General Approach for the Synthesis of Ajmaline/Sarpagine Indole Alkaloids: Enantiospecific Total Synthesis of (+)-Ajmaline, Alkaloid G, and Norsuaveoline via the Asymmetric Pictet−Spengler Reaction

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Abstract: A general approach (oxyanion-Cope strategy) for the synthesis of sarpagine/ajmaline indole alkaloids has been developed. (+)-Ajmaline **1** and alkaloid G **2** as well as norsuaveoline **3** have been synthesized from D-(+)-tryptophan in enantiospecific fashion via the asymmetric Pictet−Spengler reaction and a stereocontrolled oxyanion-Cope rearrangement as key steps. The synthesis of these indole alkaloids employed a stereospecific Pictet−Spengler/Dieckmann protocol to prepare the key intermediate, (−)-N_b-benzyl tetracyclic ketone (**7a** or **7b**). This ketone was converted into α,β-unsaturated aldehyde (**8a** or **8b**) and further transformed into (+)-ajmaline **1** and alkaloid G **2** as well as norsuaveoline **3**. It was also found that reduction of **29** can be done stereospecifically to form the 2-epidiacetylajmaline derivative **30** which has the same configuration at C(2) as that of quebrachidine and of the bisindole alstonisidine. The ring closure reaction (from **27** to **28**) to form the sarpagine skeleton was completed in 91% yield. It should now be possible to prepare the antipode of (+)-ajmaline via this approach for biological screening.

(+)-Ajmaline **1** was isolated from the roots of *Rauwolfia serpentina* in 1931[1] and contains four heteroatoms, six rings, as well as nine asymmetric centers. It is a clinically important cardiovascular indole alkaloid[2−7] with historical significance[1,8] and is related to the sarpagine bases (see **2** vs **4**).[9,10] "The most prominent action of ajmaline is an antiarrhythmic effect on the heart" as was reviewed by Creasey, "that is less pronounced than that of propranolol,[7] but is superior in terms of the ratio of the refractory phase over reduced conduction to that of procaine amide and quinidine." [6,11] In a study that involved 900 patients with acute or subacute myocardial infarction, ajmaline was found to be useful in the management of both ventricular and supra ventricular arrhythmias.[12] It should be noted, however, that successful treatment with return to normal sinus rhythm in 85% or more of the subjects required two drugs, electrolyte replacement therapy, and the administration of thiamine. The action of ajmaline involves a dose-dependent reduction in the maximum rate of rise of the muscle action potential, without affecting the resting potential.[6,9] Studies still continue on (+)-ajmaline in order to develop new treatments for a variety of cardiovascular diseases.[2−4] However, the antipode, (−)-ajmaline, has never been isolated nor synthesized, the use of which might provide a new adjunct to antiarrhythmic therapy. An important review by Creasey has also detailed the ganglionic blocking activity of other ajmaline-related alkaloids.[6] The structure of ajmaline **1** was originally suggested by Robinson[13,14] and proposed correctly by Woodward.[15] The stereochemistry was assigned[16] on the basis of additional chemical and spectroscopic observations in 1962. The structure was confirmed by X-ray crystallography.[17] Ajmaline **1** can be converted into another natural product, isoajmaline, simply by heating **1** above its melting point.[13] Alkaloid G **2** recently isolated from plant cell cultures of *Rauwolfia serpentina* Benth by Stöckigt et al.[18] after feeding experiments with ajmaline is also structurally similar to **4.** Both of these bases are related by the presence of the

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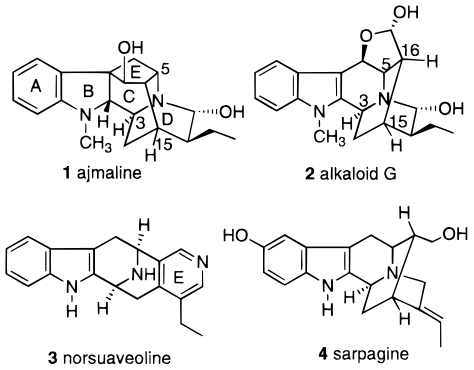


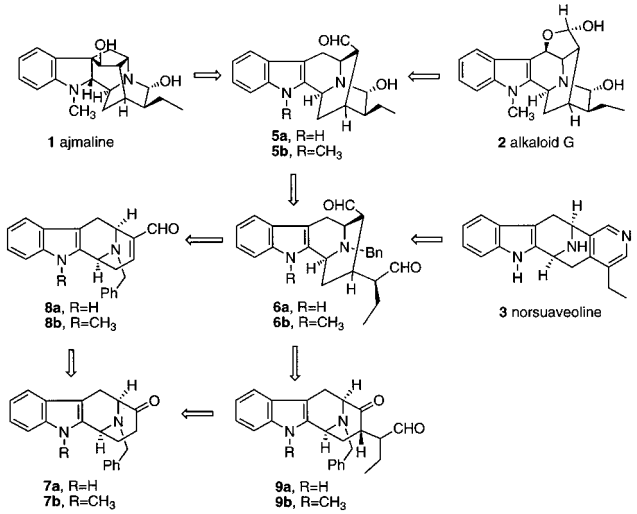
Figure 1.

quinuclidine ring and the C(5)−C(16) bond linkage. The absolute configurations of the stereogenic centers at C(3), C(5), and C(15) of members of both the sarpagine and ajmaline class of indole alkaloids are identical. The alkaloid norsuaveoline **3** is related to **1** and **2**, although ring E is fully aromatic (Figure 1).

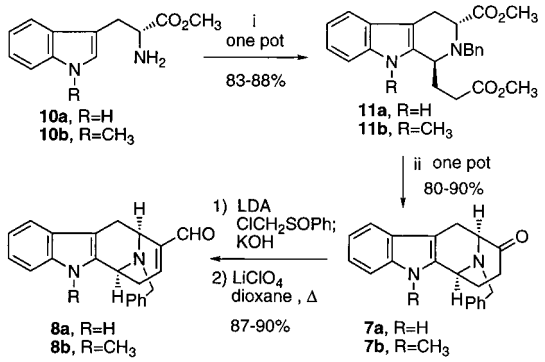
Three important reports on the synthesis of ajmaline have appeared previously.[19−22] The first was published by Masamune et al. in 1967 and involved sixteen steps; this elegant approach was unique and the chemistry employed was important for those who later worked on the synthesis of ajmaline-related indole alkaloids. However, this route was not enantiospecific, and the yields were not reported in some cases. Two years later, Mashimo and Sato converted tryptophan into an intermediate employed by Masamune in the earlier synthesis of ajmaline in order to provide a formal total synthesis of this alkaloid. Van Tamelen in 1970 employed a new synthetic route in a biogenetic approach to ajmaline and synthesized deoxyajmaline.[21−23] Since Hobson et al.[24] had earlier converted deoxyajmaline into ajmaline, a second total synthesis of ajmaline was completed. This biogenetic route involved 17 steps and shed much light on potential biogenetic pathways to **1**. We wish to report here a general approach to the synthesis of the ajmaline/sarpagine family of indole alkaloids as well as the first enantiospecific total synthesis of (+)-ajmaline, alkaloid G, and norsuaveoline.

As illustrated in Scheme 1, in a retrosynthetic sense both ajmaline **1** and alkaloid G **2** might be available via a common intermediate, the monoaldehyde **5.** This aldehyde **5** could arise from 1,5-dialdehyde **6** by a cyclization process which involves the N_b-nitrogen function. The synthesis of 1,5-dialdehyde **6** could be approached either from the α,β-unsaturated aldehyde **8** or from the monoaldehyde **9**. If both carbonyl-substituted intermediates could be obtained in high yield from the (−)-tetracyclic ketone **7**, then the 1,5-dialdehyde **6** could serve as a key intermediate in the synthesis of ajmaline **1** and alkaloid G **2** as well as norsuaveoline **3**. Furthermore, since all of the sarpagine/ajmaline alkaloids possess the same stereochemistry at C(3), C(5), and C(15), the dialdehyde **6** might also serve as a precursor for the sarpagine alkaloids.[9,10] The initial goal, therefore, was to develop a general synthetic route to 1,5-dialdehyde **6** on a multiple gram scale from readily available starting materials in an enantiospecific fashion.

Scheme 1



Scheme 2



reagents and conditions:
for **7a**: i) PhCHO, CH_3OH, rt, 2 h; $NaBH_4$, -30°C to -10°C, 3 h; $(CH_3O)_2CHCH_2CH_2COOCH_3$, TFA, CH_2Cl_2, rt, 48 h; ii) NaH, CH_3OH, $PhCH_3$, Δ, 48 h; HOAc, HCl, Δ, 12 h.
for **7b**: i) PhCHO, CH_3OH, rt, 2 h; $NaBH_4$, -30°C to -10°C, 3 h; $(CH_3O)_2CHCH_2CH_2COOCH_3$, TFA, $CHCl_3$, Δ, 12 h; ii) NaH, CH_3OH, $PhCH_3$, Δ, 4 h; HOAc, HCl, Δ, 12 h.

As illustrated above the (−)-tetracyclic ketone (**7a** or **7b**) was synthesized[25,26] via an improved route with these goals in mind, while the racemic compound had been prepared on a kilogram scale in the late 1970s in our laboratory.[27]

The synthesis of (±)-5-methyl-9-oxo-12-benzyl-6,7,8,9,10,-11-hexahydro-6,10-imino-5H-cycloocta[b]indole **7b** (R=CH_3) was first reported by Yoneda[28] and was significantly improved by Soerens.[29] The enantiospecific preparation of tetracyclic ketone **7b** in optically active form was originally developed by Zhang[26] and was recently improved to a two-pot process (Scheme 2).[30−32] The tryptophan methyl ester **10b** was converted into the N_b-benzyltryptophan derivative on stirring **10b** with benzaldehyde (1.1 equiv) in CH_3OH at room temperature for 2 h, followed by reduction of the imine which resulted with

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sodium borohydride (1.3 equiv) at −30 °C to −15 °C (3 h). Acetic acid was then added to the reaction mixture to destroy any remaining $NaBH_4$, and the solvent was removed under reduced pressure. Chloroform, methyl 4,4-dimethoxybutyrate (1.1 equiv), and TFA (3 equiv) were then added directly to the reaction vessel, and the solution was brought to reflux to provide the trans diester **11b** in high yield (overall yield >85%). The trans isomer **11b** underwent epimerization and a Dieckmann cyclization to furnish the β-ketoester after which the solvent was removed under reduced pressure. Acetic acid and hydrochloric acid were added carefully to the reaction vessel and, on heating, ketone **7b** was obtained in greater than 98% ee (overall yield from **10** >74%). The ketone **7a** was prepared via a similar process. Importantly, five chemical transformations from tryptophan methyl ester **10** to ketone **7** were accomplished in two reaction vessels. The utility of this enantiospecific two-pot sequence via the trans transfer of chirality in the asymmetric Pictet−Spengler reaction is key since these reactions can be run on a multihundred gram scale to provide the (−)-tetracyclic ketone [**7a** or **7b** (300 g scale)], which can now be considered a readily available starting material for the synthesis of optically pure macroline/sarpagine/ajmaline alkaloids. In addition, both D-(+)-tryptophan and L-(−)-tryptophan are readily available from commercial sources permitting entry into both antipodes of the natural products for biological screening.

With sufficient quantities of the tetracyclic ketone (**7a** or **7b**) in hand, attention focused on methods to convert **7** into 1,5-dialdehyde **6**. Two synthetic approaches were envisaged, the earlier of which centered on the functionalization of the α-position of the carbonyl group in ketone **7** to furnish aldehyde **9** (or its equivalent) and then to convert **9** into 1,5-dialdehyde **6**. The second route rested on the conversion of the ketone **7** via α,β-unsaturated aldehyde **8**, which could be transformed to 1,5-dialdehyde **6** in subsequent steps. A series of intermolecular processes was attempted in order to functionalize the C(15) position of **7**. These included direct alkylation reactions,[33,34,35] enamine promoted processes,[35] as well as metal promoted 1,4-addition reactions,[33−39] but with one notable exception,[36,39] all have failed (see Supporting Information for details).[33,38,39] In addition, attempts to treat α,β-unsaturated aldehyde **8b** or **8c** under conditions to promote heterodiene Diels−Alder reactions,[27,40] titanium-promoted aldol processes,[41] or cuprate-mediated additions were likewise unsuccessful (see Supporting Information for details). The inability to **intermolecularly** functionalize the tetracyclic ketone **7b** and the α,β-unsaturated aldehyde **8b** is believed to be due to steric constraints inherent in this tetracyclic [3.3.1] system and electronic effects which retard addition of reagents at C(15) from the bottom face of the π system. The approach of a nucleophilic reagent at C(15) of enone **8b** from the less hindered bottom (α) face of the molecule (equatorial position) is electronically disfavored; while approach from the top (β) face (axial position) is severely hindered by the 1,3-diaxial interactions with the cis fused diaxial-indolomethylene bridge (Figure 2).

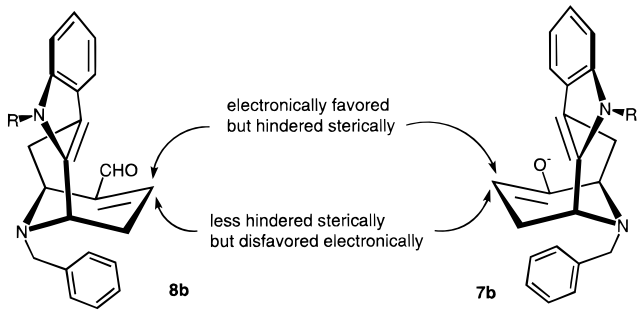
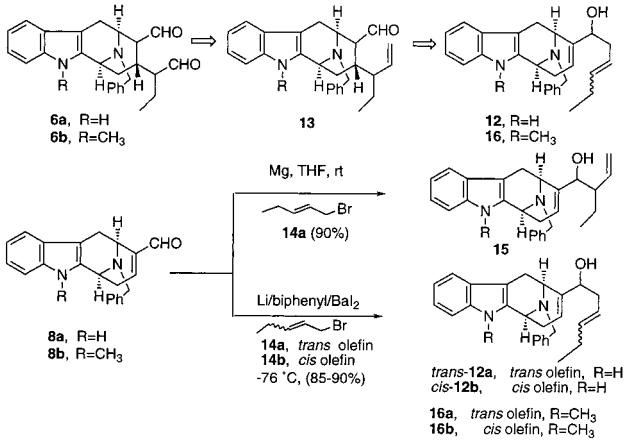


Figure 2.

Scheme 3



To overcome these steric and electronic constraints, we envisaged execution of an **intramolecular** approach for the functionalization of this tetracyclic [3.3.1] system at C(15). It was felt that an intramolecular [3,3] sigmatropic rearrangement could be employed to introduce the side chain at C(15) and generate the basic carbon skeleton of the ajmaline/sarpagine indole alkaloids. The thermal conditions of the pericyclic process would leave the remainder of the molecule unharmed.

As shown in Scheme 3, the 1,5-dialdehyde **6** might be prepared from the allylic alcohol **12** via an oxyanion-Cope rearrangement. The anionic oxy-Cope rearrangement appeared to present several advantages not the least of which rests on generation of the olefinic bond in **13**, a required latent aldehyde moiety. Oxidative cleavage of the double bond of the alkenic aldehyde **13** would provide the desired aldehyde **6** directly. More importantly, the oxyanion-Cope rearrangement of allylic alcohol **12** should take place stereoselectively from the α face of the double bond via a chair transition state to furnish the desired configuration at C(15) required for the synthesis of all ajmaline/macroline/sarpagine alkaloids.[37]

Addition of the primary Grignard reagent available from *trans*-1-bromo-2-pentene **14a** to the α,β-unsaturated aldehyde **8a** (R═H) or **8b** (R═CH_3) provided the expected but undesired alcohol **15** which resulted from allylic rearrangement of the Grignard reagent.[37] Although Benkeser et al[42] reported that the reversible Grignard addition process favored the normal addition from the α position when the initially formed adducts were heated at higher temperature in the cases of hindered carbonyl substrates, the reaction of **8b** (R═CH_3) with *trans*-1-bromo-2-pentene **14a** in refluxing THF furnished none of the desired alcohol **16a**.[37] Since barium reagents were reported by Yamamoto[43] to react with carbonyl compounds to yield regioselective

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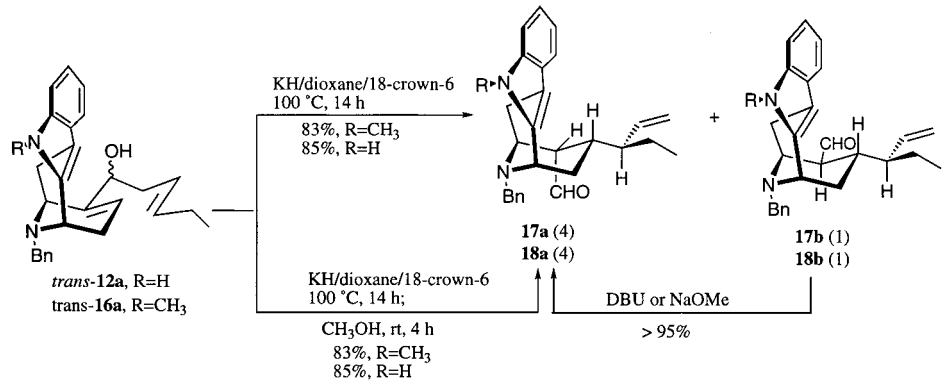
Scheme 4

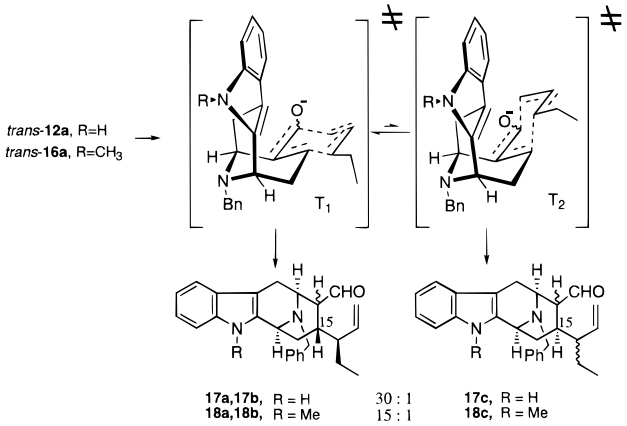


A trace of another diastereomer related to **17a** was observed by NMR spectroscopy. The amount was too small to quantify when R=H by this spectroscopic technique.

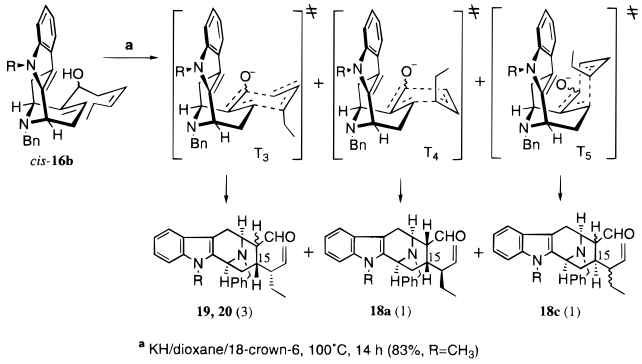
α-addition of the carbanion, this approach was examined with the unsaturated aldehyde **8**. Employment of a modified procedure of the original report in a fashion[43] similar to a Barbier−Grignard[44] process provided the desired allylic alcohol (see **12** and **16**, respectively) in high yield in both the N_a-H and N_a-methyl series.[45] With the desired allylic alcohols represented by **12** in hand, we examined both the trans and the cis alcohols under the conditions of an oxyanion-Cope rearrangement. When allylic alcohol trans-**12a** (or **16a**, R═CH_3) was heated individually with KH at 100 °C in dioxane for 14 h, two major diastereomers **17a** and **17b** were obtained in high yield accompanied by a trace of another diastereomer (Scheme 4).[32] In the N_a-methyl series **16a**, these are represented by diastereomers **18a** and **18b**. Both of the diastereomers **17a** (R═H) and **17b** (R═H) as well as isomers **18a** (R═CH_3) and **18b** (R═CH_3), respectively, contained the correct chirality at C(15), and more importantly, after treatment with DBU or NaOMe, the aldehydes **17b** (R═H) or **18b** (R═CH_3) could be converted into the desired isomers **17a** (R═H) or **18a** (R═CH_3) in almost quantitative yield, respectively. Both aldehydes **17a** (R═H) and **18a** (R═CH_3) contained the correct chirality at **C(3)**, **C(5)**, **C(15)**, **C(16)**, and **C(20)** required for the synthesis of sarpagine/macroline indole alkaloids. In addition, the reaction can be carried out in a one-pot process first by execution of the oxyanion-Cope rearrangement, followed by addition of MeOH with stirring at room temperature.

The very high stereoselectivity in the oxyanion-Cope rearrangement (>30:1) in the above system bodes well for the future synthesis of macroline/sarpagine indole alkaloids. 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,[46] while recent results[47,48] indicated that the Claisen rearrangement in this N_b-benzyl system occurred from the bottom face via a chair transition state with a stereoselectivity of about 3(α):1(β) to greater than 6:1 in the 11-methoxyindole series of Hamaker.[48]

Scheme 5



Scheme 6



[a] KH/dioxane/18-crown-6, 100°C, 14 h (83%, R=CH_3)

The diastereoselectivity for the anionic oxy-Cope rearrangement in the analogous N_b-benzyl system (trans-**12a** or **16a**) provided high α facial selectivity, presumably via a chair transition state (Scheme 5). As shown in Scheme 5, the energy of the transition state designated T_1 is lower than that of transition state T_2 and the former was favored in the oxyanion-Cope rearrangement. Execution of the oxyanion-Cope rearrangement of the cis olefinic isomer cis-**16b** under analogous conditions provided 4 diastereomers, and the diastereoselectivity at C(15) and C(20) was much lower (Scheme 6). This can be understood by examination of the possible transition states for the cis olefinic isomers (T_3-T_5) depicted in Scheme 6. It is clear that the transition states T_3-T_5 would be higher in energy than T_1 observed in the case of the trans olefinic alcohols [trans-**12a** (R═H) or trans-**16a** (R═CH_3), (Scheme 5)]. Consequently it is

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(44) Blomberg, C.; Hartog, F. A. *Synthesis* **1977**, 18.

(45) The reaction was executed by adding the mixture of the carbonyl compound **8** with the bromide **14** to the preformed barium metal; otherwise, only starting material **8** was recovered.

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

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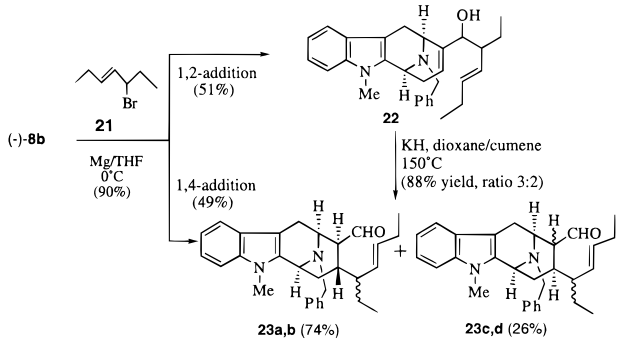
Scheme 7



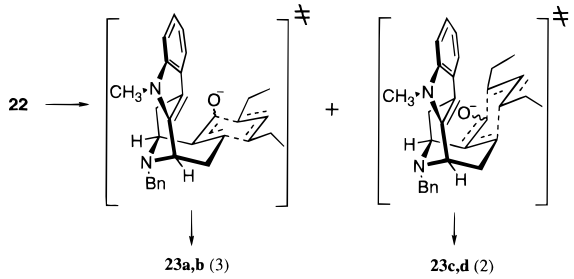
not suprising that cis-**16b** gave 4 diastereomers in a combined yield of 83% (see Scheme 6).

Although the results depicted in Schemes 4−6 are important in regard to the study of sigmatropic rearrangements in azabicyclo[3.3.1]nonane systems (ortho ester Claisen rearrangement vs Claisen rearrangement vs oxyanion-Cope rearrangement),[37,47,48] the sequence outlined in Scheme 4 also provided the first effective solution to the stereochemical problem at C(15), C(16), and C(20) in the sarpagine series of indole alkaloids.[9,10,49] Since the rearrangement from trans-**12a** (R═H) or **16a** (R═CH_3) to provide **17a** (R═H) or **18a** (R═CH_3), respectively, generated the desired chirality at C(15), C(16), and C(20) with extremely high diastereoselectivity (>30:1) in a one-pot process, the aldehydes **17a** (R═H) or **18a** (R═CH_3) can now be prepared on multigram scale and employed for the total synthesis of many macroline/sarpagine indole alkaloids. In fact, this process was employed recently in the total synthesis of talcarpine and talpinine.[31,32]

As mentioned previously, the ajmaline/raumacline alkaloids contain the same stereochemistry as the macroline/sarpagine series at C(3), C(5), and C(15) but are antipodal at C(16). Although the oxyanion-Cope rearrangement (Scheme 4) provided the desired system for the macroline/sarpagine indole alkaloids with high diastereoselectivity, this rearrangement yielded only 20% of the correct stereochemistry at the critical aldehydic position at C(16) for the synthesis of the ajmaline/raumacline indole alkaloids. The aldehydic group in this sarpagine system was contained in the more stable α (R) configuration (antipodal to the natural configuration of ajmaline) at C(16) in the reported work.[18,19,22] To synthesize (+)-ajmaline and alkaloid G, one must overcome the stereochemical problem at C(16) and epimerization of the aldehydic group at C(16) (S) to the more stable α stereochemistry must be retarded.

When **(−)-8b** was stirred with trans 3-bromo-4-heptene **21** at 0 °C under the conditions of a Barbier−Grignard process,[36] the products of 1,2-addition (allylic alcohol **22**, isolated as a mixture of diastereomers) and 1,4-addition (diastereomers **23a**,**b** and **23c**,**d**) were obtained in a combined yield of 90% in a ratio of 51(**22**):49(**23**).[36] This was the first reported case of 1,4-addition to this aldehyde **8b** and remains the only example to date to our knowledge (see Scheme 7).[29,33,36,37,50−52] The ratio of desired to undesired isomers from the 1,4-addition was 3:1 (see **23a**,**b** vs **23c**,**d**). The allylic alcohol **22** was easily separated from the mixture by flash chromatography, and it underwent the anionic oxy-Cope rearrangement at 150 °C in 88% yield to

Scheme 8

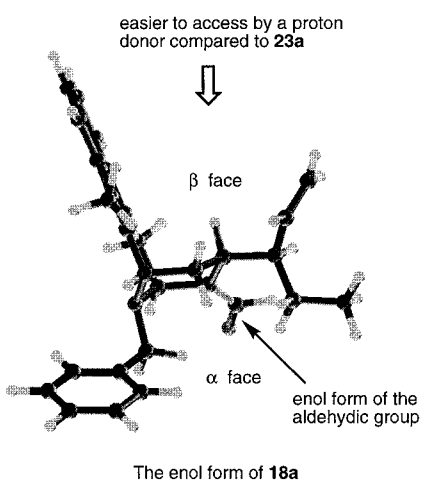


provide the same C(15) functionalized tetracyclic systems **23a**,**b** and **23c**,**d** in a ratio of 3:2 (see Scheme 8). The key diastereomers could also be obtained by executing the Barbier−Grignard process at 25 °C (only 1,2-addition) followed by the anionic oxy-Cope rearrangement. The desired aldehydes **23a**,**b**, which contained the correct stereochemistry at C(16) for the synthesis of ajmaline/raumacline indole alkaloids, were obtained (from **8b**) with 64% stereoselectivity.[37]

The conversion of **8b** into aldehydes **23a**,**b**, although not stereospecific, constitutes the first effective solution to the long standing problem of the stereochemistry at C(16) in the ajmaline series. In earlier work[19,20,22] epimerization of the aldehydic group at C(16) to the unnatural (R) configuration complicated the process, the ratio of desired to undesired diastereomers was reported as 7:43 and 3:7 from different laboratories.[19,20,22] In contrast, the presence of the ethyl group in **23a**,**b** (compared to **18a**) was found to be critical to retard epimerization of the aldehydic moiety at C(16) to the unnatural (R) configuration. Support for the importance of the ethyl group derives from the experiments mentioned previously (Scheme 4). As described above, when the anionic oxy-Cope rearrangement was carried out with the 2-pentenyl derivative **14** rather than the heptenyl analogue **21**, the diastereoselectivity at C(15) was dramatically improved; however, the ease of epimerization at C(16) to the unnatural diastereomer was increased {ajmaline requires the S configuration at this center [C(16)]}. This observation was also supported by computational results.[53] As shown in Figure 3, the enol forms of the aldehydic products are initially produced in the oxyanion-Cope rearrangement. Protonation can occur from the top face or the bottom face of the enol form at C(16), and the *β*-face of the enol appears more hindered to protonation in the R = ethyl (**23a**) case, as compared to the pentenyl case (**18a**). Protonation then occurred more readily from the α-face of the enol in the R = ethyl (**23a**) case to generate the desired (S) configuration at C(16) for ajmaline. The presence of an ethyl moiety in **23a**,**b** (from **21**) in the anionic oxy-Cope approach retarded isomerization at C(16) to the unnatural isomer. When aldehydes **23a**,**b** were stirred with base (NaOMe), it took 2 days to epimerize the aldehydic group to the unnatural isomer (the aldehyde with an R configuration). In contrast, in the pentenyl case, when **17b** (R═H) or **18b** was stirred under the same alkaline conditions, the epimerization was complete in a few hours, an epimerization process which had hindered earlier work toward **(+)-1**.[19,20,22,54]

The two diastereomers (**23a** and **23b**) were separated by flash chromatography. Because the absolute configurations of **23a**,**b** at C(3), C(5), C(15), and C(16) were identical to those of **1** and **2**, both diastereomers could be employed in the synthesis

(49) Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797.
(50) Bailey, P. D.; Hollinshead, S. P.; Mclay, N. R. *Tetrahedron Lett.* **1987**, *28*, 5177.
(51) Bailey, P. D.; McLay, N. R. *Tetrahedron Lett.* **1991**, *32*, 3895.
(52) Bailey, P. D.; Hollinshead, S. P.; McLay, N. R.; Morgan, K.; Palmer, S. J.; Prince, S. N.; Reynolds, C. D.; Wood, S. D. *J. Chem. Soc., Perkin Trans. 1* **1993**, 431.
(53) The program used for calculation was MacroModel 6.0. MMFF94S force field and MCarlo methods were employed to conduct the conformational search.
(54) Mashimo, K.; Sato, Y. *Tetrahedron* **1970**, *26*, 803.



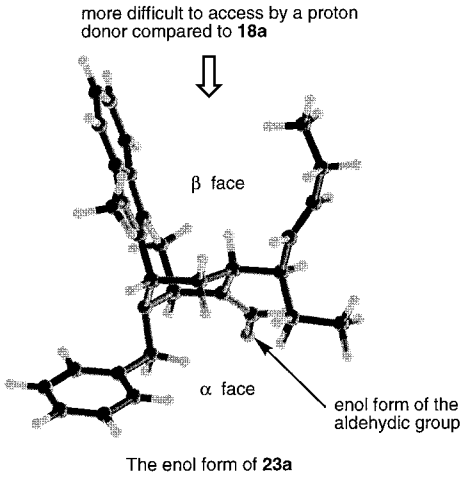
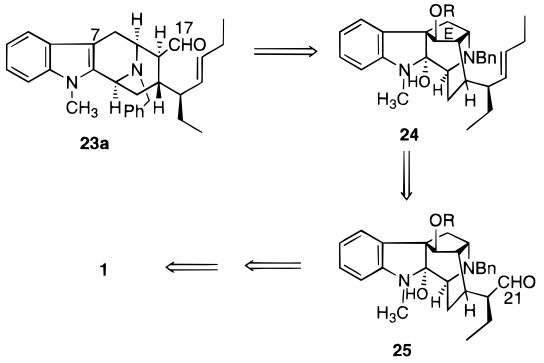


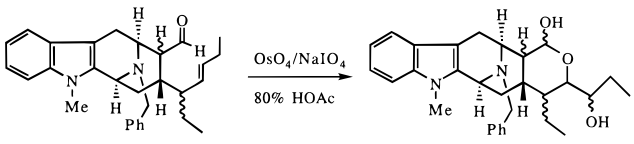
Figure 3.

Scheme 9



of **(+)-1** and **2**. The initial synthetic plan toward ajmaline **1** is shown in Scheme 9. It was planned to connect C(17) to C(7) to form the E ring or a suitable derivative and then to cleave the double bond in **24** to provide the aldehyde at C(21). An advantage of this approach rested on potential ozonolytic cleavage of the olefinic bond of **24** to generate an aldehyde at C(21) rather than use of the more expensive OsO_4.[55]

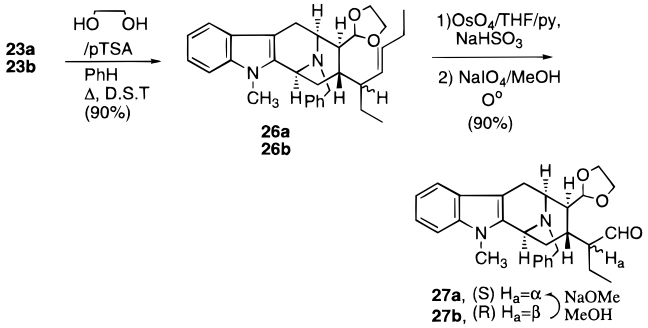
Unfortunately, after many attempts under different reaction conditions, the aldehyde **23a** was recovered unchanged or underwent decomposition.[56] Careful examination of a model of **23a** revealed that it resembled a tripod: the indole ring, the N_b-benzyl ring, and the side chain all pointed in different directions. Examination of the energy differences[53] between **23a** and **24** (R═OAc) indicated that cyclization of the upper ring (E ring) would need to overcome a large energy barrier, which was simply not possible under these circumstances (see ref 55 for details).



(55) Li, J. Ph.D. Thesis, University of Wisconsin-Milwaukee, 1999. Ozonolysis of the olefinic bond in **23a** was attempted many times and was unsuccessful due to the activity of the indole 2,3-double bond toward ozone. The olefinic bond could be selectively osmylated in the presence of the indole moiety; however if this was attempted without protection of the C(16) aldehyde, a hemiacetal resulted which prevented periodate cleavage.

(56) Some of the reaction conditions attempted are summarized below: (1) HOAc/$(Ac)_2O$/HCl(g), (2) $CF_3SO_3Si(CH_3)_3/CH_2Cl_2$, (3) Me_3SiCl/CH_2Cl_2, (4) Me_3SiI/CH_2Cl_2, (5) Me_3SiCl/CH_2Cl_2/HCl (5%), and (6) $Me_3SiCl/AlCl_3/CH_2Cl_2$ (or THF).

Scheme 10



It was therefore decided to first cyclize the lower (D) ring and then to form the upper (E) ring to provide the ajmaline skeleton. To differentiate between the aldehydic function at C(17) and the latent aldehyde at C(21), we protected the aldehyde functional groups of **23a**,**b** as the ethylene acetals **26a**,**b** in excellent yield, as illustrated in Scheme 10. Oxidative cleavage of the olefinic bond was executed via the osmium tetraoxide/sodium periodate sequence to provide aldehyde **27** in excellent yield.[23,57]

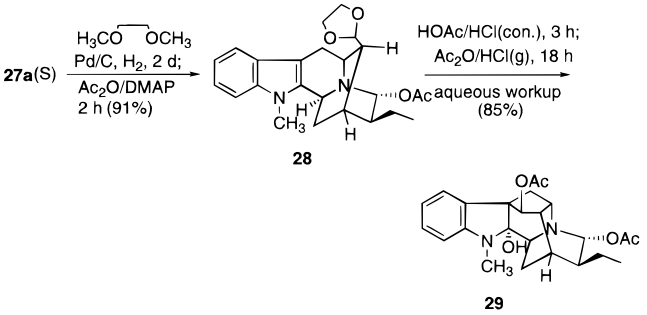
For the maximum conversion of acetals **26a** and **26b** into the aldehydes represented by **27a** and **27b**, the osmylation process was interrupted before the appearance of byproducts, which resulted from the bisosmylation of both the olefinic bond and the indole double bond. Under controlled conditions (~90% conversion of **26a** and **26b**), 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 functions to furnish the desired aldehydes **27a** (S) and **27b** (R) in greater than 90% overall yield.

The desired aldehyde **27a** [C(20S)] contained all of the required chirality for the preparation of ajmaline **1** and alkaloid G **2**. For this reason, the epimeric aldehyde **27b** was treated with base and converted into an equilibrium mixture of **27a** and **27b** (1:1), which again was subjected to flash chromatography (silica gel, EtOAc/hexane = 2:8). In this manner, the conversion of **27b** into the required **27a** could be increased to greater than 80%. This approach could also be employed to provide **27b** [C(20R)] for a synthesis of isoajmaline by reversal of the process, if desired.

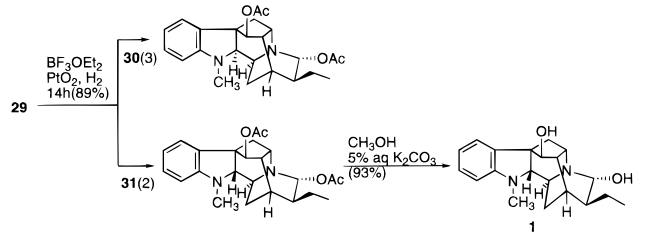
The (−)-(*S*)-aldehyde **27a** was converted into the sarpagine system present in **28** in 91% yield by catalytic debenzylation

(57) Schröder, M. *Chem. Rev.* **1980**, *80*, 187.

Scheme 11

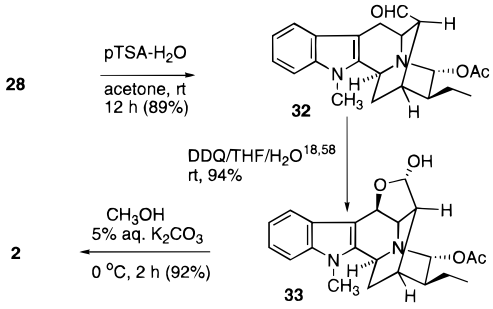


Scheme 12



followed by addition of acetic anhydride in a one-pot process (two chemical transformations, Scheme 11). This acetal **28** was then treated with acetic acid and concentrated aqueous HCl for 3 h (hydrolysis of the acetal group to provide the aldehyde moiety), after which this mixture was stirred with acetic anhydride/HCl(g) to effect smooth cyclization to furnish the 2-hydroxyajmaline derivative **29** as a single diastereomer in 85% yield. The structure of this carbinolamine was determined by NMR spectroscopy and verified by single-crystal X-ray analysis of a derivative **29** (21-OCbz).[30] The hydroxyl group in **29** was clearly in the α configuration. This demonstrated effectively the hindered nature of the β face of the caged structure of **29**. Although conversion of the α-hydroxyl group in **29** to a β hydrogen atom would provide the correct stereochemistry of ajmaline, this was expected to be difficult due to the hindered (caged) nature of the β-face. After many attempts (see Table in Supporting Information) under many reaction conditions,[55] 2-epiajmaline (α-hydrogen) could be formed with 100% diastereoselectivity (Et_3SiH, TFA) in 91% yield, as expected.[55] The only reaction conditions which provided the correct stereochemistry at the C(2) position of ajmaline were found to be H_2/platinum oxide in dry CH_2Cl_2 in the presence of BF_3 etherate or the analogous reaction in the presence of BCl_3.[55] The former process afforded 2-epidiacetylajmaline **30** and diacetylajmaline **31** in a ratio of 3:2 in 89% yield as illustrated in Scheme 12. Reaction conditions such as $(C_2H_5CHCH_3)_3B/PtO_2$, H_2; $NaBH_4$/DME; $SOCl_2$, Bu_3SnH; Pt/H_2/TFA, CH_2Cl_2; PtO_2/H_2/TFA/CH_2Cl_2; $Me_3SiI/PtO_2/H_2/CH_2Cl_2$; and many others[55] gave only 2-epiajmaline diacetate **30**, or products of overreduction (see Supporting Information for details). Reduction of alcohol **29** in the presence of BF_3 etherate or BCl_3 was felt to proceed in the correct fashion by complexation of the Lewis acid to the N_b-nitrogen atom, which retarded reduction[19,21−23] from the α-face of **29** (or the related iminium ion). However, this process was not successful in the presence of $(C_2H_5CHCH_3)_3B$, a Lewis acid chosen for the same purpose. The reduction of **29** in the presence of BCl_3 while successful was not as clean as the process in the presence of BF_3 etherate, presumably because HCl was generated in the former case. Mechanistically, it is felt that complexation of the N_b-nitrogen function with BF_3 etherate prevented the interaction of a palladium hydride-related species with **29** from the α-face, which would have been involved in the transfer of hydrogen (or hydride ion) to **29**, presumably through reduction of the related iminium ion.[55] Hydrolysis of **31** with aqueous K_2CO_3 in methanol furnished (+)-ajmaline **1** in 93% yield. This base was spectrometrically identical (IR, ^{1}H NMR, ^{13}C NMR, MS, co-TLC), including the optical rotation, to that of an authentic sample of ajmaline.[1,13]

Scheme 13



Hydrolysis of the acetal **28** in the presence of p-TSA·H_2O in acetone provided the aldehyde **32** in 89% yield (Scheme 13). The aldehyde **32** was converted into a derivative of alkaloid G **33** by treatment with DDQ in aqueous THF at room temperature in 94% yield.[18,58] This alcohol **33** was then hydrolyzed in 5% K_2CO_3-MeOH to provide alkaloid G **2** in 92% yield. The proton and C-13 NMR spectra of **2** were identical to those reported for the natural product by Stöckigt and Sakai.[18]

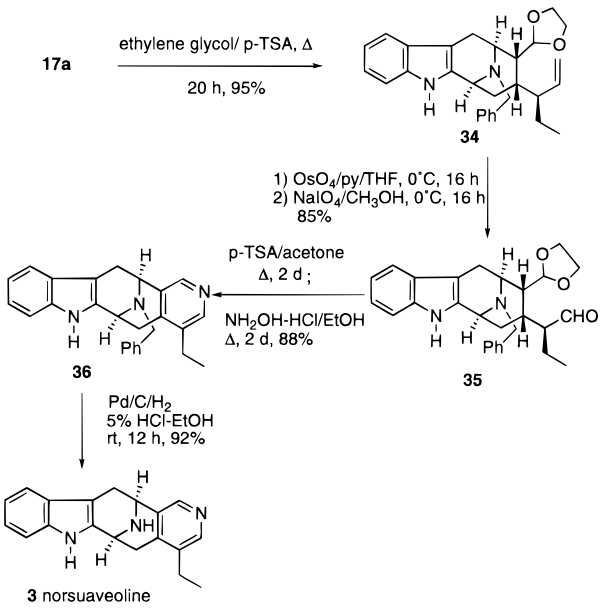
Although reduction of **29** gave only 36% of diacetylajmaline **31**, this still constitutes the highest conversion of alcohol **29** to **(+)-1**[59] reported to date. As mentioned, the α-face of **29** is much less hindered than the β-face; consequently, 2-epidiacetylajmaline **30** can be formed with 100% stereoselectivity under certain conditions (see Table 1, Supporting Information). This latter reduction process provides a potential route to alkaloids with the 2-epi configuration including quebrachidine and vincamajine as well as the bisindole alkaloid alstonisidine.[6, 8−10]

Although the oxyanion-Cope rearrangement employed in the synthesis of the ajmaline-related alkaloids was not stereospecific, the similar process (see above) in the trans pentenyl system occurred with greater than 30:1 diastereoselectivity in the N_a-H case. This provides a highly stereoselective route to the suaveoline alkaloids illustrated below for norsuaveoline (Scheme 14).

The aldehydic moiety in **17a** was protected by heating with ethylene glycol in 95% yield. The protection step was necessary since cleavage of the olefinic bond in **17a** by $OsO_4/NaIO_4$ was complicated by the presence of the C(16) aldehydic moiety in the molecule (formation of a hemiacetal, see ref 55). The olefinic bond in **34** was then cleaved by $OsO_4/NaIO_4$ to provide the acetal aldehyde **35** in 85% yield. It was originally thought that reaction of **35** directly with hydroxylamine hydrochloride might provide the pyridine ring system. However many attempts in this effort were not successful. Consequently, the acetal aldehyde **35** was hydrolyzed by heating in p-TSA/acetone for 2 days and then the residue that resulted was heated with hydroxylamine hydrochloride in ethanol to furnish N_b-benzyl norsuaveoline **36** in 88% yield in a one-pot process. The N_b-benzyl group of **36** was removed by catalytic hydrogenation (Pd/C/H_2) to provide norsuaveoline **3**[60] in 92% yield. The total synthesis of norsua-

(58) Hagen, T. J.; Narayanan, K.; Names, J.; Cook, J. M. *J. Org. Chem.* **1989**, *54*, 2170.
(59) Bartlett, M. F.; Lambert, B. F.; Werblood, H. M.; Taylor, W. I. *J. Am. Chem. Soc.* **1963**, *85*, 475−477.
(60) Nasser, A. M. A. G.; Court, W. E. *J. Ethnopharmacol.* **1984**, *11*, 99.

Scheme 14



veoline **3** depicted in Scheme 14 was completed in 10 reaction vessels with an overall yield of 28%.

In summary, a general approach (oxyanion-Cope strategy) to the synthesis of a number of indole alkaloids via the asymmetric Pictet−Spengler reaction was developed. Ajmaline **1** and alkaloid G **2** as well as norsuaveoline **3** have been successfully prepared via this approach. The oxyanion-Cope rearrangement of trans-**12a** (R═H) or **16a** (R═CH_3) to generate **17a** (R═H) or **18a** (R═CH_3), respectively, provides facile entry into the substructure of a number of sarpagine alkaloids[9,10] with extremely high diastereoselectivity (R═H, >30:1). The synthesis of norsuaveoline **3** was accomplished via this strategy. Ajmaline has been employed as a class I antiarrhythmic agent in Europe for many years but is known to exhibit serious side effects.[2−5] It is of medicinal interest to determine if the unnatural antipode, (−)-ajmaline, behaves in the same fashion as (+)-ajmaline but with fewer side effects or whether (−)-ajmaline antagonizes the activity of (+)-ajmaline at ion channels in the heart. The steps described above provide a route (from L-tryptophan) to prepare the (−)-enantiomer of ajmaline via the trans transfer of chirality in the asymmetric Pictet−Spengler reaction. The two-pot process for the improved preparation of azabicyclo[3.3.1]nonane **7a** or **7b** (300 g scale) also streamlined this enantiospecific route to **1**, **2**, and **3**. The strategy and chemistry employed in this approach will be useful for the synthesis of other alkaloids in the ajmaline/sarpagine/macroline series.

Experimental Section

Microanalysis was performed on an F and M Scientific Corp. Model 185 carbon, hydrogen, and nitrogen analyzer. Melting points were taken on a Thomas-Hoover melting point apparatus and are reported uncorrected. Proton and carbon NMR spectra were recorded on a Bruker 250 MHz, 300 MHz NMR spectrometer or a GE 500 MHz NMR spectrometer. Infrared spectra were recorded on a Mattson Polaris IR-10400 spectrometer or a Nicolet MX-1 FT-IR spectrometer. Mass spectral data (EI/CI) were obtained on a Hewlett-Packard 5985B GC-mass spectrometer or a VG Autospec (Manchester, England) mass spectrometer. Optical rotations were measured on a JASCO DIP-370 polarimeter.

All chemicals were purchased from Aldrich Chemical Co. unless otherwise noted. The analytical TLC plates used were E. Merck Brinkmann UV active silica gel (Kieselgel 60 F254) on plastic. The TLC plates were visualized under UV light or developed with spray reagents. Alkaloids were visualized with Dragendorf's reagent or a saturated solution of ceric ammonium sulfate in 50% sulfuric acid, or an aqueous solution of 2,4-dinitrophenylhydrazine in 30% sulfuric acid. Chromatography refers to flash chromatography using 230−400 mesh 60 A silica gel, grade 60 (EM reagent). Methanol was dried by distillation over magnesium metal/I_2. Tetrahydrofuran (Baker reagent), benzene (EM reagent), and toluene (EM reagent) were dried by distillation from sodium-benzophenone ketyl. Methylene chloride was dried over $MgSO_4$ and then was distilled from P_2O_5. Diisopropylamine and pyridine were dried by distillation over KOH. The preparation of **7a** (N_a-H), **8a**, and **17a** (N_a-H) on large-scale (two-pot processes) has been reported elsewhere.[62,63]

One-Pot Process for Converting D-(−)-N_a-Methyl Tryptophan Methyl Ester (10b) into *trans*-(1*S*,3*R*)-(−)-2-Benzyl-3-methoxycarbonyl-1-methoxycarbonylethyl-9-methyl-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole (11b). Benzaldehyde (100.0 g, 0.94 mol) was added to a solution of D-(−)-N_a-methyl tryptophan methyl ester (**10b**) (200.0 g, 0.87 mol) in dry methanol (1300 mL). The solution which resulted was stirred for 2 h at room temperature. The mixture was then cooled to −30 °C, and sodium borohydride (16.6 g, 0.42 mol) was added portionwise over a period of 1 h (the internal temperature was kept below −10 °C). The reaction was monitored by TLC (silica gel) with EtOAc/hexane (1:1) as the eluent (R_f = 0.59 for the product, and R_f = 0.44 for the imine), and the process was found to be complete after the addition of sodium borohydride. The solution which resulted was allowed to stir for an additional 0.5 h followed by addition of acetic acid (40 mL) at −10 °C. The solvent was removed under reduced pressure. Chloroform (1500 mL) was added to dissolve the residue, and methyl 4,4-dimethoxybutyrate (162 g, 1 mol) was then added in one portion. The reaction solution was held at reflux for 12 h. The solvent was removed under reduced pressure to provide a mixture of *trans*- and *cis*-diesters which were separated by flash chromatography (silica gel, EtOAc/hexane = 15:85) to provide the trans isomer **11b** (307.6 g, 85%) and the cis diastereomer (30.6 g, 8.4%) in pure form. The cis isomer was converted into the trans diastereomer **11b** by simply stirring in TFA/CH_2Cl_2 or heating the reaction mixture in $CHCl_3$ for a longer period of time.

***trans* 11b.** mp 119−120 °C; $[\alpha]_D^{22} = -54.6$ (c=0.95, $CHCl_3$); lit.[61] $[\alpha]_D^{28} = -54.8$ (c = 1.42, $CHCl_3$); IR (KBr) 1735 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.85−2.00 (2H, m), 2.38 (1H, dt, J = 17.5, 5.6 Hz), 2.61 (1H, ddd, J = 17.5, 9.6, 5.6 Hz), 3.05 (1H, dd, J = 15.8, 5.5 Hz), 3.12 (1H, dd, J = 15.8, 11.0 Hz), 3.39−3.81 (2H, AB_q, J = 13.1 Hz), 3.50 (3H, s), 3.65 (3H, s), 3.51 (1H, dd, J = 15.7, 5.2 Hz), 3.84 (3H, s), 4.10 (1H, dd, J = 11.0, 5.5 Hz), 7.12−7.40 (8H, m), 7.60 (1H, d, J = 8 Hz); ^{13}C NMR ($CDCl_3$) δ 20.25, 27.90, 29.60, 29.71, 51.26, 52.00, 52.79, 53.32, 56.12, 106.29, 108.90, 118.12, 119.11, 121.32, 126.52, 126.96, 128.14, 129.29, 135.67, 137.46, 139.25, 173.34, 173.87; CIMS (*m*/*e*, relative intensity) 421 (M + 1, 100%).

Anal. calcd for $C_{25}H_{28}N_2O_4$: C, 71.40; H, 6.71; N, 6.67. Found: C, 71.61; H, 6.64; N, 6.57.

cis Isomer. mp 115−116 °C; $[\alpha]_D^{28} = +20.2$ (c=1.46, $CHCl_3$); lit.[37] $[\alpha]_D^{22} = +20$ (c = 0.96, $CHCl_3$); IR (KBr) 1740 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.50 (1H, m), 1.95 (1H, m), 2.51 (1H, dt, J = 18.0, 6.0 Hz), 2.81 (1H, ddd, J = 18.0, 9.8, 6.0 Hz), 3.05 (1H, dd, J = 18.6, 6.3 Hz), 3.37 (1H, dd, J = 18.6, 2.1 Hz), 3.56 (3H, s), 3.65 (3H, s), 3.69 (3H, s), 3.75 (1H, d, J = 9.5 Hz), 3.89 (2H, s), 3.92 (1H, dd, J = 6.3, 2.1 Hz), 7.10−7.48 (8H, m), 7.58 (1H, d, J = 9.4 Hz); ^{13}C NMR (62.87 MHz, $CDCl_3$) δ 17.95, 29.10, 29.66, 29.66, 51.30, 51.83, 54.09, 57.44, 61.16, 104.70, 108.79, 118.25, 118.93, 121.28, 126.58, 127.31, 128.36, 129.07, 134.65, 137.49, 138.93, 174.07, 174.25; CIMS (*m*/*e*, relative intensity) 421 (M + 1, 100%).

Anal. calcd for $C_{25}H_{28}N_2O_4$: C, 71.40; H, 6.71; N, 6.67. Found: C, 71.37; H, 6.54; N, 6.77.

One-Pot Process for Converting *trans*-(1*S*,3*R*)-(−)-2-Benzyl-3-methoxycarbonyl-1-methoxycarbonylethyl-9-methyl-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole 11b into (6*S*,10*S*)-(−)-5-Methyl-9-oxo-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5H-cycloocta[b]indole (−)-7b. The trans diester **11b** (208.0 g, 0.5 mol) was dissolved in

(61) Cox, E. D.; Hamaker, L. K.; Li, J.; Yu, P.; Czerwinski, K. M.; Deng, L.; Bennett, D. W.; Cook, J. M.; Watson, W. H.; Krawiec, M. *J. Org. Chem.* **1997**, *62*, 44.

dry toluene (400 mL) and added to a mixture of sodium hydride (60.8 g of 60% NaH) and dry toluene (2600 mL) under an atmosphere of argon. Dry methanol (52 mL) was added carefully (a large amount of H_2 was evolved at this point). The mixture was stirred at room temperature for 0.5 h and then heated to reflux for an additional 4 h. The reaction was quenched with glacial acetic acid (50 mL), and the solvent was removed under reduced pressure. At this point the reaction vessel also contained mineral oil, which was decanted. Additional glacial acetic acid (700 mL), hydrochloric acid (1000 mL, concentrated), and water (260 mL) were added to the reaction solution, and the mixture which resulted was heated at reflux for 8 h. After removal of the solvent under reduced pressure, the residue was brought to pH 9 by the addition of aq NaOH (3 N). The mixture which resulted was extracted with CH_2Cl_2 (4 × 2000 mL), and the combined organic extracts were washed with saturated aq NH_4Cl (1000 mL) and brine (2 × 1000 mL) and dried with 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 was chromatographed on silica gel with EtOAc/hexane (3:7) to provide the tetracyclic ketone **(−)-7b** (144 g, 88%).

7b. mp 142−144 °C; $[\alpha]_D^{22} = -203.4$ ($c = 0.51$, $CHCl_3$); lit.[37] $[\alpha]_D^{28} = -200.5$ ($c = 0.62$, $CHCl_3$); IR (KBr) 1710 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.95−2.20 (2H, m), 2.45 (2H, m), 2.69 (1H, d, $J = 16.2$ Hz), 3.24 (1H, dd, $J = 16.2$, 6.3 Hz), 3.61 (3H, s), 3.71 (2H, s), 3.76 (1H, d, $J = 6.3$ Hz), 4.05 (1H, t, $J = 4.0$ Hz), 7.15 (1H, t, $J = 8.1$ Hz), 7.25 (1H, t, $J = 8.2$ Hz), 7.30−7.38 (6H, m), 7.52 (1H, d, 8.2 Hz); CIMS (*m*/*e*, relative intensity) 331 (M + 1, 100%).

Anal. calcd for $C_{22}H_{22}N_2O$: C, 79.97; H, 6.71; N, 8.48. Found: C, 79.98; H, 6.75; N, 8.48.

(6*S*,10*S*)-(−)-9-Formyl-12-benzyl-6,7,10,11-tetrahydro-6,10-imino-5H-cycloocta[b]indole 8a. A solution of diisopropylamine (56.38 mL, 0.4 mol) and *n*-butyllithium (160 mL, 2.5 M in hexane) in THF (300 mL) was cooled to −78 °C under an atmosphere of argon. α-Chloromethyl phenyl sulfoxide (70 g, 0.4 mol) was dissolved in THF (80 mL) and added to the above chilled solution of freshly generated LDA. The yellow mixture which resulted was stirred for 30 min at −78 °C, after which the ketone **7a**[62,63] (50 g, 0.161 mol) in THF (400 mL) was added dropwise via a double-ended needle over a period of 1 h. The reaction solution was stirred for 2 h and then brought to room temperature and diluted with THF (2000 mL). A solution of aq KOH (1300 mL, 15 N) was added, and the heterogeneous mixture was stirred at room temperature for 16 h. The organic layer was removed, and the aqueous phase was extracted with EtOAc (3 × 1000 mL). The combined organic fractions were washed with saturated aq NH_4Cl (500 mL) and brine (500 mL) and dried with K_2CO_3. The solvent was removed under reduced pressure to provide a crude mixture of diastereomers (1:1) of the phenylsulfinyl oxirane. The crude mixture was used directly in the next step without further separation and purification. The mixture of phenylsulfinyl oxirane diastereomers was added to a solution of dioxane (2500 mL), which contained lithium perchlorate (20 g). The slurry was heated at reflux under an atmosphere of argon for 4 days. The reaction was monitored by TLC (silica gel, EtOAc/hexane = 2:3) on the basis of the disappearance of oxirane, which has a lower R_f value. The reaction solution was allowed to cool to room temperature and diluted with CH_2Cl_2 (4000 mL). The organic layer was washed with 10% aq ammonia (500 mL) and brine (500 mL) and dried with K_2CO_3. The solvent was removed under reduced pressure. The oil which resulted was chromatographed (silica gel, EtOAc/hexane = 20:80) to provide the α,β-unsaturated aldehyde **8a** as an amorphous solid (45 g, 87%): $[\alpha]_D^{27} = -322.8$ ($c = 1.05$, $CHCl_3$); FTIR (NaCl) 1670, 3393 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.37 (1H, dd, $J = 19.20$, 5.00 Hz), 2.65 (1H, d, $J = 16.40$ Hz), 2.95 (1H, dd, $J = 19.20$, 5.20 Hz), 3.22 (1H, dd, $J = 16.50$, 5.90 Hz), 3.71 (1H, d, $J = 13.40$ Hz), 3.85 (1H, d, $J = 13.40$ Hz), 4.01 (1H, d, $J = 5.50$ Hz), 4.22 (1H, d, $J = 5.60$ Hz), 6.72 (1H, d, $J = 2.90$ Hz), 7.12 (1H, t, $J = 6.75$ Hz), 7.17 (1H, t, $J = 6.90$ Hz), 7.25−7.50 (6H, m), 7.49 (1H, d, $J = 7.20$ Hz), 7.70 (1H, s), 9.33 (1H, s); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 22.12, 32.96, 49.36, 50.29, 56.40, 106.31, 110.99, 118.40, 119.72, 121.91, 127.33, 127.49, 128.49, 128.81, 133.28, 136.06, 138.65, 143.66, 147.81, 192.56; CIMS (*m*/*e*, relative intensity) 329 (M + 1, 100%).

Anal. calcd for $C_{22}H_{20}N_2O$: C, 80.46; H, 6.14; N, 8.53. Found: C, 79.92; H, 6.12; N, 8.45.

(6*S*,10*S*)-(−)-5-Methyl-9-formyl-12-benzyl-6,7,10,11-tetrahydro-6,10-imino-5H-cycloocta[b]indole 8b was prepared following the procedure reported in ref 37.

(6*S*, 10*S*)-5-Methyl-9-(1′-hydroxy-hex-3′-enyl)-12-benzyl-6,7,10,-11-tetrahydro-6,10-imino-5H-cycloocta[b]indole *cis*-16b. To a 100 mL flask which contained lithium metal (81.0 mg, 11.7 mmol) in dry THF (30 mL) was added biphenyl (1.8 g, 11.7 mmol). The mixture was stirred for 16 h until the lithium was consumed. Freshly dried BaI_2 (2.20 g, 5.6 mmol) was added and the reaction mixture stirred for 1 h and then cooled to −78 °C. A solution of the α,β-unsaturated aldehyde **8b** (1.03 g, 3.0 mmol) and cis 1-bromo-2-pentene **14b** (745 mg, 5. 0 mmol) in THF (10 mL) was added via a double-ended needle over 30 min. The mixture was stirred at −78 °C for an additional 2 h and then quenched with 10% NH_4OH (3 mL). The solvent was removed under reduced pressure. The residue which resulted was dissolved in a mixture of CH_2Cl_2 and H_2O (1:1, 150 mL) and the aqueous layer was extracted with CH_2Cl_2 (20 mL × 3). The combined organic layers were washed with brine (30 mL), dried (K_2CO_3), and concentrated. The residue which resulted was first passed through a short column of alumina (elution with hexane) to remove biphenyl. The crude product was then chromatographed on silica gel (ethyl acetate/hexane = 3:7) to obtain the 1,2-addition product (cis-**16b**) as a mixture of two diastereomers: major isomer, 0.77 g, (62.3%); and minor isomer, 0.28 g, (22.8%) (combined yield 85.1%).

Major Isomer of *cis*-16b. IR (KBr) 3387 cm^{-1}; ^1H NMR (250 Hz, $CDCl_3$) δ 0.97 (3H, t, $J = 7.4$ Hz), 2.01 (3H, m), 2.31 (1H, m), 2.45 (1H, m), 2.75 (1H, dd, $J = 17.3$, 5.4 Hz), 2.87 (1H, d, $J = 5.7$ Hz), 3.13 (1H, dd, $J = 16$, 5.7 Hz), 3.57 (3H, s), 3.80 (3H, m), 4.02 (2H, d, $J = 5.6$ Hz), 5.30 (1H, m), 5.50 (1H, m), 5.6 (1H, s), 7.30 (9H, m); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 14.09 (CH_3), 20.71 (CH_2), 22.93 (CH_2), 29.15 (CH_3), 29.99 (CH_2), 33.31 (CH_2), 48.32 (CH), 52.49 (CH), 56.54 (CH_2), 73.44 (CH), 105.28 (C), 108.62 (C), 118.10 (CH), 118.80 (CH), 120.06 (CH), 120.83 (CH), 124.60 (CH), 126.95 (CH), 128.22 (CH), 128.72 (CH), 134.72 (CH), 135.71 (C), 137.08 (C), 139.13 (C), 141.42 (C); EIMS (*m*/*e*, relative intensity) 412 (M^+, 100%).

Anal. calcd for $C_{28}H_{32}N_2O \cdot {}^1/_2H_2O$: C, 79.81; H, 7.83; N, 6.65. Found: C, 79.54; H, 7.66; N, 6.63.

Minor Isomer of *cis*-16b. IR (KBr) 3386 cm^{-1}; ^1H NMR (250 Hz, $CDCl_3$) δ 0.96 (3H, t, $J = 7.5$ Hz), 2.05 (3H, m), 2.31 (2H, m), 2.69 (2H, m), 3.09 (1H, dd, $J = 15.7$, 5.6 Hz), 3.52 (1H, m), 3.64 (3H, s), 3.72 (2H, dd, $J = 31.9$, 13.5 Hz), 4.02 (2H, d, $J = 5.6$ Hz), 5.39 (1H, m), 5.51 (1H, m), 5.71 (1H, s), 7.23 (9H, m); ^{13}C NMR (62.8 Hz, $CDCl_3$) δ 14.19 (CH_3), 20.75 (CH_2), 22.85 (CH_2), 29.21 (CH_3), 29.59 (CH_2), 34.99 (CH_2), 48.78 (CH), 52.94 (CH), 56.67 (CH_2), 72.17 (CH), 105.19 (C), 108.70 (CH), 117.41 (CH), 118.03 (CH), 118.88 (CH), 120.91 (CH), 124.55 (CH), 127.03 (CH), 128.29 (CH), 128.72 (CH), 134,85 (CH), 135.85 (C), 135.85 (C), 137.11 (C), 139.11 (C), 142.61 (C); EIMS (*m*/*e*, relative intensity) 412 (M^+, 100%).

Anal. calcd for $C_{28}H_{32}N_2O \cdot {}^1/_3H_2O$: C, 80.38; H, 7.81; N, 6.69. Found: C, 80.43; H, 7.68; N, 6.55.

(6*S*,10*S*)-5-Methyl-9-(1′-hydroxy-hex-3′-enyl)-12-benzyl-6,7,10,-11-tetrahydro-6,10-imino-5H-cycloocta[b]indole *trans*-16b. Lithium metal (220 mg, 31.7 mmol) was added to a solution of biphenyl (5.04 g, 32.7 mmol) in THF (100 mL) at 0 °C. The solution was allowed to stir at room temperature for 12 h and then was cooled to −78 °C. Freshly dried BaI_2 (6.04 g, 15.4 mmol) was added to the above solution at −78 °C. The mixture was stirred at room temperature for 2 h and then cooled to −78 °C. A solution of trans 1-bromo-2-pentene **14a** (2.14 g, 14.3 mmol) and α,β-unsaturated aldehyde **8b** (1.18 g, 3.6 mmol) in THF (60 mL) was added to the above reaction mixture at −78 °C dropwise over a period of 1 h. The reaction solution was stirred at −78 °C for 4 h and then was brought to pH 7 with an aqueous solution of NH_4Cl and then extracted with EtOAc (3 × 50 mL). The organic layer was washed with brine (2 × 50 mL) and dried (K_2CO_3). The solvent was removed under reduced pressure. The oil which resulted was chromatographed (silica gel, EtOAc/hexane = 30:70) to

(62) Yu, P., Ph.D. Thesis, University of Wisconsin-Milwaukee, 1999.
(63) Yu, P.; Wang, T.; Li, J.; Cook, J. M. manuscript in preparation.

provide the allylic alcohol trans-**16b** (1.28 g, 90%) as a mixture of two diastereomers in a ratio of 4:1.

Major Isomer of *trans*-16b. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (3H, t, J = 7.3 Hz), 2.02 (2H, m), 2.29 (1H, t, J = 7.4), 2.75 (1H, dd, J = 17.0, 7.5 Hz), 2.85 (1H, d, J = 16 Hz), 3.10 (1H, dd, J = 16.0, 6.0 Hz), 3.56 (3H, s), 3.68 (2H, dd, J = 19.0, 14.8 Hz), 3.85 (1H, t, J = 5.66 Hz), 4.02 (1H, t, J = 5.8 Hz), 5.27−5.43 (1H, m), 5.56−5.61 (2H, m), 7.06 (1H, t, J = 7.6 Hz), 7.17 (1H, t, J = 7.7 Hz), 7.24−7. 36 (6H, m), 7.41 (1H, d, J = 7.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.76, 23.04, 25.65, 29.22, 29.98, 38.88, 48.51, 52.58, 56.67, 73.23, 105.43, 108.68, 118.19, 118.86, 119.98, 120.91, 125.05, 127.08, 127.30, 128.30, 128.78, 135.84, 136.06, 137.19, 139.24, 141.47; EIMS (*m*/*e*, relative intensity) 412 (M^+, 100%).

Anal. calcd for $C_{28}H_{32}N_2O$: C, 81.35; H, 7.99; N, 6.78. Found: C, 81.25; H, 8.03; N, 6.57.

Minor Isomer of *trans*-16a. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (3H, t, J = 7.3 Hz), 2.02 (2H, m), 2.20 (1H, t, J = 7.4), 2.35 (1H, m), 2.60−2.80 (2H, m), 2.71 (1H, d, J = 16.7 Hz), 3.08 (1H, dd, J = 16.5, 7.5 Hz), 3.57 (3H, s), 3.61 (1H, d, J = 13.5 Hz), 3.80 (1H, d, J = 13.5 Hz), 4.03 (1H, d, J = 6.0 Hz), 5.40−5.72 (3H, m), 7.07 (1H, t, J = 7.6 Hz), 7.17 (1H, t, J = 7.7 Hz), 7.24−7. 36 (6H, m), 7.47 (1H, d, J = 7.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.78, 23.00, 25.64, 29.20, 29.51, 40.50, 48.86, 52.95, 56.73, 72.01, 105.30, 108.70, 117.41, 118.06, 118.89, 120.91, 124.91, 127.04, 127.30, 128.31, 128.70, 136.04, 137.16, 139.71, 142.00; EIMS (*m*/*e*, relative intensity) 412 (M^+, 100%).

Anal. calcd for $C_{28}H_{32}N_2O$: C, 81.35; H, 7.99; N, 6.78. Found: C, 81.00; H, 7.69; N, 7.03.

1,2-Addition of *trans*-1-Bromo-2-pentene 14a to the α,β-Unsaturated Aldehyde 8a To Provide the Diastereomers of (6*S*,10*S*)-9-(1′-Hydroxy-3′-hexenyl)-12-benzyl-6,7,10,11-tetrahydro-6,10-imino-5H-cycloocta[b]indole *trans*-12a. A mixture of lithium metal (1.72 g, 0.248 mol) and biphenyl (40.0 g, 0.260 mol) in freshly distilled THF (400 mL) was stirred at room temperature overnight. Freshly dried BaI_2 (47.0 g, 0.120 mol) was then added to the above dark blue solution, and the mixture which resulted was stirred at room temperature for 1 h. The dark red solution which formed was cooled to −78 °C in a cooling bath of dry ice/EtOAc. A solution of α,β-unsaturated aldehyde **8a** (10.0 g, 0.0305 mol) and *trans*-1-bromo-3-pentene (18.8 g, 0.126 mol) in THF (160 mL) was added dropwise to the above chilled solution of barium metal after which the mixture was stirred at −78 °C for an additional 2 h. The reaction mixture was poured into an ice cooled aqueous solution of NH_4OH (10%, 100 mL) and extracted with EtOAc (3 × 200 mL). The combined organic layers were washed with water (100 mL) and brine (100 mL) and then dried with K_2CO_3. The solvent was concentrated to give a crude oil which was purified by flash chromatography (EtOAc/hexane = 20:80) to provide the isomers of allylic alcohol trans-**12a** (11.0 g, 90%) as a mixture of two diastereomers in a ratio of 4:1.

Major Isomer of *trans*-12a. FTIR (NaCl) 1457, 1470, 1654, 2958, 3439 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.98 (3H, t, J = 7.40 Hz), 1.95−2.05 (4H, m), 2.31 (2H, t, J = 6.30 Hz), 2.67 (1H, dd, J = 17.20, 5.50 Hz), 2.85 (1H, d, J = 16.0 Hz), 3.12 (1H, dd, J = 15.70, 5.20 Hz), 3.70 (1H, d, J = 13.40 Hz), 3.81 (1H, d, J = 13.90 Hz), 3.89 (2H, bs), 4.03 (1H, t, J = 6.10 Hz), 5.25−5.60 (3H, m), 7.15−7.45 (8H, m), 7.50 (1H, d, J = 7.00 Hz), 7.73 (1H, s); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 13.64, 22.99, 25.71, 30.69, 38.83, 49.45, 52.66, 56.54, 73.24, 106.14, 110.92, 118.21, 119.35, 120.43, 121.37, 125.05, 127.10, 127.68, 128.35, 128.91, 134.79, 135.93, 136.08; CIMS (*m*/*e*, relative intensity) 399 (M + 1, 100%).

Anal. calcd for $C_{27}H_{30}N_2O$: C, 81.37; H, 7.59; N, 7.03. Found: C, 81.48; H, 7.41; N, 6.90.

Minor Isomer of *trans*-12a. FTIR (NaCl) 1457, 1470, 1654, 2958, 3439 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.98 (3H, t, J = 7.50 Hz), 1.98−2.10 (4H, m), 2.20−2.50 (2H, m), 2.67 (1H, d, J = 16.0 Hz), 2.95−3.15 (1H, m), 3.05 (1H, s), 3.56 (1H, d, J = 5.63 Hz), 3.69 (1H, d, J = 13.60 Hz), 3.80 (1H, d, J = 13.60 Hz), 3.92 (1H, d, J = 4.43 Hz), 4.15 (1H, bs), 4.80−5.70 (3H, m), 7.10−7.45 (8H, m), 7.46 (1H, d, J = 4.75 Hz), 7.67 (1H, s); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 13.62, 22.88, 25.69, 30.26, 40.52, 49.60, 53.01, 56.60, 71.90, 106.30, 110.83, 117.78, 118.11, 119.39, 121.39, 124.90, 127.11, 127.69, 128.34, 128.81, 135.85, 136.01, 139.10, 140.00, 141.86; CIMS (*m*/*e*, relative intensity) 399 (M + 1, 100%).

Anal. calcd for $C_{27}H_{30}N_2O$: C, 81.37; H, 7.59; N, 7.03. Found: C, 81.48; H, 7.41; N, 6.90.

Oxy-anion Cope Rearrangement To Convert (6*S*,10*S*)-9-(1′-Hydroxy-3′-hexenyl)-12-benzyl-6,7,10,11-tetrahydro-6,10-imino-5H-cycloocta[b]indole *trans*-12a into (6*S*,10*S*)-8-(1′-Ethyl-2′-propenyl)-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5H-cycloocta[b]indole-9-carboxaldehydes 17a and 17b. A solution of both diastereomers of allylic alcohol trans-**12a** (10.2 g, 25.7 mmol) obtained from the last step and 18-crown-6 (14.5 g, 54.9 mmol) in dry dioxane (1000 mL) was added to a suspension of KH (5.60 g, 140 mmol) in dry dioxane (500 mL). The light yellow-colored mixture which resulted was stirred at room temperature for 2 h and then heated to reflux under argon for 14 h. The reaction mixture was allowed to cool to room temperature, after which it was quenched by careful addition of methanol (50 mL) and then extracted with methylene chloride (3 × 500 mL). The combined organic extracts were washed with water (200 mL) and brine (200 mL), dried (K_2CO_3), and concentrated under reduced pressure. The residue which resulted was chromatographed on silica gel (EtOAc/hexane = 2:8) to provide alkenic aldehydes **17a** and **17b** which were the rearrangement products from the α face (8.7 g, 85%); the ratio of **17a** to **17b** was 4:1 on the basis of the isolated material. Only a trace of the mixture of alkenic aldehydes which arose from rearrangement from the β face was detected by ^{1}H NMR.

Major Isomer 17a. FTIR (NaCl) 1452, 1708, 2954, 3396 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.69−0.90 (4H, m), 1.40−1.65 (2H, m), 1.83 (1H, d, J = 12.70 Hz), 2.16 (1H, dt, J = 12.70, 4.10 Hz), 2.29 (1H, dq, J = 9.90, 3.15 Hz), 2.48 (1H, d, 16.80 Hz), 2.49 (1H, d, J = 1.70 Hz), 3.34 (1H, dd, J = 16.80, 7.40 Hz), 3.59 (1H, s), 3.69 (1H, dd, J = 7.20, 1.90 Hz), 4.00 (1H, s), 4.87−5.04 (2H, m), 5.15−5.70 (1H, m), 7.15−7.39 (8H, m), 7.57 (1H, dd, J = 6.68, 2.10 Hz), 7.75 (1H, s), 9.94 (1H, s); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 11.55, 21.88, 24.60, 31.85, 33.10, 46.94, 52.41, 53.65, 55.86, 57.78, 107.48, 111.08, 116.79, 118.11, 119.55, 121.56, 127.05, 127.17, 128.38, 128.65, 133.29, 135.84, 139.04, 140.67, 204.66; CIMS (*m*/*e*, relative intensity) 399 (M + 1, 100%).

Anal. Calcd for $C_{27}H_{30}N_2O$: C, 81.37; H, 7.59; N, 7.03. Found: C, 81.48; H, 7.61; N, 6.70.

Minor Isomer 17b. FTIR (NaCl) 1449, 1709, 2913, 2958, 3396 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.78 (3H, t, J = 7.20 Hz), 0.85−1.30 (2H, m), 1.35−1.50 (1H, m), 1.70−2.05 (3H, m), 2.57 (1H, d, J = 17.00 Hz), 2.91 (1H, dt, J = 11.90, 4.13 Hz), 3.08 (1H, dd, J = 17.10, 6.70 Hz), 3.62 (1H, t, J = 6.10 Hz), 3.70 (2H, q, J = 9.40 Hz), 3.89 (1H, t, J = 3.10 Hz), 4.88−5.03 (2H, m), 5.30−5.50 (1H, m), 7.14−7.39 (8H, m), 7.53 (1H, dd, J = 6.60, 1.80 Hz), 7.71 (1H, s), 9.75 (1H, d, J = 3.50 Hz); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 12.44, 18.99, 22.36, 32.34, 33.12, 49.01, 51.52, 53.29, 56.61, 57.08, 107.30, 111.04, 116.92, 118.16, 119.57, 121.58, 127.05, 127.17, 128.41, 128.65, 133.40, 135.92, 139.01, 140.26, 205.76; CIMS (*m*/*e*, relative intensity) 399 (M + 1, 100%).

Anal. calcd for $C_{27}H_{30}N_2O$: C, 81.37; H, 7.59; N, 7.03. Found: C, 80.78; H, 7.51; N, 6.65.

Oxy-anion Cope Rearrangement To Convert (6*S*,10*S*)-5-Methyl-9-(1′-hydroxy-hex-3′-enyl)-12-benzyl-6,7,10,11-tetrahydro-6,10-imino-5H-cycloocta[b]indole *cis*-16b into (6*S*,10*S*)-5-Methyl-8-(1′-ethyl-2′-propenyl)-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5H-cycloocta[b]indole-9-carboxaldehydes 18a, 18c, 19, and 20. A solution of allylic alcohol *cis*-**16b** (100 mg, 0.243 mmol) and 18-crown-6 (128 mg, 0.48 mmol) in dry dioxane (5 mL) was added to a suspension of KH (60 mg, 1.54 mmol) in dry dioxane (5 mL). The light yellow-colored mixture which resulted was stirred at room temperature for 0.5 h and then heated to reflux under argon for 2 h. The reaction mixture was allowed to cool to room temperature and quenched by careful addition of ethanol (2 mL). A saturated solution of NH_4Cl (50 mL) and ethyl acetate (100 mL) was added to the above mixture. The aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with water and brine, dried (K_2CO_3), and concentrated under reduced pressure. The residue which formed was chromatographed on silica gel (EtOAc/hexane =

20:80) to provide alkenic aldehydes **18a**, **19**, **20**, and **18c** in a ratio of 2:3:3:2. The combined yield for the rearrangement was 83%.

20. IR (KBr) 1722 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.69 (3H, t, $J = 7.3$ Hz), 1.12 (1H, m), 1.78 (2H, m), 2.05 (2H, m), 2.50 (1H, d, $J = 17.1$ Hz), 2.91 (1H, m), 3.09 (1H, dd, $J = 6.9$, 17.1 Hz), 3.58 (3H, s), 3.59 (1H, m), 3.61 (1H, d, $J = 13.4$ Hz), 3.71 (1H, d, $J = 13.4$ Hz), 3.98 (1H, m), 4.91 (1H, dd, $J = 1.8$, 17 Hz), 5.12 (1H, dd, $J = 2.1$, 10.2 Hz), 5.56 (1H, m), 7.23 (8H, m), 7.50 (1H, d, $J = 7.4$ Hz), 9.74 (1H, d, $J = 2.3$ Hz); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 12.07, 19.00, 25.27, 28.97, 29.26, 32.00, 46.70, 50.34, 52.12, 56.62, 57.35, 106.56, 108.86, 117.67, 118.13, 119.02, 121.01, 126.24, 127.11, 128.32, 128.67, 134.01, 138.10, 139.92, 204.53; EIMS (*m*/*e*, relative intensity) 412 (M^+, 100%).

18a. IR (KBr) 1718 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.69 (3H, t, $J = 7$ Hz), 1.61 (3H, m), 1.74 (1H, m), 2.12 (1H, dd, $J = 4.2$, 12.7 Hz), 2.25 (1H, m), 2.45 (1H, m), 2.46 (1H, d, $J = 16.9$ Hz), 3.31 (1H, dd, $J = 7.5$, 16.9 Hz), 3.54 (1H, d, $J = 4.4$ Hz), 3.55 (1H, m) 3.55 (3H, s), 3.68 (1H, dd, $J = 2.1$, 7.3 Hz), 4.06 (1H, m), 4.86 (1H, dd, $J = 2.3$, 16.8 Hz), 5.00 (1H, dd, $J = 2.3$, 10.2 Hz), 5.18 (1H, m), 7.2 (8H, m), 7.56 (1H, d, 7.4 Hz), 9.92 (1H, t, $J = 1.5$ Hz); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 11.46, 21.90, 24.54, 28.91, 31.19, 32.87, 46.94, 50.96, 53.63, 55.73, 57.86, 106.12, 108.95, 116.71, 118.08, 118.98, 121.02, 126.12, 127.13, 128.31, 128.67, 134.44, 138.97, 140.61, 204.49; EIMS (*m*/*e*, relative intensity) 412 (M^+, 100%).

19. IR (KBr) 1721 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.69 (3H, t, $J = 7.3$ Hz), 1.55 (3H, m), 1.68 (1H, m), 1.97 (1H, dd, $J = 4.2$, 12.8 Hz), 2.11 (1H, m), 2.48 (1H, d, $J = 16.8$ Hz), 2.49 (1H, m), 3.39 (1H, dd, $J = 7.5$, 16.9 Hz), 3.51 (1H, m), 3.56 (3H, s), 3.62 (1H, d, $J = 8.5$ Hz), 3.69 (1H, d, $J = 4.4$ Hz), 4.06 (1H, m), 4.82 (2H, m), 5.09 (1H, m), 7.2 (8H, m), 7.52 (1H, d $J = 7.2$ Hz), 10.06 (1H, t, $J = 0.7$ Hz); EIMS (*m*/*e*, relative intensity) 412 (M^+, 100%).

18c was composed of a mixture of two isomers which were not separable by chromatography. ^1H NMR (250 MHz, $CDCl_3$) δ 2.6 (1H, dd, $J = 4.9$, 17.2 Hz), 3.05 (1H, m), 3.19 (1H, m), 5.61 (1H, m), 9.97 (1H, s).

(6*S*,10*S*)-5-Methyl-8-(1′-ethyl-pent-2′-enyl)-12-benzyl-6,7,8,9,10,-11-hexahydro-6,10-imino-cycloocta[b]indole-9-carboxaldehydes 23a,b,c,d, 26a,b, and 27a,b were prepared following the procedure reported in ref 37. The spectral properties of these bases were identical to the reported values.[37]

21-*O*-Acetylajmalal A Ethylene Acetal 28. The *S*-aldehyde **27a** (100 mg, 0.218 mmol)[37] was dissolved in dry DME (5 mL), and the Pd/C catalyst (10%, 10 mg) was added. The slurry which resulted was allowed to stir at room temperature under 1 atm of H_2 for 48 h. Examination of the mixture by TLC (silica gel, hexane/EtOAc = 1:1) indicated the disappearance of starting **27a** and the appearance of a new component (lower R_f). Acetic anhydride (44.5 mg, 0.436 mmol) and DMAP (26.7 mg, 0.218 mmol) were then added directly to the flask, and this mixture was stirred for an additional 2 h. The catalyst was filtered from the reaction mixture and washed with DME (5 mL × 3), and the filtrate was concentrated under reduced pressure. The residue which resulted was dissolved in $CHCl_3$ (150 mL) and washed with a solution of aq $NaHCO_3$ (10%, 40 mL) and brine (40 mL). The $CHCl_3$ layer was dried ($MgSO_4$), and the solvent was concentrated under reduced pressure. The residue was passed through a short wash column of silica gel (hexane/EtOAc = 4:1) to provide 81.4 mg of 21-*O*-acetylajmalal A ethylene acetal **28** (91%).

28. IR (KBr) 1467, 1740, 2932 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.95 (3H, t, $J = 6.8$ Hz), 1.48−1.72 (5H, m), 1.78 (1H, t, $J = 10.5$ Hz), 1.98 (1H, t, $J = 9$ Hz), 2.08 (1H, s), 2.12 (3H, s), 3.01 (1H, dd, $J = 16.2$, 6.4 Hz), 3.31 (1H, d, $J = 16.3$ Hz), 3.65 (2H, m), 3.66 (3H, s), 3.82 (2H, m), 4.45 (1H, dd, $J = 3.8$, 6.8 Hz), 4.48 (1H, d, $J = 8.3$ Hz), 5.39 (1H, d, $J = 3.8$ Hz), 7.06 (1H, dt, $J = 7.8$, 1.1 Hz), 7.19 (1H, dt, $J = 7.8$, 1.1 Hz), 7.26 (1H, d, $J = 7.6$ Hz), 7.48 (1H, d, $J = 7.3$); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 11.68, 21.44, 22.76, 24.61, 27.21, 29.23, 30.39, 37.43, 42.20, 45.98, 49.85, 64.04, 64.62, 89.18, 103.34, 104.87, 108.55, 118.43, 118.73, 120.62, 126.49, 137.46, 138.46, 168.48; HR EIMS $C_{24}H_{30}N_2O_4$ requires (*m*/*e*, relative intensity) 410.2205, found 410.2214 (100%).

Anal. calcd for $C_{24}H_{30}N_2O_4$: C, 70.24; H, 7.32; N, 6.83. Found: C, 70.05; H, 7.51; N, 6.67.

2-Epihydroxydiacetylajmaline 29. 21-*O*-Acetylajmalal A ethylene acetal **29** (100 mg, 0.244 mmol) was added to a mixture of acetic acid (3 mL) and aqueous concentrated HCl (0.2 mL), and the mixture which resulted was stirred for 3 h at room temperature. Acetic anhydride (3 mL) was then added, and the reaction mixture was saturated with HCl gas and then stirred at room temperature for 2 days. The solvent was removed under reduced pressure. The residue which resulted was dissolved in a mixture of CH_2Cl_2 and $NaHCO_3$ (2:1, 150 mL), and the aqueous layer was extracted with CH_2Cl_2 (20 mL × 3). The combined organic layers were washed with brine (30 mL), dried (K_2CO_3), and concentrated under reduced pressure. The crude product was chromatographed on silica gel (hexane/ethyl acetate = 3:7) to obtain 88.3 mg of the hydroxyl compound **29** as a single diastereomer (85%). The structure of this material was confirmed by X-ray crystallography.[30]

29. IR (KBr) 1471, 1738, 3187, 3495 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.94 (3H, t, $J = 7.1$ Hz), 1.4 (4H, m), 1.93 (3H, s), 1.97 (1H, t, $J = 6.0$ Hz), 2.11 (3H, s), 2.30 (2H, d, $J = 2.7$ Hz), 2.38 (2H, m), 2.72 (3H, s), 2.82 (1H, s), 3.23 (1H, m), 3.40 (1H, d, $J = 10$ Hz), 5.14 (1H, s), 5.31 (1H, s), 6.59 (1H, d, $J = 7.8$ Hz), 6.75 (1H, t, $J = 7.5$ Hz), 7.09 (1H, d, $J = 7.4$ Hz), 7.15 (1H, t, $J = 7.7$ Hz); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 12.12, 21.09, 21.26, 24.42, 25.67, 27.90, 28.53, 31.18, 39.48, 47.06, 53.01, 57.08, 61.72, 78.58, 87.94, 97.14, 108.46, 118.58, 124.34, 127.68, 128.46, 151.77, 169.28, 169.88; HR EIMS $C_{24}H_{30}N_2O_5$ requires (*m*/*e*, relative intensity) 426.2154, found 426.2140-(100%).

Anal. calcd for $C_{24}H_{30}N_2O_5$: C, 67.61; H, 7.04; N, 6.57. Found: C, 67.38; H, 7.19; N, 6.28.

2-Epidiacetylajmaline 30 and Diacetylajmaline 31. 2-Epihydroxydiacetylajmaline **29** (50 mg, 0.12 mmol) was dissolved in dry CH_2Cl_2 (5 mL), and BF_3·etherate (0.4 mL) was added dropwise over 5 min, after which PtO_2 (30 mg) was added. The mixture was hydrogenated (benchtop) under 1 atm H_2 for 24 h. The reaction mixture was diluted with CH_2Cl_2 (100 mL), washed with an aqueous solution of $NaHCO_3$ (10%, 30 mL) and brine (30 mL), and dried ($MgSO_4$). The solvent was removed under reduced pressure. The residue was separated by preparative TLC (silica gel, hexane/ethyl acetate = 3:7) to provide 2-epidiacetylajmaline (**30**) (25.6 mg, 53.4%) and diacetylajmaline (**31**) (17.1 mg, 35.6%).

30. IR (KBr) 1463, 1609, 1738, 2930 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.95 (3H, t, $J = 7.3$ Hz), 1.4 (2H, m), 1.52 (2H, m), 1.72 (1H, d, $J = 11.8$ Hz), 1.93 (3H, s), 2.01 (1H, m), 2.11 (3H, s), 2.35 (2H, m), 2.49 (1H, dd, $J = 11.7$, 4.9 Hz), 2.63 (3H, s), 3.18 (2H, dd, $J = 11.1$, 5.7), 3.65 (1H, d, $J = 9.8$, 4.8 Hz), 5.12 (1H, s), 5.26 (1H, s), 6.63 (1H, d, $J = 7.5$ Hz), 6.75 (1H, t, $J = 7.3$), 7.09 (1H, d $J = 7.5$ Hz), 7.19 (1H, dt, $J = 7.7$, 1.3); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 12.17, 21.17, 21.31, 23.54, 25.49, 25.91, 34.14, 37.21, 40.04, 47.51, 47.91, 55.89, 57.00, 74.90, 78.33, 88.65, 109.10, 118.81, 123.87, 128.27, 129.78, 154.39, 169.39, 170.03; HR EIMS $C_{24}H_{30}N_2O_4$ requires (*m*/*e*, relative intensity) 410.2207, found 410.2227 (100%).

Anal. calcd for $C_{24}H_{30}N_2O_4$: C, 70.24; H, 7.32; N, 6.83. Found: C, 70.28; H, 7.40; N, 6.73.

31. IR (KBr) 1611, 1738, 3052, 3187, 3495 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.95 (3H, t, $J = 7.1$ Hz), 1.42 (1H, m), 1.47 (1H, m), 1.70 (1H, m), 1.74 (1H, m), 1.77 (1H, m), 1.93 (1H, dd, $J = 12.7$, 5.5 Hz), 2.07 (1H, m), 2.10 (3H, s), 2.15 (1H, d, $J = 12$ Hz), 2.21 (3H, s), 2.50 (1H, m), 2.72 (1H, s), 2.78 (3H, s), 3.05 (1H, t, $J = 5.9$ Hz), 3.63 (1H, d, $J = 8$ Hz), 5.25 (1H, s), 5.28 (1H, s), 6.68 (1H, d, $J = 7.8$ Hz), 6.80 (1H, t, $J = 7.6$ Hz), 7.1 (1H, t, $J = 7.6$ Hz), 7.30 (1H, d, $J = 7.3$ Hz);^{13}C NMR (62.8 MHz, $CDCl_3$) δ 12.17, 21.23, 21.34, 25.11, 27.40, 31.91, 34.63, 36.22, 43.11, 43.76, 48.53, 53.66, 54.50, 79.36, 80.16, 88.91, 109.78, 119.33, 122.45, 127.73, 132.23, 153.99, 169.13, 170.43; HR EIMS $C_{24}H_{30}N_2O_4$ requires (*m*/*e*, relative intensity) 410.2205, found 410.2232 (100%).

(+)-Ajmaline 1. Diacetylajmaline **31** (20 mg, 0.049 mmol) was dissolved in CH_3OH (3 mL), and a solution of aq K_2CO_3 (20%, 0.5 mL) was added, after which the reaction mixture was stirred at room temperature for 2 days. The solvent was removed under reduced pressure. The residue which resulted was dissolved in a mixture of CH_2Cl_2 and H_2O (1:1, 150 mL), and the aqueous layer was extracted with CH_2Cl_2 (20 × 3). The combined CH_2Cl_2 extracts were washed with brine (30 mL), dried (K_2CO_3), and concentrated under reduced

pressure to provide 14.8 mg of (+)-ajmaline (**1**) (93%), which was identical in all respects (co-TLC, NMR, optical rotation)[1,13] with that of an authentic sample (purchased from Sigma Company).

1. IR (KBr) 1463, 1605, 2952, 3402 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.97 (3H, t, J = 7 Hz), 1.36 (1H, m), 1.46 (1H, m), 1.48 (2H, m), 1.84 (1H, dd, J = 14, 10 Hz), 1.95 (1H, dd, J = 12, 5 Hz), 2.02 (1H, m), 2.04 (1H, m), 2.27 (1H, m), 2.62 (1H, s), 2.76 (3H, s), 3.03 (1H, m), 3.58 (1H, d, J = 10 Hz), 4.21 (1H, s), 4.41 (1H, s), 6.62 (1H, d, J = 7.7 Hz), 6.73 (1H, t, J = 7.4 Hz), 7.10 (1H, t, J = 7.7 Hz), 7.43 (1H, d, J = 7.4 Hz); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 15.35, 26.67, 31.55, 34.76, 37.29, 37.97, 46.38, 48.62, 51.32, 56.00, 59.46, 81.19, 82.57, 91.46, 112.66, 122.29, 125.85, 130.45, 136.46, 157.01; EIMS (*m*/*e*, relative intensity) 326 (100%). The spectral data for **1** were identical to the published values including the optical rotation; $[\alpha]_D^{27}$ = +145.8 (c = 0.48, $CHCl_3$), lit.[14] $[\alpha]_D^{20}$ = +144 (c = 0.8, $CHCl_3$).

21-*O*-Acetylajmalal A 32. 21-*O*-Acetylajmalal A ethylene acetal **28** (100 mg, 0.244 mmol) was dissolved in acetone (6 mL), and p-TSA hydrate (19 mg, 0.101 mmol) was added. The reaction mixture was stirred at room temperature for 14 h. The solvent was removed under reduced pressure. The residue which resulted was dissolved in a mixture of CH_2Cl_2 and aqueous $NaHCO_3$ (2:1, 150 mL). The aqueous layer was extracted with CH_2Cl_2 (20 mL × 3). The combined organic layers were washed with brine (30 mL), dried (K_2CO_3), and concentrated under reduced pressure. The residue was chromatographed on silica gel (ethyl acetate/hexane = 1:4) to provide 79.9 mg of pure 21-*O*-acetylajmalal A **32** in 89% yield.

32. IR (KBr) 1463, 1698, 1736, 2934 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.95 (3H, t, J = 7.1 Hz), 1.46 (1H, dt, J = 12.8, 7.4 Hz), 1.54 (2H, m), 1.72 (1H, dt, J = 12.6, 6.5 Hz), 1.80 (2H, m), 2.15 (3H, s), 2.25 (1H, s), 2.52 (1H, dd, J = 8.9, <1 Hz), 3.12 (2H, d, J = 4.3 Hz), 3.61 (3H, s), 3.75 (1H, m), 4.50 (1H, dd, J = 9.2, 3.2 Hz), 5.43 (1H, d, J = 2.8 Hz), 7.06 (1H, t, J = 7.7 Hz), 7.17 (1H, t, J = 6.8 Hz), 7.24 (1H, d, J = 6.8 Hz), 7.41 (1H, d, J = 7.6 Hz), 9.32 (1H, s); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 11.78, 21.28, 23.62, 25.27, 26.11, 29.19, 29.37, 42.87, 43.41, 46.27, 50.63, 88.49, 103.58, 108.86, 118.13, 119.28, 121.48, 126.11, 137.89, 138.14, 169.22, 202.54; HR EIMS $C_{22}H_{27}N_2O_3$ requires (*m*/*e*, relative intensity) 366.1943, found 366.1958 (100%).

21-*O*-acetylalkaloid G 33. The aldehyde **32** (30 mg, 0.082 mmol) was dissolved in a mixture of THF/H_2O (THF/H_2O = 9:1, 3 mL). DDQ (21 mg, 0.093 mmol) was added to the above solution in one portion with stirring.[58] The reaction mixture was stirred at room temperature for 30 min. The reaction mixture was then diluted with EtOAc (100 mL), and the solution which resulted was washed with aqueous NH_4-OH (10%, 30 mL) and brine (30 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was passed through a short column of silica gel to provide the 21-*O*-acetyl alkaloid G **33** (29.4 mg, 94%).[18]

33. IR (KBr) 1742, 3373 cm^{-1};^1H NMR (250 MHz, $CDCl_3$) δ 0.94 (3H, t, J = 6.9 Hz), 1.46 (4H, m), 1.81 (2H, m), 1.92 (1H, m), 2.08 (3H, s), 3.52 (3H, s), 3.87 (1H, dd, J = 8.2, 11.3 Hz), 4.09 (1H, dd, J = 3.9, 10.4 Hz), 4.68 (1H, m), 4.75 (1H, m), 5.30 (1H, d, J = 4.0 Hz), 5.60 (1H, d, J = 8.0 Hz), 7.14 (3H, m), 7.54 (1H, d, J = 7.4 Hz); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 11.59, 21.31, 24.63, 28.27, 29.23, 30.75, 39.78, 41.10, 44.75, 56.27, 70.33, 87.94, 98.72, 106.63, 108.72, 118.36, 119.94, 121.51, 126.03, 138.12, 142.81, 170.34; EIMS (*m*/*e*, relative intensity) 382 (100%).

Alkaloid G 2. 21-*O*-Acetylalkaloid G **33** (20 mg, 0.052 mmol) was dissolved in CH_3OH (3 mL), and an aqueous solution of K_2CO_3 (20%, 0.5 mL) was added, after which the reaction mixture was stirred at room temperature for 2 h. The solvent was removed under reduced pressure. The residue which resulted was dissolved in a mixture of CH_2Cl_2 and H_2O (1:1, 150 mL), and the aqueous layer was extracted with CH_2Cl_2 (20 mL × 3). The combined CH_2Cl_2 extracts were washed with brine (30 mL), dried (K_2CO_3), and concentrated under reduced pressure to provide 16.2 mg of alkaloid G **2** (91%). The spectral data for **2** were identical to the published values.[18]

2. IR (KBr) 1463, 2918, 3373 cm^{-1};^1H NMR (250 MHz, DMSO-d_6) δ 0.96 (3H, t, J = 7.03 Hz), 1.29 (1H, m), 1.39 (1H, m), 1.50 (2H, m), 1.63 (1H, m), 1.69 (1H, m), 1.76 (1H, m), 1.84 (1H, m), 3.63 (3H, s), 3.77 (1H, dd, J = 11.1, 8.1 Hz), 4.09 (1H, m), 4.34 (1H, dd, J = 10.3, 4.0 Hz), 4.93 (1H, d, J = 5.3 Hz), 5.48 (1H, d, J = 8.0 Hz), 5.67 (1H, m), 6.22 (1H, d, J = 5.9 Hz), 7.03 (1H, ddd, J = 7.9, 7.0, 0.9 Hz), 7.14 (1H, ddd, J = 8.0, 7.2, 1.0 Hz), 7.42(1H, d, J = 8.0 Hz), 7.51(1H, d, J = 7.6 Hz); ^{13}C NMR (62.8 MHz, DMSO-d_6) δ 12.46, 25.08 28.69, 29.36, 30.80, 46.59, 55,76, 69.36, 88.02, 98.37, 105.54, 109.99, 118.24, 119,39, 120.85,126.22, 136,99; EIMS (*m*/*e*, relative intensity) 340 (100%).

(6*S*,10*S*)-8-(1′-Ethyl-2′-propenyl)-9-(2′,5′-dioxacyclopentanyl)-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5H-cycloocta[b]indole 34. The alkenic aldehyde **17a**[62,63] (4.66 g, 11.72 mmol) and ethylene glycol (6.68 g, 127.6 mmol) were dissolved in benzene (200 mL), and *p*-toluenesulfonic acid monohydrate (2.24 g, 11.8 mmol) was added. The mixture which resulted was heated at reflux with a DST for 20 h under argon. Examination of the reaction mixture by TLC (silica gel, EtOAc/hexane = 2:8) indicated the disappearance of starting aldehyde. The solution was then cooled to room temperature and concentrated under reduced pressure. The residue which formed was dissolved in a mixture of EtOAc/saturated aqueous $NaHCO_3$. The aqueous layer was extracted with ethyl acetate (3 × 200 mL). The combined organic layers were washed with water and brine, dried (K_2CO_3), and concentrated under reduced pressure to provide alkenic acetal **34** (4.92 g, 95%).

34. FTIR (NaCl) 1110, 1308, 1453 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.64 (3H, t, J = 6.90 Hz), 0.69−0.95 (1H, m), 1.26 (1H, d, J = 2.00 Hz), 1.55 (1H, d, J = 1.80 Hz), 1.63 (1H, d, J = 12.70 Hz), 1.85−2.10 (2H, m), 2.31 (1H, s), 2.41 (1H, d, J = 20.40 Hz), 3.26 (1H, dd, J = 16.80, 7.40 Hz), 3.49 (1H, d, J = 13.80 Hz), 3.62 (1H, d, J = 13.81 Hz), 3.70 (1H, d, J = 7.20 Hz), 3.82−3.93 (4H, m), 4.22 (1H, s), 4.87−5.05 (2H, m), 5.25−5.45 (1H, m), 5.48 (1H, d, J = 8.30 Hz), 7.12−7.35 (8H, m), 7.53 (1H, d, J = 6.60 Hz), 7.62 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.51, 22.60, 24.14, 28.55, 32.89, 47.77, 49.11, 51.98, 56.72, 64.59, 64.66, 104.50, 105.51, 107.47, 110.71, 115.65, 118.02, 119.34, 121.26, 126.69, 128.09, 128.43, 134.86, 135.87, 139.97, 143.08; CIMS (*m*/*e*, relative intensity) 443 (M + 1, 100%).

(6*S*,10*S*)-8-(1′-Ethyl-2′-acetyl)-9-(2′,5′-dioxacyclopentanyl)-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5H-cycloocta[b]indole 35. The alkenic acetal **34** (2.31 g, 5.22 mmol) was dissolved in freshly distilled THF (100 mL) which contained distilled pyridine (35 mL) and was then added to a cold solution of OsO_4 (1.22 g, 4.80 mmol) in THF (25 mL) and pyridine (20 mL) at 0 °C under argon. The black solution which resulted was allowed to stir at 0 °C for an additional 20 h. An aqueous solution of $NaHSO_3$ (15 g, 50 mL) was added, and the mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was diluted with EtOAc (200 mL). The organic layer was concentrated under reduced pressure to provide the crude acetal diol (2.236 g, 90%). The acetal diol was not subjected to further characterization but used directly in the next step. Acetal diol (2.236 g, 4.72 mmol) was dissolved in methanol (100 mL) and cooled to 0 °C. An aqueous solution of $NaIO_4$ (2.70 g in 80 mL of H_2O) was then added to the above solution. The reaction flask was covered by aluminum foil to exclude light. The mixture was stirred at 0 °C for 16 h and then concentrated under reduced pressure. The residue was dissolved in EtOAc/H_2O (5:1, 200 mL). The aqueous layer was extracted with EtOAc (3 × 100 mL). The organic layers were combined, washed with water (50 mL) and brine (50 mL), and dried (K_2CO_3). The solvent was removed under reduced pressure, and the crude material was chromatographed (silica gel, EtOAc/hexane = 8:2) to provide pure acetal aldehyde **35** (1.75 g, 85%).

35. FTIR (NaCl) 1134, 1446, 1609, 1666, 1715, 2952, 3385 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.64 (3H, t, J = 7.48 Hz), 1.30 (1H, m), 1.50 (1H, m), 1.61 (1H, dt, J = 12.56, 3.82 Hz), 1.88 (1H, t, J = 4.00 Hz), 1.97 (1H, dt, J = 12.71, 4.09 Hz), 2.16 (1H, tt, J = 10.41, 2.57 Hz), 2.48 (1H, d, J = 16.89 Hz), 2.72 (1H, m), 3.29 (1H, dd, J = 16.90, 7.73 Hz), 3.50 (1H, d, J = 13.77 Hz), 3.63 (1H, d, J = 13.77 Hz), 3.73 (1H, d, J = 7.75 Hz), 3.84−3.92 (5H, m), 5.49 (1H, d, J = 7.62 Hz), 7.11−7.20 (2H, m), 7.21−7.34 (6H, m), 7.55 (1H, dd, J = 6.44, 2.36 Hz), 7.67 (1H, s), 9.63 (1H, d, J = 2.26 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.39, 20.69, 22.42, 28.59, 30.83, 47.18, 51.22, 53.01, 53.64, 57.56, 63.76, 64.91, 104.17, 108.14, 110.82, 118.18, 119.25, 121.17, 126.76, 127.09, 128.04, 128.56, 132.95, 135.63, 139.69, 205.52; CIMS (*m*/*e*, relative intensity) 445 (M + 1, 100%).

(−)-N_b-Benzylnorsuaveoline 36. The acetal aldehyde **35** (300 mg, 0.68 mmol) and *p*-toluenesulfonic acid (1.50 g, 7.9 mmol) were

dissolved in acetone (75 mL). The mixture which resulted was stirred at reflux for 2 days under argon. The solution was then cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in absolute EtOH (40 mL), and hydroxylamine hydrochloride (500 mg, 7.19 mmol) was added. The reaction mixture was heated to reflux for 2 d under an argon atmosphere. The solution which resulted was allowed to cool to room temperature, and the solvent was removed under reduced pressure. The residue was dissolved in a mixture of EtOAc/saturated aqueous $NaHCO_3$ (4:1, 250 mL). The aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with water (50 mL) and brine (50 mL) and then dried (K_2CO_3). The solvent was removed under reduced pressure, and the crude material was flash chromatographed (silica gel, EtOAc/hexane = 6:4) to provide pure N_b-benzylnorsuaveoline (210 mg, 88%).

36. $[\alpha]_D^{27} = -143.2$ ($c = 1.00$, $CHCl_3$); FTIR (NaCl) 1458, 2910 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.05 (3H, t, $J = 7.30$ Hz), 2.38 (2H, q, $J = 7.28$ Hz), 2.63 (1H, d, $J = 16.04$ Hz), 2.82 (1H, d, $J = 17.14$ Hz), 3.18 (1H, dd, $J = 17.20, 5.64$ Hz), 3.42 (1H, dd, $J = 16.03, 5.20$), 3.73 (1H, d, $J = 13.37$ Hz), 3.85 (1H, d, $J = 13.35$ Hz), 4.24 (1H, d, $J = 4.90$ Hz), 4.35 (1H, d, $J = 4.93$ Hz), 6.99 (1H, t, $J = 7.00$ Hz), 7.05 (1H, t, $J = 6.77$ Hz), 7.18−7.35 (7H, m), 7.99 (1H, s), 8.20 (1H, s), 8.26 (1H, bs); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.92, 23.23, 26.27, 32.48, 49.89, 53.75, 56.77, 105.27, 111.45, 118.60, 120.03, 122.33, 127.44, 127.93, 128.93, 129.26, 133.40, 136.00, 136.53, 138.00, 138.34, 142.96, 144.51, 144.90; CIMS (*m*/*e*, relative intensity) 380 (M + 1, 100%).

Anal. calcd for $C_{26}H_{25}N_3$: C, 82.29; H, 6.64; N, 11.07. Found: C, 82.78; H, 6.41; N, 11.19.

(−)-Norsuaveoline 3. (−)-N_b-Benzylnorsuaveoline **36** (40 mg, 0.11 mmol) was dissolved in ethanolic HCl (5%, 8 mL), after which Pd on activated carbon (10%, 60 mg) was added. The mixture which resulted was allowed to stir at room temperature under an atmosphere of hydrogen for 12 h. Analysis by TLC (silica gel plate was exposed to NH_3 vapors) indicated the absence of starting material **36**. The catalyst was removed by filtration and was washed with EtOH (3 × 25 mL). The solvent was removed under reduced pressure. The residue was dissolved in a mixture of $CHCl_3$ and aqueous NH_4OH (5:1, 60 mL). The aqueous layer was extracted with $CHCl_3$ (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried (K_2CO_3), and flash chromatographed on silica gel ($CHCl_3$/EtOH = 9:1) to provide pure norsuaveoline **3**[60] (28 mg, 92%).

3. $[\alpha]_D^{27} = -3.2$ ($c = 1.00$, $CHCl_3$); FTIR (NaCl) 1416, 1447, 1589, 3052, 3184 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.12 (3H, t, $J = 7.55$ Hz), 2.44 (2H, q, $J = 7.53$ Hz), 2.81 (1H, s), 2.83 (1H, d, $J = 14.90$ Hz), 2.86 (1H, d, $J = 15.0$ Hz), 3.19 (1H, dd, $J = 17.10, 5.70$ Hz), 3.34 (1H, dd, $J = 15.80, 5.45$ Hz), 4.60 (1H, d, $J = 5.40$ Hz), 4.66 (1H, d, $J = 5.20$ Hz), 7.05 (1H, t, $J = 7.40$ Hz), 7.12 (1H, t, $J = 7.30$ Hz), 7.28 (1H, d, $J = 8.30$ Hz), 7.39 (1H, d, $J = 7.50$ Hz), 8.14 (1H, s), 8.31 (1H, s), 8.54 (1H, s); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 13.90, 22.84, 31.15, 31.92, 45.78, 48.40, 105.99, 111.02, 118.21, 119.67, 121.99, 127.32, 134.25, 135.11, 136.06, 137.11, 139.91, 146.17, 147.03; CIMS (*m*/*e*, relative intensity) 290 (M + 1, 100%).

Anal. calcd for $C_{19}H_{19}N_3$: C, 78.86; H, 6.62; N, 14.52. Found: C, 78.59; H, 6.44; N, 14.16.

Supporting Information Available: Unsuccessful attempts to convert ketone **7** (see **7b**−**7f**, Schemes 15−17) or α,β-unsaturated aldehyde **8** (see **8b**−**8d**, Scheme 18) into 1,5-dialdehyde **6** or a related derivative and unsuccessful approaches to conversion of **29** into **30** (Table 1), as well as preparations of **7a** and **11a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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