amino-2-carbethoxy-3-methylene-4-cyanobutanoate was placed in 600 mL of 20% HCl, and the mixture was stirred in a 40 °C oil bath under a nitrogen-filled balloon. After 22 h, the solvent was removed under vacuum, yielding 3.208 g (94%) of yellow foam. Trituration with 150 mL of 50:1 acetone–EtOH solution gave 2.030 g (60%) of brown solid. The NMR showed that the solid was a 1.6:1 mixture of β-methylene-D,L-glutamine hydrochloride and 4-amino-3-methylbut-2-enamide hydrochloride. When the mixture was triturated with five 150-mL portions of 50:1 acetone–EtOH, 0.790 g (23%) of pure β-methylene-D,L-glutamine hydrochloride (II-HCl) was obtained as a white solid, mp 123–131 °C dec.

The 300-MHz proton NMR spectrum (D_2O) showed a one-proton doublet at δ 5.58 (J = 2.2 Hz), a one-proton singlet at 5.17, and a two-proton singlet at 3.75. The proton-decoupled ^{13}C NMR spectrum (D_2O) showed six lines at 35.2, 64.7, 113.0, 134.9, 170.6, and 172.4 ppm. The coupled ^{13}C NMR spectrum (D_2O) showed a carbonyl singlet at δ 172.4, a carbonyl singlet at 170.6, a quaternary vinyl singlet at 134.9, a vinyl triplet at 113.0 (J = 163.6 Hz), a methine doublet at 64.7 (J = 161.1 Hz), and a methylene triplet at 35.2 (J = 139.2 Hz). The IR spectrum (KBr) showed bands at 3340 (m, NH), 3200–2900 (s, OH), 1680 (s, CO), 1430 (m), and 1390 cm^{-1} (m). The positive LD mass spectrum showed m/z (relative intensity) 194 (27, M^+), 141 (19), 97 (84, $M^+ - HCl - NH_2 - CO_2H$), 80 (35), 38 (55), and 23 (100). The negative LD mass spectrum showed m/z (relative intensity) 174 (40), 172 (85), 170 (100), 168 (61), 163 (28), 161 (38), 159 (37, $M^- - Cl$), 35 (36), and 26 (69).

The combined acetone–EtOH solution was evaporated and triturated once again with 150 mL of 50:1 acetone–EtOH, yielding 0.230 g (7%) of pure 4-amino-3-methylbut-2-enamide hydrochloride as a brown solid. The 300-MHz proton NMR spectrum (D_2O) showed a one-proton singlet at δ 6.21, a two-proton singlet at 4.37, and a three-proton singlet at 2.18. The proton-decoupled ^{13}C NMR spectrum (D_2O) showed a carbonyl singlet at δ 167.8, a quaternary vinyl singlet at 166.3, a vinyl doublet at 116.7 (J = 178.2 Hz), a methylene triplet at 57.2 (J = 144.0 Hz), and a methyl quartet at 14.0 (J = 126.9 Hz). The IR spectrum (KBr) showed bands at 3200–3000 (m, NH, OH), 2310 (w), and 1655 cm^{-1} (s, C=O). The amide does not have a sharp melting point, it begins to decompose at 185 °C, becoming progressively darker at higher temperatures.

β-Methylene-D,L-glutamine (II). In a 10-mL, round-bottomed flask, 0.400 g (2.06 mmol) of β-methylene-D,L-glutamine hydrochloride (II-HCl) was dissolved in 1 mL of deionized water, and the solution was stirred at 0 °C in an ice bath. An excess of propylene oxide (0.360 g, 6.18 mmol) was added, and the mixture was stirred at 0 °C under a nitrogen-filled balloon. After 1 h, the pH of the mixture became 2.77 and a white solid had precipitated. An additional 0.360 g (6.18 mmol) of propylene oxide was added. After 3.5 h, the pH of the mixture became 5.93. At this point the white precipitate was centrifuged and washed three times each with 1 mL of cold EtOH yielding 0.216 g (66%) of white solid, mp 130–144 °C dec.

The IR spectrum (KBr) showed bands at 3300–2800 cm^{-1} (br s, NH, OH), 1720–1580 (br s, C=O), and 1350 cm^{-1} (br s). The NMR spectrum were taken as the hydrochloride and were identical with those of (II-HCl) described above.

Decarboxylation of β-Methylene-D,L-glutamic Acid (I). In a 50-mL, round-bottomed flask 0.030 g (0.194 mmol) of β-methylene-D,L-glutamic acid (I) was placed in 5 mL of 20% HCl. The mixture was stirred under a nitrogen-filled balloon in a 50 °C oil bath. After 2 days, evaporation of the solvent under vacuum gave 0.029 g of white amorphorous solid. The 300-MHz proton NMR spectrum (D_2O) showed a one-proton singlet at δ 5.85, a two-proton singlet at 4.03, a three-proton singlet at 2.10 together with starting material. The peaks resulting from decarboxylation are identical with those of the amino acid VI.

Decarboxylation of β-Methylene-D,L-glutamine Hydrochloride (II-HCl). In a 50-mL, round-bottomed flask 0.010 g (0.05 mmol) of β-methylene-D,L-glutamine hydrochloride was placed in 5 mL of deionized water, and the mixture was stirred under nitrogen in a 50 °C oil bath. After 2 days, evaporation of the solvent under vacuum gave 0.009 g of white amorphorous solid. The 300-MHz proton NMR spectrum (D_2O) showed a one-proton singlet at δ 6.21, a two-proton singlet at 4.37, and a three-proton singlet at 2.18, together with starting material. The new peaks in the spectrum correspond to the decarboxylated product (X).

Registry No. I, 97402-98-7; I-HCl, 102831-40-3; II, 97402-99-8; II-HCl, 102831-41-4; III, 1068-90-2; IV, 14369-81-4; V, 102831-42-5; VI, 102831-43-6; VII, 1001-56-5; VIII, 102831-44-7; IX, 102831-45-8; X, 102831-39-0; ethyl (triphenylphosphoranylidene)acetate, 1099-45-2; acetyl chloride, 75-36-5; diethyl aminomalonate, 6829-40-9; di-*tert*-butyl dicarbonate, 24424-99-5.

Studies in Biomimetic Alkaloid Syntheses. 14. Controlled, Selective Syntheses of Catharanthine and Tabersonine, and Related Desethyl Compounds, through Generation of 15-Oxosecodine Intermediates

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Received March 12, 1986

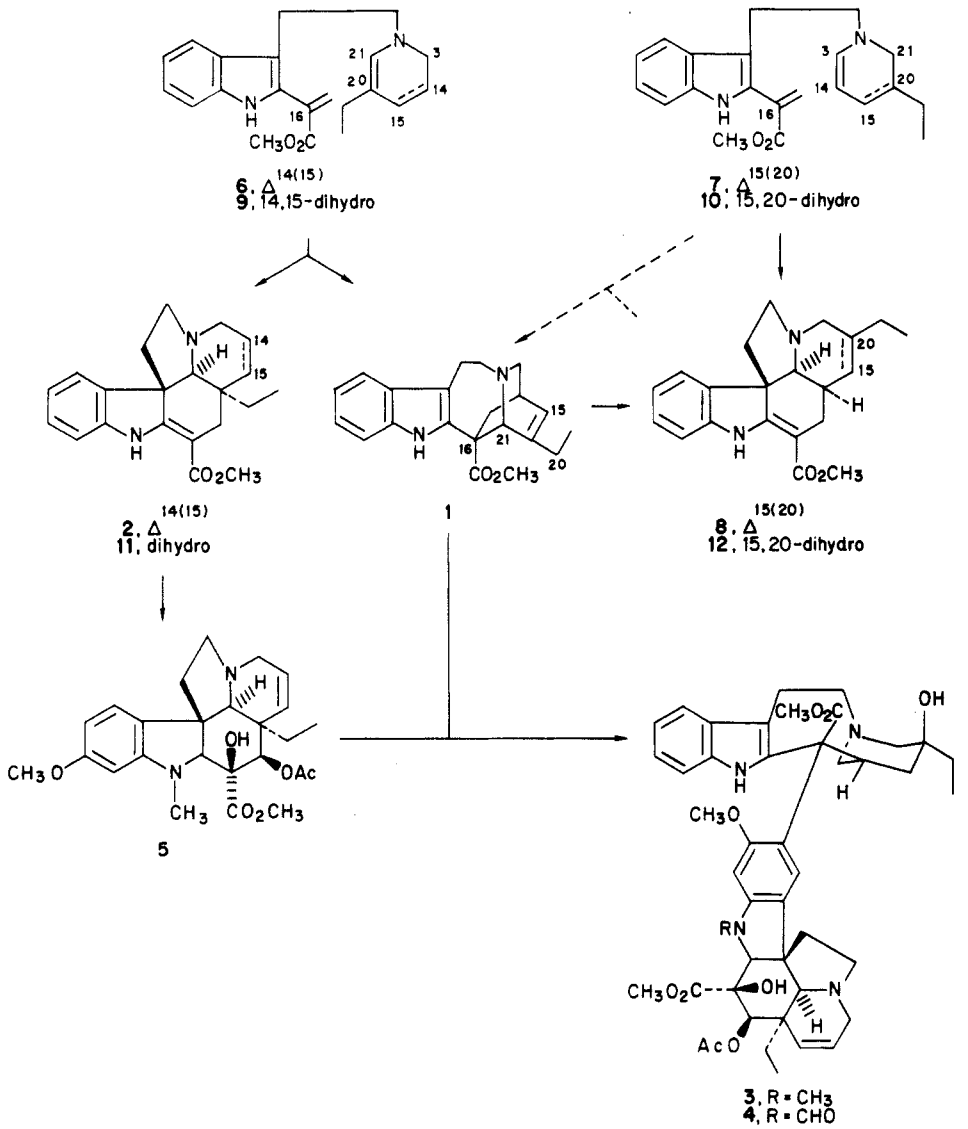
The syntheses of isolated 15-oxo-$\Delta^{20(21)}$-secodine (**13**) and desethyl-15-oxo-$\Delta^{20(21)}$-secodine (**32**) from methyl 1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-5-carboxylate (**14**) by spiroquaternization, or alternatively by a bridged azepine pathway, are described. Thermolyses of these compounds gave 15-oxovincadifformine (**18**) and desethyl-15-oxovincadifformine (**41**). Subsequent transformations led to tabersonine (**2**) and desethylvincadifformine (**43**), respectively. On O-silylation of the 15-oxosecodines **13** and **32** 15-(silyloxy)catharanthine (**23**) and the corresponding desethyl compound (**44**) were formed. Transformation to 15-oxo- and 15-β-hydroxycoronanidines (**25**, **27**) and their desethyl analogues, **47** and **48**, and to catharanthine (**1**) and desethylcatharanthine (**50**) are discussed.

Without rival in modern alkaloid chemistry has been the sustained interest in solutions to the syntheses of the catharanthine (**1**) and the tabersonine (**2**) classes of alkaloids. The stimulus for these endeavors derives from more than an intrinsic challenge inherent in the demands of stereochemically controlled assembly of polycyclic molecules, that is piqued in the catharanthine–ibogamine class by the unique isoquinuclidine skeleton. Further attention to the problem comes from biogenetic considerations of a common origin of the structurally very dissimilar molecular frameworks of catharanthine (**1**) and tabersonine (**2**), which was proposed, with differing organic chemical rationales, to explain the formation of these alkaloids.[1-4]

(1) Taylor, W. I. *Experientia* **1957**, *13*, 454.
(2) Wenkert, E.; Bringi, N. V. *J. Am. Chem. Soc.* **1959**, *81*, 1474, 6535.

0022-3263/86/1951-2913$01.50/0

Scheme I



Subsequent biosynthetic experiments with labeled precursors demonstrated the reality of a common, diverging pathway in the natural biosynthesis of the two alkaloid classes.[5]

Not least among the motivating factors for syntheses of such alkaloids has been the extensive clinical use of vinblastine (VLB, **3**) and vincristine (VCR, **4**), dimeric alkaloids obtained in plant biosynthesis[6] and synthetically,[7-9] from coupling of catharanthine (**1**), as its *N*-oxide, with vindoline (**5**), an oxygenated derivative of tabersonine (**2**).

While the numerous synthetic steps culminating in VLB and VCR can be assembled from the efforts of many research groups working in this field,[10-14] actual total syntheses of these compounds by all of the steps required for the syntheses of catharanthine and vindoline, and coupling of these synthetic intermediates, have left such a VLB–VCR total synthesis in the realm of spiritual, rather than substantive, accomplishment. Again, a possible communality of precursors for the two halves of these

(3) Thomas, R. *Tetrahedron Lett.* **1961**, *544*.
(4) Wenkert, E. *J. Am. Chem. Soc.* **1962**, *84*, 98.
(5) Battersby, A. R.; Brown, R. T.; Knight, J. A.; Martin, J. A.; Plunkett, A. O. *Chem. Commun.* **1966**, 346. Loew, P.; Goeggel, H.; Arigoni, D. *Ibid.* **1966**, 347. Hall, E. S.; McCapra, F. M.; Money, T.; Fukumoto, K.; Hanson, J. R.; Mootoo, B. S.; Phillips, G. T.; Scott, A. I. *Ibid.* **1966**, 348. Leete, E.; Ueda, S. *Tetrahedron Lett.* **1966**, 4915. Qureshi, A. A.; Scott, A. I. *Chem. Commun.* **1968**, 948. Battersby, A. R.; Byrne, J. C.; Kapil, R. S., Martin, J. A.; Payne, T. G.; Arigoni, D.; Loew, P. *Ibid.* **1968**, 951. Kutney, J. P. *Heterocycles* **1977**, *7*, 593. Kutney, J. P.; Badger, R. A.; Beck, J. F.; Bosshardt, H.; Mataugh, F. S.; Ridaura-Sanz, V. E.; So, Y. H.; Sood, R. S.; Worth, B. R. *Can. J. Chem.* **1979**, *57*, 289. Kutney, J. P.; Badger, R. A.; Cullen, W. R.; Greenhouse, R.; Noda, M.; Ridaura-Sanz, V. E.; So, Y. H.; Zanarotti, Z.; Worth, B. R. *Ibid.* **1979**, *57*, 300.
(6) Scott, A. I.; Gueritte, F.; Lee, S. L. *J. Am. Chem. Soc.* **1978**, *100*, 6253. Stuart, K. L.; Kutney, L. P.; Worth, B. R. *Heterocycles* **1978**, *9*, 1015. Stuart, K.L.; Kutney, J. P.; Honda, T.; Worth, B. R. *Ibid.* **1978**, *9*, 1391, 1419. McLauchlan, W. R.; Hasan, M.; Baxter, R. L.; Scott, A. I. *Tetrahedron* **1983**, *39*, 3777. Kutney, J. P.; Aweryn, B.; Choi, L. S. L.; Honda, T.; Kolodziejczyk, P.; Lewis, N. G.; Sato, T.; Sleigh, S. K.; Stuart, K. L.; Worth, B. R.; Kurz, W. G. W.; Chatson, K. B.; Constabel, F. *Ibid.* **1983**, *39*, 3781.
(7) Potier, P.; Langlois, N.; Langlois, Y.; Gueritte, G. *J. Chem. Soc., Chem. Commun.* **1975**, 670.
(8) Kutney, J. P.; Ratcliffe, A. H.; Treasurywala, A. M.; Wunderly, S. *Heterocycles* **1975**, *3*, 639.
(9) Langlois, N.; Gueritte, F.; Langlois, Y.; Potier, P. *J. Am. Chem. Soc.* **1976**, *98*, 7017.
(10) Mangeney, P.; Andriamialisoa, R. Z.; Langlois, N.; Langlois, Y.; Potier, P. *J. Am. Chem. Soc.* **1979**, *101*, 2243.
(11) Atta-ur-Rahman; Basha, A.; Ghazala, M. *Tetrahedron Lett.* **1976**, 2351.
(12) Jovanovics, K.; Szasz, K.; Fekete, G.; Bittner, E.; Dezseri, E.; Eles, J. Ger. Patent 27 259 447 **1974**, *Chem. Abstr.* **1974**, *81*, 91780. U.S. Patent 3 899 493, **1975**; *Chem. Abstr.* **1975**, *83*, 179360. Can. Patent989 829, **1976**; *Chem. Abstr.* **1976**, *84*, 1777621.
(13) Richter, G. Fr. Patent 2 210 393, **1975**; *Chem. Abstr.* **1975**, *82*, 73294. Belg. Patent 823 560 **1976**; *Chem. Abstr.* **1976**, *84*, 59835.
(14) Kutney, J. P.; Balsevich, J.; Honda, T.; Liao, P. H.; Thiellier, H. P. M.; Worth, B. R. *Heterocycles* **1978**, *9*, 201; *Can. J. Chem.* **1978**, *56*, 2560.

dimeric alkaloids tantalizes the synthetic chemist concerned with efficacy of a synthetic strategy directed at these compounds.

The synthetically interesting key biogenetic postulates linking formation of the catharanthine (1), tabersonine (2), and pseudotabersonine (8) classes of alkaloids, which are reconcilable with biosynthetic and interconversion experiments, are the generation of a $\Delta^{14(15),20(21)}$-dehydrosecodine (6) and its alternative modes of Diels–Alder-type cyclizations. More circuitous is the generation, from a common precursor, of a $\Delta^{3(14),15(20)}$-dehydrosecodine (7) intermediate. The latter, on Diels–Alder-type cyclization, could yield pseudotabersonine (8, "pseudocatharanthine") and indirectly, stepwise, with imonium double bond 3–21 exchange and 16–21 bonding, also lead to catharanthine (1).[15-20] It may be noted, however, that catharanthine is converted to pseudotabersonine in hot acetic acid.[17]

We had found that the generation of transient $\Delta^{20(21)}$ and $\Delta^{3(14)}$-secodines (9, 10) furnished vincadifformine (11) and the 20-epimeric pseudovincadifformines 12 in 70–84% and 46% yields, respectively.[21-23] However, this mode of cyclization does not seem to occur on generation of the transient N^{α}-benzyl-$\Delta^{14(15),20(21)}$-dehydrosecodine (N^{α}-benzyl-6), which resulted only in N^{α}-benzylcatharanthine (N^{α}-benzyl-1), in 1.5% yield, while on generation of transient N^{α}-benzyl-$\Delta^{3(14),15(20)}$-dehydrosecodine (N^{α}-benzyl-7) a 22% yield of the N^{α}-benzylpseudotabersonine (N^{α}-benzyl-8), but no isoquinuclidine product was obtained.[24]

Intermolecular additions of electron-deficient olefins to 1,2-dihydropyridines,[25-27] analogous to a dehydrosecodine cyclization, were utilized in the Büchi and Ban syntheses of ibogamine and epiibogamine, where these early key cycloaddition steps gave isoquinuclidines in modest (16% and 14%) yields.[28,29] In still closer analogy, intermolecular addition of an indole-2-acrylate to *N*-benzyl-3-ethyl-1,6-dihydropyridine by Das provided the desired isoquinuclidine in 11% yield, with 1.5% of its stereoisomer, but apparently without generation of a tabersonine-type product.[30] This result was paralleled by an analogous reaction with an *N*-carbomethoxydihydropyridine lacking the ethyl substituent, where an additional reaction of the terminal double bond of the dihydropyridine as a dienophile was also observed.[31] Remarkably, however, Fowler, reported a 1:2.3 ratio (37%) of catharanthine to tabersonine-type cycloaddition products with *N*-methyl-1,2-dihydropyridine and an *N*-methylindole-2-acrylate.[32]

For a synthesis of desethylcatharanthine, Sundberg was able to obtain an isoquinuclidine product in 62% yield from *N*-carbethoxy-1,2-dihydropyridine and *N*-(phenylsulfonyl)indole-2-acrylate. A five-fold excess of the *N*-acyldihydropyridine was required in this intermolecular reaction at 100 °C.[33]

The best yield of isoquinuclidines (96%) derived from Diels–Alder addition of an acrylate to a 1,2-dihydropyridine was found in the reaction of *N*-carbomethoxy-3-ethyl-5,6-dihydropyridine with methyl α-chloroacrylate, where two epimeric esters (1:1.4) were obtained.[34a]

Attempted dehydrosecodine-type intramolecular cycloadditions, in which the dihydropyridine moiety was stabilized as an amide, resulted only in the ubiquitous acrylate reduction and generation of a pyridinium salt,[34b] also observed by others in the search for dehydrosecodine cyclizations.[24,30,35,36]

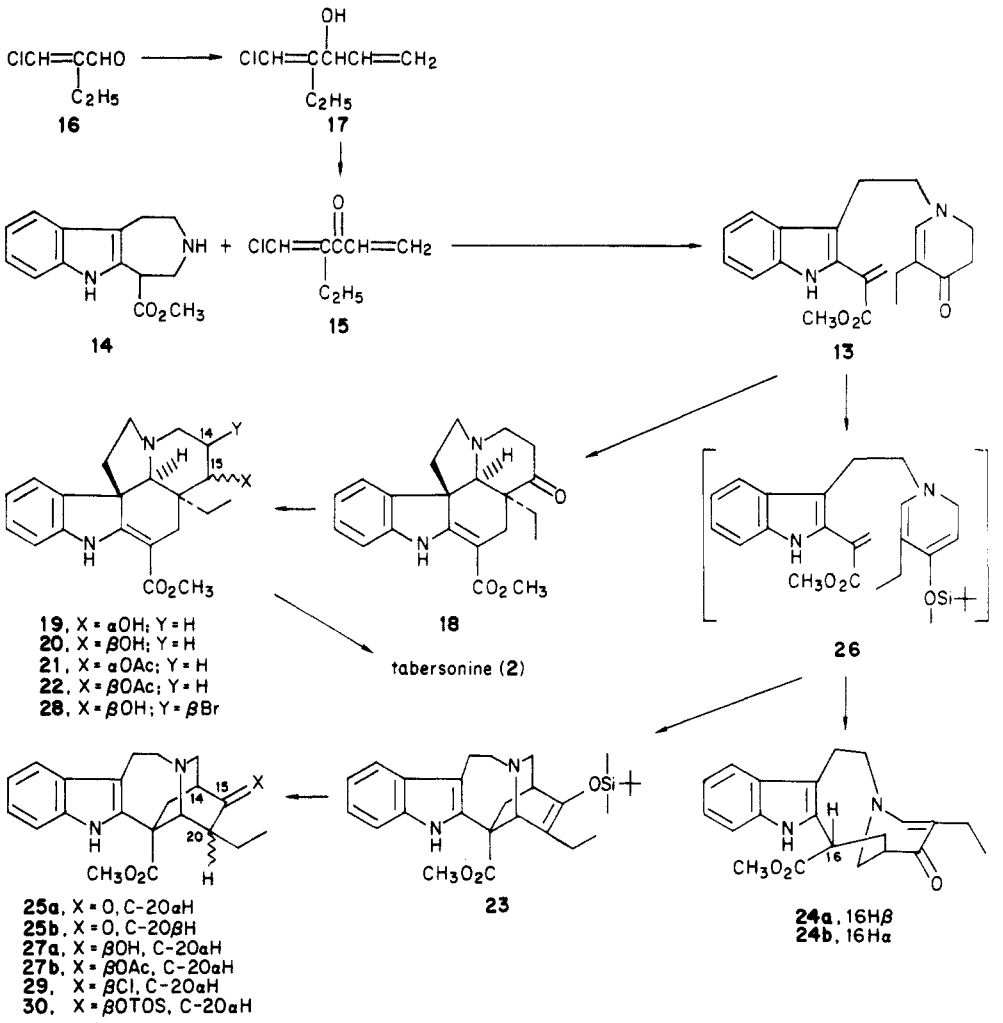
Selective Syntheses of Catharanthine (1) and Tabersonine (2). On the basis of these findings, a glum prognosis might be made for achieving practical syntheses of the catharanthine (1) and tabersonine (2) ring systems from a common intermediate which is based on the principle of dehydrosecodine (6) cyclizations. However, if one considers modifications of the dehydrosecodine (6), which create activation of the dihydropyridine diene system with respect to its reaction with an acrylate function on the one hand, or disruption of the diene function and its exclusive reaction as a mono enamine on the other, one can expect regioselective, high yielding reactions, which will selectively result in formation of the catharanthine (1) or the tabersonine (2) ring systems. The answer to how one could accomplish such a separation of dehydrosecodine reactivities arose from the experience gained with 19-oxo-$\Delta^{20(21)}$-secodine and its analogues, utilized in our syntheses of minovincine.[37,38]

The required keystone of our synthetic strategy was thus defined as a 15-oxo-$\Delta^{20(21)}$-secodine (13). In an enolized form this compound is an exceptionally reactive diene, while as the ketone tautomer, the vinylogous amide function provides a stabilized enamine, available for thermal cyclization in reaction with the indoloacrylate moiety.

A synthesis of the required 15-oxosecodine (13) could be readily accomplished by condensation of the indoloazepine 14 with 1-chloro-2-ethylpenta-1,4-dien-3-one (15). The latter was obtained from the Vilsmeier reaction product 16 of butyraldehyde and *N*,*N*-dimethylformamide.[39] A reaction of the chloro aldehyde 16 with vinylmagnesium bromide provided the allylic alcohol 17 and a Swern oxidation[40] of this sensitive intermediate with dimethyl sulfoxide and oxalyl chloride then gave the required dienone 15. When this compound was stirred with the indoloazepine 14 in methanol, the 15-oxosecodine (13)

(15) Qureshi, A. A.; Scott, A. I. *J. Chem. Soc. D* **1968**, *945*, 947.
(16) Scott, A. I.; Cherry, P. C. *J. Am. Chem. Soc.* **1969**, *91*, 5872.
(17) Gorman, M.; Neuss, N.; Cone, N. J. *J. Am. Chem. Soc.* **1965**, *87*, 93.
(18) Brown, R. T.; Hill, J. S.; Smith, G. F.; Stapleford, K. S. J.; Poisson, J.; Muget, M.; Kunesch, N. *J. Chem. Soc. D* **1969**, 1475.
(19) Scott, A. I.; Wei, C. C. *J. Am. Chem. Soc.* **1972**, *94*, 8262, 8263, 8264.
(20) Wen, R.; Laronze, J.-Y.; Levy, J. *Heterocycles* **1984**, *22*, 1061.
(21) Kuehne, M. E.; Roland, D. M.; Hafter, R. *J. Org. Chem.* **1978**, *43*, 3705.
(22) Kuehne, M. E.; Huebner, J. A.; Matsko, T. H. *J. Org. Chem.* **1979**, *44*, 2477.
(23) Kuehne, M. E.; Kirkemo, C. L.; Bohnert, J. C.; Matsko, T. H. *J. Org. Chem.* **1980**, *45*, 3259.
(24) Kutney, J. P.; Karton, Y.; Kawamura, N.; Worth, B. R. *Can. J. Chem.* **1982**, *60*, 1269.
(25) Mumm, O.; Diederichsen, J. *Liebigs Ann. Chem.* **1939**, *538*, 195.
(26) Agawa, T.; Miller, S. I. *J. Am. Chem. Soc.* **1961**, *83*, 449.
(27) Schenker, K.; Druey, J. *Helv. Chim. Acta* **1959**, *42*, 1971; **1962**, *45*, 1344.
(28) Buchi, G.; Coffen, D.; Kocsis, K.; Sonnet, P.; Ziegler, F. *J. Am. Chem. Soc.* **1966**, *88*, 3099.
(29) Ban, Y.; Wakamatsu, T.; Fujimoto, Y.; Oishi, T. *Tetrahedron Lett.* **1968**, 3383.
(30) Marazano, C.; Le Goff, M.-T.; Fourrey, J.-L.; Das, B. C. *J. Chem. Soc., Chem. Commun.* **1981**, 389.
(31) Marazano, C.; Fourrey, J.-L.; Das, B. C. *J. Chem. Soc., Chem. Commun.* **1981**, 37.
(32) Weinstein, B.; Lin, L.-C. C.; Fowler, F. W. *J. Org. Chem.* **1980**, *45*, 1657.
(33) Sundberg, R. J.; Bloom, J. D. *J. Org. Chem.* **1980**, *45*, 3382; **1981**, *46*, 4836.
(34) (a) Raucher, S.; Bray, B. L. *J. Org. Chem.* **1985**, *50*, 3237. (b) Raucher, S.; Lawrence, R. F. *Tetrahedron* **1983**, *39*, 3731.
(35) Wilson, R. M.; Farr, R. A.; Burlett, D. J. *J. Org. Chem.* **1981**, *46*, 3293.
(36) An alternative mechanism may be considered for the products obtained by Atta-ur-Rahman; Sultana, M.; Hassan, I. *Tetrahedron Lett.* **1983**, *24*, 1846.
(37) Kuehne, M. E.; Earley, W. G. *Tetrahedron* **1983**, *39*, 3707.
(38) Kuehne, M. E.; Earley, W. G. *Tetrahedron* **1983**, *39*, 3715.
(39) Arnold, Z.; Zemlicka, J. *Collect. Czech. Chem. Commun.* **1959**, *24*, 2385.
(40) Mancuso, A. J.; Huang, S. L.; Swern, D. J. *J. Org. Chem.* **1978**, *43*, 2480.

Scheme II



was formed (78%) at room temperature with completion of the reaction in 30 min. The two reaction pathways that can be considered for this transformation are discussed in connection with the corresponding desethyl analogue (below).

The 15-oxosecodine (**13**) displayed characteristic acrylic protons at δ 6.51 and 6.02 (J = 1 Hz) and a singlet at δ 6.58 for the vinylogous amide proton in its NMR spectrum. Its UV spectrum with λ_{max} 215, 227, and 336 nm was also consistent with the indoloacrylate and vinylogous amide functionalities.[37]

On heating in toluene the 15-oxosecodine (**13**) was converted to 5-oxovincadifformine (**18**). No other products were found in the reaction mixture. Reductions of 15-oxovincadifformine (**18**) with sodium borohydride gave an 8:92 mixture of the 15α:15β-hydroxyvincadifformines (**19**, **20**) and with L-Selectride (Aldrich) only the latter isomer was obtained. The alcohols **19** and **20** were characterized as their acetate derivatives (**21**, **22**).

The alternative desired cyclization of the 15-oxosecodine (**13**) could be achieved by its reaction with *tert*-butyldimethylsilyl chloride or triflate and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).[41] Thus, the 15-((trialkylsilyl)oxy)catharanthine **23** was formed in nearly quantitative yield in some reactions. However, in some instances, substantial amounts of the unsaturated 15-oxocleavamines **24a,b** were obtained.[42] The formation of the latter compounds could be suppressed by high dilution of the reactants and by inclusion of sodium hydride in the reaction mixture, to assure minimization of proton transfer and by minimizing chromatographic contact time of the silyl enol ether **23** with silica gel during purification. Cleavage of the silyl enol ether with fluoride ion then gave 15-oxocoronaridine **25a** and its C-20 epimer **25b**.[43] On chromatography the α-ethyl ketone **25b** epimerized completely to 15-oxocoronaridine **25a**.

These ketonic products could not be detected in the initial cyclization reaction mixture and no cyclization of the 15-oxosecodine (**13**) to these ketones could be found with bases in the absence of the silylating reagent. Thus, one can assume that the formation of 15-((trialkylsilyl)oxy)catharanthine **23** arises from initial generation of a 15-((trialkylsilyl)oxy)dehydrosecodine (**26**), which then undergoes an intramolecular cycloaddition.

Reduction of 15-oxocoronaridine (**25a**) with L-Selectride gave the corresponding alcohol **27a**. A relative cis configuration of the ethyl and hydroxyl substituents in this product was established by an NMR spectrum of the acetate derivative **27b**, which showed the anticipated C_{15}–C_{20} proton coupling constant (J = 8.2 Hz) and the C_{14}–C_{15} coupling (J = 4.5 Hz) and chemical shifts in agreement with data reported for the single enantiomer

(41) Taniguchi, Y.; Inanaga, J.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 3229.

(42) One enantiomer of this compound has been reported as a derivative of natural catharanthine: Andriamialisoa, Z.; Langlois, N.; Langlois, Y. *Heterocycles* **1981**, *15*, 245.

(43) Langlois, Y.; Langlois, N.; Potier, P. *C. R. Acad. Sci., Paris* **1977**, *284 C*, 809.

derived from natural sources.[43,44]

While tabersonine (2) and catharanthine (1) were now only one dehydration step away from the alcohol products **19**, **20**, and **27a**, such direct dehydrations in fact yielded only minute amounts of the desired olefins **2** and **1** under acid catalysis, by reaction with triphenylphosphine and carbon tetrachloride in acetonitrile or by tosylation and reaction with base. In the major epimeric tabersonine precursor **20**, one is faced with an equatorial, neopentyl-type alcohol, prone to rearrangement, while in the catharanthine precursor **27a** one confronts the need for a trans but noncoplanar proton and oxygen elimination and thus a need for drastic reaction conditions,[45] which are not tolerated by the product.

The synthesis of tabersonine (2) was cleanly solved by bromination of the ketone **18** and reduction of the product with sodium borohydride to a bromohydrin (**28**). On reaction with $TiCl_3$–$LiAlH_4$ reagent[46] the latter gave, by elimination through a radical process, tabersonine in 71% yield.

Unfortunately, this strategy could not be extended to 15-oxocoronaridine (**25**).

In alternative attempts to reach catharanthine (1) it was found that the enol phosphate derivative of 15-oxocoronaridine (**25a**) resisted reduction with excess Ti,[47] while a reaction of this enol phosphate with excess lithium in ethylamine led to reduction of the indole moiety.[48-51]

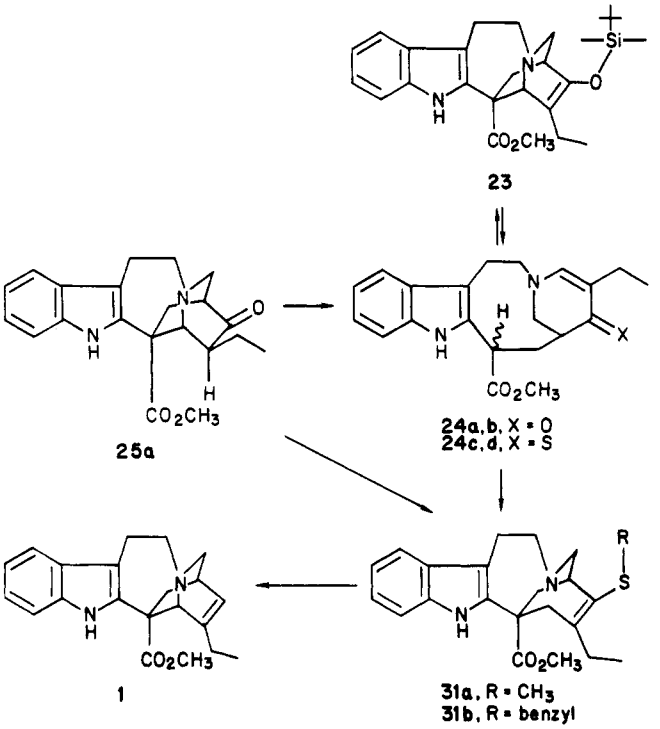
A thermolysis or photolysis of the phenylaziridine hydrazone derivative of the ketone also did not yield catharanthine, presumably because of the product's thermal and photochemical lability.[52] At 200 °C catharanthine undergoes a retro-Diels–Alder fragmentation at a rate (2 min) faster than the decomposition of the hydrazone.

Although 15β-hydroxycoronaridine (**27a**) on reaction with triphenylphosphine and CCl_4 in acetonitrile also yielded some catharanthine (**1**, 7%), the major product of this reaction was 15β-chlorocoronaridine (**29**), formed with retention of stereochemistry.[53-55] This chloride was stable to attempted elimination with DBU in refluxing toluene and it was destroyed by *tert*-butoxide in refluxing toluene. A 15β-hydroxycoronaridine tosylate (**30**) was recovered from attempted displacement reactions with sodium phenyl selenide and from attempted elimination with DBU in refluxing toluene.

A good conversion of 15-oxocoronaridine (**25a**) into catharanthine (1) was finally achieved by exploiting the observation that quantitative transformation of the iboga skeleton of 15-oxocoronaridine (**25a**) to the corresponding cleavamines (**24a,b**) under acidic conditions can be reversed by O-silylation on prolonged treatment with *tert*-butyldimethylsilyl chloride or triflate and base.

Consequently, the cleavamines **24a,b** were converted to their corresponding thione derivatives **24c,d** (83% yield) by reaction with P_2S_5. On treatment with methyl iodide these sensitive derivatives underwent S-alkylation and cyclization of the isolable *S*-methyl salt to give 15-*S*-methylcatharanthine (**31a**) (Scheme III).

Scheme III



Although 15-oxocoronaridine (**25a**) resisted attempts at conversion to a thioketal derivative under standard conditions with ethanedithiol, it was found that with benzyl mercaptan in acetic acid and BF_3 catalysis, a thio enol ether, **31b**, was readily obtained. When the thio enol ethers **31a,b** were subjected to desulfurization with Raney nickel, (±)-catharanthine (1) was obtained in 70% and 82% yield, respectively.

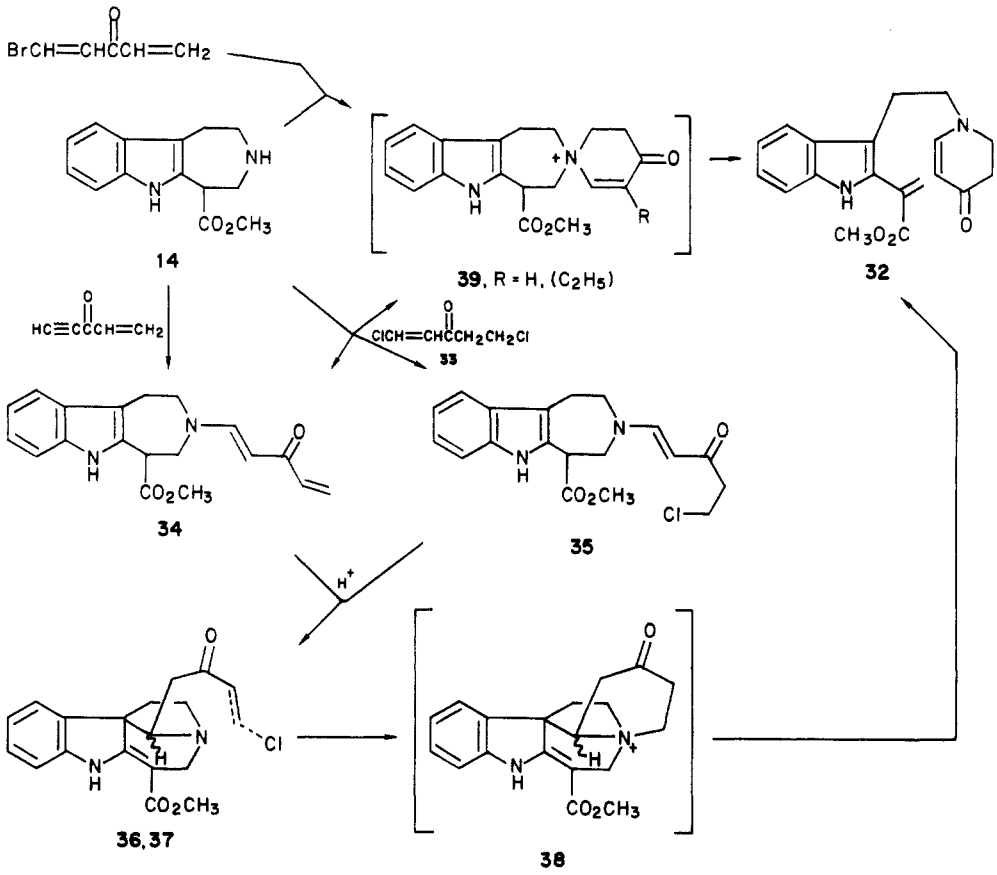
Syntheses of Desethylvincadifformine (43) and Desethylcatharanthine (50) and Mechanistic Considerations. The cyclizations leading to 15-oxygen-substituted vincadifformine **18** and -catharanthine **23** were also studied with the desethyl-15-oxosecodine (**32**). This compound was rapidly formed at room temperature (38% yield) by a reaction of the indoloazepine **14** with 1-bromo-1,4-pentadien-3-one (as an *E*/*Z* mixture).[56]

When 1,5-dichloropenten-3-one (**33**) was stirred with the indoloazepine **14** in tetrahydrofuran at room temperature, only a small amount (9%) of the desethyl-15-oxosecodine (**32**) was formed, together with a mixture of vinylogous amides **34** and **35** (62%, with at least 42% as the olefinic product **34**). Cyclization of the vinylogous amides **34** and **35** with acid and intramolecular N-alkylation of the resultant epimeric bridged indoloazepines **36** and **37**, obtained on neutralization, and fragmentation of derived quaternary salts **38**, produced additional desethyl-15-oxosecodine (**32**, 7%, total 16%). It was also possible to generate the olefinic vinylogous amide intermediate **34** selectively, by a reaction of the iodoloazepine **14** with ethynyl vinyl ketone.

The differences in spontaneous formation of 15-oxosecodine intermediates **13** and **32** seen in the reactions of the indoloazepine **14** with the foregoing halo vinyl ketones [78% from 1-chloro-2-ethyl-1,4-pentadien-3-one (**15**), 39%

(44) Langlois, N.; Andriamialisoa, R. Z.; Langlois, Y. *Tetrahedron* **1981**, *37*, 1951.
(45) (a) Hanack, M.; Eggensperger, H.; Hähnle, R. *Liebigs Ann. Chem.* **1962**, *652*, 96. (b) Hanack, M.; Hähnle, R. *Chem. Ber* **1962**, *95*, 191.
(46) McMurry, J. E.; Hoz, T. *J. Org. Chem.* **1975**, *40*, 3797.
(47) Welch, S. C.; Walters, M. E. *J. Org. Chem.* **1978**, *43*, 2715.
(48) Ireland, R. E.; Pfister, G. *Tetrahedron Lett.* **1969**, 2145.
(49) Ireland, R. E.; Muchmore, D. C.; Hengartner, U. *J. Am. Chem. Soc.* **1972**, *94*, 5098.
(50) Grieco, P. A.; Ferrine, R. L. S.; Jaw, J. Y. *J. Org. Chem.* **1982**, *47*, 601.
(51) Trost, B. M.; Renaut, P. *J. Am. Chem. Soc.* **1982**, *104*, 6668.
(52) (a) von Felix, D.; Muller, R. K.; Horn, U.; Joos, R.; Schreiber, J.; Eschenmoser, A. *Helv. Chim. Acta* **1972**, *55*, 1276. (b) Mohamadi, F.; Collumn, D. B. *Tetrahedron Lett.* **1984**, *25*, 271.
(53) Lee, J. B.; Nolan, T. J. *Tetrahedron* **1967**, *23*, 2789. Lee, J. B.; Downie, I. M. *Ibid.* **1967**, *23*, 359.
(54) Schaefer, J. P.; Weinberg, D. S. *J. Org. Chem.* **1965**, *30*, 2639.
(55) Weiss, R. G.; Snyder, E. I. *J. Chem. Soc. D* **1968**, 1358.
(56) Bundavev, G. N.; Ryzhov, V.; Chelpanoua, L. F.; Petrov, A. *J. Org. Chem. Russ.* **1967**, *3*, 785.

Scheme IV



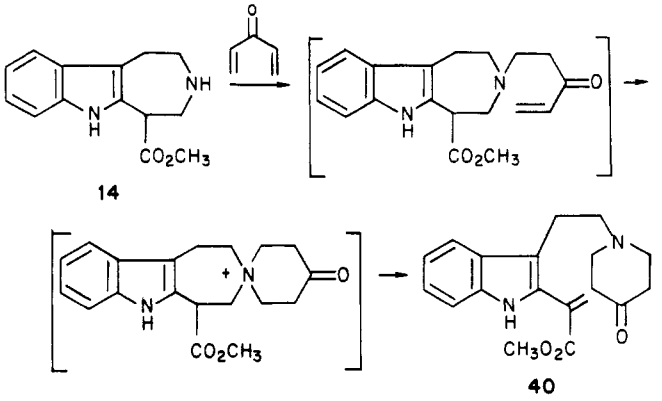
from 1-bromo-1,4-pentadien-3-one, and 9% from 1,5-dichloropenten-3-one (**33**)] and the reluctance of the vinylogous amide olefin **34** and its cyclization product **36** to form 15-oxosecodine (**32**) suggest that the oxosecodines **13** and **32** are best derived from a spirocyclic intermediate **39**. The latter could be formed either by initial amine Michael addition to the non-halogen-substituted end of the divinyl ketones followed by cyclization or, alternatively, formation of **39** may proceed by initial amine addition to a (*Z*)-β-halo enone (with known stereochemical retention on halogen displacement by amines)[57] in order to generate a (*Z*)-β-amino enone intermediate for cyclization.

In support of the preferential formation of spirocyclic intermediates **39**,[58] rather than the more usually encountered bridged indoloazepine intermediates **38**[59] in generation of 15-oxosecodines in these reactions, is also the observation that the corresponding saturated ketone **40** was formed in 73% yield in a reaction of the indoloazepine **14** with divinyl ketone.

On refluxing in toluene, the desethyl-15-oxosecodine (**32**) slowly cyclized to form desethyl-15-oxovincadifformine (**41**). Formation of thioketal derivative **42** with ethanedithiol and zinc triflate and its R/Ni desulfurization provided desethylvincadifformine (**43**), with established D/E cis stereochemistry.[59] Since, in a control experiment, desethyl-15-oxovincadifformine (**41**) was not changed by equal acidic conditions, its initially expected D/E cis stereochemistry remains likely.

Reactions of the desethyl-15-oxosecodine (**32**) with *tert*-butyldimethylsilyl triflate and the amine base DBU

Scheme V



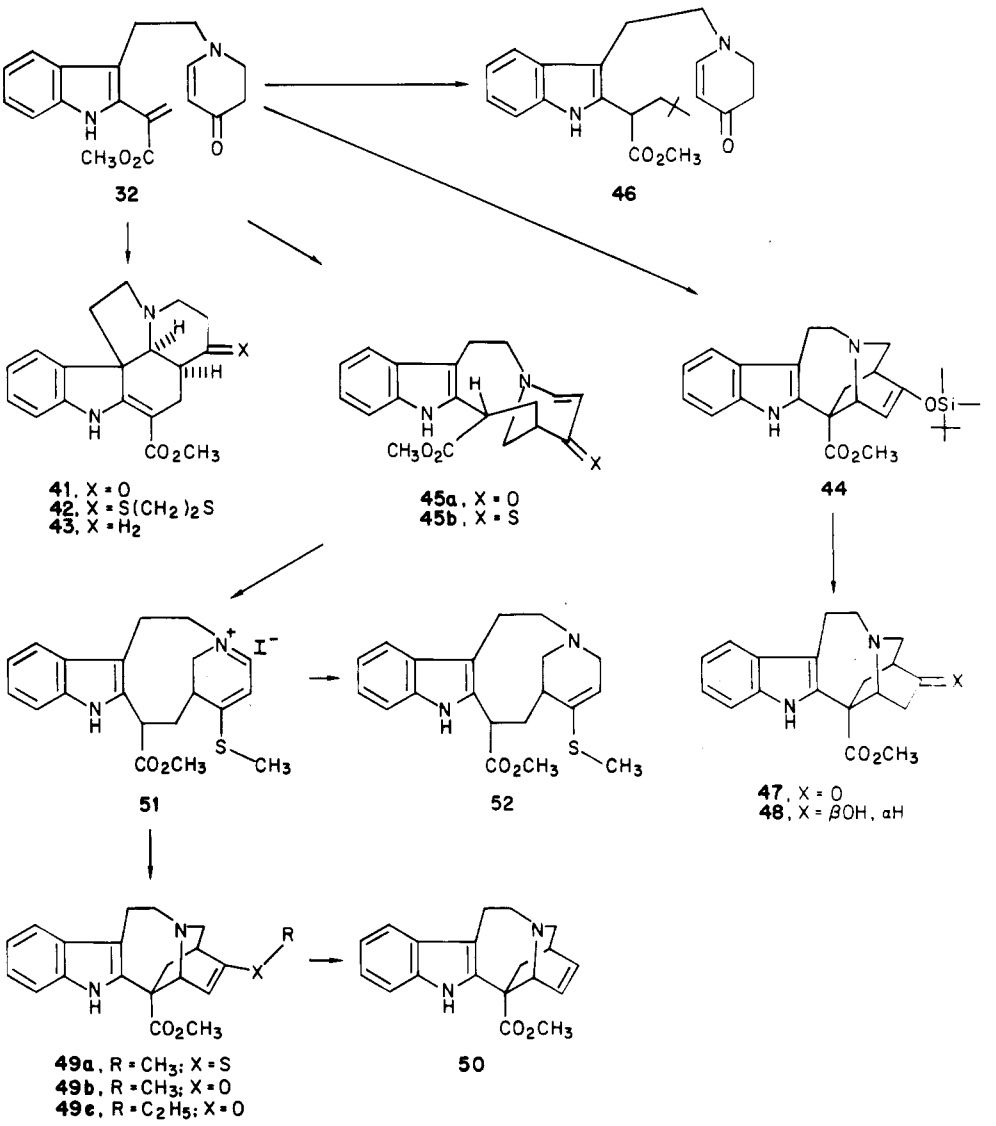
led to formation of desethyl-15-(silyloxy)catharanthine (**44**), as well as to the macrocyclic ketone **45a**. Again, no reaction was found with the same base, or with sodium hydride, in the absence of silylating agent. With *tert*-butyllithium the acrylate Michael addition product **46** was obtained.

Desilylation of the enol derivative **44** furnished the corresponding ketone **47**, which could be reduced with L-Selectride to give desethyl-15β-hydroxy-15,20-dihydrocatharanthine (**48**) in 87% yield. Attempted conversion of the ketone **47** to an *S*-benzyl thioenol ether under conditions analogous to those used above in the catharanthine synthesis gave only the thioketal. However, conversion of the enaminone **45a** to an *S*-methyl thioenol ether **49a** and desulfurization then provided desethylcatharanthine (**50**).

In this series, conversion of the cleavaminone **45a** to its thione derivative **45b** (80–92%) and its S-methylation (99%) were as readily accomplished as the corresponding reactions in the sequence leading to catharanthine.

(57) Truce, W. E.; Gorbaty, M. L. *J. Org. Chem.* **1970**, *35*, 2113.
(58) Kuehne, M. E.; Matsko, T. H.; Bohnert, J. C.; Kirkemo, C. L. *J. Org. Chem.* **1979**, *44*, 1063.
(59) Kuehne, M. E.; Matsko, T. H.; Bohnert, J. C.; Motyka, L.; Oliver-Smith, D. *J. Org. Chem.* **1981**, *46*, 2002.

Scheme VI



However, the following cyclization of the imonium intermediate **51** to the methyl thioenol ether **49a**, in methanol, was now found to diverge primarily to the corresponding methyl enol ether **49b**. This type of side reaction could be largely suppressed in ethanol, where the desired product **49a** predominated over the ethyl enol ether **49c**. A reaction in isopropyl alcohol or benzene resulted mostly in disproportionation and reduction of the imonium intermediate **51** and formation of the tetracyclic thioenol ether **52**, a minor product found also in the reaction in ethanol. In the final desulfurization reaction of **49a** it was seen that a short reaction time (30 min) led almost exclusively to desethylcatharanthine (**50**) while conditions used for the analogous generation of catharanthine (**1**) gave only the double-bond reduction product desethylcoronaridine.[33]

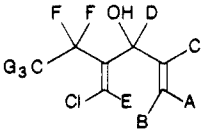
While the biogenetically postulated dual generation of catharanthine (**1**) and of tabersonine (**2**) from transient $\Delta^{14(15),20(21)}$-dehydrosecodine (**6**) has never been synthetically demonstrated and resulted only in marginal formation of the first skeletal class,[24] it could now be shown that synthesis of isolable $\Delta^{20(21)}$-15-oxosecodine (**13**) and its silyl enol ether derivative (**26**) formation allow high-yield, selective transformations to products of the aspidosperma and the iboga skeletal classes. Having build in a control of the two modes of dehydrosecodine cyclization by chemical modification, one now has the challenge of establishing the detailed mechanism by which such a control is achieved in plant biosynthesis.

Experimental Section

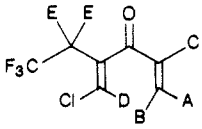
General Methods. All reactions were carried out under nitrogen or argon. Melting points were obtained in a heated oil bath or on a Kofler micro hotstage with thermometers calibrated against a National Bureau of Standards certified set. NMR spectra were recorded on Bruker 250-MHz or 270-MHz instruments.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

1-Chloro-2-ethyl-1,4-pentadien-3-ol (17). At 0 °C 15 mL of a 1.0 M solution of vinylmagnesium bromide in tetrahydrofuran was added under an argon atmosphere over 10 min to 1.77 g (14.9 mmol) of 3-chloro-2-ethyl-2-propenal,[39] dissolved in 10 mL of tetrahydrofuran. After being stirred for 1 h at 0 °C and 0.5 h at 20 °C, the reaction mixture was poured into 100 mL of saturated ammonium chloride at 0 °C and extracted with three 100-mL portions of dichloromethane. The organic extracts were dried

($MgSO_4$), concentrated under vacuum at 40 °C, and distilled at 60 °C (0.2 mm) to give 1.28 g (58%) of the allylic alcohol: TLC R_f 0.38 (SiO_2, 14% ether in hexane, detect. UV and I_2); IR (film) ν_{max} 3342, 3085, 3016, 2971, 2937, 2899, 2812, 1642, 1629, 1463, 1422, 1375, 1341, 1293, 1261, 1164, 1116, 1076, 1060, 1020, 939, 923, 875, 812, 770, 753 cm^{-1}; 250-MHz ^1H NMR ($CDCl_3$) δ 6.18 (br s, 1 H^E), 5.82 (dq, J = 17, 10, 6 Hz, 1 H^C), 5.33 (dt, J = 17, 1 Hz, 1 H^B), 5.26 (dt, J = 10, 1 Hz, 1 H^A), 4.63 (br d J = 6 Hz, 1 H^D), 2.24 (dq, J = 14, 7 Hz, 1 H^F), 2.18 (dq, J = 14, 7 Hz, 1 H^F), 1.06 (t, J = 7 Hz, 3 H^G); 62.9-MHz ^{13}C NMR ($CDCl_3$) δ 12.35, 21.29, 75.17, 116.02, 116.44, 138.20, 144.66; mass spectrum (70 eV), m/z (relative intensity) 146 (M^+, 0.6), 145 (2), 137 (4), 131 (22), 130 (6), 129 (100), 119 (3), 117 (4), 112 (3), 111 (50), 109 (5) 93 (61), 91 (10), 83 (13), 81 (18), 67 (13).

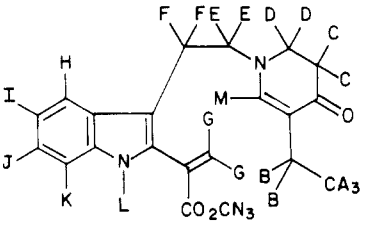


1-Chloro-2-ethyl-1,4-pentadien-3-one (15).[40] A solution of 1.40 g (11.0 mmol) of oxalyl chloride in 25 mL of dichloromethane was cooled to −60 °C under argon and 1.72 g (22.0 mmol) of dimethyl sulfoxide in 5 mL of dichloromethane was added over 2 min. After 5 min a solution of 1.10 g (7.50 mmol) of the allylic alcohol **17** in 10 mL of dichloromethane was added dropwise over 3 min. The mixture was stirred at −60 °C for 30 min and then 5.56 g (55.0 mmol) of triethylamine was added in one portion. After 5 min at −60 °C and 30 min at 20 °C the mixture was poured into 50 mL of water at 0 °C and extracted with 50 mL of dichloromethane. The organic extract was washed with 100 mL of cold brine, dried ($Mg SO_4$), and concentrated to 1.08 g at 40 °C under vacuum. Distillation at 38–40 °C (0.02 mm) gave 0.589 g (54%) of the enone: UV (ethanol) λ_{max} 251 nm; IR (film) ν_{max} 3094, 2974, 2938, 2878, 1665, 1611, 1596, 1461, 1441, 1406, 1336, 1345, 1307, 1286, 1244, 1211, 1095, 1073, 1062, 1014, 979, 919, 841, 770, 740 cm^{-1}; 250-MHz ^1H NMR ($CDCl_3$) δ 7.19 (br s, 1 H^D), 6.76 (dd, J = 17, 11 Hz, 1 H^C), 6.28 (dd, J = 17, 2, 1 H^B), 5.82 (dd, J = 11, 2 Hz, 1 H^A), 2.54 (q, J = 7 Hz, 2 H^E), 1.04 (t, J = 7 Hz, 3 H^F); 62.9-MHz ^{13}C NMR ($CDCl_3$) δ 12.08, 20.41, 124.62, 129.57, 132.18, 132.68, 189.20.



15-Oxo-$\Delta^{20(21)}$-secodine (13). To a solution of 0.100 g (0.409 mmol) of the indoloazepine **14** in 5 mL of methanol was added 0.140 g (0.968 mmol) of the enone **15** in 2 mL of methanol. After 30 min the reaction mixture was concentrated under vacuum at 40 °C and the residual foam was dissolved in 5 mL of dichloromethane and purified by centrifugal chromatography on a 2-mm SiO_2 disk, eluting with ethyl acetate at a flow rate of 2.5 mL/min. Collection of 1.2-mL fractions gave in fractions 8–22 0.112 g (78%) of the amorphous product. On a 1-g of indoloazepine scale the crude product was purified by adsorption on 20 g of SiO_2, placed on a 4 × 20 cm silica gel column and eluted with ethyl acetate/pentane (2:1). The product is labile, with spontaneous partial dimerization even at 0 °C over 24 h. At 25 °C the 15-oxosecodine is gradually converted to a major and a minor dimer, which could be isolated by centrifugal chromatography on silica gel, eluting with 4:1 ethyl acetate/ethanol.

For the 15-oxosecodine **13**: TLC R_f 0.32 (SiO_2, ethyl acetate, CAS, purple); HPLC (Microporisil, 4.1 mm × 30 cm) t_R 8.3 min at 1.3 mL/min flow of ethyl acetate; UV (ethanol) λ_{max} 215, 227, 336 nm; IR (KBr) 3263, 2954, 2929, 2868, 1724, 1681, 1588, 1494, 1458, 1436, 1398, 1360, 1326, 1283, 1239, 1199, 1160, 1103, 1049, 1067, 964, 937, 879, 809, 745, 676 cm^{-1}; 250-MHz ^1H NMR ($CDCl_3$) δ 9.40 (br s, 1 H^L), 7.54 (d, J = 8 Hz, 1 H^H), 7.36 (d, J = 8 Hz, 1 H^K), 7.21 (dt, J = 1, 8 Hz, 1 H^J), 7.12 (dt, J = 1, 7 Hz, 1 H^I), 6.02 (d, J = 1 Hz, 1 H^G), 6.58 (s, 1 H^M), 6.51 (d, J = 1 Hz, 1 H^G), 3.83 (s, 3 H^N), 3.44 (t, J = 7 Hz, 2 H^E), 3.34 (t, J = 8 Hz, 2 H^D), 3.08 (t, J = 7 Hz, 2 H^F), 2.36 (t, J = 8 Hz, 2 H^C), 2.01 (q, J = 7 Hz, 2 H^B), 0.85 (t, J = 7 Hz, 3 H^A); mass spectrum (70 eV), m/z (relative intensity) 353 (32), 352 (M^+, 45), 256 (5), 245 (4), 244 (11), 229 (5), 228 (4), 215 (20), 214 (86), 202 (12), 183 (3), 182 (12), 170 (6), 169 (4), 168 (12), 167 (12), 156 (7), 155 (12), 154 (54), 140 (6), 139 (30), 138 (100), 137 (7), 129 (7), 128 (11), 127 (15), 126 (3), 117 (9), 110 (22), 109 (18), 86 (12), 84 (21), 81 (10), 80 (7), 79 (7), 69 (18), 55 (48), 53 (24); 62.9-MHz ^{13}C NMR ($CDCl_3$) 190.89 167.41, 152.29, 136.00, 132.40, 130.87, 128.13, 127.95, 123.52, 120.19, 118.93, 111.84, 111.64, 111.41, 56.01, 52.82, 47.72, 36.07, 24.77, 20.29, 14.36,

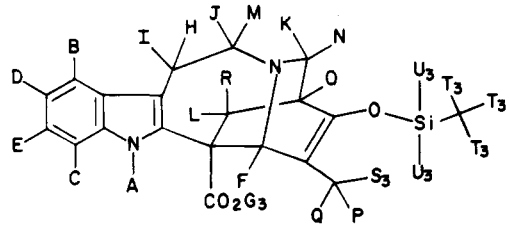


15-((*tert*-Butyldimethylsilyl)oxy)catharanthine (23) and C-16 Epimeric Carbomethoxy Δ^{20}-15-Oxocleavamines (24a,b). Method A. To 0.182 g (0.516 mmol) of the 15-oxosecodine **13** in 10 mL of dichloromethane, under argon, was added 79 mg (77 μL, 0.516 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in one portion at 0 °C. After 5 min 136 mg (118 μL, 5.164 mmol) of *tert*-butyldimethylsilyl trifluoromethanesulfonate was added in one portion. Progress of the reaction was monitored by TLC by consumption of the starting oxosecodine **13**. At completion the reaction mixture was diluted with 50 mL of dichloromethane and adsorbed under vacuum onto 10 g of SiO_2, which was then placed on a 4 cm × 5 cm silica gel column. Elution with ethyl acetate/pentane (1:1), concentration of the first 250 mL of eluate at 40 °C, and further purification by centrifugal chromatography on SiO_2, eluting with ethyl acetate/pentane (1:5) and crystallization from ether gave 0.178 g (98.4%) of product **23** with mp 173–174 °C after recrystallization from aqueous methanol.

Method B. To 0.200 g (0.567 mmol) of the 15-oxosecodine **13** in 10 mL of dichloromethane, cooled to 0 °C, was added 85 mg (0.567 mmol) of *tert*-butyldimethylsilyl chloride in 3 mL of dichloromethane, followed by 95 mg (93 μL, 0.642 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Progress of the reaction was followed by TLC until all of the 15-oxosecodine has been consumed. At that point the reaction mixture was poured into 50 mL of cold, saturated sodium bicarbonate solution and the mixture was extracted with two 25-mL portions of dichloromethane. The combined organic extracts were washed with saturated brine, dried over magnesium sulfate, and concentrated at 40 °C under vacuum. The residue was dissolved in 50 mL of dichloromethane, adsorbed onto 10 g of silica gel under vacuum, and placed on a 4 × 10 cm dry silica gel column. Elution with 250 mL of ethyl acetate/pentane (1:1) and concentration at 40 °C under vacuum gave a crude product which was purified by centrifugal chromatography on silica gel, eluting with ethyl acetate/pentane (1:4). Crystallization from ether gave 188 mg (71%) of product **23**.

When this reaction was repeated with 1 g of the oxosecodine **13**, a 47% yield of the product **23** was obtained as well as a 53% yield of the seco product **24a**, mp 225–226 °C, recrystallized from aqueous methanol. This product was isolated by elution of the Chromatotron plate with ethyl acetate, subsequent to elution of the silyl enol ether, and crystallization from ether or dichloromethane and hexane. For **23**: TLC R_f (SiO_2) 0.49 (1:1 ether/hexane), 0.74 (1:3 ethyl acetate/pentane), 0.60 (5% methanol in chloroform); HPLC t_R (4.1 mm × 30 cm Microporisil column) 1.2 mL/min (1:5 ethyl acetate/pentane) 15.0 min; UV (ethanol) λ_{max} 231, 275, 284, 292 nm; IR (KBr) 3350, 2958, 2929, 2883, 2856, 1709, 1682, 1461, 1448, 1430, 1363, 1254, 1226, 1200, 1171,, 1085, 927, 838, 780, 745 cm^{-1}; direct insertion probe mass spectrum (70 eV), m/z (relative intensity) 467 (20), 466 (M^+, 58), 465 (15), 381 (6), 352 (4), 266 (13), 265 (73), 252 (13), 251 (47), 238 (31), 229 (12), 228 (15), 214 (11), 209 (27), 196 (8), 182 (13), 180 (76), 172 (12), 169 (46), 167 (17), 154 (17), 89 (11), 75 (14), 73 (100); 250-MHz ^1H NMR ($CDCl_3$) δ 7.61 (br s, 1 H^A), 7.48 (dd, J = 7, 1 Hz, 1 H^B), 7.24 (dd, J = 7, 1 Hz, 1 H^C), 7.14 (td, J = 6, 1 Hz, 1 H^D), 7.09 (td, J = 7, 1 Hz, 1 H^E), 4.28 (s, 1 H^F), 3.72 (s, 3 H^G), 3.56 (ddd, J = 14, 11, 5 Hz, 1 H^H), 3.33 (td, J = 14, 5, 5 Hz, 1 H^I), 3.24 (ddd, J = 16, 11, 5 Hz, 1 H^J), 3.07 (dt, J = 9, 3 Hz, 1 H^K), 2.94 (dt, J

= 13, 3 Hz, 1 H^L), 2.88 (ddd, J = 16, 5, 3 Hz, 1 H^M), 2.76 (br d, J = 9 Hz, 1 H^N), 2.49 (m, 1 H^O), 2.37 (sextet, J = 14, 7 Hz, 1 H^P), 1.87 (sextet, J = 14, 7 Hz, 1 H^Q), 1.75 (dd, J = 13, 2 Hz, 1 H^R), 1.04 (t, J = 7 Hz, 3 H^S), 0.95 (s, 9 H^T), 0.16 (s, 3 H^U), 0.13 (s, 3 H^F); 62.9-MHz ^{13}C NMR ($CDCl_3$) δ 173.9, 148.1, 136.7, 135.0, 129.1, 122.5, 121.9, 119.5, 118.2, 110.9, 110.4, 61.7, 56.7, 52.9, 52.3, 49.4, 38.3, 37.1, 25.7, 21.4, 20.7, 18.1, 12.5, -3.8, -4.1. Anal. Calcd for $C_{27}H_{38}N_2O_3Si$: C, 69.49; H, 8.20; N, 6.00. Found: C, 69.25; H, 7.99; H, 6.11.



For **24a**: TLC R_f (SiO_2) 0.51 (ethyl acetate), 0.31 (5% methanol in dichloromethane); HPLC t_R 5.1 min (4.1 mm × 30 cm Microporisil column) 1.3 mL/min (ethyl acetate); UV (ethanol) λ_{max} 228, 276, 292, 345 nm; IR (KBr) ν_{max} 3375, 3248, 3212, 3174, 3156, 3111, 3055, 3029, 2951, 2927, 2868, 2847, 1735, 1627, 1578, 1499, 1462, 1434, 1399, 1358, 1330, 1308, 1284, 1248, 1227, 1197, 1180, 1160, 1098, 1011, 744 cm^{-1}; direct insertion probe mass spectrum (70 eV), m/z (relative intensity) 353 (18), 352, (M^+, 57), 293 (4), 229 (10), 228 (9), 214 (8), 180 (4), 170 (7), 169 (8), 168 (8), 167 (9), 156 (5), 155 (4), 154 (10), 152 (7), 151 (100), 138 (20), 137 (17), 136 (11), 129 (4), 128 (5), 127 (4), 124 (7), 123 (21), 110 (5), 109 (4), 108 (6), 84 (7), 55 (9); 250-MHz ^1H NMR ($CDCl_3$) δ 8.72 (s, 1 H), 7.50 (d, J = 8 Hz, 1 H), 7.38 (d, J = 8 Hz, 1 H), 7.24–7.10 (m, 2 H), 7.08 (s, 1 H), 4.13 (d, J = 10 Hz, 1 H), 3.77–3.59 (m, 2 H), 3.65 (s, 3 H), 3.20 (d, 16 Hz, 1 H), 3.02–2.81 (m, 3 H), 2.42–2.17 (m, 5 H), 1.09 (t, J = 7 Hz, 3 H). Anal. Calcd for $C_{21}H_{24}N_2O_3$: C, 71.57; H, 6.86; N, 7.95. Found: C, 71.25; H, 6.94; N, 7.99.

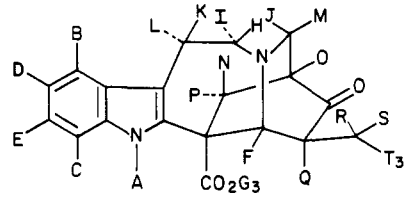
From larger scale reactions, small amounts of the C-16 epimer **24b**, mp 238–239 °C, was obtained on chromatography and crystallization from ether and from aqueous methanol.

For **24b**: TLC R_f (SiO_2) 0.38 (ethyl acetate), 0.23 (5% methanol in dichloromethane); UV (ethanol) λ_{max} 230, 278, 285, 295, 344 nm; IR (KBr) ν_{max} 3248, 3216, 3179, 3161, 3113, 3074, 3061, 3027, 2985, 2948, 2934, 2919, 2889, 2876, 2843, 1735, 1614, 1558, 1499, 1457, 1437, 1389, 1363, 1348, 1327, 1286, 1255, 1230, 1208, 1190, 1178, 1159, 1140, 958, 943, 746 cm^{-1}; direct insertion probe mass spectrum (70 eV), m/z (relative intensity) 353 (14), 352 (M^+, 52), 351 (6), 337 (8), 293 (5), 229 (12), 228 (8), 214 (9), 182 (7), 180 (7), 176 (8), 170 (7), 169 (17), 168 (13), 167 (10), 156 (12), 155 (7), 154 (15), 152 (12), 151 (100), 150 (35), 139 (9), 138 (38), 137 (26), 135 (13), 129 (7), 128 (10), 127 (6), 124 (12), 123 (30), 122 (7), 115 (6), 110 (9), 109 (6), 108 (8), 86 (10), 84 (20), 55 (21); 250-MHz NMR ($CDCl_3$) δ 8.92 (s, 1 H), 7.47 (d, J = 8 Hz, 1 H), 7.34 (d, 8 Hz, 1 H), 7.22–7.09 (m, 2 H), 6.75 (s, 1 H), 3.89 (dd, J = 3, 10 Hz, 1 H), 3.67 (s, 3 H), 3.64–3.19 (m, 6 H), 2.43–1.89 (m, 5 H), 0.92 (t, J = 7 Hz, 3 H): Anal. Calcd for $C_{21}H_{24}N_2O_3$: C, 71.57, H, 6.86, N, 7.95. Found, C, 71.67; H, 7.14; N, 7.87.

15-Oxocoronaridine (25a) and 20-*epi*-15-Oxocoronaridine (25b). At -78 °C 138 μL (67 mg, 0.26 mmol) of a 1 M solution of tetrabutylammonium fluoride in tetrahydrofuran was added to 60 mg (0.13 mmol) of the silyl enol ether **23** in 10 mL of tetrahydrofuran, under an argon atmosphere. After 10 min at -78 °C and 20 min at 20 °C the reaction mixture was poured into 30 mL of cold saturated sodium bicarbonate and extracted with three 25-mL portions of dichloromethane. The combined organic extracts were washed with 50 mL of cold brine, dried ($MgSO_4$), and concentrated at 40 °C. This product consisted of a 46:54 mixture of C-20 epimeric ketones as determined by HPLC (Microporasil column, 4.1 mm × 30 cm, 2% methanol in dichloromethane, 1.3 mL/min, t_R 2.9 and 3.1 min, respectively). The minor, first eluted product is 15-oxocoronaridine. The residue was purified by centrifugal chromatography on SiO_2, eluting with 2% methanol in dichloromethane. Concentration under vacuum gave 46 mg (100%) of 15-oxocoronaridine, mp 192–193 °C, after crystallization from ether and then aqueous methanol. Thus, its C-20 epimer had isomerized on chromatography. An analogous epimerization was found in trifluoroacetic acid.

In subsequent experiments, analogous chromatography yielded small amounts of the 20-α-ethyl epimer **25b**, mp 178–179 °C, recrystallized from ether and then from aqueous methanol.

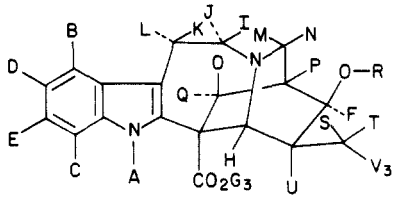
For 15-Oxocoronaridine (25a): TLC (SiO_2) R_f 0.54 (2% methanol in dichloromethane), 0.63 (1:3 ethyl acetate/pentane); HPLC t_R 2.9 min (4.1 mm × 30 cm Microporisil column, 2% methanol in dichloromethane, 1.3 mL/min); UV (ethanol) λ_{max} 226, 278, 285, 293 nm; IR (KBr) ν_{max} 3357, 3056, 3036, 2954, 2939, 2918, 2901, 2872, 2837, 1725, 1711, 1461, 1434, 1368, 1346, 1332, 1298, 1287, 1262, 1251, 1229, 1201, 1176, 1153, 1131, 1101, 1077, 1061, 1051, 1023, 1010, 978, 868, 818, 803, 784, 757, 741, 722, 682, 655 cm^{-1}; direct insertion probe mass spectrum (70 eV), m/z (relative intensity) 353 (20), 352 (M^+, 93), 267 (5), 229 (17), 228 (7), 214 (12), 194 (3), 182 (5), 181 (3), 180 (8), 170 (5), 169 (3), 168 (9), 167 (9), 155 (4), 154 (16), 152 (12), 151 (100), 150 (13), 139 (3), 138 (21), 137 (19), 128 (4), 127 (4), 124 (8), 123 (16), 110 (4), 84 (23), 55 (30); 250-MHz ^1H NMR ($CDCl_3$) δ 7.97 (s, 1 H^A), 7.51 (d, J = 8 Hz, 1 H^B), 7.28 (d, J = 7 Hz, 1 H^C), 7.19 (dt, J = 1, 7 Hz, 1 H^D), 7.12 (dt, J = 1, 7 Hz, 1 H^E), 4.10 (d, J = 2 Hz, 1 H^F), 3.75 (s, 3 H^G), 3.45 (ddd, J = 19, 10, 7 Hz, 1 H^H), 3.24 (ddd, J = 19, 6, 1 Hz, 1 H^I), 3.22 (dt, J = 9, 3, 2 Hz, 1 H^J and 1 H^K), 3.15 (m, 1 H^L), 3.09 (dd, J = 9, 3 Hz, 1 H^M), 2.90 (dd, J = 14, 2 Hz, 1 H^N), 2.50 (m, 1 H^O), 2.26 (dd, J = 14, 4 Hz, 1 H^P), 1.93 (m, 1 H^Q), 1.91 (m, 1 H^R), 1.70 (m, 1 H^S), 1.01 (t, J = 7 Hz, 3 H^T); 62.9-MHz ^{13}C NMR ($CDCl_3$) δ 215.27, 174.39, 135.66, 135.26, 128.70, 122.54, 119.66, 118.60, 110.63, 110.57, 60.05, 55.18, 54.06, 52.91, 52.80, 49.65, 44.42, 34.13, 21.90, 19.46, 11.93. Anal. Calcd for $C_{21}H_{24}N_2O_3$: C, 71.57; H, 6.86; N, 7.95. Found: C, 71.61; H, 7.09; N, 8.02.



For 20-*epi*-15-oxocoronaridine (25b): TLC (SiO_2) R_f 0.39 (2% methanol in dichloromethane); HPLC t_R 3.1 min (conditions as above); UV (ethanol) λ_{max} 228, 277, 285, 293 nm; IR (KBr) ν_{max} 3383, 2955, 2929, 2875, 2859, 2783, 1724, 1489, 1460, 1435, 1401, 1360, 1344, 1296, 1253, 1221, 1195, 1161, 1120, 1100, 1057, 1009, 789, 744 cm^{-1}; direct insertion probe mass spectrum (70 eV) m/z (relative intensity) 353 (11), 352 (M^+, 54), 267 (4), 229 (12), 228 (7), 214 (19), 195 (4), 194 (5), 182 (7), 181 (5), 180 (14), 170 (4), 168 (11), 167 (20), 155 (6), 154 (30), 152 (11), 151 (100), 139 (5), 138 (27), 137 (20), 130 (8), 127 (9), 124 (8), 123 (16), 114 (6), 110 (8), 84 (70), 77 (8), 75 (67), 68 (8), 59 (9), 55 (76); 250-MHz ^1H NMR ($CDCl_3$) δ 7.80 (s, 1 H), 7.51 (d, J = 8 Hz, 1 H), 7.27 (d, J = 6 Hz, 1 H), 7.19 (dt, J = 1, 7 Hz, 1 H), 7.12 (dt, J = 1, 7 Hz, 1 H), 4.32 (d, J = 3 Hz, 1 H), 3.68 (s, 3 H), 3.60 (m, 1 H), 3.29–3.23 (m, 1 H), 3.18–3.08 (m, 3 H), 3.03 (dd, J = 9, 1 Hz, 1 H), 2.88 (dt, J = 14, 2 Hz, 1 H), 2.52 (m, 2 H), 2.34 (dd, J = 14, 4 Hz, 1 H), 1.73 (m, 1 H), 1.21 (m, 1 H), 1.07 (t, J = 5 Hz, 3 H); 62.9-MHz ^{13}C NMR ($CDCl_3$) δ 215.24, 174.19, 135.64, 135.50, 128.42, 122.51, 119.65, 118.60, 110.65, 110.56, 60.10, 58.22, 52.54, 52.32, 51.81, 49.11, 44.70, 33.70, 21.76, 21.64, 13.00.

15β-Hydroxycoronaridine (27a). To a solution of 60 mg (0.17 mmol) of 15-oxocoronaridine (**25a**) in 5 mL of tetrahydrofuran at 0 °C, under argon, was added 178 μL (34 mg, 0.18 mmol) of a 1.0 M solution of lithium tri-*sec*-butylborohydride (L-Selectride) in tetrahydrofuran. After complete reduction of the ketone (monitored by TLC) the reaction mixture was poured into 25 mL of iced brine and extracted with three 20-mL portions of dichloromethane. The dried ($MgSO_4$) extracts were concentrated under vacuum at 40 °C and the residue subjected to centrifugal chromatography on SiO_2, eluting with ether, with 0.5-mL fractions collected at 1 mL/min. Fractions 10–23 on concentration and precipitation of the residue from ether gave 60 mg (99%) of 15β-hydroxycoronaridine (**27a**): mp 116–117 °C; TLC (SiO_2) R_f 0.51 (ether), 0.49 (5% methanol in dichloromethane), 0.49 (1:1 chloroform/ethyl acetate); HPLC t_R 6.6 min (4.1 mm × 30 cm Microporisil column, 5% methanol in dichloromethane at 1.2 mL/min); UV (ethanol) λ_{max} 229, 276, 286, 293 nm; IR (KBr) ν_{max}

3375, 2955, 2928, 2870, 1708, 1489, 1461, 1434, 1386, 1343, 1309, 1261, 1231, 1217, 1173, 1156, 1135, 1095, 1050, 1012, 804, 741 cm^{-1}; direct insertion probe mass spectrum (70 eV), m/z (relative intensity) 355 (29), 354 (M^+, 100), 352 (17), 339 (17), 337 (18), 336 (9), 325 (11), 268 (9), 267 (17), 224 (18), 215 (8), 214 (14), 194 (11), 182 (14), 181 (9), 180 (23), 177 (8), 170 (10), 169 (12), 168 (25), 167 (30), 166 (9), 156 (13), 155 (13), 154 (52), 152 (29), 151 (90), 144 (17), 143 (15), 140 (33), 139 (27), 138 (80), 137 (51), 135 (25), 130 (22), 128 (13), 127 (13), 124 (17), 123 (12), 122 (14), 115 (11), 112 (9), 110 (14), 108 (8), 98 (9), 96 (8), 94 (8), 93 (8), 91 (17), 84 (83), 82 (15), 77 (13); 250-MHz ^1H NMR ($CDCl_3$) δ 7.90 (s, 1 H^A), 7.48 (d, J = 7 Hz, 1 H^B), 7.26 (d, J = 7 Hz, 1 H^C), 7.16 (dt, J = 1, 7 Hz, 1 H^D), 7.09 (dt, J = 1, 7 Hz, 1 H^E), 3.84 (m, 1 H^F), 3.69 (s, 3 H^G), 3.65 (s, 1 H^H), 3.44–3.30 (m, 1 H^I), 3.18–3.07 (m, 4 H^{JKLM}), 2.80 (d, J = 9 Hz, 1 H^N), 2.42 (dd, J = 12, 2 Hz, 1 H^O), 2.23–2.08 (m, 3 H^{PQR}), 1.73 (dq, J = 14, 7 Hz, 1 H^S), 1.51 (dq, J = 14, 7 Hz, 1 H^T), 1.41–1.34 (m, 1 H^U), 1.00 (t, J = 7 Hz, 3 H^V); 62.9-MHz ^{13}C NMR ($CDCl_3$) δ 175.05, 135.68, 135.33, 128.58, 122.23, 119.41, 118.48, 110.45, 69.16, 57.57, 53.78, 53.37, 52.64, 45.86, 44.43, 33.88, 33.64, 21.88, 19.47, 12.38. Anal. Calcd for $C_{21}H_{26}N_2O_3$: C, 71.16; H, 7.39; N, 7.90. Found: C, 70.89; H, 7.40; N, 8.07.



The acetate derivative **27b** was prepared by solution of 20 mg (0.056 mmol) of the alcohol **27a** in 3 mL of acetic anhydride (distilled from P_2O_5) at 0 °C, followed by addition of 1 mL of dry pyridine. After being stirred under argon at 0 °C for 8 h and at 20 °C for 16 h, the mixture was poured into 50 mL of ice saturated sodium bicarbonate solution. Extraction with 3 × 30 mL of dichloromethane, washing of the extracts with 70 mL of brine, drying ($MgSO_4$), filtration, and concentration at 42 °C under vacuum gave a residual solid foam which was subjected to centrifugal chromatography on a 1-mm SiO_2 plate, eluting with 1:1 ether/hexane to provide 19 mg (87%) of the acetate: TLC R_f (SiO_2, 1:1 ether/hexane) 0.24; UV (ethanol) λ_{max} 228, 285, 294 nm; IR (KBr) λ_{max} 3407, 3393, 3377, 2960, 2928, 2874, 2856, 1729, 1461, 1249, 1053, 1037, 1027, 807, 743 cm^{-1}; mass spectrum (70 eV), m/z (relative intensity) 397 (7), 396 (7), 396 (M^+, 29), 338 (22), 337 (100), 336 (11), 229 (23), 228 (8), 214 (8), 194 (7), 182 (7), 180 (10), 170 (9), 169 (8), 168 (24), 167 (17), 156 (7), 155 (6), 154 (19), 152 (8), 149 (14), 144 (7), 139 (8),, 138 (15), 136 (16), 135 (38), 130 (9), 127 (7), 124 (7), 123 (7), 122 (21), 121 (11), 110 (8), 108 (9), 107 (10), 94 (9), 93 (9), 84 (19), 69 (8), 67 (8), 57 (15), 55 (18); 250-MHz ^1H NMR ($CDCl_3$) δ 7.78 (s, 1 H), 7.48 (d, J = 7.4 Hz, 1 H), 7.25 (d, J = 5.9 Hz, 1 H), 7.16 (t, J = 5.9, Hz, 1 H), 7.11 (t, J = 6.3 Hz, 1 H), 5.08 (dd, J = 8.1, 4.5 Hz, 1 H), 3.71 (s, 3 H), 3.68 (s, 1 H), 3.46–3.34 (m, 1 H), 3.28–2.96 (m, 4 H), 2.74 (d, J = 8.7 Hz, 1 H), 2.58 (d, J = 14.2 Hz, 1 H), 2.10 (s, 3 H), 2.07 (m, 2 H), 1.70–1.42 (m, 3 H), 0.91 (t, J = 7.0 Hz, 3 H).

15β-(Tosyloxy)coronaridine (30). A solution of 41 mg (0.11 mmol) of 15β-hydroxycoronaridine (**27a**, 23 mg (0.12 mmol) of *p*-toluenesulfonyl chloride and a catalytic amount of 4-(dimethylamino)pyridine in 3 mL of dry pyridine was stirred under argon at 40 °C for 6 h and then stored at 0 °C for 24 h. The reaction mixture was concentrated at 0.05 mm with slight warming and the residual solid dissolved in 30 mL of dichloromethane. The solution was washed with ice saturated sodium bicarbonate and brine solutions, dried ($MgSO_4$), filtered, and concentrated at 42 °C under vacuum. The residue was subjected to centrifugal chromatography on a 1-mm silica gel plate, eluting with ether/hexane (1:1) to provide 58 mg (99%) of the tosylate: TLC (SiO_2, ether/hexane, 1:1) R_f 0.28 (gray-blue, CAS); UV (ethanol) λ_{max} 230, 285, 294 nm; IR (KBr) ν_{max} 3442, 3387, 3059, 3027, 2959, 2931, 2874, 1723, 1618, 1598, 1490, 1461, 1436, 1354, 1294, 1265, 1250, 1233, 1188, 1175, 1142, 1096, 1053, 1034, 1018, 950, 909, 887, 872, 852, 815, 743, 725, 705, 667; mass spectrum (70 eV), m/z (relative intensity) 508 (M^+, <1), 338 (12), 337 (31), 336 (46), 307 (11), 228 (14), 216 (21), 184 (10), 168 (13), 167 (12), 155 (44), 135 (33), 122 (12), 120 (12), 92 (36), 91 (100), 79 (22), 65 (23), 55 (10), 51 (11).

Hydrolytic Formation of the C-16 Epimeric Δ²⁰-15-Oxocleavamines (24a,b). To a stirred solution of 233 mg (0.500 mmol) of 15-((*tert*-butyldimethylsilyl)oxy)catharanthine (**23**) in 10 mL of tetrahydrofuran and 5 mL of water, at 22 °C, was added 1.5 mL (1.5 mmol) of a 1 M solution of tetrabutylammonium fluoride in tetrahydrofuran, followed after 2 h by an additional 1 equiv of the ammonium fluoride. After a further 1 h, TLC (SiO_2, ethyl acetate) showed the absence of starting material. A 5% aqueous $KHCO_3$ solution (15 mL) and 20 mL of dichloromethane were added, the layers were separated, and the aqueous portion was extracted with 3 × 20 mL of dichloromethane. The combined organic extracts were dried (Na_2SO_4) and concentrated, and the residue, dissolved in 3 mL of dichloromethane, was stirred at 22 °C with 1 g of silica gel for several hours until 15-oxocoronaridine was absent by TLC. Chromatography on 9 g of silica gel, eluting with 200 mL of 1:3 ethyl acetate/pentane, followed by ethyl acetate, provided 160 mg (90%) of the two epimeric oxocleavamines **24a,b**.

Cyclization of Δ²⁰-15-Oxocleavamines (24a,b) to 15-((*tert*-Butyldimethylsilyl)oxy)catharanthine (23). A solution of 37 mg (0.11 mmol) of the oxocleavamines **24a,b** in 3 mL of dichloromethane, 16 mg (0.18 mmol) of *tert*-butyldimethylsilyl chloride, and 17.5 μL (0.117 mmol) of DBU was stirred for 2 h at 22 °C. A further 48 mg (0.35 mmol) of the silyl chloride and 54 μL (0.35 mmol) of DBU were added and the mixture was refluxed for 2 days. The cooled mixture was then concentrated under vacuum and subjected to centrifugal chromatography on a 1-mm Chromatotron plate, eluting with 1:3 ethyl acetate/pentane to provide 15 mg (30%) of the (silyloxy)catharanthine **23**, followed by 19 mg (55%) of the starting oxocleavamines **24a,b**. A third product of intermediate retention time (CAS, blue) [UV 295, 328 nm; MS (M^+, 466)] was obtained in less than 10%.

Δ²⁰-15-Thionocleavamines 24c,d. A mixture of 0.105 g (0.298 mmol) of the cleavamines **24a** (major) and **24b** (very minor), 15 mL of dry benzene, and 0.195 g (0.438 mmol) of phosphorus pentasulfide was stirred at reflux for 30 min. After cooling to 22 °C, 20 mL of 5% aqueous $KHCO_3$ solution was added and stirring continued for 10 min. The aqueous layer was extracted with 2 × 40 mL of dichloromethane, and the extracts were dried ($NaHCO_3$) and concentrated. Chromatography on 20 mL of silica gel, eluting with 200 mL of dichloromethane, followed by ethyl acetate, and trituration of the concentrated eluate with 1:1 ether/pentane, concentration, and trituration with ether gave 91 mg (83%) of product, mp 131–132 °C; TLC (SiO_2, ethyl acetate) R_f 0.62, yellow (CAS, green with yellow center); UV (ethanol) λ_{max} 225, 285, 293 nm; mass spectrum (70 eV), m/z (relative intensity) 370 (15), 368 (M^+, 100), 354 (12), 353 (83), 337 (3), 243 (2), 229 (3), 168 (4), 167 (8), 151 (6), 129 (2), 85 (2), 71 (2), 69 (3), 61 (4), 57 (7), 55 (4); 270-MHz NMR (acetone-d_6) δ 9.7 (s, 1 H), 7.2 (d, J = 7.4 Hz, 1 H), 7.15 (s, 1 H), 7.10 (d, J = 7.4 Hz, 1 H), 6.75 (t, J = 7.4 Hz, 1 H), 6.65 (t, J = 7.4 Hz, 1 H), 3.80 (d, J = 11.1 Hz, 1 H), 3.55 (br d, J = 7 Hz, 1 H), 3.20 (s, 3 H), 3.20 (m, 1 H), 2.95 (br d, $J \simeq$ 15 Hz, 1 H), 2.80–2.40 (m, 4 H), 2.35 (d, sextet, J = 7.4 Hz, 1 H), 2.17 (d, sextet, J = 7.4 Hz, 1 H), 2.0 (m, 2 H), 0.85 (t, J = 7.4 Hz, 3 H); IR (film) ν_{max} 3350, 2490, 2900, 1725, 1580, 1450, 1390, 1100, 1070 cm^{-1}.

15-*S*-Methylcatharanthine (31a). To a solution of 10 mg (0.027 mmol) of the 15-thionocleavamine(s) **24c(d)** in 1 mL of dry benzene and 1 mL of CH_2Cl_2 was added 150 μL (2.4 mmol) of methyl iodide. The red color of the solution faded rapidly and a yellow precipitate formed. After stirring for 2 h at 20 °C, the mixture was concentrated under vacuum and the residue triturated with dry ether to provide 13 mg (95%) of the *S*-methyl imonium salt, mp 165–167 °C; TLC (SiO_2, methanol) R_f 0.1, yellow; UV (ethanol) λ_{max} 225, 280, 293 nm; mass spectrum (70 eV), m/z (relative intensity) 382 (M^+ – HI, 59), 181 (63), 166 (38), 153 (40), 141 (100), 127 (37); IR ν_{max} 2908, 2862, 1719, 1627, 1507, 1651, 1433, 1350, 1230, 732 cm^{-1}; 270-MHz NMR (acetone-d_6) δ 9.95 (s, 1 H), 8.58 (s, 1 H), 7.26 (d, J = 7.7 Hz, 1 H), 7.10 (d, J = 7.7 Hz, 1 H), 6.80 (t, J = 7.7 Hz, 1 H), 6.72 (t, 7.7 Hz, 1 H), 4.25 (br d, J = 8.0 Hz, 1 H), 3.85 (d, J = 11.5 Hz, 1 H), 3.60 (m, 2 H), 3.25 (s, 3 H), 3.15 (m, 3 H), 2.50 (m, 2 H), 2.39 (s, 3 H), 2.20 (m, 3 H) 0.85 (t, 7.4 Hz, 3 H).

To 10 mg (1.96×10^{-5} M) of the *S*-methyl salt, dissolved in 2 mL of dry methanol, was added 15 μL (7.84×10^{-5} M) of *N,N*-diisopropylethylamine. The stirred solution was heated at 80 °C

for 1.5 h, cooled, and concentrated under vacuum. Preparative TLC (SiO_2, 1:3 ethyl acetate/CH_2Cl_2) afforded 6 mg (82%) of **31a**, mp 172–174 °C: TLC (SiO_2, 1:3 ethyl acetate/CH_2Cl_2) R_f 0.4, (ether) R_f 0.6 (CAS blue-green); UV λ_{max} 230, 285, 295 nm; 70 eV mass spectrum, m/z (relative intensity) 382 (M^+, 74), 229 (21), 228 (19), 181 (69), 167 (87), 153 (100), 84 (51), 77 (31), 71 (50), 57 (92); 270-MHz NMR ($CDCl_3$) δ 7.62 (s, 1 H), 7.44 (d, J = 7.2 Hz, 1 H), 7.22 (d, J = 7.2, 1 H), 7.15 (t, J = 7.2 Hz, 1 H), 7.10 (t, J = 7.2 Hz, 1 H), 4.30 (s, 1 H), 3.70 (s, 3 H), 3.70 (m, 1 H), 3.55 (m, 1 H), 3.30 (m, 2 H), 2.95–2.80 (m, 5 H), 2.65 (sextet, J = 7 Hz, 1 H), 2.25 (s, 3 H), 2.05 (sextet, J = 7 Hz, 1 H), 1.10 (t, 7.1 Hz, 3 H); IR (film) ν_{max} 3350, 2940, 2900, 2835, 1720, 1670, 1600, 1450, 1430, 730 cm^{-1}.

The compounds **24c,d** and **31a**, while recrystallizable, were found to undergo gradual decomposition or oxidation at room temperature within hours. Consequently, elemental analyses gave low C values.

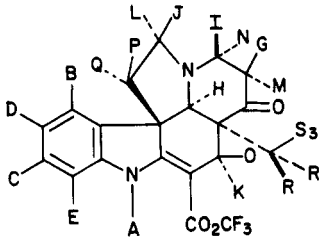
15-*S*-Benzylcatharanthine (13b). To 50 mg (0.14 mmol) of 15-oxocoronaridine (**25a**) in 5 mL of acetic acid was added 50 μL (0.42 mmol) of benzyl mercaptan, followed after 5 min by 330 μL (2.7 mmol) of boron trifluoride etherate. After being stirred for 24 h at 22 °C, the reaction mixture was poured into 50 mL of iced 10% NH_4OH and extracted with 4 × 25 mL of dichloromethane. The dried ($MgSO_4$) extracts were concentrated under vacuum and the residue was subjected to centrifugal chromatography on a 2-mm SiO_2 disk, eluting with 2% methanol in dichloromethane, to provide 45 mg (70%) of the *S*-benzyl thioenol ether **31b**: TLC R_f (SiO_2) 0.41 (1:3 EtOAc/pentane), 0.22 (2% MeOH in CH_2Cl_2); UV (EtOH) λ_{max} 230, 278, 285, 292 nm; IR (KBr) ν_{max} 3378, 2963, 2926, 2867, 2844, 1710, 1493, 1460, 1434, 1364, 1343, 1279, 1254, 1228, 1194, 1176, 1079, 745, 710, 700; 250-MHz ^1H NMR ($CDCl_3$) δ 7.67 (br s, 1 H), 7.47 (d, J = 7.7 Hz, 1 H), 7.36–7.06 (m, 8 H), 4.31 (s, 1 H), 3.89 (s, 2 H), 3.68 (s, 3 H), 3.58–3.48 (m, 2 H), 3.35–3.18 (m, 2 H), 2.92–2.45 (m, 5 H), 2.01 (septet, J = 7.1 Hz, 1 H), 1.79 (dd, J = 13.0, 2.0 Hz, 1 H), 1.03 (t, J = 7.5, 3 H); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 12.67, 21.51, 25.02, 37.30, 37.81, 38.59, 49.23, 52.32, 52.62, 55.91, 61.86, 110.44, 110.84, 118.25, 119.50, 121.98, 126.97, 128.47, 128.72, 129.03, 129.43, 135.07, 136.17, 138.52, 150.15, 173.63; 70 eV mass spectrum, m/z (relative intensity) 460 (M^+ + 2, 2), 459 (6) 458 (M^+, 30), 257 (16), 243 (11), 230 (6), 229 (15), 168 (13), 167 (8), 166 (5), 154 (8), 138 (5), 96 (6), 92 (9), 91 (100), 81 (8), 77 (7), 67 (6), 65 (27), 63 (8), 57 (15), 56 (5), 55 (17), 51 (9), 50 (8).

Catharanthine (1). Raney nickel (Aldrich, 1 mL of 50% aqueous suspension, pH 10) was washed under argon (5×) with water and (4×) with acetone and then heated in acetone at reflux for 2 h. The solvent was withdrawn by pipet, washed (4×) with methanol, and covered with 5 mL of methanol. To this R/Ni was added 9 mg of the methyl thioenol ether **31a** in 1 mL of methanol, and the suspension was stirred for 1 h at 22 °C and 15 min at reflux. The cooled mixture was filtered, the solids were washed with 3 × 5 mL of methanol, and the combined filtrates were concentrated to 5 mg (70%) of *dl*-catharanthine.

The *S*-benzyl compound **31b** was desulfurized by the same procedure to provide the product (82% yield) with mp 165–168 °C dec, recrystallized from methanol to mp 175–176 °C dec. A reported mp of 60–62 °C[28] could not be observed and the higher melting point was similarly found for *dl*-catharanthine obtained by the Raucher synthesis[34a] (private communication, Prof. Raucher). The melt contained no catharanthine but primarily a product of higher TLC R_f (for analogous products consider ref 24, 30, 34b, 35, 36).

The racemic catharanthine matched natural *d*-catharanthine in TLC behavior and 250-MHz NMR and electron impact 70 eV mass spectra.

15-Oxovincadifformine (18). A solution of 100 mg (0.284 mmol) of the 15-oxosecodine **13** in 20 mL of toluene was heated at 110 °C under argon for 10 h. From the cooled reaction mixture the solvent was evaporated at 50 °C under vacuum and the residual foam, dissolved in 5 mL of dichloromethane, was purified by centrifugal chromatography on a 2-mm SiO_2 disk, eluting with ethyl acetate/pentane (1:5) at 2 mL/min, collecting 1-mL fractions. Fractions 8–18 on concentration and crystallization of the residue from ether gave 99 mg (99%) of product **18**, recrystallized from aqueous methanol to mp 168–169 °C: TLC (SiO_2) R_f 0.47 (2% methanol in dichloromethane), 0.54 (1:3 ethyl acetate/pentane); HPLC t_R 12.6 min on a 4.1 mm × 30 cm Microporisil column eluted with 1:4 ethyl acetate/pentane at 1 mL/min; UV (ethanol) λ_{max} 215, 230, 300, 330 nm; IR (KBr) 2970, 2945, 2924, 2914, 2806, 2795, 1706, 1676, 1609, 1477, 1465, 1437, 1382, 1330, 1313, 1283, 1255, 1237, 1221, 1193, 1151, 1138, 1123, 1102, 1090, 1041, 1019, 846, 801, 747, 668 cm^{-1}; direct insertion probe mass spectrum (70 eV), m/z (relative intensity) 354 (11), 353 (50), 352 (M^+, 100), 229 (5), 215 (13), 214 (75), 182 (6), 180 (7), 168 (5), 167 (6), 154 (14), 139 (14), 138 (39), 110 (5), 69 (5), 59 (5), 57 (8), 56 (8), 55 (8); 250-MHz ^1H NMR ($CDCl_3$) δ 9.04 (s, 1 H^A), 7.25 (d, J = 7 Hz, 1 H^B), 7.18 (ddd, J = 8, 7, 1 Hz, 1 H^C), 6.90 (ddd, J = 8, 7, 1 Hz, 1 H^D), 6.83 (d, J = 8 Hz, 1 H^E), 3.77 (s, 3 H^F), 3.38 (dt, J = 9, 6 Hz, 1 H^G), 3.19 (d, J = 1 Hz, 1 H^H), 3.08 (m, 1 H^I), 3.05 (dd, J = 9, 6 Hz, 1 H^J), 2.97 (dd, J = 15, 2 Hz, 1 H^K), 2.74 (dq, J = 4, 12 Hz, 1 Hz, 1 H^L), 2.71 (dt, J = 6, 9 Hz, 1 H^M), 2.55 (dq, J = 9, 4 Hz, 1 H^N), 2.40 (d, J = 15 Hz, 1 H^O), 2.14 (dt, J = 12, 6 Hz, 1 H^P), 1.80 (dd, J = 12, 4 Hz, 1 H^Q), 1.13 (dq, J = 19.7 Hz, 2 H^R), 0.66 (t, J = 7, 3 H^S); 62.9-MHz ^{13}C NMR ($CDCl_3$) δ 214.04, 169.39, 164.97, 143.61, 137.80, 128.49, 122.05, 121.10, 109.84, 91.40, 72.02, 56.48, 55.45, 51.58, 51.14, 46.92, 44.21, 37.43, 24.62, 24.38, 8.64. Anal. Calcd for $C_{21}H_{24}N_2O_3$: 71.57; H, 6.86; N, 7.95. Found: C, 71.29; H, 6.90; 7.99.

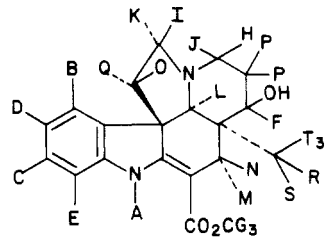


15α- and 15β-Hydroxyvincadifformine (19 and 20). To 0.184 g (0.522 mmol) of 15-oxovincadifformine (**18**) in 10 mL of methanol at 0 °C was added 0.019 g (0.52 mmol) of sodium borohydride. The reaction mixture was stirred until no starting ketone could be detected by TLC. It was then poured into 30 mL of cold brine and extracted with three 20-mL portions of dichloromethane. The combined extracts were dried ($MgSO_4$) and concentrated to 0.180 g (98%) of an epimeric mixture of 15-hydroxyvincadifformines. HPLC (conditions below) indicated a 92:8 ratio of products. The mixture was separated by centrifugal chromatography on SiO_2, eluting with 3.5% methanol in dichloromethane. Collection of 0.7-mL fractions every 0.5 min gave the major epimer in fractions 8–30, recrystallized from ether–hexane to mp 92–93 °C, and the minor epimer in fractions 46–69, recrystallized from ether–hexane to mp 98–99 °C.

A reduction of 0.111 g (0.315 mmol) of the ketone with 314 μL of a 1 M solution of L-Selectride (lithium tri-*sec*-butylborohydride, 59.8 mg, 0.315 mmol) in 10 mL of tetrahydrofuran at 0 °C, followed by the same workup, gave only the major 15-hydroxy product found above.

For the major epimer **20**: TLC (SiO_2) R_f 0.53 (ethyl acetate), 0.26 (5% methanol in dichloromethane); HPLC 6.2 min on a 4.1 mm × 30 cm Microporisil column with 5% methanol in dichloromethane at 1.2 mL/min; UV (ethanol) λ_{max} 228, 301, 330 nm; IR (KBr) ν_{max} 3420, 3375, 2930, 2877, 2859, 2777, 2711, 2625, 1972, 1607, 1476, 1463, 1436, 1380, 1364, 1329, 1313, 1297, 1278, 1253, 1235, 1212, 1191, 1112, 1055, 1039, 1015, 745 cm^{-1}; direct insertion probe mass spectrum (70 eV), m/z (relative intensity) 355 (4), 354 (M^+, 27), 253 (2), 228 (3), 220 (3), 180 (3), 177 (4), 170 (4), 169 (3), 168 (6), 167 (6), 154 (5), 141 (10), 140 (100), 134 (3), 115 (2), 110 (6), 108 (3), 107 (18), 106 (12), 101 (4), 100 (2), 96 (5), 93 (3), 92 (19), 91 (4), 86 (3), 84 (4), 79 (6), 77 (4), 73 (6), 69 (2), 65 (6), 57 (13), 56 (6), 55 (5); 250-MHz ^1H NMR ($CDCl_3$) δ 8.95 (s, 1 H, H^A), 7.18 (d, J = 7 Hz, 1 H, H^B), 7.13 (d, t, J = 1, 8 Hz, 1 H, H^C), 6.86 (dt, J = 1, 7 Hz, 1 H, H^D), 6.80 (d, J = 8, 1 H, H^E), 3.76 (s, m, 4 H, H^F, H^G), 3.14 (ddd, J = 10, 6, 4 Hz, 1 H, H^H), 2.92 (dd, J = 8, 6 Hz, 1 H, H^I), 2.49 to 2.67 (m, 5 H, H^{J-N}), 2.11 (dt, J = 11, 6 Hz, 1 H, H^O), 1.79–2.02 (m, 2 H, H^P), 1.73 (dd, J = 11, 4 Hz, 1 H, H^Q), 1.04 (dq, J = 14, 7 Hz, 1 H, H^R), 0.96 (dq, J = 14, 7 Hz, 1 H, H^S), 0.68 (t, J = 7 Hz, 3 H, H^T); 62.9-MHz ^{13}C NMR ($CDCl_3$) δ 169.28, 167.25, 143.35, 137.50, 127.67, 121.06, 120.56, 109.47, 92.20, 73.86, 70.51, 55.37, 51.39, 50.98, 47.54, 45.57, 43.79, 30.55, 26.28, 22.40, 8.50.

For the minor epimer **19**: TLC (SiO_2) R_f 0.49 (ethyl acetate), 0.21 (5% methanol in dichloromethane); HPLC t_R 7.4 min (conditions as above); UV (ethanol) λ_{max} 229, 302, 330 nm; IR (KBr) ν_{max} 3369, 2957, 2945, 2925, 2900, 2877, 2863, 2793, 2770, 2715, 1674, 1609, 1465, 1431, 1384, 1350, 1334, 1315, 1296, 1276, 1253, 1236, 1223, 1212, 1180, 1157, 1114, 1098, 1057, 1037, 1015, 746 cm^{-1}: direct insertion probe mass spectrum (70 eV), *m/z* (relative intensity) 355 (9), 354 (M^+, 24), 336 (2), 180 (2), 168 (2), 167 (2), 154 (3), 141 (7), 140 (100), 115 (1), 110 (8), 108 (1), 101 (4), 100 (7), 93 (1), 86 (1), 84 (2), 77 (1), 73 (5), 72 (1), 57 (9), 56 (5), 55 (2); 25/-MHz ^1H NMR ($CDCl_3$) δ 8.90 (s, 1 H, H^A), 7.21 (d, J = 7 Hz, 1 H, H^B), 7.12 (dt, J = 1, 8 Hz, 1 H, H^C), 6.86 (dt, J = 1, 7 Hz, 1 H, H^D), 6.80 (d, J = 8 Hz, 1 H, H^E), 3.90 (t, J = 3 Hz, 1 H, H^F), 3.77 (s, 3 H, H^G), 2.88–2.95 (m, 2 H, H^{H-K}), 2.81 (s, 1 H, H^L), 2.65 (d, J = 15 Hz, 1 H, H^M), 2.61 (m, 2 H, H^{H-K}), 2.33 (dd, J = 14, 2 Hz, 1 H, H^N), 2.00–2.19 (m, 2 H H^{O-Q}), 1.67–1.75 (m, 2 H, H^{O-Q}), 1.11 (dq, J = 14, 7 Hz, 1 H, H^R), 6.80 (dq, J = 14, 7 Hz, 1 H, H^S) 0.61 (t, J = 7 Hz, 3 H, H^T); 62.9-MHz ^{13}C NMR ($CDCl_3$) δ 169.04, 143.24, 137.85, 127.51, 121.70, 120.70, 112.94, 109.39, 92.19, 67.86, 68.46, 55.51, 51.54, 51.01, 45.43, 44.82, 43.40, 30.45, 24.64, 21.79, 6.58.



15α- and 15β-Acetoxyvincadifformine (21 and 22). A solution of 200 mg (0.564 mmol) of the epimeric product mixture of 15-hydroxyvincadifformines (**19** and **20**) in 6 mL of acetic anhydride was cooled to 0 °C. After addition of 2 mL of pyridine, the mixture was stirred at 0 °C for 1 h and at 20 °C for 24 h. It was then poured onto ice and extracted with 3 × 50 mL of dichloromethane. The extracts were washed with cold saturated sodium bicarbonate solution, dried ($MgSO_4$), and concentrated at 45 °C (10–0.05 mm). The residual material was subjected to centrifugal chromatography on silica gel, eluting with ethyl acetate/pentane (1:4) at 1.8 mL/min. The major 15β-acetate **22** was obtained in elution fractions 5–22 mL and the minor 15α-acetate **21** in fractions 44–68 mL.

The major product, **22**, crystallized from ether: mp 196–197 °C; UV (ethanol) λ_{max} 230, 300, 330 nm; IR (KBr) ν_{max} 3431, 3422, 3407, 3375, 2967, 2947, 2916, 2798, 1727, 1671, 1611, 1475, 1462, 1438, 1376, 1362, 1331, 1314, 1297, 1279, 1256, 1236, 1213, 1191, 1179, 1155, 1122, 1112, 1099, 1046, 1025, 752 cm^{-1}; direct insertion probe mass spectrum (70 eV), *m/z* (relative intensity) 397 (7), 396 (M^+, 19), 337 (6), 222 (5), 221 (5), 183 (12), 182 (100), 180 (6), 168 (9), 167 (7), 154 (7), 122 (6), 110 (22), 83 (7), 57 (15), 56 (9); 250-MHz ^1H NMR ($CDCl_3$) δ 0.56 (t, J = 8 Hz, 3 H, C-18), 0.97 (q, J = 8 Hz, 2 H, C-19), 1.73 (dd, J = 12, 5 Hz, 1 H, C-6β), 1.85–1.93 (m, 2 H, C-14α,14β), 2.08 (s, 3 H, $COCH_3$), 2.12 (dt, J = 11, 7 Hz, 1 H, C-6α), 2.46–2.58 (m, 2 H, C-3α,5α), 2.57 (dd, J = 15, 2 Hz, 1 H, C-17α), 2.65 (br s, 1 H, C-21), 2.79 (d, J = 15 Hz, 1 H, C-17β), 2.91 (t, J = 7 Hz, 1 H, C-5β), 3.11 (dt, J = 11, 4 Hz, 1 H, C-3β), 3.79 (s, 3 H, CO_2CH_3), 4.96 (dd, J = 9, 8 Hz, 1 H, C-15α), 6.80 (d, J = 8 Hz, 1 H, C-12), 6.87 (t, J = 7 Hz, 1 H, C-10), 7.13 (td, J = 8, 1 Hz, 1 H, C-11), 7.19 (d, J = 7 Hz, 1 H, C-9), 8.88 (s, 1 H, NH); 62.9-MHz ^{13}C NMR ($CDCl_3$) δ 8.20, 21.41, 23.32, 26.43, 27.70, 42.31, 46.17, 47.49, 51.07, 51.49, 55.65, 69.95, 76.52, 92.11, 109.51, 120.71 (2), 127.69, 137.14, 143.24, 167.85, 169.20, 170.62.

For the minor amorphous 15α-acetate **21**: UV (ethanol) λ_{max} 231, 301, 330 nm; IR (KBr) ν_{max} 3362, 2960, 2946, 2799, 1738, 1676, 1608, 1477, 1464, 1436, 1372, 1313, 1299, 1279, 1241, 1211, 1180, 1156, 1114, 1100, 1045, 1030, 1016, 746 cm^{-1}; direct insertion probe mass spectrum (70 eV), *m/z* (relative intensity) 397 (7), 396 (M^+, 24), 337 (7), 222 (5), 221 (5), 213 (5), 183 (11), 182 (100), 180 (7), 168 (10), 167 (8), 154 (7), 122 (6), 110 (24), 84 (6), 83 (6), 57 (14), 56 (9); 250-MHz ^1H NMR ($CDCl_3$) δ 0.49 (t, J = 7 Hz, 3 H, C-18), 0.76 (septet, J = 7 Hz, 1 H, C-19 or 19′), 0.96 (septet, J = 7 Hz, 1 H, C-19′ or 19), 1.73 (dd, J = 12, 4 Hz, 1 H, C-6β), 2.06 (s, 3 H, $COCH_3$), 2.01–2.16 (m, 2 H, C-14α,14β), 2.39 (dd, J = 15, 1.4 Hz, 1 H, C-17α), 2.57–2.75 (m, 2 H, C-3α,5α), 2.70 (d, J = 15 Hz, 1 H, C-17β), 2.81 (br s, 1 H, C-21), 2.93 (t, J = 7, 1 H, C-5β), 2.94–2.99 (m, 1 H, C-3β), 3.76 (s, 3 H, CO_2CH_3), 5.04 (t, J = 3 Hz, 1 H, C-15β), 6.80 (d, J = 8 Hz, 1 H, C-12), 6.88 (t, J = 7 Hz, 1 H, C-10), 7.13 (td, J = 8, 1 Hz, C-11), 7.23 (d, J = 7 Hz, 1 H, C-9), 8.94 (br s, 1 H, NH); 62.9-MHz ^{13}C NMR ($CDCl_3$) δ 6.56, 21.19, 22.20, 24.38, 27.69, 42.61, 45.25, 45.46, 51.04, 51.53, 55.46, 68.46, 71.45, 91.83, 109.47, 120.66, 121.03, 127.59, 137.62, 143.26, 168.20, 168.97, 170.03.

Bromination of 15-Oxovincadifformine. To a solution of 160 μL (1.13 mmol) of diisopropylamine in 2 mL of tetrahydrofuran, at 0 °C, under argon, was added 0.436 mL of a 2.6 N solution of *n*-butyllithium in hexane (1.13 mmol). After 30 min at 0 °C the mixture was cooled to −78 °C and 0.200 g (0.567 mmol) of 15-oxovincadifformine and 342 μL (2.27 mmol) of tetramethylethylenediamine in 3 mL of tetrahydrofuran was added. The yellow solution was stirred for 30 min at −78 °C and then 29 μL (0.567 mmol) of bromine in 2 mL of dichloromethane was added dropwise over 1 min (declorization of bromine). After stirring at −78 °C for 20 min the cold reaction mixture was poured into 25 mL of iced saturated aqueous sodium bicarbonate. Extraction with 3 × 25 mL of dichloromethane, washing of the extracts with 100 mL of cold saturated brine, drying ($MgSO_4$), filtration, and concentration at 42 °C under vacuum gave 0.245 g (100%) of the bromo ketone as a foam. This was used for the subsequent reduction but in an alternative experiment centrifugal chromatography on a 2-mm silica gel disk, in the dark, under argon and elution with dichloromethane provided a sample which crystallized from ether with mp 164–165 °C. The chromatography resulted in extensive decomposition of the crude product: UV (ethanol) λ_{max} 230, 300, 333 nm; IR (KBr) ν_{max} 3370, 2975, 2943, 2920, 2850, 2798, 1720, 1671, 1607, 1470, 1452, 1434, 1384, 1327, 1314, 1303, 1282, 1254, 1236, 1220, 1205, 1174, 1157, 1138, 1112, 1074, 1052, 1034, 924, 802, 755 cm^{-1}; mass spectrum, *m/z* (relative intensity) 432 (4), 431 (4), 351 (13), 222 (4), 218 (5), 216 (5), 215 (14), 214 (100), 182 (7), 180 (7), 168 (10), 167 (9), 155 (5), 154 (26), 138 (10), 128 (5), 127 (6), 108 (7), 84 (5), 57 (13), 56 (10), 55 (32), 54 (6).

14β-Bromo-15β-hydroxyvincadifformine (28). The 14-bromo 15-ketone (0.210 g, 0.487 mmol) was dissolved in 10 mL of methanol, and at 0 °C 0.020 g (0.53 mmol) of sodium borohydride was added over 15 min. After stirring at 0 °C for 5 min the mixture was poured into 50 mL of iced, saturated brine and extracted with 3 × 100 mL of dichloromethane. The dried ($MgSO_4$) extracts were concentrated at 42 °C under vacuum and the residual material subjected to centrifugal chromatography on a 2-mm silica gel plate. Elution with ethyl acetate/pentane (1:5) gave 0.129 g (61%) of the 15-β-ol **28** as an amorphous solid. Subsequent elution with ethyl acetate/pentane (1:2) gave 6 mg (3%) of the 15-α-ol, followed by 28 mg (15%) of a 14-methoxy 15-ol. Elution with ethyl acetate gave 35 mg (20%) of alcohol **20**.

28: 250-MHz NMR ($CDCl_3$) δ 8.98 (br s, 1 H), 7.16 (d, t, J = 7.5, 0.91 Hz, 1 H), 7.15 (d, J = 7.2 Hz, 1 H), 6.87 (t, J = 7.03 Hz, 1 H), 6.81 (dt, J = 0.82, 8.3 Hz, 1 H), 4.46 (ddd, 1 H), 3.78 (s, 3 H), 3.73 (dd, J = 10.8, 3.2 Hz, 1 H), 3.54 (dd, J = 12.0, 5.0 Hz, 1 H), 3.25 (dd, J = 12.0, 5.1 Hz, 1 H), 3.02 (dd, 8.4, 6.3 Hz, 1 H), 2.83 (d, J = 15.6 Hz, 1 H), 2.70 (ddd, J = 4.5 Hz, 1 H), 2.66 (dd, J = 14.8, 2.7 Hz, 1 H), 2.63 (br s, 1 H), 2.48 (d, J = 10.5 Hz, 1 H), 2.12 (dd, 11.7, 6.3 Hz, 1 H), 1.76 (dd, J = 11.6, 4.3 Hz, 1 H), 1.04 (septet, J = 14.6, 7.2 Hz, 1 H), 0.89 (septet, J = 14.3, 7.3 Hz, 1 H), 0.70 (t, J = 7.3 Hz, 3 H).

(±)-Tabersonine (2). To 0.056 g (0.35 mmol) of McMurry reagent (4:1 $TiCl_3/LiAlH_4$, Aldrich),[46] under argon, was added 10 mL of dry tetrahydrofuran. After stirring for 20 min, a solution of 0.050 g (11 mmol) of the bromohydrin **28** in 3 mL of tetrahydrofuran was added. The reaction mixture was heated at reflux, with rapid stirring, for 2 h, then cooled, and poured into 50 mL of 2 N ammonium hydroxide in saturated brine at 0 °C. Extraction with 3 × 25 mL of dichloromethane, drying of the extracts ($MgSO_4$), concentration at 42 °C under vacuum, and centrifugal chromatography of the residue on a 1-mm SiO_2 disk, eluting with 3:2 hexane/ether, gave 0.027 g (71%) of amorphous (±)-tabersonine,[65] which matched TLC, IR, NMR and mass spectroscopic

(60) Bundarev, G. N.; Ryzohov, V.; Chelpanoua, L. F.; Petrov, A. *J. Org. Chem. Russ.* **1967**, *3*, 785.

data obtained with *l*-tabersonine.

Desethyl-15-oxosecodine (32). To a mixture of 10 mL of dichloromethane and 0.230 g (0.94 mmol) of the indoloazepine **14** at 0 °C was added 0.165 g (1.0 mmol) of 1-bromo-1,4-pentadien-3-one.[60] The reaction mixture was stirred for 20 min and then poured into 10 mL of 10% NaOH at 0 °C. The reaction mixture was extracted three times with 25 mL of dichloromethane. Concentration and adsorption on 20 g of silica gel, eluting with 5:1 ethyl acetate/ethanol yielded, on concentration and crystallization from ethyl acetate, 0.120 g (39%) of desethyl-15-oxosecodine (**32**); mp 173–175 °C. TLC of the melt showed a 1:1 mixture of **32** and its thermal cyclization product **41**: TLC R_f 0.55 (silica gel, 4:1 ethyl acetate/ethanol, CAS, purple), R_f 0.04 (silica gel, ether); UV (ethanol) λ_{max} 226, 325 nm; IR (KBr) ν_{max} 3216, 2936, 1726, 1627, 1592, 1574, 1454, 1432, 1325, 1238, 1204, 1178, 1165, 743 cm^{-1}; 250-MHz NMR ($CDCl_3$) δ 9.07 (s, 1 H), 7.54 (d, J = 8 Hz, 1 H), 7.39 (d, J = 8 Hz, 1 H), 7.27–7.11 (m, 2 H), 6.70 (d, J = 7 Hz, 1 H), 6.57 (d, J = 1 Hz, 1 H), 6.04 (d, J = 1 Hz, 1 H), 4.80 (d, J = 7 Hz, 1 H), 3.83 (s, 3 H), 3.52–3.40 (m, 4 H), 3.13 (t, J = 7 Hz, 2 H), 2.93 (t, J = 8 Hz, 2 H); direct exposure mass spectrum (70 eV), m/z (relative intensity) 325 (3), 324 (M^+, 14), 215 (8), 214 (66), 168 (6), 167 (9), 155 (15), 154 (83), 128 (16), 127 (32), 111 (12), 110 (56), 86 (16), 84 (36), 82 (100), 55 (31). Anal. Calcd for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.21; N, 8.64. Found C, 69.78; H, 6.56; N, 8.28.

Alternative Method: Desethyl-15-oxosecodine (32). To a mixture of 1.00 g (4.09 mmol) of the indoloazepine **14**, 0.494 g (4.90 mmol) of triethylamine, and 15 mL of tetrahydrofuran was added 0.764 g (4.90 mmol) of 1,5-dichloropenten-3-one (**35**).[61] The reaction mixture was stirred for 30 min at 25 °C. Then 10 mL of cold 5% NaOH was added to the mixture and it was partitioned with 2 × 20 mL of dichloromethane. The organic extracts were concentrated, adsorbed on 25 g of silica gel, and eluted with ethyl acetate to yield three compounds: 0.113 g (8.5%) of the secodine **31** as crystals from ethyl acetate, with NMR, IR, and UV spectra comparable to the product of the alternative synthesis, 0.620 g (42%) of the vinylogous amide **34** as an amorphous foam [TLC R_f 0.38 (silica gel, ethyl acetate, CAS, green); UV (ethanol) λ_{max} 236, 286, 293, 335 nm; mass spectrum (80 eV), m/z (relative intensity) 325 (5), 324 (M^+, 17), 244 (6), 214 (69), 202 (10), 183 (12), 169 (12), 168 (11), 156 (21), 154 (43), 110 (59), 55 (100)], and 0.171 g (12.1%) of perhaps the chloro vinylogous amide **35** as an amorphous foam [TLC R_f 0.64 (silica gel, ethyl acetate, CAS, green); UV (ethanol) λ_{max} 230, 287, 294, 332 nm]. In addition another 0.120 g of a mixture of **34** and **35** was isolated. The compounds **34** and **35** were combined in 10 mL of tetrahydrofuran, and then 4 drops of CF_3CO_2H were added to yield the bridged indoloazepines **36** and **37**, identified by TLC with R_f 0.4 (silica gel, 5:1 ethyl acetate/ethanol, CAS, blue), R_f 0.6 (silica gel, 5:1 ethyl acetate/ethanol, CAS, blue green). This reaction mixture containing the bridged azepines **36** and **37** was partitioned between 10 mL of 10% NaOH and 2 × 20 mL of dichloromethane, concentrated, and redissolved in 5 mL of tetrahydrofuran. After stirring for 24 h, filtration gave 0.146 g of the bridged azepine salts **38**: TLC R_f 0.0 (silica gel, 4:1 ethyl acetate/ethanol, CAS, blue); UV (ethanol) λ_{max} 228, 298, 330 nm. The salts **38** were dissolved in 5 mL of methanol and the mixture was heated at reflux for 2 h. The mixture was then cooled and partitioned between 5 mL of 10% NaOH and 2 × 10 mL of dichloromethane. The organic layer was concentrated and the residue crystallized from ethyl acetate to yield 0.098 g (7.3%) of 15-oxosecodine (**32**), for a total 15-oxosecodine yield of 15.8%. (Identical by UV, IR, and NMR with the product prepared above.)

Desethyl-15-oxovincadifformine (41). A mixture of 0.052 g (0.16 mmol) of the 15-oxoacrylate **32**, 2 drops of triethylamine, and 5 mL of toluene was refluxed for 22 h. The concentrated solution was adsorbed on 10 g of silica and eluted with ether to yield 0.039 g (75%) of 15-oxodexethylvincadifformine (**41**) as white crystals, crystallized from ether, mp 130–131 °C: TLC R_f 0.48 (silica gel, ether, CAS, blue), R_f 0.69 (silica gel, 4:1, ethyl acetate/ethanol); UV (ethanol) λ_{max} 328, 298, 327 nm; IR (KBr) ν_{max} 3382, 2944, 2808, 1699, 1674, 1606, 1479, 1466, 1433, 1232, 1184, 1115, 799, 753 cm^{-1}; 250-MHz NMR ($CDCl_3$) δ 9.03 (s, 1 H), 7.28–7.14 (m, 2 H), 6.94–6.82 (m, 2 H), 3.75 (s, 3 H), 3.40 (m, 2 H), 3.15–3.09 (m, 1 H), 3.61–3.87 (m, 3 H), 2.76–2.62 (m, 1 H), 2.56–2.43 (m, 2 H), 2.21–2.09 (m, 2 H), 1.98–1.91 (m, 1 H); direct exposure probe mass spectrum (70 eV), m/z (relative intensity) 325 (15), 324 (46), 293 (3), 229 (2), 215 (10), 214 (100), 182 (6), 180 (4), 167 (6), 154 (17), 139 (3), 127 (3), 11 (6), 110 (16). Anal. Calcd for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.21; N, 8.64. Found: C, 70.12; H, 6.49; N, 8.51.

Alternative Synthesis of 34. To a mixture of 0.500 g (2 mmol) of indoloazepine **14** and 30 mL of tetrahydrofuran at 25 °C was added 0.180 g (2 mmol) of pent-4-en-1-yn-3-one.[60] The mixture was stirred for 1 h. The mixture was then concentrated under vacuum and chromatographed on 10 g of silica gel. Elution with 5:1 ethyl acetate/ethanol yielded 0.18 g (35%) of the vinylogous amide **34** and 2 unidentified compounds; R_f 0.71, 0.21 (silica gel, 4:1 ethyl acetate/ethanol, CAS, blue-yellow and blue/green).

Dithioethylene Ketal of 15-Oxodesethylvincadifformine (42). A stirred mixture of 0.168 g (0.50 mmol) of 15-oxodesethylvincadifformine (**41**), 0.144 g (0.67 mmol) of zinc triflate,[62] 0.063 g (0.67 mmol) of ethanedithiol, and 20 mL of dichloroethane was heated at reflux for 48 h. The solution was cooled and partitioned between 10 mL of water and 3 × 10 mL of dichloromethane. The organic layer was concentrated under vacuum and chromatographed on 20 g of silica gel, eluting with ether, to yield 0.115 g (56%) of a white solid 15-ethylene dithioketal of desethylvincadifformine **42**: TLC R_f 0.6 (silica gel, ether, CAS, blue); UV (ethanol) λ_{max} 227, 298, 331 nm; IR ($CHCl_3$) ν_{max} 2945, 2922, 1795, 1675, 1640, 1609, 1477, 1464, 1434, 1313, 1296, 1279, 1254, 1235, 1189, 1176, 1119, 1105, 1043, 754, 610 cm^{-1}; 250-MHz NMR ($CDCl_3$) δ 8.90 (s, 1 H), 7.29–7.26 (m, 1 H), 7.18–7.11 (m, 1 H), 6.92–6.73 (m, 2 H), 3.77 (s, 3 H), 3.30–3.08 (m, 6 H), 2.96–2.90 (m, 1 H), 2.86–2.79 (m, 1 H), 2.78–2.55 (m 3 H), 2.40 (dt, J = 5, 12 Hz, 1 H), 2.06–2.97 (m, 2 H), 1.83–1.73 (m, 2 H); direct exposure probe mass spectrum (70 eV), m/z (relative intensity) 401 (7), 400 (M^+, 26), 228 (4), 225 (4), 214 (7), 199 (17), 186 (100), 168 (13), 167 (12), 154 (15), 126 (10), 119 (9), 80 (15), 57 (56), 50 (65).

Desethylvincadifformine (43). A mixture of 0.015 g (0.03 mmol) of the dithioethylene ketal of 15-oxodesethylvincadifformine, 0.100 g of Raney Ni (activity W-2), and 5 mL of ethanol was refluxed for 4 h, cooled, and filtered. The solids were washed with 2 mL of hot methanol and the filtrate concentrated under vacuum and adsorbed on 10 g of silica gel. Elution with ether yielded 8.0 mg (68%) of desethylvincadifformine (**43**) as a white foam. TLC, UV, NMR, and MS were identical with those of desethylvincadifformine **43** synthesized previously by this research group.[59]

Control Experiment for Dithioketalization of 41. A stirred mixture of 10 mg (0.03 mmol) of 15-oxodesethylvincadifformine (**41**) and 0.0072 g (0.033 mmol) of zinc triflate in 15 mL of dichloromethane was heated to reflux for 48 h. The solution was cooled and partitioned between 10 mL of water and 3 × 10 mL of dichloromethane. The organic layer was concentrated under vacuum, chromatographed on 10 g of silica gel, and eluted with ether to give 8.0 mg (80%) of recovered **41** with the same TLC, UV, and NMR data as an authentic sample.

Desethyl-15-((*tert*-butyldimethylsilyl)oxy)catharanthine (44) and 16-Carbomethoxydesethyl-15-oxo-20,21-didehydrocleavamine (45). To a mixture of 20 mL of dichloromethane and 1.0 g (3 mmol) of 15-oxosecodine **32** was added rapidly a solution of 3 mL of dichloromethane and 0.558 g (3.7 mmol) of *tert*-butyldimethylsilyl chloride, immediately followed by a solution of 0.610 g (4 mmol) of DBU in 3 mL of dichloromethane. The reaction mixture was stirred for 15 min, then concentrated, adsorbed on 30 g of silica gel, and eluted with ethyl acetate. Concentration and crystallization from ether yielded 0.38 g (28%) of 15-((*tert*-butyldimethylsilyl)oxy)desethylcatharanthine (**44**), mp 166.5–167 °C. Further elution with 5:1 ethyl acetate/ethanol yielded, upon concentration and crystallization from ethyl acetate, 0.365 g (36.6%) of 15-oxodesethylcleavamine (**45**), mp 269–271 °C. Data for **44**: TLC R_f 0.56 (silica gel, ethyl acetate, CAS,

(61) Groves, L.; Swan, G. *J. Chem. Soc.* **1952**, 650.
(62) Corey, E. J.; Shimoji, K. *Tetrahedron Lett.* **1983**, *24*, 169.
(63) Owen, G.; Reese, C. *J. Chem. Soc. C* **1970**, 2401.
(64) Jung, M.; McCombs, C.; Takeda, Y.; Guo Pan, Y. *J. Am. Chem. Soc.* **1981**, *103*, 6677.
(65) Kuehne, M. E.; Okuniewicz, F. J.; Kirkemo, C. L.; Bohnert, J. C. *J. Org. Chem.* **1982**, *47*, 1335.

orange); UV (ethanol) λ_{max} 229, 286, 293 nm; IR (KBr) ν_{max} 3361, 2956, 2928, 2910, 2855, 1710, 1637, 1616, 1482, 1460, 1437, 1376, 1352, 1281, 1258, 1227, 1150, 1082, 1008, 908, 839, 737 cm^{-1}; 250-MHz NMR ($CDCl_3$) δ 7.67 (s, 1 H), 7.49–7.45 (m, 1 H), 7.26–7.24 (m, 1 H), 7.17–7.08 (m, 2 H), 5.36 (dd, J = 3, 7 Hz, 1 H), 4.35 (d, J = 7 Hz, 1 H), 3.74 (s, 3 H), 3.63–3.12 (m, 4 H), 2.94–2.80 (m, 3 H), 2.53 (d, J = 2 Hz, 1 H), 1.81 (dd, J = 2, 13 Hz, 1 H), 0.93 (s, 9 H), 0.17 (s, 3 H), 0.14 (s, 3 H); direct exposure probe mass spectrum (70 eV), m/z (relative intensity) 439 (18), 438 (M^+, 62), 353 (5), 239 (5), 238 (18), 236 (100), 229 (9), 228 (11), 224 (9), 223 (31), 214 (8), 210 (14), 173 (7), 168 (22), 167 (10), 154 (13), 152 (45), 147 (11), 89 (14), 75 (3), 73 (54). Anal. Calcd for $C_{25}H_{34}O_3N_2Si$: C, 68.45; H, 7.81; N, 6.38. Found: C, 68.22; H, 7.89; N, 6.32.

Data for **45**: TLC R_f 0.4 (silica gel, 4:1 ethyl acetate/ethanol, CAS, blue-green); UV (ethanol) λ_{max} 227, 285, 294, 335 nm; IR (KBr) ν_{max} 3419, 3226, 2928, 1740, 1620, 1584, 1461, 1434, 1353, 1305, 1229, 1196, 1162, 746 cm^{-1}; 250-MHz NMR ($CDCl_3$) δ 8.74 (s, 1 H), 7.50 (d, J = 8 Hz, 1 H), 7.39–7.30 (m, 1 H), 7.25–7.11 (m, 9 lines, 3 H), 5.27 (d, J = 7 Hz, 1 H), 4.19–4.14 (m, 1 H), 3.66 (s, 3 H), 3.28–3.20 (m, 1 H), 3.08–2.86 (m, 4 H), 2.45–2.29 (m, 4 H); direct exposure probe mass spectrum (70 eV), m/z (relative intensity) 325 (25), 324 (M^+, 71), 265 (7), 229 (10), 214 (22), 169 (10), 154 (12), 129 (30), 123 (100), 115 (12), 114 (80), 113 (31), 85 (20), 84 (26), 83 (13), 82 (21), 72 (47). Anal. Calcd for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.20; N, 8.63. Found C, 70.14; H, 6.32; N, 8.44.

Alternative Method for 15-((*tert*-Butyldimethylsilyl)oxy)desethylcatharanthine (44) and 16-Carbomethoxydesethyl-15-oxo-20,21-didehydrocleavamine (45). To a mixture of 15 mL of dichloromethane and 0.618 g (1.9 mmol) of 15-oxosecodine (**32**) was added 0.554 g (0.48 mL, 2.09 mmol) of *tert*-butyldimethylsilyl triflate and then immediately a solution of 0.347 g (2.28 mmol) of DBU in 3 mL of dichloromethane. The mixture was stirred for 5 min, then poured into 2 mL of cold 10% NaOH, and extracted with 2 × 10 mL of CH_2Cl_2. Concentration, adsorption on 20 g of silica gel and elution with ethyl acetate yielded as crystals from ether, 0.225 g (27%) of 15-((*tert*-butyldimethylsilyl)oxy)desethylcatharanthine (**44**). The mp, UV, IR, and NMR spectra compared with the above data. Further elution with 5:1 ethyl acetate/ethanol yielded, as crystals from ethyl acetate, 0.289 g (45.5%) of 15-oxodesethylcleavamine (**45**) with mp, UV, IR, and NMR spectral data comparable to those given above.

Desethyl-15-oxo-15,20-dihydrocatharanthine (47). To a mixture of 3 mL of dichloromethane and 0.080 g (0.18 mmol) of the 15-(silyloxy)catharanthine **44** were added 5 drops of tetra-*n*-butylammonium fluoride as a 1 M solution in tetrahydrofuran. The reaction mixture was stirred for 5 min, then concentrated, adsorbed on 10 g of silica gel, and eluted with ethyl acetate to yield, as white crystals, from ether 0.054 g (91%) of 15-oxo-15,20-dihydrocatharanthine (**47**): mp 116–117 °C; TLC R_f 0.63 (silica gel, ethyl acetate, CAS, yellow-orange); UV (ethanol) λ_{max} 232, 286, 294 nm; IR (KBr) ν_{max} 3350, 2843, 1728, 1460, 1439, 1304, 1257, 1240, 1232, 1218, 1196, 1189, 1155, 1069, 1031, 743 cm^{-1}; 250-MHz NMR ($CDCl_3$) δ 7.85 (s, 1 H), 7.52–7.49 (m, 5 lines, 1 H), 7.30–7.10 (m, 3 H), 4.23 (d, J = 2 Hz, 1 H), 3.77 (s, 3 H), 3.56–3.48 (m, 1 H), 3.36–3.26 (m, 1 H), 3.25–3.15 (m, 2 H), 3.12–3.03 (m, 2 H), 2.95 (dt, J = 2, 14 Hz, 1 H), 2.67 (dd, J = 4, 19 Hz, 1 H), 2.54 (dd, J = 1, 2 Hz, 1 H), 2.27 (dd, J = 4, 15 Hz, 2 H); direct exposure probe mass spectrum (70 eV), m/z (relative intensity) 325 (19), 324 (M^+, 100), 265 (2), 229 (7), 214 (18), 169 (6), 167 (12), 154 (14), 123 (16), 55 (23). Anal. Calcd for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.21; N, 8.63. Found: C, 70.11; H, 6.29; N, 8.33.

15-Hydroxydesethyl-15,20-dihydrocatharanthine (48). To a mixture of 5 mL of tetrahydrofuran and 0.040 g (0.123 mmol) of 15-oxodesethylcatharanthine (**47**) at 0 °C was added 0.173 mL (0.172 mmol) of 1 M L-Selectride. The mixture was stirred for 10 min at 0 °C and then cooled to −78 °C and 2 mL of brine added. After warming to 25 °C the reaction mixture was extracted with 2 × 10 mL of dichloromethane. Concentration and adsorption on 10 g of silica gel, eluting with 4:1 ethyl acetate/ethanol, yielded as an amorphous foam 0.035 g (87%) of 15-hydroxydesethylcatharanthine (**48**): TLC R_f 0.23 (silica gel, 4:1 ethyl acetate/ethanol, CAS, blue green to grey); UV (ethanol) λ_{max} 234, 285, 293 nm; IR ($CHCl_3$) ν_{max} 3452, 3385, 3376, 3018, 2952, 2937, 2892, 2865, 1722, 1461, 1431, 1253, 1215, 1154, 1090 cm^{-1}; 250-MHz NMR ($CDCl_3$) δ 7.84 (s, 1 H), 7.47 (d, J = 7 Hz, 1 H), 7.26 (d, J = 7 Hz, 1 H), 7.19–7.07 (m, 6 lines, 2 H), 3.95–3.92 (m, 1 H), 3.87 (app d, J = 4 Hz, 1 H), 3.72 (s, 3 H), 3.49–3.41 (m, 1 H), 3.32 (dd, J = 3, 10 Hz, 1 H), 3.23–3.12 (m, 2 H), 3.06–2.95 (m, 1 H), 2.83 (d, J = 9 Hz, 1 H), 2.52 (d, J = 13 Hz, 1 H), 2.21 (br s, 1 H), 2.1–2.0 (m, 2 H), 1.98–1.86 (m, 2 H); direct exposure probe mass spectrum (70 eV), m/z (relative intensity) 327 (4), 326 (M^+, 14), 324 (3), 267 (4), 207 (4), 169 (4), 154 (4), 130 (4), 128 (5), 127 (3), 126 (2), 86 (100), 85 (3), 84 (4), 68 (6).

Desethyl-17-*tert*-butyl-16,17,15,20-tetrahydro-15-oxo-20,21-didehydrosecodine 46. To a mixture of 5 mL of tetrahydrofuran and 0.050 g (0.154 mmol) of the 15-oxosecodine **32** at −78 °C was added 0.065 mL (0.169 mmol) of 2.3 M *tert*-butyllithium in pentane. The reaction mixture was stirred for 10 min, then poured into 1 mL of brine, and partitioned with 2 × 10 mL of dichloromethane. Concentration, adsorbtion on 10 g of silica gel, and elution with 5:1 ethyl acetate/ethanol, yielded as an oil, 0.029 g (49%) of the *tert*-butyl adduct **46**: TLC R_f 0.51 (silica gel, 4:1 ethyl acetate/ethanol, CAS, blue green-grey); UV (ethanol) λ_{max} 230, 286, 293, 328 nm; IR ($CHCl_3$) (NaCl) ν_{max} 3341, 3267, 3196, 3006, 2958, 2867, 1730, 1628, 1591, 1584, 1459, 1437, 1366, 1348, 1238, 1215, 1179, 761 cm^{-1}; 250-MHz NMR ($CDCl_3$) δ 8.47 (s, 1 H), 7.47 (d, J = 7 Hz, 1 H), 7.34 (d, J = 8 Hz, 1 H), 7.21–7.07 (m, 2 H), 6.81 (d, J = 7 Hz, 1 H), 4.84 (d, J = 7 Hz, 1 H), 3.94 (dd, J = 4, 10 Hz, 1 H), 3.68 (s, 3 H), 3.62–3.42 (m, 4 H), 3.15–2.8 (m, 9 lines, 2 H), 2.44 (t, J = 8 Hz, 2 H), 2.27 (dd, J = 14, 10 Hz, 1 H), 1.62 (dd, J = 4, 14 Hz, 1 H), 0.93 (s, 9 H); direct exposure probe mass spectrum (70 eV), m/z (relative intensity) 383 (4), 382 (M^+, 14), 326 (4), 325 (4), 286 (4), 273 (33), 272 (84), 228 (12), 214 (8), 180 (11), 170 (22), 169 (13), 168 (19), 156 (55), 154 (12), 143 (6), 135 (9), 130 (7), 129 (7), 110 (42), 82 (40), 57 (100), 55 (22).

Desethyl-15,20-dihydro-15-oxosecodine (40). To a mixture of 10 mL of tetrahydrofuran, 1 g (4.09 mmol) of the indoloazepine **14**, and 0.529 g (0.71 mL, 4.09 mmol) of diisopropylethylamine was added 0.369 g (4,5 mmol) of divinyl ketone.[63,64] After stirring at 25 °C for 1 h, concentration under vacuum and adsorbtion on 20 g of silica gel, eluting with 4:1 ethyl acetate/ethanol, yielded as an amorphous foam 0.98 g (73%) of the saturated ketone acrylate **40**: UV (ethanol) 231, 294, (330) nm; IR ($CHCl_3$) ν_{max} 3433, 3416, 3019, 2953, 2909, 2813, 1717, 1678, 1609, 1468, 1288, 1216, 1155, 758 cm^{-1}; 250-MHz NMR ($CDCl_3$) δ 9.19 (s, 1 H), 7.66–7.59 (m, 1 H), 7.40–7.32 (m, 1 H), 7.28–7.09 (m, 2 H), 6.54 (s, 1 H), 6.15 (s, 1 H), 3.87 (s, 3 H), 3.16–3.06 (m, 2 H), 2.88–2.67 (m, 5 H), 2.60–2.40 (m, 4 H); direct exposure probe mass spectrum (70 eV), m/z (relative intensity) 327 (8), 326 (15), 244 (2), 228 (1), 215 (2), 214 (7), 168 (2), 167 (2), 154 (10), 128 (3), 127 (3), 113 (7), 112 (100), 84 (7). This compound slowly dimerizes to a presecamine type product, which gives rise to a 330-nm absorption.

Desethyl-15-thiono-20,21-didehydro-16α-carbomethoxycleavamine (45b). To a suspension of 96 mg (0.30 mmol) of oxocleavamine **45a** in 15 mL of dry dioxane was added 195 mg (0.439 mmol) of P_2S_5. The heterogeneous mixture was heated at reflux for 40 min and the resulting red solution was cooled to 20 °C. After addition of 15 mL of dichloromethane and 15 mL of 5% aqueous $KHCO_3$ solution, the mixture was stirred for 5 min and the layers were then separated. Extraction of the aqueous phase with 4 × 15 mL of dichloromethane and concentration of the dried ($NaHCO_3$) extracts gave an orange-red foam, which was chromatographed on 30 mL of silica gel (23 mm column). After dichloromethane (200 mL), elution with 5% methanol in dichloromethane and concentration afforded 85 mg (85%) of the thione **45b**, which could be recrystallized from cold acetone to mp 212–213 °C. Repeated reactions gave 80–92% yields.

45b: TLC (silica gel) ethyl acetate: R_f 0.67, 5% methanol in dichloromethane: R_f 0.40, without reagent yellow, with CAS green; UV (ethanol) λ_{max} 225, 285, 293 nm; IR (KBr) ν_{max} 3091, 2947, 2927, 1735, 1587, 1485, 1460, 1434, 1397, 1347, 1316, 1249, 1230, 1167, 1126, 1106, 747 cm^{-1}; 270-MHz NMR (acetone-d_6) δ 10.0 (br s, 1 H), 7.45 (d, J = 6 Hz, 1 H), 7.35 (d, J = 6 Hz, 1 H), 7.22 (d, J = 4.7 Hz, 1 H), 7.00 (dt, J = 6, 1 Hz, 1 H), 6.95 (dt, J = 6, 1 Hz, 1 H), 6.15 (d, J = 5 Hz, 1 H), 4.05 (d, J = 8 Hz, 1 H), 3.75 (dt, J = 9, 1 Hz, 1 H), 3.50 (t, J = 5 Hz, 1 H), 3.45 (s, 3 H), 3.20 (br d, J = 11 Hz, 1 H), 3.00–2.75 (m, 4 H), 2.60 (d, J = 11 Hz, 1 H), 2.30 (m, 1 H); direct insertion probe mass spectrum (70 eV), m/z (relative intensity) 340 (M^+, 57), 168 (10), 154 (20), 139 (100),

126 (11), 111 (32), 73 (34), 64 (39).

Desethyl-15-thiono-20,21-didehydro-16α-carbomethoxycleavamine Methiodide (51). A solution of 103 mg (0.300 mmol) of the thionocleavamine **45b** and 5 mL of methyl iodide in 10 mL of dichloromethane and 10 mL of benzene was stirred for 2 h, resulting in precipitation of a red methiodide and complete reaction of the thione (TLC). Concentration, trituration with ether, and drying for 30 min at 0.1 mm provided 145 mg (99%) of the unstable product, mp 170–175 °C: TLC (SiO_2, methanol–triethylamine) R_f 0.2 yellow, CAS, green; UV (ethanol) λ_{max} 228, 285, 293 nm; 270-MHz NMR ($CDCl_3$) δ 9.30 (br d, J = 3 Hz, 1 H), 9.05 (br s, 1 H), 7.50–7.40 (2d, J = 6 Hz, 2 H), 7.20 (t, J = 6 Hz, 1 H), 7.15 (t, J = 6 Hz, 1 H), 6.55 (d, J = 3 Hz, 1 H), 4.70 (m, 1 H), 3.90 (d, J = 8 Hz, 1 H), 3.80 (m, 1 H), 3.70 (s, 3 H), 3.45 (m, 1 H), 3.25–3.10 (m, 1 H), 3.70 (s, 3 H), 3.45 (m, 1 H), 3.25–3.10 (m, 3 H), 2.60 (s, 3 H), 2.50 (m, 3 H); direct insertion probe mass spectrum (70 eV), m/z (relative intensity) 354 (M^+ – HI, 9), 322 (5), 309 (13), 228 (4), 142 (100), 127 (65).

Desethyl-15-methoxycatharanthine (49b). A solution of desethyl-15-thiono-20,21-didehydro-16α-carbomethoxycleavamine methiodide (**51**, 20 mg, 0.04 mmol) and 0.5 mL of diisopropylethylamine in 4 mL of dry methanol was heated at reflux for 40 min. Cooling, concentration under vacuum, and preparative TLC on silica gel with ethyl acetate provided 9 mg of the enol ether **49b** (70%) (R_f 0.2) and 1.5 mg (10%) of the thioenol ether **49a**, R_f 0.3. For **49b**: UV (ethanol) λ_{max} 230, 285, 293 nm; 270-MHz NMR ($CDCl_3$) δ 7.70 (s, 1 H), 7.50 (d, J = 6 Hz, 1 H), 7.25 (d, J = 6 Hz, 1 H), 7.12 (t, J = 6 Hz, 1 H), 7.10 (t, J = 6 Hz, 1 H), 5.25 (dd, J = 6, 2 Hz, 1 H), 4.45 (br d, J = 6 Hz, 1 H), 3.85 (s, 3 H), 3.55 (s, 3 H), 3.40–2.80 (m, 7 H), 2.65 (br s, 1 H), 1.85 (dd, J = 11, 2 Hz, 1 H); direct insertion probe mass spectrum, m/z (relative intensity) 338 (M^+, 60), 214 (9), 168 (21), 154 (18), 137 (100), 123 (37), 109 (55), 95 (16), 83 (23). For **49a**, see below.

Desethyl-15-*S*-methylcatharanthine (49a), Desethyl-15-ethoxycatharanthine (49c), and Desethyl-15,20-didehydro-15-*S*-methylcleavamine (52). Repetition of the preceding reaction with 35 mg (0.073 mmol) of the methiodide in 8 mL of absolute ethanol and centrifugal chromatography of the product on silica gel with ethyl acetate provided 17 mg (66%) of the thioenol ether **49a** [TLC R_f 0.2 (CAS, blue-green)] and small amounts of the ethoxy compound **49c** [R_f 0.1 (CAS, violet)] and the reduction product **52** [R_f 0.6 (CAS pink)]. For **49a**: UV (ethanol) λ_{max} 230, 285, 293 nm; IR (film) ν_{max} 3383, 3364, 2945, 2919, 2877, 2847, 1728, 1494, 1460, 1434, 1343, 1272, 1255, 1229, 1086, 744 cm^{-1}; 270-MHz NMR ($CDCl_3$) δ 7.80 (s, 1 H), 7.40 (d, J = 6 Hz, 1 H), 7.15 (d, J = 6 Hz, 1 H), 7.10 (t, J = 6 Hz, 1 H), 7.05 (t, J = 6 Hz, 1 H), 6.00 (dd, J = 5, 1 Hz, 1 H), 4.42 (br d, $J \simeq$ 5 Hz, 1 H), 3.75 (s, 3 H), 3.65–2.80 (m, 7 H), 2.65 (br s, 1 H), 2.20 (s, 3 H), 1.85 (dd, J = 10, 1 Hz, 1 H); direct inlet probe mass spectrum, m/z (relative intensity) 354 (M^+, 38), 167 (12), 153 (30), 149 (25), 139 (17), 125 (33), 111 (15), 86 (49), 84 (96), 69 (73), 57 (89), 55 (100). The enol ether **49c** structure could be tentatively assigned by comparison of the NMR spectrum with that of the corresponding methoxy compound **49b** (above). A reduction product structure **52** was tentatively assigned to the third product on the basis of one olefin and one (C-16) NMR proton signal at δ 5.65 and 5.25[23] and a mass spectrum with m/z 357 (M^+ + 1, 100%) and 355 (M^+ – 1, 80%).

Desethylcatharanthine (50). Under argon, 300 mg of Raney nickel (50% in water at pH 10–11) was washed with 5 × 10 mL of distilled water and with 4 × 10 mL of acetone and then heated at reflux for 2 h with 15 mL of acetone. The liquid phase was withdrawn and the solid catalyst washed with 5 × 10 mL of methanol and then suspended in 10 mL of methanol. Addition of 10 mg of the thioenol ether **49a** in 1 mL of methanol and heating at reflux for 30 min resulted in complete conversion to desethylcatharanthine (**50**). A longer reaction time produced the corresponding dihydro product desethylcoronaridine (mass spectrum, NMR). For desethylcatharanthine (**50**): no real mp could be observed under a microscope for a sample crystallized from ethyl acetate. Decomposition started around 160 °C (see note under *dl*-catharanthine). Reported mp 155–160 °C.[33] TLC (SiO_2, diethyl ether–triethylamine) R_f 0.30; for the thioenol ether **49a** R_f 0.35; for desethylcoronaridine R_f 0.47. Direct insertion probe mass spectrum, m/z (relative intensity) 308 (M^+, 49), 229 (12), 214 (15), 170 (8), 168 (13), 167 (9), 154 (18), 124 (8), 108 (11), 107 (100), 94 (36), 93 (28), 85 (21), 79 (23), 77 (7), 67 (20), 65 (7), 59 (8), 57 (7), 55 (10). The product gave a 270-MHz NMR spectrum which matched a 90-MHz spectrum provided by Prof. R. J. Sundberg. It had the same TLC R_f value as a comparison sample from Virginia.[33]

Acknowledgment. This work was supported by Grant R01-12010 from the National Cancer Institute of the National Institutes of Health. We thank Timothy Spitzer, Patricia Matson, and Bruce Pitner of our group for mass spectra. A valuable comparison sample of desethylcatharanthine was kindly provided by Professor R. J. Sundberg.

Synthesis of the Disaccharide Moiety of Bleomycin. 2-*O*-(3-*O*-Carbamoyl-α-D-mannopyranosyl)-L-gulopyranose Derivatives

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Received January 14, 1986

The synthesis of the carbohydrate moiety of bleomycin [2-*O*-(3-*O*-carbamoyl-α-D-mannopyranosyl)-L-gulopyranose] is described. A key parameter in defining a successful strategy was the lability of the carbamoyl group. Several approaches were investigated; the most successful involved the coupling of 1,6-di-*O*-acetyl-3,4-di-*O*-benzyl-β-L-gulopyranose (**19**) and 2,4,6-tri-*O*-acetyl-3-*O*-carbamoyl-α-D-mannopyranosyl chloride (**17**) via the agency of silver trifluoromethanesulfonate and tetramethylurea. Also reported is the synthesis of 1,6-di-*O*-acetyl-3,4-di-*O*-benzyl-2-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl)-L-gulopyranose (**16**), a dissacharide useful for the synthetic elaboration of decarbamoyl bleomycin.

Our continuing interest in the synthesis of bleomycin group antibiotics[1] necessitated the synthesis of the carbohydrate moiety of bleomycin [2-*O*-(3-*O*-carbamoyl-α-D-mannopyranosyl)-L-gulopyranose (**1**)] on a preparative scale and in a form suitable for further elaboration. The successful synthesis of **1**[1b] required access to suitably blocked derivatives of L-gulose[2] and to activated 3-*O*-

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(1) (a) Minster, D. K.; Hecht, S. M. *J. Org. Chem.* **1978**, *43*, 3987. (b) Pozsgay, V.; Ohgi, T.; Hecht, S. M. *J. Org. Chem.* **1981**, *46*, 3761. (c) Aoyagi, Y.; Katano, K.; Suguna, H.; Primeau, J. L.; Chang, L.-H.; Hecht, S. M. *J. Am. Chem. Soc.* **1982**, *104*, 5537.

0022-3263/86/1951-2927$01.50/0