Details of molecular geometry, atomic coordinates, calculated hydrogen coordinates, torsion angles, anisotropic thermal parameters, mean planes, and structure factors are available as Supplementary Material. Diagrams of molecule A (Figure 1,1b) were prepared with ORTEP.[39]

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(38) B. Frenz & Associates, Inc. *SDP-Plus*, College Station, TX, 1973, and Enraf-Nonius, Delft, Holland.
(39) Johnson, C. K. ORTEP II, Report ORNL-5138, Oak Ridge National Laboratory, Oak Ridge, TN, 1986.

Supplementary Material Available: Structure numbering (Figure 1b) and tables of molecular dimensions (bond lengths and angles), positional parameters, calculated hydrogen coordinates, torsion angles, anisotropic thermal parameters, and mean planes for $41 \cdot H_2O$ (16 pages); structure factors for $41 \cdot H_2O$ (21 pages). Ordering information is given on any current masthead page.

Synthesis of Vallesiachotamine[1]

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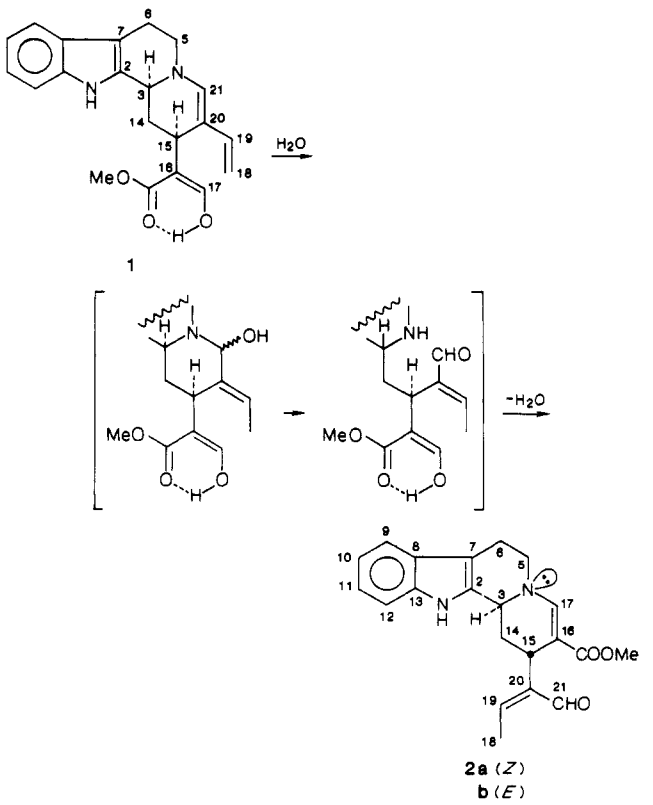
Interaction of methyl *N*-tryptophylnicotinate bromide with the lithium salt of ethyl α-(trimethylsilyl)acetate and acid-catalyzed cyclization has yielded a tetracyclic ester, whose condensation with acetaldehyde has produced ethyl vallesiachotamate. Reactions of lithiated, alkylthiolated esters with the nicotinate salt (followed by cyclization) have afforded related adducts. Ester-to-aldehyde group conversion has led to the alkaloid vallesiachotamine in the 19*Z* and 19*E* forms.

Vallesiachotamine (**2**), a minor constituent of the Peruvian plant *Vallesia dichotoma* Ruiz et Pav,[2a] of the Asian shrub *Rhazya orientalis*,[2b] and of the Cameroonian plant *Strychnos tricalysioides* Hutch. and M. B. Moss[2c] is an indole alkaloid of (at first glance) unusual structure but related by hydration, ring-chain tautomerization, and dehydration (Scheme I) to dehydrogeissoschizine (**1**), the vital, biosynthetic link connecting the large number of corynanthoid, heteroyohimboid, and yohimboid bases with those of the Strychnos family and others of like structural complexity.[3] The tetracyclic, urethane vinylogue structure of the alkaloid (**2**) with the trans H(3) -H(15) configuration was an ideal candidate for a short synthesis by way of the time-tested, two-step route of carbon nucleophile addition to 1-tryptophyl-3-acylpyridinium salts, followed by acid-induced ring closure (Scheme II).[4,5] Therefore a study of the alkaloid synthesis via this route was initiated.

The nicotinic ester derivative **3** (Y = OMe) was the starting pyridinium salt of choice. Whereas it already had been converted into tetracycle **4** (R = $CH(CO_2Me)_2$, Y = OMe) with malonic ester anion acting as the carbon nucleophile,[4b] alternative paths more readily introducing the crotonaldehyde side chain of vallesiachotamine were sought. For this reason the lithium salt of ethyl (trimethylsilyl)acetate was exposed to the methyl nicotinate

Scheme I



1

2a (*Z*)
b (*E*)

(1) For a preliminary communication, see: Spitzner, D.; Wenkert, E. *Angew. Chem.* **1984**, *96*, 972; *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 984.
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(3) Stöckigt, J.; Höfle, G.; Pfitzner, A. *Tetrahedron Lett.* **1980**, *21*, 1925 and references therein.
(4) (a) Wenkert, E.; Reynolds, G. D. *Synth. Commun.* **1973**, *3*, 241. (b) Wenkert, E.; Chang, C.-J.; Chawla, H. P. S.; Cochran, D. W.; Hagaman, E. W.; King, J. C.; Orito, K. *J. Am. Chem. Soc.* **1976**, *98*, 3645; **1982**, *104*, 6166. (c) Wenkert, E.; Halls, T. D. J.; Kunesch, G.; Orito, K.; Stephens, R. L.; Temple, W. A.; Yadav, J. S. *Ibid.* **1979**, *101*, 5370; **1982**, *104*, 6166. (d) Wenkert, E. *Pure Appl. Chem.* **1981**, *53*, 1271.
(5) For a partial synthesis from strictosidine, see: De Silva, K. T. D.; Smith, G. N.; Warren, K. E. H. *J. Chem. Soc. D* **1971**, 905.

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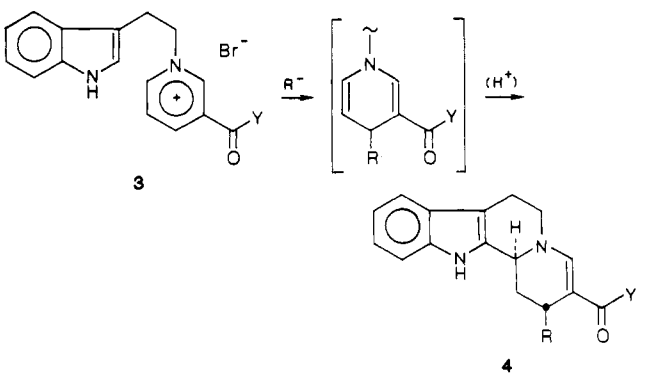
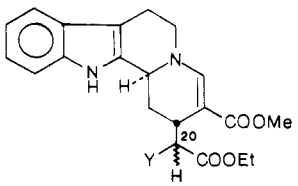
Scheme II

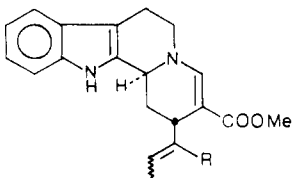


3 4

salt **3** (Y = OMe) and the adduct treated with hydrogen bromide. Not only was the product (**5a**) obtained (as mixture of 16-epimers) in higher yield (48%) than the malonic ester adduct[4b] but it also was substituted ideally for the next step of the reaction sequence, a Peterson olefination. Conversion of the silyl ester **5a** into its dianion with lithium diisopropylamide and interaction with acetaldehyde produced crotonic ester **6a** (69%) in a 4:1 *Z*/*E* ratio. Carefully controlled reduction of **6a** (as a mixture of diastereomers) with lithium aluminum hydride at ice-bath temperature furnished the allylic alcohol **6b** (81%), whose manganese dioxide oxidation led to (±)-vallesiachotamine (**2a**/**b**) in a 1:1 *Z*/*E* ratio.[6]



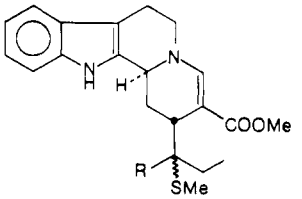
5a, Y = $SiMe_3$
b, Y = SMe
c, Y = H



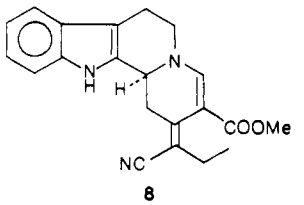
6a, R = CO_2Et
b, R = CH_2OH
c, R = CN
d, R = CO_2Me

It recently was shown that the first step of Scheme II is mechanistically more complex than a mere nucleophile–electrophile collapse and, in the absence of yet other, prior reactions, involves single-electron transfer between the carbanion and the pyridinium nucleus followed by radical coupling.[7] This had led to the use of anions whose radical equivalents are reasonably long-lived,[8] e.g., the utilization of the lithium salt of ethyl (methylthio)acetate in the reaction with salt **3** (Y = OMe) yielding tetracycle **5b** after acid treatment.[7] Raney nickel desulfurization of the latter had afforded ester **5c**,[7] a product identical with that formed on fluoride-induced desilylation (70%) of ester **5a**. It now became of interest to investigate the behavior of α-(methylthio)butyric acid derivatives in the first step of Scheme II, in view of this reaction constituting the direct introduction of a four-carbon side chain at C(15) of the vallesiachotamine (**2**) skeleton.

Treatment of α-(methylthio)butyronitrile[9] with lithium diisopropylamide and then with salt **3** (Y = OMe) and acid-catalyzed cyclization of the product yielded cyanide **7a** (23%) in the form of a ca. 1:1 mixture of 20-epimers. Oxidation of each isomer with *m*-chloroperbenzoic acid and pyrolysis of the resultant sulfoxides in benzene solution caused one epimer to be transformed into cyanide (*E*)-**6c** (71%) and the other into **8** (100%). A similar reaction sequence, starting with methyl α-(methylthio)butyrate,[10] led to ester **7b** (24%) as a ca. 1:1 mixture of 20-epimers and the oxidative elimination of the methylthio group converted each isomer into ester (*E*)-**6d** (23% and 20%).

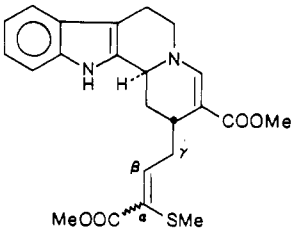


7a, R = CN
b, R = CO_2Me

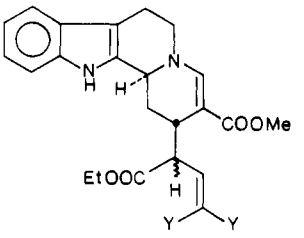


8

In an attempt to introduce an intact crotonic ester unit (in thiolated form) into the pyridinium nucleus, methyl α-(methylthio)crotonate[11] was treated at first with lithium diisopropylamide, next with salt **3** (Y = OMe), and finally with acid. The product was unfortunately ester **9** (11%), the new carbon–carbon bond having been formed at the sterically less demanding crotonic ester γ-carbon site.[12] On the other hand, the trio of reactions, when imposed on ethyl 4,4-bis(ethylthio)-3-butenoate,[13] gave ester **10a** (34%) in a ca. 3:1 20-epimer mixture. Desulfurization of the major isomer with deactivated Raney nickel[14] afforded ester **10b** (95%), whose treatment with ethanolic sodium ethoxide produced ester **6a** (100%) in ca. a 1:1 *Z*/*E* ratio. The reduction–oxidation conversion of this ester into (±)-vallesiachotamine (**2a**/**b**) has been described above.



9



10a, Y = SEt
b, Y = H

Experimental Section

Melting points were determined on a Reichert micro hotstage and a Büchi SMP-20 apparatus and are uncorrected. Ultraviolet spectra of methanol solutions were recorded on an IBM 9420 spectrophotometer and infrared spectra of chloroform solutions on a Perkin-Elmer 1320 spectrophotometer. ^1H NMR spectra of deuteriochloroform solutions were obtained on a Varian EM-390 spectrometer and ^{13}C NMR spectra of deuteriochloroform solutions on Nicolet QE-300 and Bruker WM 250 spectrometers (operating at 75.5 MHz and 62.88 MHz, respectively, in the Fourier transform mode). The carbon shifts are in ppm downfield from Me_4Si: $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm. Mass spectra were taken on a Varian MAT 311A spectrometer (low and high resolution). Extracts of crude products were dried over anhydrous Na_2SO_4 and chromatography was carried out on Florisil columns (when not stated otherwise).

Diester 5a. To a stirred suspension of 3.61 g (10 mmol) of salt **3** (Y = OMe) in 50 mL of dry tetrahydrofuran under an argon

(6) We thank Professor G. Höfle, GBF, Braunschweig, for samples of natural material and for their NMR spectra. This natural vallesiachotamine was a 1:1 mixture of *Z* and *E* isomers.
(7) Wenkert, E.; Angell, E. C.; Drexler, J.; Moeller, P. D. R.; Pyrek, J. S.; Shi, Y.-J.; Sultana, M.; Vankar, Y. D. *J. Org. Chem.* **1986**, *51*, 2995.
(8) Cf. Viehe, H. G.; Janousek, Z.; Merényi, R.; Stella, L. *Acc. Chem. Res.* **1985**, *18*, 148.
(9) (a) Gundermann, K. D. *Chem. Ber.* **1960**, *93*, 883. (b) Kadin, S. B. *J. Org. Chem.* **1966**, *31*, 620.
(10) Manfred, L. *J. Chem. Res., Synop.* **1982**, 286.
(11) Gundermann, K. D. *Chem. Ber.* **1959**, *92*, 1503.
(12) A similar regiochemistry is observed in the reactions of *tert*-butyl α-(trimethylsilyl)crotonate (D. Spitzner, unpublished observations).
(13) Bates, G. S.; Ramarswarmy, S. *Can. J. Chem.* **1983**, *61*, 2466.
(14) Cf. Autrey, R. L. *J. Am. Chem. Soc.* **1968**, *90*, 4917.

atmosphere and cooling (−50 °C) was added a freshly prepared solution of 2.1 equiv of lithium salt of ethyl (trimethylsilyl)acetate [from 3.5 g (22 mmol) of ethyl (trimethylsilyl)acetate and 23 mmol of lithium diisopropylamide] in dry tetrahydrofuran (50 mL). The reaction mixture was allowed to warm to 0 °C. Tetrahydrofuran was stripped off and replaced by dry benzene (50 mL), and the reaction mixture was acidified by the addition of a solution of hydrogen bromide in benzene (pH 3). After the removal of the solvent in vacuo, the residue was dissolved in methylene chloride (100 mL) and filtered through silica gel (150 g). Concentration of the filtrate gave 2.10 g (48%) of diester **5a** (as a mixture of epimers). One isomer was obtained pure: mp 173 °C; ^{1}H NMR δ 0.17 (s, 9, $SiMe_3$), 1.30 (t, 3, J = 7 Hz, ester Me), 3.68 (s, 3, ester Me), 4.1–4.2 (m, 2, ester CH_2), 4.72 (br d, 1, J = 12 Hz, H-3), 7.1–7.5 (m, 4, Ar Hs), 7.56 (s, 1, H-17), 7.84 (s, 1, NH); ^{13}C NMR δ −1.5 ($SiMe_3$), 14.6 (ester Me), 22.1 (C-6), 29.2 (C-15), 33.9 (C-14), 44.3 (C-20), 48.3 (C-3), 50.6 (OMe), 51.0 (C-5), 60.1 (ester CH_2), 96.7 (C-16), 108.2 (C-7), 111.1 (C-12), 118.1 (C-9), 119.8 (C-10), 122.1 (C-11), 133.1 (C-2), 136.4 (C-13), 146.7 (C-17), 168.7 (C=O), 174.9 (C-21); MS, m/e (relative intensity) 440 (70), 381 (30), 281 (100), 279 (70), 221 (80); exact mass, m/e 440.2130 (calcd for $C_{24}H_{32}N_2O_4Si$ m/e 440.2131).

Ethyl Vallesiachotamate (6a). To a stirring solution of 1.4 mmol of lithium diisopropylamide [freshly prepared from 0.65 mL of n-butyllithium (2.2 M) and 0.150 g of diisopropylamine in 10 mL of dry tetrahydrofuran] under an argon atmosphere was added a solution of 0.260 g (0.6 mmol) of diester **5a** in 10 mL of dry tetrahydrofuran at −40 °C. Stirring was continued for 30 min after which a solution of 0.1 g (2.3 mmol) of acetaldehyde in 2 mL of dry tetrahydrofuran was added. The temperature was allowed to rise to 20 °C within 2 h and the reaction was quenched with 50 mL of saturated ammonium chloride solution. The mixture was extracted with methylene chloride and chromatographed on silica gel (1:1 pentane–ether) to give 0.385 g of **6a** as a 4:1 mixture of Z/E diastereomers: ^{1}H NMR δ 1.29 and 1.39 (2 t, 3, J = 7 Hz, ester Me), 1.92 (d, 2.4, J = 7 Hz, (Z) H-18), 3.65 (s, 2.4, Me of Z ester), 3.67 (s, 0.6, Me of E ester), 4.17 (q, 1.6, J = 7 Hz, CH_2 of Z ester), 4.33 (q, 0.4, J = 7 Hz, CH_2 of E ester), 4.69 (br d, 1, J = 11 Hz, H-3), 5.93 (qd, 0.2, J = 7, 1 Hz, H-19 E isomer), 6.93 (q, 0.8, J = 7 Hz, H-19 Z isomer), 7.1–7.5 (m, 4, Ar Hs), 7.64 (s, 0.8, H-17 Z isomer), 7.72 (s, 0.2, H-17 E isomer), 7.82 and 7.86 (br s, 1 NH); MS, m/e (relative intensity) 394 (100), 379 (40), 335 (90); exact mass, m/e 394.1857 (calcd for $C_{23}H_{26}O_4N_2$ m/e 394.1824).

A solution of 60 mg (0.15 mmol) of ester **10b** in 10 mL of 10% ethanolic sodium ethoxide solution was stirred at room temperature for 4 h. It was poured into 50 mL of 10% ammonium chloride solution and extracted exhaustively with methylene chloride. The extract was washed with brine and dried. Evaporation gave 60 mg (100%) of ester **6a** in ca. a 1:1 Z/E ratio, NMR spectrally identical with the sample of the **5a** → **6a** conversion.

Alcohol 6b. To a stirring solution of 0.073 g (0.19 mmol) of ester **6a** [4:1 Z/E isomer mixture] in 10 mL of dry tetrahydrofuran at ice-bath temperature was added 0.010 g of lithium aluminum hydride. The reaction was quenched by careful addition of 1 N hydrochloric acid (pH 5) after stirring for 2 h. The mixture was extracted with methylene chloride, and the organic layer was dried and evaporated. Chromatography on silica gel and elution with ether gave 0.053 g (81.5%) of alcohol **6b** as a 4:1 stereoisomer mixture.

Major alcohol [(Z)-**6b**]: ^{1}H NMR δ 1.73 (d, J = 7 Hz, 3, Me), 3.66 (s, 3, OMe), 4.40 (br d, J = 12 Hz, 1, H-3), 5.37 (q, J = 7 Hz, H-18), 7.1–7.5 (m, 4, Ar Hs), 7.68 (s, 1, H-17).

Minor alcohol [(E)-**6b**]: mp 233 °C (ether–pentane) dec; IR [NH] 3400 (m), [OH] 3260 (m), [C=O] 1660 (s), 1605 (s) cm^{-1}; ^{1}H NMR δ 1.80 (d, J = 7 Hz, 3, Me), 3.67 (s, 3, OMe), 3.98 and 4.06 (AB, J = 12 Hz, 2, H-21), 4.63 (br d, J = 11 Hz, 1, H-3), 5.70 (q, J = 7 Hz, H-18), 7.1–7.5 (m, 4, Ar Hs), 7.68 (s, 1, H-17), 8.00 (br s, 1, NH); MS, m/e (relative intensity) 352 (40), 281 (40), 279 (100); exact mass, m/e 352.1776 (calcd for $C_{21}H_{24}N_2O_3$ m/e 352.1777).

(±)-Vallesiachotamine (2a,b). To a solution of 10 mg (0.28 mmol) of **6b** in 10 mL of methylene chloride was added 100 mg of manganese dioxide (Fluka, Buchs, Switzerland) and the suspension stirred for 5 h. Filtration and evaporation gave a semisolid foam which was chromatographed on silica gel and eluted with ether to give 6 mg (60%) of a 1:1 **2a,b** isomer mixture. This mixture proved to be identical in TLC behavior and spectroscopically (IR, UV, and ^{1}H NMR) with a sample from plant cell cultures.

19,20-Dihydro-20-(methylthio)vallesiachotamonitrile (7a). A solution of 2.0 mL (14.1 mmol) of diisopropylamine in 40 mL of anhydrous tetrahydrofuran under nitrogen at −78 °C was mixed with 10.0 mL (14.1 mmol) of a 1.5 M hexane solution of n-butyllithium. The temperature was allowed to rise to 0 °C and the mixture stirred for 0.5 h. A solution of 1.43 g (14.1 mmol) of α-(methylthio)butyronitrile[8] in 10 mL of dry tetrahydrofuran was added to the stirring mixture at −78 °C and the stirring continued for 1 h. Salt **3** (Y = OMe) (3.84 g, 10.7 mmol) was added in one portion and the suspension stirred at −78 °C for 2 h. The temperature was permitted to rise to 0 °C and the mixture stirred for another 2 h. Enough dry benzene, saturated with hydrogen bromide, was added dropwise to bring the pH to 5 and stirring was continued at 0 °C for 1 h. The mixture was poured into 200 mL of saturated sodium bicarbonate solution and extracted with ether. The extract was dried and evaporated. Chromatography and elution with 2:1 hexane–ethyl acetate gave 0.963 g (23%) of semisolid cyanide **7a** as a 4:3 stereoisomer mixture.

MPLC separation led to major cyanide **7a**: mp 204–205 °C (Et_2O); UV λ_{max} 223 nm (log ϵ 4.60), 287 (4.60), 291 (4.61); IR [NH] 3450 (m), [C≡N] 2220 (w), [C=O] 1670 (s), 1605 (s), [C=C] 1590 (s) cm^{-1}; ^{1}H NMR δ 1.19 (t, 3, J = 7 Hz, Me), 2.25 (s, 3, SMe), 3.70 (s, 3, OMe), 5.20 (br d, 1, J = 12 Hz, H-3), 7.13 (t, 1, J = 7 Hz, H-10), 7.20 (t, 1, J = 7 Hz, H-11), 7.37 (d, 1, J = 7 Hz, H-9), 7.49 (d, 1, J = 7 Hz, H-12), 7.81 (s, 1, H-17); ^{13}C NMR δ 8.5 (C-18), 12.6 (SMe), 21.9 (C-6), 28.4 (C-19), 30.6 (C-14), 34.3 (C-15), 48.1 (C-3), 50.6 (OMe), 51.1 (C-5), 52.6 (C-20), 91.4 (C-16), 107.9 (C-7), 110.9 (C-12), 118.0 (C-9), 119.6 (C-10), 120.9 (C-21), 122.0 (C-11), 126.5 (C-8), 131.9 (C-2), 136.1 (C-13), 148.4 (C-17), 168.7 (C=O); exact mass, m/e 395.1691 (calcd for $C_{22}H_{25}O_2N_3S$ m/e 395.1668).

Minor cyanide **7a**: mp 216–218 °C (Et_2O); UV λ_{max} 223 nm (log ϵ 4.60), 287 (4.60), 291 (4.61); IR [NH] 3450 (m), [C≡N] 2220 (w), [C=O] 1670 (s), 1605 (s), [C=C] 1590 (s) cm^{-1}; ^{1}H NMR δ 1.23 (t, 3, J = 7 Hz, Me), 2.25 (s, 3, SMe), 3.65 (s, 3, OMe), 5.11 (br d, 1, J = 12 Hz, H-3), 7.0–7.6 (m, 4, Ar Hs), 7.72 (s, 1, H-17); ^{13}C NMR δ 10.2 (C-18), 13.8 (SMe), 21.9 (C-6), 31.2 (C-14), 32.9 (C-15, C-19), 48.6 (C-3), 50.7 (OMe), 51.2 (C-5), 54.0 (C-20), 89.5 (C-16), 107.8 (C-7), 110.9 (C-12), 117.9 (C-9), 119.5 (C-10, C-21), 121.9 (C-11), 126.4 (C-8), 131.9 (C-2), 136.2 (C-13), 148.5 (C-17), 168.8 (C=O).

Methyl 19,20-Dihydro-20-(methylthio)vallesiachotamate (7b). The same reaction and workup with the use of 1.5 mL (10.5 mmol) of diisopropylamine in 30 mL of anhydrous tetrahydrofuran, 7.0 mL of 1.5 M hexane solution of n-butyllithium, and 1.55 g (10.5 mmol) of methyl α-(methylthio)butyrate[10] in 5 mL of dry tetrahydrofuran led to 0.510 g (24%) of ester **7b** as a 4:3 stereoisomer mixture.

MPLC separation yielded major ester **7b**: mp 221–223 °C (pentane); UV λ_{max} 223 nm (log ϵ 4.60), 292 (4.60); IR [NH] 3450 (m), [C=O] 1710 (s), 1660 (s), 1605 (s), [C=C] 1590 (s), 1550 (m) cm^{-1}; ^{1}H NMR δ 0.93 (t, 3, J = 7 Hz, Me), 2.11 (s, 3, SMe), 3.68 (s, 3, OMe), 3.81 (s, 3, 21-OMe), 5.32 (dd, 1, J = 12, 2 Hz, H-3), 7.11 (t, 1, J = 7 Hz, H-10), 7.18 (t, 1, J = 7 Hz, H-11), 7.35 (d, 1, J = 7 Hz, H-9), 7.48 (d, 1, J = 7 Hz, H-12), 7.69 (s, 1, H-17); ^{13}C NMR δ 9.7 (C-18), 12.5 (SMe), 22.0 (C-6), 28.3 (C-19), 31.4 (C-14), 37.0 (C-15), 49.0 (C-3), 50.6 (OMe), 51.1 (C-5), 52.3 (21-OMe), 63.8 (C-20), 91.4 (C-16), 107.6 (C-7), 110.9 (C-12), 117.9 (C-9), 119.5 (C-10), 121.8 (C-11), 126.5 (C-8), 133.0 (C-2), 136.0 (C-13), 147.8 (C-17), 169.1 (C=O), 173.9 (C-21); exact mass, m/e (M + 1) 429.1880 (calcd for $C_{23}H_{29}O_4N_2S$ m/e 429.1846).

Minor ester **7b**: mp 225–227 °C (Et_2O); UV λ_{max} 222 nm (log ϵ 4.68), 286 (4.63), 292 (4.66); IR [NH] 3460 (m), [C=O] 1710 (s), 1660 (s), 1610 (s), [C=C] 1590 (s), 1540 (m) cm^{-1}; ^{1}H NMR δ 0.92 (t, 3, J = 7 Hz, Me), 1.98 (s, 3, SMe), 3.60 (s, 3, 21-OMe), 3.67 (s, 3, OMe), 4.40 (br d, 1, J = 12 Hz, H-3), 7.0–7.5 (m, 4, Ar Hs), 7.57 (s, 1, H-17); ^{13}C NMR δ 9.6 (C-18), 10.8 (SMe), 22.0 (C-6), 26.4 (C-19), 30.1 (C-14), 35.7 (C-15), 48.0 (C-3), 50.6 (OMe), 51.1 (C-5), 51.8 (21-OMe), 65.8 (C-20), 92.0 (C-16), 107.2 (C-7), 111.0 (C-12), 117.8 (C-9), 119.3 (C-10), 121.7 (C-11), 126.3 (C-8), 132.8 (C-2), 136.1 (C-13), 147.3 (C-17), 169.5 (C=O), 173.8 (C-21); exact mass, m/e (M + 1) 429.1834 (calcd for $C_{23}H_{29}O_4N_2S$ m/e 429.1846).

Vallesiachotamonitrile (6c). Following the procedure of **7b** → **6d** conversion (see below), 62 mg (0.16 mmol) of cyanide **7a** (minor isomer) was transformed [32 mg of 85% *m*-chloroperbenzoic acid (0.16 mmol); sulfoxide refluxed for 5.5 h] into 39 mg (71%) of cyanide (*E*)-**6c**: mp 212–214 °C (Et_2O); UV λ_{max} 222 nm (log ϵ 4.51), 288 (4.48), 291 (4.49); IR [NH] 3460 (m), [C≡N] 2210 (w), [C=O] 1670 (s), 1610 (s), [C=C] 1590 (s) cm^{-1}; ^1H NMR δ 2.04 (d, 3, J = 7 Hz, Me), 3.63 (s, 3, OMe), 4.41 (d, 1, J = 11 Hz, H-3), 6.26 (q, 1, J = 7 Hz, H-9), 7.12 (t, 1, J = 7 Hz, H-10), 7.20 (t, 1, J = 7 Hz, H-11), 7.37 (d, 1, J = 7 Hz, H-9), 7.49 (d, 1, J = 7 Hz, H-12), 7.72 (s, 1, H-17); ^{13}C NMR δ 17.1 (C-18), 21.8 (C-6), 32.5 (C-14), 35.0 (C-15), 47.3 (C-3), 50.8 (OMe), 51.0 (C-5), 91.5 (C-16), 108.4 (C-7), 111.0 (C-12), 117.9 (C-9), 119.0 (C-21), 119.6 (C-10), 122.1 (C-11), 126.4 (C-8), 131.4 (C-2), 136.0 (C-13), 144.8 (C-19), 147.7 (C-17), 167.8 (C=O); exact mass, m/e 347.1629 (calcd for $C_{21}H_{21}O_2N_3$ m/e 347.1634).

15,20-Didehydro-19,20-dihydrovallesiachotamonitrile (8). When the **7b** → **6d** conversion procedure (see below) was used on 0.336 g (0.85 mmol) of cyanide **7a** (major isomer), it [0.173 g of 85% *m*-chloroperbenzoic acid (0.85 mmol); sulfoxide refluxed for 5 h] led to 0.295 g (100%) of cyanide **8**: mp 235–237 °C (Et_2O); UV λ_{max} 222 nm (log ϵ 4.75), 276 (4.43), 290 (4.30), 337 (4.46); IR [NH] 3460 (m), [C≡N] 2220 (s), [C=O] 1660 (s), [C=C] 1590 (s), 1560 (s) cm^{-1}; ^1H NMR δ 1.20 (t, 3, J = 7 Hz, Me), 3.72 (s, 3, OMe), 4.78 (br d, 1, J = 12 Hz, H-3), 7.13 (t, 1, J = 7 Hz, H-10), 7.22 (t, 1, J = 7 Hz, H-11), 7.42 (d, 1, J = 7 Hz, H-9), 7.50 (d, 1, J = 7 Hz, H-12), 7.66 (s, 1, H-17); ^{13}C NMR δ 12.4 (C-18), 22.1 (C-6), 25.1 (C-9), 36.6 (C-14), 51.0 (OMe), 51.3 (C-5), 53.4 (C-3), 95.2 (C-16), 107.6 (C-15), 107.9 (C-7), 111.2 (C-12), 118.1 (C-9), 119.6 (C-10), 120.2 (C-21), 122.3 (C-11), 126.1 (C-8), 130.6 (C-2), 136.0 (C-13), 142.2 (C-20), 149.9 (C-17), 166.3 (C=O); exact mass, m/e 347.1635 (calcd for $C_{21}H_{21}O_2N_3$ m/e 347.1634).

Methyl Vallesiachotamate (6d). A solution of 58 mg of 85% *m*-chloroperbenzoic acid (0.29 mmol) in 10 mL of methylene chloride was added dropwise over a 5-min period into a stirring solution of 122 mg (0.29 mmol) of ester **7b** (minor isomer) in 10 mL of methylene chloride at −78 °C and the stirring continued for 5 min. The mixture was diluted with 100 mL of ether, washed with 50 mL of 10% sodium sulfite solution and then exhaustively with saturated sodium bicarbonate, dried, and evaporated under vacuum. A mixture of the residual, foamy sulfoxide (127 mg) and a few crystals of calcium carbonate in 30 mL of benzene was stirred and refluxed for 6 h. It was filtered and the filtrate evaporated. Chromatography of the residue and elution with 9:1 hexane–ethyl acetate yielded 25 mg (23%) of ester (*E*)-**6d**: mp 220–222 °C (hexane–methylene chloride); UV λ_{max} 223 nm (log ϵ 4.51), 292 (4.49); IR [NH] 3460 (m), [C=O] 1700 (s), 1670 (s), 1620 (s), [C=C] 1590 (m) cm^{-1}; ^1H NMR δ 2.02 (d, 3, J = 7 Hz, Me), 3.67 (s, 3, OMe), 3.84 (s, 3, 21-OMe), 4.36 (br d, 1, J = 12 Hz, H-3), 5.96 (q, 1, J = 7 Hz, H-19), 7.11 (t, 1, J = 7 Hz, H-10), 7.17 (t, 1, J = 7 Hz, H-11), 7.31 (d, 1, J = 7 Hz, H-9), 7.48 (d, 1, J = 7 Hz, H-12), 7.73 (s, 1, H-17); ^{13}C NMR δ 15.7 (C-18), 21.9 (C-6), 33.1 (C-15), 33.9 (C-14), 47.2 (C-3), 50.7 (OMe), 50.8 (C-5), 51.4 (21-OMe), 94.1 (C-16), 108.5 (C-7), 110.8 (C-12), 117.9 (C-9), 119.6 (C-10), 121.9 (C-11), 126.6 (C-8), 132.1 (C-2), 135.6 (C-20), 136.1 (C-13), 138.6 (C-19), 147.2 (C-17), 168.1 (C=O), 168.6 (C-21); exact mass, m/e 380.1747 (calcd for $C_{22}H_{24}O_4N_2$ m/e 380.1733).

The same two reactions with 100 mg (0.23 mmol) of ester **7b** (major isomer) [48 mg of 85% *m*-chloroperbenzoic acid (0.23 mmol)] gave 18 mg (20%) of ester (*E*)-**6d**.

Ester 9. A hexane solution of *n*-butyllithium (3.34 mL, 5.0 mmol) was poured dropwise into a stirring solution of 0.71 mL (5 mmol) of isopropylamine in 20 mL of anhydrous tetrahydrofuran under nitrogen at −78 °C and the stirring continued for 0.5 h. A solution of 730 mg (5.0 mmol) of methyl α-(methylthio)-crotonate[11] in 5 mL of dry tetrahydrofuran was added dropwise and the stirring continued at −78 °C for 1 h. Salt **3** (Y = OMe) (900 mg, 2.5 mmol) was added in one portion and the stirring mixture kept for 5 h at −78 °C and then allowed to warm to 0 °C. Enough benzene, saturated with hydrogen bromide, was added dropwise to bring the pH to 5 and the mixture was stirred at 0 °C for 1 h. It was poured into 100 mL of saturated sodium bicarbonate solution and extracted with methylene chloride. The extract was washed with brine, dried, and evaporated. Chromatography of the residue and elution with 4:1 hexane–ethyl acetate led to 116 mg (11%) of amorphous ester **9**: UV λ_{max} 222 nm (log ϵ 4.42), 287 (4.37), 292 (4.39),; IR [NH] 3450 (m), [C=O] 1710 (s), 1665 (s), 1610 (s), [C=C] 1590 (s) cm^{-1}; ^1H NMR δ 2.33 (s, 3, SMe), 3.71 (s, 3, 21-OMe), 3.86 (s, 3, crotonate OMe), 4.70 (br d, 1, J = 12 Hz, H-3), 7.11 (t, 1, J = 7 Hz, H-10), 7.17 (t, 1, J = 7 Hz, H-11), 7.31 (t, 1, J = 8 Hz, β-H), 7.37 (d, 1, J = 7 Hz, H-9), 7.48 (d, J = 7 Hz, H-12), 7.59 (s, 1, H-17); ^{13}C NMR δ 17.3 (SMe), 21.9 (C-6), 30.5 (C-15), 31.4 (C-14), 37.0 (γ-C), 47.7 (C-3), 50.6 (C-5), 50.9 (OMe), 52.6 (crotonate OMe), 97.0 (C-16), 108.3 (C-7), 111.0 (C-12), 117.9 (C-9), 119.6 (C-10), 122.0 (C-11), 126.6 (C-8), 130.0 (α-C), 132.3 (C-2), 136.1 (C-13), 146.4 (β-C), 148.6 (C-17), 165.5 (crotonate C=O), 168.4 (C=O); exact mass, m/e 426.1622 (calcd for $C_{23}H_{26}O_4N_2S$ m/e 426.1610).

Ethyl 18,19-Didehydro-19,20-dihydro-18,18-bis(ethylthio)vallesiachotamate (10a). A hexane solution of *n*-butyllithium (4.50 mL, 6.0 mmol) was poured dropwise into a stirring solution of 0.84 mL (6.0 mmol) of diisopropylamine in 40 mL of anhydrous tetrahydrofuran under nitrogen at −78 °C and the stirring continued for 0.5 h. A solution of 1.18 g (5.0 mmol) of ethyl 4,4-bis(ethylthio)-3-butenoate[13] in 5 mL of dry tetrahydrofuran was added dropwise and the stirring was continued at −78 °C for 1 h. Salt **3** (Y = OMe) (1.80 g, 5.0 mmol) was added in one portion and the stirring mixture kept at −78 °C for 3 h and then permitted to warm slowly to 0 °C. Enough benzene, saturated with hydrogen bromide, was added dropwise to bring the pH to 5 and the mixture was stirred at 0 °C for 1 h. It was poured into 100 mL of saturated sodium bicarbonate solution and extracted with methylene chloride. The extract was washed with brine, dried, and evaporated. Chromatography of the residue and elution with 4:1 hexane–ethyl acetate gave 973 mg (34%) of ester **10a** in a 3:1 stereoisomer mixture.

MPLC separation yielded amorphous major ester **10a**: UV λ_{max} 223 nm (log ϵ 4.51), 292 (4.49); IR [NH] 3460 (m), [C=O] 1710 (s), 1670 (s), 1605 (s), [C=C] 1590 (s) cm^{-1}; ^1H NMR δ 1.19, 1.28 (t, 3 each, J = 7 Hz, SEt methyls), 1.30 (t, 3, J = 7 Hz, Me of OEt), 3.68 (s, 3, OMe), 4.00 (dd, 1, J = 10, 8 Hz, H-20), 4.14 (q, 2, J = 7 Hz, OCH_2), 4.74 (dd, 1, J = 11, 1 Hz, H-3), 6.34 (d, 1, J = 10 Hz, H-19), 7.11 (t, 1, J = 7 Hz, H-10), 7.18 (t, 1, J = 7 Hz, H-11), 7.35 (d, 1, J = 7 Hz, H-9), 7.48 (d, 1, J = 7 Hz, H-12), 7.62 (s, 1, H-17); ^{13}C NMR δ 14.1 (2 SEt methyls), 14.8 (Me of OEt), 21.9 (C-6), 27.0 (SCH_2), 27.6 (SCH_2), 30.9 (C-14), 34.1 (C-15), 48.3 (C-3), 50.5 (OMe), 50.9 (C-5), 51.9 (C-20), 60.7 (OCH_2), 94.4 (C-16), 108.2 (C-7), 110.9 (C-12), 118.0 (C-9), 119.6 (C-10), 122.0 (C-11), 126.6 (C-8), 132.5 (C-2), 133.0 (C-18), 133.6 (C-19), 136.0 (C-13), 146.6 (C-17), 168.3 (C=O), 172.3 (C-21); exact mass, m/e 514.1954 (calcd for $C_{27}H_{34}O_4N_2S_2$ m/e 514.1958).

Minor ester **10a**: UV λ_{max} 223 nm (log ϵ 4.51), 286 (4.39), 292 (4.44); IR [NH] 3460 (m), [C=O] 1710 (s), 1670 (s), 1605 (s), [C=C] 1590 (s) cm^{-1}; ^1H NMR δ 1.18, 1.29 (t, 3 each, J = 7 Hz, SEt methyls), 1.31 (t, 3, J = 7 Hz, Me of OEt), 3.66 (s, 3, OMe), 4.09 (t, 1, J = 10 Hz, H-20), 4.22 (q, 2, J = 7 Hz, OCH_2), 4.79 (br d, 1, J = 12 Hz, H-3), 6.26 (d, 1, J = 10 Hz, H-19), 7.11 (t, 1, J = 7 Hz, H-10), 7.18 (t, 1, J = 7 Hz, H-11), 7.35 (d, 1, J = 7 Hz, H-9), 7.48 (d, 1, J = 7 Hz, H-12), 7.55 (s, 1, H-17); ^{13}C NMR δ 14.1 (2 SEt methyls), 14.8 (Me of OEt), 21.9 (C-6), 26.8 (SCH_2), 27.3 (SCH_2), 32.3 (C-14), 32.9 (C-15), 47.8 (C-3), 50.5 (OMe), 50.9 (C-5), 53.5 (C-20), 60.7 (OCH_2), 94.1 (C-16), 108.3 (C-7), 110.9 (C-12), 118.0 (C-9), 119.6 (C-10), 122.0 (C-11), 126.7 (C-8), 132.4 (C-2), 132.5 (C-18), 133.2 (C-19), 136.1 (C-13), 146.6 (C-17), 168.5 (C=O), 172.5 (C-21); exact mass (M + 1), m/e 515.2099 (calcd for $C_{27}H_{35}O_4N_2S_2$ m/e 515.2036).

Ethyl 18,19-Didehydro-19,20-dihydrovallesiachotamate (10b). A vigorously stirring mixture of 1.5 mL of 50% aqueous Raney nickel slurry (pH 10, deactivated by a literature procedure[14]) and 150 mg (0.29 mmol) of ester **10a** (minor isomer) in 30 mL of methanol was refluxed for 2.5 h and then filtered. The precipitate was washed with methanol and the combined filtrate and washings were evaporated. A methylene chloride solution of the residue was washed with saturated ammonium chloride solution and with brine, dried, and evaporated. Chromatography of the residue and elution with 4:1 hexane–ethyl acetate gave 109 mg (95%) of ester **10b**: mp 183–185 °C (Et_2O); UV λ_{max} 223 nm (log ϵ 4.61), 292 (4.65); IR [NH] 3460 (m), [C=O] 1710 (s), 1670 (s), 1610 (s), [C=C] 1590 (s) cm^{-1}; ^1H NMR δ 1.31 (t, 3, J = 7 Hz, Me), 3.16 (t, 1, J = 10 Hz, H-20), 3.66 (s, 3, OMe), 4.22 (q, 2, J = 7 Hz, OCH_2), 4.68 (br d, 1, J = 12 Hz, H-3), 5.0–6.1 (m, 3, H_2-18, H-19), 7.11 (t, 1, J = 7 Hz, H-10), 7.17 (t, 1, J = 7 Hz,

H-11), 7.32 (d, 1, J = 7 Hz, H-9), 7.47 (d, 1, J = 7 Hz, H-12), 7.58 (s, 1, H-17); exact mass, m/e 394.1890 (calcd for $C_{23}H_{26}O_4N_2$ m/e 394.1891).

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"*tert*-Amino Effect" in Heterocyclic Synthesis. The Effect of a *p*-Quinone Moiety on the [1,6] H-Transfer and 1,5-Electrocyclization Reactions

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(Dialkylamino)benzo*quinone* **15** and (dialkylamino)naphtho*quinones* **32** and **34–37** undergo a thermal cyclization to the corresponding pyrrolo[1,2-*a*]indoles **41**, **43**, and **45–47** and to the pyrido[1,2-*a*]indole **44**, respectively. A corresponding *hydroquinone*, viz. (*E*/*Z*)-2,5-dimethoxy-α-(phenylmethylene)-3,6-di(1-pyrrolidinyl)benzeneacetonitrile (**18**), cyclizes only slowly to pyrrolo[1,2-*a*]indole **42**. The naphtho*hydroquinones* **38–40** do not undergo a thermal rearrangement. The results demonstrate the accelerating effect of the *quinone* function on the rate of the reaction, as a result of stabilization of the "*negative* end" of the intermediate 1,5-dipole. The presence of an electron-donating group at the β-carbon atom of the vinyl moiety lowers the rate of the reaction. Moreover, this influence is demonstrated by oxidation of one of the sulfur atoms in **35** to the ketene dithioacetal *S*-monooxide **36**, which undergoes a fast thermal isomerization to **47**. Cyclization of the pyrrolidinylnaphthoquinones **32**, **34**, and **35** yielded exclusively products in which H-11a and CN have a trans relationship, while in the case of piperidinylnaphthoquinone **37** predominantly *trans*-1*H*-benzo[*f*]pyrido[1,2-*a*]indole **44a** was formed. The trans stereochemistry of **43** was determined by single-crystal X-ray analysis. Heating of (dialkylamino)naphthoquinone **33** afforded the indoline **50** in low yield.

Introduction

In our studies on the "*tert*-amino effect" in heterocyclic chemistry[1,2] we have shown that 1-(1-pyrrolidinyl)-2-vinylbenzene derivatives **1** (Chart I) rearrange thermally to 2,3,9,9a-tetrahydro-1*H*-pyrrolo[1,2-*a*]indoles **2**.[3] This isomerization proceeds via two consecutive pericyclic reactions, viz. a [1,6] hydrogen transfer to give the 1,5-dipole **3** which undergoes a concerted 1,5-dipolar cyclization.[4] A prerequisite for this thermal isomerization is the stabilization of the negative charge in the 1,5-dipole **3** by an electron-withdrawing group (EWG). Furthermore, we have demonstrated the effect of both the substituent R and of different dialkylamino groups on the [1,6] hydrogen transfer and subsequent 1,5-electrocyclization.[5] Intermediates related to **3** in the formation of pyrrolo[1,2-*a*]indoles have been postulated by several other groups.[6,7]

The main reason for our current interest in the *tert*-amino effect is the possible application in the synthesis of isomitosanes,[8] analogues of the antitumor antibiotic mitomycin C.[5,9,10] In mitomycin C the basic skeleton contains a *p-quinone* function and therefore we have studied the influence of this oxidation state of 1-(1-pyrrolidinyl)-2-vinylbenzene derivatives on the rate of the thermal cyclization.

Previously, we reported the formation of the Michael adduct **4** in the reaction of 5,5-dimethyl-3-(1-pyrrolidinyl)-2-cyclohexen-1-one and dimethyl acetylenedicarboxylate (DMAD).[11] However, **4** could not be isomerized thermally into the corresponding pyrrolizine.[12] This lack of reactivity might be attributed to the less reactive "vinylogous amide" structure in **4**. On the other hand, 5,10-dioxo-1*H*-benzo[*f*]pyrrolo[1,2-*a*]indole **5** is formed by

Chart I

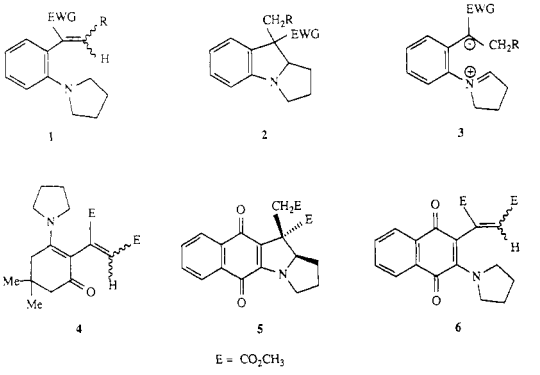
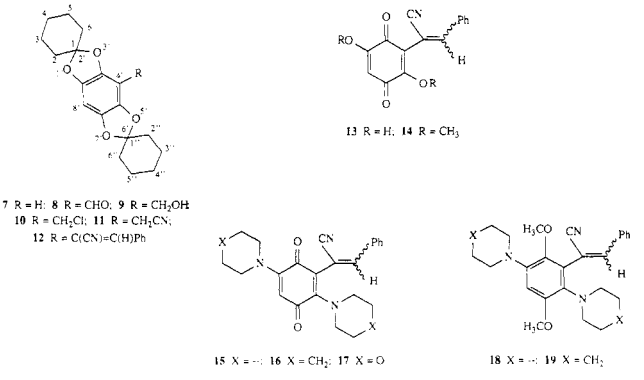


Chart II



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