Nonoxidative Coupling Methodology for the Synthesis of the Antitumor Bisindole Alkaloid Vinblastine and a Lower-Half Analogue: Solvent Effect on the Stereochemistry of the Crucial C-15/C-18′ Bond

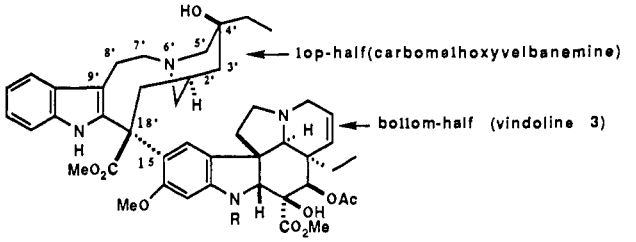
Philip Magnus,*,† José S. Mendoza,† Andrew Stamford,† Mark Ladlow,‡ and Paul Willis†

Contribution from the Department of Chemistry and Biochemistry, The University of Texas at Austin, Austin, Texas 78712, and Department of Chemistry, Indiana University, Bloomington, Indiana 47405. *Received July 16, 1992*

Abstract: The overall strategy for the synthesis of vinblastine (**1**) is based upon the nonoxidative cleavage of the tertiary amine (+)-**18** to generate the intermediate delocalized cation **18a**, which in the presence of an electron-rich aromatic nucleophile can be trapped at C-18′ to give the bisalkaloid analogues **19**, **20**, and **21**. To ascertain the effect on C-18′ stereochemistry with respect to C-2′ and C-4′ stereochemistry, we have made a number of stereoisomers of the tetracyclic amine **30**. Treatment of (−)-**30** with $ClCO_2CH_2C_6H_4NO_2$-*p*/vindoline/CH_2Cl_2/25 °C gave two compounds (**40** and **41**) and none of the correct C-18′*S* isomer **57**, whereas treatment of (−)-**30** with $ClCO_2CH_2C_6H_4NO_2$-*p*/vindoline/CH_3NO_2 at −20 °C gave the correct 18′*S* stereoisomer **57** (46%), along with **40** (33%) and traces of **41**. Hydrolysis of **57** gave the diol **59** (85%), which was oxidized using pyridine/SO_3 to the α-hydroxy aldehyde **60** (77%). Hydrogenolysis of **60** (Pd/C/MeOH) gave vinblastine (**1**) (89%). A shorter and more stereoselective synthesis of (−)-**30** is described, and the synthesis of the non-vindolinyl analogue **73** is given. This study establishes that of all the various stereoisomers of the top-half precursors to vinblastine, only the (−)-(9*R*,2*S*,2′*S*)-**30** diastereomer couples to vindoline to give the correct C-18′*S* stereochemistry for conversion into vinblastine.

Introduction

First isolated in 1958, vinblastine (**1**) and vincristine (**2**) have gained a prominent place in cancer chemotherapy.[1] Extensive



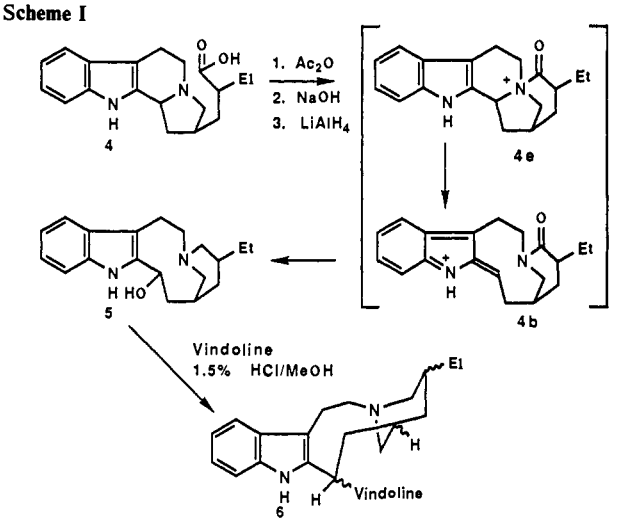
1 (R = Me, Vinblastine)
2 (R = CHO, Vincristine)

review articles summarize the massive literature associated with these two important antitumor agents.[2] The structure of vincristine was established by X-ray crystallography,[3] and heralded investigations of structure–activity relationships and total synthesis.[4] Synthetic studies have focused almost exclusively on the stereospecific formation of the crucial C-15/C-18′ bond that connects the top half (carbomethoxyvelbanamine) to the bottom half (vindoline, **3**).

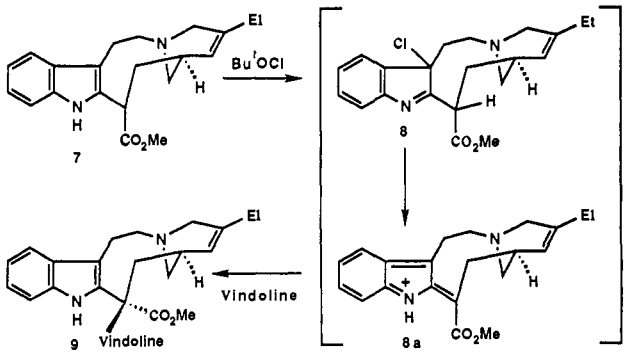
The earliest reported coupling reaction involved intramolecular acylation of the tetracyclic amine **4** to give, after reductive cleavage, the alcohol **5**. Solvolysis of **5** in the presence of vindoline gave the bis-alkaloid **6** with no control of the crucial C-18′ stereochemistry and lacking the C-18′ CO_2Me group (Scheme I).[5] This represents the only nonoxidative coupling reaction other than the work described here. It is somewhat surprising that the approach in Scheme I was not pursued further, especially the possibility of trapping the presumed iminium ions **4a**/**4b** directly with vindoline.

The so-called chloroindoline approach oxidatively activates the indole ring in **7** by chlorination to give **8**, which when treated with vindoline in the presence of acid gave the bis-alkaloid **9** in good yield but with the opposite stereochemistry at C-18′. The presumed delocalized iminium ion **8a** is attacked by vindoline from

Scheme I



Scheme II



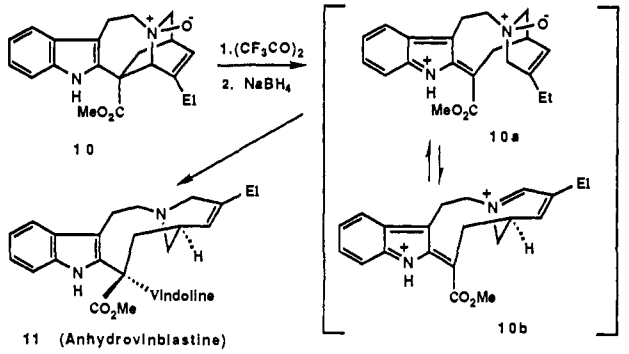
the top face, resulting in the unnatural C-18′*R* isomer (Scheme II).[6] Vinblastine and vinblastine-like alkaloids with the opposite

† The University of Texas at Austin.
‡ Indiana University.

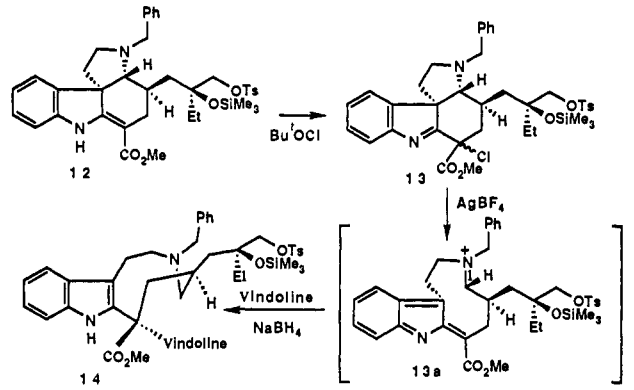
(1) Noble, R. L.; Beer, C. T.; Cutts, J. H. *Ann. N.Y. Acad. Sci.* **1958**, *76*, 882. Svoboda, G. H.; Neuss, N.; Gorman, M. J. *J. Am. Pharm. Assoc. Sci. Ed.* **1959**, *48*, 659.

0002-7863/92/1514-10232$03.00/0

Scheme III



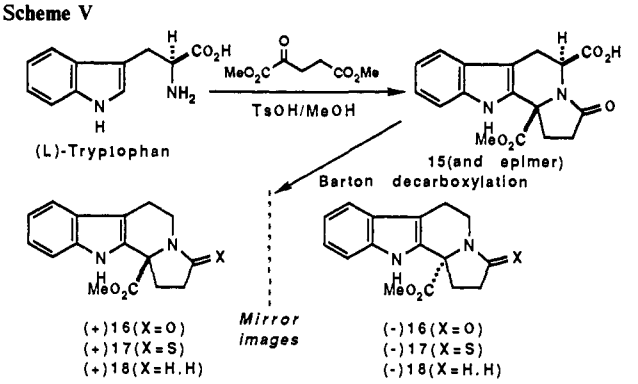
Scheme IV



18′ configuration (18′*R* rather than the natural 18′*S*) exhibit considerably reduced biological activity, although this comparison has only been made in the anhydrovinblastine series, the compounds of which are much less active (ca. $^1/_{100}$) than vinblastine.[7]

Potier[8] and Kutney[9] have described a solution to this problem which uses the Polonovski reaction to fragment catharanthine *N*-oxide (**10**) to putative bis-iminium ions **10a**/**10b**, which are trapped by vindoline to give anhydrovinblastine (**11**) after hydride reduction. The control of the C-15/C-18′ stereochemistry is highly temperature dependent. At −50 °C, the C-18′*S* natural stereoisomer is formed, whereas at 0 °C, the C-18′*R* isomer predominates (Scheme III). The C-18′ stereochemistry temperature dependence is explained by a change in the conformation of the intermediate iminium ion. When **10a** is generated from catharanthine *N*-oxide at −50 °C, the conformation of the iminium ion resembles that of **10**, and, as a consequence, electrophilic

Scheme V



substitution with vindoline takes place from the least hindered face (α-face) to establish the natural C-18′ configuration. At higher temperatures conformation equilibration becomes more rapid and the unnatural C-18′ epimer is formed from the iminium ion **10b** (coupling opposite the methylene bridge).

More recently, Kuehne[10] has described extensive studies that utilize a variant on the chloroindolenine approach to establish the correct absolute stereochemistry at C-18′. Chlorination of **12** gave **13**, which was fragmented to the iminium ion **13a** and trapped by vindoline, followed by reduction to give **14** with the correct C-18′ stereochemistry (Scheme IV).

Background to Nonoxidative Coupling Methodology

Before the syntheses of vinblastine and various stereoisomers are described, some salient features of the background to this study warrant discussion.[11] While it is clear that the conformation of the intermediate iminium ions **4b**, **8a**, **10a**/**10b**, and **13a** must influence the stereochemistry at C-18′, all the compounds examined have the C-2′ substituent present, which can also affect the C-18′ stereochemistry. Our preliminary model studies sought to separate these two aspects and examine the nine-membered ring iminium ion without any substituents. In order to do this we required a convenient synthesis of both antipodes of the tetracyclic amine (+)-**18** and (−)-**18** (Scheme V).

Starting with L-tryptophan we were able to make (+)-**18** and (−)-**18** in large amounts via the Pictet–Spengler product **15**.[12] The absolute configuration of **15**, and hence **16**–**18**, was unambiguously established by the X-ray structure of the (*R*)-α-methylbenzylamine amide derivative of **15**.

The overall strategy we have adopted is based upon the nonoxidative cleavage of the tertiary amine (+)-**18** to generate the intermediate delocalized cation **18a**, which in the presence of an electron-rich aromatic nucleophile can be trapped at C-18′ to give the bis-alkaloid analogues **19**, **20**, and **21** (Scheme VI). To effect the cleavage of **18**, we have examined a large range of chloroformates with the following restrictions in mind: (i) the chloroformate must cleave the tertiary amine without reacting with vindoline and (ii) the resulting carbamates (for example, **19**, **20**, and **21**) must be deprotected under mild conditions that do not affect the vindoline portion of the molecule. The only chloroformate that is in good accord with these requirements is *p*-nitrobenzyl chloroformate.

In experiments designed to investigate whether or not the iminium ion **18a** can retain chirality, because of potentially slow conformational processes associated with the nine-membered ring we treated (+)-**18** with $ClCO_2CH_2C_6H_4NO_2$-*p*/CH_2Cl_2/25 °C for 48 h in the presence of 3-$MeOC_6H_4NMe_2$ to give **19** (72%), $[\alpha]^{23}_D$ −30° (*c* 0.52 in CH_2Cl_2). The enantiomeric excess was

(2) For a comprehensive review of this area, see: Antitumor Bisindole Alkaloids from *Catharanthus roseus* (L.). *The Alkaloids*; Brossi, A., Suffness, M., Eds.; Academic Press Inc.: San Diego, 1990; Vol. 37. For a general review of bisindole alkaloids, see: Cordell, G. A.; Saxton, J. E. Bisindole Alkaloids. *The Alkaloids*; Rodrigo, R. G. A., Ed.; Academic Press Inc.: San Diego, 1981; Vol. 20.

(3) Moncrief, J. W.; Lipscomb, W. N. *J. Am. Chem. Soc.* **1965**, *87*, 4963.

(4) Lounasmaa, M.; Nemes, A. *Tetrahedron* **1982**, *38*, 223.

(5) Harley-Mason, J.; Rahman, A-ur. *J. Chem. Soc., Chem. Commun.* **1967**, 1048. Harley-Mason, J.; Rahman, A-ur. *Tetrahedron* **1980**, *36*, 1057. Büchi, G.; Manning, R. E.; Monti, S. A. *J. Am. Chem. Soc.* **1964**, *86*, 4631.

(6) Neuss, N.; Gorman, M.; Cone, N. J.; Huckstep, L. L. *Tetrahedron Lett.* **1968**, 783. Kutney, J. P.; Beck, J.; Bylsma, F.; Cook, J.; Cretney, W. J.; Fuji, K.; Imhof, R.; Treasurywala, A. M. *Helv. Chim. Acta* **1975**, *58*, 1690. Rahman, A-ur.; Basha, A.; Ghazala, M. *Tetrahedron Lett.* **1976**, 2351. Recent work using the chlorindolenine method has been applied to analogues: Schill, G.; Priester, C. U.; Windhovel, U. F.; Fritz, H. *Tetrahedron* **1987**, *43*, 3747.

(7) Pearce, H. L. In Medicinal Chemistry of Bisindole Alkaloids from *Catharanthus. The Alkaloids*; Brossi, A., Suffness, M., Eds.; Academic Press Inc.: San Diego, 1990; Vol. 37.

(8) Langlois, N.; Gueritte, F.; Langlois, Y.; Potier, P. *J. Am. Chem. Soc.* **1976**, *98*, 7017. Potier, P. *J. Nat. Prod.* **1980**, *43*, 72. For a recent example of the Potier coupling, see: Raucher, S.; Bray, B. L.; Lawrence, R. F. *J. Am. Chem. Soc.* **1987**, *109*, 442.

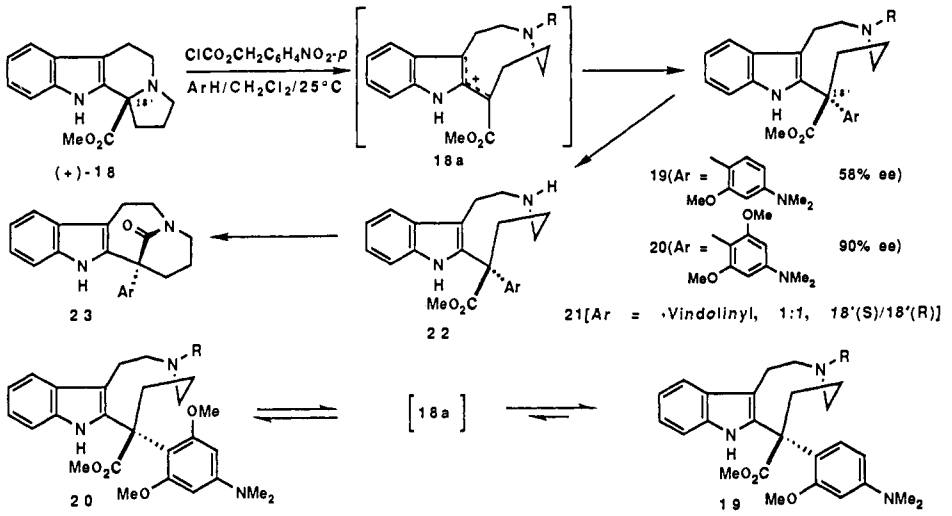
(9) Kutney, J. P. *Lloydia* **1977**, *40*, 107. This paper discusses the effect of solvent and temperature on the C-18′(*S*/*R*) ratio in the Polonovski coupling reaction. Kutney, J. P. *Lect. Heterocycl. Chem.* **1978**, *4*, 59.

(10) Kuehne, M. E.; Bornmann, W. G. *J. Org. Chem.* **1989**, *54*, 3407. Kuehne, M. E.; Zebovitz, T. C.; Bornmann, W. G.; Marko, I. *J. Org. Chem.* **1987**, *52*, 4340. Synthesis of vinblastine: Kuehne, M. E.; Matson, P. A.; Bornmann, W. G. *J. Org. Chem.* **1991**, *56*, 513.

(11) Magnus, P.; Stamford, A.; Ladlow, M. *J. Am. Chem. Soc.* **1990**, *112*, 8210. Magnus, P.; Ladlow, M.; Elliott, J.; Kim, C. S. *J. Chem. Soc., Chem. Commun.* **1989**, 518.

(12) Magnus, P.; Ladlow, M.; Kim, C. S.; Boniface, P. *Heterocycles* **1989**, *28*, 951.

Scheme VI[a]



[a] R = $CO_2CH_2C_6H_4NO_2$-*p*.

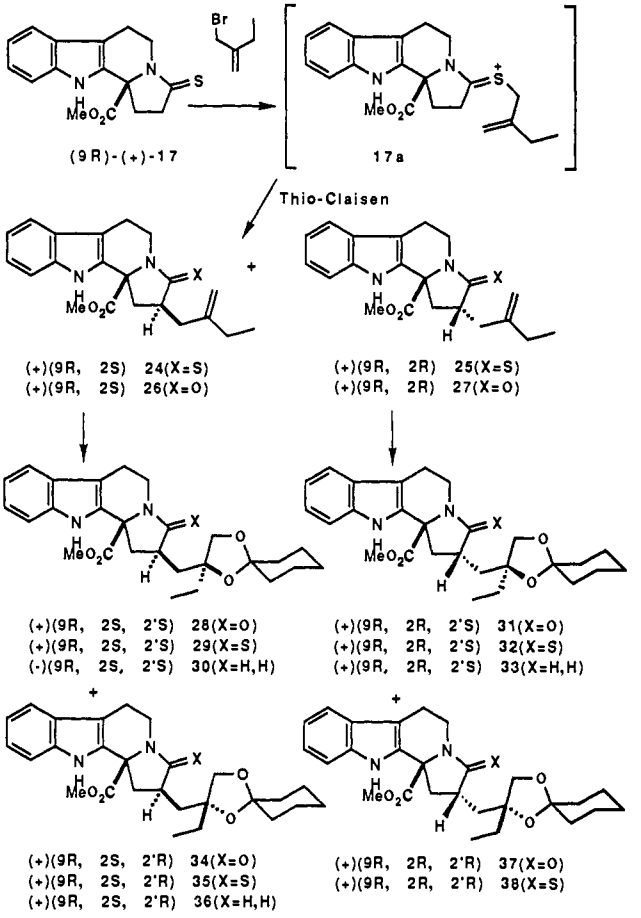
shown to be 58% after transfer hydrogenation to give **22** and conversion into the bridged amide **23**. Optical rotatory dispersion (ORD)/circular dichroism (CD) studies on the enantiomerically enriched adduct **19** demonstrated that the conversion of (+)-**18** into **19** occurs with predominant retention of configuration at C-18′. This appears to be an example of the translation of the overall dissymmetry (atropoisomerism) of the iminium ion **18a** into a single stereogenic center at C-18′. Treatment of (+)-**18** under the same conditions as above, except that the aromatic nucleophile was 3,5-$(MeO)_2C_6H_3NMe_2$, gave **20** with an ee > 90%. It appears that the more reactive aromatic system is able to capture the iminium ion **18a** before substantial racemization has taken place. The electrophilic aromatic substitution reaction of the iminium ion **18a** is reversible. This is nicely illustrated by the following experiment. Treatment of **20** (ee > 90%) with 3-$MeOC_6H_4NMe_2/CH_2Cl_2/CF_3CO_2H$ at 25 °C cleanly gave **19** (ee 58%) and 3,5-$(MeO)_2C_6H_3NMe_2$. The adduct **20** was treated with vindoline/CH_2Cl_2/CF_3CO_2H to give the bis-alkaloid **21** as a 1:1 mixture of stereoisomers at C-18′. Similarly, (+)-**18** on treatment with vindoline/$ClCO_2CH_2C_6H_4NO_2$-*p*/CH_2Cl_2/25 °C for 48 h gave **21** (1:1 C-18′ epimers). Consequently, we can conclude that the iminium ion **18a** undergoes racemization if the electrophilic substitution is slow (vindoline) and retention of configuration with respect to (+)-**18** when the aromatic electrophilic substitution is fast.

The real tetracyclic amine **30** (Scheme VII) must have a side chain at C-2 that can eventually become the piperidine ring (C-3′, -4′, and -5′). This substituent may slow the conformation inversion of the nine-membered ring and allow coupling with vindoline to proceed with retention of configuration at C-18′. To ascertain the effect on C-18′ stereochemistry with respect to C-2′ and C-4′ stereochemistry, we have made a number of stereoisomers of the tetracyclic amine **30**. The epimers at the C-4′ position correspond to the leurosidine series and, as expected, did not affect the stereochemical outcome at C-18′. Initially we required a nonstereospecific synthesis that would allow access to all of the stereoisomers of the top-half precursor. In principle, if the coupling reaction takes place with retention of configuration at C-18′, only the (−)-(9*R*,2*S*,2′*S*)-**30** tetracyclic amine can eventually lead to vinblastine.

Synthesis of the Stereoisomeric Precursors of the Top Half

The tetracyclic lactam (+)-**16** could not be efficiently alkylated by treatment with lithium diisopropylamide followed by 2-(bromomethyl)but-1-ene, consequently, we resorted to the Takano thio-Claisen methodology.[13] Treatment of the thiolactam (+)-**17**

Scheme VII

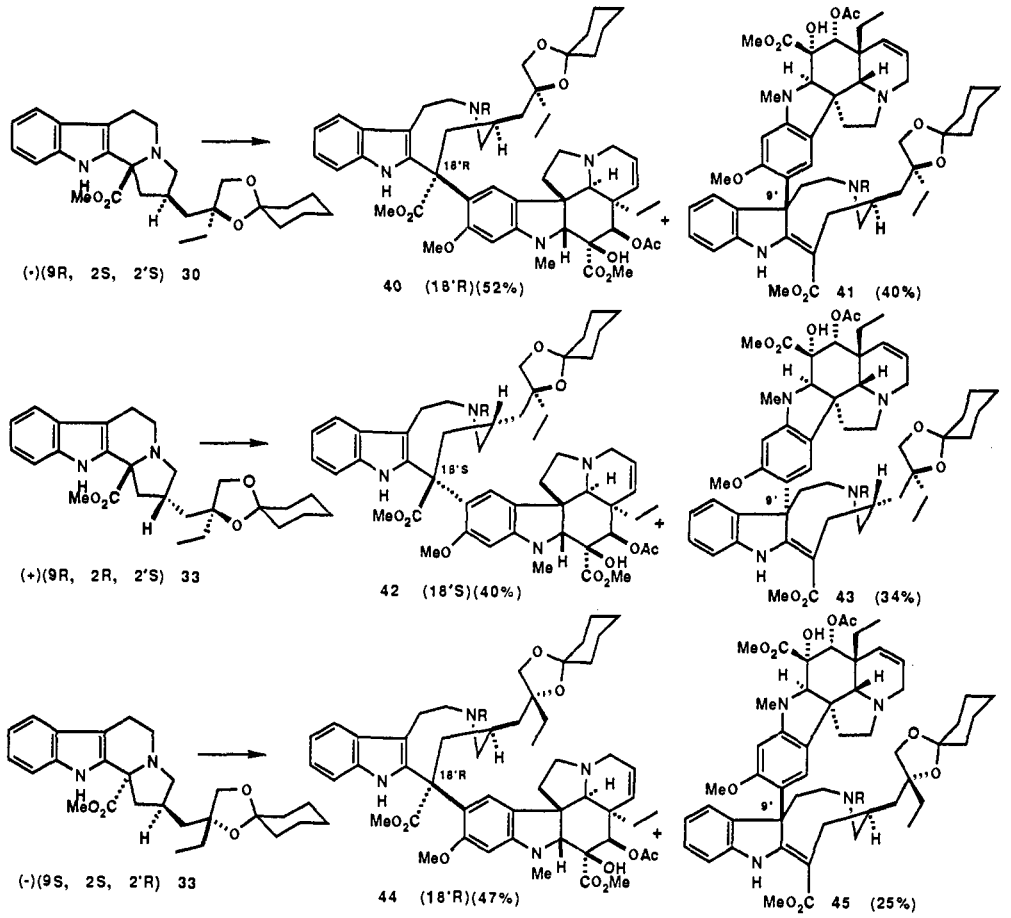


with 2-(bromomethyl)but-1-ene in nitromethane gave the thioiminium salt **17a**, which underwent thio-Claisen rearrangement upon exposure to diazabicyclo[5.4.0]undecene-5 (DBU) in tetrahydrofuran at 25 °C for 4 h to give the diastereomeric cis and trans allylated derivatives **24** and **25**, respectively, in a combined yield of 75% and in a ratio of approximately 1.0:2.2. The relative (and therefore absolute) configuration of these diastereoisomers was established by a single-crystal X-ray structure determination on the highly crystalline cis isomer **24**.[14] Rather than separating the thiolactam diastereomers on a large scale, it proved expedient

(13) Takano, S.; Yonaga, M.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1981**, 1153. Takano, S.; Hirama, M.; Araki, T.; Ogasawara, K. *J. Am. Chem. Soc.* **1976**, *98*, 7084. Tamura, Y.; Harada, T.; Yoshida, Z. *Tetrahedron Lett.* **1978**, *19*, 2167.

(14) Details of the X-ray crystallographic structure determination of **24** and **29** are available in the supplementary material.

Scheme VIII[a]



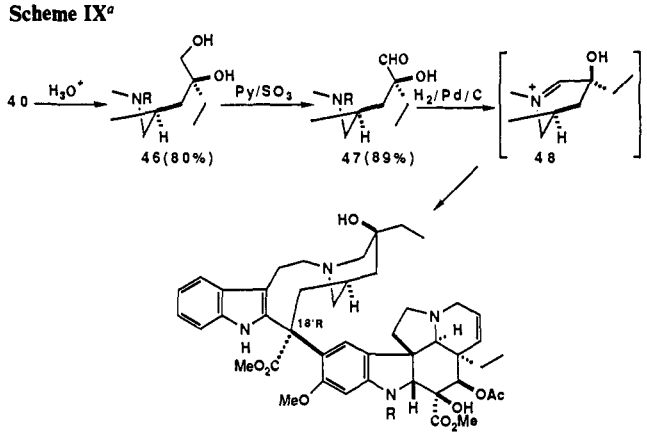
[a] R = $CO_2CH_2C_6H_4NO_2$-*p*. Coupling Conditions: $ClCO_2CH_2C_6H_4NO_2$-*p*/vindoline/CH_2Cl_2/25 °C.

to first convert them into the corresponding lactams **26** and **27** by treatment with *m*-chloroperoxybenzoic acid (87%). This was necessary because it was not possible to effect the subsequent catalytic osmylation (hydroxylation) of the double bond in the presence of the thiolactam functionality. The separation of **26** and **27** was best effected using HPLC. Treatment of the separated lactams **26** and **27** with osmium tetraoxide (cat.)/*N*-methylmorpholine oxide,[15] followed by exposure to cyclohexanone methyl enol ether in the presence of Amberlyst H-15, gave a 1.0:1.32 mixture of the two diastereomeric cyclohexylidene ketals **28**/**34** and **31**/**37** in a combined yield of 80%. This latter conversion was necessary both to protect the diol and to facilitate the separation of the two diastereomeric products.

The amides **28**/**34** and **31**/**37** (both as mixtures and the as separated diastereomers) were converted into the corresponding thiolactams **29**/**35** (90%) and **32**/**38** (90%) by treatment with Lawesson's reagent[16] in toluene at 80 °C. The absolute configuration at C-2′ was established by a single-crystal X-ray structure determination on the (+)-9*R*,2*S*,2′*S* isomer **29**.[14]

Reductive desulfurization of the thiolactams using Raney nickel in tetrahydrofuran proceeded without any loss of stereochemical integrity at C-2: (+)-**29** gave (-)-**30** (94%), (+)-**35** gave (+)-**36**, and (+)-**32** gave (+)-**33**. In the antipodal series starting from (-)-(9*S*)-**17**, we have made (-)-**26**, (-)-**27**, (-)-**32**, (-)-**38**, and (-)-**33**. While this sequence is cumbersome and involves the conversion of a lactam into a thiolactam twice, it does allow access to a range of diastereoisomers of **30** for evaluation in the nonoxidative coupling reaction. A more concise and stereoselective synthesis of the top-half precursor is described later in Scheme XIV.

Scheme IX[a]



[a] R = $CO_2CH_2C_6H_4NO_2$-*p*.

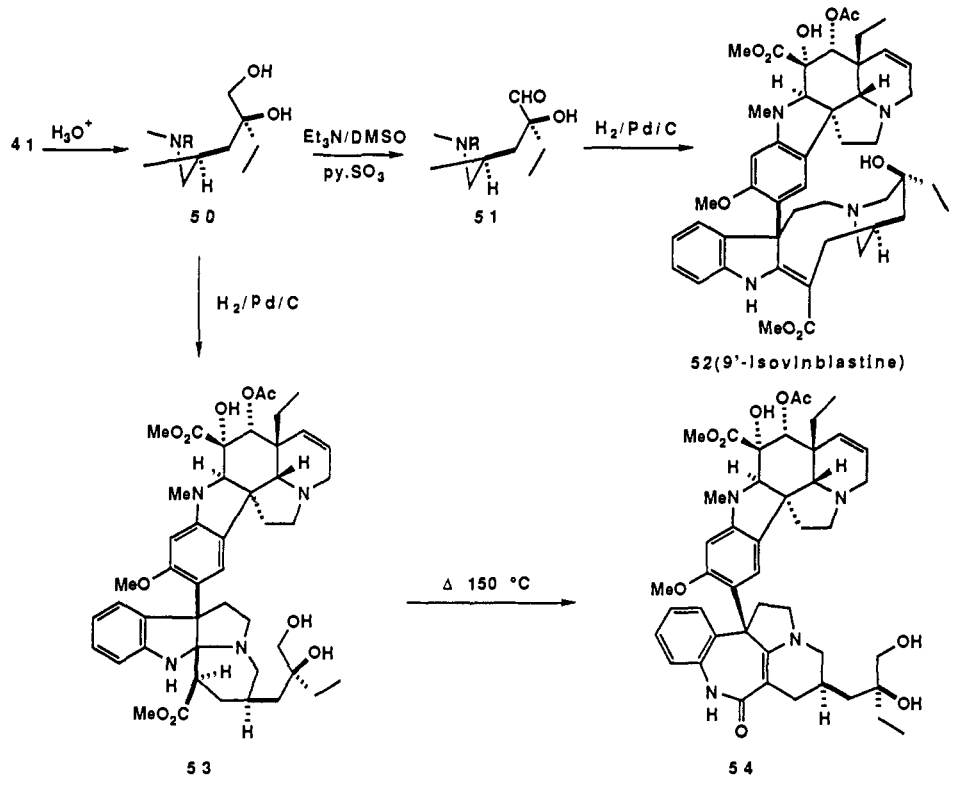
Coupling of the Stereoisomeric Precursors of the Top Half to Vindoline in Dichloromethane. Treatment of (-)-**30** with $ClCO_2CH_2C_6H_4NO_2$-*p*/vindoline/CH_2Cl_2 (ϵ_r 8.9)/25 °C for 72 h gave the two compounds **40** (52%) and **41** (40%) (Scheme VIII). The unnatural C-18′*R* stereochemistry of **40** was apparent from the CD curve (MeOH), λ_{max} ($\Delta\epsilon$) 212 (+38.5), 225 (-31.9), 277 (+5.5), 308 (+6.6) (mirror image of vinblastine). The structure of **40** was further confirmed by converting it into 18′-epivinblastine (**49**). Hydrolysis of **40** gave the diol **46** (80%), which on oxidation with pyridine SO_3/Et_3N/DMSO gave the α-hydroxy aldehyde **47** (89%). Hydrogenolysis of the (4-nitrobenzyl)oxy carbamate generated the iminium species **48**, which was reduced in situ to give **49** (92%) (structure by X-ray)[17] (Scheme IX).

(15) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *17*, 1973.

(16) Scheibye, S.; Pederson, B. S.; Lawesson, S.-O. *Bull. Soc. Chim. Belg.* **1978**, *87*, 229.

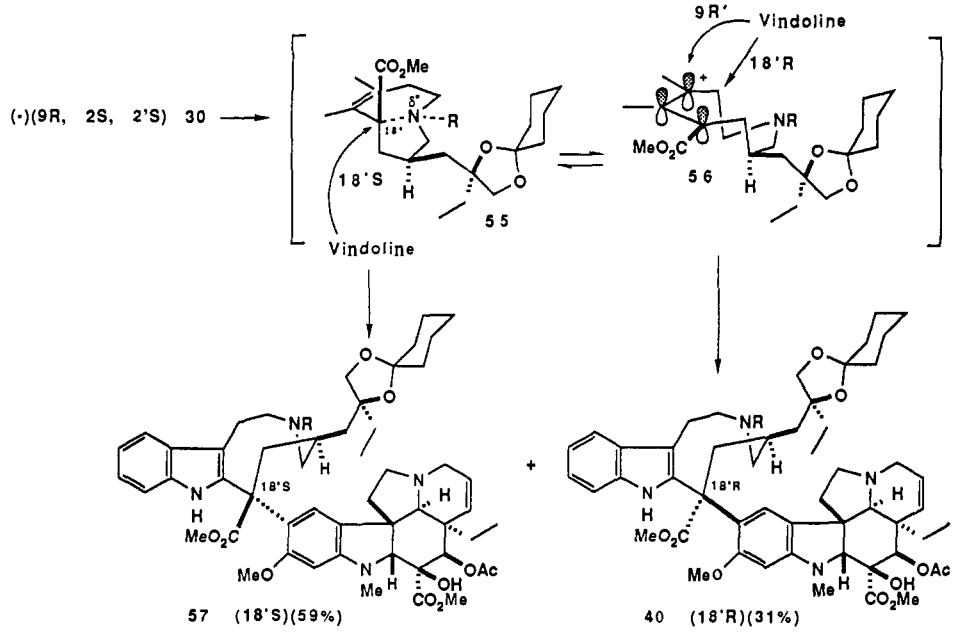
(17) Lynch, V. M.; Stamford, A.; Magnus, P.; Davis, B. E. *Acta Crystallogr.* **1991**, *C47*, 1563.

Scheme X[a]



[a] R = $CO_2CH_2C_6H_4NO_2$-*p*.

Scheme XI[a]



[a] R = $CO_2CH_2C_6H_4NO_2$-*p*. Coupling Conditions: $ClCO_2CH_2C_6H_4NO_2$-*p*/vindoline/CH_3NO_2/−20 °C.

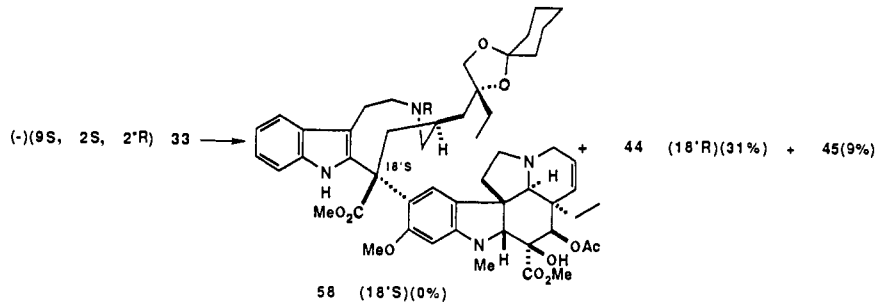
At first we thought that **41** was the C-18′*S* isomer of **40**, since its CD curve strongly resembled that of vinblastine [CD (MeOH), λ_{max} ($\Delta\epsilon$) 208 (−34), 275 (+13.2), 301 (+1.1), 335 (−13.2)].[18] The clue to the unprecedented structure of **41** came from the infrared and ultraviolet spectra. The infrared spectrum of **40** exhibits two carbonyl absorptions, at 1741 and 1694 cm^{-1}, whereas **41** has three, at 1741, 1697, and 1657 cm^{-1}. The ultraviolet spectrum of **40** has λ_{max} at 302 nm, whereas **41** has λ_{max} at 342 nm and is fluorescent. These data indicate the presence of a β-aminoacrylate functionality, and therefore suggest that coupling of vindoline has taken place at C-9′ resulting in **41**.

To umambiguously establish the unprecedented structure of the C-9′ coupled adduct **41** it was hydrolyzed to the diol **50**, which upon hydrogenolysis resulted in conjugate addition of N-6′ to the β-aminoacrylate functionality to give **53** (structure by X-ray)[19] (Scheme X). Heating **53** resulted in β-elimination and formation of the lactam **54**. The diol **50** was oxidized to the α-hydroxy

(18) Potier, P.; Langlois, N.; Langlois, Y.; Gueritte, F. *J. Chem. Soc., Chem. Commun.* **1975**, 670. Kutney, J. P.; Gregonis, D. E.; Imhof, R.; Itoh, I.; Jahngen, E.; Scott, A. I.; Chan, W. K. *J. Am. Chem. Soc.* **1975**, *97*, 5013.

(19) Lynch, V. M.; Stamford, A.; Magnus, P.; Davis, B. E. *Acta Crystallogr.* **1991**, *C47*, 1342.

Scheme XII[a]



[a] R = $CO_2CH_2C_6H_4NO_2$-*p*. Coupling Conditions: $ClCO_2CH_2C_6H_4NO_2$-*p*/vindoline/CH_2NO_2/−20 °C.

Table I

amine	*T*, °C	18′*S*:18′*R*	products, isolated yields[c]
(−)-**30**[a]	−20	60:40	**57** (46%), **40** (33%), **41** (0%)
(−)-**30**[b]	−20	67:33	**57** (59%), **40** (31%), **41** (0%)
(−)-**30**	25	11:89	HPLC ratios, trace of **41**
(−)-**33**	−20	1:99	**58** (0%), **44** (31%), **45** (9%)
(−)-**33**	25	4:96	**58** (0%), **44** (45%), **45** (4%)

[a] All reactions were run in nitromethane (ϵ_r 35.9), 0.06 M in amine, 2.6 equiv of 4-nitrobenzyl chloroformate, 4.0 equiv of vindoline. [b] 3.0 equiv of 2,6-di-*tert*-butyl-4-methylpyridine added. [c] Purified by HPLC.

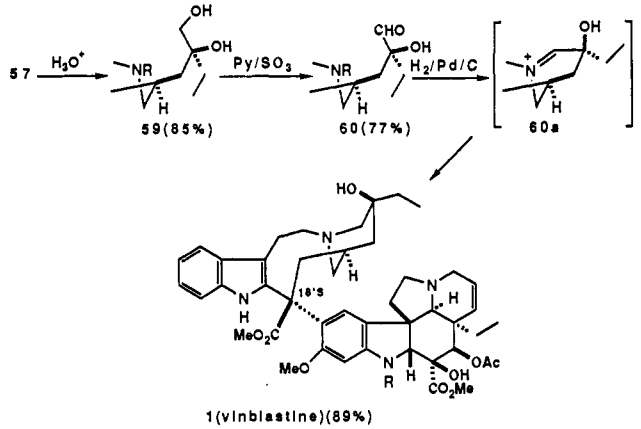
aldehyde **51**, which upon hydrogenolysis gave the new vinblastine isomer 9′-isovinblastine (**52**).

Coupling of (+)-**33** (opposite C-2 stereochemistry) with vindoline/$ClCO_2CH_2C_6H_4NO_2$-*p*/CH_2Cl_2/25 °C gave the two products **42** (40%) and **43** (34%). Paralleling the previous example, the reaction is stereospecific (α-face attack) but not regiospecific. When (−)-**33** was exposed to the above coupling conditions, it gave the two compounds **44** (47%) and **45** (25%), identical to **40** and **41** but antipodal at C-2′. Therefore, we can conclude that aromatic electrophilic substitution of (−)-**30**, (+)-**33**, and (−)-**33** takes place syn to the C-2 side chain and that under the described reaction conditions conformational equilibration of the putative intermediate iminium ion **56** (Scheme XI) is faster than the former. These results indicated that if coupling always takes place syn to the C-2 side chain, then the stereochemical relationship necessary for vinblastine (**1**) is not accessible using this strategy. In dichloromethane, the coupling reaction proceeds with inversion at C18′ (**40**, **42**, and **44**), and for the regioisomers, inversion occurs at C-9′ (**41**, **43**, and **45**). Only (+)-**33** gave the correct C-18′*S* stereochemistry but inverted at C-2.

If the rate of coupling can be increased relative to conformational equilibration of the putative iminium ions **55**/**56**, it might be possible to trap the desired conformer **55**. There are two obvious ways to achieve a change in the balance between the relative rates without resorting to major structural alterations: classically, increase the solvent polarity and lower the temperature.[20] All the coupling reactions described so far were run in CH_2Cl_2 (ϵ_r 8.9) at 25 °C.

Coupling of the Stereoisomeric Precursors of the Top Half to Vindoline in Nitromethane and Acetonitrile. Treatment of (−)-**30** with $ClCO_2CH_2C_6H_4NO_2$-*p*/vindoline/CH_3NO_2 (ϵ_r 35.9) at −20 °C gave the correct 18′*S* stereoisomer **57** (46%), along with **40** (33%) and traces of **41**, Table I. Carrying out the same coupling procedure as above but in the presence of 2,6-di-*tert*-butyl-4-methylpyridine gave **57** (59%) and **40** (31%) (Scheme XI). Hydrolysis of **57** gave the diol **59** (85%), which was oxidized using pyridine/SO_3 to the α-hydroxy aldehyde **60** (77%). Hydrogenolysis of **60** (Pd/C/MeOH) gave vinblastine (**1**) (89%) (Scheme XIII). This last transformation presumably proceeds via the iminium ion **60a**, which is the intermediate in Kutney's biomimetic conversion of 3′,4′-anhydrovinblastine (**11**) into vinblastine (**1**).[21]

Scheme XIII[a]



[a] R = $CO_2CH_2C_6H_4NO_2$-*p*.

Table II

amine	*T*, °C	18′*S*:18′*R*	products, isolated yields[b]
(−)-**30**[a]	−20	34:66	**57** (25%), **40** (48%), **41** (25%)
(−)-**30**[c]	−15	84:16	**57** (51%), **40** (11%), **41** (0%)

[a] All reactions were run in acetonitrile (ϵ_r 35.9), 0.06 M in amine, 2.6 equiv of 4-nitrobenzyl chloroformate, 4.0 equiv of vindoline. [b] Purified by HPLC. [c] Solvent CH_3CN/H_2O 15:1.

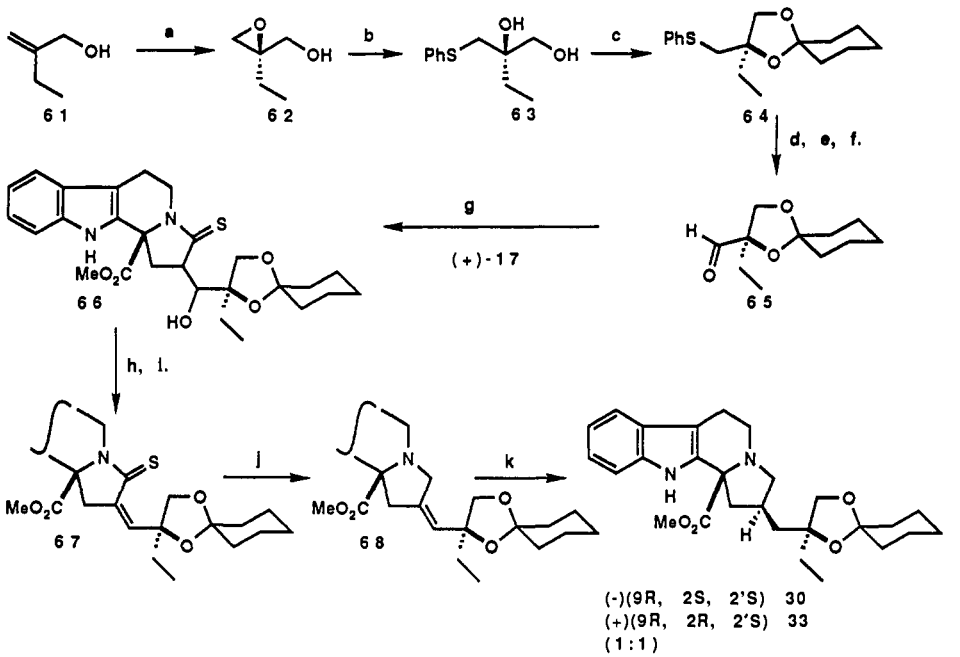
Coupling (−)-**30** with $ClCO_2CH_2C_6H_4NO_2$-*p*/vindoline/CH_3NO_2 at 25 °C reversed the stereoselectivity and gave the incorrect 18′*R* stereoisomer as the major product **57**/**40** (11:89, HPLC). Coupling of the C-9 amine epimer (−)-**33** to vindoline using the above conditions either at −20 °C or at 25 °C gave **44** and **45**, and none of the correct C-18′*S* stereoisomer **58** could be isolated (Scheme XII). Carrying out the coupling reaction in acetonitrile at −20 °C gave the correct C-18′*S* stereoisomer **57**, the 18′*R* epimer **40**, and, in contrast to the reaction in nitromethane solvent, a small amount of the 9′ regioisomer **41**. Increasing the dielectric constant of the acetonitrile by the addition of water (ϵ_r 78.3) gave the best ratio of 18′*S*/18′*R* (84:16) and no detectable amount of **41** (Table II).

The pronounced favorable solvent effect in reversing the stereochemistry at C-18′ could be attributed to preferential solvation of the "closed" iminium ion **55** versus the more delocalized "open" iminium ion **56**, Scheme XI. The more localized charge in the closed ion should be lowered in energy by solvation with nitromethane or acetonitrile more than the delocalized open ion.

(20) For general discussions of the effects of solvent polarity on reaction rates, see: Frost, A. A.; Pearson, R. G. *Kinetics and Mechanism. A Study of Homogeneous Chemical Reactions*; Wiley: New York, 1963. Alder, R. W.; Baker, R.; Brown, J. M. *Mechanism in Organic Chemistry*; Wiley: New York, 1975.

(21) Kutney, J. P.; Choi, L. S. L.; Nakano, J.; Tsukamoto, H.; McHugh, M.; Boulet, C. A. *Heterocycles* **1988**, *27*, 1845. Kutney, J. P.; Choi, L. S. L.; Nakano, J.; Tsukamoto, H. *Heterocycles* **1988**, *27*, 1827, 1837. For earlier work on the role of anhydrovinblastine in the biosynthesis of bisindole alkaloids, see: Scott, A. I.; Gueritte, F.; Lee, S.-L. *J. Am. Chem. Soc.* **1978**, *100*, 6253. The conversion of anhydrovinblastine into vinblastine: Mangeney, P.; Andriamialisoa, R. Z.; Langlois, N.; Langlois, Y.; Potier, P. *J. Am. Chem. Soc.* **1979**, *101*, 2243. Potier, P. *Pure Appl. Chem.* **1986**, *58*, 737. Mangeney, P.; Andriamialisoa, R. Z.; Lallemand, J-Y.; Langlois, N.; Langlois, Y.; Potier, P. *Tetrahedron* **1979**, *35*, 2175.

Scheme XIV[a]



[a] (a) Sharpless asymmetric epoxidation, D-(−)-DET, 85% ee. (b) PhSH/1.0 N aqueous NaOH/dioxane Δ. (c) H^+/1-methoxycyclohexene (28% from **61**). (d) MCPBA (94%). (e) Ac_2O/NaOAc/Δ (78%). (f) K_2CO_3/MeOH/Δ (88%). (g) $Sn(OTf)_2$/*N*-ethylpiperidine/THF (75%). (h) Ts_2O/Et_3N (91%). (i) DBU/CH_2Cl_2 (88%). (j) Raney nickel (deact). (k) H_2/10% Pd/C (44% from 67).

The closed ion occupies a conformation that allows electrophilic substitution with vindoline to take place from the least hindered face (α-face) to establish the natural C-18′ configuration. The conversion of the coupled product **57** into vinblastine is a very efficient process and proceeds in four steps in an overall yield of 34%.

While having access to different stereoisomers of **30** allowed us to delineate the factors that are required to control the stereochemistry of the crucial C-15/C-18′ bond, the synthesis of (−)-**30** was not stereospecific. Consequently, to improve the synthesis of vinblastine and to allow ready access to analogues, we have investigated a stereospecific synthesis of (−)-**30**.

Since we were able to alkylate the thioamide (+)-**17** using the thio-Claisen methodology, we decided to examine the aldol reaction of the thioamide and the aldehyde **65**.[22] Sharpless's asymmetric epoxidation[23] of 2-ethyl-2-propen-1-ol (**61**) gave (2*R*)-2-ethyl-2,3-epoxypropanol (**62**) (85% ee). Using the methodology developed by Williams,[24] the epoxide **62** was treated with thiophenol/1.0 N sodium hydroxide to give the diol **63**, which was directly converted into the crystalline ketal **64** (28% from **61**). Oxidation of the sulfide **64** to the corresponding sulfoxides and treatment with acetic anhydride–sodium acetate followed by hydrolysis gave the aldehyde **65** (88%). Aldol condensation of the aldehyde **65** with the (+)-thiolactam (+)-**17** to give **66** (75%) was best carried out using the Mukaiyama conditions, $Sn(OTf)_2$/*N*-ethylpiperidine.[25] It appears that **66** is a single diastereomer, although we could not determine the stereochemistry. Furthermore while desulfurization of **66** (Raney nickel) was straightforward, we could not form derivatives of the secondary hydroxyl group that would undergo deoxygenation. Dehydration (Ts_2O/Et_3N, DBU/CH_2Cl_2) of **66** gave the α,β-unsaturated thiolactam **67**, which when treated with Raney nickel under a variety of conditions gave the wrong epimer (+)-**33** as the major diastereomer (ca. 8:1, α/β). Desulfurization of **67** with deactivated Raney nickel (acetone) gave the alkene **68**, which upon hydrogenation over 10% Pd on carbon gave (−)-**30** (44%) and its 2α-epimer (+)-**33** (43%) (Scheme XIV).

Table III. IC-50 for 72-h Cytotoxicity Assay

	IC-50 (μg/mL)
1 (vinblastine)	0.000 50
49 (18′-epivinblastine)	0.006 92
11 (anhydrovinblastine)	0.050

Treatment of (−)-**30** with *m*-methoxy-*N*,*N*-dimethylaniline in nitromethane with *p*-$O_2NC_6H_4CH_2OCOCl$/DMBP/23 °C for 108 h gave **69** and **70** (74%, 4:1). The mixture of C-18′ stereoisomers was hydrolyzed to the readily separable diols **71** and oxidized to the α-hydroxy aldehyde **72**. Hydrogenolysis of **72** gave **73** (90%) via the iminium species **72a**. The assignment of absolute configuration at C-18′ was made by comparison of the CD curve with vinblastine (Scheme XV). The synthesis of **73** requires only one separation and provides access to the simple non-vindolinyl analogue of vinblastine for antitumor evaluation.[26]

Summary

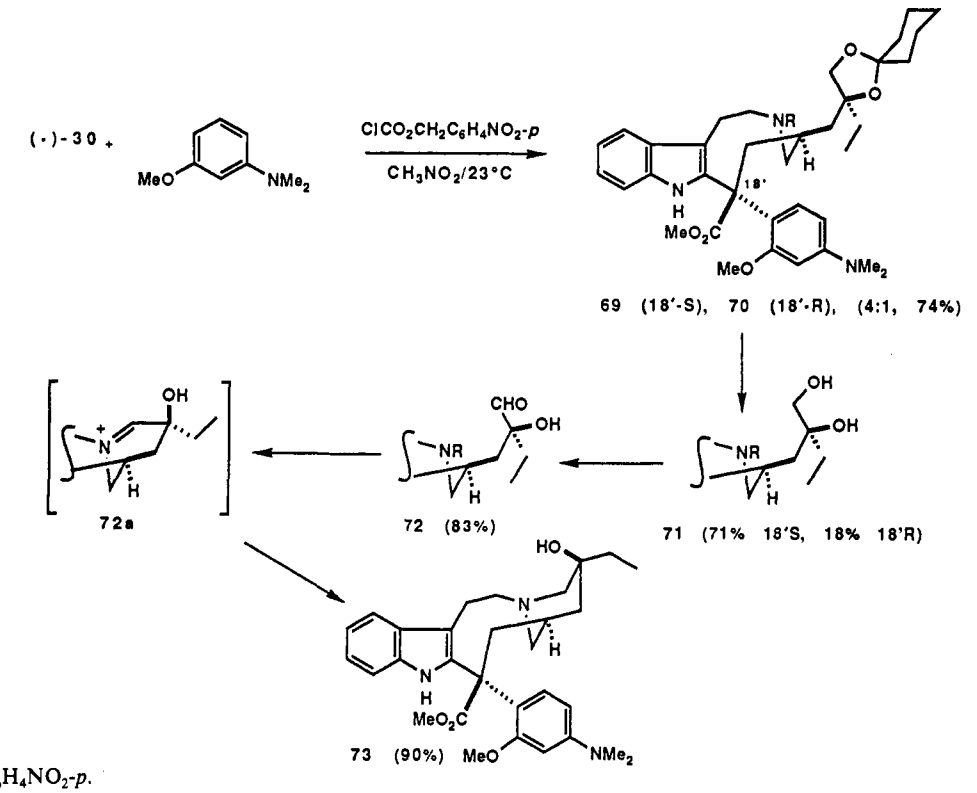
This study establishes that of all the various stereoisomers of the top-half precursors to vinblatsine, only the (−)-(9*R*,2*S*,2′*S*)-**30** diastereomer couples to vindoline to give the correct C-18′*S* stereochemistry. The in vitro activity of 18′-epivinblastine is approximately 1/14 that of vinblastine, which is not a drastic change when compared to anhydrovinblastine (Table III). This supports the notion that the C-4′ hydroxyl group is important for full activity.[27]

Experimental Section[28]

(+)-(9*R*,2*S*)-3-Thioxo-9-(methoxycarbonyl)-2-(2′-ethyl-2′-propenyl)hexahydroindolizino[8,7-*b*]indole (24) and the (+)-9*R*,2*R* Diastereoisomer 25. To a solution of the thiolactam (+)-**17** (12.05 g, 0.040

(22) Tamura, Y.; Harada, T.; Nishi, S.; Mizutani, M.; Hioki, T.; Yoshida, Z. *J. Am. Chem. Soc.* **1980**, *102*, 7806.
(23) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765. Rossiter, B. E. Synthetic Aspects and Applications of Asymmetric Epoxidation. *Asymmetric Synthesis*. Academic Press: New York, 1985; Vol. 5, p 227.
(24) Dung, J.-S.; Armstrong, R. W.; Anderson, O. P.; Williams, R. M. *J. Org. Chem.* **1983**, *48*, 3592.
(25) Mukaiyama, T.; Iwasawa, N. *Chem. Lett.* **1982**, 1903.
(26) Compound is currently undergoing biological evaluation.
(27) Borman, L. S.; Kuehne, M. E. Functional Hot Spot at the C-20′(12′) Position of Vinblastine. Medicinal Chemistry of Bisindole Alkaloids from *Catharanthus. The Alkaloids*; Brossi, A.; Suffness, M., Eds.; Academic Press Inc.: San Diego, 1990; Vol. 37. We have used the numbering system adopted by Pearce in ref 7, and therefore C-20′ is C-4′.
(28) Author numbering of the indolizino[8,7-*b*]indole ring system does not follow the systematic numbering given in the *Ring Systems Handbook*.

Scheme XV[a]



[a] R = $CO_2CH_2C_6H_4NO_2$-*p*.

mol) in dry nitromethane (250 mL) under argon was added 2-(bromomethyl)but-1-ene (10.5 mL, 3 equiv). The mixture was stirred at 25 °C for 78 h, and the nitromethane evaporated in vacuo to give the sulfonium salt **17a**. The yellow salt was added to dry tetrahydrofuran (225 mL), cooled to 0–5 °C, and treated with 1,5-diazabicyclo[5.4.0]undecene-5 (DBU) (12.1 mL). The mixture was warmed to 25 °C and stirred for 4.5 h. The solvent was evaporated in vacuo, and the residue was dissolved in ethyl acetate (400 mL) and washed with 2 N hydrochloric acid (200 mL), saturated aqueous sodium bicarbonate solution (200 mL), and saturated aqueous sodium chloride solution (200 mL). The organic layer was dried ($MgSO_4$), filtered, and evaporated in vacuo to give a yellow solid. Purification by flash chromatography over silica gel, eluting with 20% EtOAc–light petroleum ether, gave a mixture of **24** and **25** (11.10 g, 75%) in a 1:2.2 ratio (^{1}H NMR). For characterization, 200 mg of the mixture was separated by chromatography over silica gel (200 g), eluting with 30% ether–hexane, to give **24** and **25** as pure compounds.

For the less polar diastereoisomer (+)-**24**: mp 187–188 °C (MeOH); IR ($CHCl_3$) 3465, 2965, 1732, 1468, 1440, 1348, 1310, 1290, 1260, 1180, 1070, 1035, 905 cm^{-1}; UV (MeCN) λ_{max} (ϵ) 220 (28 000), 271 (24 000) nm; $[\alpha]^{25}_D$ +150° (*c* 0.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (1 H, s), 7.42 (1 H, dd, *J* = 8.0, 1.1 Hz), 7.28 (1 H, dd, *J* = 7.9, 0.9 Hz), 7.14 (1 H, ddd, *J* = 8.2, 7.1, 1.1 Hz), 7.05 (1 H, ddd, *J* = 8.0, 7.0, 1.0 Hz), 5.27 (1 H, ddd, *J* = 13.7, 5.7, 1.0 Hz), 4.78 (1 H, s), 4.57 (1 H, s), 3.72 (3 H, s), 3.48 (1 H, ddd, *J* = 13.0, 11.4, 5.2 Hz), 3.18 (1 H, m), 2.97–2.75 (3 H, m), 2.70 (1 H, dd, *J* = 13.0, 1.6 Hz), 2.33 (1 H, dd, *J* = 13.2, 9.2 Hz), 2.02–1.85 (3 H, m), 0.98 (3 H, t, *J* = 7.3 Hz); EIMS *m/e* 368 (M, 23), 309 (100), 281 (17), 240 (41), 231 (17), 219 (19), 208 (29), 180 (28), 169 (34), 131 (20), 119 (27); HRCIMS *m/e* calcd for $C_{21}H_{24}N_2O_2S$ 368.1558 (M), found *m/e* 368.1553. Anal. Calcd for $C_{21}H_{24}N_2O_2S$: C, 68.45; H, 6.56; N, 7.60. Found: C, 68.68; H, 6.84; N, 7.40. Crystals suitable for single-crystal X-ray crystallography were grown from chloroform–pentane by diffusion.

For the more polar diastereoisomer (+)-**25**: mp 122–123 °C (Et_2O/hexanes); IR ($CHCl_3$) 3465, 2970, 2940, 2880, 2860, 1730, 1460, 1432, 1345, 1290, 1250, 1220, 1192, 1153, 1070, 1035, 1010, 987, 898 cm^{-1}; UV (MeCN) λ_{max} (ϵ) 220 (26 000), 271 (29 000) nm; $[\alpha]^{25}_D$ +134° (*c* 0.8, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (1 H, s), 7.52 (1 H, dd, *J* = 7.8, 0.9 Hz), 7.38 (1 H, d, *J* = 8.1 Hz), 7.24 (1 H, td, *J* = 8.1, 1.1 Hz), 7.17 (1 H, td, *J* = 7.8, 1.0 Hz), 5.43 (1 H, m), 4.78 (1 H, s), 4.68 (1 H, s), 3.81 (3 H, s), 3.50 (1 H, m), 3.26 (1 H, m), 3.12–2.91 (4 H, m), 2.10–1.83 (4 H, m), 1.05 (3 H, t, *J* = 7.5 Hz); EIMS *m/e* 368 (20), 309 (100), 281 (18), 267 (10), 241 (14), 239 (65), 231 (28), 219 (28), 208 (57), 181 (46), 169 (69), 131 (40), 119 (71); HRCIMS *m/e* calcd for $C_{21}H_{24}N_2O_2S$ 368.1558 (M), found *m/e* 368.1557. Anal. Calcd for $C_{21}H_{24}N_2O_2S$: C, 68.45; H, 6.56; N, 7.60. Found: C, 68.65; H, 6.85; N, 7.44.

(+)-(9*R*,2*S*)-3-Oxo-9-(methoxycarbonyl)-2-(2′-ethyl-2′-propenyl)-hexahydroindolizino[8,7-*b*]indole (26) and the (+)-9*R*,2*R* Diastereoisomer 27. A solution of the thiolactams **24** and **25** (11.73 g, 31.9 mmol) in dichloromethane (300 mL) under argon was cooled to 4 °C, and a solution of *m*-chloroperoxybenzoic acid (7.34 g, 38.3 mmol) was added dropwise over 0.5 h. A further quantity of peracid (1.0 g) was added, and the mixture was stirred at 25 °C for 1 h. The mixture was washed with saturated aqueous sodium bicarbonate (500 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo to give an oil. Purification by chromatography over silica gel gave (+)-**26** (0.80 g, 7%), (+)-**26**/(+)-**27** (6.50 g, 58%), and (+)-**27** (2.28 g, 20%). The mixed fraction was purified by preparative HPLC (Dynamax Microsorb 70% hexanes–30% EtOAc, 1.5 μL/min, 900 psi) to give (+)-**26** (2.23 g, t_R 4.9) and (+)-**27** (3.38 g, t_R 5.9).

For the less polar diastereoisomer (+)-**26**: mp 68–73 °C (Et_2O/hexanes); IR ($CHCl_3$) 3286, 2964, 2849, 1742, 1683, 1622, 1493, 1452, 1423, 1350, 1322, 1299, 1255, 1189, 1168, 1116, 1073, 1056, 1024, 1009, 989, 936, 895, 739 cm^{-1}; $[\alpha]^{23}_D$ +90° (*c* 2.6, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (1 H, br s), 7.47 (1 H, d, *J* = 7.7 Hz), 7.35 (1 H, d, *J* = 8.2 Hz), 7.20 (1 H, td, *J* = 7.2, 0.8 Hz), 7.11 (1 H, td, *J* = 7.3, 0.9 Hz), 4.83 (1 H, d, *J* = 0.8 Hz), 4.65 (1 H, s), 4.55 (1 H, dd, *J* = 13.5, 5.4 Hz), 3.78 (3 H, s), 3.29 (1 H, ddd, *J* = 13.2, 11.4, 5.3 Hz), 2.92–2.56 (5 H, m), 2.43 (1 H, dd, *J* = 13.2, 9.4 Hz), 2.06–1.89 (3 H, m), 1.02 (3 H, t, *J* = 7.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.67, 172.67, 148.17, 136.48, 130.52, 126.17, 122.76, 119.86, 118.62, 111.21, 110.34, 109.68, 64.22, 53.04, 40.39, 37.71, 28.00, 20.61, 12.15; EIMS *m/e* 352 (M, 2), 293 (70), 223 (100); HREIMS *m/e* calcd for $C_{21}H_{24}N_2O_3$ 352.1787, found *m/e* 352.1798. Anal. Calcd for $C_{21}H_{24}N_2O_3$: C, 71.57; H, 6.86; N, 7.95. Found: C, 71.63; H, 6.92; N, 7.92.

For the more polar diastereoisomer (+)-**27**: mp 137–138 °C (Et_2O/hexanes); IR ($CHCl_3$) 3288, 3062, 2964, 2935, 2850, 2747, 1739, 1695, 1493, 1454, 1418, 1373, 1351, 1322, 1300, 1252, 1204, 1165, 1116, 1087, 1069 cm^{-1}; $[\alpha]^{25}_D$ +91.8° (*c* 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (1 H, br s), 7.59 (1 H, d, *J* = 7.7 Hz), 7.35 (1 H, d, *J* = 8.0 Hz), 7.21 (1 H, td, *J* = 7.7, 0.9 Hz), 7.11 (1 H, td, *J* = 7.7, 0.8 Hz), 4.74 (1 H, d, *J* = 1.0 Hz), 4.65 (1 H, s), 4.57 (1 H, m), 3.78 (3 H, s), 3.21 (1 H, dt, *J* = 13.3, 8.2 Hz), 2.93–2.72 (5 H, m), 2.08–1.84 (4 H, m), 1.00 (3 H, t, *J* = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.28, 172.15, 148.12, 136.49, 130.57, 126.13, 122.76, 119.87, 118.66, 111.22, 109.71, 109.25, 63.57, 53.15, 39.84, 39.12, 37.56, 36.58, 28.29, 20.90, 12.17; EIMS *m/e* 352 (M, 3), 293 (85), 223 (100); HREIMS *m/e* calcd for $C_{21}H_{24}N_2O_3$ 352.1787, found *m/e* 352.1766. Anal. Calcd for $C_{21}H_{24}N_2O_3$: C, 71.57; H, 6.86; N, 7.95. Found: C, 71.41; H, 6.86; N, 7.90.

(−)-(9*S*,2*R*)-3-Oxo-9-(methoxycarbonyl)-2-(2′-ethyl-2′-propenyl)-hexahydroindolizino[8,7-*b*]indole (26) and the (−)-9*S*,2*S* Diastereoisomer 27. Using a sequence identical to that above, starting from (−)-(9*S*)-**17** gave (−)-**26** and (−)-**27**.

For the less polar diastereomer (−)-**26**: foam; $[\alpha]^{25}_D$ −99° (*c* 1.17, $CHCl_3$); HRCIMS *m/e* calcd for $C_{21}H_{24}N_2O_3$ 352.1787 (M), found *m/e* 352.1805. Anal. Calcd for $C_{21}H_{24}N_2O_3$: C, 71.57; H, 6.86; N, 7.95. Found: C, 71.74; H, 6.90; N, 7.86.

For the more polar diastereomer (−)-**27**: foam; $[\alpha]^{25}_D$ −86° (*c* 0.76, $CHCl_3$); HRCIMS *m/e* calcd for $C_{21}H_{24}N_2O_3$ 352.1787 (M), found *m/e* 352.1779. Anal. Calcd for $C_{21}H_{24}N_2O_3$: C, 71.57; H, 6.86; N, 7.95. Found: C, 71.61; H, 6.92; N, 7.75.

(+)-(9*R*,2*S*,2′*S*)-3-Oxo-9-(methoxycarbonyl)-2-(2′-ethyl-2′,3′-dihydroxypropyl)hexahydroindolizino[8,7-*b*]indole Cyclohexylidene Ketal (28) and the (+)-9*R*,2*S*,2′*R* Diastereoisomer 34. To a solution of the alkene **26** (1.92 g, 5.45 mmol) in a mixture of acetone–water (160 mL) was added *N*-methylmorpholine *N*-oxide (1.99 g, 17.0 mmol), followed by a 2.5 wt% solution of osmium tetraoxide in *tert*-butyl alcohol (0.90 mL). The solution was stirred at 25 °C for 15 h. A 10% aqueous solution of sodium bisulfite (100 mL) was added to the mixture, and the acetone was evaporated in vacuo. The aqueous emulsion was acidified to pH 1 with 2 M hydrochloric acid and extracted with dichloromethane (3 × 150 mL). The combined extracts were washed with saturated aqueous sodium bicarbonate solution (150 mL), dried ($MgSO_4$), and evaporated in vacuo to give a white foam. The foam was dissolved in tetrahydrofuran (60 mL), and cyclohexanone methyl enol ether (0.90 mL) was added, followed by Amberlyst H 15 resin (50 mg). The mixture was stirred at 25 °C for 16 h, filtered, and washed with tetrahydrofuran. The mixture was evaporated in vacuo, and the residue was purified by flash chromatography over silica gel, eluting with 30% EtOAc–hexane, to give the diastereoisomeric ketals **28** and **34** (1:1.32) (2.03 g, 80%). A small sample (20 mg) of the mixture was separated by PLC (85% Et_2O–hexane and 5% MeOH–Et_2O).

For the less polar diastereoisomer (+)-**28**: foam; IR ($CHCl_3$) 3460, 2935, 2850, 1725, 1680, 1410, 1090, 920 cm^{-1}; $[\alpha]^{25}_D$ +35° (*c* 0.60, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 8.30 (1 H, br s), 7.49 (1 H, d, *J* = 7.9 Hz), 7.38 (1 H, d, *J* = 7.9 Hz), 7.23 (1 H, t, *J* = 7.8 Hz), 7.23 (1 H, t, *J* = 8.1 Hz), 4.55 (1 H, dd, *J* = 13.3, 5.9 Hz), 3.88 (1 H, d, *J* = 8.5 Hz), 3.79 (3 H, s), 3.66 (1 H, d, *J* = 8.5 Hz), 3.31 (1 H, ddd, *J* = 13.2, 11.8, 4.9 Hz), 2.88–2.60 (4 H, m), 2.18 (1 H, dd, *J* = 14.3, 2.6 Hz), 1.66–1.31 (13 H, m), 0.88 (3 H, t, *J* = 7.6 Hz); CIMS *m/e* 466 (M, 3), 477 (66), 369 (39), 351 (28), 309 (100), 291 (25), 281 (13), 243 (19), 237 (17), 231 (25), 223 (61); HRCIMS *m/e* calcd for $C_{27}H_{34}N_2O_5$ 466.2468 (M), found *m/e* 466.2483.

For the more polar diastereoisomer (+)-**34**: foam; IR ($CHCl_3$) 3480, 2940, 2860, 1725, 1680, 1410, 1160, 1090, 935 cm^{-1}; $[\alpha]^{25}_D$ +75° (*c* 0.80, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 8.30 (1 H, br s), 7.48 (1 H, d, *J* = 8.1 Hz), 7.38 (1 H, d, *J* = 8.1 Hz), 7.22 (1 H, td, *J* = 7.6, 0.9 Hz), 7.13 (1 H, td, *J* = 7.6, 0.8 Hz), 4.55 (1 H, dd, *J* = 13.3, 5.8 Hz), 3.82 (1 H, d, *J* = 8.5 Hz), 3.80 (3 H, s), 3.76 (1 H, d, *J* = 8.5 Hz), 3.31 (1 H, ddd, *J* = 13.2, 11.6, 5.3 Hz), 2.83 (1 H, ddd, *J* = 16.5, 11.3, 6.2 Hz), 2.76 (1 H, dd, *J* = 15.8, 4.7 Hz), 2.72–2.62 (2 H, m), 2.10 (1 H, d, *J* = 14.1 Hz), 1.72–1.28 (13 H, m), 0.90 (3 H, t, *J* = 7.5 Hz); CIMS *m/e* 466 (M, 4), 407 (80), 369 (41), 351 (33), 309 (100), 291 (41), 281 (21), 243 (34), 230 (49), 223 (62); HRCIMS *m/e* calcd for $C_{27}H_{34}N_2O_5$ 466.2468 (M), found *m/e* 466.2448.

(+)-(9*R*,2*S*,2′*S*)-3-Thioxo-9-(methoxycarbonyl)-2-(2′-ethyl-2′,3′-dihydroxypropyl)hexahydroindolizino[8,7-*b*]indole Cyclohexylidene Ketal (29) and the (+)-9*R*,2*S*,2′*R* Diastereoisomer 35. To a solution of the amides **28** and **34** (2.71 g, 5.82 mmol) in dry toluene (100 mL) under argon was added Lawesson's reagent (1.41 g, 0.6 equiv). The suspension was heated at 80 °C for 4 h, cooled to 25 °C, and stirred for a further 12 h. The mixture was evaporated to dryness in vacuo, and the residue was purified by flash chromatography to give **29** (0.704 g, 25%) and a mixed fraction (1.7 g, 61%). The mixed fraction was purified by preparative HPLC (Dynamax Microsorb 12.5% EtOAc–hexane 1.5 μL/min, 1000 psi) to give (+)-**29** (0.265 g, *t* 6.3) and (+)-**35** (1.16 g, t_R 8.9).

For the less polar diastereoisomer (+)-**29**: mp 201–202 °C (Et_2O); IR ($CHCl_3$) 3460, 2935, 2860, 1735, 1465, 1435, 1345, 1255, 1182, 1090, 1040, 925 cm^{-1}; UV (MeOH) λ_{max} (ε) 217 (28 000), 273 (20 000), 284 (19 000), 289 (13 000) nm; $[\alpha]^{25}_D$ +89° (*c* 0.8, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 8.26 (1 H, br s), 7.49 (1 H, d, *J* = 7.7 Hz), 7.37 (1 H, d, *J* = 7.9 Hz), 7.22 (1 H, t, *J* = 7.7 Hz), 7.12 (1 H, t, *J* = 7.9 Hz), 5.32 (1 H, dd, *J* = 13.0, 5.5 Hz), 3.90 (1 H, d, *J* = 8.6 Hz), 3.78 (3 H, s), 3.63 (1 H, d, *J* = 8.6 Hz), 3.53 (1 H, td, *J* = 12.3, 5.1 Hz), 3.24–3.13 (2 H, m), 2.99 (1 H, ddd, *J* = 15.8, 11.7, 5.9 Hz), 2.83 (1 H, dd, *J* = 15.8, 4.6 Hz), 2.56 (1 H, dd, *J* = 13.3, 9.9 Hz), 2.44 (1 H, m), 1.70–1.20 (13 H, m), 0.92 (3 H, t, *J* = 7.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.21, 171.40, 136.68, 129.98, 125.94, 123.02, 120.11, 118.77, 111.29, 110.10, 109.82, 83.14, 72.80, 71.72, 53.31, 50.99, 42.61, 41.06, 37.93, 36.59, 29.50, 25.11, 23.94, 23.88, 20.03, 8.95; CIMS *m/e* 482 (M, 3), 449 (32), 423 (27), 385 (24), 367 (17), 342 (17), 331 (20), 325 (22), 316 (16), 304 (20), 293 (33), 281 (57), 267 (24), 255 (34), 243 (74), 231 (100); HRCIMS *m/e* calcd for $C_{27}H_{34}N_2O_4S$ 482.2239 (M), found *m/e* 482.2239. Anal. Calcd for $C_{27}H_{34}N_2O_4S$: C, 67.19; H, 7.10; N, 5.80. Found: C, 67.13; H, 6.96; N, 5.78. Crystals suitable for single-crystal X-ray crystallography were grown from ether.

For the more polar diastereoisomer (+)-**35**: foam; IR ($CHCl_3$) 3461, 3008, 2938, 2880, 2856, 1749, 1733, 1474, 1443, 1435, 1367, 1345, 1296, 1282, 1257, 1179, 1165, 1143, 1118, 938, 1094 cm^{-1}; UV (MeOH) λ_{max} (ε) 217 (27 000), 273 (19 000), 284 (18 000), 289 (12 000) nm; $[\alpha]^{23}_D$ +35° (*c* 1.1, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 8.24 (1 H, br s), 7.51 (1 H, d, *J* = 7.6 Hz), 7.39 (1 H, d, *J* = 7.3 Hz), 7.24 (1 H, td, *J* = 8.3, 1.0 Hz), 7.14 (1 H, m), 5.34 (1 H, dd, *J* = 13.0, 5.5 Hz), 3.96 (1 H, d, *J* = 8.8 Hz), 3.82 (3 H, s), 3.82 (1 H, d, *J* = 8.8 Hz), 3.57 (1 H, ddd, *J* = 13.3, 12.0, 5.2 Hz), 3.22 (1 H, m), 3.06–2.83 (3 H, m) 2.57 (1 H, dd, *J* = 14.5, 1.3 Hz), 1.80–1.30 (13 H, m), 0.91 (3 H, t, *J* = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.4, 171.57, 136.64, 129.73, 125.93, 123.01, 120.10, 118.75, 111.26, 110.01, 109.77, 85.29, 71.55, 71.49, 53.38, 50.87, 42.53, 40.12, 39.11, 36.82, 36.47, 32.47, 25.06, 23.88, 20.10, 8.28 (2 methylene carbons coincident); CIMS *m/e* 482 (3), 449 (32), 423 (27), 385 (24), 331 (20), 325 (22), 293 (33), 280 (57), 267 (24), 255 (34), 253 (22), 243 (74), 215 (100); HRCIMS *m/e* calcd for $C_{27}H_{34}N_2O_4S$ 482.2239 (M), found *m/e* 482.2245.

(−)-(9*R*,2*S*,2′*S*)-3*H*-9-(Methoxycarbonyl)-2-(2′-ethyl-2′,3′-dihydroxypropyl)hexahydroindolizino[8,7-*b*]indole Cyclohexylidene Ketal (30) and the (+)-9*R*,2*S*,2′*R* Diastereoisomer 36. A suspension of Raney nickel (5 g) and the thiolactam **29** (482 mg, 1.0 mmol) in tetrahydrofuran (9 mL) was stirred at 25 °C for 16 h. Additional Raney nickel in tetrahydrofuran (5 mL) was added, and stirring was continued for 4 h. The mixture was filtered through Celite and washed with methanol. The filtrate was evaporated in vacuo to give (−)-**30** (423 mg, 94%): IR ($CHCl_3$) 4362, 3006, 2937, 2859, 1745, 1717, 1461, 1436, 1367, 1330, 1321, 1281, 1266, 1143, 1119, 1096, 1034, 938 cm^{-1}; UV (MeOH) λ_{max} (ε) 222 (31 000), 274 (8000), 282 (9000), 291 (5000) nm; $[\alpha]^{25}_D$ −3.8° (*c* 2.36, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.27 (1 H, s), 7.51 (1 H, d, *J* = 7.7 Hz), 7.35 (1 H, d, *J* = 7.9 Hz), 7.21 (1 H, dt, *J* = 7.5, 0.6 Hz), 7.10 (1 H, t, *J* = 7.3 Hz), 3.76 (3 H, s), 3.73 (1 H, d, *J* = 8.5 Hz), 3.61 (1 H, d, *J* = 8.5 Hz), 3.33–3.29 (2 H, m), 3.16 (1 H, m), 3.05–2.92 (2 H, m), 2.62 (1 H, dd, *J* = 12.5, 6.9 Hz), 2.52 (1 H, dt, *J* = 15.5, 2.5 Hz), 2.26 (1 H, dd, *J* = 12.4, 9.3 Hz), 2.11 (1 H, m), 1.75–1.26 (14 H, m), 0.79 (3 H, t, *J* = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.94, 136.19, 131.78, 126.84, 122.20, 119.40, 118.38, 111.06, 110.85, 109.72, 82.94, 72.28, 67.71, 56.37, 52.70, 44.19, 43.91, 41.51, 36.59, 36.55, 32.05, 30.34, 25.11, 23.92, 23.85, 15.71, 8.74; HRMS calcd for $C_{27}H_{36}N_2O_4$ 452.2675, found *m/e* 452.2641.

Prepared in the same manner from **35**, for (+)-**36**: foam; IR ($CHCl_3$) 3461, 3008, 2938, 2863, 1745, 1717, 1461, 1449, 1436, 1367, 1330, 1281, 1235, 1162, 1096, 1035, 938, 909, 927 cm^{-1}; $[\alpha]^{23}_D$ +29° (*c* 4.2, MeOH); UV (MeOH) λ_{max} (ε) 220 (25 000), 274 (8000), 280 (8000), 289 (7000) nm; ^1H NMR (300 MHz, $CDCl_3$) δ 8.18 (1 H, br s), 7.52 (1 H, d, *J* = 7.7 Hz), 7.36 (1 H, d, *J* = 7.8 Hz), 7.20 (1 H, t, *J* = 7.5 Hz), 7.11 (1 H, t, *J* = 7.8 Hz), 3.77 (3 H, s), 3.72 (1 H, d, *J* = 8.3 Hz), 3.59 (1 H, d, *J* = 8.3 Hz), 3.31–2.97 (4 H, m), 2.56–2.49 (2 H, m) 2.14–2.10 (2 H, m), 1.72–1.26 (15 H, m), 0.79 (3 H, t, *J* = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.10, 136.19, 131.71, 126.87, 122.24, 119.43, 118.43, 111.34, 111.03, 109.72, 82.89, 72.31, 67.34, 56.44, 52.78, 44.83, 44.28, 41.34, 36.59, 32.36, 30.32, 25.12, 23.91, 15.90, 8.70; CIMS *m/e* 453 (M + 1, 8), 393 (100), 295 (15), 209 (13); HRCIMS *m/e* calcd for $C_{27}H_{36}N_2O_4$ 452.2675 (M), found *m/e* 452.2674.

(+)-(9*R*,2*R*,2′*S*)-3-Oxo-9-(methoxycarbonyl)-2-(2′-ethyl-2′,3′-dihydroxypropyl)hexahydroindolizino[8,7-*b*]indole Cyclohexylidene Ketal (31) and the (+)-9*R*,2*R*,2′*S* Diastereoisomer 37. Prepared in the same manner as **28**/**34**, except from **27**. For the less polar diastereomer (+)-**31**: mp 218–219 °C (Et_2O); IR ($CHCl_3$) 3461, 3010, 2938, 2882, 2859, 1749, 1728, 1688, 1461, 1453, 1449, 1415, 1350, 1298, 1162, 1096, 938, 920 cm^{-1}; $[\alpha]^{23}_D$ +103° (*c* 0.61, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.32 (1 H, br s), 7.50 (1 H, d, *J* = 7.7 Hz), 7.38 (1 H, d, *J* = 8.0 Hz), 7.23 (1 H, t, *J* = 7.8 Hz), 7.13 (1 H, t, *J* = 7.4 Hz), 4.58 (1 H, dt, *J* = 12.7, 3.6 Hz), 3.79 (3 H, s), 3.77 (2 H, s), 3.27–3.18 (2 H, m), 2.85–2.70 (3 H, m), 2.43 (1 H, dd, *J* = 14.7, 2.0 Hz), 1.95 (1 H, t, *J* = 12.2 Hz), 1.67–1.36 (12 H, m), 1.45 (1 H, dd, *J* = 14.7, 9.7 Hz), 0.86 (3 H, t, *J* = 7.4 Hz); CIMS *m/e* 467 (M + 1, 65), 407 (49), 369 (100), 309 (26), 223 (31), 101 (23); HRCIMS *m/e* calcd for $C_{27}H_{34}N_2O_5$ 466.2468 (M), found *m/e* 466.2460. Anal. Calcd for $C_{27}H_{34}N_2O_5$: C, 69.51; H, 7.35; N, 6.00. Found: C, 69.69; H, 7.44; N, 6.00.

For the more polar diastereomer (+)-**37**: foam; IR ($CHCl_3$) 3461, 3009, 2938, 2878, 2859, 1748, 1728, 1686, 1462, 1449, 1435, 1416, 1365, 1351, 1321, 1298, 1269, 1165, 1094, 1071, 1035, 938, 927 cm^{-1}; $[\alpha]^{23}_D$

+66.4° (*c* 0.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.30 (1 H, br s), 7.51 (1 H, d, *J* = 7.8 Hz), 7.40 (1 H, d, *J* = 8.1 Hz), 7.23 (1 H, t, *J* = 8.0 Hz), 7.13 (1 H, t, *J* = 7.9 Hz), 4.58 (1 H, dt, *J* = 12.6, 3.5 Hz), 3.85 (1 H, d, *J* = 8.7 Hz), 3.80 (3 H, s), 3.78 (1 H, d, *J* = 8.7 Hz), 3.25–3.15 (2 H, m), 2.85–2.66 (3 H, m), 2.41 (1 H, dd, *J* = 14.5, 2.4 Hz), 2.01 (1 H, t, *J* = 12.3 Hz), 1.75–1.25 (12 H, m), 1.41 (1 H, dd, *J* = 14.6, 10.8 Hz), 0.90 (3 H, t, *J* = 7.5 Hz); CIMS *m/e* 467 (M + 1, 34), 407 (62), 369 (100), 351 (23), 309 (32), 223 (42); HRCIMS *m/e* calcd for $C_{27}H_{34}N_2O_5$ 466.2468 (M), found *m/e* 466.2464.

(+)-(9*R*,2*R*,2′*S*)-3-Thioxo-9-(methoxycarbonyl)-2-(2′-ethyl-2′,3′-dihydroxypropyl)hexahydroindolizino[8,7-*b*]indole Cyclohexylidene Ketal (32) and the (+)-9*R*,2*R*,2′*R* Diastereoisomer 38. Prepared in the same manner as **29**/**35**, except from **31**/**37**. For the less polar diastereomer (+)-**32**: foam; IR ($CHCl_3$) 3460, 3006, 2969, 2938, 2881, 2856, 2747, 1735, 1468, 1442, 1434, 1381, 1367, 1345, 1330, 1317, 1297, 1252, 1169, 1162, 1152, 1117, 1096, 1072, 1041, 1032, 1010, 1000, 967 cm^{-1}; UV (MeOH) λ_{max} (ε) 217 (37 000), 273 (34 000), 284 (31 000), 289 (20 000) nm; $[\alpha]^{25}_D$ +107° (*c* 0.61, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.35 (1 H, br s), 7.50 (1 H, d, *J* = 7.7 Hz), 7.37 (1 H, d, *J* = 8.0 Hz), 7.23 (1 H, m), 7.13 (1 H, m), 5.42 (1 H, m), 3.82 (2 H, ABq), 3.79 (3 H, s), 3.49 (1 H, m), 3.35 (1 H, dd, *J* = 12.6, 7.0 Hz), 3.00–2.89 (4 H, m), 1.94 (1 H, t, *J* = 12.2 Hz), 1.70–1.30 (12 H, m), 1.50 (1 H, dd, *J* = 15.0, 9.7 Hz), 0.88 (3 H, t, *J* = 7.5 Hz); CIMS *m/e* 482 (M, 20), 449 (15), 423 (44), 385 (100), 367 (16), 325 (21), 297 (11), 253 (15), 239 (14), 208 (23), 154 (28); HRCIMS *m/e* calcd for $C_{27}H_{34}N_2O_4S$ 482.2239 (M), found *m/e* 482.2237. Anal. Calcd for $C_{27}H_{34}N_2O_4S$: C, 67.19; H, 7.10; N, 5.80. Found: C, 66.86; H, 7.17; N, 5.65.

For the less polar diastereomer (−)-**32**: foam; $[\alpha]^{23}_D$ −105° (*c* 0.61, $CHCl_3$); CIMS *m/e* 483 (M + 1, 33), 449 (12), 423 (22), 385 (100), 325 (21), 253 (15), 239 (14), 208 (19), 154 (32); HRCIMS *m/e* calcd for $C_{27}H_{34}N_2O_4S$ 482.2239 (M), found *m/e* 482.2237. Anal. Calcd for $C_{27}H_{34}N_2O_4S$: C, 67.19; H, 7.10; N, 5.80. Found: C, 67.03; H, 7.16; N, 5.52.

For the more polar diastereomer (+)-**38**: mp 206–208 °C (Et_2O/hexanes); IR ($CHCl_3$) 3460, 3007, 2982, 2940, 2879, 2856, 1747, 1732, 1469, 1442, 1364, 1345, 1297, 1284, 1251, 1192, 1165, 1110, 1071, 1031, 1010, 979, 937 cm^{-1}; UV (MeOH) λ_{max} (ε) 218 (38 000), 274 (29 000), 282 (26 000), 289 (16 000) nm; $[\alpha]^{23}_D$ +145° (*c* 0.30, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.28 (1 H, br s), 7.52 (1 H, d, *J* = 7.8 Hz), 7.47 (1 H, d, *J* = 8.0 Hz), 7.25 (1 H, td, *J* = 7.6, 0.9 Hz), 7.15 (1 H, t, *J* = 7.6 Hz), 5.43 (1 H, m), 3.89 (1 H, d, *J* = 8.6 Hz), 3.82 (3 H, s), 3.68 (1 H, d, *J* = 8.6 Hz), 3.48 (1 H, m), 3.32 (1 H, dd, *J* = 12.9, 6.9 Hz), 3.00–2.90 (4 H, m), 2.02 (1 H, t, *J* = 12.8 Hz), 1.74–1.31 (13 H, m), 0.93 (3 H, t, *J* = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.75, 170.80, 136.73, 129.90, 126.01, 123.06, 120.18, 118.86, 111.34, 109.97, 109.60, 82.87, 72.76, 70.64, 53.55, 48.59, 42.76, 42.50, 41.66, 36.64, 36.44, 29.72, 25.12, 23.93, 23.89, 20.47, 9.09; CIMS *m/e* 483 (M + 1, 48), 423 (79), 385 (100), 325 (16), 284 (46), 253 (25), 240 (13), 238 (28), 235 (22), 233 (26), 215 (12), 163 (69), 135 (55), 107 (87); HRCIMS *m/e* calcd for $C_{27}H_{34}N_2O_4S$ 482.2239 (M), found *m/e* 482.2236. Anal. Calcd for $C_{27}H_{34}N_2O_4S$: C, 67.19; H, 7.10; N, 5.80. Found: C, 67.40; H, 7.17; N, 5.68.

For the more polar diastereomer (−)-**38**: mp 219–220 °C (Et_2O); $[\alpha]^{23}_D$ −147° (*c* 0.30, $CHCl_3$); CIMS *m/e* 483 (M + 1, 9), 423 (16), 385 (31), 208 (14), 154 (23), 147 (11), 133 (13), 127 (12), 115 (100); HRCIMS *m/e* calcd for $C_{27}H_{35}N_2O_4S$ 483.2318 (M + 1), found *m/e* 483.2321. Anal. Calcd for $C_{27}H_{34}N_2O_4S$: C, 67.19; H, 7.10; N, 5.80. Found: C, 67.36; H, 7.17; N, 5.55.

(+)-(9*R*,2*R*,2′*S*)-3*H*-9-(Methoxycarbonyl)-2-(2′-ethyl-2′,3′-dihydroxypropyl)hexahydroindolizino[8,7-*b*]indole Cyclohexylidene Ketal (33). Prepared in the same manner as **30**, except from **32**. (+)-**33**: UV (MeOH) λ_{max} (ε) 222 (32 000), 275 (9000), 282 (9000), 291 (7000) nm; $[\alpha]^{25}_D$ +40.1° (*c* 0.665, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.22 (1 H, s), 7.52 (1 H, d, *J* = 7.6 Hz), 7.35 (1 H, d, *J* = 7.9 Hz), 7.26–7.08 (2 H, m), 3.77 (3 H, s), 3.74 (1 H, d, *J* = 8.5 Hz), 3.58 (1 H, d, *J* = 8.5 Hz), 3.42–3.24 (3 H, m), 2.97–2.81 (2 H, m), 2.67 (1 H, m), 2.57 (1 H, m), 2.46 (1 H, m), 1.90–1.82 (2 H, m), 1.74–1.37 (13 H, m), 0.82 (3 H, t, *J* = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.57, 136.28, 133.50, 126.66, 122.22, 119.51, 118.52, 111.00, 109.66, 108.77, 82.87, 72.46, 65.51, 56.60, 52.87, 46.11, 43.76, 39.98, 36.76, 36.68, 33.00, 30.05, 25.15, 23.95, 23.89, 15.93, 8.72; HRMS calcd for $C_{27}H_{36}N_2O_4$ 452.2675, found *m/e* 452.2679.

(−)-**33**: $[\alpha]^{25}_D$ −39.0° (*c* 0.78, $CHCl_3$); HRMS calcd for $C_{27}H_{36}N_2O_4$ 452.2675, found *m/e* 452.2643.

Coupling Reactions in Dichloromethane. Coupling of Vindoline with (−)-(9*R*,2*S*,2′*S*-(30) To Give 40 and 41. To a stirred solution of the amine (−)-**30** (254 mg, 0.56 mmol) in dry dichloromethane (5 mL) under argon was added (4-nitrobenzyl)chloroformate (314 mg, 2.6 equiv) followed by vindoline (1.027 g, 4.0 equiv). The mixture was stirred at 25 °C for 72 h, and the reaction was quenched with methanol (300 μL). The solution was diluted with dichloromethane (25 mL), washed with saturated aqueous sodium bicarbonate (25 mL), dried ($MgSO_4$), and evaporated in vacuo to give a mixture of vindoline and the bis-alkaloids **40** and **41**. The mixture was partially purified by flash chromatography over silica gel, eluting with 5% (1% NH_3–MeOH)/75% EtOAc–hexanes to separate the vindoline. The impure fractions, consisting mainly of **40** and **41**, were separated by HPLC (Rainin Si 83-121- 60-Å SiO_2 column) 7% (1% NH_3–MeOH)/20% EtOAc–hexanes, 15 mL/min, 200 psi) to give **40** (315 mg, 52%): t_R 8.4 min; IR ($CHCl_3$) 3453, 3007, 2953, 2934, 2877, 2856, 1741, 1694, 1615, 1525, 1498, 1462, 1434, 1373, 1348, 1320, 1303, 1152, 1098, 1041, 937 cm^{-1}; CD (MeOH) λ_{max} (Δε) 212 (+38.5), 225 (−31.9), 277 (+5.5), 308 (+6.6); UV (MeOH) λ_{max} (ε) 213 (40 000), 261 (16 000), 288 (11 000), 302 (8000) nm; $[\alpha]^{25}_D$ −37° (*c* 2.9, CH_2Cl_2); ^1H NMR (500 MHz, DMSO-d_6, 100 °C) δ 10.01 (1 H, s), 8.36 (1 H, br s), 8.15 (2 H, d, *J* = 8.7 Hz), 7.46 (1 H, d, *J* = 8.2 Hz), 7.44 (2 H, d, *J* = 8.7 Hz), 7.34 (1 H, d, *J* = 7.9 Hz), 7.05 (1 H, s), 6.99 (1 H, t, *J* = 8.7 Hz), 6.87 (1 H, t, *J* = 8.5 Hz), 6.18 (1 H, s), 5.81 (1 H, dd, *J* = 10.1, 3.3 Hz), 5.24 (1 H, s), 5.13 (1 H, d, *J* = 10.1 Hz), 5.04 (2 H, ABq, J_{AB} = 13.2 Hz), 4.03 (1 H, m), 3.71 (1 H, m), 3.65 (3 H, s), 3.64 (3 H, s), 3.61 (3 H, s), 3.57 (1 H, d, *J* = 8.5 Hz), 3.55 (1 H, s), 3.52 (1 H, d, *J* = 8.5 Hz), 3.44 (1 H, m), 3.35–3.25 (2 H, m), 3.16 (1 H, m), 3.06 (1 H, dd, *J* = 14.0, 5.5 Hz), 3.3–2.6 (5 H, m), 2.56 (3 H, s), 2.54 (1 H, s), 2.42–2.37 (2 H, m), 2.32–2.17 (2 H, m), 2.10 (1 H, m), 2.0–1.8 (2 H, m), 1.93 (3 H, s), 1.7–1.0 (12 H, m), 0.75 (3 H, t, *J* = 7.3 Hz), 0.46 (3 H, t, *J* = 7.3 Hz); HRMS (FAB) calcd for $C_{60}H_{74}N_5O_{14}$ 1088.5232 (M^+), found *m/e* 1088.5153.

41: t_R 11.0 min; IR ($CHCl_3$) 3463, 3330, 3009, 2937, 2878, 2859, 1741, 1697, 1657, 1612, 1583, 1524, 1501, 1465, 1436, 1374, 1348, 1154, 1106, 1044 cm^{-1}; CD (MeOH) λ_{max} (Δε) 208 (−34), 275 (+13.2), 301 (+1.1), 335 (−13.2); UV (MeOH) λ_{max} (ε) 212 (37 000), 261 (26 000), 303 (14 000), 342 (14 000) nm; $[\alpha]^{25}_D$ −194° (*c* 2.1, $CHCl_3$); ^1H NMR (500 MHz, DMSO-d_6, 100 °C) δ 10.45 (1 H, br s), 8.41 (1 H, s), 8.18 (2 H, d, *J* = 8.4 Hz), 7.53 (2 H, br m), 7.30 (1 H, s), 7.01 (1 H, br m), 6.89 (1 H, d, *J* = 7.3 Hz), 6.70 (1 H, t, *J* = 7.8 Hz), 6.12 (1 H, s), 5.84 (1 H, dd, *J* = 10.4, 3.4 Hz), 5.20 (1 H, s), 5.25–4.86 (2 H, br m), 5.17 (1 H, d, *J* = 10.4 Hz), 3.8–3.3 (10 H, m), 3.65 (3 H, s), 3.58 (1 H, s), 3.38 (3 H, s), 3.05–2.40 (4 H, m), 2.90 (3 H, br s), 2.75 (1 H, s), 2.57 (3 H, s), 2.35–2.17 (3 H, m), 2.01 (1 H, m), 1.92 (3 H, s), 1.7–1.2 (15 H, m), 1.08 (1 H, m), 0.95–0.65 (3 H, br m), 0.49 (3 H, t, *J* = 7.3 Hz); HRMS (FAB) calcd for $C_{60}H_{74}N_5O_{14}$ 1088.5232 (M^+), found *m/e* 1088.5164.

Coupling of Vindoline with (+)-(9*R*,2*R*,2′*S*)-33 To Give 42 and 43. Experimental details are the same as for **40**/**41**, except the amine is (+)-**33**. **42** (40%): t_R 8.8 min; IR ($CHCl_3$) 3460, 3009, 2940, 2880, 2863, 1741, 1684, 1614, 1595, 1522, 1502, 1464, 1434, 1373, 1348, 1337, 1316, 1298, 1143, 1097, 1041, 938 cm^{-1}; CD (MeOH) λ_{max} (Δε) 212 (−59.6), 225 (+64.7), 258 (+39.3), 309 (−10.1); UV (MeOH) λ_{max} (ε) 214 (59 000), 264 (24 000), 290 (18 000), 310 (11 000) nm; $[\alpha]^{25}_D$ −2.8° (*c* 0.72, $CHCl_3$); ^1H NMR (500 MHz, DMSO-d_6, 100 °C) δ 9.57 (1 H, br s), 8.37 (1 H, br s), 8.07 (2 H, d, *J* = 8.6 Hz), 7.36 (1 H, d, *J* = 7.4 Hz), 7.34 (1 H, d, *J* = 7.2 Hz), 7.25–7.17 (2 H, br m), 7.04 (1 H, s), 6.94 (1 H, ddd, *J* = 7.5, 7.2, 0.9 Hz), 6.80 (1 H, t, *J* = 7.5 Hz), 6.18 (1 H, s), 5.75 (1 H, ddd, *J* = 10.1, 4.8, 1.3 Hz), 5.11 (1 H, s), 5.06 (1 H, d, *J* = 10.1 Hz), 4.5–4.9 (2 H, br m), 3.73–3.54 (4 H, m), 3.68 (3 H, s), 3.66 (3 H, s), 3.63 (3 H, s), 3.55 (1 H, s), 3.38 (1 H, m), 3.17–3.10 (2 H, m), 3.0–2.8 (2 H, m), 2.93 (3 H, s), 2.70 (1 H, m), 2.59 (3 H, s), 2.46 (1 H, m), 2.22–2.19 (2 H, m), 2.16 (1 H, dd, *J* = 15.2, 3.9 Hz), 2.05 (1 H, m), 1.88 (3 H, s), 1.65–1.63 (2 H, m), 1.6–1.4 (10 H, m), 1.4–1.2 (3 H, m), 0.85 (1 H, sextet, *J* = 7.6 Hz), 0.75–0.65 (3 H, br m), 0.77 (3 H, t, *J* = 7.3 Hz). HRMS (FAB) calcd for $C_{60}H_{74}N_5O_{14}$ (M + 1) 1088.5232, found *m/e* 1088.5235.

43 (34%): t_R 11.0 min; IR ($CHCl_3$) 3332, 3009, 2966, 2938, 2878, 2865, 1744, 1697, 1658, 1614, 1583, 1524, 1502, 1482, 1465, 1436, 1373, 1348, 1155, 1149, 1129, 1106, 1040, 939 cm^{-1}; CD (MeOH) λ_{max} (Δε) 206 (+36.0), 236 (+18.0), 273 (−4.5), 332 (+13.5); UV (MeOH) λ_{max} (ε) 214 (51 000), 261 (23 000), 310 (19 000), 340 (21 000) nm; $[\alpha]^{25}_D$ +132° (*c* 0.08, $CHCl_3$); ^1H NMR (500 MHz, DMSO-d_6, 100 °C) δ 10.95–10.84 (1 H, br m), 8.50 (1 H, s), 8.17 (2 H, d, *J* = 9.7 Hz), 7.61–7.46 (2 H, br m), 7.34 (1 H, s), 7.08–6.90 (2 H, br m), 6.78–6.68 (2 H, br m), 6.12 (1 H, s), 5.86 (1 H, dd, *J* = 10.0, 4.4 Hz), 5.19 (1 H, s), 5.17 (1 H, d, *J* = 10.0 Hz), 3.8–3.3 (10 H, m), 3.64 (3 H, s), 3.57 (1 H, s), 3.33 (3 H, s), 3.16 (1 H, br t, *J* = 13.8 Hz), 3.03–2.8 (2 H, m), 2.93 (3 H, br s), 2.79 (1 H, br s), 2.66–2.50 (2 H, m), 2.57 (3 H, s), 2.25–2.22 (2 H, m), 2.05–1.95 (2 H, m), 1.92 (3 H, s), 1.6–1.2 (15 H, br m), 1.05 (1 H, sextet, *J* = 7.1 Hz), 0.9–0.7 (3 H, br m), 0.60 (3 H, t, *J* = 7.3 Hz); HRMS (FAB) calcd for $C_{60}H_{74}N_5O_{14}$ (M + 1) 1088.5232, found *m/e* 1088.5266.

Coupling of Vindoline with (−)-(9*S*,2*S*,2′*R*)-33 To Give 44 and 45. Experimental details are the same as for **40**/**41**, except the amine is (−)-**33**. **44** (47%): t_R 9.0 min; IR ($CHCl_3$) 3456, 3008, 2963, 2939,

2878, 2863, 1741, 1728, 1692, 1616, 1524, 1498, 1463, 1449, 1434, 1373, 1348, 1144, 1105, 1098, 1041, 1015, 938 cm^{-1}; CD (MeOH) λ_{max} ($\Delta\epsilon$) 211 (+37.7), 223 (−52.6), 259 (−16.5), 280 (+8.6), 307 (+11.0); UV (MeOH) λ_{max} (ϵ) 215 (58 000), 264 (24 000), 283 (19 000), 290 (18 000), 311 sh (12 000) nm. $[\alpha]^{25}_D$ −59.2° (*c* 0.59, $CHCl_3$); ^1H NMR (500 MHz, DMSO-d_6, 100 °C) δ 9.91 (1 H, br s), 8.51 (1 H, br s), 8.11 (2 H, d, *J* = 9.0 Hz), 7.43 (1 H, d, *J* = 8.1 Hz), 7.40 (1 H, d, *J* = 7.9 Hz), 7.28 (2 H, br d, *J* = 9.4 Hz), 7.12 (1 H, s), 6.95 (1 H, ddd, *J* = 8.0, 7.1, 0.9 Hz), 6.83 (1 H, t, *J* = 7.9 Hz), 6.17 (1 H, s), 5.82 (1 H, ddd, *J* = 10.1, 4.7, 1.4 Hz), 5.21 (1 H, s), 5.13 (1 H, d, *J* = 10.1 Hz), 5.0–4.6 (2 H, br m), 3.79 (1 H, m), 3.7–3.6 (2 H, m), 3.65 (3 H, s), 3.643 (3 H, s), 3.641 (3 H, s), 3.54 (1 H, m), 3.53 (1 H, s), 3.45 (1 H, ddd, *J* = 17.2, 4.7, 0.9 Hz), 3.29 (1 H, td, *J* = 9.1, 3.8 Hz), 3.25 (1 H, dd, *J* = 14.9, 3.1 Hz), 3.16 (1 H, m), 3.01–2.92 (2 H, m), 2.80 (1 H, m), 2.65 (1 H, s), 2.55 (3 H, s), 2.50 (1 H, m), 2.21–1.97 (4 H, m), 1.93 (3 H, s), 1.63–1.40 (13 H, m), 1.35–1.26 (3 H, br m), 1.02 (1 H, sextet, *J* = 7.3 Hz), 0.70 (3 H, br m), 0.49 (3 H, t, *J* = 7.3 Hz); HRMS (FAB) calcd for $C_{60}H_{74}N_5O_{14}$ (M + 1) 1088.5232, found *m/e* 1088.5256.

45 (25%): t_R 10.9 min; IR ($CHCl_3$) 3330, 3008, 2964, 2938, 2878, 2863, 1742, 1696, 1656, 1612, 1583, 1524, 1500, 1481, 1464, 1449, 1436, 1373, 1349, 1152, 1106, 1099, 1041, 938, 928, 852 cm^{-1}; CD (MeOH) λ_{max} ($\Delta\epsilon$) 207 (−44.5), 261 (+19.2), 333 (−13.8); UV (MeOH) λ_{max} (ϵ) 214 (50 000), 261 (23 000), 308 (17 000), 340 (19 000) nm; $[\alpha]^{25}_D$ −203° (*c* 0.32, $CHCl_3$); ^1H NMR (500 MHz, DMSO-d_6, 100 °C) δ 10.45 (1 H, br m), 8.43 (1 H, br m), 8.18 (2 H, m), 7.65–7.45 (2 H, br m), 7.36 (1 H, s), 7.06–6.90 (2 H, br m), 6.84 (1 H, d, *J* = 7.3 Hz), 6.70 (1 H, br m), 6.10 (1 H, s), 5.86 (1 H, ddd, *J* = 10.1, 4.9, 1.4 Hz), 5.20 (1 H, s), 5.19 (1 H, d, *J* = 10.1 Hz), 5.2–4.7 (2 H, br m), 3.85–3.50 (6 H, br m), 3.65 (3 H, s), 3.58 (1 H, s), 3.46 (1 H, ddd, *J* = 16.2, 5.8, 1.0 Hz), 3.35 (1 H, td, *J* = 9.2, 3.9 Hz), 3.33 (3 H, s), 3.03–2.92 (2 H, m), 2.87 (1 H, br d, *J* = 16.3 Hz), 2.81 (1 H, s), 2.77 (1 H, br t, *J* = 13.3 Hz), 2.67–2.62 (2 H, m), 2.57 (3 H, s), 2.37–2.31 (2 H, m), 2.04–2.02 (2 H, m), 1.92 (3 H, s), 1.8–1.2 (17 H, br m), 1.13 (1 H, sextet, *J* = 7.3 Hz), 0.9–0.7 (3 H, br m), 0.56 (3 H, t, *J* = 7.3 Hz); HRMS (FAB) calcd for $C_{60}H_{74}N_5O_{14}$ (M + 1) 1088.5232, found *m/e* 1088.5268.

(18′*R*)-Epivinblastine (49). To a stirred solution of the ketal **40** (47 mg, 43 μmol) in tetrahydrofuran (2 mL) at 25 °C was added 2 N hydrochloric acid (2 mL). After 7.5 h, the mixture was added to ice-cold 2 N sodium hydroxide solution (5 mL), and the solution was extracted with dichloromethane (5 mL). The aqueous phase was saturated with brine and further extracted with dichloromethane (2 × 5 mL). The combined extracts were dried ($MgSO_4$), filtered, and evaporated in vacuo to give the diol **46** (34.5 mg, 80%). Purified by PLC, 10% (1% NH_3–MeOH/Et_2O: IR ($CHCl_3$) 3600–3260, 3545, 3459, 3005, 2964, 2953, 2939, 2878, 1741, 1674, 1615, 1522, 1498, 1461, 1434, 1373, 1348, 1304, 1143, 1121, 1041 cm^{-1}; CD (MeOH) λ_{max} ($\Delta\epsilon$) 208 (+20.4), 224 (−58.0), 259 (−15.3), 279 (+6.1), 307 (+8.1); UV (MeOH) λ_{max} (ϵ) 212 (37 000), 260 (13 000), 287 (10 000), 303 (7000) nm; $[\alpha]^{25}_D$ −110° (*c* 0.48, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 9.47 (1 H, br s), 9.04 (1 H, s), 8.03 (2 H, d, *J* = 8.6 Hz), 7.39 (1 H, d, *J* = 7.9 Hz), 7.30 (1 H, d, *J* = 8.0 Hz), 7.12 (1 H, t, *J* = 7.5 Hz), 6.93 (2 H, d, *J* = 8.6 Hz), 6.88 (1 H, t, *J* = 7.8 Hz), 6.74 (1 H, s), 5.97 (1 H, s), 5.87 (1 H, dd, *J* = 10.1, 3.9 Hz), 5.42 (1 H, s), 5.24 (1 H, d, *J* = 10.1 Hz), 4.72 (1 H, d, *J* = 13.6 Hz), 4.5–4.2 (2 H, br m), 4.18 (1 H, d, *J* = 13.6 Hz), 4.13 (1 H, d, *J* = 14.7 Hz), 3.77 (3 H, s), 3.76 (3 H, s), 3.74 (3 H, s), 3.68 (1 H, s), 3.55–3.25 (5 H, br m), 3.2–2.9 (3 H, m), 2.88 (1 H, br d, *J* = 16.0 Hz), 2.71 (1 H, m), 2.60 (4 H, s), 2.52–2.40 (2 H, m), 2.25 (1 H, m), 2.2–2.0 (2 H, m), 2.07 (3 H, s), 1.9–1.4 (6 H, m), 1.12 (1 H, sextet, *J* = 7.2 Hz), 0.89 (3 H, t, *J* = 7.3 Hz), 0.54 (3 H, t, *J* = 7.2 Hz); HRMS (FAB) *m/e* calcd for $C_{54}H_{65}N_5O_{14}$ 1007.4528 (M^+), found *m/e* 1007.4481.

To a stirred solution of the diol **46** (70 mg, 69 μmol) and triethylamine (144 μL, 15 equiv) in dry dimethyl sulfoxide (2 mL) under argon at 25 °C was added dropwise a solution of pyridine/sulfur trioxide (111 mg, 10 equiv) in dimethyl sulfoxide (2 mL). The mixture was stirred for 2.5 h and then quenched with saturated aqueous sodium bicarbonate solution (5 mL). The mixture was extracted with dichloromethane (2 × 10 mL), washed with water (2 × 20 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo to give a residue which was purified by chromatography over silica gel, eluting with 5% (1% NH_3–MeOH)/EtOAc to give the aldehyde **47** (62 mg, 89%): IR ($CHCl_3$) 3458, 3350, 3009, 2968, 2953, 2880, 2843, 1741, 1680, 1616, 1596, 1523, 1499, 1461, 1435, 1373, 1348, 1320, 1303, 1170, 1144, 1121, 1110, 1042 cm^{-1}; CD (MeOH) λ_{max} ($\Delta\epsilon$) 212 (+39.7), 224 (−62.8), 258 (−12.0), 279 (+10.2), 306 (+10.2); UV (MeOH) λ_{max} (ϵ) 215 (64 000), 262 (26 000), 284 sh (21 000), 291 sh (19 000), 310 sh (12 000) nm; $[\alpha]^{25}_D$ −90° (*c* 0.30, $CHCl_3$); ^1H NMR (500 MHz, DMSO-d_6, 100 °C) δ 9.79 (1 H, br s), 9.46 (1 H, s), 8.46 (1 H, br s), 8.10 (2 H, br m), 7.42 (1 H, d, *J* = 8.1 Hz), 7.36 (1 H, d, *J* = 7.9 Hz), 7.28 (2 H, br m), 7.01 (1 H, s), 6.96 (1 H, ddd, *J* = 8.0, 7.1, 1.0 Hz), 6.84 (1 H, td, *J* = 7.8, 0.7 Hz), 6.18 (1 H, s), 5.82 (1 H, ddd, *J* = 10.1, 4.7, 1.4 Hz), 5.66 (1 H, s), 5.21 (1 H, s), 5.13 (1 H, d, *J* = 10.1 Hz), 5.0–4.6 (2 H, br m), 3.76 (1 H, m), 3.68 (3 H, s), 3.67 (3 H, s), 3.64 (3 H, s), 3.52 (1 H, s), 3.48–3.41 (2 H, m), 3.27 (1 H, m), 3.17–3.12 (2 H, m), 3.0–2.9 (3 H, m), 2.78 (1 H, br d, *J* = 17.0 Hz), 2.60 (1 H, s), 2.56 (3 H, s), 2.43 (1 H, dd, *J* = 17.7, 9.7 Hz), 2.20–2.13 (2 H, m), 2.05 (1 H, m), 1.93 (3 H, s), 1.82 (1 H, m), 1.70–1.68 (2 H, m), 1.60–1.42 (3 H, m), 1.03 (1 H, sextet, *J* = 7.3 Hz), 0.73 (3 H, t, *J* = 7.4 Hz), 0.50 (3 H, t, *J* = 7.3 Hz); HRMS (FAB) calcd for $C_{54}H_{64}N_5O_{14}$ (M + 1) *m/e* 1006.4450, found *m/e* 1006.4401.

A solution of the aldehyde **47** (22 mg, 22 μmol) in methanol (2 mL) containing 10% Pd/C (12 mg) was stirred under an atmosphere of hydrogen at 25 °C for 4 h. The mixture was filtered and evaporated in vacuo, and the residue was purified by PLC, eluting with 10% (1% NH_3–MeOH)/EtOAc to give **49** (13 mg, 93%): mp 250–252 °C (dec) (MeOH/H_2O); IR ($CHCl_3$) 3439, 2966, 2951, 2933, 2879, 2841, 2812, 1740, 1616, 1595, 1500, 1489, 1461, 1433, 1373, 1333, 1171, 1144, 1038 cm^{-1}; CD (MeOH) λ_{max} ($\Delta\epsilon$) 213 (+31.4), 226 (−29.5), 252 (−15.7), 312 (+7.9); UV (MeOH) λ_{max} (ϵ) 215 (42 000), 261 (12 000), 289 (10 000), 295 (11 000), 306 (9000) nm. $[\alpha]^{25}_D$ −59° (*c* 0.67, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 9.67 (1 H, br s), 9.05 (1 H, s), 7.31 (1 H, d, *J* = 7.8 Hz), 7.22 (1 H, d, *J* = 8.1 Hz), 7.06 (1 H, t, *J* = 7.4 Hz), 7.00 (1 H, s), 6.91 (1 H, t, *J* = 7.4 Hz), 6.00 (1 H, s), 5.89 (1 H, dd, *J* = 10.2, 3.9 Hz), 5.32 (1 H, s), 5.30 (1 H, d, *J* = 10.2 Hz), 4.43 (1 H, br t, *J* = 13.4 Hz), 3.90 (3 H, s), 3.76 (3 H, s), 3.74 (3 H, s), 3.65 (1 H, s), 3.54–2.95 (11 H, m), 2.90 (1 H, s), 2.70–2.55 (2 H, m), 2.63 (3 H, s), 2.10–1.20 (10 H, m), 2.08 (3 H, s), 0.92 (3 H, t, *J* = 7.4 Hz), 0.68 (3 H, t, *J* = 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.32, 171.49, 170.82, 156.06, 151.75, 135.12, 134.57, 130.36, 128.15, 126.02, 124.61, 123.97, 121.43, 119.92, 118.37, 117.83, 110.41, 110.24, 94.24, 82.69, 79.94, 76.46, 70.08, 65.06, 64.34, 56.04, 55.33, 53.25, 52.87, 52.11, 52.03, 50.49, 50.38, 48.47, 43.67, 41.12, 39.15, 38.22, 34.25, 30.64, 21.11, 7.60, 6.81 (6 signals are coincident); HRMS (FAB) calcd for $C_{46}H_{59}N_4O_9$ (M + 1) 811.4282, found *m/e* 811.4282. Crystals suitable for single-crystal X-ray crystallography were grown from methanol–water.

9′-Isovinblastine (52). A solution of the ketal **41** (105 mg, 97 μmol) in tetrahydrofuran and 2 M hydrochloric acid (10 mL, 1:1) was stirred at 25 °C for 7 h. Workup and purification as for **46** gave the diol **50** (83 mg, 85%): IR ($CHCl_3$) 3552, 3433, 3332, 3019, 2966, 2951, 2935, 2878, 2842, 1742, 1692, 1658, 1612, 1583, 1524, 1501, 1482, 1469, 1435, 1410, 1373, 1348, 1148, 1149, 1121, 1106, 1088, 1040 cm^{-1}; CD (MeOH) λ_{max} ($\Delta\epsilon$) 207 (−31.6), 260 (+11.2), 294 (+1.0), 332 (−11.2); UV (MeOH) λ_{max} (ϵ) 214 (49 000), 264 (22 000), 308 (17 000), 342 (18 000) nm; $[\alpha]^{25}_D$ −191° (*c* 0.23, MeOH); ^1H NMR (300 MHz, $CDCl_3$) δ 10.51 (0.6 H, s), 10.41 (0.4 H, s), 9.42 (1 H, br s), 8.21 (0.8 H, d, *J* = 8.7 Hz), 8.17 (1.2 H, d, *J* = 8.7 Hz), 7.52 (0.8 H, d, *J* = 8.6 Hz), 7.36 (1.2 H, d, *J* = 8.6 Hz), 7.10–6.37 (5 H, m), 5.94 (1 H, s), 5.85 (1 H, m), 5.37–4.95 (4 H, m), 3.76–3.28 (16 H, m), 3.06–2.63 (10 H, m), 2.40–1.74 (10 H, m), 1.63–1.00 (6 H, m), 0.86 (1.8 H, t, *J* = 7.5 Hz), 0.73 (1.2 H, t, *J* = 7.5 Hz), 0.45 (3 H, br m) (5:3 mixture of conformational isomers in $CDCl_3$ at 298 K); HRMS (FAB) calcd for $C_{54}H_{66}N_5O_{14}$ (M + 1) *m/e* 1008.4606, found *m/e* 1008.4587.

Oxidation of the diol **50** (25 mg, 25 μmol) using the same procedure as for **47** gave the aldehyde **51** (21 mg, 83%): IR ($CHCl_3$) 3514, 3331, 3009, 2968, 2951, 2935, 2879, 1743, 1735, 1700, 1696, 1656, 1612, 1584, 1524, 1500, 1481, 1436, 1410, 1373, 1153, 1150, 1107, 1044 cm^{-1}; CD (MeOH) λ_{max} ($\Delta\epsilon$) 210 (−22.7), 232 (+2.1), 261 (+22.7), 333 (−12.4); UV (MeOH) λ_{max} (ϵ) 214 (55 000), 261 (25 000), 302 (20 000), 340 (21 000) nm; $[\alpha]^{25}_D$ −155° (*c* 0.40, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 10.54 (0.5 H, s), 10.50 (0.5 H, s), 9.53 (0.5 H, s), 9.50 (1 H, br s), 9.47 (0.5 H, s), 8.27 (1 H, d, *J* = 8.7 Hz), 8.16 (1 H, d, *J* = 8.7 Hz), 7.51 (1 H, d, *J* = 8.6 Hz), 7.36 (1 H, d, *J* = 8.6 Hz), 7.09–6.34 (5 H, m), 5.95 (1 H, s), 5.89 (1 H, m), 5.38–4.93 (4 H, m), 3.82–3.40 (14 H, m), 3.04–2.46 (7 H, m), 2.63 (3 H, s), 2.42–1.92 (6 H, m), 2.06 (3 H, s), 1.78–1.12 (6 H, m), 0.83–0.75 (3 H, m), 0.50–0.43 (3 H, br m) (1:1 mixture of conformational isomers in $CDCl_3$ at 298 K); HRMS (FAB) calcd for $C_{54}H_{64}N_5O_{14}$ (M + 1) *m/e* 1006.4450, found *m/e* 1006.4401.

A solution of the aldehyde **51** (15 mg, 15 μmol) was hydrogenolyzed using the procedure described for **49** to give 9′-isovinblastine (**52**) (6 mg, 49%): IR ($CHCl_3$) 3304, 3007, 2966, 2952, 2934, 2878, 2843, 1742, 1650, 1614, 1571, 1502, 1482, 1467, 1460, 1448, 1435, 1374, 1160, 1152, 1101, 1045, 1020 cm^{-1}; CD (MeOH) λ_{max} ($\Delta\epsilon$) 216 (+23.3), 242 (+11.0), 264 (+22.7), 332 (−32.5) nm; UV (MeOH) λ_{max} (ϵ) 216 (24 000), 265 (8000), 306 (11 000), 331 (12 000) nm; $[\alpha]^{23}_D$ −296° (*c* 0.50, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 11.03 (1 H, s), 9.79 (1 H, s), 7.22 (1 H, d, *J* = 7.4 Hz), 6.96 (1 H, t, *J* = 7.3 Hz), 6.73–6.66 (2 H, m), 6.64 (1 H, s), 6.07 (1 H, s), 5.75 (1 H, dd, *J* = 10.1, 3.5 Hz), 5.30 (1 H, s), 5.02 (1 H, d, *J* = 10.1 Hz), 4.07 (1 H, m), 3.90 (3 H, s), 3.76 (6 H, s), 3.70 (1 H, s), 3.45–3.14 (5 H, m), 2.84–2.81 (2 H, m), 2.65 (3 H, s), 2.58 (1 H, m), 2.44–2.23 (3 H, m), 2.33 (1 H, s), 2.17–1.96 (2 H, m), 2.02 (3 H, s), 1.78–1.61 (4 H, m), 1.33–1.23 (5 H, m), 0.85

(3 H, br t, J = 7.2 Hz), 0.48 (1 H, sextet, J = 7.0 Hz), −0.34 (3 H, t, J = 7.1 Hz); HRMS (FAB) calcd for $C_{46}H_{59}N_4O_9$ (M + 1) m/e 811.4282, found m/e 811.4257.

(3a*R*-[3aα,4β,5aβ,9[1*R*,3*R*(2*S*),5*R*,7a*S*,12a*S*],10b*R*,13aα])-Methyl 4-(Acetyloxy)-3a-ethyl-1,3a,4,5,5a,6,11,13a-octahydro-9-[1,2,3,4,6,7,7a,12-octahydro-3-(2-hydroxy-2-(hydroxymethyl)butyl)-1-(methoxycarbonyl)indolizino[1,2-*b*]indol-7a-yl]-5-hydroxy-8-methoxy-6-methyl-1*H*-indolizino[8,1-*cd*]carbazole-5-carboxylate Methanol Hydrate Solvate (53). A solution of the diol **50** (16.5 mg, 16.4 μmol) in methanol (2 mL) containing 10% Pd/C (5 mg) was stirred under an atmosphere of hydrogen gas for 8 h at 25 °C. The mixture was filtered through Celite and washed with methanol. The filtrate was evaporated in vacuo and purified by PLC, eluting with 10% (1% NH_3–MeOH)/EtOAc to give **53** (10.3 mg, 76%): mp 243–245 °C dec ($MeOH/H_2O$); IR ($CHCl_3$) 3686, 3600, 2967, 2953, 2937, 2880, 2837, 2813, 1742, 1727, 1614, 1605, 1502, 1490, 1466, 1433, 1372, 1323, 1040 cm^{-1}; CD (MeOH) λ_{max} ($\Delta\epsilon$) 207 (+26.6), 217 (−25.1), 230 (+16.0), 261 (+25.1), 304 (+0.8), 322 (−1.6); UV (MeOH) λ_{max} (ϵ) 214 (40 000), 251 (14 000), 307 (8000) nm; $[\alpha]^{25}_D$ −67.8° (c 0.36, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.45 (1 H, br s), 7.08 (1 H, br t, J = 7.2 Hz), 6.88 (1 H, m), 6.78–6.74 (2 H, m), 6.50 (1 H, br s), 6.13 (1 H, s), 5.86 (1 H, dd, J = 10.3, 4.1 Hz), 5.35 (1 H, s), 5.29 (1 H, d, J = 10.3 Hz), 3.98 (3 H, br s), 3.77 (3 H, s), 3.75 (1 H, s), 3.61 (2 H, ABq, J_{AB} = 11.6 Hz), 3.41–3.00 (4 H, m), 3.05 (3 H, br s), 2.83–2.68 (2 H, m), 2.70 (3 H, s), 2.56 (1 H, s), 2.56–2.37 (2 H, m), 2.20–1.43 (14 H, m), 2.07 (3 H, s), 1.28 (1 H, m), 0.94 (3 H, t, J = 7.4 Hz), 0.67 (3 H, t, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.95, 171.49, 170.75, 160.23, 152.48, 150.52, 135.92, 130.34, 127.74, 126.73, 126.54, 124.14, 122.47, 119.11, 118.92, 110.63, 94.08, 89.47, 83.22, 79.98, 76.10, 75.23, 68.49, 65.92, 63.72, 55.24, 53.28, 52.12, 50.98, 50.59, 50.51, 49.52, 47.97, 44.03, 42.66, 38.89, 38.57, 36.66, 33.57, 30.31, 29.01, 28.41, 21.11, 8.01, 7.81 (two signals, coincident quaternary carbon atoms); HRMS (FAB) calcd for $C_{46}H_{61}N_4O_{10}$ (M + 1) 829.4388, found m/e 829.4412. Anal. Calcd for $C_{46}H_{60}N_4O_{10}\cdot CH_3OH$: C, 65.56; H, 7.49; N, 6.51. Found: C, 65.88, H, 7.31; N, 6.55. Crystals for X-ray analysis were grown from aqueous methanol.

Thermolysis of 53 To Give 54. A solution of **53** (24.4 mg, 29.4 μmol) in o-dichlorobenzene (5 mL) was heated to 150 °C under argon. After 3 h, the solvent was removed by Kugelrohr distillation (50 °C, 0.1 mm), and the residue was purified by PLC, eluting with 15% (1% NH_3–MeOH)/EtOAc to give **54** (13.8 mg, 59%); IR ($CHCl_3$) 3700–3200, 3390, 3005, 2969, 2933, 2879, 2840, 1742, 1615, 1598, 1582, 1499, 1464, 1434, 1404, 1373, 1041, 908 cm^{-1}; CD (MeOH) λ_{max} ($\Delta\epsilon$) 215 (−7.6), 253 (+15.6), 285 (−12.0), 317 (+10.3) nm; UV (MeOH) λ_{max} (ϵ) 206 (35 000), 210 (34 000), 253 (17 000), 311 (13 000) nm; $[\alpha]^{25}_D$ +135° (c 0.50, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (1 H, d, J = 6.9 Hz), 7.20–7.10 (2 H, m), 6.91 (1 H, br s), 6.79 (1 H, d, J = 7.3 Hz), 6.36 (1 H, s), 5.95 (1 H, s), 5.78 (1 H, dd, J = 10.1, 3.8 Hz), 5.30 (1 H, s), 5.19 (1 H, s), 5.17 (1 H, d, J = 10.1 Hz), 3.76 (3 H, s), 3.65 (1 H, s), 3.52 (3 H, s), 3.52–3.26 (6 H, m), 3.03–2.79 (3 H, m), 2.66–2.53 (1 H, m), 2.60 (3 H, s), 2.39 (1 H, s), 2.39–2.25 (5 H, m), 2.13–1.95 (2 H, m), 2.05 (3 H, s), 1.65–1.48 (6 H, m), 1.25 (1 H, br s), 1.09 (1 H, sextet, J = 7.1 Hz), 0.88 (3 H, t, J = 7.4 Hz), 0.45 (3 H, t, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$), δ 172.04, 170.81, 168.19, 160.54, 158.52, 152.72, 138.03, 133.21, 130.09, 127.92, 127.33, 124.19, 124.06, 122.86, 121.42, 120.98, 120.71, 95.34, 91.81, 83.27, 79.38, 76.29, 74.99, 67.31, 56.29, 55.99, 52.76, 52.45, 52.34, 52.21, 50.90, 50.79, 43.89, 42.88, 39.58, 38.20, 34.60, 31.63, 31.15, 29.91, 27.37, 21.05, 8.07, 7.85 (two methine signals coincident); HRMS (FAB) calcd for $C_{45}H_{57}N_4O_9$ (M + 1) 797.4126, found m/e 797.4133.

Coupling Reactions in Nitromethane. Coupling of Vindoline with (−)-(9*R*,2*S*,2′*S*)-30 To Give 57 and 40. To a stirred solution of the amine (−)-**30** (5 mg, 11 μmol) and 2,6-di-*tert*-butyl-4-methylpyridine (7 mg, 3.0 equiv) in dry nitromethane (185 μL) at −20 °C under argon was added 4-nitrobenzyl chloroformate (6 mg, 2.6 equiv) followed by vindoline (20 mg, 4.0 equiv). The mixture was stirred at −20 °C for 64 h and quenched with saturated aqueous sodium bicarbonate (1 mL). The mixture was extracted with dichloromethane (2 × 2 mL), dried ($MgSO_4$), and evaporated in vacuo to give a mixture of vindoline and the bis-alkaloids **57** and **40**. The mixture was purified by HPLC (Rainin Si 83-121-) (60-Å SiO_2 column) 7% (1% NH_3–MeOH)/20% EtOAc–hexanes, 15 mL/min, 250 psi, to give **57** (7.1 mg, 59%) and **40** (3.7 mg, 31%).

57: t_R 6.9 min (Dynamax 60-Å Si 83-121-C, 4.6 mm × 25 cm, 7% MeOH/20% EtOAc/0.007% NH_4OH/hexanes; 2.0 mL/min: 1400 psi); IR ($CHCl_3$) 3467, 3453, 3008, 2949, 2938, 2877, 2863, 2846, 1741, 1734, 1685, 1613, 1595, 1523, 1501, 1461, 1446, 1432, 1348, 1107, 1042, 937, 856 cm^{-1}; CD (MeOH) λ_{max} ($\Delta\epsilon$) 212, (−85.4), 227 (+23.5), 239 (−7.1), 259 (+18.8), 302 (+8.2); UV (MeOH) λ_{max} (ϵ) 214 (56 000), 265 (25 000), 286 sh (20 000), 296 sh (16 000), 311 sh (8 000) nm; $[\alpha]^{25}_D$ −72.5° (c 0.80, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.47 (1 H, br s), 7.89 (1 H, s), 7.87 (2 H, d, J = 8.3 Hz), 7.48 (1 H, d, J = 7.9 Hz), 7.22–7.15 (2 H, m), 7.03 (1 H, m), 6.68 (1 H, s), 6.50 (2 H, d, J = 8.3 Hz), 6.09 (1 H, s), 5.71 (1 H, dd, J = 10.1, 4.0 Hz), 5.47 (1 H, s), 5.25 (1 H, d, J = 10.1 Hz), 4.69 (1 H, d, J = 13.8 Hz), 4.56 (1 H, d, J = 13.8 Hz), 4.14 (1 H, td, J = 13.5, 4.2 Hz), 3.78 (6 H, s), 3.71 (1 H, s), 3.62 (2 H, ABq, J_{AB} = 14.1 Hz), 3.56 (3 H, s), 3.6–3.35 (3 H, m), 3.30–3.03 (4 H, m), 2.66 (3 H, s), 2.65–2.44 (3 H, m), 2.38 (1 H, s), 2.20–1.85 (3 H, m), 2.04 (3 H, s), 1.82–1.10 (17 H, m), 0.67 (3 H, t, J = 7.2 Hz), 0.36 (3 H, t, J = 7.2 Hz); HRMS (FAB) calcd for $C_{60}H_{74}N_5O_{14}$ 1088.5232 (M^+ + 1), found m/e 1088.5251.

Vinblastine (1). To a stirred solution of the ketal **57** (27 mg, 25 μmol) in tetrahydrofuran (3 mL) at 25 °C was added 2 N hydrochloric acid (3 mL). After 10 h, the mixture was added to saturated aqueous sodium bicarbonate solution (8 mL) and extracted with dichloromethane (10 mL). The aqueous phase was saturated with brine and further extracted with dichloromethane (2 × 5 mL). The combined extracts were dried ($MgSO_4$), filtered, and evaporated in vacuo to give the diol **59** (20.7 mg, 83%). Purified by PLC, 10% (1% NH_3–MeOH): IR ($CHCl_3$) 3457, 3450, 3419, 3008, 2966, 2952, 2938, 2880, 2840, 1741, 1674, 1611, 1594, 1524, 1503, 1461, 1434, 1348, 1122, 1109, 1041, 1013, 892 cm^{-1}; CD (MeOH) λ_{max} ($\Delta\epsilon$) 213 (−78.4), 227 (+18.3), 238 (−6.1), 262 (+18.3), 302 (+9.2); UV (MeOH) λ_{max} (ϵ) 214 (53 000), 266 (24 000), 288 sh (19 000), 297 sh (15 000), 312 sh (6000) nm; $[\alpha]^{25}_D$ −50° (c 0.30, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.41 (1 H, br s), 7.97 (1 H, br s), 7.79 (2 H, d, J = 8.7 Hz), 7.51 (1 H, d, J = 7.9 Hz), 7.30–7.22 (2 H, m), 7.07 (1 H, ddd, J = 7.9, 6.5, 1.6 Hz), 6.55 (1 H, s), 6.47 (2 H, d, J = 8.7 Hz), 6.12 (1 H, s), 5.68 (1 H, dd, J = 10.2, 4.0 Hz), 5.44 (1 H, s), 5.23 (1 H, d, J = 10.2 Hz), 5.09 (1 H, d, J = 14.4 Hz), 4.25 (1 H, td, J = 13.5, 4.0 Hz), 3.96 (1 H, d, J = 14.0 Hz), 3.81 (3 H, s), 3.77 (3 H, s), 3.75 (1 H, s), 3.71 (1 H, m), 3.60 (3 H, s), 3.52 (1 H, m), 3.28–3.13 (5 H, m), 2.77 (1 H, dd, J = 14.6, 10.0 Hz), 2.71 (3 H, s), 2.53–2.16 (5 H, m), 2.26 (1 H, s), 2.08 (3 H, s), 1.88–1.48 (6 H, m), 1.54 (1 H, dd, J = 14.6, 10.7 Hz), 1.42–1.20 (3 H, m), 0.80–0.69 (6 H, m); HRMS (FAB) calcd for $C_{54}H_{65}N_5O_{14}$ 1007.4528 (M^+), found m/e 1007.4586.

To a stirred solution of the diol **59** (14.0 mg, 13.9 μmol) and triethylamine (39 μL, 20 equiv) in dry dimethyl sulfoxide (250 μL) under argon at 25 °C was added dropwise a solution of pyridine/sulfur trioxide (22 mg, 10 equiv) in dimethyl sulfoxide (250 μL). The mixture was stirred for 3 h and quenched with saturated aqueous sodium bicarbonate solution (1 mL). The mixture was extracted with dichloromethane (2 × 3 mL), washed with water (3 × 10 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo to give a residue which was purified by chromatography over silica gel, eluting with 5% (1% NH_3–MeOH)/EtOAc to give the aldehyde **60** (10.7 mg, 77%): IR ($CHCl_3$) 3467, 3453, 3009, 2966, 2952, 2880, 2838, 1735, 1678, 1612, 1594, 1524, 1502, 1461, 1433, 1412, 1373, 1294, 1121, 1109, 1043, 1013 cm^{-1}; CD (MeOH) λ_{max} ($\Delta\epsilon$) 212 (−73.2), 226 (+17.3), 249 (−6.1), 260 (+17.3), 301 (+8.1); UV (MeOH) λ_{max} (ϵ) 214 (52 000), 265 (24 000), 285 (19 000), 295 (15 000), 312 (7000) nm; $[\alpha]^{25}_D$ −44° (c 0.15, $CHCl_3$). The NMR spectrum of **60** shows a single formyl hydrogen signal that integrates as 0.7 H; many of the other signals are doubled. This is consistent with **60** and its derived aldehyde hydrate: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.49 (1 H, br s), 8.87 (0.7 H, s), 7.96–7.76 (3.3 H, m), 7.50 (1 H, m), 7.30–7.16 (3 H, m), 6.69–6.39 (3 H, m), 5.70 (1 H, m), 5.45 (1 H, s), 5.27–5.10 (2 H, m), 4.71–4.64 (1.3 H, m), 4.33 (0.7 H, s), 4.20 (1 H, m), 4.08–3.05 (8 H, m), 3.82 (2.1 H, s), 3.80 (0.9 H, s), 3.79 (0.9 H, s), 3.78 (2.1 H, s), 3.60 (2.1 H, s), 3.56 (0.9 H, s), 2.76–2.37 (4 H, m), 2.71 (2.1 H, s), 2.70 (0.9 H, s), 2.31–1.91 (3 H, m), 2.21 (1 H, s), 2.08 (3 H, s), 1.80–1.22 (7 H, m), 0.76–0.61 (6 H, m); ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 9.07 (1 H, s), 8.78 (1 H, br s), 8.31 (1 H, br s, exchanged with D_2O), 7.85 (2 H, br d, J = 8.1 Hz), 7.51 (1 H, d, J = 7.9 Hz), 7.27 (1 H, d, J = 8.1 Hz), 7.07 (1 H, ddd, J = 8.1, 7.1, 1.0 Hz), 6.94, (1 H, ddd, J = 7.4, 7.1, 0.7 Hz), 6.78 (2 H, br m), 6.55 (1 H, s), 6.32 (1 H, s), 5.65 (1 H, dd, J = 10.1, 4.0 Hz), 5.24 (1 H, s), 5.15 (1 H, d, J = 10.1 Hz), 4.76 (2 H, br s), 4.40 (1 H, s, exchange D_2O), 3.98 (1 H, br m), 3.76 (3 H, s), 3.66 (3 H, s), 3.65 (1 H, m), 3.55 (3 H, s), 3.54 (1 H, s), 3.53 (1 H, m), 3.4–3.3 (2 H, br m), 3.20–3.11 (2 H, m), 3.05 (1 H, m), 2.82 (1 H, dd, J = 14.0, 10.6 Hz), 2.49 (3 H, s), 2.41 (1 H, br d, J = 15.9 Hz), 2.34 (1 H, m), 2.26 (1 H, br s), 2.08 (1 H, m), 1.94 (3 H, s), 1.83 (1 H, br m), 1.58 (1 H, sextet, J = 7.3 Hz), 1.42 (1 H, dd, J = 14.6, 9.1 Hz), 1.32–1.14 (6 H, m), 0.59, (3 H, t, J = 7.4 Hz), 0.55 (3 H, t, J = 7.3 Hz); HRMS (FAB) calcd for $C_{54}H_{64}N_5O_{14}$ 1006.4450 (M + 1), found m/e 1006.4452.

A solution of the aldehyde **60** (7.8 mg, 8 μmol) in methanol (1 mL) containing 10% Pd/C (6 mg) was stirred under an atmosphere of hydrogen at 25 °C for 2 h. The mixture was filtered and evaporated in vacuo, and the residue was purified by PLC, eluting with 10% (1% NH_3–MeOH)/EtOAc to give **1** (5.6 mg, 89%): IR ($CHCl_3$) 3468, 3453, 3006, 2966, 2951, 2941, 2880, 2840, 2816, 1740, 1614, 1595, 1503, 1459,

1434, 1373, 1332, 1146, 1130, 1041, 1008, 885 cm^{-1}; CD (MeOH) λ_{max} ($\Delta\epsilon$) 212 (−53.7), 224 (+33.7), 256 (+16.4), 302 (+6.4); UV (MeOH) λ_{max} (ϵ) 213 (39000), 260 (13000), 287 (10000), 295 (9000) nm; $[\alpha]^{25}_D$ +36° (*c* 0.34, $CHCl_3$), $[\alpha]^{25}_D$ −13° (*c* 0.34, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.87 (1 H, br s), 8.04 (1 H, s), 7.52 (1 H, d, J = 7.4 Hz), 7.18–7.07 (3 H, m), 6.63 (1 H, s), 6.10 (1 H, s), 5.85 (1 H, dd, J = 10.1, 3.8 Hz), 5.47 (1 H, s), 5.30 (1 H, d, J = 10.1 Hz), 3.96 (1 H, t, J = 14.1 Hz), 3.79 (6 H, s), 3.77 (1 H, s), 3.75 (1 H, m), 3.73 (3 H, s), 3.45–3.24 (3 H, m), 3.20–3.07 (2 H, m), 2.85–2.77 (2 H, m), 2.71 (3 H, s), 2.67 (1 H, s), 2.44 (1 H, m), 2.28 (1 H, m), 2.15 (1 H, m), 2.11 (3 H, s), 1.88–1.73 (2 H, m), 1.70–1.25 (10 H, m), 0.89 (3 H, t, J = 7.4 Hz), 0.81 (3 H, t, J = 7.3 Hz). Identical with an authentic sample.

(2*R*)-2-Ethyl-2,3-epoxypropanol (62). To a stirred suspension of powdered activated 3-Å molecular sieves (6 g) in dry dichloromethane (450 mL) cooled to −20 °C was added D-(−)-diethyl tartrate (2.48 g, 12 mmol), followed by titanium(IV) isopropoxide (3 mL, 10 mmol). After 30 min, *tert*-butyl hydroperoxide (133.4 mL, 0.4 mol, 3.0 M in 2,2,4-trimethylpentane) was added, the mixture was stirred for 30 min, and 2-ethyl-2-propen-1-ol (17.2 g, 0.2 mol) in 20 mL of dichloromethane was added dropwise. The mixture was stirred for 4.5 h at −20 °C, and quenched with water (60 mL) and stirred for 1 h, allowing the reaction mixture to warm to room temperature. The tartrate was hydrolyzed by addition of 60 mL of a 30% aqueous solution of sodium hydroxide saturated with sodium chloride and stirred for 30 min. The mixture was filtered through Celite, the organic layer was separated, and the aqueous phase was extracted with dichloromethane (2 × 100 mL). The combined organic layers were dried over sodium sulfate, filtered, and evaporated in vacuo to afford the crude epoxide **62** (25 g, contaminated with some of the starting reagents), which was used directly for the next step without further purification. A pure sample could be obtained by column chromatography (silica gel, eluting with 6:4 hexane/ethyl acetate) as a clear colorless oil. The epoxidation reaction in this case proceeded with ca. 85% ee as indicated by ^{1}H NMR studies using Eu(fod)$_3$ as a chiral shift reagent: $[\alpha]^{23}_D$ +32° (*c* 1.9, $CHCl_3$); IR ($CHCl_3$) 3584, 3012, 2974, 2883, 1462, 1226, 1072, 1034, 912, 889, 816 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.72 (1 H, dd, J = 12.3, 4.8 Hz), 3.56 (1 H, dd, J = 12.3, 8.2 Hz), 2.81 (1 H, d, J = 4.6 Hz), 2.61 (1 H, d, J = 4.6 Hz), 2.32–2.28 (1 H, m), 1.80–1.64 (1 H, m), 1.58–1.42 (1 H, m), 0.89 (3 H, t, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$) δ 62.61, 60.54, 49.35, 24.48, 8.57; HRMS calcd for $C_5H_{10}O_2$ 102.068, found *m/e* 102.067.

(*R*)-(−)-2-Ethyl-1-(phenylthio)-2,3-propanediol (63). To a solution of the crude epoxide **62** (10 g, ca. 79.94 mmol) and thiophenol (8.6 mL, 83.75 mmol) in dioxane (25 mL) was added dropwise a 1.0 N NaOH solution (25 mL). The reaction mixture was stirred at reflux for 4.5 h. After the mixture was allowed to cool to room temperature, dichloromethane (100 mL) was added, the organic layer was separated, and the aqueous layer was extracted with dichloromethane (2 × 100 mL). The combined organic extracts were dried over sodium sulfate, filtered, and evaporated in vacuo to afford the crude diol **63** (10 g) as a clear oil, which was directly used for the next step without further purification. An analytical sample was obtained by column chromatography (silica gel, eluting with 6:4 hexane/ethyl acetate) as a clear colorless oil: $[\alpha]^{23}_D$ −0.6° (*c* 6.4, $CHCl_3$), $[\alpha]^{23}_D$ −5.5° (*c* 2.2, MeOH); IR ($CHCl_3$) 3567, 3016, 2971, 2935, 2884, 1584, 1481, 1462, 1440, 1052, 1026 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.40–7.17 (5 H, m), 3.54, 3.49 (2 H, ABq, J = 11.2 Hz), 3.17, 3.10 (2 H, ABq, J = 13.2 Hz), 2.43 (2 H, s), 1.62–1.58 (2 H, m), 0.86 (3 H, t, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 136.53, 129.57, 129.00, 126.38, 74.72, 66.65, 40.87, 28.86, 7.64; HRMS calcd for $C_{11}H_{16}SO_2$ 212.0871, found *m/e* 212.0866.

Phenylthioacetonide 64. A solution of the crude diol **63** (10 g, ca. 47.17 mmol) in tetrahydrofuran (100 mL) was stirred with cyclohexanone methyl enol ether (6 mL) and Amberlyst-H15 (0.7 g) for 7 h at room temperature. The reaction mixture was filtered, and the solvent was evaporated in vacuo. The crude residue was purified by column chromatography (silica gel, eluting with hexane, then with 98:2 hexane/ethyl acetate) to afford 8.5 g (28% overall from 2-ethyl-2-propen-1-ol) of the acetonide **64** as a white solid material: mp 44–45 °C (methanol); $[\alpha]^{23}_D$ +3.3° (*c* 1.35, $CHCl_3$); IR ($CHCl_3$) 3011, 2940, 2864, 1584, 1481, 1449, 1439, 1368, 1126, 1096, 937 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.34–7.12 (5 H, m), 3.90 (1 H, d, J = 8.6 Hz), 3.70 (1 H, d, J = 8.6 Hz), 3.20, 3.10 (2 H, ABq, J = 12.6 Hz), 1.69 (2 H, q, J = 7.5 Hz), 1.62–1.50 (8 H, m), 1.36–1.30 (2 H, m), 0.87 (3 H, t, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 137.06, 129.32, 128.84, 125.99, 110.23, 83.00, 71.24, 41.20, 36.82, 36.24, 29.51, 25.05, 23.88, 23.82, 8.22; HRMS calcd for $C_{17}H_{24}SO_2$ 292.1497, found *m/e* 292.1496.

(*R*)-(+)-Aldehyde 65. To a stirred solution of the sulfide **64** (5.84 g, 20 mmol) in dry dichloromethane (120 mL) was added *m*-chloroperbenzoic acid (0.5 g) at room temperature. After 1 h, sequential additions of 0.5-g portions of *m*-chloroperbenzoic acid were carried out every hour until the total amount reached 3.6 g. The mixture was diluted with dichloromethane, poured into a 0.5 N NaOH solution (100 mL), and thoroughly extracted with dichloromethane. The combined extracts were dried over sodium sulfate, filtered, and evaporated in vacuo to give 5.8 g (94%) of homogeneous crude material as a 1:1 mixture of diastereomers. The crude material was used directly for the subsequent Pummerer reaction without purification: IR ($CHCl_3$) 3005, 2940, 2860, 1463, 1445, 1368, 1224, 1208, 1096, 1041, 790, 775 cm^{-1}; HRMS calcd for $C_{17}H_{24}SO_3$ 308.1446, found *m/e* 308.1439.

A stirred suspension of the above sulfoxides (3.08 g, 10 mmol), anhydrous sodium acetate (4.92 g, 60 mmol), and acetic anhydride (90 mL) was heated to reflux for 6 h. The reaction mixture was allowed to cool to room temperature, diluted with dichloromethane, slowly poured into a 1.0 N NaOH solution (130 mL), and thoroughly extracted with dichloromethane. The combined organic extracts were dried over sodium sulfate, filtered, and evaporated in vacuo, and the residue was purified on column chromatography (silica gel, eluting with 95:5 hexane/ethyl acetate) to afford 2.73 g (78%) of the α-acetoxy sulfides as a 1:1 mixture of diastereomers: $[\alpha]^{23}_D$ +19.5° (*c* 1.05, $CHCl_3$); IR ($CHCl_3$) 3008, 2939, 2863, 1748, 1449, 1440, 1370, 1230, 1094, 1045, 1019, 938, 795 cm^{-1}; HRMS calcd for $C_{19}H_{26}SO_4$ 350.1552, found *m/e* 350.1551.

To a stirred solution of the above α-acetoxy sulfides (5.0 g, 14.28 mmol) in methanol (180 mL) was added anhydrous potassium carbonate (1.52 g), and the mixture was refluxed for 4 h. The mixture was cooled to room temperature, and the solvent was carefully evaporated in vacuo. Ethyl ether (200 mL) was then added, and the mixture filtered. After careful evaporation of the solvent and column chromatography of the residue (silica gel, eluting with 98:2 pentane/ethyl acetate), the aldehyde **65** (2.5 g, 88%) was obtained as a clear colorless oil: bp 125–130 °C/15 mmHg; $[\alpha]^{23}_D$ +8.1° (*c* 1.43, $CHCl_3$); IR ($CHCl_3$) 2943, 2864, 2813, 1736, 1450, 1369, 1161, 1095, 927, 849 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.61 (1 H, s), 4.13 (1 H, d, J = 8.8 Hz), 3.69 (1 H, d, J = 8.8 Hz), 1.76–1.64 (2 H, m), 1.62–1.55 (8 H, m), 1.36 (2 H, br s), 0.87 (3 H, t, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 203.57, 111.51, 87.32, 68.50, 36.25, 35.80, 26.36, 24.97, 23.79 (2), 7.62; HRMS calcd for $C_{11}H_{18}O_3$ 198.1256, found *m/e* 198.1263.

(+)-(9*R*,2*S*,2′*S*)-3-Thioxo-9-(methoxycarbonyl)-2-(2′-ethyl-2′,3′-dihydroxypropyl)hexahydro-1-hydroxyindolizino[8,7-*b*]indole Cyclohexylidene Ketal (66). To a stirred solution of (+)-**17** (1.2 g, 4.0 mmol), aldehyde (+)-**65** (0.792 g, 4.0 mmol), and *N*-ethylpiperidine (0.72 mL, 5.2 mmol) in tetrahydrofuran (20 mL) was added dropwise a solution of stannous triflate (2.01 g, 4.8 mmol) in tetrahydrofuran (10 mL) at room temperature under argon. The reaction mixture was stirred for 10 h at room temperature (two more equivalents of *N*-ethylpiperidine and stannous triflate were added portionwise during this period) and then diluted with dichloromethane. The reaction was quenched with a pH = 7 phosphate buffer solution (40 mL). The precipitated white mass was removed through Celite. After separation of the organic layer, the aqueous layer was extracted with dichloromethane several times, and then the combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and evaporated in vacuo. The residue was purified by column chromatography (silica gel, eluting with 80:20 hexane/ethyl acetate) to afford the aldol product **66** (1.5 g, 75%) as a white solid material: mp 203–205 °C dec; $[\alpha]^{23}_D$ +88.6° (*c* 0.56, $CHCl_3$); IR ($CHCl_3$) 3460, 3332, 2941, 2859, 1737, 1483, 1436, 1297, 1190, 892 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.34 (1 H, s), 7.48 (1 H, d, J = 7.8 Hz), 7.36 (1 H, d, J = 8.0 Hz), 7.22 (1 H, dt, J = 7.3, 0.8 Hz), 7.12 (1 H, dt, J = 7.2, 0.8 Hz), 5.40–5.10 (1 H, br s), 5.32 (1 H, dd, J = 13.1, 5.6 Hz), 4.11 (1 H, d, J = 9.4 Hz), 3.95 (1 H, d, J = 9.4 Hz), 3.80 (3 H, s), 3.72 (1 H, d, J = 10.0 Hz), 3.56 (1 H, dt, J = 12.8, 5.0 Hz), 3.45 (1 H, dd, J = 13.9, 4.1 Hz), 3.19 (1 H, dt, J = 10.1, 4.0 Hz), 3.07–2.96 (1 H, m), 2.82 (1 H, dd, J = 15.8, 4.6 Hz), 2.60 (1 H, dd, J = 13.8, 10.2 Hz), 1.78–1.45 (12 H, m), 0.93 (3 H, t, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$) δ 203.79, 170.66, 136.74, 129.77, 125.81, 123.18, 120.21, 118.76, 111.34, 110.42, 109.90, 84.25, 77.26, 72.06, 70.83, 55.56, 53.35, 42.63, 36.26, 35.80, 34.12, 25.13 (2), 23.98, 23.86, 19.88, 8.08; HRMS calcd for $C_{27}H_{35}N_2O_5S$ (M^+ + 1) 499.2267, found *m/e* 499.2272.

(+)-(9*R*,2′*S*)-3-Thioxo-9-(methoxycarbonyl)-2-(2′-ethyl-2′,3′-dihydroxypropenylhexahydroindolizino[8,7-*b*]indole Cyclohexylidene Ketal (67). To a solution of the alcohol **66** (2.6 g, 5.22 mmol) in dichloromethane (125 mL) was added triethylamine (3.64 mL, 26.14 mmol) at room temperature under argon, followed by *p*-toluenesulfonic anhydride (2.55 g, 7.82 mmol). The reaction mixture was stirred at room temperature for 5 h, during which one more equivalent of *p*-toluenesulfonic anhydride was added. The reaction mixture was washed with brine, dried over sodium sulfate, and evaporated in vacuo. Column chromatography of the residue (silica gel, eluting with 80:20 hexane/ethyl acetate) afforded 3.1 g (91%) of the derived tosylate as a yellow glass material: IR ($CHCl_3$) 3459, 2939, 1756, 1732, 1465, 1434, 1369, 1345, 1190, 1178, 937 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.15 (1 H, s), 7.81 (2 H, d, J = 8.3 Hz), 7.45 (1 H, d, J = 7.8 Hz), 7.34 (1 H, d, J = 8.1 Hz), 7.25 (2 H, d, J

= 8.4 Hz), 7.21 (1 H, dt, J = 8.2, 1.0 Hz), 7.11 (1 H, dt, J = 7.4, 0.8 Hz), 5.24 (1 H, d, J = 4.6 Hz), 5.17 (1 H, dd, J = 12.9, 5.6 Hz), 3.97 (1 H, d, J = 9.2 Hz), 3.81 (3 H, s), 3.76 (1 H, d, J = 9.2 Hz), 3.40–3.34 (1 H, m), 3.17 (1 H, dd, J = 13.4, 5.1 Hz), 3.12–2.91 (1 H, m), 2.72 (1 H, dd, J = 15.9, 4.5 Hz), 2.64 (1 H, dd, J = 13.4, 10.2 Hz), 2.36 (3 H, s), 1.84–1.40 (13 H, m), 0.94 (3 H, t, J = 7.5 Hz); HRMS calcd for $C_{34}H_{40}N_2O_7S_2$ 652.2277, found m/e 652.2255.

To a solution of the tosylate (3.1 g, 4.75 mmol) in dichloromethane (120 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (1.05 mL, 7.03 mmol). The yellow reaction mixture was stirred at room temperature for 15 min and then diluted with dichloromethane (30 mL) and washed with water. The organic layer was separated, dried over sodium sulfate, and evaporated in vacuo. The residue was purified by column chromatography (silica gel, eluting with 80:20 hexane/ethyl acetate) to afford 2.0 g (88%) of **67** as a yellowish solid material: mp 205–208 °C dec; $[\alpha]^{23}_D$ +83.8° (c 0.6, $CHCl_3$); IR ($CHCl_3$) 3459, 2940, 1735, 1463, 1430, 1283, 1177, 1094, 780 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.31 (1 H, s), 7.49 (1 H, d, J = 7.8 Hz), 7.37 (1 H, d, J = 8.1 Hz), 7.21 (1 H, t, J = 8.0 Hz), 7.13 (1 H, t, J = 7.8 Hz), 6.99 (1 H, m), 5.50 (1 H, dd, J = 13.3, 5.7 Hz), 4.26 (1 H, dd, J = 16.9, 1.6 Hz), 3.97 (1 H, d, J = 8.4 Hz), 3.88 (1 H, d, J = 8.3 Hz), 3.74 (3 H, s), 3.66–3.56 (1 H, m), 3.03 (1 H, dd, J = 16.9, 3.1 Hz), 3.07–2.86 (2 H, m), 1.78–1.40 (12 H, m), 0.83 (3 H, t, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 194.66, 170.90, 139.97, 137.74, 136.82, 129.49, 125.95, 123.16, 120.21, 118.86, 111.34, 110.86, 110.23, 83.69, 72.92, 69.85, 53.38, 42.82, 37.97, 36.63, 35.56, 31.96, 25.15, 23.97 (2), 20.42 8.52; HRMS calcd for $C_{27}H_{33}N_2O_4S$ (M^+ + 1) 481.2161, found m/e 481.2158.

(−)-(9*R*,2*S*,2′*S*)-3*H*-9-(Methoxycarbonyl)-2-(2′-ethyl-2′,3′-dihydroxypropyl)hexahydroindolizino[8,7-*b*]indole Cyclohexylidene Ketal (30). To a stirred solution of the olefin **67** (480 mg, 1.0 mmol) in acetone (30 mL) was added partially deactivated Raney Ni in portions until the reaction was complete as indicated by TLC. The reaction mixture was diluted with dichloromethane and filtered through Celite, the cake was washed several times with a solution of dichloromethane/acetone/methanol (1:1:1) and then with a warm solution of dichloromethane/methanol (1:1), and the solvent was evaporated in vacuo.

The crude residue **68** was taken up in methanol (30 mL) and stirred overnight at room temperature under hydrogen at 1 atm with a catalytic amount of 10% Pd/C. The mixture was filtered through Celite, and the solvent was evaporated in vacuo. Purification of the residue by column chromatography (silica gel, eluting with 65:35 hexane/ethyl acetate) afforded 200 mg (44%) of the β isomer (−)-**30** and 196 mg (43%) of the α isomer (+)-**33**, shown by ^1H NMR, IR, TLC, and optical rotation to be identical with authentic samples.

Vinblastine Analogue 73. To a solution of (−)-**30** (480 mg, 1.06 mmol) in nitromethane (30 mL) at room temperature under argon was added 2,6-di-*tert*-butyl-4-methylpyridine (660 mg, 3.21 mmol), and then *p*-nitrobenzyl chloroformate (600 mg, 2.78 mmol), followed by 3-(dimethylamino)anisole (660 mg, 4.36 mmol). The mixture was stirred at room temperature for 108 h and quenched by addition of a saturated solution of sodium bicarbonate. The mixture was then extracted several times with dichloromethane. The organic layer was dried over sodium sulfate and evaporated in vacuo. The residue was purified by column chromatography (silica gel, eluting with 70:30 hexane/ethyl acetate) to give **69**/**70** (615 mg, 74%), consisting of a mixture of diastereomers at C-18′ (4:1). This mixture was used directly for the subsequent reaction.

To a solution of **69**/**70** (a mixture of diastereomers at C-18′) (610 mg, 0.78 mmol) in tetrahydrofuran (50 mL) was added a 2.0 M HCl solution (50 mL). The mixture was stirred for 20 h at room temperature, and then the reaction was quenched with a saturated solution of sodium bicarbonate until basic pH. The mixture was extracted with dichloromethane, and the combined organic layers were dried over sodium sulfate, filtered, and evaporated in vacuo. Purification of the residue by column chromatography (silica gel, eluting with 30:60 hexane/ethyl acetate, then 10:90 hexane/ethyl acetate) gave 390 mg (71%) of **71** (correct 18′*S* stereoisomer), along with 98 mg (18%) of the 18′*R* stereoisomer. The assignment of the absolute configuration at C-18′ could be made from the comparison of the CD curves with vinblastine and vinblastine precursors. Diastereomer **71** showed the following properties: $[\alpha]^{23}_D$ +5.6° (c 1.2, EtOAc); CD (methanol) λ_{max} ($\Delta\epsilon$) 210 (−9), 220 (+5), 235 (−10), 265 (+10); IR ($CHCl_3$) 3431, 2922, 1726, 1610, 1521, 1458, 1345, 1240, 735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.06 (1 H, s), 7.92 (2 H, d, J = 8.6 Hz), 7.56 (1 H, d, J = 7.9 Hz), 7.30 (1 H, d, J = 7.8 Hz), 7.24 (1 H, t, J = 7.4 Hz), 7.11 (1 H, dt, J = 7.2, 0.7 Hz), 6.53 (2 H, d, J = 8.5 Hz), 6.20 (1 H, br s), 6.19 (1 H, d, J = 8.5 Hz), 5.81 (1 H, dd, J = 8.6, 2.1 Hz), 4.93 (1 H, d, J = 13.2 Hz), 4.54 (1 H, d, J = 13.1 Hz), 4.29 (1 H, dt, J = 13.7, 4.6 Hz), 4.04 (1 H, br s), 3.99 (1 H, d, J = 14.9 Hz), 3.76 (3 H, s), 3.51 (3 H, s), 3.48–3.36 (1 H, m), 3.23–3.05 (3 H, m), 2.92 (6 H, s), 2.73–2.65 (2 H, m), 2.50 (1 H, br d, J = 10.2 Hz), 2.33 (1 H, d, J = 15.7 Hz), 1.76–1.61 (1 H, br s), 1.43–1.21 (5 H, m), 0.71 (3 H, t, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 174.44, 157.68, 156.31, 151.32, 147.10, 143.97, 135.07, 132.07, 131.26, 128.66, 128.12, 123.30, 122.50, 119.22, 118.03, 117.44, 111.61, 110.54, 103.56, 95.92, 73.93, 65.09, 65.37, 55.69, 55.44, 52.57, 47.42, 42.95, 42.42, 40.47, 30.61, 29.68, 28.78, 24.62, 7.51; HRMS calcd for $C_{38}H_{46}N_4O_9$ 702.3265, found m/e 702.3254.

To a solution of diol **71** (532 mg, 0.76 mmol) and triethylamine (2.12 mL, 15.20 mmol) in anhydrous dimethyl sulfoxide (25 mL) was added sulfur trioxide pyridine complex (1.21 g, 7.60 mmol) at room temperature under argon in one portion. The reaction mixture was stirred for 6 h and quenched with a saturated solution of sodium bicarbonate, followed by water, and the whole was extracted with dichloromethane. The combined organic extracts were washed with brine, dried over sodium sulfate, and evaporated in vacuo. Purification of the residue by column chromatgraphy (silica gel, eluting with 1:1 hexane/ethyl acetate) afforded 440 mg (83%) of **72** as a yellow glass material: $[\alpha]^{23}_D$ +14.1° (c 0.75, $CHCl_3$); CD (MeOH) λ_{max} ($\Delta\epsilon$) 211 (−4), 221 (+16), 236 (−13), 266 (+18); IR ($CHCl_3$) 3404, 2922, 1729, 1676, 1612, 1517, 1460, 1345, 1240, 1119 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.24 (1 H, s), 7.99 (1 H, s), 7.94 (2 H, d, J = 8.6 Hz), 7.53 (1 H, d, J = 7.9 Hz), 7.28–7.20 (2 H, m), 7.09 (1 H, dt, J = 7.6, 1.5 Hz), 6.63 (2 H, d, J = 8.6 Hz), 6.22 (1 H, br s), 6.03 (1 H, d, J = 8.6 Hz), 5.9 (1 H, br d, J = 8.0 Hz), 5.01 (1 H, s), 4.97 (1 H, d, J = 13.2 Hz), 4.53 (1 H, d, J = 12.9 Hz), 4.27 (1 H, dt, J = 13.4, 4.3 Hz), 3.98 (1 H, d, J = 14.2 Hz), 3.77 (3 H, s), 3.49 (3 H, s), 3.46–3.37 (1 H, m), 3.22–3.13 (2 H, m), 3.06 (1 H, dd, J = 15.2, 3.1 Hz), 2.95 (6 H, s), 2.66 (1 H, dd, J = 14.2, 8.9 Hz), 2.29 (1 H, dd, J = 15.5, 1.2 Hz), 1.58–1.23 (5 H, m), 0.65 (3 H, t, J = 7.4 Hz); HRMS calcd for $C_{38}H_{44}N_4O_9$ 700.3108, found m/e 700.3117.

A solution of aldehyde **72** (440 mg, 0.63 mmol) in methanol (60 mL) containing 10% Pd/C (200 mg) was stirred under hydrogen at 1 atm at room temperature until the reaction was complete as indicated by TLC. The mixture was filtered through Celite, the cake was washed with methanol, and the filtrate was evaporated in vacuo. The residue was purified by column chromatography (silica gel, eluting with 60:40 hexane/ethyl acetate, then with 30:70 hexane/ethyl acetate) to afford **73** (286 mg, 90%): $[\alpha]^{23}_D$ +53.6° (c 1.4, $CHCl_3$); CD (MeOH) λ_{max} ($\Delta\epsilon$) 209 (−23), 220 (+34), 255 (+18); IR ($CHCl_3$) 3428, 2915, 1715, 1610, 1511, 1453, 1239 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.26 (1 H, s), 7.48 (1 H, d, J = 7.8 Hz), 7.20 (1 H, d, J = 7.6 Hz), 7.14 (1 H, t, J = 8.0 Hz), 7.06 (1 H, dt, J = 7.2, 0.9 Hz), 6.86 (1 H, d, J = 8.6 Hz), 6.28 (1 H, d, J = 2.4 Hz), 6.18 (1 H, dd, J = 8.7, 2.4 Hz), 3.98 (1 H, t, J = 13.8 Hz), 3.80 (3 H, s), 3.73–3.62 (1 H, m), 3.58 (3 H, s), 3.46–3.25 (2 H, m), 3.13 (2 H, d, J = 13.8 Hz), 2.96 (6 H, s), 2.83 (2 H, br s), 2.42 (1 H, d, J = 13.4 Hz), 2.30 (1 H, dd, J = 14.9, 2.8 Hz), 1.86 (1 H, br s), 1.50–1.25 (4 H, m), 1.05–0.99 (1 H, m), 0.88 (3 H, t, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 175.06, 157.64, 150.89, 134.67, 131.45, 130.61, 128.98, 122.03, 118.71, 118.38, 118.28, 116.00, 110.19, 103.58, 96.57, 69.78, 64.43, 55.68, 55.43, 55.26, 52.25, 48.55, 41.40, 40.43, 34.61, 34.17, 30.06, 29.10, 6.93; HRMS calcd for $C_{30}H_{39}N_3O_4$ 505.2941, found m/e 505.2945.

Acknowledgment. The National Institutes of Health (GM 29801) are thanked for their support of this research. Dr. John C. Huffman (Department of Chemistry, Indiana University, Bloomington) is thanked for the X-ray structure determinations of **24** and **29**. Dr. Vince Lynch (X-ray lab, Department of Chemistry and Biochemistry, UT Austin) is thanked for the X-ray structure determinations of **49** and **53**. Dr. Homer Pearce (Eli Lilly) is thanked for supplies of vindoline and vinblastine.

Supplementary Material Available: Details of the X-ray determination of **24** and **29** (26 pages). Ordering information is given on any current masthead page.