Syntheses of 20′-Deoxyvinblastine, 20′-Deoxyleurosidine, 20′-Deoxyvincovaline, 20′-*epi*-20′-Deoxyvincovaline, and 20′-Deoxyvincristine and Its 20′-Epimer through Racemic and Enantioselectively Generated Intermediates. New Syntheses of *D/E-cis*- and -*trans*-Ψ-Vincadifformines and *D/E-cis*- and -*trans*-20-*epi*-Ψ-Vincadifformines

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Vindoline (**20**), on reaction with chloro imine derivatives of the *D-seco-D/E-trans*-Ψ- and -20-*epi*-Ψ-vincadifformines **18** and **19**, followed by cyclization and debenzylation steps, provided the natural products 20′-deoxyvinblastine (**4**) and 20′-deoxyleurosidine (**5**) and their diastereomers **6** and **7**, in two atropisomeric forms. These reactions gave exclusively the pharmacologically critical C16′–C14′ parf stereochemistry. Intermediates **18** and **19** were generated as mixtures of racemates or, alternatively, as enantiomerically unique diastereomers, by initial enantioselection of C20. Cyclization and debenzylation of the intermediates furnished *D/E-cis*- and/or -*trans*-Ψ- and -20-*epi*-Ψ-vincadifformines **14**, **52**, **15**, and **55**. Coupling of the *D/E-cis*-Ψ-vincadifformines **14** and **15** with vindoline (**20**) gave C16′–C14′ pref products **63** and **66**. Mechanistic implications of the coupling and cyclization steps are discussed.

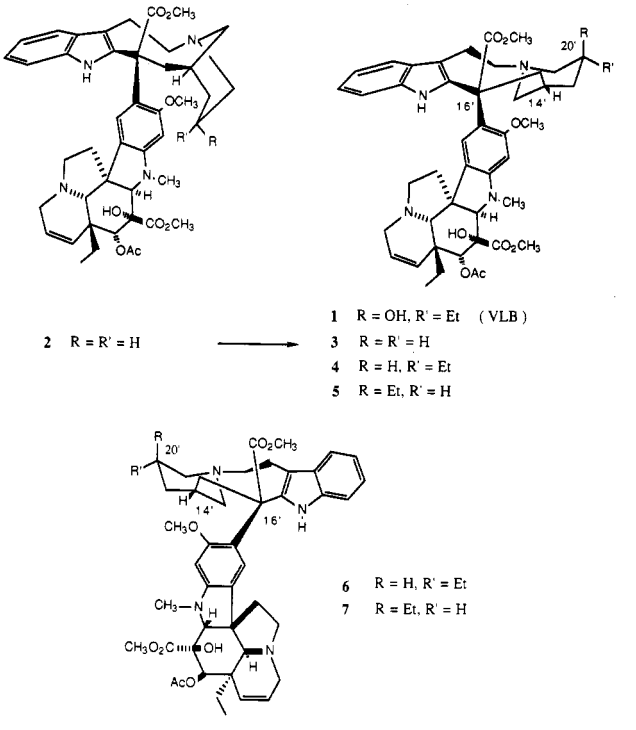
In a preceding publication we could report a reaction sequence leading selectively to indole–indoline compounds having the pharmacologically critical C14′–C16′ parf relative configuration of vinblastine (VLB, **1**).[1] In that synthesis we generated a novel piperidine ring atropisomer of 20′-desethyl-20′-deoxyvinblastine (**2**) and followed its formation with a thermally induced conformational inversion to give the product **3** in the natural conformation of vinblastine (Scheme I). A determination that the initial atropisomer **2** lacked the vinblastine-like cytotoxicity for L1210 leukemia cells, which was found for 20′-desethyl-20′-deoxyvinblastine (**3**) in its lower energy conformation (albeit less potently than with VLB), suggested that such an atropisomer might serve as a prodrug for in-tumor *site activation chemotherapy* (SAC). To that end, it was of interest to determine the effects of piperidine ring substitution on the following: (1) the ability to form and isolate analogous atropisomeric pairs of compounds; (2) the energy required for their conformational inversions; and (3) the biological activity of the two conformational isomers for each structure modification.

Not least in our motivation for extensions of our previous syntheses was the consideration that while our key coupling reaction had been found to be highly C16′–C14′ parf stereoselective,[1] two diastereomeric products are, of course, formed on coupling of a racemic intermediate to one enantiomer of vindoline. That process consequently results in the sacrifice of half of the valuable latter alkaloid, by production of a noncarcinostatic diastereomeric coproduct. Thus our next synthetic extensions advanced with an eye on their asymmetric synthetic potential. As seen in this report, each of the above points could be addressed, with eventual syntheses of the natural products 20′-deoxyvinblastine (**4**)[2a–c] and 20′-deoxyleurosidine (**5**)[2a–c] and of 20′-deoxyvincovaline (**6**)[2b] and its 20′-epimer **7**.[2b]

The starting material for these studies was 4-carbomethoxyhexanal (**8**), which was readily made by α-ethylation of δ-valerolactone,[3] followed by methanolysis of the lactone, and pyridinium chlorochromate oxidation of the resultant methyl 2-ethyl-5-hydroxyvalerate (Scheme II). Condensation of this aldehyde ester **8** with the indoloazepine **9**[4] resulted in formation of a diastereomeric mixture of bridged indoloazepines **10**. A stereochemical mixture of products at this point is inconsequential to our synthetic scheme since, in the subsequent transformation, the bridging carbon of the intermediate **10** loses its chirality by becoming trigonal. On N^b-benzylation of the intermediates **10** and reaction of the resultant quaternary salts with base, two *D/E-trans-D-seco*-Ψ- and -*20-epi*-Ψ-vincadifformines **11** and **12** were formed in a ratio of 3:2. These esters could be separated by chromatography.

The preferential cyclization of an intermediate *E*-enamine **13** to a product **11** with the C14–C20 pref relative

Scheme I



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

(2) (a) Neuss, N.; Gorman, M.; Cone, N. J.; Huckstep, T. L. *Tetrahedron Lett.* **1968**, 783. (b) Kutney, J. P.; Hibino, T.; Jahngen, E.; Okutani, T.; Ratcliffe, A. H.; Treasurywala, A. M.; Wunderly, S. *Helv. Chim. Acta* **1976**, *59*, 2858. (c) Langlois, N.; Gueritte, Y.; Langlois, Y.; Potier, P. *J. Am. Chem. Soc.* **1976**, *98*, 7017.

(3) Cregge, R. J.; Hermann, J. L.; Lee, C. S.; Richman, J. E.; Schlessinger, R. H. *Tetrahedron Lett.* **1975**, 2425.

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

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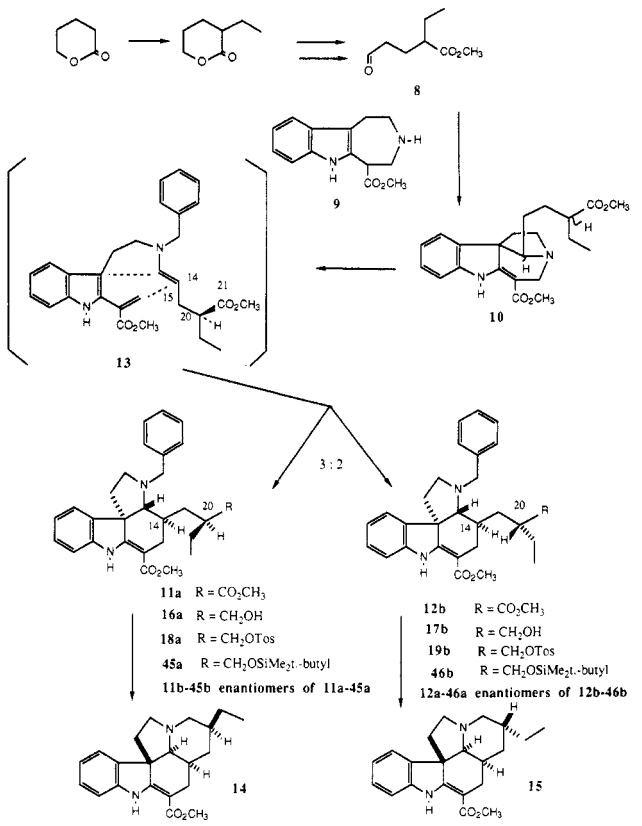
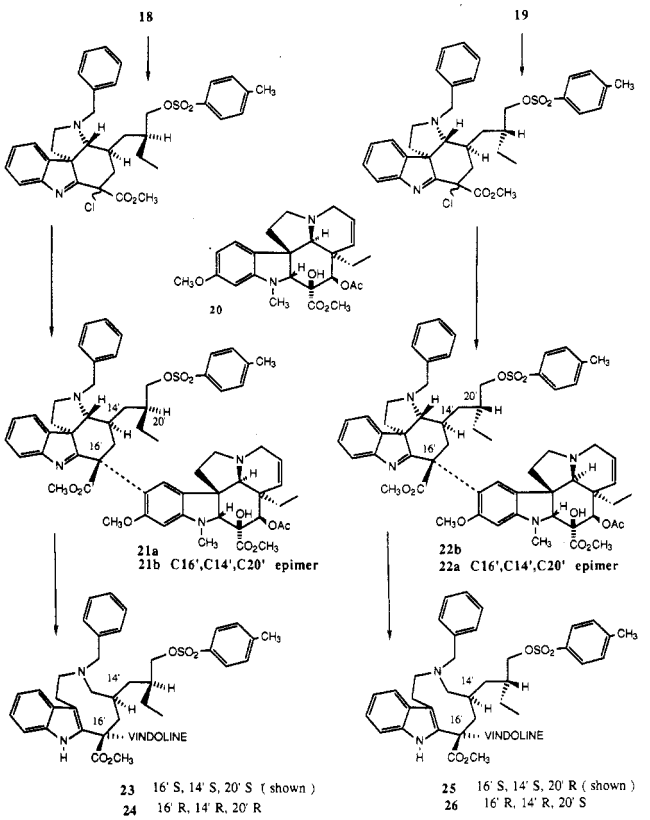
Scheme II



Scheme III



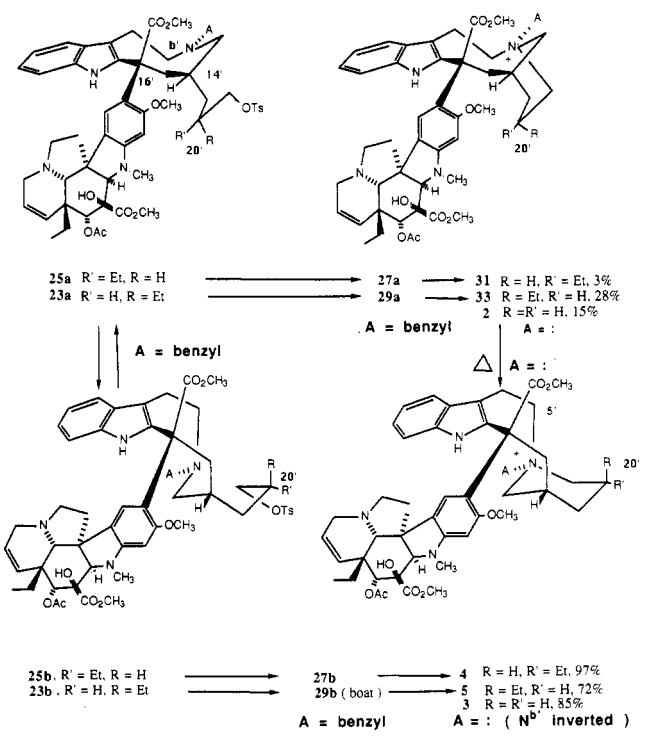
stereochemistry may be understood in terms of a Diels–Alder-like transition-state geometry, with some preference for orientation of the C15–C21 chain so that C14 and the ethyl substituent have an anti relationship and the C21 carbomethoxy group is least encumbered, but possibly interacting with the terminus (C14) of the enamine function (see **13**). The stereochemical assignments for the two diastereomeric rearrangement products **11** and **12** were based on their conversions to Ψ-vincadifformine (**14**) and 20-*epi*-Ψ-vincadifformine (**15**), respectively (see below).

Reaction of the two rearrangement products **11** and **12** with lithium aluminum hydride led selectively to reduction of the C21 ester function, without reduction of the vinylogous urethane group. The alcohol products **16** and **17**, in contrast to their ester precursors **11** and **12**, could be easily separated by preparative medium-pressure chromatography. A reaction of each of these diastereomeric alcohols with *p*-toluenesulfonic anhydride then provided the corresponding tosylate derivatives **18** and **19**.

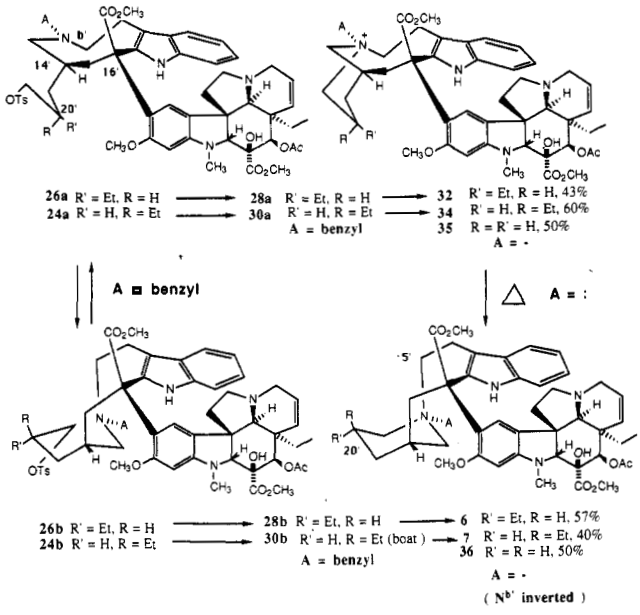
Chlorination of the two racemic tosylates **18** and **19** with *tert*-butyl hypochlorite and reaction of the resultant crude chloro imine derivatives with silver tetrafluoroborate, in the presence of protonated vindoline (**20**), led to formation of the isolable imine products **21a,b** and **22a,b**, respectively (Scheme III). Without purification, these individual coupling products were subjected to reduction with potassium borohydride in acetic acid. While only the C16′–C14′ parf products were obtained in each of the C20′-diastereomeric series, coupling of the racemic intermediates **18** and **19** to (–)-vindoline (**20**) gave, as expected, two products each (C16′*S*,C14′*S* vs C16′*R*,C14′*R*) in about equal amounts in each series. Chromatographic separation of the diastereomeric amines **23** vs **24** and **25** vs **26** provided an enantiomeric resolution of the synthetic carbomethoxy cleavamine half of the indole–indolines.

When the amino tosylates **23–26** were heated in toluene, dramatic differences were found in their rates of intramolecular N^b-alkylation (Schemes IV and V). The C14′–C20′ parf diastereomers **25** and **26** gave quantitative cyclization at a rate (24 h) comparable to that of the corresponding desethyl compound,[1] while for the C14′–C20′ pref isomers **23** and **24** over 4 days (105 h) of heating was required for complete cyclization. The resultant quaternary salts **27–30** (as mixtures of $N^{b'}$-epimers **a** and **b**) were then debenzylated to the corresponding amines **31–34** and **4–7** by catalytic hydrogenolysis.

Scheme IV



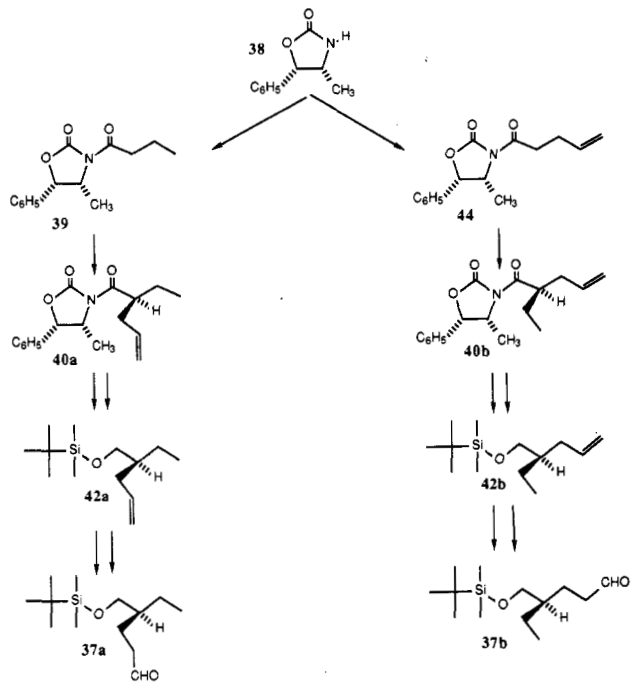
Scheme V



We had previously found in the desethyl series that an analogous cyclization to the cleavamine ring system lacking the vindoline substituent resulted in generation of essentially only the "unnatural" piperidine conformer with a C17 equatorial orientation,[5] while the same cyclization with the C16′ vindoline substituent gave just 15% of that atropisomer of desethyldeoxyvinblastine **2** (vs 85% of **3**).[1] From the diastereomeric precursor, desethyldeoxyvincovaline was generated as a 50/50 mixture of atropisomers **35** and **36**.[1]

The cyclization and debenzylation sequence in the C14′–C20′ parf 20′-deoxyvinblastine series provided the higher energy (unnatural) atropisomer **31**, which now bears an axial ethyl substituent, in only 3% yield, vs 97% of the lower energy piperidine ring conformer **4** with an equatorial ethyl substituent. For the other C14′–C20′ parf diastereomer, 20′-deoxyvincovaline, the corresponding amounts of higher and lower energy atropisomers **32** and **6** were 43% and 57%, respectively. Cyclization and debenzylation of the C14′–C20′ pref amino tosylate **23** led to 20′-deoxyleurosidine in a 28:72 ratio of high and low energy atropisomers **33** and **5**, while its 14′,16′,20′-epi diastereomer **24** gave the high- and low-energy atropisomers **34** and **7** in a ratio of 60:40. Thus, the presence of a C20′ axial ethyl substituent diminishes the formation of that atropisomer relative to the conformer with an equatorial ethyl substituent in each of the four diastereomeric possibilities, but this effect is not large enough to drive the amino tosylate cyclization completely to the formation of a single quaternary ammonium diastereomer. A boat or deformed chair like conformation (rather than one with three axial piperidine substituents) can be assumed for the major diastereomer of *N*-benzyldeoxyleurosidine (**29b**) and its 14′,16′,20′-epimer **30b**. On heating in toluene, all four higher energy atropisomers **31**, **32**, **33**, and **34** were completely converted into the corresponding lower energy conformers **4**, **6**, **5**, and **7**, which showed the decreased chromatographic retention anticipated for indole–indolines with a sterically shielded $N^{b'}$ axial electron pair (C5′ equatorial).[1,6]

Scheme VI



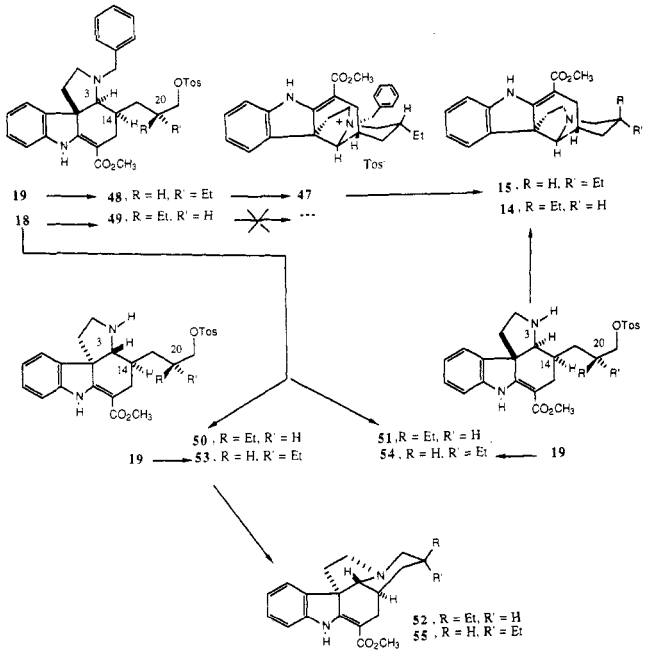
The foregoing syntheses of the diastereomeric pairs of 20′-deoxyvinblastine (**4**,**6**) and 20′-deoxyleurosidine (**5**,**7**) were initially desired to establish, for the four products, relative activities in influencing reversible tubulin–microtubule transformations, as well as for determination of the relative cytotoxicities of these compounds with leukemia cell lines. Such stereochemical structure/activity information having been obtained,[7] it became important to find a simple synthetic route, which would allow coupling of vindoline to one stereochemically specified, enantiomerically pure precursor of the carbomethoxy cleavamine moiety of the indole–indoline product. To this end we decided, for a first strategy, to fix the absolute stereochemistry at C20 in our synthetic precursors, thus allowing their resolution by diastereomeric separation prior to the coupling to vindoline step. A loss of half of the invested vindoline, due to generation of (noncytotoxic) C14′*R*,C16′*R* diastereomers, would thus be avoided.

A chiral 4-ethyl-5-(silyloxy)pentanal **37**, required for this purpose, was readily generated through the use of the cyclic urethane of (+)-norephedrine (**38**).[8] On reaction with sodium hydride and acylation by butyryl chloride, an imide **39** was obtained (94%), which, as its lithium enolate, could be alkylated with allyl bromide to provide the chromatographically purified olefinic imide **40a**, enantiomerically pure, in 84% yield (Scheme VI). Reduction of the imide with lithium aluminum hydride gave recovered norephedrine and an alcohol **41a**, which was silylated with *tert*-butyldimethylsilyl chloride. The resultant olefinic silyl ether **42a** was hydroborated with 9-borabicyclo[3.3.1]nonane and then treated with hydrogen peroxide and sodium hydroxide to give an alcohol **43a**, which could be oxidized with pyridinium chlorochromate to the (4*S*)-4-ethyl-5-(silyloxy)pentanal **37a** (overall yield 16%).

Alternatively, the 4*R* enantiomer **37b** of this aldehyde could be prepared by acylation of the same cyclic urethane **38** with 4-pentenoyl chloride (90%), alkylation of the

(5) Kuehne, M. E.; Zebovitz, T. C. *J. Org. Chem.* **1987**, *52*, 4331.
(6) The kinetic data for these conformational inversions and corresponding energy barriers will be reported together with the data for a number of alternatively substituted compounds.
(7) Details of biochemical and pharmacologicaly evaluations will be presented together with data for several analogous compounds.
(8) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.

Scheme VII

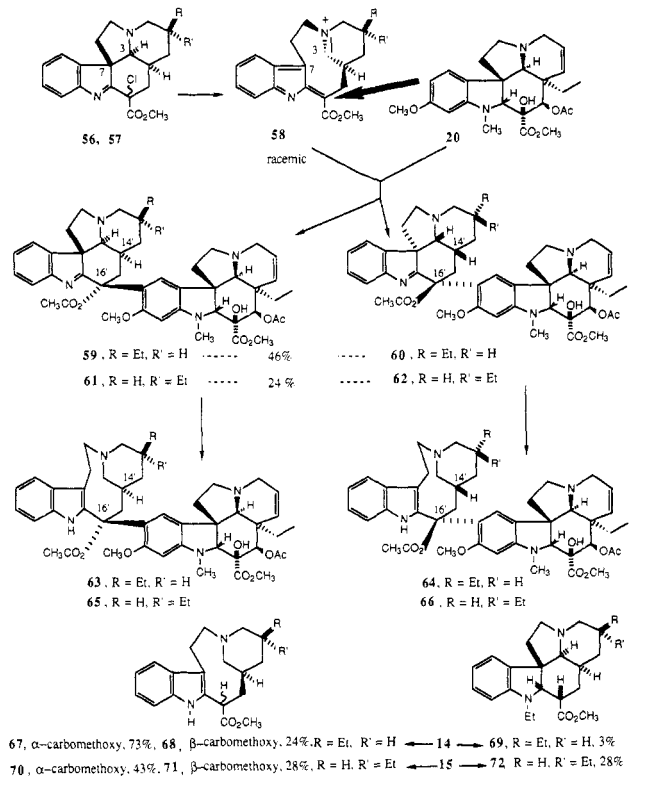


product's (**44**) lithium enolate with ethyl iodide (68%), and completion of the same subsequent steps (overall yield 11%). A generation of both of the separated enantiomeric aldehydes **37a** and **37b**, useful for the syntheses of 20′-deoxyleurosidine (**5**) and 20-deoxyvinblastine (**4**), respectively, could also be achieved by acylation of the urethane **38** with racemic 2-ethyl-4-pentenoyl chloride and chromatographic separation of the diastereomeric products **40a,b** (23% each from methyl butyrate).

Condensation of the enantiomerically pure aldehydes **37a** and **37b** with the indoloazepine **9**, followed by benzylation and treatment with triethylamine, provided the 20*S* and 20*R* *D-seco-D/E-trans*-Ψ- and *D-seco-D/E-trans*-20-*epi*-Ψ-vincadifformines **45a**, **46a** and **45b**, **46b** in 81% for each diastereomeric pair (Scheme II). Chromatographic separation of these diastereomeric pairs (**45**, **46**) then gave the enantiomerically pure precursors for coupling to vindoline (**20**).

In order to establish the relative configurations of the tetracyclic tosylates **18** and **19**, these compounds were converted to racemic Ψ-vincadifformine (**14**) and 20-*epi*-Ψ-vincadifformine (**15**), compounds we had previously obtained by alternative syntheses, which had allowed the first stereochemical structure definition of these alkaloids through X-ray crystallography.[9] When the tosylates were subjected to heating in refluxing toluene, it was found that one isomer (**19**) would undergo complete cyclization in 10 h while the other (**18**) was recovered unchanged after heating for 4 days (Scheme VII). An analogous cyclization with the 20′-desethyl analogue had resulted in prior C3 and C7 epimerization and given only the D/E cis-fused pentacyclic product.[5] Conforming with that result, debenzylation by hydrogenolysis of the quaternary cyclization product **47**, derived from an unisolated epimerization product **48** gave the expected 20-*epi*-Ψ-vincadifformine (**15**). Lack of cyclization of the racemic *D-seco*-Ψ-vincadifformine tosylate **49** can be understood in terms of two additional 1,3-diaxial interactions (or an equivalent conformationally deformed piperidine ring), which would arise here relative to the cyclization of the epimer **48**. To avoid

Scheme VIII



this energy barrier, the *N*-benzyl substituent of the amino tosylate **18** was removed first by hydrogenolysis in acid and the resulting secondary amine tosylates **50** and **51** (C3/14 hydrogens trans and cis), obtained by partial epimerization, were then brought to cyclization by heating at 110 °C for 10 h. The resulting mixture of Ψ-vincadifformine (**14**) and *D/E-trans*-Ψ-vincadifformine (**52**) was readily separated by chromatography.

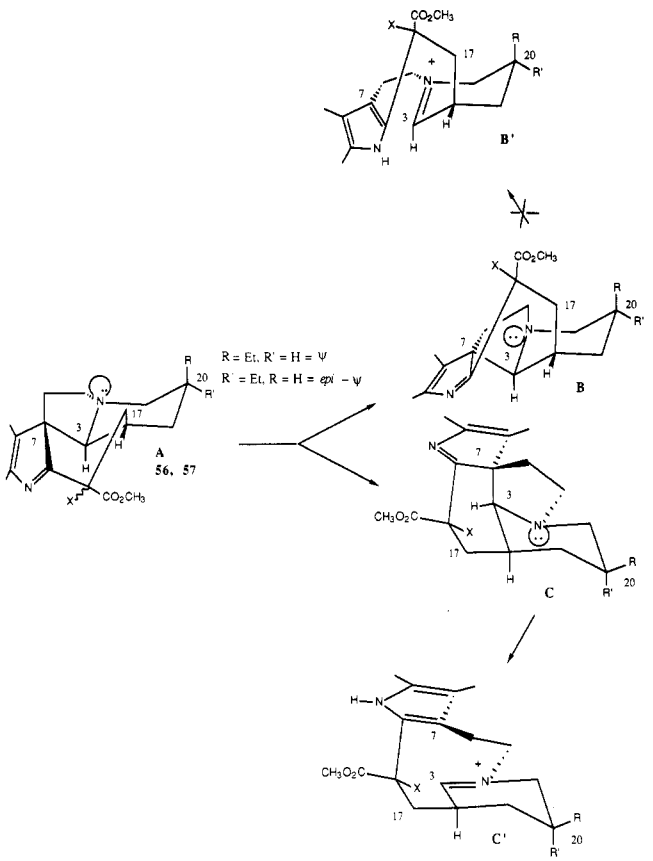
Similarly, the debenzylation–cyclization sequence with the epimeric ethyl compound **19** proceeded through an intermediate mixture of *D/E-trans*- and *cis-D-seco*-Ψ-vincadifformines **53** and **54**, which cyclized to 20-*epi*-Ψ-vincadifformine (**15**) and its D/E trans diastereomer **55**. The difference in cyclization energy found for the tosylates **48** and **49** was also seen for the debenzylated products, where 20-*epi*-Ψ-vincadifformine (**15**) was formed much more readily from the secondary amine **54** than Ψ-vincadifformine (**14**) was from the ethyl epimer **51**.

Syntheses of the racemic Ψ- and 20-*epi*-Ψ-vincadifformines (**14** and **15**) allowed a study of their coupling to vindoline (**20**), Scheme VIII. We had originally explained the C16′–C14′ pref coupling products of such systems as a result of rupture of the C3–C7 bond on reaction of a pair of chloro imine derivatives **56** and **57** (R = R′ = H) with silver tetrafluoroborate, followed by an attack of vindoline, with concerted reformation of the C3–C7 bond in an imonium intermediate **58**.[1] The present examples provide further evidence that the propensity for coupling of a chloro imine to vindoline (**20**) is equated to the ease of a reversible C3–C7 bond rupture. While racemic Ψ-vincadifformine (**14**) on chlorination with *tert*-butyl hypochlorite, and then reaction with silver tetrafluoroborate and vindoline at 20 °C, gave C14′–C16′ pref coupling products **59** and **60** in yields (46%) equivalent to those obtained with the 20-desethyl compound,[1,10] essentially no

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

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

Scheme IX



coupling product was obtained when racemic 20-*epi*-Ψ-vincadifformine (**15**) was used. Instead, the precipitation of metallic silver and formation of unidentified oxidation products was found. Only when the coupling reaction of 20-*epi*-Ψ-vincadifformine derived chloro imines (**56** and **57**, R = H, R′ = Et) was tried at 56 °C did some amount (24%) of coupling products **61** and **62** form. Reduction of the imine pairs **59**, **60** and **61**, **62** with potassium borohydride and chromatographic separation of the products provided the respective C14′–C16′ pref indole–indolines **63–66**.

In another set of experiments, it was again seen that rupture of the C3–C7 bond is influenced by the stereochemistry of substitution at C20. While reduction of Ψ-vincadifformine (**14**) with sodium borohydride in hot acetic acid readily gave the tetracyclic indolic carbomethoxy cleavamines **67** and **68** and little of the indoline **69** (C2, C16 stereochemistry suggested),[9] an analogous treatment of 20-*epi*-Ψ-vincadifformine (**15**) resulted in more extensive formation of a pentacyclic indoline **72** (C2, C16 stereochemistry suggested),[9] at the expense of formation of the indolic products **70** and **71**.

These demonstrations of a more facile C3–C7 bond rupture for Ψ-vincadifformine (**14**) vs 20-*epi*-Ψ-vincadifformine (**15**) now allow a distinction between two conformational alternatives for the reversible C3–C7 bond rupture (Scheme IX): The transition of conformations B → B′, on formation of the bridged imonium ring from the imine precursors **56** and **57**, with C17 as an axial substituent, might be considered to be conformationally preferable to the transition of conformations C → C′, with C17 equatorial and a resultant greater ring strain due to 1,3 diequatorial bridging.[5] However, this stereochemical aspect is now found to be less important for the fragmentation reaction than the stereoelectronic one of preferential orbital overlap of a trans diaxial (C) vs an (acceptable) trans diequatorial[11] (B) arrangement of the nitrogen lone pair and the C3–C7 bond. Such an experimental distinction could not previously be made in the coupling, nor in the reduction reactions of the 20-desethyl compounds, which proceed as readily as those with Ψ-vincadifformine (**14**).[1,5]

For pharmacological evaluation, 20′-deoxyvinblastine (**4**) and 20′-deoxyleurosidine (**5**) were oxidized with permanganate to the corresponding vindolinyl *N*-formyl derivatives (vincristine, VCR, type analogues).[12] The deoxy VLB and VCR compounds showed tubulin polymerization inhibition at a concentration equal to that of the 20′-hydroxy compounds. For cytotoxicity against L1210 leukemia cells, the deoxy VLB and deoxy VCR ID_{50} was 10^{-9} M vs 10^{-10} M for vinblastine or vincristine. In vivo activity with P388 leukemia in mice (50% long-term survivors) was obtained at 3 mg/kg for 20′-deoxy VLB vs 0.2 mg/kg for VLB, and at 0.05 mg/kg for 20′-deoxy VCR vs 0.2 mg/kg for VCR. The corresponding 20′-deoxyleurosidine compounds required about 5–10-fold-greater concentrations for cytotoxicity and in vivo activity.[7,13]

Experimental Section

General Methods. All reactions were carried out under nitrogen or argon. Melting points were obtained in a heated oil bath or on a Kofler micro hot stage with thermometers calibrated against a National Bureau of Standards certified set. NMR spectra were recorded on Bruker 250-MHz or 270-MHz instruments. Mass spectra were obtained with a Finnegan 4610 quadrupole instrument at 70 eV, calibrated with perfluorotributylamine and bis(pentafluorophenyl)phenylphosphine for compounds below MW 600 and with tris(perfluorononyl)-*s*-triazine for higher MW compounds. IR spectra were obtained with a Nicolet 6000 FT or a Perkin-Elmer 267 grating instrument. UV spectra were recorded on Perkin-Elmer 202 or 402 instruments. TLC data were obtained with E. Merck 60F-254 precoated silica on alumina sheets. For centrifugal chromatography, a Harrison Chromatotron was used with E. Merck 60 PF 254 silica with gypsum. For column chromatography, 60–200-mesh Baker R3405 silica was used. Microanalyses were provided by George Robertson, Robertson Laboratories, Florham Park, NJ.

Methyl 2-Ethyl-5-hydroxyvalerate. A solution of 30.0 g (0.234 mol) of 2-ethylvalerolactone in 150 mL of dry methanol and 0.5 mL of concentrated sulfuric acid was stored under argon for 17 h at 20 °C. Then 10.0 g of potassium carbonate was added and the mixture stirred for 20 min. After filtration and concentration at 40 °C under vacuum, the residue was dissolved in 100 mL of ether. The solution was washed with 200 mL of saturated sodium carbonate and 100 mL of saturated brine, dried over $MgSO_4$, filtered, and concentrated and the residue distilled to give 32.1 g (86%) of product: bp 58–60 °C (0.5 mm); IR (neat) ν_{max} 3441, 2950, 2878, 1735, 1460, 1436, 1385, 1320, 1265, 1201, 1165, 1087, 1067, 1000 cm^{-1}; 250-MHz NMR ($CDCl_3$) δ 3.68 (s, 3 H), 3.61 (dd, J = 6, 12 Hz, 2 H) 2.37–2.26 (m, 1 H), 2.54–2.41 (m, 1 H), 1.69–1.50 (m, 6 H), 0.89 (t, J = 7 Hz, 3 H).

Methyl 2-Ethyl-5-oxopentanoate (8). To 50.46 g (0.234 mol) of pyridinium chlorochromate, under argon, was added 100 mL of dichloromethane followed, with rapid stirring, by 25.0 g (0.156 mol) of methyl 2-ethyl-5-hydroxypentanoate in 20 mL of dichloromethane. After stirring at 20 °C for 2.5 h, 15 g of silica gel was added, followed by 200 mL of ether. Filtration through a 3.5 × 40 cm silica gel column (60–200 mesh), eluting with ether, and concentration at 40 °C under vacuum gave an oil which was redissolved in 100 mL of dichloromethane. Washing with 3 × 100 mL of cold 1 N HCl, 3 × 100 mL of saturated $NaHCO_3$, drying over $MgSO_4$, filtration, concentration at 40 °C, and distillation gave 14.64 g (59%) of product: bp 104–105 °C (16 mm); mass

(11) See example 58 in: Grob, C. A. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 535.
(12) Hannart, J. Eur. Pat. Appl. EP 117,861; *Chem. Abstr.* **1984**, *101*, 230832f.
(13) Thompson, G. L. U.S. Pat. 4,143,041, March 6, 1979.

spectrum, m/z (relative intensity) 159 (M + 1, 75), 129 (38), 127 (97), 115 (14), 102 (62), 100 (13), 99 (17), 98 (24), 97 (11), 87 (77), 83 (21), 81 (45), 71 (17), 70 (32), 69 (40), 59 (52), 57 (13), 56 (15), 55 (100), 53 (17); IR (neat) ν_{max} 2965, 2939, 2879, 2844, 2726, 1732, 1461, 1451, 1436, 1414, 1386, 1310, 1267, 1203, 1168, 1088, 1049, 1027, 996, 832 cm^{-1}; 250-MHz NMR ($CDCl_3$) δ 9.75 (t, J = 1 Hz, 1 H), 3.68 (s, 3 H), 2.47 (t, d, J = 7, 1 Hz, 2 H), 2.40–2.28 (m, 1 H), 1.92–1.82 (m, 2 H), 1.69–1.51 (m, 2 H), 0.90 (t, J = 7 Hz, 3 H).

Condensation of Methyl 1,2,3,4,5,6-Hexahydroazepino[4,5-*b*]indole-5-carboxylate (9) with Methyl 2-Ethyl-5-oxopentanoate (8). To a solution of 6.00 g (24.6 mmol) of the indoloazepine in 50 mL of dry methanol, under argon, was added 4.00 g (25.3 mmol) of the aldehyde ester. After 12 h at 20 °C, the mixture was concentrated under vacuum at 40 °C and the residue dissolved in dichloromethane. The solution was adsorbed on 20 g of SiO_2, which was then placed on a 4 × 15 cm dry column of silica gel. Elution with ethyl acetate, concentration, solution of the concentrated eluate in 100 mL of dichloromethane, drying over $MgSO_4$, filtration, and concentration gave an oily product, from which two successive 100-mL portions of toluene were distilled at 40 °C under vacuum. Drying at 20 °C (0.05 mm) provided, as a foam, 7.70 g (82%) of a mixture of four diastereomeric ester products **10**.

Two pairs of ethyl epimers were obtained from the initial and final chromatographic functions. Each had UV (ethanol) λ_{max} 228, 303, 330 nm. For the fraction with TLC (SiO_2, ethyl acetate) R_f 0.62: mass spectrum, m/z (relative intensity) 385 (12), 384 (52), 353 (7), 341 (11), 315 (4), 283 (21), 242 (20), 227 (9), 215 (20), 214 (100), 196 (11), 184 (26), 182 (14), 170 (18), 168 (15), 167 (15), 155 (12), 154 (59), 128 (8), 127 (22), 126 (15), 115 (11), 113 (9), 110 (16), 102 (23), 100 (13), 87(30), 83 (19), 82 (10), 81 (17), 71 (12), 70 (20), 69 (20), 59 (26). For the fraction with TLC (SiO_2, ethyl acetate) R_f 0.22: mass spectrum, m/z (relative intensity) 385 (14), 384 (46), 353 (5), 283 (25), 227 (2), 228 (3), 215 (20), 214 (100), 184 (1), 183 (3), 182 (11), 170 (19), 168 (10), 167 (10), 155 (9), 154 (44), 141 (8), 128 (7), 127 (17), 126 (2), 115 (4), 111 (8), 110 (14), 102 (2), 87 (5), 83 (6), 82 (3), 81 (4), 71 (7), 70 (4), 69 (6), 59 (6).

C20 Epimeric N^b-Benzyl-21-hydroxy-*D*-*seco*-Ψ-vincadifformines 16 and 17. A solution of 6.182 g (16.08 mmol) of the bridged azepine esters **10** and 2.750 g (16.08 mmol) of benzyl bromide in 100 mL of anhydrous ether was stirred for 48 h at 20 °C under argon. Filtration, washing of the solids with 3 × 100 mL of ether, and drying at 15 mm and 0.01 mm of pressure gave 8.422 g (94%) of quaternary salts.

A solution of 4.000 g (7.201 mmol) of the quaternary salts in 40 mL of methanol and 1.100 g (10.80 mmol) of triethylamine was heated at reflux under argon for 5 h. At 40 °C (15 mm), the solution was then concentrated to a residual orange gum and the latter dissolved in 50 mL of dichloromethane. Washing with iced 15% ammonium hydroxide and saturated brine, with back-extraction of the aqueous wash with 50 mL of dichloromethane, drying of the combined organic solutions ($MgSO_4$), filtration, and concentration at 40 °C (15 mm and 0.01 mm) gave a foam, which was chromatographed on a 3 × 15 cm silica gel column, eluting with 1:4 ethyl acetate–pentane. The diastereomeric mixture of esters (**11**, **12**) (2.737 g, 80% yield) showed almost no separation on TLC (SiO_2): R_f 0.61, 2:1 ether–hexane; R_f 0.43, 2% methanol in dichloromethane; R_f 0.41, 1:4 ethyl acetate–pentane. The C20 epimeric mixture could be separated by HPLC on a 22.1 mm × 50 cm 10-μm Rainin prep silica column with ether–hexane (1:3) at a flow rate of 8.0 mL/min, giving the C14, C20 pref isomer **11** with t_R = 50 min and the parf **12** isomer with t_R 57 min in a 1.47:1.00 ratio.

For the pref isomer **11**: 250-MHz NMR ($CDCl_3$) δ 0.75 (t, J = 7 Hz, 3 H), 0.95–1.07 (m, 1 H), 1.13–1.37 (m), 1.39–1.57 (m, 1 H), 1.61–1.68 (m, 1 H), 1.79–1.87 (m, 1 H), 1.95–2.07 (m, 1 H), 2.21–2.32 (m), 2.49 (dd, J = 3, 15 Hz), 2.58–2.67 (m, 1 H), 2.73 (d, J = 15 Hz, 1 H), 2.85–2.91 (m, 2 H), 3.61 (s, 3 H), 3.78 (s, 3 H), 3.69 (d, J = 13 Hz, 1 H), 4.09 (d, J = 13 Hz, 1 H), 6.79–7.39 (m, 8 H), 8.89 (s, 1 H); mass spectrum, m/z (relative intensity) 475 (4), 474 (15), 443 (4), 415 (3), 342 (9), 341 (44), 332 (5), 315 (8), 308 (3), 261 (16), 260 (100), 241 (5), 238 (5), 228 (4), 227 (7), 195 (3), 194 (5), 180 (7), 168 (6), 167 (7), 154 (6), 134 (5), 92 (6), 91 (80); UV (ethanol) λ_{max} 220, 300, 330 nm; IR (KBr) ν_{max} 3379, 3059, 3028, 2964, 2948, 2874, 2863, 2797, 1732, 1677, 1610, 1478, 1466, 1437, 1383, 1345, 1294, 1280, 1249, 1203, 1160, 1136, 1105, 1079, 1046, 1028, 1019, 800, 773, 740, 701 cm^{-1}.

For the parf isomer **12**: 250-MHz NMR ($CDCl_3$) δ 0.75 (t, J = 7 Hz, 3 H), 0.91–1.02 (m, 1 H), 1.21–1.50 (m, 3 H), 1.62–1.69 (m, 1 H), 1.80–1.87 (m, 1 H), 1.96–2.08 (m, 1 H), 2.19–2.25 (m, 1 H), 2.49–2.69 (m, 3 H), 2.87–2.93 (m, 1 H), 2.96 (s, 1 H), 3.60 (s, 3 H), 3.77 (s, 3 H), 3.72 (d, J = 13 Hz, 1 H), 4.12 (d, J = 13 Hz, 1 H), 6.78–7.41 (m, 8 H), 8.95 (s, 1 H); mass spectrum, m/z (relative intensity) 475 (6), 474 (20), 443 (3), 415 (2), 373 (3), 342 (11), 341 (55), 332 (5), 342 (11), 341 (55), 332 (5), 315 (8), 261 (17), 260 (100), 241 (6), 238 (4), 228 (4), 227 (8), 195 (2), 194 (4), 180 (5), 168 (5), 167 (6), 154 (5), 134 (7), 92 (5), 91 (65); UV (ethanol) λ_{max} 220, 301, 330 nm; IR (KBr) ν_{max} 3385, 3085, 3057, 3028, 2965, 2949, 2876, 2857, 2797, 2741, 1731, 1677, 1611, 1478, 1466, 1437, 1383, 1346, 1280, 1266, 1250, 1205, 1166, 1133, 1105, 1050, 1028, 1019, 801, 7722, 739, 702 cm^{-1}.

A solution of 2.147 g (4.526 mmol) of the mixture of diastereomeric esters **11** and **12** in 20 mL of dry tetrahydrofuran, under an argon atmosphere, was cooled to 0 °C. With rapid stirring, 5.40 mL of a 1.0 M solution of lithium aluminum hydride in tetrahydrofuran (5.43 mmol) was added dropwise over 10 min. After stirring at 0 °C for a further 20 min, the reaction mixture was poured into 100 mL of iced 30% ammonium hydroxide and extracted with 3 × 50 mL of dichloromethane. The combined extracts were washed with 100 mL of cold saturated brine, dried ($MgSO_4$), filtered, and concentrated at 40 °C (15 mm and 0.01 mm) to 1.744 g (66% yield) of alcohols **16** and **17** as a foam. TLC (SiO_2, ether): **16**, R_f 0.50; **17**, R_f 0.56. A 0.50-g portion of this product was subjected to centrifugal chromatography on a 2-mm silica gel plate. Application in 5 mL of dichloromethane was followed by elution with 4:1 ether–hexane at 2.2 mL/min and collection of 1-min fractions. Fractions 5–30 and 52–90 contained the two nearly pure diastereomers **17** and **16**. UV (ethanol) for **16** and **17**: λ_{max} 224, 300, 330 nm.

For **17**: IR (KBr) ν_{max} 3640–3390, 3380, 2957, 2920, 2871, 2856, 2820, 2795, 1674, 1609, 1478, 1466, 1437, 1381, 1344, 1294, 1280, 1249, 1203, 1134, 1117, 1078, 1047, 745, 699 cm^{-1}; 250-MHz NMR ($CDCl_3$) δ 0.72 (t, J = 7 Hz, 3 H), 0.63–0.93 (m, 2 H), 1.04 (m, 1 H), 1.21–1.38 (m, 3 H), 1.67 (m, 1 H), 1.89 (m, 1 H), 2.04 (m, 1 H), 2.49 (dd, J = 3, 15 Hz, 2 H), 2.64 (d, J = 15 Hz, 1 H), 2.69 (m, 1 H), 2.88 (s, 1 H), 2.95 (m, 1 H), 3.37 (8-line m, 2 H), 3.75 (s, 3 H), 3.79 (d, J = 13 Hz, 1 H), 4.06 (d, J = 13 Hz, 1 H), 6.80–7.42 (m, 8 H), 8.98 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 11.32, 22.11, 24.25, 31.47, 36.64, 39.33, 42.13, 50.90, 50.97, 55.28, 58.63, 64.83, 72.68, 90.42, 109.24, 120.53, 122.27, 127.12, 127.80, 128.33, 129.03, 137.97, 139.20, 143.02, 165.20, 169.08; mass spectrum, m/z (relative intensity) 446 (M^+, 5), 332 (2), 313 (10), 287 (2), 241 (5), 238 (2), 233 (6), 232 (44), 228 (2), 227 (4), 214 (2), 209 (2), 206 (2), 195 (2), 194 (4), 193 (2), 182 (2), 181 (3), 180 (6), 169 (2), 168 (5), 167 (11), 155 (2), 154 (7), 134 (3), 127 (2), 125 (3), 120 (3), 92 (7), 91 (100).

Anal. Calcd for $C_{28}H_{34}N_2O_3$: C, 75.31; H, 7.67; N, 6.27. Found: C, 74.93; H, 7.59; N, 6.32.

For **16**: IR (KBr) ν_{max} 3640–3442, 3429, 3412, 3384, 3367, 2957, 2918, 2872, 2857, 2797, 1674, 1609, 1478, 1466, 1437, 1382, 1345, 1295, 1280, 1250, 1204, 1131, 1103, 1079, 1047, 1018, 745, 700 cm^{-1}; 250-MHz NMR ($CDCl_3$) δ 0.74 (t, J = 7 Hz, 3 H), 0.63–0.77 (m, 1 H), 0.86–0.98 (m, 1 H), 1.10–1.40 (m, 5 H), 1.67 (m, 1 H), 1.93 (m, 1 H), 2.04 (m, 1 H), 2.51 (dd, J = 3, 15 Hz, 1 H), 2.63 (d, J = 15 Hz, 1 H), 2.66 (m, 1 H), 2.91 (s, 1 H), 2.93 (m, 1 H), 3.58 (m, 2 H), 3.72 (d, J = 13 Hz, 1 H), 3.77 (s, 3 H), 4.09 (d, J = 13 Hz, 1 H), 6.70–7.40 (m, 8 H), 8.90 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 10.84, 22.40, 22.66, 22.81, 29.72, 31.88, 36.66, 39.50, 42.24, 50.76, 51.01, 55.22, 58.42, 65.57, 72.53, 90.59, 109.22, 120.51, 122.21, 127.09, 127.78, 128.33, 128.94, 137.91, 139.09, 143.00, 165.20, 169.11; mass spectrum, m/z (relative intensity) 446 (M^+, 14), 332 (3), 314 (4), 313 (24), 287 (5), 241 (8), 238 (2), 233 (9), 232 (70), 228 (2), 227 (6), 220 (2), 215 (2), 214 (3), 209 (2), 206 (2), 195 (2), 194 (7), 182 (2), 181 (3), 180 (6), 169 (3), 168 (6), 167 (13), 155 (2), 154 (8), 143 (2), 134 (4), 127 (2), 125 (5), 120 (3), 107 (3), 92 (7), 91 (100).

Anal. Calcd for $C_{28}H_{34}N_2O_3$: C, 75.31; H, 7.67; N, 6.27. Found: C, 75.10; H, 7.51; N, 6.22.

C20 Epimeric N^b-Benzyl-21-(tosyloxy)-*D*-*seco*-Ψ-vincadifformines 18 and 19. Under an argon atmosphere, 0.980 g (2.19 mmol) of the C20 epimeric mixture of alcohols **16** and **17** was combined with 0.460 g (2.41 mmol) of *p*-toluenesulfonyl chloride

and 5 mg of 4-(dimethylamino)pyridine. At 0 °C, 10 mL of dry pyridine was added, and the reaction mixture was stirred at 0 °C for 4 h and at 4 °C for 24 h. The red solution was then poured into 50 mL of cold 1 N ammonium hydroxide and extracted with 3 × 50 mL of dichloromethane. The combined extracts were washed with 100 mL of cold saturated brine, dried ($MgSO_4$), filtered, and concentrated at 40 °C (15 mm). Two 100-mL portions of toluene were then added and distilled at 40 °C under vacuum, providing 0.991 g (75% yield) of tosylates **18** and **19**. TLC (SiO_2): R_f 3.0 and 3.7 (1:4 ethyl acetate–pentane), R_f 4.6 and 5.1 (5% methanol in dichloromethane).

The C20 epimeric mixture of tosylates could be separated by centrifugal chromatography on a 4-mm SiO_2 plate, with application in 10 mL of dichloromethane and elution with ethyl acetate–pentane (1:5). At 2.2 mL/min and with collection of 1-min fractions, the C14, C20 pref isomer **18** was obtained in fractions 6–26 and the parf isomer **19** in fractions 99–170. Rechromatography of central fractions (5×) gave a final 0.420 g of combined pref isomer **18** and 0.391 g of combined parf isomer **19** (total 0.811 g, 61% yield).

Alternatively, separation of the diastereomeric tosylates was accomplished by preparative high-pressure liquid chromatography. For this, the crude reaction product was first passed through a 3 × 10 cm silica gel column, eluting with ethyl acetate–pentane (1:2). The concentrated eluates (200 mg) were then subjected to HPLC on a 22.1 mm × 50 cm 10-μm Rainin prep silica column, eluting with ethyl acetate–pentane (1:4), 20 mL/min. Collection of 24-mL fractions gave, in fractions 6–9, 76 mg and, in fractions 12–17, 112 mg of the respective diastereomers (94% recovery).

For the pref isomer **18**: IR (KBr) ν_{max} 3427, 3398, 3378, 3056, 3030, 2962, 2932, 2918, 2875, 2855, 2830, 2797, 2743, 2728, 2700, (1734), 1677, 1637, 1610, 1495, 1478, 1466, 1437, 1382, 1359, 1304, 1293, 1279, 1249, 1205, 1189, 1176, 1134, 1116, 1099, 1046, 1028, 1019, 996, 946, 914, 881, 849, 831, 815, 790 cm^{-1}; 250-MHz NMR ($CDCl_3$) δ 0.62 (t, J = 7 Hz, 3 H), 0.53–0.86 (m, 2 H), 1.10–1.27 (m, 2 H), 1.43–1.53 (m, 1 H), 1.63–1.69 (m, 2 H), 1.78–1.81 (m, 1 H), 1.98–2.07 (m, 1 H), 2.38 (s, 3 H), 2.43–2.50 (m, 2 H), 2.54–2.68 (m, 1 H), 2.81 (s, 1 H), 2.88–2.95 (m, 1 H), 3.75–3.65 (m, 3 H), 4.00 (d, J = 13 Hz, 1 H), 3.77 (s, 3 H), 7.77–6.80 (m, 12 H), 8.91 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 10.36, 21.55, 22.20, 22.40, 31.43, 36.19, 36.34, 42.23, 50.79, 51.04, 55.19, 58.43, 72.68, 72.26, 90.39, 109.25, 120.54, 122.20, 127.15, 127.85, 128.88, 129.71, 132.91, 137.79, 139.00, 142.99, 144.52, 164.96, 168.87; mass spectrum, m/z (relative intensity) 429 (M – Tos, 3), 428 (12), 339 (11), 338 (50), 307 (3), 293 (6), 239 (3), 214 (8), 186 (6), 182 (7), 181 (3), 180 (4), 172 (9), 168 (4), 167 (10), 166 (4), 165 (4), 156 (4), 155 (6), 154 (3), 125 (12), 124 (100), 122 (4), 108 (7), 107 (55), 92 (24), 91 (86), 79 (8), 77 (9), 65 (16), 63 (4), 58 (4), 55 (3), 51 (4).

Anal. Calcd for $C_{35}H_{40}N_2O_5S$: C, 69.97; H, 6.71; N, 4.66; S, 5.34. Found: C, 69.73; H, 6.75; N, 4.81; S, 5.38.

For the parf isomer **19**: IR (KBr) ν_{max} 3434, 3380, 3295, 3056, 3029, 2961, 2947, 2932, 2875, 2860, 2797, (1735), 1676, 1610, 1495, 1478, 1466, 1437, 1382, 1359, 1304, 1294, 1280, 1250, 1204, 1189, 1176, 1147, 1133, 1116, 1100, 1078, 1060, 1045, 1028, 1019, 946, 926, 867, 849, 830, 815, 792, 772, 747, 700 cm^{-1}; 250-MHz NMR ($CDCl_3$) δ 0.62 (t, J = 7 Hz, 3 H), 0.59–0.73 (m, 1 H), 0.79–0.91 (m, 1 H), 1.03 (m, 1 H), 1.21–1.39 (m, 1 H), 1.42–1.55 (m, 1 H), 1.61–1.72 (m, 1 H), 1.80–1.90 (m, 1 H), 1.92–2.06 (m, 1 H), 2.37 (s, 3 H), 2.46–2.50 (m, 2 H), 2.61–2.69 (m, 1 H), 2.81 (s, 1 H), 2.87–2.93 (m, 1 H), 3.73 (s, 3 H), 3.68–3.82 (m, 3 H), 4.01 (d, J = 13 Hz, 1 H), 6.79–7.70 (m, 12 H), 8.96 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 10.93, 21.55, 24.31, 31.02, 36.16, 36.59, 42.09, 50.51, 50.86, 55.16, 58.16, 71.98, 72.19, 89.98, 109.21, 120.62, 122.24, 127.14, 127.79, 128.32, 129.03, 129.76, 133.06, 137.79, 138.83, 142.88, 144.58, 165.15, 168.87; mass spectrum, m/z (relative intensity) 600 (M^+, trace), 429 (6), 428 (18), 400 (9), 339 (15), 338 (57), 295 (8), 293 (9), 239 (3), 238 (4), 214 (34), 186 (9), 182 (8), 180 (5), 172 (12), 168 (4), 167 (10), 156 (5), 155 (8), 125 (10), 124 (98), 122 (4), 108 (10), 107 (71), 106 (5), 92 (29), 91 (100), 89 (5), 79 (10), 77 (9), 65 (17), 63 (4), 58 (4), 55 (3), 51 (4).

Anal. Calcd for $C_{35}H_{40}N_2O_5S$: C, 69.97; H, 6.71; N, 4.66; S, 5.34. Found: C, 69.67; H, 6.78; N, 4.77; S, 5.29.

For each diastereomer **18**, **19**: UV (ethanol) λ_{max} 228, 300, 330 nm.

Coupling Reaction of Vindoline and 14,20-*parf*-*D*-*seco*-21-(Tosyloxy)-Ψ-vincadifformine (19). A solution of 0.636 g (1.06 mmol) of the 14,20-parf isomer **19** in 10 mL of dichloromethane and 0.118 g (0.162 μL, 1.16 mmol) of triethylamine was cooled to 0 °C under argon. With vigorous stirring, 135 μL (0.126 g, 1.16 mmol) of *tert*-butyl hypochlorite was added. After 20 min at 0 °C, the yellow reaction mixture was poured into 20 mL of iced water and the mixture extracted with 3 × 10 mL of dichloromethane. The combined extracts were dried ($MgSO_4$), filtered, and concentrated at 20 °C at 15 mm and subsequently at 0.05 mm of pressure to a tan foam (0.672 g, 100%). This chloroindolenine (0.636 g, 1.00 mmol) product and 0.374 g (0.720 mmol) of vindoline 1.5 hydrochloride were placed under argon, and 10 mL of dry acetone was added. After stirring for 5 min, 0.618 g (3.18 mmol) of silver tetrafluoroborate in 4 mL of dry acetone was added in one portion, with shielding from light. After stirring in the dark for 20 min, the brown suspension was poured into 50 mL of 10% ammonium hydroxide saturated with sodium chloride, and the mixture was extracted with 3 × 25 mL of dichloromethane. The combined dried ($MgSO_4$) extracts were filtered and concentrated at 40 °C, 15 mm, to a brown glass. TLC (SiO_2, ethyl acetate) indicated two imines (R_f 0.13 and 0.46) and the absence of vindoline (R_f 0.32). The imine mixture was dissolved in 25 mL of acetic acid, and 0.571 g (10.6 mmol) of potassium borohydride was added in portions over 15 min, with rapid stirring. The reaction mixture was then poured into cold ammonium hydroxide solution and extracted with 3 × 50 mL of dichloromethane. The combined extracts were dried ($MgSO_4$), filtered, and concentrated at 40 °C at 15 mm, and subsequently at 0.05 mm, to give 0.660 g (87% yield based on vindoline used) of the two amine tosylates **26** and **25** as a tan foam. TLC (SiO_2, ethyl acetate): R_f 0.37 and 0.49 (ceric ammonium sulfate (CAS) grey-purple). Centrifugal chromatography on a 4-mm silica gel plate, with application of the mixture in 10 mL of dichloromethane, followed by elution with 10 mL of dichloromethane and then with 80% ethyl acetate in pentane at 2.1 mL/min, and collection of fractions every minute, gave the separated diastereomers in fractions 3–30 (**25**) and 52–90 (**26**). Rechromatography of fractions 31–51 provided additional separated compounds, for a combined 0.300 g of **25** and 0.271 g of **26** (66% total based on vindoline).

For **25**: UV (ethanol) λ_{max} 225, 262, 284, 297 nm; IR (KBr) ν_{max} 3472, 3057, 3027, 2960, 2876, 2858, 2796, 1740, 1614, 1501, 1460, 1432, 1364, 1337, 1305, 1293, 1244, 1226, 1188, 1176, 1131, 1120, 1108, 1097, 1041, 947, 931, 907, 891, 833, 781, 761, 739, 700, 666, 555 cm^{-1}; 250-MHz NMR ($CDCl_3$) δ 0.43 (t, J = 7 Hz, 3 H), 0.54–0.72 (m, 2 H), 0.85 (t, J = 7 Hz, 3 H), 2.10 (s, 3 H), 2.42 (s, 3 H), 2.67 (s, 3 H), 3.60 (s, 3 H), 3.68 (s, 1 H), 3.78 (s, 6 H), 5.30 (d, J = 10 Hz, 1 H), 5.45 (s, 1 H), 5.81 (dd, J = 4, 10 Hz, 1 H), 6.10 (s, 1 H), 6.76–7.72 (m, 13 H), 7.99 (s, 1 H), 9.84 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 8.56, 10.26, 21.14, 21.61, 21.88, 25.52, 30.87, 33.69, 35.78, 36.07, 36.36, 38.44, 42.69, 44.75, 49.03, 50.69, 53.22, 53.28, 52.26, 52.18, 55.75, 56.10, 60.95, 63.55, 65.42, 72.63, 79.68, 83.45, 94.04, 110.44, 115.03, 118.14, 118.94, 121.69, 122.01, 124.48, 123.02, 125.23, 126.55, 127.82, 128.08, 129.38, 129.77, 130.03, 132.37, 133.08, 134.91, 140.02, 144.58, 152.88, 157.90, 170.90, 171.66, 174.73; mass spectrum, m/z (relative intensity) 885 (M^+ – OTos, 0.2), 795 (0.5), 794 (0.4), 793 (0.4), 792 (0.4), 764 (1.5), 735 (1), 635 (1), 633 (1), 627 (1.5), 555 (0.3), 496 (0.4), 469 (1), 355 (0.6), 338 (1), 325 (1), 311 (1), 307 (1), 197 (0.8), 282 (2), 280 (1), 279 (6), 272 (1), 262 (2), 261 (1), 252 (1), 221 (1), 220 (1), 214 (2), 210 (1), 209 (2), 207 (1), 202 (1), 201 (2), 188 (2), 186 (6), 182 (2), 181 (1), 172 (2), 168 (1), 167 (5), 165 (2), 157 (1), 156 (2), 155 (6), 152 (1), 149 (4), 148 (2), 139 (2), 138 (7), 135 (5), 134 (4), 128 (4), 124 (4), 121 (3), 119 (6), 108 (8), 107 (42), 106 (7), 105 (10), 93 (6), 92 (57), 91 (100), 90 (5), 89 (14), 85 (5), 79 (8), 77 (12), 71 (6), 65 (30), 63 (15), 62 (7), 57 (10), 55 (8), 52 (5), 51 (21), 50 (7).

For **26**: UV (ethanol) λ_{max} 222, 260, 290, 299 nm; IR (KBr) ν_{max} 3427, 3028, 2960, 2946, 2935, 2877, 2838, 2804, 2735, 1740, 1614, 1499, 1460, 1432, 1413, 1362, 1337, 1295, 1245, 1226, 1188, 1176, 1153, 1120, 1109, 1097, 1041, 983, 947, 906, 836, 816, 783, 763, 740, 700, 666, 555 cm^{-1}; 250-MHz NMR ($CDCl_3$) δ 0.37 (t, J = 7 Hz, 3 H), 0.56 (t, J = 8 Hz, 3 H), 2.06 (s, 3 H), 2.38 (s, 3 H), 2.73 (s, 3 H), 2.73 (s, 3 H), 3.57 (s, 3 H), 3.78 (s, 3 H), 3.79 (s, 3 H), 5.23 (d, J = 10 Hz, 1 H), 5.41 (s, 1 H), 5.81 (dd, J = 4, 10 Hz, 1 H), 6.10 (s, 1 H), 6.84–7.70 (m, 13 H), 8.04 (s, 1 H), 9.74 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 8.25, 10.25, 21.06, 21.48, 21.61, 26.37, 30.59, 34.04, 35.61, 35.72, 35.87, 38.62, 42.70, 45.29, 50.37, 52.25, 52.37, 53.53,

54.11, 55.55, 55.69, 58.77, 64.91, 65.94, 73.25, 76.01, 79.71, 83.65, 93.59, 110.21, 115.94, 118.27, 126.77, 127.88, 128.24, 128.31, 129.14, 130.06, 131.94, 132.95, 134.90, 140.26, 144.44, 153.16, 158.20, 170.55, 171.67, 174.12; mass spectrum, m/z (relative intensity) 885 (M^+ - OTos, 0.05), 796 (0.1), 795 (0.1), 794 (0.2), 793 (0.2), 792 (0.2), 764 (0.2), 735 (0.4), 635 (0.6), 633 (0.2), 555 (0.1), 524 (0.1), 469 (0.8), 428 (0.4), 415 (0.4), 381 (0.5), 379 (0.4), 369 (0.4), 357 (0.6), 355 (0.4), 339 (0.7), 338 (3), 325 (0.6), 323 (0.9), 311 (0.9), 310 (1), 307 (2), 282 (1), 280 (0.5), 279 (2), 262 (2), 252 (0.8), 223 (0.8), 221 (0.7), 220 (0.7), 217 (0.7), 215 (0.9), 214 (2), 210 (0.7), 209 (0.6), 208 (0.7), 207 (0.4), 205 (0.6), 202 (0.7), 201 (0.7), 200 (0.8), 186 (4), 182 (4), 181 (1), 172 (2), 168 (1), 167 (6), 165 (2), 156 (2), 155 (7), 149 (8), 148 (3), 139 (2), 138 (5), 135 (4), 134 (6), 133 (4), 128 (4), 126 (7), 124 (5), 120 (4), 119 (16), 108 (7), 107 (31), 106 (5), 105 (9), 92 (31), 91 (100), 89 (9), 85 (4), 79 (10), 77 (18), 73 (5), 71 (8), 69 (7), 65 (28), 63 (14), 62 (5), 57 (12), 55 (9), 52 (5), 51 (16), 50 (11).

20′-Deoxyvinblastine (4) and Atropisomer 31. Under an argon atmosphere, 0.907 g (0.863 mmol) of the tosylate **25** in 100 mL of dry toluene was heated at reflux for 24 h with rapid stirring. At that point, the starting amino tosylate had reacted completely. The cooled reaction mixture was concentrated under vacuum and the residual solid washed with three 50-mL portions of dry ether. The resulting quaternary salts **27a** and **27b** (0.873 g, 96%), which were free of starting amine by TLC (ethyl acetate–ethanol, 1:1), were dissolved in 20 mL of methanol. Addition of 0.060 g of 10% Pd–charcoal and stirring under a hydrogen atmosphere at −6 °C for 5 h resulted in an uptake of 20.5 mL of hydrogen. The reaction mixture was filtered through a 1 × 3 cm plug of Celite 545, with subsequent washing of the Celite with 100 mL of methanol. Concentration at 20 °C under vacuum, solution of the residue in 200 mL of dichloromethane, washing of the solution with 2 × 30 mL of 3% ammonium hydroxide and saturated brine, drying ($MgSO_4$), filtration, and concentration under vacuum, gave a mixture of 20′-deoxyvinblastine (**4**) and its bridged piperidine conformational isomer **31**. This mixture was separated by centrifugal chromatography on a 2-mm silica gel plate and eluted with 10% methanol in dichloromethane. Collection of 1 mL/min fractions gave 0.527 g (80%) of 20′-deoxyvinblastine (**4**) in fractions 8–27 and 0.0198 g (3%) of its atropisomer **31** in fractions 30–42. For product **4**, crystallized from methanol: mp 202–205 °C; TLC R_f 0.53 (silica gel, 10% methanol in dichloromethane); UV (ethanol) λ_{max} 225, 252, 288, 298 nm; IR (KBr) ν_{max} 3470, 2960, 2930, 2902, 2877, 2839, 2808, 2736, 2685, 1744, 1616, 1502, 1459, 1432, 1370, 1332, 1294, 1245, 1224, 1146, 1128, 1107, 1094, 1078, 1063, 1042, 1019, 807, 740 cm^{-1}; 250-MHz NMR ($CDCl_3$) δ 0.73 (t, J = 7 Hz, 3 H), 0.83 (t, J = 7 Hz, 3 H), 2.03 (s, 3 H), 2.64 (s, 3 H), 3.55 (s, 3 H), 3.66 (s, 1 H), 3.72 (s, 3 H), 3.73 (s, 3 H), 5.27 (d, J = 10 Hz, 1 H), 5.38 (s, 1 H), 5.77 (dd, J = 4, 10 Hz, 1 H), 6.00 (s, 1 H), 6.50 (s, 1 H), 6.90–7.10 (m, 3 H), 7.42 (d, J = 7 Hz, 1 H), 7.94 (s, 1 H), 9.81 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 8.36, 11.23, 21.16, 27.20, 28.80, 30.32, 30.84, 32.80, 33.83, 38.41, 38.80, 42.70, 44.58, 47.62, 50.62, 52.20, 52.31, 53.34, 55.52, 55.81, 57.08, 60.16, 65.43, 79.74, 83.39, 94.12, 110.51, 117.42, 118.40, 118.84, 121.30, 122.30, 122.71, 123.50, 124.56, 129.35, 130.06, 130.53, 135.15, 152.76, 158.11, 170.93, 171.70, 175.04; mass spectrum (relative intensity) 794 (M^+, 3) 764 (5), 763 (4), 735 (8), 664 (2), 635 (3), 555 (3), 527 (3), 469 (2), 338 (2), 282 (5), 281 (5), 228 (4), 223 (3), 221 (3), 209 (9), 207 (9), 180 (7), 167 (5), 151 (7), 139 (3), 138 (56), 137 (5), 136 (14), 135 (13), 134 (14), 124 (20), 122 (13), 121 (8), 119 (100), 110 (6), 108 (5), 107 (8), 105 (13), 99 (5), 96 (7), 93 (16), 92 (9), 83 (18), 82 (42), 79 (11), 77 (71). An analytical sample was prepared by centrifugal chromatography on silica gel. It was eluted with ethyl acetate–ethanol, and then crystallized from methanol. NMR ($CDCl_3$): δ 3.32 for 2 equiv of CH_3OH. Anal. Calcd for $C_{46}H_{58}N_4O_8 \cdot 2CH_3OH$: C, 67.19; H, 7.64; N, 6.53. Found: C, 66.83, H, 7.46, N, 6.79. Exact mass calcd 794.4254, found 794.4258.

For compound **31**: TLC R_f 0.49 (silica gel, 10% methanol in dichloromethane); HPLC t_R 17.5 min (C-18 5-μm spherical reverse-phase Microsorb column, 4.6 mm × 25 cm with a 3-cm guard column, eluted with 9:1:0.1 methanol–water–triethylamine at 1 mL/min, 1260 psi; UV (ethanol) λ_{max} 217, 225, 265, 284, 293, 307 nm; IR (KBr) ν_{max} 3381, 2964, 2950, 2936, 2930, 2877, 2861, 1735, 1616, 1506, 1498, 1458, 1432, 1372, 1235, 1146, 1039, 747, 667 cm^{-1}; IR ($CHCl_3$) ν_{max} 3446, 3029, 3009, 2968, 2939, 2881, 2863, 2844, 2811, 1616, 1498, 1490, 1458, 1435, 1374, 1241, 1146, 1041 cm^{-1}; 270-MHz NMR ($CDCl_3$) (broadened signals prevented accurate integration) δ 0.25 (m, 1 H), 0.92 (m, 6 H), 1.09–1.02 (m, 4 H), 2.08 (br s, 4 H), 2.42 (m, 4 H), 2.94–2.61 (m, 5 H), 3.56–2.95 (m, 6 H), 3.66 (s, 3 H), 3.82 (s, 6 H), 3.85 (s, 1 H), 5.16 (m, 1 H), 5.44 (br s, 1 H), 5.81 (m, 1 H), 6.11 (br s, 1 H), 7.00 (br s, 1 H), 7.30–7.15 (m, 3 H), 7.43 (d, J = 8 Hz, 1 H), 8.75 (br s, 1 H) 9.75 (br s, 1 H); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 171.94, 170.81, 165.19, 160.03, 153.98, 134.54, 130.05, 127.37, 124.14, 122.45, 120.46, 118.17, 115.10, 111.52, 94.40, 83.23, 79.19, 55.71, 53.07, 52.92, 52.26, 51.41, 43.75, 43.17, 37.65, 34.78, 33.86, 31.72, 31.65, 30.80, 29.65, 26.53, 26.46, 21.06, 20.95, 10.76, 8.87; mass spectrum, m/z (relative intensity) 796 (0.2), 795 (0.5), 794 (M^+, 0.3), 764 (0.4), 738 (0.5), 737 (0.7), 736 (0.4), 256 (0.3), 172 (0.2), 149 (0.7), 147 (0.2), 135 (2), 133 (1), 126 (2), 115 (1), 101 (5), 99 (5), 97 (6), 88 (13), 86 (67), 85 (22), 84 (100), 83 (27), 51 (83), 50 (48).

20′-Deoxyvincovaline (6) and Atropisomer 32. Cyclization of the amine tosylate **26** and debenzylation of the resultant quaternary salts **28a,b** by the above procedure provided the title products **6** (49%) and **32** (37%). For **6** crystallized from methanol: mp 203–206 °C (reported: 190–194 °C,[2b] 214 °C[2c]); TLC R_f 0.82 (silica gel, 10% methanol in dichloromethane); UV (ethanol) λ_{max} 225, 257, 290, 298, 310 nm; IR (KBr) ν_{max} 3471, 3037, 3016, 2960, 2926, 2901, 2877, 2839, 2805, 1742, 1616, 1501, 1459, 1432, 1370, 1333, 1296, 1245, 1223, 1192, 1172, 1146, 1120, 1108, 1095, 1080, 1064, 1038, 1003, 956, 741 cm^{-1}; 250-MHz ^1H NMR ($CDCl_3$) δ 0.40 (t, J = 7 Hz, 3 H), 0.90 (t, J = 7 Hz, 3 H), 0.93–1.25 (m, 5 H), 1.42–1.77 (m, 4 H), 2.07 (s, 3 H), 2.13–2.35 (m, 2 H), 2.41 (s, 1 H), 2.37–2.57 (m, 4 H), 2.72 (s, 3 H), 2.72–2.78 (m, 1 H), 2.98–3.43 (m, 8 H), 3.57 (s, 3 H), 3.57–3.69 (m, 1 H), 3.78 (s, 1 H), 3.80 (s, 3 H), 3.81 (s, 3 H), 5.23 (d, J = 10 Hz, 1 H), 5.49 (s, 1 H), 5.79 (dd, J = 10, 4 Hz, 1 H), 6.14 (s, 1 H), 6.74 (s, 1 H), 7.06–7.23 (m, 3 H), 7.50 (d, J = 8 Hz, 1 H), 8.08 (s, 1 H), 9.66 (s, 1 H); 62.9-MHz ^{13}C NMR ($CDCl_3$) δ 8.41, 11.29, 21.11, 27.61, 29.35, 30.35, 30.96, 33.13, 33.88, 38.50, 39.15, 42.96, 44.59, 48.55, 50.64, 51.17, 52.29, 53.46, 55.69, 56.50, 60.25, 67.16, 76.08, 79.57, 83.60, 94.18, 110.24, 117.22, 118.50, 118.88, 121.22, 122.22, 123.73, 123.89, 129.17, 130.03, 130.91, 135.15, 153.15, 158.21, 170.76, 171.94, 174.94; mass spectrum, m/z (relative intensity) 795 (11), 794 (M^+, 24), 793 (5), 765 (5), 763 (20), 736 (11), 735 (23), 664 (6), 636 (5), 635 (9), 556 (11), 527 (6), 526 (4), 496 (8), 469 (39), 397 (4), 381 (4), 339 (5), 338 (15), 327 (4), 326 (4), 325 (10), 311 (5), 309 (5), 297 (5), 296 (5), 282 (22), 267 (7), 266 (5), 265 (6), 252 (5), 222 (5), 207 (5), 188 (9), 170 (4), 158 (4), 149 (20), 144 (7), 139 (6), 138 (100), 136 (12), 135 (66), 134 (7), 133 (4), 130 (5), 125 (6), 124 (52), 123 (4), 122 (25), 121 (20), 119 (6), 110 (19), 109 (5), 108 (10), 107 (15), 105 (7), 97 (7), 96 (18), 95 (7), 93 (23), 92 (5), 91 (19), 83 (13), 82 (26), 81 (10), 77 (8), 71 (13), 70 (5), 69 (14), 68 (5), 58 (18), 57 (31), 56 (10), 55 (32). An amorphous analytical sample was prepared by centrifugal chromatography, as above, dissolved in methanol, and filtered and the concentrate dried under vacuum. Anal. Calcd for $C_{46}H_{58}N_4O_8 \cdot 2H_2O$: C, 66.49; H, 7.52; N, 6.74. Found: C, 66.58; H, 7.48; N, 6.55. Exact mass calcd 794.425, found 794.419.

For **32**: TLC R_f 0.47 (silica gel, 10% methanol in dichloromethane); HPLC t_R 20.5 min (conditions as for **31**); UV λ_{max} 218, 226, 263, 285, 294, 309 nm; IR (KBr) ν_{max} 3401, 3001, 2963, 2929, 2876, 2862, 2836, 2814, 1740, 1617, 1500, 1488, 1459, 1432, 1372, 1335, 1302, 1249, 1242, 1192, 1176, 1148, 1130, 1120, 1106, 1092, 1065, 1040, 1004, 746, 665; (in $CHCl_3$ separation of ester absorptions 1743, 1723 cm^{-1}); 250-MHz ^1H NMR ($CDCl_3$) δ 0.52 (t, J = 7 Hz, 3 H), 0.98 (t, J = 7 Hz, 3 H), 1.16–1.26 (m, 2 H), 1.45–1.51 (m, 1 H), 1.71–1.92 (m, 2 H), 2.07 (s, 3 H), 2.16–2.34 (m, 2 H), 2.41–2.74 (m, 5 H), 2.68 (s, 3 H), 2.64 (s, 1 H), 2.80–3.22 (m, 4 H), 3.11 (s, 3 H), 3.52–3.81 (m, 5 H), 3.58 (s, 3 H), 3.80 (s, 3 H), 3.84 (s, 1 H), 5.25 (d, J = 10 Hz, 1 H), 5.47 (s, 1 H), 5.86 (dd, J = 10, 4 Hz, 1 H), 5.93 (s, 1 H), 6.91 (s, 1 H), 7.06 (t, J = 7 Hz, 1 H), 7.17 (t, J = 7 Hz, 1 H), 7.28 (d, J = 7 Hz, 1 H), 7.40 (d, J = 8 Hz, 1 H), 9.07 (s, 1 H), 10.82 (s, 1 H); 67.9-MHz ^{13}C NMR ($CDCL_3$) δ 7.67, 11.04, 20.11, 20.92, 26.84, 27.49, 30.78, 32.38, 34.29, 35.06, 38.00, 43.02, 44.76, 45.25, 48.13, 51.34, 52.06, 52.23, 52.44, 52.77, 52.99, 53.13, 53.30, 55.99, 67.56, 76.24, 79.39, 83.26, 95.68, 111.14, 117.72, 119.52, 119.85, 121.85, 124.15, 127.10, 130.35, 133.96, 153.07, 160.12, 170.79, 171.74; mass spectrum, m/z (relative intensity) 795 (0.5), 794 (0.5), 793 (0.7), 736 (0.5), 469 (0.8), 282 (0.5), 139 (0.5), 138 (3.0), 135 (1.5), 125 (0.6), 124 (0.9), 123 (0.7), 121 (0.8), 107 (1.5), 106 (0.7), 98 (0.6), 97 (0.7), 96 (1), 92 (1), 91 (0.8), 88 (1), 86 (6.9), 85 (2), 84 (12), 83 (1.8), 82 (0.9), 73 (7), 71 (1), 70

(1), 69 (2), 68 (2), 67 (0.8), 65 (0.7), 61 (2), 66 (5), 58 (1), 57 (3), 56 (3), 55 (3), 52 (37), 51 (17), 50 (100).

20′-Deoxyleurosidine (5) and Atropisomer 33. Cyclization of the amine tosylate **23** and debenzylation of the resultant quaternary salts **29a,b** by the above procedure provided the title products **5** (59%) and **33** (23%). For **5**: TLC R_f 0.47 (silica gel, 10% methanol in dichloromethane); UV (ethanol) λ_{max} 221, 229, 264, 280, 290, 296 nm; IR (KBr) ν_{max} 3470, 2960, 2926, 2909, 2875, 2853, 2811, 1741, 1616, 1502, 1459, 1432, 1370, 1333, 1296, 1243, 1226, 1145, 1129, 1119, 1108, 1039, 734 cm^{-1}; 250-MHz ^1H NMR ($CDCl_3$) δ 0.70 (t, J = 12 Hz, 1 H), 0.84 (t, J = 7 Hz, 3 H), 0.87 (t, J = 7 Hz, 3 H), 1.05–1.19 (m, 1 H), 1.20–1.43 (m, 3 H), 1.73–1.93 (m, 3 H), 1.98–2.20 (m, 2 H), 2.11 (s, 3 H), 2.29 (d, J = 15 Hz, 1 H), 2.37–2.51 (m, 1 H), 2.68 (s, 1 H), 2.72 (s, 3 H), 2.74–2.92 (m, 3 H), 2.74–2.92 (m, 5 H), 3.10–3.42 (m, 6 H), 3.61 (s, 3 H), 3.61–3.69 (m, 1 H), 3.69 (s, 3 H), 3.75 (s, 1 H), 3.80 (s, 3 H), 5.32 (d, J = 9 Hz, 1 H), 5.47 (s, 1 H), 5.86 (dd, J = 10, 4 Hz, 1 H), 6.11 (s, 1 H), 6.59 (s, 1 H), 7.09–7.21 (m, 3 H), 7.54 (d, J = 8 Hz, 1 H), 7.93 (s, 1 H), 9.87 (s, 1 H); 62.9-MHz ^{13}C NMR ($CDCl_3$) δ 8.47, 11.46, 21.17, 28.23, 30.52, 30.89, 35.29, 35.72, 38.36, 40.17, 42.78, 44.52, 44.64, 50.39, 52.23, 52.34, 52.55, 53.34, 54.19, 55.75, 55.88, 67.75, 70.58, 79.73, 83.48, 94.32, 110.58, 117.48, 118.34, 119.03, 121.10, 122.39, 122.98, 123.72, 124.57, 129.45, 130.07, 130.50, 135.09, 152.85, 158.09, 170.94, 171.73, 174.52; mass spectrum, m/z (relative intensity) 795 (1), 794 (1), 794 (M^+, 3), 765 (2), 764 (4), 736 (3), 635 (2), 555 (1), 527 (1), 526 (1), 469 (3), 372 (2), 342 (5), 339 (2), 338 (7), 325 (2), 283 (3), 282 (7), 273 (2), 272 (2), 265 (2), 252 (3), 214 (2), 197 (2), 196 (2), 177 (9), 144 (3), 140 (3), 139 (5), 138 (37), 135 (10), 133 (32), 131 (5), 125 (6), 124 (29), 122 (4), 121 (5), 117 (10), 115 (4), 110 (5), 108 (3), 107 (6), 103 (5), 102 (5), 101 (19), 96 (5), 91 (12), 90 (6), 89 (100), 88 (35), 87 (57), 86 (21), 84 (8), 83 (7), 81 (12), 75 (6), 73 (79), 72 (34), 71 (15), 70 (25), 60 (10). An analytical sample was prepared as described for isomer **4**. Anal. Calcd for $C_{46}H_{58}N_4O_8 \cdot 3H_2O$: C, 65.07; H, 7.60; N, 6.60. Found: C, 65.10; H, 7.33; N, 6.51. Exact mass calcd 794.425, found 794.427.

For **33**: TLC R_f 0.42 (silica gel, 10% methanol in dichloromethane); HPLC t_R 25.0 min (conditions as for **31**); UV (ethanol) λ_{max} 220, 223, 269, 284, 295, 310 nm; IR (KBr) ν_{max} 3448, 2998, 2962, 2957, 2949, 2938, 2932, 2877, 2843, 2814, 1739, 1616, 1594, 1502, 1459, 1433, 1372, 1335, 1321, 1301, 1245, 1237, 1159, 1143, 1129, 1110, 1085, 1042, 748 cm^{-1}; 270-MHz ^1H NMR ($CDCl_3$, broadening of most signals) δ 0.53 (br t, 3 H), 0.79–0.99 (br m, 1 H), 0.81 (t, J = 7 Hz, 3 H), 1.04–1.40 (m, 6 H), 1.56–1.79 (m, 3 H), 1.80–2.05 (m, 2 H), 2.09 (s, 3 H), 2.22–2.74 (m, 5 H), 2.84–3.07 (m, 4 H), 3.14–3.24 (m, 1 H), 2.77 (br s, 3 H), 3.41–3.56 (m, 3 H), 3.67 (br s, 3 H), 3.82 (s, 3 H), 3.89 (br s, 1 H), 5.25 (d, J = 10 Hz, 1 H), 5.45 (s, 1 H), 5.91 (dd, J = 10, 4 Hz, 1 H), 6.09 (br s, 1 H), 7.12–7.25 (m, 5 H), 7.47 (m, 2 H), 9.62 (br s, 1 H); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 7.53, 10.79, 20.89, 21.66, 21.74, 26.41, 29.52, 30.78, 33.84, 33.89, 36.61, 36.67, 37.70, 42.99, 44.01, 50.99, 51.74, 51.87, 52.18, 52.65, 52.81, 52.96, 53.09, 55.88, 66.94, 76.19, 79.39, 83.27, 94.44, 110.44, 112.23, 117.76, 119.64, 121.88, 124.17, 124.79, 129.45, 130.33, 133.34, 133.78, 153.90, 159.67, 170.67, 171.71; mass spectrum, m/z (relative intensity) 795 (0.1), 794 (M^+, 0.1), 793 (0.1), 738 (0.2), 737 (0.5), 736 (0.2), 735 (0.2), 661 (0.2), 612 (0.4), 598 (0.2), 577 (0.2), 575 (0.2), 470 (0.2), 469 (0.8), 468 (0.2), 467 (0.2), 466 (0.2), 464 (0.2), 455 (0.2), 452 (0.2), 451 (0.2), 438 (0.2), 393 (0.2), 380 (0.2), 340 (0.2), 339 (0.5), 338 (0.5), 313 (0.2), 312 (0.2), 309 (0.2), 308 (0.2), 283 (0.3), 282 (0.9), 281 (0.3), 278 (0.3), 252 (0.4), 222 (0.3), 214 (0.3), 212 (0.5), 200 (0.3), 188 (0.4), 171 (0.5), 169 (0.3), 167 (0.3), 155 (0.6), 149 (0.8), 139 (0.9), 138 (0.5), 135 (0.2), 126 (0.7), 125 (1), 124 (2), 123 (0.6), 122 (1), 121 (1), 120 (0.4), 119 (0.5), 111 (0.7), 110 (0.9), 109 (0.6), 108 (1), 107 (2), 106 (2), 101 (1), 98 (1), 97 (1), 96 (2), 95 (1), 93 (1), 92 (2), 91 (4), 88 (3), 87 (1), 86 (14), 85 (3), 84 (19), 83 (4), 82 (2), 81 (1), 79 (1), 77 (1), 74 (1), 73 (1), 71 (2), 70 (2), 69 (3), 68 (2), 67 (1), 65 (1), 63 (1), 61 (2), 60 (5), 59 (2), 57 (5), 56 (4), 55 (5), 53 (5), 52 (31), 51 (24), 50 (100).

20′-*epi*-20′-Deoxyvincovaline (7) and Atropisomer 34. Cyclization of the amine tosylate **24** and debenzylation of the resultant quaternary salts **30a,b** by the above procedure gave the title products **7** (31%) and **34** (46%). For **7**: TLC R_f 0.49 (silica gel 10% methanol in dichloromethane); UV (ethanol) λ_{max} 220, 257, 291, 298, 307 nm; IR (KBr) ν_{max} 3467, 2960, 2925, 2875, 2854, 2811, 1742, 1615, 1501, 1460, 1432, 1370, 1333, 1297, 1246, 1224, 1146, 1120, 1108, 1093, 1065, 1038, 1003, 740 cm^{-1}; 250-MHz ^1H NMR δ 0.35 (t, J = 7 Hz, 3 H), 0.73 (t, J = 12 Hz, 1 H), 0.89 (t, J = 7 Hz, 3 H), 0.98–1.23 (m, 1 H), 1.26–1.46 (m, 3 H), 1.52–1.81 (m, 2 H), 1.90–2.66 (m, 5 H), 2.07 (s, 3 H), 2.46 (s, 1 H), 2.74 (s, 3 H), 2.81–2.93 (m, 5 H), 3.09–3.47 (m, 6 H), 3.55 (s, 3 H), 3.62–3.72 (m, 1 H), 3.69 (s, 1 H), 3.80 (s, 3 H), 3.81 (s, 3 H), 5.24 (d, J = 10 Hz, 1 H), 5.45 (s, 1 H), 5.82 (dd, J = 10, 4 Hz, 1 H), 6.14 (s, 1 H), 6.72 (s, 1 H), 7.09–7.27 (m, 3 H), 7.54 (d, J = 8 Hz, 1 H), 8.00 (s, 1 H), 9.71 (s, 1 H); 62.9-MHz ^{13}C NMR ($CDCl_3$) δ 8.21, 11.47, 21.12, 21.37, 28.33, 30.23, 30.78, 35.32, 35.98, 38.55, 40.46, 42.82, 44.94, 50.54, 50.86, 52.14, 52.28, 53.55, 54.02, 55.70, 55.77, 66.66, 70.64, 79.69, 83.61, 94.31, 110.33, 117.32, 118.42, 119.10, 120.59, 122.38, 123.57, 123.86, 124.06, 129.15, 130.03, 130.62, 135.12, 153.18, 158.18, 170.77, 171.82, 174.41; mass spectrum, m/z (relative intensity) 795 (1), 794 (M^+, 4), 735 (1), 579 (2), 555 (1), 470 (1), 469 (4), 381 (1), 380 (1), 339 (2), 338 (5), 325 (1), 312 (1), 311 (1), 283 (1), 282 (4), 279 (1), 273 (1), 252 (1), 222 (1), 202 (1), 188 (1), 177 (6), 167 (2), 149 (3), 144 (2), 140 (1), 139 (3), 138 (27), 135 (10), 134 (2), 133 (16), 131 (4), 126 (3), 125 (5), 124 (17), 122 (4), 121 (5), 110 (2), 117 (7), 115 (2), 110 (6), 107 (3), 103 (2), 101 (12), 96 (5), 93 (3), 91 (6), 90 (4), 89 (100), 88 (28), 87 (57), 86 (14), 85 (7), 84 (20), 83 (6), 82 (11), 75 (4), 74 (3), 73 (36), 72 (21), 71 (19), 70 (12), 69 (11). An analytical sample was prepared as described for isomer **6**. Anal. Calcd for $C_{46}H_{58}N_4O_8 \cdot 2CH_3OH$: C, 67.19; H, 7.64; N, 6.53. Found: C, 67.04; H, 7.51; N, 6.53. Exact mass calcd 794.425, found 794.409.

For **34**: TLC R_f 0.36 (silica gel, 10 methanol in dichloromethane); HPLC t_R 25.5 min (conditions as for **31**); UV (ethanol) λ_{max} 218, 225, 269, 285, 293, 307 nm; IR (KBr) ν_{max} 3451, 3017, 2998, 2959, 2929, 2876, 2862, 2854, 2849, 2817, 1740, 1615, 1593, 1500, 1459, 1433, 1371, 1334, 1322, 1300, 1247, 1157, 1144, 1131, 1120, 1110, 1084, 1042, 1012, 748, 665 cm^{-1}; 270-MHz ^1H NMR ($CDCl_3$, most signals broad) δ 0.59 (br t, 3 H), 0.75–0.93 (m, 2 H), 0.78 (t, J = 7 Hz, 3 H), 0.96–1.44 (m, 4 H), 1.46–1.96 (m, 3 H), 2.11 (s, 3 H), 2.20–2.54 (m, 4 H), 2.56–3.12 (m, 8 H), 2.74 (br s, 3 H), 3.29–3.99 (m, 2 H), 3.51 (br s, 3 H), 3.74 (br s, 3 H), 3.82 (br s, 3 H), 3.86 (br s, 1 H), 5.26 (d, J = 10 Hz, 1 H), 5.51 (s, 1 H), 5.89 (dd, J = 10, 4 Hz, 1 H), 6.10 (s, 1 H), 5.89 (dd, J = 10, 4 Hz, 1 H), 6.10 (s, 1 H), 7.07–7.27 (m, 5 H), 7.51 (d, J = 7 Hz, 1 H), 9.67 (br s, 1 H); 67.9-MHz ^{13}C NMR ($CDCl_3$, missing C's due to broadening) δ 8.09, 11.15, 20.95, 23.09, 27.19, 31.14, 37.85, 38.26, 38.48, 38.57, 43.11, 43.79, 51.03, 51.17, 52.61, 52.23, 52.49, 52.79, 53.19, 55.92, 67.21, 79.47, 83.46, 94.69, 110.25, 118.24, 119.17, 121.49, 121.59, 121.72, 122.04, 124.46, 124.62, 130.16, 132.83, 133.69, 153.74, 159.72, 170.87, 171.83, 178.73; mass spectrum, m/z (relative intensity) 795 (0.2), 794 (M^+, 0.4), 793 (0.3), 792 (0.5), 765 (0.2), 763 (0.5), 738 (0.2), 737 (0.3), 736 (0.4), 735 (0.2), 469 (0.2), 380 (0.2), 354 (0.2), 353 (0.5), 341 (0.6), 340 (2), 339 (0.6), 338 (0.7), 325 (0.2), 311 (0.3), 282 (0.9), 178 (0.8), 177 (3), 171 (0.9), 167 (1), 164 (2), 161 (2), 155 (1), 151 (1), 150 (1), 149 (6), 143 (2), 141 (1), 140 (2), 139 (2), 138 (6), 137 (2), 136 (2), 135 (4), 134 (2), 133 (2), 127 (2), 126 (1), 125 (2), 124 (2), 123 (2), 121 (4), 119 (3), 113 (2), 112 (2), 111 (3), 110 (3), 109 (3), 108 (2), 107 (2), 106 (2), 105 (2), 104 (1), 101 (2), 99 (3), 98 (4), 97 (9), 96 (7), 95 (4), 94 (2), 93 (4), 91 (6), 89 (2), 88 (12), 87 (5), 86 (63), 85 (14), 84 (100), 83 (18), 82 (5), 81 (7), 79 (3), 73 (7), 71 (12), 70 (11), 69 (12), 68 (13), 67 (5), 61 (10), 60 (10), 59 (5), 57 (23), 56 (10), 55 (17), 54 (3), 53 (5), 52 (13), 51 (58), 50 (61).

20′-Deoxyvincristine and Its C14′,16′,20′ Diastereomer. A solution of 20′-deoxyvinblastine methanesulfonate (21 mg, 0.023 mmol) in dichloromethane (2.5 mL) and acetic acid (320 μL, 5.6 mmol) was cooled to −78 °C, and with rapid stirring, a solution of potassium permanganate (8.2 mg, 0.052 mmol) and 1,4,7,10,13,16-hexaoxacyclooctadecane (17 mg, 64 mmol) in dichloromethane (1 mL) was added dropwise over 1 min. After 30 min at −78 °C, the reaction mixture was poured into 50 mL of a 4.5% sodium bisulfite solution at 0 °C and extracted with three 20-mL portions of cold dichloromethane. The combined organic extracts were washed with 50 mL of 8% sodium bicarbonate at 0 °C, dried over magnesium sulfate, and concentrated. Purification of the residue by high-pressure liquid chromatography on a 50 × 2.5 cm 10-μm SiO_2 column with 1:1 ethyl acetate–ethanol at 15 mL/min gave 8.0 mg (50% yield) of 20′-deoxyvincristine with a retention time of 17 min, TLC R_f 0.34 (SiO_2, 2:1 ethyl acetate–ethanol), IR (KBr) 1687 cm^{-1} (formamide), 250-MHz ^1H NMR ($CDCl_3$) δ 8.17 (0.5 H), 7.74 (0.5 H), and mass spectroscopic m/z M^+ = 808.

The C14′,16′,20′ diastereomer, prepared analogously by oxidation of 20′-deoxyleurosidine methanesulfonate, gave TLC R_f 0.18, HPLC t_R 34 min, IR 1685 cm^{-1}, ^1H NMR δ 8.17 (0.5 H), 7.77 (0.5 H), and mass spectrum M^+ = 808, using identical analytical conditions. Rotational isomerism of these formamides resulted in multiplicity of NMR signals, thus precluding meaningful full spectroscopic data.

(*S*)-4-Ethyl-5-[(*tert*-butyldimethylsilyl)oxy]pentanal (37a). At −78 °C, 122 mL (0.196 mol) of a 1.6 M solution of *n*-butyllithium was added dropwise to a stirred solution of 34.90 g (0.197 mol) of (4*R*,5*S*)-4-methyl-5-phenyloxazolidone in 300 mL of tetrahydrofuran (distilled from sodium–benzophenone). After stirring for 1 h at −78 °C, 20.46 mL (0.197 mol) of butyryl chloride in 25 mL of tetrahydrofuran was then injected over a 30-min period. The mixture was then allowed to come to 20 °C and stirred at 20 °C for 24 h. It was then poured into 200 mL of saturated ammonium chloride. The organic layer was separated and the aqueous portion extracted with 3 × 200 mL of dichloromethane. The combined organic solutions were washed with 200 mL of saturated sodium bicarbonate and 200 mL of saturated brine, dried ($MgSO_4$), and concentrated under vacuum. The residue was adsorbed onto 50 g of silica gel, which was then placed on a 4 × 30 cm dry column of silica gel. Elution with 10% ethyl acetate in hexanes, collecting 50-mL fractions, gave 43.1 g (88%) of the imide **39**, mp 55–56 °C, on concentration of fractions 5–16: 250-MHz ^1H NMR ($CDCl_3$) δ 0.89 (d, J = 7 Hz, 3 H), 1.00 (t, J = 7 Hz, 3 H), 1.71 (sex., J = 7 Hz, 2 H), 2.80–3.04 (m, 2 H), 4.77 (p, J = 7 Hz, 1 H), 5.67 (d, J = 7 Hz, 1 H), 7.29–7.32 (m, 2 H), 7.36–7.45 (m, 3 H).

Lithium diisopropylamide was prepared by dropwise addition (over 30 min) of 97.5 mL (0.151 mol) of *n*-butyllithium in hexanes to 21.1 mL (0.151 mol) of diisopropylamine in 300 mL of dry tetrahydrofuran at 0 °C. The solution was then cooled to −78 °C, and 34.94 g (0.141 mol) of the imide **39**, in 100 mL of dry tetrahydrofuran, was then added dropwise over a 1-h period. After stirring at −78 °C for 2 h, 36.7 mL (0.424 mol) of allyl bromide in 50 mL of tetrahydrofuran was then added dropwise over 30 min. After stirring at −78 °C for 6 h and at 0 °C for 10 h, 200 mL of saturated ammonium chloride solution was added. The organic solution was separated and the aqueous phase extracted with 3 × 200 mL of dichloromethane. Washing of the combined organic solutions with 300 mL of 1 N HCl, 300 mL of saturated sodium bicarbonate, and 300 mL of saturated brine and concentration of the dried ($MgSO_4$) solutions under vacuum gave an oil, which was chromatographed. Adsorption of the concentrate onto 50 g of silica gel, which was then placed on a 4 × 30 cm dry column of silica gel, and elution with 5% ethyl acetate in hexanes, collecting 50-mL fractions, gave in fractions 3–11, after concentration and distillation at 170 °C (0.05 mm, Kugelrohr), 27.85 g (61%) of the olefin **40a**. HPLC of this product showed only the diastereomer **40a**, t_R 1.82 min, and none of the diastereomer **40b**, t_R 1.79 min (silica gel Microsorb column, 4.6 mm × 25 cm, 5-μm spherical SiO_2, 15% ethyl acetate in hexane, 1.0 mL/min, 450–550 psi, R.I. detector); 250-MHz ^1H NMR ($CDCl_3$): δ 0.86 (d, J = 6 Hz, 3 H), 0.94 (t, J = 7 Hz, 3 H), 1.58 (sept, J = 8 Hz, 1 H), 1.73 (sept, J = 8 Hz, 1 H), 2.33 (sept, J = 7 Hz, 1 H), 2.42 (sept, J = 7 Hz, 1 H), 2.87 (p, J = 7 Hz, 1 H), 4.98–5.08 (m, 2 H), 5.66 (d, J = 7 Hz, 1 H), 5.81 (ddt, J = 17, 10, 7 Hz, 1 H), 7.27–7.35 (m, 2 H), 7.37–7.46 (m, 3 H).

To 14.68 g (51.1 mmol) of the imide **40a** in 200 mL of dry tetrahydrofuran was added dropwise 153.3 mL (153.3 mmol) of a 1 M solution of lithium aluminum hydride in tetrahydrofuran at 0 °C, over 2 h. The mixture was stirred for 6 h at 0 °C, and then 5.8 mL of 15% sodium hydroxide solution was added dropwise, over 2 h, at 0 °C, followed by 17 mL of water. Addition of 600 mL of 2 N HCl, extraction with 3 × 300 mL of dichloromethane, washing of the combined extracts with 300 mL of brine, and concentration of the dried ($MgSO_4$) solutions produced a yellow oil. This crude product was adsorbed on 50 g of silica gel and then placed on a 4 × 30 cm dry silica gel column. Elution with 2:1 hexane–ether, collecting 50-mL fractions, gave 2.47 g (59%), bp 70 °C (17 mm), of (*S*)-2-ethyl-4-pentenol (**41a**) from concentration of fractions 2–28 and distillation: 250-MHz ^1H NMR ($CDCl_3$) δ 0.91 (t, J = 7 Hz, 3 H), 1.32 (sex., J = 7 Hz, 1 H), 1.34 (sept, J = 7 Hz, 1 H), 1.52 (sex., J = 6 Hz, 1 H), 2.11 (t, J = 6 Hz, 2 H), 2.38 (s, 1 H), 3.53 (d, J = 6 Hz, 2 H), 4.98–5.09 (m, 2 H), 5.80 (ddt, J = 17, 10, 7 Hz, 1 H); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 137.06, 115.84, 64.96, 41.98, 35.22, 23.17, 11.07; IR (neat) ν_{max} 3341, 3030, 2963, 2925, 2877 1639, 1457, 1438, 1040, 1014, 911, 667 cm^{-1}.

To 2.18 g (19.1 mmol) of (*S*)-2-ethyl-4-pentenol (**41a**) in 100 mL of dry dichloromethane and 5.02 mL (28.7 mol) of *N*,*N*-diisopropylethylamine was added, dropwise, 3.46 g (22.9 mmol) of *tert*-butyldimethylsilyl chloride in 10 mL of dichloromethane. After 24 h, 10 mL of water was added and the mixture stirred for 30 min. It was then partitioned between 200 mL of saturated sodium bicarbonate and 2 × 100 mL of dichloromethane. The dried ($MgSO_4$) organic extract was then concentrated and the residue subjected to chromatography on a 4 × 30 cm dry column of silica gel. Elution with hexanes gave the silyl ether **42a** on concentration of the first 1.55 L of eluate. The compound was distilled, at bp 100 °C (18 mm), to provide 3.68 g (84%): IR (neat) ν_{max} 3078, 2958, 2930, 2899, 2859, 1472, 1464, 1438, 1255, 1096, 1065, 1006, 994, 912, 837, 775, 667 cm^{-1}; 250-MHz ^1H NMR ($CDCl_3$) δ −0.01 (s, 6 H), 0.84 (t, J = 7 Hz, 3 H), 0.88 (s, 9 H), 1.30 (sex., J = 7 Hz, 1 H), 1.33 (sex., J = 6 Hz, 1 H), 1.45 (sex., J = 6 Hz, 1 H), 3.47 (d, J = 5 Hz, 1 H), 4.95–5.03 (m, 2 H), 5.76 (ddt, J = 17, 10, 7 Hz, 1 H); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 137.43, 115.61, 64.85, 42.25, 35.22, 25.99, 23.33, 18.35, 11.32, −2.38, −2.44.

Hydroboration of 2.25 g (9.87 mmol) of the olefin **42a** in 50 mL of dry tetrahydrofuran was obtained by dropwise addition of 21.7 mL (10.9 mmol) of a 0.5 M solution of 9-borabicyclo[3.3.1]nonane in tetrahydrofuran over 15 min. After stirring of the mixture for 24 h at 20 °C, it was cooled to 0 °C and 5 mL of water was added. The reaction mixture was allowed to warm to 20 °C, and then a solution of 10 mL of 3 M sodium hydroxide was added dropwise, over 15 min, followed by 10 mL of 30% hydrogen peroxide, added over 1.5 h. The heterogeneous mixture was stirred for 18 h and then poured into 150 mL of saturated brine. Separation of the organic layer, extraction of the organic phase with 3 × 100 mL of dichloromethane, and concentration of the dried ($MgSO_4$) organic solutions under vacuum provided a crude product, which was subjected to chromatography on a 4 × 20 cm silica gel dry column. Elution with hexane–ether (2:1) and collection of 50-mL fractions gave, after distillation, 1.89 g (78%) of alcohol product **43a**: bp 94 °C (0.01 mmol, Kugelrohr); IR (neat) ν_{max} 3325, 2957, 2930, 2899, 2859, 1472, 1463, 1254, 1095, 1069, 1006, 837, 814, 775, 668 cm^{-1}; 250-MHz ^1H NMR ($CDCl_3$) δ −0.01 (s, 6 H), 0.82 (t, J = 7 Hz, 3 H), 0.84 (s, 9 H), 1.20–1.39 (m, 5 H), 1.46 (p, J = 8 Hz, 2 H), 2.13 (s, 1 H), 3.43–3.46 (m, 2 H), 3.56 (t, J = 7 Hz, 2 H); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 65.26, 63.12, 41.79, 30.89, 26.71, 25.87, 18.22, 11.09, −2.48, −2.55.

The preceding alcohol product **43a**, 3.782 g (15.3 mmol), dissolved in 15 mL of dry dichloromethane, was added to 4.962 g (23.0 mmol) of pyridinium chlorochromate and 0.60 g (7.3 mmol) of sodium acetate in 50 mL of dry dichloromethane, resulting in an exothermic reaction. The mixture was stirred at 20 °C for 2 h, when TLC analysis showed the absence of the starting alcohol. Silica gel (50 g) and 100 mL of diethyl ether were then added to the stirred reaction mixture, and the resultant slurry was then poured onto a 4 × 20 cm dry column of silica gel. The column was eluted with 3 L of ether, the eluate concentrated under vacuum, and the residue dissolved in 200 mL of dichloromethane. The solution was washed with 2 × 200 mL of 10% copper sulfate solution, followed by 100 mL of brine. Concentration of the dried ($MgSO_4$) solution under vacuum and distillation of the residual oil gave 2.72 g (72%) of the aldehyde **37a**: bp 64–65 °C (0.1 mm); IR (neat) ν_{max} 2958, 2931, 2899, 2881, 2859, 1712, 1472, 1463, 1413, 1255, 1142, 1097, 1065, 1007, 939, 837, 813, 756 cm^{-1}; 250-MHz ^1H NMR ($CDCl_3$) δ −0.02 (s, 6 H), 0.83 (s, 9 H), 0.83 (t, J = 7 Hz, 3 H), 1.17–1.40 (m, 3 H), 1.53–1.69 (m, 2 H), 2.40 (t, d, J = 7, 2 Hz, 2 H), 3.38–3.51 (m, 2 H), 9.71 (t, J = 2 Hz, 1 H); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 202.66, 64.86, 41.56, 31.73, 25.87, 23.53, 23.28, 18.23, 11.17, −2.40, −2.47.

(*R*)-4-Ethyl-5-[(*tert*-butyldimethylsilyl)oxy]pentanal (37b). Acylation of 10.0 g (0.056 mol) of (4*R*,5*S*)-4-methyl-5-phenyloxazolidone with 8.27 g (0.056 mol) of 4-pentenoyl chloride, according to the procedure given above for preparation of the imide **39**, provided 14.58 g (90%) of the imide **44**, mp 73–74 °C.

A reaction of 32.79 g (0.126 mol) of the imide **44**, as its lithium enolate, with 30.33 mL (0.379 mol) of ethyl iodide, using the procedure given above for alkylation of the imide **39** with allyl

bromide, provided 25.83 g (71%) of the alkylation product **40b**, bp 171 °C (0.05 mm, Kugelrohr). HPLC analysis of this product showed a 92:8 ratio of diastereomers **40b**:**40a** with t_R 1.79 min, 1.82 min (HPLC conditions as given for preparation of **40a**, above).

Transformation of the imide alkylation product **40b** to the aldehyde **37b** was carried out by the procedure given for the transformation of the diastereomer **40a** to **37a**. Thus the lithium aluminum hydride step gave a 56% yield, the silylation 77%, the hydroboration and oxidation 70%, and the PCC oxidation 58%.

Syntheses and Separation of the Diastereomeric *N*-Acyl-4-methyl-5-phenyloxazolidones 40a and 40b. At −78 °C, 10.2 g (0.0999 mol) of methyl butanoate, in 25 mL of dry tetrahydrofuran, was added dropwise, over 1 h, to lithium diisopropylamide, prepared at 0 °C in 75 mL of tetrahydrofuran from 14.28 mL (0.102 mol) of *N,N*-diisopropylamine and 66 mL (0.102 mol) of 1.5 M *n*-butyllithium in hexane. After 2 h at −78 °C, a solution of 18.12 g (0.150 mol) of allyl bromide in 30 mL of tetrahydrofuran was added dropwise over 1 h. The mixture was stirred at −78 °C for 5 h and at 0 °C for 15 min. It was then poured into 400 mL of 10% aqueous HCl and extracted with 3 × 100 mL of dichloromethane. The extracts were washed with 200 mL of saturated sodium bicarbonate and brine solutions, dried ($MgSO_4$), concentrated, and distilled to give 12.34 g (86.9%) of methyl 2-allylbutyrate, bp 88–89 °C (15 min). This ester was hydrolyzed by heating with 30 mL of water and 5.70 g (0.144 mmol) of sodium hydroxide at reflux for 2 h. Addition of 200 mL of 2 N HCl to the cooled reaction mixture and extraction with dichloromethane gave, after drying ($MgSO_4$), concentration, and distillation, 9.10 g (82%) of 2-allylbutyric acid, bp 112 °C (15 mm).

To 9.10 g (0.071 mol) of 2-allylbutyric acid in 100 mL of dry dichloromethane was added, at 0 °C, 7.45 mL (0.085 mol) of oxalyl chloride, over a 1-h period. After 1 h at 0 °C and 1 h at 20 °C, the mixture was concentrated and distilled to give 10.4 g (100%) of the acid chloride, bp 57 °C (21 mm).

Acylation of (4*R*,5*S*)-4-methyl-5-phenyloxazolidone with this acid chloride, following the procedure given above for butyryl chloride, produced an 81% yield of a mixture of diastereomers **40a** and **40b**. Separation of 1.0 g of this mixture by medium-pressure chromatography on one 25 mm × 50 cm and two 25 mm × 1 m tandem columns of Merck silica gel 60, 230–400 mesh, eluting with 15% ethyl acetate in hexane at 11 mL/min and collecting 25-mL fractions, gave 0.27 g of the (2*R*)-2-allylbutyramide **40b** in fractions 6–17, an overlap of diastereomers **40a** and **40b** in fractions 18–29 (0.43 g), and 0.30 g of the 2*S* isomer **40a** in fractions 30–46. Rechromatography with the same system then provided a further 0.19 g of **40b** and 0.21 g of **40a**.

Formation of N^b-Benzyl-21-[(*tert*-butyldimethylsilyl)oxy]-*D*-*seco*-Ψ-vincadifformines 45a and 46a. A solution of 1.50 g (6.1 mmol) of the indoloazepine **9** and 1.50 g (6.1 mmol) of the aldehyde **37a** in 50 mL of dry tetrahydrofuran was stirred for 24 h. The solvent was evaporated under vacuum and the residue dissolved in 25 mL of dichloromethane and adsorbed onto 50 g of silica gel, with evaporation of the solvent. The resulting material was placed on a 4 × 30 cm dry column of silica gel. Elution with 50:15:1 pentane–ether–triethylamine, collecting 10-mL fractions, gave in fractions 6–30 one diastereomeric isomer pair and in fractions 41–73 the other diastereomeric isomer pair of the bridged indoloazepine. The eluate fractions were combined and concentrated under vacuum. Addition of 100 mL of dry toluene and concentration under vacuum provided 2.54 g (81%) of the bridged indoloazepine isomers.

To a solution of 2.00 g (4.25 mmol) of this condensation product in 125 mL of dry diethyl ether was added 0.51 mL (4.25 mmol) of benzyl bromide. The mixture was heated at reflux for 93 h, when TLC indicated completed consumption of the starting amine. Filtration of the cooled mixture and drying of the quaternary salts under vacuum gave 2.65 g (97%).

A mixture of 2.50 g (3.89 mmol) of the quaternary salts, 75 mL of methanol, and 1.09 mL (7.8 mmol) of triethylamine was heated at reflux for 10 h. The cooled solution was then poured into 300 mL of 1 M ammonium hydroxide in saturated brine. Extraction with 3 × 100 mL of dichloromethane and concentration of the dried ($MgSO_4$) extracts under vacuum provided a foam, which was subjected to centrifugal chromatography on a 4-mm silica gel plate. Elution with 1:3 ether–hexanes and concentration of the eluate provided 1.89 g (86%) of the compounds **45a** and **46a**; 250-MHz ^{1}H NMR ($CDCl_3$), 1:1 mixture of **45a** and **46a**: δ 9.05, 8.99 (s, NH, 1 H), 3.80, 3.79 (s, CO_2CH_3, 3 H), 0.76, 0.75 (t, J = 7 Hz, CH_2CH_3, 3 H).

Hydrolysis of these silyl ethers was achieved by solution of 1.00 g (1.78 mmol) in 35 mL of tetrahydrofuran and 17 mL of water and addition of 6.78 g (35.6 mmol) of *p*-toluenesulfonic acid. After being stirred for 80 min, the solution was basified to pH 10 with saturated potassium carbonate and extracted with 3 × 100 mL of ether and 2 × 100 mL of dichloromethane. The dried ($MgSO_4$) combined extracts were concentrated under vacuum and then chromatographed on a 3 cm × 25 cm column of silica gel, which was eluted with diethyl ether to provide 0.729 g (92%) of a 1:1 mixture of the diastereomeric alcohols **16a** and **17a**.

Formation of N^b-Benzyl-21-[(*tert*-butyldimethylsilyl)oxy]-*D*-*seco*-Ψ-vincadifformines 45b and 46b. Condensation of 2.00 g (8.19 mmol) of the indoloazepine **9** with 2.00 g (8.19 g) of the aldehyde **37b**, according to the procedure given for the enantiomer **37a**, provided 2.94 g (76%) of the condensation products. On N-benzylation of 1.14 g of these products, 1.50 g (96%) of quaternary salts was obtained. Rearrangement of these salts with triethylamine in methanol, according to the preceding procedure, gave 1.10 g (84%) of the title products; 250-MHz ^{1}H NMR ($CDCl_3$), 1:1 mixture of **45b** and **46b**: δ 9.05, 8.96 (s, NH, 1 H), 3.81 (s, CO_2CH_3, 3 H), 0.76, 0.74 (t, J = 7 Hz, CH_2CH_3, 3 H). Hydrolysis of the silyl ether function then provided the alcohols **16b** and **17b** (92%).

20-*epi*-Ψ-Vincadifformine (15). A solution of 0.100 g (0.166 mmol) of the tosylate **19** in 50 mL of dry toluene was heated at reflux under argon for 30 h, when TLC showed the absence of starting material. The solvent was evaporated under vacuum and the residual quaternary salt dissolved in 10 mL of acetic acid. Addition of 15 mg of 10% Pd–C and hydrogenation at atmospheric pressure resulted in a 4-mL uptake of hydrogen in 3 h. Filtration and partitioning of the filtrate between 60 g of ice, 50 mL of concentrated ammonium hydroxide, and 3 × 60 mL of dichloromethane and concentration of the dried extracts gave a crude product, which was subjected to centrifugal chromatography on a 2-mm silica gel plate eluted with 1:3 ether–hexane, to give 0.050 g (89%) of 20-*epi*-Ψ-vincadifformine. The product was matched by comparison spectra with an authentic sample.[9] (Under the same conditions, tosylate **18** did not react and it was recovered unchanged.)

20-*epi*-Ψ-Vincadifformine (15) and Its D/E-Trans Diastereomer 55. A solution of 0.100 g (0.166 mmol) of the tosylate **19** in 10 mL of acetic acid was subjected to hydrogenation over 0.20 g of 10% Pd–C. After stirring for 4 h at atmospheric pressure, 4.1 mL of hydrogen had been consumed. The mixture was filtered and the filtrate poured into 70 g of ice and 50 mL of concentrated ammonium hydroxide. Extraction with 3 × 75 mL of dichloromethane and concentration of the dried ($MgSO_4$) extract gave the secondary amines **53** and **54**. A solution of the debenzylation product in 50 mL of dry toluene was heated at reflux for 24 h. The solvent was evaporated under vacuum and the residue partitioned between 25 mL of 10% ammonium hydroxide saturated with sodium chloride and 50 mL of dichloromethane. The dried ($MgSO_4$) extract was concentrated. HPLC on a 5-μm Microsorb silica gel column (4.6 mm × 25 cm) and a 4.6 mm × 3 cm guard column, eluted with 6% methanol in dichloromethane at 1 mL/min, showed a 3:1 ratio of *D/E-cis*-Ψ-vincadifformine **15**, t_R 3.8 min, and its D/E-trans diastereomer **55**, t_R 6.7 min. Preparative separation of products **15** and **55** was obtained by centrifugal chromatography on a 2-mm silica gel plate, eluted with 1:1 ether–hexane at 1.5 mL/min. Fractions 2–8 gave the D/E-cis compound **15**, and fractions 11–18 gave the D/E-trans product **55**. Further purification by preparative HPLC under the above conditions provided 0.041 g (73%) of product **55** and 0.0125 g (22%) of product **15**.

For **15**: TLC R_f 0.54 (1:1 ether–hexane, CAS blue-yellow center).[9] NMR and mass spectra matched those of an authentic sample.[9] For **55**: TLC R_f 0.25 (1:1 ether–hexane), 0.29 (5% methanol in dichloromethane), CAS purple-yellow center; UV (ethanol) λ_{max} 200, 222, 293, 327 nm; IR (KBr) ν_{max} 3354, 3049, 3012, 2955, 2944, 2921, 2858, 2808, 2789, 1679, 1608, 1475, 1464, 1435, 1379, 1357, 1336, 1320, 1282, 1264, 1239, 1215, 1195, 1168, 1133, 1093, 1038, 1014, 987, 878, 777, 748, 662, 653 cm^{-1}; 250-MHz ^{1}H NMR ($CDCl_3$) δ 0.97 (t, J = 7 Hz, 3 H), 1.47–1.82 (m, 7 H),

1.90–2.12 (m, 2 H), 2.43–2.64 (m, 2 H), 2.88 (dd, J = 13, 5 Hz, 1 H), 3.09 (t, d, J = 10, 2 Hz, 1 H), 3.23 (d, d, J = 13, 4 Hz, 1 H), 3.46 (d, d, J = 18, 9 Hz, 1 H), 3.74 (s, 3 H), 6.76 (d, J = 8 Hz, 1 H), 6.84 (t, d, J = 7, 1 Hz), 7.10 (t, d, J = 7, 1 Hz, 1 H), 7.50 (d, J = 7 Hz, 1 H), 9.01 (s, 1 H); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 168.91, 164.05, 144.25, 137.35, 127.59, 122.98, 120.78, 109.13, 94.44, 65.08, 55.24, 52.45, 50.83, 50.21, 40.97, 36.15, 34.26, 30.81, 28.31, 27.97, 12.51; mass spectrum, m/z (relative intensity) 339 (14), 338 (M^+, 64), 279 (5), 278 (5), 240 (7), 206 (5), 194 (13), 193 (9), 182 (5), 181 (5), 180 (14), 168 (9), 167 (24), 166 (11), 154 (8), 139 (5), 125 (11), 124 (100), 110 (7), 91 (9), 88 (5), 86 (32), 85 (7), 84 (69), 83 (19), 73 (65), 63 (7), 61 (6), 59 (6), 58 (9), 57 (16), 56 (9), 55 (23), 51 (28), 50 (8). Anal. Calcd for $C_{21}H_{26}N_2O_2$: C, 74.51; H, 7.75; N, 8.28. Found: C, 74.21; H, 8.01; N, 8.16.

Ψ-Vincadifformine (14) and Its D/E-Trans Diastereomer 52. The preceding procedure for preparation of the 20-epi diastereomers **15** and **55**, but using 0.10 g of the tosylate **18**, required 120 h for completion of the ring-closure reaction of the secondary amine tosylates. HPLC under the above conditions, except for elution with 2% methanol in dichloromethane, showed a 73:19 ratio of D/E-trans product **52**, HPLC t_R 4.5 min, to D/E-cis product **14**, t_R 5.3 min. Preparative separation gave 0.040 g (71%) of **52** and 0.010 g (18%) of **14**.

For **14**: TLC R_f 0.70 (1:1 ether–hexane), CAS blue-yellow center. NMR and mass spectra matched those of an authentic sample.[9]

For **52**: TLC R_f (1:1 ether–hexane) 0.32 (2% methanol–dichloromethane), CAS purple-yellow center; UV (ethanol) λ_{max} 202, 223, 296, 325 nm; IR (KBr) ν_{max} 3358, 3052, 2983, 2965, 2956, 2926, 2911, 2884, 2870, 2854, 2836, 1665, 1607, 1478, 1466, 1455, 1432, 1380, 1367, 1350, 1340, 1337, 1315, 1304, 1278, 1265, 1233, 1211, 1199, 1163, 1153, 1130, 1120, 1103, 1082, 1075, 1053, 1039, 1015, 974, 882, 775, 752, 668 cm^{-1}; 250-MHz ^{1}H NMR ($CDCl_3$) δ 0.80–0.95 (m, 2 H), 0.92 (t, J = 7 Mz, 3 H), 1.12–1.27 (m, 2 H), 1.67–2.02 (m, 6 H), 2.36–2.66 (m, 2 H), 2.72 (t, J = 10 Hz, 1 H), 3.04–3.26 (m, 2 H), 3.73 (s, 3 H), 6.74 (d, J = 8 Hz, 1 H), 6.82 (t, d, J = 7, 1 Hz, 1 H), 7.08 (t, d, J = 7, 1 Hz, 1 H), 7.51 (d, J = 7 Hz, 1 H), 9.03 (s, 1 H); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 169.09, 164.22, 143.97, 137.65, 127.40, 123.14, 120.86, 111.00, 109.09, 94.35, 66.78, 55.01, 54.11, 50.83, 46.33, 44.22, 36.84, 32.24, 32.07, 30.02, 27.12, 11.23. Anal. Calcd for $C_{21}H_{26}N_2O_2$: C, 74.51; H, 7.75; N, 8.28. Found: C, 74.27; H, 8.00; N, 8.17.

Reduction of 20-*epi*-Ψ-Vincadifformine (15). A solution of 0.386 g (1.14 mmol) of 20-*epi*-Ψ-vincadifformine (**15**) in 25 mL of acetic acid was heated at 90 °C, and with rapid stirring, 0.443 g (11.4 mmol) of sodium borohydride was added in small portions over 30 min. After 10 min the reaction mixture was poured into 100 mL of concentrated ammonium hydroxide and 100 mL of crushed ice and extracted with 3 × 50 mL of dichloromethane. The dried ($MgSO_4$) extract was then concentrated under vacuum and subjected to centrifugal chromatography on a 2-mm silica gel plate, eluting with dichloromethane and ethyl acetate (15:1). fractions 6–24 mL gave 0.166 g (43%) of the 16α-carbomethoxy product **70**, and a mixture of products **71** and **72** was obtained in fractions 26–77 mL. Rechromatography of the latter and elution with 10:1 hexane–acetone gave 0.110 g (28%) of the indoline **72** in fractions 7–28 mL and 0.097 g (25%) of the indole **71** in fractions 33–47 mL.

For **70**: from methanol, mp 137–138 °C (120–121 °C); UV (ethanol) λ_{max} 232, 279, 286, 293 nm; IR (KBr) ν_{max} 3394, 3059, 3043, 3021, 3002, 2961, 2951, 2922, 2840, 2774, 2772, 2705, 2643, 1720, 1489, 1460, 1434, 1372, 1336, 1309, 1300, 1283, 1263, 1245, 1233, 1194, 1117, 1151, 1132, 1090, 1078, 1044, 1005, 982, 959, 910, 810, 762, 744, 617 cm^{-1}; 250-MHz ^{1}H NMR ($CDCl_3$) δ 0.93 (t, J = 7 Hz, 3 H), 0.98–1.28 (m, 3 H), 1.64 (d, J = 16 Hz, 1 H), 1.76–1.90 (m, 2 H), 1.96 (d, J = 14 Hz, 1 H), 2.09 (t, J = 10 Hz, 2 H), 2.21–2.38 (m, 2 H), 2.46–2.64 (m, 2 H), 2.81–2.90 (m, 2 H), 3.04 (dd, J = 15, 4 Hz, 1 H), 3.68 (s, 3 H), 5.53 (dd, J = 12, 1 Hz, 1 H), 7.07 (t, d, J = 7, 1 Hz, 1 H), 7.13 (t, d, J = 7, 1 Hz, 1 H), 7.32 (d, J = 7 Hz, 1 H), 7.49 (d, J = 7 Hz, 1 H), 8.59 (s, 1 H); 62.9-MHz ^{13}C NMR ($CDCl_3$) δ 11.39, 26.54, 27.79, 31.23, 36.17, 39.23, 40.43, 42.05, 52.04, 54.18, 55.90, 60.75, 110.63, 111.63, 118.19, 118.95, 121.45, 127.86, 133.92, 135.86, 175.68; mass spectrum, m/z (relative intensity) 341 (9), 340 (M^+, 38), 281 (4), 254 (4), 216 (4), 215 (27), 210 (24), 182 (4), 180 (5), 170 (10), 169 (9), 168 (7), 167 (6), 156 (8), 155 (5), 154 (9), 144 (5), 143 (4), 141 (5), 140 (6), 139 (12), 138 (100), 137 (13), 136 (4), 130 (6), 129 (7), 128 (7), 127 (6), 126 (24), 125 (9), 124 (32), 123 (6), 122 (6), 115 (5), 112 (5), 110 (10), 108 (7), 103 (5), 97 (4), 96 (14), 95 (4), 94 (4), 86 (8), 84 (15), 83 (11), 82 (28), 81 (6), 77 (5), 70 (5), 69 (5), 68 (8), 67 (9). Anal. Calcd for $C_{21}H_{28}N_2O_2$: C, 74.08; H, 8.29; N, 8.23. Found: C, 74.27; H, 8.15; N, 8.11. Exact mass calcd 340.215, found 340.208.

For **71**: from methanol, mp 214–215 °C; UV (ethanol) λ_{max} 233, 278, 286, 293 nm; IR (KBr) ν_{max} 3396, 3084, 3060, 3043, 3018, 2994, 2959, 2949, 2925, 2888, 2815, 2782, 2753, 1724, 1484, 1459, 1430, 1369, 1348, 1334, 1302, 1262, 1245, 1234, 1221, 1204, 1190, 1167, 1131, 1116, 1093, 1064, 1035, 1008, 968, 942, 932, 907, 807, 741, 725, 711, 626 cm^{-1}; 250-MHz ^{1}H NMR ($CDCl_3$) δ 0.71 (t, J = 7 Hz, 3 H), 0.96–1.16 (m, 3 H), 1.38–1.52 (m, 2 H), 1.86–2.05 (m, 4 H), 2.18–2.33 (m, 2 H), 2.42–2.55 (m, 2 H), 2.87–2.95 (m, 2 H), 3.51 (d, J = 11 Hz, 1 H), 3.75 (s, 3 H), 3.93 (dd, J = 6, 1 Hz, 1 H), 7.07 (td, J = 7, 1 Hz, 1 H), 7.13 (td, J = 7, 1 Hz, 1 H), 7.33 (dd, J = 7, 1 Hz, 1 H), 7.50 (d, J = 7 H, 1 H), 8.97 (s, 1 H); 62.9-MHz ^{13}C NMR ($CDCl_3$) δ 11.37, 22.21, 27.38, 32.96, 33.29, 36.46, 36.96, 39.19, 50.80, 52.26, 52.64, 61.49, 109.83, 110.75, 117.72, 118.81, 121.90, 128.07, 135.21, 135.33, 176.51; mass spectrum, m/z (relative intensity) 341 (5), 340 (M^+, 23), 281 (3), 211 (4), 210 (34), 182 (3), 180 (4), 170 (8), 169 (7), 168 (5), 167 (4), 156 (6), 155 (4), 154 (7), 144 (4), 143 (3), 141 (3), 140 (5), 139 (13), 138 (100), 137 (13), 136 (3), 130 (5), 129 (5), 128 (6), 127 (3), 126 (3), 125 (6), 124 (19), 123 (5), 122 (5), 115 (4), 110 (8), 108 (6), 97 (4), 96 (11), 95 (3), 94 (3), 89 (4), 84 (4), 83 (9), 82 (25), 81 (4), 77 (3), 70 (4), 69 (4), 68 (7), 67 (7). Anal. Calcd for $C_{21}H_{28}N_2O_2$: C, 74.08; H, 8.29; N, 8.23. Found: C, 74.00; H, 8.25; N, 8.07. Exact mass calcd 340:215, found 340:210.

Reduction of Ψ-Vincadifformine (14). According to a procedure analogous to the one used for the 20-epi compound **15**, 0.406 g (1.20 mmol) of Ψ-vincadifformine was reduced in hot acetic acid with sodium borohydride to give 0.297 g (73%) of the 16α-carbomethoxy product **67**, 0.10 g (24%) of its 16β-carbomethoxy epimer **68**, and 0.013 g (3%) of the indoline **69**.

For **67**: from methanol, mp 179–180 °C; UV (ethanol) λ_{max} 234, 279, 287, 294 nm; IR (KBr) ν_{max} 3394, 3052, 3031, 2997, 2957, 2920, 2904, 2887, 2873, 2860, 2797, 1716, 1459, 1442, 1431, 1328, 1306, 1282, 1267, 1245, 1167, 1135, 1122, 1104, 1073, 1061, 1044, 1018, 1008, 928, 803, 726, 686, 597 cm^{-1}; 250-MHz ^{1}H NMR ($CDCl_3$) δ 0.89 (t, J = 7 Hz, 3 H), 1.23–1.42 (m, 3 H), 1.43–1.55 (m, 2 H), 1.74–1.81 (m, 1 H), 1.84 (d, J = 13 Hz, 1 H), 2.04 (d, J = 12 Hz, 1 H), 2.13–2.38 (m, 3 H), 2.43–2.54 (m, 2 H), 2.65 (t, J = 9 Hz, 1 H), 2.87–2.91 (m, 2 H), 3.69 (s, 3 H), 5.08 (d, J = 10 Hz, 1 H), 7.07 (td, J = 7, 1 Hz, 1 H), 7.14 (td, J = 7, 1 Hz, 1 H), 7.32 (d, J = 7 Hz, 1 H), 7.48 (d, J = 7 Hz, 1 H), 8.65 (s, 1 H); 62.9-MHz ^{13}C NMR ($CDCl_3$) δ 11.67, 26.49, 28.66, 31.09, 32.15, 34.82, 37.63, 38.62, 51.29, 51.90, 52.11, 59.01, 110.66, 111.93, 118.25, 119.02, 121.57, 127.78, 133.99, 136.01, 175.56; mass spectrum, m/z (relative intensity) 341 (9), 340 (M^+, 34), 254 (5), 215 (15), 211 (5), 210 (35), 182 (4), 180 (4), 170 (9), 169 (8), 168 (6), 167 (5), 156 (7), 155 (5), 154 (8), 144 (5), 143 (4), 141 (5), 140 (6), 139 (12), 138 (100), 137 (19), 130 (5), 129 (6), 128 (7), 127 (5), 126 (16), 125 (8), 124 (36), 122 (4), 112 (4), 110 (12), 97 (6), 96 (15), 95 (4), 94 (4), 86 (4), 84 (10), 83 (11), 82 (29), 81 (5), 77 (8), 70 (5), 69 (6), 68 (8), 67 (8). Anal. Calcd for $C_{21}H_{28}N_2O_2$: C, 74.08; H, 8.21; N, 8.23. Found: C, 74.16; H, 8.40; N, 8.18. Exact mass calcd 340.215, found 340.212.

For **68**: from methanol, mp 172–174 °C; UV (EtOH) λ_{max} 231, 280, 286, 294 nm; IR (film) ν_{max} 3440, 3058, 3028, 2955, 2929, 2874, 2792, 2758, 1726, 1663, 1609, 1461, 1437, 1370, 1337, 1320, 1299, 1269, 1244, 1198, 1167, 1123, 1109, 1079, 1065, 1041, 1009, 908, 734, 648, 599 cm^{-1}; 250-MHz ^{1}H NMR ($CDCl_3$) δ 0.58 (t, J = 7 Hz, 3 H), 0.87–1.04 (m, 3 H), 1.20–1.32 (m, 2 H), 1.62 (dt, J = 13, 6 Hz, 1 H), 1.85–2.00 (m, 1 H), 2.04–2.19 (m, 3 H), 2.25–2.40 (m, 2 H), 2.52–2.62 (m, 1 H), 2.81–3.04 (m, 2 H), 3.36 (dd, J = 11, 1 Hz, 1 H), 3.72 (s, 3 H), 3.97 (dd, J = 8, 2 Hz, 1 H), 7.05 (td, J = 7, 1 Hz, 1 H), 7.11 (td, J = 7, 1 Hz, 1 H), 7.30 (dd, J = 7, 1 Hz, 1 H), 7.48 (dd, J = 8, 1 Hz, 1 H), 8.77 (s, 1 H); 62.9-MHz ^{13}C NMR $CDCl_3$) δ 12.79, 22.28, 28.67, 32.93, 33.96, 36.48, 37.67, 39.96, 49.65, 52.34, 52.24, 58.49, 110.71, 111.33, 117.80, 118.80, 121.10, 127.86, 133.79, 135.47, 175.90; mass spectrum, m/z (relative intensity) 341 (6), 340 (M^+, 20), 339 (6), 338 (7), 281 (4), 211 (5), 210 (35), 182 (4), 180 (4), 170 (8), 169 (8), 168 (7), 167 (6), 156 (8), 155 (5), 154 (11), 144 (5), 142 (5), 140 (7), 139 (13), 138 (100), 137 (17), 136 (9), 130 (7), 129 (7), 128 (6), 127 (4), 126 (4), 125 (7), 124 (45), 123 (4), 122 (9), 115 (6), 110 (11), 109 (4), 108 (8),

97 (5), 96 (14), 95 (4), 94 (5), 84 (4), 83 (11), 82 (30), 81 (6), 79 (4), 77 (6); exact mass calcd 340.215, found 340.210.

Syntheses of the C16′–C14′ Pref 20′-Deoxyvinblastine Diastereomers 63–66. To a solution of 0.410 g (1.21 mmol) of racemic Ψ-vincadifformine (**14**) in 50 mL of dichloromethane and 0.18 mL (1.33 mmol) of triethylamine, at 0 °C, was added 0.155 mL (1.33 mmol) of *tert*-butyl hypochlorite. After 10 min at 0 °C, the mixture was washed with 50 mL of iced water, and the latter was back-extracted with 2 × 25 mL of dichloromethane. The dried ($MgSO_4$) organic solutions were concentrated under vacuum and the resulting chloroimines **56** dissolved in 10 mL of acetone, which had been dried over boron oxide. Addition of 0.553 g (1.21 mmol) of vindoline was followed by 0.707 g (3.63 mmol) of silver tetrafluoroborate in 2 mL of dry acetone. The mixture was stirred at 20 °C for 20 min, then poured into 200 mL of 10% ammonium hydroxide, saturated with sodium chloride, and extracted with 3 × 100 mL of dichloromethane. The combined and dried ($MgSO_4$) extracts were concentrated under vacuum and the residual imines **59** and **60** subjected to LPLC on two 2.5 × 100 cm and one 2.5 × 50 cm tandem silica gel columns, eluted with 1:1 acetone–hexane, containing 1% of triethylamine, at 12 mL/min. The 14′*R* product **60** was collected in fractions 18–32 and the 14′*S* product **59** in fractions 44–74. Further purification of each isomer by centrifugal chromatography on a 2-mm silica gel plate and elution with 4% methanol in dichloromethane for **60** and with 5% methanol in dichloromethane for **59** gave 0.24 g (25%) and 0.20 g (21%), respectively.

The imine **60** (0.240 g, 0.303 mmol) was dissolved in 9 mL of acetic acid, and 0.338 g of potassium borohydride was added in small portions. The mixture was then poured onto 50 g of ice, basified with 50 mL of concentrated ammonium hydroxide, and extracted with 3 × 40 mL of dichloromethane. The dried ($MgSO_4$) extracts were concentrated under vacuum, and the residue was subjected to centrifugal chromatography on a 2-mm silica gel plate eluted at 1.2 mL/min with 5% methanol in dichloromethane, to produce 0.192 g (80%) of 14′-*epi*-20′-deoxyvinblastine (**64**) in fractions 24–42: TLC (silica gel) R_f 0.34 (2:1 ethanol–ethyl acetate), 0.33 (10% methanol in dichloromethane); UV (ethanol) λ_{max} 216, 222, 262, 288, 296, 305 nm; IR (KBr) ν_{max} 3446, 3016, 2958, 2937, 2930, 2918, 2876, 2853, 2812, 2804, 1741, 1617, 1597, 1500, 1461, 1432, 1371, 1334, 1300, 1246, 1193, 1176, 1145, 1130, 1119, 1108, 1086, 1065, 1040, 1008, 741 cm^{-1}; 250-MHz ^1H NMR ($CDCl_3$) δ −0.12 (t, *J* = 7 Hz, 3 H), 0.48–0.60 (m, 1 H), 0.81 (t, *J* = 12 Hz, 1 H), 0.94 (t, *J* = 7 Hz, 3 H), 1.21–1.42 (m, 3 H), 1.82–2.00 (m, 2 H), 2.02 (s, 3 H), 2.16–2.25 (m, 2 H), 2.36–2.45 (m, 2 H), 2.56 (s, 1 H), 2.60–2.93 (m, 5 H), 2.65 (s, 3 H), 3.00–3.08 (m, 1 H), 3.18–3.57 (m, 8 H), 3.73 (s, 1 H), 3.75 (s, 3 H), 3.76 (s, 3 H), 3.91 (s, 3 H), 5.06 (d, *J* = 10 Hz, 1 H), 5.22 (s, 1 H), 5.79 (d, d, *J* = 10, 3 Hz, 1 H), 6.06 (s, 1 H), 6.97 (s, 1 H), 6.98 (dd, *J* = 7, 2 Hz, 1 H), 7.08 (d, d, *J* = 7, 1 Hz, 1 H), 7.22 (d, *J* = 8 Hz, 1 H), 7.31 (d, *J* = 8 Hz, 1 H), 8.86 (s, 1 H), 9.66 (s, 1); 62.9-MHz ^{13}C NMR ($CDCl_3$) δ 6.77, 11.34, 20.68, 22.55, 28.31, 30.75, 31.64, 36.42, 38.19, 42.83, 43.41, 43.97, 44.93, 51.02, 51.87, 52.17, 53.02, 53.37, 53.50, 53.87, 55.88, 67.31, 76.89, 79.41, 83.52, 94.49, 110.42, 111.48, 117.61, 118.56, 119.74, 121.56, 123.70, 125.32, 128.30, 130.42, 133.13, 134.90, 152.28, 156.36, 170.31, 171.74, 174.94; mass spectrum, *m/z* (relative intensity) 795 (7), 794 (M^+, 52), 765 (4), 764 (9), 763 (15), 736 (12), 735 (16), 706 (7), 705 (6), 664 (6), 636 (5), 635 (25), 633 (5), 624 (5), 540 (5), 527 (20), 512 (5), 498 (7), 497 (8), 496 (21), 490 (10), 468 (5), 457 (4), 402 (9), 397 (6), 381 (9), 380 (23), 366 (5), 357 (4), 356 (5), 355 (9), 343 (4), 342 (11), 341 (9), 339 (11), 338 (38), 326 (5), 325 (14), 323 (5), 313 (5), 312 (6), 311 (7), 310 (4), 298 (5), 297 (8), 295 (6), 283 (7), 282 (31), 279 (4), 273 (12), 272 (11), 267 (10), 254 (12), 252 (5), 222 (6), 202 (5), 188 (5), 170 (11), 168 (4), 149 (6), 144 (9), 141 (5), 140 (6), 139 (9), 138 (88), 136 (8), 135 (46), 129 (5), 126 (4), 125 (48), 124 (23), 122 (15), 121 (14), 112 (4), 110 (19), 108 (6), 107 (11), 97 (6), 96 (24), 93 (9), 92 (7), 91 (14), 88 (5), 86 (24), 84 (43), 82 (19), 81 (7), 73 (6), 71 (8), 70 (8), 69 (10), 68 (5), 67 (5), 60 (7), 59 (5), 58 (12), 57 (21), 56 (7), 55 (22), 52 (24), 51 (19), 50 (100); exact mass calcd 794.425, found 794.407.

According to the same imine reduction procedure, 0.20 g of the diastereomer **59** provided 0.188 g (94%) of 14′-*epi*-20′-deoxyvincovaline (**63**): TLC (silica gel) R_f 0.36 (2:1 ethanol–ethyl acetate), 0.38 (10% methanol in dichloromethane); UV (ethanol) λ_{max} 216, 221, 263, 289, 296, 306 nm; IR (KBr) ν_{max} 3445, 3018, 2959, 2949, 2931, 2910, 2876, 2854, 2808, 1741, 1617, 1597, 1500, 1461, 1436, 1371, 1334, 1300, 1246, 1226, 1194, 1174, 1144, 1130, 1121, 1108, 1087, 1041, 1008, 741 cm^{-1}; 250-MHz ^1H NMR ($CDCl_3$) δ 0.65–0.78 (m, 1 H), 0.68 (t, *J* = 7 Hz, 3 H), 0.93 (t, *J* = 7 Hz, 3 H), 1.19–1.40 (m, 3 H), 1.59–1.71 (m, 1 H), 1.85–1.98 (m, 2 H), 2.01–2.27 (m, 4 H), 2.09 (s, 3 H), 2.55–2.68 (m, 1 H), 2.64 (s, 3 H), 2.81–2.99 (m, 5 H), 3.05–3.60 (m, 7 H), 3.69 (s, 1 H), 3.76 (s, 6 H), 3.74–3.85 (m, 1 H), 3.90 (s, 3 H), 5.34 (d, *J* = 12 Hz, 1 H), 5.36 (s, 1 H), 5.93 (d, d, *J* = 10, 4 Hz, 1 H), 6.00 (s, 1 H), 6.97 (s, 1 H), 7.04 (t, *J* = 8 Hz, 1 H), 7.11 (t, *J* = 8 Hz, 1 H), 7.26 (d, *J* = 8 Hz, 1 H), 7.41 (d, *J* = 8 Hz, 1 H), 9.01 (s, 1 H), 9.60 (s, 1 H); 62.9-MHz ^{13}C NMR ($CDCl_3$) δ 7.58, 11.39, 21.01, 22.03, 28.39, 30.58, 31.81, 34.51, 36.17, 38.72, 43.74, 44.09, 44.74, 50.75, 50.93, 52.06, 53.02, 53.15, 53.95, 55.97, 65.85, 76.37, 79.81, 82.86, 94.33, 110.48, 111.17, 117.75, 118.49, 119.49, 121.52, 124.15, 124.37, 125.80, 128.14, 130.38, 133.55, 134.68, 151.92, 156.18, 170.73, 171.47, 175.09; mass spectrum, *m/z* (relative intensity) 794 (M^+, 3), 793 (0.7), 737 (0.5), 736 (0.5), 636 (0.5), 634 (0.4), 580 (0.5), 541 (0.4), 528 (0.4), 497 (0.5), 470 (0.7), 469 (0.7), 381 (0.4), 380 (0.9), 379 (0.4), 356 (0.4), 355 (0.5), 354 (0.5), 341(0.4), 340 (0.5), 339 (1), 338 (3), 337 (0.7), 336 (0.7), 325 (0.7), 311 (0.5), 308 (0.4), 297 (0.4), 296 (0.4), 284 (0.6), 283 (0.5), 282 (2), 281 (0.4), 279 (0.4), 268 (0.5), 267 (0.5), 266 (0.9), 264 (0.4), 256 (0.5), 254 (0.7), 253 (0.4), 252 (0.4), 225 (0.4), 223 (0.4), 222 (0.6), 215 (0.4), 214 (0.5), 210 (0.4), 202 (0.4), 201 (0.4), 200 (0.5), 196 (0.7), 172 (0.9), 171 (0.7), 170 (0.8), 169 (0.9), 168 (0.8), 167 (1), 157 (1), 155 (0.7), 152 (0.9), 151 (0.7), 147 (4), 144 (1), 139 (3), 138 (19), 137 (1), 136 (2), 135 (5), 129 (2), 175 (3), 124 (4), 123 (1), 122 (2), 121 (4), 119 (3), 115 (1), 113 (2), 112 (1), 111 (2), 110 (2), 109 (1), 108 (2), 107 (2), 105 (1), 99 (2), 98 (3), 97 (3), 96 (3), 95 (2), 89 (1), 88 (19), 87 (4), 86 (84), 85 (10), 84 (100), 83 (10), 82 (5), 81 (3), 74 (2), 73 (4), 72 (4), 71 (9), 70 (6), 69 (10), 68 (2), 67 (3), 65 (2), 60 (9), 59 (5), 58 (6), 57 (11), 56 (2), 55 (10), 52 (28), 51 (45), 50 (61); exact mass calcd 794.425, found 794.447.

For coupling of racemic 20-*epi*-Ψ-vincadifformine (**15**) to vindoline, the initial silver ion promoted reaction of the chloro imine derivative **57** had to be carried out in refluxing acetone since only 4% of coupling product was obtained at room temperature. Thus 0.350 g (1.03 mmol) of **15** provided 0.103 g (13%) of the imine **62** (fractions 12–34) and 0.098 g (12%) of the imine **61** (fractions 48–70) on centrifugal chromatography of the crude reaction products on a 4-mm silica gel plate, eluted with 3% methanol in dichloromethane at 1.2 mL/min.

Individual reduction of the imines **62** and **61** with potassium borohydride, according to the above procedure, produced 0.081 g (78%) of 14′-*epi*-20′-deoxyleurosidine (**66**), obtained in fractions 18–77 on centrifugal chromatography on a 2-mm silica gel plate, eluted with ethyl acetate at 1.2 mL/min, and 0.053 g (55%) of the 14′,16′,20′-*epi*-diastereomer **65**, eluted similarly in fractions 8–26 with 5% methanol in dichloromethane. For **66**: TLC (silica gel) R_f 0.18 (ethyl acetate), 0.17 (5% methanol in dichloromethane); UV (ethanol) λ_{max} 214, 222, 262, 291, 296, 305 nm; IR (KBr) ν_{max} 3440, 2995, 2987, 2958, 2951, 2943, 2937, 2931, 2924, 2876, 2854, 2840, 2823, 2804, 1742, 1678, 1614, 1597, 1529, 1500, 1461, 1433, 1416, 1390, 1371, 1335, 1299, 1247, 1235, 1227, 1196, 1169, 1152, 1145, 1110, 1087, 1041, 1010, 739 cm^{-1}; 250-MHz ^1H NMR ($CDCl_3$) δ −0.13 (t, *J* = 7 Hz, 3 H), 0.56 (t, d, *J* = 7, 1 Hz, 1 H), 0.65–0.95 (m, 1 H), 0.92 (t, *J* = 7 Hz, 3 H), 1.02–1.33 (m, 3 H), 1.66 (m, 3 H), 1.92–2.15 (m, 2 H), 2.00 (s, 3 H), 2.34–2.58 (m, 5 H), 2.50 (s, 1 H), 2.65 (s, 3 H), 2.86 (d, *J* = 16 Hz, 1 H), 2.93–3.25 (m, 6 H), 3.40–3.52 (m, 2 H), 3.73 (s, 1 H), 3.76 (s, 3 H), 3.75 (s, 3 H), 3.67–3.83 (m, 1 H) 3.91 (s, 3 H), 3.97 (t, *J* = 13 Hz, 1 H), 5.06 (d, *J* = 10 Hz, 1 H), 5.28 (s, 1 H), 5.78 (d, d, *J* = 10, 4 Hz, 1 H), 6.06 (s, 1 H), 6.94 (t, *J* = 7 Hz, 1 H), 6.97 (s, 1 H), 7.06 (t, *J* = 7 Hz, 1 H), 7.20 (d, *J* = 7 Hz, 1 H), 7.27 (d, *J* = 6 Hz, 1 H), 8.87 (s, 1 H), 9.67 (s, 1 H); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 175.27, 171.88, 170.51, 156.30, 152.23, 134.87, 133.93, 130.49, 128.36, 126.51, 125.24, 123.81, 121.45, 119.72, 118.31, 117.80, 111.32, 110.39, 94.55, 83.57, 79.44, 76.35, 67.17, 60.46, 56.00, 53.10, 53.02, 52.18, 52.09, 51.96, 51.02, 48.75, 43.98, 42.81, 39.21, 38.38, 37.80, 33.41, 31.74, 30.83, 29.66, 27.52, 20.87, 11.24, 6.91; mass spectrum, *m/z* (relative intensity) 794 (M^+, 1.7), 793 (0.5), 636 (0.6), 528 (0.4), 339 (0.4), 338 (1), 294 (0.6), 293 (0.5), 282 (1), 272 (6), 254 (0.6), 240 (1), 227 (0.6), 226 (3), 225 (0.7), 224 (0.4), 213 (1), 212 (6), 211 (7), 199 (0.5), 198 (1), 197 (0.5), 196 (0.4), 183 (2), 182 (0.8), 169 (2), 168 (1), 155 (4), 154 (2), 141 (4), 140 (3), 138 (2), 135 (3), 127

(4), 126 (4), 125 (1), 124 (1), 122 (0.9), 121 (0.8), 114 (0.8), 113 (7), 112 (4), 111 (2), 110 (1), 99 (10), 98 (6), 97 (7), 96 (2), 88 (5), 86 (30), 85 (33), 84 (53), 83 (11), 82 (3), 81 (2), 71 (55), 70 (11), 69 (11), 68 (3), 67 (2), 58 (6), 57 (100), 56 (22), 55 (21); exact mass calcd 794.425, found 794.418.

For **65**: TLC (silica gel) R_f 0.18 (ethyl acetate), 0.17 (5% methanol in dichloromethane); UV (ethanol) λ_{max} 216, 222, 262, 289, 295, 305 nm; IR (KBr) ν_{max} 3441, 3023, 2959, 2952, 2931, 2895, 2877, 2849, 2843, 2816, 1741, 1672, 1617, 1597, 1500, 1461, 1433, 1371, 1335, 1299, 1247, 1234, 1227, 1198, 1169, 1144, 1132, 1120, 1111, 1087, 1040, 1010, 738 cm^{-1}; 250-MHz ^1H NMR ($CDCl_3$) δ 0.69 (t, J = 7 Hz, 3 H), 0.91 (t, J = 7 Hz, 3 H), 0.95-1.33 (m, 5 H), 1.56-1.68 (m, 3 H), 1.91-2.15 (m, 3 H), 2.09 (s, 3 H), 2.47-2.73 (m, 3 H), 2.65 (s, 3 H), 2.90 (s, 1 H), 2.93-3.25 (m, 6 H), 3.36-3.52 (m, 2 H), 3.69 (s, 1 H), 3.76 (s, 6 H), 3.69-3.84 (m, 1 H), 3.90 (s, 3 H), 4.02 (br t, 1 H), 5.32 (s, 1 H), 5.35 (d, J = 11 Hz, 1 H), 5.93 (d, d, J = 11, 4 Hz, 1 H), 6.00 (s, 1 H), 6.98 (s, 1 H), 6.98 (t, J = 7 Hz, 1 H), 7.09 (t, J = 7 Hz, 1 H), 7.24 (d, J = 9 Hz, 1 H), 7.36 (d, J = 8 Hz, 1 H), 9.05 (s, 1 H), 9.61 (s, 1 H); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 175.32, 171.43, 170.70, 156.29, 151.78, 134.76, 134.41, 130.52, 128.29, 126.48, 124.41, 123.92, 121.36, 119.70, 118.28, 117.91, 111.14, 110.39, 94.32, 82.83, 80.00, 65.51, 60.60, 56.08, 55.98, 53.25, 52.60, 52.01, 51.91, 50.74, 48.81, 43.78, 42.80, 39.20, 38.47, 38.19, 33.63, 31.74, 30.53, 29.63, 27.33, 21.00, 11.20, 7.45; mass spectrum, m/z (relative intensity) 794 (M^+, 3), 793 (1), 736 (0.4), 636 (0.6), 528 (0.3), 340 (0.4), 339 (1), 338 (0.3), 282 (0.6), 254 (0.5), 240 (1), 227 (1), 226 (4), 225 (0.5), 213 (1), 212 (7), 199 (7), 198 (2), 197 (0.4), 183 (1), 182 (0.7), 171 (0.5), 170 (0.9), 169 (3), 168 (1), 156 (0.5), 155 (3), 154 (2), 149 (0.8), 142 (0.9), 141 (7), 140 (3), 138 (2), 135 (2), 127 (5), 126 (5), 125 (1), 113 (9), 112 (6), 111 (3), 108 (1), 107 (1), 106 (1), 105 (1), 101 (1), 100 (2), 99 (15), 98 (7), 97 (5), 96 (1), 93 (1), 92 (6), 91 (7), 88 (4), 87 (2), 86 (24), 85 (43), 84 (42), 83 (10), 82 (3), 81 (1), 73 (1), 72 (5), 71 (71), 70 (13), 69 (13), 68 (2), 67 (2), 65 (2), 60 (1), 59 (2), 58 (6), 57 (100), 56 (20), 55 (22); exact mass calcd 794.425, found 794.404.

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Palladium-Catalyzed Synthesis of Alkynylamino Nucleosides. A Universal Linker for Nucleic Acids

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A method for attaching alkynylamino "linkers" to nucleosides and nucleotides is described. Protected or unprotected alkynylamines are coupled to iodonucleosides in dimethylformamide using a 1:2 mol ratio of tetrakis(triphenylphosphine)palladium(0) and copper(I) iodide, a catalyst system superior to the standard system using palladium(II) species. The resulting alkynylamino nucleosides are useful for enzymatic or chemical labeling of all four bases of DNA.

In connection with our program on automated sequencing of DNA, we wanted to prepare chain-terminating,[1] fluorescence-tagged substrates for DNA polymerases.[2] One critical feature of these substrates is the "linker" or group which covalently attaches the fluorescent moiety to the nucleotide substrate without interfering with enzymatic processing of the molecule. Although several linkers are known which meet these requirements,[3] no *general* method is currently available for attaching fluorescent dyes or other reporters[4] to all of the nucleotides found in DNA. Since acetylenes are small and can be attached to some aromatic rings under mild conditions, preparation of nucleosides with alkynylamino groups linked to the heterocyclic ring was investigated.

Robins and Barr[5] had shown that 5-iodouridines with protected hydroxy groups can be coupled with a variety of non-nitrogenous terminal alkynes by treatment with bis(triphenylphosphine)palladium(II) dichloride and copper(I) iodide in warm triethylamine.[6] Attempts to couple propargylamine with unprotected 5-iodouridine under these conditions failed, at least in part because of the insolubility of the iodonucleoside in triethylamine. After some experimentation, it was discovered that couplings between iodonucleosides and alkynylamines could be effected in dimethylformamide by using copper(I) iodide and a palladium(0) catalyst.[7] Specifically, treatment of a

(1) A "chain terminating" substrate for a polymerase is one which, when incorporated onto the 3'-end of an oligonucleotide, blocks enzymatic chain extension of the oligonucleotide. The chain terminators used most often for DNA sequencing are 2',3'-dideoxynucleoside 5'-triphosphates: Sanger, F.; Nicklen, S.; Coulson, A. R. *Proc. Natl. Acad. Sci. U.S.A.* **1977**, *74*, 5463.

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(3) (a) An allylamino linker has been attached to C5 of uridine: Langer, P. R.; Waldrop, A. A.; Ward, D. C. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 6633. An alkylamino linker has been attached to N4 of cytidine and N6 of adenosine: Gebeyehu, G.; Rao, P. Y.; Soochan, P.; Simms, D. A.; Klevan, L. *Nucleic Acids Res.* **1987**, *15*, 4513. (c) Derivatives of 3' α-aminonucleoside triphosphates were reported to function as alternative substrates, but the chain terminating species present in these experiments was not unambiguously identified: Krayevsky, A.; Kukhanova, M.; Azhayev, A.; Chidgeavadze, Z.; Beabealashvilli, R. *Nucleic Acids Res. Symposium Ser.* **1984**, *14*, 283. Bililashvili, R. Sh.; Chidzhavadze, Z. G.; Kraevskii, A. A.; Kukhanova, M. K.; Atrazhev, A. M.; Azhaev, A. V.; Kutateladze, T. V. *Biopolim. Kletka* **1985**, *1*, 293-307.

(4) A "reporter" or "reporter group" is a group placed in or attached to a nucleic acid which creates a signal permitting a small quantity of the nucleic acid to be detected. Useful reporters include radioactive isotopes, biotin, and fluorescent dyes. As little as 10^{-18} mol of some of these reporters can be detected.[2]

(5) (a) Robins, M. J.; Barr, P. J. *Tetrahedron Lett.* **1981**, *22*, 421. (b) Robins, M. J.; Barr, P. J. *J. Org. Chem.* **1983**, *48*, 1854. (c) Similar products had also been prepared by palladium-catalyzed coupling of alkynylzinc halides to iodouridines: Vincent, P.; Beaucourt, J. P.; Pichat, L. *Tetrahedron Lett.* **1981**, *22*, 945.

(6) This type of coupling was first reported by: Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett* **1975**, 4467.

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