stituted olefins without detectable epimerization at the adjacent stereogenic center, suggesting potential for application of the method in asymmetric synthesis. Entries 2, 3, 5, and 6 illustrate syntheses of trisubstituted olefins and further define the requirements for selectivity in olefin formation. Thus, additions with 2-lithio-1-butene (entries 2 and 5) exhibit little or no selectivity while additions with (*E*)-2-lithio-2-butene (entries 3 and 6) produce a single stereoisomer, within the limits of detection. The transformations exemplified in the latter entries are particularly significant; we are unaware of another means by which to accomplish this bond construction with the observed selectivity and efficiency. Together these examples reinforce the notion that $A_{1,3}$ steric interactions dominate the transition state for diazene rearrangement (see entries 3 and 6), but caution that $A_{1,2}$ terms can become important where $A_{1,3}$ interactions diminish (see entries 2 and 5).

In conclusion, *N-tert*-butyldimethylsilyl tosylhydrazones are demonstrated to be valuable precursors for the constructive synthesis of carbon–carbon double bonds. The method is efficient and offers unique solutions to problems in the stereoselective synthesis of di- and trisubstituted olefins.

Acknowledgment. We are indebted to Mr. Narayanan Kurur and Professor John D. Roberts for their assistance in obtaining ^{15}N NMR spectra. This research was generously supported by the Caltech Consortium in Chemistry and Chemical Engineering; members: E. I. du Pont de Nemours & Co., Inc., Eastman Kodak Company, and Minnesota Mining and Manufacturing Company. Financial support from the National Science Foundation is also gratefully acknowledged.

Supplementary Material Available: Experimental procedures for the preparation of the optically active aldehydes and organolithium precursors of Table I (6 pages). Ordering information is given on any current masthead page.

Synthesis of the Antitumor Bisindole Alkaloid Vinblastine: Diastereoselectivity and Solvent Effect on the Stereochemistry of the Crucial C-15–C-18′ Bond

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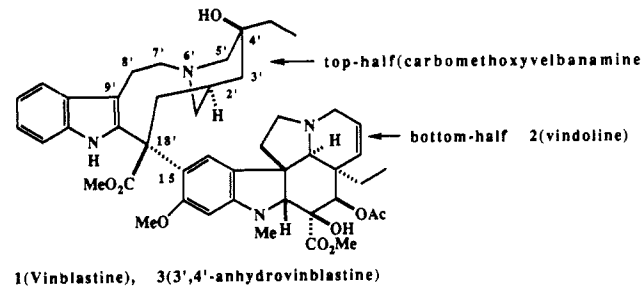
Received August 13, 1990

The clinically valuable antitumor agent vinblastine (**1**) has been the object of intensive chemical and pharmacological investigations for the past 25 years.[1] Synthetic studies have focused on how to control the absolute stereochemistry of the crucial C-15–C-18′ bond linking the bottom half, vindoline (**2**), and the top half, carbomethoxyvelbanamine, Scheme I.[2] Potier[3] and Kutney[4] have described a solution to this problem using the Polonovski reaction to fragment catharanthine *N*-oxide to a putative bis iminium ion which is trapped by **2** to give anhydrovinblastine **3** 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. More recently, Kuehne has described extensive studies that utilize a variant on the chloroindolenine approach to establish the correct absolute stereochemistry at C-18′.[5]

Scheme I



1(Vinblastine), 3(3′,4′-anhydrovinblastine)

Despite the formidable and extensive literature in this area, there has not been a systematic examination of how the various stereogenic centers in the top half influence the stereochemistry of the C-15–C-18′ bond. Previously, we had reported that treatment of (+)-**4** with *m*-$MeOC_6H_4NMe_2$/*p*-nitrobenzyl chloroformate-/CH_2Cl_2 gave **6** with 60% ee (retention of C-18′ configuration). Coupling with more nucleophilic aryl components, such as 3,5-$(MeO)_2C_6H_3NMe_2$ gave **7** with >90% ee.[6] The same reaction with vindoline (**2**) gave **8** as a 1:1 mixture of diastereomers at C-18′, indicating that the more slowly the putative iminium ion **5** is captured by the aromatic nucleophile, the more conformational isomerization, in this case racemization, can take place. The transition states leading to **6**/**7** are enantiomeric, whereas for **8** they are diastereomeric. Starting with (−)-**4**, the antipodes of **6**/**7** are formed, whereas coupling with vindoline gave the same result, namely **8** (1:1, 18′-epimers), Scheme II.

We reasoned that a substituent at C-2′ in **4**,[7] fashioned to eventually become the piperidine ring (C-3′, -4′, and -5′), would sufficiently slow the conformational inversion of the nine-membered ring to allow coupling with vindoline to proceed with retention of configuration at C-18′. To ascertain the effect of C-18′/C-2′/C-4′ stereochemistry, we made all possible stereoisomers (only three are shown); the epimers at the C-4′ position correspond to the leurosidine series and did not affect the stereochemical outcome at C-18′. The details of the syntheses of **9**, **10**, and **11**, Scheme III, will be reported in a full account of this research.

Treatment of **9** with $ClCO_2CH_2C_6H_4NO_2$-*p*/vindoline/CH_2Cl_2/25 °C for 72 h gave two compounds, **12** (52%) and **13** (42%). The structure of **12** was established by converting it into 18′-epivinblastine **17**, via **14** (80%), **15** (89%) and **16**, to give **17** (92%) (structure by X-ray).[8] To establish the unprecedented structure of the C-9′ coupled adduct **13**, it was hydrolyzed to the

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(1) For a comprehensive review of this area, see: The Alkaloids. *Antitumor Bisindole Alkaloids from Catharanthus roseus (L.)*; Brossi, A., Suffness, M., Eds.; Academic Press Inc.: San Diego, 1990; Vol. 37.

(2) 3′,4′-Anhydrovinblastine has been converted into vinblastine. Mangeney, P.; Andriamialisoa, R. Z.; Langlois, N.; Langlois, Y.; Potier, P. *J. Am. Chem. Soc.* **1979**, *101*, 2243. For a biomimetic equivalent, see reference 10.

(3) 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 review, see: Lounasmaa, M.; Nemes, A. *Tetrahedron* **1982**, *38*, 223.

(4) 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.

(5) For a modification of the chloroindolenine route that produces the correct 18′ configuration, see: Kuehne, M. E.; Zebovitz, T. C.; Bornmann, W. G.; Marko, I. *J. Org. Chem.* **1987**, *52*, 4340. Kuehne, M. E.; Bornmann, W. G. *J. Org. Chem.* **1989**, *54*, 3407. For earlier examples of the chloroindolenine approach that produces the C-18′ *R* stereochemistry, see: 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. Rahmann, ur-A.; Basha, A.; Ghazala, M. *Tetrahedron Lett.* **1976**, 2351. Recent work using the chloroindolenine method has been applied to analogues: Schill, G.; Priester, C. U.; Windhovel, U. F.; Fritz, H. *Tetrahedron* **1987**, *43*, 3747.

(6) Magnus, P.; Ladlow, M.; Elliott, J.; Kim, C. S. *J. Chem. Soc., Chem. Commun.* **1989**, 518.

(7) The compound **4** and C-2′-substituted derivatives are made from D- or L-tryptophan: Magnus, P.; Ladlow, M.; Kim, C. S.; Boniface, P. *Heterocycles* **1989**, *28*, 951.

(8) The full details of the single-crystal X-ray crystallographic structure determination of **17** and **19** will be given in a full account of this research.

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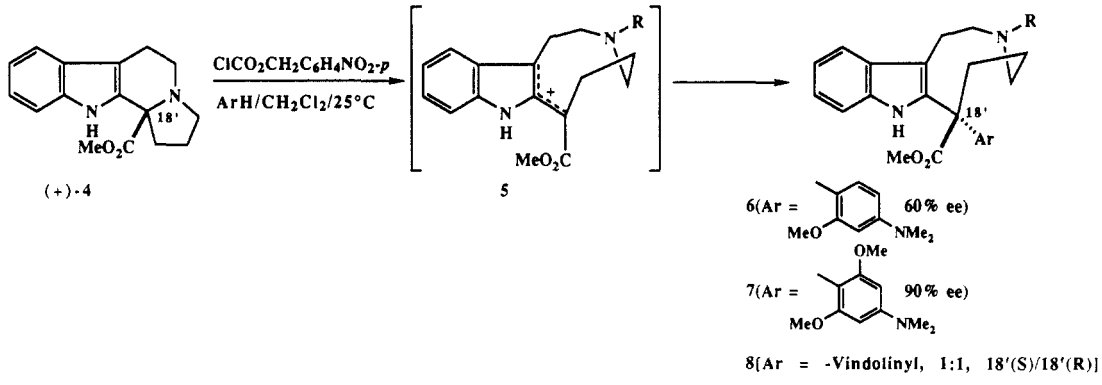
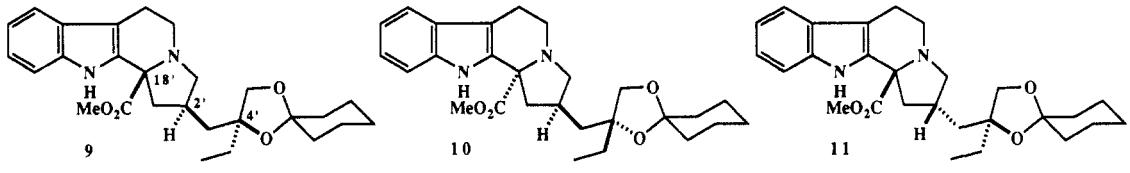
Scheme II[a]



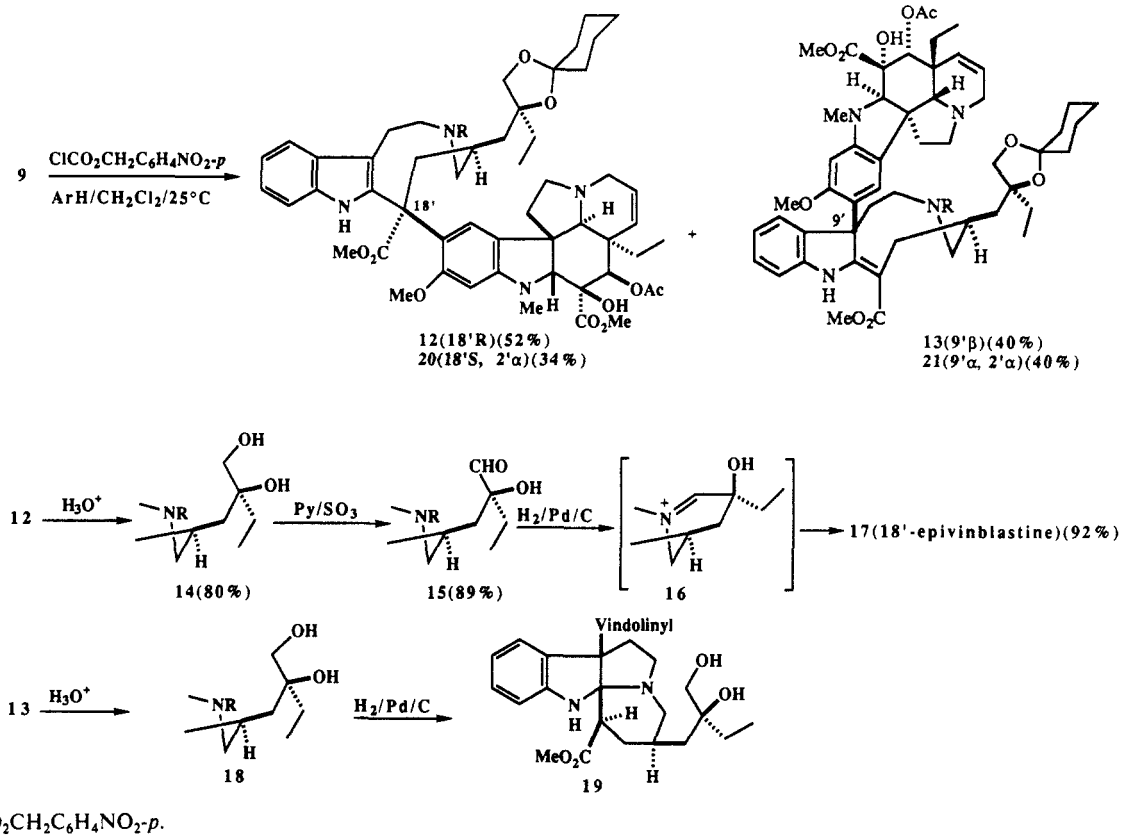
[a] R = $CO_2CH_2C_6H_4NO_2$-*p*.

Scheme III[a]



[a] All structures are shown with their correct absolute stereochemistry.

Scheme IV[a]

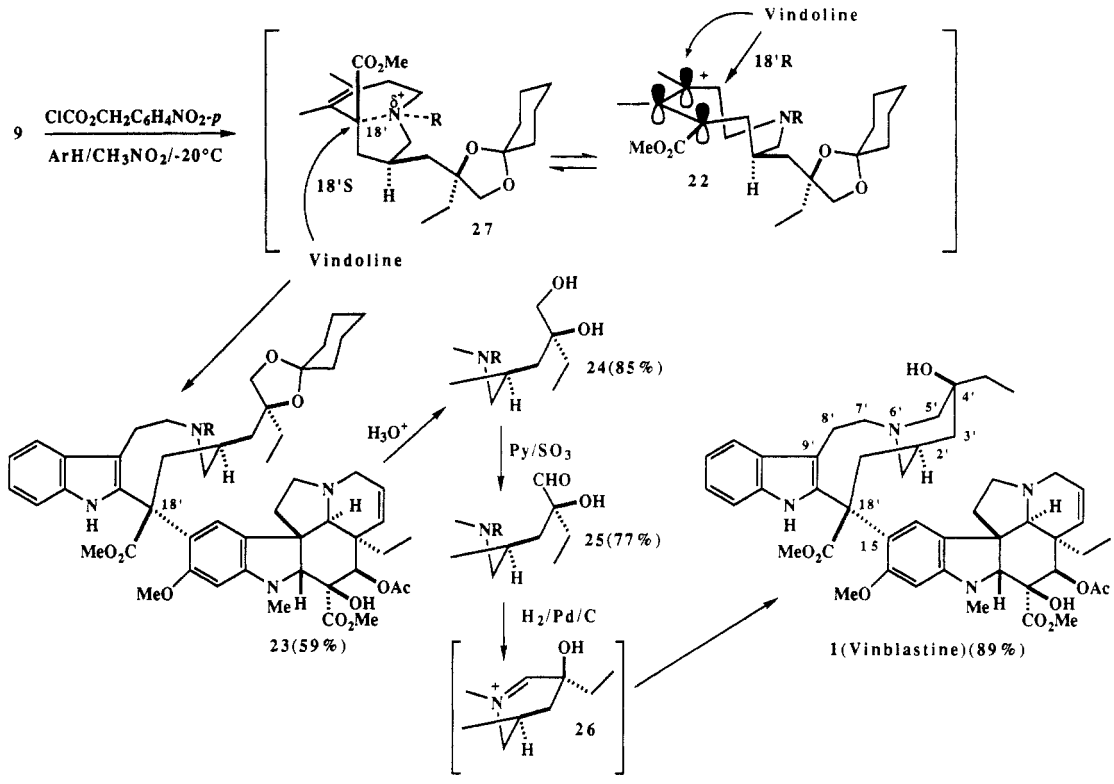


[a] R = $CO_2CH_2C_6H_4NO_2$-*p*.

diol **18**, which upon hydrogenolysis resulted in conjugate addition of N-6′ to the β-aminoacrylate functionality to give **19** (structure by X-ray).[8] Therefore, somewhat surprisingly, especially given the information in Scheme II, the coupling reaction of **9** is stereospecific (β-face attack, inversion at C-18′), but not regiospecific! Coupling of **11** (opposite C-2′ stereochemistry) with vindoline/$ClCO_2CH_2C_6H_4NO_2$-*p*/CH_2Cl_2/25 °C gave two products, **20** and **21**. Paralleling the previous example, the reaction is stereospecific (α-face attack) but not regiospecific, Scheme IV.

Again surprisingly, when **10** was exposed to the above coupling conditions, it gave the same two compounds as **9**, namely, **12** and **13**, but antipodal at C-4′. Therefore we can conclude that aromatic electrophilic substitution of **9**, **10**, and **11** takes place syn to the C-2′ side chain and that, under the described reaction conditions for **9** and **10**, conformational equilibration of the putative intermediate iminium ion **22** is faster than the former. The results described so far indicate that if coupling always take place syn to the C-2′ side chain, then the stereochemical relationship necessary for vinblastine (**1**) is not accessible. If the rate of coupling can be increased relative to conformational equilibration of the iminium ion **22**, it might be possible to trap the desired conformer. There are two obvious ways to achieve a change in

Scheme V[a]



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

the balance between the relative rates without resorting to major structural alterations. Classically, increase the solvent polarity and lower the temperature.[9] All the coupling reactions were run in CH_2Cl_2 (ϵ, 8.9) at 25 °C. On the basis of the results shown in Scheme II (retention of configuration at C-18′), we treated **9** with $ClCO_2CH_2C_6H_4NO_2$-*p*/vindoline/CH_3NO_2 (ϵ, 35.9) at −20 °C and obtained the correct 18′*S* stereoisomer **23** (46%) along with **12** (33%) and traces of **13**. Carrying out the same coupling procedure as above but in the presence of 2,6-di-*tert*-butyl-4-methylpyridine gave **23** (59%) and **12** (31%). Hydrolysis of **23** gave the diol **24** (85%), which was oxidized, by using pyridine/SO_3, to the α-hydroxy aldehyde **25** (77%). Hydrogenolysis of **25** (Pd/C/MeOH) gave vinblastine (**1**) (89%), Scheme V. This last transformation presumably proceeds via the iminium ion **26**, which is the intermediate in Kutney's biomimetic conversion of 3′,4′-anhydrovinblastine (**3**) into vinblastine (**1**).[10]

The pronounced favorable solvent effect in reversing the stereochemistry at C-18′ could be attributed to preferential solvation of the "closed" iminium ion **27** versus the more delocalized "open" iminium ion **22**. Trapping of the "closed" ion leads to the correct C-18′ *S* stereochemistry with overall retention of configuration.[11] The overall yield from **9** to vinblastine is 34% (four steps).[12] Finally it should be noted that coupling of the C-18′ epimer **10** to vindoline using the above conditions gave none of the correct C-18′ *S* stereochemistry.

Acknowledgment. The National Institutes of Health (GM 29801) are thanked for their support of this research. Dr. Vince Lynch (X-ray lab, Department of Chemistry and Biochemistry, The University of Texas at Austin) is thanked for the X-ray structure determinations of **17** and **19**. Dr. Homer Pearce (Eli Lilly) is gratefully thanked for supplies of vindoline and vinblastine. Dr. J. P. Kutney is thanked for FAB mass spectra.

Supplementary Material Available: Spectral data for compounds **9–15**, **17**, **19–21**, **23–25**, **1**, and the C-4′ epimers of **12** and **13** and details of the X-ray determination of **17** and **19** (48 pages). Ordering information is given on any current masthead page.

(9) 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.

(10) Kutney, J. P.; Choi, L. S. L.; Nakano, J.; Tsukamoto, H. *Heterocycles* **1988**, *27*, 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.

(11) Assignment of the absolute configuration at C-18′ is made by comparison of the CD curves with **1**. These correlations can only be used with any reliability if the alkaloids are very similar to the natural bis alkaloids. 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.

(12) Coupling 4′-epi **9** (leurosidine series) to vindoline using the described procedure with CH_3NO_2 gave the corresponding 18′*S* bis alkaloid in 77% yield, clearly suggesting that there is ample room for improvement in the vinblastine series. We are currently investigating the optimization of this reaction.

Activation of Dioxygen by Bis[(2-carboxy-6-carboxylato)pyridine]iron(II) for the Bromination (via $BrCCl_3$) and Monooxygenation (via PhNHNHPh) of Saturated Hydrocarbons: Reaction Mimic for the Methane Monooxygenase Proteins

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Received May 17, 1990

The activation of dioxygen for the monooxygenation of saturated hydrocarbons by the methane monooxygenase (MMO, μ-oxo-

0002-7863/90/1512-8212$02.50/0