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General Approach for the Synthesis of Sarpagine Indole Alkaloids. Enantiospecific Total Synthesis of (+)-Vellosimine, (+)-Normacusine B, (−)-Alkaloid Q_3, (−)-Panarine, (+)-N_a-Methylvellosimine, and (+)-N_a-Methyl-16-epipericyclivine

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The first total synthesis of (+)-N_a-methyl-16-epipericyclivine (**9**) was completed [from D-(+)-tryptophan methyl ester] in an overall yield of 42% (eight reaction vessels). The optical rotation [$[\alpha]_D$ +22.8 (*c* 0.50, $CHCl_3$)] obtained on this material confirmed that the reported optical rotation [$[\alpha]_D$ 0 (*c* 0.50, $CHCl_3$)][47] was biogenetically unreasonable. The total syntheses of (+)-vellosimine, (+)-normacusine B, (−)-alkaloid Q_3, (−)-panarine, and (+)-N_a-methylvellosimine are also described. Moreover, a mixed sample (1:1) of synthetic (−)-panarine and natural (−)-panarine yielded only one set of signals in the ^{13}C NMR; this indicated that the two compounds are identical and further confirmed the correct configuration of (+)-vellosimine, (+)-normacusine B, and (−)-alkaloid Q_3. In this approach, the key templates, (−)-N_a-H,N_b-benzyltetracyclic ketone **15a** and (−)-N_a-methyl,N_b-benzyltetracyclic ketone **43** were synthesized on multihundred gram scale by the asymmetric Pictet—Spengler reaction and a stereocontrolled Dieckmann cyclization via improved sequences. An intramolecular palladium (enolate-mediated) coupling reaction was employed to introduce the C(19)—C(20) *E*-ethylidene function in the sarpagine alkaloids for the first time in stereospecific fashion.

Introduction

Sarpagine alkaloids have long held a prominent position in natural products chemistry because of their structural similarity to the essential amino acid tryptophan and related metabolites, such as the neurotransmitter serotonin. Over 100 sarpagine alkaloids have been isolated from various plant genera, principally in the *Apocynaceae*, the most important genus of which are *Rauwolfia*, *Corynanthe*, *Alstonia*, and *Strychnos*.[1−3] Many sarpagine alkaloids comprise a key component of bioactive bisindole alkaloids;[4−10] the structures of a few of these are illustrated in Figure 1.

As early as 1958 and again in 1967, it was reported that the bisindole alkaloid macralstonine was able to lower blood pressure.[11,12] More recent studies by Houghton et al.[13,14] have demonstrated that a number of alkaloids from various parts of *Alstonia scholaris*, *A. macrophylla*, and *A. glaucescens*, collected from Thailand, exhibited pronounced antiplasmodial activity. To date, villalstonine and macrocarpamine have been shown to be the most active and are much more potent than the monomeric units which comprise them against *Plasmo-*

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TABLE 1. IC_{50} Values of Alkaloids Tested Against *Plasmodium falciparum* (K1 and T9−96 Strains)[13,14]

alkaloid	K1 (μM, $n = 3$)[a]	T9−96 (μM, $n = 3$)[a]	K1/T9−96 ratio
O-acetylmacralstonine	0.53 ± 0.09	12.4 ± 1.6	0.04
villalstonine	0.27 ± 0.06	0.94 ± 0.07	0.29
alstomacroline	1.12 ± 0.35	10.2 ± 0.4	0.11
macrocarpamine	0.36 ± 0.06	>39[b]	<0.009
chloroquine diphosphate	0.20 ± 0.07	0.019 ± 0.002	10.53

[a] K1: the multidrug-resistant strain, which is highly resistant to chloroquine. T9−96: the chloroquine-sensitive strain. *n*: number of independent experiments. [b] Percent inhibition at 39 μM (7.5 μg/mL); the highest concentration tested was 32.6 ± 4.1 μM.

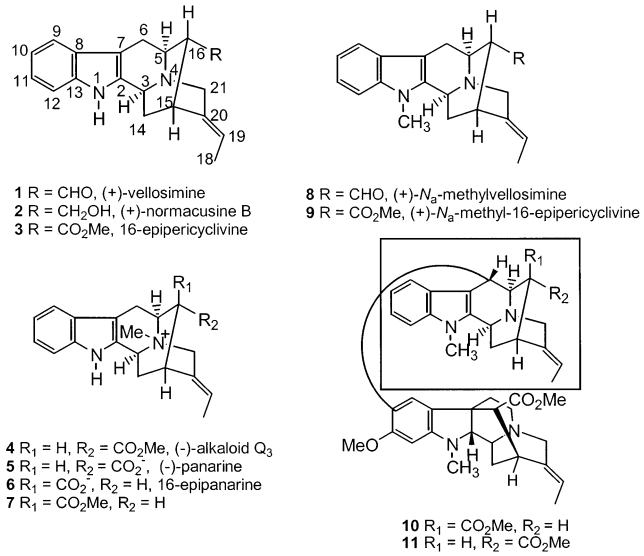

FIGURE 1. Sarpagine indole alkaloids.

dium falciparum malaria.[13,14] The enhanced activity may result from the unique interaction of dimers with DNA or proteins or from increased lipophilicity. This latter property would facilitate their transport across cell membranes of red blood cells and of the parasites. These results were in agreement with the same activity profile previously reported from *A. angustifolia* in which bisindoles were shown to be far more potent than the monomeric indole alkaloids.[15]

Importantly, for the two strains (K1 and T9−96 strains) of *P. falciparum* which were evaluated, chloroquine diphosphate has shown extremely high affinity to the T9−96 (chloroquine-sensitive) strain compared to the K1 (chloroquine-resistant) strain (see Table 1). In contrast, the active bisindole alkaloids were almost as potent as chloroquine diphosphate against the K1 strain but far less (about 50-fold to 2000-fold) active against the T9−96 strain. "It is apparent that these active alkaloids," as reported by Houghton, "have significantly higher affinity to the chloroquine-resistant K1 strain than to the chloroquine-sensitive strain T9−96 and it is possible that these potent blood schizontocidal bisindole alkaloids might act against the parasites through a mechanism fundamentally different from that of chloroquine."[14] Although the two most active alkaloids (villalstonine and macrocarpamine) are similar in structure, they interact in the two strains (K1 and T9−96) quite differently. Villalstonine (which is the rigid dimer of macroline and pleiocarpamine) is active against both the K1 and T9−96 strains, even though the activity against the T9−96 (chloroquine diphosphate sensitive strain) is far less potent than chloroquine diphosphate. Macrocarpamine (which is the flexible linear dimer of macroline and pleiocarpamine), however, is active only against the K1 strain (chloroquine-resistant). Obviously, the T9−96 strain of *P. falciparum* which is sensitive to chloroquine diphosphate (even to villalstonine) appears completely resistant to macrocarpamine. These differences perhaps can be employed to study the mechanism of drug resistance of *P. falciparum*. One of the principal mechanisms of multi-drug resistance in malaria involves a P-glycoprotein. Since the P-glycoprotein in resistant strains of *P. falciparum* has been shown to be identical to the major P-glycoprotein in some resistant forms of cancer, understanding the effect of the alkaloids on the K1 strain versus the T9−96 strain is important. The difference in the effect of the bisindole alkaloids villalstonine and macrocarpamine as well as their analogues and chloroquine on the T9−96 strain vs the K1 strain may prove of value in the solution to multi-drug resistance in many diseases including cancer.

The World Health Organization (WHO) estimates (WHO Fact Sheet No. 94) that malaria affects between 300 and 500 million people a year, resulting in death for 2−3 million. Moreover, drug-resistant strains of malaria (principally some strains of *P. falciparum*) are now spreading rapidly throughout Southeast Asia, India, and sub-Saharan Africa. The design of new drugs to treat chloroquinine-resistant malaria has become very important in the past few years. Further investigation into the mode of action of the antiplasmodial activity of these active bisindole alkaloids would provide additional evidence of the mechanism of action of chloroquine-resistant strains of *P. falciparum* and might lead to the discovery of novel pharmacological targets.

The sarpagine alkaloid (+)-vellosimine (**1**) was first isolated from the tree *Geissospermum vellosii* in 1958 by Rapoport et al.[4,16] Amorphous extracts of this bark, known as *pao pereria*, have long enjoyed a reputation as a febrifuge[17,18] in Brazilian folk medicine and have also been reported to exhibit curare-like activity.[19] During the following years, (+)-vellosimine (**1**) has also been isolated from various species of *Rauwolfia* which are broadly distributed throughout Asia and Africa.[20−27] These plants

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are widely employed in traditional herbal medicine for the treatment of neuralgia, migrain,[26] and hypertension.[22,24,28] The structure of (+)-vellosimine (**1**) was elucidated on the basis of NMR spectroscopy as well as a comparison with the data from other indole alkaloids[4] and confirmed by analysis of its 2D NMR spectrum.[25] The related base, (+)-normacusine B (**2**), was isolated from various species of *Alstonia*[29] and *Rauwolfia*[30,31] as well as other plants.[32−34] Its structure was determined on the basis of extensive studies of NMR spectroscopy[33,35−41] and confirmed by the partial synthesis of **2** from the known indole alkaloid (+)-perivine.[42]

Among these bases, a few sarpagine-related monomeric alkaloids form a subgroup of alkaloids which contain a methyl ester function at C-16. Quaisuddin[43] in 1980 isolated a quaternary alkaloid **4** from *Aspidosperma perba* which was designated as alkaloid Q_3. On the basis of chemical transformations, alkaloid Q_3 (**4**) was converted into 16-epipericyclivine (**3**), a material which had not yet been isolated as a natural product. However, the optical rotation of **3** reported by Quaisuddin[43] [$[\alpha]_D$ +37.7 (*c* 0.13, MeOH)] was not consistent with that reported by Büchi et al.[44] [$[\alpha]_D$ +3.6 (*c* 1.00, MeOH)]. Furthermore, because only a few physical properties were reported, the identity of alkaloid Q_3 could not be established unambiguously. Angenot et al.[45] in 1988 isolated two closely related quaternary alkaloids including panarine (**5**) from a Venezuelan curare. This material was prepared by the Panare Indians from the bark of *Strychnos toxifera* Rob. Schomb. Ex Lindley. Its structure has been established unequivocally by ^{1}H and ^{13}C NMR spectra and X-ray crystallographic analysis.[45] Another related quaternary alkaloid 16-epipanarine (**6**) was isolated from *Stemmadenia minima* in 1991 by Achenbach et al.[46] To directly compare an authentic sample of **6** with **5** and establish the correct configuration of **6**, chemical correlations were carried out. The three steps included esterification with thionyl chloride in methanol to provide **7**, epimerization on treatment of **7** with potassium *tert*-butyl alcoholate to obtain **4**, and alkaline hydrolysis to afford **5** as the only product. However, no report of the total synthesis of these quaternary alkaloids has appeared in the literature to date.

Interestingly, N_a-methyl-16-epipericyclivine (**9**)[47] and bisindole alkaloids such as desformoundulatine (**10**)[48] had also been isolated from *Alstonia undulata*. It has previously been demonstrated by Le Men-Olivier et al.[49] that natural N_a-methyl-16-epipericyclivine (**9**) couples with the natural monomeric alkaloid cabucraline to provide bisindole **11** on treatment with DDQ. Importantly, the optical rotation of **9** was reported as 0,[47] which was biogenetically unreasonable. As a consequence, the total synthesis of **9** and eventually bisindoles **10** and **11** has become of interest.

The common structural features of the sarpagine ring system usually contain a double bond at C(19)−C(20) and lack other functionality at C(21). Many of these natural products contain oxygen substituents on the indole ring. In all cases known to date, the more stable *S* stereochemistry is found at C(3). The rigid ring system also requires the *S* stereochemistry at C(5) and the β-configuration at C(15). Consequently, three of the stereochemical centers contain a fixed configuration because of the rigid nature of the molecular structure. The C(19)−C(20) double bond is normally present with the *E* stereochemistry.

Sakai[50] previously reported the partial synthesis (from ajmaline) of (−)-koumidine, which contained a skeleton similar to that of (+)-vellosimine (**1**); however, the double bond in (−)-koumidine was present in the *Z*-configuration and the chirality at C-16 was *S* rather than *R*. Establishment of the stereochemistry of the C(19)−C(20) double bond in (−)-koumidine by Sakai via an elimination process yielded the *Z*-configuration required for koumidine in a 5:1 ratio. This was opposite to the characteristic *E*-configuration for the C(19)−C(20) double bond in the sarpagine alkaloids. Magnus[51] reported the total synthesis of the antipode of (−)-koumidine (from L-tryptophan); however, establishment of the double bond (Z/E = 1:5.7) was still not stereospecific. Several other groups have encountered a similar problem during the synthesis of the C(19)−C(20) related alkaloid geissoschizine; the ratio of *E* to *Z* was very good but not reported as stereospecific.[52−54] Recently, Martin reported the total synthesis

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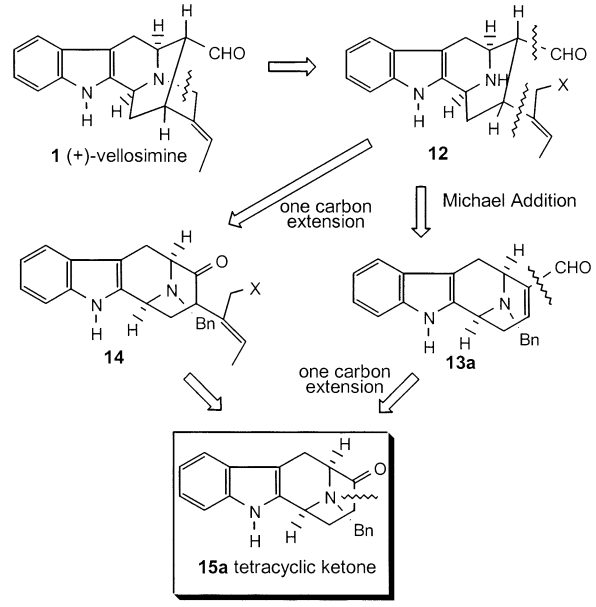
of geissoschizine with stereoselective establishment of the double bond by an elimination process.[55] Furthermore, Rawal and Bosch reported the total synthesis of *Strychnos* alkaloids with stereocontrolled establishment of the double bond by a Heck coupling reaction,[56−58] and this novel method has been applied toward the enantiospecific total synthesis of the *Corynanthe* indole alkaloids.[59] We wish to report here a general approach to the enantiospecific, stereospecific total synthesis of sarpagine indole alkaloids in which an enolate-mediated palladium-catalyzed cross coupling reaction has been employed to solve this problem at C(19)−C(20) in the sarpagine series.

Results and Discussion

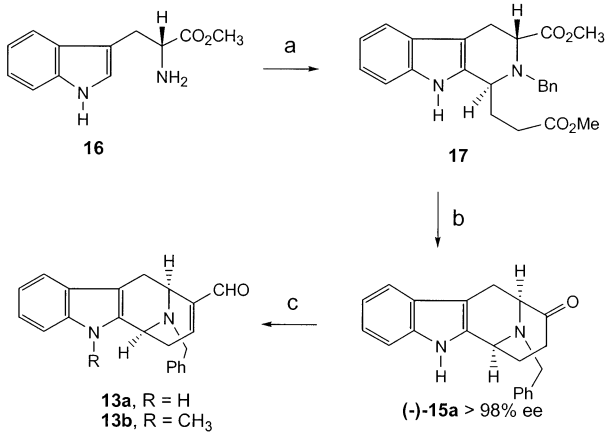
Recently, a number of N_a-methyl-substituted macroline, ajmaline, and suaveoline indole alkaloids were prepared in enantiospecific fashion by employing the asymmetric Pictet−Spengler reaction.[60] Extension of this strategy for the enantiospecific total synthesis of these sarpagine indole alkaloids comprises the contents of this effort.

The strategy rests on the stereospecific total synthesis of vellosimine and N_a-methylvellosimine, which could be converted into the other sarpagine indole alkaloids, including alkaloid Q_3 (**4**), panarine (**5**), and N_a-methyl-16-epipericyclivine (**9**). As shown in Scheme 1, in a retrosynthetic sense, vellosimine (**1**) could arise by a cyclization process which involves the N_b-nitrogen function. The synthesis of the key intermediate **12** for the cyclization reaction could be approached from either the α,β-unsaturated aldehyde **13a** by the Michael addition reaction or from the α-functionalized ketone **14**. If both carbonyl-substituted intermediates could be obtained in high yield from the ketone **15a**, then the ketone **15a** could serve as a common intermediate for the synthesis of many sarpagine indole alkaloids. These two synthetic approaches have been examined, the earlier of which centered on the functionalization of the α-position of the carbonyl group in ketone **15a** to furnish ketone **14** (or its equivalent) followed by conversion of **14** into aldehyde **12**. The second route rested on the conversion of the ketone **15a**, *via* α,β-unsaturated aldehyde **13a**, into **12** in subsequent steps. The initial goal, therefore, was to develop an efficient approach to synthesize the key intermediate (−)-tetracyclic ketone **15a** in an enantiospecific fashion.

SCHEME 1. Retrosynthetic Approach toward (+)-Vellosimine (Route 1)



SCHEME 2[a]



[a] Reagents and conditions: (a) PhCHO, CH_3OH, rt, 5 h, $NaBH_4$, −5 °C, 4 h; $(CH_3O)_2CHCH_2CH_2CO_2Me$, TFA (2.4 equiv), CH_2Cl_2, rt, 10 d, 83%, one pot (400 g scale); (b) NaH (10 equiv), CH_3OH, toluene, reflux, 72 h; HOAc, HCl, H_2O, reflux, 10 h, 80%, one pot (150 g scale); (c) $PhSOCH_2Cl$, LDA, THF; KOH (aq), THF, 16 h; $LiClO_4$, dioxane, reflux, 4 d, 87%.

As illustrated here, the (−)-tetracyclic ketone **15a** was synthesized via an improved two-pot process on a multihundred gram scale with these goals in mind,[61,62] while the racemic compound had been prepared on a kilogram scale in the late 1970s in our laboratory.[63] The utility of this enantiospecific two-pot sequence via the transfer of chirality in the asymmetric Pictet−Spengler reaction[60a,c,64] was key since both of these reactions could be run on a multihundred gram scale to provide (−)-ketone **15a** (>98% ee), which could now be considered a readily available starting material for the synthesis of optically

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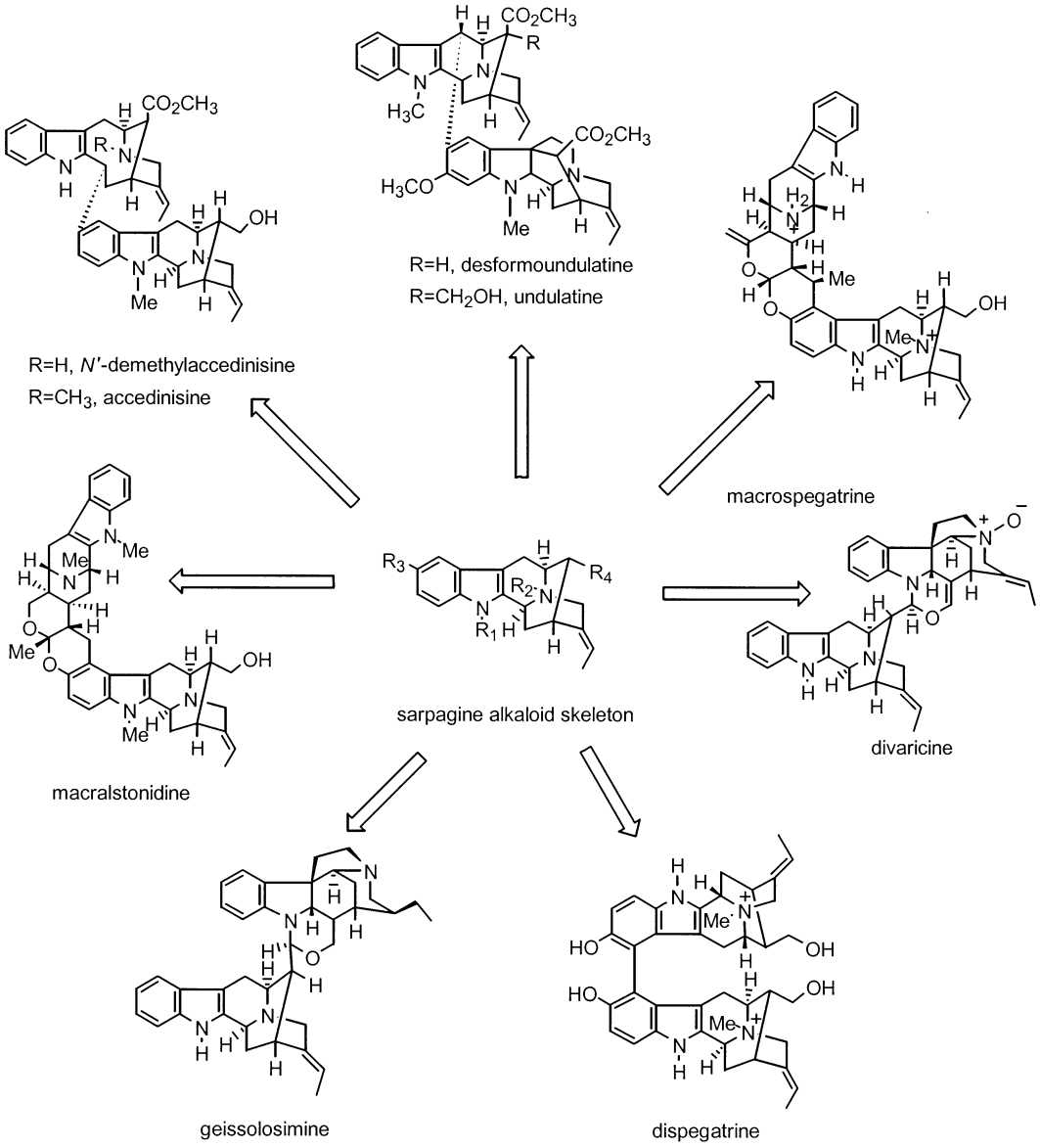


FIGURE 2. Potential bisindole alkaloid targets from sarpagine alkaloids.

pure sarpagine alkaloids. The conversion of the ketone **15a** into the α,β-unsaturated aldehyde moiety of **13a** was achieved in good yield via the spirooxiranophenylsulfoxide of Satoh by an improved procedure similar to published methods.[65] As shown in Scheme 2, the N_a-H,N_b-benzyltetracyclic ketone **15a** was treated with the anion of α-chloromethylphenyl sulfoxide generated in situ to furnish a chlorohydrin intermediate. When the mixture of diastereomeric chlorohydrins was stirred with a solution of KOH (10 N) in water−THF (3:7) for 16 h at room temperature, this material was converted into the spirooxirane phenylsulfoxide isolated as a mixture of diastereomers. The mixture of spirooxirane phenylsulfoxides was then dissolved in a solution of dioxane that contained lithium perchlorate. The slurry that resulted was heated to 100 °C under nitrogen (1 atm) to provide the desired α,β-unsaturated aldehyde **13a** in 84% yield. Dioxane was employed to dissolve the catalytic amount of lithium perchlorate, which permitted replacement of the original solvent (toluene) to avoid the use of tri-*n*-butylphosphine oxide. The phosphine oxide had been difficult to remove after the reaction was completed; consequently, the use of dioxane/$LiClO_4$ represented an important improvement especially on large scales.

A series of intermolecular processes were attempted earlier in order to functionalize the C(15) position of N_a-methyl tetracyclic ketone **15b** as well as the N_a-methyl α,β-unsaturated aldehyde **13b**. These included direct alkylation reactions,[66−68] enamine-promoted processes,[68] as well as metal-promoted 1,4-additions,[60b,66−70] but with one notable exception:[60b,70] all have failed. In addition, attempts to treat α,β-unsaturated aldehyde **13b** under

(64) (a) Cox, E. D.; Hamaker, L. K.; Li, J.; Yu, P.; Czerwinski, K. M.; Deng, L.; Bennett, D. W.; Cook, J. M.; Watson, W. H.; Krawiec, M. *J. Org. Chem.* **1997**, *62*, 44. (b) Zhang, L. H.; Trudell, M. L.; Hollinshead, S. P.; Cook, J. M. *J. Am. Chem. Soc.* **1989**, *111*, 8263. (c) Zhang, L. H.; Cook, J. M. *Hetereocycles* **1988**, *27*, 2795. (d) Zhang, L. H.; Gupta, A. G.; Cook, J. M. *J. Org. Chem.* **1989**, *54*, 4708. (e) Hamaker, L. K. Ph.D. Thesis, University of Wisconsin—Milwaukee, 1995.

(65) Satoh, T.; Itoh, M.; Ohara, T.; Yamakawa, K. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1839.

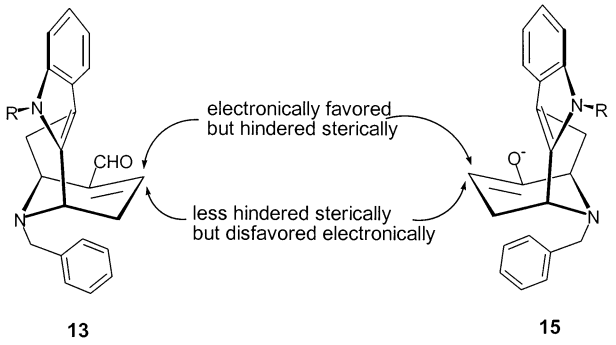


FIGURE 3.

conditions to promote heterodiene Diels−Alder reactions,[63,71] titanium-promoted aldol processes,[72] or cuprate-mediated additions were likewise unsuccessful (see the Supporting Information for these attempts).

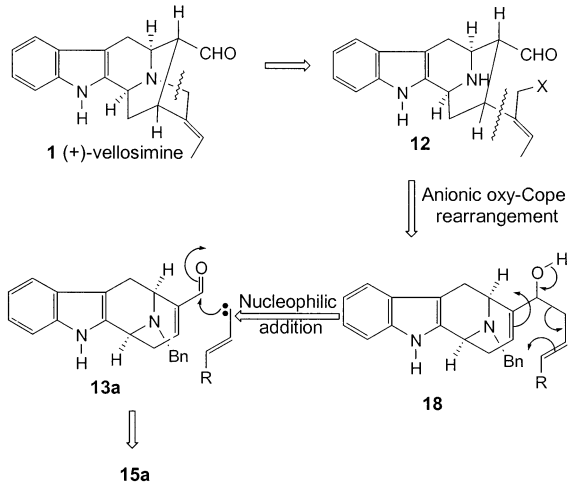
The inability to intermolecularly functionalize the tetracyclic ketone **15** and the α,*β*-unsaturated aldehyde **13** as well as their equivalents was believed to be due to steric constraints inherent in this tetracyclic [3.3.1] system and electronic effects which retarded addition of reagents at C(15) from the bottom face of the *π* system. The approach of a nucleophilic reagent at C-15 of enone **13** from the less hindered bottom (α) face of the molecule (equatorial position) was electronically disfavored, while approach from the top (*β*) face (axial position electronically favored by stereoelectronic control) was severely hindered by the 1,3-diaxial interactions with the cis-fused diaxial-indolomethylene bridge (Figure 3).

To overcome these steric and electronic constraints, execution of an intramolecular approach for the functionalization of this tetracyclic [3.3.1] 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 the ajmaline/sarpagine indole alkaloids. The thermal conditions of the pericyclic process would leave the remainder of the molecule unharmed.

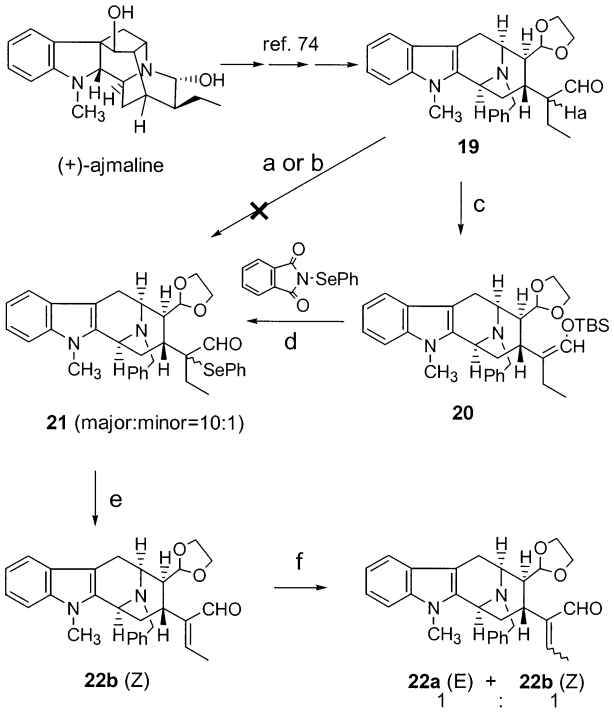
As shown in Scheme 3, the aldehyde **12** might be prepared from the allylic alcohol **18** via an anionic oxy-Cope rearrangement. The anionic oxy-Cope rearrangement appeared to present several advantages not the least of which rested on generation of the olefinic bond in **18**, a required latent aldehyde moiety. More importantly, the oxy-anion Cope rearrangement of allylic alcohol **18** should take place stereoselectively from the α face of the double bond via a chair transition state[60d,e,73] to furnish the desired configuration at C(15) required for the synthesis of all ajmaline/macroline/ sarpagine alkaloids.

During the studies to construct the skeleton of 19-hydroxy-N_b-methylraumacline,[74] (+)-ajmaline had been

SCHEME 3. Retrosynthetic Approach toward (+)-Vellosimine (Route 2)



SCHEME 4[a]



[a] Reagents and conditions: (a) LDA, THF, −76 °C, PhSeBr; (b) PhSeBr, EtOAc; (c) TBSOTf, Et_3N, CH_2Cl_2, 93%; (d) CH_2Cl_2, *p*-TSA, 72%; (e) $NaIO_4$, THF, H_2O, 90%; (f) I_2, benzene, reflux.

degraded to provide the acetals represented by **19**. The initial approach focused on the conversion of the aldehydic moiety in **19** into the α,*β*-unsaturated aldehyde functionality present in **22** (see Scheme 4).

Several methods were available for conversion of aldehyde **19** into an α,*β*-unsaturated aldehyde **22**. One of these approaches was to convert the aldehyde **19** directly into an α-substituted phenylselenide moiety, which could be oxidized to an α,*β*-unsaturated aldehyde **22**. As depicted in Scheme 4, the aldehyde **19** was

(66) Weber, R. W. Ph.D. Thesis, University of Wisconsin−Milwaukee, 1984.
(67) Cloudsale, I. S.; Kluge, A. F.; McClure, N. L. *J. Org. Chem.* **1982**, *47*, 919.
(68) Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovicz, J.; Terrell, R. *J. Am. Chem. Soc.* **1963**, *85*, 207.
(69) Hollinshead, S. Ph.D. Thesis, University of York, 1987.
(70) Trudell, M. L. Ph.D. Thesis, University of Wisconsin−Milwaukee, 1989.
(71) Desimoni, G.; Tacconi, G. *Chem. Rev.* **1975**, *75*, 5.
(72) Narasaka, K.; Soai, K.; Mukaiyama, T. *Chem. Lett.* **1974**, 1223.
(73) Wang, T.; Xu, Q.; Yu, P.; Liu, X.; Cook, J. M. *Org. Lett.* **2001**, *3*, 345.
(74) Li, J., Ph.D. Thesis, University of Wisconsin−Milwaukee, 1999.

dissolved in THF and then cooled to −78 °C. The LDA (1.5 equiv) was then added to the above solution through a syringe, according to the literature procedure.[75] After the solution was allowed to stir for 20 min, the PhSeBr was added in one portion. The reaction was monitored by TLC; however, only starting material **19** was recovered. Since it was reported that aldehydes could react with phenylselenyl bromide in ethyl acetate to provide α-phenylselenium-substituted aldehydes,[75] the aldehyde **19** was dissolved in ethyl acetate and phenylselenyl bromide was added. Again no reaction was observed by TLC.

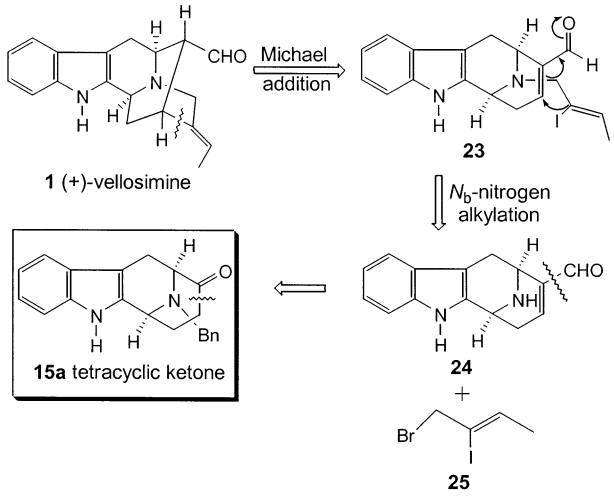
An alternate synthetic approach was attempted. It was well-known that enol ethers can be converted into α,*β*-unsaturated aldehydes in two steps;[76] consequently, it was decided to convert the aldehyde **19** into an enol ether **20**. Therefore, the mixture of aldehydes **19** was reacted with 1.2 equiv of TBSOTf in the presence of triethylamine in CH_2Cl_2 at 0 °C to provide the desired enol ether **20** in 93% yield. The enol ether **20** was reacted with *N*-phenylselenophthalimide to provide the desired α-substituted selenoaldehyde **21** in 72% yield which was isolated as a mixture of two diastereomers in a ratio of 10:1. Since *N*-phenylselenophthalimide was expensive, other reagents including PhSeBr and NBS were employed; however, with **20** the latter two reagents did not provide the desired material.

With the desired α-phenylselenoaldehyde **21** in hand, conversion of this phenylselenoaldehyde into the α,*β*-unsaturated aldehyde **22a** was carried out. Unfortunately, when the major isomer of the mixture of aldehydes represented by **21** was oxidized with $NaIO_4$, the process provided the α,*β*-unsaturated aldehyde **22b** in 90% yield isolated as a single isomer with the undesired *Z* olefinic configuration. When aldehyde **22b** was heated in benzene in the presence of a catalytic amount of I_2,[77] it was converted into the desired isomer **22a** isolated from a mixture of the two olefinic isomers (*E* and *Z*) and present in a ratio of **22a** (*E*) to **22b** (*Z*) of 1:1. In fact, separation of the two isomers proved impractical for the purposes of total synthesis and this approach was discontinued.

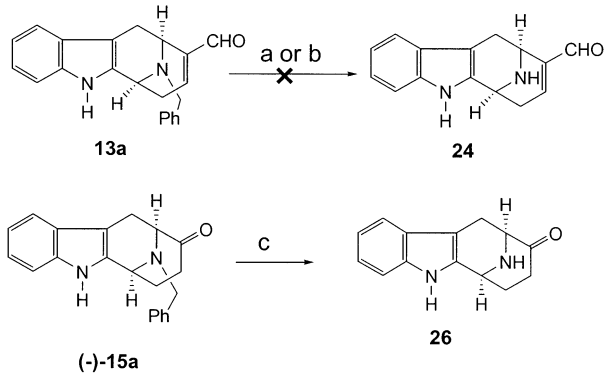
To solve the problems encountered in the first two routes, another approach was designed, as shown in Scheme 5. It was now decided to first introduce the C(19)−C(20) double bond with the *E* configuration stereospecifically rather than generating the olefin at a later stage.

With this goal in mind, attempts to remove the benzyl group from the N_b-nitrogen moiety of **13a** to provide N_a-H, N_b-H unsaturated aldehyde **24** have been made under various conditions and have failed, as shown in Scheme 6. The inability to remove the benzyl group via catalytic hydrogenation (Pd/C, H_2) was believed to arise from coordination of the palladium to the double bond of the unsaturated aldehyde system, while the failure of ACECl

SCHEME 5. Retrosynthetic Approach toward (+)-Vellosimine (Route 3)



SCHEME 6[a]



[a] Reagents and conditions: (a) Pd/C/H_2, HCl−EtOH, 1 atm or 50 atm; (b) ACECl, diglyme, 0 °C, rt; reflux, MeOH; (c) Pd/C/H_2, 1 atm, 1 equiv of HCl−EtOH, 95% (see improved procedure).

was felt to be due to steric constraints in the N_b-benzyl-[3.3.1]azabicyclononane system.[74,78]

When the starting N_a-H,N_b-benzyltetracyclic ketone **15a** was stirred with palladium on carbon under 1 atm of hydrogen under acidic conditions, the benzyl group was successfully removed. After the formation of the N_a-H,N_b-benzyltetracyclic ketone **15a** hydrochloride salt, the solvent was removed under reduced pressure. The residue was dissolved again in dry EtOH (80 mL), and the solvent was removed. This process was recycled three times, which removed the excess HCl. The debenzylation (10% Pd/C, H_2) process in EtOH now afforded only **26** (5 h) in 95% yield (10 g scale).

Conversion of the N_a-H, N_b-H tetracyclic ketone **26** into the N_a-H, N_b-H unsaturated aldehyde **24** failed in all attempts, as anticipated (Scheme 7). It was believed the tertiary N_b-nitrogen moiety was necessary for successful transformation of ketone **15a** into the unsaturated aldehyde **13a** for the exposed secondary amine (N_b-H) in **26** disrupted the formation of the oxirane precluding the oxirane rearrangement to aldehyde **24**. It was then decided to prepare the tertiary amine **27** by alkylation

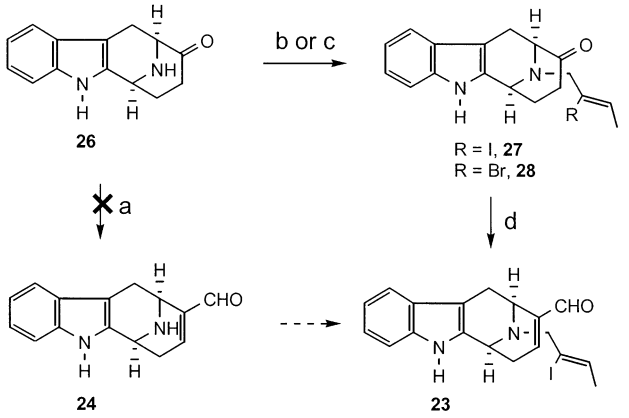
(75) (a) Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1972**, *94*, 7154. (b) Sharpless, K. B.; Lauer, R. F.; Teranishi, A. T. *J. Am. Chem. Soc.* **1973**, *95*, 6137. (c) Sharpless, K. B.; Young, M. W.; Lauer, R. F. *Tetrahedron Lett.* **1973**, *14*, 1979.

(76) Gan, T. Ph.D. Thesis, University of Wisconsin−Milwaukee, 1997.

(77) Jain, N. F.; Cirillo, P. F.; Schaus, J. V.; Panek, J. S. *Tetrahedron Lett.* **1995**, *36*, 8723.

(78) Wang, T. Ph.D. Thesis, University of Wisconsin−Milwaukee, 2001.

SCHEME 7[a]



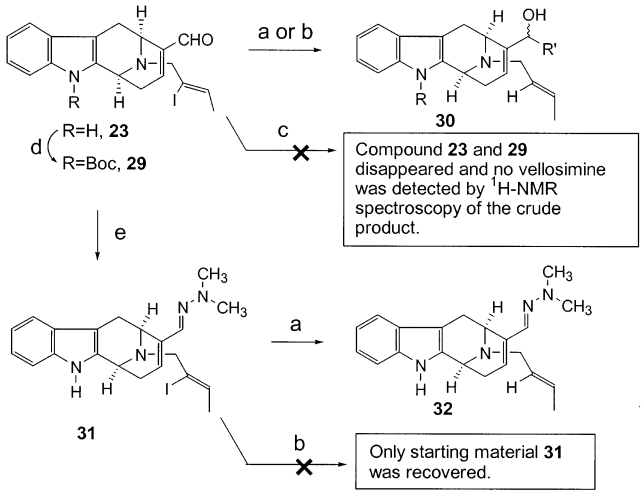
[a] Reagents and conditions: (a) $ClCH_2SOPh$, LDA/THF, −78 °C, KOH (aq THF), 8 h; $LiClO_4$, dioxane, reflux, 24 h; (b) **25**, rt, 24 h; reflux, 24 h; K_2CO_3, rt, 24 h, 87%; (c) Z-1,2-dibromobutene, K_2CO_3, THF, rt, 3 d, 80%; (d) $ClCH_2SOPh$, LDA/THF, −78 °C; KOH (aq THF), 16 h; $LiClO_4$, dioxane, reflux, 4 d, 83%.

of **26** with (*Z*)-1-bromo-2-iodo-2-butene **25** and then convert the tertiary amine **27** into the desired α,*β*-unsaturated aldehyde **23**.

The required (*Z*)-1-bromo-2-iodo-2-butene **25** was synthesized in three steps by following the procedure of Corey[79] and Ensley.[80] This bromide **25** has been employed by several groups in the total syntheses of geissoschizine and strychnine.[56−59,81] Alkylation of the N_a-H, N_b-H tetracyclic ketone **26** with (*Z*)-1-bromo-2-iodo-2-butene **25** under basic conditions smoothly took place to provide the N_a-H,N_b-(*Z*)-2′-iodo-2′-butenyl tetracyclic ketone **27** in 87% yield (the N_a-H, N_b-*Z*-2′-bromo-2′-butenyl tetracyclic ketone **28** was also prepared by the alkylation of the N_a-H, N_b-H tetracyclic ketone **26** with (*Z*)-1,2-dibromo-2-butene under the same conditions). Conversion of the ketone **27** into the α,*β*-unsaturated aldehyde **23** was achieved in 83% yield under the same conditions employed earlier in the N_b-benzyl series.

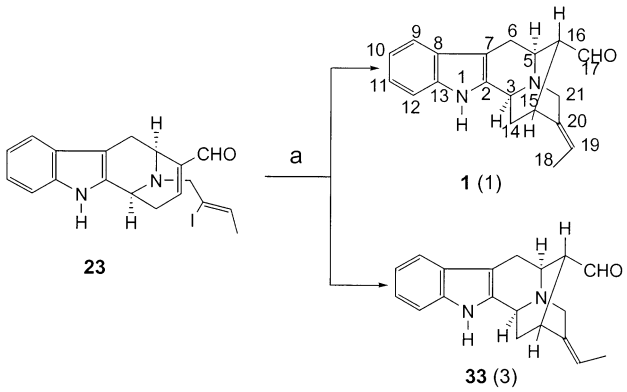
Numerous attempts to effect the intramolecular Michael addition in **23** to construct the sarpagine skeleton have been made. When the unsaturated aldehyde **23** was treated with *n*-BuLi or *t*-BuLi, the products of 1,2-addition to the aldehyde were isolated; moreover, the iodine atom had been replaced with a hydrogen moiety. When the N_a-H acidic function was protected as an N_a-Boc moiety (Scheme 8), the same result was realized. To avoid the 1,2-addition reaction, the unsaturated aldehyde **23** was converted into the hydrazone **31**[82] (Scheme 8). When the hydrazone **31** was treated with *n*-BuLi, replacement of the iodo group with a hydrogen atom occurred, while in the case of *t*-BuLi, only starting material **31** was recovered. Treatment of the α,*β*-unsaturated aldehyde **23** or the N_a-Boc α,*β*-unsaturated aldehyde **29** with freshly prepared active Rieke metals such as Rieke magnesium, Rieke barium, Rieke zinc, Rieke copper, or Rieke lithium gave complex mixtures

SCHEME 8[a]



[a] Reagents and conditions: (a) BuLi, THF, −78 °C; (b) *t*-BuLi, THF, −78 °C; (c) freshly made Rieke metals including Li*, Mg*, Ba*, Zn*, Cu*; (d) $(Boc)_2O$, DMAP, CH_3CN, rt, 12 h, >90%; (e) $MgSO_4$, Me_2NNH_2, CH_2Cl_2, Δ, 2 h, >90%.

SCHEME 9[a]



[a] Reagents and conditions: (a) AIBN/Bu_3SnH, benzene, Δ, 12 h, 40%.

of products. The α,*β*-unsaturated aldehyde disappeared on analysis by TLC; however, no signals from vellosimine or its equivalent were ever detected in the proton NMR spectrum of the crude product. The failure to achieve the cyclization by the Michael addition was believed to be due to the relative acidity inherent at the *γ*-position [C(14)] of the α,*β*-unsaturated aldehydic system. Although the vinyl anion could be generated under some circumstances it was felt is was quenched immediately by the acidic hydrogen atom at C(14) or on workup.

To overcome this problem, it was decided to employ radical conditions[81] to achieve the cyclization. As shown in Scheme 9, a premixed solution composed of 2 equiv of tributyltin hydride and 0.1 equiv of AIBN was added to a refluxing benzene solution of α,*β*-unsaturated aldehyde **23** through a syringe pump over a period of 12 h. The α,*β*-unsaturated aldehyde **23** was converted into a mixture of two isomers which were isolated in a ratio of 3:1 (^{1}H NMR) in 40% overall yield. The spectroscopic properties (MS, IR, NMR) of the minor isomer were in excellent agreement with those reported in the literature[4,20−26,83] for (+)-vellosimine (**1**) [[α]$_D$ +45.3 (*c* 0.60, CH_3OH); lit.[83b]

(79) Corey, E. J.; Kirst, H. A.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1970**, *92*, 6314.
(80) Ensley, H. E.; Buescher, R. R.; Lee, K. *J. Org. Chem.* **1982**, *47*, 404.
(81) Kuehne, M. E.; Wang, T.; Seraphin, D. *J. Org. Chem.* **1996**, *61*, 7873.
(82) Corey, E. J.; Enders, D. *Tetrahedron Lett.* **1976**, *17*, 3.

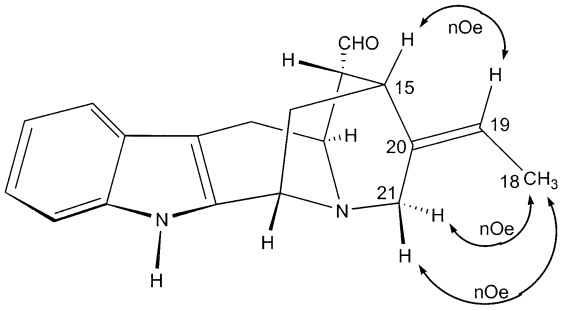


FIGURE 4. NOE interactions in the major isomer **1**.

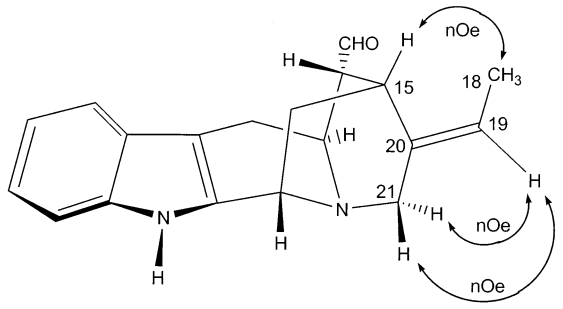


FIGURE 5. NOE interactions in the minor isomer **33**.

$[\alpha]_D$ +48.0 (CH_3OH)]; while the structure of the major isomer was found to be 16-*epi*-koumidine aldehyde **33** by 2D NMR experiments.

The stereochemistry of the two isomers was examined by analysis of data from the 2D NOESY experiments. As shown in Figure 4, examination of the data from the NOESY experiment on the major isomer **33** clearly indicated that the methine proton at C(15) and the vinyl proton at C(19) experienced a strong NOE interaction, while the methylene protons at C(21) experienced a strong NOE interaction with the methyl protons at C(18). Examination of the data from the NOESY experiment on the minor isomer **1** indicated very different interactions. The major NOE interactions in the spectrum of the minor isomer were observed between the methine proton at C(15) and the methyl protons at C(18) as well as between the vinyl proton at C(19) and the methylene protons at (21), as shown in Figure 5. The above evidence suggested that the olefinic double bond underwent epimerization during the cyclization process under radical conditions, as expected. The desired isomer **1** with the *E* configuration was obtained as the minor product in a 1:3 (*E*/*Z*) ratio. The result was not surprising, however, for analysis of MM2 calculations (MacroModel version 6.0-MM2 force field) indicated the major isomer **33** was 0.71 kcal/mol more stable than vellosimine (**1**). In addition, Magnus[51] and Sakai[50,84] had demonstrated that the *Z* olefinic isomer **33** was contained in the more stable configuration in the koumidine system. Interestingly, under similar radical reaction conditions in a different indole system Kuehne observed the formation of the *E* isomer.[81] Kuehne reported that the double bond underwent epimerization under radical conditions to provide a mixture of olefins which was dominated by the desired isomer with the *E* configuration in a ratio of 3:1. No details for the determination of the configuration of the double bond in that synthesis were reported.[81] Certainly, epimerization of such systems would be expected to provide the thermodynamically more stable olefin as the major isomer. It is also necessary to point out that two ^{13}C NMR signals (50.5 and 53.8 ppm) were misassigned by Banerji et al.[25] The value of 50.5 ppm should be assigned to C(3) which was previously assigned to C(5); while the value of 53.8 ppm should be assigned to C(5) which was misassigned as C(3). The new assignment was based on examination of the HSQC experiment.

Although the target (+)-vellosimine (**1**) and other sarpagine indole alkaloids as well as analogues could be synthesized by the approach discussed above, the yield and stereoselectivity for the last step were disappointing. Semmelhack et al.[85] in 1973 reported the first examples of transition metal (Ni) catalyzed reactions of soft, non-organometallic, carbon nucleophiles.[86] Recently, Rawal reported a new approach to construct the D-ring in geissoschizine by employing a Heck reaction as the key step.[87] The advantage of a Heck reaction stems from the stability of the olefin, no epimerization of the double bond was observed.[87] It was decided, therefore, to employ a Heck (Pd^0) reaction to build up the sarpagine ring system. The α,*β*-unsaturated aldehyde **23** was first converted into allylic alcohol **34** by reduction with sodium borohydride followed by Pd^0-mediated cyclization of **34** under the Heck reaction conditions employed by Rawal.[87] Only the product of elimination **35** was observed even under modified reaction conditions. A related coupling process was reported recently by Muratake and Natsume.[88] Direct palladium-mediated arylation at the *γ*-position of a simple α,*β*-unsaturated aldehyde had been achieved under basic conditions in high yield.[88] When the α,*β*-unsaturated aldehyde **23** was stirred under similar conditions, the C(14) insertion product (aldehyde **36**) was isolated in 71% yield. It was believed the cyclization took place in this manner due to the relative acidity of the methylene protons at the *γ*-position of the unsaturated aldehyde. Examination of molecular models suggested the α,*β*-unsaturated aldehyde **23** tautomerized to its enolate form **36a** under basic conditions, followed by a palladium-mediated coupling reaction to provide the α,*β*-unsaturated aldehyde **36**, as shown in Scheme 10.

Although the process provided the wrong ring system in which C(14) was coupled to C(20), it was felt a similar mechanism could be encouraged to occur with **27**; the relative acidity inherent at the α-position of the ketone **27** would facilitate the Pd^0-mediated conversion of N_a-H,N_b-(*Z*)-2′-iodo-2′-butenyltetracyclic ketone **27** into the desired sarpagine system in **37**. As hoped, when the above conditions were employed directly with ketone **27**, the key cyclized ketone **37** was received in 80% yield (Scheme 11). It is worthy of note that the optimized

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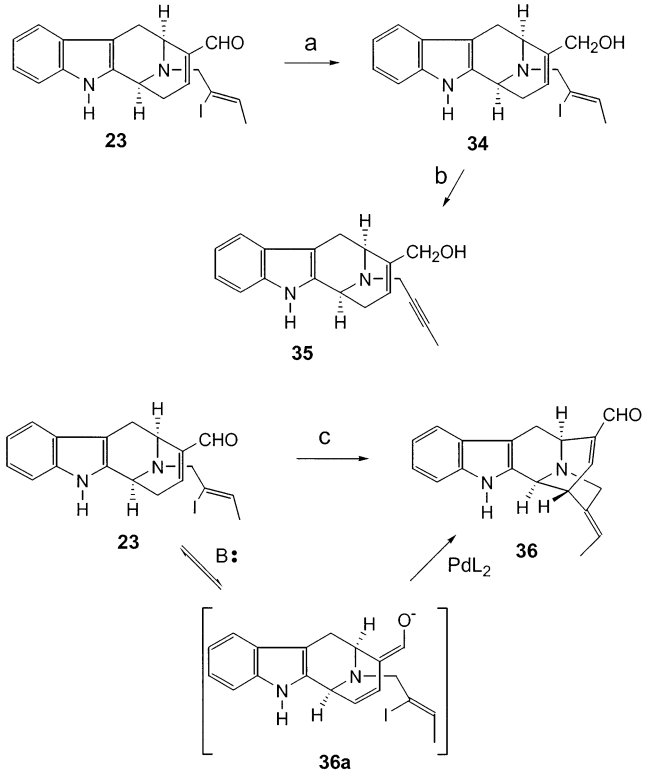
(87) Birman, V. B.; Rawal, V. H. *Tetrahedron Lett.* **1998**, *39*, 7219.

(88) Muratake, H.; Natsume, M. *Tetrahedron Lett.* **1997**, *38*, 7581.

SCHEME 10[a]



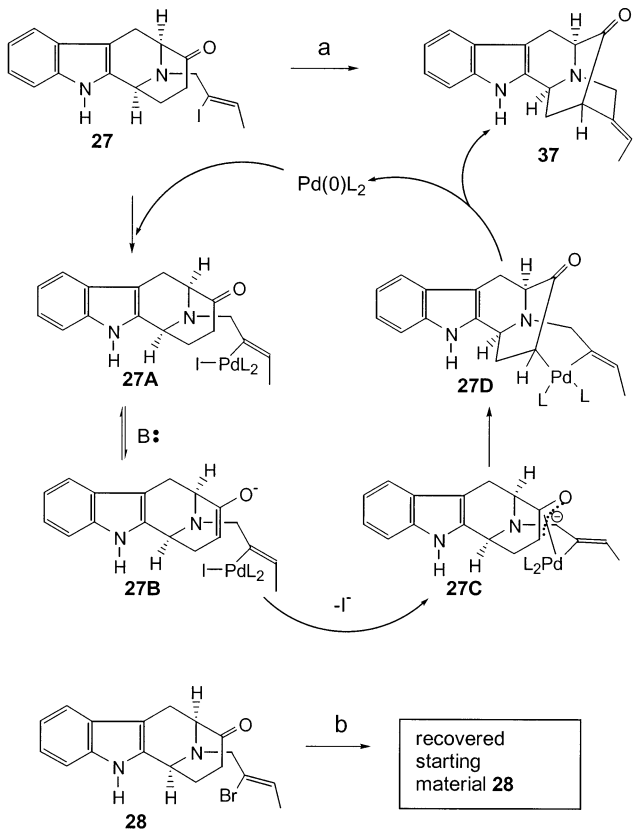
[a] Reagents and conditions: (a) $NaBH_4$, MeOH, >99%; (b) $Pd(OAc)_2$, PPh_3, Bu_4NBr, K_2CO_3, DMF−H_2O (9:1); (c) $Pd(OAc)_2$, PPh_3, Bu_4NBr, K_2CO_3, DMF−H_2O (9:1), 70 °C, 5 h, 71%.

amount of $Pd(OAc)_2$ (3 mol %) and PPh_3 (30 mol %) resulted in a cleaner process as compared to the amount of $Pd(OAc)_2$ (5 mol %) and PPh_3 (20 mol %) initially employed, although this took longer to go to completion. The structure of the cyclic ketone **37** was determined by analysis of NMR experiments and the stereochemistry of the cyclized ketone **37** was examined by analysis of 2D NMR experiments (NOESY). As shown in Figure 6, examination of the data from the NOESY spectrum clearly illustrated the NOE interaction between the methine protons at C(14) with the methyl protons at C(18) as well as between the vinyl proton at C(19) with the methylene protons at C(21). Consequently, it could be concluded that the geometry of this cyclic ketone **37** was *E*. This was the required configuration for the sarpagine alkaloids.

The stereochemistry of this key intermediate, cyclic ketone **37**, was later confirmed by single-crystal X-ray crystallography. Crystal data and structural refinement data as well as the coordinates are available in the Supporting Information. The significance of this palladium-mediated α-vinylation was that it provided a very efficient approach to construct the sarpagine alkaloid system as well as introduce the C(19)−C(20) olefinic bond with the *E* configuration stereospecifically. Recently, this palladium-mediated α-vinylation process has been extended to ring-A methoxy substituted indole systems and successfully employed to prepare ring-A methoxy substituted indole alkaloids.[89,90] The process appeared to be general for indole containing systems if the vinyl halide was a vinyl iodide. To date, vinyl bromides have not reacted successfully under these conditions.[78] Palladium-mediated direct α-arylation of ketones has been reported by several groups;[91] however, the palladium-mediated

(89) Zhao, S.; Liao, X.; Cook, J. M. *Org. Lett.* **2002**, *4*, 687.
(90) Liu, X.; Deschamps, J. R.; Cook, J. M. *Org. Lett.* **2002**, *4*, 3339.

SCHEME 11[a]



[a] Reagents and conditions: (a) $Pd(OAc)_2$, PPh_3, Bu_4NBr, K_2CO_3, DMF−H_2O (9:1), 70 °C, 5 h, 80%; (b) $Pd(OAc)_2$, PPh_3, Bu_4NBr, K_2CO_3, DMF−H_2O (9:1), 70 °C, 5 h.

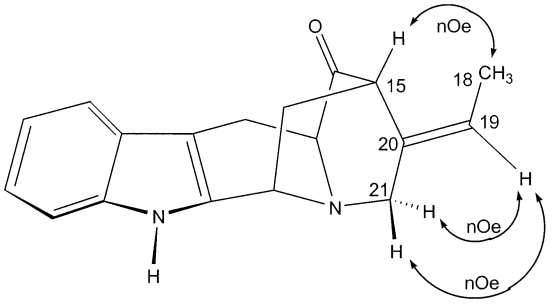


FIGURE 6. NOE interactions in the cyclic ketone **37**.

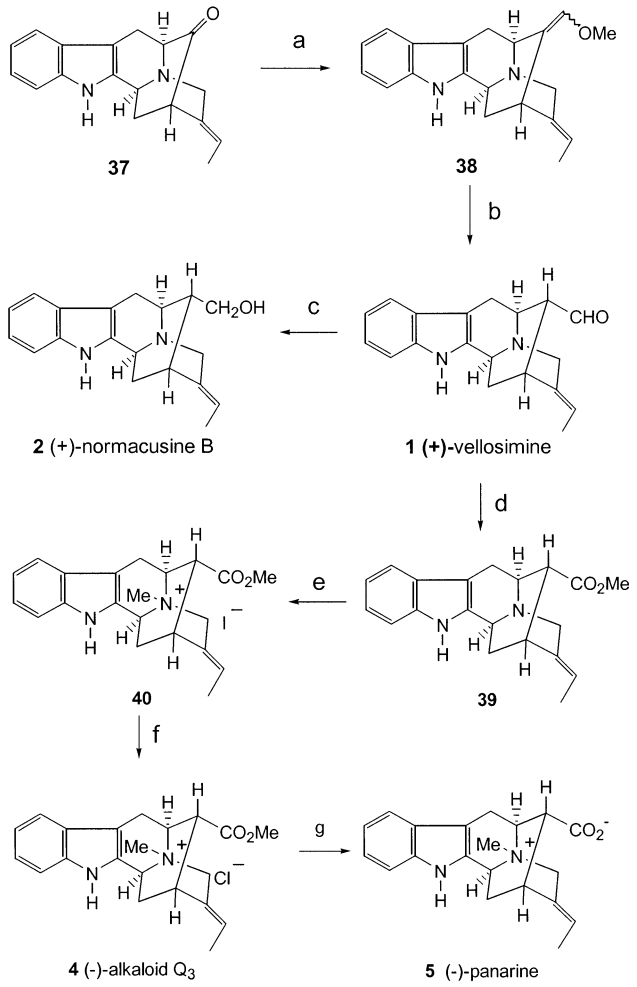
(91) (a) Palucki, M. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108. (b) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 12382. (c) Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1740. (d) Satoh, T.; Inoh, J.-I.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2239. (e) Terao, Y.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **1998**, *39*, 6203. (f) Satoh, T.; Kametani, Y.; Terao, Y.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **1999**, *40*, 5345. (g) Shaughnessy, K. H.; Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *63*, 6546. (h) Wang, D.; Wu, Z. *J. Chem. Soc., Chem. Commun.* **1999**, 529. (i) Ahman, J.; Wolfe, J. P.; Troutman, M. V.; Palucki, M. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 1918. (j) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473.

direct α-vinylation of ketones has been reported in only a few cases.[92] Although very little mechanistic information has been obtained in regard to the palladium-catalyzed α-vinylation of ketones, by analogy to previous coupling processes[91a,b] it was believed that the reaction proceeds via the set of steps illustrated in Scheme 11. Oxidative addition of the $Pd(0)L_2$ with the vinyl iodide followed by an equilibrium between the ketone **27A** and its enolate would afford the Pd(II) organometallic intermediate **27B**. Coordination of the enolate to the palladium species then provided an intermediate **27C** which could rearrange to provide the Pd(II) organometallic intermediate **27D**. Finally, **27D** can undergo reductive elimination to provide the cyclic ketone **37** and regenerate the $Pd(0)L_n$ catalyst.[91] In this reaction cycle, the oxidative addition of the $Pd(0)L_2$ to the vinyl iodide was the key step (it is not necessarily the rate determining step) to execute the reaction cycle. The analogous vinyl halide **28** of ketone **27** which contained a bromine atom at C(20) in place of the iodide was studied under the same reaction conditions. Only starting material was recovered. The reason for the difference in results between the vinyl bromide and vinyl iodide was not clear. It was felt, execution of the oxidative addition of the vinyl iodide to the palladium catalyst occurred faster than interaction of Pd(0) with the electron rich indole ring; while the less active vinyl bromide may allow the palladium catalyst to complex with the indole removing it from the reaction cycle. The reaction cycle shown in Scheme 11 was drawn according to the classic neutral pathway[93] although the anionic pathway would also accurately describe the catalytic cycle.[94]

The sarpagine system **37** was converted into (+)-vellosimine (**1**) in two steps, as shown in Scheme 12. The ketone **37** was subjected to the Wittig reaction with methoxylmethyl triphenylphosphonium chloride and anhydrous potassium *tert*-butoxide to provide a mixture of two stereoisomeric enol ethers represented by **38**. After a short wash column, the mixture of enol methyl ethers **38** was hydrolyzed to provide (+)-vellosimine (**1**) in 90% yield (overall yield for two steps). Since the aldehyde at C(16) is in the more stable (α) configuration because of a *syn* pentane interaction with the indole methylene bridge, the mixture was simply stirred until all of the *β* epimer was converted into the more stable, natural α epimer in **1**. The spectral data (^{1}H and ^{13}C NMR, IR, MS, and co-TLC) for this base were identical to those reported for the natural product[4,20−26,83] and the synthetic vellosimine obtained earlier under radical conditions.

A second sarpagine alkaloid, (+)-normacusine B (**2**), was synthesized in enantiospecific fashion by this route. Synthetic (+)-vellosimine (**1**) was reduced with sodium borohydride to provide (+)-normacusine B (**2**) in over 90% yield. The spectral data (^{1}H and ^{13}C NMR, IR, and MS) for (+)-normacusine B (**2**) were identical to those reported for the natural product [$[\alpha]_D$ +40.5 (*c* 0.75, C_2H_5OH); lit. $[\alpha]_D$ +42.0 (*c* 1.0, C_2H_5OH)].[29−42] The structure of (+)-normacusine B (**2**) was further confirmed by single-crystal X-ray crystallography. Crystal data and structural refinement data as well as the coordinates are available in the Supporting Information. Oxidation of the aldehyde **1** at C-17 to provide the ester **39** was accomplished in 85% yield by using I_2 and KOH in MeOH.[95,96] The optical rotation of synthetic **39** [$[\alpha]_D$ +4.6 (*c* 1.00, MeOH)] was in agreement with that of Büchi and not of Quaisuddin.[43,44] Subsequent quaternization of the N_b-nitrogen moiety in **39** with MeI provided the N_b-methiodide salt **40** which was, upon exposure to AgCl,[97] converted into the chloride **4** in 85% yield. The ^{1}H NMR spectrum and optical rotation of **4** were in good agreement with that of the reported values.[46] Hydrolysis of the ester function of **4** with 0.1 N NaOH followed by neutralization with 0.1 HCl afforded panarine (**5**) in 90% yield. The ^{1}H and ^{13}C NMR spectra of synthetic **5** were identical to that of

SCHEME 12[a]



[a] Reagents and conditions: (a) $H_3COCH_2PPh_3$, KO-t-Bu, PhH, rt, 24 h; (b) HCl (2 N, aq) Δ, 6 h, 90% (overall yield for two steps); (c) $NaBH_4$, THF, 0 °C, 12 h, 90%; (d) KOH, I_2, MeOH, rt, 2 h, 88%; (e) MeI, MeOH, rt, 4 h, 90%; (f) AgCl, MeOH, 85%; (e) 0.1 N NaOH, then 0.1 N HCl, 90%.

(92) (a) Piers, E.; Marais, P. C. *J. Org. Chem.* **1990**, *55*, 3454. (b) Piers, E.; Renaud, J. *J. Org. Chem.* **1993**, *58*, 11.

(93) Heck, R. F. *Palladium-catalyzed vinylation of organic halides*; Dauben, W. G., Boswell, G. A., Danishefsky, S., Gschwend, H. W., Heck, R. F., Hirschmann, R. F., Kende, A. S., Paquette, L. A., Posner, G. H., Eds.; John Wiley & Sons: New York, 1982; Vol. 27, p 345.

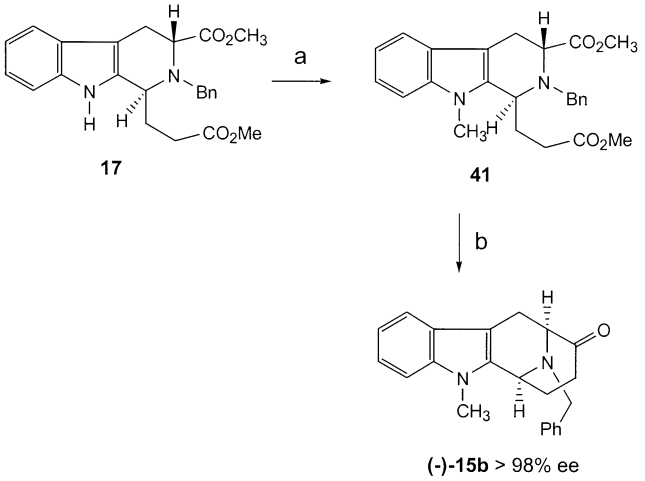
(94) Amatore, C.; Jutand, A. *Acc. Chem. Res.* **2000**, *33*, 314.

(95) Yamada, S.; Morizano, D.; Yamamoto, K. *Tetrahedron Lett.* **1992**, *33*, 4329.

(96) Roush, W. R.; Limberakis, C.; Kunz, R. K.; Barda, D. *Org. Lett.* **2002**, *4*, 1543.

(97) Yamazaki, N.; Dokoshi, W.; Kibayashi, C. *Org. Lett.* **2001**, *3*, 193.

SCHEME 13[a]



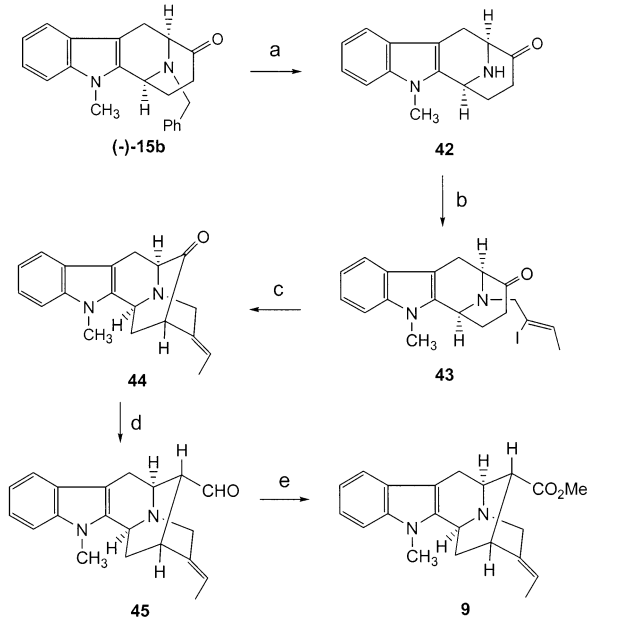
[a] Reagents and conditions: (a) CH_3I, NaH, DMF, rt 2 h, 95%; (b) NaH (10 equiv), CH_3OH, toluene, reflux, 72 h; HOAc, HCl, H_2O, reflux, 10 h, 80%, one pot (150 g scale).

natural panarine kindly supplied by Professor Luc Angenot. Moreover, a mixed sample (1:1) of synthetic panarine and natural panarine yielded only one set of signals in the ^{13}C NMR; the two compounds are identical.[98]

The synthesis of N_a-methylvellosimine **8** and N_a-methyl-16-epipericyclivine **9** began from N_a-methyl N_b-benzyl tetracyclic ketone **15b** which could be prepared on 150 g scale (>98% ee) from D-(+)tryptophan methyl ester in three reaction vessels via the asymmetric Pictet−Spengler reaction/Dieckmann protocol as described above (Scheme 13).[60d,98]

The N_b-benzyl group was removed via catalytic hydrogenation under acidic conditions to afford the N_b-H ketone **42** in 94% yield (Scheme 14). This base was reacted with the (*Z*)-1-bromo-2-iodo-2-butene **25** in the presence of K_2CO_3 to afford alkylated ketone **43** in 90% yield. Palladium-mediated enolate driven intramolecular cyclization took place stereospecifically to afford the desired ketone **44** in 82% yield.[99] Ketone **44** was then converted into N_a-methylvellosimine (**8**)[98] which had also been isolated from *Rauvolfia nitida*.[100] The optical rotation of synthetic N_a-methylvellosimine (**8**) [[α]$_D$ +98.0 (*c* 0.50, $CHCl_3$)] was different from the literature value [[α]$_D$ +23 (*c* 0.01, $CHCl_3$)]; however, it was consistent with that of the *ent*-N_a-methylvellosimine [[α]$_D$ −99 (*c* 0.50, $CHCl_3$)] which was previously reported.[101] Furthermore, N_a-methylvellosimine (**8**) was converted into another natural product, affinisine, by reduction of the C-17 aldehydic group of **8** to its corresponding alcohol with $NaBH_4$. The optical rotation of synthetic affinisine [[α]$_D$ +31 (*c* 0.31, $CHCl_3$)] was in excellent agreement with that of the natural affinisine [[α]$_D$ +30 (*c* 0.01, $CHCl_3$)].[102] Consequently, the correct configuration of **8** was established, *vide infra*. Oxidation of the C-17 aldehyde function of **8** to the desired ester afforded N_a-methyl-16-epipericyclivine (**9**) in 94% yield on treatment with I_2 and KOH in MeOH. This sequence provided enantiospecific, stereospecific access to N_a-methyl-16-epipericyclivine (**9**) in eight reaction vessels (42% overall yield). All spectral data (e.g., ^1H and ^{13}CNMR, IR, and MS) for synthetic **9** were in good agreement with data reported for the natural product.[47] However, the optical rotation of synthetic N_a-methyl-16-epipericyclivine (**9**) [[α]$_D$ +22.8 (*c* 0.50, $CHCl_3$)] was different from that reported [[α]$_D$ 0 (*c* 0.50, $CHCl_3$)].[47]

SCHEME 14[a]



[a] Reagents and conditions: (a) 5% Pd/C, H_2, 1 equiv of EtOH/HCl, rt 5 h, 94%; (b) (*Z*)-1-bromo-2-iodo-2-butene, K_2CO_3, THF, reflux, 90%; (c) $Pd(OAc)_2$, PPh_3, Bu_4NBr, K_2CO_3, DMF−H_2O (9:1), 65 °C, 30 h, 82%; (d) KO-t-Bu, $MeOCH_2PPh_3Cl$, benzene, rt, 24 h; 2 N HCl/THF, 55 °C, 5 h, 90%; (e) KOH, I_2, MeOH, rt, 2 h, 94%.

In summary, the first enantiospecific, stereospecific total synthesis of the sarpagine indole alkaloids (+)-vellosimine (**1**) and (+)-normacusine B (**2**), (−)-alkaloid Q_3 (**4**), (−)-panarine (**5**), (+)-N_a-methylvellosimine (**8**), and (+)-N_a-methyl-16-epipericyclivine (**9**) has been accomplished from commercially available D-(+)-tryptophan methyl ester **16**. The asymmetric Pictet−Spengler reaction and a stereocontrolled intramolecular palladium-mediated coupling reaction are the two key steps in this approach employed to establish the stereochemistry at all chiral centers. This approach provides the first stereospecific solution to the problem of the stereochemistry of the C(19)−C(20) *E*-ethylidene function in the sarpagine alkaloids.

Experimental Section

General Methods. Reagent and solvent purification, work-up procedures, and analyses were in general performed as described previously.[60e]

(6*S*,10*S*)-(−)-9-Formyl-12-benzyl-6,7,10,11-tetrahydro-6,10-imino-5*H*-cycloocta[*b*]indole (13a). A solution of di-

(98) Yu, J.; Wearing, X. Z.; Cook, J. M. *Tetrahedron Lett.* **2003**, *44*, 543.

(99) For enantiomers of ketone **44** and N_a-methylvellosimine **8**, see: Liu, X, Zhang, C.; Liao, X.; Cook, J. M. *Tetrahedron Lett.* **2002**, *43*, 7373.

(100) Amer, M. A.; Court, W. E. *Phytochemistry* **1981**, *20*, 2569.

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(102) Banerji, A.; Chakrabarti, R.; Mukherjee, R. *Phytochemistry* **1972**, *11*, 2605.

isopropylamine (56.4 mL, 0.4 mol) and *n*-butyllithium (160 mL, 2.5 M in hexane) in THF (300 mL) was cooled to −78 °C under an atmosphere of argon in a round-bottom flask (5000 mL). It was equipped with an overhead stirrer. α-Chloromethyl phenyl sulfoxide (70 g, 0.4 mol) was dissolved in THF (80 mL) and added to the above chilled solution of freshly generated LDA. The yellow mixture that resulted was stirred for 30 min at −78 °C after which time the ketone (−)-**15a** (50 g, 0.161 mol) in THF (400 mL) was added dropwise via a cannula over a period of 1 h. The reaction solution that resulted was stirred for 2 h after which time it was then brought to rt and diluted with THF (2000 mL). A solution of aq KOH (1300 mL, 15 N) was added, and the heterogeneous mixture was stirred at rt for 16 h. The organic layer was removed, and the aqueous phase was extracted with EtOAc (3 × 1000 mL). The combined organic fractions were washed with a saturated solution of aq NH_4Cl (500 mL) and brine (500 mL) and dried (K_2CO_3). The solvent was removed under reduced pressure to provide a crude mixture of diastereomers (1:1) of the phenylsulfinyl oxirane. The crude mixture was used directly in the next step without further separation or purification. The mixture of phenylsulfinyl oxiranes was added to a solution of dry dioxane (2500 mL) that contained lithium perchlorate (20 g) in a round-bottom flask (5000 mL). The slurry that resulted was heated at reflux under an atmosphere of argon for 4 d. The reaction was monitored by TLC (silica gel, EtOAc/hexane = 2:3) based on the disappearance of oxirane which has a lower R_f value. The reaction solution was allowed to cool to rt and diluted with CH_2Cl_2 (4000 mL). The organic layer was washed with 10% aq NH_4OH (500 mL) and brine (500 mL) and dried (K_2CO_3). The solvent was removed under reduced pressure. The oil that resulted was purified by chromatography on silica gel (EtOAc/hexane = 1:4) to provide the α,*β*-unsaturated aldehyde **13a** as an amorphous solid (45 g, 87%): $[\alpha]_D = -322.86$ (*c* 1.05, $CHCl_3$); FTIR (NaCl) 3393, 1670 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.37 (1H, dd, J = 19.2, 5.0 Hz), 2.65 (1H, d, J = 16.4 Hz), 2.95 (1H, dd, J = 19.2, 5.2 Hz), 3.22 (1H, dd, J = 16.5, 5.9 Hz), 3.71 (1H, d, J = 13.4 Hz), 3.85 (1H, d, J = 13.4 Hz), 4.01 (1H, d, J = 5.5 Hz), 4.22 (1H, d, J = 5.6 Hz), 6.72 (1H, d, J = 2.9 Hz), 7.12 (1H, t, J = 6.8 Hz), 7.17 (1H, t, J = 6.9 Hz), 7.25−7.50 (6H, m), 7.49 (1H, d, J = 7.2 Hz), 7.70 (1H, s), 9.33 (1H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.83, 33.00, 49.23, 50.13, 56.21, 106.11, 110.91, 118.33, 119.65, 121.88, 127.33, 127.35, 128.44, 128.79, 133.31, 135.84, 138.69, 143.65, 147.87, 192.50; CIMS (*m/e*, relative intensity) 329 ($M^+ + 1$, 100). Anal. Calcd for $C_{22}H_{20}N_2O$: C, 80.16; H, 6.14; N, 8.53. Found: C, 79.92; H, 6.12; N, 8.45.

Catalytic Debenzylation of (6*S*,10*S*)-(−)-9-Oxo-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole (15a) To Provide (6*S*,10*S*)-(−)-9-Oxo-12-H-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole (26) over Pd/C/H_2. Tetracyclic ketone **15a** (10 g, 31.7 mmol) was suspended in anhydrous EtOH (100 mL), and saturated ethanolic HCl (15 mL) was added dropwise to form a clear solution. The solvent was removed under reduced pressure. Then the residue was dissolved again in dry EtOH (80 mL), and the solvent was removed. This process was recycled three times after which Pd/C (10%, 2.0 g) was added. The mixture that resulted was allowed to stir at rt under an atmosphere of hydrogen for 5 h. Analysis by TLC (silica gel plate was exposed to NH_3 vapors) indicated the absence of starting material **15a**. The catalyst was removed by filtration and was washed with EtOH (3 × 50 mL). The solvent was removed under reduced pressure. The residue was dissolved in a mixture of CH_2Cl_2 and aq NH_4OH (5:1, 100 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine (20 mL) and dried (K_2CO_3). Removal of the solvent under reduced pressure afforded the crude product, which was purified by chromatography on silica gel ($CHCl_3$/MeOH = 20:1) to provide pure N_a-H, N_b-H tetracyclic ketone **26** (6.8 g, 95%): FTIR (NaCl) 3393, 3382, 1705 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.08−2.15 (2H, m), 2.36−2.50 (3H, m), 2.80 (1H, d, J = 16.4 Hz), 3.09 (1H, dd, J = 16.5, 6.8 Hz), 3.92 (1H, d, J = 6.7 Hz), 4.27 (1H, d, J = 3.9 Hz), 7.10 (1H, d, J = 7.4 Hz), 7.16 (1H, d, J = 7.4 Hz), 7.29 (1H, d, J = 7.9 Hz), 7.44 (1H, d, J = 7.6 Hz), 8.06 (1H, bs); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 25.79, 31.98, 35.02, 46.08, 59.75, 107.50, 110.91, 118.12, 119.71, 122.08, 126.87, 133.95, 135.71, 210.95; CIMS (*m/e*, relative intensity) 227 ($M^+ + 1$, 100). Anal. Calcd for $C_{14}H_{14}N_2O$: C, 74.31; H, 6.24; N, 12.38. Found: C, 74.39; H, 6.35; N, 12.41.

Alkylation of (6*S*,10*S*)-(−)-9-Oxo-12-H-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole (26) To Provide (6*S*,10*S*)-(−)-9-Oxo-12-((*Z*)-2′-iodo-2′-butenyl)-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole (27). A solution of N_a-H, N_b-H tetracyclic ketone **26** (25.0 g, 110.6 mmol) and (*Z*)-1-bromo-2-iodo-2-butene[79,80] (40.0 g, 153.8 mmol) was dissolved in THF (500 mL), stirred at rt for 24 h, and then heated to 60 °C for 24 h. Analysis by TLC (silica gel, $CHCl_3/C_2H_5OH$ = 4:1) indicated there was still a small amount of tetracyclic ketone **26** that remained. The reaction solution was cooled to rt, and K_2CO_3 (10.0 g) was added. The mixture that resulted was stirred at rt for 24 h. Analysis by TLC (silica gel, $CHCl_3/C_2H_5OH$ = 4:1) indicated the absence of tetracyclic ketone **26**. The K_2CO_3 was removed by filtration and was washed with EtOAc (3 × 100 mL). After removal of the solvent under reduced pressure, the crude product was purified by chromatography on silica gel (EtOAc/hexane = 1:9) to provide N_b-(*Z*)-2′-iodo-2′-butenyl tetracyclic ketone **27** (39.0 g, 87%): FTIR (NaCl) 3393, 1705, 1450 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.73 (3H, d, J = 6.3 Hz), 2.19−2.05 (2H, m), 2.37−2.47 (2H, m), 2.65 (1H, d, J = 16.9 Hz), 3.05 (1H, dd, J = 16.9, 6.7 Hz), 3.19−3.37 (2H, m), 3.64 (1H, d, J = 6.4 Hz), 3.96 (1H, bs), 5.76 (1H, q, J = 6.2 Hz), 6.97−7.16 (2H, m), 7.25 (1H, d, J = 7.7 Hz), 7.40 (1H, d, J = 7.5 Hz), 8.05 (1H, bs); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.60, 21.71, 30.35, 34.49, 49.73, 63.36, 64.07, 106.69, 108.47, 110.94, 118.09, 119.62, 121.97, 126.72, 132.11, 132.76, 135.79, 210.40; CIMS (*m/e*, relative intensity) 407 ($M^+ + 1$, 100). Anal. Calcd for $C_{18}H_{19}N_2OI$: C, 53.22; H, 4.71; N, 6.90. Found: C, 53.15; H, 4.80; N, 6.64.

Alkylation of (6*S*,10*S*)-(−)-9-Oxo-12*H*-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole (26) To Provide (6*S*,10*S*)-(−)-9-Oxo-12-((*Z*)-2′-bromo-2′-butenyl)-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole (28). A solution of N_a-H, N_b-H tetracyclic ketone **26** (20.0 g, 88.5 mmol) and (*Z*)-1,2-dibromo-2-butene (37.5 g, 176.9 mmol) was dissolved in THF (500 mL), and K_2CO_3 (15.0 g) was added. The mixture that resulted was stirred at rt for 3 d. Analysis by TLC (silica gel, $CHCl_3/C_2H_5OH$ = 6:1) indicated the presence of a trace amount of the tetracyclic ketone **26**. The K_2CO_3 was removed by filtration and was washed with EtOAc (3 × 100 mL). After removal of the solvent under reduced pressure, the crude product was purified by chromatography on silica gel (EtOAc/hexane = 1:9) to provide N_b-(*Z*)-2′-bromo-2′-butenyl tetracyclic ketone **28** (25.3 g, 80%): FTIR (NaCl) 3395, 1706 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.79 (3H, d, J = 7.7 Hz), 1.99−2.16 (2H, m), 2.44−2.53 (2H, m), 2.70 (1H, d, J = 20.3 Hz), 3.14 (1H, dd, J = 20.3, 7.9 Hz), 3.43 (2H, m), 3.75 (1H, d, J = 7.7 Hz), 4.08 (1H, bs), 5.97 (1H, q, J = 7.7 Hz), 7.10−7.25 (2H, m), 7.34 (1H, d, J = 8.9 Hz), 7.48 (1H, d, J = 8.5 Hz), 7.95 (1H, bs); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 16.75, 20.55, 30.37, 34.52, 50.34, 60.83, 64.43, 106.97, 111.04, 118.30, 119.69, 122.23, 125.77, 126.62, 126.96, 132.09, 136.01, 210.11; CIMS (*m/e*, relative intensity) 359 ($M^+ + 1$, 100). Anal. Calcd for $C_{18}H_{19}N_2OBr$: C, 60.18; H, 5.33; N, 7.80. Found: C, 59.91; H, 5.34; N, 7.53.

(6*S*,10*S*)-(−)-9-Formyl-12-((*Z*)-2′-iodo-2′-butenyl)-6,7,10,11-tetrahydro-6,10-imino-5*H*-cycloocta[*b*]indole (23). A solution of diisopropylamine (34.7 mL, 0.25 mol) and *n*-butyllithium (100 mL, 2.5 M in hexane) in THF (200 mL) was cooled to −78 °C under an atmosphere of argon in a round-bottom flask (5000 mL) equipped with a magnetic stir bar. α-Chloromethyl phenyl sulfoxide (43 g, 0.25 mol) was dissolved in THF (50 mL) and added to the above chilled solution of freshly generated LDA. The yellow mixture that resulted was

stirred for 30 min at −78 °C, after which time the ketone **27** (25 g, 61.58 mmol) in THF (300 mL) was added dropwise via a double-ended needle over a period of 1 h. The reaction solution was stirred for 6 h at −78 °C, after which time it was brought to rt and diluted with THF (1000 mL). A solution of aq KOH (800 mL, 15 N) was added, and the heterogeneous mixture was stirred at rt for 16 h. The organic layer was removed, and the aqueous phase was extracted with EtOAc (3 × 1000 mL). The combined organic fractions were washed with a saturated aqueous solution of NH_4Cl (500 mL) and brine (500 mL) and dried (K_2CO_3). The solvent was removed under reduced pressure to provide a crude mixture of diastereomers of the phenylsulfinyl oxirane. The crude mixture was used directly in the next step without further separation or purification. The mixture of phenylsulfinyl oxiranes was added to a solution of dry dioxane (1500 mL) that contained lithium perchlorate (12 g) in a round-bottom flask (3000 mL) equipped with a magnetic stir bar. The slurry that resulted was heated at reflux under an atmosphere of argon for 4 d. The reaction was monitored by TLC (silica gel, EtOAc/hexane = 2:3) on the basis of the disappearance of oxirane, which had a lower R_f value. The reaction solution was allowed to cool to rt and diluted with CH_2Cl_2 (4000 mL). The organic layer was washed with a 10% solution of aq NH_4OH (500 mL) and brine (500 mL) and dried (K_2CO_3). The solvent was then removed under reduced pressure. The oil that resulted was purified by chromatography on silica gel (EtOAc/hexane = 1:4) to provide the α,*β*-unsaturated aldehyde **23** as an amorphous solid (21.4 g, 83%): FTIR (NaCl) 3394, 1672, 1640 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.79 (3H, d, J = 6.3 Hz), 2.42 (1H, dd, J = 19.2, 4.9 Hz), 2.63 (1H, d, J = 26.7 Hz), 3.06 (2H, dt, J = 16.6, 5.9 Hz), 3.31 (1H, d, J = 13.9 Hz), 3.44 (1H, d, J = 13.9 Hz), 4.06 (1H, d, J = 5.4 Hz), 4.14 (1H, d, J = 5.8 Hz), 5.83 (1H, q, J = 6.3 Hz), 6.71 (1H, d, J = 3.0 Hz), 7.05−7.17 (2H, m), 7.28 (1H, d, J = 7.9 Hz), 7.43 (1H, d, J = 7.6 Hz), 7.77 (1H, bs), 9.32 (1H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.79, 33.40, 49.17, 49.45, 63.66, 106.44, 108.66, 110.87, 118.31, 119.67, 121.92, 127.20, 132.75, 132.79, 135.78, 143.37, 148.02, 192.48; CIMS (*m*/*e*, relative intensity) 419 (M^+ + 1, 100), 420 (M^+ + 2, 20). Anal. Calcd for $C_{19}H_{19}N_2OI$: C, 54.56; H, 4.58; N, 6.70. Found: C, 54.40; H, 4.52; N, 6.20.

Radical-Mediated Cyclization of (6*S*,10*S*)-(−)-9-Formyl-12-((*Z*)-2′-iodo-2′-butenyl)-6,7,10,11-tetrahydro-6,10-imino-5*H*-cycloocta[*b*]indole (23) To Provide (+)-3-Ethylidene-1,3,4,7,12,12b-hexahydro-2*H*,6*H*-2,6-methanoindole[2,3-α]quinolizine-13-carboxaldehyde (Vellosimine, 1) and 16-*epi*-Koumidine Aldehyde (33). The α,*β*-unsaturated aldehyde **23** (1.0 g, 2.4 mmol) was dissolved in dry benzene (120 mL), and the solution was heated to reflux. A mixture of Bu_3SnH (1.2 mL, 4.5 mmol) and AIBN (140 mg, 0.85 mmol) in dry benzene (8 mL) was added to the above solution through a syringe pump over 12 h. Analysis by TLC (silica gel, EtOAc/hexane = 4:1) indicated the absence of α,*β*-unsaturated aldehyde **23**. Removal of the solvent under reduced pressure afforded an oil that was purified by chromatography (preparative TLC, silica gel, EtOAc/hexane = 3:7) to provide (+)-vellosimine (**1**) (70 mg, 10%) and 16-*epi*-koumidine aldehyde **33** (210 mg, 30%). **1**: $[\alpha]_D$ = +45.3 (*c* 0.60, CH_3OH) [lit.[83b] $[\alpha]_D$ = +48.0 (CH_3OH)]; FTIR (NaCl) 3395, 1710, 1626 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.56 (3H, d, J = 6.8 Hz), 1.93 (1H, d, J = 13.3 Hz), 2.16 (1H, t, J = 10.4 Hz), 2.59 (1H, s), 2.63 (2H, d, J = 9.2 Hz), 3.22 (1H, s), 3.25−3.36 (1H, m), 3.58 (1H, d, J = 16.5 Hz), 3.80 (1H, t, J = 6.0 Hz), 4.44 (1H, d, J = 9.4 Hz), 5.25 (1H, q, J = 6.9 Hz), 7.04−7.16 (2H, m), 7.35 (1H, d, J = 7.8 Hz), 7.41 (1H, d, J = 7.7 Hz), 9.16 (1H, bs), 9.56 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.65, 26.49, 26.71, 32.59, 50.69, 50.85, 54.50, 55.38, 103.69, 111.26, 118.15, 118.20, 119.65, 121.97, 127.10, 131.05, 136.15, 136.46, 201.34; CIMS (*m*/*e*, relative intensity) 293 (M^+ + 1, 100); EIMS (*m*/*e*, relative intensity) 292 (M^+, 65), 291 (10), 264 (15), 263 (80), 249 (15), 182 (16), 169 (100), 168 (70). Anal. Calcd for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.89; N, 9.58. Found: C, 78.20; H, 6.51; N, 9.28. **33**: FTIR (NaCl) 3395, 1710, 1626 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.53 (3H, d, J = 6.8 Hz), 1.73−1.79 (1H, m), 2.01−2.05 (1H, m), 2.38 (1H, d, J = 7.3 Hz), 2.57 (1H, d, J = 15.6 Hz), 2.70 (1H, bs), 3.14 (1H, dd, J = 15.7, 5.1 Hz), 3.48 (1H, d, J = 16.1 Hz), 3.57 (1H, t, J = 6.2 Hz), 3.72 (1H, d, J = 15.9 Hz), 4.08 (1H, d, J = 9.0 Hz), 5.28 (1H, qt, J = 6.7, 2.4 Hz), 7.05−7.16 (2H, m), 7.25 (1H, d, J = 7.4 Hz), 7.44 (1H, d, J = 7.3 Hz), 7.92 (1H, bs), 9.60 (1H, t, J = 5.9 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.49, 27.36, 34.09, 34.41, 50.14, 50.89, 53.34, 54.36, 104.12, 110.90, 117.69, 118.19, 119.53, 121.62, 127.55, 134.78, 136.33,137.91, 203.32; CIMS (*m*/*e*, relative intensity) 293 (M^+ + 1, 100).

Sodium Borohydride Mediated Reduction of (6*S*,10*S*)-(−)-9-Formyl-12-((*Z*)-2′-iodo-2′-butenyl)-6,7,10,11-tetrahydro-6,10-imino-5*H*-cycloocta[*b*]indole (23) To Provide (6*S*,10*S*)-(−)-9-Hydroxymethyl-12-((*Z*)-2′-iodo-2′-butenyl)-6,7,10,11-tetrahydro-6,10-imino-5*H*-cycloocta[*b*]indole (34). The unsaturated aldehyde **23** (100 mg, 0.24 mmol) was dissolved in EtOH (5 mL). $NaBH_4$ (8 mg, 0.22 mmol) was added to the above solution in one portion. The mixture was then stirred at 0 °C for 8 h. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and poured into cold water (10 mL). The aqueous layer was extracted with additional CH_2Cl_2 (3 × 20 mL), and the combined organic layers were washed with brine (10 mL) and dried (K_2CO_3). Removal of the solvent under reduced pressure afforded the crude product, which was purified by chromatography on silica gel to provide allylic alcohol **34** (100 mg, 99%): FTIR (NaCl) 3397, 3299 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.79 (3H, d, J = 6.3 Hz), 2.07 (1H, dd, J = 17.5, 4.4 Hz), 2.67 (1H, d, J = 16.1 Hz), 2.75 (1H, dd, J = 17.2, 3.9 Hz), 3.01 (1H, dd, J = 16.1, 5.7 Hz), 3.33 (1H, d, J = 14.0 Hz), 3.43 (1H, d, J = 14.0 Hz), 3.74 (1H, d, J = 5.3 Hz), 3.98 (1H, s), 5.60 (1H, d, J = 0.8 Hz), 5.87 (1H, q, J = 6.3 Hz), 7.06−7.16 (2H, m), 7.27 (1H, d, J = 7.4 Hz), 7.45 (1H, d, J = 7.2 Hz), 7.75 (1H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.78, 31.44, 49.20, 52.13, 63.80, 65.03, 106.07, 108.89, 110.86, 118.01, 119.41, 120.71, 121.48, 127.30, 132.17, 133.86, 135.66, 139.10; EIMS (*m*/*e*, relative intensity) 420 (M^+, 55), 402 (2), 293 (15), 222 (30), 221 (100); HRMS (*m*/*e*, relative intensity) required for $C_{19}H_{21}N_2OI$ 420.0699, found 420.0676.

Attempted Cyclization of (6*S*,10*S*)-(−)-9-Hydroxymethyl-12-((*Z*)-2′-iodo-2′-butenyl)-6,7,10,11-tetrahydro-6,10-imino-5*H*-cycloocta[*b*]indole (34) into (+)-3-Ethylidene-1,3,4,7,12,12b-hexahydro-2*H*,6*H*-2,6-methanoindole[2,3-α]quinolizine-13-carboxaldehyde (1) via a Palladium-Mediated Heck Reaction. A mixture of allylic alcohol **34** (100 mg, 0.24 mmol), $Pd(OAc)_2$ (5.36 mg, 0.024 mmol), Bu_4NBr (88 mg, 0.27 mmol), PPh_3 (25 mg, 0.095 mmol), and K_2CO_3 (132 mg, 0.95 mmol) in a solution of DMF−H_2O (9:1, 2.5 mL) was degassed under reduced pressure. The mixture was then heated to 70 °C (oil bath temperature) under an atmosphere of argon for 5 h. Analysis by TLC (silica gel, EtOAc/hexane = 4:1) indicated the absence of allylic alcohol **34** and the presence of a new indole component at higher R_f value. The mixture was cooled to room temperature, diluted with EtOAc (250 mL), washed with H_2O (5 × 50 mL), and dried (K_2CO_3). The solvent was removed under reduced pressure, and the oil that resulted was purified by chromatography on silica gel (EtOAc/hexane = 3:7) to provide allylic alcohol **35** (48.4 mg, 70%): FTIR (NaCl) 3394, 3252, 2243 cm^{-1}; ^1H NMR δ 1.80 (3H, s), 2.07 (1H, dd, J = 17.5, 4.4 Hz), 2.66 (1H, d, J = 16.3 Hz), 2.72 (1H, d, J = 16.2 Hz), 2.97 (1H, dd, J = 17.4, 5.7 Hz), 3.27−3.35 (4H, m), 3.96 (1H, d, J = 5.7 Hz), 4.25 (1H, d, J = 5.7 Hz), 5.59 (1H, d, J = 3.6 Hz), 7.05−7.12 (2H, m), 7.39 (1H, d, J = 7.5 Hz), 7.49 (1H, d, J = 7.5 Hz), 7.87 (1H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 3.68, 20.86, 31.33, 41.79, 49.76, 51.68, 64.79, 75.08, 80.24, 105.46, 110.86, 118.01, 119.33, 120.27, 121.45, 127.18, 133.11, 135.78, 138.97; HRMS (*m*/*e*, relative intensity) required for $C_{19}H_{22}N_2O$ 292.1576, found 292.1568.

Palladium-Catalyzed Cyclization of (6*S*,10*S*)-(−)-9-Formyl-12-((*Z*)-2′-iodo-2′-butenyl)-6,7,10,11-tetrahydro-6,10-imino-5*H*-cycloocta[*b*]indole (23) To Provide the Cyclic Unsaturated Aldehyde 36. A mixture of α,β-unsaturated aldehyde **23** (100 mg, 0.24 mmol), $Pd(OAc)_2$ (5.36 mg, 0.024 mmol), Bu_4NBr (88 mg, 0.27 mmol), PPh_3 (25 mg, 0.095 mmol), and K_2CO_3 (132 mg, 0.95 mmol) in a solution of DMF−H_2O (9:1, 2.5 mL) was degassed under reduced pressure. The mixture was then heated to 70 °C (oil bath temperature) under an atmosphere of argon for 5 h. Analysis by TLC (silica gel, EtOAc/hexane = 4:1) indicated the absence of α,β-unsaturated aldehyde **23** and the presence of a new indole component (indole spray reagent) of lower R_f value. The mixture was cooled to rt, diluted with EtOAc (250 mL), washed with H_2O (5 × 50 mL), and dried (K_2CO_3). The solvent was removed under reduced pressure, and the oil that resulted was purified by chromatography on silica gel (EtOAc/hexane = 3:7) to provide cyclic unsaturated aldehyde **36** (49.4 mg, 71%): FTIR (NaCl) 1670 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.69 (3H, d, J = 7.5 Hz), 2.89 (1H, dd, J = 15.7, 1.6 Hz), 3.17 (1H, dd, J = 15.7, 4.6 Hz), 3.42 (1H, d, J = 16.1 Hz), 3.55 (1H, d, J = 6.5 Hz), 3.85 (1H, d, J = 17.3 Hz), 4.01 (1H, d, J = 3.2 Hz), 4.06 (1H, s), 5.22 (1H, q, J = 7.4 Hz), 6.69 (1H, d, J = 10.6 Hz), 7.00−7.10 (2H, m), 7.27 (1H, d, J = 7.4 Hz), 7.51 (1H, d, J = 7.3 Hz), 9.14 (1H, s), 9.23 (1H, bs); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 15.36, 26.65, 42.77, 57.76, 57.83, 57.97, 108.60, 111.00, 114.48, 118.27, 119.14, 121.47, 128.59, 131.96, 136.34, 137.95, 143.13, 149.77, 192.95; CIMS (*m*/*e*, relative intensity) 291 (M^+ + 1, 100). Anal. Calcd for $C_{19}H_{18}N_2O$: C, 78.59; H, 6.25; N, 9.65. Found: C, 78.41; H, 6.54; N, 9.22.

Palladium-Catalyzed Cyclization of (6*S*,10*S*)-(−)-9-Oxo-12-((*Z*)-2′-iodo-2′-butenyl)-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole (28a) To Provide Pentacyclic Ketone 37. A mixture of N_b-(*Z*)-2′-iodo-2′-butenyl tetracyclic ketone **28a** (4.0 g, 10.0 mmol), $Pd(OAc)_2$ (66 mg, 0.30 mmol), Bu_4NBr (3.26 g, 10.0 mmol), PPh_3 (790 mg, 3.0 mmol), and K_2CO_3 (5.56 g, 40.0 mmol) in a solution of DMF−H_2O (9:1, 131 mL) was degassed under reduced pressure. The mixture was then heated to 70 °C (oil bath temperature) under an atmosphere of argon for 30 h. Analysis by TLC (silica gel, EtOAc/hexane = 4:1) indicated the absence of N_b-(Z)-2′-iodo-2′-butenyl tetracyclic ketone **28a** and the presence of a new indole component of lower R_f value. The mixture was cooled to rt, diluted with EtOAc (2 L), washed with H_2O (5 × 100 mL), and dried (K_2CO_3). The solvent was removed under reduced pressure, and the oil that resulted was purified by chromatography on silica gel (EtOAc/hexane = 3:7) to provide pentacyclic ketone **37** (2.18 g, 80%) whose structure was confirmed by single-crystal X-ray analysis: FTIR (NaCl) 1723 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.63 (3H, d, J = 6.9 Hz), 2.15−2.20 (1H, m), 2.38 (1H, t, J = 9.9 Hz), 2.97 (1H, dd, J = 15.6, 6.2 Hz), 3.27 (1H, d, J = 14.4 Hz), 3.37 (1H, bs), 3.59 (1H, d, J = 5.7 Hz), 3.78 (2H, bs), 4.26 (1H, d, J = 9.1 Hz), 5.49 (1H, q, J = 6.9 Hz), 7.05−7.15 (2H, m), 7.25 (1H, d, J = 7.3 Hz), 7.47 (1H, d, J = 7.3 Hz), 7.92 (1H, bs); ^{13}CNMR (75.5 MHz, $CDCl_3$) δ 12.68, 22.39, 36.40, 44.55, 50.83, 55.24, 64.17, 105.62, 110.89, 118.54, 119.69, 121.26, 122.00, 126.88, 131.88, 135.87, 136.34, 217.00; CIMS (*m*/*e*, relative intensity) 291 (M^+ + 1, 100); EIMS (*m*/*e*, relative intensity) 278 (M^+, 10), 250 (75), 249 (85), 182 (6), 169 (100), 168 (5); HRMS (*m*/*e*, relative intensity) required for $C_{18}H_{18}N_2O$ 278.1419, found 278.1437. This material was used directly in a later step.

Conversion of the Pentacyclic Ketone 37 into (+)-3-Ethylidene-1,3,4,7,12,12b-hexahydro-2*H*,6*H*-2,6-methanoindole[2,3-α]quinolizine-13-carboxaldehyde [(+)-Vellosimine (1)] via the Wittig Reaction Followed by Acid-Mediated Hydrolysis. A mixture of anhydrous potassium *tert*-butoxide (12.8 g, 0.114 mol) and methoxymethyltriphenylphosphonium chloride (36 g, 0.105 mol) in dry benzene (500 mL) was allowed to stir at rt for 1 h. The pentacyclic ketone **37** (4.0 g, 14.4 mmol) in THF (160 mL) was then added to the above orange solution dropwise at rt. The mixture that resulted was stirred at rt for 24 h (the reaction progress was monitored by ^1H NMR spectroscopy). The mixture was diluted with EtOAc (3 × 700 mL), washed with H_2O (3 × 50 mL) and brine (50 mL), and dried (K_2CO_3). The solvent was removed under reduced pressure to afford an oil. The baseline materials were removed by a quick wash through a column of silica gel. The solvent was removed under reduced pressure, and the residue was dissolved (without further purification) in a solution of aq HCl (2 N) in H_2O−THF (1:1, 400 mL). The solution that resulted was stirred at 55 °C (oil bath temperature) under an atmosphere of argon for 6 h (the reaction progress was monitored by ^1H NMR spectroscopy). The reaction mixture was cooled to 0 °C and extracted with ethyl ether (5 × 100 mL) to remove phosphorus-based byproducts, and the water layer was then brought to pH 8 with an ice cold aqueous solution of NaOH (1 N). The aqueous layer was extracted with CH_2Cl_2 (3 × 1 L), and the combined organic layers were washed with H_2O (3 × 100 mL) and brine (100 mL) and dried (K_2CO_3). The solvent was removed under reduced pressure to afford an oil that was crystallized to provide (+)-vellosimine (**1**) (3.15 g, 75%). The mother liquor was concentrated, and the residue was purified by chromatography on silica gel (EtOAc/hexane = 3:2) to provide additional (+)-vellosimine (**1**) (0.63 g, 15%). The combined yield was 90%. The spectral data for (+)-vellosimine (**1**) were identical to those obtained directly from unsaturated aldehyde **23** via the radical reaction and were in good agreement with the published values.[4,20−27,83]

Sodium Borohydride Mediated Reduction of (+)-3-Ethylidene-1,3,4,7,12,12b-hexahydro-2*H*,6*H*-2,6-methanoindole[2,3-α]quinolizine-13-carboxaldehyde [(+)-Vellosimine (1)] To Provide the (+)-3-Ethylidene-1,3,4,7,12,12b-hexahydro-13-hydroxymethyl-2*H*,6*H*-2,6-methanoindole[2,3-α]quinolizine [(+)-Normacusine B (2)]. The (+)-vellosimine (**1**) (100 mg, 0.34 mmol) was dissolved in EtOH (5 mL). The $NaBH_4$ (12 mg, 0.33 mmol) was added to the above solution in one portion. The mixture was then stirred at 0 °C for 8 h. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and poured into cold water (10 mL). The aqueous layer was extracted with additional CH_2Cl_2 (3×20 mL), and the combined organic layers were washed with brine (10 mL) and dried (K_2CO_3). The solvent was removed under reduced pressure to afford the crude product, which was purified by chromatography on silica gel to provide (+)-normacusine B (**2**) (90 mg, 90%): $[\alpha]_D$ = +40.5 (*c* 0.75, C_2H_5OH) [lit.[29−42] $[\alpha]_D$ = +42.0 (*c* 1.0, C_2H_5OH)]; FTIR (NaCl) 3198 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.57 (3H, d, J = 6.8 Hz), 1.66 (1H, dt, J = 12.5, 3.7 Hz), 1.78 (1H, q, J = 7.5 Hz), 1.93 (1H, t, J = 10.0 Hz), 2.61 (1H, d, J = 15.4 Hz), 2.72 (1H, s), 2.74 (1H, d, J = 6.5 Hz), 3.03 (1H, dd, J = 15.4, 5.1 Hz), 3.43−3.49 (4H, m), 4.07 (1H, d, J = 10.3 Hz), 5.26 (1H, q, J = 6.7 Hz), 7.03−7.14 (1H, m), 7.28 (1H, d, J = 6.0 Hz), 7.42 (1H, d, J = 7.0 Hz), 8.22 (1H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.75, 26.95, 27.58, 33.37, 44.14, 50.48, 54.47, 55.85, 64.90, 104.52, 110.99, 116.84, 118.07, 119.35, 121.44, 127.59, 135.33, 136.33, 137.80; EIMS (*m*/*e*, relative intensity) 294 (M^+, 84), 293 (85), 279 (10), 263 (30), 169 (100), 168 (79); HRMS (*m*/*e*, relative intensity) required for $C_{19}H_{22}N_2O$ 294.1732, found 294.1705.

Conversion of Vellosimine (1) into (+)-Methyl-3-ethylidene-1,3,4,7,12,12b-hexahydro-2*H*,6*H*-2,6-methanoindole[2,3-α]quinolizine-13-carboxylate (39). Aldehyde **1** (29 mg, 0.10 mmol) was dissolved in anhydrous MeOH (2 mL), and a solution of KOH (2.6 equiv, 17.2 mg, 0.26 mmol) and iodine (1.3 equiv, 33 mg, 0.13 mmol) in anhydrous MeOH (each 0.5 mL)[95,96] was successively added at 0 °C. After 2 h, the reaction was quenched by adding AcOH to neutralize the solution to pH 7. The solution was diluted with CH_2Cl_2, washed with 10% $Na_2S_2O_3$ (20 mL) and brine (2 × 20 mL), and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue that resulted was purified by chromatography

on silica gel ($CHCl_3$/MeOH = 40:1) to provide ester **39** (28 mg, 88%): $[\alpha]_D = +4.6$ (*c* 1.0, MeOH) [lit.[44] $[\alpha]_D = +3.6$ (*c* 1.0, MeOH)]; FTIR ($CHCl_3$) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.54 (3H, d, $J = 6.7$ Hz), 1.66 (1H, dt, $J = 12.0$, 2.6 Hz), 1.95 (1H, t, $J = 10.6$ Hz), 2.42 (1H, d, $J = 7.7$ Hz), 2.51 (1H, d, $J = 15.2$ Hz), 2.90 (1H, dd, $J = 15.2$, 5.1 Hz), 3.09 (1H, m), 3.45 (3H, m), 3.59 (3H, s), 3.59 (3H, s), 4.09 (1H, d, $J = 8.6$ Hz), 5.24 (1H, q, $J = 7.8$ Hz), 6.93 (1H, t, $J = 6.9$ Hz), 7.01 (1H, t, $J = 6.0$ Hz), 7.28 (1H, d, $J = 7.9$ Hz), 7.36 (1H, d, $J = 7.5$ Hz), 10.71 (1H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.86, 27.25, 28.87, 33.21, 46.84, 49.45, 51.80, 52.75, 55.59, 102.49, 111.43, 115.77, 117.89, 118.64, 120.76, 127.44, 136.01, 136.51, 139.39, 173.86; EIMS (*m*/*e*, relative intensity) 322 (M^+, 36), 307 (11), 263 (19), 168 (100). Anal. Calcd for $C_{20}H_{22}N_2O_2 \cdot 0.3H_2O$: C, 73.26; H, 6.76; N, 8.55. Found: C, 73.13; H, 6.86; N, 8.29.

Conversion of the (+)-Methyl-3-ethylidene-1,3,4,7,12,12b-hexahydro-2*H*,6*H*-2,6-methanoindole[2,3-α]quinolizine-13-carboxylate (39) into (−)-Alkaloid Q_3 (4). Ester **39** (32 mg, 0.1 mmol) was dissolved in anhydrous THF (2 mL), and then MeI (5 equiv, 161 mg, 0.5 mmol) was added at 0 °C. The mixture that resulted was stirred at rt for 4 h. The solvent was removed under reduced pressure, and the residue was chromatographed (flash) on silica gel ($CHCl_3$/MeOH = 9:1) to provide iodomethylated salt **40** (42 mg, 90%). The salt was dissolved in anhydrous MeOH (2 mL), and this was followed by addition of AgCl[97] (72 mg, 0.5 mmol). The mixture that resulted was stirred at rt for 2 days. The excess AgCl and formed AgI were removed by filtration and washed with MeOH (3×10 mL). After removal of the solvent under reduced pressure, the crude product was purified by chromatography on silica gel ($CHCl_3$/MeOH = 9:1) to afford alkaloid Q_3 (**4**) (29 mg, 85%): $[\alpha]_D = -21.3$ (*c* 0.15, MeOH) [lit.[46] $[\alpha]_D = -23$ (*c* 0.15, MeOH)]; FTIR (NaCl) 3040, 1594 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 1.68 (3H, ddd, $J = 8.3$, 2.3, 2.2 Hz), 2.26 (1H, dd, $J = 13.3$, 3.2 Hz), 2.58 (1H, ddd, $J = 12.1$, 10.3, 1.7 Hz), 3.03 (1H, dd, $J = 7.7$, 1.8 Hz), 3.08 (1H, br d, $J = 17.5$ Hz), 3.17 (3H, s), 3.33 (1H, m), 3.41 (1H, dd, $J = 17.4$, 4.9 Hz), 3.60 (1H, m), 3.76 (3H, s), 4.30 (1H, d, $J = 15.5$ Hz), 4.45 (1H, m), 4.56 (1H, dt, $J = 15.5$, 2.4 Hz), 4.98 (1H, d, $J = 10.2$ Hz), 5.58 (1H, q, $J = 6.8$ Hz), 7.1 (1H, ddd, $J = 8.0$, 7.1, 1.1 Hz), 7.2 (1H, ddd, $J = 8.2$, 7.1, 1.2 Hz), 7.40 (1H, dt, $J = 8.1$, 0.8 Hz), 7.52 (1H, dt, $J = 7.8$, 0.9 Hz); ^{13}C NMR (75.5 MHz, CD_3OD) δ 11.43, 23.41, 27.20, 30.95, 46.83, 47.17, 51.57, 60.39, 62.51, 64.24, 100.02, 111.17, 117.93, 119.53, 120.79, 122.46, 125.87, 126.59, 130.52, 137.38, 170.52; EIMS (*m*/*e*, relative intensity) 336 (M^+, 14), 322 (100), 307 (37), 291 (11), 263 (44), 225 (20), 168 (71). The spectral data were in complete agreement with the natural product.

Conversion of (−)-Alkaloid Q_3 (4) into (−)-Panarine (5). Alkaloid Q_3 (**4**) (37 mg, 0.1 mmol) was treated with 0.1 N NaOH (1 mL) in MeOH (4 mL) at rt for 6 h. The solution that resulted was brought with 0.1 N HCl to pH 7. The solvent was removed, and the crude product was purified by chromatography on silica gel ($CHCl_3$/MeOH = 6:1) to afford panarine (**5**) (29 mg, 90%): $[\alpha]_D = -24.0$ (*c* 0.10, MeOH) [lit.[46] $[\alpha]_D = -28 \pm 10$ (*c* 0.05, MeOH)]; IR (KBr) 1738 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 1.53 (3 H, d, $J = 6.7$ Hz), 2.07 (1 H, dd, $J = 13.2$, 3.8 Hz), 2.43 (1 H, t, $J = 12.3$ Hz), 2.51 (1 H, d, $J = 7.6$ Hz), 2.88 (1 H, d, $J = 17.3$ Hz), 3.03 (1 H, s), 3.24 (1 H, dd, $J = 17.3$, 5.0 Hz), 3.36 (1 H, bs), 4.11 (1 H, d, $J = 15.4$ Hz), 4.16 (1 H, t, $J = 6.4$ Hz), 4.28 (1 H, d, $J = 15.4$ Hz), 4.80 (1 H, d, $J = 5.0$ Hz), 5.47 (1 H, q, $J = 6.7$ Hz), 7.11 (1 H, t, $J = 7.3$ Hz), 7.22 (1 H, t, $J = 7.1$ Hz), 7.43 (1 H, d, $J = 8.1$ Hz), 7.51 (1 H, d, $J = 7.9$ Hz). ^{13}C NMR (75 MHz, CD_3OD) δ 12.06, 23.41, 28.21, 31.03, 47.13, 49.03, 60.18, 64.23, 64.69, 100.84, 111.86, 118.39, 119.93, 120.70, 122.74, 125.61, 126.61, 131.59, 136.67, 176.95; EIMS (*m*/*e*, relative intensity) 336 [$(M + Me)^+$, 8], 322 (M^+, 81), 307 (47), 291(7), 278 (21), 263 (79), 249 (32), 247 (41), 169 (87), 168 (100). A carbon 13 NMR spectrum of a mixed sample of synthetic and natural panarine indicated the two compounds were identical since there was only one set of signals.

Catalytic Debenzylation of (6*S*,10*S*)-(−)-9-Oxo-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5-methylcyclooct-[*b*]indole (15b) To Provide (6*S*,10*S*)-5-Methyl-(−)-9-oxo-12*H*-6,7,8,9,10,11-hexahydro-6,10-iminocyclooct[*b*]indole (42). Tetracyclic ketone **15b** (10.0 g, 30.3 mmol) was suspended in anhydrous EtOH (100 mL), and ethanolic HCl (5%, 15 mL) was added dropwise to form a clear solution. The solvent was removed under reduced pressure. The residue was then dissolved again in dry EtOH (80 mL), and the solvent was removed under reduced pressure. This process was repeated for three times after which Pd/C (10%, 2.0 g) was added. The mixture that resulted was allowed to stir at rt under an atmosphere of hydrogen (Parr hydrogenator) for 5 h. Analysis by TLC (silica gel plate was exposed to NH_3 vapor) indicated the absence of starting material **15b**. The catalyst was removed by filtration, and the solid was washed with EtOH (3 × 100 mL). The solvent was removed under reduced pressure. The residue was dissolved in a mixture of CH_2Cl_2 and 15% aq NH_4OH (5:1, 500 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were washed with brine (2 × 200 mL) and dried (K_2CO_3). Removal of the solvent under pressure afforded the crude product, which was purified by chromatography on silica gel ($CHCl_3$/MeOH = 25:1) to provide pure N_a-Me, N_b-H tetracyclic ketone **42** (6.80 g, 94%): FTIR ($CHCl_3$) 3419, 1705 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.15 (2H, m), 2.25 (1H, bs), 2.85 (1H, d, $J = 16.5$ Hz), 3.16 (1H, dd, $J = 16.5$, 6.9 Hz), 3.70 (3H, s), 3.97 (1H, d, $J = 6.8$ Hz), 4.42 (1H, m), 7.13 (1H, t, $J = 6.8$ Hz), 7.25 (1H, t, $J = 6.9$ Hz), 7.33(1H, d, $J = 8.1$ Hz), 7.50 (1H, d, $J = 7.8$ Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 25.80, 29.26, 31.38, 34.86, 44.86, 59.66, 106.42, 108.80, 118.70, 119.23, 121.56, 126.44, 135.07, 136.89, 210.53; EIMS (*m*/*e*, relative intensity) 240 (M^+, 28), 183 (100), 168 (17). Anal. Calcd for $C_{15}H_{16}N_2O \cdot 0.25H_2O$: C, 73.59; H, 6.79; N, 11.44. Found: C, 73.60; H, 6.57; N, 11.19.

Alkylation of (6*S*,10*S*)-5-Methyl-9-oxo-12*H*-6,7,8,9,10,-11-hexahydro-6,10-iminocyclooct[*b*]indole (42) To Provide (6*S*,10*S*)-5-Methyl-9-oxo-12-((*Z*)-2′-iodo-2′-butenyl)-6,7,8,9,10,11-hexahydro-6,10-iminocyclooct[*b*]indole (43). A solution of N_a-methyl, N_b-H tetracyclic ketone **42** (10.0 g, 41.7 mmol) and (*Z*)-1-bromo-2-iodo-2-butene (15.1 g, 58.2 mmol) was dissolved in THF (200 mL). At this point, K_2CO_3 (31.5 g, 228.3 mmol) was added, and the mixture was heated at 60 °C for 24 h. Analysis by TLC (silica gel, $CHCl_3$/MeOH = 6:1) indicated the absence of tetracyclic ketone. The K_2CO_3 was removed by filtration, and the solid was washed with EtOAc (3 × 100 mL). The solvent was removed from the combined organic layers under reduced pressure after which the crude product was purified by chromatography on silica gel (EtOAc/hexanes = 15:1) to provide N_b-(*Z*)-2′-iodo-2′-butenyl tetracyclic ketone **43** (14.95 g, 85%): ^1H NMR (300 MHz, $CDCl_3$) δ 1.84 (3H, d, $J = 6.4$ Hz), 2.10 (2H, m), 2.53 (2H, m), 2.78 (1H, d, $J = 17.0$ Hz), 3.16 (1H, dd, $J = 16.9$, 6.6 Hz), 3.44 (2H, s), 3.69 (3H, s), 3.78 (1H, d, $J = 6.4$ Hz), 4.21 (1H, m), 5.94 (1H, q, $J = 6.4$ Hz), 7.15 (1H, t, $J = 6.9$ Hz), 7.26 (1H, t, $J = 6.9$ Hz), 7.36 (1H, d, $J = 8.2$ Hz), 7.50 (1H, d, $J = 7.7$ Hz); ^{13}C NMR (75.5 Hz, $CDCl_3$) 20.58, 21.87, 29.35, 34.15, 48.86, 63.30, 63.90, 105.73, 108.89, 118.18, 119.35, 121.72, 126.20, 137.14, 209.80; EIMS (*m*/*e*, relative intensity) 420 (M^+, 35), 363 (100), 293 (8.5), 183 (35). Anal. Calcd for $C_{19}H_{21}N_2OI$: C, 54.30; H, 5.04; N, 6.67. Found: C, 54.06; H, 5.17; N, 6.47.

Palladium-Catalyzed Cyclization of (6*S*,10*S*)-5-Methyl-9-oxo-12-((*Z*)-2′-iodo-2′-butenyl)-6,7,8,9,10,11-hexahydro-6,10-iminocyclooct[*b*]indole (43) To Provide 3-Ethylidene-12-methyl-1,3,4,7,12,12b-hexahydro-2*H*,6*H*-2,6-methanoindolo[2,3-*a*]quinolizin-13-one (44). A mixture of N_b-(*Z*)-2′-iodo-2′-butenyl tetracyclic ketone **43** (3.0 g, 7.14 mmol), $Pd(OAc)_2$ (47 mg, 0.21 mmol), Bu_4NBr (1.88 g, 7.14 mmol), PPh_3 (566 mg, 2.14 mmol), and K_2CO_3 (3.98 g, 28.56 mmol) was placed in a solution of DMF−H_2O (9:1, 131 mL) after which it was degassed under reduced pressure at rt. The mixture was then heated to 70 °C (oil bath temperature) for 40 h under an

atmosphere of Ar. Analysis by TLC (silica gel, $CHCl_3$/MeOH = 9:1) indicated the absence of N_b-(*Z*)-2′-iodo-2′-butenyl tetracyclic ketone **43** and the presence of a new indole component of lower R_f value. The mixture was cooled to rt, diluted with EtOAc (1000 mL), washed with H_2O (5 × 200 mL), and dried (K_2CO_3). The solvent was removed under reduced pressure, and the oil that resulted was purified by chromatography on silica gel ($CHCl_3$/MeOH = 20:1) to provide pentacyclic ketone **44** (1.69 g, 82%): $[\alpha]_D = -145.07$ (*c* 0.43, $CHCl_3$); FTIR ($CHCl_3$) 1721 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.68 (1H, d, *J* = 6.9 Hz), 2.18 (1H, dt, *J* = 12.7, 3.3 Hz), 2.57 (1H, ddd, *J* = 12.2, 11.0, 1.7 Hz), 3.10 (1H, dd, *J* = 15.6, 6.2 Hz), 3.37 (1H, d, *J* = 16.3 Hz), 3.42 (1H, m), 3.58 (3H, s), 3.67 (1H, d, *J* = 5.4 Hz), 3.96 (2H, m), 4.48 (1H, d, *J* = 9.4 Hz), 5.56 (1H, q, *J* = 6.9 Hz), 7.11 (1H, t, *J* = 7.5 Hz), 7.22 (1H, t, *J* = 6.9 Hz), 7.28 (1H, d, *J* = 8.1 Hz), 7.51 (1H, d, *J* = 7.5 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.65, 22.33, 29.25, 35.49, 44.11, 49.69, 55.39, 64.11, 104.40, 108.76, 118.52, 119.14, 119.52, 121.54, 126.40, 132.07, 136.93, 137.40, 215.77; EIMS (*m*/*e*, relative intensity) 292 (M^+, 100). Anal. Calcd for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.89; N, 9.58. Found: C, 78.45; H, 6.87; N, 9.24.

Conversion of the Pentacyclic Ketone 44 into (+)-3-Ethylidene-12-methyl-1,3,4,7,12,12b-hexahydro-2*H*,6*H*-2,6-methanoindole[2,3-α]quinolizine-13-carboxaldehyde [N_a-Methylvellosimine (8)] via the Wittig Reaction Followed by Acid-Mediated Hydrolysis. A mixture of anhydrous potassium *tert*-butoxide (6.73 g, 0.06 mol) and methoxymethyltriphenylphosphonium chloride (17.1 g, 0.05 mol) in dry benzene (400 mL) was allowed to stir at rt for 1 h. The pentacyclic ketone **44** (2 g, 6.9 mmol) in THF (100 mL) was then added to the above orange solution dropwise at rt. The mixture that resulted was stirred at rt for 24 h. The mixture was diluted with EtOAc (1000 mL), washed with H_2O (3 × 200 mL) and brine (2 × 200 mL), and dried (K_2CO_3). The solvent was removed under reduced pressure to afford an oil. The baseline materials were removed by quick filtration through a column of silica gel. The solvent was removed under reduced pressure, and the residue was dissolved (without further purification) in a solution of aq HCl (2 N) in H_2O−THF (1:1, 400 mL). The solution that resulted was stirred at 55 °C (oil bath temperature) under an atmosphere of argon for 6 h (the reaction progress was monitored by ^1H NMR spectroscopy). The reaction mixture was cooled to 0 °C and extracted with ethyl ether (5 × 100 mL) to remove phosphorus-based byproducts, and the water layer was then brought to pH 8 with an ice-cold aqueous solution of NaOH (1 N). The aqueous layer was extracted with CH_2Cl_2 (3 × 1 L), and the combined organic layers were washed with H_2O (3 × 100 mL) and brine (100 mL) and dried (K_2CO_3). The solvent was removed under reduced pressure to afford an oil that was crystallized to provide N_a-methylvellosimine (**8**) (1.89 g, 90%): $[\alpha]_D = +98.0$ (*c* 0.50, $CHCl_3$) [lit.[100] $[\alpha]_D = +23$ (*c* 0.01, $CHCl_3$)]; FTIR ($CHCl_3$) 2911, 1709, 1469 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.64 (3H, d, *J* = 6.8), 1.85 (1H, m), 2.20 (1H, ddd, *J* = 11.2, 9.9, 1.9 Hz), 2.56 (1H, d, *J* = 7.6 Hz), 2.66 (1H, dd, *J* = 15.8, 1.1 Hz), 3.27 (2H, m), 3.60 (3H, s), 3.76 (3H, m), 4.46 (1H, d, *J* = 9.4 Hz), 5.42 (1H, q, *J* = 7.0 Hz), 7.12 (1H, t, *J* = 7.9 Hz), 7.21 (1H, t, *J* = 8.2 Hz), 7.48 (2H, d, *J* = 7.7 Hz), 9.58 (1H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.62, 26.29, 26.71, 29.31, 31.88, 49.45, 50.74, 54.43, 55.73, 102.89, 108.90, 118.24, 119.16, 121.37, 126.84, 128.37, 131.28, 132.06,137.38, 201.43; EIMS (*m*/*e*, relative intensity) 306 (M^+, 68), 277 (91), 196 (20), 183 (100), 182 (76), 168 (43). Anal. Calcd for $C_{20}H_{22}N_2O$·1/9 H_2O: C, 77.92; H, 7.14; N, 9.09. Found: C, 77.78; H, 7.21; N, 8.96. The spectral data were in complete agreement with the literature values.

Conversion of the N_a-Methylvellosimine (8) into N_a-Methyl-16-epipericyclivine (9). Aldehyde **8** (50 mg, 0.16 mmol) was dissolved in anhydrous MeOH (2 mL), and solutions of KOH (2.6 equiv, 27.3 mg, 0.416 mmol) and iodine (1.3 equiv, 52.4 mg, 0.208 mmol) in anhydrous MeOH (each 0.5 mL) were successively added at 0 °C. After 2 h, the reaction was quenched by adding AcOH to neutralize the solution to pH 7. The solution was diluted with CH_2Cl_2, washed with 10% $Na_2S_2O_3$ (20 mL) and brine (2 × 20 mL), and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue that resulted was purified by chromatography on silica gel ($CHCl_3$/MeOH = 40:1) to provide ester **9** (52 mg, 94%): $[\alpha]_D = +22.8$ (*c* 0.50, $CHCl_3$) [lit.[47] $[\alpha]_D = 0$ (*c* 0.50, $CHCl_3$)]; IR (KBr) 1730, 1470 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.64 (3 H, dt, *J* = 6.8, 1.9 Hz), 1.76 (1 H, ddd, *J* = 12.6, 2.6, 1.4 Hz), 2.18 (1 H, ddd, *J* = 12.2, 10.0, 1.9 Hz), 2.61 (1 H, dd, *J* = 7.8, 1.4 Hz), 2.74 (1 H, dd, *J* = 15.8, 1.0 Hz), 3.25 (2 H, m), 3.61 (3 H, s), 3.70 (3 H, s), 3.76 (3 H, m), 4.40 (1 H, d, *J* = 9.1 Hz), 5.42 (1 H, q, *J* = 6.7 Hz), 7.11 (1 H, ddd, *J* = 8.9, 7.9, 1.2 Hz), 7.23 (1 H, td, *J* = 6.9, 1.2 Hz), 7.29 (1 H, d, *J* = 7.7 Hz), 7.50 (1 H, d, *J* = 7.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.69, 26.80, 28.28, 29.30, 32.11, 46.50, 48.98, 51.74, 53.00, 55.82, 103.10, 108.82, 117.89, 118.22, 119.03, 121.21, 126.99, 132.67, 137.36, 137.88, 173.39; EIMS (*m*/*e*, relative intensity) 336 (M^+, 82), 277 (21), 241 (21), 182 (100), 168 (36). Anal. Calcd for $C_{21}H_{24}N_2O_2$: C, 74.97; H, 7.19; N, 8.33. Found: C, 74.72; H, 6.85; N, 7.97.

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Supporting Information Available: A complete description of experimental details and characterization data for compounds **20**, **21**, **22b**, **29**, and **31**; details of X-ray structures and data for **2** and **37**. This material is available free of charge via the Internet at http://pubs.acs.org.

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