General Approach for the Synthesis of Ajmaline-Related Alkaloids. Enantiospecific Total Synthesis of (−)-Suaveoline, (−)-Raumacline, and (−)-N_b-Methylraumacline

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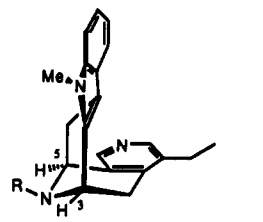
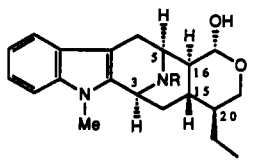
(−)-Raumacline (3) and (−)-N_b-methylraumacline (4), isolated from plant cell cultures of *Rauwolfia serpentina* Benth., have been synthesized from D-(+)-tryptophan in enantiospecific fashion. In addition, (−)-suaveoline (1) has also been prepared via this strategy. The synthesis of these indole alkaloids employed a stereospecific Pictet–Spengler/Dieckmann protocol to prepare the key intermediate, (−)-N_b-benzyltetracyclic ketone 12. This ketone 12 was converted into the C-15 functionalized system 16 via an anionic oxy-Cope rearrangement; 16 had also been obtained by 1,4-addition of a Grignard reagent to the α,β-unsaturated aldehyde (−)-8 generated from (−)-12. Conversion of 16 into either (−)-N_b-benzylsuaveoline (23) or (−)-N_b-benzylraumacline (28), respectively, is described. Catalytic debenzylation of the hydrochloride salts of 23 and 28 in ethanol provided the corresponding alkaloids (−)-1 and (−)-3 in excellent yield. In contrast to the published reports, the optical rotation of (−)-suaveoline (>98% ee) was found to be $[\alpha]^{25}_D = -9.3°$ (c = 0.30, $CHCl_3$) rather than 0° as previously reported. Treatment of 23 or 28 (individually) with excess Pd/C and hydrogen in methanol yielded (−)-N_b-methylsuaveoline and (−)-N_b-methylraumacline in excellent yield, respectively.

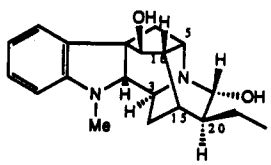
Suaveoline (1) was isolated by Potier et al.[1] in 1972, along with eight other indoles from the alkaloidal components of the trunk bark of *Rauwolfia suaveolens* S. Moore collected in New Caledonia and has been found in other species of *Rauwolfia*.[2] The structure of suaveoline was elucidated on the basis of mass and proton NMR spectroscopy.[1] However, suaveoline was reported by Potier et al.[1] to have no optical rotation, although the related N_b-methylsuaveoline (2) was levorotatory. More recently, the natural products raumacline (3) and N_b-methylraumacline (4) were isolated from plant cell cultures of *Rauwolfia serpentina* Benth. by Stöckigt, Sakai, and coworkers[3] after feeding experiments with ajmaline.[3-5] The tropical Indian plant *R. serpentina* has been used as a traditional herbal medicine for treatment of heart disease.[6] It has been the object of extensive phytochemical,[7] pharmacological,[8] and biosynthetic[9] studies since the initial isolation of ajmaline (5) by Siddiqui et al.[10] more than 60 years ago. The stereochemistry of suaveoline (1) and raumacline (3) was confirmed by partial synthesis of 2[1] and 3[3] from ajmaline. From a biosynthetic perspective, both the suaveoline and raumacline indole alkaloids appear to arise from the catabolism of the biologically important alkaloid ajmaline (5).[11-13] Interesting structural relationships exist in the members of the sarpagine/macroline (6)[14] and ajmaline classes of alkaloids. The absolute configurations of the stereogenic centers at C-3, C-5, and C-15



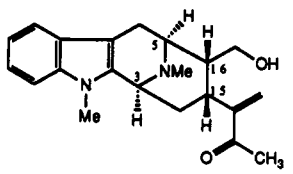
1, R = H
suaveoline
2, R = CH_3
N_b-methylsuaveoline



3, R = H
raumacline
4, R = CH_3
N_b-methylraumacline



5, ajmaline



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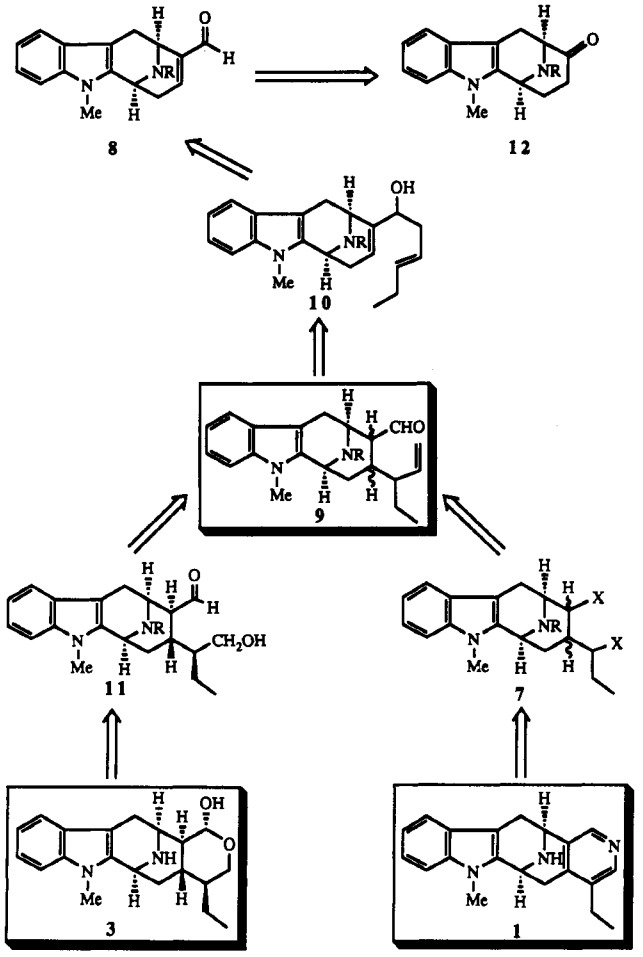
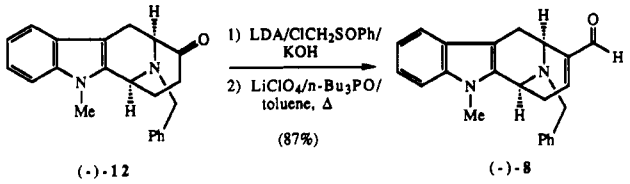
Scheme I



Scheme II[a]



[a] The details of the stereospecific synthesis of (−)-12 are fully described in reference 21.

of both classes of alkaloids are identical; however, the chirality of the ajmaline series is antipodal at C-16 with respect to that of the sarpagine alkaloids. More importantly, the five chiral centers in 3 and 4 at C-3, C-5, C-15, C-16, and C-20 are identical to those found in ajmaline (5), providing additional interest in an approach to these alkaloids. Recently, the synthesis of the macroline/sarpagine base alstonerine was reported from this laboratory.[15] Extension of this approach for the enantiospecific synthesis of the ajmaline-related indole alkaloids suaveoline (1), raumacline (3), and N_b-methylraumacline (4) is described below.

The strategy for the synthesis of suaveoline (1) was envisaged to employ a 1,5-dialdehyde 7 (or equivalent) as a latter intermediate for the construction of the annulated pyridine (E)-ring of 1 (Scheme I). Three different routes for the construction of the 1,5-dialdehyde 7 were recently proposed by Trudell et al.[16] However, only the ortho ester Claisen rearrangement successfully resulted in the preparation of the desired 1,5-dialdehyde 7 and eventually led to the first total synthesis of (±)-1.[16,17]

In regard to a simple route for an enantiospecific construction of 7 (Scheme I), the anionic oxy-Cope rearrangement[18] appeared to present several advantages. Oxidative cleavage of the double bond of the alkenic aldehyde 9 should provide 7 directly. The intermediate 9 could be obtained from α,β-unsaturated aldehyde 8 in just two steps via an allylic alcohol 10, since the aldehyde function at C-16 would be regenerated in the oxy-Cope process. More importantly, the anionic oxy-Cope rearrangement of the allylic alcohol 10 should take place stereoselectively from the α face of the double bond to furnish the desired configuration at C-15 required for the synthesis of the ajmaline/sarpagine alkaloids.

From a retrosynthetic (Scheme I) point of view, the hemiacetal function of raumacline (3) could be formed from the 1,5-hydroxy aldehyde 11 or an equivalent. The anionic oxy-Cope rearrangement of 10 would be expected to occur stereoselectively from the α face via a chair transition state to provide 11 with the desired configuration at C-15 and C-16. The allylic alcohol 10 could then be obtained from a Grignard reagent or other nucleophilic addition to the α,β-unsaturated aldehyde 8 which had already been prepared in racemic form from tryptophan via the tetracyclic ketone 12 in the synthesis of (±)-suaveoline by Trudell.[16]

The optically active (−)-N_b-benzyl tetracyclic ketone 12 was prepared from D-(+)-tryptophan, as described previously, in greater than 98% ee.[21,22] The optical purity was based on an analysis by NMR spectroscopy (a chiral shift reagent)[21] and HPLC.[22] Conversion of the carbonyl function of (−)-12 into the α,β-unsaturated aldehyde moiety of 8 (Scheme II) via the spirooxirano phenyl sulfoxide[23,24] was accomplished in 87% overall yield by the published methods of Trudell in the racemic series and Zhang in the N_b-methyl series.[15,16,19b] The α,β-unsaturated aldehyde (−)-8 (>98% ee) contains the desired absolute configuration at C-3 and C-5 and serves as the key intermediate for the total synthesis of alkaloids in both the sarpagine and ajmaline series.

With large quantities of (−)-8 in hand, plans to functionalize the C-15 position of the tetracyclic framework turned to the conversion of 8 into an allylic alcohol with a C_5 unit to be followed by an anionic oxy-Cope rear-

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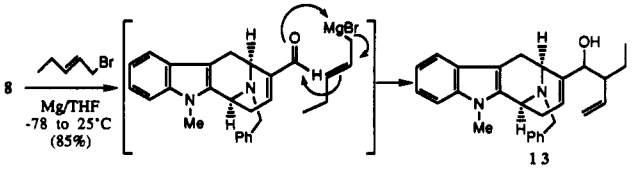
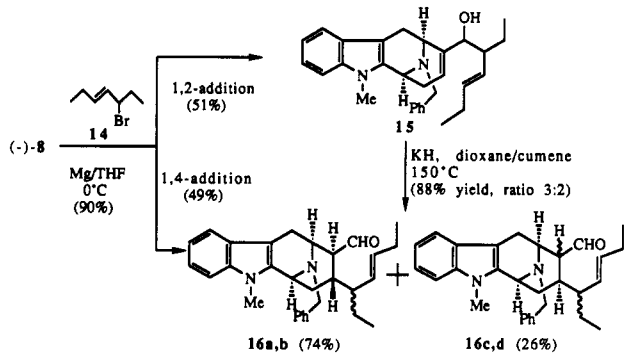
Scheme III



Scheme IV

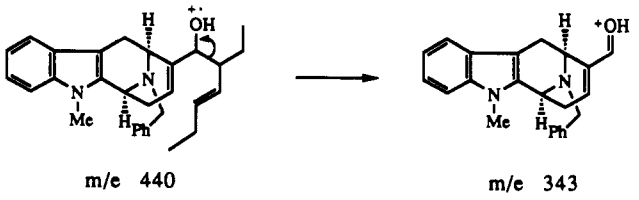


rangement. Numerous attempts to add reagents 1,4 to the enal system of **8** had previously been unsuccessful in several laboratories[25-27] promoting the intramolecular strategy.

Addition of the primary Grignard reagent available from 1-bromo-2-pentene to the α,β-unsaturated aldehyde **8** provided the expected but undesired alcohol **13** which resulted from the allylic rearrangement of the Grignard reagent[28] (Scheme III). Although Benkeser et al.[29] reported that the reversible Grignard addition process favored the "normal" addition from the α position when the adduct initially formed was heated at higher temperature in the cases of hindered carbonyl substrates, the reaction of **8** with 1-bromo-2-pentene in refluxing THF furnished none of the desired alcohol. Since the olefinic bond in **9** served as a latent aldehyde function, the primary Grignard reagent was replaced with a pseudosymmetric secondary Grignard reagent available from 5-bromo-3-heptene (**14**). Generation of the anion followed by an allylic rearrangement[28] would provide the same carbanion as in the case of **14**. When the aldehyde **8** was reacted with **14** at 0 °C under the conditions of a Barbier–Grignard process (Scheme IV),[30] the products of 1,2-addition (allylic alcohols **15**) and 1,4-addition (diastereomers **16a–d**) were obtained in a combined yield of 90% in a ratio of 51 (**15**):49 (**16**).

The allylic alcohols represented by **15** were easily separated from the mixture of aldehydes **16** by flash chromatography. The mixture of monols **15** consisted of at least four diastereomers (^{13}C-NMR spectroscopy) which could not be separated, all of which, however, could be employed for the synthesis of **1** and **3**. The relatively intense ion observed at *m/e* 343 from β-fragmentation (Scheme V) in the mass spectrum of **15** is characteristic

Scheme V



of the allylic alcohol function.[31] The aldehydes from the 1,4-addition were separated by flash chromatography. The structures of these aldehydes **16a,b** and **16c,d** were confirmed spectroscopically.

In the fixed chair conformation of ring-D in **16**, the coupling constants between H-16 and H-15 are diagnostic for the configurations of C-15 and C-16. If protons H-15 and H-16 are diaxial, a large coupling (ca. 10 Hz) should be observed. In contrast, when H-15 and H-16 are disposed in a diequatorial or equatorial/axial (vice verse) configuration, the coupling constants between these hydrogen atoms would be small (<6 Hz).[31] In the COSY NMR spectrum of **16a**, a clear crosspeak between the aldehydic proton (δ 9.72) and the proton located at H-16 (δ 2.87) was observed.

Further examination of the signal at H-16 indicated the presence of a 12-Hz coupling constant which must be due to H-15 and H-16 since H-16 was coupled with H-17 (aldehydic proton) with a *J* value of 2 Hz and with H-5 of ca. 4.5 Hz. Consequently, the 12-Hz coupling between H-16 and H-15 permitted the assignment of H-16 and H-15 as diaxial. This can only occur if H-15 occupies the β configuration and the proton located at H-16 is α.

In a similar fashion, the aldehydic proton at H-17 (δ 9.65) was correlated with H-16 (δ 2.79) in the COSY spectrum of **16b**. The signal at H-16 was observed as a doublet of triplets with coupling constants of 11.6 and 4.3 Hz, respectively. Again the large coupling (11.6 Hz) observed between H-16 and H-15 permitted the assignment of configurations at C-15 and C-16 as the same as those in **16a**. The double bond in both **16a** and **16b** was assigned as trans on the basis of the large coupling constant (15.3 Hz) observed for the olefinic protons. The configurations of C-20 in **16a** and **16b** were not assigned unambiguously at this stage.

The structures of **16c** and **16d** were assigned in a slightly different fashion. Since the aldehydic protons in both **16c** and **16d** resonate as singlets, direct identification of the signals at H-16 was difficult. However, the interaction between the protons at H-20 (δ 1.19) and H-21 (δ 4.73) permitted unequivocal identification of the multiplet (δ 2.16) at H-15 in the COSY NMR spectrum of **16d**. Although it was difficult to determine the individual coupling constants associated with H-15, only one small crosspeak was observed between H-15 and H-14 (δ 1.95). This result indicated that the proton located at H-15 (α) exhibited a small coupling only with H-16 (δ 2.48). The configurations of C-16 and C-20 were not unequivocally determined and were not important in this context since the configuration of C-15 was antipodal to that desired for the construction of the ajmaline-related alkaloids. The same conclusion with respect to the configuration of C-15 was reached for **16c** upon comparison of its ^{1}H-NMR

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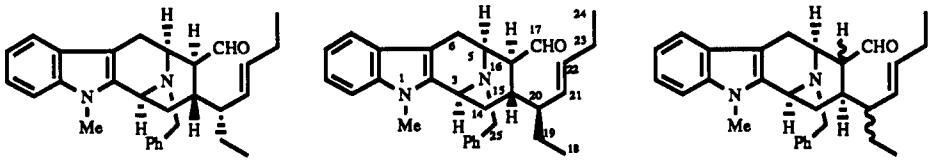
Table I. ^{1}H-NMR Spectral Data for Aldehydes 16a, 16b, and 16d



	16a		16b		16d	
proton	δ (ppm)	J (Hz)	δ (ppm)	J (Hz)	δ (ppm)	J (Hz)
H-17	9.72	H17-H16 = 2.2	9.65	H17-H16 = 3.8	9.78	s
aromatic	7.48	7.7	7.50	7.9	7.52	7.7
	7.29	m	7.28	m	7.30	m
	7.20	7.5	7.21	7.7	7.23	7.6
	7.11	7.2	7.12	7.2	7.14	7.4
H-22	5.31	H22-H21 = 15.2 H22-H23 = 6.3	5.32	H22-H21 = 15.3 H22-H23 = 6.2	4.11	H22-H21 = 15.2 H22-H23 = 6.5
H-21	5.11	H21-H22 = 15.3 H21-H20 = 9.6	4.94	H21-H22 = 15.4 H21-H20 = 9.4	4.73	H21-H22 = 15.2 H21-H20 = 9.5
H-3	3.95	H3-H14β < 2 H3-H14α < 2	3.94	H3-H14β = 3.1	3.81	H3-H14β = 2.5
H-25	3.67	gem = 13.4	3.68	gem = 13.6	3.69	gem = 13.5
H-5	3.63	H5-H6α = 7.4 H5-H16 = 4.9	3.54	m	3.78	H5-H6α = 6.8 H5-H16 = 1.9
H-25	3.60	gem = 13.4	3.60	gem = 113.5	3.63	gem = 13.6
N_a-Me	3.53	s	3.54	s	3.53	s
H-6α	3.05	gem = 16.9 H6α-H5 = 6.9	3.04	gem = 17.0 H6α-H5 = 6.8	3.37	gem = 16.6 H6α-H5 = 7.1
H-16	2.87	H16-H15 = 11.9 H16-H5 = 4.5 H16-H17 = 2.4	2.79	H16-H15 = 11.6 H16-H5 = 4.3 H16-H17 = 4.3	2.48	br. s
H-6β	2.48	gem = 16.9	2.55	gem = 17.0	2.56	gem = 16.6
H-15	1.95	m	1.93	m	2.16	m
H-14β	1.79	gem = 12.6 H14β-H3 = 4.09 H14β-H15 = 4.09	1.79	m	1.95	m
H-14α	1.66	gem = 12.5 H14α-H3 = 3.75 H14α-H15 = 3.75	1.93	m	1.86	gem = 16.4
2H-23	2.05	H23-H24 = 7.2 H23-H22 = 7.2	1.93	m	1.80	H23-H24 = 7.4 H23-H22 = 6.7
H-20	2.00	m	1.79	m	1.19	m
H-19	1.10	m	1.45	m	1.34	m
H-19	1.09	m	1.02	m	0.83	m
3H-24	0.99	H24-H23 = 7.4	0.90	H24-H23 = 7.5	0.82	H24-H23 = 7.4
3H-18	0.66	H18-H19 = 7.3	0.71	H18-H19 = 7.3	0.50	H18-H19 = 7.3

spectrum with that of **16d**. The assignments of the ^{1}H-NMR spectral data for **16a**, **16b**, and **16d** are summarized in Table I.

The 1,4-addition of **14** to **8** is unprecedented in these systems and provided diastereomers **16a** and **16b** with the ajmaline configuration at C-15 and C-16 in a ratio of 3 (**16a,b**):1 (**16c,d**), although the addition of penten-2-ylmagnesium bromide and allylmagnesium bromide (see **17**)[32] provided only the products of 1,2-addition, respectively. The allylic alcohols **17a** and **17b** obtained in the simple system (90% yield) were separated. Each of these monols was subjected to the anionic oxy-Cope rearrangement (KH, dioxane, 102 °C) to provide aldehydes **18** and **19** in a ratio of approximately 3 (α-face attack): 2 (β-face attack) in a 90% combined yield (Scheme VI).[32] Again the preferred mode of attack was observed from the bottom face of the double bond.

When the allylic alcohol **15** from 1,2-addition was treated with ethylmagnesium bromide at 0 °C to 24 °C for 1 day, no aldehydic material from the corresponding anionic oxy-Cope rearrangement was detected. This result indicated that the aldehydes represented by **16** isolated from the Grignard reaction (under the Barbier conditions) were indeed produced from 1,4-addition. However, the allylic alcohol **15** underwent the anionic oxy-Cope rearrangement at 150 °C in 88% yield to provide the same C-15 functionalized tetracyclic systems **16a,b** and **16d,e** in a ratio of 3:2 (Scheme VI). The aldehyde **16e** was a diastereomer of **16c** and **16d** and resulted from rearrangement from the β face of the double bond. It is important to note that the anionic oxy-Cope rearrangement has provided the same diastereomers as the reaction by 1,4-addition. This demonstrated the importance of the pseudosymmetric secondary Grignard reagent the olefinic bond of which also served as a latent aldehyde function.

The hindered nature of the N_b-benzylazabicyclo[3.3.1]-nonane system is evident for the anionic oxy-Cope rearrangement (KH, 150 °C) would not take place at temperatures normally required for this pericyclic process.[33,34] The ortho ester Claisen rearrangement in a related N_b-benzyl system occurred with a diastereofacial selectivity of 13:1 from the top face of the double bond principally via boat transition states,[35] while recent results[36] indicate that the Claisen rearrangement in this

(32) Yu, F.; Fu, X.; Cook, J. M. Unpublished results.

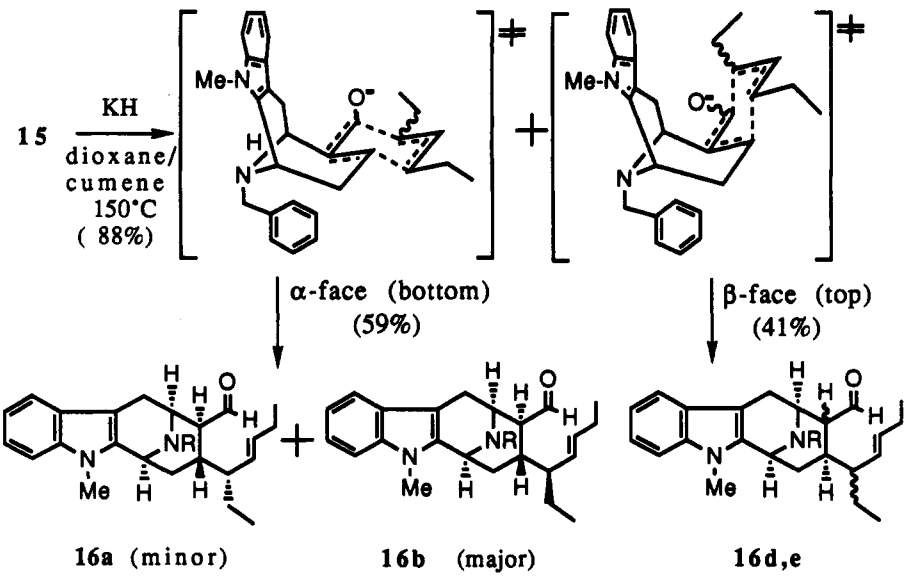
(33) Evans, D. A.; Nelson, J. V. *J. Am. Chem. Soc.* **1980**, *102*, 774.

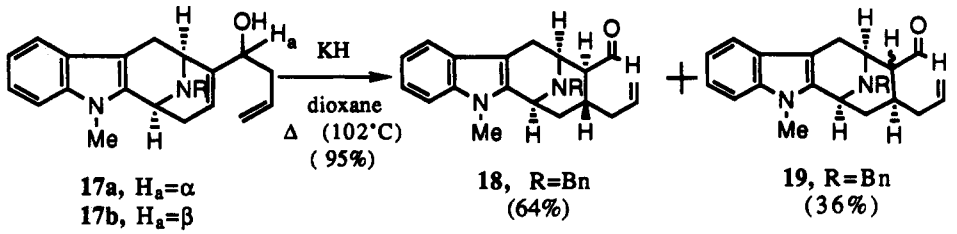
(34) For a recent review on the anionic oxy-Cope rearrangement see: Paquette, L. A. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 609.

(35) Zhang, L.-H.; Trudell, M.; Hollinshead, S. P.; Cook, J. M. *J. Am. Chem. Soc.* **1989**, *111*, 8263.

(36) Bi, Y.; Cook, J. M. Unpublished results.

Scheme VI

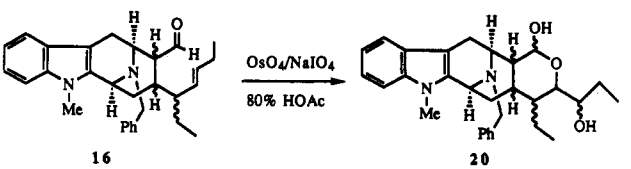




N_b-benzyl system occurs with a stereoselectivity of about 3(α):2(β). The diastereofacial selectivity for the anionic oxy-Cope rearrangement in the analogous N_b-benzyl systems **15** (KH, 150 °C) and **17** (KH, 102 °C) favored attack from the desired bottom face of the double bond, although the selectivity was only 3:2. The selectivity in the N_b-benzyl series is important for the Claisen rearrangement in the related N_b-methyl series appears to occur with high stereoselectivity from the bottom face of the double bond.[35] This indicates that the stereofacial selectivity of the anionic oxy-Cope process may be significantly increased in the N_b-H series. This possibility is currently under investigation with respect to the synthesis of ajmaline (**5**).[37]

The overall conversion of (−)-**8** into the mixture of C-15 functionalized aldehydes **16** required for the synthesis of suaveoline (**1**) and N_b-methylsuaveoline (**2**) was greater than 84%. With alkenic aldehyde **16** in hand, attention turned to the oxidative cleavage of the olefinic bond to generate the desired 1,5-dialdehyde intermediate. Initial attempts via ozonolysis were unsuccessful due to the reactivity of the indole 2,3-double bond toward ozone.[38] Of the many bishydroxylation reactions available, osmylation has been considered a selective process.[39] Encouraged by van Tamelen's report on the synthesis of yohimbine wherein an olefinic bond was selectively osmylated in the presence of the indole moiety,[40] the osmium tetraoxide mediated bishydroxylation was attempted with intermediate **16**. When a mixture of diastereomers represented by **16** was treated with a catalytic amount of osmium tetraoxide in 80% acetic acid in the presence of sodium periodate, a mixture of stereoisomeric hemiacetals (see **20**), rather than the desired dialdehyde, was isolated from the process (Scheme VII). Obviously, the formation of **20** resulted from the interaction of the hydroxyl function with the aldehyde at C-16 to provide a stable six-membered hemiacetal. Although the hemiacetal **20** was not useful here, this result implied that chemoselectivity existed in this system with osmylation.

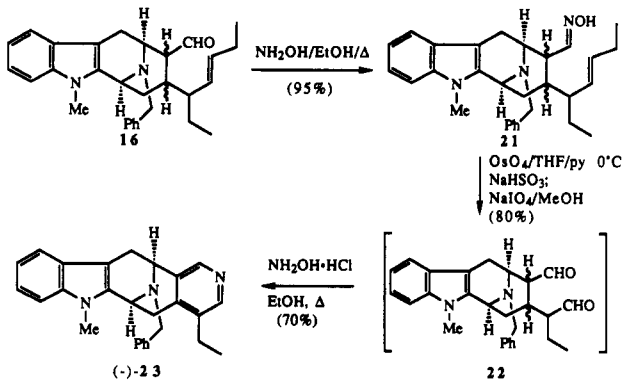
Scheme VII



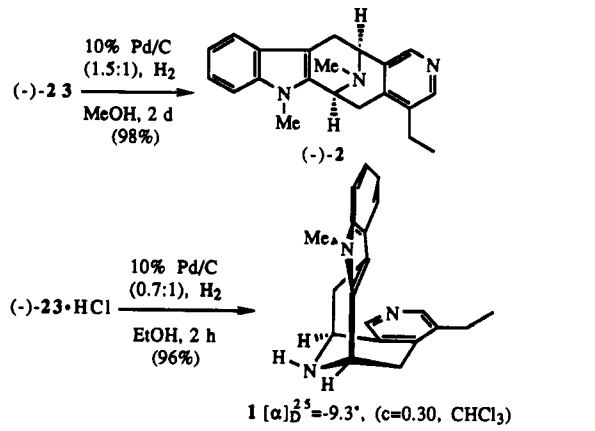
Protection of the aldehyde function of alkenic aldehyde **16** as an oxime instead of an acetal would facilitate formation of the pyridine E-ring of suaveoline in situ by an intramolecular condensation. The aldehyde function in **16** was treated with hydroxylamine hydrochloride in ethanol at reflux to provide a mixture of diastereomeric oximes represented by **21** (95% yield). The mixture of oximes was osmylated and subsequently hydrolyzed reductively with aqueous $NaHSO_3$ solution to provide the desired diol which was subjected directly to the oxidative cleavage[41] sequence with $NaIO_4$. The desired dialdehyde

(37) Peterson, A.; Fu, X.; Cook, J. M. Unpublished results.
(38) Ockenden, D. W.; Schofield, K. *J. Chem. Soc.* **1953**, 612.
(39) For a review on osmium tetraoxide *syn*-dihydroxylation see: Schroder, M. *Chem. Rev.* **1980**, *80*, 187.
(40) van Tamelen, E. E.; Shamma, M.; Burgstahler, A. W.; Wolinsky, J.; Tamm, R.; Aldrich, P. E. *J. Am. Chem. Soc.* **1969**, *91*, 7315.
(41) For a review on periodic acid oxidation see: Jackson, E. L. *Organic Reactions*; Adams, R., Ed.; Wiley & Sons: New York, 1944; Vol. II, p 341.

Scheme VIII

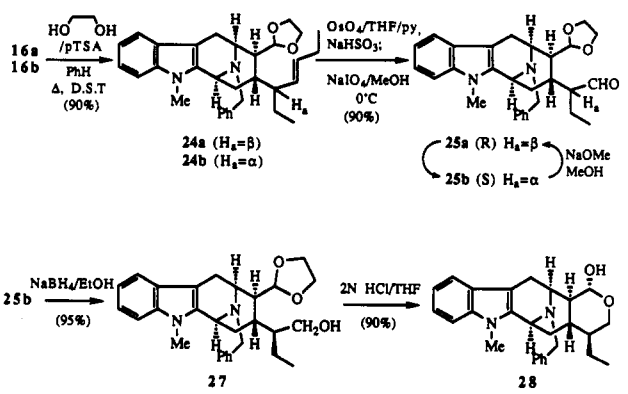


Scheme IX

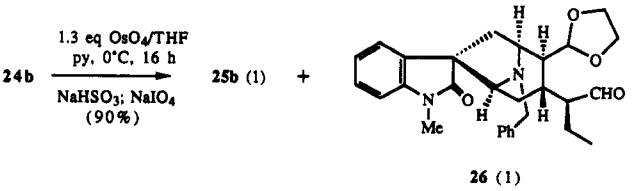


22 was obtained in 80% overall yield based on recovered starting oxime **21**. The C-16 aldehyde function was believed to be regenerated by oxidative hydrolysis of the oxime function with $NaIO_4$.[42a] This process is closely related to the oxidative hydrolysis of dimethylhydrazones reported by Corey et al.[42b] The mixture of bisaldehydes **22** was cyclized in situ with hydroxylamine hydrochloride to provide (-)-N_b-benzylsuaveoline (**23**) in 70% yield (Scheme VIII). When (-)-N_b-benzylsuaveoline (**23**) was subjected to catalytic debenzylation with excess (ca 1.5:1, w/w) Pd/C (10%) and hydrogen in methanol, a 98% yield of (-)-N_b-methylsuaveoline (**2**) ($[\alpha]^{25}_D$ = -89.5°, c = 0.35, $CHCl_3$) was realized in greater than 98% ee. Although the mechanism of this benzyl/methyl transformation is not clear, this provides a simple method to execute a benzyl/methyl transfer in the latter stages of the synthesis and can be employed in the preparation of a number of macroline/sarpagine/ajmaline alkaloids.[43] Catalytic debenzylation of the hydrochloride salt of N_b-benzylsuaveoline (**23**) with 10% Pd/C (0.7:1, w/w) and hydrogen in ethanol provided a 96% yield of (-)-suaveoline (**1**) (Scheme IX). The specific optical rotation of **1** was found to be -9.3° (c = 0.30, $CHCl_3$) rather than the 0° previously reported.[1] The spectral properties of both **1** and **2** were identical, respectively, to those reported earlier for these

Scheme X



Scheme XI



indole bases by Potier[1] and Trudell.[16,17] The synthesis described above constitutes the first enantiospecific synthesis of **1** and **2**, and the seven-step route from (-)-tetracyclic ketone **12** represents an important improvement with respect to the approach in the racemic series.[16,17]

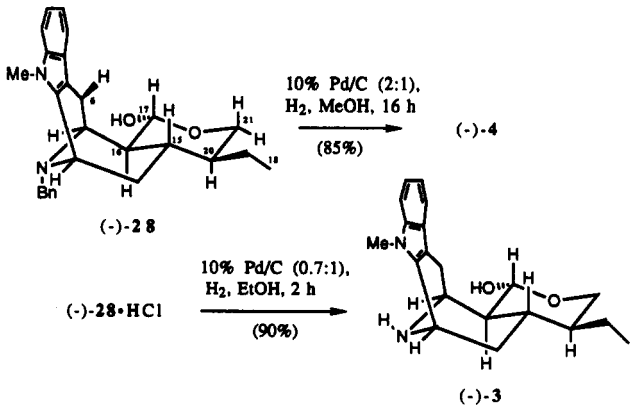
For the synthesis of (-)-raumacline (**3**) and (-)-N_b-methylraumacline (**4**), execution of the chemistry in Schemes IV and VI provided a 57% overall yield (64% stereoselectivity) of **16a** and **16b** [from (-)-**8**], epimeric about the C-20 ethyl moiety. These two diastereomers (**16a** and **16b**) were separated by flash chromatography. Because the absolute configurations of **16a,b** at C-3, C-5, C-15, and C-16 were identical to those of **3** and **4**, both diastereomers could be employed for the synthesis. In order to differentiate between the aldehyde function at C-17 and the latent aldehyde at C-21, the aldehyde functions of **16a** and **16b** were protected as the ethylene acetals (see **24a** and **24b**, respectively) in excellent yield, as illustrated in Scheme X. Oxidative cleavage of the olefinic bond was again executed via the osmium tetraoxide/sodium periodate sequence.[39-41] For the maximum conversion of the acetals **24a** and **24b** into the aldehydes represented by **25a** and **25b**, the osmylation process was interrupted before the appearance of byproducts which resulted from the bisosmylation of both the olefinic bond and the indole double bond. Under controlled conditions (ca. 80% conversion of **24a** and **24b**), the osmates which resulted were reductively hydrolyzed with aqueous $NaHSO_3$ solution to provide the corresponding diols, respectively. This was followed by sodium periodate cleavage of the diol function to furnish the desired aldehydes **25a** and **25b** in greater than 90% overall yield based on recovered **24** (see Experimental Section for details).

When the alkenic acetal **24b** was treated with 1.3 equiv of osmium tetraoxide (in three portions) and stirred for a longer period, (16 h) this sequence (Scheme XI) produced the desired **25b** and the undesired oxindole **26** in 90% combined yield (1:1). The structure of **26** was assigned by mass and high resolution NMR spectroscopy. The configuration of C-7 is believed to be (*S*). This was based on the assumption that osmylation should occur from the

(42) (a) Araujo, H. C.; Ferreira, G. A. L.; Mahajam, T. R. *J. Chem. Soc. Perkin Trans. 1* **1974**, 2257. (b) Corey, E. J.; Enders, D. *Tetrahedron Lett.* **1976**, 3.

(43) (a) Bi, Y.; Hamaker, L. K.; Cook, J. M. *Bioactive Natural Products, Studies in Natural Products Chemistry*; Basha, F.-Z.; Atta-ur-Rahman, Eds.; Elsevier Science: New York, 1992, in press. (b) Ingham, J. L.; Koskinen, A.; Lounasmaa, M. *Progress in the Chemistry of Organic Natural Products*; Springer-Verlag: New York, 1983, p 268. (c) Esmond, P. W.; LeQuesne, P. W. *J. Am. Chem. Soc.* **1980**, *102*, 7116. Takayama, H.; Phisalalaphong, C.; Kitajima, M.; Aimi, N.; Sakai, S. *Tetrahedron*, **1991**, *47*, 1383.

Scheme XII

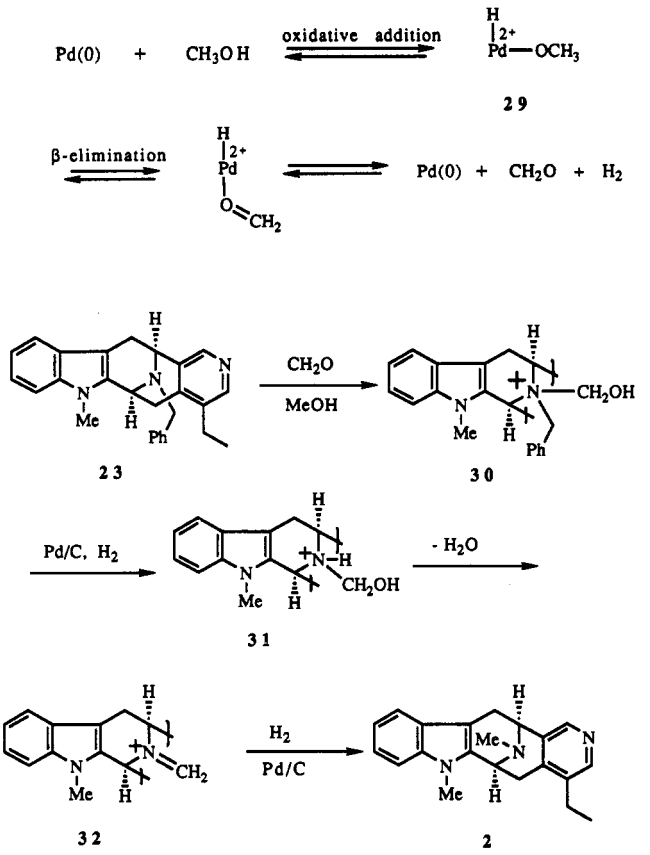


less hindered α face of the molecule to generate the α-bishydroxyl intermediate. A stereospecific pinacol rearrangement would provide the $C_7(S)$[44] oxindole **26**. Conversion of an indole into oxindole function with osmium tetraoxide has been well-documented in the literature.[44] The desired aldehyde **25b** [C-20(*S*)] contains the required chirality for the preparation of raumacline (**3**), **4**, and ajmaline (**5**). For this reason, the epimeric aldehyde **25a** was treated with base and converted into an equilibrium mixture of **25a** and **25b** (1:1), which again was subjected to flash chromatography (silica gel, EtOAc/hexane, 2:8). In this manner, the conversion of **24a** and **24b** into the required **25b** could be increased to greater than 85%. This approach could also be employed to provide **25a** [C-20(*R*)] for a synthesis of isoajmaline[13] by reversing the process.

The (−)-(*S*)-aldehyde **25b** was converted into the alcohol **27** in 95% yield with sodium borohydride. Deprotection of the aldehyde function of **27** and cyclization to (−)-N_b-benzylraumaline (**28**) was effected under acidic conditions (2 N HCl, THF) in excellent yield. The structure of the N_b-benzyl derivative **28** was assigned based on high-resolution NMR spectroscopy (2D-COSY, NOESY). In particular, the *S*-configuration of C-20 was elucidated from the coupling constant (11.3 Hz) between the diaxial protons at H-20 (α) and H-21 (β). In the NOESY spectrum, NOE correlations were observed between the C-18 methyl group and H-21 (α), as well as H-21 (β), and suggested that the C-20 ethyl group has to be located between H-21 (α) and H-21 (β). This is possible only when the C-20 ethyl group lies in an equatorial position of the chair conformation. The NOE enhancements between H-17 and H-21 (β), H-17 and H-15, H-17 and H-6 (β), as well as H-16 and H-20 further confirmed the configurations of all stereogenic centers as illustrated. The structure and stereochemistry of **28** was eventually confirmed by conversion into natural (−)-raumacline (**3**).

The conversion of **25b** into **28** is stereospecific providing only **28** which contains the correct absolute configuration at all six chiral centers for the preparation of **3** and **4**. Catalytic debenzylation (10% Pd/C, H_2) of the hydrochloride salt of **28** in ethanol provided (−)-raumacline (**3**) ($[\alpha]^{27}_D = -26.5°$, $c = 0.28$, $CHCl_3$) in 91% yield (Scheme XII). The proton and carbon-13 NMR spectra of (−)-**3** were identical to those reported for the natural product

Scheme XIII



by Stöckigt and Sakai.[3] When (−)-**28** was subjected to catalytic debenzylation in methanol with excess (2:1, w/w) Pd/C (10%) and H_2, an 85% yield of natural (−)-N_b-methylraumacline (**4**) was realized (Scheme XII).

The benzyl/methyl transfer reaction appears to be general in these systems (**23** and **28**). This process could involve the oxidation of methanol on the surface of the catalyst (Pd/C). Oxidative addition of methanol to palladium should provide complex **29**. This would be followed by β elimination to furnish formaldehyde (Scheme XIII). The formation of formaldehyde from methanol in this reaction is the reverse of a Fischer–Tropsch reaction.[45] The aldehyde could then add to the N_b nitrogen atom of **23** or **28**, respectively, to produce a quaternary carbinolamine **30**. This quaternary benzylamine **30** should exhibit higher reactivity[46] with regard to the debenzylation which is catalyzed by Pd/C. Debenzylation of **30** could provide a carbinolamine **31** followed by dehydration to form an iminium ion **32**. Reduction of the iminium intermediate then would produce the N_b-methyl analogs **2** and **4**. An alternate route to the formation of **2** and **4** would originate from the reaction of **1** and **3** with formaldehyde to produce the iminium ion **32** directly. In the case of N_b-benzylsuaveoline (**23**), the debenzylation process provided only N_b-methylsuaveoline (**2**); suaveoline (**1**) was not observed at any time during the process. The related reductive alkylation reaction is well-documented.[1,46]

Summary. Since the Pictet–Spengler/Dieckmann approach to (−)-**12** is stereospecific,[19–21] all three ajmaline-related alkaloids **1**, **3**, and **4** have been synthesized in

(44) (a) Kitajima, M.; Takayama, H.; Sakai, S. *J. Chem. Soc. Perkin Trans 1*, **1991**, 1773. (b) Takayama, H.; Masubuchi, K.; Kitajima, M.; Aimi, N.; Sakai, S. *Tetrahedron* **1989**, *45*, 1327. (c) Takayama, H.; Odaka, H.; Aimi, N.; Sakai, S. *Tetrahedron Lett.* **1990**, *31*, 5483.

(45) Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987; pp 653–660.

(46) Freifelder, M. *Catalytic Hydrogenation in Organic Synthesis Procedures and Commentary*, John Wiley & Sons: New York, 1978.

greater than 98% ee. The synthesis of these indoles described herein represents the first enantiospecific preparation of members of ajmaline family of alkaloids and demonstrates that the strategy employed in the macroline-related series[15] can be extended to other families. The seven-step synthesis of (−)-suaveoline (1) [from (−)-12] provided material in greater than 98% ee on which an accurate optical rotation could be obtained. The benzyl/methyl transfer reaction (excess Pd/C, MeOH, H_2) is noteworthy for it provides a simple procedure with which to convert the N_b-benzyl analogs into the natural N_b-methyl alkaloids. The anionic oxy-Cope rearrangement of 15 to provide 16 constitutes the first application of this concerted process in the synthesis of sarpagine/ajmaline alkaloids. Although the stereoselectivity of this rearrangement (N_b-benzyl series) is only 3:2, the conversion of 15 into 16 (Scheme VII) in 88% yield bodes well for this strategy in the N_b-H series. Further work in regard to an enantiospecific synthesis of ajmaline (5) will be reported in due course.

Experimental Section

The experimental details are analogous to those previously published.[16,21] The N_b-benzyl tetracyclic ketone 12 was prepared according to the literature procedure[21] with $[\alpha]^{28}_D = -201°$, c = 0.62, $CHCl_3$ (lit.[21] $[\alpha]^{22}_D = -203°$, c = 0.50, $CHCl_3$), and the α,β-unsaturated aldehyde (−)-8 was prepared by the method of Zhang[19b] with $[\alpha]^{24}_D = -310.5°$ (c = 0.55, $CHCl_3$).

Grignard Addition to the α,β-Unsaturated Aldehyde 8 To Provide (6*S*,10*S*)-5-Methyl-9-(2′-ethyl-1′-hydroxy-3′-butenyl)-12-benzyl-6,7,10,11-tetrahydro-6,10-imino-5*H*-cyclooct[*b*]indole (13). To a two-neck flask which contained magnesium turnings (20 mg) and iodine (one crystal) in dry ether (0.5 mL) was added 1-bromo-2-pentene (0.1 mL, 126 mg, 0.85 mmol) in dry ether (0.5 mL) dropwise via a syringe under an atmosphere of argon. The color of I_2 disappeared upon addition of the bromide, and the mixture which resulted was allowed to stir at 23 °C for 4 h. The Grignard reagent which was prepared was cooled to −78 °C in a cooling bath of dry ice/EtOAc. The α,β-unsaturated aldehyde 8 (60 mg, 0.175 mmol) in dry THF (2 mL) was added dropwise to the above mixture, and the temperature was allowed to warm to 23 °C and the mixture stirred for 16 h. The reaction was quenched by careful addition of aqueous HCl (1 N, 5 mL) and brought to alkaline pH with NH_4OH. The cloudy mixture was extracted with EtOAc (3 × 50 mL). The organic layers were washed with H_2O and brine, dried ($MgSO_4$), and concentrated to give a crude oil which was purified by flash chromatography (EtOAc/hexane, 27:75) to provide the allylic alcohol 13 (52 mg, 72%): ^{1}H-NMR (250 MHz, $CDCl_3$) δ 0.70–0.95 (3 H, m), 1.40 (2 H, m), 1.95–2.25 (2 H, m), 2.75 (1 H, m), 3.05 (2 H, m), 3.55 (3 H, m), 3.75 (2 H, m), 3.89 (1 H, m), 4.05 (1 H, m), 4.80–5.70 (5 H, m), 7.05–7.50 (9 H, m); ^{13}C-NMR (DEPT, 125.76 MHz, $CDCl_3$) δ 10–12 (2 × CH_3), 22–25 (5 × CH_2), 29.5 (CH_3), 29.7–30.5 (3 × CH_2), 48–54 (8 × CH), 75–80 (3 × CH), 108.52 (CH), 108.55 (CH), 108.60 (CH), 116.57 (CH_2), 117.82 (CH_2), 117.89 (CH), 118.10 (CH), 118.19 (CH), 118.49 (CH_2), 118.68 (CH), 118.72 (CH), 118.73 (CH), 119.44 (CH), 120.73 (CH), 122.35 (CH), 122.81 (CH), 126.84 (CH), 126.88 (CH), 126.89 (CH), 128.13 (CH), 128.18 (CH), 128.51 (CH), 128.53 (CH), 128.61 (CH), 138.08 (CH), 138.71 (CH), 139.70 (CH); mass spectrum (EI 70 eV) m/e (rel inten) 412 (M^+, 5.2%), 343 (100%).

***trans*-4-Hepten-3-ol.** Ethylmagnesium chloride (24 mL, 2 M in ethyl ether) was placed in a 250-mL round bottom flask under an atmosphere of argon and cooled to 0 °C with an ice bath. To this solution was added *trans*-2-pentenal (4.0 g, 47.6 mmol) in dry THF (5 mL) dropwise via syringe over a period of 30 min. The mixture was allowed to warm to 25 °C and stirred for 2 h. The reaction progress was monitored by GC (t_R = 4.88 min under the conditions: oven temperature, 40 °C; initial time, 2 min; oven temperature program rate 5 °C/min; final oven temperature, 150 °C). The reaction was quenched by addition of an aqueous solution of HCl (1 N), which was followed by addition of ethyl ether (50 mL) to the dilute solution. The organic layer was separated and the aqueous layer was extracted with ether (4 × 100 mL). The combined organic layers were washed with H_2O and brine and dried ($MgSO_4$). The solvent was removed by distillation and the residue was distilled under vacuum [water aspirator (about 230 mmHg)] at 89 °C to provide pure *trans*-4-hepten-3-ol (4.84 g, 89%): bp 153–155 °C (lit.[47] 154–156 °C).

***trans*-5-Bromo-3-heptene (14).** trans-4-Hepten-3-ol (2.0 g, 17.5 mmol) was dissolved in dry ethyl ether (15 mL) and cooled to 0 °C with an ice-bath. Phosphorus tribromide (0.85 mL, 8.97 mmol) was then injected into the above solution dropwise via a syringe under argon. The mixture was stirred at 0 °C and the reaction progress was monitored by GC (t_R = 7.47 min, oven temperature, 40 °C; initial time, 2 min; oven temperature program rate, 5 °C/min; oven temperature final value, 150 °C). The reaction was complete after stirring at 0 °C for 2 h. The reaction was quenched by careful addition of methanol (0.5 mL) at 0 °C. The mixture was then poured into ice–H_2O. The ethereal layer was separated and diluted with ether (50 mL). The combined organic layers were washed quickly with ice-cold saturated aqueous $NaHCO_3$ solution and brine and dried ($MgSO_4$). The solvent was removed under reduced pressure at a temperature lower than 20 °C to provide the bromide (2.95 g, 95%) 14: bp 36.5 °C (14.5 mmHg); ^{1}H-NMR (250 MHz, $CDCl_3$) δ 0.97 (3 H, t, J = 7.30 Hz), 0.98 (3 H, t, J = 7.50 Hz), 1.90 (2 H, m), 2.05 (2 H, m), 4.45 (1 H, m), 5.66 (2 H, m); mass spectrum (EI) m/e (rel inten) 97 (M^+ − Br, 27.3%).

Grignard Addition of *trans*-5-Bromo-3-heptene (14) to the α,β-Unsaturated Aldehyde (−)-8 To Provide (−)-(6*S*,10*S*)-5-Methyl-9-(2′-ethyl-1′-hydroxy-3′-hexenyl)-12-benzyl-6,7,10,11-tetrahydro-6,10-imino-5*H*-cyclooct[*b*]indole (15) and (−)-(6*S*,10*S*)-5-Methyl-8-(1′-ethyl-2′-pentenyl)-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole-9-carboxaldehydes 16a–d. The α,β-unsaturated aldehyde (−)-8 (3.5 g 10.2 mmol) was dissolved in dry THF (25 mL) and added to a 100-mL round bottom flask which contained magnesium turnings (freshly cut into small pieces, 1.7 g) under an atmosphere of argon. The mixture which resulted was then cooled to 0 °C in an ice/salt bath. The 5-bromo-3-heptene (14) (freshly prepared, 4.2 g, 23.7 mmol) was diluted with dry THF (5 mL), and added dropwise to the above mixture via a double-ended needle. The mixture was stirred at 0 °C for an additional 2 h. The reaction solution was poured into ice-cold water (25 mL). Solid ammonium chloride (20 g) was then added, and this was followed by addition of ethyl acetate (100 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 150 mL). The combined organic layers were washed with brine (2 × 50 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue which resulted was chromatographed on silica gel (gradient elution with hexane, ethyl acetate/hexane, 7:93, 10:90, 15:85, 25:75, 35:65) to provide the 1,4-addition products 16a–d (combined yield, 1.764 g, 39%), 1,2-addition products 15 (combined yield, 1.879 g, 42%), and the recovered α,β-unsaturated aldehyde (0.350 g). The combined yield for 1,4- and 1,2-addition products was 90% based on recovered starting material.

15: FTIR (KBr) 3439 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.78–1.05 (6 H, m), 1.15 (1 H, m), 1.42 (1 H, m), 1.75 (1 H, m), 1.95–2.15 (5 H, m), 2.65–2.80 (1 H, m), 3.02–3.20 (1 H, m), 3.55–3.60 (3 H, 4 s), 3.67 (1 H, m), 3.70–3.80 (2 H, m), 4.05 (1 H, m), 5.03–5.75 (3 H, m), 7.10–7.50 (9 H, m); ^{13}C-NMR (125.75 MHz, $CDCl_3$) δ 11.81, 12.00, 13.92, 13.96, 14.13, 14.25, 21.19, 21.57, 22.75, 23.08, 23.18, 24.05, 24.47, 25.71, 25.73, 25.78, 29.21, 29.23, 29.56, 30.13, 30.23, 30.24, 43.94, 45.43, 48.86, 49.13, 49.30, 49.76, 50.90, 51.42, 51.87, 52.84, 53.40, 56.66, 75.67, 75.93, 78.26, 78.40, 105.40, 105.44, 108.56, 108.65, 117.98, 118.03, 118.27, 118.28, 118.72, 118.78, 119.56, 120.75, 120.79, 122.35, 122.61, 126.92, 126.94, 126.98, 127.24, 128.23, 128.57, 128.61, 128.64, 129.16, 129.88, 136.30, 136.51, 137.01, 137.08, 137.18, 139.24, 139.43, 139.48; mass spectrum (EI, 15 eV) m/e (rel inten) 440 (M^+, 9.9%), 343 (M^+ − C_7H_{13}, 100%). Anal. Calcd for $C_{30}H_{36}N_2O$: C, 81.82; H, 8.18; N, 6.36. Found: C, 82.38; H, 8.15; N, 6.97.

16a (640 mg): FTIR (KBr) 1718 cm^{-1}; ^{13}C-NMR (125.75 MHz, $CDCl_3$) δ 12.24, 14.24, 19.00, 25.72, 25.82, 29.00, 29.20, 32.22, 45.27,

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50.21, 52.15, 56.55, 57.24, 106.56, 108.87, 118.10, 118.91, 120.89, 126.50, 127.07, 128.08, 128.31, 128.67, 134.34, 135.61, 137.04, 138.93, 205.08; mass spectrum (EI, 15 eV) *m/e* (rel inten) 440 (M^+, 53.9%), 273 (100). Anal. Calcd for $C_{30}H_{36}N_2O$: C, 81.82; H, 8.18; N, 6.36. Found: C, 81.63; H, 8.05; N, 6.28.

16b (664 mg): FTIR (KBr) 1715 cm^{-1}; ^{13}C-NMR (125.75 MHz, $CDCl_3$) δ 15.69, 16.81, 21.92, 26.19, 28.20, 31.54, 34.80, 35.46, 50.42, 51.52, 54.93, 57.80, 57.99, 104.74, 107.22, 115.92, 116.73, 118.62, 123.83, 124.44, 125.62, 125.90, 127.67, 131.59, 132.30, 133.88, 135.66, 199.23; mass spectrum (EI, 15 eV) *m/e* (rel inten) 440 (M^+, 36.4%), 273 (100%). Anal. Calcd for $C_{30}H_{36}N_2O$: C, 81.82; H, 8.18; N, 6.36. Found: C, 81.93; H, 8.04; N, 6.68.

16c (150 mg): ^1H-NMR (500 MHz, $CDCl_3$) δ 0.68 (3 H, t, J = 7.22 Hz), 0.88 (3 H, t, J = 7.63 Hz), 0.96 (1 H, m), 1.50 (1 H, m), 1.91 (2 H, m), 2.03 (3 H, m), 2.45 (1 H, bs), 2.47 (1 H, d, J = 16.48 Hz), 3.33 (1 H, dd, J = 16.68, 7.42 Hz), 3.53 (3 H, s), 3.55 (1 H, d, J = 14.40 Hz), 3.59 (1 H, d, J = 14.37 Hz), 3.66 (1 H, m), 4.03 (1 H, bs), 4.71 (1 H, dd, J = 15.09, 9.43 Hz), 5.33 (1 H, dt, J = 15.18, 6.41 Hz), 7.14 (1 H, t, J = 7.23 Hz), 7.21 (1 H, t, J = 7.61 Hz), 7.28 (6 H, m), 7.53 (1 H, d, J = 6.94 Hz), 10.07 (1 H, d, J = 1.93 Hz); ^{13}C-NMR (125.75 MHz, $CDCl_3$) δ 11.45, 14.23, 22.00, 24.41, 25.56, 28.90, 32.56, 32.85, 45.97, 50.93, 54.15, 55.20, 57.80, 106.50, 108.98, 118.10, 118.90, 120.06, 126.60, 127.15, 128.31, 128.70, 131.50, 134.46, 135.45, 137.00, 138.98, 206.15; mass spectrum (EI, 15 eV) 440 (M^+, 29.4%), 273 (100%).

16d (310 mg): FTIR (KBr) 1722 cm^{-1}; ^{13}C-NMR (125.75 MHz, $CDCl_3$) δ 11.34, 14.09, 21.74, 25.43, 26.26, 28.64, 28.91, 33.06, 45.75, 49.20, 51.25, 54.40, 57.39, 105.29, 108.63, 117.93, 118.89, 121.00, 126.64, 127.11, 128.30, 128.63, 131.44, 133.39, 136.08, 137.00, 139.04, 205.14; mass spectrum (EI, 15 eV) *m/e* (rel inten) 440 (M^+, 40.1%), 273 (100%). Anal. Calcd for $C_{30}H_{36}N_2O$: C, 81.82; H, 8.18; N, 6.36. Found: C, 82.13; H, 8.11; N, 6.69.

Anionic Oxy-Cope Rearrangement To Convert (−)-(6*S*,10*S*)-5-Methyl-9-(2′-ethyl-1′-hydroxy-3′-hexenyl)-12-benzyl-6,7,10,11-tetrahydro-6,10-imino-5*H*-cyclooct[*b*]indole (15) into (−)-(6*S*,10*S*)-5-Methyl-8-(1′-ethyl-2′-pentenyl)-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole-9-carboxaldehydes 16a,b,d,e. A solution of allylic alcohol **15** (50 mg, 0.11 mmol) and 18-crown-6 ether (64 mg, 0.24 mmol) in dry dioxane (1 mL) was added to a suspension of KH (30 mg, 0.77 mmol) in dry dioxane (1 mL). The light yellow-colored mixture which resulted was stirred at room temperature for 2 h. Dry cumene (15 mL) was added and then the slurry was heated to reflux (oil bath temperature 160 °C) for 14 h. Analysis of the mixture by TLC indicated the presence of two new components and the disappearance of starting material. The reaction mixture was allowed to cool to room temperature, quenched by careful addition of methanol (1 mL), and then extracted with ethyl acetate (50 mL). The combined organic extracts were washed with water and brine, dried (K_2CO_3), and concentrated under reduced pressure. The residue which resulted was purified by preparative TLC (EtOAc/hexane, 2:8) to provide alkenic aldehydes **16a,b** from rearrangement from the bottom face (26.0 mg, 52%, **16b** as a major product) and alkenic aldehydes **16d,e** from rearrangement from the top face of the double bond (18.0 mg, 36%, **16e** as the major component). The combined yield for the rearrangement was 88%.

16e: ^1H-NMR (500 MHz, $CDCl_3$) δ 0.22 (3 H, t, J = 7.28 Hz), 0.86 (1 H, m), 0.87 (3 H, t, J = 6.39 Hz), 1.10 (1 H, m), 1.86 (4 H, m), 1.98 (1 H, m), 2.10 (1 H, m), 2.53 (1 H, bs), 2.58 (1 H, d, J = 16.44 Hz), 3.30 (1 H, dd, J = 16.45, 7.05 Hz), 3.58 (3 H, s), 3.65 (1 H, d, J = 13.44 Hz), 3.70 (1 H, d, J = 13.79 Hz), 3.74 (1 H, bs), 3.83 (1 H, bs), 4.71 (1 H, dd, J = 15.30, 7.05 Hz), 4.93 (1 H, dt, J = 15.22, 6.36 Hz), 7.12 (1 H, t, J = 7.32 Hz), 7.20 (1 H, t, J = 7.67 Hz), 7.28 (6 H, m), 7.50 (1 H, d, J = 7.76 Hz), 9.69 (1 H, s); ^{13}C-NMR (125.75 MHz, $CDCl_3$) δ 11.32, 14.14, 21.14, 25.05, 25.52, 27.66, 29.07, 33.14, 45.59, 49.35, 51.49, 55.04, 57.38, 106.29, 108.78, 117.99, 119.08, 121.11, 126.75, 127.12, 128.31, 128.64, 132.87, 134.66, 135.57, 137.21, 139.08, 205.49; mass spectrum (EI, 15 eV) *m/e* (rel inten) 440 (M^+, 45%).

Attempted Oxidative Cleavage of Alkenic Aldehyde 16 with OsO_4/$NaIO_4$ Which Provided the hemiacetal 20. The alkenic aldehyde **16** (20 mg) was dissolved in HOAc (80%, 2 mL). Solid osmium tetraoxide (3.4 mg) was added. The dark solution which resulted was stirred for an additional 2 h. Sodium periodate (2 × 8 mg) was added in two portions over an 8-h period. The mixture was stirred for 24 h. The solvent was evaporated under reduced pressure and the residue was dissolved in EtOAc (25 mL) and washed with aqueous $NaHCO_3$ solution (10%), H_2O, and brine, and dried (K_2CO_3). The oil was purified by flash chromatography to provide diastereomeric hemiacetals **20** (12 mg, 56%): ^1H-NMR (250 MHz, $CDCl_3$) δ 0.55 (CH_3, t), 0.65 (CH_3, t), 0.85–1.00 (m), 1.20–2.40 (m), 2.58 (d), 2.62 (d), 3.00–3.25 (m), 3.50–3.57 ($3CH_3$, 3 s), 3.50–4.10 (m), 4.67 (d), 4.95 (d), 5.50 (d), 7.10–7.40 (m), 7.50 (d), 7.65 (m); mass spectrum (EI, 70 eV) *m/e* (rel inten) 474 (M^+, 15.5%), 456 ($M^+ - H_2O$, 11.1%), 273 (100%).

(−)-(6*S*,10*S*)-5-Methyl-8-(1′-ethyl-2′-pentenyl)-9-[(hydroxyimino)methyl]-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole (21). The mixture of diastereomeric alkenic aldehydes (−)-**16** (**16c,d** as the major components, 200 mg, 0.45 mmol) was dissolved in absolute ethyl alcohol (10 mL), and hydroxylamine hydrochloride (200 mg) was added. The mixture which resulted was heated at reflux for 3 h under argon. Examination of the reaction mixture by TLC ($CHCl_3$/MeOH, 6:0.1) indicated the disappearance of starting aldehyde. The solution was then cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in EtOAc/saturated aqueous $NaHCO_3$. The aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with water and brine, dried (K_2CO_3), and concentrated under reduced pressure to provide a mixture of diastereomeric oximes **21** (201 mg, 97%): FTIR (KBr) 1616, cm^{-1}; ^1H-NMR (500 MHz, $CDCl_3$) δ (diastereomeric mixture with two major isomers) 0.69 (t, J = 7.25 Hz), 0.80 (t, J = 7.44 Hz), 0.82 (t, J = 7.56 Hz), 0.90–1.15 (m), 1.45 (m), 1.56 (m), 1.63 (m), 1.83 (m), 2.00 (m), 2.22 (m), 2.34 (d, J = 6.92 Hz), 2.50 (m), 3.18 (dd), 3.30 (m), 3.51 (s), 3.52 (s), 3.53–3.68 (m), 3.84 (m), 4.55–4.80 (m), 7.12 (m), 7.17–7.35 (m), 7.50 (d, J = 7.74 Hz), 7.69 (1 H, d, J = 7.85 Hz); ^{13}C-NMR (125.75 MHz, $CDCl_3$) δ 11.76, 11.89, 14.04, 14.07, 14.18, 14.22, 22.02, 22.52, 22.71, 25.49, 25.57, 25.99, 26.03, 26.06, 28.65, 28.92, 29.07, 36.57, 43.30, 45.72, 48.12, 48.38, 53.40, 54.44, 56.39, 56.85, 104.72, 108.58, 108.61, 108.87, 118.02, 118.07, 118.77, 120.68, 120.75, 120.80, 126.82, 126.86, 126.94, 128.27, 128.48, 128.64, 129.66, 129.69, 130.99, 133.33, 133.67, 133.91, 136.32, 137.05, 139.28, 139.39, 139.45, 156.08, 156.66; mass spectrum (EI, 15 eV) *m/e* (relative intensity) 455 (M^+, 9.3%), 273 (100%). This material was employed directly in the next experiment.

(−)-N_b-Benzylsuaveoline (23). The alkenic oxime **21** (180 mg, 0.397 mmol) was dissolved in freshly distilled THF (8 mL) which contained distilled pyridine (0.5 mL) and added to a cold solution of OsO_4 (112 mg, 0.437 mmol) in THF (2 mL) and pyridine (1.5 mL) at 0 °C under argon. The black solution which resulted was allowed to stir at 0 °C for an additional 3 h. An aqueous solution of $NaHSO_3$ (1.2 g, 4 mL) was added and the mixture was allowed to warm to room temperature and stirred for 4 h. The reaction mixture was diluted with ethyl acetate (25 mL). The organic layer was washed with water. The aqueous layers were extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with brine and dried (K_2CO_3). Removal of solvent under reduced pressure provided a crude material (185 mg). Flash chromatography with EtOAc/hexane (1:1.5) provided the starting oxime (45 mg) and with EtOAc/hexane (1.5:1) provided the desired diol oxime (110 mg, 76% based on recovered starting material): mass spectrum (EI, 15 eV) *m/e* (rel inten) 489 (M^+, 1.5%), 471 ($M^+ - H_2O$, 10.5%), 456 (9.5%), 273 (100%). The diol was not subjected to further characterization but used directly in the next step.

The diol oxime (110 mg, 0.22 mmol) was dissolved in methanol (6 mL) and cooled to 0 °C. Aqueous $NaIO_4$ solution (122 mg, 0.57 mmol in 3 mL of H_2O) was then added to the above solution. The reaction flask was covered by aluminum foil to omit light. The mixture was stirred at 0 °C for 10 h and then concentrated under reduced pressure. The residue was dissolved in ethyl acetate/water (25:5). The aqueous layer was extracted with EtOAc (3 × 25 mL). The organic layers were washed with water and brine and dried (K_2CO_3). Removal of solvent provided diastereomeric bisaldehydes **22** (95 mg, 77% from **21**): mass spectrum (EI, 15 eV) *m/e* (rel inten) 414 (M^+, 42.3%), 273 (100%), 249 (33.0%), 182 (60.5%), 170 (40.2%), 159 (37.8%).

The dialdehyde **22** (48 mg, 0.12 mmol) was dissolved in absolute ethanol (8 mL), and hydroxylamine hydrochloride (100 mg, 1.45 mmol) was added. The reaction mixture was heated to reflux

(oil bath temperature, 105 °C) for 21 h under an atmosphere of argon. The brown solution which resulted was allowed to cool to room temperature and the solvent was removed under reduced pressure. The oil which resulted was dissolved in EtOAc/aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with water, brine, and dried (K_2CO_3). The solvent was removed under reduced pressure and the crude material was chromatographed (EtOAc/hexane, 8:2) to provide pure N_b-benzylsuaveoline (**23**) (32 mg, 70%): $[\alpha]^{24}_D$ = −126.67° (*c* = 0.33, $CHCl_3$); ^{13}C-NMR (125.75 MHz, $CDCl_3$) δ 13.80 (1 C, q), 22.92 (1 C, t), 25.97 (1 C, t), 29.41 (1 C, q), 31.16 (1 C, t), 48.42 (1 C, d), 53.35 (1 C, d), 56.56 (1 C, t), 104.49 (1 C, s), 108.79 (1 C, d), 118.21 (1 C, d), 119.09 (1 C, d), 121.29 (1 C, d), 126.83 (1 C, s), 127.28 (1 C, d), 128.45 (2 C, d), 128.75 (2 C, d), 134.48 (1 C, s), 135.19 (1 C, s), 136.81 (1 C, s), 137.24 (1 C, s), 138.54 (1 C, s), 139.80 (1 C, s), 146.33 (1 C, d), 146.81 (1 C, d); mass spectrum (EI, 15 eV) *m/e* (rel inten) 393 (M^+, 100%), 273 (66.5%). The ^{1}H-NMR spectrum[48] of **23** is in complete agreement with that reported for (±)-N_b-benzylsuaveoline by Trudell.[16]

(−)-N_b-Methylsuaveoline (2). (−)-N_b-Benzylsuaveoline (**23**) (9.0 mg, 0.023 mmol) was added to a slurry of Pd/C (10%, 3.0 mg) in MeOH (Aldrich, 99.99%, 2.5 mL) in a 5-mL flask. The system was maintained under vacuum for 1 min and then flushed with H_2. This process was repeated three times. The mixture was stirred under an atmosphere of H_2 (1 atm) for 5 h. Analysis by TLC (EtOH/$CHCl_3$, 0.7:9.3, basified with NH_3) indicated no reaction had occurred. Additional quantities of catalyst (three portions, 4 mg each) were added over a period of 2 d. Reaction progress was monitored by TLC which indicated a decrease and eventual disappearance of the starting **23** and an increase of a new component. The catalyst was removed by filtration and then washed with methanol (10 × 5 mL). The methanol was removed under reduced pressure, and the residue was dissolved in chloroform (10 mL). The solution which resulted was dried over K_2CO_3 to reverse salt formation and then was passed through a small wash column (pipette size, silica gel). The column was eluted with EtOH/$CHCl_3$ (15:85). The solvent was removed under reduced pressure to provide pure N_b-methylsuaveoline (**2**) (7.1 mg, 98%): $[\alpha]^{25}_D$ = −89.25° (*c* = 0.37, $CHCl_3$), lit.[1,2] $[\alpha]_D$ = −93° (*c* = 0.89, $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.14 (3 H, t, *J* = 7.57 Hz), 2.47 (2 H, q, *J* = 7.55 Hz), 2.58 (3 H, s), 2.72 (1 H, d, *J* = 15.75 Hz), 2.78 (1 H, d, *J* = 16.94 Hz), 3.32 (1 H, dd, *J* = 16.95, 6.03 Hz), 3.43 (1 H, dd, *J* = 15.82, 5.51 Hz), 3.70 (3 H, s), 4.26 (1 H, d, *J* = 5.80 Hz), 4.29 (1 H, d, *J* = 5.36 Hz), 7.03 (1 H, t, *J* = 7.78, 7.37 Hz), 7.15 (1 H, dt, *J* = 8.10, 7.03, 0.90 Hz), 7.25 (1 H, d, *J* = 7.32 Hz), 7.40 (1 H, d, *J* = 7.77 Hz), 8.12 (1 H, s), 8.30 (1 H, s); ^{13}C-NMR (125.75 MHz, $CDCl_3$) δ 13.82 (1 C, q), 22.91 (1 C, t), 25.46 (1 C, t), 29.42 (1 C, q), 30.68 (1 C, t), 40.69 (1 C, q), 51.13 (1 C, d), 54.49 (1 C, d), 104.05 (1 C, s), 108.75 (1 C, d), 118.20 (1 C, d), 119.06 (1 C, d), 121.29 (1 C, d), 126.73 (1 C, s), 134.09 (1 C, s), 134.80 (1 C, s), 136.81 (1 C, s), 137.23 (1 C, s), 139.20 (1 C, s), 146.30 (1 C, d), 146.87 (1 C, d); mass spectrum (EI, 15 eV) *m/e* (rel inten) 317 (M^+, 66.9%), 197 (100%). The ^{1}H-NMR spectrum of (−)-**2** is in complete agreement with that reported for N_b-methylsuaveoline by Potier[1] and by Trudell.[16]

(−)-Suaveoline (1). (−)-N_b-Benzylsuaveoline (**23**) (8.0 mg, 0.02 mmol) was dissolved in ethanolic HCl (15%, 1 mL). The solution which resulted was allowed to stand at room temperature for 1 h. Analysis by TLC (EtOH/$CHCl_3$, 0.6:9.4) indicated salt formation. The ethanol was removed under reduced pressure. The residue was flashed with ethanol (2 × 2 mL) under reduced pressure to remove the excess HCl. The residue was then dissolved in absolute ethanol (2.0 mL) in a vial. Palladium on activated carbon (10%, 6 mg) was added. The mixture which resulted was allowed to stir at room temperature under an atmosphere of hydrogen for 2 h. Analysis of the reaction mixture by TLC (plate was exposed to NH_3 vapors) indicated the absence of starting material. The catalyst was removed by filtration and was washed with ethanol (5 × 5 mL). The solvent was removed under reduced pressure. The residue was dissolved in a mixture of $CHCl_3$/aqueous NH_4OH (10:2). The organic layer was dried (K_2CO_3) and and it was passed through a small wash column (pipette, silica gel). Additional solvent ($CHCl_3$/EtOH, 9:1) was employed to elute the compound from the column. Removal of solvent under reduced pressure provided suaveoline (**1**) (5.9 mg, 96%). For the purpose of obtaining a sample of high purity for the optical rotation, sauveoline (**1**) was repurified by preparative TLC (EtOH/$CHCl_3$, 7:93, developed twice). Suaveoline was removed from the silica gel with EtOH/$CHCl_3$ (15:85) to provide a homogeneous (TLC, NMR) sample: $[\alpha]^{25}_D$ = −9.33° (*c* = 0.30, $CHCl_3$). lit.[1,2] $[\alpha]_D$ = 0 ± 2°, (*c* = 1.0, $CHCl_3$); ^{13}C-NMR (125.75 MHz, C_6D_6), δ 13.86 (1 C, q), 22.95 (1 C, t), 28.61 (1 C, q), 31.36 (1 C, t), 31.55 (1 C, t), 44.57 (1 C, d), 48.58 (1 C, d), 105.53 (1 C, s), 108.83 (1 C, d), 118.70 (1 C, d), 119.48 (1 C, d), 121.57 (1 C, d), 135.20 (1 C, s), 136.64 (1 C, s), 136.70 (1 C, s), 137.52 (1 C, s), 139.37 (1 C, s), 147.03 (1 C, d), 147.54 (1 C, d); mass spectrum (EI, 15 eV) *m/e* (rel inten) 303 (M^+, 66.5%), 183 (100%). The proton NMR spectrum (see ref 48 supplementary material for details) of (−)-**1** was identical to that reported by Potier[1] and Trudell.[16]

(−)-(6*S*,8*S*,9*S*,10*S*,1′*S*)-5-Methyl-8-(1′-ethyl-2′-pentenyl)-9-(1′,3′-dioxolan-2′-yl)-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole (24b). The alkenic aldehyde **16b** (500 mg, 1.13 mmol) was dissolved in benzene (5 mL) and added to a solution of ethylene glycol (543 mg, 8.75 mmol) in benzene (15 mL) which contained *p*TSA (217 mg, 1.22 mmol). The mixture which resulted was heated to reflux for 3 h with removal of water via a Dean–Stark trap. Analysis of the mixture by TLC (EtOH/$CHCl_3$, 5:95) indicated the absence of starting material at this time. The mixture was allowed to cool to room temperature and poured into aqueous NH_4OH (10%, 30 mL). The aqueous layer was separated and then extracted with ethyl acetate (3 × 100 mL). The combined benzene and ethyl acetate layers were washed with water (2 × 50 mL) and brine and dried (K_2CO_3). The solvent was removed under reduced pressure to provide an oil. The oil was chromatographed (short wash column, silica gel, hexane/EtOAc, 8:2) to provide the oily ethylene acetal **24b** (510 mg, 92%): ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.80 (3 H, t, *J* = 7.25 Hz), 0.83 (3 H, t, *J* = 7.47 Hz), 1.07 (1 H, m), 1.60 (3 H, m), 1.77 (1 H, m), 1.86 (2 H, m), 2.15 (1 H, t, *J* = 9.35 Hz), 2.35 (1 H, dt, *J* = 11.50, 4.68 Hz), 2.77 (1 H, d, *J* = 16.88 Hz), 3.04 (1 H, dd, *J* = 16.87, 7.1 Hz), 3.48 (3 H, s), 3.53 (1 H, d, *J* = 13.67 Hz), 3.58 (1 H, dd, *J* = 6.77, 4.57 Hz), 3.67 (1 H, d, *J* = 13.66 Hz), 3.79 (1 H, dd, *J* = 12.86, 6.43 Hz), 3.86 (2 H, m), 3.93 (1 H, dd, *J* = 12.16, 6.84 Hz), 3.99 (1 H, dd, *J* = 12.75, 6.37 Hz), 4.77 (1 H, d, *J* = 5.15 Hz), 5.07 (1 H, dd, *J* = 15.37, 7.94 Hz), 5.22 (1 H, dt, *J* = 15.33, 6.24 Hz), 7.11 (1 H, t, *J* = 7.52 Hz), 7.18 (1 H, t, *J* = 7.22 Hz), 7.28 (6 H, m), 7.53 (1 H, d, *J* = 7.66 Hz); ^{13}C-NMR (125.75 MHz, $CDCl_3$) 11.16, 12.64, 18.39, 20.44, 25.62, 28.83, 30.76, 34.87, 43.67, 45.95, 50.10, 53.42, 57.32, 63.87, 64.88, 106.02, 107.42, 108.71, 118.05, 118.51, 120.38, 126.72, 126.78, 128.14, 128.61, 131.51, 132.35, 135.14, 137.01, 139.77; mass spectrum (EI, 15 eV) *m/e* (rel inten) 484 (M^+, 100%). Anal. Calcd for $C_{32}H_{40}N_2O_2$: C, 79.33; H, 8.26; N, 5.78. Found: C, 78.91; H, 8.57; N, 5.61.

(6*S*,8*S*,9*S*,10*S*,1′*R*)-5-Methyl-8-(1′-ethyl-2′-pentenyl)-9-(1′,3′-dioxolan-2′-yl)-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole (24a). Alkenic aldehyde **16a** was employed to prepare the ethylene acetal **24a** in 89% yield by the same procedure described above for the preparation of **24b**.

24a: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.64 (3 H, t, *J* = 7.32 Hz), 1.00 (1 H, m), 1.01 (3 H, t, *J* = 7.42 Hz), 1.17 (1 H, m), 1.60 (1 H, dt, *J* = 12.19, 3.21 Hz), 1.68 (1 H, tt, *J* = 12.15, 3.31 Hz), 1.89 (1 H, m), 2.07 (2 H, m), 2.19 (1 H, m), 2.27 (1 H, dt, *J* = 11.83, 4.60 Hz), 2.87 (1 H, d, *J* = 16.76 Hz), 3.00 (1 H, dd, *J* = 16.77, 6.83 Hz), 3.50 (3 H, s), 3.55 (1 H, d, *J* = 13.73 Hz), 3.72 (1 H, d, *J* = 13.72 Hz), 3.80 (1 H, m), 3.87 (2 H, m), 3.97 (3 H, m), 4.91 (1 H, d, *J* = 4.73 Hz), 5.28 (1 H, dd, *J* = 15.42, 8.91 Hz), 5.45 (1 H, dt, *J* = 15.33, 6.34 Hz), 7.10 (1 H, t, *J* = 7.58 Hz), 7.18 (1 H, t, *J* = 7.69 Hz), 7.28 (6 H, m), 7.52 (1 H, d, *J* = 7.75 Hz); ^{13}C-NMR (125.75 MHz, $CDCl_3$) δ 12.32, 14.40, 18.39, 25.87, 26.06, 28.91, 30.25, 33.91, 43.42, 45.40, 49.91, 52.81, 57.23, 63.90, 64.80, 105.12, 107.64, 108.69, 118.07, 118.51, 120.34, 126.70, 126.78, 128.14, 128.64, 128.88, 134.38, 134.91, 137.03, 139.75; mass spectrum (EI, 15 eV) *m/e* (rel inten) 484 (M^+, 79.7%), 182 (100%). Anal. Calcd for $C_{32}H_{40}N_2O_2 \cdot {}^1/_2H_2O$: C, 77.89; H, 8.31; N, 5.68. Found: C, 77.74; H, 8.40; N, 5.46.

(6*S*,8*S*,9*S*,10*S*,1′*S*)-5-Methyl-8-(1′-ethyl-2′-oxoethyl)-9-(1′,3′-dioxolan-2′-yl)-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole (25b). Alkenic ethylene acetal **24b** (180

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mg, 0.37 mmol) was dissolved in dry THF (8 mL) and pyridine (freshly distilled, 0.7 mL) and added to a lightly yellow-colored solution of OsO_4 (95 mg, 0.37 mmol) in dry THF (5 mL) which contained freshly distilled pyridine (1 mL) at 0 °C. The black-colored mixture which resulted was stirred at 0 °C for 8 h under argon. Aqueous sodium bisulfite solution (1.5 g dissolved in 6 mL of H_2O) was then added and the slurry was stirred at room temperature for 2 h. The mixture was diluted with ethyl acetate (20 mL) and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (5 × 50 mL). The combined organic layers were washed with brine (2 × 30 mL), dried (K_2CO_3), and concentrated under reduced pressure to provide the crude product as a lightly black-colored oil. The oil was chromatographed to provide an initial fraction as starting material (18 mg) with ethyl acetate/hexane (20:80) and to provide the desired diol (165 mg, 86%, it was 95%, based on the recovered starting material) with EtOAc/hexane (35:65) [R_f = 0.49 (EtOAc/hexane, 7:3)]. Analysis of both the ^{1}H-NMR and ^{13}C-NMR spectra indicated the presence of two isomers: ^{1}H-NMR (500 MHz, $CDCl_3$) δ major isomer (75% by ^{1}H-NMR) 0.53 (3 H, t, J = 7.31 Hz), 0.89 (1 H, m), 0.92 (3 H, t, J = 7.25 Hz), 3.48 (3 H, s), 4.71 (1 H, d, J = 4.31 Hz), 7.07 (1 H, t, J = 7.25 Hz), 7.15 (1 H, t, J = 8.15 Hz), 7.28 (6 H, m), 7.49 (1 H, d, J = 7.59 Hz); minor isomer (25% by ^{1}H-NMR) 0.58 (3 H, t, J = 7.46 Hz), 0.99 (3 H, t, J = 7.34 Hz), 3.45 (3 H, s), 4.81 (1 H, d, J = 3.70 Hz), other signals overlapped with those of the major isomer; ^{13}C-NMR (125.75 MHz, $CDCl_3$) δ major isomer 9.47, 12.61, 18.23, 18.26, 25.88, 28.96, 29.37, 32.16, 40.06, 45.60, 50.27, 53.69, 57.40, 63.67, 64.91, 74.33, 74.40, 105.99, 107.49, 108.73, 117.96, 118.59, 120.52, 126.59, 126.75, 128.17, 128.58, 134.93, 137.08, 139.70; minor isomer 9.98, 14.87, 20.18, 26.06, 28.92, 31.16, 31.80, 41.61, 45.32, 50.15, 53.45, 63.57, 65.01, 72.94, 75.91, 105.77, 107.01, 108.67, 118.06, 118.69, 120.69, 126.84, other signals overlapped with those of the major isomer; mass spectrum (EI, 15 eV) m/e (rel inten) 518 (M^+, 100%) 273 (46.7%), 224 (78.2%). Both diols, without further separation, were employed directly for the sodium periodate oxidative cleavage of the *cis*-diol function.

The mixture of diols (62 mg, 0.12 mmol) was dissolved in distilled methanol (3 mL) in a roundbottom flask (10 mL) which was coated with aluminum foil to exclude light. The solution which resulted was cooled to 0 °C, and an aqueous solution of $NaIO_4$ (70 mg, 0.33 mmol, in 2 mL of H_2O) was added to the chilled solution. The mixture was stirred at 0 °C for 16 h. Examination of the mixture by TLC (EtOAc/hexane, 1:1) indicated the presence of a new component (R_f = 0.71) which was active to 2,4-DNP spray reagent, and starting material had disappeared. Methanol was removed under reduced pressure, and the residue which resulted was dissolved in EtOAc/water (2:1). The two layers were separated and the aqueous layer was extracted with ethyl acetate (4 × 25 mL). The combined organic layers were washed with water and brine and dried (K_2CO_3). The solvent was removed under reduced pressure to provide the acetal aldehyde **25b** (53 mg, 97%): FTIR (KBr) 1722 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.87 (3 H, t, J = 7.33 Hz), 1.24 (1 H, m), 1.47 (1 H, m), 1.60 (1 H, m), 1.79 (1 H, dt, J = 12.61, 4.05 Hz), 2.21 (1 H, m), 2.36 (1 H, dt, J = 11.84, 4.90 Hz), 2.60 (1 H, bd, J = 10.48 Hz), 2.79 (1 H, d, J = 17.02 Hz), 3.07 (1 H, dd, J = 16.97, 7.06 Hz), 3.44 (3 H, s), 3.53 (1 H, d, J = 13.60 Hz), 3.57 (1 H, dd, J = 6.77, 4.53 Hz), 3.67 (1 H, d, J = 13.60 Hz), 3.80 (1 H, dd, J = 12.67, 6.32 Hz), 3.85 (2 H, m), 3.92 (1 H, dd, J = 12.09, 6.85 Hz), 3.98 (1 H, dd, J = 12.70, 6.53 Hz), 4.74 (1 H, d, J = 5.08 Hz), 7.11 (1 H, t, J = 7.47 Hz), 7.19 (1 H, t, J = 7.80 Hz), 7.27 (6 H, m), 7.53 (1 H, d, J = 7.70 Hz), 9.36 (1 H, s); ^{13}C-NMR (125.75 MHz, $CDCl_3$) δ 13.00, 15.85, 18.17, 28.90, 28.97, 31.93, 45.86, 49.69, 53.55, 54.77, 57.32, 63.78, 65.00, 105.76,, 107.31, 108.96, 118.09, 118.76, 120.80, 126.56, 126.92, 128.24, 128.60, 134.31, 137.09, 139.32, 205.19; mass spectrum (EI, 15 eV) m/e (rel inten) 458 (M^+, 92.3%), 273 (52.3%), 182 (100%). Anal. Calcd for $C_{29}H_{34}N_2O_3 \cdot {}^1/_2H_2O$: C, 74.52; H, 7.49; N, 6.00. Found: C, 74.88; H, 7.60; N, 5.92.

When the alkenic acetal **24b** was treated with OsO_4 (1.3 equiv in three portions over an 8-h period) for 16 h at 0 °C, the above described sequence provided the desired aldehyde **25b** and the undesired oxindole **26** in 90% combined yield in a ratio of 1:1. They were separated by flash chromatography (EtOAc/hexane, 3:7).

26: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.00 (3 H, t, J = 7.33 Hz), 1.20 (1 H, m), 1.51 (1 H, m), 1.71 (1 H, m), 1.92 (1 H, m), 2.17 (1 H, dd, J = 13.41, 7.50 Hz), 2.46 (1 H, ddd, J = 11.66, 5.05, 2.85 Hz), 2.58 (1 H, d, J = 13.42 Hz), 2.84 (1 H, bd, J = 10.03 Hz), 3.14 (3 H, s), 3.74 (3 H, m), 3.85 (3 H, m), 3.98 (2 H, m), 4.79 (1 H, d J = 5.13 Hz), 6.71 (1 H, t, J = 7.66 Hz), 6.99 (1 H, t, J = 7.09 Hz), 7.19 (2 H, m), 7.28 (2 H, t, J = 7.36 Hz), 7.37 (2 H, d, J = 7.23 Hz), 7.44 (1 H, d, J = 7.05 Hz), 9.84 (1 H, s); ^{13}C-NMR (125.75 MHz, $CDCl_3$) δ 13.42, 15.70, 21.10, 26.22, 29.67, 34.96, 37.66, 50.56, 54.89, 56.53, 57.13, 63.84, 64.99, 65.80, 106.64, 107.03, 122.44, 123.76, 127.05, 127.42, 128.28, 128.97, 138.07, 138.56, 141.91, 177.81, 205.56; mass spectrum (EI, 15 eV) m/e (rel inten) 474 (M^+, 33.0%), 170 (100%).

(−)-(6*S*,8*S*,9*S*,10*S*,1′*R*)-5-Methyl-8-(1′-ethyl-2′-oxoethyl)-9-(1′,3′-dioxolan-2′-yl)-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole (25a). Alkenic ethylene acetal (−)-**24a** was employed to prepare the acetal aldehyde (−)-**25a** by the same procedure as employed for **25b** described above. The yields for the corresponding diol (note, only one isomer) and the aldehyde were 92 and 93%, respectively.

Diol: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.38 (3 H, t, J = 7.09 Hz), 0.81 (1 H, m), 0.93 (3 H, t, J = 7.26 Hz), 1.00 (1 H, m), 1.17 (1 H, m), 1.60 (4 H, m), 1.87 (2 H, m), 2.10 (1 H, m), 2.68 (1 H, d, J = 16.92 Hz), 2.87 (1 H, m), 3.04 (1 H, dd, J = 16.86, 7.06 Hz), 3.15 (1 H, m), 3.31 (1 H, d, J = 9.56 Hz), 3.41 (1 H, m), 3.51 (3 H, s), 3.54 (1 H, d, J = 13.79 Hz), 3.68 (1 H, d, J = 13.69 Hz), 3.82 (1 H, m), 3.90 (1 H, dd, J = 8.01, 1.87 Hz), 3.95 (1 H, bs), 4.01 (2 H, bs), 4.74 (1 H, d, J = 5.01 Hz), 7.09 (1 H, t, J = 7.29 Hz), 7.17 (1 H, t, J = 7.82 Hz), 7.28 (6 H, m), 7.50 (1 H, d, J = 7.99 Hz); ^{13}C-NMR (125.75 MHz, $CDCl_3$) δ 10.48, 12.51, 14.19, 18.14, 22.46, 27.46, 28.93, 30.80, 40.73, 48.35, 50.49, 54.51, 57.50, 63.82, 64.99, 73.13, 75.03, 106.86, 107.76, 108.73, 118.04, 118.61, 120.53, 126.60, 126.77, 128.16, 128.66, 134.91, 137.05, 139.65; mass spectrum (EI, 15 eV) m/e (rel inten) 518 (M^+, 98.5%), 273 (49.3%), 224 (100%).

25a: FTIR (KBr) 1715 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.78 (3 H, t, J = 7.33 Hz), 1.12 (1 H, m), 1.71 (1 H, dt, J = 12.12, 3.92 Hz), 1.79 (1 H, m), 1.95 (1 H, m), 2.04 (1 H, m), 2.52 (1 H, m), 2.58 (1 H, m), 2.84 (1 H, d, J = 16.96 Hz), 3.11 (1 H, dd, J = 16.96, 6.96 Hz), 3.54 (3 H, s), 3.60 (1 H, d, J = 13.62 Hz), 3.62 (1 H, m), 3.74 (1 H, d, J = 13.61 Hz), 3.82–4.01 (5 H, m), 4.85 (1 H, d, J = 5.29 Hz), 7.17 (1 H, t, J = 7.30 Hz), 7.24 (1 H, t, J = 7.85 Hz), 7.32 (6 H, m), 7.59 (1 H, d, J = 7.71 Hz), 9.92 (1 H, s); ^{13}C-NMR (125.75 MHz, $CDCl_3$) δ 12.79, 17.93, 19.59, 28.83, 31.86, 32.38, 46.30, 49.77, 53.37, 53.43, 57.14, 63.68, 64.81, 105.51, 107.38, 108.76, 118.01, 118.66, 120.67, 126.42, 126.81, 128.14, 128.50, 133.95, 136.98, 139.23, 206.50; mass spectrum (EI, 15 eV) m/e (rel inten) 458 (M^+, 72.1%), 273 (50.2%), 182 (100%). This material was employed directly in the next experiment.

Equilibration of (−)-(6*S*,8*S*,9*S*,10*S*,1′*R*)-5-Methyl-8-(1′-ethyl-2′-oxoethyl)-9-(1′,3′-dioxolan-2′-yl)-12-benzyl-6,7,8,9,-10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole (25a) to (−)-(6*S*,8*S*,9*S*,10*S*,1′*S*)-5-Methyl-8-(1′-ethyl-2′-oxoethyl)-9-(1′,3′-dioxolan-2′-yl)-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole (25b). Sodium methoxide was freshly prepared by addition of metallic sodium (20 mg) to dry methanol (3 mL) which was followed by stirring at room temperature until the sodium dissolved (20 min). Acetal aldehyde **25a** (5 mg) in THF (1 mL) was added to the above solution. The mixture was allowed to stir at room temperature for 2 d. Analysis of the reaction mixture by TLC (EtOAc/hexane, 2:8) indicated the appearance of two components which were active to the 2,4-DNP spray reagent. Direct comparison with authentic samples (mixed TLC) suggested the two aldehydes were **25b** (R_f = 0.39) and **25a** (R_f = 0.30). The reaction mixture was worked up by addition of saturated aqueous NH_4Cl solution. Methanol was removed under reduced pressure. The residue was dissolved in EtOAc and washed with H_2O and brine and dried (K_2CO_3). The solvent was removed under reduced pressure to provide a mixture of aldehydes (4.9 mg, 98%). Integration of the two aldehydic signals of the ^{1}H-NMR spectrum of the mixture indicated the two aldehydes (**25b**/**25a**) were present in a 1:1 ratio. The aldehydes **25a** and **25b** could be separated by flash chromatography on silica gel (EtOAc/hexane, 1.5:8.5).

(−)-(6*S*,8*S*,9*S*,10*S*,1′*S*)-5-Methyl-8-(1′-ethyl-2′-hydroxyethyl)-9-(1′,3′-dioxolan-2′-yl)-12-benzyl-6,7,8,9,10,11-hexahydro-

6,10-imino-5*H*-cyclooct[*b*]indole (27). Alkenic aldehyde (-)-(*S*)-**25b** (45 mg, 0.098 mmol) was dissolved in anhydrous ethyl alcohol (2 mL) and cooled to 0 °C. Sodium borohydride (5.0 mg, 0.13 mmol) was added to the above solution in two portions over a period of 5 min. The mixture which resulted was allowed to stir at 0 °C for 1 h. Analysis of the mixture by TLC (EtOAc/hexane, 1:1) indicated the appearance of a new component (R_f = 0.36) and the absence of starting material. The reaction was quenched by addition of cold water (5 drops). Ethanol was removed under reduced pressure. The residue was dissolved in ethyl acetate (50 mL) and washed with water (10 mL) and brine (15 mL) and dried (K_2CO_3). Removal of solvent under reduced pressure provided an alcoholic acetal (44.5 mg, 99%) **27**: FTIR (KBr) 3431 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.92 (3H, t, J = 6.89 Hz), 1.25 (1 H, m), 1.58 (2 H, m), 1.76 (2 H, m), 1.86 (1 H, m), 2.37 (1 H, dt, J = 11.78, 4.20 Hz), 2.76 (1 H, d, J = 16.88 Hz), 3.03 (1 H, dd, J = 16.94, 7.13 Hz), 3.28 (1 H, t, J = 9.45 Hz), 3.46 (1 H, m), 3.49 (3 H, s), 3.51 (1 H, d, J = 13.56 Hz), 3.57 (1 H, m), 3.66 (1 H, d, J = 13.60 Hz), 3.78 (1 H, dd, J = 12.97, 6.54 Hz), 3.85 (2 H, m), 3.91 (1 H, dd, J = 12.28, 6.57 Hz), 3.99 (1 H, dd, J = 12.59, 6.33 Hz), 4.74 (1 H, d, J = 4.93 Hz), 7.09 (1 H, t, J = 7.27 Hz), 7.17 (1 H, t, J = 7.50 Hz), 7.26 (6 H, m), 7.51 (1 H, d, J = 7.75 Hz); ^{13}C-NMR (125.75 MHz, $CDCl_3$) δ 12.96, 18.36, 19.00, 28.96, 30.51, 30.53, 42.11, 45.66, 49.90, 53.48, 57.37, 63.79, 64.21, 64.93, 105.96, 107.40, 108.82, 118.09, 118.60, 120.54, 126.71, 126.78, 128.17, 128.62, 134.82, 137.04, 139.65; mass spectrum (EI, 15 eV) m/e (rel inten) 460 (M^+, 39.6%), 182 (100%). Anal. Calcd. for $C_{29}H_{36}N_2O_3 \cdot {}^1/_2H_2O$: C, 74.20; H, 7.89; N, 5.97. Found: C, 74.51; H, 7.93; N, 5.63.

(-)-N_b-Benzylraumacline (28). The hydroxyl acetal **27** (38 mg, 0.083 mmol) was dissolved in distilled THF (6 mL). Aqueous hydrochloric acid solution (2 mL, 2 N) was added. The solution which resulted was allowed to stir at room temperature for 7 days under argon. The reaction progress was monitored by TLC (EtOAc/hexane, 1.2:1; TLC plates were exposed to NH_4OH vapor before development). The reaction mixture was diluted with ethyl acetate (25 mL) and brought to alkaline pH with aqueous NH_4OH (5 mL, 10%). The two layers were separated, and the aqueous layer was extracted with ethyl acetate (5 × 25 mL). The combined organic layers were washed with brine (2 × 25 mL), dried (K_2CO_3), and concentrated under reduced pressure to provide (-)-N_b-benzylraumacline (**28**) (33 mg, 96%) as a colorless oil: $[\alpha]^{26}_D$ = -106.67° (c = 0.30, $CHCl_3$); ^{13}C-NMR (125.75 MHz, $CDCl_3$) δ 11.44 (1 C, q), 17.57 (1 C, t), 20.96 (1 C, t), 28.99 (1 C, q), 33.76 (1 C, t), 34.14 (1 C, d), 42.13 (1 C, d), 49.86 (1 C, d), 51.24 (1 C, d), 51.63 (1 C, d), 57.33 (1 C, t), 69.78 (1 C, t), 97.23 (1 C, d), 106.99 (1 C, s), 108.89 (1 C, d), 118.03 (1 C, d), 118.82 (1 C, d), 120.78 (1 C, d), 126.57 (1 C, s), 126.90 (1 C, d), 128.23 (2 C, d), 128.65 (2 C, d), 134.81 (1 C, s), 137.00 (1 C, s), 139.43 (1 C, s); mass spectrum (EI, 15 eV) m/e (rel inten) 416 (M^+, 100%), 273 (73.0%). The ^{1}H-NMR spectrum was reported in reference 48 (supplementary material). This material was employed directly in the next step.

(-)-Raumacline (3). The (-)-N_b-benzylraumacline hydrochloride salt was prepared from the corresponding free base **28** (4.5 mg, 0.011 mmol) and ethanolic hydrogen chloride. The solvent was removed under reduced pressure and the residue was dissolved in absolute ethanol (1 mL). The 10% Pd/C (3 mg) was added and the slurry was allowed to stir at room temperature under 1 atm of hydrogen for 1 h. Examination of the mixture by TLC ($CHCl_3$/MeOH, 10:1) indicated the disappearance of starting material and the appearance of a new component. The catalyst was filtered from the medium and washed with ethanol (5 × 10 mL). The solvent was removed under reduced pressure. The residue which resulted was dissolved in a mixture of $CHCl_3$ and aqueous NH_4OH. The aqueous layer was extracted with $CHCl_3$ (4 × 5 mL). The combined $CHCl_3$ layers were dried (K_2CO_3) and passed through a wash column (pipette, silica gel). The compound which remained on the column was eluted with $CHCl_3$/EtOH (8.5:1.5). The solvent was removed under reduced pressure to provide (-)-raumacline (**3**) (3.2 mg, 91%): $[\alpha]^{26}_D$ = -26.43° (c = 0.28, $CHCl_3$); ^{13}C-NMR (125.75 MHz, $CDCl_3$) δ 11.35 (1 C, q), 20.75 (1 C, t), 21.94 (1 C, t), 28.93 (1 C, q), 32.91 (1 C, t), 34.26 (1 C, d), 41.96 (1 C, d), 45.88 (1 C, d), 46.12 (1 C, d), 50.45 (1 C, d), 69.70 (1 C, t), 96.95 (1 C, d), 107.37 (1 C, s), 108.93 (1 C, d), 118.06 (1 C, d), 119.05 (1 C, d), 121.18 (1 C, d), 126.47 (1 C, s), 136.38 (1 C, s), 136.81 (1 C, s); mass spectrum (EI, 15 eV) m/e (rel inten) 326 (M^+, 14.4%), 183 (100%). The ^{1}H-NMR spectrum was reported in ref 48. The NMR data for **3** are in complete agreement with that reported for natural raumacline.[3]

(-)-N_b-Methylraumacline (4). (-)-N_b-Benzylraumacline (**28**) (13 mg, 0.031 mmol) was dissolved in freshly distilled methanol (10 mL), and 10% Pd/C (15 mg) was added to the solution. The mixture which resulted was allowed to stir at room temperature for 5 h under H_2 (1 atm). Analysis of the reaction mixture by TLC ($CHCl_3$/MeOH, 10:1) indicated the disappearance of starting material. The catalyst was filtered from the medium and washed with methanol (5 × 20 mL). The combined methanol solution was concentrated in vacuo to provide a crude oil (10.3 mg). Analysis of the oil by TLC (plate was exposed to NH_3 vapors before development) and by NMR spectroscopy indicated the presence of two major components which were separated by preparative TLC ($CHCl_3$/MeOH, 10:1.2) to provide (-)-raumacline (**3**) (5.8 mg, 57%) and (-)-N_b-methylraumacline (**4**) (3.4 mg, 32%). (-)-Raumacline (**3**) was identical in all respects (co-TLC, NMR) with that from the previous experiment.

(-)-N_b-Methylraumacline (**4**): $[\alpha]^{25}_D$ = -67.50° (c = 0.16, $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.72 (3 H, m), 1.12 (1 H, m), 1.27 (3 H, m), 1.73 (1 H, m), 1.81 (1 H, m), 1.90 (1 H, m), 2.44 (3 H, s), 2.63 (1 H, d, J = 17.1 Hz), 3.01 (1 H, t, J = 11.10 Hz), 3.04 (1 H, dd, J = 16.83, 7.35 Hz), 3.52 (1 H, dd, J = 6.30, 4.59 Hz), 3.62 (3 H, s), 3.94 (1 H, dd, J = 11.70, 4.19 Hz), 4.05 (1 H, bs), 4.56 (1 H, d, J = 8.56 Hz), 7.11 (1 H, t, J = 7.25 Hz), 7.20 (1 H, t, J = 7.23 Hz), 7.30 (1 H, d, J = 8.13 Hz), 7.51 (1 H, d, J = 7.74 Hz); ^{13}C-NMR (125.75 MHz, $CDCl_3$) δ 11.35, 16.91, 20.93, 29.11, 33.37, 33.40, 41.21, 41.94, 50.79, 52.58, 53.21, 69.75, 97.02, 106.33, 108.94, 118.11, 118.98, 121.03, 126.30, 133.54, 137.09; mass spectrum (EI, 15 eV) m/e (rel inten) 340 (M^+, 45.0%), 197 (100%).

The yield for (-)-N_b-methylraumacline can be optimized by stirring the reaction mixture for a longer period. When the same reaction with (-)-N_b-benzylraumacline **28** (3.0 mg, 0.007 mmol) and 10% Pd/C (6 mg) was stirred in methanol (1 mL) for 2 d under hydrogen, (-)-N_b-methylraumacline (**4**) (2.1 mg) was obtained in 85% yield. All analytical data for this sample were identical to those described above. The NMR spectrum of (-)-**4** was identical to that reported for N_b-methylraumacline.[3]

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