Enantiospecific Synthesis of (-)-Alstonerine and (+)-Macroline as Well as a Partial Synthesis of (+)-Villalstonine[1,2]

Yingzhi Bi, Lin-Hua Zhang, Linda K. Hamaker, and James M. Cook*

Contribution from the Department of Chemistry, University of Wisconsin—Milwaukee, Milwaukee, Wisconsin 53201

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Abstract: The enantiospecific synthesis of (-)-alstonerine (**5**) and (+)-macroline (**8**), as well as a partial synthesis of the *Alstonia* bisindole alkaloid villalstonine (**2**) has been completed. In addition, a more stable macroline equivalent **9** was prepared. The stereochemistry at C(15) and C(16) in **5** and **8** has been successfully installed by a stereoselective Claisen rearrangement followed by stereospecific hydroboration–oxidation of the exocyclic methylene function at C-16. The E ring in alstonerine **5** was constructed by a regioselective cyclization followed by a novel Swern oxidation under modified conditions [$(COCl)_2$/DMSO/CH_2Cl_2, -78 °C to -10 °C/1.5 h; Et_3N], whereas the C(20)–C(21) enone system in macroline (**8**) was generated *via* a convenient one pot process from the β-diol **45**. Condensation of either synthetic (+)-macroline (**8**) or the macroline equivalent **9** with natural pleiocarpamine **7** in 0.2 N HCl furnished the antiamoebic, antimalarial bisindole alkaloid villalstonine **2**. This constitutes the first partial synthesis of any of the *Alstonia* bisindoles from a synthetically derived indole moiety.

During recent years an increasing number of macroline related alkaloids have been isolated from various species of *Alstonia*.[3-9] At the present time this group contains over 70 indole alkaloids, at least 18 of which are bisindoles. The hypotensive base macralstonine **1** (Figure 1) isolated from *Alstonia macrophylla* Wall[10,11] is a member of this family, as well as the bisindole villalstonine **2** isolated from *Alstonia spectabilis*,[12-14] *A. macrophylla*,[12-14] and *A. muelleriana*.[15,16] The latter alkaloid has been shown to exhibit antiamoebic activity as well as antimalarial activity against *Plasmodium falciparum*. The macroline bases contain a unit derived from macroline as a common structural feature and consist of both monomeric and bisindole alkaloids,[17-19] the majority of which have not fallen to total synthesis. The macroline alkaloids are related, structurally, to the sarpagine/ajmaline class of bases. The latter relationship may provide new strategies for the preparation of potential Class I antiarrhythmic agents in the ajmaline series, including (+)- or (-)-ajmaline (**3**).

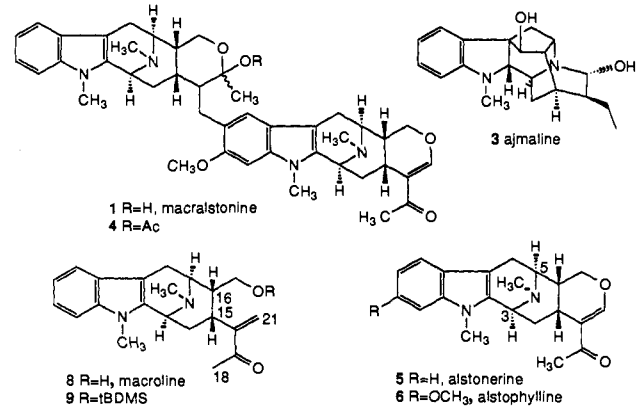

Figure 1.

With respect to the macroline/sarpagine alkaloids, Wright *et al.*[7] reported their findings on the antiprotozoal activity of nine alkaloids from *Alstonia angustifolia* against *Entamoeba histolytica* and *P. falciparum in vitro*. Of the bases tested, villalstonine **2** was found to be the most potent alkaloid against *P. falciparum* and was about 15 times less potent than the antimalarial drug chloroquine. These results, therefore, explain the use of *A. angustifolia* in traditional medicine for the treatment of malaria, as well as amoebic dysentery, although the potencies of even the most active alkaloids are less than the standard drugs tested. Wright *et al.* also assessed the toxicity of villalstonine **2** against KB cells (human epidermoid cancer of the mouth) using a microdilution method similar to the antiamoebic test used above. The cytotoxic activity of villalstonine **2** against KB cells [ED_{50} (95% CI) = 11.6 (10.2–13.0) μM] was also found to be similar to its antiamoebic activity. This similarity suggests there is no selective toxicity for amoebae in this series. However, the standard antiamoebic drug emetine is highly toxic to KB cells [ED_{50} = 0.673 μM (SEM = 0.20)] but is 3 times less toxic to amoebae than to KB cells. Therefore, villalstonine **2** appears to have a more favorable antiamoebic/cytotoxic ratio as compared with emetine.[7]

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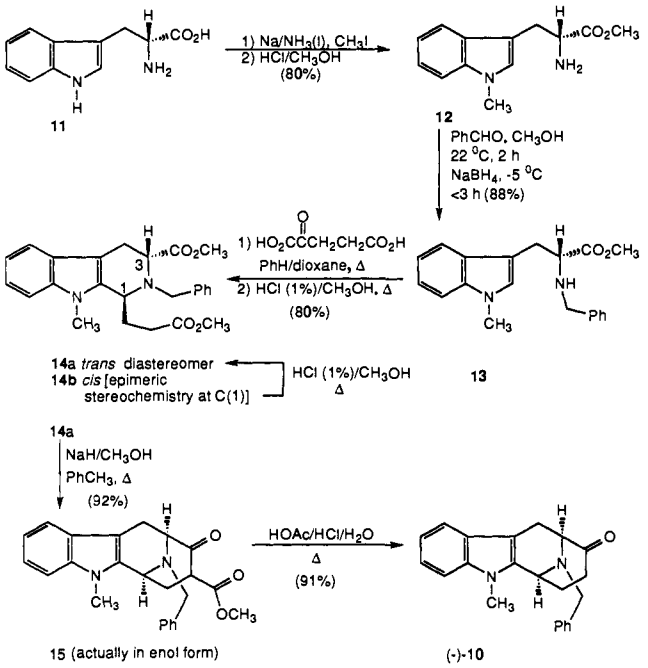
Scheme 1



Macralstonine (**1**) is comprised of a unit of macroline (**8**) and a unit of alstophylline (**6**), yet macralstonine (**1**) is more active than alstophylline (**6**) or alstonerine (**5**). Villalstonine (**2**) and pleiocarpamine (**7**) also exhibit a similar relationship. Since the monomeric alstonerine (**5**) and pleiocarpamine (**7**) elicit practically no antiprotozoal activity, at least part of both ring systems of the bisindoles appears to be necessary for activity.[7] Further studies on the bisindole alkaloids of *Alstonia* may lead to more selective antiprotozoal agents in the future.

The macroline/sarpagine/ajmaline alkaloids have very similar skeletons; consequently, an ideal approach to these bases might rest on the multigram synthesis of a common, optically active intermediate that could be employed for the synthesis of many related natural products. The (-)-tetracyclic ketone **10** (Scheme 1) was synthesized in 1988 with these goals in mind[20-24] while the racemic compound had been prepared on kilogram scale in the late 1970s in our laboratory.[25]

The synthesis of (±)-5-methyl-9-oxo-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole (**10**) was first reported by Yoneda[24] and was improved by Soerens.[23] The enantiospecific preparation of tetracyclic ketone **10** in optically active form was developed by Zhang[20,21] and is illustrated in Scheme 1. The synthesis of **10** began with D-(+)-tryptophan (**11**) since Zhang had found earlier that the Pictet–Spengler reaction of aldehydes with N_b-benzyl substituted tryptophan methyl esters exhibited a strong preference for the enantiomerically pure *trans* diester. The enantiomeric purity of this ketone (-)-**10** was shown to be greater than 98% ee by use of both ^{1}H NMR spectroscopy with the chiral shift reagent[26] tris[3-[(heptafluoropropyl)hydroxymethylene]-(+)-camphorato]europium-(III) and by HPLC on a diastereomeric urea derivative of **10**.[27] The utility of this enantiospecific seven step sequence *via* the Pictet–Spengler reaction[28] rests on the fact that these reactions can be run on multigram scale to provide the (-)-tetracyclic ketone **10**[29] (100–300 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.

The monomeric alkaloid alstonerine (**5**) was first isolated from *A. muelleriana* Domin by Elderfield and Gilman,[15,16] and its structure was elucidated by LeQuesne *et al.*[16] This indole base **5** is the desmethoxy analogue of alstophylline (**6**), the latter alkaloid of which comprises the southern unit of macralstonine (**1**). In keeping with our interest in the total synthesis of *Alstonia* bisindole alkaloids including **1** and villalstonine (**2**), we report an enantiospecific synthesis of (-)-alstonerine (**5**) and (+)-macroline (**8**) *via* a route amenable to preparation of **6**, as well as the preparation of a more stable macroline equivalent **9**. In addition, a partial synthesis of villalstonine (**2**) has been completed by condensation of synthetic (+)-macroline (**8**) or the macroline equivalent **9** with natural pleiocarpamine (**7**). The synthesis of **6** when coupled with that of (+)-**8** will eventually result in the total synthesis of bisindole alkaloid **1**. The strategy developed here can be employed for the enantiospecific synthesis of other macroline/sarpagine/ajmaline alkaloids.

The approach for the synthesis of alstonerine (**5**) and macroline (**8**) was envisaged to employ the hydroxy β-keto aldehyde **16** or an equivalent as a common intermediate for further elaboration. This key intermediate could be formed from ene aldehyde **17** *via* a facial selective hydroboration–oxidation from the top face of the olefinic bond to set the correct configuration at C(16). The Claisen rearrangement of **18** would be expected to occur stereoselectively from the α-face of the azabicyclo[3.3.1] system *via* a chair transition state to afford **17** with the desired configuration at C(15). The precursor for the Claisen rearrangement could be generated by a Michael addition of 3-butyn-2-one to the allylic alcohol **19** which can be obtained from the tetracyclic ketone **21** in three steps *via* α,β-unsaturated aldehyde **20**. A retrosynthetic analysis of this strategy is depicted in Figure 2.

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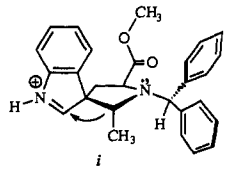
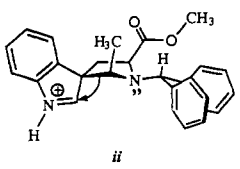
(28) The Pictet–Spengler cyclization has been utilized for many years for the synthesis of indole alkaloids.[21,23,24,30-39] With the increasing interest in the enantiospecific synthesis of alkaloids, many improvements have been made toward stereochemical control of this important condensation. Ungemach demonstrated the utility of the Pictet–Spengler reaction by reporting the 100% stereoselective formation of *trans*-1,3-disubstituted-1,2,3,4-tetrahydro-β-carbolines in aprotic media when various bulky aldehydes were heated with N_b-benzyltryptophan methyl ester.[34,40] The realization of this 100% stereoselective cyclization in this series is largely due to steric constraints placed upon the transition state by the N_b-benzyl and C(3) carbomethoxy groups. More importantly, there was no racemization at C(3). Under the aprotic conditions involving α-ketoglutaric acid, Zhang observed almost complete *trans* stereospecificity after esterification. The remaining small amount of *cis* isomer had been converted, with no loss of optical activity, into the *trans* diastereomer upon heating in 1% methanolic HCl. Hence, a sequence had been developed to provide the *trans* isomer in high enantiomeric purity even in the N_a-methyl series in the absence of time consuming separations. Recently, Czerwinski *et al.* have achieved complete *trans* stereoselectivity in the Pictet–Spengler cyclization even when aldehydes as small as acetaldehyde are employed in the condensation.[41] Czerwinski went on to note that the *trans*-favored diastereoselectivity correlated extremely well with the energy difference between the two possible spiroindolenine intermediates (see figure). MacroModel version 2.5-MM2 force field calculations revealed that the *anti* spiroindolenine intermediate *i* was 2.1 kcal/mol more stable than the corresponding *syn* isomer *ii*.



i
anti
spiroindolenine



ii
syn
spiroindolenine

Outlined in Figure 3 is a doubly convergent route toward the antiprotozoal bisindole alkaloid villalstonine (**2**). As planned, villalstonine (**2**) could be synthesized by condensation of macroline (**8**) with pleiocarpamine (**7**) *via* a convergent process.[17] More importantly, in this strategy both monomeric alkaloids **7** and **8** could be approached *via* a common intermediate such as **22** [from D-(+)-tryptophan], hence the description of the process as doubly convergent.

Numerous attempts have been made to effect a 1,4-addition to **20**, but with one notable exception,[50,51] all have failed.[25,46,52,53] The inability to intermolecularly functionalize the α,β-unsaturated

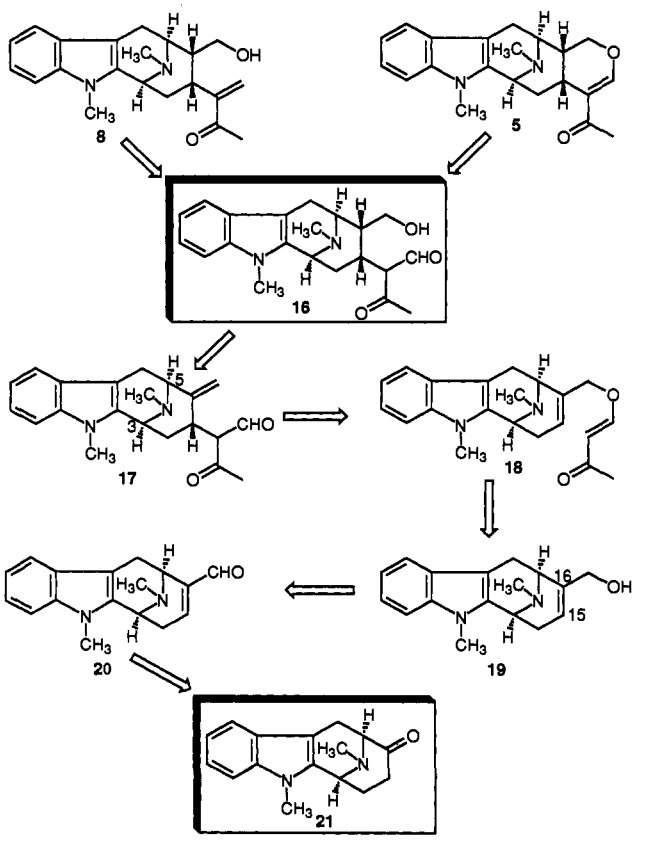


Figure 2.

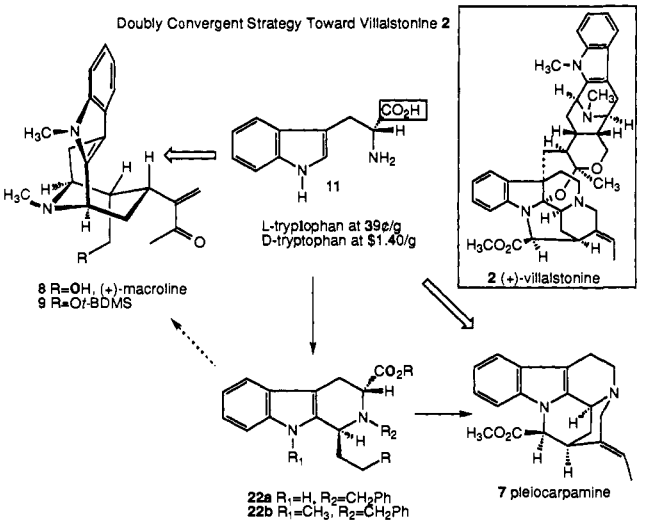
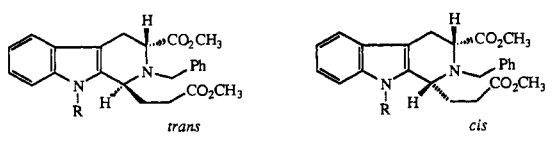


Figure 3.

aldehyde **20** is believed to be due to the steric constraints inherent in this tetracyclic system from the top face of the C(15)–C(16) olefinic bond and electronic effects which retard addition of nucleophiles at C(15) from the bottom face. The approach of a nucleophilic reagent to **20** at C(15) from the less hindered bottom (α) face of the molecule (equatorial position) is electronically not favored, while approach from the top (β) face (axial

(29) There are contrasting reports on the Dieckmann cyclization (**14** to **15**) with regard to time of reaction. Yoneda reported that the *cis* diastereomer of diester **14b** (N_a-methyl series) could not be coerced to undergo the Dieckmann reaction to provide the antipode of tetracyclic β-keto ester **15** under conditions employed for cyclization of *trans* diester **14a**. Zhang in 1988 demonstrated that the *trans* diastereomer **14a** (under these Dieckmann conditions) in the N_a-methyl series was converted into the β-keto ester **15** more rapidly than the corresponding *cis* diastereomer underwent the cyclization under conditions similar to those reported by Yoneda.[24] Zhang was, however, able to effect cyclization of the *cis* diastereomer to produce the tetracyclic system by employing additional quantities of base and longer reaction times.[21] In contrast, Magnus *et al.* in 1990 reported that the antipode of the *cis* diester *iv* (see figure) in the related N_a-benzyl series underwent the Dieckmann reaction faster than the corresponding antipode of the *trans* diester *iii*.[42,43] Examination of the experimental results clearly indicated that the *trans* diastereomer in both series is the thermodynamically more stable isomer.[21] The *cis* diastereomer was completely converted into the corresponding *trans* diastereomer, respectively, under either acidic or alkaline conditions.[21,27] Evidence indicated that the *cis* diastereomer epimerized to the *trans* diastereomer and then underwent the Dieckmann reaction, but with *cis* stereochemistry.[27] Because the rate of these cyclizations is highly dependent on the amount of sodium hydride and methanol present, an equimolar mixture of *cis* (*iv*) and *trans* (*iii*, R = CH_2Ph) diastereomers was subjected to the Dieckmann reaction. It was found that both the *cis* (*iii*) and *trans* (*iv*) diastereomers in the mixture in the N_a-benzyl, N_b-benzyl series underwent the Dieckmann reaction at the same rate in contrast to the earlier reports of Magnus.[42,43] Although the *trans* diastereomer **14a** in the N_a-methyl, N_b-benzyl series cyclized to completion (see **15**) consistently faster than the corresponding *cis* diastereomer, under the conditions of Zhang,[27] an equimolar mixture of the two diastereomers (*cis*/*trans*) yielded both the (+) and (-) β-keto esters (**15**) at the same rate.[27] This is in agreement with the results of the same experiment in the N_a-benzyl, N_b-benzyl series and is in contrast to the earlier reports of Magnus *et al.*[42,43] It should be pointed out, however, in agreement with Magnus, the rate of this cyclization is very sensitive to the amount of methanol present in the solution.[44] The importance of the discrepancies between the rates of the Dieckmann cyclization among laboratories is not significant from an experimental point of view, but is important from a stereochemical point of view. Enantiospecific synthesis of indole alkaloids in the macroline/sarpagine/ajmaline series rests on the accurate identification of the stereogenic centers at C(1) and C(3) in the 1,3-disubstituted tetrahydro-β-carbolines. Although Bailey *et al.* have reported a ^{13}C NMR method to differentiate between the *cis* and *trans* diastereomers in the N_a-H, N_b-benzyl series, this method is not 100% effective as noted by the authors.[45,46] Moreover, Toth *et al.* have examined this method for stereochemical assignments and also found exceptions.[47] Consequently, if the rates of the Dieckmann cyclization were ever taken as evidence of *cis* stereochemistry at C(1) and C(3), the rate differences encountered in the various laboratories could be problematic. Rate differences between laboratories in this series generally stem from the scale of the reaction and the amount of sodium hydride and methanol employed in the cyclization.[21,24] To date, accurate stereochemical assignments for the *cis* and *trans* 1,3-disubstituted N_b-benzyltetrahydro-β-carbolines in this series can only be made in 100% of these cases by removal of the N_b-benzyl group (catalytic transfer hydrogenation) followed by identification of the diastereomers by the ^{13}C NMR method developed earlier by Sandrin[48] and Ungemach[40,49] in these laboratories.



iii R=CH_2Ph *iv* R=CH_2Ph

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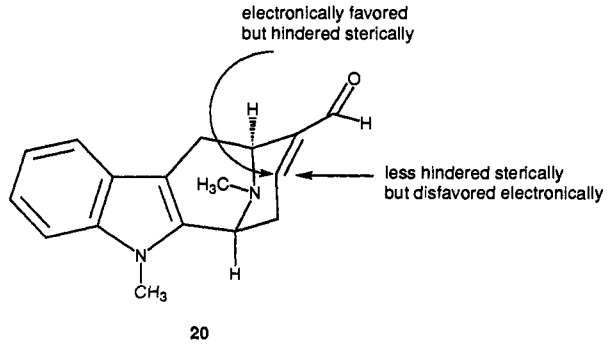

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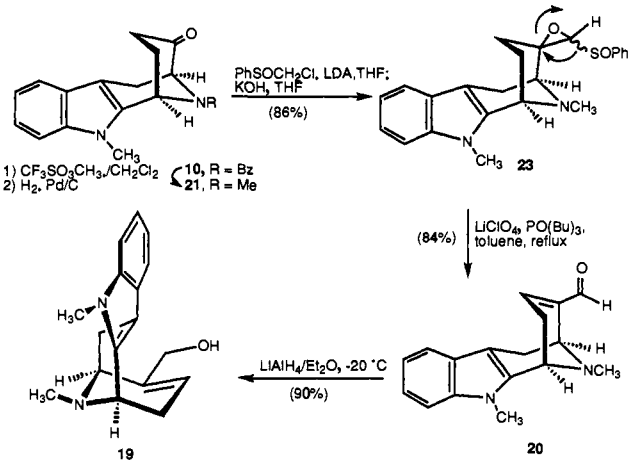
Figure 4.

Scheme 2

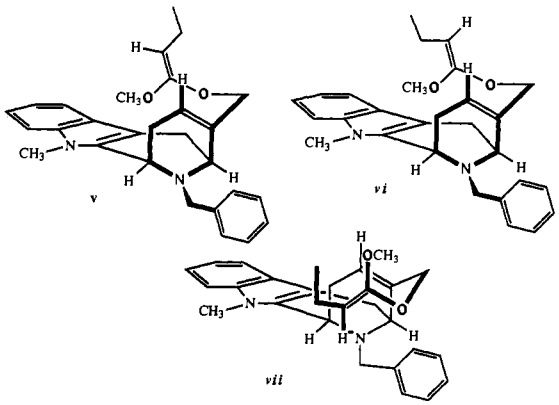


position) is severely hindered by the 1,3-diaxial interactions with the *cis* fused diaxial indolomethylene bridge (Figure 4). To overcome these steric and electronic constraints, execution of an intramolecular approach for the functionalization of this tetracyclic system at C(15) was envisaged. It was 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 macroline (**8**) and alstonerine (**5**). The thermal conditions of the pericyclic process would also leave the remainder of the molecule unharmed as opposed to exposure to chemical reagents.

The acid catalyzed ortho ester Claisen rearrangement has been successfully employed in the total synthesis of (±)-suaveoline.[52] This method, however, cannot be employed in this study, since the ortho ester Claisen rearrangement occurred predominantly from the β-face[54] of the molecule to install a new chiral center at C(15) with a configuration opposite to that in (-)-alstonerine (**5**) and (+)-macroline (**8**). In order to overcome this drawback a Claisen rearrangement was chosen, since it has been well-documented that Claisen rearrangements prefer to adopt a chair or a chair-like transition state.[56-58] In this fashion rearrangement from the α-face of the C(15)–C(16) olefinic bond might be possible.

The desired N_a-methyl, N_b-methyl allylic alcohol **19** was prepared as outlined in Scheme 2. Since both alstonerine (**5**) and macroline (**8**) contain a methyl substituent on the N_b-nitrogen function, the N_b-benzyl tetracyclic ketone **10** was first converted into N_b-methyl tetracyclic ketone **21**. This was accomplished easily on large scale by methylation of **10** with methyl trifluoromethanesulfonate and this was followed by catalytic debenzylation under 1 atm of hydrogen to provide **21** in 84% overall yield $\{[\alpha]^{22}_D$ -129.6° (c = 0.52 in $CHCl_3$)$\}$. The N_b-methyl tetracyclic ketone **21** was then reacted with the anion of α-chloromethyl phenyl sulfoxide generated *in situ* to furnish a chlorohydrin intermediate which on treatment with KOH afforded the spirooxirane phenyl sulfoxide **23** as a mixture of diastereomers (86–90%) in this one pot process. The spirooxirane phenyl sulfoxide **23** was dissolved in toluene which contained lithium perchlorate and tri-*n*-butylphosphine oxide, and the mixture which resulted was heated to 110 °C under nitrogen (1 atm) to afford the desired α,β-unsaturated aldehyde **20** (84%), $\{[\alpha]^{22}_D$ -233.5° (c = 0.5 in $CHCl_3$)$\}$. The Lewis acid catalyzed oxirane rearrangement had been followed by a *syn* elimination process to generate **20**, according to the procedures of Taber[59] and Yamakawa.[60] The desired aldehyde **20** was also obtained by a thermally-induced rearrangement–elimination sequence when **23** was heated in refluxing xylene, albeit the yield was lower. The α,β-unsaturated aldehyde **20** was then reduced to the allylic alcohol **19** $\{[\alpha]^{22}_D$ -100° (c = 0.5 in $CHCl_3$)$\}$ under standard conditions.

The required enone ether **18** was prepared by Michael addition[61] of the allylic alcohol **19** to 3-butyn-2-one (Scheme 3). The reaction must be carried out in the dark due to the polymerization of



A reviewer has pointed out that the inversion of stereoselectively between the orthoester Claisen rearrangement and the Claisen rearrangement in **19** may also be influenced by stereoelectronic effects. One possibility: the electron-rich ketene acetal, which probably contributes its HOMO to the reaction, may prefer to attack from the face of the molecule where maximum mixing is possible between the LUMO of the ring olefin (i.e., the π^* orbital) and the σ^* orbital of the N–C bond, an effect that would lower the LUMO energy of the ring olefin. In contrast, the analogous reaction of the alkoxyenone substrate may primarily involve a $HOMO_{(ring\ olefin)}$–$LUMO_{(enone)}$ interaction. This being the case, the opposite topological course would be favored, because mixing of the $\sigma_{[ring\ C\text{-}indole\ C\text{-}2]}$ orbital and the ring olefin π orbital may be required to raise the ring olefin π energy as close as possible to the enone π^* orbital. Although the reviewer has pointed out that these matters can be explored even at the unsophisticated semiempirical level (EHMO, MNDO, etc.), at the present we have synthesized the indolobicyclo[3.3.0] analog of ketone **10** and will carry out the two rearrangements in systems devoid of a N_b-nitrogen function before proceeding with the computational work.

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(52) Trudell, M. L.; Cook, J. M. *J. Am. Chem. Soc.* **1989**, *111*, 7504.
(53) Weber, R. W. Ph.D. Thesis, 1984, University of Wisconsin—Milwaukee.
(54) The steric outcome of this process has been rationalized on examination of the potential chair and boat transition states of the orthoester Claisen rearrangement.[55] It was found that the major products were obtained *via* the boatlike transition states *v* and *vi*, while the minor product [with the natural configuration at C(15)] was obtained through a chairlike transition state *vii*, as depicted below.
(55) Zhang, L. H.; Trudell, M. L.; Hollinshead, S. P.; Cook, J. M. *J. Am. Chem. Soc.* **1989**, *111*, 8263.
(56) Bennett, G. B. *Synthesis* **1977**, 589.
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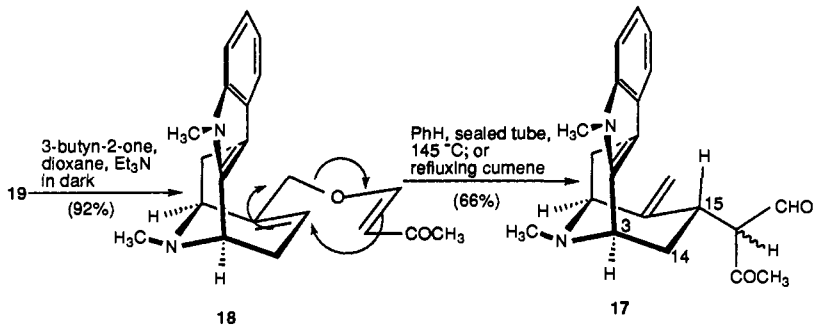
(61) Rackur, G.; Stahl, M.; Walkowiak, M.; Winterfeldt, E. *Chem. Ber.* **1976**, *109*, 3817.

Scheme 3



3-butyn-2-one. Upon completion of the reaction, the mixture which resulted was first passed through a short wash column (silica gel, dioxane) directly to remove the dark polymeric material generated from excess 3-butyn-2-one. After removal of the solvent, the residue was then chromatographed (silica gel, EtOAc/THF) to provide the pure enone ether **18** in 92% yield. The Claisen rearrangement was first executed in benzene in a sealed tube (145 °C). The reaction provided cleanly the desired β-keto aldehyde **17** with the natural configuration at C(15) in 65% yield, accompanied by an inseparable mixture of alkaloidal byproducts of much higher R_f (silica gel, MeOH/$CHCl_3$, 1:9). The byproducts were easily separated from **17** by flash chromatography. The structure and stereochemistry of **17** were determined by high resolution NMR experiments. All protons were assigned by 2D-COSY experiments and the coupling constants then defined. The proton designated H-3 of **17** appeared as a broad singlet at δ 3.9 ppm, indicating that the D ring of the molecule existed in a chair conformation with H-3 in an equatorial position lying on a plane which bisected the two protons at C(14). This observation was found to be consistent with the appearance of this proton in most related alkaloids with the exception of the talpinine series. In this latter group the geometry of the alkaloids requires that the D ring exist in a boat conformation, wherein the proton at C(3) is observed as a doublet of doublets. The coupling constant between the two protons at C(14) was observed as 11 Hz while the coupling constant between H(14α) and H(15) was found to be 9.5 Hz. These coupling constants indicated that H(15) was in the axial (β) position with a dihedral angle of about 180° with respect to H(14α). If this nucleus occupied the equatorial (α) position, the dihedral angle would have been about 60° with respect to both protons at C(14) and a coupling constant smaller than 6 Hz would be expected. Attempts to increase the yield of the Claisen rearrangement at higher reaction temperatures (180 °C) afforded two enone ethers **24** and **25** *via* an intramolecular cyclization from the dicarbonyl intermediate **17**. This was further confirmed by first isolation of **17** and then conversion into the mixture of **24** and **25** at 180 °C. Although both pentacycles were byproducts of continued heating, the rigid nature of these structures was critical to the determination of stereochemistry at C(15) for **17** as well as other intermediates in this research. The stereochemistry of the rigid pentacyclic enone ethers was determined by 1D and 2D NMR spectroscopy. The chemical shifts and coupling constants between H(3) and H(14α,β), H(5) and H(6α,β) of **24** and **25** were found to be consistent with a chair conformation for the D ring. The coupling constants between protons located at H(15) and H(14α) indicated that H(15) was located on the β-face of the molecule with a dihedral angle of about 150° with respect to H(14α) (J = 9 Hz), and about 20° with respect to H(14β) (J = 9.5 Hz). Examination of the NOESY spectra of **24** and **25** clearly indicated the presence of crosspeaks between the methyl group at C(17) and H(15), as well as H(6β). The NOE difference spectrum measured by 1D experiments was shown to be 9.0% between the methyl group at C(17) and the H(6β), as well as an enhancement of 8.7% between the methyl group at C(17) and H(15) in **24**. In enone ether **25**, the enhancement was observed to be 6.5% and 5.4%, respectively

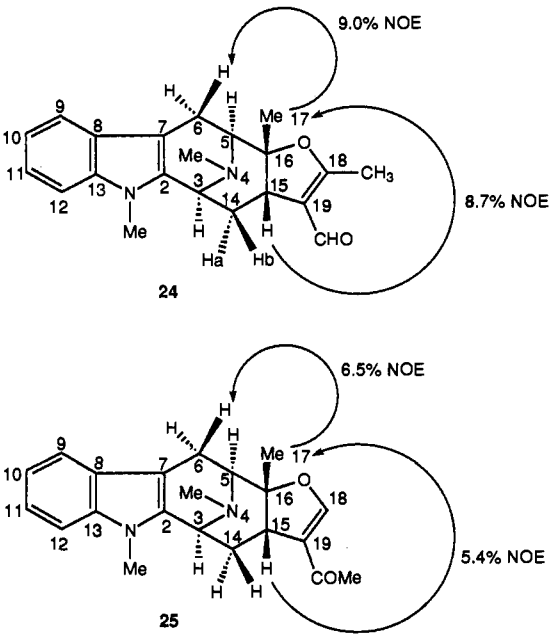


Figure 5,

(Figure 5). The structural information provided on **24** and **25** further confirmed that the Claisen rearrangement had occurred stereoselectively, as indicated, from the desired α-face of the azabicyclo[3.3.1]nonene system to provide **17**.

Attempts to improve the yield of this pericyclic process in a sealed tube were not successful; consequently, an open system was investigated in order to scale up the process and improve the yield as well. When the enone ether **18** was heated to 145 °C in cumene, the desired β-keto aldehyde **17** was formed in 66% yield accompanied by the same alkaloidal byproducts (TLC) observed previously. Although the byproducts were easily separated from **17**, they could not be partitioned from each other. Examination of the ^{1}H NMR spectrum of the mixture of these byproducts indicated it contained one major component (~16% of the total reaction mixture) accompanied by at least two minor compounds. The structure of the major component was deduced by analysis of the ^{1}H NMR spectrum of the mixture and the reaction mechanism. Comparison of the proton signals in the spectrum of **17** to the signals at δ 15.4 ppm and δ 7.71 ppm in the ^{1}H NMR spectrum of **26b** indicated that this dicarbonyl compound existed as an enol. The observation of a singlet at δ 5,02 ppm and a triplet at δ 4.60 ppm in the vinyl region with a small coupling constant (long range coupling) suggested the presence of the exocyclic double bond at C(16). Consequently, the major byproduct from this rearrangement appears to be a diastereomer of the desired β-dicarbonyl compound **17**. Since there was no interconversion between **17** and this mixture (TLC, NMR) on heating, it was felt that **26b** is diastereomeric with **17** at C(15). This result suggests that a small amount of the product of the rearrangement arises from attack from the β-face of the C(15)–C(16) olefinic bond. Although the pericyclic process did

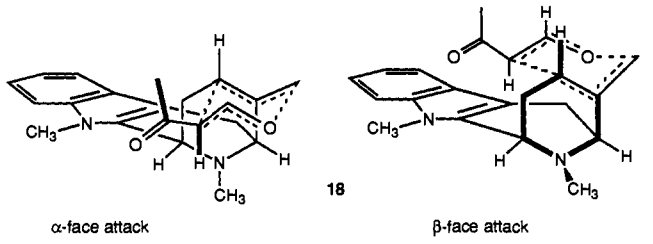


Figure 6.

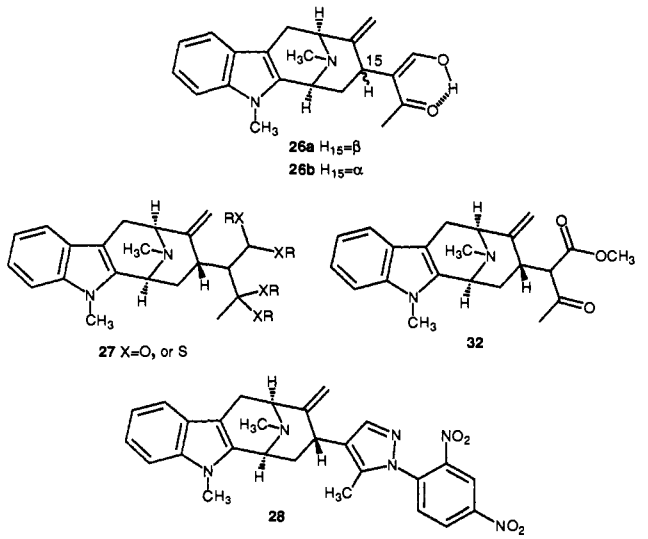


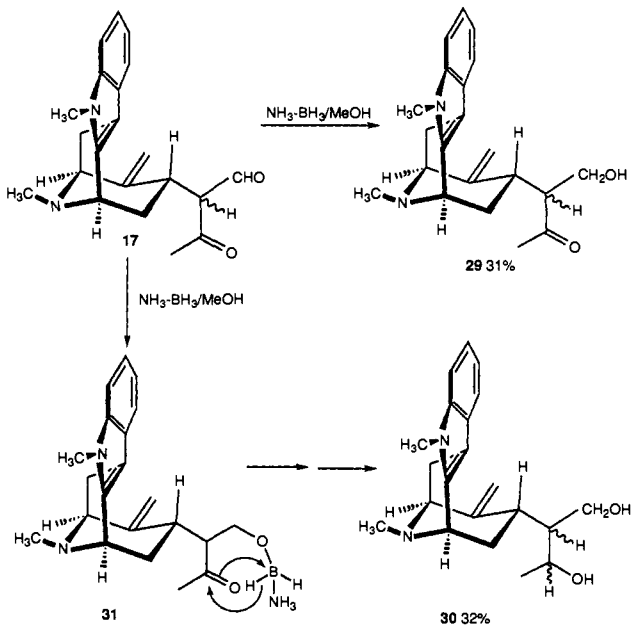
Figure 7.

not take place with as high a diastereoselectivity as originally believed,[55] the selectivity was, however, at least greater than 4:1 (82% combined yield) from the bottom face of the C(15)–C(16) olefinic bond. Attempts to increase the selectivity at lower temperature (refluxing xylene, 134 °C) resulted only in recovered starting enone ether **18**. Grieco *et al.*[62] has reported that Claisen rearrangements can be accelerated in water; however, under these conditions [H_2O, 1.0 N NaOH, H_2O–MeOH (2.5:1), and H_2O–py (3:1)], the enone ether **18** reverted back to the allylic alcohol **19**, as expected.

This preference for rearrangement from the α-face of the C(15)–C(16) olefinic bond was anticipated to occur *via* a chair transition state from the least hindered α-face of **18**. As illustrated in Figure 6, the α-face is more accessible to attack for approach from the β-face of the double bond would encounter steric interactions with the indolomethylene bridge. Execution of the Claisen rearrangement, stereoselectively, from the desired α-face of **18** has important implications for the total synthesis of macroline related and ajmaline alkaloids, since this intermediate has been functionalized at C(15) with the natural stereoconfiguration common to both alkaloid families. This important transformation represents the first successful stereoselective Claisen rearrangement in this rigid indolomethylene azabicyclo[3.3.1]nonene system and will have a variety of applications in the total synthesis of macroline/sarpagine/ajmaline alkaloids.

With the β-keto aldehyde **17** in hand, a route was devised to protect the two carbonyl groups as ketals **27** (Figure 7) before further elaboration at C(16). However, when the β-keto aldehyde **17** and ethylene glycol, or β-mercaptoethanol,[63] were heated in benzene in the presence of PTSA, the two enone ethers **24** and **25** were obtained. Similar results were obtained when **17** was treated with ethanedithiol in the presence of boron trifluoride[64] even at room temperature. The protection of **17** with dinitrophenylhydrazine[65] was also prohibited due to the formation of a stable pyrazole **28** which resisted hydrolysis back to the parent β-keto aldehyde under both conditions of ozonolysis or of Amberlyst 15.[65] A number of other mild conditions, such as montmorillonite clay K-10/trimethyl orthoformate,[66] ($TMSOT_f$)/methoxytrimethylsilane,[67] and cerium(III) chloride/trimethyl orthoformate,[68,69] have been attempted with the β-keto aldehyde **17**, but none were successful. From the experimental data it was apparent that strongly acidic catalysts promoted the intramolecular ring closure to form enone ethers **24** and **25**, while reactions with mildly acidic and neutral catalysts were not active enough to effect ketalization of **17**. Consequently, a synthetic route through a ketal intermediate such as **27** had to be revised.

Scheme 4



It appeared that the formation of the enone ether byproducts **24** and **25** could be prevented if the β-keto aldehyde could be chemoselectively reduced to the corresponding β-hydroxyl ketone **29**, the carbonyl of which might be protected as a β-hydroxyl ketal. There have been a number of reports of chemoselective reducing agents which are capable of distinguishing between aldehyde and ketone functionalities in a predictable manner. It appeared that commercially available ammine–borane reagents were worthy of investigation because of the high chemoselectivity (97%) reported in the reduction of a variety of aldehydes in the presence of ketone functions.[70] However, when the β-keto aldehyde **17** was reacted with ammine–borane, only 31% of the desired β-hydroxy ketone **29** was obtained, accompanied by 32% of the β-dihydroxyalkene **30**. The latter diol might have originated by intramolecular hydride transfer from intermediate **31** (Scheme 4). Similar results with tetra-*n*-butylammonium triacetoxyborohydride and β-keto aldehydes have been reported.[71,72] Zinc borohydride has been reported to reduce β-keto aldehydes to hydroxy ketones;[73] however, when this reagent was applied to **17**, similar results to those from ammine–borane were obtained. When *tert*-butylammine–borane[70] was employed in place of ammine–borane for this sequence, only starting material was recovered. The poor chemoselectivity of these reagents (see **29**, Scheme

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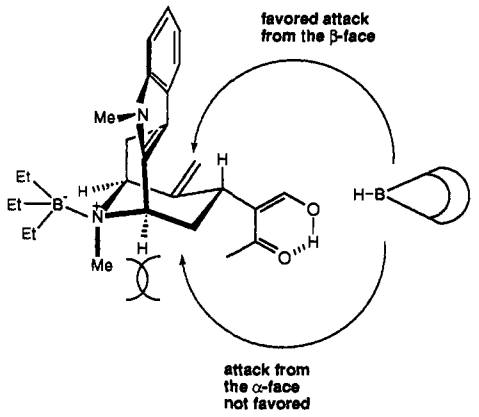

Figure 8,

4) with β-keto aldehyde **17** limited application of this strategy in these studies.

Because of the difficulty encountered in the chemoselective reduction of the β-keto aldehyde **17** into the corresponding β-hydroxy ketone **29**, a different approach to the synthesis of **29** was envisaged. Oshima *et al.* recently reported a Lewis acid catalyzed reductive Claisen rearrangement.[74] The vinyl ether employed in this reaction underwent a Claisen rearrangement, the aldehydic product of which was reduced in the presence of triisobutylaluminum or diisobutylaluminum hydride to the required alcohol. Unfortunately, under conditions analogous to those employed by Oshima no rearrangement took place; the vinyl enone ether **18** underwent bond scission to the allylic alcohol **19**, presumably, through a retro-Michael reaction.

The failure of the above attempts to prepare the β-hydroxy ketone **29** prompted the investigation of the oxidation of the aldehyde functionality of **17** to its corresponding carboxyl group (see **32**). Perhaps the required chemoselective differentiation between the aldehydic and ketone carbonyl groups of **17** could be effected in this fashion. However, when the β-keto aldehyde **17** was treated with silver oxide[75] or PDC,[76] only starting materials were recovered. The resistance of the β-keto aldehyde toward oxidation with mild oxidation reagents was, presumably, due to the presence of a conjugated form of **17** (see **26a**). When Jones reagent[77] was used in the oxidation of **17**, an unresolvable mixture of alkaloidal material was obtained.

Careful examination of the stereochemistry and the functionality of the intermediate alkenic β-keto aldehyde indicated that protection of the β-keto aldehyde might not be necessary. The hydroboration–oxidation of the intermediate **17** would convert this alkenic β-keto aldehyde into a triol **33** which possesses the essential functionality for further elaboration to the two monomeric bases **5** and **8**, It was felt that the hydroborating agent would approach the methylene function at C(15) from the β-face of the exocyclic C(16)–C(17) double bond because the α-face of the molecule would be hindered by the four carbon side chain (C(15)), as well as by a 1,3-diaxial interaction with the N_b-methyl group when the nitrogen atom was complexed with the boron reagent (Figure 8). In order to provide the expected stereochemical outcome, a bulky hydroborating agent such as 9-BBN would be employed in this process.

Triethylborane was chosen as an agent to complex with the N_b-nitrogen functionality in **17** because this Lewis acid is devoid of an active hydride atom on the boron nucleus preventing possible intramolecular hydroboration from the α-face of the double bond.

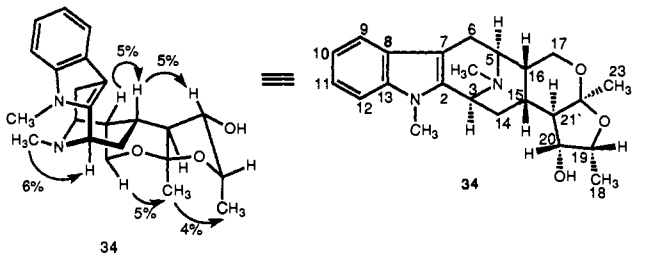

Figure 9,

Treatment of **17** with triethylborane followed by hydroboration–oxidation with 9-BBN; H_2O_2, OH^- gave the hydroxy ketal **34** in 38% yield. The mass spectrum of this ketal contained a molecular ion at m/e 382 amu. The structure of **34** was assigned on the basis of ^1H NMR, 2D COSY, and NOE experiments.[78] On the basis of the analysis of the structure of **34**, it was assumed that one ethyl group had added to the β-keto aldehyde **17**. The complex nature of this reaction with triethylborane prevented the use of this reagent in the hydroboration of **17**. However, this reaction did provide evidence that the 9-BBN added from the desired top (β) face of the molecule to install the correct chiral center at C-16.

When the alkenic β-keto aldehyde **17** was reacted with 3.3 equiv of 9-BBN, the triol **33** was formed as expected (37%), accompanied by the intermediate hemiketal **35** (41%), the product of incomplete reduction (Scheme 5). The structure of this hemiketal was determined by oxidation with PDC followed by dehydration to afford the α,β-unsaturated aldehyde **36** (Scheme 5). Examination of the mass spectrum of **36** indicated that the base had a molecular weight of 336 amu, and this material had a ^{13}C NMR spectrum similar to that reported for (-)-alstonerine (**5**).[16,79] The similar chemical shifts of C(15) and C(16) of **36** with the corresponding carbon atoms in alstonerine **5** indicated these two carbon atoms had the same configurations as those found in alstonerine (**5**). On the basis of the data from the ^{13}C NMR spectrum, it was believed that the 9-BBN had added to the exocyclic carbon–carbon double bond from the top (β) face of the molecule. This was further verified by the coupling constants [at H(16)] in **36**. The proton at C(16) in the NMR spectrum appeared as a doublet of triplets with coupling constants of 6.0 and 12.0 Hz. This indicated that H(16) was located with a dihedral angle of 180° with respect to H(17α), 60° to H(17β), and approximately 5° in regard to H(15). Therefore, H(15) and H(16) must be *cis* to each other. The structural assignment of **36** was further confirmed by comparison of the NMR (^1H, ^{13}C) data of **36** to that of the 10-methoxy analog **37**, a newly isolated alkaloid from *A. angustifolia* Wall.[80] The synthesis of **36**, although the yield has not been maximized to date, provides the first enantiospecific entry into the stereochemical framework of **37**. The enantiospecific synthesis of the natural product, 19,-20-dehydro-10-methoxytalcarpine, **37**, should now be possible

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(78) In the ^1H NMR spectrum of **34** the chemical shifts and coupling constants of H(6β) (δ 2.51 ppm, J = 16.2 Hz), H(6α) (δ 2.91 ppm, J = 16.2 and 6.3 Hz), H(14α) (δ 1.42 ppm, J = 12.4 Hz), and H(14β) (δ 2.39 ppm, m) were consistent with the skeleton of the tetracyclic ketone. This indicated that the basic structural unit of **17** was unchanged during the reaction. Three methyl singlets were observed in the ^1H NMR spectrum of **34** and assigned to the N_a-methyl (δ 3.61 ppm), N_b-methyl (δ 2.42 ppm), and ketal methyl functions (δ 0.98 ppm), respectively. A doublet (δ 0.22 ppm) which represented three protons was assigned to the methyl group at C(18) for it was coupled with H(19) (δ 1.79 ppm) based on a crosspeak in the 2D COSY NMR spectrum of **34**. Moreover, in the 2D COSY NMR spectrum, the proton at C(20) was coupled to H(19) (δ 3.82 ppm) and H(21). The proton at C(20) appeared as a triplet with a coupling constant of 6 Hz which indicated this nucleus was located with a dihedral angle of about 30° with respect to H(19) and 150° in regard to H(21). Examination of the NOE data on **34**, as shown in Figure 9, indicated that H(15) and H(16) are *cis* to each other. This conclusion was supported by the coupling constant between H(15) and H(16) (J = 8.6 Hz) with a dihedral angle of approximately 10°.
(79) Szatmáry, L.; Czakó, E.; Rényi-Vámos, F.; Bodor, E.; Rablóczky, G. *Acta Med. Hung.* **1986**, *43*, 321.
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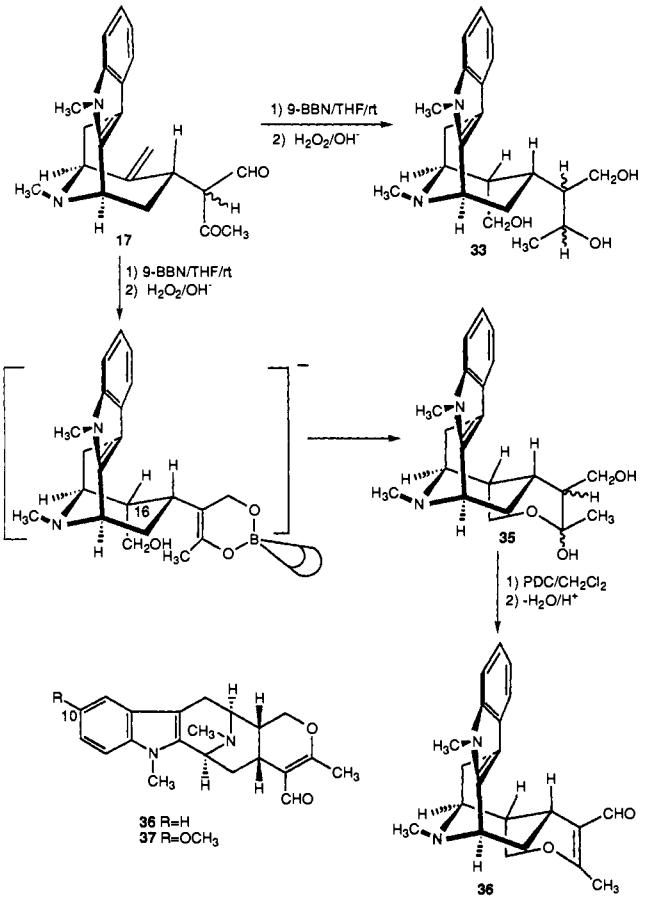
Scheme 5



Scheme 6

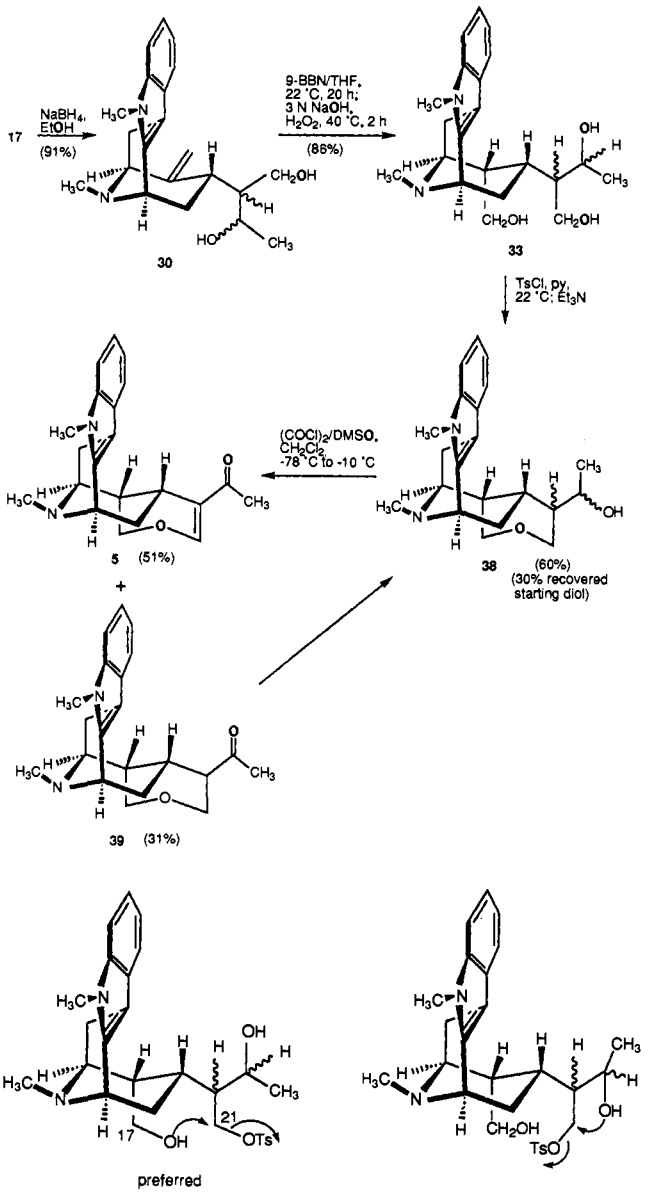


Figure 10.

by replacement of D-(+)-tryptophan with 5-methoxy-D-(+)-tryptophan and completion of the sequence of steps depicted in Schemes 2, 3, and 5,

The drawback of incomplete hydroboration was soon overcome by reduction of the alkenic β-keto aldehyde **17** to a diol **30** (86–91%) with sodium borohydride followed by hydroboration–oxidation with 9-BBN, $H_2O_2/NaOH$ to afford the triol **33** in 86% yield (Scheme 6). The mass spectrum of this triol contained a molecular ion at m/e 358 amu. The triol was obtained as a mixture of diastereoisomers, and they were not readily separable by flash column chromatography. The ^1H NMR spectrum of the mixture of the diastereoisomers of **33** was complicated and the protons at C(15) and C(16) could not be unequivocally assigned by either COSY or NOESY experiments due to signal overlap. However, it was believed that 9-BBN had attacked the exocyclic carbon–carbon double bond from the top face of the molecule based on comparison of the spectral data to that for **34** and **36**, as mentioned above. This was further confirmed by the synthesis of (–)-alstonerine from triol **33** (see below).

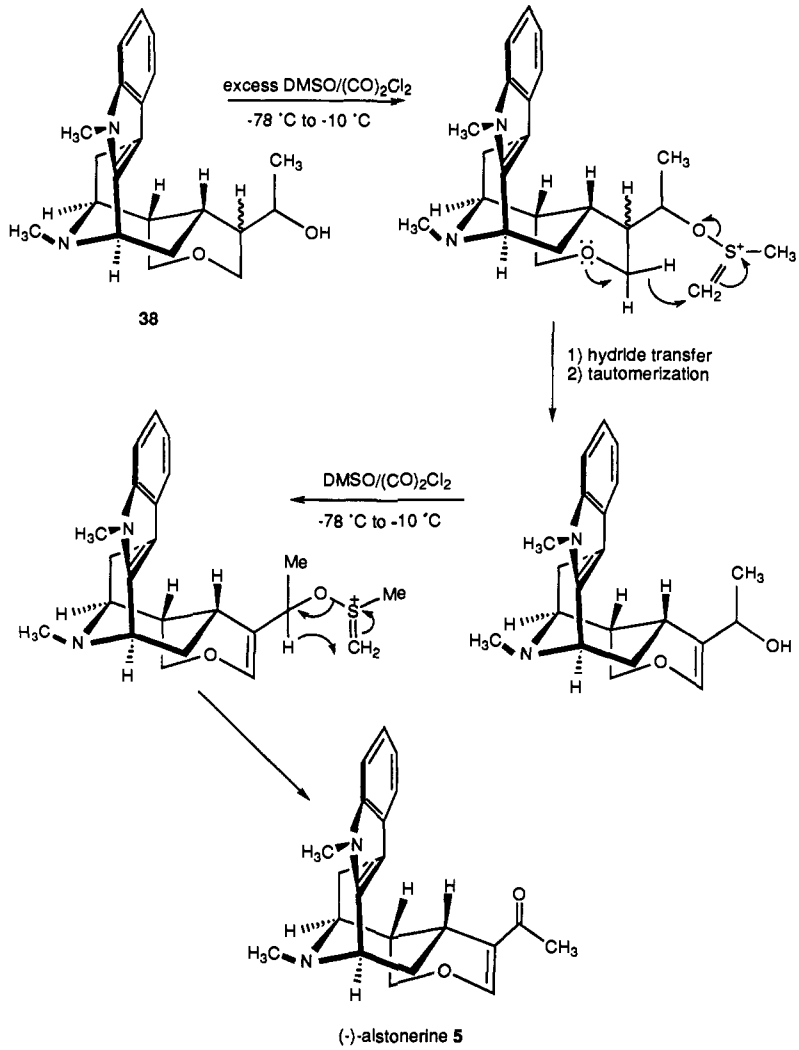
With the mixture of triols in hand, attention turned to the construction of the tetrahydropyran ring, the E ring of (–)-alstonerine (**5**). Anker *et al.*[81] had reported earlier the HMPA catalyzed cyclodehydration of 1,4- and 1,5-diols to afford tetrahydrofurans and tetrahydropyrans, respectively. When heated under the same conditions, triol **33** gave only unresolvable tars for the high reaction temperature (200 °C) led to decomposition. The construction of the tetrahydropyran skeleton was achieved by reacting the triol with 1 equiv of tosyl chloride (40 h, room temperature) followed by a base-promoted ring closure (Scheme 6) on addition of either KOH, K_2CO_3, or Et_3N to the reaction mixture. This one pot process occurred as expected to provide tetrahydroalstonerine (**38**), since the primary hydroxyl group at C(21) was more reactive toward tosyl chloride than the secondary hydroxyl group at C(19) (see Figure 10). Furthermore, the primary hydroxyl group located at C(21) was more exposed as expected than the corresponding group at C(17) in agreement with the observations of Trudell during the synthesis of (±)-suaveoline.[10] Presumably, the tosylate at C(21) reacted with the hydroxyl group at C(17) by an intramolecular S_N2 process (Figure 10). Even if a small amount of the tosylate at C(17) forms, cyclization with the free hydroxyl group at C(21) would provide the same tetrahydropyran **38**. This procedure resulted in the construction of the tetrahydropyran ring in 60% yield, accompanied by 33% of recovered starting diol which could be recycled. This intramolecular nucleophilic substitution involved a six-membered transition state which was more favorable than its four-membered counterpart, The latter would have arisen if the secondary hydroxyl group had participated in the process of ring closure (Figure 10).

No reaction occurred when tetrahydroalstonerine (**38**) was treated with the Swern reagent under normal conditions (–78 °C, 20 min).[82] (–)-Alstonerine (**5**), however, was the major product (51%) when tetrahydroalstonerine (**38**) was stirred with

(81) Diab, J.; Assalt, M. A.; Gervais, C.; Anker, D. *Tetrahedron Lett.* **1985**, *26*, 1051.

(82) Mancuso, A. J.; Huang, S.-L.; Swern, S. *J. Org. Chem.* **1978**, *43*, 2480.

Scheme 7



excess Swern reagent under modified conditions (−78 °C to −10 °C, 1 h and 15 min). This material was accompanied by (−)-dihydroalstonerine (**39**) (31%) which could be reduced back to monol **38** and recycled to **5** when desired. This constitutes the first total synthesis of an *Alstonia* macroline related alkaloid and was executed *via* a route amenable to the synthesis of alstophylline **6**, as well as many other macroline/sarpagine/ajmaline alkaloids. The enone system of **5** obtained from tetrahydroalstonerine (**38**) under modified Swern conditions is important for a number of *Alstonia* alkaloids contain this chromophore including alstophylline (**6**), alstonisine, and N_b-desmethylalstophylline oxindole, as well as N_a-desmethylalstophylline. The latter base constitutes the nonmacroline portion of bisindole alkaloid-H. Since the methyl ketone, dihydroalstonerine (**39**), could not be converted into (−)-alstonerine under the modified conditions of the Swern reaction, carbon–carbon double bond formation in the tetrahydropyran ring must have occurred before the formation of the carbonyl group. A possible sequence of steps to account for this new reaction is illustrated in Scheme 7. The process is felt to involve an intramolecular hydrogen abstraction by the nearby oxidizing agent at C(19) (CH_3—S=CH_2) assisted by one of the lone pairs on the ether oxygen atom. After the formation of the double bond followed by tautomerization, a second molecule of the oxidizing agent presumably converts the secondary hydroxyl group into the methyl ketone **5**. This process provides the unique enone structural feature inherent in (−)-alstonerine (**5**) (Scheme 7). The spectral and physical data of (−)-alstonerine [mp 171–172 °C, IR, MS, UV, ^{1}H NMR, ^{13}C NMR and $[\alpha]^{22}_D$ −190° (*c* 0.32 in EtOH)] are in complete agreement with the data reported in the literature (mp 172–173 °C, $[\alpha]^{25}_D$ −195°) for this indole alkaloid.[16,83] The synthesis of (−)-alstonerine has been achieved in greater than 98% ee *via* this approach.

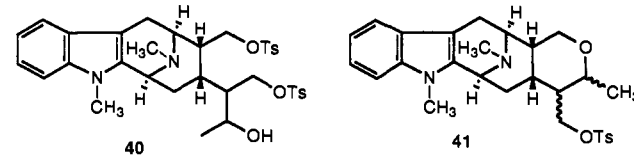


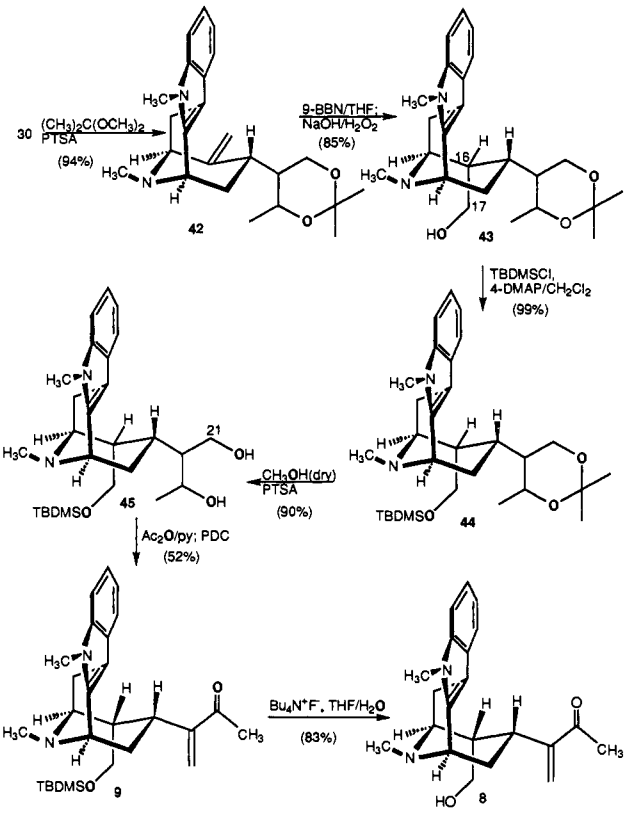
Figure 11.

For the synthesis of (+)-macroline **8**, it was felt that triol **33** might be amenable for selective manipulation of the hydroxyl group to provide an enone function present in macroline **8**. Attempts to functionalize the primary alcohol functions at C(17) and C(21) in the presence of the secondary hydroxyl group at C(19) were not successful except in the case of tosylation. Unfortunately, the ditosylate **40** was not stable under the alkaline reaction conditions and underwent intramolecular cyclization directly to furnish the monotosylated tetrahydropyran intermediate **41** along with tetrahydroalstonerine (**38**) (Figure 11). The sequence outlined in Scheme 8 was, therefore, designed to circumvent the above mentioned problems.

Macroline (**8**) is known to cyclize to dihydroalstonerine (**39**) when exposed to base and is not stable in a vial for long periods of time; therefore, the synthesis of (+)-macroline (**8**) is presented

(83) Ratnayake, C. K.; Arambewela, L. S. R.; DeSilva, K. T. D.; Rahman, A.; Alvi, K. A. *Phytochemistry* **1987**, *26*, 868.

Scheme 8



along with the preparation of a stable macroline equivalent **9** that can be employed for the synthesis of *Alstonia* bisindole alkaloids.

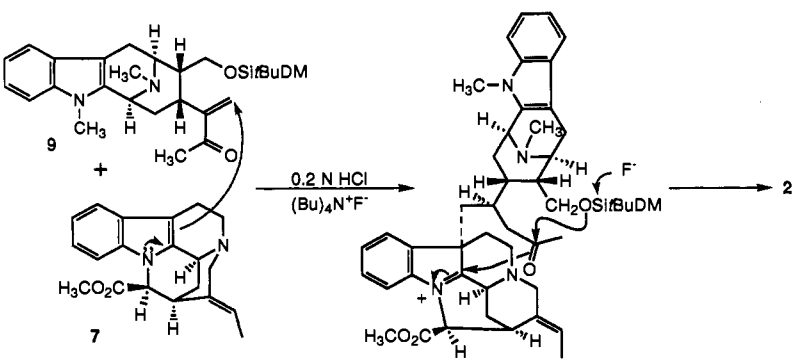
The alkenic 1,3-diol **30** was converted into the acetonide **42** in 94% yield by treatment of the diol **30** with 2,2-dimethoxypropane in the presence of *p*-toluenesulfonic acid. Hydroboration–oxidation of **42** with 9-BBN occurred exclusively from the β-face of the C(16)–C(17) olefinic bond to furnish the desired primary alcohol **43** at C(17) with the natural configuration at C(16). The hydroxyl group at C(17) of **43** was converted into its *tert*-butyldimethylsilyl ether **44**, after which the acetonide was selectively removed by stirring with *p*-toluenesulfonic acid in dry methanol under argon. Moisture must be excluded from this process, otherwise the silyl group will be adversely affected. This process permitted the protection of the more hindered hydroxyl group [C(17)] in the triol intermediate **33** and prevented its participation in other reactions. The diol **45** which resulted was treated with tosyl chloride in pyridine–methylene chloride at 20 °C for 48 h and later at 35 °C for 24 h. Unfortunately, only starting **45**, accompanied by a small amount of unresolved alkaloidal material, was isolated from this process. Mesylation of **45** did take place but, as expected, with very little regioselectivity.

On the basis of a report by Helquist[84] in 1981, an acetyl group was then employed as both the chemoselective protecting group at C(21) and as the desired leaving group. The primary hydroxyl group in **45** at C(21) was converted into the monoacetate upon treatment with acetic anhydride in the presence of pyridine, after which the mixture was exposed to oxidation with PDC (methylene chloride). Elimination of the acetate function occurred spontaneously upon oxidation of the secondary alcohol to provide the α,β-unsaturated ketone present in the stable macroline equivalent **9**. Both transformations were carried out in a one-pot process to provide enone **9** in 52% overall yield. When **9** was stirred in THF with tetrabutylammonium fluoride,[85] (+)-macroline (**8**) was obtained in 83% yield. The spectral properties of **8** were identical to those reported earlier by Schmid *et al.*[13,14]

According to the biomimetic methods developed by LeQuesne,[17] the (+)-macroline equivalent **9** was reacted with natural pleiocarpamine **7** in 0.2 N hydrochloric acid in the presence of fluoride ion. After the mixture was stirred at room temperature (~22 °C) for 24 h, villalstonine (**2**) was obtained as the only product (TLC). This material was indistinguishable from authentic material (Scheme 9). Since (+)-macroline (**8**) also reacted with **7** to provide **2** under the same conditions, it is difficult to tell whether the condensation took place as depicted in Scheme 9 or whether **8** was formed (from **9**) first. Nonetheless, this synthesis represents the first partial synthesis of any of the *Alstonia* bisindole alkaloids from a totally synthetic material.

In summary, the enantiospecific synthesis of (–)-alstonerine (**4**) and (+)-macroline (**8**) have been completed in greater than 98% ee starting from the optically active tetracyclic ketone **10** which had been prepared by an enantiospecific Pictet–Spengler reaction[28] and stereocontrolled Dieckmann cyclization.[29] The synthesis of (–)-alstonerine (**4**) and (+)-macroline (**8**) described herein represents the first enantiospecific synthesis of members of the *Alstonia* class of indole alkaloids. Moreover, the synthesis of the indole base **36** (the desmethoxy analog of **37**), a newly isolated alkaloid from *A. angustifolia* Wall, has been accomplished in enantiospecific fashion. Since the three intramolecular reactions (the Pictet–Spengler reaction, the stereocontrolled Dieckmann cyclization, and the Claisen rearrangement) employed in the synthesis provide an intermediate (**17**) which possesses the same stereoconfiguration at C(3), C(5), and C(15) as those in the macroline, sarpagine, and ajmaline alkaloids with high stereoselectivity, a general approach for the preparation of the macroline/sarpagine/ajmaline alkaloids has been developed. The significance of the synthesis of (+)-macroline becomes apparent when one considers that over 70 macroline related alkaloids have been isolated and it is known that macroline serves as a biogenetic precursor for one portion of most of the bisindole alkaloids as well as some of the monomeric bases in this group.[17-19] Macroline (**8**) is known to cyclize to dihydroalstonerine when exposed to base and is not stable in a vial for long periods of time; therefore, the synthesis of the stable macroline equivalent **9** described herein will obviously facilitate the synthesis of bisindole alkaloids which exhibit greater biological activity than the monomers that

Scheme 9



constitute them. Synthetic (+)-macroline **8** has now been coupled stereospecifically with natural pleiocarpamine **7** to furnish the antiprotozoal alkaloid villalstonine **2** which contains 11 chiral centers and 11 carbocyclic rings. The novel Swern oxidation discovered during the conversion of tetrahydroalstonerine to alstonerine is noteworthy for it provides a simple procedure with which to convert a tetrahydropyran into an enone system. Further work regarding the scope and application of this reaction to indole alkaloid synthesis will be reported in due course.

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 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 5855 GC-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, 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 distilled from P_2O_5. Diisopropylamine and pyridine were dried by distillation over KOH.

(6*S*,10*S*)-(–)-5,12-Dimethyl-9-oxo-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole [(–)-21]. A solution of (–)-N_b-benzyl tetracyclic ketone **10** (10.0 g, 0.03 mol) and methyl trifluoromethanesulfonate (5.4 g, 0.033 mol) in dry CH_2Cl_2 (100 mL) was heated at reflux under an atmosphere of nitrogen for 8 h. The reaction mixture was diluted with CH_2Cl_2 (700 mL), washed with saturated aqueous $NaHCO_3$ (2 × 100 mL) and brine (100 mL), and dried ($MgSO_4$). After the removal of solvent under reduced pressure, the residue (14.1 g, 95%) was dissolved in ethanol (200 mL, 95%) and hydrogenated under an atmosphere of hydrogen over Pd/C (3 g, 10%) until the hydrogen adsorption had ceased (1 L). The slurry which remained was filtered through Celite and the solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (800 mL), washed with saturated aqueous $NaHCO_3$ (2 × 100 mL) and brine (100 mL), and dried (K_2CO_3). After the removal of solvent under reduced pressure, the residue was dissolved in ethyl acetate (10 mL) and passed through a wash column (silica gel), after which the residue was crystallized from ethyl acetate to afford (–)-**21** (6.4 g, overall yield 84%): mp 140–141 °C; $[\alpha]^{22}_D$ –129.6° (c = 0.52 in $CHCl_3$); IR (KBr) 1710 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.03 (m, 2 H), 2.38 (dd, J = 16.7 and 7.7 Hz, 1 H), 2.48 (s, 3 H), 2.51 (m, 1 H), 2.64 (d, J = 16.8 Hz, 1 H), 3.22 (dd, J = 16.8 and 6.8 Hz, 1 H), 3.62 (d, J = 6.8 Hz, 1 H), 3.67 (s, 3 H), 4.04 (m, 1 H), 7.10 (t, J = 8.0 Hz, 1 H), 7.21 (t, J = 8.0 Hz, 1 H), 7.30 (d, J = 8.0 Hz, 1 H), 7.47 (d, J = 8.0 Hz, 1 H); ^{13}C NMR (125.75 MHz, $CDCl_3$) δ 19.99, 29.36, 29.47, 33.78, 40.42, 51.83, 65.91, 105.41, 108.86, 118.23, 119.25, 121.52, 126.38, 132.87, 137.20, 210.06; CIMS (CH_4) m/e (relative intensity) 255 (M + 1, 100). Anal. Calcd for $C_{16}H_{18}ON_2$: C, 75.56; H, 7.13; N, 11.01. Found: C, 75.57; H, 7.19; N, 10.98.

α-(Chloromethyl)phenyl Sulfoxide. A solution of sulfuryl chloride (22.9 g, 0.166 mol) in CH_2Cl_2 (125 mL) was added dropwise to a stirred mixture of wet silica gel (12.5 g of silicic acid, 12.5 g of H_2O), and chloromethyl phenyl sulfide (25 g, 0.158 mol) in CH_2Cl_2 (125 mL) at room temperature. The mixture was stirred for an additional 2 h and then poured into a solution of aqueous $NaHCO_3$ (10%, 50 mL), and this was followed by extraction with CH_2Cl_2 (3 × 70 mL). The combined extracts were washed with water (30 mL) and brine (2 × 50 mL) and dried (K_2CO_3). The solvent was removed under reduced pressure to provide an oil. The oil was chromatographed (silica gel, EtOAc/hexane, 50:50) to provide the sulfoxide (20.5 g, 80.8%): $bp_{0.2mm}$ = 120–123 °C (lit.[86] $bp_{0.3mm}$ = 120–130 °C); IR (NaCl) 3100, 3000, 1480, 1090, 1045, 760, 740, 700 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.38 (s, 2 H), 7.55 (m, 3 H), 7.65 (m, 2 H); CIMS (CH_4) m/e (relative intensity) 175 (M + 1, 100).

(6*S*,10*S*)-(–)-2′-(Phenylsulfinyl)-5,12-dimethyl-6,7,8,9,10,11-hexahydrospirooxirane[2′,9]-6,10-imino-5*H*-cyclooct[*b*]indole (23). A solution of lithium diisopropylamide [12 mmol, from diisopropylamine (1.34 g, 13.2 mmol) in THF (5 mL) and n-butyllithium (4.8 mL of a 2.5 M solution in hexane)] was cooled to –78 °C under an atmosphere of argon. A solution of α-(chloromethyl)phenyl sulfoxide (2.10 g, 12 mmol) in THF (1 mL) was added to the solution of LDA. The yellow mixture was stirred for 10 min at –78 °C, after which the ketone **21** (2.54 g, 10 mmol) in THF (15 mL) was added dropwise over a 5 min period. The reaction mixture was stirred for 40 min, then brought to room temperature, and diluted with THF to 70 mL. A solution of aqueous KOH (10 N, 30 mL) was added, and the heterogeneous mixture was stirred for 10 h at room temperature. The organic layer was removed, and the aqueous phase was extracted with $CHCl_3$ (4 × 100 mL). The combined organic fractions were washed with saturated aqueous NH_4Cl (2 × 50 mL) and brine (2 × 50 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue was dissolved in ethyl acetate. This solution was percolated through a wash column of silica gel, after which the mixture of diastereomers of the (phenylsulfinyl)oxirane represented by **23** was obtained as an amorphous solid (3.37 g, 86%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.05 (m, 1 H), 1.90 (m, 1 H), 2.54 (s, 3 H), 2.78 (d, J = 17.5 Hz, 1 H), 3.02 (dd, J = 17.5 and 5.9 Hz, 1 H), 3.27 (dd, J = 17.5 and 7.5 Hz, 1 H), 3.55 (dd, J = 17.5 and 7.5 Hz, 1 H), 3.63 (s, 3 H), 3.60–3.68 (m, 1 H), 3.92 (s, 1 H), 4.01 (dd, J = 4.7 and 1.2 Hz, 1 H), 7.05 (t, J = 7.4 Hz, 1 H), 7.15–7.60 (m, 8 H). Anal. Calcd for $C_{23}H_{24}N_2O_2S$: C, 70.38; H, 6.16; N, 7.13. Found: C, 70.06; H, 6.08; N, 7.03.

(6*S*,10*S*)-(–)-5,12-Dimethyl-9-formyl-6,7,10,11-tetrahydro-6,10-imino-5*H*-cyclooct[*b*]indole [(–)-20]. The mixture of (phenylsulfinyl)oxiranes **23** (3.0 g, 7.7 mmol) was added to a solution of toluene (45 mL) which contained lithium perchlorate (0.8 g, 7.7 mmol) and tri-n-butylphosphine oxide (1.7 g, 7.7 mmol). The mixture was heated at reflux under an atmosphere of argon for 2 h. The orange solution which resulted was allowed to cool to room temperature and diluted with toluene to a volume of 400 mL. The organic mixture was washed with 10% aqueous NH_3 (50 mL), and brine (2 × 50 mL), and dried (K_2CO_3). The solvent was removed under reduced pressure. The oil which resulted was chromatographed (silica gel, MeOH/EtOAc, 8/92) to provide the α,β-unsaturated aldehyde (–)-**20** (1.7 g, 84%) as an amorphous solid: $[\alpha]^{22}_D$ –100° (c = 0.52 in $CHCl_3$); IR (neat) 2890, 1678, 1450 cm^{-1}; ^{1}H NMR (500 MHz $CDCl_3$) δ 2.39 (dd, J = 19.2 and 5.0 Hz, 1 H), 2.50 (s, 3 H), 2.62 (d, J = 16.3 Hz, 1 H), 3.06 (dd, J = 19.2 and 5.5 Hz, 1 H), 3.35 (dd, J = 16.3 and 6.0 Hz, 1 H), 3.65 (s, 3 H), 4.07 (d, J = 6 Hz, 1 H), 4.09 (d, J = 5.5 Hz, 1 H), 6.69 (dd, J = 5.0 and 2.0 Hz, 1 H), 7.06 (t, J = 8.5 Hz, 1 H), 7.17 (t, J = 8.5 Hz, 1 H), 7.26 (d, J = 8.4 Hz, 1 H), 7.44 (d, J = 8.4 Hz, 1 H), 9.32 (s, 1 H); ^{13}C NMR (125.75 MHz, $CDCl_3$) 21.40, 29.36, 31.99, 40.39, 50.83, 50.98, 104.87, 108.72, 118.31, 119.11, 121.34, 126.74, 133.79, 137.01, 143.50, 146.94, 192.44; CIMS (CH_4) m/e (relative intensity) 267 (M + 1, 100). Anal. Calcd for $C_{17}H_{18}N_2O$: C, 76.66; H, 7.81; N, 10.52. Found: C, 76.81; H, 7.69; N, 10.48.

Alternative Route To Prepare (–)-20 from 23. A solution of the (phenylsulfinyl)oxiranes **23** (1 g, 2.6 mmol) in xylenes (100 mL) was heated at reflux for 3 h under an atmosphere of argon. The solution was allowed to cool to room temperature and diluted with ethyl acetate (100 mL). The organic layer was washed with brine (2 × 30 mL) and dried (K_2CO_3). The solvent was removed under reduced pressure and the residue dissolved in ethyl acetate (1 mL). The solution was percolated through a wash column (silica gel, MeOH/EtOAc, 2:98) to yield the α,β-unsaturated aldehyde **20** (0.52 g, 75%). This aldehyde was obtained as an amorphous solid which was identical in all respects to an authentic sample of (–)-**20** obtained from the previous experiment.

(6*S*,10*S*)-(–)-5,12-Dimethyl-9-(hydroxymethyl)-6,7,10,11-tetrahydro-6,10-imino-5*H*-cyclooct[*b*]indole [(–)-19]. The α,β-unsaturated aldehyde **20** (1.06 g, 4 mmol) was dissolved in dry ether (20 mL), and the solution was added dropwise to a mixture of lithium aluminum hydride (188 mg, 4.8 mmol) in ether (50 mL) at –20 °C (CCl_4–dry ice). The mixture which resulted was stirred for 2 h at –20 °C, after which ethanol (2 mL) was added to destroy the excess hydride. The solution was brought to room temperature, poured into aqueous KOH (6 N, 80 mL), and extracted with EtOAc (3 × 200 mL). The combined organic extracts were washed with saturated aqueous NH_4Cl (2 × 50 mL) and brine (2 × 50 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue was crystallized from CH_3OH to afford the allylic alcohol **19** as a colorless solid (0.97 g, 90%): mp 185.5–186.5 °C; $[\alpha]^{22}_D$ –100.0°

(84) Bornack, W. K.; Bhagwat, S. S.; Ponton, J.; Helquist, P. *J. Am. Chem. Soc.* **1981**, *103*, 4647.
(85) Esmond, R. W.; LeQuesne, P. W. *J. Am. Chem. Soc.* **1980**, *102*, 7116.
(86) Hojo, M.; Masuda, R. *Tetrahedron Lett.* **1976**, 613.

(c = 0.52 in $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 2.05 (dd, J = 17.4 and 4.8 Hz, 1 H), 2.47 (s, 3 H), 2.67 (d, J = 16.1 Hz, 1 H), 2.85 (dd, J = 17.4 and 5.5 Hz, 1 H), 3.06 (dd, J = 16.1 and 5.8 Hz, 1 H), 3.62 (s, 3 H), 3.74 (d, J = 5.8 Hz, 1 H), 3.99 (d, J = 5.8 Hz, 1 H), 4.05 (AB q, J = 13.0 Hz, 2 H), 5.56 (d, J = 4.0 Hz, 1 H), 7.07 (t, J = 7.5 Hz, 1 H), 7.15 (t, J = 7.5 Hz, 1 H), 7.26 (d, J = 7.5 Hz, 1 H), 7.47 (d, J = 7.5 Hz, 1 H); ^{13}C NMR (125.75 MHz, $CDCl_3$) 20.60, 29.26, 30.72, 40.32, 50.92, 53.12, 64.96, 104.55, 108.72, 118.06, 118.91, 119.37, 121.00, 126.89, 134.29, 136.99, 140.22; CIMS (CH_4) m/e (relative intensity) 269 (M + 1, 100). Anal. Calcd for $C_{17}H_{20}N_2O$: C, 76.11; H, 7.48; N, 10.44. Found: C, 76.33; H, 7.53; N, 10.15. This reaction was run on scales greater than 10 g with no loss in yield.

Michael Addition Reaction. (6*S*,10*S*)-(−)-5,12-Dimethyl-9-[[(3-oxo-1(*E*)-butenyl)oxy]methyl]-6,7,10,11-tetrahydro-6,10-imino-5*H*-cyclooct-[*b*]indole (18). The allylic alcohol **19** (1.00 g, 3.73 mmol) was dissolved in a solution of dry dioxane (80 mL), and freshly distilled triethylamine (1 mL) was added. This mixture was maintained at 22 °C. A solution of 3-butyn-2-one (1 mL) in dry dioxane (1 mL) was added dropwise over 5 min. The light brown solution which resulted was stirred in the dark for 3 days at room temperature. The reaction mixture was rapidly passed through a short wash column without removal of solvent (silica gel, dioxane). The residue was then chromatographed (silica gel, EtOAc, then THF) to provide the allylic enone ether **18** as an oil (1.16 g, 92%): $[\alpha]^{22}_D$ −111.6° (c = 0.62 in $CHCl_3$); IR (NaCl) 1660, 1600 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.08 (dd, J = 17.5 and 5.0 Hz, 1 H), 2.12 (s, 3 H), 2,49 (s, 3 H), 2.65 (d, J = 16.0 Hz, 1 H), 2.86 (dd, J = 17.5 and 4.0 Hz, 1 H), 3.14 (dd, J = 16.0 and 6.0 Hz, 1 H), 3.63 (s, 3 H), 4.03 (d, J = 6.0 Hz, 1 H), 4.20–4.42 (AB q, J = 11.9 Hz, 2 H), 5.62 (d, J = 12.7 Hz, 1 H), 5.71 (d, J = 4.0 Hz, 1 H), 7.07 (t, J = 8.0 Hz, 1 H), 7.17 (t, J = 8.0 Hz, 1 H), 7.25 (d, J = 8.0 Hz, 1 H), 7.46 (d, J = 7.9 Hz, 1 H), 7.52 (d, J = 12.7 Hz, 1 H); ^{13}C NMR (125.75 MHz, $CDCl_3$) 21.08, 27.71, 29.19, 30.02, 40.34, 50.49, 53.40, 73.17, 104.23, 107.75, 108.67, 117.90, 121.02, 124.13, 126.65, 134.12, 134.37, 136.89, 161.79, 197.16; CIMS (CH_4) m/e (relative intensity) 337 (M + 1, 69.9), 251 (100). Anal. Calcd for $C_{21}H_{24}N_2O_2$: C, 74.97; H, 7.19; N, 8.33. Found: C, 75.06; H, 7.09; N, 8.04.

Claisen Rearrangement. (6*S*,8*S*,10*S*)-(−)-1-Formyl-1-(5,12-dimethyl-9-methylene-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indol-8-yl)propan-2-one (17). A solution of the allylic enone **18** (100 mg, 0.30 mmol) in freshly distilled dry benzene (10 mL) was placed in a glass tube, flushed with argon, and then evacuated three times. The tube was sealed under vacuum. This tube was heated at 145 °C for 20 h. The reaction mixture was cooled to room temperature and then opened. The solvent was removed under reduced pressure to afford an oil. The oil was chromatographed (silica gel, MeOH/EtOAc, 10:90) to provide the alkenic β-keto aldehyde as an enolic tautomer represented by **17** (65.5 mg, 65%): IR (NaCl) 1660, 1600 cm^{-1}; ^1H NMR (500 MHz $CDCl_3$) δ 1.77 (br d, J = 11.0 Hz, 1 H), 1.88 (s, 3 H), 2.31 (t, J = 10.3 Hz, 1 H), 2.46 (s, 3 H), 2.56 (d, J = 16.8 Hz, 1 H), 3.10 (d, J = 9.4 Hz, 1 H), 3.35 (dd, J = 16.8 and 6.3 Hz, 1 H), 3.65 (s, 3 H), 3.83 (d, J = 6.3 Hz, 1 H), 4.14 (br s, 1 H), 4.55 (s, 1 H), 4.98 (s, 1 H), 7.10 (t, J = 7.5 Hz, 1 H), 7.21 (t, J = 7.5 Hz, 1 H), 7.28 (d, J = 8.0 Hz, 1 H), 7.50 (d, J = 7.9 Hz, 1 H), 7.95 (s, 1 H), 15.4 (s, 1 H); ^{13}C NMR (125.75 MHz, $CDCl_3$) δ 23.17, 29.09, 33.62, 35.71, 41.26, 53.73, 61.56, 106.59, 108.85, 109.46, 112.32, 118.13, 119.01, 121.17, 126.31, 133.07, 137.16; EIMS m/e (relative intensity) 336 (M^+, 100.0), 293 (16), 212 (19.6), 197 (91), 182 (26.4), 170 (59.0). Anal. Calcd for $C_{21}H_{24}N_2O_2$: C, 74.97; H, 7.19; N, 8.33. Found: C, 75.04; H, 7.01; N, 8.11.

5,9,12-Trimethyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]-indole (24) and 5,9,12-Trimethyl-6,7,8,9,10,11-hexahydro-8,9-[(1-acetylethylene)oxy]-6,10-imino-5*H*-cyclooct[*b*]indole (25). A solution of the allylic enone **18** (50 mg, 0.15 mmol) in freshly distilled dry benzene (5 mL) was placed in a glass tube and was flushed with argon. The tube was evacuated three times and then sealed under vacuum. The sealed tube was heated at 180 °C for 20 h. The tube was cooled to room temperature and then opened. The solvent was removed under reduced pressure to afford an oil. The oil was chromatographed (silica gel, MeOH/EtOAc) to provide the two isomeric enone ethers **24** (21.6 mg) and **25** (10.8 mg). The overall yield of the process was 65%. **24**: IR (NaCl) 1660, 1600 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.15 (s, 3 H), 1.72 (ddd, J = 13.1, 9.0, and 5.0 Hz, 1 H), 2.21 (s, 3 H), 2.34 (dd, J = 9.0 and 9.0 Hz, 1 H), 2.42 (ddd, J = 13.1, 9.0, and 2.0 Hz, 1 H), 2.53 (s, 3 H), 2.77 (d, J = 17.0 Hz, 1 H), 3.11 (dd, J = 17.0 and 6.0 Hz, 1 H), 3.52 (d, J = 6.0 Hz, 1 H), 3.63 (s, 3 H), 3.79 (dd, J = 5.0 and 2.0 Hz, 1 H), 7.05 (t, J = 8.0 Hz, 1 H), 7.15 (t, J = 8.0 Hz, 1 H), 7.25 (d, J = 7.9 Hz, 1 H), 7.50 (d, J = 7.9 Hz, 1 H), 8.71 (s, 1 H); EIMS m/e (relative intensity) 336 (M^+, 100). **25**: IR (NaCl) 1660, 1600 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.18 (s, 3 H), 1.73 (ddd, J = 13.1, 9.1, and 2.0 Hz, 1 H), 2.23 (s, 3 H), 2.39 (dd, J = 9.0 and 9.0 Hz, 1 H), 2.49 (ddd, J = 13.1, 9.0, and 2.0 Hz, 1 H), 2.54 (s, 3 H), 2.77 (d, J = 17.0 Hz, 1 H), 3.10 (dd, J = 17.0 and 6.0 Hz, 1 H), 3.53 (d, J = 6.0 Hz, 1 H), 3.63 (s, 3 H), 3.73 (dd, J = 5.0 and 2.0 Hz, 1 H), 7.09 (t, J = 8.0 Hz, 1 H), 7.20 (t, J = 8.0 Hz, 1 H), 7.23 (s, 1 H), 7.27 (d, J = 7.9 Hz, 1 H), 7.45 (d, J = 7.9 Hz, 1 H), 9.63 (s, 1 H); EIMS m/e (relative intensity) 336 (M^+, 100); HRMS calcd for $C_{21}H_{24}N_2O_2$ 336.1842, found 336.1838.

Conversion of 1-Formyl-1-(5,12-dimethyl-9-methylene-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indol-8-yl)propan-2-one (17) into the Corresponding Enone Ethers 5,9,12-Trimethyl-6,7,8,9,10,11-hexahydro-8,9-[(1-methyl-2-formylethylene)oxy]-6,10-imino-5*H*-cyclooct[*b*]-indole (24) and 5,9,12-Trimethyl-6,7,8,9,10,11-hexahydro-8,9-[(1-acetylethylene)oxy]-6,10-imino-5*H*-cyclooct[*b*]indole (25) under Thermal Conditions (180 °C). A solution of the alkenic β-keto aldehyde **17** (20 mg) in freshly distilled dry benzene (5 mL) was placed in a glass tube, flushed with argon, and evacuated three times. It was then sealed under vacuum. This sealed tube was heated at 180 °C for 20 h in an oven. The tube was cooled to room temperature and then opened. The solvent was removed under reduced pressure to afford an oil. The oil was chromatographed (silica gel, MeOH/EtOAc) to provide **24** and **25** both of which were identical to the enol ethers **24** and **25**, respectively, produced in the previous experiment (67% overall yield).

Claisen Rearrangement in Cumene. (6*S*,8*S*,10*S*)-1-Formyl-1-(5,12-dimethyl-9-methylene-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct-[*b*]indol-8-yl)propan-2-one (17). A solution of the allylic enone **18** (2 g, 0.30 mmol) in freshly distilled dry cumene (300 mL) was heated at 145 °C under an atmosphere of argon until the starting material disappeared (~6 h). The solvent was removed under reduced pressure to afford an oil. The oil was chromatographed (silica gel, MeOH/$CHCl_3$, 10:90) to provide the alkenic β-keto aldehyde as an enolic tautomer represented by **17** (1.31 g, 66%) and a mixture of byproducts represented by **26b** (0.32 g 16%). The properties of **17** were identical in all respects to that of the β-keto aldehyde produced in the previous sealed tube experiment. The mixture of byproducts was comprised of three components the major one of which appears to be **26b**: IR (NaCl) 1660, 1600 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.93 (s, 3 H), 2.44 (s, 3 H), 2.71 (d, J = 17.0 Hz, 1 H), 3.22 (dd, J = 17.0 and 5.1 Hz, 1 H), 3.58 (s, 3 H), 4.0 (m, 2 H), 4.60 (t, J = 2.2 Hz, 1 H), 5.02 (br s, 1 H), 7.11 (t, J = 7.5 Hz, 1 H), 7.20 (t, J = 7.5 Hz, 1 H), 7.26 (d, J = 8.0 Hz, 1 H), 7.49 (d, J = 7.9 Hz, 1 H), 7.71 (d, J = 4.5 Hz, 1 H), 15.4 (d, J = 4.5 Hz, 1 H); EIMS m/e (relative intensity) 336 (M^+, 100.0), 293 (16), 212 (19.6), 197 (91), 182 (26.4), 170 (59.0).

Attempted Chemoselective Reduction of the Alkenic β-Keto Aldehyde 17 To Provide 1-Methoxy-1-(5,12-dimethyl-9-methylene-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indol-8-yl)propan-2-one (29). The alkenic β-keto aldehyde **17** (34 mg, 0.1 mmol) was dissolved in CH_3OH (3 mL), and ammine–borane (1.05 mg, 0.034 mmol) was added. The reaction mixture was stirred at 0 °C for 20 min and then quenched by addition of aqueous HCl (2 N). The reaction mixture was brought to pH 9.5 with ammonium hydroxide (10%) and then extracted with dichloromethane (2 × 30 mL). The combined organic extracts were washed with H_2O (20 mL) and brine (2 × 20 mL) and dried (K_2CO_3). The solvent was removed under reduced pressure to afford an oil. This oil was chromatographed (silica gel, 8% MeOH/EtOAc) to give β-hydroxy ketone **29** (10.5 mg, 31%), β-dihydroxyl derivative **30** (11 mg, 32%), and starting material (β-keto aldehyde) **17** (6.8 mg, 20%). **29**: IR (NaCl) 1725 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.50 (s, 3 H), 1.51 (d, J = 14.0 Hz, 1 H), 1.90 (m, 1 H), 2.19 (br s, 1 H), 2.35 (m, 1 H), 2.49 (s, 3 H), 2.51 (d, J = 16.9 Hz, 1 H), 2.95 (dd, J = 12.1 and 6.2 Hz, 1 H), 3.31 (dd, J = 16.9 and 5.1 Hz, 1 H), 3.35 (dd, J = 9.8 and 6.2 Hz, 1 H), 3.61 (s, 3 H), 3.72 (d, J = 6.2 Hz, 1 H), 3.88 (s, 1 H), 4.95 (s, 1 H), 5.15 (s, 1 H), 7.11 (t, J = 7.9 Hz, 1 H), 7.19 (t, J = 7.9 Hz, 1 H), 7.30 (d, J = 8.0 Hz, 1 H), 7.49 (d, J = 8.2 Hz, 1 H); EIMS m/e (relative intensity) 338 (M^+, 100). Anal. Calcd for $C_{21}H_{26}N_2O_2$: C, 74.52; H, 7.74; N, 8.28. Found: C, 75.04; H, 7.84; N, 7.87. **35**: ^1H NMR δ 1.01 (d, J = 7.1 Hz, 3 H), 1.95 (m, 2 H), 2.08 (dd, J = 15.6 and 4.2 Hz, 1 H), 2.38 (s, 3 H), 2.45 (br s, 1 H), 2.52 (d, J = 17.2 Hz, 1 H), 3.22 (dd, J = 17.2 and 5.0 Hz, 1 H), 3.35 (br s, 1 H), 3.59 (s, 3 H), 3.71 (m, 3 H), 3.88 (d, J = 5.0 Hz, 1 H), 3.92 (d, J = 4.8 Hz, 1 H), 3.98 (s, 1 H), 4.72 (s, 1 H), 4.98 (s, 1 H), 7.05 (t, J = 7.9 Hz, 1 H), 7.12 (t, J = 7.9 Hz, 1 H), 7.25 (d, J = 8.0 Hz, 1 H), 7.43 (d, J = 8.0 Hz, 1 H); EIMS m/e (relative intensity) 340 (M^+, 80.3), 197 (100); HRMS calcd for $C_{21}H_{28}N_2O_2$ 340.2154, found 340.2151.

Hydroboration of the Alkenic β-Keto Aldehyde 17 in the Presence of Triethylborane. The alkenic β-keto aldehyde **17** (50 mg, 0.15 mmol) was dissolved in dry THF (1 mL) under an atmosphere of argon. Trieth-

ylborane in THF (0.15 mL, 0.15 mmol) was added in one portion, and the mixture was stirred at 22 °C for 30 min, after which 9-BBN in THF (0.6 mL, 0.3 mmol) was added. The solution was stirred at 22 °C for an additional 20 h, after which H_2O (0.1 mL) was added to quench the excess borohydride. The reaction mixture which resulted was warmed to 40 °C, and aqueous NaOH (3 N, 0.3 mL, 0.9 mmol) was added followed by dropwise addition of H_2O_2 (30%, 0.15 mL). The reaction mixture was stirred at 40 °C for 2 h. The solution was saturated with NaCl, and the organic layer was decanted. The residue was extracted with EtOAc (3 × 40 mL), and the combined organic layers were washed with brine (2 × 30 mL) and dried (K_2CO_3). The solvent was removed under reduced pressure, and the residue was chromatographed (silica gel, MeOH/$CHCl_3$, 8:92) to provide **34** (21.8 mg, 38%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.22 (d, J = 6.6 Hz, 3 H), 0.98 (s, 3 H), 1.42 (d, J = 12.4 Hz, 1 H), 1.43 (d, J = 13.5 Hz, 1 H), 1.62 (dd, J = 13.5 and 6.2 Hz, 1 H), 1.79 (m, 1 H), 1.80 (m, 1 H), 1.85 (br s, 1 H), 2.39 (m, 1 H), 2.42 (s, 3 H), 2.51 (d, J = 16.2 Hz, 1 H), 2.75 (ddd, J = 8.5, 8.5, and 6.0 Hz, 1 H), 2.91 (dd, J = 16.2 and 6.3 Hz, 1 H), 3.12 (ddd, J = 8.6, 8.6, and 3.1 Hz, 1 H), 3.52 (dd, J = 6.2 and 3.1 Hz, 1 H), 3.62 (s, 3 H), 3.85 (t, J = 6.0 Hz, 1 H), 3.91 (d, J = 6.3 Hz, 1 H), 7.05 (t, J = 7.8 Hz, 1 H), 7.20 (t, J = 8.0 Hz, 1 H), 7.31 (d, J = 7.6 Hz, 1 H), 7.50 (d, J = 7.9 Hz, 1 H); EIMS m/e (relative intensity) 382 (M^+, 0.4), 339 (17.2), 338 (71.1), 337 (10.2), 198 (15.7), 197 (100), 182 (18.7), 181 (13.8).

Direct Hydroboration of the Alkenic β-Keto Aldehyde 17 with 9-BBN. The alkenic β-keto aldehyde **17** (50 mg, 0.15 mmol) was dissolved in dry THF (1 mL) under an atmosphere of argon. A solution of 9-BBN in THF (1 mL, 0.5 mmol) was added in one portion, and the mixture was stirred at 22 °C for 20 h, after which H_2O (0.1 mL) was added to quench the excess borohydride. The reaction mixture which resulted was warmed to 40 °C, and aqueous NaOH (3 N, 0.5 mL, 1.5 mmol) was added followed by dropwise addition of H_2O_2 (30%, 1.5 mL). The reaction mixture was stirred at 40 °C for 2 h. The solution was saturated with NaCl, and the organic layer was decanted. The residue was extracted with EtOAc (3 × 50 mL), after which the combined organic layers were washed with brine (2 × 30 mL) and dried (K_2CO_3). The solvent was removed under reduced pressure to afford a colorless foam which was chromatographed (silica gel, EtOH) to provide the triol **33** (19.7 mg, 37%) and hemiketal **35** (21.9 mg, 41%): EIMS (**35**) m/e (relative intensity) 356 (M^+, 2.4), 326 (27.3), 199 (14.6), 198 (16.9), 197 (100), 181 (22.9). The hemiketal **35** (18.0 mg, 0.05 mmol) was dissolved in dry CH_2Cl_2 (0.5 mL), and the solution which resulted was added to a mixture of pyridinium dichlorochromate (30 mg, 0.09 mmol) in dry CH_2Cl_2 (0.2 mL). The mixture which resulted was stirred at room temperature for 8 h and then diluted with dry ether (50 mL). The slurry was filtered through a short column of Florisil, and the solvent was removed under reduced pressure. The residue was dissolved in ethanol (5% HCl), and the solution which resulted was stirred at 25 °C for 4 h to afford the α,β-unsaturated aldehyde **36** (11.9 mg, 71% overall yield): ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.77 (dd, J = 12.2 and 4.2 Hz, 1 H), 1.89 (ddd, J = 12.2, 11.4, and 1.5 Hz, 1 H), 2.15 (s, 3 H), 2.10 (m, 1 H), 2.30 (s, 3 H), 2.49 (d, J = 16.4 Hz, 1 H), 2.60 (m, 1 H), 3.08 (d, J = 6.8 Hz, 1 H), 3.31 (dd, J = 16.4 and 6.8 Hz, 1 H), 3.62 (s, 3 H), 3.85 (br s, 1 H), 4.15 (ddd, J = 11.2, 4.0, and 1.5 Hz, 1 H), 4.39 (t, J = 11.2 Hz, 1 H), 7.08 (t, J = 8.1 Hz, 1 H), 7.18 (t, J = 7.0 Hz, 1 H), 7.30 (d, J = 8.1 Hz, 1 H), 7.45 (d, J = 7.6 Hz, 1 H), 9.68 (s, 1 H); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 16.56, 22.42, 22.82, 29.07, 31.88, 38.57, 41.78, 53.74, 54.77, 68.12, 105.87, 109.00, 117.82, 118.72, 120.82, 126.58, 129.73, 133.20, 137.25, 157.37, 188.62. Anal. Calcd for $C_{21}H_{24}N_2O_2$: C, 74.97; H, 7.19; N, 8.33. Found: C, 74.93; H, 7.06; N, 8.03.

1-(Hydroxymethyl)-2-hydroxy-1-(5,12-dimethyl-9-methylene-6,7,8,9,-10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indol-8-yl)propane (30). To a solution of the alkenic β-keto aldehyde **17** (1.0 g, 3.0 mmol) in anhydrous ethanol (10 mL) was added portionwise sodium borohydride (117 mg, 3.0 mmol) over 2 h at 0 °C. The mixture which resulted was stirred at room temperature for an additional 18 h. Water (1 mL) was then added followed by a solution of aqueous HCl (6 N, 1 mL). The solvent was removed under reduced pressure, and the residue was brought to pH 9.5 with cold aqueous Na_2CO_3 (5%). The aqueous layer was extracted with CH_2Cl_2 (5 × 100 mL). The combined extracts were washed with water (50 mL) and brine (100 mL) and dried (K_2CO_3). The solvent was removed under reduced pressure, and the residue was chromatographed (silica gel, EtOH) to afford the β-dihydroxy intermediate **30** as a mixture of two diastereoisomers (0.87 g, 86%). **30a**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.01 (d, J = 7.1 Hz, 3 H), 1.95 (m, 2 H), 2.08 (dd, J = 15.6 and 4.2 Hz, 1 H), 2.38 (s, 3 H), 2.45 (br s, 1 H), 2.52 (d, J = 17.2 Hz, 1 H), 3.22 (dd, J = 17.2 and 5.0 Hz, 1 H), 3.35 (br s, 1 H), 3.59 (s, 3 H), 3.71 (m, 3 H), 3.88 (d, J = 5.0 Hz, 1 H), 3.92 (d, J = 4.8 Hz, 1 H), 3.98 (s, 1 H), 4.72 (s, 1 H), 4.98 (s, 1 H), 7.05 (t, J = 7.9 Hz, 1 H), 7.12 (t, J = 7.9 Hz, 1 H), 7.25 (d, J = 8.0 Hz, 1 H), 7.43 (d, J = 8.0 Hz, 1 H); EIMS: m/e (relative intensity) 340 (M^+, 80.3), 197(100). **30b**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.25 (d, J = 7.1 Hz, 3 H), 1.69 (m, 2 H), 2.05 (dd, J = 6.1 and 2.0 Hz, 1 H), 2.21 (dd, J = 14.2 and 5.2 Hz, 1 H), 2.32 (s, 3 H), 2.42 (d, J = 17.2 Hz, 1 H), 2.80 (br s, 2 H), 3.20 (dd, J = 17.2 and 5.0 Hz, 1 H), 3.60 (s, 3 H), 3.75 (m, 3 H), 3.85 (dd, J = 12.2 and 4.8 Hz, 1 H), 4.02 (d, J = 4.8 Hz, 1 H), 4.52 (s, 1 H), 4.85 (s, 1 H), 7.05 (t, J = 7.9 Hz, 1 H), 7.12 (t, J = 7.9 Hz, 1 H), 7.25 (d, J = 8.0 Hz, 1 H), 7.43 (d, J = 8.0 Hz, 1 H); EIMS m/e (relative intensity) 340 (M^+, 80.3), 197 (100); HRMS calcd for $C_{21}H_{28}N_2O_2$ 340.2154, found 340.2151. Anal. Calcd for $C_{21}H_{28}N_2O_2$: C, 74.08; H, 8.29; N, 8.23. Found: C, 73.63; H, 8.10; N, 8.11.

1-(Hydroxymethyl)-2-hydroxy-1-[5,12-dimethyl-9-(hydroxymethyl)-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indol-8-yl]propane (33). The alkenic dihydroxy compound **30** (500 mg, 1.5 mmol) was dissolved in dry THF (5 mL) under an atmosphere of argon. A solution of 9-BBN in THF (0.5 M, 3 mL, 1.5 mmol) was added in one portion, and the mixture was stirred at 22 °C for 1 h, after which additional 9-BBN (6 mL, 3.0 mmol) was added. The solution was stirred at 22 °C for an additional 20 h, after which H_2O (1 mL) was added to quench the excess borohydride. The reaction mixture which resulted was warmed to 40 °C, and aqueous NaOH (3 N, 4.0 mL, 12.0 mmol) was added followed by dropwise addition of H_2O_2 (30%, 1.5 mL, 13.2 mmol). The reaction mixture was stirred at 40 °C for 2 h. The solution was saturated with NaCl, and the organic layer was decanted. The aqueous residue was extracted with EtOAc (3 × 70 mL), and the combined organic layers (containing triol **33**) were washed with brine (3 × 50 mL) and dried (K_2CO_3). The solvent was removed under reduced pressure to afford a colorless foam which was chromatographed (silica gel, EtOH) to provide the triol **33** as a mixture of two diastereomers (456 mg, 86%). **33a**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.95 (d, J = 6.7 Hz, 3 H), 1.30 (br s, 1 H), 1.61 (t, J = 8.5 Hz, 1 H), 1.86 (dt, J = 14.0 and 3.2 Hz, 1 H), 1.90 (br s, 2 H), 2.15 (ddd, J = 14.0, 8.5, and 3.1 Hz, 1 H), 2.42 (s, 3 H), 2.52 (m, 1 H), 2.55 (m, 1 H), 2.67 (d, J = 16.7 Hz, 1 H), 2.95 (m, 1 H), 3.06 (dd, J = 16.7 and 5.2 Hz, 1 H), 3.35 (d, J = 5.2 Hz, 1 H), 3.67 (s, 3 H), 3.70–3.76 (AB q, J = 12.5 Hz, 2 H), 3.80–3.87 (AB q, J = 12.8 Hz, 2 H), 3.89 (t, J = 3.1 Hz, 1 H), 7.11 (t, J = 7.9 Hz, 1 H), 7.20 (t, J = 7.9 Hz, 1 H), 7.31 (t, J = 8.0 Hz, 1 H), 7.49 (d, J = 8.0 Hz, 1 H); EIMS m/e (relative intensity) 358 (M^+, 78.8), 197 (100). **33b**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.10 (d, J = 6.7 Hz, 3 H), 1.11 (m, 1 H), 1.30 (br s, 1H), 1.65 (dt, J = 14.0 and 3.2 Hz, 1 H), 1.79 (m, 1 H), 1.90 (br s, 2 H), 2.15 (ddd, J = 14.0, 9.5, and 3.1 Hz, 1 H), 2.38 (s, 3 H), 2.55 (m, 1 H), 2.78 (d, J = 16.7 Hz, 1 H), 3.05 (dd, J = 16.7 and 5.2 Hz, 1 H), 3.42 (d, J = 5.2 Hz, 1 H), 3.45 (dq, J = 6.7 and 2.0 Hz, 1 H), 3.55 (dd, J = 11.6 and 1.5 Hz, 1 H), 3.64 (s, 3 H), 3.65–3.85 (m, 3 H), 3.89 (t, J = 3.1 Hz, 1 H), 7.11 (t, J = 7.9 Hz, 1 H), 7.20 (t, J = 7.9 Hz, 1 H), 7.31 (t, J = 8.0 Hz, 1 H), 7.50 (d, J = 8.0 Hz, 1 H); EIMS m/e (relative intensity) 358 (M^+, 78.8), 197 (100); HRMS calcd for $C_{21}H_{30}N_2O_3$ 358.2252, found 358.2256. Anal. Calcd for $C_{21}H_{30}N_2O_3$: C, 70.36; H, 8.43; N, 7.81. Found: C, 69.70; H, 8.25; N, 7.82.

Synthesis of Tetrahydroalstonerine (38). The triol **33** (360 mg, 1 mmol) was dissolved in a solution of dry CH_2Cl_2 (5 mL), and freshly distilled dry pyridine (0.2 mL) was added. The solution was cooled to 0 °C, and a solution of tosyl chloride (191 mg, 1 mmol) in dry CH_2Cl_2 (1 mL) was added dropwise over 3 min. The light brown solution which resulted was stirred at 0 °C for 4 h and then warmed to 27 °C (room temperature) for an additional 44 h. Freshly distilled triethylamine (0.2 mL) was then added, and the reaction was continued for an additional 24 h. The reaction mixture was diluted with CH_2Cl_2 (300 mL), washed with aqueous NaOH (1 N, 2 × 30 mL), water (30 mL), and brine (2 × 50 mL), and dried (K_2CO_3). The solvent was removed under reduced pressure, and the residue was chromatographed (silica gel, MeOH/$CHCl_3$, 8:92) to provide tetrahydroalstonerine **38** (204 mg, 60%) and recovered triol **33** (100.8 mg, 33%). **38**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.77 (d, J = 6.6 Hz, 3 H), 0.83 (m, 1 H), 1.79 (ddd, J = 12.2, 6.1, and 4.2 Hz, 1 H), 2.19 (m, 1 H), 2.21 (m, 1 H), 2.22 (br s, 1 H), 2.31 (d, J = 15.1 Hz, 1 H), 2.47 (s, 3 H), 2.76 (t, J = 11.1 Hz, 1 H), 3.07 (dd, J = 16.6 and 6.9 Hz, 1 H), 3.20 (d, J = 16.6 Hz, 1 H), 3.23 (dd, J = 5.9 and 5.9 Hz, 1 H), 3.43 (quintet, J = 5.7 Hz, 1 H), 3.56 (dd, J = 11.1 and 4.3 Hz, 1 H), 3.60 (dd, J = 12.2 and 4.7 Hz, 1 H), 3.67 (s, 3 H), 3.86 (br s, 1 H), 3.95 (d, J = 12.2 Hz, 1 H), 7.08 (t, J = 7.5 Hz, 1 H), 7.18 (t, J = 7.6 Hz, 1 H), 7.27 (t, J = 8.1 Hz, 1 H), 7.49 (d, J = 7.8 Hz, 1 H); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 18.11, 18.21, 29.19, 30.81, 32.52, 39.38, 41.02, 41.58, 51.53, 57.62, 67.46, 68.31, 71.00, 106.53, 108.63, 118.60, 119.04, 121.14, 126.68, 134.91, 136.95; EIMS m/e (relative

intensity) 340 (M^+, 100), 197 (62.8); HRMS calcd for $C_{21}H_{28}N_2O_2$ 340.2158, found 340.2151.

Synthesis of Alstonerine (5) and 20,21-Dihydroalstonerine (39). A solution of oxalyl chloride (2.0 M, 0.1 mL, 0.2 mmol) in CH_2Cl_2 was added to a solution of dry DMSO (31.0 mg, 0.40 mmol) in CH_2Cl_2 (3 mL) at −78 °C under an atmosphere of argon. The mixture was stirred for 15 min followed by dropwise addition of a solution of tetrahydroalstonerine **38** (50 mg, 0.15 mmol) in CH_2Cl_2 (1 mL) over a 2 min period. The mixture which resulted was stirred for 1 h and 15 min at a temperature which was allowed to warm from −78 °C to −10 °C. Triethylamine (0.1 mL) was added, and the mixture was allowed to warm to room temperature with stirring over a 15 min period. Water (10 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were washed with brine (2 × 20 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to provide an oil which was chromatographed (silica gel, MeOH/$CHCl_3$, 8:92) to provide (−)-alstonerine (**5**) (25.2 mg, 51%) and dihydroalstonerine (**39**) (15.3 mg, 31%). **39**: mp (EtOH) 212–213 °C; IR (NaCl) 2920, 1700, 1475 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.25 (m, 1 H), 1.42 (s, 3 H), 1.63 (d, J = 14.1 Hz, 1 H), 1.93 (ddd, J = 11.1, 11.0, and 4.1 Hz, 1 H), 2.28 (m, 1 H), 2.35 (dd, J = 14.6 and 6.8 Hz, 1 H), 2.51 (s, 3 H), 2.76 (t, J = 10.9 Hz, 1 H), 3.10 (dd, J = 16.7 and 6.6 Hz, 1 H), 3.17 (d, J = 16.8 Hz, 1 H), 3.28 (br s, 1 H), 3.57 (dd, J = 10.9 and 4.2 Hz, 1 H), 3.60 (dd, J = 11.1 and 4.4 Hz, 1 H), 3.61 (s, 3 H), 3.90 (br s, 1 H), 3.97 (d, J = 11.3 Hz, 1 H), 7.11 (t, J = 7.2 Hz, 1 H), 7.22 (t, J = 7.4 Hz, 1 H), 7.30 (d, J = 8.0 Hz, 1 H), 7.55 (d, J = 7.8 Hz, 1 H); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 17.87, 29.16, 30.16, 30.70, 33,02, 38.30, 41.25, 50.78, 51.15, 57.02, 69.01, 70.60, 106.59, 108.58, 118.65, 119.15, 121.34, 126.78, 135.10, 137.19, 210.02; EIMS m/e (relative intensity) 338 (M^+, 12.2), 308 (100), 265 (52.5), 251 (50.0), 234 (57.6), 208 (24.7), 197 (88.8). **5**: mp (Et_2O) 171–172 °C (lit.[16,79] mp 172–173 °C); $[\alpha]^{22}_D$ −190° (c = 0.32 in EtOH) {lit.[16,79] $[\alpha]^{25}_D$ −195° in EtOH}; IR (NaCl) 1650, 1621 cm^{-1} (lit.[16,79] 1650, 1621 cm^{-1}); UV λ_{max} 231, 261 nm, λ_{min} 245 nm, two shoulders at 284 and 293 nm (lit.[16,79] 231, 261, 245, 284 and 294 nm); ^1H NMR (250 MHz, $CDCl_3$) δ 1.77 (dd, J = 12.2 and 4.2 Hz, 1 H), 1.89 (ddd, J = 12.2, 11.4, and 1.5 Hz, 1 H), 2.10 (s, 3 H), 2.11 (ddd, J = 11.2, 4.6 and 4.0 Hz, 1 H), 2.30 (s, 3 H), 2.49 (d, J = 16.4 Hz, 1 H), 2.60 (ddd, J = 12.4, 4.6 and 4.6 Hz, 1 H), 3.08 (d, J = 6.8 Hz, 1 H), 3.31 (dd, J = 16.4 and 6.8 Hz, 1 H), 3.63 (s, 3 H), 3.86 (t, J = 1.5 Hz, 1 H), 4.15 (ddd, J = 11.2, 4.0, and 1.5 Hz, 1 H), 4.39 (t, J = 11.2 Hz, 1 H), 7.10 (t, J = 8.1 Hz, 1 H), 7.18 (t, J = 7.0 Hz, 1 H), 7.30 (d, J = 8.1 Hz, 1 H), 7.45 (d, J = 7.6 Hz, 1 H), 7.52 (s, 1 H); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 22.82, 22.88, 25.05, 29.07, 32.36, 38.51, 41.78, 53.77, 54.68, 67.76, 105.86, 108.97, 117.82, 118.70, 120.78, 126.53, 129.73, 133.20, 137.18, 157.43, 195.45 (lit.[16,79] 22.42, 22.96, 25.04, 29.12, 32.29, 38.67, 41.75, 54.02, 54.86, 67.75, 105.93, 109.36, 117.91, 118.87, 121.02, 126.50, 133.39, 137.39, 157.45, 195.44); EIMS m/e (relative intensity) 337 (M^+ + 1, 26.2), 336 (M^+, 100), 197 (70.5), 181 (35.9), 170 (50.7); HRMS calcd for $C_{21}H_{24}N_2O_2$ 336.1846, found 336.1838.

Oxidation of Tetrahydroalstonerine (38) to 20,21-Dihydroalstonerine (39) with PDC. The tetrahydroalstonerine **38** (170 mg, 0.5 mmol) was dissolved in dry CH_2Cl_2 (2 mL), and the solution which resulted was added to a mixture of pyridinium dichlorochromate (284 mg, 0.75 mmol) in dry CH_2Cl_2 (3 mL). The mixture which resulted was stirred at room temperature for 8 h and then diluted with dry ether (200 mL). The slurry was filtered through a short Florisil column to afford dihydroalstonerine **39** (137 mg, 81%), which was spectroscopically (NMR, IR, MS) identical to that of authentic **39**.

2,2,4-Trimethyl-5-(5,12-dimethyl-9-methylene-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indol-8-yl)-1,3-dioxane (42). To a solution of diols **30** (245 mg, 0.72 mmol) in 2,2-dimethoxypropane (25 mL) was added *p*-toluenesulfonic acid (260 mg, 1.5 mmol). The solution which resulted was stirred at room temperature for 24 h. The reaction mixture was then diluted with CH_2Cl_2 (150 mL), washed with saturated aqueous $NaHCO_3$ (50 mL), and dried (K_2CO_3). The solvent was removed under reduced pressure, and the residue was chromatographed (silica gel, MeOH/$CHCl_3$, 5:95) to provide the alkenic acetonide **42** as a mixture of diastereomers (257 mg, 94%). **42a**: ^1H NMR (500 MHz, $CDCl_3$) δ 1.14 (d, J = 6.6 Hz, 3 H), 1.31 (s, 3 H), 1.33 (s, 3 H), 1.63 (m, 1 H), 1.90 (m, 1 H), 2.09 (dd, J = 11.0 and 6.1 Hz, 1 H), 2.13 (br d, J = 11.3 Hz, 1 H), 2.38 (s, 3 H), 2.49 (d, J = 17.1 Hz, 1 H), 3.26 (dd, J = 17.1 and 6.8 Hz, 1 H), 3.52 (dd, J = 10.5 and 5.5 Hz, 1 H), 3.63 (s, 3 H), 3.71 (m, 2 H), 3.92 (dd, J = 11.5 and 5.1 Hz, 1 H), 4.06 (br s, 1 H), 4.87 (s, 1 H), 5.03 (s, 1 H), 7.08 (t, J = 7.3 Hz, 1 H), 7.19 (t, J = 7.5 Hz, 1 H), 7.30 (d, J = 8.0 Hz, 1 H), 7.41 (d, J = 7.6 Hz, 1 H); ^{13}C NMR (125.75 MHz, $CDCl_3$) 14.15, 20.61, 21.63, 23.34, 28.43, 29.10, 31.77, 33.51, 41.18, 41.31, 53.30, 59.86, 62.20, 67.36, 98.01, 106.70, 108.57, 118.12, 118.86, 120.96, 133.36, 137.11, 149.78; EIMS m/e (relative intensity) 380 (M^+, 21.4), 252 (71.9), 197 (96.5), 182 (31.5), 170 (100). **42b**: ^1H NMR (500 MHz, $CDCl_3$) δ 0.75 (d, J = 6.7 Hz, 3 H), 1.32 (s, 3 H), 1.38 (s, 3 H), 1.69 (m, 1 H), 1.95 (m, 1 H), 2.05 (dd, J = 10.9 and 6.0 Hz, 1 H), 2.22 (br s, 1 H), 2.52 (d, J = 17.0 Hz, 1 H), 3.29 (dd, J = 17.0 and 6.8 Hz, 1 H), 3.58 (dd, J = 10.4 and 5.5 Hz, 1 H), 3.63 (s, 3 H), 3.75 (m, 2 H), 3.98 (dd, J = 11.5 and 5.0 Hz, 1 H), 4.06 (br s, 1 H), 4.78 (s, 1 H), 5.00 (s, 1 H), 7.06 (t, J = 7.5 Hz, 1 H), 7.18 (t, J = 7.8 Hz, 1 H), 7.29 (d, J = 7.8 Hz, 1 H), 7.41 (d, J = 7.5 Hz, 1 H); ^{13}C NMR (125.75 MHz, $CDCl_3$) 19.46, 20.53, 23.62, 28.40, 29.11, 30.62, 33.56, 41.14, 41.45, 53.28, 60.31, 62.15, 62.64, 66.89, 98.40, 106.76, 107.99, 108.73, 118.14, 118.89, 126.38, 133.06, 137.17, 149.47; EIMS m/e (relative intensity) 380 (M^+, 34.3), 251 (18), 197 (100), 181 (23.3), 170 (80.3). Anal. Calcd for $C_{24}H_{32}N_2O_2$: C, 75.75; H, 8.48; N, 7.36. Found: C, 75.46; H, 8.45; N, 7.06.

2,2,4-Trimethyl-5-[5,12-dimethyl-9-(hydroxymethyl)-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indol-8-yl]-1,3-dioxane (43). The alkenic acetonide **42** (380 mg, 1.0 mmol) was dissolved in dry THF (5 mL) under an atmosphere of argon. A solution of 9-BBN in THF (0.5 M, 2 mL, 1.0 mmol) was added in one portion, and the mixture was stirred at 22 °C for 1 h, after which additional 9-BBN (4 mL, 2.0 mmol) was added. The solution was stirred at 22 °C for an additional 24 h, after which H_2O (1 mL) was added to quench the excess borohydride. The reaction mixture which resulted was warmed to 45 °C, and aqueous NaOH (3 N, 2 mL, 6.0 mmol) was added followed by dropwise addition of H_2O_2 (30%, 2 mL, 8.8 mmol). The reaction mixture was stirred at 45 °C for 2.5 h. The solution was saturated with NaCl, and the organic layer was decanted. The aqueous residue was extracted with EtOAc (3 × 100 mL), and the combined organic layers were washed with brine (2 × 100 mL) and dried (K_2CO_3). The solvent was removed under reduced pressure, and the residue was chromatographed (silica gel, MeOH/$CHCl_3$, 5:95) to provide the hydroxyl acetonide **43** as a mixture of two diastereomers (337 mg, 85%). **43a**: IR (KBr) 3300, 1105 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.87 (d, J = 7.0 Hz, 3 H), 1.18 (s, 3 H), 1.24 (m, 1 H), 1.29 (s, 3 H), 1.54 (m, 1 H), 1.73 (m, 1 H), 1.98 (m, 1 H), 2.33 (dd, J = 10.7 and 6.7 Hz, 1 H), 2.35 (s, 1 H), 2.47 (d, J = 16.8 Hz, 1 H), 3.30 (dd, J = 16.8 and 7.5 Hz, 1 H), 3.55 (d, J = 7.4 Hz, 1 H), 3.58 (dd, J = 11.9 and 7.5 Hz, 1 H), 3.61 (s, 3 H), 3.73 (dd, J = 11.9 and 4.0 Hz, 1 H), 4.00 (m, 2 H), 4.07 (m, 2 H), 7.08 (t, J = 7.2 Hz, 1 H), 7.18 (t, J = 7.4 Hz, 1 H), 7.27 (d, J = 8.3 Hz, 1 H), 7.47 (d, J = 7.7 Hz, 1 H); ^{13}C NMR (125.75 MHz, $CDCl_3$) δ 18.38, 22.20, 25.57, 26.84, 27.40, 28.91, 32.20, 38.10, 41.23, 41.97, 53.31, 58.70, 60.81, 65,18, 69.25, 97.86, 106.24, 108.84, 117.96, 118.93, 120.99, 126.18, 132.43, 137.10; EIMS m/e (relative intensity) 398 (M^+, 23.7), 383 (5.6), 340 (12.0), 209 (31.4), 197 (100.0), 181 (42.7), 170 (24.6). **43b**: IR (KBr) 3300, 1105 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.63 (d, J = 6.6 Hz, 3 H), 1.33 (s, 4 H), 1.37 (s, 3 H), 1.66 (m, 1 H), 1.86 (d, J = 9.6 Hz, 1 H), 2.15 (dt, J = 14.5 and 3.4 Hz, 1 H), 2.36 (m, 1 H), 2.45 (s, 3 H), 2.60 (d, J = 17.0 Hz, H), 3.03 (dd, J = 17.0 and 6.9 Hz, 1 H), 3.49 (m, 2 H), 3.63 (s, 3 H), 3.65 (m, 1 H), 3.92 (dd, J = 12.5 and 4.2 Hz, 1 H), 4.00 (br s, 1 H), 4.10 (m, 2 H), 7.08 (t, J = 7.1 Hz, 1 H), 7.17 (t, J = 7.3 Hz, 1 H), 7.27 (d, J = 8.0 Hz, 1 H), 7.48 (d, J = 7.4 Hz, 1 H); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 18.68, 20.88, 22.49, 25.38, 28.88, 29.02, 31.77, 38.13, 41.47, 46.26, 53.82, 59.75, 62.23, 66.45, 68.40, 97.93, 106.00, 108.75, 117.94, 118.81, 120.88, 126.33, 133.01, 137.25; mass spectrum (EI), m/e (relative intensity) 398 (M^+, 22.3), 383 (6.5), 340 (11.0), 209 (30.0), 197 (100.0), 181 (42.9), 170 (26.1). Anal. Calcd for $C_{24}H_{34}N_2O_3 \cdot H_2O$: C, 69.23; H, 8.65; N, 6.73. Found: C, 69.59; H, 8.35; N, 6.48.

2,2,4-Trimethyl-5-[5,12-dimethyl-9-[[(*tert*-butyldimethylsilyl)oxy]-methyl]-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indol-8-yl]-1,3-dioxane (44). To a solution of hydroxyacetonide **43** (100 mg, 0,25 mmol) in dry CH_2Cl_2 (10 mL) were added 4-(dimethylamino)pyridine (122 mg, 1.0 mmol) and *tert*-butyldimethylsilyl chloride (120 mg, 0.8 mmol). The solution which resulted was stirred at room temperature for 18 h. The reaction mixture was then chromatographed directly (silica gel, MeOH/$CHCl_3$, 5:95) to afford the acetonidosilyl ether **44** as a mixture of two diastereomers (129 mg, 99%). **44a**: ^1H NMR (500 MHz, $CDCl_3$) δ 0.06 (s, 3 H), 0.08 (s, 3 H), 0.68 (d, J = 6 Hz, 3 H), 0.91 (s, 9 H), 1.32 (s, 3 H), 1.40 (s, 3 H), 1.51 (dd, J = 13.5 and 3.7 Hz, 1 H), 1.58 (dt, J = 12.6 and 3.1 Hz, 1 H), 1.96 (dt, J = 3.8 and 13.9 Hz, 1 H), 2.05 (m, 1 H), 2.40 (s, 3 H), 2.69 (d, J = 17.0 Hz, 1 H), 2.93 (dd, J = 17.0 and 7.0 Hz, 1 H), 3.40 (m, 1 H), 3.50 (t, J = 9.8 Hz, 1 H), 3.60 (s, 3 H), 3.61 (m, 1 H), 3.75–3.85 (m, 4 H), 3.96 (br s, 1 H), 7.08 (t, J = 7.6 Hz, 1 H), 7.17 (t, J = 7.6 Hz, 1 H), 7.27 (d, J = 8.0 Hz, 1 H), 7.49 (d, J = 7.8 Hz, 1 H); ^{13}C NMR (125.75 MHz, $CDCl_3$) δ −3.57, −3.52, 15.90,

18.10, 18.90, 19.52, 25.87, 28.22, 29.02, 29.54, 30.15, 40.35, 41.65, 43.47, 53.12, 54.80, 59.86, 62.73, 66.98, 97.83, 107.25, 108.70, 118.12, 118.77, 120.80, 126.32, 133.02, 137.11; EIMS *m/e* (relative intensity) 512 (M^+, 7.8), 209 (21.6), 197 (100.0), 181 (38.4), 170 (25.3). **44b**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.03 (s, 3 H), 0.04 (s, 3 H), 0.63 (d, J = 6.6 Hz, 3 H), 0.87 (s, 9 H), 1.34 (s, 4 H), 1.38 (s, 3 H), 1.70 (br t, J = 11.9 Hz, 1 H), 2.13 (dt, J = 13.7 and 3.3 Hz, 1 H), 2.22 (dd, J = 11.9 and 5.5 Hz, 1 H), 2.38 (m, 1 H), 2.42 (s, 3 H), 2.62 (d, J = 16.8 Hz, 1 H), 2.96 (dd, J = 16.8 and 6.8 Hz, 1 H), 3.38 (dd, J = 6.4 and 4.4 Hz, 1 H), 3.49 (m, 3 H), 3.62 (s, 3 H), 3.90 (dd, J = 12.3 and 4.3 Hz, 1 H), 3.98 (m, 2 H), 4.10 (dd, J = 6.6 and 3.9 Hz, 1 H), 7.04 (t, J = 7.6 Hz, 1 H), 7.15 (t, J = 7.5 Hz, 1 H), 7.27 (d, J = 7.9 Hz, 1 H), 7.47 (d, J = 7.4 Hz, 1 H); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ -5.57, -5.52, 16.68, 17.96, 18.12, 19.15, 25.85, 28.57, 28.96, 29.20, 33.96, 35.05, 41.56, 44.59, 53.74, 56.18, 59.84, 64.17, 98.10, 106.91, 108.64, 117.88, 118.51, 120.42, 126.49, 134.29, 137.16; EIMS *m/e* (relative intensity) 512 (M^+, 7.8), 209 (21.6), 197 (100.0), 181 (38.4), 170 (25.3). Anal. Calcd for $C_{30}H_{48}N_2O_3 \cdot 1.25H_2O$: C, 67.35; H, 9.44; N, 5.23. Found: C, 67.38; H, 9.29; N, 4.86.

1-(Hydroxymethyl)-2-hydroxy-1-[5,12-dimethyl-9-[[(*tert*-butyldimethylsilyl)oxy]methyl]methyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct-[*b*]indol-8-yl]-propane (45). The N_b-methyl TBDMS acetonide **44** (103 mg, 0.20 mmol) was dissolved in freshly distilled dry CH_3OH (10 mL) under an atmosphere of argon, and then dry PTSA (43 mg, 0.25 mmol) in dry methanol (2 mL) was added. The solution was stirred for 5 h at ~22 °C. The reaction mixture was brought to pH = 8 with cold aqueous $NaHCO_3$ solution. After filtration, the solvent was removed under reduced pressure. The residue was then dissolved in CH_2Cl_2 (200 mL), washed with water (30 mL) and brine (2 × 30 mL), and dried over K_2CO_3. After removal of the solvent under reduced pressure, the residue was chromatographed (silica gel, MeOH/$CHCl_3$, 1:9) to provide the TBDMS diol **45** (85 mg, 90%) as a mixture of two diastereomers. **45a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.07 (s, 3 H), 0.08 (s, 3 H), 0.89 (s, 9 H), 1.24 (d, J = 6.0 Hz, 3 H), 1.50–1.65 (m, 3 H), 1.80 (br d, J = 4.9 Hz, 1 H), 2.17 (dt, J = 3.9 and 13.9 Hz, 1 H), 2.40 (s, 3 H), 2.71 (d, J = 6.9 Hz, 1 H), 2.94 (dd, J = 16.9 and 7.1 Hz, 1 H), 3.10 (dd, J = 10.6 and 5.2 Hz, 1 H), 3.39 (t, J = 5.7 Hz, 1 H), 3.56 (s, 3 H), 3.62 (m, 2 H), 3.83 (dd, J = 10.6 and 5.1 Hz, 1 H), 3.98 (m, 1 H), 4.03 (br s, 1 H), 7.08 (t, J = 7.5 Hz, 1 H), 7.17 (t, J = 7.5 Hz, 1 H), 7.26 (d, J = 8.1 Hz, 1 H), 7.46 (d, J = 7.5 Hz, 1 H); ^{13}C NMR (125.75 MHz, $CDCl_3$) δ -5.36, -5.34, 16.52, 18.23, 21.90, 25.95, 29.04, 30.78, 32.24, 41.35, 45.12, 46.86, 53.67, 56.34, 63.21, 64.25, 67.00, 106.78, 108.86, 118.86, 120.93, 126.16, 132.76, 137.13; EIMS *m/e* (relative intensity) 472 (M^+, 42.7), 271 (11.1), 229 (52.7), 197 (100.0), 183 (55.2), 172 (56.5). **45b**: ^{1}H NMR (250 MHz $CDCl_3$) δ 0.07 (s, 3 H), 0.08 (s, 3 H), 0.73 (d, J = 6.2 Hz, 3 H), 0.89 (s, 9 H), 1.54 (m, 3 H), 1.88 (dt, J = 3.7 and 14.0 Hz, 1 H), 2.18 (m, 1 H), 2.39 (s, 3 H), 2.71 (d, J = 17.1 Hz, 1 H), 2.93 (dd, J = 17.1 and 6.8 Hz, 1 H), 3.39 (m, 1 H), 3.55 (m, 1 H), 3.58 (s, 3 H), 3.78 (m, 3 H), 3.94 (br s, 1 H), 3.98 (m, 1 H), 7.08 (t, J = 7.6 Hz, 1 H), 7.17 (t, J = 8.0 Hz, 1 H), 7.26 (d, J = 7.7 Hz, 1 H), 7.48 (d, J = 7.5 Hz, 1 H); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ -4.63, -4.62, 16.30, 18.18, 22.04, 25.92, 28.99, 30.42, 30.96, 41.58, 44.55, 45.86, 53.44, 55.65, 62.50, 63.30, 71.64, 107.22, 108.72, 118.11, 118.80, 120.83, 126.37, 133.12, 137.19; EIMS *m/e* (relative intensity) 472 (M^+, 42.7), 271 (11.1), 229 (52.7), 197 (100.0), 183 (55.2), 172 (56.5). Anal. Calcd for $C_{27}H_{44}N_2O_3Si \cdot H_2O$: C, 66.08; H, 9.45; N, 5.71. Found: C, 66.35; H, 9.16; N, 5.58.

Preparation of the Macroline Equivalent (9). The β-dihydroxy silyl ether **45** (16 mg, 0.034 mmol) was dissolved in dry CH_2Cl_2 (0.5 mL), and pyridine (40 μL) was added in one portion. The solution which was generated was stirred at room temperature for 15 min, after which a solution of acetic anhydride (5.0 mg, 0.05 mmol) in CH_2Cl_2 (0.2 mL) was added dropwise to the solution. The reaction mixture was stirred at room temperature for 15 h, after which additional acetic anhydride (3.0 mg) in CH_2Cl_2 (0.1 mL) was added to the solution, and the mixture was stirred for an additional 12 h. Pyridinium dichromate (20.0 mg, 0.053 mmol) was then added to the solution, and this suspension was stirred further for 8 h. The reaction mixture was passed through a wash column (silica gel, THF), and the residue was separated by preparative TLC (silica gel, MeOH/$CHCl_3$ 10:90) to provide the macroline equivalent **9** (8 mg 52%): IR (NaCl) 1680, 1624 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.03 (s, 6 H), 0,86 (s, 9 H), 1.65 (dt, J = 12.8 and 3.3 Hz, 1 H), 1.90 (m, 2 H), 2.22 (s, 3 H), 2.46 (s, 3 H), 2.75 (d, J = 16.4 Hz, 1 H), 2.94 (dd, J = 16.4 and 6.8 Hz, 1 H), 3.40 (m, 2 H), 3.58 (s, 3 H), 3.70 (m, 2 H), 3.84 (br s, 1 H), 5.88 (s, 1 H), 6.08 (s, 1 H), 7.07 (t, J = 7.4 Hz, 1 H), 7.18 (t, J = 7.4 Hz, 1 H), 7.28 (d, J = 8.2 Hz, 1 H), 7.46 (d, J = 7.7 Hz, 1 H); EIMS (15 eV) *m/e* (relative intensity) 452 (M^+, 41.2), 409 (9.6), 251 (18.3), 197 (71.2), 181 (100.0). This material was employed directly in the next experiment.

(+)-Macroline (8). The macroline equivalent **9** (7.1 mg, 0.016 mmol) was dissolved in dry THF (2 mL). Tetrabutylammonium fluoride (1.0 M in THF, 0.03 mL) was added in one portion, and the solution was stirred at room temperature for 5 h. The reaction mixture was diluted with $CHCl_3$ (25 mL), washed with water (2 × 10 mL) and brine (2 × 10 mL), and dried (Na_2SO_4). After removal of the solvent under reduced pressure, the residue was separated by preparative TLC (silica gel, MeOH/$CHCl_3$, 10:90) to afford macroline (**8**) (4.4 mg, 83%): $[\alpha]^{25}_D$ +18.7° (c = 0.35, $CHCl_3$) {lit.[14] $[\alpha]^{22}_D$ +19° ± 5° (c = 0.41)}; IR (NaCl) 3200, 1680, 1624 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.65 (dt, J = 12.8 and 3.3 Hz, 1 H), 2.10 (m, 2 H), 2.23 (s, 3 H), 2.42 (s, 3 H), 2.70 (d, J = 16.4 Hz, 1 H), 2.97 (dd, J = 16.4 and 6.8 Hz, 1 H), 3.55 (m, 2 H), 3.60 (s, 3 H), 3.70 (m, 2 H), 3.86 (br s, 1 H), 5.92 (s, 1 H), 6.14 (s, 1 H), 7.06 (t, J = 7.4 Hz, 1 H), 7.19 (t, J = 7.3 Hz, 1 H), 7.28 (d, J = 8.0 Hz, 1 H), 7.49 (d, J = 7.7 Hz, 1 H); EIMS *m/e* (relative intensity) 338 (M^+, 23.0), 251 (5.0), 208 (11.8), 197 (100.0), 181 (75.3), 170 (18.3). The spectral properties of synthetic macroline **8** were identical in all respects to those of macroline prepared by degradation of villalstonine by Schmid *et al.*[13,14]

(+)-Villalstonine (2). Pleiocarpamine **7** (4.0 mg) was added to a solution of macroline **8** (3.5 mg) in 0.2 N aqueous hydrochloric acid (1 mL), and the mixture was stirred at room temperature (~22 °C) for 24 h. After basification with aqueous NH_4OH, the solution was diluted with CH_2Cl_2 (50 mL) and washed with brine (2 × 10 mL). The CH_2Cl_2 layer was dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was separated by preparative TLC (silica gel, MeOH/$CHCl_3$, 1:9) to afford villalstonine **2** as an oil (3.2 mg, 41%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.08 (d, J = 14.6 Hz, 1 H), 1.14 (dd, J = 12.9 and 4.6 Hz, 1 H), 1.22 (s, 3 H), 1.42 (ddd, J = 12.9, 4.6, and 2.3 Hz, 1 H), 1.53 (d, J = 6.5 Hz, 3 H), 1.58 (m, 1 H), 1.66 (dt, J = 12.7 and 3.3 Hz, 1 H), 2.02 (dd, J = 9.5 and 4.4 Hz, 1 H), 2.07 (m, 1 H), 2.29 (s, 3 H), 2.41 (m, 3 H), 2.67 (m, 1 H), 2.90 (m, 1 H), 3.10 (dt, J = 2.4 and 13.8 Hz, 1 H), 3.19 (q, J = 3.2 Hz, 1 H), 3.28 (dd, J = 16.4 and 6.8 Hz, 1 H), 3.60 (s, 3 H), 3.66 (s, 3 H), 3.70 (m, 2 H), 3.83 (br s, 1 H), 3.98 (t, J = 12.1 Hz, 1 H), 4.17 (br d, J = 12.2 Hz, 1 H), 4.42 (d, J = 3.5 Hz, 1 H), 5.34 (q, J = 6.5 Hz, 1 H), 6.12 (d, J = 7.8 Hz, 1 H), 6.67 (t, J = 7.3 Hz, 1 H), 6.85 (d, J = 7.1 Hz, 1 H), 6.96 (t, J = 8.0 Hz, 1 H), 7.12 (t, J = 7.6 Hz, 1 H), 7.21 (t, J = 7.6 Hz, 1 H), 7.31 (d, J = 8.2 Hz, 1 H), 7.52 (d, J = 7.8 Hz, 1 H); EIMS *m/e* (relative intensity) 660 (M^+, 45.7), 617 (14.3), 601 (16.1), 338 (32.7), 322 (12.8), 197 (71.5), 182 (32.4), 170 (35.9), 121 (100.0). The TLC and spectral properties of the synthetic villalstonine were identical in all respects to those of the natural product reported by Schmid.[13,14] When the same experiment was repeated with **9** in the presence of fluoride ion, **2** was again produced as the sole isolable compound. Traces of pleiocarpamine **7** remained (TLC). The yield of this condensation was 60% based on NMR and TLC. However, the yield of pure material isolated by preparative TLC was 40%.

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