Studies in Biomimetic Alkaloid Syntheses. 5. Total Syntheses of ψ-Vincadifformine, 20-Epi-ψ-vincadifformine, Pandoline, 20-Epipandoline, and the C-16 Epimeric (Carbomethoxy)velbanamines

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The title racemic pentacyclic alkaloids (**5b–e**) were synthesized by respective reactions of the indoloazepines **8b,c** with the halopentanals **10a,b** or the epoxypentanal **23**. Reductive opening of pandoline (**5d**) gave the racemic seco compounds **28a,b**, and reductive opening of 20-epipandoline (**5e**) gave the seco epimers **28c,d**.

Running parallel to the biosyntheses of numerous alkaloids with the tabersonine (**1a**) skeleton generated from a preakuammicine (**2**) through the $\Delta^{14,20}$-dehydrosecodine **3**,[1] one finds the formation of alkaloids which are also derived from the same preakuammicine (**2**) but for which the alternative $\Delta^{3(14),15(20)}$-dehydrosecodine (**4**) can be proposed as a precursor.[2] These compounds are represented by the ψ-tabersonine structure **5a**.[3] Formation of this alkaloid's $\Delta^{15(20)}$-dihydro derivatives ψ-vincadifformine (**5b**)[3] and 20-epi-ψ-vincadifformine (**5c**) can be postulated to arise from reduction of the dehydrosecodine **4** to a $\Delta^{3(14)}$-secodine isomer **6**, in analogy with the generation of vincadifformine (**1b**) from the alternative Δ^{20}-secodine isomer **7**[2,4-6] (Scheme I). The alkaloids pandoline[7-9] (**5d**) and 20-epipandoline[3,8] (**5e**) in turn can be ascribed to a biosynthetic hydroxylation of the corresponding $\Delta^{15(20)}$-dehydro or dihydro compounds in the chain of biosynthetic intermediates and products and could plausibly be derived from reduction of C15–C20 epoxides.

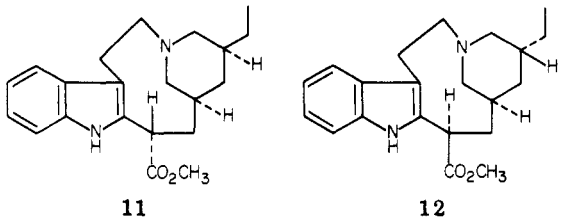
In this report we present total syntheses of ψ-vincadifformine (**5b**), 20-epi-ψ-vincadifformine (**5c**), pandoline (**5d**), and 20-epipandoline (**5e**) with implication of a synthetic $\Delta^{3(14)}$-secodine precursor for the ψ-vincadifformines. The specific synthetic results support the postulated intermediacy and stereodirectional reactivity of a secodine in the natural biosynthesis of the ψ-vincadifformine class of alkaloids.

For these syntheses the indoloazepine ester **8b** served as a convenient starting material. We had previously obtained this compound through a biomimetic oxidative alkylation of *N*-benzyltetrahydro-β-carboline with *tert*-butyl methyl malonate, followed by selective decarboalkoxylation and debenzylation of the diester **9a**[4] (see Scheme II). Since a corresponding dimethyl ester precursor **9b** was also readily synthesized,[5] its monodecarbomethoxylation was studied. It was found that an 83% yield of the monoester **8a** could be obtained by heating the diester in dimethylformamide with lithium chloride.[10]

Debenzylation and condensation of the resultant amino ester **8b** with 5-bromo- or 5-chloro-4-ethylpentanal **10a,b** furnished, in 41% yield, a material with the typical UV chromophore (328 nm) of a β-anilinoacrylate and the mass fragmentation of natural "ψ-vincadifformine". High-pressure liquid chromatography of this product indicated a mixture of two compounds in a ratio of 4:1. Preparative medium-pressure and high-pressure LC, or fractional crystallizations, provided the individual C-20 epimeric ψ-vincadifformines **5b** and **5c**.

When a comparison sample of natural "ψ-vincadifformine" became available, it was found to consist of the same two epimeric (but not racemic) components, in the same ratio, as the synthetic product.[11]

Two stereochemical assignments had previously been given for "ψ-vincadifformine", differing in relative configuration at C-20 (**5b** or **5c**).[3,12,13] In each instance a series of transformations starting from catharanthine had provided the (carbomethoxy)cleavamines **11** and **12**, epimeric



at the ethyl-bearing carbon. The respective compounds were subjected to oxidative cyclization with mercuric acetate. In each instance the (different) resulting "ψ-vincadifformine" product was claimed to be identical with the (same) hydrogenation product of ψ-tabersonine (**5a**).

(1) The numbering system used in this publication is one based on a biogenetic interrelationship of indole alkaloids as proposed by J. LeMen and W. I. Taylor, *Experientia*, **21**, 508 (1965). All synthetic compounds are racemic and structures are written in the absolute configurations of the natural products.

(2) (a) A. I. Scott, *Acc. Chem. Res.*, **3**, 151 (1970); (b) *Bioorg. Chem.*, **3**, 398 (1974).

(3) M. Zeches, M. M. Debray, G. Ledouble, L. LeMen-Olivier, and J. Le Men, *Phytochemistry*, **14**, 1122 (1975).

(4) M. E. Kuehne, D. M. Roland, and R. Hafter, *J. Org. Chem.*, **43**, 3705 (1978).

(5) M. E. Kuehne, T. H. Matsko, J. C. Bohnert, and C. L. Kirkemo, *J. Org. Chem.*, **44**, 1063 (1979).

(6) M. E. Kuehne, T. H. Matsko, and J. A. Huebner, *J. Org. Chem.*, **44**, 2477 (1979).

(7) (a) M. J. Hoizey, M. M. Debray, L. Le Men-Olivier, and J. Le Men, *Phytochemistry*, **13**, 1995 (1974); (b) J. Le Men, G. Lukacs, L. Le Men-Olivier, J. Lévy, and M. J. Hoizey, *Tetrahedron Lett.*, 483 (1974); (c) M. J. Hoizey, C. Sigaut, M. J. Jacquier, L. Le Men-Olivier, J. Lévy, and J. Le Men, *ibid.*, 1601 (1974).

(8) (a) J. Bruneton, A. Cavé, E. W. Hagaman, N. Kunesch, and E. Wenkert, *Tetrahedron Lett.*, 3567 (1976); (b) J. Le Men, G. Hugel, M. Zeches, M.-J. Hoizey, L. Le Men-Olivier, and J. Lévy, *C. R. Hebd. Seances Acad. Sci., Ser. C*, 759 (1976).

(9) F. Khoung-Huu, M. Cesario, J. Guilhem, and R. Goutarel, *Tetrahedron*, **32**, 2539 (1976).

(10) For analogous use of LiCl in Me_2SO and alternatives, see A. P. Krapcho, J. F. Weimaster, J. M. Eldridge, E. G. E. Jahngen, Jr., A. J. Lovey, and W. P. Stephens, *J. Org. Chem.*, **43**, 138 (1978).

(11) We thank Professors J. Le Men and J. Lévy for exceptional cooperation in providing complete sets of comparison samples of natural "ψ-vincadifformine", pandoline, and epipandoline and their corresponding IR, UV, and NMR spectra.

(12) J. Le Men, C. Caron-Sigaut, G. Hugel, L. Le Men-Olivier, and J. Lévy, *Helv. Chim. Acta*, **61**, 566 (1978).

(13) J. P. Kutney, R. T. Brown, E. Piers, and J. R. Hadfield, *J. Am. Chem. Soc.*, **92**, 1708 (1970).

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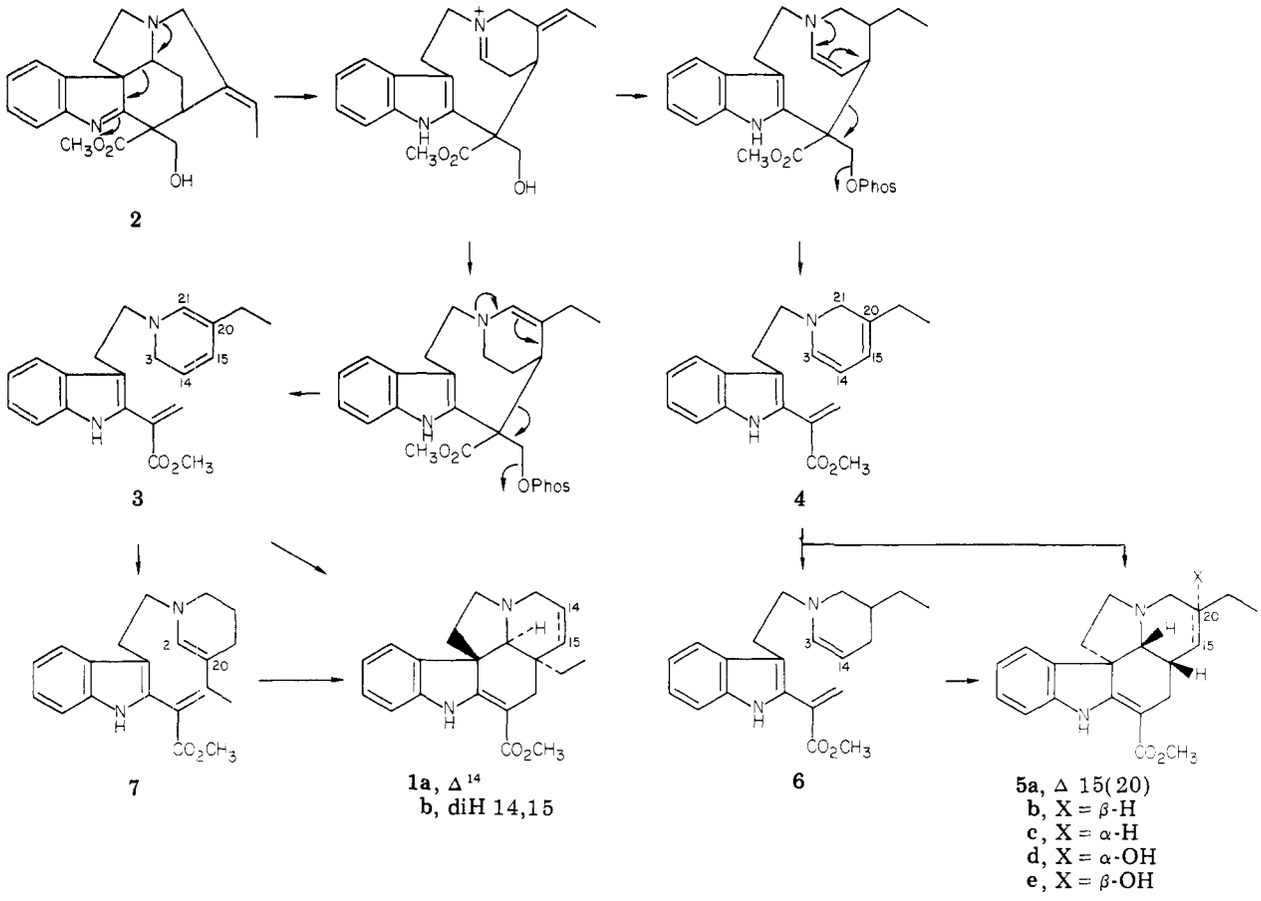
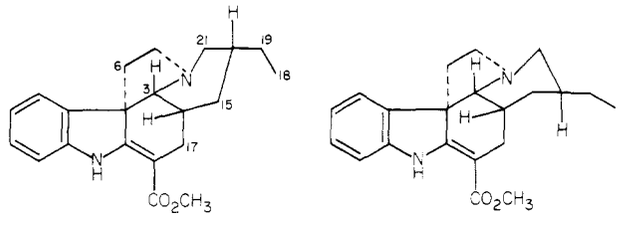
Scheme I. Biosynthetic Origin of Tabersonine and ψ-Tabersonine Alkaloid Types



One may attribute this discrepancy and uncertainty in stereochemical assignments to the amorphous character of the ψ-vincadifformines derived from natural sources, by the above partial syntheses or by plant extraction. The crystalline ψ-vincadifformines **5b,c**, obtained by total synthesis, now allowed X-ray crystallographic definition of their structures.[14] Hydrogenation of ψ-tabersonine and high-pressure LC of the product clearly allowed matching with the major synthetic and natural epimer (**5a** → **5b** but **5a** ↛ **5c**).

X-ray definition of both epimers was required since the minor natural or synthetic ψ-vincadifformine isomer could have a structure epimeric with **5b** only at the ethyl-bearing center C-20 (i.e., **5c**) or alternatively it could conceivably have been derived from a C/D trans-fused skeleton. The latter possibility could not be easily excluded by 270-MHz NMR proton spectra, which were remarkably different and complex for the two epimers **5b,c**.[15] While the ^{13}C NMR spectra showed a difference in the ethyl methylene and at C-3 of the ψ-vincadifformine epimers **5b,c** (C-19: Δ1.4; C-3: Δ1.5) analogous to the pandoline epimers **5d,e**, they differed considerably from the pandoline spectra by showing larger differences at C-6 (Δ1.6), C-15 (Δ1.1), C-17 (Δ1.7), C-18 (Δ0.8), and C-21 (Δ1.1) between the epimers **5b,c** than those reported for the two pandolines **5d,e**.[8] Remarkably strong IR Wenkert–Bohlmann bands[16] in solution and KBr powder spectra of each epimer suggested that both **5b** and **5c** have conformations with a trans-diaxial nitrogen to C-3 proton relationship (conformations **13a,b**), rather than a conformation with an inverted nitrogen. The data are consistent with a replacement of the chair conformation of ring D in 20-epi-ψ-vincadifformine (**13b**) by a deformed boat in ψ-vincadifformine (**13a**) in solutions of these compounds. This conformational difference allows relief of an ethyl to C-17 1,3-diaxial interaction in a ψ-vincadifformine ring D chair.



The same epimeric mixture of ψ-vincadifformine (**5b**) and 20-epi-ψ-vincadifformine (**5c**) was also obtained in 46% yield on reaction of the halopentanals **10a,b** with the indoloazepine diester **8c**. We had previously established a spiroenammonium intermediate **14** (R = C_2H_5, R′ = H) in an analogous vincadifformine synthesis starting from the diester **8c** and found a concerted fragmentation of this quaternary salt to a Δ^{20}-secodine (**7**) with subsequent formation of the pentacyclic alkaloid structure.[5] By analogy, the corresponding $\Delta^{3(14)}$-secodine (**6**) intermediate could now also arise in the present ψ-vincadifformine synthesis starting from the same diester **8c**.[17]

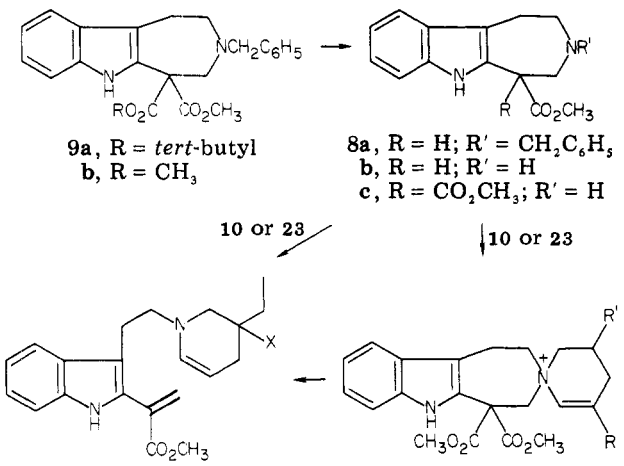
(14) We thank Dr. James P. Springer of the Merck Institute for Therapeutic Research for providing these analyses.

(15) We thank Mr. Peter Demov of the Yale University regional NMR service facility for providing these NMR spectra. An analysis of the NMR spectra of these and related compounds will be published subsequently.

(16) I. A. Crabb, R. F. Newton, and D. Jackson, *Chem. Rev.*, 71, 121 (1971).

(17) The formation of spiroenammonium salts such as **14** as intermediates is only rigorously established in the vincadifformine synthesis starting from the diester **8c** and an α-substituted δ-halo aldehyde.[5] Investigation of additional alternative pathways to secodine intermediates and the alkaloid products will be described in a subsequent paper.

Scheme II



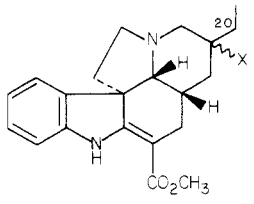
9a, R = *tert*-butyl
b, R = CH_3

8a, R = H; R′ = $CH_2C_6H_5$
b, R = H; R′ = H
c, R = CO_2CH_3; R′ = H

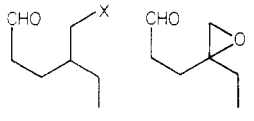
10 or 23 | 10 or 23

6, X = H or OH

14



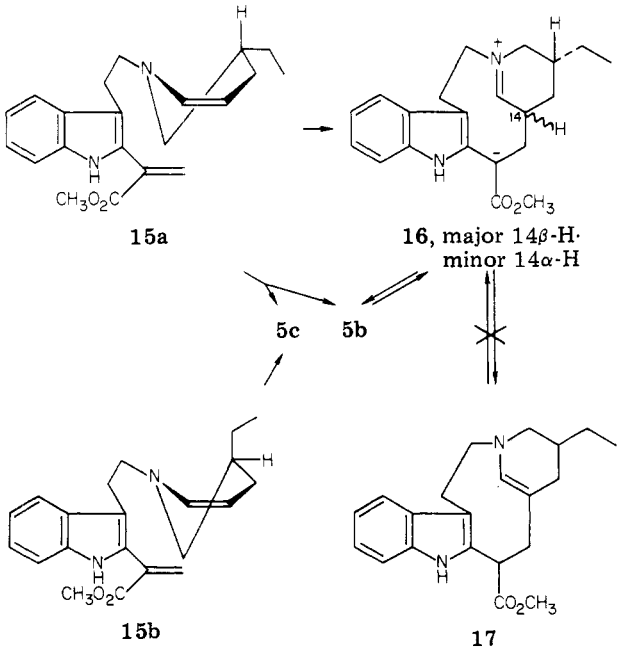
5b, 20β-H
c, 20α-H
d, 20α-OH
e, 20β-OH



10a, X = Br
b, X = Cl

23

Scheme III



15a

16, major 14β-H·
minor 14α-H

5c 5b

15b

17

As there seems to be no difference between the in vivo and in vitro reactions of the secodine intermediate **6** in formation of the 4:1 mixture of ψ- and 20-epi-ψ-vincadifformine,[18] the origin of this isomeric ratio is of interest. The isomeric ratio could be shown to be a kinetic result ascribed to cyclization of the secodine intermediate **6**, where addition of the indoloacrylate to the enamine function occurs predominantly cis to the ethyl substituent on the piperideine ring. This stereochemical preference could be due to a favored attack on the face of the piperideine ring away from an equatorial ethyl-substituted carbon (conformation **15a**), with minor attack in this conformation from the other side. Alternatively, constant attack of the piperideine ring from one side, with a major equatorial or minor axial substituent (conformations **15a** and **15b**), would provide the same result.[19] With these considerations the cyclization could proceed by a concerted (Diels–Alder) reaction or by a stepwise process through an immonium intermediate **16** (Scheme III).

Since one can also consider generation of the immonium intermediate **16** to arise from C/E ring juncture cleavage of a ψ-vincadifformine product, this process could conceivably allow equilibration with a seco enamine structure **17** and consequently lead to epimerization of the C-14 stereochemistry relative to C-20. However, such an explanation of the epimeric product mixture of the ψ-vincadifformines **5b,c** was ruled out by a lack of isomerization of either pure epimer under the reaction condtions or on more forceful treatment with anhydrous acid or base.

The halo aldehydes **10a,b** used in this synthesis were obtained from methyl 4-formylhexanoate (**18**). Sodium borohydride reduction of the latter gave the hydroxy ester **19**, which then provided the mesylate derivative **20** (81% overall); or, alternatively, **19** could be cyclized to the δ-lactone **21** (58% overall). Displacement of the mesyl function with lithium bromide furnished bromo ester **22a** (74%). This compound and the corresponding chloride **22b** could also be obtained by opening of the lactone **21** with hydrogen bromide or hydrogen chloride and methanol (83%, 94%). Reduction of the halo esters (**22a,b**) with diisobutylaluminum hydride then gave the halo aldehydes **10a,b** (84%, 77%) (Scheme IV).

For syntheses of the 20-hydroxylated alkaloids pandoline (**5d**) and 20-epipandoline (**5e**), the epoxy aldehyde **23** was desired. This compound was prepared from intermediates available in our research group by opening of the lactone **21** with sodium phenyl selenide,[20] followed by esterification, which provided the selenide ester **24** (55%). Oxidation of the latter to a selenoxide and its fragmentation gave the olefinic ester **25** (74%). Alternatively, this ester can be prepared from the corresponding acid which is readily prepared from the trichloride **26** on reaction with magnesium and carbon dioxide.[21] Oxidation to the epoxide **27** (81%) and a reduction of the epoxy ester with diisobutylaluminum hydride then provided the required

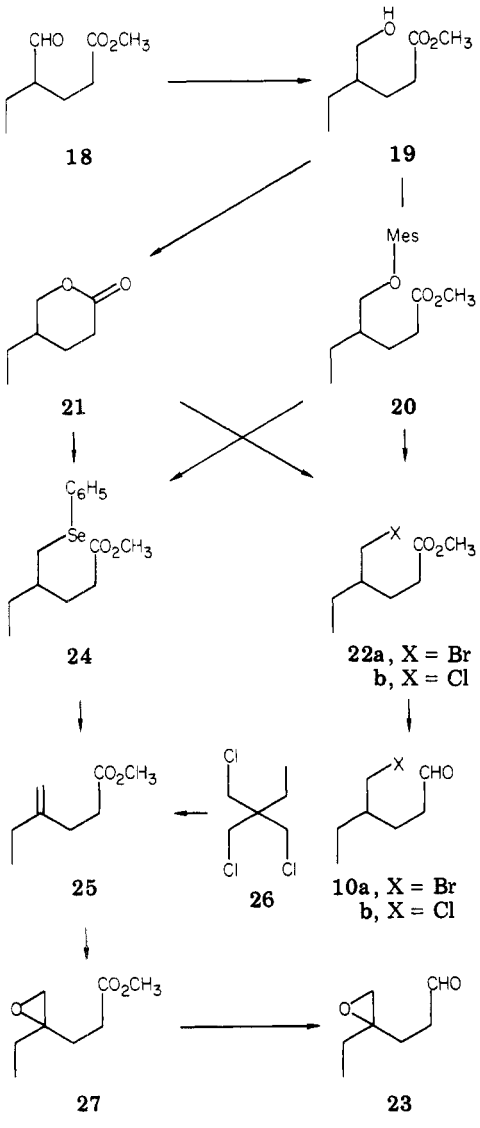
(18) Unfortunately insufficient natural ψ- and 20-epi-ψ-vincadifformine mixture was available to explore whether the two natural epimers have the same absolute configuration at C-20 and are enantiomeric at C-3, C-7, and C-14, as expected for cyclization of an enantiomerically pure secodine, in analogy to the synthetic racemic secodine cyclization, or if the natural epimers are identical at C-3, C-7, and C-14 and enantiomeric at C-20.

(19) This unifacial attack could arise from steric or stereoelectronic control based on ground-state conformations **15a** and **15b** with a quasi-equatorial indole ethyl N-substituent and quasi-axial nonbonded-electron localization on nitrogen in a stereoelectronically optimum configuration for delocalization. Preferred attack at C-14 cis to the ethyl group is more difficult to rationalize on the basis of structures with trigonal nitrogen geometry. The intermolecular Diels–Alder reaction of butadiene with 5-methylcyclohex-2-enone, analogous to the latter geometry, leads to exclusive addition trans to the methyl group (T. Harayama, H. Cho, M. Ohtani, and Y. Inubushi, *Chem. Pharm. Bull.*, **22**, 2784 (1974).

(20) R. M. Scarborough, Jr., and A. B. Smith, III, *Tetrahedron Lett.*, 4361 (1977).

(21) E. L. McCaffery and S. W. Shalaby, *J. Organomet. Chem.*, 8, 17 (1967).

Scheme IV

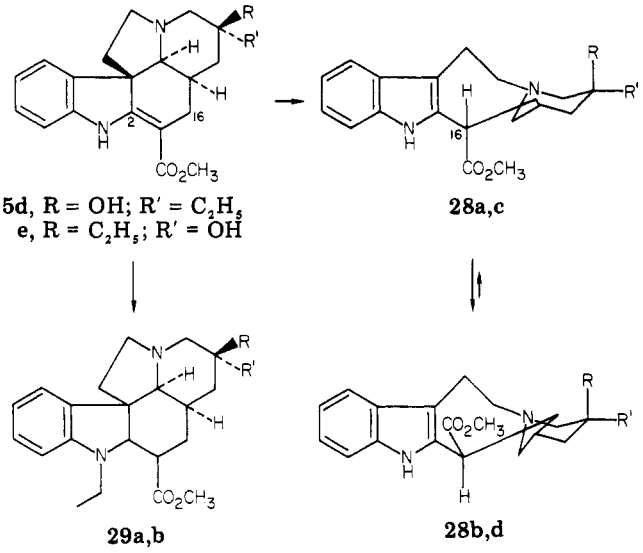


epoxy aldehyde **23** in yields which varied in repeated runs. The epoxy aldehyde **23** was found to be relatively unstable and to decompose on distillation or chromatography.

Condensation of the amino ester **8b** with an excess of the impure epoxy aldehyde **23** resulted in formation of pandoline **5d** and epipandoline **5e** in 64% yield. The crystalline alkaloids, obtained in equal quantities, were readily separated by chromatography. They matched the natural products in all spectroscopic and chromatographic respects.[11]

The selective mode of cyclization of an amino epoxide intermediate leading to formation of a six-membered ring in this instance is the result of preferential displacement at a primary vs. tertiary carbon in our reaction and is in accord with other cyclizations arising from unsymmetrically substituted epoxides.[17,22]

In accord with the previous reductive generation of seco alkaloids,[8] established for the natural products, the racemic 16-epimeric (carbomethoxy)velbanamines **28a–d** could be obtained by reactions of pandoline (**5d**) and epipandoline (**5e**) with sodium borohydride in acetic acid, thus providing a total synthesis of the second half structure[6,23] **28b** of the oncolytic alkaloid vinblastine (VLB). It was found that these reductions result in rapid stereospecific generation of the respective 16α-carbomethoxy products **28a** and **28c**. The latter are epimerized in hot acetic acid to give mostly the 16β-carbomethoxy compounds **28b** and **28d**. (Racemic compounds **28a–d** are depicted in the absolute configuration of VLB.)



The isomers **28a** and **28c** were readily identified by their C-16 proton NMR signals at δ 5.71 and 5.04 which are shifted to δ 3.96 and 3.84, respectively, in the epimers **28b** and **28d**.[8] These consecutive stereospecific reactions are in accord with the preferential electrophilic attack of the vinylogous urethane double bond in the vincadifformine series, trans to the C/D ring junction substituents, while the epimerizations are governed by the relatively greater steric repulsions in velbanamines with 16α vs. 16β substituents.

In addition to products **28a** and **c**, the reductions of **5d** and **e** in acetic acid also gave small amounts of products tentatively identified as *N*-ethyl-2,16-dihydropandoline and epipandoline (**29a,b**), showing *n*-alkylindoline UV spectra and corresponding molecular ions.

Experimental Section

Methyl 3-Benzyl-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-5-carboxylate (8a). Diester **9b** (9.3 g, 24 mmol),[5] lithium chloride (1.3 g, 30 mmol), and water (620 mg, 34 mmol) were dissolved in anhydrous dimethylformamide (20 mL) under nitrogen and the stirred solution was placed in a preheated (160–165 °C) oil bath for 1 h. The solution immediately became cloudy and began evolving CO_2. After cooling, the reaction was poured into water (400 mL) with vigorous stirring. The gummy solid which formed was collected by filtration through glass wool, dissolved in dichloromethane, and dried ($MgSO_4$). After the solution was concentrated under vacuum, the residual product was purified by column chromatography on silica gel, eluting with dichloromethane. This yielded a solid which was recrystallized from hexane to provide 6.6 g (83%) of **8a**, mp 135–136 °C, identical with a previously prepared sample.[4]

Methyl 4-(Methanesulfonylmethyl)hexanoate (20). Methyl 4-formylhexanoate (18,[24] 6 g, 38 mmol) was dissolved in methanol (60 mL) and cooled to 0 °C. Sodium borohydride (0.75 g, 20 mmol) was added slowly, keeping the reaction temperature below 10 °C. The solution was stirred for an additional 15 min, then taken up in dichloromethane, washed with water and saturated brine, and dried ($MgSO_4$). Solvent removal under vacuum at 30 °C gave the alcohol **19** which was dissolved in dichloromethane (60 mL) with triethylamine (5.2 g, 51 mmol) and cooled to 0 °C. Methanesulfonyl chloride (5.5 g, 48 mmol) was added dropwise followed

(22) (a) G. Stork and J. F. Cohen, *J. Am. Chem. Soc.*, **96**, 5270 (1974); (b) G. Stork, L. D. Cama, and D. R. Coulson, *ibid.*, **96**, 5268 (1974).
(23) G. Buechi, *Chimia*, **29**, 172 (1975).
(24) G. Stork, A. Brizzolara, H. K. Landesman, J. Smuszkovicz, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963).

by 30 min of stirring. An additional 40 mL of dichloromethane was then added and the solution was washed with 3% HCl and saturated aqueous sodium bicarbonate and dried ($MgSO_4$). Concentration under vacuum and distillation, bp 145–150 °C (0.3 mm), gave the pure mesylate **20** (7.6 g, 81%): IR (neat) 2965, 1734, 1350, 1175 cm^{-1}; NMR ($CDCl_3$) δ 1.0 (3 H, t), 1.3–1.9 (5 H, m), 2.45 (2 H, t), 3.1 (3 H, s), 3.8 (3 H, s), 4.3 (2 H, d).

4-Ethyl-5-hydroxypentanoic Acid Lactone (21). Methyl 4-formylhexanoate (18,[24] 15.3 g, 97 mmol) was cooled to 0 °C in anhydrous methanol (125 mL) and sodium borohydride (1.84 g, 48 mmol) was added at a rate such that the reaction temperature stayed below 20 °C. The solution was stirred for 30 min after the addition was completed and then poured into water. The aqueous solution was extracted with ether (3 × 75 mL). The combined extracts were washed with saturated brine, dried ($MgSO_4$), and concentrated under vacuum. The residual alcohol **19** was taken up in benzene (200 mL) and *p*-toluenesulfonic acid (1 g) was added. The solution was refluxed for 15 h, using a Dean–Stark trap filled with anhydrous calcium chloride. After cooling, the reaction mixture was washed with saturated sodium bicarbonate and dried ($MgSO_4$) and the solvent evaporated. Distillation of the crude material gave lactone **21**: bp 70–75 °C (0.25 mm); 7.2 g (58%); IR (neat) 2986, 1730, 1180, 1056 cm^{-1}; NMR ($CDCl_3$) δ 0.98 (3 H, t), 1.2–2.2 (5 H, m), 2.58 (2 H, m), 4.0 (1 H, d of d), 4.35 (1 H, m). Anal. Calcd for $C_7H_{12}O_2$: C, 65.66; H, 9.42. Found: C, 65.43; H, 9.64.

For an alternative preparation of the hydroxy ester **19**, sodium borohydride was adsorbed on alumina. To 6.0 g of this $NaBH_4/Al_2O_3$ reagent,[25] being vigorously stirred in 18 mL of diethyl ether, was added 1.0 g of the aldehyde ester **18** in 15 mL of ether. After being stirred for 10 min, the mixture was filtered, the solid was washed with three 15-mL portions of ether, and the combined filtrates were concentrated to yield 0.83 g of **19** (82%) as a colorless oil: NMR ($CDCl_3$) δ 3.65 (3 H, s), 3.5 (2 H, d), 2.8–2.2 (4 H, br m), 1.8–1.1 (9 H, br m), 0.9 (3 H, t); IR (neat) 3400, 2940, 2860, 1725, 1450, 1430, 1230, 1190, 1165, 1050 cm^{-1}.

Methyl 4-(Bromomethyl)hexanoate (22a). A. Anhydrous lithium bromide (4.7 g, 54 mmol) was dissolved (Caution: exothermic) in anhydrous dimethylformamide (30 mL). After the mixture cooled to room temperature, the mesylate **20** (3.0 g, 12 mmol) was added and the reaction mixture was heated at 40 °C for 5 h. The solution was poured into water (150 mL) and extracted with hexane (2 × 75 mL). The combined extracts were washed with water, dried ($MgSO_4$), and concentrated, and the residual bromo ester **22** was distilled: bp 70–75 °C (0.1 mm); 1.95 g (74%); IR (neat) 2955, 1733, 1170 cm^{-1}; NMR ($CDCl_3$) δ 0.98 (3 H, t), 1.3–2.0 (5 H, m), 2.45 (2 H, t), 3.6 (2 H, d), 3.82 (3 H, s).

B. Anhydrous HBr gas was bubbled into lactone **21** (3 g, 23 mmol) at 60 °C for 30 min. The solution was allowed to cool and methanol (15 mL) with trimethyl orthoformate (2.5 g, 23 mmol) was added. The solution was stirred for 8 h, then concentrated, and distilled, bp 70–75 °C (0.1 mm), to produce the desired bromo ester **22a** (4.3 g, 83%) with spectroscopic data as shown above.

Methyl 4-(Chloromethyl)hexanoate (22b). Hydrogen chloride gas was passed into a solution of 2.0 g of the lactone **21** in 20 mL of methanol and the above procedure for the analogous bromide formation was then followed to produce a 94% yield of the chloride: bp 38–40 °C (0.02 mm); NMR ($CDCl_3$) δ 0.90 (3 H, t), 1.30–1.55 (3 H, m), 1.70 (2 H, t), 2.30 (2 H, t), 3.41 (2 H, d), 3.60 (3 H, t).

4-(Bromomethyl)hexanal (10a). The bromo ester **22a** (1.9 g, 8.5 mmol) was dissolved in anhydrous dichloromethane (20 mL) and cooled to −78 °C. With vigorous stirring, diisobutylaluminum hydride (10.2 mL, 1 M in hexane) was added dropwise over 10 min. The solution was stirred for an additional 20 min at −78 °C and then quenched by the addition of methanol (2 mL). The solution was poured into 3% HCl, extracted with dichloromethane (3 × 30 mL), and dried ($MgSO_4$). Concentration under vacuum gave a light oil which was purified by distillation: bp 78 °C (0.4 mm), 1.38 g (84%); IR (neat) 2959, 2720, 1720 cm^{-1}; NMR ($CDCl_3$) δ 0.97 (3 H, t), 1.3–2.0 (5 H, m), 2.57 (2 H, t), 3.6 (2 H, d), 10.15 (1 H, t).

(25) E. Santaniello, I. Ponti, and A. Manzocchi, *Synthesis*, 12, 891 (1978).

4-(Chloromethyl)hexanal (10b). This aldehyde, bp 45–50 °C (0.2 mm), was obtained in 77% from the corresponding ester **22b** by the above procedure: NMR ($CDCl_3$) δ 0.90 (3 H, t), 1.25–1.75 (3 H, m), 1.70 (2 H, t), 2.42 (2 H, t), 3.43 (2 H, d), 9.64 (1 H, t); 2,4-dinitrophenylhydrazone, mp 110–111 °C. Anal. Calcd for $C_{13}H_{17}N_4O_4Cl$: C, 47.49; H, 5.21; N, 17.04. Found: C, 47.63; H, 5.50; N, 16.76.

Pseudovincadifformine (5b) and 20-Epipseudovincadifformine (5c). A. The indoloazepine monoester **8b** (1.0 g, 4.1 mmol) was dissolved in methanol (30 mL) at room temperature and the bromo aldehyde **10a** (1.0 g, 5.3 mmol) was added. The solution was stirred for 4 h and then triethylamine (1 mL, excess) was added and the solution was heated at 40 °C with stirring for 16 h. The methanol was removed under vacuum and the residue was taken up in dichloromethane (75 mL), washed with saturated aqueous sodium carbonate, dried ($MgSO_4$), and concentrated. High-pressure LC (using a 10-in. commercial Waters Microporacil column with a flow rate of 0.9 mL/min), eluting with chloroform, showed two components, **5b** (retention time 10.3 min) and **5c** (retention time 8.5 min), with a ratio of 4:1 which corresponds to the two components (ratio 4:1) in a sample of natural "pseudovincadifformine". Medium-pressure (100 psi) column chromatography (4 ft × 1.25 in., silica gel), eluting with chloroform, allowed isolation of the major isomer as a homogeneous material (by high-pressure LC), which crystallized and was recrystallized from methanol–water (95:5): mp 118–119 °C; 155 mg (11%). For **5b** (major isomer): IR (KBr) 3365, 2955, 2773, 1666, 1605, 740 cm^{-1}; NMR ($CDCl_3$) δ 0.95 (3 H, t), 1.1–1.6 (4 H, m), 1.6–2.15 (4 H, m), 2.15–2.65 (3 H, m), 2.65–2.95 (4 H, m), 3.68 (3 H, s), 6.5–6.7 (2 H, m), 6.8–7.2 (2 H, m), 8.7 (1 H, br); UV (MeOH) λ_{max} 228, 298, 328 nm; mass spectrum (80eV), *m/e* (% at 100 °C, % at 120 °C) 124 (100, 100), 125 (37, 65), 139 (6, 12), 141 (10, 18), 153 (8, 16), 154 (8, 18), 167 (13, 29), 168 (7, 18), 169 (10, 25), 180 (9, 25), 193 (6, 16), 206 (5, 12), 239 (6, 14), 293 (9, 25) 307 (7, 18), 338 (92, 116), 339 (22, 61). Anal. Calcd for $C_{21}H_{26}N_2O_2$: C, 74.53; H, 7.74; N, 8.23. Found: C, 74.75, H, 7.75; N, 8.04.

Fractional crystallization of the remaining mixture of epimers, 415 mg (30%) from aqueous methanol, yielded the minor isomer 20-epi-ψ-vincadifformine (**5c**), mp 127–128 °C. This compound gave UV and solution IR spectra which matched those of the major isomer **5b**. A small difference was seen in IR spectra (KBr) in the fingerprint region: **5c** (975, 955, 935, 920, 900 cm^{-1}) vs. **5b** (960, 945, 930, 920, 910 cm^{-1}). The 270-MHz NMR[15] proton spectra were identical in the aromatic region and showed the same *O*-methyl (δ 3.77, s) and *C*-methyl (δ 0.93, t) signals but differed at all signals in between. Most notable was a symmetrical 9-line signal at δ 1.45 for **5b** contrasted with δ 1.59 (s) and δ 1.23 (t) for **5c**. The signal at δ 3.2 (d of d, 2 H) for **5c** was absent for **5b**. The mass spectrum of **5c** differed from that of epimeric **5b** primarily by the increased intensity of the fragment peak at 293: mass spectrum, *m/e* (% at 100 °C, % at 120 °C) 124 (100, 100), 125 (35, 69), 139 (6, 21), 141 (9, 9), 153 (7, 22), 154 (7, 25), 167 (15, 47), 168 (7, 24), 169 (11, 31), 180 (12, 37), 193 (12, 19), 206 (6, 16), 239 (5, 29), 293 (17, 56), 307 (7, 24), 338 (93, 120), 339 (23, 76).

B. By use of the same procedure with the indoloazepine diester **8c**, a 4:1 mixture of ψ-vincadifformines (**5b,c**) was obtained in 46% yield. When chloro aldehyde **10b** was used in place of the bromo aldehyde **10a**, the rate of product formation was decreased but the epimer ratio and final yield were unchanged. Heating the separate epimer **5b** or **5c** in methanol or THF with triethylamine or *p*-toluenesulfonic acid did not produce the respective other epimer.

Methyl 4-[(Phenylselenyl)methyl]hexanoate (24). A. Diphenyl diselenide (1.7 g, 5.3 mmol) was dissolved in anhydrous dimethylformamide (30 mL) and sodium borohydride (690 mg, 18 mmol) was carefully added (vigorous evolution of H_2). The solution changed from orange to nearly colorless as the reduction reached completion. After the reaction mixture was purged with nitrogen the mesylate **20** (2.1 g, 8.8 mmol) was added. The reaction mixture was stirred for 24 h at room temperature, followed by 3 h at 45 °C, and was then poured into water (150 mL). Extraction with pentane (4 × 75 mL), washing with water, drying ($MgSO_4$), and concentration gave a yellow oil which was column chromatographed on silica gel. Elution with hexane until the yellow diselenide band was removed and then elution with 1:1 ether–hexane gave the pure selenide **24** (2.2 g, 83%): IR (neat) 3060,

2960, 1735, 1558 cm^{-1}; NMR ($CDCl_3$) δ 0.85 (3 H, t), 1.2–1.9 (5 H, m), 2.3 (2 H, t), 2.9 (2 H, d), 3.6 (3 H, s), 7.15 (3 H, m), 7.44 (2 H, m).

B. Diphenyl diselenide (3.65 g, 11.7 mmol) was dissolved in freshly distilled dimethylformamide (15 mL) and sodium borohydride (0.89 g, 23 mmol), dissolved in dimethylformamide (10 mL), was carefully added (vigorous evolution of H_2) under a nitrogen atmosphere. The lactone **21** (3 g, 23 mmol) was then added and the solution was heated to 120 °C for 8 h. After cooling, the solution was made acidic with 3% HCl and extracted with ether (4 × 50 mL). The ether solution was washed with water, dried ($MgSO_4$), and concentrated. The crude carboxylic acid product was esterified by stirring for 15 h at reflux in anhydrous methanol (20 mL) with trimethyl orthoformate (2.5 g, 23 mmol) and *p*-toluenesulfonic acid (100 mg). Removal of the methanol in vacuo, followed by column chromatography of the residue on silica gel, eluting with hexane until the yellow diselenide band was removed and subsequently with ether, gave the pure selenide (3.8 g, 55%). In other runs the yield varied from 25% to 55%. See above for spectroscopic data.

Methyl 4-Ethyl-4-pentenoate (25). A. To a solution of selenide **24** (1.8 g, 6.0 mmol) in dichloromethane (15 mL), at −78 °C, was added *m*-chloroperbenzoic acid (1.28 g, 85%, 6.3 mmol). The solution was allowed to warm to room temperature over 30 min, then washed with water and saturated sodium carbonate, and dried ($MgSO_4$). The solvent was removed under vacuum and the residual selenoxide was taken up in carbon tetrachloride (15 mL). Triethylamine (640 mg, 6.3 mmol) was added and the solution was refluxed under nitrogen for 2 h. The mixture was then poured into dichloromethane (25 mL), washed with saturated aqueous sodium bicarbonate, dried ($MgSO_4$), and concentrated on a rotoevaporator. The olefin **25** was distilled, bp 70–75 °C (25 mm), to give a colorless oil (630 mg, 74%): IR (neat) 3070, 2960, 1740, 1645, 1160 cm^{-1}; NMR ($CDCl_3$) δ 1.0 (3 H, t), 2.03 (2 H, q), 2.2–2.6 (4 H, m), 3.64 (3 H, s), 4.7 (2 H, d).

B. Alternatively, 10 g of 4-ethyl-4-pentenoic acid, prepared from 1-chloro-2,2-dichloromethylbutane,[21] was esterified by refluxing for 16 h with 20 mg of *p*-toluenesulfonic acid in 30 mL of methanol and 100 mL of benzene, followed by washing with 10% aqueous sodium hydroxide, to give 9.14 g (82%) of **25**.

Methyl 4-Ethyl-4-oxiranylpentanoate (27). At 0 °C *m*-chloroperbenzoic acid (3.30 g, 85%, 17.9 mmol) was added to a stirred solution of olefin **25** (2.00 g, 14.1 mmol) in 100 mL of dichloromethane and 50 mL of 0.5 N aqueous $NaHCO_3$. The mixture was allowed to warm to room temperature over 1 h and was then washed twice with 100 mL of 5% aqueous sodium hydroxide, dried ($MgSO_4$), and concentrated under vacuum. The product was column chromatographed on silica, eluting with hexane followed by 2:8 ether–hexane, to furnish 2.08 g (93% yield) of **27**. The product could be distilled at 43 °C (0.3 mm): IR (neat) 2965, 1735, 1165 cm^{-1}; NMR ($CDCl_3$) δ 0.95 (3 H, t), 1.6 (2 H, m), 1.98 (2 H, t), 2.4 (2 H, t), 2.65 (2 H, s), 3.8 (3 H, s).

4-Ethyl-4-oxiranylpentanal (23). Ester **27** (1.90 g, 12.7 mmol) was dissolved in anhydrous dichloromethane (20 mL) and cooled to −78 °C under nitrogen. Diisobutylaluminum hydride (14 mL, 1 M in hexane) was added dropwise over 10 min, followed by continued stirring at −78 °C for 20 min. The reaction was then quenched by addition of methanol (1.3 mL), and after 5 min 2 g of magnesium sulfate heptahydrate was added. After being stirred for 10 min at −78 °C and 5 min at 20 °C, the reaction mixture was diluted with 50 mL of ether, washed twice with 25 mL of brine, and centrifuged. The separated salts were washed with ether, and the combined organic fractions were dried ($MgSO_4$) and concentrated under vacuum. The crude product (1.54 g) was flash distilled at a bath temperature of 60 °C (0.1 mm) to give 0.91 g of an unstable oil estimated to contain 40% aldehyde and 20% ester from NMR integration values of the aldehyde proton and methoxy protons: IR (neat) 2965, 2720, 1725, 1040 cm^{-1}; NMR ($CDCl_3$) δ 0.95 (3 H, t), 1.2–1.8 (2 H, m), 2.0 (2 H, t), 2.5 (1.2 H, t), 2.62 (1.2 H, s), 3.62 (0.6 H, s), 9.70 (0.4 H, t).

Pandoline (5d) and 20-Epipandoline (5e). Amine **8b** (1.00 g, 4.1 mmol) and epoxy aldehyde **23** (1.4 g crude, estimated to contain about 0.56 g pure, 4.3 mmol) were stirred under nitrogen in methanol (40 mL) for 10 h. TLC on silica gel (CH_2Cl_2–MeOH, 99:1) showed two main products (visualized as blue spots by spraying with 10% ceric ammonium sulfate in 85% phosphoric acid). After 1 h of reflux, the methanol was removed under vacuum and the residue was column chromatographed on silica gel, eluting with dichloromethane–methanol (99:1). Two principal components were obtained. The first, pandoline (**5d**, 440 mg, 31%), recrystallized from acetonitrile, had mp 150–151 °C; the second, 20-epipandoline (**5e**, 473 mg, 32%), recrystallized from acetonitrile–water (9:1), had mp 114–116 °C. Each was identical in all spectroscopic and TLC chromatographic respects (except optical rotation) with natural samples.[11] For pandoline (**5d**): IR (KBr) 3500, 3400, 2965, 2800, 1678, 1620 cm^{-1}; NMR ($CDCl_3$) δ 0.96 (3 H, t), 1.3–1.7 (4 H, m), 1.7–2.3 (4 H, m), 2.5–2.8 (3 H, m), 2.8–3.1 (4 H, m), 3.79 (3 H, s), 6.8–7.05 (2 H, m), 7.15–7.4 (2 H, m), 9.05 (1 H, br); UV (MeOH) λ_{max} 228, 298, 326 nm; mass spectrum *m/e* 354 (M^+), 239, 141, 140 (100%), 110, 88. Anal. Calcd for $C_{21}H_{26}N_2O_3$: C, 71.16; H, 7.39; N, 7.90. Found: C, 70.90; H, 7.35; N, 7.78.

For 20-epipandoline (**5e**): IR (KBr) 3450 (br), 3400, 2960, 2805, 1682, 1620 cm^{-1}; NMR ($CDCl_3$) δ 0.96 (3 H, t), 1.2–2.2 (8 H, m), 2.45 (2 H, m), 2.5–2.95 (3 H, m), 3.05 (1 H, s), 3.1 (1 H, d), 3.78 (3 H, s), 6.7–7.0 (2 H, m), 7.05–7.3 (2 H, m), 8.9 (1 H, br); UV (MeOH) λ_{max} 228, 298, 326 nm; mass spectrum, *m/e* 354 (M^+), 239, 141, 140 (100%), 110, 88. The mass spectra of **5d** and **5e** differed slightly, with *m/e* 88 and 239 more intense in **5d** than in **5e**.

16α- and 16β-(Carbomethoxy)velbanamines (28a,b) and N_a-Ethyl-2,16-dihydropandoline (29a). Over 10 min, 500 mg of $NaBH_4$ (13.2 mmol) was added to a solution of 800 mg of *dl*-pandoline (2.26 mmol) in 6 mL of acetic acid held at 90 °C. The mixture was poured into 50 mL of ice water, made basic with ammonium hydroxide, and extracted with 3 × 30 mL of dichloromethane. The combined organic extracts were filtered through phase-separating paper and concentrated under vacuum to 737 mg of solid, which was taken up in hot methanol. When the solution cooled, 314 mg (39%) of 16α-(carbomethoxy)velbanamine (**28a**) crystallized. Chromatography of the concentrated mother liquor on neutral alumina (activity III) and elution with dichloromethane gave an additional 137 mg (17%) of **28a** and 164 mg (20%) of the 16β-carbomethoxy isomer **28b** as well as 32 mg of the N_a-ethyl-2,16-dihydropandoline (**29a**).

Following the reaction progress by TLC, it was found that after 2 min the 16α-carbomethoxy isomer **28a** was almost the exclusive product with subsequent generation of isomer **28b** and decrease of isomer **28a**.

Isomer **28a**: recrystallized from methanol, mp 218–220 °C (methanolate); TLC (Merck silica, dichloromethane–5% methanol), R_f 0.8, brown-purple with ceric ammonium sulfate (CAS) spray; UV (ethanol) λ_{max} (log ϵ) 228 (4.40), 286 (3.85), 291 (3.82) nm; IR (KBr) ν_{max} 3550, 3375, 1715, 1460, 1440, 1370, 1335, 1315, 1260, 1250, 1200, 1170, 1130, 1035, 1000, 960, 935, 905, 855, 765, 750 cm^{-1}; NMR ($CDCl_3$) δ 8.70 (1 H, br), 7.55–6.92 (4 H, m), 5.71 (1 H, dd), 3.62 (3 H, s), 3.45 (CH_3OH), 0.93 (3 H, t); mass spectrum (80 eV), *m/e* 83, 124, 140, 142, 153, 154, 155, 215, 226, 257, 270, 297, 327, 338, 356, (357). Anal. Calcd for $C_{21}H_{28}N_2O_3 \cdot CH_3OH$: C, 68.01; H, 8.30; N, 7.21. Found: C, 68.18; H, 8.19; N, 7.01.

Isomer **28b**: perchlorate, recrystallized from methanol, mp 241–242 °C; TLC (as above), R_f 0.5, purple with CAS; R_f values of **28a** and **28b** reverse on alumina; UV (ethanol, $HClO_4$ salt) λ_{max} (log ϵ) 228 (4.44), 276 (4.05), 286 (4.05), 296 (3.85) nm; IR (KBr) ν_{max} ($HClO_4$ salt, KBr) 3450, 3350, 3110, 1730, 1720, 1460, 1440, 1340, 1215, 1115, 1065, 755 cm^{-1}; NMR ($CDCl_3$, free base) δ 8.92 (1 H, br), 7.48–6.92 (4 H, m), 3.92 (1 H, dd), 3.64 (3 H, s), 0.71 (3 H, t); mass spectrum, as for isomer **28a** except that fragment peaks *m/e* 257, 143, 124 were decreased and *m/e* 226 was increased in **28b**.

The N_a-ethyl-2,16-dihydropandoline (**29a**) showed R_f 0.7 in the above described TLC system and orange coloration with CAS spray: UV (ethanol) λ_{max} 214, 256 nm; mass spectrum (80 eV), *m/e* 140, 158, 172, 226, 264, 298, 353, 384, (385); NMR ($CDCl_3$) δ 7.3–6.4 (4 H, m), 3.8 (1 H, s), 3.7 (3 H, s), 0.97 (3 H, t), 0.87 (3 H, t).

Equilibration of Seco Pandoline Isomers 28a and 28b. A solution of 250 mg (0.71 mmol) of the above isomer **28a** in 2 mL of acetic acid was carefully purged with nitrogen and heated at 100 °C for 1.5 h. The cooled mixture was diluted with water, basified with ammonium hydroxide, and extracted with 3 × 25 mL of dichloromethane. A solid obtained on vacuum concen-

tration showed primarily isomer **28b** and only a trace of **28a** by TLC (above). Chromatography on alumina (neutral, activity III) and elution with ethyl acetate–hexane (1:4) gave 151 mg (63%) of isomer **28b**. Equilibration of 15 mg of pure isomer **28b** under the same conditions showed a small amount of isomer **28a** by TLC.

16α- and 16β-(Carbomethoxy)-20-epivelbanamines (28c,d). Reduction of 490 mg (1.38 mmol) of *dl*-20-epipandoline with 400 mg (10.6 mmol) of sodium borohydride in 6 mL of acetic acid for 10 min, as above, gave 208 mg (42%) of the 16α-carbomethoxy isomer **28c** on crystallization from methanol and another 65 mg (13%) after chromatography of the mother liquors on alumina (neutral, activity III), eluting with 4:1 hexane–ethyl acetate, in addition to 33 mg (6.7%) of isomer **28d**. Two further minor products were detected by TLC, giving orange color reactions with CAS spray like the *N*-ethyl-2,16-dihydropandoline (**29a**).

Isomer **28c** (methanolate): recrystallized from methanol, mp 203–206 °C; TLC (Merck silica, dichloromethane–5% methanol), R_f 0.7, grey-green with CAS spray; UV (ethanol) λ_{max} (log ϵ) 230 (4.36), 286 (3.86), 291 (3.83) nm; IR (KBr) ν_{max} 3550, 3375, 1725, 1460, 1435, 1330, 1315, 1260, 1200, 1170, 1040, 1010, 930, 800, 750 cm^{-1}; NMR ($CDCl_3$) δ 8.62 (1 H, br s), 7.54–6.98 (4 H, m), 5.04 (1 H, d), 3.68 (3 H, s), 3.45 (CH_3OH), 0.93 (3 H, t); mass spectrum identical with that of **28a**. Anal. Calcd for $C_{21}H_{28}N_2O_3 \cdot CH_3OH$: C, 68.01; H, 8.30; N, 7.21. Found: C, 68.14; H, 8.24; N, 7.05.

Isomer **28d**: perchlorate, recrystallized from methanol, mp 238–241 °C; TLC (as above), R_f 0.3, green with CAS spray; UV (HCl salt, ethanol) λ_{max} (log ϵ) 228 (4.44), 285 (4.0), 2.93 (3.97); IR ($HClO_4$ salt, KBr) ν_{max} 3510, 3390, 3170, 1730, 1720 (shoulder), 1460, 1440, 1340, 1305, 1290, 1230, 1165, 1105, 1060, 1025, 935, 905, 840, 750 cm^{-1}; NMR ($CDCl_3$ free base) δ 8.92 (1 H, br s), 7.48–6.92 (4 H, m), 3.84 (1 H, dd), 3.64 (3 H, s), 0.71 (3 H, t); mass spectrum, as for **28c** except for decreased fragment peaks at *m/e* 257, 143, 124 and an increased peak at *m/e* 226 for **28d**.

Equilibration of the seco 20-epipandolines **28c,d** under the conditions described for the seco pandolines **28a,b** showed analogous conversions but a relatively decreased rate of conversion of **28c** to **28d**.

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Registry No. (±)-**5b**, 73837-57-7; (±)-**5c**, 73836-92-7; (±)-**5d**, 73824-79-0; (±)-**5e**, 73805-38-6; (±)-**8a**, 66859-30-1; (±)-**8b**, 66859-22-1; **8c**, 69069-71-2; **9b**, 69069-58-5; (±)-**10a**, 73816-12-3; (±)-**10b**, 73805-39-7; (±)-**10b** DNP, 73805-40-0; (±)-**18**, 66757-48-0; (±)-**19**, 73805-41-1; (±)-**20**, 73805-42-2; (±)-**21**, 73805-43-3; (±)-**22a**, 73805-44-4; (±)-**22b**, 73805-45-5; (±)-**23**, 73805-46-6; (±)-**24**, 73805-47-7; **25**, 73805-48-8; (±)-**27**, 73805-49-9; (±)-**28a**, 73836-93-8; (±)-**28b**, 56596-08-8; (±)-**28b** perchlorate, 73836-94-9; (±)-**28c**, 73836-95-0; (±)-**28d**, 73837-58-8; (±)-**28d** perchlorate, 73889-50-6; (±)-**29a**, 73816-13-4; diphenyl diselenide, 1666-13-3; 4-ethyl-4-pentenoic acid, 13722-73-1.

Secotropane Alkaloids of *Physalis peruviana*

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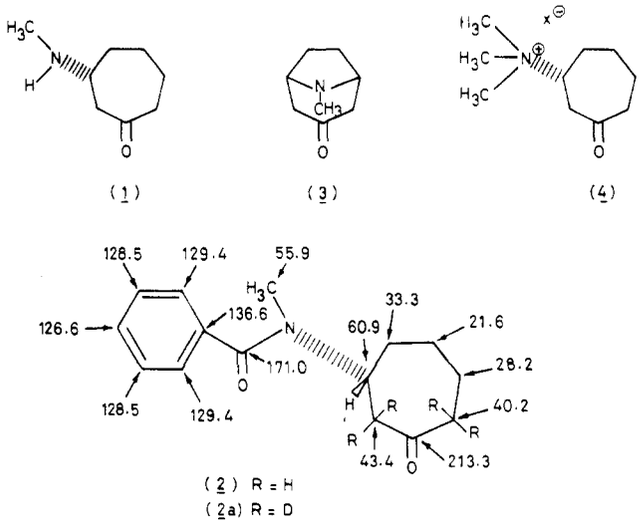
(+)-Physoperuvine, (±)-physoperuvine, and (+)-*N,N*-dimethylphysoperuvinium salt (anion unknown) were isolated from the roots of *Physalis peruviana*. Their structures were advanced on the basis of spectral and chemical evidence. These alkaloids comprise the first group of biogenetically interesting secotropane alkaloids.

The genus *Physalis* is reputed for elaborating C_{28} steroidal lactones, physalins and withanolides.[1] In addition to the isolation[2-5] of these groups of compounds from the leaves of *Physalis peruviana* L. (Solanaceae family), the presence of the alkaloids[6] tigloidine and 3-α-(tigloyloxy)-tropane was also detected in the roots of this plant. In the present paper we report that systematic fractionation of the alkaloidal constituents of the roots of *P. peruviana* yielded three alkaloids, none of which corresponded to either of the alkaloids[6] earlier reported from this source, and these were proved to be altogether new alkaloids. In a previous paper[7] we reported the structure of physoperuvine (1), the major alkaloid of this plant, exclusively on



^1H NMR and mass spectral evidence. We present here the detailed data in support of the structure and absolute configuration of physoperuvine and two of its congeners which comprise a new group of alkaloids and may appro-

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