$C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.21. Found: C, 75.02; H, 5.25; N, 9.07.

7-Methyl-12-hydropyrido[3,2-*b*:5,4-*b*']diindole (4). (A) From 3. The β-carboline **3** (100 mg, 0.33 mmol) was added to phenylhydrazine (5 mL), and the mixture was heated at 150 °C for 7 h. The reaction mixture was cooled, anhydrous hydrazine (4 mL) was added and the reaction mixture was refluxed for 16 h. The reaction mixture was then cooled to room temperature, and the yellow precipitate that resulted was collected by vacuum filtration to provide **4** (68 mg; 77% yield): mp >300 °C; MS (CI, CH_4), *m/e* 272 (M + 1); IR (KBr) 3450, 1460, 1325, 730 cm^{-1}; ^1H NMR (DMSO-d_6) δ 13.10 (s, 1 H), 9.45 (s, 1 H), 8.97 (d, *J* = 7.9 Hz, 1 H), 8.55 (d, *J* = 7.9 Hz, 1 H), 7.96 (d, *J* = 8.4 Hz, 1 H), 7.93 (d, *J* = 8.4 Hz, 1 H), 7.85 (t, *J* = 8.1 Hz, 1 H), 7.65 (t, *J* = 7.2 Hz, 1 H), 7.55 (t, *J* = 7.0 Hz, 1 H), 7.43 (t, *J* = 7.2 Hz, 1 H), 4.20 (s, 3 H). The hydrochloride salt was prepared by adding **4** to a cold saturated solution of methanolic hydrogen chloride. The precipitate that resulted was collected by vacuum filtration to afford **4**·HCl (73 mg, 95%): mp >300 °C. Anal. Calcd for $C_{18}H_{13}N_3$·HCl: C, 70.24; H, 4.38; N, 13.65. Found: C, 69.94; H, 4.48; N, 13.54.

(B) By Methylation of 1. A solution of **1** (100 mg, 0.39 mmol) in DMSO (1 mL) was added to a solution of KH (16 mg, 0.40 mmol) in dry DMSO (1 mL) at 25 °C. The reaction mixture was maintained under an atmosphere of Ar and stirred for 15 min. Methyl iodide (55 mg, 0.44 mmol) was then added directly, and the mixture was stirred for an additional 30 min. The solution was then poured into water (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic portions were washed with water (2 × 50 mL) and brine (2 × 50 mL) and dried over Na_2SO_4. The solvent was removed in vacuo to provide an oil. A cold saturated solution of methanolic hydrogen chloride was added. The precipitate that resulted was collected by vacuum filtration to afford **4**·HCl (85 mg, 71%).

7-Hydro-12-methylpyrido[3,2-*b*:5,4-*b*']diindole Hydrochloride (5·HCl). A 250-mL three-neck round-bottom flask equipped with a mechanical stirrer and dry-ice condenser was cooled in a dry ice/acetone bath and filled with liquid ammonia (150 mL). Metallic sodium (115 mg, 5.0 mmol) and a catalytic amount of $Fe(NO_3)_3$·$9H_2O$ were added with stirring. After 1 h, **1** (500 mg, 2 mmol) was added in one portion and the mixture was stirred for 10 min. Methyl iodide (430 mg, 3 mmol) was added dropwise, and the reaction mixture was removed from the cooling bath. The ammonia was allowed to evaporate overnight. The residue that resulted was dissolved in MeOH and added to a solution of saturated methanolic hydrogen chloride. The excess solvent was removed in vacuo to provide a mixture of **5** and **7** as their hydrochloride salts. The solid mixture was dissolved in MeOH/CH_3CN (1:1). Upon standing at room temperature, **5** crystallized as its hydrochloride salt selectively from the mixture. The filtrate was concentrated, and the dimethylpyridodiindole **7** was obtained in pure form as the hydrochloride salt by repeated recrystallizations from MeOH.

7-Hydro-12-methylpyrido[3,2-*b*:5,4-*b*']diindole Hydrochloride (5·HCl) (275 mg; 40%): mp >300 °C; MS (CI, CH_4), *m/e* 272 (M + 1); IR (KBr) 3300, 1450, 1310, 700 cm^{-1}; ^1H NMR (DMSO-d_6) δ 13.0 (s, 1 H), 9.15 (s, 1 H), 8.82 (d, *J* = 8.3 Hz, 1 H), 8.62 (d, *J* = 8.2 Hz, 1 H), 7.96 (d, *J* = 7.3 Hz, 1 H), 7.86 (d, *J* = 8.3 Hz, 1 H), 7.75 (t, *J* = 8.0 Hz, 1 H), 7.69 (t, *J* = 7.3 Hz, 1 H), 7.50 (t, *J* = 7.0 Hz, 1 H) 7.42 (t, *J* = 7.3 Hz, 1 H), 4.60 (s, 3 H). Anal. Calcd for $C_{18}H_{13}N_3$·HCl·$^1/_4H_2O$: C, 69.23; H, 4.67; N, 13.46. Found: C, 69.04; H, 4.46; N, 13.08.

7,12-Dimethylpyrido[3,2-*b*:5,4-*b*']diindole Hydrochloride (7·HCl) (190 mg; 30%): mp >300 °C; MS (CI, CH_4), *m/e* 286 (M + 1); IR (KBr) 3400, 1450, 1310, 725 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.45 (s, 1 H), 8.90 (d, *J* = 7.6 Hz, 1 H) 8.60 (d, *J* = 7.5 Hz, 1 H), 8.00 (d, *J* = 7.3 Hz, 1 H), 7.91 (d, *J* = 7.3 Hz, 1 H), 7.85 (t, *J* = 7.5 Hz, 1 H), 7.75 (t, *J* = 7.5 Hz, 1 H), 7.55 (t, *J* = 7.5 Hz, 1 H), 7.45 (t, *J* = 7.5 Hz, 1 H), 4.70 (s, 3 H), 4.20 (s, 3 H). Anal. Calcd for $C_{19}H_{15}N_3$·HCl: C, 70.91; H, 5.01; N, 13.06. Found: C, 71.19; H, 5.04; N, 13.09.

Acknowledgment. This work was supported by grants from the National Institutes of Health (MH 36644 and NS 22287). We would also like to thank Michael J. Martin, Dr. Suzanne Wehrli, and Frank Laib for their technical assistance and Anju Gupta for her help in the preparation of this manuscript.

Registry No. 1, 98263-45-7; 2, 98263-41-3; 3, 116130-38-2; 4, 116130-39-3; 4·HCl, 116130-40-6; 5, 116130-41-7; 5·HCl, 116130-42-8; 6a, 116130-43-9; 6b, 116130-44-0; 6c, 116130-45-1; 7, 116130-46-2; 7·HCl, 116130-47-3; $PhNHNH_2$, 100-63-0.

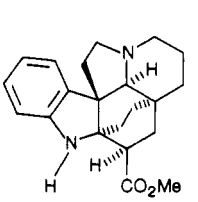
A Formal Total Synthesis of Kopsinine

Ernest Wenkert* and Mauricio J. Pestchanker

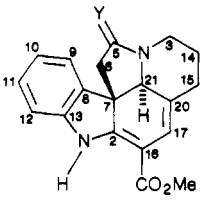
Department of Chemistry (D-006), University of California—San Diego, La Jolla, California 92093

Received May 17, 1988

Recently a three-step reaction sequence (Scheme I) was put forward as a facile mode of construction of the pentacyclic nucleus of the Aspidosperma alkaloids.[1] The substitution pattern of the product **1** made the substance ideally suited for conversion into kopsinine (**2**), a hexacyclic indoline alkaloid biosynthetically related to the Aspidosperma alkaloid family. The keto ester **1** required transformation into diene esters **3** on the assumption of the latter being amenable to Diels–Alder chemistry as an approach to the kopsinine skeleton. The functional group manipulation needed for the **1** → **3** transformation is the subject of the present paper.



2



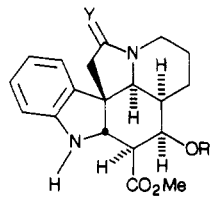
3a: Y = O
b: Y = H_2

The keto ester **1** had been converted earlier into the olefinic ester **5a** by way of sodium borohydride reduction and polyphosphoric acid induced dehydration of the resultant hydroxy ester **4a**.[1] The water extrusion now could be improved by treatment of alcohol **4a** with methanesulfonyl chloride and triethylamine and β-elimination of the resultant mesylate **4b** with potassium hydride. Oxidation of indoline **5a** with lead tetraacetate led to dienamine ester **3a**. An alternate route to the latter involved the lead tetraacetate oxidation of hydroxy ester **4a**. The product mixture consisted of vinylogous urethane **6**, its dehydration product (**3a**), and the aryl acetate **7**. Exposure of alcohol **6** to methanesulfonyl chloride and diisopropylethylamine furnished more dienamine ester **3a**.

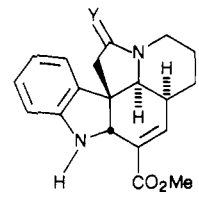
The keto ester **1** had been transformed earlier into the hyroxy ester **4c** via diborane reduction of the lactam moiety and subsequent sodium borohydride reduction of the ketone unit.[1] Treatment of alcohol **4c** now with methanesulfonyl chloride and diisopropylethylamine afforded mesylate **4d**, whose solvolysis in acetonitrile led to a mixture of olefinic esters **5b** and **8**, but whose β-elimination with potassium hydride gave exclusively the conjugated olefinic ester **5b**. Lead tetraacetate oxidation of the latter produced dienamine ester **3b**.[2,3] In view of the recent transmutation of this diene ester into (±)-kopsinine

(1) Wenkert, E.; Orito, K.; Simmons, D. P.; Ardisson, J.; Kunesch, N.; Poisson, J. *J. Org. Chem.* **1983**, *48*, 5006.
(2) Kuehne, M. E.; Seaton, P. J. *J. Org. Chem.* **1985**, *50*, 4790.
(3) Ogawa, M.; Kitigawa, Y.; Natsume, M. *Tetrahedron Lett.* **1987**, *28*, 3985.

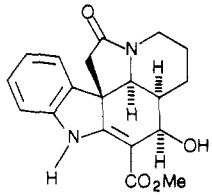
0022-3263/88/1953-4875$01.50/0



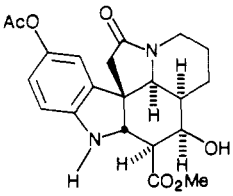
4a: R = H; Y = O
b: R = SO_2Me; Y = O
c: R = H; Y = H_2
d: R = SO_2Me; Y = H_2



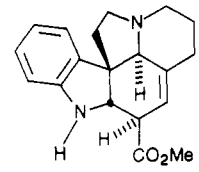
5a: Y = O
b: Y = H_2



6



7



8

(2) (cycloaddition with phenyl vinyl sulfone and subsequent, reductive desulfonylation and double bond saturation),[2] the present work constitutes the completion of a formal total synthesis of the alkaloid.[4]

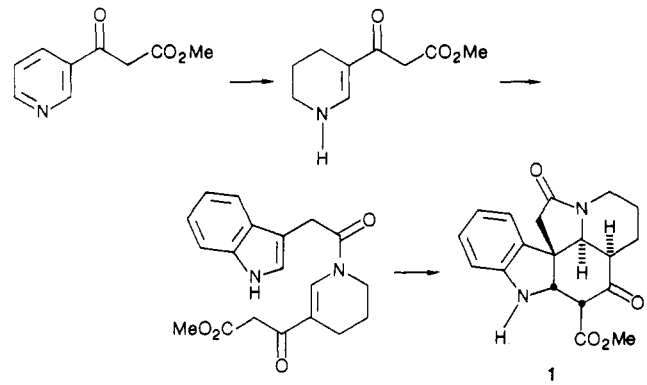
Experimental Section

Melting points were recorded on a Reichert microhotstage apparatus and are uncorrected. Ultraviolet spectra of methanol solutions and infrared spectra of methylene chloride solutions were measured on IBM 9400 and Perkin-Elmer 1330 spectrophotometers, respectively. ^1H NMR spectra of deuteriochloroform solutions (internal standard: Me_4Si) were obtained on Varian EM-390 and Nicolet QE-300 spectrometers and ^{13}C NMR spectra of deuteriochloroform solutions on the latter instrument, operating at 75.5 MHz in the Fourier transform mode. The carbon shifts are in parts per million downfield from Me_4Si; $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm. All crude products were extracted with methylene chloride, and the extracts were washed with brine, dried over anhydrous Na_2SO_4, and evaporated. All chromatographic separations were carried out on medium-pressure, Lichoprep Si 60 (40–63 μm) Lobar columns with the use of a Fluid Metering, Inc., pump.

20-Deethyl-17-dehydro-2β-hydro-5-oxovincadifformine (5a). A solution of 300 mg (0.88 mmol) of hydroxy ester **4a**,[1] 100 μL (1.2 mmol) of methanesulfonyl chloride, and 1 mL of triethylamine in 10 mL of ethylene dichloride was stirred at 0 °C for 1 h and then poured into saturated sodium bicarbonate solution. Extraction, drying, and evaporation led to crude, metastable mesylate **4b**, whose solution in 10 mL of dry tetrahydrofuran was treated with 77 mg (1.9 mmol) of potassium hydride. The suspension was stirred at room temperature for 10 h and then poured into a saturated solution of sodium bicarbonate. Normal workup and chromatographic elution with 4:1 hexane–ethyl acetate yielded 185 mg (65%) of solid, amorphous olefinic ester **5a**: UV, IR, ^1H NMR, and ^{13}C NMR[5] spectrally identical with an authentic sample.[1]

17,20-Didehydro-20-deethyl-5-oxovincadifformine (3a). A suspension of 800 mg (2.6 mmol) of indoline **5a** and 1.40 g (4.2 mmol) of lead tetraacetate in 50 mL of dry methylene chloride was stirred at 0 °C for 2 h and then poured into saturated sodium bicarbonate solution. The usual workup and chromatographic elution with 9:1 hexane–ethyl acetate led to the recovery of 200 mg of starting indoline **5a**. The early eluates yielded 120 mg (20% based on consumed **5a**) of colorless, crystalline diene ester **3a**: mp 153–155 °C (MeOH); UV $\lambda_{shoulder}$ 225 nm (log ε 4.56), λ_{max} 248 (4.56), 306 (4.15), 374 (4.42); IR 3420 (NH, w), 3374 (m), 1690 (C=O, s), 1642 (m), 1603 (C=C, s) cm^{-1}; ^1H NMR δ 1.6–2.6 (m, 4, 2 CH_2), 2.36, 2.92 (d, 1 each, J = 17 Hz, C-6 H's), 2.97 (ddd, 1, J = 13, 13, 3 Hz, H-3), 3.80 (s, 3, OMe), 4.33 (dd, 1, J = 13, 1 Hz, H-3), 4.41 (s, 1 H-21), 6.17 (s, 1, H-17), 6.91, 7.36 (d, 1 each, J = 7 Hz, H-9, H-12), 6.92, 7.23 (t, 1 each, J = 7 Hz, H-10, H-11); ^{13}C NMR δ 26.2 (C-14), 31.0 (C-15), 41.9 (C-3), 46.7 (C-6), 48.7 (C-7), 51.1 (OMe), 64.2 (C-21), 91.9 (C-16), 110.0 (C-12), 116.0 (C-17), 121.6 (C-10 or C-9), 121.9 (C-9 or C-10), 122.0 (C-20), 128.9 (C-11), 134.3 (C-8), 143.0 (C-13), 161.9 (C-2), 167.0 (C-5), 173.3 (C=O); exact mass; m/e 322.1324 (calcd for $C_{19}H_{18}O_3N_2$ m/e 322.1315).

Scheme I



1

A solution of 300 mg (0.88 mmol) of vinylogous urethane **6** (see below), 100 μL (1.2 mmol) of methanesulfonyl chloride, and 1 mL of diisopropylethylamine in 10 mL of dry methylene chloride was stirred at room temperature for 24 h and then poured into saturated sodium bicarbonate solution. Normal workup, chromatographic elution with 9:1 hexane–ethyl acetate, and crystallization from ethanol furnished 238 mg (83%) of crystalline diene ester **3a**.

20-Deethyl-17β-hydroxy-5-oxovincadifformine (6). A suspension 2.40 g (7.0 mmol) of hydroxy ester **4a** and 3.70 g (8.4 mmol) of lead tetraacetate in 50 mL of dry methylene chloride was stirred at room temperature for 72 h and then poured into saturated sodium bicarbonate solution. Normal workup and chromatographic elution with 7:1 hexane–ethyl acetate gave 384 mg (24% based on consumed **4a**) of colorless, crystalline diene ester **3a**, melting and mixed melting points and spectrally identical with the above sample. Elution with 3:1 hexane–ethyl acetate yielded 480 mg (30% based on consumed **4a**) of amorphous, colorless, solid vinylogous urethane **6**: UV $\lambda_{shoulder}$ 227 nm (log ε 4.55), λ_{max} 296 (4.53), 325 (4.64); IR 3590 (OH, w), 3414 (NH, w), 3371 (w), 1681 (C=O, s), 1640 (m), 1611 (C=C, s) cm^{-1}; ^1H NMR δ 1.6–2.3 (m, 5, H-20, 2 C-14, 2 C-15 H's), 2.57, 3.10 (d, 1 each, J = 17 Hz, C-6 H's), 2.92 (dt, 1 J = 13, 3 Hz, H-3), 3.79 (s, 3, OMe), 4.10 (d, 1, J = 6 Hz, H-21), 4.32 (dd, 1, J = 12, 2 Hz, H-3), 5.04 (t, 1, J = 2 Hz, H-17), 6.90, 7.28 (d, 1 each, J = 7 Hz, H-9, H-12), 6.98, 7.22 (t, 1 each, J = 7 Hz, H-10, H-11); ^{13}C NMR δ (added trace of DMSO-d_6) 20.6 (C-14), 26.8 (C-15), 36.1 (C-20), 40.4 (C-3), 48.3 (C-6), 49.9 (C-7), 50.5 (OMe), 60.0 (C-21), 69.4 (C-17), 98.7 (C-16), 109.4 (C-12), 120.7 (C-10), 121.4 (C-9), 127.9 (C-11), 136.5 (C-8), 142.2 (C-13), 165.7 (C-2), 167.1 (C-5), 170.0 (C=O); exact mass m/e 340.1428 (calcd for $C_{19}H_{20}O_4N_2$ m/e 340.1421).

Elution with 1:1 hexane–ethyl acetate led to the recovery of 800 mg of starting hydroxy ester **4a** and with 1.5:1 ethyl acetate–hexane afforded 520 mg (30% based on consumed **4a**) of colorless, liquid diester **7**: UV λ_{max} 250 nm (log ε 4.14), 306 (3.88); IR 3590 (OH, w), 3395 (NH, w), 1759 (C=O, s), 1730 (s), 1714 (s), 1685 (s), 1611 (C=C, m) cm^{-1}; ^1H NMR δ 1.5–2.3 (m, 5, H-20, 2 C-14, 2 C-15 H's), 2.25, 2.97 (d, 1 each, J = 17 Hz, C-6 H's), 2.26 (s, 3, COMe), 2.37 (d, 1, J = 10 Hz, H-16), 2.74 (dt, 1, J = 13, 3 Hz, H-3), 3.79 (s, 1, OMe), 3.94 (d, 1, J = 5 Hz, H-21), 4.05 (d, 1, J = 10 Hz, H-2), 4.15 (dd, 1, J = 13, 4 Hz, H-3), 6.63 (d, 1, J = 8 Hz, H-12), 6.80 (dd, 1, J = 8, 2 Hz, H-11), 6.83 (d, 1, J = 2 Hz, H-9); ^{13}C NMR δ 20.0 (C-14), 20.6 (Me), 27.2 (C-15), 34.3 (C-20), 40.1 (C-3), 44.5 (C-6), 48.1 (C-7), 49.9 (C-16), 51.9 (OMe), 58.0 (C-21), 62.0 (C-2), 71.2 (C-17), 169.8 (acetyl C=O), 171.8 (C-5), 173.3 (C=O), 109.8, 115.4, 121.2 (aromatic methines), 131.3, 143.0, 146.4 (aromatic, nonprotonated carbons); exact mass m/e 400.1619

(4) It is noteworthy that the dienamine ester **3a** does not undergo cycloaddition with phenyl vinyl sulfone, but at elevated temperature is changed into a substance of as yet undetermined structure.

(5) Wenkert, E.; Porter, B.; Simmons, D. P.; Ardisson, J.; Kunesch, N.; Poisson, J. *J. Org. Chem.* **1984**, *49*, 3733.

(calcd for $C_{21}H_{24}O_6N_2$ m/e 400.1631).

20-Deethyl-2β,16α-dihydro-17β-[(methylsulfonyl)oxy]-vincadifformine (4d). A solution of 200 mg (0.61 mmol) of hydroxy ester **4c**,[1] 60 μL (0.72 mmol) of methanesulfonyl chloride, and 0.5 mL of diisopropylethylamine in 6 mL of ethylene dichloride was stirred at 0 °C for 1 h and then poured into a saturated sodium bicarbonate solution. Extraction, drying, and evaporation gave a residue, whose crystallization from acetone–hexane afforded 197 mg (82%) of colorless, crystalline ester **4d**: mp 94–96 °C, UV λ_{max} 245 nm (log ε 4.27), 297 (3.91); IR 3400 (NH, w), 1738 (C=O, s), 1611 (C=C, m), 1340 (SO_2, s), 1180 (s) cm^{-1}; ^1H NMR δ 1.5–2.6 (m, 11, methylenes, methines), 3.06 (s, 3, SMe), 3.0–3.2 (m, 2, H-3, H-5), 3.75 (s, 3, OMe), 4.01 (d, 1, J = 10 Hz, H-2), 5.35 (d, 1, J = 2 Hz, H-17), 6.62, 7.09 (d, 1 each, J = 8 Hz, H-9, H-12), 6.73, 7.02 (t, 1 each, J = 8 Hz, H-10, H-11); ^{13}C NMR δ 21.7 (C-14), 26.2 (C-15), 35.8 (C-20), 38.4 (C-6), 39.0 (SMe), 50.2 (OMe), 52.2 (C-16), 52.9 (C-3), 53.6 (C-7), 54.0 (C-5), 63.0 (C-2), 65.1 (C-21), 80.1 (C-17), 110.0 (C-12), 118.8 (C-10), 121.7 (C-9), 128.0 (C-11), 133.4 (C-8), 148.3 (C-13), 172.0 (C=O); exact mass m/e (M^+ – 80) 310.1681 (calcd for $C_{19}H_{22}O_2N_2$ m/e 310.1691). Anal. Calcd for $C_{20}H_{26}O_5N_2S$: C, 59.07; H, 6.45; N, 6.89. Found: C, 58.85; H, 6.32; N, 6.74.

Olefinic Esters 5b and 8. A solution of 60 mg (0.15 mmol) of mesylate **4d** in 7.5 mL of dry acetonitrile was refluxed for 24 h and then poured into a saturated sodium bicarbonate solution. Workup as before and chromatographic elution with 2:1 hexane–ethyl acetate gave 20 mg (40%) of colorless, crystalline 20-deethyl-17-dehydro-2β-hydrovincadifformine (**5b**): mp 137–138 °C (hexane–acetone); UV $\lambda_{shoulder}$ 242 nm (log ε 4.34), λ_{max} 300 (3.97); IR 3410 (NH, w), 1708 (C=O, s), 1653 (C=C, m), 1612 (m) cm^{-1}; ^1H NMR δ 1.5–2.6 (m, 10, methylenes, methines), 3.05 (dd, 1, J = 11, 3 Hz, H-3 or H-5), 3.18 (dt, 1, J = 9, 4 Hz, H-3 or H-5), 3.76 (s, 3, OMe), 4.35 (d, 1, J = 1 Hz, H-2), 6.53, 7.01 (d, 1 each, J = 8 Hz, H-9, H-12), 6.68, 6.98 (t, 1 each, J = 8 Hz, H-10, H-11), 6.92 (d, 1, J = 1 Hz, H-17); ^{13}C NMR δ 22.4 (C-14), 28.7 (C-15), 32.8 (C-20), 39.9 (C-6), 51.6 (OMe), 52.5 (C-3 or C-5), 52.7 (C-5 or C-3), 53.5 (C-7), 62.9 (C-2), 68.3 (C-21), 108.7 (C-12), 118.2 (C-10), 122.7 (C-9), 128.0 (C-11), 131.0 (C-8 or C-16), 131.8 (C-16 or C-8), 144.7 (C-17), 150.6 (C-13), 167.2 (C=O); exact mass m/e 310.1655 (calcd for $C_{19}H_{22}O_2N_2$ m/e 310.1679). Anal. Calcd for $C_{19}H_{22}O_2N_2$: C, 73.05; H, 7.15; N, 9.03. Found: C, 72.98; H, 7.08; N, 8.67.

Elution with 1:1 hexane–ethyl acetate led to 12.5 mg (25%) of colorless, liquid 20-deethyl-17,20-didehydro-2β,16α-dihydrovincadifformine (**8**): UV $\lambda_{shoulder}$ 245 nm (log ε 4.30), λ_{max} 301 (3.95); ^1H NMR δ 1.6–3.3 (m, 12, methylenes, methines), 3.64 (d, 1, J = 9 Hz, H-2), 3.76 (s, 3, OMe), 5.55 (s, 1, H-17), 6.71, 7.15 (d, 1 each, J = 7 Hz, H-9, H-12), 6.77, 7.07 (t, 1 each, J = 7 Hz, H-10, H-11); exact mass m/e 310.1674 (calcd for $C_{19}H_{22}O_2N_2$ m/e 310.1679).

A suspension of 460 mg (1.13 mmol) of mesylate **4d** and 124 mg (3.1 mmol) of potassium hydride in 50 mL of dry tetrahydrofuran was stirred at 0 °C for 5 h and then at room temperature for 12 h. The mixture was poured into saturated sodium bicarbonate solution and worked up as above. Chromatographic elution with 2:1 hexane–ethyl acetate and crystallization from acetone–hexane led to 281 mg (81%) of colorless, crystalline olefinic ester **5b**.

20-Deethyl-17,20-didehydrovincadifformine (3b). A suspension of 150 mg (0.48 mmol) of ester **5b** and 230 mg (0.52 mmol) of lead tetraacetate in 15 mL of dry methylene chloride was stirred at 0 °C for 2 h and then at room temperature for 4 h. The mixture was poured into a saturated sodium bicarbonate solution and worked up as before. Chromatographic elution with 11:1 hexane–ethyl acetate led to the recovery of 50 mg of starting ester **5b**. The earlier eluates gave 60 mg (60% based on consumed **5b**) of colorless, crystalline diene ester **3b**:[2,3] mp 140–142 °C (hexane–acetone) (lit.[2] mp 139–140.5 °C); IR 3431 (NH, w), 3382 (m), 3342 (w), 1730 (C=O, s), 1678 (s), 1639 (C=C, s), 1605 (s) cm^{-1}; ^1H NMR δ 1.4–3.2 (m, 10, methylenes), 3.78 (s, 3, OMe), 3.83 (s, 1, H-21), 6.10 (s, 1, H-17), 6.87, 7.57 (d, 1 each, J = 8 Hz, H-9, H-12), 6.93, 7.17 (t, 1 each, J = 8 Hz, H-10, H-11); ^{13}C NMR δ 20.2 (C-14), 31.9 (C-15), 41.0 (C-6), 46.5 (C-5 or C-3), 47.6 (C-3 or C-5), 49.6 (C-7), 50.7 (OMe), 66.0 (C-21), 90.8 (C-16), 109.1 (C-12), 115.5 (C-17), 121.3 (C-10), 123.2 (C-9), 124.9 (C-20), 127.5 (C-11), 136.4 (C-8), 143.0 (C-13), 164.4 (C-2), 167.4 (C=O); exact mass m/e 308.1554 (calcd for $C_{19}H_{20}O_2N_2$ m/e 308.1523).

Acknowledgment. We are indebted to the Public Health Service for support for this work. M.J.P., expresses his gratitude to the Consejo Nacional de Investigaciones Cientificas y Technológicas (Argentina) for a 1986–1988 fellowship.

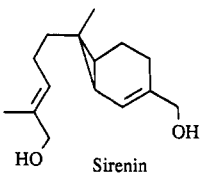
A New Synthesis of (±)-Sirenin and a Physiologically Active Analogue

Kenn E. Harding,* J. Byron Strickland, and Jeffrey Pommerville

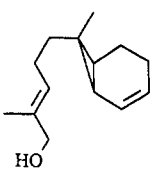
Department of Chemistry and Department of Biology, Texas A&M University, College Station, Texas 77843

Received March 29, 1988

As part of a project to elucidate the chemical and biological processes involved in the chemotactic response of gametes of the aquatic fungus *Allomyces*,[1] it became necessary to prepare authentic samples of the female sexual pheromone sirenin (**1**)[2] for calibration of biological tests. Although several syntheses of sirenin have been reported,[3] it was decided to elaborate the synthesis of demethylsesquicarene developed earlier in these laboratories[4] into a new synthesis of racemic sirenin. Model studies conducted to develop the reactions necessary for the synthesis of sirenin resulted in the synthesis of the deoxy-nor analogue **2**. This compound has proven to be first sirenin analogue that exhibits chemotactic activity at physiological concentrations.



Sirenin
1



2

The method used[4] for synthesis of the bicyclo[4.1.0]-heptane skeleton involves the stereoselective addition of

(1) For a recent review, see: Pommerville, J. In *Sexual Interactions in Eukaryotic Microbes*; O'Day, D. H.; Horgen, P. A., Eds.; Academic: New York, 1981; pp 53–72.

(2) For discussions of the isolation and structure elucidation of sirenin, see: (a) Machlis, L. *Physiol. Plant.* **1958**, *11*, 181–192. (b) Machlis, L. *Physiol. Plant* **1958**, *11*, 845–854. (c) Machlis, L. *Nature (London)* **1958**, *181*, 1790–1791. (d) Machlis, L., Nutting, W. H.; Williams, M. W.; Rapoport, H. *Biochemistry* **1966**, *5*, 2147–2152. (e) Machlis, L.; Nutting, W. H.; Rapoport, H. *J. Am. Chem. Soc.* **1968**, *90*, 1674–1676. (f) Nutting, W. H.; Rapoport, H.; Machlis, L. *J. Am. Chem. Soc.* **1968**, *90*, 6434–6438.

(3) For previous syntheses of sirenin, see: (a) Corey, E. J.; Achiwa, K.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1969**, *91*, 4318–4320. (b) Plattner, J. J.; Bhalerao, U. T.; Rapoport, H. *J. Am. Chem. Soc.* **1969**, *91*, 4933–4934. (c) Bhalerao, U. T.; Plattner, J. J.; Rapoport, H. *J. Am. Chem. Soc.* **1970**, *92*, 3429–3433. (d) Plattner, J. J.; Rapoport, H. *J. Am. Chem. Soc.* **1971**, *93*, 1758–1761. (e) Corey, E. J.; Achiwa, K. *Tetrahedron Lett.* **1970**, 2245–2246. (f) Katzenellenbogen, J. A. *Diss. Abstr. Int. B* **1970**, *31*, 1826. (g) Grieco, P. A. *J. Am. Chem. Soc.* **1969**, *91*, 5660–5661. (h) Grieco, P. A. *Diss. Abstr. Int. B* **1971**, *32*, 1449. (i) Mori, K.; Matsui, M. *Tetrahedron Lett.* **1969**, 4435–4438. (j) Mori, K.; Matsui, M. *Tetrahedron* **1970**, *26*, 2801–2814. (k) Garbers, C. F.; Steenkamp, J. A.; Visagie, H. E. *Tetrahedron Lett.* **1975**, 3753–3756. (l) DuPreez, H. E.; Garbers, C. F.; Steenkamp, J. A. *S. Afr. J. Chem.* **1980**, *33*, 21–26. (m) Kitatani, K.; Hiyama, T.; Nozaki, H. *J. Am. Chem. Soc.* **1976**, *98*, 2362–2364. (n) Mandai, T.; Hara, K.; Kawada, M.; Nokami, J. *Tetrahedron Lett.* **1983**, *24*, 1517–1518. (o) Ono, T.; Tamaoka, T.; Yuasa, Y.; Matsuda, T.; Nokami, J.; Wakabaya-shi, S. *J. Am. Chem. Soc.* **1984**, *106*, 7890–7893. (p) Uyehara, T.; Yamada, J.; Ogata, K.; Kato, T. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 211–216.

(4) (a) Harding, K. E.; Trotter, J. W. *J. Org. Chem.* **1977**, *42*, 4157–4159. (b) Trotter, J. W. Ph.D. Dissertation, Texas A & M University, College Station, TX, December, 1975.

0022-3263/88/1953-4877$01.50/0