over $MgSO_4$. The solution was filtered and evaporated, and the residue was purified by flash chromatography on silica gel (10% MeOH–$CHCl_3$) to give **38** (63.3 mg, 75.4%) as an oil: R_f 0.23 (10% MeOH–$CHCl_3$); IR ($CHCl_3$) 3425, 3343, 2912, 1737, 1727, 1710, 1691, 1502 cm^{-1}; ^1H NMR (200 MHz, CD_3CN) δ 7.36 (5 H, s, CH_2Ph), 7.3–6.9 (8 H, m, aromatic Hs), 6.02 (1 H, br, $NHCOCH_2NH$), 5.50 (1 H, br, $NHCOCH_2NH$), 5.44 (1 H, d, J = 7.2 Hz, phenylglycine chiral center), 5.09 (2 H, s, CH_2Ph), 5.09 (1 H, br, NHBoc, overlapping with CH_2Ph), 4.35 (1 H, br, phenylalanine chiral center), 4.16 (2 H, m, $CO_2CH_2CH_3$), 3.79 (2 H, d, J = 6 Hz, $NHCOCH_2NH$), 3.16 (1 H, dd, J = 14 and 4 Hz, ArCHH), 2.94 (1 H, dd, J = 14 and 6 Hz, ArCHH), 1.37 (9 H, s, $C(CH_3)_3$), 1.17 (3 H, t, J = 7 Hz, $CO_2CH_2CH_3$). The optical rotation was not taken because of minor impurities found in both ^1H and ^{13}C NMR spectra, which were not removed by usual purification methods. FAB MS analysis did not give a molecular ion peak.

D-*N*-[(1,1-Dimethylethoxy)carbonyl]-*O*-[D-3-[1-[*N*-(2-aminoacetyl)amino]-2-oxo-2-ethoxyethyl]phenyl]tyrosine (39). To a stirred solution of 116.8 mg (0.18 mmol) of **38** in 2 mL of absolute ethanol were added 170.1 μL (1.8 mmol, 10 equiv) of 1,3-cyclohexadiene and 100 mg of 10% Pd–C. The mixture was refluxed overnight. The removal of the catalyst and solvent gave 68.5 mg of yellow powder. Attempted purification of a 10-mg sample by ether trituration resulted in deterioration of the compound. An ^1H NMR spectrum of the crude sample showed clear disappearance of the Cbz peak. **39**: R_f 0.09 (10% MeOH–$CHCl_3$); ^1H NMR (DMSO-d_6) δ 8.63 (1 H, br, NH), 8.17 (1 H, br, NH), 7.4–6.7 (8 H, m, aromatic Hs), 5.46 (1 H, br s, phenylglycine chiral center), 4.95 (1 H, br s, phenylalanine chiral center), 4.1–3.8 (4 H, m, $NHCOCH_2NH_2$ and $CO_2CH_2CH_3$), 1.3 (9 H, s, $C(CH_3)_3$), 1.2 (3 H, overlapping with impurities, $CO_2CH_2CH_3$).

Acknowledgment. We are grateful to the U.S. Public Health Service, National Institutes of Health, for financial support (GM 36925), and A. Russell, S. Yang, and Y. Chuang for carrying out preliminary experiments.

Supplementary Material Available: Experimental details for the preparation of compounds **25, 26, 28,** and **30,** together with physical and spectroscopic data, details of attempted macrolactamization of **39,** and proton NMR spectra of selected compounds (32 pages). Ordering information is given on any current masthead page.

A Common Intermediate Providing Syntheses of Ψ-Tabersonine, Coronaridine, Iboxyphylline, Ibophyllidine, Vinamidine, and Vinblastine

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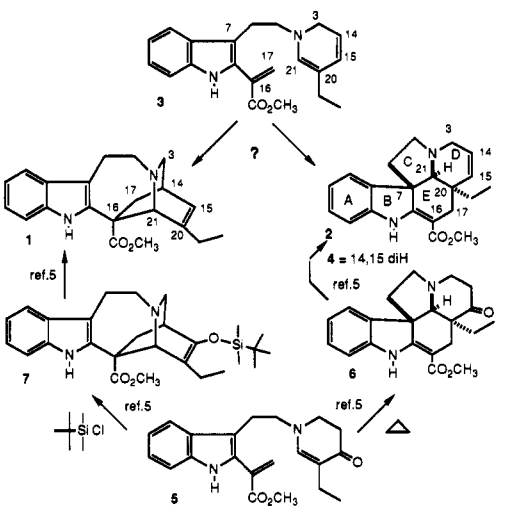
Generation of the key tetracyclic intermediates **14a,b** in six steps (42% overall) and subsequent short reduction, oxidation, and arylation sequences results in total syntheses of the title compounds **8, 9, 10, 11, 12,** and **13.**

The biogenetic postulate of derivation of catharanthine (**1**) and tabersonine (**2**) from the common precursor dehydrosecodine (**3**, Scheme I)[1,2] had provided the stimulus for our synthetic studies on intramolecular enamine–acrylate reactions, which led, with great efficacy, to pentacyclic aspidosperma alkaloids such as vincadifformine (**4**).[3] While the actual generation of catharanthine (**1**) and tabersonine (**2**) from dehydrosecodine (**3**) was never realized, in spite of widespread efforts,[4] we could nevertheless exploit the underlying concept of two alternative modes of (formal) intramolecular Diels–Alder reactions by use of a common oxosecodine intermediate (**5**), which provided, selectively, 15-oxovincadifformine (**6**) on heating or 15-(silyloxy)catharanthine **7** on O-silylation. Subsequent deoxygenation steps then gave the racemic alkaloids tabersonine (**2**) and catharanthine (**1**).[5] Intrigued by the possibility of other common precursors for a diversity of alkaloid structures, we developed a generalized synthetic strategy for members of the aspidosperma and iboga manifold and thus obtained as well Ψ-tabersonine (**8**, formerly Ψ-catharanthine), coronaridine (**9**), iboxyphylline (**10**), ibophyllidine (**11**), and the binary alkaloids vinamidine (**12**, formerly catharinine) and vinblastine (**13**) from a common tetracyclic intermediate "versatiline" (**14a,b**), generated as a mixture of C-20 epimers (Scheme II).

Scheme I



Our key intermediates **14a,b** were generated from methyl acrylate and the pyrrolidine enamine derivative of butyraldehyde (Scheme III). The initial monoalkylation product **15** was derivatized to an acetal (**16**) with ethylene glycol and that ester was then converted to the corre-

(1) Wenkert, E. *J. Am. Chem. Soc.* **1962**, *84*, 98.
(2) Scott, A. I. *Acc. Chem. Res.* **1970**, *3*, 151.
(3) (a) Kuehne, M. E.; Roland, D. M.; Hafter, R. *J. Org. Chem.* **1978**, *43*, 3705. (b) Kuehne, M. E.; Huebner, J. A.; Matsko, T. H. *J. Org. Chem.* **1979**, *44*, 2477.
(4) For a review, see footnote 5. For a summary of alternative syntheses of alkaloids described here, see footnote 16 and Overman, L. E.; Sworin, M. *Alkaloids: Chemical and Biological Perspectives*; New York, 1985; Vol. 3, p 275.
(5) Kuehne, M. E.; Bornmann, W. G.; Early, W. G.; Markó, I. *J. Org. Chem.* **1986**, *51*, 2913.

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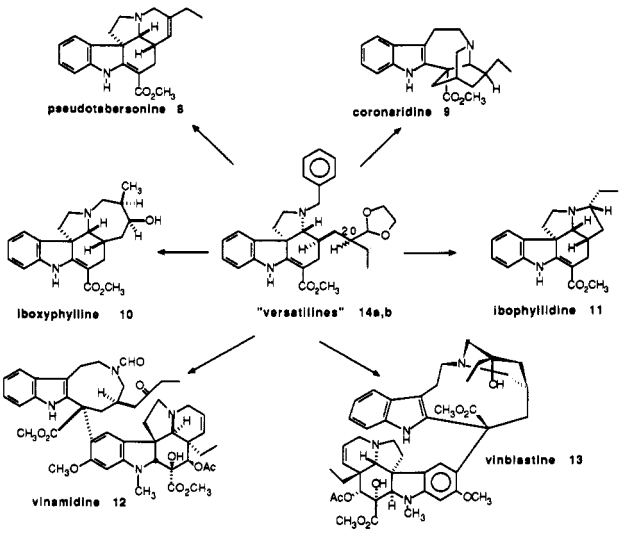
Scheme II



sponding aldehyde **17** by reduction with lithium aluminum hydride, followed by oxidation of the alcohol product with pyridinium chlorochromate. Condensation of the half-masked glutaraldehyde **17** with the indoloazepine **18**,[6] in methanol, provided a diastereomeric mixture of bridged azepines **19**. Without isolation, these amines were alkylated with benzyl bromide and the resulting quaternary salts then subjected to base-catalyzed fragmentation with triethylamine. Spontaneous cyclization of the transient enamine acrylate **20** provided the pivotal tetracyclic "versatiline" (**14a,b**). This product was formed (42% overall yield) with complete diastereoselectivity at the carbocyclic centers, presumably because of high selectivity for an *E*-enamine configuration in the intermediate **20** and its retention on cyclization. The chiral center on the chain at C-20 was, however, generated without selectivity. While the resulting two diastereomers of the "versatiline" (**14a,b**) product could be separated by low-pressure chromatography, this separation was not required for the overall syntheses since eventual generation of a trigonal C-20 carbon would eliminate this diastereomeric difference.

For syntheses of the isoquinuclidine alkaloids of the iboga family (Scheme IV), an initial cleavage of the C-3 to C-7 bond of the "versatiline" intermediates **14a,b** with sodium borohydride in acetic acid provided the indoloazonines **21a-1,21a-2** (3:1) and **21b-1,21b-2** (3:1) as C-14/C-16 diastereomers from the respective C-20 epimeric precursors **14a,b**. Molecular modeling calculations gave an energy difference of 1.8 kcal/mol for the C-14/C-16 trans/cis isomers.[7] Each major diastereomer **21a-1** and **21-b1** showed the hydrogen at C-16 shifted downfield (at δ 5.6) due to its interaction with the N^b lone pair, in analogy to a corresponding observation with 16-(methoxycarbonyl)cleavamines.[8a,9]

Debenzylation by hydrogenolysis and hydrolysis of the acetal function provided, by cyclization, a common enamine (**22**) from each of the indoloazonines **21a-1,21a-2, 21b-1, 21b-2**. While the C-16 ^{1}H NMR signal for this compound was not informative, reduction of the enamine function with sodium borohydride furnished our previously synthesized C-20 epimeric 16-(methoxycarbonyl)cleavamines **23a,b** with C-16 ^{1}H NMR signals at δ 5.08/5.53,[9] thus establishing the relative stereochemistry at C-16 and C-14 in the compounds **21**, **22**, and **23a,b**.

On storage under vacuum for several days, the crude, dry enamine **22** was quantitatively (and stereoselectively!) converted to racemic coronaridine (**9**). It may be noted that oxidation of a carbomethoxycleavamine (**23**) with mercuric acetate had already been shown to yield coronaridine (**9**, 10%) and its C-20 epimer (9%), as well as a Ψ-vincadifformine (**28**, 24%), by a nonregioselective and nonstereoselective generation of analogous imonium intermediates.[10] Finally, the racemic coronaridine (**9**) was decarbomethoxylated to ibogamine (**24**) in 98% yield.[11]

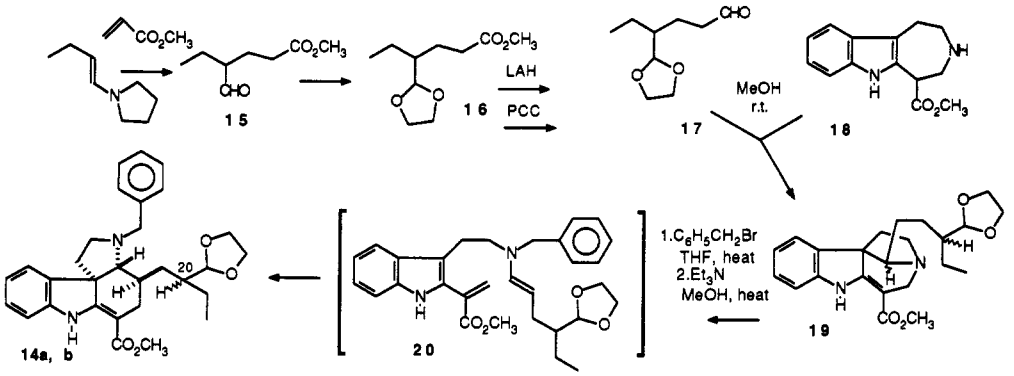
For a synthesis of Ψ-tabersonine (Ψ-catharanthine, **8**) the "versatiline" (**14a,b**) intermediates were subjected to debenzylation by hydrogenolysis, followed by hydrolytic deprotection of the acetal function in the secondary amines **25a,b** (Scheme V). The resulting enamine **26** was seen to have preserved the trans stereochemistry at the D/E ring juncture because, on reduction of the enamine function by hydrogenation in acetic acid, two C-20 epimeric *D/E-trans*-Ψ-vincadifformines (**27a,b**) were obtained. These products did not correspond to the D/E-cis compounds Ψ-vicadifformine **28a** and 20-epi-Ψ-vincadifformine **28b**, which we had synthesized earlier,[8a] but they matched our D/E-trans products.[9]

However, when the D/E-trans enamine **26** was subjected to oxidation with dibenzoyl peroxide, followed by reduction with sodium borohydride, *D/E-cis*-Ψ-tabersonine (**8**) was obtained. Apparently, initial formation of an α,β-unsaturated imonium salt, and its equilibration with an unsaturated enamine (**29**), provides epimerization at C-14. Catalytic hydrogenation of racemic Ψ-tabersonine (**8**) then resulted in formation of Ψ-vincadifformine (**28a**) in accord with reduction of the enantiomer derived from catharanthine.[8b-d] The $\Delta^{15,20}$ position of the double bond in the synthetic product **8** (rather than $\Delta^{14,15}$) follows from its identity with the dehydration product of the 20-hydroxy compound, racemic pandoline.[8a,12]

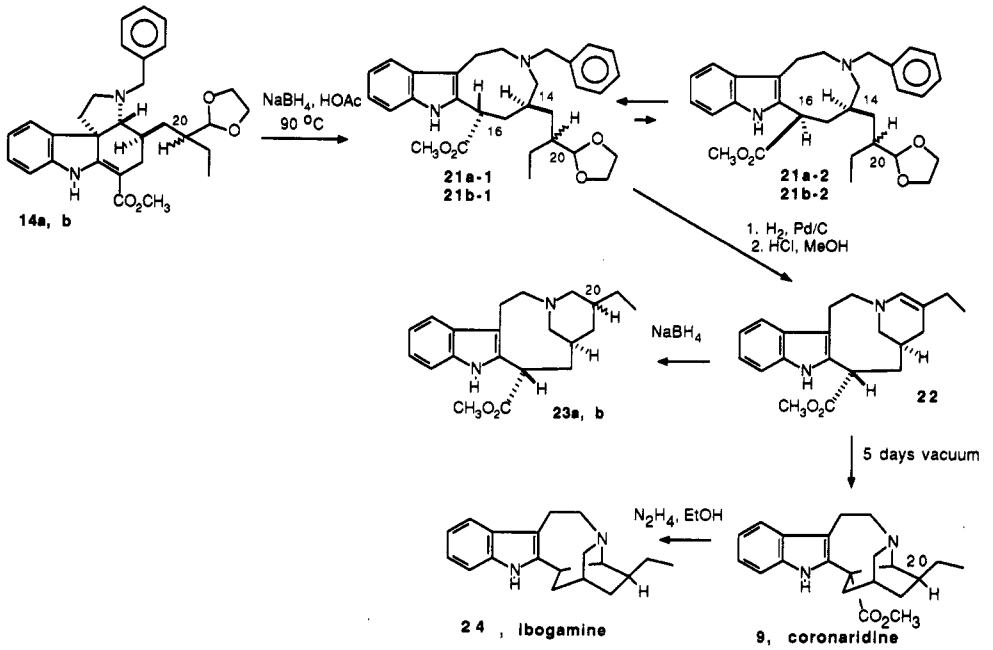
The D/E-trans enamine **26** also gave access to the D-homo and D-nor aspidosperma alkaloids iboxyphylline (**10**) and ibophyllidine (**11**) through an initial photochemical oxidative cleavage of the enamine function, with formation of the formamide ketone **30** (Scheme VI). Methanolysis of its formamide function, with cyclization and hydrogenation, provided an alternative to our previous synthesis of ibophillidine (**11**).[13] Alternatively, conversion to a ketal, followed by methanolysis, gave new access to the amino ketal **31**, which on condensation with formaldehyde, hydrolysis and reduction, had been taken to iboxyphylline (**10**).[14] In these syntheses the D/E cis stereochemistry is obtained before cyclization by acid-catalyzed, reversible, rupture of the C-3 to C-7 bond (which is not possible with a preformed D/E trans-fused 5-, 6-, or 7-membered ring D,[14,15] i.e., enamine **26**).

(6) Kuehne, M. E.; Bohnert, J. C.; Bornmann, W. G.; Kirkemo, C. L.; Kuehne, S. E.; Seaton, P. J.; Zebovitz, T. C. *J. Org. Chem.* **1985**, *50*, 919.
(7) Calculations with the MACROMODEL computer program which was kindly provided by Prof. Clark Still.
(8) (a) Kuehne, M. E.; Kirkemo, C. L.; Matsko, T. H.; Bohnert, J. C. *J. Org. Chem.* **1980**, *45*, 3259. Hydrogenation of Ψ-tabersonine (**8**), derived from catheranthine, was reported and the product Ψ-vincadifformine ascribed structures **28a** and **28b**. (b) Kutney, J. P.; Brown, R. T.; Piers, E.; Hadfield, J. R. *J. Am. Chem. Soc.* **1970**, *92*, 1708. (c) Brown, R. T.; Hill, J. S.; Smith, G. F.; Stapleford, K. J. S. *Tetrahedron* **1971**, *27*, 5217. (d) LeMen, J.; Caron-Sigaut, C.; Hugel, G.; LeMen-Olivier, L.; Lévy, J. *Helv. Chim. Acta* **1978**, *61*, 566.
(9) Kuehne, M. E.; Bornmann, W. G. *J. Org. Chem.* **1989**, *54*, 3407.
(10) Kutney, J. P.; Brown, R. T.; Piers, E.; Hadfield, J. R. *J. Am. Chem. Soc.* **1970**, *92*, 1708.
(11) Renner, U.; Prins, D. A.; Stoll, W. G. *Helv. Chim. Acta* **1959**, *42*, 1572.
(12) Hoizey, M.-J.; Sigaut, C.; Jacquier, M. J.; LeMen-Olivier, L.; Lévy, J.; LeMen, J. *Tetrahedron Lett.* **1974**, *17*, 1601.
(13) Kuehne, M. E.; Bohnert, J. C. *J. Org. Chem.* **1981**, *46*, 3443.
(14) Kuehne, M. E.; Pitner, B. J. *J. Org. Chem.* **1989**, *54*, 4553.
(15) Kuehne, M. E.; Zebovitz, T. C. *J. Org. Chem.* **1987**, *52*, 4331.

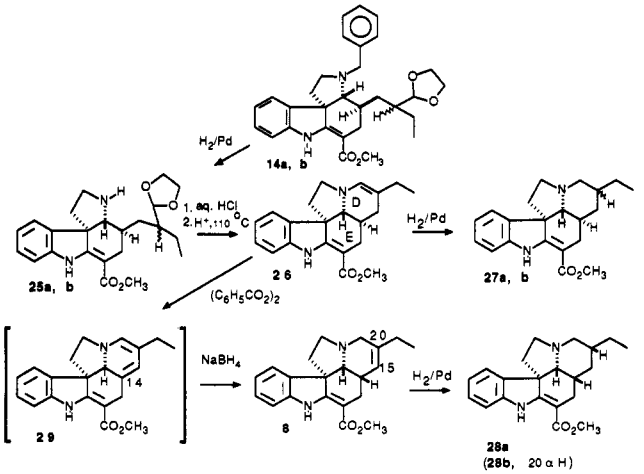
Scheme III



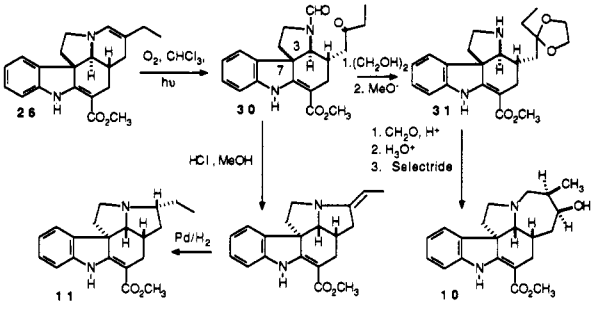
Scheme IV



Scheme V



Scheme VI



The pivotal "versatiline" (**14a,b**) intermediates even proved to be useful for syntheses of binary alkaloids (Scheme VII).[16] On chlorination of **14a** with *tert*-butyl hypochlorite and treatment of the resulting chloro imine with vindoline (**32**) hydrochloride and silver tetrafluoroborate, followed by reduction of the resulting arylated imines **33** and **34** (and the C16′ epimeric minor products) with potassium borohydride in acetic acid, the vindolinylazonines **35** and **36** were generated with the now expected C-14′/C-16′ *parf* stereoselectivity.[9,17,18] It should be noted, however, that in contrast to the exclusive formation of C-14′/C-16′ *parf*[19] coupling products that were formed in our laboratory on generation of about 100 VLB congeners, the present coupling reaction repeatedly produced about 10% of the undesired C-14′/16′ *pref*[19] products **35a** and

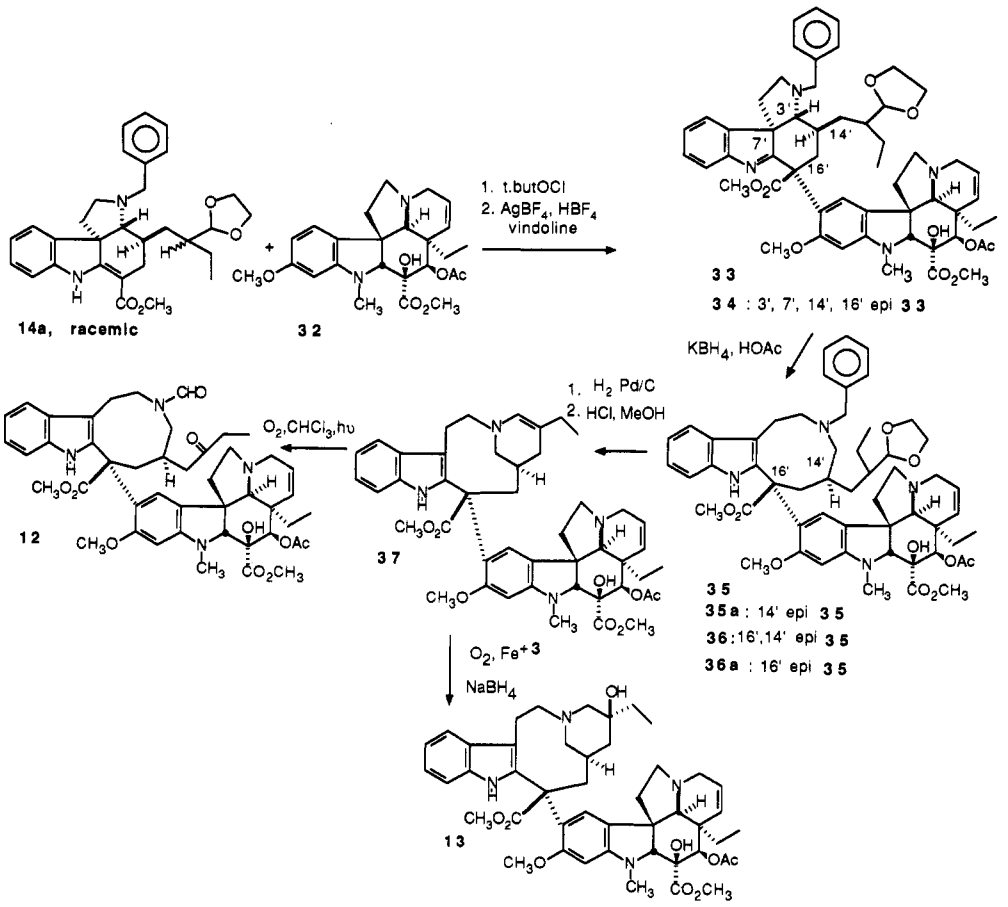
(16) For a review of alternative syntheses, see: (a) Kuehne, M. E.; Markó, I. *Syntheses of Vinblastine-Type Alkaloids, The Alkaloids*; Academic Press: New York, 1990; Vol. 37, p 77. (b) Magnus, P.; Stamford, A.; Ladlow, M. *J. Am. Chem. Soc.* **1990**, *112*, 8210.

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

(18) Kuehne, M. E.; Matson, P. A.; Bornmann, W. G. *J. Org. Chem.* **1991**, *56*, 513.

(19) Carey, A. F.; Kuehne, M. E. *J. Org. Chem.* **1982**, *47*, 3811.

Scheme VII



36a[20] in addition to **35** and **36**. Debenzylation and acetal hydrolysis of the azonine **35** then provided, through cyclization, the enamine **37** (previously obtained by oxidation of the corresponding dihydro compound[21,22]).

The photochemical oxygenation of enamine **37** resulted in formation of vinamidine (catharinine, **12**),[23,24] while its oxygenation in the presence of ferric ion, and a following reduction with sodium borohydride,[25] led to vinblastine (**13**). Although the stereoselective coupling of the racemic "versatiline" intermediates (**14a,b**) with vindoline (**32**) and subsequent formation of the enamine **37** gave good yields, oxidation of this penultimate intermediate to vinblastine (**13**) is not yet sufficiently productive to make this synthesis competitive (even if a nonracemic "versatiline" intermediate is considered) with our previously reported total synthesis of vinblastine (22% overall yield).[18] Oxidation of the enamine **37** with thallium triacetate was even less productive in our hands.[21,22]

Experimental Section

For standard methodology, see ref 18. Anhydrous $MgSO_4$ was used for drying of extract solutions. IR and MS data for all compounds are included in the supplementary material.

Methyl 4-(1,3-Dioxolan-2-yl)hexanoate (16). A mixture of 30.24 g (0.1912 mol) of the aldehyde **15**,[26] 200 mL of dry benzene, 60 mg of *p*-toluenesulfonic acid monohydrate, and 11.86 g (0.1912 mol) of ethylene glycol was purged with argon for 1 h and the clear, colorless reaction mixture was then heated at reflux, with vigorous stirring, for 24 h. During this time 3.4 mL of water was collected in a Dean–Stark trap. After the orange-colored reaction mixture was allowed to cool to room temperature, the benzene was removed at 40 °C under reduced pressure with a rotary evaporator to leave a dark red liquid. This was then taken up into 300 mL of dichloromethane and washed with one 100-mL portion of saturated sodium bicarbonate solution and one 100-mL portion of saturated sodium chloride, dried, filtered, washing the salts with 40 mL of dry dichloromethane, and concentrated at 40 °C under vacuum to a deep red liquid, which was then distilled under vacuum (0.4 mm) to give 32.11 g of a colorless liquid: bp 83–84 °C (83% yield); 250-MHz ^1H NMR ($CDCl_3$) δ 0.94 (t, J = 7 Hz, 3 H), 1.35 (septet, J = 7 Hz, 1 H), 1.45–1.60 (m, 2 H), 1.62–1.87 (m, 2 H), 2.41 (t, J = 7 Hz, 2 H), 3.66 (s, 3 H), 3.80–3.86 (m, 2 H), 3.89–3.97 (m, 2 H), 4.76 (d, J = 4 Hz, 1 H); 62.9-MHz ^{13}C NMR ($CDCl_3$) δ 11.41, 22.17, 23.79, 32.08, 42.43, 51.41, 64.81, 64.96, 106.50, 174.29. Anal. Calcd for $C_{10}H_{18}O_4$: C, 59.39; H, 8.97. Found: C, 59.54; H, 8.73.

4-(1,3-Dioxolan-2-yl)-1-hexanol. With stirring 128 mL of a 1 M solution of lithium aluminum hydride (0.128 mol) in tetrahydrofuran (THF) was added dropwise, over 1 h, at 0 °C, to a solution of 25.6 g (0.127 mol) of the acetal ester **16** in 100 mL of dry THF under an atmosphere of argon. The mixture was then heated at reflux for 5 h and cooled to 0 °C, and 5 mL of water in 25 mL of THF was added dropwise with rapid stirring. Over 1 h, 5 mL of 15% aqueous sodium hydroxide was then added at 0 °C, followed by 15 mL of water. The mixture was then filtered and the solids were washed with 300 mL of ether. Concentrating the filtrate at 42 °C under vacuum, solution of the concentrate in 400 mL of ether, washing with 100 mL of 5% aqueous sodium hydroxide and 100 mL of saturated brine, drying, concentration at 42 °C, and distillation at 85 °C (0.4 mm) gave 19.0 g (86% yield)

(20) This stereochemical assignment was based on ^1H NMR chemical shift values of C19 (vindolinyl ethyl), which is found characteristically upfield for **35a** in the set of four diastereomers of **35**.[17]

(21) Atta-ur-Rahman, Pakistani Patent 126852, 1978.

(22) Mangeney, P.; Andriamialisoa, R. Z.; Langlois, N.; Langlois, Y.; Potier, P. *J. Am. Chem. Soc.* **1979**, *101*, 2243.

(23) Andriamialisoa, R. Z.; Langlois, N.; Potier, P.; Chiaroni, A.; Riche, C. *Tetrahedron* **1978**, *34*, 677.

(24) Kutney, J. P.; Choi, L. S. L.; Nakano, J.; Hiroki, T. *Heterocycles* **1988**, *27*, 1837.

(25) Kutney, J. P.; Choi, L. S. L.; Nakano, J.; Tsukamoto, H.; McHugh, M.; Boulet, C. A. *Heterocycles* **1988**, *27*, 1845.

(26) Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovicz, J.; Terrell, R. *J. Am. Chem. Soc.* **1963**, *85*, 207.

of the alcohol: 250-MHz ^{1}H NMR ($CDCl_3$) δ 0.93 (t, J = 7 Hz, 3 H), 1.29–1.44 (m, 2 H), 1.46–1.67 (m, 5 H), 3.13 (t, J = 5 Hz, 1 H), 3.59 (q, J = 6 Hz, 2 H), 3.81–3.88 (m, 2 H), 3.90–3.98 (m, 2 H), 4.77 (d, J = 4 Hz, 1 H), 62.9-MHz ^{13}C NMR ($CDCl_3$) δ 11.44, 22.08, 24.58, 30.34, 42.67, 62.87, 64.86, 106.65.

4-(1,3-Dioxolan-2-yl)hexanal (17). To 35.26 g (0.1636 mol) of pyridinium chlorochromate, 2.683 g (0.0327 mol) of sodium acetate, and 200 mL of dichloromethane, stirred vigorously with a mechanical paddle stirrer, was added 19.0 g (0.109 mol) of 4-(1,3-dioxolan-yl)-1-hexanol in 50 mL of dry dichloromethane, resulting in an exothermic reaction and reflux of the solvent. The mixture was then stirred at room temperature for 3 h, when TLC indicated complete consumption of the starting alcohol. Addition of 100 g of silica gel and 200 mL of ether, placement of this slurry onto a 4- × 20-cm dry column of silica gel, and elution with ether (3 L) gave, after concentration at 42 °C, under vacuum, a crude product. This was dissolved in 200 mL of dichloromethane and washed with 2 × 200 mL of 10% copper sulfate, followed by 200 mL of saturated brine. The dried solution was concentrated and distilled at 81 °C (0.5 mm) to give 16.1 g (86%) of the aldehyde 17: 250-MHz ^{1}H NMR ($CDCl_3$) δ 0.94 (t, J = 7 Hz, 3 H), 1.36 (septet, J = 7 Hz, 1 H), 1.46–1.62 (m, 2 H), 1.64–1.87 (m, 2 H), 2.54 (td, J = 8, 2 Hz, 2 H), 3.80–3.89 (m, 2 H), 3.90–3.98 (m, 2 H), 4.76 (d, J = 4 Hz, 1 H), 9.76 (t, J = 2 Hz, 1 H); 62.9-MHz ^{13}C NMR ($CDCl_3$) δ 11.38, 20.76, 22.28, 41.87, 42.38, 64.78, 64.90, 106.40, 202.68.

Methyl (3a*RS*,4*SR*)-3-Benzyl-2,3,3a,4,5,7-hexahydro-4-[2-ξ-(1,3-dioxolan-2-yl)-1-butyl]-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylates (14a,b). A mixture of 2.00 g (8.19 mmol) of the indoloazepine **18**, 1.41 g (8.19 mmol) of the aldehyde **17**, and 50 mL of dry methanol was stirred for 24 h under argon at room temperature. The solution was then concentrated at 42 °C under vacuum, diluted with 20 mL of dichloromethane, and adsorbed onto 50 g of silica gel. The slurry was placed on a 4- × 30-cm dry column of silica gel and eluted with ethyl acetate. Collection of 50-mL fractions gave methyl 11α/β-[4-ξ-(1,3-dioxolan-2-yl)-1-hexyl]-1,2,4,6-tetrahydro-3,10b-methanoazepino-[4,5-*b*]indole-5-carboxylates (**19**) with the 11β-isomer (TLC R_f 0.91, silica gel, EtOAc) in fractions 8–21 and the 11α-isomer (TLC R_f 0.36, silica gel, EtOAc) in fractions 42–79. The product fractions were combined and concentrated under vacuum at 42 °C. The concentrate was dissolved in 100 mL of dichloromethane, dried, and reconcentrated. Addition of 100 mL of dry toluene and evaporation at 42 °C (10 mm) and room temperature (0.05 mm) produced 2.74 g of a colorless foam (84% yield), which was used directly in the following N-benzylation step.

To the combined bridged indoloazepine epimers **19** (1.36 g, 3.41 mmol) in 100 mL of anhydrous ether was added 0.58 g (0.40 mL, 3.41 mmol) of benzyl bromide. The mixture was heated at reflux for 72 h with stirring under argon. Filtration and washing of the quaternary salts with 3 × 100 mL of ether and drying under vacuum (0.05 mm) gave 1.90 g (98%) of N-benzylated products.

A mixture of 1.5 g (2.63 mmol) of the quaternary salts, 50 mL of dry methanol, and 0.73 mL (0.53 g, 5.4 mmol) of triethylamine was heated at reflux for 8 h under argon. The cooled mixture was then poured into 200 mL of 1 N ammonium hydroxide in saturated brine and extracted with 3 × 100 mL of dichloromethane. The dried extracts were concentrated under vacuum at 42 °C and the resulting foam was dissolved in 10 mL of a 9:1 mixture of (ether/hexane 1:1):triethylamine and subjected to low-pressure liquid chromatography (Altex, 25-mm × 100-cm and 25-mm × 50-cm silica gel (200–400 mesh) columns in series, equilibrated with 1:1 ether/hexane, and eluted with 1:1 ether/hexane). After 925 mL, collection of 20-mL fractions at a flow rate of 11 mL/min (38–40 psi) gave the C20 epimeric acetals **14a,b** in fractions 6–21 and 28–51, respectively. Concentration at 42 °C and drying at 0.05 mm gave 0.46 g and 0.59 g (81% combined yield) of the respective product fractions. For the less polar product: TLC (SiO_2) R_f 0.33 (1:1 ether/hexane), 0.47 (9:1 [1:1 ether/hexane]:triethylamine), 0.48 (1:4 ethyl acetate/pentane), CAS blue with yellow center, becomes purple with yellow center; 250-MHz ^{1}H NMR in $CDCl_3$ (H assignments by C number) δ (18) 0.75 (t, J = 7 Hz, 3 H), (15α/15β) 0.84–0.93 (m, 2 H), (19α or -β) 1.04 (m, J = 7, 19 Hz, 1 H), (20/19α or -β) 1.36–1.52 (m, 2 H), (6β) 1.66 (dd, J = 12, 4 Hz, 1 H), (14/6α) 1.97–2.11, (m, 2 H), (17β) 2.54, (dd, J = 15, 3 Hz, 1 H), (5β) 2.58–2.66 (m, 1 H), (17α) 2.70 (d, J = 15 Hz, 1 H), (5α) 2.90 (dd, J = 9, 6 Hz, 1 H), (3) 2.97 (s, 1 H), (ethylenedioxy and benzyl) 3.58–3.89 (m, 5 H), (CO_2CH_3) 3.75 (s, 3 H), (benzyl) 4.13 (d, J = 13 Hz, 1 H), (21) 4.65 (d, J = 3 Hz, 1 H), (12) 6.81 (d, J = 8 Hz, 1 H), (10) 6.83 (td, J = 7, 0.9 Hz, 1 H), (9) 6.98 (d, J = 7 Hz, 1 H), (11) 7.13 (td, J = 8, 1 Hz, 1 H), (phenyl) 7.25–7.43 (m, 5 H), (NH) 9.02 (s, 1 H); 62.9-MHz ^{13}C NMR in $CDCl_3$ (C assignment) δ 11.80 (18), 22.56 (15), 23.12 (19), 30.19 (17), 37.38 (14), 40.90 (20), 42.49 (6), 50.59 (5), 50.84 (OMe), 55.14 (7), 55.12 (benzyl), 64.66 (ethylenedioxy), 64.96 (ethylenedioxy), 72.17 (3), 90.78 (16), 106.71 (21), 109.13 (12), 120.45 (10), 122.30 (9), 127.00 (11), 127.65 (Ph), 128.32 (Ph), 128.95 (Ph), 138.15 (Ph), 139.35 (8), 143.09 (13), 165.62 (2), 169.20 (CO_2Me); UV (abs EtOH) λ_{max} 214, 227, 301, 332 nm; HRMS M+ calcd 488.26751, found 488.26785.

For the more polar epimer: TLC (SiO_2) R_f 0.30 (1:1 ether/hexane), 0.40 (9:1 [1:1 ether/hexane]:Et_3N), 0.44 (1:4 EtOAc/pentane), blue with yellow center; 250-MHz ^{1}H NMR in $CDCl_3$ (H assignment by C number) δ (18) 0.72 (t, J = 7 Hz, 3 H), (15α or -β) 0.69–0.79 (m, 1 H), (15α or -β) 1.01–1.13 (m, 1 H), (19α or -β) 1.14–1.30 (m, 1 H), (19α or -β) 1.33–1.43 (m, 1 H), (20) 1.53–1.46 (m, 1 H), (6β) 1.67 (dd, J = 12, 4 Hz, 1 H), (14/6α) 1.97–2.09 (m, 2 H), (17β) 2.52 (dd, J = 15, 3 Hz, 1 H), (17α, 5β) 2.58–2.69 (m, 2 H), (5α) 2.91 (dd, J = 9, 6 Hz, 1H), (3) 2.94 (s, 1 H), (ethylenedioxy, benzyl) 3.69–3.85 (m, 5 H), (CO_2Me) 3.76 (s, 3 H), (benzyl) 4.13 (d, J = 13 Hz, 1 H), (21) 4.62 (d, J = 4 Hz, 1 H), (12) 6.79 (d, J = 8 Hz, 1 H), (10) 6.81 (td, J = 8, 1 Hz, 1 H), (9) 6.95 (d, J = 7 Hz, 1 H), (11) 7.12 (td, J = 8, 1 Hz, 1 H), (phenyl) 7.25–7.42 (m, 5 H), (NH) 8.97 (s, 1 H); 62.9-MHz ^{13}C NMR in $CDCl_3$ (C number) δ 11.42 (18), 22.05 (15), 22.60 (19), 29.74 (17), 36.82 (14), 40.25 (20), 42.38 (6), 50.63 (5), 50.87 (Me), 53.40 (7), 55.13 (benzyl), 64.75 (ethylenedioxy), 64.84 (ethylenedioxy), 72.05 (3), 90.89 (16), 106.92 (21), 109.16 (12), 120.44 (10), 122.21 (9), 127.04 (11), 127.71 (Ph), 128.33 (Ph), 128.97 (Ph), 138.00 (Ph), 139.24 (8), 143.15 (13), 165.31 (2), 169.20 (CO_2Me); UV (ethanol) λ_{max} 214, 228 (sh), 301, 330 nm; HRMS M+ calcd 488.26751, found 488.26799.

Methyl 3-Benzyl-1,2,3,4,5,6,7,8-octahydro-5β-[2-ξ-(1,3-dioxolan-2-yl)-1-butyl]azonino[6,7-*b*]indole-7α- and -β-carboxylates (21a-1, 21a-2 and 21b-1, 21b-2). A solution of 2.258 g (4.608 mmol) of the less polar isomer **14a** in 25 mL of acetic acid was heated at 90 °C and 1.049 g (27.72 mmol) of sodium borohydride was added in portions over 5 min. The mixture was then poured onto 100 mL of crushed ice and 100 mL of concentrated ammonium hydroxide was added. The mixture was extracted with 3 × 100 mL of dichloromethane and the combined, dried extracts were concentrated at 42 °C under vacuum and dried at 0.05 mm. The crude reduction product was dissolved in dichloromethane and subjected to centrifugal chromatography on a 4-mm silica gel plate, eluting with 1:2 ether/hexane. Collection of 2 mL/min fractions gave, in fractions 11–39, the major diasteromer **21a-1**, and, in fractions 55–83, the minor diastereomer (**21a-2**) of the C16 epimeric esters. Rechromatography of the major isomer **21a-1**, eluting the centrifugal plate with dichloromethane, provided 1.399 g of product and chromatography of the minor isomers **21a-2** with ether/hexane, 1:2, gave 0.485 g of product (combined yield 83%).

For **21a-1**: TLC (SiO_2, ether/hexane 1:1) R_f 0.83; UV (EtOH) λ_{max} 203, 225, 278, 284, 292 nm; ^{1}H NMR in $CDCl_3$ δ 0.69 (t, J = 7 Hz, 3), 0.85–0.99 (m, 1 H), 1.01–1.12 (m, 2 H), 1.23–1.38 (m, 3 H), 1.44–1.55 (m, 1 H), 2.01 (t, J = 13 Hz, 1 H), 2.29–2.32 (m, 2H), 2.46–2.36 (m, 1 H), 2.57–2.68 (m, 1 H), 2.80–2.91 (m, 2 H), 3.29–3.44 (m, 4 H), 3.63 (d, J = 13 Hz, 1 H), 3.76 (s, 3 H) 3.83 (d, J = 13 Hz, 1 H), 4.33 (d, J = 4 Hz, 1H), 5.58 (dd, J = 12, 5 Hz, 1 H), 7.01 (td, J = 7, 1 Hz, 1 H), 7.08 (td, J = 7 Hz, 1 H), 7.21–7.44 (m, 7 H), 8.70 (s, NH, 1 H); ^{13}C NMR in $CDCl_3$ δ 11.50, 22.98, 26.15, 34.77, 36.14, 39.93, 40.03, 40.55, 52.09, 52.64, 60.01, 61.08, 64.77, 64.84, 106.46, 110.64, 111.71, 118.11, 119.03, 121.56, 126.71, 127.90, 128.21, 128.64, 134.09, 136.03, 140.46, 175.34. Anal. Calcd for $C_{30}H_{38}N_2O_4$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.36; H, 8.04; N, 5.63.

For 21a-2: TLC (SiO_2, ether/hexane 1:1) R_f 0.40; UV (EtOH) λ_{max} 203, 225, 276, 284, 290 nm; ^{1}H NMR ($CDCl_3$) δ 0.89 (t, J = 7 Hz, 3 H), 0.94–1.02 (m, 1 H), 1.13–1.22 (m, 1 H), 1.31 (sept, J = 7 Hz, 1 H), 1.48 (sept, J = 7 Hz, 1 H), 1.51–1.62 (m, 1 H), 1.81–1.92 (m, 2 H), 2.28–2.38 (m, 4 H), 2.65–2.86 (m, 3 H), 3.35 (d, J = 14 Hz, 1 H), 3.73 (s, 3 H), 3.73–3.87 (m, 5 H), 4.71 (d, J

= 4 Hz, 1 H), 5.11 (d, J = 8 Hz, 1 H), 7.03 (td, J = 7 Hz, 1 H), 7.12 (td, J = 7 Hz, 1 Hz, 1 H), 7.19–7.41 (m, 7 H), 8.62 (s, NH, 1 H); ^{13}C NMR ($CDCl_3$) δ 11.10, 22.80, 25.05, 31.17, 33.09, 40.05, 41.65, 51.92, 56.14, 62.46, 63.22, 64.30, 64.42, 106.31, 110.54, 114.29, 117.66, 118.75, 121.14, 126.85, 128.05, 128.18, 129.40, 131.76, 135.83, 139.81, 175.90. Anal. Calcd for $C_{30}H_{38}N_2O_4$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.39; H, 8.12; N, 5.67.

Following the same procedure with the more polar diastereomer **14b**, the C16 epimeric esters **21b-1** and **21b-2** were obtained in analogous ratio in 88% combined yield.

For **21b-1**: TLC (SiO_2, ether/hexane 1:1) R_f 0.80; UV (EtOH) λ_{max} 205, 225, 276, 283, 292 nm; ^{1}H NMR ($CDCl_3$) δ 0.62 (t, J = 7 Hz, 3 H), 0.81–1.27 (m, 5 H), 1.40–1.58 (m, 2 H), 1.94–1.84 (t, J = 13 Hz, 1 H), 2.26 (t, J = 11 Hz, 1 H), 2.36–2.68 (m, 3 H), 2.81–2.90 (m, 2 H), 3.36–3.53 (m, 4 H), 3.63 (d, J = 13 Hz, 1 H), 3.76 (s, 3 H), 3.84 (d, J = 13 Hz, 1 H), 4.51 (d, J = 3 Hz, 1 H), 5.58 (dd, J = 12 Hz, 1 H), 7.02 (td, J = 7, 1 Hz, 1 H), 7.09 (td, J = 6, 1 Hz, 1 H), 7.22–7.45 (m, 7 H), 8.71 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 11.27, 23.07, 25.06, 31.02, 32.91, 39.94, 40.61, 41.74, 51.89, 56.03, 62.05, 63.27, 64.28, 64.53, 106.60, 110.51, 114.36, 117.65, 118.79, 121.21, 126.84, 127.99, 128.17, 129.38, 131.84, 135.80, 139.83, 175.88. Anal. Calcd for $C_{30}H_{38}N_2O_4$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.34; H, 8.04; N, 5.63.

For **21b-2**: TLC (SiO_2, ether/hexane 1:1) R_f 0.29; UV (EtOH) λ_{max} 203, 225, 278, 284, 292 nm; ^{1}H NMR ($CDCl_3$) δ 0.86 (t, J = 7 Hz, 3 H), 0.91–1.02 (m, 1 H), 1.14–1.33 (m, 2 H), 1.40–1.48 (m, 1 H), 1.56–1.60 (m, 1 H), 1.80–1.89 (m, 2 H), 1.98–2.01 (m, 1 H), 2.27–2.35 (m, 4 H), 2.67–2.80 (m, 3 H), 3.33 (d, J = 14 Hz, 1 H), 3.74 (s, 3 H), 3.78–3.90 (m, 5 H), 4.73 (d, J = 4 Hz, 1 H), 5.14 (d, J = 9 Hz, 1 H), 7.05 (td, J = 7, 1 Hz, 1 H), 7.14 (td, J = 7, 1 Hz, 1 H), 7.24–7.43 (m, 7 H), 8.60 (d, 1 H); ^{13}C NMR δ 11.29, 22.49, 26.21, 34.80, 35.79, 39.99, 39.56, 40.45, 52.09, 52.72, 60.53, 61.14, 64.76, 64.91, 106.74, 110.67, 111.70, 118.11, 119.04, 121.57, 126.73, 127.88, 128.22, 128.71, 134.15, 136.03, 140.47, 170.34. Anal. Calcd for $C_{30}H_{38}N_2O_4$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.36; H, 8.04; N, 5.64.

Methyl 1,2,3,4,5,6,7,8-Octahydro-5β-[2-ξ-(1,3-dioxolan-2-yl)-1-butyl]azonino[6,7-*b*]indole-7α-carboxylates. A solution of 1.100 g (2.243 mmol) of the major indoloazonine C16 epimer (**21a-1**) in 25 mL of acetic acid and 0.412 g of 10% Pd/C was subjected to hydrogenation at atmospheric pressure for 4.5 h. Filtration through a 1- × 4-cm Celite 454 plug, washing with 10 mL of acetic acid, and addition to 100 g of crushed ice and 100 mL of concentrated ammonium hydroxide was followed by extraction with 3 × 100 mL of dichloromethane. Concentration of the dried extracts at 42 °C, under vacuum, and centrifugal chromatography on a 4-mm silica gel plate, eluting with 5% methanol in dichloromethane and collecting 2 mL/min fractions, gave 0.815 g (91% yield) of secondary amine from fractions 6–31, after drying at 0.05 mm.

The same product was obtained by hydrogenolysis and spontaneous C16 epimerization from the minor epimer **21a-2**: TLC (SiO_2, 5% MeOH in CH_2Cl_2) R_f 0.32; UV (EtOH) λ_{max} 203, 224, 276, 284, 291 nm; ^{1}H NMR ($CDCl_3$) δ 0.72 (t, 7 Hz, 3 H), 0.93–1.15 (m, 4 H), 1.26–1.43 (m, 2 H), 1.66–1.77 (m, 2 H), 2.11 (t, J = 12 Hz, 1 H), 2.22 (t, J = 12 Hz, 1 H), 2.48 (t, J = 12 Hz, 1 H), 2.65–2.73 (m, 2 H), 2.92 (dd, J = 14, 3 Hz, 1 H), 3.32–3.48 (m, 5 H), 3.72 (s, 3 H), 4.34 (d, J = 4 Hz, 1 H), 5.46 (dd, J = 12, 5 Hz, 1 H), 7.03 (td, J = 7 Hz, 1 Hz, 1 H), 7.09 (td, J = 7, 2 Hz, 1 H), 7.29 (dd, J = 7, 1 Hz, 1 H), 7.47 (d, J = 8 Hz, 1 H), 8.67 (s, NH, 1 H); ^{13}C NMR ($CDCl_3$) δ 11.13, 22.78, 27.52, 31.62, 39.74, 40.27, 41.81, 49.65, 51.81, 57.27, 64.48, 64.36, 106.37, 110.56, 114.18, 117.75, 118.81, 121.23, 128.05, 132.04, 135.98, 175.79; HRMS M+ calcd 400.2362, found 400.2364.

Analogously, debenzylation of the other C20′ diastereomers **21b-1** and **21b-2** provided 89% yields of the secondary amine corresponding to **21b-1** from centrifugal chromatography fractions 11–50: TLC (silica gel, 5% MeOH in CH_2Cl_2) R_f 0.29; UV (EtOH) λ_{max} 203, 223, 276, 284, 291 nm; ^{1}H NMR δ 0.63 (t, J = 7 Hz, 3 H), 0.83–1.09 (m, 3 H), 1.11–1.23 (m, 2 H), 1.39–1.48 (m, 1 H), 1.68–1.79 (m, 2 H), 2.23 (t, J = 12 Hz, 1 H), 2.01 (t, J = 12 Hz, 1 H), 2.46 (t, J = 12 Hz, 1 H), 2.61–2.72 (m, 2 H), 2.92 (dd, J = 3, 14 Hz, 1 H), 3.36 (dt, J = 3, 14 Hz, 1 H), 3.43–3.58 (m, 4 H), 3.73 (s, 3 H), 4.53 (d, J = 4 Hz, 1 H), 5.45 (dd, J = 5, 12 Hz, 1 H), 7.04 (td, J = 1, 6 Hz, 1 H), 7.16 (td, J = 1, 6 Hz, 1 H), 7.29 (d, J = 7 Hz, 1 H), 7.48 (d, J = 7 Hz, 1 H), 8.67 (s, 1 H); ^{13}C NMR δ 11.23, 22.94, 27.56, 31.64, 33.22, 46.16, 40.32, 41.95, 49.60, 51.74, 57.04, 64.37, 64.59, 106.79, 110.53, 114.26, 117.75, 118.87, 121.30, 128.08, 132.15, 136.04, 175.70; HRMS M+ calcd 400.2362, found 400.2356.

16-(Methoxycarbonyl)-Δ^{20}-cleavamine (22). To a solution of 0.200 g (0.499 mmol) of debenzyl aminoacetal **21a-1** in 10 mL of methanol, rapidly stirred at room temperature, was added 10 mL of 1 N aqueous HCl. After 2 h the starting material had been consumed (TLC). The mixture was cooled to 0 °C and basified with 10% ammonium hydroxide in saturated brine. The mixture was extracted with three 25-mL portions of dichloromethane. The dried extracts were concentrated under vacuum at 42 °C and dried at 0.005 mm to give 0.175 g (98%) of the title product: UV (EtOH) λ_{max} 225, 275, 282, 292 nm; ^{1}H NMR ($CDCl_3$) δ 0.83–1.08 (m, 2 H), 1.05 (t, J = 7 Hz, 3 H), 1.72 (d, J = 17 Hz, 1H), 1.97–2.15 (m, 5 H), 2.38–2.56 (m, 3 H), 2.59–2.82 (m, 2 H), 2.86–2.90 (m, 1 H), 3.16–3.33 (m, 2 H), 3.66 (s, 3 H), 4.52 (d, J = 10 Hz, 1 H), 5.88 (s, 1 H), 7.08 (tt, J = 7, 1 Hz, 1 H), 7.15 (tt, J = 7, 1 Hz, 1 H), 7.32 (d, J = 8 Hz, 1 H), 7.49 (d, J = 7 Hz, 1 H), 8.60 (s, NH); ^{13}C NMR ($CDCl_3$) δ 13.82, 25.58, 28.11, 29.04, 32.30, 39.84, 41.83, 49.34, 51.81, 52.69, 107.16, 110.69, 117.92, 119.00, 121.59, 127.54, 127.84, 133.95, 136.21, 175.57.

Reductions of Enamine 22. a. A sample of the crude enamine **22**, obtained from 80 mg (0.20 mmol) of the amino acetal **21a-1** by the above procedure, was dissolved in 15 mL of methanol and warmed to 45 °C. Over 5 min, 75 mg (10 equiv) of $NaBH_4$ was added and the reaction mixture was then poured onto crushed ice and basified with NH_4OH. Extraction with 3 × 20 mL of dichloromethane and concentration of the dried extracts was followed by flash chromatography on silica gel, eluting with 3:2 ether/hexane. The product (30 mg, 44%) gave a TLC with R_f 0.53 (silica gel, 3:2 ether/hexane, CAS green-grey). An NMR spectrum indicated a 5:1 mixture of C14,20 cis:trans hydrogens (δ 5.1:5.5) and only the C14,16 *pref* products.[9]

b. A solution of 0.030 g (0.089mmol) of the enamine **22** in 10 mL of freshly distilled MeOH was cooled to 0 °C and 15 mg of 10% Pd/C was added. After allowing the mixture to warm to room temperature, it was subjected to hydrogenation at atmospheric pressure. When there was no further uptake of hydrogen, the mixture was filtered with methanol washes. The filtrate was concentrated to a foam, for which TLC (ether:hexane, 3:2) and NMR indicated only the C14,20 cis H product formed in **a**.

Coronaridine (9). The crude enamine **22** (0.175 g) was dissolved in 25 mL of chloroform, and, after 20 min, the solution was concentrated under vacuum and the residue stored at 0.005 mm. After 1 week (TLC monitoring) the enamine had been converted to coronaridine. The crude product was dissolved in 20 mL of dichloromethane, washed with 10 mL of 10% ammonium hydroxide in saturated brine, dried, and concentrated. Centrifugal chromatography on 2 mm of silica, eluting with 1:1 hexane/ether, provided 0.169 g (95% yield) of product from fractions 19–61. The racemic coronaridine (**9**) was matched with a sample of the natural alkaloid in TLC (R_f 0.73, silica gel, 2% MeOH in CH_2Cl_2), NMR, and mass spectra. Anal. Calcd for $C_{21}H_{26}N_2O_2$: C, 74.96; H, 7.19; N, 8.33. Found: C, 75.03; H, 7.24; N, 8.24.

Ibogamine (24).[11] A solution of 0.200 g (0.561 mmol) of racemic coronaridine (**9**) and 10 mL of hydrazine hydrate in 10 mL of ethanol was heated at reflux for 116 h, when TLC indicated completion of the decarbomethoxylation. The reaction mixture was poured into saturated brine at 0 °C and extracted with 3 × 25 mL of dichloromethane. The extracts were dried and concentrated under vacuum, and the residue was subjected to centrifugal chromatography on silica gel, eluting with 2% methanol in dichloromethane, to give 0.153 g (92% yield) of crystalline racemic ibogamine (TLC R_f 0.62, 20% MeOH in CH_2Cl_2), which matched an authentic sample, obtained previously by an alternative synthesis,[27] in mp, NMR, and MS. Anal. Calcd for $C_{19}H_{24}N_2$: C, 81.37; H, 8.63; N, 10.00. Found: C, 81.23; H, 8.93; N, 9.80.

***D*/*E*-*trans*-20,21-Didehydro-Ψ-vincadifformine (26).** Debenzylation of the "versatiline" intermediates **14a,b** by hydrogenolysis according to the procedure given for the cleavamine **21a-1** provided the secondary amines **25a** and **25b**. HRMS: M+

(27) Kuehne, M. E.; Reider, P. J. *J. Org. Chem.* **1985**, *50*, 1464.

calcd 398.22056, found 398.22079 (**25a**), 398.21982 (**25b**).

A solution of 0.200 g (0.502 mmol) of the acetal **25a** in 15 mL of methanol and 10 mL of 1 N HCl was stirred at room temperature, under argon for about 1 h, when TLC showed absence of the starting material. The mixture was made basic by addition of ice and cold 10% ammonium hydroxide in saturated brine. Extraction with 3 × 50 mL of dichloromethane, drying, and concentration of the extracts at 42 °C under vacuum gave a crude product, which was subjected to centrifugal chromatography on silica gel. Elution with 2% methanol in dichloromethane provided a product, which was recrystallized from methanol: mp 139–141 °C, 0.654 g (98% yield).

The same product was obtained with the same yield from the acetal **25b**: TLC R_f 0.61 (SiO_2, 5% MeOH in CH_2Cl_2); UV (EtOH) λ_{max} 202, 205, 293, 326 nm; 250-MHz ^1H NMR ($CDCl_3$) δ 0.95 (t, J = 7 Hz, 3 H), 1.67 (dd, J = 7, 12 Hz, 1 H), 1.76–2.01 (m, 6 H), 2.39 (q, J = 11 Hz, 1 H), 2.74 (dd, J = 16, 5 Hz, 1 H), 2.90–3.01 (m, 2 H), 2.47 (ddd, J = 10, 7 Hz, 1 H), 3.67 (s, 3 H), 5.91 (s, 1 H), 6.70 (d, J = 8 Hz, 1 H), 6.76 (td, J = 7, 1 Hz, 1 H), 7.04 (td, J = 7, 1 Hz), 7.29 (d, J = 7 Hz, 1 H), 8.95 (br s, 1 H); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 13.06, 28.00, 29.68, 30.78, 32.77, 40.33, 49.76, 50.95, 55.29, 62.29, 94.58, 109.18, 118.67, 120.52, 122.94, 127.77, 129.17, 136.39, 144.20, 163.52, 168.80. Anal. Calcd for $C_{21}H_{24}N_2O_2$: C, 74.96; H, 7.19; N, 8.33. Found: C, 75.03; H, 7.24; N, 8.24.

***D/E-trans*-Ψ- and -20-*epi*-Ψ-Vincadifformine (27a,b).** Hydrogenation of 0.100 g (0.097 mmol) of the enamine **26** in 10 mL of dry acetic acid with 50 mg of 10% Pd/C catalyst at 1 atm of hydrogen was stopped when 7.8 mL (1 equiv) of hydrogen was consumed. Filtration, addition of the filtrate to 100 g of crushed ice, addition of 40 mL of concd ammonium hydroxide, extraction with 5 × 50 mL of dichloromethane, and concentration of the dried extracts provided a product mixture, which was subjected to centrifugal chromatography on silica gel. Elution with 1:1 ether/hexane gave 40 mg of *D/E-trans*-Ψ-vincadifformine (**27a**) and 36 mg of its C-20 epimer **27b**. The products were matched by TLC, ^1H NMR, IR, and mass spectra with authentic samples obtained by an alternative synthesis.[9]

Ψ-Tabersonine (8). To 0.100 g (0.298 mmol) of the enamine **26** in 10 mL of freshly distilled dichloromethane was added 0.072 g (0.298 mmol) of benzoyl peroxide, in 1 mL of dichloromethane, over a 2-min period. The deep red solution was stirred at 20 °C for 15 min and the solvent was then evaporated at 24 °C under vacuum. The residual oil was dissolved in 10 mL of methanol and 50 mg of sodium borohydride was added. The resulting pale orange solution was stirred for 15 min and then poured into 50 mL of 10% ammonium hydroxide in saturated brine. Three extractions with 50 mL of dichloromethane and concentration of the dried extracts under vacuum gave an oily residue, which was subjected to centrifugal chromatography on silica gel. Elution with 0.5% methanol in dichloromethane gave 12 mg (12%) of the title product: TLC R_f 0.57 (SiO_2, 5% MeOH in CH_2Cl_2); UV (EtOH) λ_{max} 203, 223, 297, 325 nm; 250-MHz ^1H NMR ($CDCl_3$) δ 1.06 (t, J = 7 Hz, 3 H), 1.61 (m, 1 H), 1.78 (m, 1 H), 1.90 (dd, J = 12, 4 Hz 1 H), 2.01–2.20 (m, 3 H), 2.68 (dd, J = 15, 3 Hz, 1 H), 2.77 (ddd, J = 14, 9, 5 Hz, 1 H), 3.03 (d, J = 11 Hz, 1 H), 3.03 (s, 1 H), 3.27 (d, J = 16 Hz, 1 H), 3.37 (d, J = 15 Hz, 1 H), 3.77 (s, 3 H), 5.51 (d, J = 4 Hz, 1 H), 6.81 (d, J = 8 Hz, 1 H), 6.88 (t, J = 8 Hz, 1 H), 7.15 (t, J = 8 Hz, 1 H), 7.30 (d, J = 7 Hz, 1 H), 8.98 (s, NH). The IR, MS, and NMR spectra of this product matched those of Ψ-tabersonine obtained by dehydration of pandoline.[8a,12] HRMS: M+ calcd 336.18376, found 336.18375.

Ψ-Vincadifformine (28a). A mixture of 5 mg of Ψ-tabersonine (**8**) and 3 mg of 10% Pd/C in 2 mL of freshly distilled ethyl acetate was prepared at 0 °C and then stirred at room temperature for 5 h under an atmosphere of hydrogen. Filtration, rinsing of the catalyst with 5 mL of ethyl acetate, and concentration at 42 °C under vacuum, followed by drying for 24 h under high vacuum, gave 4.7 mg (93% yield) of **28a**. An NMR spectrum matched that of a sample previously obtained by alternative syntheses.[8a,9]

Methyl (3a*SR*,4*SR*)-3-Formyl-2,3,3a,4,5,7-hexahydro-4-(2-oxobut-1-yl)-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate (30). At 0 °C, a stirred solution of 0.300 g (0.893 mmol) of the enamine **26** in 50 mL of dichloromethane was irradiated with a Sylvania 275-W sunlamp and oxygen was bubbled through for about 1 h (consumption of **26** seen by TLC). Concentration under vacuum and centrifugal chromatography on a 4-mm silica gel plate, eluted with 2.5% methanol in dichloromethane, and concentration, gave 0.301 g (91%) of the formamide **30**: TLC R_f 0.61 (5% MeOH in CH_2Cl_2); UV (ethanol) λ_{max} 205, 221, 296, 327 nm; 250-MHz ^1H NMR ($CDCl_3$) δ [0.98 (t, J = 7 Hz) and 1.01 (t, J = 7 Hz), 3 H], 1.95–1.96 (m, 1 H), 2.24–2.51 (m, 4 H), 2.53–2.62 (m, 4 H), 3.65–3.88 (m, 2 H), [3.79 (s) and 3.74 (s), 3 H], 3.88 (s, 1 H), 6.89 (d, J = 7 Hz, 1 H), 6.90 (td, J = 7 Hz, 1 H), 7.06 (d, J = 7 Hz, 1 H), 7.21 (td, J = 8, 1 Hz, 1 H), [8.87 (s) and 8.43, 2:1, 1 H], 9.04 (br s, 1 H), 67.9-MHz ^{13}C NMR δ 209.53, 168.34, 162.34, 161.35 (161.27), 143.46 (143.15), 135.55 (135.29), 128.67, 121.73, 121.48 (121.20), 109.63, 91.12 (91.86), 64.95 (63.13), 54.87, 50.97 (50.89), 45.58, 42.13 (44.07), 37.97 (38.25), 37.01, 36.35 (36.21), 25.48 (25.00), 7.59 (7.69).

Ibophyllidine (11). A solution of 0.200 g (0.543 mmol) of the formamide **30** in 15 mL of methanol and 10 mL of 1 N HCl was stirred at 24 °C for 36 h. Addition of 50 mL of ice-cold 10% sodium hydroxide in saturated brine, extraction with 3 × 50 mL of dichloromethane, and concentration of the dried extract under vacuum at 42 °C provided a crude enamine (0.181 g, 98%). This was dissolved in 20 mL of acetic acid and subjected to hydrogenation (1 atm H_2) with 100 mg of 10% Pd/C catalyst. After 2 h the reaction vessel was flushed with nitrogen and the mixture filtered through Celite. The filtrate was poured onto 100 g of ice, made basic with 50 mL of concentrated ammonium hydroxide, and extracted with 3 × 75 mL of dichloromethane. The dried extracts were concentrated and the residue was subjected to centrifugal chromatography. Elution with 10% methanol in dichloromethane and concentration provided 0.151 g (87%) of ibophyllidine (**11**), which could be matched spectroscopically with an authentic sample.[13] **11**: TLC R_f 0.48 (SiO_2, 10% MeOH in CH_2Cl_2); UV (EtOH) λ max 204, 224, 298, 327 nm; 250–MHz ^1H NMR ($CDCl_3$) δ 1.04 (t, J = 7 Hz, 3 H), 1.24–1.36 (m, 1 H), 1.48–1.65 (m, 1 H), 1.82 (dd, J = 11, 15 Hz, 1 H), 1.83–2.34 (m, 5 H), 2.80 (m, 1 H), 3.08–3.34 (m, 3 H), 3.57 (d, J = 8 Hz, 1 H), 3.76 (s, 3 H), 6.81 (d, J = 8 Hz, 1 H), 6.93 (td, J = 7 Hz, 1 H), 7.15 (td, J = 8 Hz, 1 H), 7.56 (d, J = 7 Hz, 1 H), 9.13 (s, NH); 67.9-MHz ^{13}C NMR δ 12.36, 25.50, 31.76, 35.05, 37.67, 41.30, 47.49, 50.86, 55.89, 75.46, 92.08, 108.77, 121.39, 123.31, 127.74, 138.41, 164.81, 168.60. The product matched an authentic sample prepared by an alternative route in all of these spectra.[13]

Methyl (3a*SR*,4*SR*)-2,3,3a,4,5,7-Hexahydro-4-[(2-ethyl-1,3-dioxolan-2-yl)methyl]-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate (31). A solution of 0.099 g (0.27 mmol) of the formamide ketone **30**, 0.018 g (0.29 mmol) of ethylene glycol, and a catalytic amount of boron trifluoride etherate in 15 mL of dry benzene was heated at reflux with a Dean–Stark trap filled with 4A molecular sieves until TLC indicated complete consumption of the ketone. The mixture was washed with 25 mL of 10% ammonium hydroxide in brine, dried, and concentrated under vacuum. The residual oil was dissolved in 20 mL of dry methanol, which contained a catalytic amount of sodium methoxide. The solution was heated at reflux for 2 h and then concentrated under vaccum. The residue was partitioned between 25 mL of dichloromethane and 30 mL of water, the aqueous layer was extracted with 3 × 15 mL of dichloromethane, and the combined organic solutions were then concentrated under vacuum. Centrifugal chromatography on a 2-mm silica gel plate, eluting with 5% methanol in dichloromethane, gave 0.063 g of product, which matched by TLC a sample recently prepared by an alternative route.[14]

(7*S*,5*R*)- and (7*R*,5*S*)-Methyl 3-Benzyl-1,2,3,4,5,6,7,8-octahydro-5-[2-ξ-(1,3-dioxolan-2-yl)but-1-yl]-7-(15-vindolinyl)azonino[5,4-*b*]indole-7-carboxylate (35 and 36) and Their C5 Epimers 35a and 36a. To 0.79 g (1.6 mmol) of the less polar acetal **14a** in 100 mL of dichloromethane was added 0.25 mL (0.18 g, 1.8 mmol) of triethylamine. The solution was cooled to 0 °C and 0.21 mL (0.19 g, 1.78 mmol) of *tert*-butylhypochlorite was added. After 30 min at 0 °C the mixture was poured into 100 mL of ice-cold water and extracted with 3 × 50 mL of dichloromethane. The dried extracts were concentrated at 42 °C under vacuum to give 0.84 g of crude chloroindolenines.

From an analogous preparation, 1.723 g (2.554 mmol) of the chloroindolenines and 1.259 g (2.554 mmol) of vindoline hydrochloride were dissolved in 10 mL of dry acetone. Addition of 1.924 g (9.885 mmol) of silver tetrafluoroborate in 4 mL of dry acetone, in one portion, and stirring in the dark for 20 min, resulted in

precipitation of AgCl. The mixture was poured into 50 mL of 10% ammonium hydroxide in saturated brine and extracted with 3 × 25 mL of dichloromethane. The dried extracts were concentrated at 40 °C under vacuum and the resulting major imines **33** and **34** and the minor C16′ epimers were then dissolved in 50 mL of glacial acetic acid. Addition of 1.77 g (32.9 mmol) of KBH_4, over 15 min, was followed by partitioning between ice-cold 50% ammonium hydroxide and 3 × 50 mL of dichloromethane. The dried extracts were concentrated at 40 °C under vacuum to provide 2.107 g (87% yield) of crude products. Preparative low-pressure chromatography on tandem (1) 15- × 250-mm and (2) 25- × 1000-mm columns of silica gel 60 (230–400 mesh, ASTM 0.04–0.063 mm) and elution with ether/acetone/triethylamine 100:20:1, at a flow rate of 10 mL/min, collecting 22-mL fractions after 700 mL, provided in fractions 26–54 crude product **36** and in fractions 70–103 crude product **35**. Rechromatography of each product under the same conditions provided 0.805 g of **36** preceded by 0.120 g of **35a** and 1.07 g of **35** preceded by 0.11 g of **36a**.

For **36a**: HPLC t_R 11.7 min (SiO_2, 5% MeOH/CH_2Cl_2); UV (EtOH) λ_{max} 210, 224, 262, 268, 288, 294, 304, 313, 320 nm; 250-MHz ^1H NMR ($CDCl_3$) δ 0.60 (t, J = 7 Hz, 3 H), 0.87 (t, J = 7 Hz, 3 H), 1.16–1.26 (m, 3 H), 1.43–1.76 (m, 5 H), 1.98 (d, J = 14 Hz, 1 H), 2.10 (s, 3 H), 2.26–2.36 (m, 4 H), 2.54–2.71 (m, 2 H), 2.82–2.89 (m, 2 H), 2.80 (s, 1 H), 2.97 (d, J = 16 Hz, 1 H), 3.44–3.87 (m, 9 H), 3.67 (s, 3 H), 3.69 (s, 3 H), 3.71 (s, 1 H), 3.77 (s, 3 H), 4.22 (m, 1 H), 4.73 (d, J = 2 Hz, 1 H), 5.29 (d, J = 10 Hz, 1 H), 5.47 (s, 1 H), 5.93 (dd, J = 10, 4 Hz, 1 H), 5.94 (s, 1 H), 6.97 (t, J = 8 Hz, 1 H), 7.09 (t, J = 7 Hz, 1 H), 7.22–7.34 (m, 6 H), 7.43 (d, J = 7 Hz, 2 H), 9.64 (br s, 1 H), 9.67 (br s, 1 H); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 7.53, 11.21, 20.87, 22.15, 26.35, 30.79, 34.04, 35.58, 38.05, 38.33, 40.05, 42.85, 43.87, 51.11, 51.42, 51.87, 51.96, 52.99, 54.27, 55.49, 56.56, 64.67, 64.76, 76.52, 79.50, 83.29, 94.49, 106.23, 110.35, 110.45, 117.68, 118.19, 118.92, 120.80, 123.57, 124.12, 124.60, 126.50, 127.52, 127.94, 128.22, 130.44, 133.98, 134.17, 141.22, 152.03, 157.45, 170.68, 171.69, 176.38; HRMS M+ calcd 944.4935, found 944.4884.

For **35**: HPLC t_R 11.9 min (SiO_2, 5% MeOH/CH_2Cl_2); UV (EtOH) λ_{max} 210, 226, 258, 266, 278, 288, 296, 314 nm; 250-MHz ^1H NMR ($CDCl_3$) δ 0.64 (t, J = 7 Hz, 3 H), 0.84 (t, J = 7 Hz, 3 H), 0.81–1.01 (m, 2 H), 1.08–1.25 (m, 3 H), 1.33–1.43 (m, 3 H), 1.61–1.82 (m, 3 H), 1.89–2.01 (m 1 H), 2.10 (s, 3 H), 2.27 (d, J = 16 Hz, 1 H), 2.42–2.72 (m, 7 H), 2.66 (s, 3 H), 2.93–3.42 (m, 5 H), 3.58–3.76 (m, 7 H), 3.61 (s, 1 H), 3.63 (s, 3 H), 3.81 (s, 3 H), 3.78 (s, 3 H), 4.31 (d, J = 3 Hz, 1 H), 5.28 (d, J = 10 Hz, 1 H), 5.45 (s, 1 H), 5.81 (dd, J = 10, 4 Hz, 1 H), 6.11 (s, 1 H), 6.74–6.83 (m, 4 H), 6.94 (s, 1 H), 6.95–7.02 (m, 2 H), 7.10–7.18 (m, 2 H), 7.37 (d, J = 7 Hz, 1 H), 8.04 (br s, 1 H), 9.91 (br s, 1 H); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 8.36, 11.32, 20.95, 21.51, 25.24, 36.76, 33.90, 34.89, 38.10, 38.36, 40.30, 42.63, 44.68, 49.46, 49.87, 52.00, 52.08, 52.75, 53.10, 55.58, 56.47, 60.21, 62.71, 64.70, 64.76, 65.33, 76.41, 79.58, 83.69, 94.05, 105.90, 110.19, 114.71, 118.08, 118.75, 121.82, 122.18, 122.85, 124.33, 125.47, 126.20, 127.63, 127.81, 129.38, 129.93, 132.46, 134.82, 140.15, 152.62, 157.87, 170.71, 171.60, 174.86; HRMS M+ calcd 944.4935, found 944.4885.

For **35a**: HPLC t_R 10.9 min (SiO_2, 5% MeOH/CH_2Cl_2); UV (EtOH) λ_{max} 210, 228, 262, 286, 294, 308, 316 nm; 250-MHz ^1H NMR ($CDCl_3$) δ 0.13 (t, J = 7 Hz, 3 H), 0.91 (t, J = 7 Hz, 3 H), 1.23–1.37 (m, 2 H), 1.44–1.52 (m, 3 H), 1.64–1.77 (m, 4 H), 2.03 (s, 3 H), 2.10 (s, 1 H), 2.32–2.59 (m, 7 H), 2.65 (s, 3 H), 2.82–2.99 (m, 4 H), 3.46–3.89 (m, 12 H), 3.70 (s, 3 H), 3.73 (s, 3 H), 3.77 (s, 4 H), 4.02–4.06 (m, 1 H), 4.74 (d, J = 3 Hz, 1 H), 5.15 (d, J = 10 Hz, 1 H), 5.39 (s, 1 H), 5.82 (dd, J = 10, 3 Hz, 1 H), 5.98 (s, 1 H), 6.96 (t, J = 7 Hz, 1 H), 7.11 (t, J = 7 Hz, 1 H), 7.15–7.37 (m, 9 H), 9.48 (s, 1 H), 9.52 (s, 1 H); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 7.47, 11.16, 20.78, 22.19, 26.82, 30.71, 34.12, 35.13, 38.00, 38.51, 39.79, 42.83, 44.03, 51.00, 51.93, 51.98, 52.09, 52.20, 53.08, 54.33, 55.60, 64.63, 64.75, 64.82, 67.40, 76.12, 79.30, 83.38, 94.02, 106.29, 110.33, 110.61, 117.71, 118.17, 119.29, 120.84, 123.70, 124.40, 124.57, 126.39, 127.85, 128.31, 130.33, 133.97, 134.06, 140.98, 152.32, 157.28, 170.34, 171.76, 175.98; HRMS M+ calcd 944.4935, found 944.4863.

For **36**: HPLC t_R 11.0 min (SiO_2, 5% MeOH/CH_2Cl_2); UV (EtOH) λ_{max} 214, 228, 256, 280, 290, 300; 250-MHz ^1H NMR ($CDCl_3$) δ 0.43 (t, J = 7 Hz, 3 H), 0.88 (t, J = 7 Hz, 3 H), 1.03–1.11 (m, 2 H), 1.25–1.28 (m, 2 H), 1.43–1.74 (m, 5 H), 2.06 (s, 3 H), 2.16–2.56 (m, 8 H), 2.68 (d, J = 16 Hz, 1 H), 2.74 (s, 3 H), 2.82–3.13 (m, 3 H), 3.26–3.47 (m, 4 H), 3.57 (s, 3 H), 3.58 (s, 1 H), 3.70 (s, 3 H), 3.72–3.75 (m, 6 H), 3.80 (s, 3 H), 4.21 (d, J = 3 Hz, 1 H), 5.21 (d, J = 10 Hz, 1 H), 5.47 (s, 1 H), 5.80 (dd, J = 10, 4 Hz, 1 H), 6.13 (s, 1 H), 6.86 (s, 1 H), 7.05 (t, J = 8 Hz, 1 H), 7.12–7.27 (m, 7 H), 7.43 (d, J = 8 Hz, 1 H), 8.06 (br s, 1 H), 9.95 (br s, 1 H); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 8.01, 11.58, 20.79, 21.45, 26.27, 29.10, 30.88, 32.78, 33.76, 34.11, 38.64, 39.23, 42.55, 45.24, 50.16, 50.46, 51.96, 52.00, 53.27, 53.97, 55.21, 55.69, 58.01, 64.64, 64.74, 65.90, 76.09, 79.36, 83.83, 93.40, 104.85, 109.87, 115.50, 118.07, 118.08, 121.70, 121.88, 123.25, 123.79, 124.00, 126.29, 127.87, 127.94, 129.63, 129.96, 131.88, 134.66, 140.44, 152.91, 158.12, 170.31, 171.61, 175.61; HRMS M+ calcd 944.4935, found 944.4865.

Δ^{20-21}-Anhydrovinblastine (37). To a solution of 0.257 g (0.252 mmol) of the binary acetal **35** in 10 mL of glacial acetic acid was added 0.268 g of 10% Pd/C. Hydrogenolysis at atmospheric pressure and room temperature was completed in 45 min (11.7 mL H_2 uptake). The mixture was filtered and the filtrate poured onto 200 g of ice. Neutralization with 150 mL of ammonium hydroxide, extraction with 3 × 75 mL of dichloromethane, and concentration of the dried extracts at 42 °C under vacuum produced a 2° amine, which was purified by centrifugal chromatography on silica gel. Elution with 90:10:1 CH_2Cl_2/MeOH/Et_3N gave 0.232 g (100%) of amine with TLC R_f 0.36 (SiO_2, 90:10:1 CH_2Cl_2/MeOH/Et_3N); EIMS m/z 854 (M+). Addition of 10 mL of methanol and 10 mL of 1 N HCl, and stirring for 30 min at room temperature, resulted in hydrolysis of the acetal. The solution was poured into 100 mL of 10% ammonium hydroxide in saturated brine and extracted with 3 × 50 mL of dichloromethane. The dried extracts were concentrated under vacuum and the residue purified by HPLC to provide 0.200 g (93% yield) of the enamine **37**: TLC R_f 0.53 (5% MeOH–CH_2Cl_2); Prep HPLC t_R 13.6 min; 2.54- × 25-cm silica gel column (4% MeOH/CH_2Cl_2, 10 mL/min); UV (EtOH) λ_{max} 214, 256, 287, 296, 307 nm; 250-MHz ^1H NMR ($CDCl_3$) δ 0.83 (t, J = 7 Hz, 3 H), 0.99 (t, J = 8 Hz, 3 H), 0.89–1.01 (m, 1 H), 1.26–1.41 (m, 2 H), 1.79–1.87 (m, 2 H), 1.92–2.07 (m, 3 H), 2.08–2.28 (m, 3 H), 2.12 (s, 3 H), 2.41–2.51 (m, 1 H), 2.67–2.75 (m, 2 H), 2.73 (s, 3 H), 2.70 (s, 1 H), 2.85 (br t, J = 12 Hz, 2 H), 3.04–3.48 (m, 5 H), 3.58 (s, 3 H), 3.77 (s, 1 H), 3.81 (s, 3 H), 3.81 (s, 3 H), 5.32 (d, J = 10 Hz, 1 H), 5.51 (s, 1 H), 5.72 (s, 1 H), 5.87 (dd, J = 4, 10 Hz, 1 H), 6.14 (s, 1 H), 6.72 (s, 1 H), 7.08–7.27 (m, 3 H), 7.52 (d, J = 7 Hz, 1 H), 7.97 (s, 1 H), 9.85 (br s, 1 H); 62.9-MHz ^{13}C NMR ($CDCl_3$) δ 8.45, 13.40, 21.04, 26.91, 27.32, 28.46, 30.81, 33.69, 34.14, 38.25, 42.72, 44.54, 46.93, 50.38, 50.55, 52.16, 53.24, 54.59, 55.67, 55.85, 66.00, 76.39, 79.60, 83.43, 94.36, 109.82, 110.45, 116.82, 118.14, 118.90, 121.51, 122.22, 123.02, 123.52, 124.40, 127.60, 129.21, 129.99, 131.10, 134.93, 152.80, 158.12, 170.82, 171.67, 174.39; HRMS M+ calcd 792.4098, found 792.3993.

Vinamidine (12). A stream of oxygen was passed through a solution of 0.100 g (0.126 mmol) of the enamine **37** in 30 mL of dichloromethane while irradiating the solution with a Sylvania 275-W sunlamp. After about 1 h, the enamine **37** was consumed (TLC) and the mixture was concentrated under vacuum. Centrifugal chromatography on a 1-mm silica gel plate, eluting with 5% methanol in dichloromethane, gave a crude product, which was subjected to HPLC on silica gel. Elution with 5% methanol in dichloromethane gave 71 mg (70%) of vinamidine (**12**): TLC R_f 0.48 (SiO_2, 5% MeOH, CH_2Cl_2); Prep HPLC t_R 11.5 min (SiO_2, 5% MeOH, CH_2Cl_2; 250-MHz ^1H NMR ($CDCl_3$) δ 0.79 (t, J = 7 Hz, 3 H), 0.86 (t, J = 8 Hz, 3 H), 1.27–1.38 (m, 1 H), 1.76–1.85 (m, 2 H), 2.03–2.29 (m, 6 H), 2.11 (s, 3 H), 2.44–2.47 (m, 2 H), 2.59–2.84 (m, 3 H), 2.70 (s, 3 H), 3.00–3.19 (m, 6 H), 3.36–3.66 (m, 5 H), 3.55 (s, 3 H), 3.75 (s, 1 H), 3.80 (s, 6 H), 5.31 (d, J = 10 Hz, 1 H), 5.48 (s, 1 H), 5.87 (dd, J = 10, 4 Hz, 1 H), 6.10 (br s 1 H), 6.64 (br s 1 H), 7.11–7.18 (m, 3 H), 7.49–7.50 (m, 1 H), 7.96 (s, 1 H), 9.86 (br s, 1 H); 62.9-MHz ^{13}C NMR ($CDCl_3$) δ 7.84, 8.35, 21.03, 25.33, 29.60, 30.84, 34.91, 37.40, 38.23, 42.81, 43.87, 49.43, 50.54, 51.27, 52.09, 52.28, 52.37, 53.31, 55.70, 66.40, 79.72, 83.71, 93.76, 110.76, 111.45, 117.66, 119.34, 119.46, 122.49, 123.79, 124.54, 128.36, 129.99, 132.92, 135.33, 153.13, 158.04, 163.47, 170.87, 171.77, 174.22, 210.24; UV (EtOH) λ_{max} 224, 265, 286, 294, 311 nm; HRMS M+ calcd 824.3996, found 824.3978. These data correspond to the selected values reported for the natural product.[24]

Vinblastine (13). Method A.[21,22] To 0.100 g (0.126 mmol) of the enamine **37** in 4 mL of dry dichloromethane, at 0 °C, was added 0.106 g (0.28 mmol) of $Tl(OAc)_3$. After stirring at 0 °C for

15 min the mixture was concentrated under vacuum at 0 °C and the residue dissolved in 4 mL of dry methanol. Addition of 0.105 g (2.78 mmol) of sodium borohydride, at room temperature, resulted in decolorization. The mixture was partitioned between 20 mL of 10% ammonium hydroxide in saturated brine and 3 × 50 mL of dichloromethane. The extracts were concentrated under vacuum and the residue was subjected to centrifugal chromatography on a 1-mm silica gel plate. Elution with 10% methanol in dichloromethane provided the product, which was purified by preparative HPLC on silica gel, eluting with 10% methanol in dichloromethane, to give 3.7 mg (3.6%) of vinblastine, which matched (MS, HPLC, and TLC) authentic natural and synthetic samples.[18]

Method B.[25] To 0.100 g (0.126 mmol) of the enamine **37** in 100 mL of dry methanol was added, in one portion, 0.0409 g (0.252 mmol) of ferric chloride. The solution was cooled to 0 °C and, with stirring, air was bubbled through for 1 h and then 0.105 g (1.26 mmol) of sodium borohydride was added. The reaction mixture was then worked up as in method A to provide 0.0318 g (31%) of purified vinblastine (**13**).

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Supplementary Material Available: Compound characterization data (including full IR and EIMS data) and a ^{13}C NMR spectrum for each new compound (43 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

π-Conjugated Systems with Unique Electronic Structure: A Case of "Planarized" 1,3-Connected Polyarylmethyl Carbodianion and Stable Triplet Hydrocarbon Diradical

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The effect of "planarization" on π-conjugated 1,3-connected polyarylmethyls in connection with the electronic structure and magnetic properties is examined. The synthesis, ESR and UV–vis spectroscopy, voltammetry, and magnetic studies of triplet diradical $\mathbf{6}^{2\bullet}$ are reported. The corresponding dianion $\mathbf{6}^{2-}$, $2M^+$ (M = Li, K) is studied using NMR and UV–vis spectroscopy.

Introduction

The understanding of the electronic structure associated with the high spin molecules is related to the problem of magnetism.[1,2] Polyradicals, polycarbenes, and polynitrenes based upon 1,3-connected polyarylmethyl (methylene) π-conjugated systems are promising candidates for very high spin organic molecules.[3-5] For example, pentacarbene **1** (Chart I) is the highest spin, $S = 5$, organic molecule and tetraradical **2** is one of the highest spin, $S = 2$, polyradicals.[3d,4a] Polyanions and radical anions related to **2**, e.g., 1,3-connected polyarylmethyl decaanion **3** and radical anion **4**, possess an unusual uniform charge density distribution and localized spin density, respectively.[6] Such π-conjugated systems have been considered as ensembles of weakly coupled arylmethyl units via 1,3-phenylene bridges. In the related work, 1,3-connected polyarylmethyl diradical **5b** has been found to interact ferromagnetically in the solid state.[7] Because of the steric interactions, the above 1,3-connected polyarylmethyls are forced to be nonplanar. Out-of-plane twisting would hamper π-conjugation and might contribute to the weakness of the interactions between the arylmethyl units and influence magnetic interactions.

In order to examine if the unusual properties represented by decaanion **3** and diradicals **5a–c** are intrinsic to their electronic structure or caused by the out-of-plane twisting, we prepare a model system where the out-of-plane

(1) Proceedings of the Symposium on Ferromagnetic and High Spin Molecular Based Materials, 197th National Meeting of the American Chemical Society, Dallas, TX. Miller, J. S.; Dougherty, D. A. *Mol. Cryst. Liq. Cryst.* **1989**, *176*, 1–562. Iwamura, H. *Adv. Phys. Org. Chem.* **1990**, *26*, 179. Dougherty, D. A. *Acc. Chem. Res.* **1991**, *24*, 88.

(2) Allemand, P.-M.; Khemani, K. C.; Koch, A.; Wudl, F.; Holczer, K.; Donovan, S.; Gruner, G.; Thompson, J. D. *Science* **1991**, *253*, 301.

(3) High spin tetraradicals ($S = 2$). (a) Seeger, D. E.; Berson, J. A. *J. Am. Chem. Soc.* **1983**, *105*, 5144, 5146. Seeger, D. E.; Lahti, P. M.; Rossi, A. R.; Berson, J. A. *J. Am. Chem. Soc.* **1986**, *108*, 1251. Berson, J. A. in *The Chemistry of Quinoid Compounds*; Patai, S., Rappaport, Z., Eds.; Wiley: New York, 1988, Vol. II, Chapter 10. (b) Novak, J. A.; Jain, R.; Dougherty, D. A. *J. Am. Chem. Soc.* **1989**, *111*, 7618. Dougherty, D. A. *Mol. Cryst. Liq. Cryst.* **1989**, *176*, 25. (c) Kirste, B.; Grimm, M.; Kurreck, H. *J. Am. Chem. Soc.* **1989**, *111*, 108. (d) Rajca, A. *J. Am. Chem. Soc.* **1990**, *112*, 5890.

(4) High spin polycarbenes. (a) ($S = 5$) Fujita, I.; Teki, Y.; Takui, T.; Kinoshita, T.; Itoh, K.; Miko, F.; Sawaki, Y.; Iwamura, H.; Izuoka, A.; Sugawara, T. *J. Am. Chem. Soc.* **1990**, *112*, 4074. (b) ($S = 4$) Sugawara, T.; Bandow, S.; Kimura, K.; Iwamura, H.; Itoh, K. *J. Am. Chem. Soc.* **1984**, *106*, 6449. Sugawara, T.; Bandow, S.; Kimura, K.; Iwamura, H.; Itoh, K. *J. Am. Chem. Soc.* **1986**, *108*, 368. (c) ($S = 3$) Takui, T.; Itoh, K. *Chem. Phys. Lett.* **1973**, *19*, 120. (d) ($S = 2$) Itoh, K. *Chem. Phys. Lett.* **1967**, *1*, 235. Wasserman, E.; Murray, R. W.; Yager, W. A.; Trozzolo, A. M.; Smolinsky, G. *J. Am. Chem. Soc.* **1967**, *89*, 5076.

(5) Polynitrenes: Murata, S.; Iwamura, H. *J. Am. Chem. Soc.* **1991**, *113*, 5547.

(6) (a) Utamapanya, S.; Rajca, A. *J. Am. Chem. Soc.* **1991**, *113*, 9242. Rajca, A. *J. Am. Chem. Soc.* **1990**, *112*, 5889. (b) Rajca, A. *J. Org. Chem.* **1991**, *56*, 2557.

(7) Rajca, A.; Utamapanya, S.; Xu, J. *J. Am. Chem. Soc.* **1991**, *113*, 9235.

0022-3263/92/1957-1760$03.00/0