(1.05 g, 13.2 mmol) in dichloromethane (12 mL). After 10 min, **20a** (4.20 g, 12.9 mmol) in dichloromethane (25 mL) was added. After 15 min, diisopropylethylamine (9.0 g, 69 mmol) was added and the mixture was allowed to warm to 20 °C. Workup with water furnished the crude aldehyde (**27a**), which was immediately oxidized to the acid. Crude **27a** (4.0 g) in *tert*-butyl alcohol (25 mL) was treated with phosphate buffer until pH 6 was reached. Aqueous 1 M potassium permanganate was added dropwise, until no starting material was left (TLC). Sodium sulfite was added to destroy unreacted permanganate, and the mixture was acidified to pH 3 with diluted HCl and extracted with ether. The ether phase was dried ($MgSO_4$) and concentrated to give the crude acid (**27b**). **27b** in ether (10 mL) was treated dropwise at 0 °C with ethereal diazomethane, until the mixture was faintly yellow. One drop of acetic acid was added, and the ether was removed under reduced pressure. The residue was purified by column chromatography to give **27c** (3.10 g, 68%) as a colorless oil.

(2*S*,3*S*,4*S*)-*N*-Benzoyl-3-(benzyloxy)-4-methylproline methyl ester (27c): $[\alpha]^{20}_D$ −22.1° (*c* 0.8, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.06 (d, *J* = 7 Hz, CH_3), 2.48 (m, H-4), 3.39 (t, *J* = 10 Hz, H-5), 3.66 (dd, *J* = 10, 2.5 Hz, H-5), 3.80 (s, OMe), 3.94 (d, *J* = 5 Hz, H-3), 4.55 (d, *J* = 11 Hz, benzyl H), 4.80 (d, *J* = 11 Hz, benzyl H), 4.86 (br s, H-2), 7.28–7.56 (phenyl H); ^{13}C NMR ($CDCl_3$) δ 10.81, 37.11, 52.31, 54.14, 64.54, 71.28, 81.74, 127.11, 127.73, 127.82, 128.15, 128.37, 128.98, 136.03, 137.41, 169.70, 170.45; IR (film) 1745, 1635, 1400, 1415, 1210, 1180, 735 cm^{-1}. Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.52; H, 6.40; N, 3.87.

(2*S*,3*S*,4*S*)-*N*-Benzoyl-3-hydroxy-4-methylproline Methyl Ester (27d). **27c** (3.00 g, 8.48 mmol) in methanol (150 mL) was treated with 0.5 mL of concentrated HCl. Pd/C (10%) (300 mg) was added, and the mixture was hydrogenated at 22 °C (3 bar). After 3 h, the catalyst was removed by filtration and the solvent was evaporated. Column chromatography (silica gel, hexane–ethyl acetate 1:1) furnished **27d**: 2.10 g, 94%; colorless crystals, mp 106–107 °C; $[\alpha]^{20}_D$ −13.8° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.03 (d, *J* = 7 Hz, CH_3), 1.73 (s, OH), 2.44 (m, H-4), 3.38 (dd, *J* = 10, 9 Hz, H-5), 3.67 (dd, *J* = 10, 7.5 Hz, H-5), 3.80 (s, OMe), 4.28 (br s, H-3), 4.68 (s, H-2), 7.36–7.60 (m, phenyl H); ^{13}C NMR ($CDCl_3$) δ 10.81, 37.45, 52.41, 53.75, 68.27, 75.23, 127.20, 128.25, 130.17, 170.63; IR (KBr) 1745, 1625–1610, 1450, 1432, 1206, 1178, 732 cm^{-1}; MS *m/e* calcd. for $C_{14}H_{17}NO_4^{\bullet+}$ 263.115 759, found 263.115 862.

(2*S*,3*S*,4*S*)-3-Hydroxy-4-methylproline (HMP) (4). Sodium methoxide (40% in methanol, 70 mL) was diluted with water (30 mL). **27d** (2.00 g, 7.57 mmol) in methanol (5 mL) was added, and the mixture was refluxed for 36 h. After neutralization with diluted HCl, the solvent was evaporated and the solid residue was dried under reduced pressure and then extracted with methanol. The methanol solution was evaporated to deliver crude **4**, which was purified by dissolving it in diluted HCl (pH 2) and treating the solution with acidic ion-exchange resin (Dowex 50×4). The resin was washed with water and then eluted with 1 N aqueous ammonia. Evaporation of the elute delivered **4** (710 mg, 64%) as a colorless solid: $[\alpha]^{22}_D$ −26.4° (*c* 1.3, H_2O) [lit.[15] −27° (*c* 0.8, H_2O)]; ^1H NMR (D_2O) δ 1.08 (d, *J* = 7 Hz, CH_3), 2.26 (m, H-4), 3.05 (t, *J* = 12 Hz, H-5), 3.60 (dd, *J* = 12, 8 Hz, H-5), 4.06 (s, H-2), 4.45 (d, *J* = 4 Hz, H-3); ^{13}C NMR (D_2O + acetone-d_6) δ 11.79, 38.95, 51.63, 71.73, 78.20, 174.05; IR (KBr) 3320, 3030, 1620, 1575, 1380 cm^{-1}. Anal. Calcd for $C_6H_{11}NO_3$: C, 49.65, H, 7.64; N, 9.65. Found: C, 50.11; H, 7.58; N, 9.69.

Acknowledgment. This work was generously supported by Fonds der Chemischen Industrie and the Schering AG Berlin-Bergkamen.

Registry No. 4, 54615-51-9; **5a**, 121964-06-5; **5a** (mesylate), 121964-11-2; **5b**, 122045-92-5; **5c**, 121964-07-6; **5d**, 93170-28-6; **5e**, 122045-93-6; **6a**, 121964-08-7; **6a** (1,2-*O*-isopropylidene), 121964-12-3; **6a** (1-*O*-benzoate), 121964-16-7; **6b**, 122045-94-7; **6c**, 121964-09-8; **6d**, 121964-10-1; **6e**, 122045-95-8; **7a**, 121964-13-4; **7b**, 122045-96-9; **7c**, 121964-14-5; **7d**, 121964-15-6; **7e**, 122045-97-0; **8a**, 121964-17-8; **8b**, 122045-98-1; **8c**, 121964-18-9; **8d**, 121964-19-0; **8e**, 122045-99-2; **9a**, 121964-21-4; **9b**, 122046-04-2; **9c**, 121964-22-5; **9d**, 121964-23-6; **9e**, 122046-05-3; **10a**, 121964-24-7; **10b**, 122046-11-1; **10c**, 121964-25-8; **10d**, 121964-26-9; **10e**, 122087-62-1; **11a**, 122046-00-8; **11b**, 122046-01-9; **11c**, 122046-02-0; **11d**, 122046-03-1; **11e**, 121964-20-3; **12a**, 122046-06-4; **12b**, 122046-07-5; **12c**, 122046-08-6; **12d**, 122046-09-7; **12e**, 122046-10-0; **20a**, 121964-27-0; **20b**, 121964-28-1; **21b**, 121964-29-2; **21b** (3-*O*-deblocked), 121964-39-4; **22**, 121964-30-5; **22** (triol), 121964-40-7; **22** (triol, *N*-deblocked), 13042-55-2; **23**, 121964-31-6; **24a**, 121964-32-7; **24b**, 121964-33-8; **25a**, 121987-72-2; **25b**, 122087-63-2; **25c**, 121987-73-3; **27a**, 121964-34-9; **27a** (*N*-BOC analog), 121964-38-3; **27b**, 121964-35-0; **27c**, 121964-36-1; **27c** (free acid), 121964-41-8; **27d**, 121964-37-2; (2*R*,3*S*,4*S*)-1,2-*O*-isopropylidene-3-*O*-benzyl-4-methyl-5-hexene, 100572-69-8; (2*R*,3*R*,4*R*)-1,2-*O*-isopropylidene-3-*O*-benzyl-4-methyl-5-hexene, 100758-79-0; (2*R*,3*S*)-1,2-*O*-isopropylidene-3-*O*-benzyl-5-hexene, 87604-53-3; (2*R*,3*R*)-1,2-*O*-isopropylidene-3-*O*-benzyl-5-hexene, 87604-54-4; D-mannitol, 69-65-8; 3,4-di-*O*-benzyl-1,2:5,6-di-*O*-isopropylidene-D-mannitol, 111476-62-1; 3,4-di-*O*-benzyl-1,2-*O*-isopropylidene-D-mannitol, 121964-05-4.

Supplementary Material Available: Experimental details for the preparation of **5c** and ^1H and ^{13}C NMR and IR data and optical rotation for compounds **5c, 8, 9, 10b,c, 11, 12b–d, 23, 25b,c,** and some derivatives of **20/21b** and **23** (9 pages). Ordering information is given on any current masthead page.

Total Synthesis of (±)-Suaveoline†

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Contribution from the Department of Chemistry, University of Wisconsin—Milwaukee, Milwaukee, Wisconsin 53201. *Received March 2, 1989. Revised Manuscript Received May 15, 1989*

Abstract: The first total synthesis of the indole alkaloid (±)-suaveoline (**1**) (a macroline-related base and a member of the sarpagine/ajmaline class of alkaloids) was completed in a stereocontrolled fashion. The serial synthesis employed three intramolecular reactions, the Pictet–Spengler cyclization (**2** → **3**), the Dieckmann condensation (**3** → **4**), and the ortho ester Claisen rearrangement (**7** → **9**), all of which occurred with high stereoselectivity. Construction of the unique 3,4,5-trisubstituted pyridine ring (*E*) of **1** was executed by addition of hydroxylamine hydrochloride to an ethanolic solution of the corresponding 1,5-dialdehyde **13** followed by heating.

The indole alkaloid suaveoline (**1**) was first isolated from *Rauwolfia suaveolens* S. Moore in 1972.[1,2] The structure of **1** was elucidated by mass spectrometry, ^1H NMR (100 MHz) and UV spectroscopies, and partial synthesis from ajmaline.[1,2] Suaveoline (**1**) is a member of the sarpagine/ajmaline family of alkaloids and is structurally reminiscent of the macroline-related

† This paper is dedicated to Elmer Fike on the occasion of his 70th birthday.

(1) Majumdar, S. P.; Potier, P.; Poissen, J. *Phytochemistry* **1973**, *12*, 1167.
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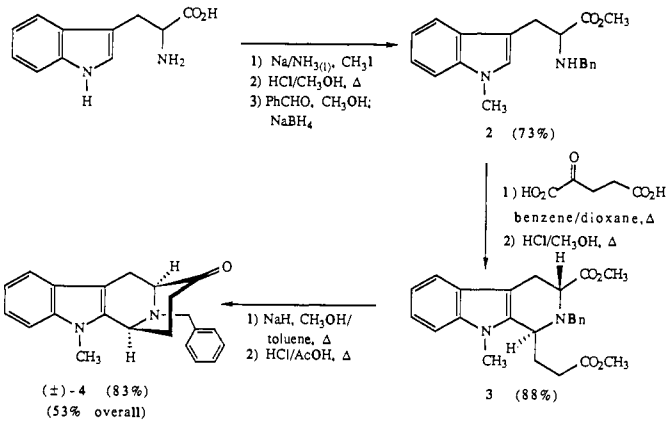
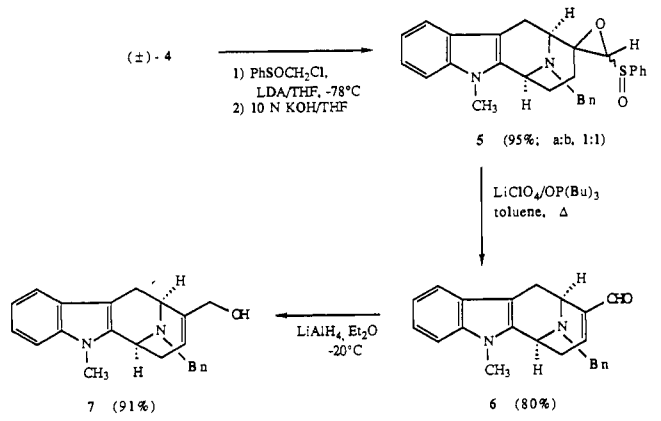
0002-7863/89/1511-7504$01.50/0

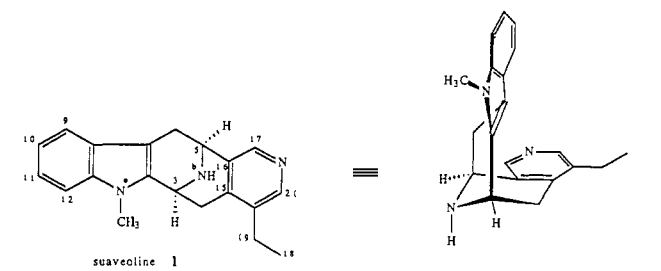
Scheme I



Scheme II



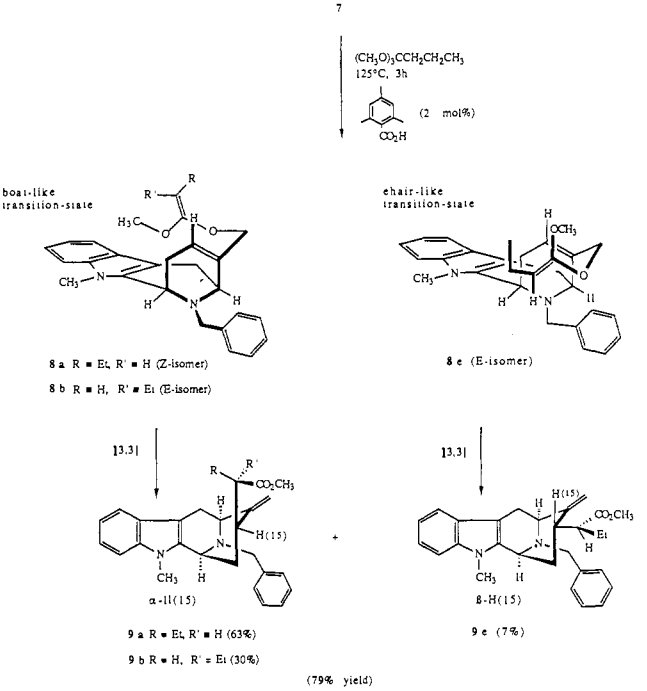
alkaloids isolated from the related botanical genus species *Alstonia*.[3a] Although the biomimetic synthesis of a number of bisindoles in this class has been reported by LeQuesne et al.,[3b] as well as interconversions in the monomeric series,[3c] these alkaloids have not yet fallen to total synthesis.



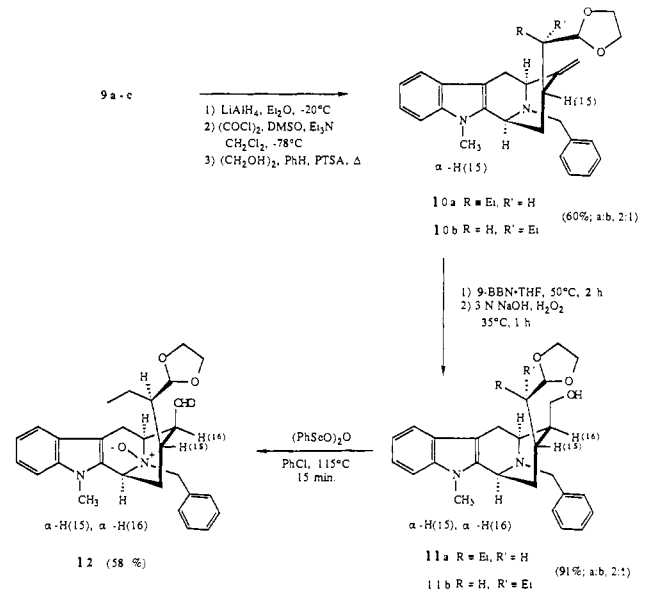
Here we report the first total synthesis of (±)-suaveoline (**1**). The synthetic strategy employs three stereoselective intramolecular reactions, the Pictet–Spengler reaction, the Dieckmann condensation, and the ortho ester Claisen rearrangement, for the construction of the basic carbon skeleton of the alkaloid.

Kilogram quantities of the (±)-tetracyclic ketone **4** were prepared from (±)-tryptophan in seven steps in an overall yield of 53% by a method previously developed in these laboratories.[4]

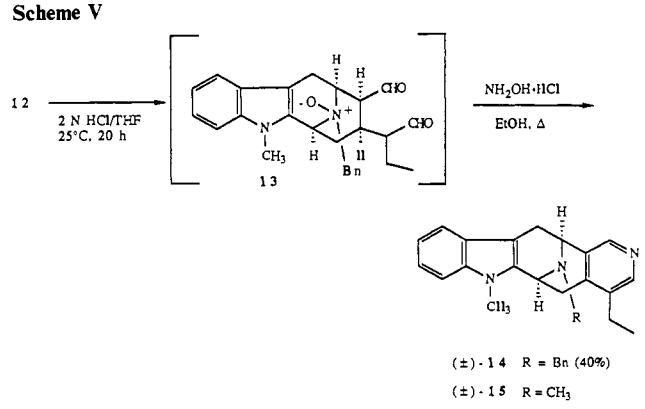
Scheme III



Scheme IV



Scheme V



In this procedure, stereospecific construction of the *trans*-1,3-disubstituted-1,2,3,4-tetrahydro-β-carboline intermediate **3** was

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achieved by performing a Pictet–Spengler reaction with tryptophan derivative **2** and 2-ketoglutaric acid in aprotic media (PhH/*p*-dioxane/reflux), followed by esterification with MeOH/HCl/reflux. Base-mediated epimerization at C-3 accompanied by cyclization of **3** under Dieckmann conditions ($PhCH_3$/MeOH/NaH/reflux), followed by acid-mediated decarboxylation (AcOH/HCl/reflux), furnished the desired (±)-tetracyclic ketone **4**.[3a] Moreover, this ketone has recently been prepared in optically active form in a stereospecific fashion via the method of Zhang.[5]

The ketone **4** was treated with the anion generated from chloromethyl phenyl sulfoxide/LDA/THF/−78 °C.[6] The chlorohydrin which resulted was stirred in a heterogeneous solution of 10 N KOH/THF/25 °C/24 h to provide the oxirane **5** in 95% yield. A solution of **5** in $PhCH_3$/$LiClO_4$/$OP(n\text{-}Bu)_3$ was heated to reflux for 1 h, which furnished the α,β-unsaturated aldehyde **6** in 80% yield.[7] Chemoselective reduction of the carbonyl moiety with $LiAlH_4/Et_2O$/−20 °C provided the allylic alcohol **7** in 91% yield.[8]

With **7** in hand, an intramolecular synthetic approach was utilized for functionalization of C-15. Previous studies have shown that intermolecular reactions (i.e., alkylation reactions with **4**[4a] and Michael reactions with **6**[4b]) gave poor yields of the desired products. This is presumably due to the steric influences of the indole–methylene bridge and the N_b-benzyl group. The allylic alcohol **7** was subjected to the conditions of an ortho ester Claisen rearrangement with $(CH_3O)_3CCH_2CH_2CH_3$/2,4,6-trimethylbenzoic acid (2%)/125 °C/3 h.[9] This facile one-pot reaction generated the basic carbon skeleton of (±)-**1** as a mixture of diastereomers in 79% yield. The [3,3]-sigmatropic rearrangement of the intermediate ketene acetals, **8a–c**, generated in situ, occurred with a high degree of stereofacial selectivity, predominately via a boatlike transition state from the β-face of the molecule to provide a mixture of diastereomers in a ratio of 13:1 (**9a**:**9b**:**9c**).[10,11] The stereochemical outcome of the ortho ester Claisen rearrangement was determined by ^1H NMR spectroscopy and confirmed by single-crystal X-ray crystallography of the major isomer **9a**.[12]

Conversion of the ester group of **9a–c** into the ethylene acetal of **10** was effected in a straightforward fashion with $LiAlH_4/Et_2O$/−20 °C, $(COCl)_2$/DMSO/Et_3N/−78 °C/CH_2Cl_2, and $(CH_2OH)_2$/PhH/PTSA/reflux in an overall yield of 60%. Hydroboration of the *exo*-methylene carbon–carbon double bond with 9-BBN·THF/THF/50 °C occurred from the α-face of the molecule and was followed by alkaline oxidative workup with 3 N $NaOH/H_2O_2$/35 °C/1 h to afford **11** in 91% yield.

The hydroxyl moiety of **11** was resistant to oxidation by a variety of oxidative reagents and reaction conditions (i.e., $(COCl)_2$/DMSO/Et_3N/−78 °C,[13] SO_3·pyr/DMSO/Et_3N,[14] PDC/CH_2Cl_2,[15] activated MnO_2,[16] and RuO_4[16]). Intramolecular oxidation of the hydroxymethyl group of **11** was successfully achieved with $(PhSeO)_2O$/PhCl/120 °C/15 min to provide **12** as the N_b-oxide in 58% yield.[17] Formation of the N_b-oxide is believed to have resulted from the disproportionation of selenenic and/or seleninic acids present as byproducts in the reaction mixture.[18] Hydrolysis of the ethylene acetal with 2 N HCl/THF/25 °C/24 h furnished the intermediate dialdehyde **13** which was immediately converted into (±)-N_b-benzylsuaveoline (**14**) by treatment with NH_2OH·HCl/EtOH/reflux in an overall yield of 40% from **12**.[19]

Hydrogenolysis of **14** with H_2 over 10% Pd/C/MeOH afforded (±)-**1** in 69% yield. The spectral data of (±)-**1** (^1H NMR, MS) were in complete agreement with the published data of the natural product.[2] Furthermore, the structure of (±)-**1** was confirmed by the synthesis of (±)-N_b-methylsuaveoline (**15**) from (±)-**14** by hydrogenolysis with H_2, 10% Pd/C/MeOH in the presence of formic acid (78% yield). The spectral data of (±)-**15** (^1H NMR, MS) were in complete agreement with the previously reported data on this synthetic derivative.[2]

(±)-Suaveoline (**1**) represents the first macroline-related alkaloid to fall to total synthesis.[20] The Claisen chemistry developed here to functionalize the sterically hindered C-15 and C-16 positions of these indolo-substituted azabicyclo[3.3.1]nonane alkaloids (see **1** and **4**) coupled with the recent work of Zhang[5,11,21] will be invaluable for the construction of other macroline-related sarpagine/ajmaline alkaloids. Further work in this area will be reported in due course.

Experimental Section

Ortho Ester Claisen Rearrangement. Methyl α-Ethyl-5-methyl-9-methylene-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct-[*b*]indole-8-acetate (9a–c). The allyl alcohol **7** (500 mg, 1.45 mmol) was dissolved in trimethyl orthobutyrate (2.00 g, 13.5 mmol). A catalytic amount of 2,4,6-trimethylbenzoic acid (10 mg) was added, and the mixture was heated at 125 °C (oil bath temperature) under an atmosphere of argon for 3 h. The reaction mixture was allowed to cool to room temperature and the excess ortho ester was removed under reduced pressure. The oil which resulted was chromatographed (SiO_2, EtOAc/hexane, 20:80) to provide the alkenic ester **9** as a mixture of diastereomers (490 mg, 79%) in the ratio of **a**:**b**:**c**, 63:30:7, respectively. mp 172–174 °C; IR (KBr) 1720, 1590 cm^{-1}; MS (CI, CH_4), *m/e* (relative intensity) 429 (M + 1, 100).

Anal. Calcd for (**9a–c**) $C_{28}H_{32}N_2O_2$: C, 78.47; H, 7.53; N, 6.54. Found: C, 78.72; H, 7.61; N, 6.41.

9a. ^1H NMR (benzene-d_6) δ 7.70–7.00 (m, 9 H_{arom}), 4.90 (d, J_{17AB} = 2.0 Hz, H_{17a}), 4.81 (d, J_{17AB} = 2.0 Hz, H_{17b}), 3.70 (d, J_{5-6a} = 7.0 Hz, H_5), 3.67 (t, J_{3-14} = 4.0 Hz, H_3), 3.64 (s, NCH_3), 3.57–3.48 (q, J_{AB} = 13.5 Hz, 2 H_{benzyl}), 3.21 (s, OCH_3), 3.17 (dd, J_{6AB} = 15.0, J_{6a-5} = 6.9 Hz, H_{6a}), 2.88 (m, H_{15}), 2.73 (d, J_{6AB} = 15.0 Hz, H_{6b}), 2.15 (m, J_{14AB} = 14.0, J_{14a-15} = 7.0, J_{14a-3} = 4.0 Hz, H_{14a}), 1.65 (dt, J_{20-15} = 10.0, J_{20-19a} = 10.0, J_{20-19b} = 3.0 Hz, H_{20}), 1.62 (m, H_{14b}), 1.28 (m, $2H_{19}$), 0.33 (t, J_{18-19} = 6.5 Hz, CH_3).

9b. ^1H NMR (benzene-d_6) δ 7.70–7.00 (m, 9 H_{arom}), 4.81 (d, J_{17AB} = 2.0 Hz, H_{17a}), 4.74 (d, J_{17AB} = 2.0 Hz, H_{17b}), 3.85 (t, J_{3-14} = 4.0 Hz, H_3), 3.67 (d, J_{5-6a} = 6.8 Hz, H_5), 3.57–3.48 (q, J_{AB} = 13.5 Hz, 2 H_{benzyl}), 3.20 (dd, J_{6AB} = 16.0, J_{6a-5} = 7.0 Hz, H_{6a}), 3.05 (s, NCH_3), 2.81 (s, OCH_3), 2.78 (m, H_{15}), 2.68 (dt, J_{20-15} = 8.0, J_{20-19} = 5.5 Hz, H_{20}), 2.54 (d, J_{6AB} = 16.0 Hz, H_{6b}), 1.85 (dt, J_{14AB} = 12.0, J_{14a-15} = 12.0, J_{14a-3} =

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4.0 Hz, H_{14a}), 1.65 (m, H_{14b}), 1.60 (m, 2 H_{19}), 0.75 (t, J_{18-19} = 6.5 Hz, CH_3).

α-Ethyl-5-methyl-9-formyl-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cycloocta[*b*]indole-8-acetaldehyde Ethylene Acetal N_b-Oxide (12). The hydroxy acetal **11** (200 mg, 0.43 mmol) was added to a solution of dry chlorobenzene (2 mL) and benzeneseleninic anhydride (78 mg, 0.21 mmol). The colorless mixture was heated to 110 °C (oil bath temperature) for 15 min. The orange solution which resulted was cooled to room temperature, and the solvent was removed under reduced pressure. The oil which resulted was dissolved in EtOAc (20 mL) and poured into a solution of 1 N NaOH (30 mL). The mixture was then extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford an oil. The oil was chromatographed (SiO_2, EtOAc/hexane, 30:70) to furnish the aldo acetal N_b-oxide **12** as a single isomer (104 mg, 53%): IR (NaCl) 2950, 2850, 1730, 1470, 1330, 1240, 1035, 730 cm^{-1}; MS (CI, CH_4), *m/e* (relative intensity) 474 (M + 1, 100) 458 (M + 1 - 16, 35.6); ^1H NMR ($CDCl_3$) δ 9.30 (s, 1 H), 7.49 (d, *J* = 7.8 Hz, 1 H), 7.30-7.10 (m, 7 H), 7.05 (t, *J* = 7.8 Hz, 1 H), 4.79 (d, *J* = 4.9 Hz, 1 H), 4.02-3.45 (m, 8 H), 3.51 (s, 3 H), 3.09 (dd, *J* = 16.8, *J* = 7.0 Hz, 1 H), 2.90 (m, 1 H), 2.53 (m, 1 H), 2.48 (d, *J* = 16.8 Hz, 1 H), 1.73-1.53 (m, 2 H), 1.15 (m, 2 H), 0.60 (t, *J* = 7.0 Hz, 3 H). ^{13}C NMR ($CDCl_3$) δ 205.00 (d), 140.11 (s), 139.03 (s), 138.20 (s), 129.11 (d), 127.98 (d), 126.85 (d), 127.00 (s), 122.11 (d), 119.94 (d), 119.01 (d), 109.14 (d), 106.50 (d), 104.81 (s), 81.91 (d), 66.00 (t), 65.22 (t), 63.15 (d), 55.80 (t), 48.00 (d), 39.91 (d), 38.2 (d), 29.9 (d), 26.00 (q), 21.92 (t), 20.21 (t), 11.93 (q). Exact mass calcd for $C_{29}H_{34}N_2O_4$: 474.2519. Found: 474.2520.

(±)-N_b-Benzylsuaveoline (14). The aldoacetal N_b-oxide **12** (200 mg, 0.41 mmol) was added to a 5% solution of 2 N HCl in THF (2 mL). The reaction mixture was stirred at 25 °C for 24 h and then poured into a cold aqueous solution of $NaHCO_3$ (10%, 10 mL). The aqueous mixture was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (20 mL) and dried (K_2CO_3). The solvent was removed under reduced pressure to afford the crude dialdehyde **13** as an oil (160 mg, 0.37 mmol, 91%). The crude dialdehyde was dissolved in anhydrous EtOH (5 mL) and hydroxylamine hydrochloride (128 mg, 1.86 mmol) was added. The reaction mixture was heated to reflux for 16 h under an atmosphere of nitrogen. The red solution which resulted was cooled to room temperature, and the solvent was removed under reduced pressure. The oil which resulted was dissolved in CH_2Cl_2 (10 mL) and poured into an aqueous solution of $NaHCO_3$ (10%, 10 mL). The aqueous mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with brine and dried (K_2CO_3). The solvent was removed under reduced pressure to afford an oil. The oil was chromatographed (SiO_2, EtOH/$CHCl_3$, 7:93) to afford N_b-benzylsuaveoline (**14**) (R_f = 0.42) as an oil (64 mg, 40% yield from **12**). MS (CI, CH_4), *m/e* (relative intensity) 394 (M + 1, 100); ^1H NMR ($CDCl_3$) δ 8.30 (s, H_{17}), 8.15 (s, H_{21}), 7.45 (d, J_{9-10} = 8.0 Hz, H_9), 7.40-7.20 (m, $H_{12,phenyl}$), 7.19 (t, $J_{11-10(12)}$ = 7.9 Hz, H_{11}), 7.09 (t, $J_{10-9(11)}$ = 7.9 Hz, H_{10}), 4.41 (d, J_{5-6a} = 6.5 Hz, H_5), 4.27 (d, J_{3-14a} = 6.6 Hz, H_3), 3.98-3.75 (q, J_{AB} = 13.8 Hz, 2 H_{benzyl}), 3.65 (s, N_aCH_3), 3.48 (dd, J_{6AB} = 16.4, J_{6a-5} = 6.6 Hz, H_{6a}), 3.25 (dd, J_{14AB} = 16.9, J_{14a-3} = 6.6 Hz, H_{14a}), 2.77 (d, J_{6AB} = 16.4 Hz, H_{6b}), 2.75 (d, J_{14AB} = 16.9 Hz, H_{14b}), 2.50 (q, J_{19-18} = 7.1 Hz, 2 H_{19}), 1.15 (t, J_{18-19} = 7.0 Hz, 3 H_{18}). This material was converted into (±)-suaveoline (**1**) on treatment with hydrogen over Pd/C (see supplementary material for details).

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Supplementary Material Available: Experimental procedure and spectral data for compounds **1**, **5**, **6**, **7**, **10a,b**, **11a,b**, and **15** (13 pages). Ordering information is given on any current masthead page.

Free-Radical Cyclizations: Application to the Total Synthesis of *dl*-Pleurotin and *dl*-Dihydropleurotin Acid†

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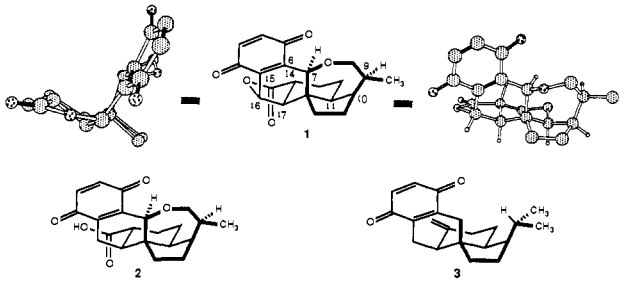
Abstract: Total syntheses of the antitumor antibiotic pleurotin (**1**) and dihydropleurotin acid (**2**) are described. Early stages of the synthesis feature the construction of a trans perhydroindan substructure using a stereoselective free-radical cyclization, and the final stage of the synthesis involves the biomimetic conversion of dihydropleurotin acid (**2**) to pleurotin (**1**).

Pleurotin (**1**) is an fungal metabolite first isolated from *Pleurotus grieseus* and later obtained from *Hohenbuehelia geogenius*.[1,2] Two structurally related natural products, dihydropleurotin acid (**2**) and pleurogrisein (**3**), have also been isolated from fungal sources.[3] Pleurotin displays antibiotic activity against Gram-positive bacteria and antitumor activity against Erlich ascites carcinoma, L-1210 lymphoid leukemia, and mammary tumors.[1,2] The structure of pleurotin was originally assigned on the basis of degradative studies[4] and later confirmed by X-ray crystallographic analysis of a derivative[5] and the natural product itself.[2]



Although the carbocyclic nucleus of **1** is uncommon, pleurotin does contain two substructures that appear in a variety of natural products. One of these substructures is the trans-fused perhydroindan common to numerous terpenoids. The other is a

† This paper is dedicated to Professor William G. Dauben on the occasion of his 70th birthday.

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