placed 291 mg (0.75 mmol) of **10b** and 3 mL of dry $CHCl_3$ (previously distilled over P_2O_5). The solution was flushed with N_2 several times, and the flask then was fitted with a rubber septum. Bromotrimethylsilane (4.5 mL, 5.22 g, 34.2 mmol) was introduced via syringe, and the resulting mixture was stirred overnight at ambient temperature. The excess Me_3SiBr and $CHCl_3$ were then removed under high vacuum to give the bis-Me_3Si ester of **10b** in quantitative yield: ^1H NMR ($CDCl_3$) δ 2.36 (2 H, d, $P(=O)CH_2\overline{COO}$, J = 19 Hz) and all other peaks observed in the ^1H NMR spectra of **10b**, with the exception that a peak at δ 0.37 (27 H, s, $(CH_3)_3Si$) replaced the peak at δ 3.65 in **10b**. The Me_3Si ester was then treated with 10 mL of acetone containing a few drops of H_2O, and resulting solution was stirred at ambient temperature overnight. The solvent was then removed in vacuo, and the residue was subjected to several acetone wash-evaporation cycles before a final drying at high vacuum. The resulting amorphous keto phosphonate was sufficiently pure for subsequent transformations: ^1H NMR (D_2O) δ 1.48-1.78 (2 H, m, CH_2), 2.58 (2 H, t, $CH_2C{=}O$), 2.68 (2 H, d, $P(=O)CH_2C{=}O$, J = 21 Hz), 2.93 (3 H, s, NCH_3), 3.16 (2 H, t, CH_2N), 7.21-7.88 (4 H, AA'BB', aromatic H).

For further purification, the free β-keto phosphonic prepared above could be converted to its dilithium salt by addition of a saturated ethanolic solution of LiOH to an ethanolic solution of the free phosphonic acid, until a pH 8.0 was obtained. The precipitated Li_2 phosphonate was isolated by centrifugation, followed by successive washes of the precipitate with ethanol (three times) and ether (three times). The precipitate was then dried under high vacuum for several hours to give 166 mg (68%) of the dilithio salt of **11b**: ^1H NMR (D_2O, 5% CD_3COOD) δ 1.40-1.70 (2 H, m, CH_2), 2.31-2.70 (2 H, m, $CH_2C{=}O$), 2.60 (3 H, s, NCH_3), 2.78 (2 H, d, $P(=O)CH_2C{=}O$, J = 21 Hz), 3.08 (2 H, t, CH_2N), 6.43-7.56 (4 H, AA'BB', aromatic H).

***N*-(4-(((2,4-Diaminopteridin-6-yl)methyl)methylamino)benzoyl)-5-amino-2-oxopentanephosphonic Acid (13a).** The keto phosphonate **10b** (97 mg, 0.25 mmol) was converted to the free keto phosphonic acid **11b** as described above. The resulting amorphous product was dissolved in 1 mL of H_2O, and solid $KHCO_3$ was added to adjust the pH to ca. 7.5. 2,4-Diamino-6-(bromomethyl)pteridine-hydrobromide (**12**)[14] (110 mg, 0.3 mmol) was then added as a fine powder, and the resulting mixture was heated at 45 ± 5 °C. After ca. 24 h, 60 mL of H_2O was added to the reaction mixture, and stirring was continued at the same temperature for an additional period of ca. 24 h. Insoluble material was then removed by filtration of the reaction mixture, the filtrate pH was adjusted to ca. 3-4 with dilute HCl, and water was removed by lyophilization. The desired product was extracted from the crude solid residue by several triturations with CH_3OH. This process removed the insoluble inorganic salts, and evaporation of the solvent CH_3OH afforded crude **13a** as an oily residue. The crude product was dissolved in 500 mL of H_2O (pH adjusted to 8.2 with dilute NH_4OH) and applied to a DEAE-cellulose column (0.9 × 30 cm), previously equilibrated with 0.015 M NH_4HCO_3. The column was then washed with 200 mL of 0.015 M NH_4HCO_3, and the desired product was obtained by gradient elution with 0.015-0.30 M NH_4HCO_3 (total volume = 500 mL). The material eluting at 0.18 M NH_4HCO_3 accounted for ca. 95% of the UV absorbance and had spectral properties consistent with the structure **13a**. Lyophilization of the column effluent containing **13a** gave a hygroscopic fluffy yellow solid: ^1H NMR (D_2O, 200 MHz) δ 1.64-1.92 (2 H, m, CH_2), 2.80 (2 H, t, $CH_2C{=}O$), 2.92 (2 H, d, $P(=O)CH_2C{=}O$, J = 20 Hz), 3.16 (3 H, s, NCH_3), 3.35 (2 H, t, CH_2N), 6.80-7.73 (4 H, AA'BB', aromatic H), 8.60 (1 H, s, peteridine 7-H); the HOD signal at δ 4.50-4.90 obscured the pteridine 6-CH_2N resonance; UV $\lambda_{max}^{0.1NH^+}$ 241, 298, 331 (sh), 347 (sh) nm; $\lambda_{max}^{0.1NOH^-}$ 216, 257, 298, 370 nm. The overall yield of **13a** from **10b** was calculated as ca. 20%, based on absorbance at 298 nm in 0.1 N HCl. HPLC on Whatman SAX:[4] single peak at t_r = 10.2 min; mass spectrum (FAB), m/e 489 $(M + 1)^+$, 511 $(M + Na)^+$, 581 $(M + glycerol)^+$.

Acknowledgment. This research was supported by a grant from the U.S. Public Health Service, National Institutes of Health, CA-28097. We thank Drs. John Montgomery and J. Robert Piper for several helpful discussions and Dr. James A. Ellard for a generous gift of 2,4-diamino-6-(hydroxymethyl)pteridine. We thank Dr. Montgomery and his colleagues for obtaining the FAB mass spectrum of **13a**.

Registry No. **3a**, 59378-98-2; **3c**, 87517-44-0; **3d**, 87517-45-1; **4a**, 87517-46-2; **5**, 87517-56-4; 5 (bis(dicyclohexylamine) salt), 87517-57-5; **6b**, 87517-47-3; **7b**, 87517-48-4; **7c**, 87517-49-5; **8**, 87517-50-8; **9a**, 87517-51-9; **9b**, 87517-52-0; **10a**, 87517-53-1; **10b**, 87517-54-2; **10b** (bis(trimethylsilyl) ester), 87517-59-7; **11b**, 87517-55-3; **11b**·2Li, 87517-60-0; **12**, 52853-40-4; **13a**, 87531-97-3; NaN_3, 26628-22-8; monomethyl glutarate, 1501-27-5; isobutylene, 115-11-7; dimethyl methanephosphonate, 756-79-6; bromotrimethylsilane, 2857-97-8; methyl 4-chlorobutyrate, 3153-37-5; ethylene glycol, 107-21-1; *p*-nitrobenzoyl chloride, 122-04-3; *p*-[[(carbobenzoxy)methyl]amino]benzoic acid, 2528-30-5; *p*-[[(carbobenzoxy)methyl]amino]benzoyl chloride, 66891-86-9; dimethyl [[2-(3-hydrazinopropyl)-1,3-dioxolan-2-yl]methyl]-phosphonate, 87517-58-6.

An Alternate Synthesis of Deethylvincadifformine

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A synthesis of 20-deethylvincadifformine from methyl nicotinylacetate is described. The reaction scheme involved a fast construction of the pentacyclic nucleus of the *Aspidosperma* alkaloids and the early incorporation of the 16-carbomethoxy group common to these bases.

Recently there was reported a simple three-reaction scheme for the facile production of the pentacyclic nucleus of the *Aspidosperma* alkaloids starting with β-acetylpyridine (Scheme I; R = H).[2] Reductive removal of the functional groups at C(5) and C(17), followed by C(2) oxidation, had served as a route to an aspidospermidine model, whose N-carbomethoxylation and subsequent

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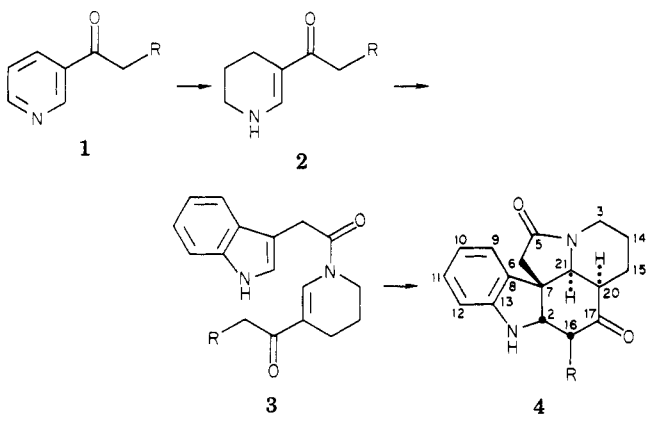
(2) (a) Wenkert, E.; Bindra, J. S.; Chauncy, B. *Synth. Commun.* **1972**, *2*, 285. (b) Wenkert, E. *Pure Appl. Chem.* **1981**, *53*, 1271. (c) Wenkert, E.; Orito, K.; Simmons, D. P.; Kunesch, N.; Ardisson, J.; Poisson, J. *Tetrahedron*, in press.

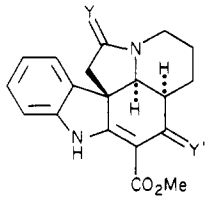
0022-3263/83/1948-5006$01.50/0

Scheme I



1 2 3 4

photorearrangement had led to deethylvincadifformine (**5a**), the basic skeleton of a large number of *Aspidosperma*

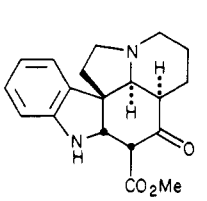


5a, Y = Y′ = H_2
b, Y = O; Y′ = H_2
c, Y = Y′ = O
d, Y = H_2; Y′ = O

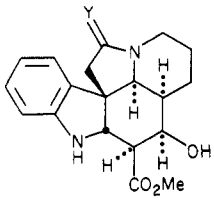
bases.[2] In order to test the flexibility of the overall reaction scheme, it became of interest to introduce the carbomethoxy group at the start of the reaction sequence and to ascertain the survivability of this function to the individual reactions to which the starting material had to be exposed.

Base-induced condensation of methyl nicotinate with methyl acetate yielded methyl nicotinylacetate (**1**, R = CO_2Me), whose palladium-catalyzed hydrogenation gave the tetrahydro derivative **2** (R = CO_2Me). N-Acylation of the latter with indoleacetic anhydride[3] afforded 2-piperideine **3** (R = CO_2Me), whose treatment with polyphosphoric acid led to pentacycle **4** (R = CO_2Me).[4,5] Thus scheme I (vide supra) could be reproduced in the presence of a sensitive β-keto ester moiety.

Whereas, in principle, several reaction sequences were available for the removal of two keto groups from keto ester **4** (R = CO_2Me) and the introduction of a double bond, i.e., the transformation of **4** (R = CO_2Me) into **5a**, several pathways proved more difficult than others. Thus even though diborane reduction of the lactam **4** (R = CO_2Me) yielded keto ester **6**, which on reduction with



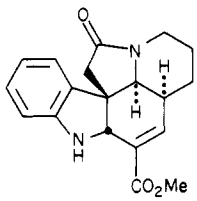
6



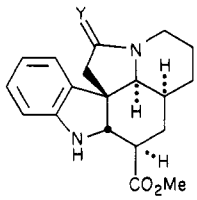
7a, Y = O
b, Y = H_2

sodium borohydride led to hydroxy ester **7b**[6], dehydration of the latter under a variety of conditions gave unsatisfactory results. Similarly, although lead tetraacetate oxidation of keto esters **4** (R = CO_2Me) and **6** yielded vinylogous amides **5c** and **5d**, respectively, removal of their conjugated keto groups presented insurmountable obstacles.[7]

Preservation of the lactam carbonyl group until the end of the synthesis permitted removal of the 17-keto function. Reduction of keto ester **4** (R = CO_2Me) with sodium borohydride afforded hydroxy ester **7a**,[6] whose dehydration with polyphosphoric acid produced olefinic ester **8**. Hydrogenation of the latter led to lactam ester **9a**, whose diborane reduction at 0 °C and oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) gave esters **9b** and **5b**, respectively.



8



9a, Y = O
b, Y = H_2

Lead tetraacetate oxidation of ester **9b** as well as mild lithium aluminum hydride reduction of lactam **5b** led to 20-deethylvincadifformine (**5a**).[2c,8]

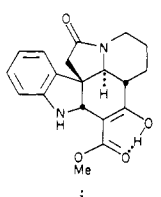
Experimental Section

Melting points were determined on a Kofler micro hotstage and are uncorrected. Infrared spectra were recorded on Perkin-Elmer 137 and 257 spectrophotometers and ultraviolet spectra of 95% ethanol solutions on Cary 14, Cary 17, and Unicam SP 1800 spectrophotometers. Mass spectra were obtained on Finnigan 3300, CEC 21-110B, and AEI MS909 spectrometers. ^1H NMR spectra of $CDCl_3$ solutions with Me_4Si as internal standard (δ 0) were taken on Varian EM-390 and XL-100-15 spectrometers and on experimental 240- and 400-MHz instruments built at the Institut d'Electronique Fondamentale, 91405 Orsay, France.[9]

Methyl Nicotinylacetate (1, R = CO_2Me). A mixture of 9.00 g of methyl nicotinate and 4.80 g of sodium hydride (50% in oil) in 20 mL of methyl acetate was refluxed for 3 h. It then was cooled to room temperature, poured onto 50 g of ice, shaken, and ex-

(3) Hart, J. C.; Matheson, E. M.; Hutzinger, O. *Can. J. Chem.* **1970**, *48*, 177.

(4) The minor side product of this reaction, tentatively assigned structure i, was also the product of photoisomerization of tetrahydro-



i

pyridine **3** (R = CO_2Me) as well as of the latter's exposure to boron trifluoride etherate at 100 °C for 20 min.

(5) The assignment of the stereochemistry of keto esters **4** (R = CO_2Me) and **6** is based on NMR spectral considerations (see Experimental Section) and on analogy with experiences in the noncarbomethoxy keto lactam series.[2a,c] A previous representation of the keto esters has their H(16) configuration portrayed incorrectly.[2b]

(6) The stereochemistry of hydroxy esters **7** is founded on their NMR analysis (see Experimental Section), including decoupling experiments. In the borohydride reduction C-16 epimerization preceded the reduction process.

(7) Conversion of vinylogous amide **5d** into the desired end product **5a** by way of formation of a vinylogous thioamide and its Raney nickel desulfurization[2b] proved to be a frequently irreproducible process.

(8) Kuehne, M. E.; Kirkemo, C. L.; Matsko, T. H.; Bohnert, J. C. *J. Org. Chem.* **1980**, *45*, 3259.

(9) Gonord, P.; Kan, S. K.; Sauzade, M. *J. Magn. Res.* **1976**, *24*, 457. Kan, S. K.; Gonord, P.; Fan, M.; Sauzade, M.; Courtieu, J. *Rev. Sci. Instrum.* **1978**, *49*, 785.

tracted with ether. The aqueous solution was brought to pH 6–7 with 6 N hydrochloric acid, saturated with NaCl, and extracted exhaustively with methylene chloride. The extract was dried (Na_2SO_4) and evaporated. Crystallization of the residual oil from hexane–ether yielded 8.46 g (72%) of ester **1** (R = CO_2Me): mp 74–75 °C; IR ($CHCl_3$) OH (enol) 3350 (m), C=O 1739 (s), 1689 (s), 1660 (s), C=C 1625 (m) cm^{-1}; ^1H NMR δ (ca. 2:1 keto–enol mixture) 3.97 (s, $^2/_3$ of 2, CH_2), 3.71 (s, $^2/_3$ of 3, keto OMe), 3.76 (s, $^1/_3$ of 3, enol OMe), 5.62 (s, $^1/_3$ of 1, enol olefinic H), 7.1–9.1 (m, 4, aromatic Hs).

Anal. Calcd for $C_9H_9O_3N$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.26; H, 5.11; N, 7.44.

Methyl 1,4,5,6-Tetrahydronicotinylacetate (2, R = CO_2Me). A mixture of 4.00 g of ester **1** (R = CO_2Me) and 500 mg of 5% palladium–charcoal in 25 mL of methanol was hydrogenated at 3 atm. Upon cessation of hydrogen uptake the mixture was filtered and the filtrate evaporated under vacuum. Crystallization of the residual oil from ethyl acetate gave 2.49 g (61%) of ester **2** (R = CO_2Me): mp 40–42 °C; IR ($CHCl_3$) NH 3460 (m), C=O 1735 (s), 1590 (s), C=C 1525 (m) cm^{-1}; ^1H NMR δ 1.6–2.1 (m, 2, CH_2), 2.1–2.6 (m, 2, allyl CH_2), 3.1–3.6 (m, 2, NCH_2), 3.47 (s, 2, $COCH_2$), 3.64 (s, 3, OMe), 7.57 (d, 1, J = 7 Hz, olefinic H).

Anal. Calcd for $C_9H_{13}O_3N$: C, 59.00; H, 7.15; N, 7.65. Found: C, 58.70; H, 7.13; N, 7.69.

Methyl 1-(2-(3-Indolinyl)acetyl)-1,4,5,6-tetrahydronicotinylacetate (3, R = CO_2Me). A solution of 7.72 g of ester **2** (R = CO_2Me) in 100 mL of tetrahydrofuran was added dropwise to a stirring suspension of 2.05 g of sodium hydride (50% in oil) in 50 mL of dry tetrahydrofuran at 0 °C and the mixture stirred for an additional 0.5 h. A solution of 14.00 g of indoleacetic anhydride[3] in 100 mL of tetrahydrofuran was added slowly and the mixture then stirred at room temperature for 24 h. The mixture was cooled to 0 °C, diluted with 30 g of ice and 300 mL of methylene chloride, washed with 1 N hydrochloric acid and saturated sodium carbonate solution, dried (Na_2SO_4), and evaporated under vacuum. Chromatography of the residual, viscous oil through silica gel and elution with 100:1 dichloromethane–methanol yielded material, whose crystallization from methanol afforded 5.16 g (36%) of ester **3** (R = CO_2Me): mp 121–123 °C; IR ($CHCl_3$) NH 3470 (m), C=O 1740 (s), 1680 (s), 1665 (m), C=C 1610 (m) cm^{-1}; ^1H NMR δ 1.5–1.9 (m, 2, CH_2), 2.23 (t, 2, J = 6 Hz, allyl CH_2), 3.4–3.7 (m, 4, NCH_2, $COCH_2CO$), 3.64 (s, 3, OMe), 3.99 (s, 2, $COCH_2$), 6.77 (d, 1, J = 3 Hz, indole α-H), 7.0–7.6 (m, 4, aromatic Hs).

Anal. Calcd for $C_{19}H_{20}O_4N_2$: C, 67.05; H, 5.92; N, 8.23. Found: C, 67.05; H, 5.94; N, 8.23.

20-Deethyl-2β,16β-dihydro-5,17-dioxovincadifformine (4, R = CO_2Me). A suspension of 1.00 g of ester **3** (R = CO_2Me) in 20 mL of Merck-Schuchardt (No.807471) polyphosphoric acid was heated under 20 torr pressure on a steam bath for 3 h. It then was cooled to 0 °C and 50 mL of methanol added slowly. The solution was poured onto 300 g of ice and saturated sodium bicarbonate solution added. The mixture was extracted with methylene chloride and the extract dried (Na_2SO_4) and evaporated under vacuum. Crystallization of the residue from methanol gave 610 mg of product. Concentration of the mother liquor, chromatography of the oily residue on silica gel and elution with 9:1 dichloromethane–acetone yielded first 122 mg of additional product and then 150 mg of its isomer.[4] Thus there was obtained 732 mg (73%) of keto ester **4** (R = CO_2Me): mp 175–183 °C (keto–enol mixture on melting); IR (Nujol) NH 3340 (m), C=O 1740 (s), 1719 (s), 1674 (s), C=C 1609 (m) cm^{-1}; UV (EtOH) λ_{max} 248 nm (log ϵ 3.88), 2.98 (3.75); ^1H NMR δ 1.2–1.7 (m, 4, 2 CH_2), 2.4–2.7 (m, 2, H-3, H-20), 2.58 (d, 1, J = 17 Hz, H-6), 3.26 (d, 1, J = 17 Hz, equatorial H-6), 3.55 (d, 1, J = 4 Hz, H-21), 3.86 (s, 3, OMe), 4.1–4.2 (m, 1, H-3), 4.23 (d, 1, J = 4 Hz, H-2), 4.95 (d, 1, J = 4 Hz, H-16), 6.6–7.2 (m, 4, aromatic Hs); MS, m/e 340 (M^+, 32%), 308 (16), 282 (5), 240 (8), 216 (6), 157 (11), 130 (base).

Anal. Calcd for $C_{19}H_{20}O_4N_2$: C, 67.05; H, 5.92; N, 8.23. Found: C, 66.88; H, 5.93; N, 8.23.

20-Deethyl-2β,16β-dihydro-17-oxovincadifformine (6). A 1 M tetrahydrofuran solution of diborane, 11 mL, was added dropwise to a solution of 1.10 g of ester **4** (R = CO_2Me) in 25 mL of tetrahydrofuran at 0 °C over a 5 h period. A 1:1 methanol–acetic acid mixture was added slowly to the solution at room temperature until hydrogen evolution had ceased. A saturated, methanolic sodium acetate solution, 75 mL, was added and the mixture refluxed for 45 min. It then was basified with sodium carbonate solution and extracted with methylene chloride. The extract was dried (Na_2SO_4) and evaporated under vacuum. Chromatography of the residual oil on silica gel and elution with methylene chloride gave 833 mg (79%) of amorphous, solid keto ester **6**: IR (film) NH 3390 (m), C=O 1740 (s), 1715 (s), C=C 1610 (s) cm^{-1}; UV (EtOH) λ_{max} 246 nm (log ϵ 3.85), 300 (3.45); ^1H NMR δ 1.1–2.5 (m, 9, methylenes, methines), 2.07 (d, 1, J = 3 Hz, H-21), 3.05 (d, 1, J = 13 Hz, H-5 or H-3), 3.19 (t, 1, J = 11 Hz, H-3 or H-5), 3.86 (s, 3, OMe), 4.07 (d, 1, J = 3 Hz, H-2), 4.66 (d, 1, J = 3 Hz, H-16), 6.5–7.1 (m, 4, aromatic Hs); MS, m/e 326 (M^+, 33%), 294 (5), 226 (25), 196 (5), 144 (11), 130 (5), 96 (base); exact mass, m/e 326.1636 (calcd for $C_{19}H_{22}O_3N_2$, m/e 326.1630).

20-Deethyl-2β,16α-dihydro-17β-hydroxyvincadifformine (7b). Sodium borohydride, 150 mg, was added in portions over a 15 min period to a stirring solution of 1.00 g of ester **6** in 5 mL of methylene chloride and 25 mL of methanol and the stirring continued for 2 h. The mixture was poured into a 10% sodium bicarbonate solution and extracted with methylene chloride. The extract was dried (Na_2SO_4) and evaporated under vacuum. Chromatography of the residual oil on alumina (activity I) and elution with 9:1 cyclohexane–acetone led to the recovery of 150 mg of starting material. The early fractions of this eluate yielded 650 mg (77% on the basis of recovered starting ketone) of amorphous, solid ester **7b**: IR (film) OH, NH 3380 (m), 3250 (m), C=O 1725 (s), C=C 1605 (s) cm^{-1}; ^1H NMR δ 1.6–2.5 (m, 11, methylenes, methines), 2.27 (dd, 1, J = 10, 2 Hz, H-16), 2.78 (d, 1, J = 3 Hz, H-21), 3.1–3.3 (m, 2, H-3, H-5), 3.76 (s, 3, OMe), 4.09 (d, 1, J = 10 Hz, H-2), 4.39 (t, 1, J = 2 Hz, H-17), 6.6–7.0 (m, 4, aromatic Hs); MS, m/e 328 (M^+, 15%), 327 (6), 227 (6), 226 (8), 144 (6), 130 (5), 98 (5), 97 (9), 96 (base); exact mass, m/e 328.1782 (calcd for $C_{19}H_{24}O_3N_2$, m/e 328.1787).

20-Deethyl-5,17-dioxovincadifformine (5c). A mixture of 300 mg of keto ester **4** (R = CO_2Me) and 390 mg of lead tetraacetate in 15 mL of dry methylene chloride was stirred for 0.5 h and then poured into saturated sodium carbonate solution. The mixture was extracted with methylene chloride and the extract dried (Na_2SO_4) and evaporated under vacuum. Chromatography of the oily residue on silica gel and elution with 4:1 dichloromethane–acetone yielded 240 mg (80%) of amorphous, solid ester **5c**, spectrally identical with authentic material.[2c]

20-Deethyl-17-oxovincadifformine (5d). A mixture of 300 mg of keto ester **6** and 410 mg of lead tetraacetate in 15 mL of dry methylene chloride was stirred for 0.5 h. Workup as above gave 244 mg (82%) of amorphous, solid ester **5d**, spectrally identical with an authentic specimen.[2c]

20-Deethyl-2β,16α-dihydro-17β-hydroxy-5-oxovincadifformine (7a). Sodium borohydride, 150 mg, was added in portions over a 15-min period to a stirring solution of 1.00 g of ester **4** (R = CO_2Me) in 5 mL of methylene chloride and 25 mL of methanol and the stirring continued for 5 min. Workup (except for chromatography) as in the preparation of hydroxy ester **7b** above and crystallization of the crude product from ether–methanol yielded 800 mg (79%) of crystalline ester **7a**: mp 179–181 °C; IR (film) OH, NH 3400 (m), 3320 (m), C=O 1720 (s), 1660 (s), C=C 1605 (m) cm^{-1}; UV (EtOH) λ_{max} 251 nm (log ϵ 3.83), 302 (3.44); ^1H NMR δ 1.5–2.8 (m, 6, methylenes, methine), 2.25 (d, 1, J = 17 Hz, H-6), 2.45 (d, 1, J = 10 Hz, H-16), 3.00 (d, 1, J = 17 Hz, H-6), 3.81 (s, 3, OMe), 4.04 (d, 1, J = 3 Hz, H-21), 4.06 (d, 1, J = 10 Hz, H-2), 4.19 (dd, 1, J = 13, 5 Hz, H-3), 4.38 (br s, 1, H-17), 7.0–7.3 (m, 4, aromatic Hs); MS, m/e 342 (M^+, 91%), 239 (7), 238 (7), 157 (11), 131 (15), 130 (base); exact mass, m/e 342.1563 (calcd for $C_{19}H_{22}O_4N_2$, m/e 342.1579).

20-Deethyl-17-dehydro-2β-hydro-5-oxovincadifformine (8). A mixture of 600 mg of ester **7a** and 10 mL of Merck-Schuchardt (No. 807471) polyphosphoric acid was heated at 100 °C for 3 h. After it was cooled to 0 °C, 50 mL of methanol was added slowly. The solution was poured onto 75 g of ice, brought to pH 8 with ammonia, and extracted with methylene chloride. The extract was dried (Na_2SO_4) and evaporated under vacuum. Chromatography of the residual oil on silica gel and elution with 1:1 cyclohexane–ethyl acetate yielded 298 mg (53%) of amorphous, solid ester **8**: IR (film) NH 3310 (m), C=O 1700 (s), 1670 (s), C=C 1600 (m) cm^{-1}; UV (EtOH) λ_{max} 245 nm (log ϵ 3.80), 303 (3.42);

^{1}H NMR δ 3.82 (s, 3, OMe), 6.3–7.2 (m, 5, aromatic and olefinic Hs); MS, *m/e* 324 (M^+, base), 309 (15%), 167 (38), 130 (66); exact mass, *m/e* 324.1468 (calcd for $C_{19}H_{20}O_3N_2$, *m/e* 324.1474).

20-Deethyl-2β,16α-dihydro-5-oxovincadifformine (9a). A mixture of 405 mg of ester **8** and 200 mg of 10% palladium–charcoal in 20 mL of methanol was hydrogenated at 50 psi for 6 h and then filtered through Celite. The filtrate was evaporated under vacuum. Crystallization of the residual solid from methanol yielded 387 mg (95%) of crystalline ester **9a**: mp 158–160 °C; IR (KBr) NH 3250 (m), C=O 1725 (s), 1660 (s), C=C 1600 (w) cm^{-1}; UV (EtOH) λ_{max} 249 nm (log ε 3.89), 302 (3.51); ^{1}H NMR δ 1.5–1.9 (m, 6, methylenes, methine), 2.18 (d, 1, *J* = 17 Hz, H-6), 2.2–2.8 (m, 2, methylene Hs), 2.87 (d, 1, *J* = 17 Hz, H-6), 3.51 (d, 1, *J* = 10 Hz, H-2), 3.76 (s, 3, OMe), 3.97 (d, 1, *J* = 3 Hz, H-21), 4.19 (d, 1, *J* = 13 Hz, H-3), 6.7–7.2 (m, 4, aromatic Hs); MS, *m/e* 326 (M^+, 94%), 240 (10), 180 (9), 157 (11), 131 (15), 130 (base); exact mass, *m/e* 326.1627 (calcd for $C_{19}H_{22}O_3N_2$, *m/e* 326.1630).

20-Deethyl-2β,16α-dihydrovincadifformine (9b). A 1 M tetrahydrofuran solution of diborane, 10 mL, was added dropwise to a solution of 326 mg of lactam **9a** in 30 mL of tetrahydrofuran at 0 °C over a 5 h period. Workup as in the preparation of ester **6** above, followed by chromatography on silica gel and elution with 1:1 cyclohexane–ethyl acetate yielded 228 mg (73%) of amorphous, solid ester **9b**: IR (film) NH 3380 (m), C=O 1735 (s), C=C 1610 (m) cm^{-1}; ^{1}H NMR δ 1.2–2.4 (m, 12, methylenes, methines), 2.50 (d, 1, *J* = 3 Hz, H-21), 3.0–3.2 (m, 2, 2 NCH), 3.62 (d, 1, *J* = 10 Hz, H-2), 3.73 (s, 3, OMe), 6.6–7.1 (m, 4, aromatic Hs); MS, *m/e* 312 (M^+, 21%), 311 (8), 226 (10), 97 (8), 96 (base); exact mass, *m/e* 312.1843 (calcd for $C_{19}H_{24}O_2N_2$, *m/e* 312.1838).

20-Deethyl-5-oxovincadifformine (5b). A mixture of 85 mg of ester **9a** and 65 mg of DDQ in 5 mL of freshly distilled dioxane was refluxed under nitrogen for 1.5 h and then poured into 5% sodium hydroxide solution. The mixture was extracted with methylene chloride. The extract was dried (Na_2SO_4) and evaporated under vacuum. The residue was chromatographed on silica gel and eluted with 2:1 cyclohexane–ether. Crystallization of the solid product, 48 mg (57%), from ether yielded lactam **5b**: mp 194–196 °C; IR (KBr) NH 3460 (m), C=O 1690 (s), 1660 (s), C=C 1610 (s) cm^{-1}; UV (EtOH) λ_{max} 230 nm (log ε 4.12), 302 (4.17), 333 (4.28); ^{1}H NMR δ 1.4–2.0 (m, 5, methylenes, methine), 2.21 (t, 1, *J* = 13 Hz, H-17), 2.48 (d, 1, *J* = 13 Hz, H-17), 2.61, 2.66, 2.75, 2.80 (AB, 2, 2 H-6), 2.85 (m, 1, H-3), 3.79 (s, 3, OMe) 4.15 (d, 1, *J* = 4 Hz, H-21), 4.35 (d, 1, *J* = 13 Hz, H-3), 6.8–7.3 (m, 4, aromatic Hs), 8.90 (s, 1, NH); MS, *m/e* 324 (M^+, base), 293 (28%), 292 (97), 265 (13), 263 (10), 215 (15), 214 (98), 182 (14), 180 (18), 167 (13), 155 (14), 154 (50), 127 (13); exact mass, *m/e* 324.1476 (calcd for $C_{19}H_{20}O_3N_2$, *m/e* 324.1474).

20-Deethylvincadifformine (5a). Lead tetraacetate, 28 mg, was added in small portions to a stirring solution of 20 mg of ester **9b** in 3 mL of dry methylene chloride under nitrogen at −15 °C over a 10 min period. Workup as in the above preparation of ester **5c**, alumina chromatography of the crude product and elution with 65:1 cyclohexane–ethyl acetate yielded 8 mg (40%) of amorphous, solid ester **5a**, spectrally identical with an authentic sample.[2c,8]

A mixture of 20 mg of lactam **5b** and 30 mg of lithium aluminum hydride in 10 mL of anhydrous ether was stirred under nitrogen at −5 to 0 °C for 4 h.[10] It then was poured slowly into 5% hydrochloric acid solution and a saturated sodium potassium tartrate solution was added. After the addition of a saturated sodium bicarbonate solution and methylene chloride the aqueous layer was extracted with more methylene chloride and the combined organic solutions dried (Na_2SO_4) and evaporated under vacuum. Chromatography of the crude product as above led to 5 mg (26%) of amorphous, solid ester **5a**, identical by IR, ^{1}H NMR spectra, and TLC with an authentic specimen.[2c,8]

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Registry No. 1 (R = CO_2Me), 54950-20-8; 2 (R = CO_2Me), 87495-03-2; 3 (R = CO_2Me), 87495-04-3; (±)-4 (R = CO_2Me), 87495-05-4; (±)-**5a**, 77080-74-1; (±)-**5b**, 87508-90-5; (±)-**5c**, 87508-87-0; (±)-**5d**, 87508-88-1; (±)-**6**, 87495-06-5; (±)-**7a**, 87495-08-7; (±)-**7b**, 87495-07-6; (±)-**8**, 87508-89-2; (±)-**9a**, 87495-09-8; (±)-**9b**, 87495-10-1; (±)-i, 87495-11-2; methyl nicotinate, 93-60-7; methyl acetate, 79-20-9; indoleacetic anhydride, 41547-05-1.

(10) Cf. Levy, J.; Laronze, J.-Y.; Laronze, J.; LeMen, J. *Tetrahedron Lett.* **1978**, 1579.

Synthesis of Two Macrolide Pheromones of the Rusty Grain Beetle, *Cryptolestes ferrugineus* (Stephens)[1]

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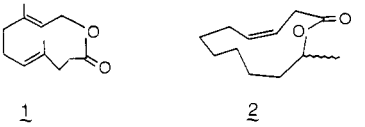
Two macrolide pheromones for *Cryptolestes ferrugineus* (Stephens), the rusty grain beetle, have been synthesized. Synthesis of 4,8-dimethyl-4(*E*),8(*E*)-decadienolide (**1**) was achieved by intramolecular alkylation of an ω-bromo (phenylthio)acetate derived from geraniol by reaction with (phenylthio)acetyl chloride and allylic functionalization of the 8(*E*)-methyl. Macrolide **1** was also synthesized by intramolecular esterification of an ω-hydroxy acid derived from geraniol by formal addition of acetate to tetrahydropyranyl-protected 8(*E*)-bromogeraniol. Synthesis of the second macrolide, 11-methyl-3(*Z*)-undecenolide (**2**), also involved intramolecular esterification of the appropriate hydroxy acid. The chiral center of **2** was introduced via chiral propylene oxides while the *Z* unsaturation was introduced by P-2 nickel reduction of the appropriate alkyne. Both chiral isomers of **2** were synthesized.

The rusty grain beetle, *Cryptolestes ferrugineus* (Stephens), is a widely distributed pest which primarily infests stored grain. Male beetles produce aggregation pheromones which are attractive to both sexes and probably function by promoting population buildup in suitable habitats.[2] Recently, we reported the isolation of two synergistic pheromones, ferrulactones I (**1**) and II (**2**), from



1 **2**

the volatile components of *C. ferrugineus* frass.[3] The

(1) Taken in part from the Ph.D. Thesis of J.W.W., Simon Fraser University, June 1982, and from the M.Sc. Thesis of V.G. V., Simon Fraser University, August 1980.

(2) J. H. Borden. M. G. Dolinski, L. Chong, V. Verigin, H. D. Pierce, Jr., and A. C. Oehlschlager, *Can. Entomol.*, 111, 681 (1979).

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