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PICTET-SPENGLER REACTIONS IN APROTIC MEDIA. THE TOTAL SYNTHESIS OF (±) SUAVEOLINE

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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 (**11** → **20**), the Dieckmann condensation (**21** → **22**) and the orthoester Claisen rearrangement (**25** → **30**), 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 **36** which was followed by heating. The related base (±)–N_b-methylsuaveoline **38** was prepared from **37** *via* catalytic debenzylation (Pd/C, H_2) in the presence of formic acid (78% yield).

The indole alkaloid suaveoline **1** was first isolated from *Rauwolfia suaveolens* S. Moore in 1972[1] and has since been found in a number of *Rauwolfia* species.[2-4] The structure of **1** was elucidated by mass spectrometry, ^{1}H NMR (100 MHz) and UV spectroscopy, while the absolute stereochemistry was confirmed by partial synthesis of **1** from the alkaloid ajmaline.[1] Recently, two additional derivatives of suaveoline, **2a** and **2b** have been isolated from *Rauwolfia caffra*[4] (Figure 1). Suaveoline **1** is a member of the sarpagine/ajmaline family of alkaloids. Similar to the bases raumacline **3a** and N_b-methyl raumacline **3b** (*Rauwolfia serpentina* Benth),[5] this alkaloid **1** is probably an extraneous metabolite of the ajmaline biosynthetic pathway.

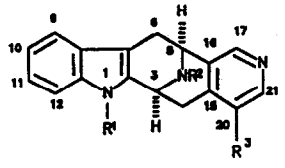
Suaveoline **1** is structurally reminiscent of the macroline-related alkaloids macroline **4**, alstonerine **5a**, and alstophylline **5b** which have been isolated from the related botanical genus *Alstonia*.[6] Macroline **4**, although not isolated from natural sources, to date, is believed to be the key biosynthetic precursor to a number of related *Alstonia* alkaloids including the bisindole alkaloid macralstonine **6**.[7] The bisindole **6** has been reported to exhibit potent hypotensive activity in dogs;[8] however, it has not been established whether this activity is derived from the dimeric form of **6** or from monomeric catabolites. In an effort to elucidate the active component of **6** a general synthetic strategy for the preparation of useful quantities of the macroline and suaveoline-related alkaloids has been under investigation. The synthesis of the monomeric units would provide a convergent route to macralstonine **6** and related dimers *via* reported

biomimetic transformations.[9]

Suaveoline 1 was chosen as an initial structural target because of the novel pyridine E-ring of these bases. Moreover, the lack of complex stereochemistry rendered suaveoline 1 an attractive target from which to develop the chemistry required to construct the five carbocyclic rings present in the macroline-related bases. The knowledge gained with respect to stereogenic centers at C(15) and C(16) during the synthesis of 1 could then be applied to an enantiospecific synthesis of the macroline-related natural products.

The strategy for the synthesis of suaveoline 1 was envisaged to employ a 1,5-dialdehyde 7 (or equivalent) as a late synthetic intermediate for the construction of the annulated pyridine (E) ring of 1. This approach offered synthetic flexibility, since a variety of functional groups disposed 1,5 can be converted into pyridines.[10] Construction of the 1,5-dialdehyde 7 was envisaged to proceed *via* one of three possible avenues illustrated retrosynthetically in Scheme I.

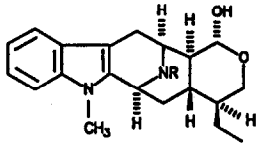
Figure 1



1, $R^1 = CH_3$, $R^2 = H$, $R^3 = C_2H_5$

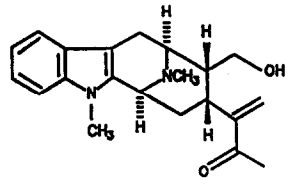
2a, $R^1 = H$, $R^2 = CH_3$, $R^3 = CH_2CH_2OH$

2b, $R^1 = H$, $R^2 = CH_3$, $R^3 = CH_2OH$



3a, R = H

3b, R = CH_3



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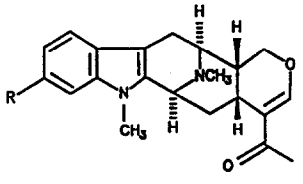
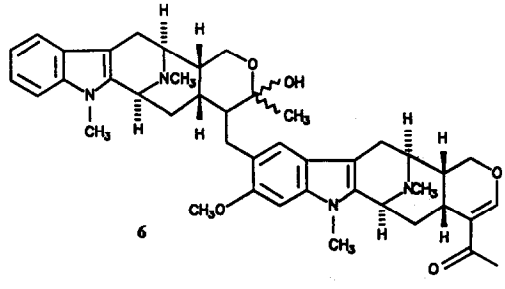


5a, R = H

5b, R = OCH_3



6

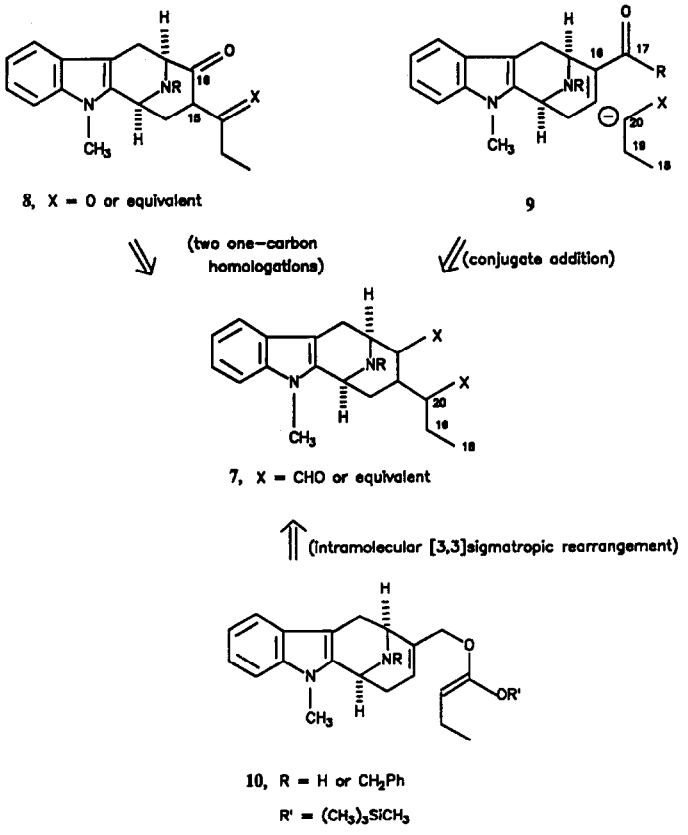
The first approach involved the construction of ß-diketone 8 with the ethyl side chain of 1 introduced at an early stage of the synthesis. This strategy exploited the mild conditions of the aprotic Pictet-Spengler reaction/Dieckmann cyclization sequence and allowed for the rapid construction of the

tetracyclic ß-diketone **8**. Two one-carbon homologations at each carbonyl moiety would then generate the carbon skeleton of **1**.

The second pathway involved the intermolecular coupling of a four-carbon fragment (C(18) - C(21)) to an α,ß-unsaturated aldelyde **9** *via* a conjugate addition. This route would add a degree of convergency to the synthesis and permit the possible introduction of a wide variety of functional groups at C(19) of the pyridine (E) ring (see **2a,b**).

Finally, an intramolecular addition of the four-carbon chain (C(18) - C(21)) was anticipated to proceed *via* a [3,3]-sigmatropic rearrangement of tetracyclic allyl keteneacetal **10**. This approach offered the advantage of stereochemical control, often inherent in [3,3]-sigmatropic rearrangements. Although this would not be an issue for the synthesis of **1**, stereochemical control at C(15) is a major concern for the preparation of the macroline-related alkaloids.

SCHEME I



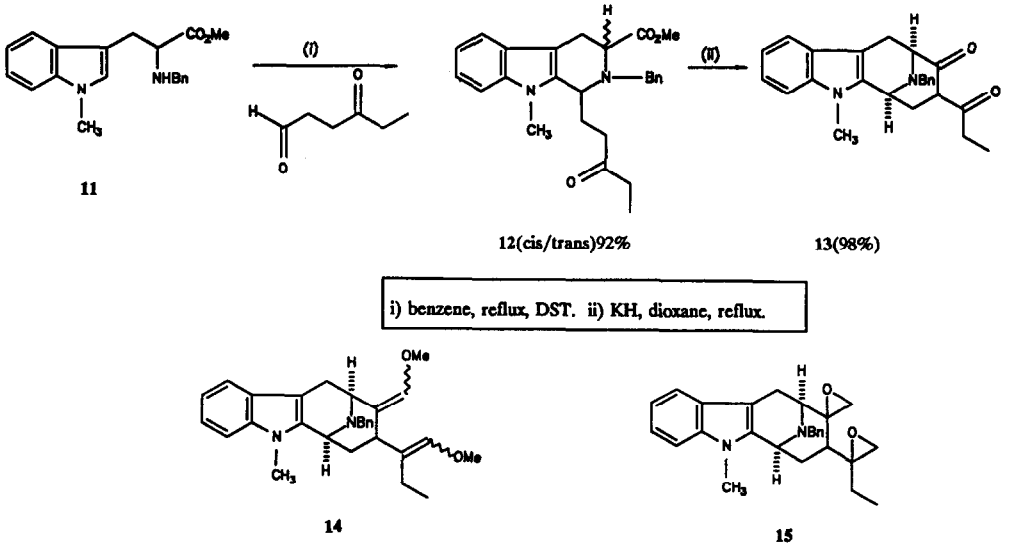
RESULTS AND DISCUSSION

The initial approach involved the synthesis of the ß-diketone **13**. As illustrated in Scheme II, the construction of **13** was achieved in a straightforward fashion using the Pictet-Spengler cyclization in aprotic

media.[11] The condensation of (±)-N_a-methyl-N_b-benzyl-tryptophan methyl ester **11**[12] with the acid labile 4-oxo-hexanal under aprotic conditions (benzene, reflux) afforded the required (±)-tetrahydro-ß-carboline **12** in 92% yield. This material was isolated as a mixture of *cis* and *trans* diastereomers. Dieckmann cyclization of this mixture **12** under the conditions of KH/dioxane gave a 98% yield of ß-diketone **13**.

With the ß-diketone **13** in hand it remained only to add the two one-carbon fragments with appropriate functionality for the generation of the target 1,5-dialdehyde equivalent. The ß-diketone **13** was treated with an excess of the phosphorane ylide generated from methoxymethyl-triphenylphosphonium chloride/LDA/THF at -70°C.[13] However, none of the masked 1,5-dialdehyde, (*bis*-methylvinyl ether **14**) was obtained and only starting material was recovered. In similar fashion **13** was treated with the sulfonium ylide generated from trimethylsulfoxonium iodide/DMSO/NaH/25°C.[14] Once again, the 1,5-difunctionalized intermediate, *bis*-oxirane **15**, was not obtained and only starting material was recovered. The lack of reactivity of **13** toward these reagents is believed to be due to the acidic nature of the α-proton. Presumably, the ylide deprotonates the ß-diketone to furnish a stable enolate anion which renders the carbonyl system completely unreactive towards the addition of nucleophiles. Attempts to convert the ß-diketone **13** into a monoketal also met with only limited success.[15]

SCHEME II

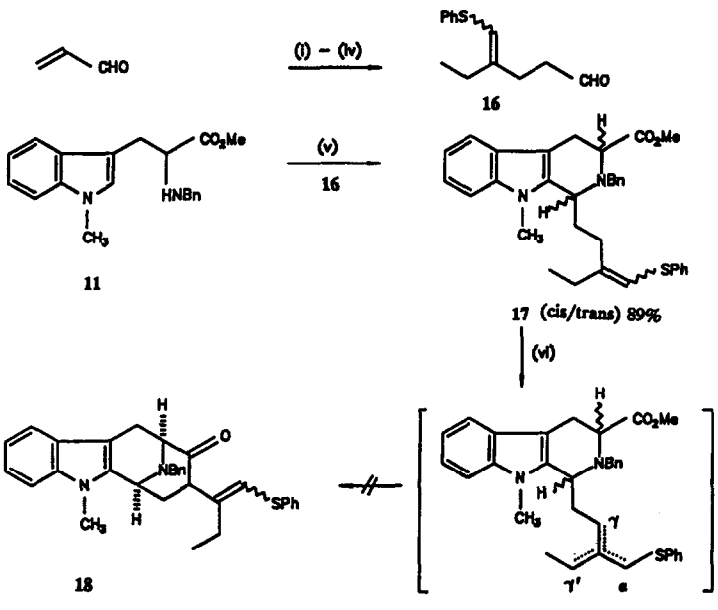


It became necessary to develop a synthetic route to **7** which would permit the construction of the tetracyclic ring system, and avoid the 1,3-dicarbonyl group. It was felt that the phenylthioenol ether **17** could be cyclized under thermodynamic conditions *via* the γ-carbanion, to afford the tetracyclic ketone **18**. The construction of the required phenylthioenol ether **17** was first attempted *via* Peterson olefination of keto-ester **12**.[16] Treatment of **12** with $(CH_3)_3SiCH_2SPh$/n-buLi/THF at -78°C afforded none of the desired phenylthioenol ether **17** and led to extensive decomposition of starting materials. Alternatively,

as illustrated in Scheme III, the tetrahydro-ß-carboline derivative 17 was prepared from the acid labile aldehyde 16 and (±)-tryptophan derivative 11 *via* a Pictet-Spengler cyclization. These conditions were ideal for the construction of 17 in either a stereoselective[11] or enantioselective fashion.[17] The phenylthio substituted aldehyde 16 was prepared in four steps from acrolein in 20% overall yield (Scheme III).[15] The aldehyde 16 was then allowed to react with (±)-tryptophan derivative 11 under aprotic conditions (PhH, reflux, DST) to furnish the desired tetrahydro-ß-carboline 17 in 89% yield.

With the necessary intermediate 17 in hand, attention turned toward the D and E ring annulation sequence *via* formation of the tetracyclic ketone 18. It was felt that generation of an equilibrium mixture of α- and γ-carbanions of 17[18] would result in cyclization of the γ-carbanion to afford the favored six-membered ring. This pathway would be favored both kinetically and thermodynamically over cyclization of other metallated species (α or γ′). Treatment of 17 with LDA(excess)/THF at -78°C, afterwhich the mixture was allowed to warm to room temperature, afforded a yellow colored solution. Unfortunately, upon workup only starting material was recovered. Alteration of the reaction conditions proved futile for 18 was never observed nor isolated. This synthetic approach was discontinued and an investigation of the convergent intermolecular strategy was begun.

SCHEME III



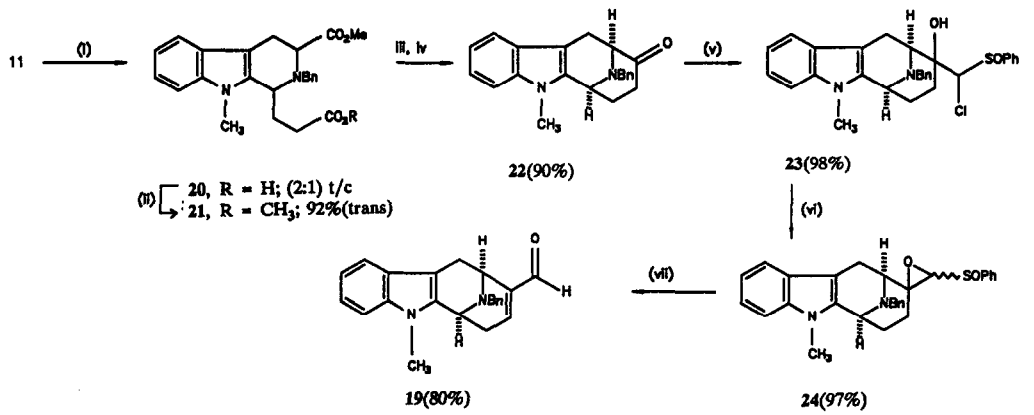
i) HBr(g), $(CH_2OH)_2$, $CHCl_3$, 0°C. ii) Mg, THF, then propionyl chloride, -70°C.
iii) $PhSCH_2Si(CH_3)_3$, n-buLi, THF, 0°C. iv) THF, 1N HCl, reflux.
v) benzene, reflux, DST, 18 h. vi) LDA, THF, -78°C → room temperature.

The initial target of the convergent approach was the α,ß-unsaturated aldehyde 19. As illustrated in Scheme IV, the synthesis of 19 employed a Pictet-Spengler reaction and a Dieckmann cyclization for

the construction of the indoloazabicyclo[3.3.1]nonane system. The (±)-tryptophan derivative **11** was treated with 2-oxoglutaric acid in a solution of benzene-dioxane (1:1) and the mixture heated at reflux with continuous removal of water *via* a Dean-Stark trap (DST). This afforded the tetrahydro-ß-carboline carboxylic acid **20** in 97% yield. Esterification was effected in 91% yield with methanolic hydrogen chloride to give the *trans*-diester **21**, exclusively.[17] This conversion has important implications for the enantiospecific synthesis of macroline-related alkaloids.[17] The Dieckmann cyclization (NaH/MeOH/-toluene/reflux) of diester **21** was followed by an acid mediated decarboxylation (HCl/AcOH) to afford the tetracyclic ketone **22** in 80% yield (53% overall yield from d,l-tryptophan).[19]

Several methods have been reported which describe the conversion of ketones into α,ß-unsaturated aldehydes.[20-22] Of these, the Yamakawa modification[23a] of the spiro-oxiranophenylsulfoxide protocol developed by Taber *et al.*[23b] was found to be the method of choice. The tetracyclic ketone **22** was stirred with the anion generated from α-chloromethylphenylsulfoxide[23c]/LDA/THF/-78°C to provide the halohydrin **23** in quantitative yield (Scheme IV). The halohydrin **23** was then stirred vigorously in a heterogeneous solution of 10N KOH/THF (1:1) for 24 h. This gave the spirooxirane **24** as a 1:1 mixture of diastereomers in 95% yield from **22**. The mixture (see **24**) was heated to reflux in toluene in the presence of $LiClO_4/Bu_3PO$ for 30 minutes. This furnished the desired α,ß-unsaturated aldehyde **19** in 80% yield.

SCHEME IV



i) 2-ketoglutaric acid, benzene, reflux, DST. ii) HCl(g)/MeOH, reflux. iii) NaH, MeOH, toluene, reflux. iv) AcOH, HCl(conc.), reflux. v) $PhSOCH_2Cl$, LDA, THF, -78°C. vi) 10 N KOH, THF, 24 h. vii) $LiClO_4$, $OPBu_3$, toluene, reflux.

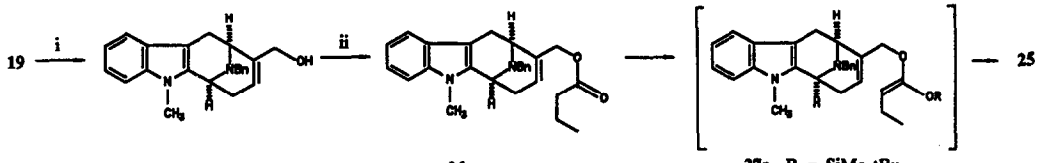
With the α,ß-unsaturated aldehyde **19** in hand, the intermolecular convergent approach was investigated. Exhaustive attempts were made at introduction of the four-carbon side chain to the α,ß-unsaturated aldehyde *via* the chemistry of Mukaiyama,[24] Posner,[25] Evans[26] or Corey;[27] however, these approaches were uniformly unsuccessful. The details of this chemistry are fully described in reference 15.

These results, however, served to further demonstrate the degree to which the ß-position [C(15)] of **19** was hindered sterically by the indolomethylene bridge (1,3-diaxial interaction) and by the N_b-benzyl group.[28a] In addition, Hollinshead later demonstrated that a related enone was resistant to 1,4-addition.[28b] To overcome the inherent steric constraints to reaction at C(15) in the indolo-bicyclo[3.3.1]nonane system, attention turned toward the intramolecular strategy for the addition of the four-carbon unit to C(15).

An ester-enolate Claisen rearrangement was initially explored in this approach for the construction of the carbon skeleton of **1**. Successful preparation of the allyl butyryl ester **26** was ultimately achieved in two steps by reduction of the α,ß-unsaturated aldehyde **19** with lithium aluminum hydride to afford allyl alcohol **25** in 92% yield. Subsequent treatment of **25** with butyryl chloride gave the desired *seco*-Claisen ester enolate intermediate **26** as shown in Scheme V.

With allylic ester **26** in hand, the ester-enolate Claisen rearrangement[29] was attempted. Based on the research of Ireland and coworkers,[29a] as well as examination of Dreiding models,[28a] it appeared the rearrangement would proceed predominately *via* a chair-transition state from the α-face of the molecule.[28a] It was believed necessary to generate the E-ketene acetal to ensure good stereoselectivity.

SCHEME V



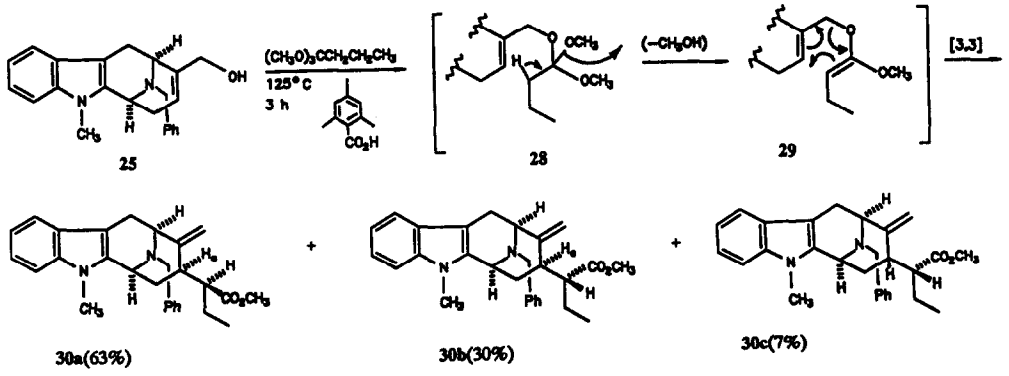
i) $LiAlH_4$, Et_2O, -20°C. ii) $CH_3CH_2CH_2COCl$, CH_2Cl_2, TEA

Ireland achieved excellent stereoselectivity by performing the rearrangement of the E-ketene silyl acetal in HMPA/THF at -78°C[29a], consequently, the allyl ester **26** was treated with LDA/HMPA/THF/(23:77)/-TBDMSCl at -78°C. The reaction solution was allowed to warm to room temperature and then heated to reflux. As illustrated in Scheme V, the only material isolated from the reaction mixture was the allyl alcohol **25** (81% yield). Initially, it was believed that the t-butyldimethylsilyl group (see **27a**) sterically inhibited the rearrangement, thus promoting a fragmentation of the ketene silyl acetal. However, attempts to minimize the steric bulk of the ketene silyl acetal, as the trimethylsilyl derivative **27b** or the lithium enolate **27c** proved to have little effect on the outcome of the reaction sequence and provided uniform yields of allyl alcohol **25**. The formation of the allyl alcohol **25** from these reactions has been proposed

to occur *via* a fragmentation of the enolate or ketene silyl acetal *via* a ketene, analogous to previous reports.[29a] The apparent steric constraints of the indoloazabicyclo[3.3.1]nonane system, as well as the lability of the ketene acetal rendered the ester-enolate Claisen rearrangement unsuitable for construction of the macroline related alkaloids.

An orthoester Claisen rearrangement was proposed to circumvent the problem of carbon-oxygen bond scission observed in the ester-enolate Claisen rearrangement. If fragmentation of the mixed orthoester **28** or ketene acetal **29** did occur to regenerate allyl alcohol **25**, it was felt the alcohol could react with excess orthoester and ultimately facilitate the cyclization (Scheme VI).[29c]

SCHEME VI



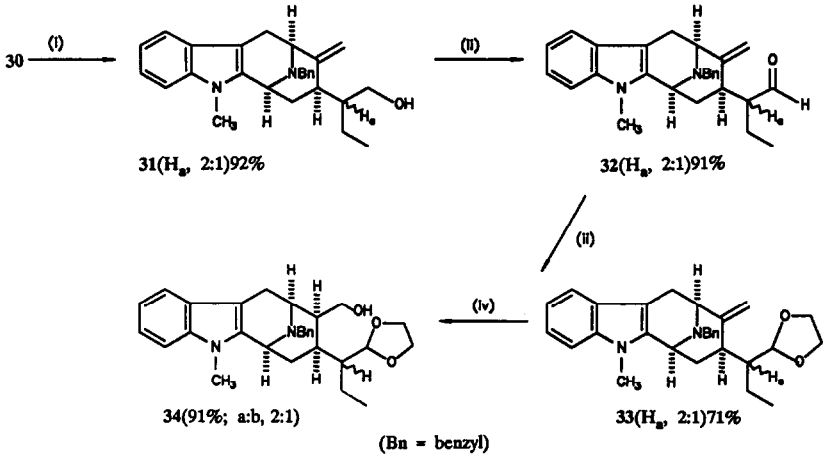
The orthoester Claisen rearrangement was effected in a 10-fold excess of trimethyl orthobutyrate in the presence of the acid catalyst, 2,4,6-trimethylbenzoic acid (2 mol %) at 125°C. This afforded the unsaturated ester **30** obtained as a mixture of diastereomers (**30a**:b:c, 63:30:7) in 79% yield. The major isomers **30a** and **30b** resulted from rearrangement of the intermediate ketene acetal from the ß-face of the molecule (ab:c, 13:1) for H_a.[30] The complete details of the stereochemical assignments for the major isomer **30a** by 1D, 2D HR-NMR and NOESY experiments have been reported.[28a] Although **30b** and **30c** could not be separated from each other, their structures were deduced by the comparison of their HR NMR spectra with those of **30a**. In addition, the structure of **30a** was confirmed by single crystal X-ray analysis.[30] The details of the stereochemical assignments are reported in reference 28a.

The transition state of the orthoester Claisen rearrangement is often partitioned between chair and boat-like conformations,[29,31] and the effect of the Z and E isomers of the ketene acetal on the stability of these conformations in the present system has been analyzed.[28a,30] Although it has been reported that E isomers are favored in the orthoester rearrangement,[29] the steric and stereoelectronic constraints imposed by the rigid indoloazabicyclo[3.3.1]nonane system has resulted in a partitioning between transition

states. The preferred conformations which are believed to lead to the transition states for formation of **30a,b,c** have been reported.[28a,30] Esters **30a** and **30b** arise predominantly *via* boat transition states, while the minor isomer **30c** arises from a chair transition state.[28a] In contrast, in the same [3.3.1]azanonane system, the Claisen rearrangement took place principally from the bottom face of the double bond.[32]

The differences in the stereochemical outcome of the Claisen *versus* orthoester Claisen rearrangement have been described.[28a] The influence of the steric and stereoelectronic effects of the indoloazabicyclo[3.3.1]nonane system on the stereoselectivity of the orthoester Claisen *versus* the Claisen rearrangement is currently under study.[32]

SCHEME VII



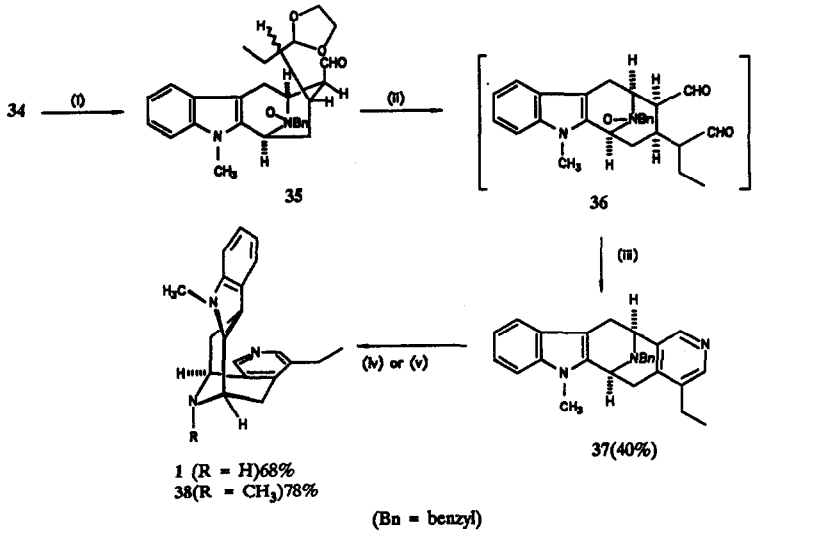
i) $LiAlH_4$, Et_2O, -20°C. ii) $(COCl)_2$, DMSO, DCM, TEA, -78°C. iii) $(CH_2OH)_2$, pTSA, benzene, reflux, DST. iv) 9-BBN•THF, THF, 50°C; then H_2O_2, 3N NaOH.

With all of the carbon atoms of suaveoline **1** in place, attention turned toward the construction of a 1,5-dialdehyde equivalent. As illustrated in Scheme VII, ester **30** was reduced to the corresponding alcohol **31** (92% yield). Swern oxidation of **31** afforded the aldehyde **32** (91% yield), which was protected as the ethylene acetal ($(CH_2OH)_2$/PTSA/benzene,reflux) to yield **33** as a mixture of two isomers (a:b; 2:1) in 60% overall yield. Hydroboration of the alkenic acetal with 9-BBN·THF/THF at 50°C was followed by subsequent alkaline/oxidative workup (H_2O_2/3N NaOH) to give the hydroxy acetal **34** in 91% yield. The stereochemistry at C(15) and C(16) was established by comparison of the HR-NMR spectra with that of lactone *i* and its corresponding hydroxy ester *ii*.[28c]

Oxidation of the hindered hydroxyl group attached to C(16) proved to be difficult. The use of

oxidative reagents such as SO_3•pyridine,[33] activated DMSO,[34,35] pyridinium dichromate (PDC),[36] MnO_2 (activated),[37] and RuO_4,[38] to list a few, proved unsuccessful in the oxidation of the alcohol function of **34** into the corresponding aldehyde. In all cases starting material was recovered in nearly quantitative yield. The steric constraints placed on **34** were overcome using benzeneseleninic anhydride[38] as the oxidant (Scheme VIII). The alcohol was heated in a solution of chlorobenzene with benzeneseleninic anhydride (0.5 eq) for 15 min. This furnished the mono-protected 1,5-dialdehyde **35** as the N_b-oxide in 53% yield as a single isomer. The formation of the N_b-oxide was an unexpected, but interesting result. It is believed that the formation of the N_b-oxide resulted from a disproportionation of benzeneseleninic acid or benzeneselenenic intermediates present in the medium as by-products of the oxidation.[39]

SCHEME VIII



i) $(PhSeO)_2O$, PhCl, 110°C, 15 min. ii) 2N HCl/THF, 25°C, 15 h. iii) NH_2OH•HCl, EtOH reflux. iv) H_2, Pd/C, MeOH. v) H_2, Pd/C, HCO_2H/MeOH.

Conversion of the mono-protected 1,5-dialdehyde **35** into the key dialdehyde **36** was achieved by stirring **35** in 2N aqueous HCl/THF at 25°C. The crude 1,5-dialdehyde N_b-oxide **36** was then heated at reflux in a solution of NH_2OH•HCl/EtOH/ for 15 hours. This resulted in generation of the pyridine ring of suaveoline with simultaneous reduction of the N_b-oxide moiety to afford N_b-benzyl suaveoline **37** in 40% overall yield from **34**. Debenzylation of **37** was effected in a solution of methanol using 10% palladium on carbon under an atmosphere of hydrogen (1 atm/25°C). This gave (±)–suaveoline **1** in pure form in 68% yield (Scheme VIII). In addition, **37** was converted into (±)–N_b-methyl suaveoline **38**[1] by hydrogenolysis in a solution of formic acid/methanol using 10% palladium on carbon under an atmosphere of hydrogen (1 atm, 25°C). The spectral data obtained for (±)–**1** and (±)–**38** were in

complete agreement with data reported by Potier *et al.* for these two compounds.[1] The replacement of an N_b-benzyl group with an N_b-methyl function under the conditions of catalytic hydrogenation is significant for it provides a general entry into N_b-functionalized macroline alkaloids from N_b-benzyl tetracyclic ketone **22**, wherein the benzyl (methyl) transfer can occur late in the synthetic pathway.

Suaveoline **1** is the first macroline-related indole alkaloid of the sarpagine/ajmaline class of alkaloids to fall to total synthesis. The chemistry developed and described herein has recently been employed in the enantioselective synthesis of the *Alstonia* alkaloid (−)–alstonerine **5b**.[32] This synthetic strategy is currently being applied to the synthesis of the proposed biogenetic intermediate macroline **4**, the alkaloid raumacline **3a** and the hypotensive *bis*indole base, macralstonine **6**. The total synthesis of these *Alstonia* alkaloids will be reported in due course.

EXPERIMENTAL

Microanalysis was performed with a F and M Scientific Corp. Model 185 carbon, hydrogen and nitrogen analyzer. Melting points were taken with a Thomas-Hoover melting point apparatus and are reported uncorrected. Proton NMR were recorded with a Bruker multiprobe 250 MHz spectrometer or a GE 500 MHz instrument. Infrared spectra were recorded with a Beckman Aculab-1 or a Mattson-Polaris IR-10400 spectrometer. Mass spectral data (EI/CI) were obtained from a Hewlett-Packard 5855 GC-mass spectrometer, while high resolution mass spectral data (exact mass) were obtained from a Finnigan HR mass spectrometer.

All chemicals were purchased from Aldrich Chemical Company, unless otherwise noted. The analytical TLC plates used were E. Merck Brinkmann UV active silica gel (Kiesel gel 60 F254) on plastic. "Chromatography" refers to flash chromatography using 230-400 mesh 60Å silica gel, grade 60 (EM reagent).[40]

Methanol was dried by distillation over magnesium metal. Tetrahydrofuran (THF, Baker reagent) ether, benzene (EM reagent) and toluene (EM reagent) were dried by distillation from sodium-benzophenone ketyl. Dichloromethane (DCM) was dried over $MgSO_4$, and then distilled over P_2O_5. Dimethylsulfoxide (DMSO) was dried by distillation under high vacuum over CaH_2. Triethylamine (TEA) and diisopropylamine (DIPA) were dried by distillation over KOH. The synthesis of **11**, **20-22** and **30abc** are described elsewhere.[19,28a]

2-Benzyl-3-methoxycarbonyl-1,2,3,4-tetrahydro-9-methyl-pyrido-[3,4b]indole-1-(3-pentanone) 12.

N_a-methyl, N_b-benzyl tryptophan methyl ester **11**,[19] (8.37 g, 0.026 mol) and 4-oxohexanal, (2.97 g 0.026 mol) were dissolved in dry benzene (150 mL) and stirred at reflux for 8 h; water was removed *via* a Dean Stark trap. Following removal of solvent under reduced pressure, the resultant oil was chromatographed on silica gel (120 g) packed in hexane and eluted with benzene to provide the tetrahydro ß-carboline (10.2 g). It was composed of a mixture of *cis* and *trans* isomers represented by **12** (93.9% yield): mp 116-119°C (high R_f isomer), mp 95-97°C (low R_f isomer); IR (KBr) 1740 (s, ester) and 1705 cm^{-1} (s, ketone); ^1H NMR ($CDCl_3$) δ 0.93 (t, 3H), 1.66 (m, 2H), 2.16 (q, 2H), 2.8 (m, 2H), 3.16 (d, 2H), 3.47 (t, 1H), 3.63 (s, 3H, NCH_3), 3.7 (s, 3H, OCH_3), 3.8 (m, 3H), 7.3 (m, 9H); mass spectrum (70 ev) m/e 481 (M^+, 6), 334 (34), 333 (100), 273 12, 184 (12), 183 (34, 182 (14), 181 (8), 170 (11), 169 (12), 168 (17), 92 (8), 91 (47).

Anal. Calcd. for $C_{26}H_{30}N_2O_3$: C, 74.61; H, 7.22; N, 6.69. Found: C, 74.90; H, 7.31; N, 6.70.

5-Methyl-8-propionyl-9-oxo-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5H-cyclooct[b]indole 13.

A solution of the keto ester **12** (8.8 g, 21 mmol) in dry dioxane (100 mL) was treated at room temperature with KH (7.5 g, 52.5 mmol, 28% of oil dispersion, previously washed with dry dioxane). After addition, the solution was heated to reflux for 90 min and allowed to cool to room temperature. A solution of aq HCl (0.5N, 104 mL) was added carefully and was followed by extraction with $CHCl_3$ (4 x 120 mL). The organic extract was washed with brine and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford an orange oil which crystallized from MeOH (20 mL) to furnish **13** (7.9 g, 98% yield): mp 144-146°C; IR (KBr) 3410 (w, broad, enol OH), 1615-1580 cm^{-1} (s, enolized beta

diketone); NMR ($CDCl_3$) δ 1.0 (t, 3H, J = 6 Hz), 2.35 (m, 4H), 3.05 (m, 2H), 2.95 (m, 1H), 3.43 (s, 3H, NCH_3), 3.67 (s, 2H, CH_2Ph), 4.1 (m, 2H), 7.0-7.6 (m, 14H); mass spectrum (70 ev) m/e 387 (M+1, 5), 386 (M^+, 16), 333 (11), 292 (10), 274 (17), 273 (58), 183 (19), 144 (29), 122 (20), 92 (22), 91 (100), 78 (20).

Anal. Calcd for $C_{25}H_{26}N_2O_2$: C, 67.69; H, 5.67; N, 9.85. Found: C, 67.38; H, 5.76; N, 9.67.

2-Benzyl-3-methoxycarbonyl-9-methyl-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-1-(3-phenylthiomethylene)pentane 17.

A solution of **11**[19] (820 mg, 2.5 mmol) and aldehyde **16** (560 mg, 2.5 mmol in benzene (25 mL)) was heated to reflux for 18 h with continuous removal of water *via* a Dean-Stark trap. Removal of the solvent under reduced pressure gave an oil which was chromatographed (SiO_2, benzene) to furnish **17** in pure form (1.1 g, 85%): IR (thin film): 2940, 1570, 1460, 730 cm^{-1}; NMR ($CDCl_3$) δ 7.64-7.15 (m, 14H), 5.83 (s, 1H), 3.80 (m, 2H), 3.65 (m, 5H), 3.38 (s, 3H), 3.14 (m, 2H), 2.12 (m, 4H), 1.70 (m, 2H), 0.98 (t, J = 8 Hz, 3H); MS (CI, NH_3) 525 (100, M + 1) 334 (32)

Anal. Calcd. for $C_{33}H_{36}N_2O_2S$: C, 75.64; H, 6.92; N, 5.34. Found: C, 75.42; H, 6.80; N, 5.21.

Methyl-2-benzyl-3-carbomethoxy-9-methyl-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-1-propionate 21.

A solution of 2-benzyl-3-carbomethoxy-9-methyl-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-1-propionic acid **20**[11c] (52.8 g, 0.13 mol) in methanolic HCl (250 mL) was heated at reflux for 3 h. After removal of the solvent under reduced pressure, the residue was dissolved in CH_2Cl_2 (400 mL) and it was brought to neutral pH with aqueous ammonia (14%, 300 mL). The organic layer was washed with brine, and dried (K_2CO_3). The product which solidified upon removal of the solvent was recrystallized from methanol to furnish the *trans*-diester **21** (49.6 g, 91%): mp 137-140°C (Lit.[12] mp 137-140°C); IR (KBr) 1730 cm^{-1}; MS (CI, CH_4) m/e (relative intensity) 421 (M+1, 100); ^1H NMR ($CDCl_3$) δ 7.33 (m, 9H), 4.02 (m, 2H), 3.76 (s, 3H), 3.73 (s, 2H), 3.61 (s, 3H), 3.43 (s, 3H), 3.05 (d, J = 8 Hz, 2H), 2.43 (m, 2H), 2.00 (m, 2H).

Anal. Calcd. for $C_{25}H_{28}N_2O_4$: C, 71.41; H, 6.72; N, 6.66. Found: C, 71.37; H, 6.43; N, 6.70.

5-Methyl-9-oxo-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5H-cyclooct[b]indole 22.

A mixture of diester **21** (42.0 g, 0.10 mol) and sodium hydride (6.5 g, 0.27 mol) in dry toluene (700 mL) was heated to reflux and a solution of dry methanol (4 mL) in toluene (16 mL) was added dropwise over 1 h. The mixture was held at reflux for an additional 6 h and then stirred at room temperature for 12 h. Glacial acetic acid (20 mL) was added to the mixture and was followed by neutralization with saturated aqueous $NaHCO_3$ solution. The mixture was extracted with benzene (3 x 300 mL) and the combined organic extracts were washed with brine and dried (K_2CO_3). Removal of the solvent under reduced pressure, followed by crystallization of the residue from methanol, provided the ß-ketoester (35.8 g, 92%): mp 146-148°C (Lit.[12] mp 148-150°C); IR (KBr) 1670, 1630 cm^{-1}; MS (CI, CH_4) m/e (relative intensity) 389 (M+1, 100); ^1H NMR ($CDCl_3$) δ 11,89 (s, 1H), 7.50 (d, J = 8.1 Hz, 1H), 7.30 (m, 8H), 4.10 (d, J = 5.3 Hz, 1H), 4.00 - 3.67 (q, J_{AB} = 11.0 Hz, 2H) 3.75 (m, 1H), 3.66 (s, 3H), 3.60 (s, 3H), 3.10 (dd, J = 16.1 Hz, J = 7.3 Hz, 1H), 2.95 (d, J = 16.2, 1H), 2.90 (dd, J = 15.9 Hz, J = 3.5 Hz, 2H), 2.32 (d, J = 16.1 Hz, 1H).

The ß-ketoester (60.0 g, 0.15 mol) was heated at reflux for 7 h in a mixture of glacial acetic acid (200 mL), hydrochloric acid (300 mL, conc.) and water (80 mL). After removal of the solvent under reduced pressure, the residue was brought to pH 8.5 with aqueous NaOH (10%). The mixture which resulted was extracted with CH_2Cl_2 (3 x 300 mL) and the combined organic extracts were washed with brine (500 mL) and dried (K_2CO_3). The organic solution was then filtered through a short column of alumina. Removal of the solvent under reduced pressure afforded an oil which crystallized from ethyl acetate to provide the tetracyclic ketone **22** (46.0 g, 90%): mp 131-133°C (Lit.[12] mp 131.5-133°C); IR (KBr) 1710 cm^{-1}; MS (CI, CH_4) m/e (relative intensity) 331 (M+1, 100); ^1H NMR ($CDCl_3$) δ 7.52 (d, J_{1-2} = 8.1 Hz, H_1), 7.32 (m, H_4, phenyl), 7.25 (t, $J_{3-2(4)}$ = 8.1 Hz, H_3), 7.15 (t, $J_{2-1(3)}$ = 8.2 Hz, H_2), 4.05 (t, $J_{6-7a'}$ = H_{6-7b} = 4.0 Hz, H_6), 3.75 (d, J_{10-11a} = 6.4 Hz, H_{10}), 3.72 (s, $2H_{benzyl}$), 3.60 (s, NCH_3), 3.25 (dd, J_{11AB} = 16.8 Hz, J_{11a-10} = 6.3 Hz, H_{11a}), 2.70 (d, J_{11AB} = 16.9 Hz, H_{11b}), 2.45 (m, $2H_8$), 2.20 - 1.95 (m, $2H_7$). ^{13}C NMR ($CDCl_3$) δ 209.74 (s, C_9), 138.23 (s), 137.21 (s), 133.16 (s), 128.59 (d), 128.36 (d), 127.25 (d), 126.47 (s), 121.48 (d, C_3), 119.21 (d, C_2), 118.15 (d, C_1), 108.83 (d, C_4), 105.74 (s), 64.78 (d, C_{10}), 56.20 (t, C_{benzyl}), 48.88 (d, C_6), 34.24 (t, C_8), 29.70 (t, C_{11}), 29.20 (q, C_5), 20.39 (t, C_7).

Anal. calcd. for $C_{22}H_{22}N_2O$: C, 79.97; H, 6.71; N, 8.48. Found: C, 80.24; H, 6.89; N, 8.78.

5-Methyl-9-hydroxy-9-α-chloro-phenylsulfinylmethyl-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5H-cyclooct[b]indole 23.

A solution of LDA [6.3 mmol, from DIPA (0.64 g, 6.3 mmol) in THF (5 mL) and n-butyllithium (2.53 mL of a 2.5 M solution in hexanes)] was cooled to -78°C under an atmosphere of nitrogen. A solution of α-chloro-methyl phenylsulfoxide (1.08 g, 6.3 mmol) in THF (1 mL) was added to the solution of LDA. The clear yellow mixture was stirred for 5 min, after which a solution of the ketone **22** (2.0 g, 6.0 mmol) in THF (15 mL) was added dropwise over 5 min. **Note: It is important to keep all of the solutions as concentrated as possible to ensure complete conversion of the ketone into the chlorohydrin 23.** The reaction mixture was stirred for 40 min and then allowed to warm to room temperature. The mixture was poured into water (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine (150 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to provide the chlorohydrin **23** (2.91 g, 96%): mp (Et_2O) 224-225°C; IR (KBr) 3600, 1570, 1050, 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.70 - 7.50 (m, 5H), 7.40 - 7.10 (m, 9H), 5.62 (s, 1H), 4.10 (d, J = 6.2 Hz, 1H), 3.98 (br s, 1H), 3.75 - 3.60 (q, J_{AB} = 12.4 Hz, 2H), 3.52 (s, 3H), 3.40 (d, J = 18.6 Hz, 1H), 3.25 (dd, J = 18.6 Hz, J = 6.0 Hz, 1H), 1.90 (m, 2H), 1.55 (m, 2H).

Anal. Calcd. for $C_{29}H_{29}N_2ClO_2S$: C, 68.96; H, 5.79; N, 5.55. Found: C, 68.92; H, 5.81; N, 5.50.

2'-Phenylsulfinyl-5-methyl-12-benzyl-6,7,8,9,10,11-hexahydro-oxirano-spiro[2',9]-6,10-imino-5H-cyclooct[b]indole 24.

Note: The chlorohydrin 23 is usually pure enough to employ in this reaction without purification in the previous step. The chlorohydrin **23** (2.91 g, 5.8 mmol) was dissolved in THF (50 mL). A solution of aqueous KOH (10 N, 50 mL) was added and the heterogeneous mixture was stirred vigorously for 24 h at room temperature. The organic layer was removed and the aqueous portion was diluted with water (100 mL) and extracted with EtOAc (3 x 50 mL). The combined organic fractions were washed with brine and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford a mixture of isomers of the phenylsulfinyl oxirane **24** (a:b, 50:50) present as an oil. The oil was dissolved in Et_2O from which one isomer (**24a**) crystallized in pure form. The supernatant was concentrated and the oil which resulted was chromatographed (SiO_2, EtOAc/hexane, 1:1) to afford **24b** as an oil (overall yield of **24**, 2.5 g, 85%). **24a**: (1.3 g); mp 145-146°C (Et_2O); IR (KBr) 1470, 1050, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.60 - 7.20 (m, 12H), 7.15 (t, J = 7.2 Hz, 1H), 7.05 (t, J = 7.3 Hz, 1H), 4.09 (t, J = 3.9 Hz, 1H), 3.80 (s, 1H), 3.61 (s, 2H), 3.58 (s, 3H), 3.07 (dd, J = 17.5 Hz, J = 5.0 Hz, 1H), 2.73 (d, J = 5.1 Hz, 1H), 2.65 (d, J = 17.5 Hz, 1H), 2.20 (m, 2H), 1.90 (m, 2H).

Anal. Calcd. for $C_{29}H_{28}N_2O_2S$: C, 74.17; H, 6.03; N, 5.98. Found: C, 74.18; H, 6.21; N, 6.03.

24b: (1.2 g); IR (NaCl) 1470, 1050, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.70 - 7.20 (m, 12H), 7.15 (t, J = 7.3 Hz, 1H), 7.07 (t, J = 7.2 Hz, 1H), 4.15 (t, J = 3.9 Hz, 1H), 3.72 (s, 2H), 3.71 (s, 1H), 3.60 (s, 3H), 3.53 (d, J = 7.0 Hz, 1H), 3.22 (dd, J = 17.5 Hz, J = 6.3 Hz, 1H), 2.65 (d, J = 17.5 Hz, 1H), 2.20 (m, 2H), 1.15 (m, 2H). This material **24** was employed directly in the next step.

5-Methyl-9-formyl-12-benzyl-6,7,10,11-tetrahydro-6,10-imino-5H-cyclooct[b]indole 19.

The phenylsulfinyl oxirane **24** (1.20 g, 2.60 mmol) was added to a solution of toluene (15 mL) which contained lithium perchlorate (270 mg, 2.60 mmol) and tri-n-butylphosphine oxide (570 mg, 2.60 mmol). The mixture was heated at reflux under an atmosphere of argon for 1 h. The orange solution was allowed to cool to room temperature and poured into benzene (100 mL). The organic mixture was washed with water (2 x 100 mL), brine (100 mL) and dried (K_2CO_3). The solvent was removed under reduced pressure. The oil which resulted was chromatographed (SiO_2, EtOAc/hexane, 1:1) to provide the α,ß-unsaturated aldehyde **19** (700 mg, 80%): mp 151-152.5°C (Et_2O); IR (KBr) 2950, 2850, 1675, 1460, 1130 cm^{-1}; MS (CI, CH_4) m/e (relative intensity) 343 (M+1, 100); ^1H NMR ($CDCl_3$) δ 9.33 (s, CHO), 7.47 (d, $J_{1\text{-}2}$ = 8.6 Hz, H_1), 7.33-7.11 (m, $7H_{aromatic}$), 7.08 (t, $J_{2\text{-}1(3)}$ = 9.1 Hz, H_2), 6.72 (t, $J_{8\text{-}7}$ = 2.5 Hz, H_8), 4.19 (d, $J_{10\text{-}11a}$ = 3.7 Hz, H_{10}), 4.09 (d, $J_{6\text{-}7a}$ = 5.6 Hz, H_6), 3.86 - 3.64 (q, J_{AB} = 13.5 Hz, $2H_{benzyl}$), 3.57 (s, NCH_3), 3.20 (dd, J_{11AB} = 16.5 Hz, $J_{11a\text{-}10}$ = 5.9 Hz, H_{11a}), 2.98 (dd, J_{7AB} = 14.0 Hz, $J_{7b\text{-}8}$ = 2.5 Hz, H_{7b}), 2.65 (d, J_{11AB} = 16.5 Hz, H_{11b}), 2.35 (dd, J_{7AB} = 13.9 Hz, $J_{7a\text{-}6}$ = 5.1 Hz, H_{7a}).

Anal. Calcd. for $C_{23}H_{22}N_2O$: C, 80.70; H, 6.43; N, 8.19. Found: C, 80.70; H, 6.42; N, 8.11.

5-Methyl-9-hydroxymethyl-12-benzyl-6,7,10,11-tetrahydro-6,10-imino-5H-cyclooct[b]indole 25.

The α,ß-unsaturated aldehyde **19** (650 mg, 1.90 mmol) was dissolved in dry Et_2O (10 mL) and the solution was added dropwise to a slurry of lithium aluminum hydride (90 mg, 2.30 mmol) in Et_2O (25 mL) at -20°C (CCl_4/CO_2). The reaction mixture was stirred for 2 h, after which the excess hydride was

destroyed on addition of EtOH (1 mL), followed by water (2 mL). The mixture was poured into aqueous KOH (6N, 25 mL) and extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with water (100 mL), brine (100 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford the allyl alcohol **25** as a colorless foam (585 mg, 91%): IR (KBr) 3350, 1450 cm^{-1}; MS (CI, CH_4) m/e (relative intensity) 345 (M+1, 100); ^1H NMR ($CDCl_3$) δ 7.50 (d, J = 7.4 Hz, H_1), 7.37 - 7.27 (m, $H_{4,phenyl}$), 7.21 (t, $J_{3\text{-}2(4)}$ = 7.4 Hz, H_3), 7.16 (t, $J_{2\text{-}3(1)}$ = 7.1 Hz, H_2), 5.64 (br s, H_8), 4.10 - 4.00 (q, J_{AB} = 14.6 Hz, $2H_{12}$), 4.05 (br s, H_6), 3.87 - 3.66 (q, J_{AB} = 13.3 Hz, $2H_{benzyl}$), 3.82 (d, J = 3.7 Hz, H_{10}), 3.56 (s, NCH_3), 3.12 (dd, J = 16.1 Hz, J = 7.2 Hz, H_{11a}), 2.76 (dd, J = 16.4 Hz, J = 3.9 Hz, H_{7a}), 2.24 (d, J = 16.4 Hz, H_{11b}), 2.20 (dd, J = 16.4 Hz, J = 4.1 Hz, H_{7b}).

Anal. Calcd. for $C_{23}H_{24}N_2O$: C, 80.20; H, 7.02; N, 8.13. Found: C, 79.98; H, 7.03; N, 8.27.

5-Methyl-9-methylbutyryl-12-benzyl-6,7,10,11-tetrahydro-6,10-imino-5H-cyclooct[b]indole 26.

The allyl alcohol **25** (90 mg, 0.26 mmol) was dissolved in a solution of CH_2Cl_2 (20 mL) and TEA (80 mg, 0.78 mmol) at 0°C. A solution of butyryl chloride (55 mg, 0.52 mmol) in DCM (1 mL) was added and the mixture stirred for 1 h. The mixture was warmed to room temperature and poured into 10% aqueous Na_2CO_3 solution (50 mL). The mixture was extracted with DCM (3 x 20 mL). The combined extracts were washed with water (50 mL), brine (50 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford an oil. The oil was chromatographed (SiO_2, EtOAc/hexane, 35:65) to provide the pure allylic ester **26** (80 mg, 74%): IR (NaCl) 2900, 1740, 1450, 1190, 720 cm^{-1}; MS (CI, CH_4) m/e (relative intensity) 415 (M+1, 100); ^1H NMR (CD_3CN) δ 7.45 (d, $J_{9\text{-}10}$ = 7.0 Hz, H_9), 7.38 - 7.20 (m, H_{12}, $5H_{phenyl}$), 7.10 (t, $J_{10\text{-}9(11)}$ = 7.1 Hz, H_{10}), 7.00 (t, $J_{11\text{-}10(12)}$ = H_{11}), 5.70 (br s, H_{15}), 4.70 - 4.30 (q, J_{17AB} = 12.5 Hz, $2H_{17}$), 4.15 (d, $J_{3\text{-}14a}$ = 4.0 Hz, H_3), 3.90 - 3.60 (q, J_{AB} = 14.0 Hz, $2H_{benzyl}$), 3.55 (s, NCH_3), 3.54 (d, $J_{5\text{-}6a}$ = 3.0 Hz, H_5), 3.05 (dd, J_{6AB} = 16.0 Hz, $J_{6a\text{-}5}$ = 3.0 Hz, H_{6a}), 2.65 (m, H_{14a}), 2.60 (d, J_{6AB} = 16.0 Hz, H_{6b}), 2.21 (t, $J_{20\text{-}19}$ = 7.1 Hz, $2H_{20}$), 2.12 (dd, J_{14AB} = 15.5 Hz, $J_{14b\text{-}15}$ = 3.0 Hz, H_{14b}), 1.50 (sextet, $J_{19\text{-}18(20)}$ = 7.2 Hz, $2H_{19}$, 0.85 (t, $J_{18\text{-}19}$ = 7.1 Hz, CH_3). Exact mass calcd. for $C_{27}H_{30}N_2O_2$: 414.2307. Found: 414.2314.

α-Ethyl-5-methyl-9-methylene-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5H-cyclooct[b]indole-8-ethanol 31.

The alkenic ester **30** (1.0 g, 2.3 mmol) was dissolved in dry Et_2O (15 mL) and added dropwise to a slurry of lithium aluminum hydride (88 mg, 2.3 mmol) in Et_2O (50 mL) at −22°C under an atmosphere of nitrogen. The mixture was stirred for 3 h and then allowed to warm to room temperature. Ethanol (1 mL) was added to destroy the excess hydride, after which the mixture was poured into aqueous NaOH (6N, 30 mL) and extracted with Et_2O (3 x 50 mL). The combined organic extracts were washed with brine (2 x 100) and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford an oil. The oil was chromatographed (Si_2O, EtOAc/hexane, 40:60) to provide a diastereomeric mixture (a:b, 2:1) of the alcohols represented by **31** (850 mg, 92%) as an oil: IR (NaCl) 3300, 2905, 1600, 1460, 1000 cm^{-1}; MS (CI, CH_4) m/e (relative intensity) 401 (M+1, 100); **31a**: ^1H NMR ($CDCl_3$) δ 7.45 (d, $J_{9\text{-}10}$ = 7.5 Hz, H_9), 7.35 - 7.10 (m, $8H_{aromatic}$), 5.05 (d, J_{17AB} = 1 Hz, H_{17a}), 4.85 (d, J_{17AB} = 1 Hz, H_{17b}), 3.90 (t, $J_{3\text{-}14}$ = 3.5 Hz, H_3), 3.83 (d, $J_{5\text{-}6a}$ = 6.1 Hz, H_5), 3.75 (d, $J_{21\text{-}20}$ = $2H_{21}$), 3.58 (s, NCH_3), 3.40 (dd, J_{6AB} = 15.5 Hz, $J_{6a\text{-}5}$ = 6.5 Hz, H_{6a}), 3.30 - 3.23 (q, J_{AB} = 11.0 Hz, $2H_{benzyl}$), 2.60 (d, J_{6AB} = 15.5 Hz, H_{6b}), 2.53 (dt, $J_{15\text{-}14a}$ = 7.0 Hz, $J_{15\text{-}20}$ = 7.0 Hz, $J_{15\text{-}14b}$ = 2.0 Hz, H_{15}), 2.25 (m, H_{14a}), 1.83 (dt, J_{14AB} = 14.0 Hz, $J_{14b\text{-}3}$ = 3.0 Hz, $J_{14b\text{-}5}$ = 3.0 Hz, H_{14b}), 1.05 (m, H_{20}), 0.95 (m, $2H_{19}$), 0.48 (t, $J_{18\text{-}19}$ = 7.1 Hz, CH_3). Exact mass calcd. for $C_{27}H_{32}N_2O$: 400.2515. Found: 400.2515.

α-Ethyl-5-methyl-9-methylene-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5H-cyclooct[b]indole-8-acetaldehyde (32).

A solution of oxalyl chloride (2.0 M, 1.1 mL, 2.1 mmol) in CH_2Cl_2 was added to a solution of DMSO (327 mg, 4.2 mmol) in CH_2Cl_2 (20 mL) at −60°C under an atmosphere of argon. The mixture was stirred for 15 min followed by dropwise addition of a solution of the alcohol **31** (850 mg, 2.1 mmol) in CH_2Cl_2 (10 mL) and the mixture which resulted was stirred for 30 min. Triethylamine (1.5 mL) was added and the mixture was allowed to warm to room temperature. The reaction mixture was poured into water (50 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were washed with brine (2 x 50 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford an oil. The oil was chromatographed (SiO_2, EtOAc/hexane, 40:60) to provide the alkenic aldehyde as a mixture of diastereomers (a:b, 2:1) represented by **32** (760 mg, 91%) as an oil: IR (NaCl) 2950, 2850, 1735, 1600, 1450 cm^{-1}; MS (CI, CH_4) m/e (relative intensity) 399 (M+1, 100); **32a**: ^1H NMR ($CDCl_3$)

δ 9.35 (d, J = 4.5 Hz, H_{21}), 7.50 (d, J = 7.3 Hz, H_9), 7.40 - 7.09 (m, $8H_{aromatic}$), 5.05 (d, J < 1 Hz, H_{17a}), 4.70 (d, J < 1 Hz, H_{17b}), 3.95 (br s, H_3), 3.77 (d, J = 6.5 Hz, H_5), 3.75 (m, $2H_{benzyl}$), 3.57 (s, NCH_3), 3.27 (dd, J = 16.5 Hz, J = 6.5 Hz, H_{6a}), 2.93 (m, H_{15}), 2.69 (d, J = 16.5 Hz, H_b), 2.35 (m, H_{14a}), 1.70 (m, H_{20}), 1.58 (m, H_{14b}), 1.25 (m, $2H_{19}$), 0.47 (t, J = 7.8 Hz, CH_3).

32b: ^{1}H NMR ($CDCl_3$) δ 9.40 (d, J = 2.0 Hz, H_{21}), 7.52 (d, J = 7.3 Hz, H_9), 7.40 - 7.09 (m, $8H_{aromatic}$), 4.98 (d, J < 1 Hz, H_{17a}), 4.65 (d, J < 1 Hz, H_{17b}), 4.05 (br s, H_3), 3.87 (d, J = 16.5 Hz, H_5), 3.75 - 3.60 (m, $2H_{benzyl}$), 3.50 (s, NCH_3), 3.32 (dd, J = 16.1 Hz, J = 6.5 Hz, H_{6a}), 2.65 (m, H_{15}), 2.60 (d, J = 16.1 Hz, H_{6b} 2.40 (m, H_{20}, H_{14a}), 1.58 (m, $2H_{19}$, H_{14b}), 0.88 (t, J = 7.8 Hz, CH_3).

Exact mass calcd. for $C_{27}H_{30}N_2O$: 398.2358. Found: 398.2362.

α-Ethyl-5-methyl-9-methylene-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5H-cyclooct[b]indole-8-acetaldehyde ethylene acetal (33).

The alkenic aldehyde **32** (880 mg, 2.2 mmol) was dissolved in benzene (25 mL). Ethylene glycol (1.0 g, 17.6 mmol) and dry *p*TSA (420 mg, 2.4 mmol) were added and the mixture which resulted was heated to reflux for 2 h with removal of water *via* a Dean-Stark trap. The mixture was allowed to cool to room temperature and then poured into aqueous ammonia (7%, 20 mL), afterwhich it was extracted with benzene (3 x 50 mL). The combined organic extracts were washed with water (100 mL), brine (100 mL) and dried (K_2CO_3). The solvent was removed under reduced pressure to provide an oil. The oil was chromatographed (SiO_2, EtOAc/hexane, 30:70) to provide the oily alkenic acetal **33** (690 mg, 71%) as a mixture of diastereomers (a:b, 2:1): IR (NaCl) 2900, 1450 cm^{-1}; MS (CI, CH_4) m/e (relative intensity) 443 (M+1, 100); **33a:** ^{1}H NMR ($CDCl_3$) δ 7.55 (d, J = 7.8 Hz, H_9), 7.40 - 7.05 (m, $8H_{aromatic}$), 5.10 (d, J < 1Hz, H_{17a}), 4.83 (d, J = 4.0 Hz, H_{21}), 4.80 (d, J < 1 Hz, H_{17b}), 4.01 (t, J = 3.0 Hz, H_3), 3.95 - 3.60 (m, 7H), 3.59 (s, NCH_3), 3.35 (m, 1H), 2.70 (d, J_{6AB} = 16.0 Hz, H_{6b}), 2.45 - 2.35 (m, 1H), 2.00 - 1.45 (m, 5H), 0.60 (t, J = 7.8 Hz, CH_3).

33b: 7.40 - 7.05 (m, $9H_{aromatic}$), 4.90 (d, J < 1 Hz, H_{17a}), 4.74 (d, J = 3.5 Hz, H_{21}), 4.65 (d, J < 1 Hz, H_{17b}), 4.05 (t, J = 3.0 Hz, H_3), 3.90 - 3.60 (m, 7H), 3.53 (s, NCH_3), 2.95 (m, 1H), 2.65 (d, J = 16.0 Hz, H_{6b}), 2.45 - 2.35 (m, 1H), 2.00 - 1.45 (m, 5H), 1.02 (t, J = 7.8 Hz, CH_3).

Exact mass calcd. for $C_{29}H_{34}N_2O_2$: 442.2648. Found: 442.2620.

α-Ethyl-5-methyl-9-hydroxymethyl-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5H-cyclooct[b]indole-8-acetaldehyde ethylene acetal (34).

The alkenic acetal **33** (380 mg, 0.87 mmol) was dissolved in dry THF (4 mL) under an atmosphere of argon. A solution of 9-BBN in THF (0.5 M, 3.5 mL, 1.75 mmol) was added and the mixture was stirred at 50°C for 2 h. The colorless solution was then cooled to 0°C and water (0.5 mL) was added dropwise under argon to quench excess borohydride. A solution of aqueous NaOH (3 N, 0.58 mL; 1.75 mmol) was added and was followed by dropwise addition of H_2O_2 (30%, 0.6 mL, 5.25 mmol). The reaction mixture was warmed to 35°C and stirred for 1.5 h. The solution was saturated with solid K_2CO_3 (anhydr., 2 g) and the organic solution was decanted into Et_2O (25 mL). The inorganic residue was washed with Et_2O (3 x 20 mL). The combined organic portions were washed with brine (2 x 100 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure. The oil which resulted was crystallized from Et_2O to furnish the major isomer, **34a** in pure form. The filtrate was concentrated and the oil which resulted was chromatographed (SiO_2, EtOAc/hexane, 9:1) to furnish the hydroxy acetal **34** as a mixture of diastereomers (a:b, 2:1) in 91% yield (364 mg). **34a:** mp 177 - 179°C; IR (KBr) 3400, 2950, 1600, 1450, 1160, 1020 cm^{-1}; MS (CI, CH_4) m/e (relative intensity) 461 (M+1, 100); ^{1}H NMR ($CDCl_3$) δ 7.50 (d, J = 7.8 Hz, 1H), 7.40 -7.05 (m, 8H), 4.75 (d, J = 4.0 Hz, 1H), 3.95 - 355 (m, 10H), 3.39 (t, J = 6.5 Hz, 1H), 3.05 (dd, J = 16.0 Hz, J = 6.5 Hz, 1H), 3.65 (m, 1H), 3.60 (d, J = 16.0 Hz, 1H), 2.40 (m, 1H), 2.30 (m, 1H), 1.85 (m, 1H), 1.35 (m, 1H), 1.00 (m, 1H), 0.50 (m, 1H), 0.31 (t, J = 7.0 Hz, 3H). Exact mass calcd. for $C_{29}H_{34}N_2O_3$: 460.2725. Found: 460.2747.

Anal. Calcd. for $C_{29}H_{34}N_2O_3 \cdot ¼H_2O$: C, 74.90; H, 7.91; N, 6.03. Found: C, 74.89; H, 7.89; N, 5.81.

α-Ethyl-5-methyl-9-formyl-12-benzyl-6,7,8,9,11-hexahydro-6,10,imino-5H-cyclooct[b]indole-8-acetaldehyde ethylene acetal N_b-oxide 35.

The hydroxy acetal **34** (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 temp.) 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) poured into a solution of 1 N NaOH (30 mL). The mixture was then extracted with EtOAC (3 x 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 oi. The oil was chromatographed (SiO_2, EtOAc/hexane, 30:70) to furnish the aldo-acetal N_b-oxide **35** 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, 3.56); ^1H NMR ($CDCl_3$) δ 9.30 (s, 1H), 7.49 (d, J = 7.8 Hz, 1H), 7.30 - 7.10 (m, 7H), 7.05 (t, J = 7.8 Hz, 1H), 4.79 (d, J = 16.8 Hz, J = 7.0 Hz, 1H), 2.90 (m, 1H), 2.53 (m, 1H), 2.48 (d, J = 16.8 Hz, 1H), 1.73 - 1.53 (m, 2H), 1.15 (m, 2), 0.60 (t, J = 7.0 Hz, 3H). ^{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-Benzyl suaveoline (37).

The aldehyde-acetal N_b-oxide **35** (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 then poured into a cold aqueous solution of $NaHCO_3$ (10%, 10 mL). The aqueous mixture was extracted with EtOAc (3 x 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 **36** as an oil (160 mg, 0.37 mmol, 91%). The crude dialdehyde was dissolved in anhydrous EtOH (5 mL) and hydroxylamine•HCl (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 x 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-benzyl suaveoline **37** (R_f = 0.42) as an oil (64 mg, 40% yield from **35**)l. 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, $J_{9\text{-}10}$ = 8.0 Hz, H_9), 7.40 - 7.20 (m, $H_{12,phenyl}$), 7.19 (t, $J_{11\text{-}10(12)}$ = 7.9 Hz, H_{11}), 7.09 (t, $J_{10\text{-}9(11)}$ = 7.9 Hz, H_{10}), 4.41 (d, $J_{5\text{-}6a}$ = 6.5 Hz, H_5), 4.27 (d, $J_{3\text{-}14a}$ = 6.6 Hz, H_3), 3.98 - 3.75 (q, J_{AB} = 13.8 Hz, $2H_{benzyl}$), 3.65 (s, N_a-CH_3), 3.48 (dd, J_{6AB} = 16.4 Hz, $J_{6a\text{-}5}$ = 6.6 Hz, H_{6a}), 3.25 (dd, J_{14AB} = 16.9 Hz, $J_{14a\text{-}3}$ = 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, $J_{19\text{-}18}$ = 7.1 Hz, $2H_{19}$), 1.15 (t, $J_{18\text{-}19}$ = 7.0 Hz, $3H_{18}$).

(±)-Suaveoline (1).

N_b-Benzyl suaveoline **37** (30 mg, 0.076 mmol) was added to a slurry of methanol and 10% palladium on carbon (30 mg). The reaction mixture was then stirred at room temperature for 20 h under an atmosphere of hydrogen (1 atm). After debenzylation was complete the reaction mixture was filtered. The solvent was removed under reduced pressure and the oil which resulted was chromatographed [SiO_2, EtOH (sat'd with NH_3(g)/$CHCl_3$, 15:85] to furnish (±)-suaveoline **1** (R_f = 0.36) as an oil (16 mg, 68%): MS (CI, CH_4) m/e (relative intensity) 304 (M+1, 100); MS (EI, 15 ev) m/e (relative intensity) 303 (M+, 100), 286 (22.9), 183 (52.9), 158 (5.2), 144 (4.3); ^1H NMR (C_6D_6) δ 8.54 (s, H_{17}), 8.35 (s, H_{21}), 7.55 (d, $J_{9\text{-}10}$ = 8.2 Hz, H_9), 7.35 - 7.15 (m, H_{10}, H_{11}), 7.11 (d, $J_{12\text{-}11}$ = 8.2 Hz, H_{12}), 4.34 (d, $J_{5\text{-}6a}$ = 6.4 Hz, H_5), 4.05 (d, $J_{3\text{-}14a}$ = 6.6 Hz, H_3), 3.05 (dd, J_{6AB} = 16.0 Hz, $J_{6a\text{-}5}$ = 6.6 Hz, H_{6a}), 3.00 (s, N_a-CH_3), 2.90 (dd, J_{14AB} = 17.6 Hz, $J_{14a\text{-}3}$ = 6.5 Hz, H_{14a}), 2.77 (d, J_{6AB} = 16.0 Hz, H_{6b}), 2.45 (d, J_{14AB} = 17.6 Hz, H_{14b}), 2.13 (q, $J_{19\text{-}18}$ = 7.4 Hz, $2H_{19}$), 1.40 (br s, N_b-H), 0.87 (t, $J_{18\text{-}19}$ = 7.4 Hz, $3H_{18}$). The ^1H NMR spectrum of (±)-**1** is in complete agreement with that reported for suaveoline[1]. The mass spectral data (EI fragmentation pattern) for (±)-**1** is also identical to that reported for suaveoline.[1]

(±)-N_b-Methyl suaveoline (38).

N_b-Benzyl suaveoline **37** (30 mg, 0.076 mmol) was added to a slurry of 4% formic acid in methanol and 10% palladium on carbon (30 mg). The reaction mixture was then stirred at room temperature for 2 h under an atmosphere of hydrogen (1 atm). After debenzylation/methylation was complete, aqueous ammonia (conc. 0.2 mL) was added and the mixture which resulted was filtered. The solvent was removed under reduced pressure and the residue which resulted was dissolved in $CHCl_3$ (30 mL). The organic solution was washed with aqueous $NaHCO_3$ (10%, 20 mL), brine (20 mL) and dried (K_2CO_3). The solvent was removed under reduced pressure to afford an oil. The oil was chromatographed (SiO_2, EtOH/$CHCl_3$, 1:9) to furnish N_b-methyl suaveoline **38** (R_f = 0.40) as an oil (19 mg, 78%): MS (CI, CH_4) m/e (relative intensity) 318 (M+1, 100); ^1H NMR ($CDCl_3$) δ 8.28 (s, H_{17}), 8.13 (s, H_{21}), 7.40 (d, $J_{9\text{-}10}$

= 8.0 Hz, H_9), 7.25 (d, J_{12-11} = 8.1 Hz, H_{12}), 7.15 (t, $J_{11-10(12)}$ = 7.9 Hz, H_{11}), 7.06 (t, $J_{10-9(11)}$ = 8.0 Hz, H_{10}), 4.30 (d, J_{6a} = 6.6 Hz, H_5), 4.25 (d, J_{3-14a} = 6.5 Hz, H_3), 3.70 (s, N_a-CH_3), 3.45 (dd, J_{6AB} = 16.0 Hz, J_{6a-5} = 6.6 Hz, H_{6a}), 3.33 (dd, J_{14AB} = 17.6 Hz, J_{14a-3} = 6.5 Hz, H_{14a}), 2.79 (d, J_{6AB} = 16.0 Hz, H_{6b}), 2.71 (d, J_{14AB} = 17.6 Hz, H_{14b}), 2.57 (s, N_b-CH_3), 2.47 (q, J_{19-18} = 7.1 Hz, $2H_{19}$), 1.15 (t, J_{18-19} = 7.0 Hz, $3H_{18}$). The data from the ^{1}H NMR spectrum of **38** is in complete agreement with that published for N_b-methyl suaveoline.[1]

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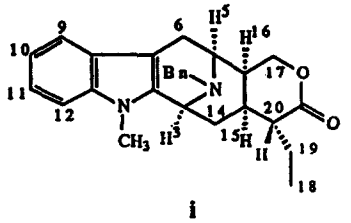

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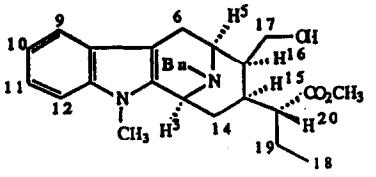

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