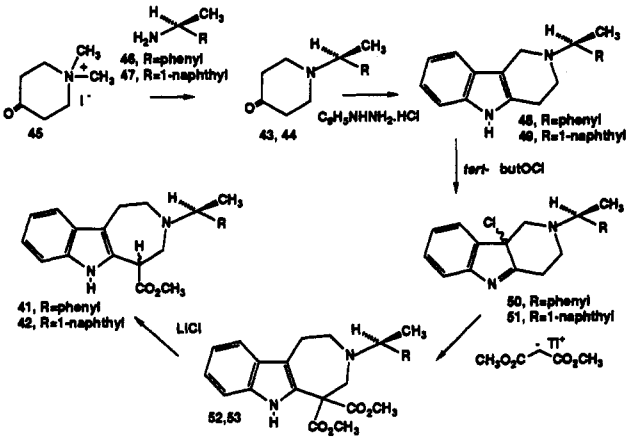
(20) Legseir, B.; Massiot, G.; Gulhem, J.; Vercauteren, J. *Tetrahedron Lett.* **1987**, *28*, 3573.

(21) Unpublished results obtained in 1980 with Linda Motyka and Stephen Kuehne.

Scheme VII



Scheme VIII

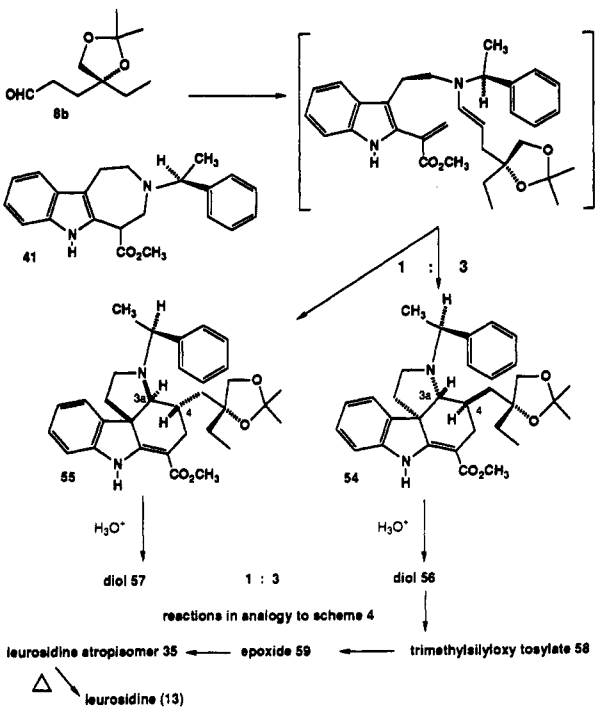


sponding N-benzylated acrylate intermediate **38** (R′ = benzyl) with a variety of aldehydes had then led (through transient secodine analogues **39**) to the formation of tetracyclic amine models **40** for the required intermediates **18** and **19**.[21]

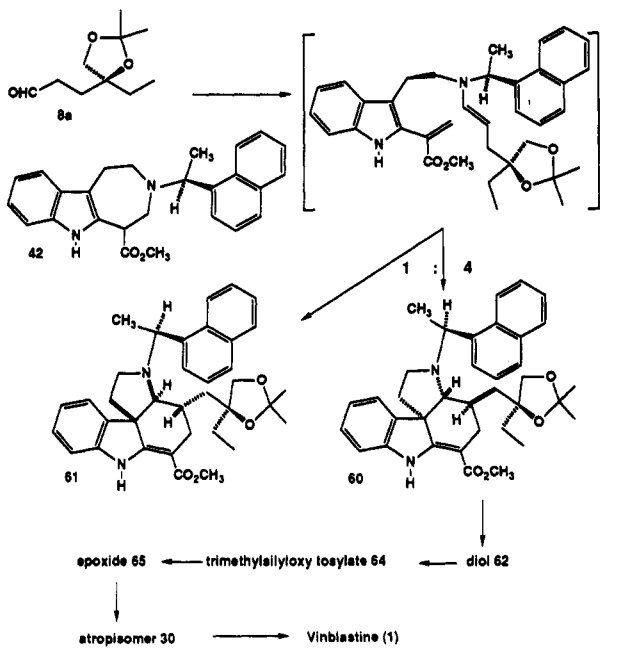
In order to maximize steric and possible π-stacking effects in this key intramolecular (formal) Diels–Alder reaction,[22] we chose chiral α-phenethyl and α-naphthylethyl N^b substituents (in place of N^b-benzyl) for our secodine-type cyclization.[18,21] The required indoloazepine intermediates **41** and **42** could be readily synthesized from corresponding N-substituted 4-piperidones (Scheme VIII). The latter compounds were obtained by replacement of dimethylamine from *N*-methyl-4-piperidone methiodide (**45**) by commercially available (S)-(−)-α-methylbenzylamine (**46**) or by (*S*)-(−)-1-(1-naphthyl)ethylamine (**47**).[23] A Fischer indole synthesis with subsequent chlorination of the resulting γ-carbolines **48** and **49** and reaction of the chloroindolenine products **50** and **51** with thallium dimethyl malonate, followed by a decarbomethoxylation of the diesters **52** and **53**,[24] provided the indoloazepines **41** (31%, overall) and **42** (27%, overall).

For a synthesis of leurosidine (**13**), the α-phenethylamine derivative **41** was heated in toluene with the 4*R* aldehyde **8b** (Scheme IX), to produce a 3:1 ratio of the 3a*R*,4*S* di-

Scheme IX



Scheme X



astereomer **54** to the 3a*S*,4*R* diastereomer **55**, as seen from integration of the N^a ^1H NMR signals at δ 8.98 and 8.87. Hydrolysis of the acetonide function of these products then allowed chromatographic separation of the corresponding diols **56** and **57** (3:1, 47% overall yield from the azepine **41**). Derivatization of the major isomer to the (trimethylsilyl)oxy tosylate **58** (73%), a coupling to vindoline, conversion to the epoxide **59** (73% overall), and its cyclization and hydrogenolysis, according to the procedures used with the $N^{b'}$-benzyl compounds **7b–31b**, again provided the higher energy atropisomer **35b** of leurosidine, which on heating gave leurosidine (**13**).

The (naphthylethyl)-substituted indoloazepine **42** was used for a synthesis of vinblastine. Its condensation with the 4*S* aldehyde **8a** provided the tetracyclic amines **60** and **61** in a 4:1 ratio (Scheme X). Chromatographic separation

(22) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 876.
(23) An analogous reaction of the piperidone methiodide **45** with tryptamine had been developed in our laboratories by R. Muth.
(24) Kuehne, M. E.; Kirkemo, C. L.; Matsko, T. H.; Bohnert, J. C. *J. Org. Chem.* **1980**, *45*, 3259.

of the diols **62** and **63**, obtained by hydrolysis of the acetonides **60** and **61**, gave the more polar 3a*R*,4*S* isomer **62** in 37% overall yield. Its conversion to the (trimethylsilyl)oxy tosylate **64** (38% yield), a coupling reaction with vindoline and formation of the epoxide **65** (72% overall), was followed by a cyclization that required 40 h of heating in methanol. Hydrogenolysis of the quaternary product's naphthylethyl substituent led exclusively to the higher energy atropisomer **30** of vinblastine. On heating in toluene, this product was also converted to vinblastine (**1**) in its natural conformation (80% overall yield in the last steps starting with the cyclization of the epoxide **65**).

Experimental Section

General Methods. All reactions were run under a nitrogen atmosphere unless otherwise stated. Melting points were obtained on a Kofler micro hotstage with thermometers calibrated against a National Bureau of Standards certified set. NMR spectra were obtained with Bruker 250-MHz or 270-MHz instruments and chemical shifts are expressed as parts per million (δ) downfield from tetramethylsilane. Mass spectra were obtained with a Finnigan 4610 quadrupole instrument at 70 eV, calibrated with perfluorotributylamine and hexafluorotriphenyl-*s*-triazine for higher molecular weight compounds. Chemical ionization spectra employed methane as the reagent gas. IR spectra were obtained with either a Nicolet 6000 FT or a Perkin-Elmer 1430 grating instrument. Perkin-Elmer 402 and Lambda instruments were used for recording UV spectra. TLC data were obtained with E. Merck 60 PF 254 precoated silica gel on aluminum sheets. Indole derivatives were characterized with a 10% solution of ceric ammonium sulfate (CAS) in phosphoric acid as a spray reagent and other compounds were visualized by either UV, iodine vapor, or treatment with an acid and heating. Flash chromatography employed Baker 7024-R 40-μm diameter silica gel. Microanalyses were provided by Robertson Laboratories, Florham Park, NJ. Circular dichroism (CD) spectra were obtained in dry methanol, using an Autodichrograph V (ISA Jobin-Yvon) instrument and Darrel R. McCaslin CD soft, V.3.1.

(2*R*)-2-Ethyl-2,3-epoxypropanol (10a). Under argon, dichloromethane (160 mL) and powdered activated 4.0-Å molecular sieves (3.0 g, Aldrich) were stirred in a three-neck flask equipped with a thermometer, a dropping funnel, and a septum and cooled to 0 °C. D-(−)-Diethyl tartrate (1.26 g, 6.11 mmol) and titanium(IV) isopropoxide (1.38 g, 4.85 mmol) were added sequentially. After 1 h the reaction was brought to −20 °C (dry ice, carbon tetrachloride) and *tert*-butyl hydroperoxide (85 mL, 25 mmol, 3.0 M in 2,2,4-trimethylpentane) was added, and the mixture stirred for 10 min and 2-ethylallyl alcohol (8.78 g, 102 mmol in 3 mL of dichloromethane) was added dropwise with vigorous stirring over 30 min.

The reaction mixture was stirred for 4 h at −20 °C, stored at −15 °C for 12 h and then quenched with water (28 mL), allowed to warm to room temperature, and stirred another 30 min. The tartrate was hydrolyzed by addition of 7.0 mL of a 30% aqueous solution of sodium hydroxide saturated with sodium chloride and stirring for 2 h. The mixture was filtered through Celite, the organic layer was separated, and the aqueous phase was extracted with dichloromethane (100 mL). The combined organic layers were dried over magnesium sulfate and filtered. Concentration, low pressure chromatography on a 4 × 25 cm column of silica gel, eluting with 2:1 ether/hexane, and distillation gave the title compound as a clear colorless oil (10.2 g, 97%, bp 77 °C, 18 mm): TLC R_f 0.24 (silica gel, 1:1 ether–hexane, CAS char tan); IR (neat) ν_{max} 3436, 3052, 2974, 2940, 2882, 1464, 1239, 1198, 1146, 1080, 1042, 1006, 912, 889, 814, 686 cm^{-1}; 270-MHz ^{1}H NMR ($CDCl_3$) δ 0.95 (t, J = 7.5 Hz, 3 H), 1.51–1.65 (m, 1 H), 1.74–1.88 (m, 1 H), 2.56–2.61 (m, 1 H, O*H*, varies), 2.68 (d, J = 4.7 Hz, 1 H), 2.86 (d, J = 4.7 Hz, 1 H), 3.62 (dd, J = 12.3, 7.90 Hz, 1H), 3.77 (dd, J = 12.3, 4.9 Hz, 1 H); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 8.43, 24.49, 49.37, 60.40, 62.84; mass spectrum m/z (rel intensity) 103 (M + 1), 91 (6), 89 (4), 87 (8), 85 (2), 79 (1), 77 (2), 73 (7), 72 (42), 71 (17), 69 (3), 59 (8), 58 (3), 57 (100), 55 (10), 54 (5), 53 (5); high resolution mass spectrum (PCI/NH_3, mass resolution 4000), calcd for M + NH_4^+ 120.10244, found 120.10258. *Note*: Chromatography prior to distillation was necessary for high yields.

A 270-MHz ^{1}H NMR analysis of the Mosher ester[17] (derived from (*R*)-(+) α-methoxy-α-(trifluoromethyl)phenylacetic acid) in $CDCl_3$ showed two doublets at δ 4.27 and 4.20 in a corresponding ratio of at least 93:7, indicating (conservatively) an 86% ee on formation of the 2*R* alcohol **10a**.

(2*S*)-2-Ethyl-2,3-epoxypropanol (10b). By the same procedure, and employing L-(+)-diethyl tartrate, a 97% yield of the enantiomeric title compound was obtained: TLC R_f 0.24 (silica gel, 1:1 ether–hexane, CAS char tan); IR (neat) ν_{max} 3430, 3062, 2980, 2945, 2888, 1465, 1400, 1366, 1328, 1274, 1240, 1198, 1150, 1082, 1040, 1008, 987, 912, 890, 814, 735, 702, 687 cm^{-1}; 270-MHz ^{1}H NMR ($CDCl_3$) δ 0.95 (t, J = 7.5 Hz, 3 H), 1.52–1.66 (m, 1 H), 1.74–1.88 (m, 1 H), 2.68 (d, J = 4.7 Hz, 1 H), 2.86 (d, J = 4.7 Hz, 1 H), 2.95–3.00 (m, 1 H, O*H*, varies) 3.61 (m, J = 12.3, 7.6 Hz, 1 H), 3.77 (m, J = 12.4, 5.1 Hz, 1 H); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 8.37, 24.32, 49.31, 60.46, 62.71; mass spectrum, m/z (rel intensity) 103 (M + 1, 23), 91 (12), 85 (30), 73 (15), 72 (39), 71 (15), 67 (14), 59 (13), 57 (100), 55 (28); high resolution mass spectrum (PCI/NH_3, mass resolution 3000), calcd for M + NH_4^+ 120.10244, found 120.10182.

A 270-MHz ^{1}H NMR ($CDCl_3$) analysis of the Mosher ester[17] (from (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenyl acetic acid), by integration of doublets at δ 4.27 and 4.20, showed a corresponding ratio of diastereomers of at most 7:93, indicating an ee of >86% on formation of the 2*S* alcohol **10b**.

(2*S*)-2-Ethyl-2-hydroxyhex-5-enol (11a). Under argon, a mixture of (2*R*)-2-ethyl-2,3-epoxypropanol (**10a**, 5.34 g, 51.8 mmol) and copper iodide (985 mg, 5.2 mmol) was stirred in tetrahydrofuran (100 mL) and brought to −30 °C (dry ice, acetonitrile). Allylmagnesium chloride (65 mL, 2 M in THF, 2.5 equiv) was added via a dropping funnel at such a rate as to maintain the temperature between −25 and −30 °C for 1 h. The reaction mixture was stirred for 6 h, stored at −15 °C for 12 h, then brought to 0 °C, and poured into 300 mL of ice-cold 1 N HCL. The THF layer was separated and the aqueous phase was extracted with ether (5 × 100 mL). The organic layers were combined, dried over magnesium sulfate, concentrated, and chromatographed on a 3 × 25 cm column of silica gel, eluting with 1:1 hexane/ether. Concentration of the eluate (fractions 360–660 mL) and distillation gave the title compound as a clear colorless oil (6.85 g, 91%, bp 74–75 °C/0.2 mm): TLC R_f 0.26 (silica gel, 5% methanol in dichloromethane, CAS char brown); IR (neat) ν_{max} 3416, 3078, 2974, 2942, 2883, 1640, 1462, 1416, 1336, 1134, 1056, 994, 909, 740, 650 cm^{-1}; 270-MHz ^{1}H NMR ($CDCl_3$) δ 0.89 (t, J = 7.5 Hz, 3 H), 1.50–1.60 (m, 4 H), 2.05–2.17 (m, 2 H), 2.21 (s, 2 H), 3.48 (s, 2 H), 4.96–5.09 (m, 2 H), 5.80–5.86 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 7.90, 27.68, 28.47, 34.52, 67.54, 74.83, 114.41, 138.72; mass spectrum, m/z (rel intensity) 145 (M + 1, 0.4), 127 (5), 115 (6), 114 (2), 113 (28), 110 (3), 109 (36), 97 (3), 89 (18), 88 (2), 86 (7), 85 (3), 84 (12), 79 (3), 72 (4), 71 (8), 69 (5), 67 (11), 57 (100), 55 (10); high resolution mass spectrum (PCI/NH_3, mass resolution 4000), M + NH_4 calcd 162.14932, found 162.14958.

(2*R*)-2-Ethyl-2-hydroxyhex-5-enol (11b). By the same procedure, starting from (2*S*)-2-ethyl-2,3-epoxypropanol (**10b**), 71 91% yield (bp 85 °C/5–6 mm) of the title compound was obtained: IR (neat) ν_{max} 3400, 3085, 2975, 2948, 2890, 1642, 1418, 1337, 1136, 1057, 992, 911, cm^{-1}; 270-MHz ^{1}H NMR ($CDCl_3$) δ 0.89 (t, J = 7.5 Hz, 3 H), 1.48–1.59 (m, 4 H), 2.03–2.12 (m, 2 H), 2.46 (br s, 1 H), 2.82 (br s, 1 H) 3.44 (s, 2 H), 4.93–5.08 (m, 2 H), 5.75–5.91 (m, 1 H); mass spectrum, m/z (rel intensity) 145 (M + 1, 4), 127 (24), 115 (8), 114 (4), 113 (38), 110 (11), 109 (100), 97 (5), 95 (6), 89 (23), 71 (13), 69 (8), 67 (21), 57 (89); high resolution mass spectrum (PCI/NH_3, mass resolution 3000), M + NH_4 calcd 162.14932, found 162.14810.

(2*S*)-2-Ethyl-2-hydroxyhex-5-enol Acetonide (12a). A solution of (2*S*)-2-ethyl-2-hydroxyhex-5-enol (**11a**, 1.7 g, 11.8 mmol) in acetone (25 mL) was stirred with 2,2-dimethoxypropane (2 mL) and a catalytic amount of *p*-toluenesulfonic acid. After 12 h, the reaction was complete as indicated by TLC. The acetone was removed under reduced pressure at room temperature, and the residue was basified with aqueous saturated sodium bicarbonate and extracted with ether (3 × 50 mL). The combined ether layers were dried over sodium sulfate. Concentration and distillation (75–80 °C, 10 mm) gave 2.1 g of the title product (99%): TLC R_f 0.72 (silica gel, 4:1 hexane–ether); IR (neat) ν_{max} 3080, 2995,

2950, 2880, 1640, 1457, 1255, 1214, 1119, 1065, 995, 912, 868, 810, 735 cm^{-1}; 270-MHz ^1H NMR ($CDCl_3$) δ 0.90 (t, J = 7.5 Hz, 3 H), 1.40 (s, 6 H), 1.56–1.71 (m, 4 H), 1.98–2.18 (m, 2 H), 3.76 (s, 2 H), 4.94–5.07 (m, 2 H), 5.77–5.91 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 8.35, 27.20, 28.45, 30.00, 36.20, 72.60, 83.60, 109.04, 114.31, 138.70; mass spectrum, m/z (rel intensity) 185 (M + 1, 3), 170 (8), 169, (80), 165 (4), 163 (15), 156 (3), 155 (36), 149 (3), 130 (8), 129 (86), 127 (13), 113 (3), 111 (6), 110 (6), 109 (74), 103 (5), 97 (12), 95 (3), 85 (7), 83 (5), 81 (9), 79 (10), 73 (7), 72 (100), 71 (26), 69 (23), 68 (15), 67 (56), 61 (4), 59 (57), 57 (20), 56 (3), 55 (36), 53 (6); high resolution mass spectrum (PCI/NH_3, mass resolution 5000), M + H calcd 185.154145, found 185.15472.

(2*R*)-2-Ethyl-2-hydroxyhex-5-enol Acetonide (12b). By the same procedure, starting from (2*R*)-2-ethyl-2-hydroxyhex-5-enol (**11b**), a 99% yield of the title compound was obtained: IR (neat) ν_{max} 3081, 2992, 2950, 2880, 1644, 1457, 1382, 1371, 1256, 1214, 1161, 1118, 1065, 995, 912, 868, 810, 735 cm^{-1}; 270-MHz ^1H NMR ($CDCl_3$) δ 0.90 (t, J = 7.5 Hz, 3 H), 1.39 (s, 6 H), 1.54–1.70 (m, 4 H), 1.99–2.20 (m, 2 H), 3.75 (s, 2 H), 4.94–5.08 (m, 2 H), 5.76–5.91 (m, 1 H); mass spectrum, m/z (rel intensity) 185 (M + 1, 8), 169 (100), 155 (42), 129 (82), 127 (22), 11 (10), 109 (97), 106 (13), 97 (16), 81 (15), 79 (21), 72 (79), 70 (14), 69 (28), 67 (51), 59 (44), 57 (32), 55 (40), 53 (11); high resolution mass spectrum (PCI/NH_3, mass resolution 3000), M + H calcd 185.154145, found 185.15419.

(4*S*)-4-Ethyl-4,5-dihydroxypentanal Acetonide (8a). A solution of (2*S*)-2-ethyl-2-hydroxyhex-5-enol acetonide (**12a**, 1.02 g, 5.54 mmol) in dichloromethane (25 mL) was brought to −78 °C (dry ice, acetone), and ozone was bubbled through until the reaction mixture turned a pale blue (approximately 15 min). The reaction mixture was then flushed with nitrogen for 1 h, triphenylphosphine (850 mg, 3.26 mmol) was added, and the mixture was allowed to slowly warm to room temperature. After 24 h the solvent was removed under reduced pressure and the residue was taken up in hexane, filtered, and again concentrated. Chromatography on 50 g of silica gel, eluting with 10% ether in hexane, gave 1.01 g (98%) of the title aldehyde: TLC R_f 0.39 (silica gel, 3:2 hexane–ether); IR (neat) ν_{max} 2995, 2948, 2889, 2828, 2725, 1731, 1460, 1382, 1371, 1255, 1212, 1185, 1117, 1063, 987, 876 cm^{-1}; 270-MHz ^1H NMR ($CDCl_3$) δ 0.90 (t, J = 7.6 Hz, 3 H), 1.39 (s, 6 H), 1.59–1.65 (m, 2 H), 1.90 (t, J = 7.4 Hz, 2 H), 2.53–2.61 (m, 2 H), 3.78 (q, J = 20.8, 8.7 Hz, 2 H), 9.82 (s, 1 H); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 8.32, 26.77, 27.00, 28.71, 30.11, 38.73, 72.22, 82.73, 109.26, 201.46; mass spectrum, m/z (rel intensity) 187 (M + 1, 10), 172 (6), 171 (62), 157 (19), 130 (4), 129 (60), 127 (18), 115 (6), 112 (4), 111 (54), 99 (37), 93 (20), 85 (12), 84 (3), 83 (16), 81 (11), 73 (8), 72 (100), 71 (30), 69 (13), 67 (9), 59 (45), 57 (22), 56 (3), 55 (39), 53 (5); high resolution mass spectrum (PCI/NH_3 mass resolution 5000), M + H calcd 187.13341, found 187.13259.

(4*R*)-4-Ethyl-4,5-dihydroxypentanal Acetonide (8b). By the same procedure, starting with (2*R*)-2-ethyl-2-hydroxyhex-5-enol acetonide (**12b**), a 98% yield of the title compound was obtained: IR (neat) ν_{max} 2988, 2940, 2882, 2820, 2720, 1729, 1458, 1413, 1380, 1369, 1252, 1210, 1182, 1160, 1150, 1115, 1060, 987, 920, 875, 795, cm^{-1}; 270-MHz ^1H NMR ($CDCl_3$) δ 0.90 (t, J = 7.6 Hz, 3 H), 1.38 (s, 6 H), 1.54–1.69 (m, 2 H), 1.90 (t, J = 7.4 Hz, 2 H), 2.41–2.61 (m, 2 H), 3.78 (q, J = 20.8, 8.7 Hz, 2 H), 9.82 (s, 1 H); mass spectrum, m/z (rel intensity) 187 (M + 1, 8), 171 (78), 157 (24), 129 (89), 111 (75), 99 (42), 93 (24), 83 (24), 72 (100), 71 (25), 69 (16), 59 (40), 57 (27), 55 (42); high resolution mass spectrum (PCI/NH_3), M + H calcd 187.1334097, found 187.13390.

(3a*R*,4*R*)- and (3a*S*,4*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-6-carboxylate (18a, 19a). A solution of 2.00 g (8.19 mmol) of methyl 1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-5-carboxylate (**15a**) and 1.68 g (9.01 mmol, 1.1 equiv) of (4*S*)-4-ethyl-4,5-dihydroxypentanal acetonide (**8a**) in 50 mL of tetrahydrofuran was heated at reflux under nitrogen until TLC showed no remaining starting material (approximately 2 h). After addition of anhydrous sodium sulfate and filtration, the solvent was removed under reduced pressure and the residue was taken up in 35 mL of dry tetrahydrofuran and 1.54 g (9.01 mmol) of benzyl bromide. The reaction mixture was heated at reflux for 12 h. Filtration gave 4.56 g (97%) of quaternary salts, which were heated for 2 h in 50 mL of methanol and 5.55 mL (39.8 mmol) of triethylamine. Flash chromatography of the residue on a 23 × 3.5 cm silica column, eluting with 3:2 hexane/ether, gave 3.78 mg of the title products (97% yield): TLC R_f 0.32 (silica gel, 1:1 ether–hexane, CAS blue); UV (ethanol) λ_{max} 327, 297, 202 nm; IR (KBr) ν_{max} 3382, 2982, 2938, 2860, 2787, 1678, 1610, 1478, 1466, 1438, 1378, 1368, 1345, 1294, 1280, 1249, 1206, 1150, 1124, 1101, 1054, 745, 700 cm^{-1}; 270-MHz ^1H NMR ($CDCl_3$) δ 0.73–0.88 (m, 3 H), 0.89–0.98 (m, 1 H), 1.02 (s, 1 H), 1.16–1.40 (m, 7 H), 1.52–1.79 (m, 3 H), 1.95–2.01 (m, 2 H), 2.51–2.96 (m, 5 H), 3.46 (t, J = 7.8 Hz, 1 H), 3.65–3.74 (m, 2 H), 3.76–3.78 (2s, 3 H), 4.18–4.28 (m, 1 H), 6.78–7.45 (m, 9 H), 8.94–8.96 (br s, 1 H); mass spectrum, m/z (rel intensity) 503 (9), 502 (M^+, 31), 487 (5), 374 (21), 373 (89), 369 (11), 341 (3), 332 (6), 289 (5), 288 (33), 261 (3), 241 (7), 238 (6), 229 (4), 228 (29), 214 (11), 200 (5), 194 (8), 180 (9), 168 (16), 167 (11), 154 (9), 129 (11), 120 (6), 91 (100), 59 (13). Anal. Calcd for $C_{31}H_{38}N_2O_4$: C, 74.08; H, 7.62; N, 5.57. Found: C, 73.81; H, 7.11; N, 5.31.

(3a*R*,4*R*)- and (3a*S*,4*S*)-Methyl 3-Benzyl-2,3,3a,4,5,7-hexahydro-4-[(2*S*)-2-ethyl-2,3-dihydroxypropyl]-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate (20a, 21a). The mixture of the title compounds' acetonide (**18a**, **19a**, 500 mg, 1.0 mmol) was heated for 15 min at reflux in 25 mL of methanol, containing 10 mL of 10% aqueous hydrochloric acid. The methanol was removed under reduced pressure, and the solution was basified with ammonium hydroxide and then extracted with ether (3 × 50 mL). Concentration gave 440 mg (95%) of the title diols. Separation of the diastereomers (400 mg) was partially effected by flash chromatography on a 5 × 12 cm silica gel column, eluting with 0.2% triethylamine in ether, to give 175 mg of the less polar 3a*S*,4*S* title isomer **21a**: TLC R_f 0.32 (silica gel, ether, CAS blue). This was followed by 110 mg of the more polar 3a*R*,4*R* title isomer **20a**, TLC R_f 0.25 (silica gel, ether, CAS blue–fade to purple), and 110 mg of a mixture of the two isomers. For the 3a*R*,4*R* isomer **20a**: UV (ethanol) λ_{max} 329, 297, 225, 202 nm; IR (KBr) ν_{max} 3440, 3390, 2970, 2934, 2880, 2855, 2790, 1674, 1610, 1480, 1466, 1438, 1382, 1344, 1304, 1296, 1280, 1250, 1202, 1128, 1102, 1076, 1050, 746, 700 cm^{-1}; 270-MHz ^1H NMR ($CDCl_3$) δ 0.78 (t, J = 7.4 Hz, 3 H), 0.88–0.91 (m, 1 H), 1.01–1.22 (m, 2 H), 1.46–1.51 (m, 2 H), 1.65 (dd, J = 11.7, 4.5 Hz, 1 H), 1.88 (br s, 1 H), 1.98–2.12 (m, 3 H), 2.49–2.68 (m, 3 H), 2.87–2.5 (m, 1 H), 3.12 (s, 1 H), 3.12 (s, 1 H), 3.3 (s, 1 H), 3.72–3.77 (m, 1 H), 3.78 (s, 3 H), 4.21 (d, J = 13.5 Hz, 1 H), 6.79–6.87 (m, 2 H), 7.00 (d, J = 7.2 Hz, 1 H), 7.13 (t, J = 7.7 Hz, 1 H), 7.25–7.43 (m, 5 H), 8.87 (br s, 1 H); 67.9–MHz ^{13}C NMR ($CDCl_3$) δ 7.95, 24.65, 28.86, 34.23, 36.56, 42.79, 50.87, 55.32, 58.40, 65.71, 67.84, 74.49, 75.25, 76.36, 91.34, 109.21, 120.64, 122.18, 126.99, 127.77, 128.13, 128.28, 128.81, 137.98, 139.56, 143.07, 165.62, 169.08; mass spectrum, m/z (rel intensity) 463 (M + 1, 6), 462 (M^+, 24), 431 (8), 374 (41), 332 (6), 329 (22), 249 (7), 248 (46), 238 (7), 228 (14), 215 (7), 194 (7), 180 (8), 168 (13), 167 (10), 154 (8), 141 (5), 120 (6), 92 (8), 91 (100), 68 (5), 57 (6); high resolution mass spectrum (EI, mass resolution 6000), calcd for $C_{28}H_{34}N_2O_4$ 462.25184, found 462.25186.

For the 3a*S*,4*S* isomer **21a**: UV (ethanol) λ_{max} 330, 297, 201, 194 nm; IR (KBr) ν_{max} 3451, 3380, 3030, 3017, 2942, 2862, 2790, 1676, 1610, 1497, 1480, 1466, 1440, 1381, 1340, 1305, 1282, 1244, 1207, 1131, 1104, 1075, 1044, 744, 700 cm^{-1}; 270-MHz ^1H NMR ($CDCl_3$) δ 0.77 (t, J = 7.3 Hz, 3 H), 0.88 (dd, J = 14.4, 4.0 Hz, 1 H), 1.09–1.22 (m, 1 H), 1.40–1.55 (m, 2 H), 1.66 (dd, J = 11.0, 4.6 Hz, 1 H), 1.95–2.20 (m, 4 H), 2.55–2.70 (m, 3 H), 2.77–2.89 (m, 1 H), 3.10 (s, 1 H), 3.29–3.30 (m, 2 H), 3.77 (d, J = 14.0 Hz, 1 H), 3.79 (s, 3 H), 4.22 (d, J = 14.0 Hz, 1 H), 6.80–6.91 (m, 2 H), 7.01 (d, J = 7.7 Hz, 1 H), 7.22 (t, J = 7.7 Hz, 1 H), 7.31–7.48 (m, 5 H), 9.00 (br s, 1 H); 67.9–MHz ^{13}C NMR ($CDCl_3$) δ 8.01, 24.40, 28.88, 34.12, 36.60, 42.77, 50.89, 55.22, 58.30, 60.59, 67.31, 74.20, 75.11, 91.09, 109.22, 120.61, 122.11, 127.00, 127.11, 128.22, 128.70, 138.01, 139.66, 143.21, 166.01, 168.92; mass spectrum, m/z (rel intensity) 463 (38), 462 (M^+, 42) 431 (17), 374 (14), 373 (71), 330 (11), 329 (55), 320 (52), 249 (16), 248 (69), 241 (12), 328 (13), 234 (16), 228 (22), 215 (16), 194 (11), 180 (14), 169 (17), 168 (21), 167 (20), 154 (27), 147 (18), 120 (21), 92 (16), 91 (100), 57 (15).

(3a*R*,4*R*)-Methyl 3-Benzyl-2,3,3a,4,5,7-hexahydro-4-[(2*S*)-2-ethyl-2-[(trimethylsilyl)oxy]-3-[(*p*-tolylsulfonyl)oxy]propyl]-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate (7a). A solution of 175 mg (0.38 mmol) of (3a*R*,4*R*)-methyl 3-benzyl-2,3,3a,4,5,7-hexahydro-4-[(2*S*)-2-ethyl-2,3-dihydroxypropyl]-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate (**20a**) and 106 μL (0.76 mmol) of triethylamine in 25 mL of dichloromethane was brought to 0 °C, and 247 mg (0.76 mmol) of *p*-toluenesulfonic anhydride

was added. The reaction flask was purged with nitrogen, and the reaction mixture was stirred for 26 h. The reaction mixture was then washed with water, dried over magnesium sulfate, and concentrated under reduced pressure. Flash chromatography on a 15 × 3.5 cm silica gel column, eluting with 1:1 ether–hexane, gave 177 mg (76%) of the primary alcohol tosylate: TLC R_f 0.45 (silica gel, 4:1 ether–hexane, CAS blue); UV (ethanol) λ_{max} 328, 295, 223, 202 nm; IR (KBr) ν_{max} 3384, 2928, 2854, 1678, 1610, 1496, 1477, 1466, 1438, 1359, 1304, 1294, 1281, 1250, 1204, 1190, 1178, 1129, 1104, 975, 841, 816, 748, 700, 668 cm^{-1}; 270-MHz ^1H NMR ($CDCl_3$) δ 0.66 (t, J = 7.4 Hz, 3 H), 0.86 (dd, J = 14.7, 4.9 Hz, 1 H), 1.10 (dd, J = 14.8, 6.1 Hz, 1 H), 1.26 (s, 1 H), 1.44 (q, J = 14.7, 7.2 Hz, 2 H), 1.64 (dd, J = 11.7, 4.4 Hz, 1 H), 1.76 (s, 1 H), 1.92–2.09 (m, 1 H), 2.39 (s, 3 H), 2.53–2.59 (br s, 3 H), 2.85–2.91 (m, 1 H), 3.03 (s, 1 H), 3.64–3.76 (m, 3 H), 3.77 (s, 3 H), 4.12 (d, J = 13.6 Hz, 1 H), 6.80–6.87 (m, 2 H), 7.00 (d, J = 7.4 Hz, 1 H), 7.15 (t, J = 7.4 Hz, 1 H), 7.24–7.40 (m, 7 H), 7.72 (d, J = 8.2 Hz, 2 H), 8.89 (s, 1 H); mass spectrum, m/z (rel intensity) 446 (13), 445 (55), 444 (100), 427 (10), 426 (13), 413 (8), 353 (14), 312 (7), 311 (26), 292 (5), 279 (11), 278 (17), 261 (5), 246 (5), 238 (6), 231 (7), 230 (50), 227 (5), 226 (5), 200 (5), 173 (6), 172 (13), 155 (12), 140 (12), 139 (41), 134 (6), 124 (7), 123 (17), 107 (12), 106 (9), 105 (8), 92 (19), 91 (78), 86 (18), 77 (13), 65 (10).

A solution of 150 mg (0.32 mmol) of (3a*R*,4*R*)-methyl 3-benzyl-2,3,3a,4,5,7-hexahydro-4-[(2*S*)-2-ethyl-2-hydroxy-3-[(*p*-tolylsulfonyl)oxy]propyl]-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate and 64 μL (1.5 equiv) of *N*,*N*-diisopropylethylamine in 25 mL of tetrahydrofuran was stirred under nitrogen and brought to 0 °C, and 71 μL (1.5 equiv) of trimethylsilyl trifluoromethanesulfonate was added by syringe. The solution was stirred for 15 min, then washed with 15 mL of aqueous saturated sodium bicarbonate, dried over magnesium sulfate, and concentrated under reduced pressure. Flash chromatography on a 12.5 × 3.5 cm silica gel column, eluting with 1:1 ether–hexane, gave 154 mg (92%) of the title product as a white foam: TLC R_f 0.37 (silica gel, 1:1 ether–hexane, CAS blue green); UV (ethanol) λ_{max} 327, 296, 223, 199 nm; IR (KBr) ν_{max} 3383, 3060, 3030, 2951, 2857, 2790, 1678, 1610, 1496, 1478, 1466, 1438, 1365, 1345, 1304, 1294, 1281, 1250, 1202, 1190, 1178, 1136, 1101, 1078, 1052, 1028, 1018, 982, 838, 814, 746, 700, 666, 554 cm^{-1}; 270-MHz ^1H NMR ($CDCl_3$) δ 0.03 (s, 9 H), 0.63 (t, J = 7.4 Hz, 3 H), 0.75 (dd, J = 14.6, 4.6 Hz, 1 H), 1.10–1.16 (dd, 1 H), 1.48–1.67 (m, 4 H), 1.9–2.12 (m, 2 H), 2.39 (s, 3 H), 2.49–2.60 (m, 3 H), 2.81–2.88 (m, 1 H), 3.05 (s, 1 H), 3.55–3.73 (m, 2 H), 3.76 (s, 3 H), 4.15 (d, J = 13.4 Hz, 1 H), 6.80–6.87 (m, 2 H), 7.07 (d, J = 7.3 Hz, 1 H), 7.16 (t, J = 7.5 Hz, 1 H), 7.24–7.39 (m, 7 H), 7.70 (d, J = 8.2 Hz, 2 H), 8.94 (br s, 1 H); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 169.0, 166.0, 144.7, 143.0, 139.6, 137.8, 133.0, 129.8, 129.7, 128.6, 128.2, 127.9, 127.7, 126.9, 122.1, 120.5, 109.1, 91.4, 77.7, 74.2, 73.6, 58.4, 55.0, 50.8, 43.0, 37.6, 33.8, 29.7, 24.7, 21.5, 8.1, 2.4; mass spectrum, m/z (rel intensity) 688 (M^+, 9), 503 (4), 475 (5), 474 (22), 374 (21), 373 (100), 332 (6), 229 (7), 228 (16), 210 (8), 207 (5), 194 (4), 180 (4), 168 (9), 167 (5), 155 (5), 92 (7), 91 (78), 86 (5), 75 (6), 73 (22).

(3a*S*,4*S*)-Methyl 3-benzyl-2,3,3a,4,5,7-hexahydro-4-[(2*S*)-2-ethyl-2-[(trimethylsilyl)oxy]-3-[(*p*-tolylsulfonyl)oxy]propyl]-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate (22a) was prepared by the above procedure from the diol **21a** in 88% yield. For the initial intermediate tosylate alcohol: UV (ethanol) λ_{max} 205, 283, 311 nm; IR (KBr) ν_{max} 3393, 3103, 3084, 3056, 3029, 2970, 2943, 2891, 2855, 1674, 1609, 1478, 1465, 1438, 1360, 1303, 1294, 1280, 1250, 1203, 1190, 1177, 1133, 1102, 1078, 1051, 1028, 1019, 974, 841, 814, 737, 701, 668 cm^{-1}; 250-MHz ^1H NMR ($CDCl_3$) δ 0.69 (t, J = 7.4 Hz, 3 H), 0.82 (dd, J = 14.7, 4.9 Hz, 1 H), 1.08 (dd, J = 14.8, 5.3 Hz, 1 H), 1.26–1.57 (m, 2 H), 1.62 (dd, J = 11.7, 4.3 Hz, 1 H), 1.90 (m, 1 H), 1.98 (ddd, J = 11.9 , 11.9, 6.2 Hz, 1 H), 2.13 (m, 1 H), 2.38 (s, 3 H), 2.52–2.65 (m, 3 H), 2.87 (dd, J = 8.5, 6.6 Hz, 1 H), 3.09 (s, 1 H), 3.64 (d, J = 11.0 Hz, 1 H), 3.69 (d, J = 13.5 Hz, 1 H), 3.75 (s, 3 H), 3.72 (d, J = 11.9 Hz, 1 H), 4.15 (d, J = 13.5 Hz, 1 H), 6.80 (d, J = 7.7 Hz, 1 H), 6.83 (t, J = 7.6 Hz, 1 H), 6.95 (d, J = 6.8 Hz, 1 H), 7.13 (t, J = 7.9 Hz, 1 H), 7.23–7.45 (m, 5 H), 7.25 (d, J = 8.2 Hz, 2 H), 7.69 (d, J = 8.2 Hz, 2 H), 8.90 (br s, 1 H); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 7.69, 21.44, 24.52, 29.10, 33.64, 36.28, 42.64, 50.55, 58.04, 73.78, 73.83, 91.02, 109.13, 120.61, 122.15, 126.94, 127.74, 127.82, 128.21, 128.84, 129.77, 132.79, 137.71, 139.20, 142.90, 144.76, 165.42, 168.85. For **22a**: TLC R_f (silica gel) (1:1 ether–hexane, CAS blue-green) 0.54 (1:4 ethyl acetate/pentanes); UV (ethanol) λ_{max} 208, 282, 311 nm; IR (KBr) ν_{max} 3378, 3050, 3029, 2965, 2951, 2885, 2857, 2830, 2794, 1678, 1611, 1494, 1478, 1466, 1453, 1438, 1366, 1345, 1303, 1293, 1281, 1250, 1203, 1190, 1177, 1137, 1102, 1078, 1051, 1028, 1019, 982, 839, 815, 668, 578, 555, 538, 528, 514 cm^{-1}; 250-MHz ^1H NMR ($CDCl_3$) δ 0.10 (s, 9 H), 0.70 (t, J = 7.3 Hz, 3 H), 0.83 (dd, J = 14.6, 4.8 Hz, 1 H), 1.19 (dd, J = 14.5, 4.6 Hz, 1 H), 1.51–1.63 (m, 2 H), 1.70 (dd, J = 11.8, 4.4 Hz, 1 H), 2.03 (ddd, J = 11.8, 11.8, 6.3 Hz, 1 H), 2.20 (m, 1 H), 2.44 (s, 3 H), 2.61 (ddd, J = 13.6, 8.1, 4.3 Hz, 1 H), 2.67 (m, 2 H), 2.91 (dd, J = 6.1, 8.8 Hz, 1 H), 3.12 (s, 1 H), 3.91 (d, J = 13.4 Hz, 1 H), 3.71 (d, J = 9.5 Hz, 1 H), 3.82 (d, J = 9.2 Hz, 1 H), 3.82 (s, 3 H), 4.21 (d, J = 13.3 Hz, 1 H), 6.88 (d, J = 7.7 Hz, 1 H), 6.93 (t, J = 7.4 Hz, 1 H), 7.14 (d, J = 7.3 Hz, 1 H), 7.21 (t, J = 7.7 Hz, 1 H), 7.30–7.45 (m, 5 H), 7.31 (d, J = 7.9 Hz, 2 H), 7.76 (d, J = 8.2 Hz, 2 H), 9.03 (br s, 1 H); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 2.43, 8.01, 21.42, 24.72, 29.54, 33.59, 37.57, 43.05, 50.67, 50.71, 55.07, 58.36, 73.23, 74.37, 77.74, 91.43, 109.10, 120.55, 122.09, 126.89, 127.72, 127.86, 128.22, 129.67, 132.98, 137.76, 139.51, 142.99, 144.63, 165.84, 168.97.

(7*S*,5*R*)-Methyl 3-Benzyl-1,2,3,4,5,6,7,8-octahydro-5-[(2*S*)-2-ethyl-2-[(trimethylsilyl)oxy]-3-[(*p*-tolylsulfonyl)oxy]propyl]-7-(15-vindolinyl)azonino[5,4-*b*]indole-7-carboxylate (27a). A solution of 0.10 g (0.14 mmol) of (3a*R*,4*R*)-methyl 3-benzyl-2,3,3a,4,5,7-hexahydro-4-[(2*S*)-2-ethyl-2-[(trimethylsilyl)oxy]-3-[(*p*-tolylsulfonyl)oxy]propyl]-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate (**7a**) and 21 μL (1.1 equiv) of triethylamine in 5 mL of dichloromethane was stirred under nitrogen and brought to 0 °C. Dropwise addition of 19 μL (1.1 equiv) of *tert*-butyl hypochlorite in 2 mL of dichloromethane and stirring for 5 min gave a solution, which by TLC was free of starting compound (CAS blue) and which contained a new, less polar chlorination product (**23a**), R_f 0.6 (2:3 hexane–ether, CAS purple). The solution was washed with 2 × 5 mL of water, dried over magnesium sulfate, and concentrated under vacuum to give a white foam, which was used in the next reaction.

To a solution of the chlorination product **23a** and 0.063 g (0.95 equiv) of vindoline (**3**) in 5 mL of dry acetone, was added 47 μL (2 equiv) of tetrafluoroboric acid–diethyl ether complex. After 5 min, 0.056 g (2 equiv) of silver tetrafluoroborate in 2 mL of dry acetone was added, causing the mixture to become heterogeneous. After 5 min, TLC showed no remaining starting material. Addition of 10 mL of 10% aqueous ammonium hydroxide, extraction with 4 × 15 mL of dichloromethane, drying ($MgSO_4$), and concentration under vacuum gave a white foam.

This material, **25a**, was dissolved in 10 mL of acetic acid and, with stirring, 0.078 g (10 equiv) of potassium borohydride was slowly added. After being stirred for 10 min, the reaction mixture was poured onto ice and made strongly basic with concentrated ammonium hydroxide. Extraction with 4 × 15 mL of dichloromethane, drying ($MgSO_4$), and concentration under vacuum gave a white foam. Flash chromatography on silica, eluting with ethyl acetate, gave 0.126 g (80% based on vindoline) of the title product. In some experiments only 65–70% yields were obtained, possibly due to cleavage of the silyl ether by fluoride: TLC R_f 0.61 (ethyl acetate, CAS dark brown-purple); UV λ_{max} 296, 288, 262, 215, 202 nm; IR (KBr) ν_{max} 3500, 3445, 3048, 2970, 2900, 2820, 1756, 1732, 1625, 1608, 1512, 1474, 1445, 1376, 1350, 1309, 1260, 1238, 1202, 1190, 1075, 1054, 990, 851, 753, 710, 682, 568 cm^{-1}; 270-MHz ^1H NMR ($CDCl_3$) δ 0.0 (s, 9 H), 0.58 (t, J = 7.1 Hz, 3 H), 0.92 (t, J = 6.8 Hz, 3 H), 1.10–1.47 (m, 6 H), 1.81–1.92 (m, 3 H), 2.18 (s, 3 H), 2.18–2.45 (m, 4 H), 2.40 (s, 3 H), 2.66 (s, 2 H), 2.80 (s, 3 H), 3.05–3.44 (m, 6 H), 3.67 (s, 3 H), 3.50–3.79 (m, 6 H), 3.84–3.91 (m, 6 H), 5.37 (d, J = 10.1 Hz, 1 H), 5.57 (s, 1 H), 5.91 (dd, J = 10.1, 4.0 Hz, 1 H), 6.26 (s, 1 H), 6.84 (s, 1 H), 6.84 (s, 1 H), 7.07–7.48 (m, 11 H), 7.75 (d, J = 8.2 Hz, 2 H), 8.07 (br s, 1 H), 9.98 (br s, 1 H); 67.9-MHz ^{13}C NMR δ 174.5, 171.6, 170.6, 157.8, 152.9, 144.5, 140.2, 134.8, 133.2, 131.8, 129.9, 129.5, 129.2, 127.9, 127.8, 127.6, 126.3, 124.4, 124.1, 123.2, 121.9, 121.3, 118.7, 117.9, 115.4, 110.1, 94.1, 83.3, 79.5, 77.4, 76.4, 72.8, 66.0, 64.5, 58.5, 55.8, 55.5, 53.5, 53.1, 51.9, 51.8, 50.2, 44.4, 42.7, 41.0, 38.1, 37.3, 32.6, 30.7, 29.5, 25.6, 21.3, 20.8, 8.37, 5.23.

(7*R*,5*S*)-Methyl 3-Benzyl-1,2,3,4,5,6,7,8-octahydro-5-[(2*S*)-2-ethyl-2-[(trimethylsilyl)oxy]-3-[(*p*-tolylsulfonyl)oxy]propyl]-7-(15-vindolinyl)azonino[5,4-*b*]indole-7-carboxylate (28a). This compound was prepared by the procedure ($CDCl_3$) for preparation of its diastereomer **27a**, providing

the title product in 78% yield and 10% of its desilylation product from the coupling of vindoline to the silyl tosylate **22a** after centrifugal chromatography (silica gel, ethyl acetate): TLC R_f 0.50 (silica gel, ethyl acetate, CAS dark brown-purple); UV (ethanol) λ_{max} 297, 288, 257, 221, 212, 196 nm; IR(KBr) ν_{max} 3415, 3028, 2950, 2911, 2893, 2878, 2838, 2803, 2748, 1742, 1615, 1598, 1497, 1461, 1432, 1412, 1368, 1338, 1321, 1297, 1249, 1225, 1190, 1177, 1151, 1131, 1121, 1109, 1097, 1064, 1042, 1001, 978, 840, 740, 667 cm^{-1}; 270-MHz ^1H NMR ($CDCl_3$) δ 0.06 (s, 9 H), 0.43 (br t, J = 7.2 Hz, 3 H), 0.56 (br t, J = 7.7 Hz, 3 H), 1.09–1.51 (m, 4 H), 1.60–1.91 (m, 2 H), 2.06–3.21 (m, 11 H), 2.12 (s, 3 H), 2.49 (s, 3 H), 2.75 (s, 3 H), 3.22–3.94 (m, 10 H), 3.85 (s, 6 H), 3.63 (s, 3 H), 5.30 (d, J = 10.8 Hz, 1 H), 5.54 (s, 1 H), 5.86 (dd, J = 10.9, 4.3 Hz, 1 H), 6.07 (s, 1 H), 6.86 (s, 1 H), 7.05–7.60 (m, 12 H), 7.83 (d, J = 7.2 Hz, 1 H), 8.13 (s, 1 H), 9.74 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 2.34, 7.93, 8.15, 20.90, 21.48, 26.07, 29.99, 30.52, 33.31, 38.39, 39.82, 42.74, 44.67, 50.50, 51.02, 52.09, 52.17, 53.19, 53.80, 55.55, 57.89, 64.59, 66.32, 73.52, 76.64, 79.41, 83.46, 94.35, 110.11, 117.95, 118.55, 121.79, 123.56, 124.04, 126.51, 127.79, 128.00, 128.09, 129.72, 130.02, 133.16, 134.62, 140.24, 144.39, 152.93, 158.21, 170.40, 171.71, 175.22.

(7*S*,5*R*)-Methyl 3-Benzyl-1,2,3,4,5,6,7,8-octahydro-5-[(2*S*)-2-ethyl-2,3-epoxypropyl]-7-(15-vindolinyl)azonino-[5,4-*b*]indole-7-carboxylate (31a). To a solution of 0.07 g (0.06 mmol) of (7*S*,5*R*)-methyl 3-benzyl-1,2,3,4,5,6,7,8-octahydro-5-[(2*S*)-2-ethyl-2-[(trimethylsilyl)oxy]-3-(*p*-tolylsulfonyl)oxy]-propyl]-7-(15-vindolinyl)azonino[5,4-*b*]indole-7-carboxylate (**27a**) in 20 mL of tetrahydrofuran was added 0.184 mL (3 equiv, 1 M in THF) of tetrabutylammonium fluoride. After 25 min, TLC showed complete conversion of starting material to a more polar product. The reaction mixture was washed with aqueous saturated sodium bicarbonate, dried ($MgSO_4$), and concentrated under vacuum. Flash chromatography on silica, eluting with ethyl acetate, gave 0.047 g (85% yield) of the title compound: TLC R_f 0.33 (silica gel, ethyl acetate, CAS brown); UV (ethanol) λ_{max} 296, 289, 258, 215, 201 nm; IR (KBr) ν_{max} 3466, 3030, 2970, 2934, 2878, 2802, 1744, 1704, 1612, 1502, 1460, 1432, 1371, 1336, 1296, 1226, 1172, 1146, 1042, 957, 886, 818, 740, 701, 480 cm^{-1}; 270-MHz ^1H NMR ($CDCl_3$) δ 0.54 (t, J = 7.2 Hz, 3 H), 0.85 (t, J = 7.2 Hz, 3 H), 0.98–1.81 (m, 12 H), 1.95–2.04 (m, 1 H), 2.10 (s, 3 H), 2.15–2.17 (m, 1 H), 2.28–2.62 (m, 6 H), 2.66 (s, 3 H), 2.73–3.34 (m, 3 H), 3.63–3.64 (m, 6 H), 3.77–3.82 (m, 8 H), 5.30 (d, J = 10.4 Hz, 1 H), 5.44 (s, 1 H), 5.81 (dd, J = 10.3, 4.0 Hz, 1 H), 6.12 (s, 1 H), 6.73–6.80 (m, 3 H), 6.83–7.01 (m, 3 H), 7.11–7.20 (m, 2 H), 7.36 (d, J = 7.7 Hz, 1 H), 8.06 (br s, 1 H), 9.81 (br s, 1 H); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 8.17, 8.37, 20.74, 25.06, 26.58, 30.61, 32.93, 37.83, 38.32, 39.86, 42.54, 44.45, 49.36, 49.78, 51.74, 51.92, 52.02, 52.81, 53.01, 55.57, 56.27, 58.11, 60.30, 62.86, 65.30, 76.24, 79.47, 83.42, 94.01, 110.08, 114.37, 117.88, 118.66, 121.73, 122.05, 122.93, 124.14, 125.38, 126.14, 127.43, 127.71, 129.18, 129.85, 132.23, 134.77, 139.78, 152.62, 158.01, 170.41, 171.34, 174.51; high resolution mass spectrum (EI, direct probe, mass resolution 12 000), calcd for $C_{53}H_{64}N_4O_9$ 900.46729, found 900.46909; mass spectrum, m/z (rel intensity) 901 (10), 900 (M^+, 17), 841 (6), 788 (6), 742 (6), 741 (10), 650 (7), 649 (13), 566 (6), 540 (6), 527 (8), 469 (9), 444 (8), 431 (10), 380 (7), 373 (9), 355 (6), 295 (6), 282 (18), 273 (7), 272 (7), 262 (6), 261 (21), 260 (7), 259 (8), 258 (7), 244 (8), 231 (6), 230 (30), 222 (8), 218 (9), 217 (9), 214 (7), 212 (6), 202 (8), 200 (7), 188 (11), 174 (6), 169 (6), 168 (9), 154 (10), 144 (12), 143 (10), 136 (14), 135 (53), 134 (19), 130 (7), 124 (6), 122 (23), 121 (21), 120 (8), 108 (9), 107 (22), 106 (8), 93 (12), 92 (19), 91 (100), 79 (6), 77 (6), 65 (17), 60 (7), 55 (7), 51 (6). Anal. Calcd for $C_{53}H_{64}N_4O_9 \cdot CH_3OH$: C, 69.51; H, 7.35; N, 6.00. Found: 69.35; H, 7.49; N, 6.22. The analytical sample was obtained by centrifugal chromatography on silica gel with 5% methanol in dichloromethane. It showed methanol signals in the NMR spectrum after drying under high vacuum.

(7*R*,5*S*)-Methyl 3-Benzyl-1,2,3,4,5,6,7,8-octahydro-5-[(2*S*)-2-ethyl-2,3-epoxypropyl]-7-(15-vindolinyl)azonino-[5,4-*b*]indole-7-carboxylate (33a). Following the procedure for preparation of the diastereomer **31a**, the *O*-silyl tosylate **28a** provided the centrifugally chromatographed (silica gel, ethyl acetate) product in 93% yield: TLC (silica gel) R_f 0.35 (ethyl acetate, CAS brown), 0.69 (5% methanol in CH_2Cl_2); UV (ethanol) λ_{max} 199, 212, 248, 270, 282, 287 nm; IR (KBr) ν_{max} 3459, 3057, 3028, 2964, 2943, 2935, 2879, 2856, 2838, 2802, 2797, 1742, 1615, 1595, 1500, 1460, 1432, 1370, 1336, 1321, 1298, 1244, 1227, 1172, 1154, 1145, 1127, 1108, 1092, 1042, 1000, 962, 817, 739 cm^{-1}; 270-MHz ^1H NMR ($CDCl_3$) δ 0.47 (t, J = 6.8 Hz, 3 H), 0.72 (t, J = 7.1 Hz, 3 H), 0.91–1.02 (m, 1 H), 1.05–1.28 (m, 3 H), 1.29–1.41 (m, 1 H), 1.50–1.73 (m, 2 H), 1.73–1.89 (m, 1 H), 2.06 (s, 3 H), 2.13–2.72 (m, 14 H), 2.76 (s, 3 H), 2.86–2.99 (m, 1 H), 3.05–3.19 (m, 2 H), 3.28–3.52 (m, 4 H), 3.55 (s, 3 H), 3.65 (t, J = 10.9 Hz, 1 H), 3.80 (s, 6 H), 5.28 (d, J = 9.1 Hz, 1 H), 5.44 (s, 1 H), 5.85 (dd, J = 9.4, 4.6 Hz, 1 H), 6.13 (s, 1 H), 6.88 (br s, 1 H), 7.00–7.34 (m, 8 H), 7.43 (d, J = 7.6 Hz, 1 H), 8.05 (br s, 1 H), 9.79 (br s, 1 H); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 7.87, 8.07, 20.87, 25.52, 26.29, 30.44, 32.33, 34.43, 38.53, 39.02, 42.20, 45.55, 50.18, 52.04, 52.12, 53.41, 53.94, 55.24, 55.42, 57.54, 58.81, 64.88, 65.72, 75.80, 79.58, 83.55, 93.38, 110.04, 115.83, 118.11, 118.84, 121.03, 122.04, 123.19, 124.03, 126.53, 127.99, 128.13, 128.98, 129.93, 131.65, 134.75, 139.93, 153.04, 158.13, 170.34, 171.46, 174.29; mass spectrum, m/z (relative intensity) 901 (42), 900 (M^+, 72) 842 (6), 811 (10), 810 (19), 809 (10), 751 (9), 741 (9), 741 (9), 617 (10), 540 (8) 527 (9), 470 (10), 469 (26), 444 (6), 432 (23), 431 (73), 413 (6), 409 (7), 380 (8), 355 (11), 341 (6), 295 (7), 282 (24), 273 (6), 272 (6), 261 (10), 231 (18), 230 (100), 222 (10), 218 (9), 217 (29), 214 (9), 212 (13), 202 (10), 200 (10), 188 (10), 174 (6), 154 (27), 144 (8), 136 (13), 135 (49), 134 (16), 122 (25), 121 (20), 120 (7), 109 (8), 107 (19), 106 (6), 93 (11), 92 (12), 91 (70), high resolution mass spectrum (EI, mass resolution 12 000), M calcd 900.46729, found 900.47003. Anal. Calcd for $C_{53}H_{64}N_4O_9 \cdot CH_3OH$: C, 69.51; H, 7.35; N, 6.00. Found: C, 69.41; H, 7.21; N, 5.86. The sample was obtained by centrifugal chromatography on silica gel with 5% methanol in dichloromethane. It showed methanol signals in the NMR spectrum after drying under high vacuum.

Vinblastine (1) and Its 17′-Equatorial Conformational Isomer 30. A solution of 0.040 g (0.044 mmol) of (7*S*,5*R*)-methyl 3-benzyl-1,2,3,4,5,6,7,8-octahydro-5-[(2*S*)-2-ethyl-2,3-epoxypropyl]-7-(15-vindolinyl)azonino[5,4-*b*]indole-7-carboxylate (**31a**) in 10 mL of methanol was heated at reflux for 26 h, at which time TLC showed no remaining starting material and a new more polar product (R_f 0.25, 2% triethylamine in methanol, CAS blue): UV (ethanol) λ_{max} 292, 266, 216 nm. The reaction mixture was cooled and flushed with nitrogen and 20 mg of 10% Pd on charcoal was added. This was stirred under a hydrogen atmosphere at room temperature for 2 h, filtered, and concentrated under vacuum. Flash chromatography on a 22 × 12 cm silica gel column, eluting with 1% triethylamine in methanol, gave 0.032 g (89%) of the 17′-equatorial conformational isomer **30** of vinblastine as a white solid. This compound crystallized to provide a sample with mp 210–213 °C, with gradual change of particles at 80–120 °C (vinblastine lit.[25] mp 211–216 °C): TLC R_f 0.23 (silica gel, 1% triethylamine in methanol, CAS purple); UV (ethanol) λ_{max} 292, 261, 222, 216, 205 nm; IR (KBr) ν_{max} 3406, 3389, 2953, 2935, 2877, 2808, 1738, 1616, 1594, 1499, 1459, 1433, 1372, 1331, 1300, 1246, 1145, 1086, 1040, 1012, 744 cm^{-1}; 250-MHz ^1H NMR ($CDCl_3$) [Most signals in this spectrum were very broad and complex due to the presence of three or more conformers, precluding meaningful analysis and integration. The observed signals were classified as broad "singlets" (br s) or sharp singlet (s)] (br s) δ 10.78, 9.74, 9.69, 9.46, 9.41, 9.12, 8.98, 8.59, 6.01, 5.93, 5.75, 5.37, 5.23, 5.10, 0.18; (s) δ 3.79, 3.76, 3.74, 3.73, 3.57, 2.29, 2.02; multiplets δ 7.35–6.74, 0.88; mass spectrum, m/z (rel intensity) 825 (M^+ + 15, 13), 8.24 (25), 811 (17), 810 (M^+, 32), 809 (9), 808 (9), 780 (11), 779 (16), 767 (7), 766 (12), 753 (15), 752 (33), 751 (23), 750 (11), 749 (6), 732 (5), 652 (6), 651 (11), 650 (8), 649 (9), 612 (6), 610 (6), 593 (5), 591 (5), 571 (7), 543 (9), 527 (5), 470 (7), 469 (17), 381 (6), 356 (7), 355 (21), 354 (6), 353 (7), 343 (5), 341 (6), 327 (5), 325 (5), 313 (5), 311 (5), 297 (6), 296 (5), 295 (9), 283 (8), 282 (22), 272 (6), 268 (6), 240 (5), 222 (7), 214 (8), 202 (8), 200 (8), 188 (12), 186 (6), 183 (5), 174 (6), 172 (6), 171 (5), 168 (6), 156 (7), 155 (12), 154 (100), 144 (10), 141 (13), 140 (11), 136 (21), 135 (52), 130 (6), 124 (16), 123 (8), 122 (30), 121 (25), 108 (10), 107 (21), 106 (7), 100 (6), 93 (12), 92 (6), 91 (5), 83 (13), 82 (9), 81 (6), 70 (10), 58 (21); high resolution mass spectrum (EI), M calcd 810.4203801, found 810.417648; CD (0.032 mg/mL methanol), λ (ellipticity) 214 (−177), 225 (4), 258 (53), (0.32 mg/mL) 307 (−13).

This product was dissolved in toluene and heated at reflux for 8 h, at which time TLC showed no remaining starting material

(25) Neuss, N.; Gorman, M.; Svoboda, G. H.; Maciak, G.; Beer, C. T. *J. Am. Chem. Soc.* **1959**, *81*, 4754.

and a new less polar product, which chromatographically matched an authentic sample of vinblastine. Concentration of the solvent and flash chromatography, eluting with 5:1:0.01 ether–acetone–triethylamine, gave 0.03 g (95% yield) of vinblastine: TLC R_f 0.36 (silica gel, 5% methanol in dichloromethane, CAS violet); IR (KBr) ν_{max} 3466, 3027, 2957, 2948, 2878, 2852, 2815, 1741, 1616, 1502, 1460, 1433, 1371, 1332, 1295, 1243, 1228, 1193, 1145, 1130, 1109, 1094, 1080, 1040, 1009, 742 cm^{-1}; 270-MHz ^{1}H NMR ($CDCl_3$) δ 0.82 (t, J = 6.8 Hz, 3 H), 0.88 (t, J = 7.4 Hz, 3 H), 1.30–1.48 (m, 4–5 H), 1.78–1.86 (m, 2 H), 2.12 (s, 3 H), 2.19–2.47 (m, 3–4 H), 2.67–2.69 (m, 1 H), 2.81 (s, 3 H), 2.81–2.87 (m, 3 H), 3.10–3.20 (m, 2 H), 3.25–3.41 (m, 4 H), 3.62 (s, 3 H), 3.68–3.74 (m, 2 H), 3.80 (s, 6 H), 3.87–4.00 (m, 1 H), 5.30 (d, J = 9.9 Hz, 1 H), 5.46 (s, 1 H), 5.85 (dd, J = 9.2, 3.7 Hz, 1 H), 6.10 (s, 1 H), 6.61 (s, 1 H), 7.13–7.26 (m, 3 H), 7.52 (d, J = 7.5, 1 H), 8.03 (s, 1 H), 9.90 (br s, 1 H); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 174.58, 171.43, 170.48, 157.90, 152.40, 134.73, 131.17, 129.77, 129.20, 124.15, 123.35, 122.64, 121.91, 120.98, 118.54, 118.15, 116.62, 110.09, 93.99, 83.16, 79.36, 76.20, 69.12, 65.58, 64.02, 55.53, 52.96, 51.95, 51.81, 50.25, 50.09, 47.81, 44.25, 42.49, 41.06, 38.05, 34.12, 30.55, 29.85, 28.19, 28.14, 20.75, 8.06, 6.63; mass spectrum, m/z (rel intensity) 825 (M + 15, 21), 824 (41), 811 (M$^+$ + 1, 19), 810 (M$^+$, 37), 809 (10), 808 (13), 780 (9), 779 (16), 767 (7), 753 (11), 752 (26), 751 (23), 720 (17), 734 (7), 652 (5), 651 (12), 650 (8), 649 (9), 571 (7), 543 (8), 525 (5), 470 (6), 469 (14), 381 (5), 356 (9), 355 (32), 354 (6), 353 (6), 325 (5), 296 (5), 295 (8), 283 (6), 282 (23), 272 (6), 268 (6), 240 (5), 222 (6), 214 (6), 202 (6), 200 (7), 188 (10), 174 (6), 170 (6), 168 (5), 156 (6), 155 (12), 154 (100), 144 (10), 142 (5), 141 (13), 140 (11), 136 (22), 135 (51), 130 (5), 124 (18), 122 (29), 121 (24), 108 (10), 107 (19), 106 (7), 93 (12), 84 (7), 83 (11), 82 (7), 81 (5), 70 (8), 58 (24); high resolution mass spectrum (EI), M calcd 810.4203801, found 810.417114; CD (0.027 mg/mL ethanol) λ (ellipticity) 214 (−383), 225 (138), 258 (84), (0.250 mg/mL) 303 (20).

20′-*epi*-Vincovaline (14a) and Its Atropisomer 35a. Following the procedure for the preparation of vinblastine but with addition of 1.5 equiv of acetic acid to 0.206 g of the epoxide **33a** in 10 mL of methanol and heating at reflux for 48 h, and with centrifugal chromatography (silica gel, 100:5:5:5 ether/toluene/methanol/triethylamine), the atropisomer **35a** of 20′-*epi*-vincovaline was obtained from the epoxide **33a** in 97% yield: TLC R_f 0.017 (100:5:5:5 ether/toluene/methanol/diethylamine), R_f 0.24 (100:1 methanol/triethylamine); HPLC t_R 3.41 min (80:20:1 methanol/water/triethylamine, 4.6 × 100 mm Rainin microsorb C-18 3 μm (100 Å) column at 1 mL/min, detection at 260 nm); UV (ethanol) λ_{max} 204, 214, 254, 278, 285, 300 nm; IR (KBr) ν_{max} 3403, 3088, 3077, 3037, 3032, 3016, 2961, 2935, 2930, 2878, 2848, 2812, 2734, 2721, 2690, 1743, 1718, 1617, 1597, 1499, 1488, 1459, 1431, 1371, 1332, 1302, 1247, 1236, 1190, 1170, 1150, 1129, 1118, 1098, 1068, 1042, 1020, 968, 946, 911, 982, 737, 712, 621 cm^{-1}; 270-MHz ^{1}H NMR ($CDCl_3$) δ 0.57 (t, J = 6.8 Hz, 3 H), 0.80–1.02 (m, 1 H), 0.95 (br t, J = 7.2, 3 H), 1.05–1.31 (m, 3 H), 1.34–1.51 (m, 4 H), 1.62–1.75 (m, 1 H), 1.90–2.09 (m, 3 H), 2.07 (s, 3 H), 2.22–2.40 (m, 1 H), 2.42–3.04 (m, 6 H), 2.66 (br s, 3 H), 3.10–3.24 (m, 3 H), 3.32–3.62 (m, 1 H), 3.55 (br s, 3 H), 3.78 (s, 6 H), 5.26 (d, J = 9.1 Hz, 1 H), 5.44 (s, 1 H), 5.88 (dd, J = 4.4, 9.2 Hz, 1 H), 5.94 (br s, 1 H), 6.95–7.30 (m, 4 H), 7.37 (d, J = 7 Hz, 1 H), 9.52 (br s, 1 H), 10.93 (br s, 1 H); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 7.05, 7.53, 20.91, 26.58, 28.20, 30.49, 34.01, 35.96, 38.22, 42.83, 43.11, 43.33, 51.17, 52.04, 52.21, 52.33, 53.22, 53.57, 53.90, 54.43, 55.84, 66.35, 66.85, 72.29, 79.53, 83.44, 95.35, 110.53, 110.94, 118.19, 118.41, 120.64, 120.99, 122.75, 123.24, 124.17, 127.94, 130.44, 133.50, 134.17; mass spectrum, m/z (rel intensity) 825 (M$^+$ + 15, 5), 824 (7), 810 (M$^+$, 4), 792 (6), 767 (5), 766 (9), 752 (6), 751 (9), 750 (11), 749 (5), 748 (5), 734 (6), 674 (5), 662 (5), 648 (5), 632 (5), 613 (7), 612 (14), 611 (6), 610 (12), 607 (5), 605 (5), 591 (7), 590 (5), 536 (5), 534 (6), 507 (5), 495 (6), 494 (10), 493 (7), 492 (11), 490 (5), 483 (6), 482 (6), 481 (5), 480 (5), 470 (5), 469 (9), 466 (5), 465 (5), 464 (6), 393 (5), 369 (5), 367 (5), 357 (5), 356 (5), 355 (9), 354 (5), 353 (6), 352 (6), 351 (8), 344 (5), 343 (9), 341 (6), 329 (6), 327 (5), 325 (5), 313 (5), 311 (10), 297 (6), 295 (8), 294 (13), 284 (9), 283 (6), 282 (17), 268 (5), 240 (7), 226 (6), 222 (6), 214 (8), 212 (5), 202 (10), 201 (6), 200 (12), 198 (6), 197 (5), 196 (6), 194 (9), 188 (13), 184 (6), 183 (6), 182 (7), 180 (7), 174 (11), 172 (6), 171 (7), 170 (9), 169 (8), 168 (9), 167 (7), 160 (5), 157 (8), 156 (10), 155 (13), 154 (100), 144 (14), 143 (7), 141 (21), 140 (7), 138 (11), 137 (5), 136 (36), 135 (49), 134 (6), 130 (14), 124 (14), 123 (13), 122 (33), 121 (31), 110 (6), 108 (16), 107 (48), 106 (32), 105 (5), 94 (6), 93 (12), 92 (36), 91 (20), 84 (11), 82 (10), 81 (6), 80 (5), 79 (11), 77 (11), 70 (10), 67 (7), 65 (12), 60 (19), 59 (8), 58 (93), 57 (9); high resolution mass spectrum (EI), M calcd 810.4203801, found 810.423035; CD (0.021 mg/mL methanol) λ (ellipticity) 210 (44.5), 224 (−145.5), 261 (+23.0), (0.21 mg/mL) 309 (10.9). On heating in toluene at reflux for 2 h the atropisomer **35a** was converted to 20′-*epi*-vincovaline (**14a**) in 90% yield: TLC (silica gel) R_f 0.36 (10% methanol in CH_2Cl_2), 0.31 (100:5:5:5 ether/methanol/toluene/diethylamine); HPLC (under conditions given for **35a**) t_R 2.5 min; UV (ethanol) λ_{max} 211, 221, 253, 291, 302 nm; IR (KBr) ν_{max} 3413, 3029, 3022, 2964, 2953, 2878, 2852, 2841, 2810, 2740, 1739, 1616, 1501, 1460, 1432, 1371, 1334, 1296, 1244, 1226, 1172, 1156, 1146, 1120, 1108, 1093, 1038, 1003, 739 cm^{-1}; 270-MHz ^{1}H NMR ($CDCl_3$) δ 0.41 (t, J = 7.2 Hz, 3 H), 0.96 (t, J = 7.1 Hz, 3 H), 0.96–1.08 (m, 2 H), 1.23–1.38 (m, 3 H), 1.55–1.80 (m, 5 H), 1.80–1.86 (m, 1 H), 2.66 (s, 3 H), 2.09–2.38 (m, 2 H), 2.43 (m, 2 H), 2.74 (s, 3 H), 2.79–2.86 (m, 2 H), 3.05–3.74 (m, 5 H), 3.55 (s, 3 H), 3.80 (s, 3 H), 3.81 (s, 3 H), 5.22 (d, J = 10.5 Hz, 1 H), 5.46 (s, 1 H), 5.80 (dd, J = 4.5, 10.5 Hz, 1 H), 6.16 (s, 1 H), 6.66 (s, 1 H), 7.14–7.25 (m, 4 H), 7.49 (d, J = 7.8 Hz, 1 H), 8.09 (br s, 1 H), 9.61 (br s, 1 H); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 6.80, 8.05, 20.25, 20.76, 27.64, 30.67, 34.49, 38.16, 38.68, 39.94, 42.52, 44.01, 44.51, 50.25, 52.20, 53.10, 53.46, 54.34, 55.14, 55.43, 66.61, 70.48, 75.69, 79.22, 83.37, 94.07, 110.27, 144.45, 117.72, 119.10, 119.45, 122.71, 123.22, 123.82, 123.86, 128.16, 129.56, 130.63, 134.76, 153.32, 157.79, 170.37, 171.52, 173.52; high resolution mass spectrum (EI, mass resolution 12 000), M calcd 810.423801, found 810.41498; mass spectrum m/z (relative intensity) 838 (10), 825 (20), 824 (37), 810 (M$^+$, 8), 792 (12), 766 (11), 752 (11), 735 (6), 734 (10),612 (6), 591 (6), 516 (8), 502 (8), 500 (31), 499 (7), 369 (8), 356 (6), 297 (5), 295 (7), 294 (6), 283 (7), 282 (23), 222 (8), 214 (8), 202 (8), 200 (8), 188 (10), 174 (6), 170 (6), 168 (6), 156 (7), 155 (11), 154 (100), 144 (11), 141 (21), 140 (14), 136 (29), 135 (57), 130 (7), 124 (16), 123 (8), 122 (33), 121 (28), 108 (12), 107 (22), 106 (8), 93 (13), 92 (7), 91 (8), 84 (9), 83 (8), 82 (8), 81 (6), 70 (8), 60 (6), 58 (41); CD (0.026 mg/mL methanol) λ (ellipticity) 211 (102.5), 222 (−189.5), 258–260 (20), (0.29 mg/mL) 304 (−21.0).

Vinblastine 20′-Trimethylsilyl Ether. A solution of 0.070 g (0.061 mmol) of (7*S*,5*R*)-methyl 3-benzyl-1,2,3,4,5,6,7,8-octahydro-5-[(2*S*)-2-ethyl-2-[(trimethylsilyl)oxy]-3-[(*p*-tolylsulfonyl)oxy]propyl]-7-(15-vindolinyl)azonino[5,4-*b*]indole-7-carboxylate (**27a**) in 10 mL of methanol was heated at reflux under nitrogen for 40 h, at which time TLC showed no remaining starting material and a new, more polar product (R_f 0.38, 2% triethylamine in methanol, CAS brown). The reaction mixture was cooled to room temperature and flushed with nitrogen, and 0.010 g of 10% palladium on carbon was added. The mixture was stirred under a hydrogen atmosphere for 2 h. TLC then showed complete conversion of starting material to a less polar compound (TLC R_f 0.36, 5% methanol in dichloromethane, CAS purple). The reaction mixture was filtered, the filtrate was washed with dichloromethane, and the combined solvents were concentrated under vacuum. Flash chromatography on silica gel eluting with 5% methanol in dichloromethane gave 0.048 g (90%) of the title compound: 270-MHz ^{1}H NMR ($CDCl_3$) δ 0.28 (s, 9 H), 0.78–0.88 (m, 6 H), 1.21–1.88 (m, 10 H), 2.10 (s, 3 H), 2.15–2.30 (m, 1 H), 2.39–2.48 (m, 2 H), 2.68 (s, 1 H), 2.70 (s, 3 H), 2.76–2.90 (m, 3 H), 3.04–3.40 (m, 5 H), 3.62 (s, 3 H), 3.72 (s, 1 H), 3.79 (s, 3 H), 3.80 (s, 3 H), 3.84–4.06 (m, 2 H), 5.29 (d, J = 10.1 Hz, 1 H), 5.47 (s, 1 H), 5.85 (dd, J = 10.1, 3.7 Hz, 1 H), 6.12 (s, 1 H), 6.62 (s, 1 H), 7.09–7.15 (m, 3 H), 7.52 (d, J = 7.1 Hz, 1 H), 8.03 (br s, 1 H), 9.91 (br s, 1 H); mass spectrum, m/z (rel intensity) 883 (M + 1, 30), 882 (M$^+$, 71), 867 (s), 854 (11), 853 (31), 852 (58), 825 (10), 823 (30), 724 (19), 668 (5), 643 (7), 549 (8), 496 (9), 495 (40), 469 (17), 426 (18), 381 (10), 380 (12), 355 (8), 282 (29), 273 (5), 228 (11), 227 (18), 226 (100), 212 (33), 205 (16), 185 (8), 172 (11), 149 (22), 144 (17), 136 (21), 135 (43), 129 (17), 122 (27), 121 (25), 111 (16), 109 (12), 108 (11), 107 (20), 103 (13), 99 (14), 97 (25), 95 (20), 93 (17), 91 (19).

The silyl ether of vinblastine (0.020 g) was dissolved in 5 mL of tetrahydrofuran, and 68 μL of tetrabutylammonium fluoride (1 M in THF, 3 equiv) was added. After 30 min, TLC showed no remaining starting material and only the presence of vinblastine in its natural conformation. Flash chromatography on silica gel

eluting with 5% methanol in dichloromethane gave 0.016 g (87%) of vinblastine.

(3a*R*,4*R*)- and (3a*S*,4*S*)-Methyl 3-Benzyl-2,3,3a,4,5,7-hexahydro-4-[(2*R*)-2-ethyl-2,3-dihydroxypropyl]-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate (20b and 21b). To a stirred solution of the N^b-benzylated indoloazepine (**15a**, 1 g, 2.99 mmol) in toluene (20 mL) at 70 °C was added (4*R*)-4-ethyl-4,5-dihydroxypentanal acetonide (**8b**, 0.67 g, 1.2 equiv) in toluene (5 mL), over 15 min. After addition was complete, the reaction mixture was heated at reflux for 12 h, at which time none of the starting azepine was present, as seen by TLC. The solvent was removed under reduced pressure, and to the residue were added methanol (20 mL) and 10% aqueous hydrochloric acid (10 mL). This was heated at reflux for 20 min., the methanol was removed under reduced pressure, and the residue was made basic with 10% aqueous ammonium hydroxide. Extraction with diethyl ether (3 × 5 mL), drying ($MgSO_4$), and concentration gave a white foam. Flash chromatography on silica gel, eluting with ether, gave 0.53 g (38%) of the less polar 3a*R*,4*R* title isomer **18b**, TLC R_f 0.32 (silica gel, ether, CAS blue). This was followed by 0.56 g (40%) of the more polar 3a*S*,4*S* title isomer **19b**, TLC R_f 0.25 (silica gel, ether, CAS blue fade to purple).

For 3a*R*,4*R*,2′*R* isomer **18b**: UV (ethanol) λ_{max} 327, 298, 201, 194 nm; IR (KBr) ν_{max} 3390, 3056, 3030, 2940, 2856, 2790, 1684, 1609, 1480, 1468, 1439, 1380, 1343, 1300, 1280, 1248, 1204, 1129, 1102, 1074, 1048, 741, 697 cm^{-1}; 250-MHz ^1H NMR ($CDCl_3$) δ 0.78 (t, *J* = 7.4 Hz, 3 H), 0.87 (dd, *J* = 14.7, 6.8 Hz, 1 H), 0.91–0.98 (m, 1 H), 1.12 (dd, *J* = 14.7, 5.8 Hz, 1 H), 1.43–1.50 (m, 2 H), 1.65 (dd, *J* = 11.8, 4.5 Hz, 1 H), 1.95–2.09 (m, 4 H), 2.61–2.65 (m, 3 H), 2.88–2.93 (m, 1 H), 3.12 (s, 1 H), 3.30 (s, 2 H), 3.77 (s, 3 H), 4.21 (d, *J* = 13.5 Hz, 1 H), 6.79–6.86 (m, 2 H), 7.00 (d, *J* = 7.3 Hz, 1 H), 7.13 (t, *J* = 7.4 Hz, 1 H), 7.25–7.43 (m, 5 H), 8.88 (br s, 1 H); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 8.03, 24.59, 28.67, 34.18, 36.36, 42.71, 50.79, 50.92, 55.24, 58.32, 67.73, 74.38, 75.29, 91.21, 109.21, 120.61, 122.16, 126.98, 127.77, 128.28, 128.78, 137.88, 139.43, 142.96, 165.61; mass spectrum, *m*/*z* (rel intensity) 462 (M^+, 33), 431 (24), 374 (18), 373 (75), 332 (11), 329 (38), 320 (14), 249 (12), 248 (69), 238 (14), 234 (14), 228 (27), 215 (16), 194 (11), 180 (14), 169 (12), 168 (20), 167 (15), 154 (12), 141 (13), 92 (9), 91 (100), 57 (14); high resolution mass spectrum (EI, mass resolution 5000), M calcd 462.2518392, found 462.25232.

For 3a*S*,4*S*,2′*R* isomer **19b**: UV (ethanol) λ_{max} 328, 298, 200, 193 nm; IR (KBr) ν_{max} 3385, 3029, 3015, 2940, 2858, 2791, 1674, 1610, 1496, 1480, 1468, 1439, 1380, 1344, 1304, 1280, 1249, 1204, 1130, 1104, 1075, 1049, 742, 699 cm^{-1}; 270-MHz ^1H NMR ($CDCl_3$) δ 0.75 (t, *J* = 7.5 Hz, 3 H), 0.87 (dd, *J* = 14.6, 4.6 Hz, 1 H), 1.11–1.20 (m, 1 H), 1.43–1.52 (m, 2), 1.65 (dd, *J* = 11.7, 4.5 Hz, 1 H), 1.95–2.15 (m, 4 H), 2.56–2.66 (m, 3 H), 2.87–2.92 (m, 1 H), 3.05 (s, 1 H), 3.31–3.33 (m, 2 H), 3.71 (d, *J* = 13.5 Hz, 1 H), 3.77 (s, 3 H), 4.20 (d, *J* = 13.5 Hz, 1 H), 6.79–6.86 (m, 2 H), 7.00 (d, *J* = 7.1 Hz, 1 H), 7.13 (t, *J* = 7.7 Hz, 1 H), 7.24–7.43 (m, 5 H), 8.88 (br s, 1 H); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 7.95, 24.38, 28.81, 34.09, 36.42, 42.71, 60.69, 50.94, 55.19, 58.27, 67.45, 74.04, 75.17, 91.15, 109.20, 120.56, 122.10, 126.98, 127.74, 128.25, 128.75, 137.82, 139.31, 142.96, 165.54, 169.05; mass spectrum, *m*/*z* (rel intensity) 463 (M + 1, 23), 462 (43), 431 (20), 374 (13), 373 (60), 330 (9), 329 (43), 320 (43), 249 (11), 248 (64), 241 (9), 238 (12), 234 (13), 228 (24), 215 (14), 194 (10), 180 (11), 169 (10), 168 (17), 167 (12), 154 (10), 141 (14), 120 (12), 92 (9), 91 (100), 57 (13); high resolution mass spectrum (EI, mass resolution 5000), M calcd 462.2518392, found 462.25256.

(3a*R*,4*R*)-Methyl 3-Benzyl-2,3,3a,4,5,7-hexahydro-4-[(2*R*)-2-ethyl-2-[(trimethylsilyl)oxy]-3-[(*p*-tolylsulfonyl)oxy]propyl]-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate (7b). A solution of 0.20 g (0.43 mmol) of (3a*R*,4*R*)-methyl 3-benzyl-2,3,3a,4,5,7-hexahydro-4-[(2*R*)-2-ethyl-2,3-dihydroxypropyl]-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate (**20b**) and triethylamine (0.12 mL, 2 equiv) in dichloromethane (20 mL) was stirred under nitrogen and brought to 0 °C. *p*-Toluenesulfonic anhydride (280 mg, 2 equiv) in dichloromethane (10 mL) was added dropwise over 30 min. After being stirred for an additional 24 h, the reaction mixture was washed with 10% aqueous ammonium hydroxide (3 × 15 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give a white solid.

This material was dissolved in tetrahydrofuran (20 mL) and triethylamine (0.120 mL, 2 equiv) was added. The solution was brought to 0 °C and trimethylsilyl trifluoromethanesulfonate (83 μL, 2 equiv) was added by syringe. After 30 min, the reaction mixture was washed with aqueous saturated sodium bicarbonate (15 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Flash chromatography on silica gel, eluting with 1:1 ether–hexane, gave 0.21 g (72%) of the title compound: TLC R_f 0.39 (silica gel, 1:1 hexane–ether, CAS blue); UV (ethanol) λ_{max} 327, 297, 223, 199 nm; IR (KBr) ν_{max} 3375, 3060, 3033, 2955, 2859, 2792, 1679, 1611, 1496, 1480, 1468, 1439, 1364, 1346, 1304, 1294, 1281, 1249, 1203, 1190, 1177, 1135, 1100, 1078, 1054, 1018, 982, 838, 812, 747, 698, 666 cm^{-1}; 270-MHz ^1H NMR ($CDCl_3$) δ 0.04 (s, 9 H), 0.55 (t, *J* = 7.3 Hz, 3 H), 0.68 (dd, *J* = 14.6, 4.7 Hz, 1 H), 1.04 (dd, *J* = 14.6, 4.7 Hz, 1 H), 1.44–1.59 (m, 3 H), 1.85–1.95 (m, 1 H), 2.05 (br s, 1 H), 2.13 (s, 3 H), 2.44–2.52 (m, 3 H), 2.74–2.77 (m, 1 H), 2.98 (s, 1 H), 3.48–3.65 (m, 3 H), 3.68 (s, 3 H), 4.07 (d, *J* = 13.4 Hz, 1 H), 6.72–6.82 (m, 2 H), 6.99 (d, *J* = 7.2 Hz, 1 H), 7.07 (t, *J* = 7.6 Hz, 1 H), 7.16–7.31 (m, 7 H), 7.62 (d, *J* = 8.2 Hz, 2 H), 8.87 (br s, 1 H); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 2.38, 8.03, 21.27, 24.80, 29.61, 33.74, 37.52, 43.00, 50.66, 55.10, 58.38, 73.50, 74.26, 77.75, 91.40, 109.18, 120.55, 122.09, 126.15, 126.90, 127.68, 127.88, 128.25, 128.56, 129.35, 129.70, 137.75, 139.62, 143.05, 144.66, 165.91, 169.10; mass spectrum, *m*/*z* (rel intensity) 688 (M^+, 1), 532 (7), 503 (7), 476 (8), 474 (30), 420 (12), 374 (24), 373 (100), 333 (8), 332 (8), 315 (9), 302 (9), 261 (9), 230 (9), 229 (29), 228 (18), 227 (27), 214 (7), 213 (12), 212 (86), 180 (8), 168 (7), 155 (60), 149 (11), 147 (8), 129 (16), 107 (8), 106 (10), 105 (14), 92 (10), 91 (81), 89 (9), 78 (16), 76 (15), 73 (20), 65 (19), 56 (10).

(3a*S*,4*S*)-Methyl 3-Benzyl-2,3,3a,4,5,7-hexahydro-4-[(2*R*)-2-ethyl-2-[(trimethylsilyl)oxy]-3-[(*p*-tolylsulfonyl)oxy]propyl]-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate (22b). By the same procedure, starting with the 3a*S*,4*S*,2′*R* diol **21b** (0.15 g, 0.32 mmol), 0.156 g (70%) of the title compound was obtained: TLC R_f 0.37 (silica gel, 1:1 ether–hexane, CAS blue); UV (ethanol) λ_{max} 327, 297, 222, 199 nm; IR (KBr) ν_{max} 3380, 3059, 3031, 2952, 2855, 2792, 1678, 1610, 1496, 1480, 1468, 1437, 1363, 1345, 1304, 1292, 1280, 1249, 1202, 1189, 1177, 1150, 1134, 1098, 1078, 1053, 1018, 980, 839, 813, 738, 698, 665 cm^{-1}; 270-MHz ^1H NMR ($CDCl_3$) δ −0.03 (s, 9 H), 0.56 (t, *J* = 7.4 Hz, 3 H), 0.84 (dd, *J* = 14.6, 5.0 Hz, 1 H), 1.04 (dd, *J* = 14.6, 4.6 Hz, 1 H), 1.34–1.63 (m, 3 H), 1.89–2.03 (m, 1 H), 2.06 (br s, 1 H), 2.34–2.35 (m, 3 H), 2.45–2.55 (m, 3 H), 2.78–2.84 (m, 1 H), 3.06 (s, 1 H), 3.55 (d, *J* = 13.4 Hz, 1 H), 3.73 (s, 3 H), 3.70–3.80 (m, 2 H), 4.11 (d, *J* = 13.4 Hz, 1 H), 6.77–6.84 (m, 2 H), 7.02–7.15 (m, 2 H), 7.20–7.35 (m, 7 H), 7.64–7.73 (m, 2 H), 8.96 (br s, 1 H); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 2.39, 8.04, 21.27, 21.43, 24.73, 29.71, 33.76, 37.61, 43.02, 50.74, 55.05, 58.37, 73.63, 74.22, 77.67, 91.32, 109.16, 120.53, 122.04, 126.11, 126.89, 127.72, 127.85, 128.22, 128.56, 129.31, 129.68, 137.72, 139.54, 142.99, 144.65, 165.91, 169.00; mass spectrum, *m*/*z* (rel intensity) 688 (M^+, 7), 475 (7), 474 (26), 374 (21), 373 (100), 332 (9), 302 (13), 229 (16), 228 (20), 180 (6), 168 (8), 167 (6), 155 (10), 149 (12), 106 (9), 92 (8), 91 (66), 89 (33), 77 (7), 75 (10), 73 (18), 65 (10), 57 (8), 56 (8).

(7*S*,5*R*)-Methyl 3-Benzyl-1,2,3,4,5,6,7,8-octahydro-5-[(2*R*)-2-ethyl-2,3-epoxypropyl]-7-(15-vindolinyl)azonino-[5,4-*b*]indole-7-carboxylate (31b). A solution of 0.09 g (0.13 mmol) of (3a*R*,4*R*)-methyl 3-benzyl-2,3,3a,4,5,7-hexahydro-4-[(2*R*)-2-ethyl-2-[(trimethylsilyl)oxy]-3-[(*p*-tolylsulfonyl)oxy]-propyl]-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate (**7b**) and 20 μL (1.1 equiv) of triethylamine in 5 mL of dichloromethane was stirred under nitrogen and brought to 0 °C. Dropwise addition of 17 μL (1.1 equiv) of *tert*-butyl hypochlorite in 2 mL dichloromethane and stirring for 5 min gave a solution, which by TLC was free of starting compound (CAS blue) and which contained a new less polar product (CAS purple). The reaction mixture was washed with water (10 mL), dried ($MgSO_4$), and concentrated to give a white foam, which was used in the next reaction.

To a solution of the chlorination product **23b** and vindoline (**3**) (0.057 g, 0.95 equiv) in 5 mL of dry acetone was added 42 μL (2 equiv) of tetrafluoroboric acid–diethyl ether complex. After 5 min, 0.051 g (2 equiv) of silver tetrafluoroborate was added. The reaction mixture was stirred for 10 min and then quenched with the addition of 10 mL of 10% aqueous ammonium hydroxide. Extraction with dichloromethane (3 × 20 mL), drying ($MgSO_4$), and concentration under reduced pressure gave a white foam, which was used in the next reaction.

The coupled imine product **25b** was dissolved in 10 mL of glacial acetic acid, and 0.071 g of potassium borohydride was slowly

added. After being stirred for 10 min, the reaction mixture was poured onto ice and made strongly basic with concentrated ammonium hydroxide. Extraction with dichloromethane (3 × 20 mL), drying ($MgSO_4$), and concentration under vacuum gave a white foam: TLC R_f 0.56 (silica, ethyl acetate, CAS brown).

This material (**27b**) was dissolved in 20 mL of tetrahydrofuran, and 0.375 mL (3 equiv, 1 M in THF) of tetrabutylammonium fluoride was added. After 30 min, TLC showed no remaining starting compound and the presence of a new, more polar product. The solution was washed with aqueous saturated sodium bicarbonate, dried ($MgSO_4$), and concentrated under vacuum. Flash chromatography on silica gel, eluting with ethyl acetate, gave 0.080 g (71%) of the title compound: TLC R_f 0.43 (silica, ethyl acetate, CAS brown); UV (ethanol) λ_{max} 288, 258, 212, 195 nm; IR (film) ν_{max} 3460, 3025, 2965, 2935, 2792, 1743, 1612, 1501, 1460, 1432, 1369, 1336, 1300, 1242, 1225, 1172, 1143, 1124, 1105, 1041, 960, 815, 738, 697 cm^{-1}; 270-MHz ^1H NMR ($CDCl_3$) δ 0.50 (t, 3 H), 0.84 (t, 3 H), 0.91–0.99 (m, 1 H), 1.28–1.84 (m, 8 H), 1.92–2.29 (m, 2 H), 2.11 (s, 3 H), 2.40–2.69 (m, 8 H), 2.68 (s, 3 H), 2.91–3.35 (m, 4 H), 3.51 (s, 3 H), 3.02–3.75 (m, 5 H), 3.78 (s, 3 H), 3.82 (s, 3 H), 5.31 (d, 1 H), 5.48 (s, 1 H), 5.84 (dd, 1 H), 6.14 (s, 1 H), 6.81–6.92 (m, 3 H), 6.99–7.07 (m, 3 H), 7.11–7.20 (m, 2 H), 7.39–7.42 (m, 1 H), 8.01 (br s, 1 H), 9.97 (br s, 1 H); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 8.43, 8.82, 20.95, 25.50, 25.89, 29.29, 30.89, 33.53, 38.53, 40.33, 42.80, 44.73, 50.07, 51.95, 52.12, 53.27, 55.66, 56.25, 58.77, 60.18, 63.44, 65.71, 79.69, 83.68, 94.24, 110.30, 115.05, 118.19, 118.95, 122.01, 123.44, 124.37, 125.52, 126.36, 127.80, 127.96, 130.04, 132.23, 135.04, 140.10, 152.93, 158.12, 170.70, 174.60; high resolution mass spectrum (EI, mass resolution 12000), M calcd 900.4672941, found 900.46303; mass spectrum, m/z (rel intensity) 901 (11), 900 (M^+, 33), 898 (6), 841 (6), 839 (7), 838 (13), 825 (29), 824 (52), 810 (10), 809 (9), 793 (7), 792 (9), 788 (7), 766 (6), 751 (7), 741 (7), 665 (6), 649 (8), 541 (6), 540 (12), 527 (10), 470 (11), 469 (21), 450 (6), 444 (9), 431 (14), 381 (7), 380 (10), 379 (8), 373 (6), 370 (6), 369 (11), 356 (10), 355 (35), 325 (6), 310 (7), 297 (6), 295 (6), 283 (7), 282 (29), 273 (18), 261 (17), 258 (7), 244 (6), 240 (6), 231 (6), 230 (31), 222 (9), 218 (7), 217 (8), 214 (8), 202 (10), 200 (9), 190 (6), 188 (13), 185 (6), 182 (6), 174 (7), 171 (6), 170 (6), 168 (8), 158 (6), 155 (8), 154 (62), 144 (13), 143 (7), 141 (15), 140 (7), 136 (24), 135 (67), 134 (25), 130 (8), 124 (9), 123 (7), 122 (36), 121 (31), 120 (8), 108 (13), 107 (30), 106 (9), 93 (17), 92 (25), 91 (100), 84 (7), 82 (6), 81 (7), 79 (7), 77 (8), 70 (6), 65 (14), 60 (7), 58 (30), 57 (9).

(7*R*,5*S*)-Methyl 3-Benzyl-1,2,3,4,5,6,7,8-octahydro-5-[(2*R*)-2-ethyl-2,3-epoxypropyl]-7-(15-vindolinyl)azonino-[5,4-*b*]indole-7-carboxylate (33b). By the same procedure, starting with 0.085 g (0.12 mmol) of the 3a*S*,4*S*,2′*R* isomer **22b** of the silyl tosylate, 0.077 g (69%) of the title compound was obtained: TLC R_f 0.41 (silica gel, ethyl acetate, CAS brown); UV (ethanol) λ_{max} 290, 258, 212, 194 nm; IR (KBr) ν_{max} 3460, 3030, 2935, 2800, 1743, 1622, 1500, 1460, 1441, 1369, 1240, 1235, 1170, 1040, 736, 695 cm^{-1}; 270-MHz ^1H NMR ($CDCl_3$) δ 0.46 (t, 3 H), 0.73 (t, 3 H), 1.10–1.36 (m, 10 H), 1.58–1.71 (m, 2 H), 2.07 (s, 3 H), 2.19–2.67 (m, 10 H), 2.79 (s, 3 H), 2.87–3.10 (m, 1 H), 3.35–3.52 (m, 3 H), 3.57 (s, 3 H), 3.63–3.73 (m, 2 H), 3.82 (s, 6 H), 5.28 (d, 1 H), 5.45 (s, 1 H), 5.85 (dd, 1 H), 6.14 (s, 1 H), 6.9–7.45 (m, 9 H), 8.09 (br s, 1 H), 9.76 (br s, 1 H); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 8.10, 8.68, 20.92, 26.26, 26.64, 29.21, 29.54, 30.60, 34.03, 38.53, 42.69, 45.15, 50.26, 50.34, 52.03, 52.14, 53.49, 53.85, 54.14, 54.44, 57.83, 58.77, 65.05, 65.93, 75.98, 76.20, 77.45, 79.71, 83.57, 93.70, 110.16, 118.11, 118.79, 121.92, 123.13, 123.99, 126.61, 128.00, 128.08, 128.16, 130.12, 134.86, 140.19, 153.05, 158.37, 170.39, 171.54; high resolution mass spectrum (EI, mass resolution 12000), M calcd 900.4672941, found 900.46083; mass spectrum, m/z (rel intensity) 901 (12), 900 (M^+, 26), 842 (6), 838 (8), 825 (10), 824 (18), 810 (8), 792 (7), 751 (6), 649 (6), 540 (11), 527 (8), 470 (7), 469 (17), 444 (7), 431 (9), 381 (6), 380 (8), 379 (7), 369 (9), 356 (6), 355 (19), 311 (6), 295 (6), 283 (6), 282 (21), 272 (8), 261 (16), 260 (6), 258 (6), 231 (6), 230 (29), 222 (8), 218 (6), 217 (8), 214 (8), 202 (9), 188 (10), 170 (6), 168 (7), 158 (6), 155 (6), 154 (40), 144 (11), 143 (8), 141 (11), 140 (8), 136 (23), 135 (60), 134 (22), 130 (9), 124 (9), 122 (27), 121 (26), 120 (8), 108 (11), 107 (26), 106 (11), 93 (13), 92 (24), 91 (100), 81 (6), 79 (7), 77 (9), 65 (18), 63 (6), 60 (7), 58 (30), 55 (6), 51 (6).

Vincovaline (14b) and Its 17′-Equatorial Conformational Isomer 34. A solution of the D-seco epoxide dimer **33b** (0.35 g, 0.39 mmol) in 10 mL of methanol was heated at reflux for 48 h at which time TLC showed no remaining starting material and a new more polar product. The reaction mixture was cooled and flushed with nitrogen, and 20 mg of 10% palladium on carbon was added. This was stirred under a hydrogen atmosphere at room temperature for 3 h, filtered, and concentrated. Flash chromatography on silica gel, eluting with 1% triethylamine in methanol, gave 0.28 g (90%) of the 17′-equatorial conformational isomer **34** of vincovaline: TLC R_f 0.32 (silica gel, 1% methanol in dichloromethane, CAS purple): UV (ethanol) λ_{max} 292, 284, 262, 223, 195 nm; IR (KBr) ν_{max} 3403, 2956, 2924, 2877, 1739, 17219, 1658, 1617, 1595, 1500, 1461, 1431, 1272, 1331, 1304, 1247, 1186, 1150, 1131, 1099, 1085, 1039, 1012, 741 cm^{-1}; 270-MHz ^1H NMR ($CDCl_3$) δ 0.50–0.56 (m, 3 H), 0.91–0.99 (m, 3 H), 1.15–1.58 (m, 3 H), 1.69–1.92 (m, 3 H), 2.10 (s, 3 H), 2.21–2.69 (m, 6 H), 2.70 (s, 3 H), 2.71–3.11 (m, 3 H), 3.41–3.58 (m, 2 H), 3.60 (s, 3 H), 3.81 (s, 3 H), 5.25 (d, J = 8.1, 1 H), 5.45 (s, 1 H), 5.82–5.91 (m, 1 H), 5.97 (s, 1 H), 6.87 (s, 1 H), 7.00–7.41 (m, 4 H), 9.35 (s, 1 H), 10.80 (br s, 1 H); mass spectrum, m/z (rel intensity) 811 (M + 1, 69), 779 (5), 752 (1), 651 (1), 469 (3), 391 (26), 283 (16), 281 (17), 279 (10), 239 (40), 237 (90), 234 (53), 222 (14), 221 (10), 201 (11), 185 (12), 179 (42), 163 (100), 157 (30), 145 (10), 143 (15), 129 (12), 121 (14), 113 (19); CD (0.024 mg/mL methanol) λ (ellipticity) 214 (12), 225 (−114), 258 (−11), 0.240 mg/mL) 307 (28).

This product was then dissolved in toluene and heated at reflux for 8 h. Concentration and flash chromatography on silica gel, eluting with 9:1 dichloromethane–methanol, gave 0.27 g (95%) of vincovaline (**14b**): TLC R_f 0.42 (silica gel, 5% methanol in dichloromethane, CAS maroon); UV (ethanol) λ_{max} 205, 216 shld, 247, 284, 292, 301 nm; IR (KBr) ν_{max} 3458, 3424, 3025, 2962, 2931, 2879, 2852, 2813, 1740, 1676, 1614, 1500, 1460, 1433, 1371, 1334, 1296, 1249, 1226, 1191, 1174, 1146, 1106, 1095, 1034, 963, 927, 903, 804, 741 cm^{-1}; 270-MHz ^1H NMR ($CDCl_3$) δ 0.38 (t, J = 7.1 Hz, 3 H), 0.89 (t, J = 7.0 Hz, 3 H), 0.98–1.80 (m, 6 H), 2.07 (s, 3 H), 2.10–2.51 (m, 4 H), 2.73 (s, 3 H), 2.17–2.82 (m, 2 H), 3.11–3.54 (m, 4 H), 3.56 (s, 3 H), 3.79 (s, 6 H), 3.98–4.11 (m, 1 H), 5.23 (d, J = 8.7 Hz, 1 H), 5.45 (s, 1 H), 5.79 (dd, J = 10.0, 4.7 Hz, 1 H), 6.14 (s, 1 H), 6.72 (s, 1 H), 7.05–7.21 (m, 3 H), 7.52 (d, J = 7.4 Hz, 1 H), 8.11 (s, 1 H), 9.68 (br s, 1 H); mass spectrum, m/z (rel intensity) CI 811 (M + 1, 14), 793 (5), 753 (3), 431 (4), 419 (3), 393 (4), 392 (22), 391 (100), 389 (12), 375 (3), 307 (6), 279 (18), 261 (9), 186 (5), 185 (3), 184 (4), 177 (3), 167 (4), 149 (14), 113 (7); high resolution mass spectrum (EI, mass resolution 12000), M calcd 810.4203801, found 810.41685; mass spectrum, m/z (rel intensity) 838 (7), 826 (7), 825 (17), 824 (32), 811 (9), 810 (17), 808 (7), 779 (9), 766 (6), 753 (7), 752 (15), 751 (13), 651 (7), 649 (7), 469 (12), 356 (9), 355 (35), 283 (7), 282 (21), 222 (7), 214 (6), 202 (6), 200 (7), 174 (6), 168 (8), 156 (6), 155 (12), 154 (100), 144 (9), 141 (15), 140 (11), 136 (21), 135 (56), 130 (6), 124 (32), 123 (6), 122 (28), 121 (25), 108 (10), 107 (22), 106 (7), 93 (12), 92 (9), 91 (16), 84 (8), 83 (9), 82 (7), 70 (8), 60 (7), 58 (34), 57 (9); CD (0.019 mg/mL methanol) λ (ellipticity) 214 (100), 225 (−167), (0.190 mg/mL) 258 (32), 307 (−32).

Leurosidine (13) and Its 17′-Equatorial Conformational Isomer 35b. By the same procedure, starting with 0.10 g (0.11 mmol) of the D-seco epoxide dimer **31b** and adding 1.5 equiv of glacial acetic acid, 0.054 g (60%) of the 17′-equatorial conformational isomer **35b** was obtained: TLC R_f 0.19 (silica gel, 1% triethylamine in dichloromethane, CAS purple); UV (ethanol) λ_{max} 291, 285, 262, 222, 195 nm; IR (KBr) ν_{max} 3457, 3407, 2957, 2930, 2877, 2852, 1740, 1616, 1595, 1498, 1458, 1432, 1371, 1332, 1301, 1250, 1191, 1172, 1147, 1132, 1110, 1085, 1042, 743, cm^{-1}; mass spectrum, m/z (rel intensity) 810 (M^+, 3), 779 (2), 651 (2), 469 (1), 308 (2), 297 (5), 282 (5), 187 (3), 182 (1), 154 (7), 149 (5), 141 (2), 140 (8), 123 (3), 122 (5), 121 (3), 112 (4), 109 (4), 107 (6); CD (0.026 mg/mL methanol) λ (ellipticity) 214 (−185), 225 (167), 258 (41), (0.260 mg/mL) 307 (−9).

After heating 0.04 g of the above compound at reflux in toluene for 72 h, 0.032 g (80%) of leurosidine (**13**) was obtained: TLC R_f 0.24 (silica gel, 5% methanol in dichloromethane, CAS brown); UV (ethanol) λ_{max} 300, 290, 260, 220, 195 nm; IR (KBr) ν_{max} 3467, 2957, 2936, 2879, 2848, 2815, 1740, 1616, 1503, 1459, 1432, 1371, 1331, 1244, 1229, 1039, 738 cm^{-1}; 270-MHz ^1H NMR ($CDCl_3$) δ 0.82 (t, J = 7.6 Hz, 3 H), 0.95 (t, J = 7.6 Hz, 3 H), 1.16–1.41 (m, 2 H), 1.52–1.59 (m, 1 H), 1.73–1.84 (m, 3 H), 2.11 (s, 3 H), 2.11–2.28 (m, 6 H), 2.40–2.50 (m, 1 H), 2.67–2.87 (m, 3 H), 2.72 (s, 3 H), 2.92–3.00 (m, 1 H), 3.11–3.21 (m, 2 H), 3.25–3.43 (m, 4 H), 3.61

(s, 3 H), 3.74 (s, 1 H), 3.80 (s, 6 H), 5.31 (d, J = 8.9 Hz, 1 H), 5.47 (s, 1 H), 5.87 (m, 1 H), 6.12 (s, 1 H), 6.56 (s, 1 H), 7.11–7.19 (m, 3 H), 7.53 (d, J = 6.8 Hz, 1 H), 7.98 (s, 1 H), 9.79 (s, 1 H); high resolution mass spectrum (EI, mass resolution 12 000), M calcd 810.4203801, found 810.41718; mass spectrum, m/z (rel intensity) 838 (11), 825 (15), 824 (32), 811 (6), 810 (17), 780 (6), 779 (10), 766 (8), 753 (7), 752 (14), 751 (8), 651 (7), 649 (6), 469 (11), 369 (9), 356 (9) 355 (34), 295 (7), 283 (6), 282 (21), 272 (6), 222 (7), 214 (7), 202 (6), 200 (7), 188 (9), 174 (6), 170 (6), 168 (6), 155 (11), 154 (100), 144 (10), 141 (15), 140 (10), 136 (21), 135 (52), 130 (6), 124 (32), 123 (6), 122 (30), 121 (25), 108 (11), 107 (21), 106 (7), 93 (12), 92 (6), 91 (8), 84 (8), 83 (10), 82 (8), 81 (6), 70 (8), 60 (6), 58 (40), 57 (9), 55 (7); CD (0.027 mg/mL) λ (ellipticity) 214 (−291), 225 (133), 258 (79), (0.270 mg/mL) 307 (20).

N-[(S)-α-Methylbenzyl]-4-piperidone (43). (S)-(−)-α-Methylbenzylamine (**46**, 2.0 g, 16.5 mmol), ethanol (25 mL), potassium carbonate (4.79 g, 34.6 mmol), and water (12 mL) were stirred in a two-necked flask equipped with a reflux condenser and a dropping funnel containing N,N-dimethyl-4-oxopiperidinium iodide (**45**, 4.21 g, 16.5 mmol) in water (12 mL). After achieving vigorous reflux the piperidone was added over 30 min, and the mixture was heated at reflux for another 30 min. The reaction mixture was then cooled, the ethanol was removed under reduced pressure, and the residue was extracted with 3 × 100 mL of ether. The ether layers were combined and dried over magnesium sulfate. Concentration and flash chromatography, eluting with ether, gave 2.5 g of the title compound (75%): TLC R_f 0.43 (silica gel, 3:2 ether–hexane, CAS char); UV (EtOH) λ_{max} 204, 321 nm; IR (neat) ν_{max} 3418, 3085, 3062, 3010, 2972, 2940, 2908, 2880, 2800, 2755, 1720, 1650, 1600, 1583, 1495, 1474, 1453, 1410, 1387, 1375, 1340, 1320, 1310, 1285, 1219, 1155, 1130, 1110, 1080, 1050, 1028, 1010, 1000, 970, 949, 930, 912, 800, 767, 734, 700, 624, 615, 604 cm^{-1}; 270-MHz ^{1}H NMR ($CDCl_3$) δ 1.42 (d, J = 6.8 Hz, 3 H), 2.41 (t, J = 5.9 Hz, 4 H), 2.66–2.81 (m, 4 H), 3.62 (q, J = 13.5, 6.7 Hz, 1 H), 7.22–7.36 (m, 5 H); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 19.11, 41.42, 49.88, 63.25, 126.98, 127.21, 128.21, 143.47, 208.93; mass spectrum m/z (rel intensity) 204 (M + 1, 19), 203 (M$^+$, 30), 189 (14), 188 (98), 143 (13), 126 (51), 118 (35), 106 (14), 105 (100), 104 (13), 103 (20), 98 (14), 91 (42), 79 (30), 78 (12), 77 (45), 56 (50), 55 (13), 51 (17).

N-[(S)-α-Methylbenzyl]tetrahydro-γ-carboline (48). Phenylhydrazine hydrochloride (2.8 g, 19.36 mmol) in glacial acetic acid (60 mL) and the N-(methylbenzyl)-4-piperidone **43** (4.32 g, 21.30 mmol) were stirred at room temperature for 3 h. Concentrated HCl (40 mL) was then added, causing the reaction to turn dark red. The mixture was heated at 65 °C for 3 h, at which time the acetic acid was removed under reduced pressure (70 °C). The residue was taken up in dichloromethane (150 mL) and basified with potassium carbonate. Water was added (50 mL), the organic layer was separated, and the aqueous layer was extracted further with 2 × 50 mL of dichloromethane. The combined dichloromethane layers were dried over magnesium sulfate. Concentration and flash chromatography on silica gel, eluting with 2:1 ether–hexane followed by crystallization from methanol, gave 4.25 g of the title compound (71%); mp (methanolate) 80–84 °C dec. TLC R_f 0.33 (silica gel, 3:2 ether–hexane, CAS blue-green); UV (ETOH) λ_{max} 207, 223, 277, 282 nm; IR (KBr) ν_{max} 3402, 3150, 3058, 3035, 2975, 2920, 2802, 2745, 1625, 1598, 1493, 1475, 1452, 1440, 1272, 1330, 1312, 1281, 1265, 1238, 1183, 1148, 1121, 1102, 1088, 1063, 1030, 1010, 970, 738, 700, 635 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.51 (d J = 6.7 Hz, 3 H), 2.09 (br s, 1 H), 2.58–2.72 (m, 3 H), 2.85–2.92 (m, 1 H), 3.36 (s, 3 H), 3.57–3.71 (m, 2 H), 3.94 (d, J = 13.5 Hz, 1 H), 7.00–7.10 (m, 2 H), 7.16–7.41 (m, 7 H), 7.97 (br s, 1 H); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 20.11, 23.97, 46.93, 47.77, 50.57, 64.09, 108.93, 110.56, 117.15, 119.15, 121.00, 126.39, 126.90, 127.56, 128.28, 132.40, 136.19, 144.54; mass spectrum, m/z (rel intensity) 277 (M + 1, 11), 276 (M$^+$, 41), 275 (9), 261 (3), 171 (14), 144 (20), 143 (100), 118 (4), 115 (7), 105 (25), 103 (7), 91 (10), 79 (8), 77 (14), 56 (5), 51 (5).

Dimethyl 3-[(S)-α-Methylbenzyl]-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole-5,5-dicarboxylate (52). To a solution of N-[(S)-α-methylbenzyl]tetrahydro-γ-carboline (methanolate) (**48**, 0.75 g, 2.43 mmol) and triethylamine (0.37 mL, 2.68 mmol) in tetrahydrofuran (20 mL), stirring at −78 °C (dry ice, acetone) under nitrogen, was added *tert*-butyl hypochlorite (0.313 mL, 2.68 mmol). The reaction mixture was stirred at −78 °C for 15 min followed by warming to 0 °C over 1 h. Thallium dimethyl malonate (1.14 g, 3.41 mmol) was added and the mixture was stirred at room temperature for 3 h and then at reflux for 20 h. The cooled reaction mixture was filtered and concentrated. Flash chromatography on silica gel, eluting with 3:2 ether–hexane, gave 0.77 g of the title compound (78%) crystallized from methanol: TLC R_f 0.50 (silica gel, 3:2 ether–hexane, CAS gray-green); UV (ETOH) λ_{max} 196, 224, 284, 292, 328 nm; IR (film) ν_{max} 3412, 3060, 3030, 2958, 2900, 2839, 1740, 1670, 1618, 1580, 1493, 1460, 1435, 1392, 1373, 1337, 1283, 1245, 1175, 1155, 1144, 1075, 1050, 1032, 960, 928, 870, 796, 742, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.42 (d, J = 6.7 Hz, 3 H), 2.74–2.89 (m, 4 H), 3.62 (d, J = 13.4 Hz, 1 H), 3.73–3.82 (m, 7 H), 4.00–4.08 (m, 1 H), 7.03–7.46 (m, 9 H), 8.39 (br s, 1 H); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 14.86, 25.38, 52.88, 52.96, 59.51, 62.81, 64.82, 110.81, 114.90, 118.42, 119.31, 122.18, 126.71, 127.54, 128.08, 128.72, 129.48, 135.14, 143.49, 169.71; mass spectrum, m/z (rel intensity) 407 (M + 1, 25), 406 (73), 391 (6), 301 (43), 275 (13), 273 (37), 272 (36), 270 (17), 269 (14), 264 (15), 260 (19), 242 (10), 241 (9), 228 (28), 227 (9), 214 (18), 209 (13), 181 (7), 169 (10), 159 (8), 155 (7), 154 (29), 140 (7), 128 (9), 127 (18), 106 (9), 105 (100), 103 (11), 91 (10), 79 (20), 77 (20), 59 (14).

Methyl 3-[(S)-α-Methylbenzyl]-1,2,3,4,5ξ,6-hexahydroazepino[4,5-b]indole-5-carboxylate (41). A solution of the diester azepine **52** (0.75 g, 1.85 mmol), lithium chloride (0.78 g, 1 equiv), and triethylamine hydrochloride (0.127 g, 0.5 equiv) in dimethylacetamide (20 mL) was heated at 120 °C for 1 h, at which time TLC (2% methanol in dichloromethane) showed no remaining starting material and the presence of a new, more polar compound. Brine (20 mL) was added to the reaction mixture and the resulting solution was extracted with ether (3 × 25 mL). The combined ether layers were dried over magnesium sulfate. Concentration and flash chromatography on silica gel, eluting with 3:2 ether–hexane, gave 0.51 g (80%) of the title compounds as two diastereomers: TLC R_f 0.41, 0.45 (silica gel, 3:2 ether–hexane, CAS blue); UV (ETOH) λ_{max} 196, 203, 225, 283, 291 nm; IR (film) ν_{max} 3392, 3060, 3030, 2952, 2829, 1733, 1600, 1494, 1465, 1454, 1435, 1370, 1340, 1286, 1245, 1208, 1163, 1050, 1025, 910, 850, 742, 717, 700 cm^{-1}; 270-MHz ^{1}H NMR ($CDCl_3$) δ 1.42 (d, J = 6.7 Hz, 3 H), 2.58–3.2 (m, 6 H), 3.4–3.53 (m, 1 H), 3.65–3.71 (2s, 3 H), 3.96–4.08 (m, 1 H), 7.02–7.16 (m, 2 H), 7.19–7.46 (m, 7 H), 8.1–8.3 (2s, 1 H); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 14.83, 17.39, 24.89; 25.32, 46.28, 46.67, 51.96, 52.09, 53.64, 54.44, 56.06, 63.69, 64.20, 110.57, 113.84, 117.92, 118.96, 121.21, 121.25, 126.66, 127.49, 127.93, 128.02, 128.53, 132.12, 132.26, 134.81, 143.30, 143.97, 172.38; mass spectrum, m/z (rel intensity) 349 (M + 1, 29), 348 (M$^+$, 56), 333 (3), 275 (8), 243 (68), 216 (14), 215 (56), 214 (78), 202 (25), 183 (10), 170 (10), 169 (15), 156 (30), 155 (10), 154 (24), 147 (11), 146 (13), 134 (9), 128 (9), 106 (9), 105 (100), 103 (9), 79 (12), 77 (18).

(3aR,4R)- and (3aS,4S)-Methyl 3-[(S)-α-Methylbenzyl]-2,3,3a,4,5,7-hexahydro-4-[(2R)-2-ethyl-2,3-dihydroxypropyl]-1H-pyrrolo[2,3-d]carbazole-6-carboxylate Acetonide (54 and 55). The mixture of the above azepines **41** (0.15 g, 0.43 mmol) in anhydrous toluene (15 mL) was stirred under nitrogen at 70 °C. (4R)-4-Ethyl-4,5-dihydroxypentanal acetonide (**8b**, 0.095 g, 1.2 eq) in toluene (2 mL) was added slowly via syringe, and the reaction mixture was heated at reflux for 24 h. Concentration and flash chromatography on silica gel, eluting with 1:1 ether–hexane, gave 0.133 g (60%) of a mixture of the title compounds: TLC R_f 0.54 (silica gel, 3:2 ether–hexane, CAS blue); 270-MHz ^{1}H NMR ($CDCl_3$) integration of indole protons (8.87, 1 H):(8.98, 1 H); mass spectrum, m/z (rel intensity) 516 (M$^+$, 4), 515 (12), 501 (3), 388 (13), 387 (44), 303 (5), 302 (23), 283 (4), 241 (3), 238 (4), 228 (7), 214 (5), 198 (6), 194 (4), 187 (20), 169 (5), 168 (8), 167 (8), 159 (8), 155 (6), 154 (7), 140 (9), 132 (8), 129 (17), 127 (41), 115 (18), 113 (9), 111 (5), 109 (6), 106 (10), 105 (100), 81 (13), 72 (53), 71 (15), 59 (52).

(3aR,4R)- and (3aS,4R)-Methyl 3-[(S)-α-Methylbenzyl]-2,3,3a,4,5,7-hexahydro-4-[(2R)-2-ethyl-2,3-dihydroxypropyl]-1H-pyrrolo[2,3-d]carbazole-6-carboxylate (56 and 57). The mixture of the acetonides **54** and **55** (0.133 g, 0.26 mmol) in methanol (20 mL) and 10% aqeuous hydrochloric acid (5 mL) was stirred at reflux for 30 min. Methanol was removed under reduced pressure, and the reaction mixture was basified with 10% ammonium hydroxide and extracted with ether (3 × 25 mL). The combined ether layers were dried over magnesium sulfate. Concentration and flash chromatography on silica

gel, eluting with ether, gave 0.085 g of the less polar 3a*R*,4*R*,2'*R* title isomer **56** (69%): TLC R_f 0.44 (silica gel, 9:1 dichloromethane–methanol, CAS blue). This was followed by 0.028 g (23%) of the more polar isomer **57** (3a*S*,4*S*,2'*R*): TLC R_f 0.32 (silica gel, 9:1 dichloromethane–methanol, CAS blue fade to purple). Diastereomeric excess: 47%.

For the 3a*R*,4*R*,2'*R* isomer **56**: UV (ethanol) λ_{max} 203, 225, 299, 328 nm; IR (film) ν_{max} 3460, 3390, 2972, 2935, 1730, 1672, 1610, 1480, 1467, 1438, 1378, 1300, 1282, 1250, 1203, 1133, 1045, 745, 700 cm^{-1}; 270-MHz ^{1}H NMR ($CDCl_3$) δ 0.80–94 (m, 5 H), 1.14 (dd, J = 14.7, 7.4 Hz, 1 H), 1.49–1.74 (m, 6 H), 1.91–2.02 (m, 1 H), 2.15–2.27 (m, 2 H), 2.49–2.67 (m, 3 H), 2.95 (t, J = 8.3 Hz, 1 H), 3.06 (br s, 1 H), 3.33–3.44 (m, 2 H), 3.77 (s, 3 H), 4.09–4.18 (m, 1 H), 5.95 (d, J = 7.3 Hz, 1 H), 6.58 (t, J = 7.3 Hz, 1 H), 6.73 (d, J = 7.7 Hz, 1 H), 7.03 (t, J = 7.7 Hz, 1 H), 7.29–7.45 (m, 5 H), 8.81 (br s, 1 H); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 8.16, 21.13, 24.05, 28.87, 34.68, 36.59, 41.06, 45.52, 50.89, 55.02, 59.11, 67.70, 71.38, 75.17, 90.50, 108.90, 120.52, 122.21, 127.07, 127.43, 128.08, 128.44, 137.77, 140.65, 142.73, 165.43, 169.10.

(3a*R*,4*R*)-Methyl 3-[(*S*)-α-Methylbenzyl]-2,3,3a,4,5,7-hexahydro-4-[(2*R*)-2-ethyl-2-hydroxy-3-[(*p*-tolylsulfonyl)oxy]propyl]-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate. A solution of 80 mg (0.17 mmol) of (3a*R*,4*R*)-methyl 3-[(*S*)-α-methylbenzyl]-2,3,3a,4,5,7-hexahydro-4-[(2*R*)-2-ethyl-2,3-dihydroxypropyl]-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate (**56**) and 47 mL (0.34 mmol) of triethylamine in 20 mL of dichloromethane was brought to 0 °C, and 110 mg (0.34 mmol) of *p*-toluenesulfonic anhydride was added. The reaction mixture was stirred under nitrogen for 30 h and then washed with 10% ammonium hydroxide. The organic layer was dried over sodium sulfate and concentrated under reduced pressure to give a white solid, which was taken directly on to the next reaction: TLC R_f 0.37 (silica gel, 4:1 ether–hexane, CAS blue).

(3a*R*,4*R*)-Methyl 3-[(*S*)-α-Methylbenzyl]-2,3,3a,4,5,7-hexahydro-4-[(2*R*)-2-ethyl-2-[(trimethylsilyl)oxy]-3-[(*p*-tolylsulfonyl)oxy]propyl]-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate (58). A solution of (3a*R*,4*R*)-methyl 3-[(*S*)-α-methylbenzyl]-2,3,3a,4,5,7-hexahydro-4-[(2*R*)-2-ethyl-2-hydroxy-3-[(*p*-tolylsulfonyl)oxy]propyl]-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate from the previous reaction and triethylamine (35 μL, 1.5 equiv) in tetrahydrofuran (20 mL) was stirred under nitrogen and brought to 0 °C. Trimethylsilyl trifluoromethanesulfonate (49 μL, 1.5 equiv) was then added by syringe. The solution was stirred for 20 min, then washed with 10 mL of aqueous saturated sodium bicarbonate, dried over sodium sulfate, and concentrated under reduced pressure. Flash chromatography on a silica gel column, eluting with 3:2 ether–hexane, gave 86 mg (73% from diol) of the title compound: TLC R_f 0.45 (silica gel, 3:2 ether–hexane, CAS blue); UV (ethanol) λ_{max} 200, 224, 255, 297, 330 nm; IR (KBr) ν_{max} 3385, 3060, 3030, 2975, 2950, 2858, 1738, 1677, 1608, 1495, 1480, 1465, 1455, 1437, 1362, 1303, 1295, 1280, 1250, 1240, 1200, 1190, 1176, 1155, 1130, 1096, 1083, 1062, 1050, 1030, 980, 910, 840, 812, 780, 750, 735, 705, 636, 552 cm^{-1}; 270-MHz ^{1}H NMR ($CDCl_3$) δ 0.0 (s, 9 H), 0.52 (J = 6.5 Hz, 3 H), 0.58–0.65 (m, 1 H), 0.98–1.14 (m, 2 H), 1.31–1.55 (m, 3 H), 1.44 (d, J = 6.9 Hz, 3 H), 1.76–1.86 (m, 1 H), 2.04–2.06 (m, 1 H), 2.30 (s, 3 H), 2.31–2.57 (m, 3 H), 2.79 (br s, 1 H), 3.58–3.71 (m, 1 H), 3.87–3.93 (m, 1 H), 5.77 (d, J = 7.3 Hz, 1 H), 6.45 (t, J = 7.5 Hz, 1 H), 6.60 (d, J = 7.7 Hz, 1 H), 6.91 (t, J = 7.5 Hz, 1 H), 7.13–7.28 (m, 7 H), 7.63 (d, J = 7.2 Hz, 2 H), 8.78 (br s, 1 H); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 2.54, 8.26, 21.19, 21.51, 23.59, 29.23, 34.52, 37.03, 41.28, 45.49, 50.60, 54.91, 59.25, 72.19, 74.11, 77.82, 90.84, 108.87, 120.44, 122.18, 127.12, 127.47, 127.98, 128.12, 128.46, 129.74, 133.01, 137.67, 140.48, 142.91, 144.70, 165.42, 169.08; mass spectrum, m/z (rel intensity) 702 (M^+, 6), 517 (6), 489 (9), 488 (28), 388 (26), 387 (100), 384 (8), 346 (10), 294 (8), 283 (11), 229 (15), 228 (17), 227 (12), 226 (6), 214 (8), 212 (30), 205 (8), 194 (6), 168 (7), 167 (7), 157 (9), 156 (6), 155 (38), 149 (10), 145 (6), 130 (11), 129 (61), 122 (7), 115 (6), 114 (56), 111 (6), 106 (12), 105 (77), 97 (7), 92 (7), 91 (59), 89 (17), 75 (14), 73 (24), 72 (55), 71 (11), 70 (10), 69 (10), 68 (10).

(7*S*,5*R*)-Methyl 3-[(*S*)-α-Methylbenzyl]-1,2,3,4,5,6,7,8-octahydro-5-[(2*R*)-2-ethyl-2,3-epoxypropyl]-7-(15-vindolinyl)azonino[6,7-*b*]indole-7-carboxylate (59). A solution of 0.080 g (0.11 mmol) of (3a*R*,4*R*)-methyl 3-[(*S*)-α-methylbenzyl]-2,3,3a,4,5,7-hexahydro-4-[(2*R*)-2-ethyl-2-[(trimethylsilyl)oxy]-3-[(*p*-tolylsulfonyl)oxy]propyl]-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate (**58**) and triethylamine (17 μL, 1.1 equiv) in dichloromethane (5 mL) was stirred under nitrogen and brought to 0 °C. *tert*-Butyl hypochlorite (14 μL, 1.1 equiv) in dichloromethane (2 mL) was added by syringe, and the mixture was stirred for 5 min at which time, by TLC, the mixture was free of starting material. The solution was washed with water (10 mL), dried over sodium sulfate, and concentrated under vacuum to give a white solid, which was used in the next reaction: R_f 0.59 (silica, ethyl acetate, CAS brown). To a solution of the chlorination product and vindoline (0.052 g, 1 equiv) in dry acetone (5 mL) was added tetrafluoroboric acid–diethyl ether complex (43 μL, 2 equiv). After 5 min, silver tetrafluoroborate (0.044 g, 2 equiv) in dry acetone (1 mL) was added. The resulting heterogeneous mixture was stirred for 10 min, at which time 10% ammonium hydroxide (5 mL) was added. Extraction with dichloromethane (3 × 15 mL), drying over sodium sulfate, and concentration under vacuum gave a white foam.

The above material was then dissolved in glacial acetic acid (10 mL) and, with stirring, potassium borohydride (0.062 g, 10 eq) was slowly added. After 15 min, the reaction mixture was poured onto ice and made strongly basic with concentrated ammonium hydroxide. Extraction with dichloromethane (3 × 15 mL), drying (Na_2SO_4), and concentration under vacuum gave a white foam: TLC R_f 0.53 (silica gel, ethyl acetate, CAS brown). This product was dissolved in tetrahydrofuran (10 mL) and brought to 0 °C. Tetrabutylammonium fluoride (0.228 mL, 2 equiv, 1.0 M in THF) was added by syringe, and the reaction mixture was stirred for 15 min, at which time TLC showed complete conversion of starting material to a more polar product. The solution was washed with aqueous saturated sodium bicarbonate, dried over sodium sulfate, and concentrated under vacuum. Flash chromatography on silica gel, eluting with ethyl acetate, gave 0.084 g (73%) of the title compound: TLC R_f 0.44 (silica gel, ethyl acetate, CAS brown); UV λ_{max} 213, 262, 289 nm; IR (film) ν_{max} 3470, 3028, 2965, 2930, 2875, 2575, 2240, 1740, 1610, 1500, 1456, 1430, 1367, 1325, 1235, 1170, 1140, 1100, 1080, 1035, 5.90 (dd, 815, 755, 730, 696, 640 cm^{-1}; 270-MHz ^{1}H NMR ($CDCl_3$) δ 0.55 (t, J = 7.2 Hz, 3 H), 0.88 (t, J = 7.3 Hz, 3 H), 1.20 (d, J = 6.6 Hz, 3 H), 1.22–1.46 (m, 5 H), 1.66–2.04 (m, 3 H), 2.12 (s, 3 H), 2.17–2.23 (m, 2 H), 2.35–2.63 (m, 6 H), 2.69 (s, 3 H), 2.74–2.80 (m, 2 H), 3.00 (d, J = 14.4 Hz, 2 H), 3.25–3.55 (m, 3 H), 3.59 (s, 3 H), 3.63–3.76 (m, 2 H), 3.81 (s, 6 H), 5.36 (d, J = 10.2 Hz, 1 H), 5.51 (s, 1 H), 5.90 (dd, J = 13.2, 6.6 Hz, 1 H), 6.10 (s, 1 H), 6.9 (s, 1 H), 7.03–7.41 (m, 9 H), 9.7 (br s, 1 H); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 8.40, 8.63, 15.36, 20.98, 25.69, 26.04, 30.89, 34.38, 36.06, 38.54, 40.11, 42.89, 44.67, 48.99, 50.61, 50.74, 52.07, 52.12, 52.96, 53.33, 55.60, 55.79, 56.62, 58.77, 63.36, 66.44, 76.41, 76.53, 79.73, 83.63, 94.31, 110.31, 116.51, 118.20, 118.92, 121.99, 122.10, 125.36, 124.38, 124.89, 126.25, 127.13, 127.94, 129.32, 130.10, 134.96, 144.64, 153.01, 158.26, 170.77, 171.60, 174.36; mass spectrum, m/z (rel intensity) 915 (M + 1, 5), 810 (5), 566 (12), 540 (7), 527 (12), 469 (6), 380 (10), 296 (5), 295 (9), 283 (5), 282 (14), 276 (11), 275 (8), 273 (6), 258 (5), 245 (5), 244 (19), 233 (13), 232 (9), 222 (5), 188 (5), 172 (6), 171 (7), 149 (6), 148 (5), 145 (6), 144 (10), 140 (8), 136 (8), 135 (33), 134 (5), 130 (6), 129 (7), 122 (12), 121 (13), 119 (6), 115 (6), 112 (5), 111 (10), 109 (5), 108 (5), 107 (10), 106 (11), 105 (100), 104 (14), 103 (10), 100 (5), 99 (9), 97 (15), 95 (5), 93 (7), 91 (10), 87 (97).

***N*-[(*S*)-1-(1-Naphthyl)ethyl]-4-piperidone (44).** (*S*)-(−)-1-(1-Naphthyl)ethylamine (**47**) (2 mL, 12.38 mmol), ethanol (25 mL), potassium carbonate (3.59 g, 25.97 mmol), and water (12 mL) were heated at reflux. *N*,*N*-Dimethyl-4-piperidone, iodide salt (**45**) (3.16 g, 12.38 mmol) in water (12 mL) was added by dropping funnel over 30 min. The mixture was then stirred for another 30 min at reflux temperature. The solution was cooled, ethanol was removed under reduced pressure, and the residue was extracted with dichloromethane (3 × 100 mL). The organic layers were combined, dried over sodium sulfate, and concentrated. Flash chromatography on silica gel, eluting with 3:2 ether–hexane, gave 2.16 g of the title compound (70%): TLC R_f 0.43 (silica gel, 3:2 ether–hexane, UV); UV (ethanol) λ_{max} 281, 271, 223, 191 nm; IR (neat) ν_{max} 3415, 3050, 2975, 2908, 2802, 1720, 1596, 1511, 1460, 1410, 1394, 1374, 1355, 1341, 1320, 1256, 1215, 1173, 1132, 1074, 1028, 1012, 998, 968, 948, 927, 860, 800, 780, 734, 650, 620 cm^{-1}; 250-MHz ^{1}H NMR ($CDCl_3$) δ 1.47 (d, J = 6.6 Hz, 3 H), 2.26–2.44 (m, 4 H), 2.67–2.87 (m, 4 H), 4.27 (q, J = 6.6 Hz, 1 H), 7.37–7.50

(m, 3 H), 7.57 (d, J = 7.1 Hz, 1 H), 7.71 (d, J = 8.1 Hz, 1 H), 7.81 (d, J = 8.6 Hz, 1 H), 8.41 (d, J = 7.8 Hz, 1 H); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 18.32, 41.59, 50.32, 60.37, 124.06, 124.34, 125.32, 125.41, 125.61, 127.69, 128.81, 131.67, 134.25, 140.13, 209.10; mass spectrum, m/z (rel intensity) 254 (M + 1, 27), 253 (M^+, 46), 238 (83), 168 (10), 156 (18), 155 (100), 153 (28), 141 (34), 128 (13), 127 (18), 126 (60), 115 (15), 98 (19); high resolution mass spectrum (EI, mass resolution 5000), M calcd 253.1466547, found 253.14771.

N-[(S)-1-(1-Naphthyl)ethyl]tetrahydro-γ-carboline (49). Phenylhydrazine hydrochloride (1 g, 6.9 mmol) and N-[(S)-1-(1-naphthyl)ethyl]-4-piperidone (44) (1.6 g, 6.3 mmol) were stirred in glacial acetic acid (25 mL) for 3 h at room temperature. Concentrated hydrochloric acid (15 mL) was added and the reaction mixture was heated at 65 °C in an oil bath for 4 h. Acetic acid was removed under reduced pressure and the residue was taken up in dichloromethane (100 mL) and made basic with potassium carbonate. Water was added (50 mL), the organic layer was separated, and the aqueous layer was further extracted with dichloromethane (3 × 50 mL). The combined organic layers were dried over magnesium sulfate and concentrated. Flash chromatography on silica gel, eluting with 4:1 ether–hexane, gave 1.45 g of the title compound (70%): TLC R_f 0.50 (silica gel, 4:1 ether–hexane, CAS green); UV (ethanol) λ_{max} 282, 224, 194 nm; IR (KBr) ν_{max} 3406, 3050, 2970, 2910, 2800, 2740, 1645, 1593, 1510, 1472, 1452, 1428, 1391, 1370, 130, 1328, 1314, 1262, 1237, 1172, 1146, 1122, 1104, 1080, 1009, 969, 800, 778, 739, 634 cm^{-1}; 250-MHz ^{1}H NMR ($CDCl_3$) δ 1.59 (d, J = 6.6 Hz, 3 H), 2.38–2.48 (m, 1 H), 2.59–2.68 (m, 2 H), 2.83–2.92 (m, 1 H), 3.64 (d, J = 13.3 Hz, 1 H), 4.10 (d, J = 13.1 Hz, 1 H), 4.38 (q, J = 6.5 Hz, 1 H), 6.99–7.15 (m, 3 H), 7.34–7.50 (m, 4 H), 7.71 (t, J = 7.9 Hz, 2 H), 7.80–7.85 (m, 1 H), 8.42–8.45 (m, 1 H); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 19.52, 24.18, 47.29, 48.18, 61.00, 109.20, 110.58, 117.47, 119.26, 121.06, 124.17, 124.17, 124.58, 125.32, 125.52, 126.45, 127.35, 128.72, 131.75, 132.61, 134.20, 136.16, 141.31; mass spectrum, m/z (rel intensity) 327 (M + 1, 11), 326 (M^+, 35), 311 (4), 171 (30), 155 (32), 144 (23), 143 (100), 128 (8), 115 (10); high resolution mass spectrum (EI, mass resolution 5000), M calcd 326.1782876, found 326.17844.

Dimethyl 3-[(S)-1-(1-Naphthyl)ethyl]-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole-5,5-dicarboxylate (53). N-[(S)-1-(1-Naphthyl)ethyl]tetrahydro-γ-carboline (49) (0.49 g, 1.5 mmole) and triethylamine (0.23 mL, 1.65 mmol) in tetrahydrofuran (20 mL) were stirred under nitrogen and brought to −78 °C (dry ice, acetone). *tert*-Butyl hypochlorite (0.19 mL, 1.65 mmol) was added by syringe, and the mixture was stirred for 15 min and then warmed to 0 °C over 1 h. Thallium dimethyl malonate (0.70 g, 2.10 mmol) was added, the mixture was stirred at room temperature for 14 h and then filtered. The filtrate was then heated at reflux for 24 h. Concentration and flash chromatography on silica gel, eluting with 3:2 ether–hexane, gave 0.56 g (82%) of the title compound: TLC R_f 0.69 (silica gel, 4:1 ether–hexane, CAS gray); UV (ethanol) γ_{max} 292, 281, 223, 196 nm; IR (film) ν_{max} 3440, 3048, 2955, 2900, 2835, 1740, 1510, 1488, 1460, 1434, 1395, 1370, 1336, 1315, 1282, 1240, 1176, 1142, 1121, 1080, 1050, 1024, 970, 930, 800, 780, 740, 700 cm^{-1}; 250-MHz ^{1}H NMR ($CDCl_3$) δ 1.55 (d, J = 6.7 Hz, 3 H), 2.95 (s, 3 H), 2.83–3.03 (m, 3 H), 3.12–3.23 (m, 1 H), 3.54 (d, J = 13.2 Hz, 1 H), 3.76 (s, 3 H), 3.81–3.84 (m, 1 H), 4.72 (q, J = 6.6 Hz, 1 H), 7.04–7.16 (m, 2 H), 7.20–7.26 (m, 1 H), 7.39–7.51 (m, 5 H), 7.73–7.83 (m, 2 H), 8.29–8.33 (m, 2 H); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 13.22, 25.45, 52.37, 53.07, 54.51, 56.82, 61.78, 61.92, 110.78, 115.10, 118.39, 119.29, 122.13, 124.48, 124.96, 125.02, 125.33, 125.61, 127.77, 128.37, 128.53, 129.53, 132.46, 134.09, 134.90, 138.94, 169.05, 169.95; mass spectrum, m/z (rel intensity) 457 (M + 1, 18), 456 (M^+, 39), 314 (11), 302 (13), 301 (36), 273 (21), 272 (19), 270 (17), 260 (7), 228 (10), 227 (13), 214 (7), 159 (35), 156 (17), 155 (100), 154 (15), 153 (13), 143 (9), 127 (31), 115 (7), 101 (73), 100 (15); high resolution mass spectrum (EI, mass resolution 5000), M calcd 456.2048916, found 456.20674.

Methyl 3-[(S)-1-(1-Naphthyl)ethyl]-1,2,3,4,5ξ,6-hexahydroazepino[4,5-b]indole-5-carboxylate (42). A solution of the diester azepine 53 (0.420 g, 0.92 mmol), lithium chloride (0.05 g, 1.18 mmol), and triethylamine hydrochloride (0.63 mg, 0.46 mmol) in dimethylacetamide (20 mL) was heated in an oil bath at 130 °C for 1 h. Brine (20 mL) was added and the mixture was extracted with ether (4 × 50 mL). The combined ether layers were dried over magnesium sulfate and concentrated. Flash chromatography on silica gel, eluting with 1:1 ether–hexane, gave 0.25 g (68%) of the title compounds: TLC R_f 0.45 (silica, 3:2 ether–hexane, CAS blue); UV (ethanol) λ_{max} 291, 281, 223, 191 nm; IR (KBr) ν_{max} 3375, 3050, 2974, 2940, 2900, 2825, 1734, 1597, 1510, 1490, 1465, 1454, 1398, 1372, 1340, 1316, 1288, 1264, 1246, 1208, 1162, 1145, 1118, 1040, 1022, 1010, 977, 910, 860, 800, 780, 740, 720, 700 cm^{-1}; 270-MHz ^{1}H NMR ($CDCl_3$) δ 1.51 (d, J = 6.7 Hz, 3 H), 2.79 (s, 3 H), 2.83–3.00 (m, 3 H), 3.24–3.30 (m, 1 H), 3.45 (d, J = 5.0 Hz, 1 H), 3.54 (dd, J = 12.9, 5.6 Hz, 1 H), 3.73 (dd, J = 5.6, 2.3 Hz, 1 H), 4.71 (q, J = 6.7 Hz, 1 H), 7.04–7.12 (m, 2 H), 7.16–7.19 (m, 1 H), 7.40–7.51 (m, 4 H), 7.77–7.85 (m, 2 H), 7.96 (br s, 1 H), 8.41 (d, J = 8.2 Hz, 1 H); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 13.58, 25.39, 46.53, 51.45, 53.15, 56.75, 61.14; mass spectrum, m/z (rel intensity (398 (M^+, 34), 244 (14), 243 (65), 215 (18), 214 (43), 202 (7), 183 (5), 169 (12), 156 (23), 155 (100), 154 (23), 153 (120), 129 (12), 128 (16), 127 (13), 115 (12); high resolution mass spectrum (EI, mass resolution 5000), M calcd 398.1994142, found 398.19968.

(3aR,4R)- and (3aS,4S)-Methyl 3-[(S)-1-(1-Naphthyl)-ethyl]-2,3,3a,4,5,7-hexahydro-4-[(2S)-2-ethyl-2,3-dihydroxypropyl]-1H-pyrrolo[2,3-d]carbazole-6-carboxylate Acetonide (60 and 61). The mixture of the above azepine diastereomers 42 (0.20 g 0.50 mmol) in toluene (15 mL) was heated at 70 °C. (4S)-4-Ethyl-4,5-dihydroxypentanal acetonide (8a) (0.14 g, 0.75 mmol) in toluene (2 mL) was added slowly by dropping funnel. Upon completion of addition, the mixture was heated at reflux for 36 h. Concentration gave a residue, which was used directly in the following reaction.

(3aR,4R)- and (3aS,4S)-Methyl 3-[(S)-1-(1-Naphthyl)-ethyl]-2,3,3a,4,5,7-hexahydro-4-[(2S)-2-ethyl-2,3-dihydroxypropyl]-1H-pyrrolo[2,3-d]carbazole-6-carboxylate (62). The mixture of the above acetonide diastereomers (60, 61) and 10% aqueous hydrochloric acid (5 mL) in methanol (20 mL) was heated at reflux for 30 min. Methanol was removed under reduced pressure, and the reaction mixture was made basic with 10% ammonium hydroxide. This solution was then extracted with ether (3 × 50 mL), and the ether layers were combined and dried over magnesium sulfate. Concentration and flash chromatography on silica gel, eluting with ether, gave 0.13 g (50%) of a mixture of the title compounds' diastereomers: TLC R_f 0.35, 0.29 (silica gel, ether, CAS blue); mixture ^{1}H NMR ($CDCl_3$) integration of ethyl triplet 0.55–0.65 (t, 3 H) to 0.75–0.85 (t, 0.75 H). Enantiomeric excess equals 60%.

Careful chromatography of the mixture on silica, eluting with ether, gave 0.026 g (10%) of the less polar 3aS,4S isomer followed by 0.098 g (37%) of the more polar 3aR,4R isomer 62.

For the 3aR,4R isomer 62: UV (ethanol) λ_{max} 328, 295, 224, 192 nm; IR (film) ν_{max} 3380, 2975, 2860, 1730, 1678, 1610, 1480, 1468, 1440, 1380, 1282, 1250, 1205, 1114, 1045, 800, 780, 743 cm^{-1}; 250-MHz ^{1}H NMR ($CDCl_3$) δ 0.78 (t, J = 7.5 Hz, 3 H), 0.83–0.92 (m, 2 H), 1.17–1.26 (m, 1 H), 1.43–1.65 (m, 2 H), 1.71 (d, J = 6.7 Hz, 3 H), 1.96–2.10 (m, 2 H), 2.29–2.32 (m, 1 H), 2.56–2.92 (m, 4 H), 3.01 (s, 1 H), 3.25–3.38 (m, 3 H), 3.77 (s, 3 H), 4.71–4.79 (m, 1 H), 6.78–6.80 (m, 2 H), 7.07–7.13 (m, 1 H), 7.46–7.53 (m, 3 H), 7.69 (d, J = 6.8 Hz, 1 H), 7.79 (d, J = 8.1 Hz, 1 H), 7.86 (d, J = 7.6 Hz, 1 H), 8.60 (br s, 1 H), 8.85 (br s, 1 H); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 7.96, 22.05, 23.14, 28.92, 36.03, 36.28, 41.33, 49.90, 50.97, 56.01, 67.51, 72.56, 74.61, 90.28, 109.15, 120.61, 122.35, 124.02, 124.98, 125.32, 125.41, 125.70, 127.50, 127.72, 128.81, 124.11, 137.11, 137.77, 139.98, 142.87, 164.84, 169.02; mass spectrum, m/z (rel intensity) 527 (M + 1, 14), 526 (M^+, 41) 495 (12), 438 (18), 437 (62), 385 (27), 371 (23), 329 (38), 313 (13), 312 (71), 283 (31), 156 (15), 155 (100), 154 (12), 153 (13), 129 (30).

(3aR,4R)-Methyl 3-[(S)-1-(1-Naphthyl)ethyl]-2,3,3a,4,5,7-hexahydro-4-[(2S)-2-ethyl-2-hydroxy-3-[(*p*-tolylsulfonyl)oxy]propyl]-1H-pyrrolo[2,3-d]carbazole-6-carboxylate. To a solution of the diol 62 (0.095 g, 0.18 mmol) and triethylamine (50 mL, 0.36 mmol) in dichloromethane (20 mL) at 0 °C was added *p*-toluenesulfonic anhydride (0.118 g, 0.36 mmol) in dichloromethane (2 mL) over a 1-h period. The reaction mixture was allowed to warm to room temperature and stirred for 24 h. The solution was then washed with 10% ammonium hydroxide, dried over sodium sulfate, and concentrated to give a white foam, which was used directly in the following reaction: TLC R_f 0.50 (silica, 4:1 ether–hexane, CAS blue).

(3aR,4R)-Methyl 3-[(S)-1-(1-Naphthyl)ethyl]-2,3,3a,4,5,7-hexahydro-4-[(2S)-2-ethyl-2-[(trimethylsilyl)-

oxy]-3-[(*p*-tolylsulfonyl)oxy]propyl]-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate (64). A solution of the hydroxy tosylate from the previous reaction and triethylamine (50 μL, 0.36 mmol) in tetrahydrofuran (20 mL) was stirred under nitrogen and cooled to 0 °C. Trimethylsilyl trifluoromethanesulfonate (70 μL, 0.36 mmol) was added by syringe and the reaction mixture was stirred for 20 min. Aqueous saturated sodium bicarbonate was added and the THF layer was separated. The aqueous layer was extracted with ether (3 × 50 mL) and the combined organic layers were then dried over sodium sulfate and concentrated. Flash chromatography on silica gel, eluting with 1:1 ether–hexane, gave 0.052 g (38%) of the title compound: TLC R_f 0.50 (silica, 3:2 ether–hexane, CAS blue); 270-MHz ^{1}H NMR ($CDCl_3$) δ 0.00 (s, 9 H), 0.55 (t, J = 7.4 Hz, 3 H), 0.83–0.94 (m, 1 H), 1.05–1.10 (m, 1 H), 1.20 (br s, 1 H), 1.31–1.53 (m, 2 H), 1.60 (d, J = 6.8 Hz, 3 H), 1.90–2.01 (m, 1 H), 2.26–3.30 (m, 1 H), 2.35 (s, 3 H), 2.48–2.64 (m, 3 H), 2.79–2.84 (m, 1 H), 3.03 (s, 1 H), 3.73 (s, 3 H), 3.78 (d, J = 9.6 Hz, 1 H), 3.90 (d, J = 9.5 Hz, 1 H), 4.61–4.63 (m, 1 H), 6.70–6.79 (m, 3 H), 7.02–7.08 (m, 1 H), 7.27 (d, J = 8.0 Hz, 2 H), 7.39–7.47 (m, 3 H), 7.60–7.66 (m, 1 H), 7.73 (d, J = 8.3 Hz, 2 H), 7.78–7.83 (m, 2 H), 8.56 (br s, 1 H), 8.90 (br s, 1 H); mass spectrum, m/z (rel intensity) 752 (M^+, 2), 611 (2), 538 (9), 437 (25), 384 (9), 302 (4), 283 (14), 279 (13), 268 (3), 229 (12), 205 (5), 180 (4), 167 (15), 155 (100), 149 (30), 91 (19).

(7*S*,5*R*)-Methyl 3-[(*S*)-1-(1-Naphthyl)ethyl]-1,2,3,4,5,6,7,8-octahydro-5-[(2*S*)-2-ethyl-2,3-epoxypropyl]-7-(15-vindolinyl)azonino[5,4-*b*]indole-7-carboxylate (65). A solution of 0.040 g (0.059 mmol) of (3a*R*,4*R*)-methyl 3-[(*S*)-1-(1-naphthyl)ethyl]-2,3,3a,4,5,7-hexahydro-4-[(2*S*)-2-ethyl-2-[(trimethylsilyl)oxy]-3-[(*p*-tolylsulfonyl)oxy]propyl]-1*H*-pyrrolo-[2,3-*d*]carbazole-6-carboxylate (64) and triethylamine (9.0 μL, 1.1 equiv) in dichloromethane (2 mL) was stirred under nitrogen and brought to 0 °C. *tert*-Butyl hypochlorite (7.7 μL, 1.1 equiv) in dichloromethane (1 mL) was added by syringe, and the mixture was stirred for 5 min, at which time, TLC showed no remaining starting material. The solution was washed with water (5 mL), dried over magnesium sulfate, and concentrated under reduced pressure to give a white foam, which was used directly in the following reaction: TLC R_f 0.50 (silica gel, 3:2 ether–hexane, CAS purple).

To a solution of the chlorination product and vindoline (**3**, 27 mg, 1 equiv) in dry acetone (2 mL) was added tetrafluoroboric acid–diethyl ether complex (19 μL, 2 equiv). The reaction was brought to 0 °C and silver tetrafluoroborate (23 mg, 2 equiv) in acetone (1 mL) was added. The resulting heterogeneous solution was stirred for 10 min, at which time 10% NH_4OH (10 mL) was added. The now homogeneous solution was extracted with dichloromethane (3 × 10 mL). The combined organic extracts were dried with magnesium sulfate and concentrated under reduced pressure to give a white foam, which was used directly in the following reaction.

The above material was dissolved in glacial acetic acid (5 mL) and with stirring potassium borohydride (32 mg, 10 equiv) was slowly added. After 15 min the solution was poured onto ice and made strongly basic with concentrated ammonium hydroxide. Extraction with dichloromethane (3 × 10 mL), drying ($MgSO_4$), and concentration gave a white foam, which was used directly in the following reaction: TLC R_f 0.57 (silica gel, ethyl acetate, CAS brown).

To a solution of the above coupled product in tetrahydrofuran (10 mL) at 0 °C was added tetrabutylammonium fluoride (180 μL, 3 equiv, 1 M in THF). The mixture was brought to room temperature and stirred for 15 min, at which time no starting material remained by TLC. The solution was washed with aqueous saturated sodium bicarbonate, dried ($MgSO_4$), and concentrated under vacuum. Flash chromatography on silica gel, eluting with ethyl acetate, gave 0.043 g (72%) of the title compound: TLC R_f 0.46 (silica gel, ethyl acetate, CAS brown). ^{1}H NMR shows mostly broad peaks presumably due to interaction of naphthyl group and remainder of compound. Selected peaks for 270-MHz ^{1}H NMR ($CDCl_3$): δ 0.49 (t, J = 7.3 Hz, 3 H, C18′), 1.01 (t, J = 7.2 Hz, 3 H, C18), 2.11 (s, 3 H, $OCOCH_3$), 3.79 (s, 6 H, 2 × CO_2CH_3); mass spectrum, m/z (rel intensity) 965 (M + 1, 59), 905 (4), 852 (4), 811 (3), 566 (3), 509 (4), 391 (6), 253 (4), 242 (7), 239 (3), 214 (5), 201 (3), 197 (3), 195 (5), 187 (13), 186 (81), 185 (64), 184 (80), 183 (21), 173 (11), 170 (10), 157 (22), 156 (23), 155 (100), 154 (17), 153 (10), 143 (9), 142 (57), 113 (4), 100 (4), 99 (6), 97 (4).

Vinblastine (1). A solution of the epoxide **65** (0.040 g, 0.041 mmol) in methanol (10 mL) was heated at reflux for 40 h, at which time no starting material was present by TLC and a new more polar spot had appeared. The mixture was cooled and 10% palladium on charcoal (5.0 mg) was added. This was then stirred under a hydrogen atmosphere at room temperature for 3 h and filtered, the residue was washed with dichloromethane and methanol, and the filtrates were concentrated under vacuum.

The resulting atropisomer **30** was dissolved in dry toluene (10 mL) and heated at reflux for 8 h, at which time TLC showed no remaining starting material and only the presence of vinblastine in its natural conformation.

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Supplementary Material Available: ^{1}H NMR and ^{13}C NMR spectra for compounds **1**, **7a**, **7b**, **13**, **14a**, **14b**, **18a**, **19a**, **20a**, **20b**, **21a**, **21b**, the monotosylates of **20a** and **21a**, **22a**, **22b**, **26a**, **27a**, **30**, **31a**, **31b**, **33a**, **33b**, **34**, **35a**, and **35b** (46 pages). Ordering information is given on current masthead page.

Conversion of D-Glucose to L-Glucose: Oxidative Decarboxylation of α-Oxy Carboxylic Acids via Their Diacyl Peroxides

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D-Glucose was converted to an L-glucose derivative. The key step was the oxidative decarboxylation of carboxylic acid **12** via its diacyl peroxide derivative. This synthetic scheme proceeds through C-glycosidic compounds and is applicable to other sugar configurations.

Because L sugars are potentially useful as safe, effective, nonnutritive sweeteners,[1] these less common enantiomers of the carbohydrates have been studied for many years. Chemical syntheses of L-glucose from L-arabinose were reported by Emil Fischer[2] in 1890 and by J. C. Sowden and

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