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A General Strategy for the Synthesis of Vincamajine-Related Indole Alkaloids: Stereocontrolled Total Synthesis of (+)-Dehydrovoachalotine, (−)-Vincamajinine, and (−)-11-Methoxy-17-epivincamajine as Well as the Related Quebrachidine Diol, Vincamajine Diol, and Vincarinol[1]

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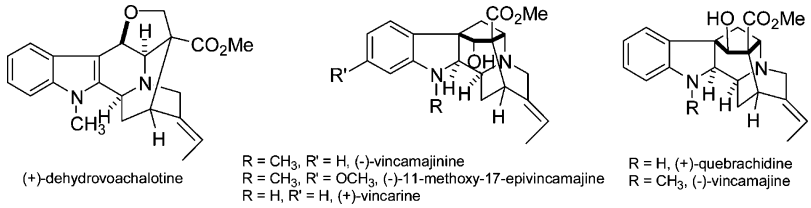
Received November 8, 2004



The highly convergent stereocontrolled total synthesis of (−)-vincamajinine (**7**), (−)-11-methoxy-17-epivincamajine (**9**), and the oxygen-bridged (+)-dehydrovoachalotine (**22**) are described. Key steps in the synthesis of **7** and **9** involved the stereospecific enolate-driven palladium-catalyzed cross-coupling reaction, a Tollens reaction, an acid-assisted intramolecular cyclization to form the C(7)−C(17) quaternary center, and two stereospecific reductions. The efficiency of this strategy is illustrated by the completion of the synthesis of **7** and **9** in 16 [from D-(+)-tryptophan methyl ester **17**] and 17 (from the Schöllkopf chiral auxiliary **27**) reaction vessels, respectively. This constitutes the first total synthesis of these indole alkaloids and provides the first regiospecific route to 11-methoxy-substituted ajmaline/vincamajine-related alkaloids. The synthesis of **22** required a novel DDQ-mediated cyclization to furnish the C(6)−O(17) bond, executed in stereospecific fashion. Completion of these syntheses illustrates a concise and versatile strategy for the synthesis of vincamajine-related alkaloids, which has also been employed to prepare the related compounds quebrachidine diol (**53**), vincamajine diol (**56**), and vincarinol (**59**).

Introduction

Indole alkaloid natural products are an important source of biologically active compounds.[2,3] Ajmaline-related indole alkaloids contain the polycyclic ajmaline ring system, the *E*-olefinic C(19)−C(20) unsaturated members of which belong to the sarpagine, vincamajine, and quebrachidine series.[4]

While more than 84 ajmaline/vincamajine/quebrachidine indole alkaloids have been isolated, which includes the bisindoles which contain at least one monomeric ajmaline/vincamajine/quebrachidine unit, those which contain a carbomethoxy group at C(16) form a unique series (Figure 1).[5] Studies by Houghton et al.[6] 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. (+)-Alstomacroline (**1**), a bisindole alkaloid, was isolated from the root bark of *A. macrophylla* collected in Thailand and exhibited potent activity against drug-resistant strains of malaria para-

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(1) Portions of this work were communicated earlier; see: (a) Yu, J.; Wearing, X. Z.; Cook, J. M. *J. Am. Chem. Soc*. **2004**, *126*, 1358−1359. (b) Yu, J.; Wearing, X. Z.; Cook, J. M. *Tetrahedron Lett*. **2004**, *45*, 3937−3940.

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(4) The "biogenetic numbering" of indole alkaloids is used in the text; see: Le Men, J.; Taylor, W. I. *Experientia* **1965**, *21*, 508−510.

(5) For a recent review, see: Lounasmaa, M.; Hanhinen, P. The Ajmaline Group of Indole Alkaloids. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: San Diego, 2001; Vol. 55, Chapter 1, pp 1−87.

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10.1021/jo040282b CCC: $30.25
Published on Web 04/19/2005

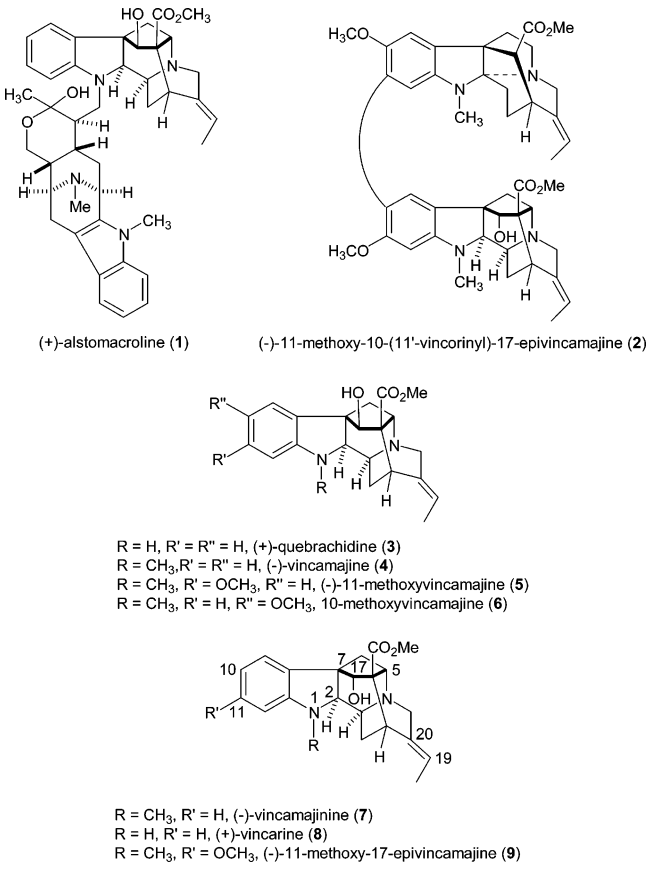

FIGURE 1. Vincamajine-related group of indole alkaloids.

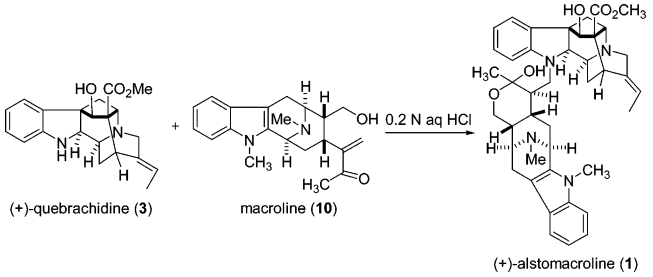

FIGURE 2. Formation of (+)-alstomacroline (**1**).[8]

sites (IC_{50} of 1.12 μM against the K1 strain of *Plasmodium falciparum*).[6,7] A partial synthesis of **1** was reported by Le Quesne et al.[8] via a biomimetic coupling process by condensation of the two components, (+)-quebrachidine (**3**) and macroline (**10**) (Figure 2). The related bisindole alkaloid (−)-11-methoxy-10-(11′-vincorinyl)-17-epivincamajine (**2**) was isolated in 1992 from the leaves of *Tonduzia pettieri* (*Alstonia pettieri*),[9a] accompanied by the monomeric base (−)-11-methoxy-17-epivincamajine (**9**).[9] The latter two alkaloids have not been evaluated for antimalarial activity to date. (+)-Quebrachidine (**3**), reported to show psychosedative and adrenergic activity,[10] was first isolated in 1963 from the extract of the basified ground leaves of *Aspidosperma quebracho-blanco*[11] and later from many other species.[10,12] The related (−)-vincamajine (**4**), an N_a-methyl analogue of (+)-quebrachidine, has also been obtained from many species.[12e,g,j,l,13] Both (−)-11-methoxyvincamajine (**5**)[9b] and 10-methoxyvincamajine (**6**)[12d,14] have only been isolated from *Alstonia* species. The isolation of (−)-vincamajinine (**7**, 17-epivincamajine) from the aerial parts of *Vinca major* was reported by Zhukovich and Vachnadze in 1985.[15] (+)-Vincarine (**8**), an N_a-H analogue of (−)-vincamajinine, was isolated from *Vinca erecta*, *Vinca herbacea*, and *Vinca major*.[16] The constitution and relative configuration of these indole alkaloids were determined on the basis of NMR studies and chemical correlation or confirmed by chemical conversion and spectral data.[9−16] These indole alkaloids typically possess a unique rigid, caged hexacyclic carbon skeleton which contains seven stereogenic centers (carbons 2, 3, 5, 7, 15, 16, and 17) as well as the key olefinic bond at C(19)−C(20) in the *E*-configuration. However, the configuration of the C(17)-hydroxyl group in **3**−**6** [17(*S*)] is different from that in **7**−**9** [17(*R*)]. Due to the paucity of these natural

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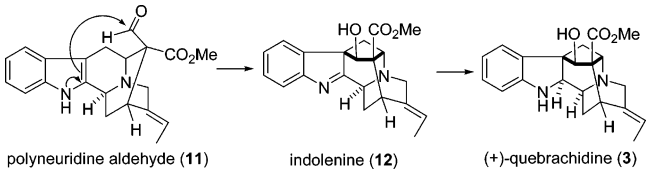


FIGURE 3. Postulated biogenesis of the vincamajine-related indole alkaloids.

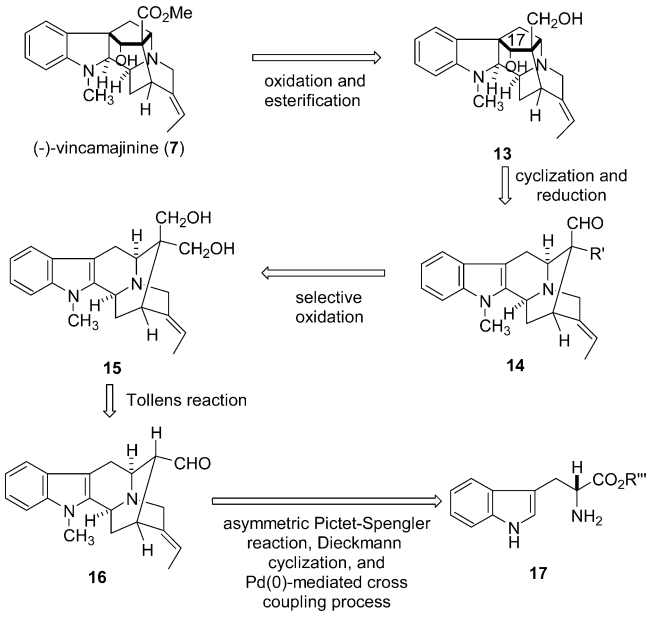
compounds isolated to date, biological activity has not been reported for alkaloids **4**−**9**.

The complex architecture of the above-mentioned indole alkaloids, coupled with their largely unexplored potential in medicine or as tools for biological studies, rendered these indoles as attractive targets for total synthesis. An approach to the synthesis of (−)-**3** has been described by Martin et al.;[17] however, no total synthesis of **1**−**9** has yet been reported. Herein, we provide a detailed account of the first synthesis of (−)-vincamajinine (**7**), the 11-methoxy analogue (−)-**9**, and (+)-dehydrovoachalotine (**22**)[18] as well as the preparation of the related compounds, (+)-quebrachidine diol (**53**), (+)-vincamajine diol (**56**), and (+)-vincarinol (**59**).

Results and Discussion

Synthetic Plan. Close inspection of the structures of these indole alkaloids (**1**−**9**) indicated the major challenges for the syntheses included the generation of the C(16) quaternary carbon center, complete control of the stereochemistry at C(2) and C(17), stereospecific generation of the C(19)−C(20) ethylidene function in the *E*-configuration, and development of an efficient route for the preparation of the rigid caged hexacyclic system which contained a C(16) carbomethoxy group. Most notably, a biogenetic scheme for formation of the these indole alkaloids has been reviewed by Lounasmaa et al.[19] which included the proposals of Bartlett, Taylor,[20] and van Tamelen,[21] amenable perhaps to formation of the quaternary C(7)−C(17) bond. As illustrated in Figure 3, cyclization of polyneuridine aldehyde (**11**) was postulated to occur by intramolecular cyclization to furnish the hexacyclic ring system in indolenine (**12**) which could stereoselectively be reduced by an NAD(P)-H-assisted process from the *si* face to provide (+)-**3**.[19] As a means to construct the strained hexacyclic framework, this biomimetic intramolecular cyclization was attractive as long as a stereospecific means to introduce the C(17) hydroxyl group could be developed. It was believed that experimental conditions could be found to take advantage of the vicinal location of the nucleophilic β-position of the indole nucleus and the electrophilic aldehyde following the elegant work of Bartlett, Taylor, and van Tamelen.[20,21]

SCHEME 1. Retrosynthetic Analysis of (−)-Vincamajinine (7)



The disconnection strategy summarized in Scheme 1 (for vincamajinine **7**) envisioned here involved oxidation of the C(16)-hydroxymethyl function of diol (**13**) available from the acid-assisted reductive cyclization of **14** via the previous contributions of Bartlett, Taylor, and van Tamelen.[20,21] The latter aldehyde **14** contained four of the seven stereogenic centers in **7** as well as the olefinic bond at C(19)−C(20) in the *E* configuration. Since the synthetic strategy for the formation of the C7−C17 bond of **13** was based on the treatment of aldehyde **14** under acidic conditions, the presence of an aldehydic group at the desired axial position (C-17) and a quaternary carbon center at C(16) in **14** rendered the formation of the quaternary carbon center at C(16) a pivotal process in this strategy. As illustrated, disconnection of aldehyde **14** unveiled N_a-methylvellosimine **16** (via **15**) as a putative synthetic precursor. It was believed that the quaternary center of aldehyde **14** could be obtained from aldehyde **16** via the Tollens reaction[22] in one step and the diol **15**, which resulted, might be selectively oxidized to give **14** in a stereoslective fashion. The required **16**, in turn, had earlier been constructed in our laboratories.[23] Efforts that resulted in completion of this strategy are described below.

Construction of the Hexacyclic Core 13 Required for the Synthesis of (−)-Vincamajinine (7). The stereocontrolled total synthesis of (−)-**13** began with the readily available N_a-methylvellosimine **16** obtained from D-(+)-tryptophan methyl ester in stereospecific fashion in eight reaction vessels in 39% overall yield.[23] This had been previously achieved via a combination of the asymmetric Pictet−Spengler reaction, Dieckmann cyclization,

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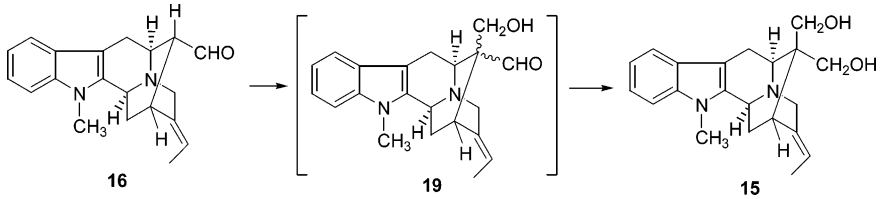
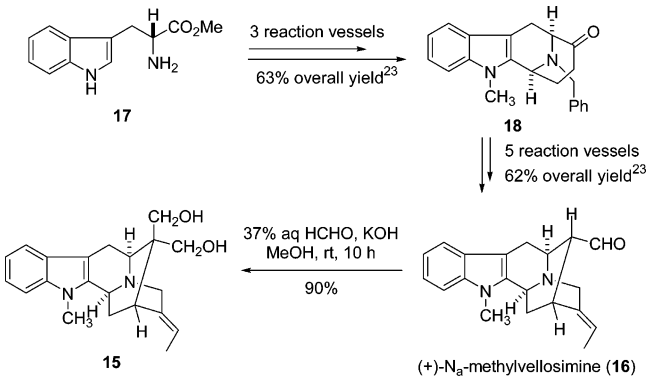
TABLE 1. Reaction Conditions for the Formation of Diol 15 via the Tollens Reaction



entry	condition	reaction time (h)	isolated yield (%)
1	37% aq HCHO (5 equiv), KOH (2 N, 10 equiv), MeOH, rt	60	85
2	37% aq HCHO (15 equiv), KOH (2 N, 10 equiv), MeOH, rt	40	88
3	37% aq HCHO (25 equiv), KOH (2 N, 10 equiv), MeOH, rt	10	90
4[28]	37% aq HCHO (123 equiv), Na_2CO_3 (3 equiv), MeOH/CH_2Cl_2 (2:1), rt	60	no reaction
5[29]	$(HCHO)_n$ (8 equiv), K_2CO_3 (8 equiv), MeOH, reflux	60	no reaction

SCHEME 2. Stereocontrolled Synthesis of the (−)-Vincamajinine (7) Core



and stereocontrolled intramolecular enolate driven palladium-mediated cross-coupling reaction (Scheme 2). The latter was reported in the total synthesis of vellosimine by Wang et al.[24] This synthetic strategy was executed efficiently to provide intermediate **16** in gram quantities.[23] Alternatively, Martin et al.[25] reported an enantioselective route for the synthesis of **16** via a biomimetic pathway. With gram quantities of (−)-**16** in hand, numerous efforts (aldolizations, alkylations, and acylations) were originally carried out to construct the quaternary carbon center at C-16, but they were not successful.[26,27] Gratifyingly, it was found that the aldehydic group at C-16 could be converted into diol **15** in 85% yield via the Tollens reaction[22] with 37% aqueous formaldehyde (5 equiv) and KOH (10 equiv) in methanol, as shown in Table 1. The prochiral quaternary carbon center at C-16, which contained the structurally hindered diol in **15**, was constructed in one step. More importantly, because of the symmetry of the two diol moieties at C-16, generation of a new chiral center with expensive reagents was avoided. Encouraged by this result, attention turned toward reduction of the reaction time for the Tollens process. The amount of 37% aqueous formaldehyde was, therefore, increased to facilitate the formation of **15** from intermediate **19**. This increase in the concentration of formaldehyde accelerated the reaction rate (Table 1, entries 2 and 3), as expected, and also slightly increased the yield. While this work was in progress, conditions appeared for two other recent examples of the Tollens reaction.[28,29] Examination of these new conditions (entries 4[28] and 5[29]), unfortunately, resulted in no reaction in this system. As illustrated in Table 1, use of the conditions reported here (entries 1−3, Table 1) provided excellent yields of the C(16) quaternary diol **15**.

With the success of the synthesis of diol **15**, the synthesis of many sarpagine-related indole alkaloids which contain a C-16 quaternary center might be realized.[30] Herein an example for the voachalotine series is illustrated which resulted in the stereospecific synthesis of the C(6)−O(17) oxygen-bridged alkaloid (+)-dehydrovoachalotine (**22**).[1b] Oxidative cyclization of diol **15** effected by DDQ[18c,31−35] in THF afforded ether **20** in 95% yield (Scheme 3). The remaining hydroxyl moiety of cyclic ether **20** was converted into the corresponding aldehyde **21** via intramolecular oxidation with $(PhSeO)_2O$/PhCl analogous to previous work of Barton et al.[36] and Trudell et al.[37] The aldehyde so formed was further oxidized with KOH/I_2/MeOH by the procedure of Yamada, Yamamoto, et al.[38] to deliver the methyl ester **22** in 90% yield. The optical rotation [$[\alpha]^{26}_D$ +125.0 (lit.[18] $[\alpha]^{26}_D$ $[\alpha]^{26}_D$ +124±2)] and spectroscopic properties of synthetic (+)-**22** were in excellent agreement with those of natural (+)-dehydrovoachalotine.[18]

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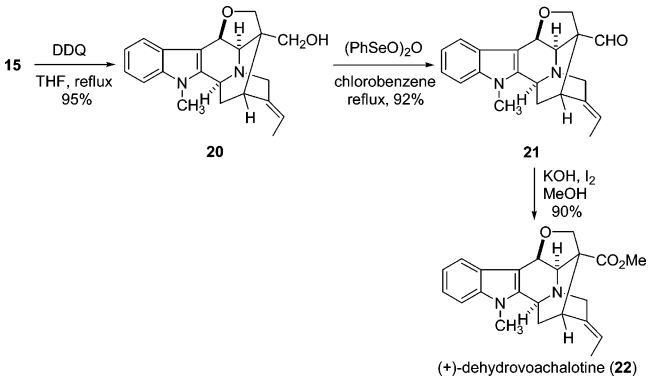
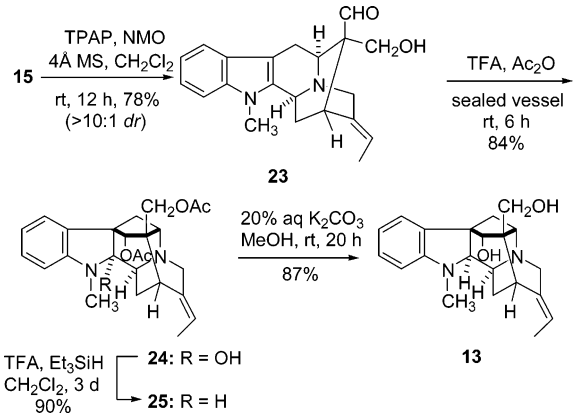
(38) Yamada, S.; Morizano, D.; Yamamoto, K. *Tetrahedron Lett*. **1992**, *33*, 4329−4332.

SCHEME 3. Total Synthesis of (+)-Dehydrovoachalotine (22)



SCHEME 4. Stereocontrolled Synthesis of the Core Structure of (−)-Vincamajinine (7)



With the key C(16) bis-hydroxymethyl intermediate **15** in hand, selective conditions for the oxidation of the 16-hydroxymethyl group present in the axial (β) position, in contrast to oxidation of the equatorial (α) hydroxymethyl group, were required. This was realized on stirring **15** with tetrapropylammonium perruthenate (TPAP)[39] to provide the desired aldehyde **23** with >10:1 diastereoselectivity in 78% yield. This oxidation was a key process required for synthesis of **7** or **9**. When β-aldehyde **23** was dissolved in a mixture of TFA/Ac_2O, the conjugate acid of the aldehyde was sufficiently electrophilic to cyclize to the indoleninium salt, which was trapped as the diacetate **24** by Ac_2O.[40] This cyclization stereospecifically provided the 17(*S*) stereochemistry in **24** in 84% yield. The use of trifluoroacetic acid was key to the stereoselectivity in this process. This reagent provided the kinetic product while cyclization of **23** with Ac_2O/HCl(g) gave the thermodynamic 17(*R*) isomer, although the ds was not 100%. Acid-assisted reduction of the carbinolamine function in **24** with Et_3SiH/TFA[41] furnished the C2(α)-H stereochemistry in indolinine **25** from the bottom face as the sole product in 90% yield. Thus, the required caged congested hexacyclic ring system, which contained the desired 17(*R*) hydroxyl function, and the C2(α)-H were efficiently constructed from **15** in three steps. To this end, further hydrolysis of diacetate **25** under basic conditions gave diol **13** in 85% yield (Scheme 4).

Construction of the Hexacyclic Core 45 Required for the Synthesis of (−)-11-Methoxy-17-epivincamajine (9). Since the hexacyclic core of **13** was efficiently synthesized from D-(+)-tryptophan methyl ester, the 6-methoxy-D-tryptophan ethyl ester (**30**) was chosen as the chiral transfer agent and starting material for the synthesis of **9**. Because of the D-stereochemistry in **30** required for the asymmetric Pictet−Spengler reaction, the Schöllkopf chiral auxiliary required for the asymmetric induction would be prepared from the inexpensive L-valine. As shown in Scheme 5, iodoaniline **26** and the propargyl unit **27**,[42] which had been prepared on a 200 g scale with high diasteroselectivity from the readily available Schöllkopf chiral auxiliary, underwent Larock heteroannulation[43] in the presence of $Pd(OAc)_2$, K_2CO_3, and LiCl in DMF at 100 °C to provide the protected 6-methoxytryptophan **28** in 77% yield on 300 g scale. The N_a-methyl analogue **29** was obtained in 95% yield simply by methylation of the indole N_a-H function with MeI and NaH. Hydrolysis of the Schöllkopf chiral auxiliary in **29** in aqueous 2 N HCl in EtOH, accompanied by concomitant loss of the indole-2-silyl group, provided optically active N_a-methyl-6-methoxy-D-tryptophan ethyl ester **30** in 93% yield. Since the 2-iodo-5-methoxyaniline **26** and the propargyl unit **27** could be readily prepared on a large scale (>200 g), this provided an efficient route to synthesize 6-methoxy-D-tryptophan with high diastereoselectivity.[44] With N_a-methyl-6-methoxy-D-tryptophan ethyl ester **30** in hand, the 11-methoxy tetracyclic ketone **35** was prepared, as illustrated in Scheme 6. The primary amine in **30** was converted into the N_b-benzyl ester **31** by reductive amination in high yield. The optical purity of this N_b-benzyltryptophan **31** was determined to be greater than 98% ee by comparison of the optical rotation with that of an authentic sample.[45] The Pictet−Spengler condensation between the aldehyde **32** and the N_b-benzylamine **31** was carried out in the presence of the catalyst (acetic acid/CH_2Cl_2) to afford a mixture (at C-1) of *trans* (**33b**) and *cis* (**33a**) diesters in nearly quantitative yield in a ratio of 72:28. If TFA/CH_2Cl_2 was employed in this process, significant decomposition of the starting 6-methoxytryptophan **31** was observed. In keeping with the mechanistic studies on the carbocation-mediated *cis*/*trans* isomerization,[44,46−48] when the Pictet−Spengler was

(39) For a review on TPAP/NMO oxidations, see: Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639−666.

(40) The first example of the intramolecular cyclization to form the hexacyclic ring system in the presence of Ac_2O/HCl(g)/AcOH was reported in the synthesis of ajmaline-related alkaloids; see: Bartlett, M. F.; Lambert, B. F.; Werblood, H. M.; Taylor, W. I. *J. Am. Chem. Soc*. **1963**, *85*, 475−477. These conditions did not work, however, in this case even after stirring for 5 days.

(41) (a) Li, J.; Wang, T.; Yu, P.; Peterson, A.; Weber, R.; Soerens, D.; Grubisha, D.; Bennett, D.; Cook, J. M. *J. Am. Chem. Soc*. **1999**, *121*, 6998−7010. (b) Li, J.; Cook, J. M. *J. Org. Chem*. **1998**, *63*, 4166−4167.

(42) Ma, C.; Liu, X.; Li, X.; Flippen-Anderson, J.; Yu, S.; Cook, J. M. *J. Org. Chem*. **2001**, *66*, 4525−4542.

(43) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc*. **1991**, *113*, 6689−6690.

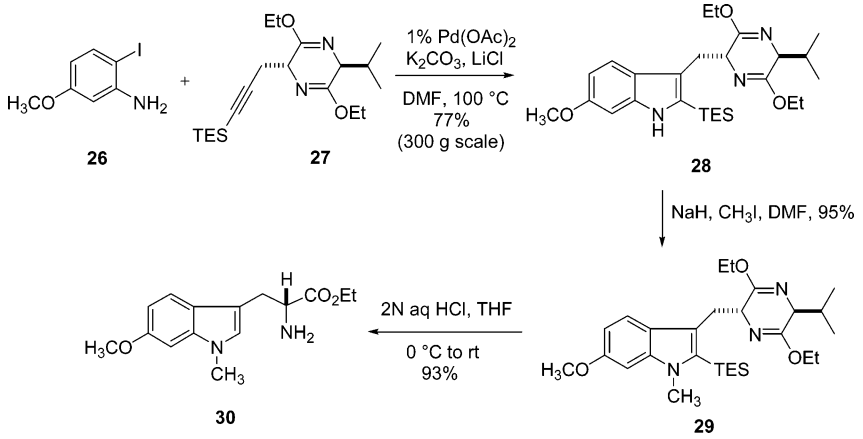
(44) (a) Liu, X.; Deschamps, J. R.; Cook, J. M. *Org. Lett*. **2002**, *4*, 3339−3342. (b) Wearing, X. Z.; Cook, J. M. 225th ACS National Meeting, New Orleans, LA, March 23−27, 2003; American Chemical Society: Washington, DC, 2003; ORGN 412.

(45) Liu, X. Ph.D. Thesis, University of Wisconsin−Milwaukee, 2002.

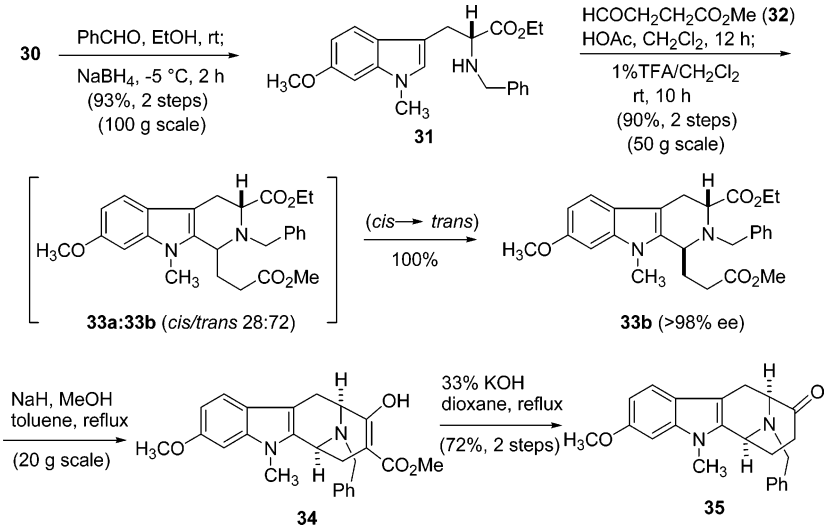
(46) Cox, E. D.; Hamaker, L. K.; Li, J.; Yu, P.; Czerwinski, K. M.; Deng, L.; Bennett, D. W.; Cook, J. M.; Watson, W. H.; Krawiec, M. *J. Org. Chem*. **1997**, *62*, 44−61.

(47) Cox, E. D.; Cook, J. M. *Chem. Rev*. **1995**, *95*, 1797−1842.

SCHEME 5. Synthesis of N_a-Methyl-6-methoxy-D-tryptophan Ethyl Ester (30)



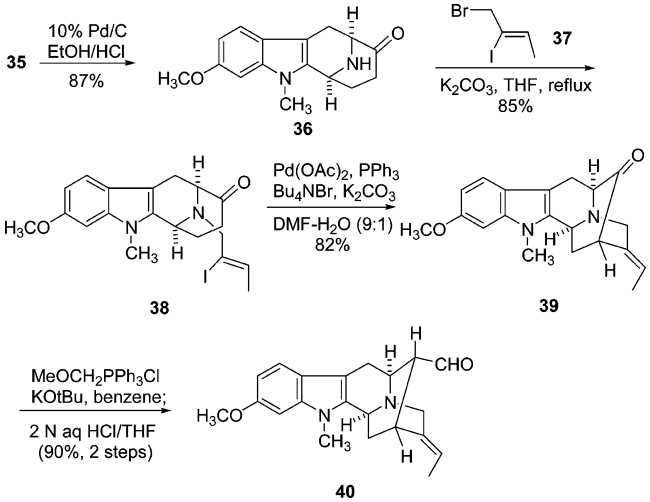
SCHEME 6. Synthesis of the 11-Methoxy Tetracyclic Ketone (35)



completed, a small amount of TFA was added to the reaction mixture after which epimerization of the stereocenter at C(1) of this *cis* diastereomer **33a** took place to give the desired *trans* diastereomer **33b** as the single isolable diastereomer. This isomerization took place in 10 h at a much faster rate than the parent 11-(H) analogue.[44,48] Dieckmann cyclization of the *trans* diester **33b**, followed by base-mediated hydrolysis/decarboxylation in a one-pot process then provided the key tetracyclic ketone **35** in 85% overall yield. The synthesis of this key ketone **35** could then be carried out in a two-pot fashion (from **28**) and was accomplished (from iodoaniline **26**) in five reaction vessels in an overall yield of 46%.

With an efficient synthesis of the 11-methoxytetracyclic ketone **35** in hand, attention turned to the synthesis of 16-*epi*-N_a-methyl gardneral **40**, a base previously obtained by Sakai from the degradation of gardnerine.[49] As illustrated in Scheme 7, the N_b-benzyl group of **35** was removed via catalytic hydrogenation, and was followed by alkylation with (*Z*)-1-bromo-2-iodo-butene **37** to provide ketone **38** in an overall yield of 74% (two steps). When this ketone **38** was subjected to the conditions of

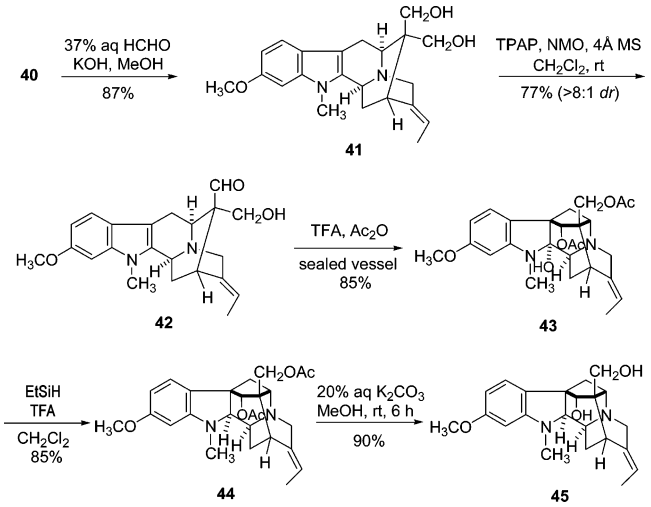
SCHEME 7. Synthesis of (+)-N_a-Methyl-16-epigardneral (40)



the enolate driven palladium-catalyzed intramolecular cyclization, the 11-methoxy pentacyclic ketone **39** was obtained in 82% yield in stereospecific fashion. This ketone **39** was then converted into 16-*epi*-N_a-methyl gardneral **40** in 90% yield via a Wittig reaction followed by hydrolysis.[44] The aldehyde **40** so formed, was subjected

(48) Zhao, S.; Liao, X.; Wang, T.; Flippen-Anderson, J.; Cook, J. M. *J. Org. Chem*. **2003**, *68*, 6279−6295.
(49) Sakai, S.; Yamamoto, Y.; Hasegawa, S. *Chem. Pharm. Bull*. **1980**, *28*, 3454−3456.

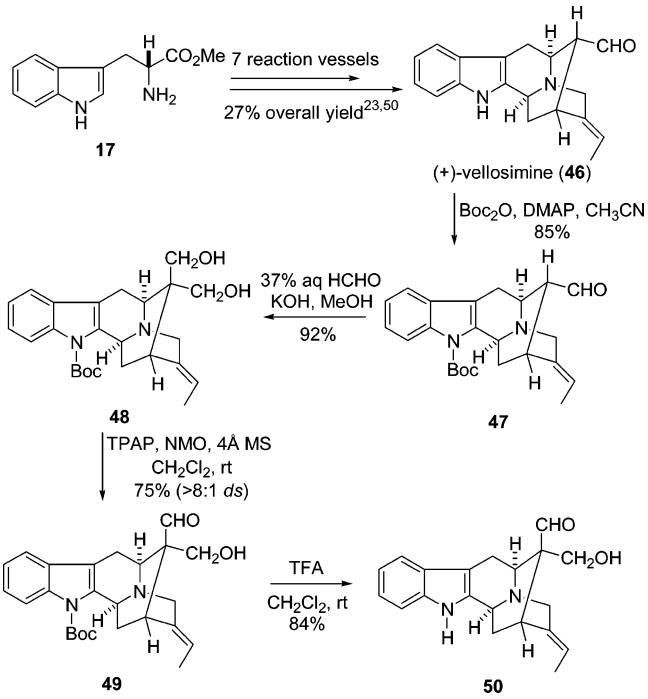
SCHEME 8. Stereocontrolled Synthesis of the Core of (−)-11-Methoxy-17-epivincamajine (9)



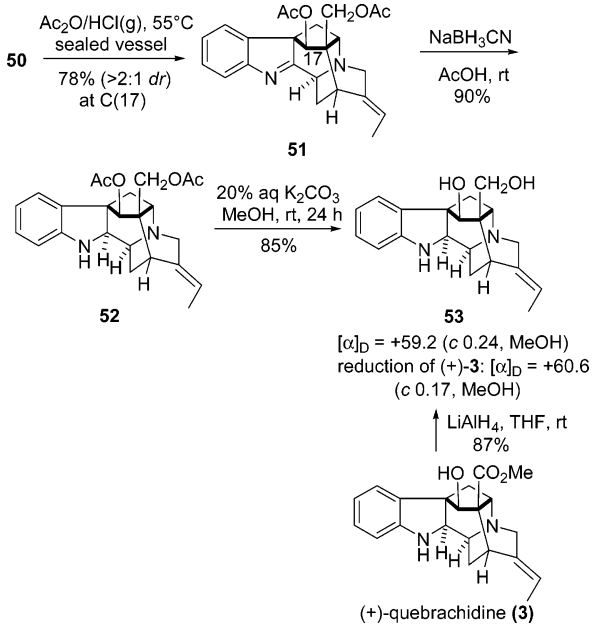
to the conditions of the Tollens reaction to afford diol **41** in 87% yield. This diol was selectively oxidized to give the desired β-aldehyde **42** via the TPAP-oxidation developed earlier in 77% yield (>8:1 dr), as depicted in Scheme 8. The acid-assisted cyclization of β-aldehyde **42** with TFA/Ac_2O stereospecifically provided the 17(*S*) stereochemistry in diacetate **43** in 85% yield. Further stereospecific reduction of carbinolamine **43** with Et_3SiH in the presence of TFA was executed in high yield and provided the crucial diacetate **44** in 85% yield. Hydrolysis of **44** with K_2CO_3 in MeOH furnished diol **45** in 90% yield, which contained the required seven stereogenic centers and the C(19)−C(20) *E*-olefinic bond. It is worthy of note that the *E*-configuration of this olefinic function is the thermodynamically less stable isomer, consequently the palladium-mediated cyclization was critical to its stereospecific formation.[23a]

Construction of the Hexacyclic Cores 53, 56, and 59 Necessary for the Synthesis of (+)-Quebrachidine (3), (−)-Vincamajine (4), and (+)-Vincarine (8). Since the synthesis of the congested hexacyclic cores **13** (for the synthesis of **7**) and **45** (for the synthesis of **9**) was successfully completed, attention turned to extension of this strategy to the synthesis of the hexacyclic cores of **3**, **4**, and **8**. As shown in Scheme 9, (+)-vellosimine (**46**) was chosen as the intermediate for the synthesis of the hexacyclic core of quebrachidine **3**. Thus, (+)-vellosimine (**46**), available in enantiospecific fashion in seven reaction vessels in 27% overall yield from D-(+)-tryptophan methyl ester,[23,50] was protected as the N_a-Boc intermediate in the presence of DMAP to afford **47** in 85% yield. The N_a-Boc-protected vellosimine **47** was next converted into the C(16)-quaternary diol **48** via the Tollens reaction, and this was followed by the TPAP oxidation to provide the desired β-aldehyde **49** with >8:1 diastereoselectivity in 69% overall yield for the two steps. The Boc group in **49** was removed using TFA in dichloromethane under standard conditions[51] to provide aldehyde **50** in 84% yield. The intramolecular cyclization of **50** occurred under modified conditions [Ac_2O/HCl(g)][20,21,40] to give the desired diacetate **51** [17(*R*)] with >2:1 diastereoselectivity in 52% yield (Scheme 10). The imine moiety of this intermediate was stereospecifically reduced using $NaBH_3CN$ in the presence of acid[52] and the acetate functions were hydrolyzed with aqueous K_2CO_3 to provide diol **53** in 77% overall yield (two steps). As anticipated, the spectroscopic data and optical rotation ($[\alpha]^{26}{}_D$ +59.2,

SCHEME 9. Stereocontrolled Synthesis of the Key 16-Hydroxymethyl-17-aldehydo Intermediate 50



SCHEME 10. Stereocontrolled Synthesis of (+)-Quebrachidine Diol 53

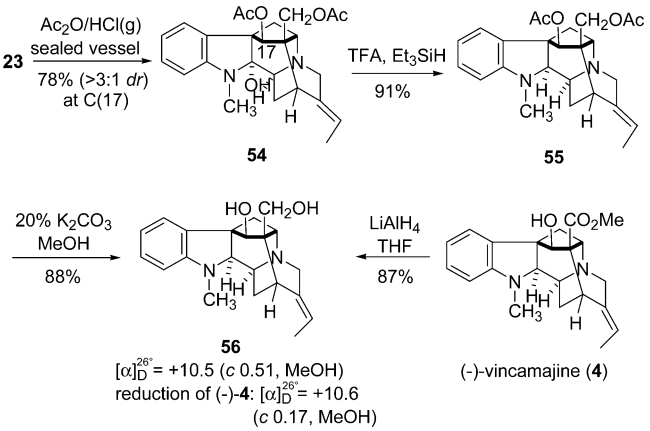


(50) Wang, T.; Cook, J. M. 219th ACS National Meeting, San Francisco, CA, March 26−30, 2000; American Chemical Society: Washington, DC, 2000; ORGN 752.

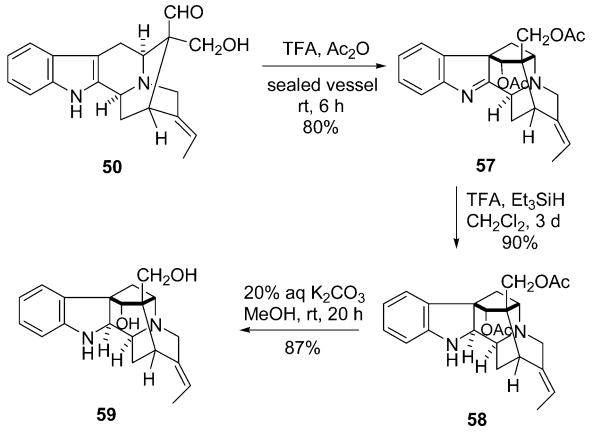
(51) Hanessian, S.; Faucher, A.-M. *J. Org. Chem.* **1991**, *56*, 2947−2949.

(52) Bornmann, W. G.; Kuehne, M. E. *J. Org. Chem.* **1992**, *57*, 1752−1760.

SCHEME 11. Stereocontrolled Synthesis of (+)-Vincamajine Diol 56



SCHEME 12. Stereocontrolled Synthesis of Vincarine Diol 59

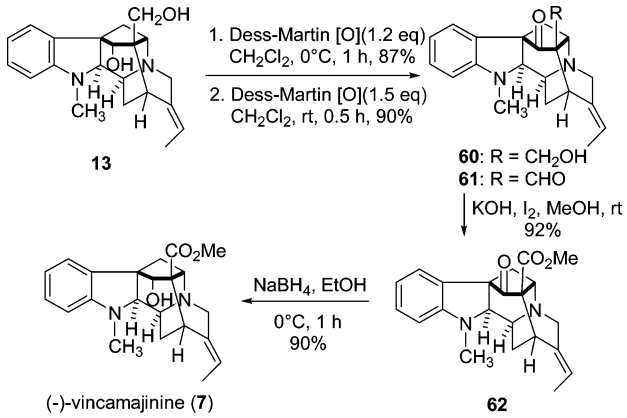


c 0.24, MeOH) of diol **53** were virtually identical to that of diol **53** ($[\alpha]^{26}{}_{D}$ +60.6, *c* 0.17, MeOH) obtained from reduction of natural (+)-quebrachidine (**3**) with $LiAlH_4$.[53] This strategy was also employed for the synthesis of the diol **56** in the vincamajine series (Scheme 11). Intramolecular cyclization of **23** using Ac_2O/HCl(g) (>3:1 dr), followed by reduction (Et_3SiH, TFA) and hydrolysis under basic conditions provided the diol **56** in 60% overall yield (three steps). Again, the spectral data and optical rotation of the synthetic diol **56** ($[\alpha]^{26}{}_{D}$ +10.5, *c* 0.51, MeOH) were in excellent agreement with an authentic sample of **56** ($[\alpha]^{26}{}_{D}$ +10.6, *c* 0.17, MeOH) obtained via the reduction of natural (−)-vincamajine (**4**) with $LiAlH_4$.[53]

Under the modified conditions (TFA/Ac_2O) developed for the synthesis of the hexacyclic cores of **13** and **45**, which contained the C-17(*R*) stereochemistry of the monol, treatment of aldehyde **50** with TFA/Ac_2O exclusively afforded the desired imine **57** in 82% yield (Scheme 12). The imine moiety of **57** was stereospecifically reduced using Et_3SiH/TFA and the acetate functions were hydrolyzed with aqueous K_2CO_3 to give diol **59** in 78% overall yield (two steps). The structure of vincarinol **59** was established with full characterization by ^1H and ^{13}C NMR, NOESY, NOE, MS, and IR spectroscopy. Furthermore, analysis indicated the proton signal at 17-H appeared at 4.10 ppm in diol **59** [17(*R*)] in contrast to the 17(*S*) stereochemistry (δ 4.30) of quebrachidine diol **53**. Thus, the hexacyclic cores contained in quebrachidine diol **53**, vincamajine diol **56**, and vincarinol **59** have been synthesized in an efficient manner, and these caged systems are available for the synthesis of the corresponding (+)-quebrachidine (**3**), (−)-vincamajine (**4**), and (+)-vincarine (**8**), respectively.

(53) Authentic samples of both (+)-quebrachidine (**3**) and (−)-vincamajine (**4**) were kindly provided by Professor Toh-Seok Kam (University of Malaya) and Professor Monique Zeches-Hanrot (University of Reims).

SCHEME 13. Completion of the Total Synthesis of (−)-Vincamajinine (7)



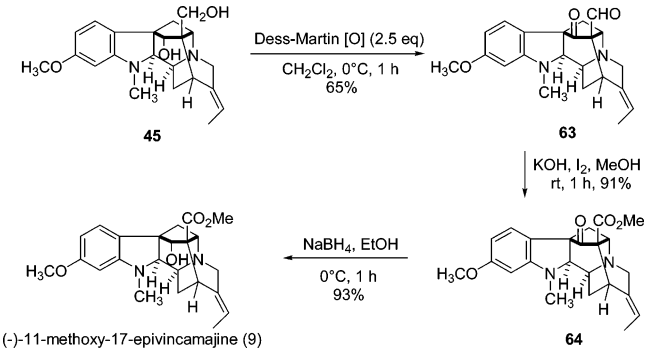
Completion of the Total Synthesis of (−)-Vincamajinine (7). The final steps required for the synthesis of vincamajinine (**7**) are shown in Scheme 13. Unexpectedly, diol **13** was labile to some conditions of oxidation [e.g., $(PhSeO)_2O$/Ph,[36,37] TPAP/NMO,[39] TEMPO/BAIB/CH_2Cl_2[54]] which ultimately resulted in cleavage of the C(7)−C(17) bond. Careful treatment of diol **13**, however, with Dess−Martin periodinane[55] furnished the ketone **60** with the C(16) primary alcohol moiety intact. After isolation, further oxidation of ketone **60** with Dess−Martin periodinane provided the desired aldehydoketone **61** (78% for two steps). These sequential oxidations were important steps in the synthesis of **7** and attempts to execute them in a one-pot process, resulted in low yields of aldehydoketone **61**.[56] The C-16(*S*) aldehydic group of **61** was converted into the methyl ester **62** upon treatment with KOH/I_2 in 92% yield.[38] The stereochemical issue of the C(17) hydroxyl group which now remained was resolved by simple reduction of ketone **62** with $NaBH_4$. Attack occurred exclusively from the least hindered face to provide (−)-vincamajinine (**7**) in 90% yield. Analysis of the proton NMR spectrum indicated the characteristic singlet at 17-H(*R*) appeared at 3.98 ppm in (−)-**7** in contrast to the 17(*S*) stereochemistry (δ 4.21) in (−)-vincamajine (**4**).[12e,g,j,l,13] The structure of (−)-**7** was fully characterized by ^1H and ^{13}C NMR, NOESY, NOE, MS, and IR. This completed the first stereocontrolled total synthesis of (−)-**7** in 16 reaction vessels from D-(+)-tryptophan methyl ester in an overall yield of 11.8%.

(54) De Mico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* **1997**, *62*, 6974−6977.

(55) (a) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287. (b) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155−4156.

(56) In the absence of the isolation of ketone **60**, further oxidation of **60** with Dess−Martin periodinane at room temperature resulted in the decomposition of ketone **60** and isolation of only a small amount of aldehydoketone **61**.

SCHEME 14. Completion of the Total Synthesis of (−)-11-Methoxy-17-epivincamajine (9)



Completion of the Total Synthesis of (−)-11-Methoxy-17-epivincamajine (9). Once the synthesis of vincamajinine (**7**) was realized, attention turned to the construction of 11-methoxy-17-epivincamajine (**9**) to illustrate the versatility of this approach. The desired diol **45**, available by the efficient process described in Schemes 6−8, was subjected to the condition of Dess−Martin oxidation. Gratifyingly, it was found that oxidation of **45** under the Dess−Martin periodinane conditions was much faster than that of the parent **13** (Scheme 14). Both primary and secondary alcohol functions of diol **45** were simultaneously converted into the corresponding aldehyde and ketone moieties to give aldehydoketone **63** in 65% yield. The aldehydic group in **63** was converted into the methyl ester **64** in 91% yield by the elegant procedure of Yamamoto et al.[38] The C(17) ketone which remained was stereoselectively reduced from the top face to furnish the synthetic (−)-11-methoxy-17-epivincamajine (**9**) in 93% yield with $NaBH_4$ in EtOH. The spectroscopic properties and optical rotation [$[\alpha]^{26}_D$ −10.5 (lit.[9b] $[\alpha]^{26}_D$ −12.0)] of synthetic (−)-**9** were in excellent agreement with those of natural (−)-11-methoxy-17-epivincamajine (**9**). See the Experimental Section and the Supporting Information for details. This synthesis required 17 reaction vessels from the Schöllkopf chiral auxiliary **27** and was completed in an overall yield of 5.4%.

Conclusion

In summary, a stereocontrolled total synthesis of (+)-dehydrovoachalotine (**22**), (−)-vincamajinine (**7**), and (−)-11-methoxy-17-epivincamajine (**9**) was accomplished by combination of the highly practical asymmetric Pictet−Spengler reaction, a Tollens reaction, an acid-assisted intramolecular cyclization, and two stereospecific reductions that provided the required hexacyclic ring systems in stereocontrolled fashion. This constitutes the first total synthesis of these alkaloids and provided the first regiospecific route to 11-alkoxy substituted ajmaline-related alkaloids. In particular, alteration of the acidic conditions during formation of the C(7)−C(17) quaternary center can be employed to stereospecifically control the intramolecular cyclization to provide the 17(*R*) configuration. This strategy was concise and versatile since the three hexacyclic cores of (+)-quebrachidine (**3**), (−)-vincamajine (**4**), and (+)-vincarine (**9**) have been synthesized in a similar manner as well. This stereocontrolled approach will permit extension of this strategy to the synthesis of many vincamajine/ajmaline-related indole alkaloids including alkaloids in the 10- and 12-methoxy series, heretofore difficult to obtain regiospecifically. Further work on the synthesis of these monomeric- and bis-indole alkaloids is underway and will be reported in due course.

Experimental Section

Microanalysis was performed on an F and M Scientific Corp. model 185 carbon, hydrogen, and nitrogen analyzer. Melting points were taken on a Thomas Hoover melting point apparatus and are reported uncorrected. Proton and carbon NMR spectra were recorded on 250 and 300 MHz NMR spectrometers. The analytical TLC plates used were UV-active silica gel on plastic. The TLC plates were visualized under UV light or developed with spray reagents. Alkaloids were visualized with Dragendorf's reagent or a saturated solution of ceric ammonium sulfate in 50% sulfuric acid or an aqueous solution of 2,4-dinitrophenylhydrazine in 30% sulfuric acid. Chromatography refers to flash chromatography using 230−400 mesh 60 A silica gel, grade 60. Methanol was dried by distillation over magnesium metal/I_2. Tetrahydrofuran, benzene, and toluene were dried by distillation from sodium−benzophenone ketyl. Methylene chloride was dried over $MgSO_4$ and then was distilled from P_2O_5.

Preparation of Voachalotinol (15). To a solution of aldehyde **16**[23] (306 mg, 1.0 mmol) in MeOH (10 mL) were added formaldehyde [(25 equiv, 25 mmol) 1.9 mL of a 37% w/w solution in water] and 85% KOH (10 equiv, 659 mg, 10 mmol) in MeOH (10 mL). The reaction mixture was stirred at rt for 10 h, diluted with brine, and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue that resulted was purified by column chromatography (silica gel, MeOH/$CHCl_3$ = 1:12) to provide diol **15** as a white solid (304 mg, 90%): FTIR 3330, 2911, 1470 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.54 (d, J = 6.6 Hz, 3 H), 1.76 (m, 2 H), 2.68 (m, 3 H), 3.01 (dd, J = 10.4, 5.0 Hz, 1 H), 3.07 (d, J = 5.4 Hz, 1 H), 3.23 (dd, J = 9.8, 5.0 Hz, 1 H), 3.41 (t, J = 4.8 Hz, 1 H), 3.50 (m, 3 H), 3.61 (s, 3 H), 4.04 (t, J = 4.7 Hz, 1 H), 4.12 (dd, J = 9.7, 3.7 Hz, 1 H), 4.46 (t, J = 4.9 Hz, 1 H), 5.26 (q, J = 6.7 Hz, 1 H), 6.98 (t, J = 7.7 Hz, 1 H), 7.08 (t, J = 7.0 Hz, 1 H), 7.39 (m, 2 H); ^{13}C NMR (300 MHz, DMSO-d_6) δ 12.7, 22.9, 27.8, 28.7, 29.3, 43.5, 48.1, 49.0, 56.2, 57.1, 58.0, 66.2, 105.4, 109.5, 113.6, 118.0, 118.7, 120.0, 137.0, 139.8, 140.2; EIMS (*m/e*, relative intensity) 338 (M^+, 100), 321 (10), 307 (23), 263 (11), 182 (25); HRMS calcd for $C_{21}H_{26}N_2O_2$ 338.1994, found 338.1993. This material was used directly in the next step.

Preparation of (2a*S*,3*S*,4*E*,7*S*,12c*R*,12d*R*)-4-Ethylidene-4,5,7,8,12c,12d-hexahydro-8-methyl-3,7-methano-2*H*-furo-[4,3,2-*ij*]indolo[3,2-*b*]quinolizine-2a(3*H*)-methanol (20). To a solution of diol **15** (34 mg, 0.10 mmol) in THF (2 mL) was added DDQ (46 mg, 0.20 mmol). The mixture which resulted was heated to reflux for 2 h. The mixture was then diluted with CH_2Cl_2 (25 mL), washed with a saturated solution of aq $NaHSO_3$ (5 mL) and brine (2 × 10 mL), and dried (K_2CO_3). The solvent was removed under reduced pressure and the residue which resulted was chromatographed (silica gel, $CHCl_3$/MeOH = 9:1) to provide the cyclic ether **20** as a white solid (32 mg, 95%): FTIR 3382, 2922, 1469, 1011 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.68 (3 H, d, J = 6.8 Hz), 1.95 (m, 2 H), 3.00 (t, J = 2.7 Hz, 1 H), 3.14 (d, J = 7.5 Hz, 1 H), 3.46 (s, 2 H), 3.50−3.74 (m, 7 H), 4.11 (dd, J = 8.5, 5.3 Hz, 1 H), 5.45 (q, J = 6.7 Hz, 1 H), 5.67 (d, J = 7.5 Hz, 1 H), 7.17 (td, J = 7.8, 1.1 Hz, 1 H), 7.24 (td, J = 7.9, 1.1 Hz, 1 H), 7.30 (t, J = 8.0 Hz, 1 H), 7.70 (d, J = 7.5 Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.8, 28.7, 29.1, 29.2, 45.9, 47.4, 55.4, 62.9, 66.7, 68.1, 72.0, 103.3, 108.9, 116.2, 118.7, 119.8, 121.4, 126.1, 136.3, 137.3, 143.0; EIMS (*m/e*, relative intensity) 336 (M^+, 36), 319 (24), 305 (9), 196 (43), 182 (100); HRMS calcd for

$C_{21}H_{24}N_2O_2$ 336.1837, found 336.1822. This material was employed directly in the next step.

Preparation of (2a*R*,3*S*,4*E*,7*S*,12c*R*,12d*R*)-4-Ethylidene-4,5,7,8,12c,12d-hexahydro-8-methyl-3,7-methano-2*H*-furo-[4,3,2-*ij*]indolo[3,2-*b*]quinolizine-2a(3*H*)-carboxaldehyde (21). The benzeneseleninic anhydride (6.6 mg, 0.025 mmol) was added to a solution of dry chlorobenzene (5 mL) and cyclic ether **20** (17 mg, 0.05 mmol). The mixture was heated to 115 °C (oil bath temperature) for 30 min. The orange solution which resulted was cooled to rt, and the solvent was removed under reduced pressure. The oil which resulted was dissolved in EtOAc (25 mL) and poured into a solution of aq 1 N NaOH (20 mL). The mixture was then extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with brine and dried (Na_2SO_4), and the solvent was removed under reduced pressure to afford an oil. The oil was chromatographed (silica gel, $CHCl_3$/MeOH = 15:1) to provide aldehyde **21** as a pale yellow solid (15 mg, 92%): FTIR 2938, 1720, 1468 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.64 (dt, J = 6.8, 1.9 Hz, 3 H), 2.08 (m, 2 H), 3.19 (t, J = 2.7 Hz, 1 H), 3.65 (s, 3 H), 3.68 (m, 2 H), 3.70 (d, J = 15.5 Hz, 2 H), 3.86 (d, J = 10.3 Hz, 1 H), 4.26 (d, J = 7.3 Hz, 2 H), 5.42 (q, J = 6.8 Hz, 1 H), 5.81 (d, J = 7.6 Hz, 1 H), 7.15−7.32 (m, 2 H), 7.68 (d, J = 7.7 Hz, 1 H), 9.59 (s, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.7, 28.4, 28.8, 29.2, 47.5, 55.2, 57.3, 59.4, 65.1, 72.8, 103.0, 109.0, 117.7, 118.9, 120.0, 121.8, 125.8, 133.3, 137.4, 142.1, 201.3; EIMS (*m*/*e*, relative intensity) 334 (M^+, 34), 305 (43), 196 (41), 182 (100); HRMS calcd for $C_{21}H_{22}N_2O_2$ 334.1681, found 334.1684. This material was employed directly in the next step.

Preparation of (+)-Dehydrovoachalotine (22). Aldehyde **21** (6.7 mg, 0.02 mmol) was dissolved in anhydrous MeOH (2 mL), and a solution of 85% KOH (2.6 equiv, 3.4 mg, 0.052 mmol) and iodine (1.3 equiv, 6.6 mg, 0.026 mmol) in anhydrous MeOH (each 0.5 mL) were successively added to **21** at 0 °C. After 30 min, the reaction mixture was quenched by addition of glacial acetic acid to bring the pH to 7. The solution was diluted with CH_2Cl_2, washed with a 10% aq solution of $NaHSO_3$ (20 mL) brine (2 × 20 mL), and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue which resulted was purified by chromatography on silica gel ($CHCl_3$/MeOH = 20:1) to provide dehydrovoachalotine **22** as a pale yellow solid (5 mg, 90%): $[\alpha]_D$ = +125.0 (*c* 0.08, MeOH) [lit.[18] $[\alpha]_D$ = +124 ± 2 (*c* 0.90, MeOH)]; IR 1736, 1467, 1238 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.60 (d, J = 7.9 Hz, 3 H), 2.03 (m, 2 H), 2.29 (t, J = 2.9 Hz, 1 H), 3.65 (s, 3 H), 3.72 (3 H, s), 3.71−3.76 (m, 3 H), 3.94 (d, J = 10.1 Hz, 1 H), 4.07 (dd, J = 9.4, 4.2 Hz, 1 H), 4.52 (d, J = 7.7 Hz, 1 H), 5.36 (q, J = 7.6 Hz, 1 H), 5.78 (d, J = 7.7 Hz, 1 H), 7.14−7.33 (m, 3 H), 7.70 (d, J = 7.5 Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.6, 29.1, 29.3, 31.0, 47.1, 52.2, 53.9, 55.4, 61.4, 68.3, 72.6, 103.4, 109.1, 116.5, 119.2, 120.1, 121.8, 126.4, 135.7, 137.7, 143.3, 175.9; EIMS (*m*/*e*, relative intensity) 364 (M^+, 26), 333 (10), 196 (30), 182 (100); HRMS calcd for $C_{22}H_{24}N_2O_3$ 364.1786, found 364.1765. The spectral data of this material were in excellent agreement with that of the literature.[18]

Preparation of (6*S*,7*R*,9*E*,10*S*,11*S*,11a*S*)-9-Ethylidene-5,6,8,9,10,11,11a,12-octahydro-11-(hydroxymethyl)-5-methyl-6,10-methanoindolo[3,2-*b*]quinolizine-11-carboxaldehyde (23). The TPAP (1.8 mg, 0.005 mmol) was added to a mixture of **15** (34 mg, 0.10 mmol), 4 Å MS (50 mg, 500 mg/mmol), and NMO (18 mg, 0.15 mmol) in CH_2Cl_2 (10 m L) under a N_2 atmosphere. The reaction mixture was stirred at rt for 12 h, at which time it was passed through a pad of Celite and washed with CH_2Cl_2 (20 mL). The filtrate was washed with brine (2 × 20 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue that resulted was purified by preparative TLC on silica gel ($CHCl_3$/MeOH = 9:1) to provide **23** and its C-16 epimer in >10:1 ratio (26 mg, 78%). **23**: FTIR 2941, 1692, 1469 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.67 (d, J = 6.7 Hz, 3 H), 1.80 (t, J = 10.4 Hz, 1 H), 1.90 (m, 1 H), 2.82 (dd, J = 15.5, 4.6 Hz, 1 H), 2.91 (d, J = 2.4 Hz, 1 H), 3.03 (d, J = 4.2 Hz, 1 H), 3.16 (d, J = 15.5 Hz, 1 H), 3.40 (dd, J = 10.3, 4.7 Hz, 1 H), 3.49 (s, 2 H), 3.54 (s, 3 H), 3.66 (m, 1 H), 4.22 (dd, J = 18.3, 7.9 Hz, 1 H), 4.79 (t, J = 4.6 Hz, 1 H), 5.34 (q, J = 6.8 Hz, 1 H), 6.99 (t, J = 7.1 Hz, 1 H), 7.09 (td, J = 8.1, 1.0 Hz, 1 H), 7.39 (t, J = 7.5 Hz, 2 H), 9.04 (s, 1 H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 13.0, 23.5, 26.4, 27.1, 29.4, 48.7, 53.1, 55.3, 58.0, 66.2, 103.9, 109.7, 115.5, 118.0, 119.0, 120.7, 125.9, 137.5, 138.4, 139.8, 202.6; EIMS (*m*/*e*, relative intensity) 336 (M^+, 16), 307 (29), 263 (22), 183 (100); HRMS calcd for $C_{21}H_{24}N_2O_2$ 336.1838, found 336.1823. This material was used directly in the next step.

Preparation of (2α,17*S*,19*E*)-17-Aceto-16-[(acetyloxy)-methyl]-19,20-didehydroajmalan-2,17-diol (24). The TFA (2 mL) was added to a solution of **23** (80 mg, 0.23 mmol) in Ac_2O (5 mL). The reaction mixture was stirred in a sealed vessel at rt for 6 h, at which time it was concentrated under reduced pressure. The residue was diluted with CH_2Cl_2 (20 mL), and a solution of 10% aq NH_4OH was added to bring the pH to 8. The organic layer was extracted with CH_2Cl_2 (20 mL), which was washed with brine (2 × 20 mL), dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residue that resulted was purified by preparative TLC on silica gel ($CHCl_3$/MeOH = 9:1) to provide **24** (84.5 mg, 84%): FTIR 2941, 1742, 1473, 1241 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.48 (m, 1 H), 1.57 (d, J = 6.7 Hz, 3 H), 1.72 (s, 3 H), 2.00 (s, 3 H), 2.04 (dd, J = 18.6, 4.4 Hz, 1 H), 2.45 (d, J = 12.3 Hz, 1 H), 2.76 (m, 4 H), 2.93 (dd, J = 13.5, 4.6 Hz, 1 H), 3.46 (m, 4 H), 3.90 (m, 2 H), 5.35 (s, 1 H), 5.40 (q, J = 6.4 Hz, 1 H), 6.54 (d, J = 7.8 Hz, 1 H), 6.76 (t, J = 7.4 Hz, 1 H), 7.06 (d, J = 7.2 Hz, 1 H), 7.13 (t, J = 7.7 Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.8, 20.5, 20.7. 22.8, 28.5, 29.4, 29.9, 43.8, 55.6, 58.7, 59.0, 62.0, 67.7, 82.0, 97.4, 107.6, 116.8, 118.6, 122.9, 126.8, 128.5, 137.0, 152.1, 169.2, 170.9; EIMS (*m*/*e*, relative intensity) 438 (M^+, 64), 422 (100), 406 (34), 378 (43), 319 (46), 253 (34), 182 (76); HRMS calcd for $C_{25}H_{30}N_2O_5$ 438.2154, found 438.2148. This material was used directly in the next step.

Preparation of (2α,17*R*,19*E*)-17-Aceto-16-[(acetyloxy)-methyl)]-19,20-didehydroajmalan-17-ol (25). The TFA (2 mL) and Et_3SiH (3 mL) were added to a solution of **24** (45 mg, 0.10 mmol) in CH_2Cl_2 (2 mL). The reaction mixture which resulted was stirred in a sealed vessel at rt for 3 d, at which time it was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (30 mL), and a solution of 10% aq NH_4OH was added to bring the pH to 8. The organic layer was separated, washed with brine (2 × 20 mL), dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residue that resulted was purified by preparative TLC on silica gel ($CHCl_3$/MeOH = 15:1) to provide **25** (38 mg, 90%): FTIR 2941, 1749, 1422, 1241 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.50 (dd, J = 13.6, 10.4 Hz, 1 H), 1.60 (d, J = 6.8 Hz, 3 H), 1.76 (s, 3 H), 1.79 (d, J = 12.0 Hz, 1 H), 2.02 (s, 3 H), 2.30 (dd, J = 11.8, 4.6 Hz, 1 H), 2.67 (s, 3 H), 2.71 (d, J = 4.7 Hz, 1 H), 2.78 (d, J = 4.4 Hz, 1H), 2.98 (dd, J = 13.4, 4.8 Hz, 1H), 3.32 (d, J = 4.7 Hz, 1 H), 3.50 (m, 1 H), 3.54 (t, J = 2.2 Hz, 1 H), 3.69 (dd, J = 9.5, 4.8 Hz, 1 H), 3.92 (m, 2 H), 5.33 (s, 1 H), 5.39 (q, J = 6.7 Hz, 1 H), 6.63 (d, J = 7.9 Hz, 1 H), 6.78 (td, J = 7.4, 0.8 Hz, 1 H), 7.10 (dd, J = 7.3, 0.7 Hz, 1 H), 7.15 (td, J = 7.8, 1.2 Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.8, 20.6, 20.7, 22.3, 28.8, 34.9, 36.5, 45.2, 53.3, 54.1, 55.8, 62.0, 68.0, 75.1, 82.7, 108.9, 116.3, 119.1, 122.5, 128.4, 128.9, 137.9, 154.9, 169.4, 171.0; EIMS (*m*/*e*, relative intensity) 422 (M^+, 100), 379 (6), 363 (20); HRMS calcd for $C_{25}H_{30}N_2O_4$ 422.2204, found 422.2206. This material was used directly in the next step.

Preparation of (+)-(2α,17*R*,19*E*)-19,20-Didehydro-17-hydroxyajmalan-16-methanol (13). A solution of 20% aq K_2CO_3 (2 mL) was added to a solution of **25** (42 mg, 0.10 mmol) in MeOH (2 mL) at rt. The mixture was stirred at rt for 24 h and concentrated under reduced pressure to remove the MeOH, after which time it was diluted with CH_2Cl_2 (20 mL) and separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residue that resulted was purified by

preparative TLC on silica gel ($CHCl_3$/MeOH = 9:1) to provide diol **13** as a white solid (29 mg, 87%): $[\alpha]_D = +8.84$ (*c* 0.52, MeOH); FTIR 3405, 2951, 1638 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.51 (m, 1 H), 1.66 (d, J = 6.8 Hz, 3 H), 1.77 (d, J = 11.8 Hz, 1 H), 2.21 (dd, J = 11.8, 4.6 Hz, 1 H), 2.66 (s, 3 H), 2.80 (d, J = 3.7 Hz, 1 H), 2.96 (m, 2 H), 3.40 (d, J = 6.8 Hz, 1 H), 3.43 (m, 1 H), 3.52 (m, 1 H), 3.54 (t, J = 2.1 Hz, 1 H), 3.60 (d, J = 10.2 Hz, 1 H), 3.73 (dd, J = 9.6, 5.0 Hz, 1 H), 4.10 (1 H, s), 5.36 (q, J = 6.6 Hz, 1 H), 6.74 (d, J = 7.9 Hz, 1 H), 6.87 (t, J = 7.4 Hz, 1 H), 7.11 (d, J = 7.2 Hz, 1 H), 7.22 (td, J = 7.7, 1.2 Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.0, 22.7, 28.2, 34.9, 35.8, 47.6, 53.7, 54.6, 55.6, 62.2, 67.0, 76.1, 85.8, 109.7, 116.2, 119.9, 121.6, 128.3, 130.7, 137.8, 154.7; EIMS (*m/e*, relative intensity) 338 (M^+, 76), 321 (9), 194 (83), 157 (100); HRMS calcd for $C_{21}H_{26}N_2O_2$ 338.1994, found 338.1993. This material was used in a later step.

Preparation of (−)-3-{[(2*R*,5*S*)-2,5-Dihydro-5-(1-methylethyl)pyrazinyl]methyl}-6-methoxy-2-(triethylsilyl)-1*H*-indole (28). To a three-neck flask (5 L) equipped with an overhead stirrer were charged 2-iodo-5-methoxyaniline **26** (300 g, 1.20 mol) and the Schöllkopf derivative **27** (530 g, 1.45 mol), as well as lithium chloride (5.1 g, 0.12 mol), sodium carbonate (318 g, 3.0 mol), palladium(II) acetate (3.50 g, 0.0156 mol), and dry DMF (4 L). The mixture was then degassed with a vacuum pump three times at rt with argon. The suspension which resulted was heated for 36 h at 100 °C under an atmosphere of Ar. After examination of the mixture by TLC (silica gel) indicated the iodoaniline **26** had been consumed, the reaction mixture was cooled to rt and the DMF was removed under reduced pressure. Methylene chloride (4 L) was added to the residue, and the suspension which resulted was filtered to remove unwanted salts. After removal of the CH_2Cl_2, the crude product was purified by flash chromatography (silica gel, 2% EtOAc/hexanes) to give the desired 6-methoxy substituted indole **28** (450 g, 77%): $[\alpha]_D = -21.4$ (*c* 1.58, $CHCl_3$); IR (NaCl) 3388, 2944, 1683 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.67 (d, J = 6.8 Hz, 3 H), 0.85−1.05 (m, 18 H), 1.20 (t, J = 7.1 Hz, 3 H), 1.30 (t, J = 7.1 Hz, 3 H), 2.25 (m,1 H), 2.80 (dd, J = 13.5, 10.6 Hz, 1 H), 3.46 (dd, J = 14.1, 3.1 Hz, 1 H), 3.84 (s, 3 H), 3.88 (t, J = 3.9 Hz, 1 H), 4.01−4.21 (m, 5 H), 6.70 (dd, J = 8.7, 2.2 Hz, 1 H), 6.82 (d, J = 2.1 Hz, 1 H), 7.60 (d, J = 8.7 Hz, 1 H), 7.77 (bs, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 4.1, 7.9, 14.7, 14.8, 17.1, 19.5, 32.1, 32.5, 56.0, 59.3, 60.9, 61.0, 61.1, 93.9, 109.3, 121.8, 124.4, 124.7, 130.5, 139.5, 157.0, 163.1, 164.2; MS (CI, CH_4) *m/e* (relative intensity) 486 (M^+ + 1, 100), 456 (13), 372 (51), 274 (27); exact mass calcd for $C_{27}H_{43}N_3O_3Si$ 485.3074, found 485.3055. This material was employed directly in the next step.

Preparation of (−)-1-Methyl-6-methoxy-D-tryptophan Ethyl Ester (29). Sodium hydride (60% in mineral oil, 12.4 g) in several portions was added to a mixture of indole **28** (100 g, 0.21 mol), methyl iodide (44 g, 0.31 mol), and anhydrous DMF (1000 mL) at 0 °C. After this mixture was stirred for 2 h, analysis by TLC (silica gel) indicated the absence of starting material. The reaction solution was quenched with water (8 mL), and the mixture which resulted was subsequently poured into hexanes (5000 mL) to precipitate out sodium hydroxide which was removed by filtration. The solvent was then removed under reduced pressure and the residue was crystallized from hexanes at 0 °C to afford the N_a-methyl derivative **29** as white needlelike crystals in several crops. The product in the mother liquor was purified by flash chromatography (silica gel, EtOAc/hexanes = 3:97). The combined material **29** (99 g) was obtained in 95% yield: $[\alpha]_D = -17.5$ (*c* 0.81, $CHCl_3$); mp 91−92 °C; IR (NaCl) 2945, 1688, 1613 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.63 (d, J = 6.8 Hz, 3 H), 0.95 (m, 15 H), 0.98 (d, J = 6.9 Hz, 3 H), 1.14 (t, J = 7.1 Hz, 3 H), 1.23 (t, J = 7.1 Hz, 3 H), 2.23 (m, 1 H), 2.80 (dd, J = 14.0, 4.5 Hz, 1 H), 3.45 (dd, J = 14.0, 3.5 Hz, 1 H), 3.73 (s, 3 H), 3.84 (s, 3 H), 3.85 (m, 1 H), 3.90−4.15 (m, 5 H), 6.65 (m, 2 H), 7.50 (d, J = 9.2 Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 4.8, 7.6, 14.3, 14.4, 16.7, 19.1, 31.6, 31.9, 33.1, 55.7, 59.2, 60.4, 60.5, 60.7, 91.9, 108.2, 121.2, 124.2, 124.6, 132.3, 140.6, 156.7, 162.7, 163.9; MS (CI, CH_4) *m/e* (relative intensity) 500 (M^+ + 1, 100), 470 (16), 386 (14), 288 (21). Anal. Calcd for $C_{28}H_{45}N_3O_3Si$: C, 67.29; H, 9.08; N, 8.41. Found: C, 67.49; H, 9.16; N, 8.34.

To a solution of optically pure (−)-3-{[(2*R*,5*S*)-2,5-dihydro-5-(1-methylethyl)pyrazinyl]methyl}-6-methoxy-1-methyl-2-(triethylsilyl)-1*H*-indole (**29**) (50 g, 0.1 mol) in THF (1000 mL) at 0 °C was slowly added a cold solution of 2 N aq HCl (875 mL). The mixture was allowed to warm to rt and stirred for 2 h. Ice (800 g) was added to the solution, and the pH of the reaction mixture was adjusted to 8 with 10% aq NH_4OH (concd) at 0 °C. The mixture was then extracted with CH_2Cl_2 (4 × 1000 mL). The combined organic layers were dried (Na_2SO_4), and the solvent was removed under reduced pressure. After all of the solvent had been removed, the residue was subjected to Kugelrohr distillation at 80 °C (0.3 mmHg) to remove L-valine ethyl ester while pure 1-methyl-6-methoxy-D-tryptophan ethyl ester **30** (25.7 g, 93%) remained. An analytical sample was obtained by flash chromatography (silica gel, EtOAc) to afford **30** as a light yellow oil: $[\alpha]_D = -7.21$ (*c* 2.01, $CHCl_3$) [lit.[49] $[\alpha]_D = -7.09$ (*c* 2.06, $CHCl_3$)]; IR (NaCl) 3374, 3311, 2980, 1736, 1623 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.30 (t, J = 7.1 Hz, 3 H), 1.62 (bs, 2 H), 2.99 (dd, J = 14.4, 7.7 Hz, 1H), 3.24 (dd, J = 14.3, 4.7 Hz, 1 H), 3.65(s, 3 H), 3.79 (dt, J = 7.4, 2.6 Hz, 1 H), 3.89 (s, 3 H), 4.18 (q, J = 7.1 Hz, 2 H), 6.75−6.83 (m, 3 H), 7.48 (d, J = 8.6 Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1, 30.6, 32.5, 55.2, 55.8, 60.6, 93.1, 108.9, 109.8, 119.6, 122.6, 126.5, 137.8, 156.6, 175.0; MS (EI) *m/e* (relative intensity) 276 (M^+, 4), 174(100), 159(11). Anal. Calcd for $C_{15}H_{20}N_2O_3$: C, 65.18; H, 7.30; N 10.14. Found: C, 64.96; H, 7.36; N, 10.24. This material was used directly in the next step.

Preparation of N_b-Benzyl-6-methoxy-1-methyl-D-tryptophan Ethyl Ester (31). Benzaldehyde (46 g, 0.435 mol) was added to a solution of tryptophan ethyl ester **30** (100 g, 0.36 mol) in dry ethanol (2 L) at rt under nitrogen. The solution which resulted was stirred at this temperature for 5 h, cooled to −10 °C, and treated portionwise with $NaBH_4$ (16.5 g, 0.435 mol) to keep the temperature below −5 °C (about 3 h). After the mixture was allowed to stir for an additional 1 h, ice−water (75 mL) was added, and the mixture was allowed to warm to rt. The ethanol was removed under reduced pressure, and the aqueous residue was extracted with EtOAc (3 × 1.8 L). The combined organic layers were washed with brine and dried (Na_2SO_4). After removal of the solvent under reduced pressure, the residue was purified by flash chromatography (ethyl acetate/hexanes = 3:1) to afford **31** as an oil (125 g, 93%): ^1H NMR (250 MHz, $CDCl_3$) δ 1.14 (t, J = 7.1 Hz, 3 H), 1.77 (bs, 1 H), 3.08 (dd, J = 6.9, 2.7 Hz, 2H), 3.61 (m, 2 H), 3.65 (s, 3 H), 3.80 (d, J = 13.2 Hz, 1H), 3.84 (s, 3 H), 4.07 (q, J = 7.1 Hz, 2 H), 6.72 (m, 3 H), 7.25 (m, 5 H), 7.40 (d, J = 9.0 Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.12, 29.21, 32.54, 52.01, 55.63, 60.49, 61.27, 92.64, 108.66, 109.73, 119.59, 122.40, 126.28, 126.86, 128.11, 128.22, 137.54, 139.72, 156.29, 174.78; CIMS *m/e* 367 (M^+ + 1, 100). Anal. Calcd for $C_{22}H_{26}N_2O_3$: C, 72.11; H, 7.15; N, 7.64. Found: C, 71.93; H, 7.10; N, 7.53. This material was used directly in the next step.

Preparation of (−)-(1S,3R)-N_b-Benzyl-3-(ethoxycarbonyl)-2,3,4,9-tetrahydro-7-methoxy-9-methyl-1*H*-pyrido-[3,4-*b*]-1-propanoic Acid Methyl Ester (33b). The methyl 4-oxobutanoate **32** (24 g, 0.208 mol) and HOAc (8.25 g, 0.138 mol) were added to a round-bottom flask (2 L) which contained a solution of optically active N_b-benzyl-6-methoxy-1-methyl-D-tryptophan ethyl ester **31** (50 g, 0.138 mol) in dry CH_2Cl_2 (300 mL) at 0 °C. The reaction mixture which resulted was stirred at rt overnight. A mixture of *trans* and *cis* diastereomers (72:28) was present at this stage. The TFA (23.75 g, 0.208 mol) in CH_2Cl_2 (500 mL) was then added at 0 °C. The reaction mixture which resulted was stirred at rt for 12 h and then cooled in an ice bath. The pH was brought to 8 with a solution of 10% aq NH_4OH. The aqueous layer was separated and extracted with CH_2Cl_2 (3 × 500 mL). After the combined

organic layers were washed with brine and dried (K_2CO_3), the solvent was removed under reduced pressure. The residue which resulted was purified by flash chromatography (silica gel, EtOAc/hexanes = 1:4) to provide **33b** (57 g, 90%): $[\alpha]_D = -34.7$ (*c* 0.3, $CHCl_3$); FTIR ($CDCl_3$) 2950, 2846, 1735, 1624 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.35 (t, $J = 7.1$ Hz, 3 H), 1.89 (m, 2 H), 2.43 (m, 2 H), 3.02 (m, 2 H), 3.36 (d, $J = 13.2$ Hz, 1 H), 3.45 (s, 3 H), 3.57 (s, 3 H), 3.78 (d, $J = 13.2$ Hz, 2 H), 3.87 (s, 3 H), 4.02 (dd, $J = 10.5$, 5.4 Hz, 1 H), 4.22 (m, 2 H), 6.77 (s, 1 H), 6.80 (d, $J = 2.2$ Hz, 1 H), 7.21−7.44 (m, 6 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 14.36, 20.47, 28.21, 29.75, 51.20, 52.69, 53.63, 56.32, 60.81, 93.57, 106.46, 108.66, 118.71, 126.96, 128.17, 129.35, 134.66, 139.54, 156.47, 172.90, 173.94; EIMS(70 eV) *m/e* (relative intensity) 464 (M^+, 7.4), 377 (100.0), 213 (37.5). Anal. Calcd for $C_{27}H_{32}N_2O_5$: C, 69.81; H, 6.94; N, 6.03. Found: C, 70.11; H, 6.94; N, 5.90. This material was used directly in the next step.

Preparation of (−)-(6*S*,10*S*)-5,6,7,8,10,11-Hexahydro-3-methoxy-5-methyl-6,10-imino-9*H*-cyclooct[*b*]indol-9-one (35). Sodium hydride (4.8 g of 60% NaH in mineral oil, 0.12 mol) was added to a solution of *trans* diester **33b** (20 g, 0.04 mol) in dry toluene (40 mL) under argon. Dry methanol (4.0 mL) was added carefully to the above mixture (a large amount of H_2 was evolved at this point). The mixture which resulted was stirred at rt for 0.5 h and then heated to reflux for an additional 4 h. The reaction mixture was then allowed to cool to rt and treated with a saturated aqueous solution of $NaHCO_3$ (40 mL). The organic layer was separated, washed with brine, and dried (Na_2SO_4). After removal of solvent under reduced pressure, the residue was purified by flash chromatography (hexanes/ethyl acetate = 3:1) to afford the β-ketoester **34** (14.4 g, 85%) as a yellow colored solid: mp 168−169 °C; FTIR ($CHCl_3$) 3053, 2924, 1660 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.27 (d, $J = 15.5$ Hz, 1 H), 2.84 (dd, $J = 15.5$, 5.5 Hz, 1 H), 2.87 (d, $J = 15.5$ Hz, 1 H), 3.14 (dd, $J = 16.2$, 5.8 Hz, 1 H), 3.53 (s, 3 H), 3.66 (s, 3 H), 3.74 (d, $J = 15.5$ Hz, 2 H), 3.75 (m, 1 H), 3.66 (s, 3 H), 4.04 (d, $J = 5.3$ Hz, 1 H,), 6.76−6.80 (m, 2 H), 7.25−7.39 (m, 6 H), 11.97 (s, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.21, 28.13, 29.39, 48.82, 51.42, 54.97, 55.95, 56.02, 93.25, 93.99, 105.32, 108.55, 118.76, 121.07, 127.28, 128.43, 128.74, 133.18, 137.68, 138.29, 156.21, 171.90, 172.54; EIMS (70 eV) *m/e* (relative intensity) 418 (M^+, 57), 303 (100.0), 295 (69). Anal. Calcd for $C_{25}H_{26}N_2O_4$: C, 71.75; H, 6.26; N, 6.69. Found: C, 71.98; H, 6.22; N, 6.74. This material was used directly in the next step.

A solution of β-ketoester **34** prepared above (4.0 g, 9.6 mmol) was dissolved in 1,4-dioxane (40 mL). The 40% aqueous solution of KOH was then added to the above mixture. The reaction mixture which resulted was heated to reflux for 3 d. The solution was allowed to cool to rt. The 1,4-dioxane was removed under reduced pressure. The mixture which remained was extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was separated, washed with brine, and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was purified by flash chromatography (hexanes/ethyl acetate = 3:1) to afford **35** as white crystals (2.9 g, 85%): mp 77−78 °C; $[\alpha]_D = -176.2$ (*c* 0.30, $CHCl_3$); FTIR ($CDCl_3$) 1713, 1625 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.89−2.17 (m, 2 H), 2.43 (m, 2 H), 2.63 (d, $J = 16.9$ Hz, 1 H), 3.20 (dd, $J = 16.9$, 6.7 Hz, 1 H), 3.52 (s, 3 H), 3.64 (s, 2 H), 3.67 (s, 3 H), 4.01 (bs, 2 H), 6.76−6.80 (m, 2 H), 7.24−7.39 (m, 6 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.55, 29.32, 29.85, 34.30, 49.04, 55.97, 56.31, 64.94, 93.54, 105.84, 108.70, 118.78, 121.12, 127.32, 128.44, 128.65, 132.10, 138.12, 138.42, 156.55, 209.98; EIMS (70 eV) *m/e* (relative intensity) 360 (M^+, 31.9), 303 (100.0). Anal. Calcd for $C_{23}H_{24}N_2O_2$: C, 76.64; H, 6.71; N, 7.77. Found: C, 76.61; H, 6.90; N, 7.63. This material was used directly in the next step.

Preparation of (−)-(6*S*,10*S*)-5,6,7,8,10,11-Hexahydro-3-methoxy-5-methyl-6,10-imino-9*H*-cyclooct[*b*]indol-9-one (36). Tetracyclic ketone **35** (7.0 g, 19.4 mmol) was dissolved in anhydrous ethanolic HCl (5%, 100 mL), after which Pd/C (10%, 1.5 g) was added. The mixture which resulted was allowed to stir at rt under an atmosphere of H_2 for 24 h. Analysis by TLC (silica gel plate was exposed to NH_3 vapors) indicated the existence of only a very small amount of starting material **33**. The catalyst was removed by filtration (Celite) and was washed with EtOH (3 × 100 mL). The solvent was removed under reduced pressure. The residue was dissolved in a mixture of $CHCl_3$ and aq NH_4OH (5:1, 500 mL). The aqueous layer was extracted with $CHCl_3$ (3 × 200 mL). The combined organic layers were washed with brine (100 mL) and dried (K_2CO_3). The solvent was removed under reduced pressure to afford the crude amine which was chromatographed (flash) on silica gel ($CHCl_3$/EtOH = 9:1) to provide pure N_a-Me, N_b-H, tetracyclic ketone **36** (4.56 g, 87%): FTIR ($CHCl_3$) 1700, 1619 cm^{-1}; $[\alpha]_D = -147.16$ (*c* 0.43, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 2.10−2.22 (m, 2 H), 2.46−2.55 (m, 2 H), 2.81 (d, $J = 16.6$ Hz, 1 H), 3.13 (dd, $J = 16.6$, 6.8 Hz, 1 H), 3.65 (s, 3 H), 3.90 (s, 3 H), 3.96 (d, $J = 6.8$ Hz, 1 H), 4.40 (bs, 1 H), 6.78 (m, 2 H), 7.36 (d, $J = 9.2$ Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 25.68, 29.32, 31.37, 34.84, 44.89, 55.75, 59.68, 93.10, 106.39, 108.53, 118.65, 120.89, 133.84, 137.69, 156.30, 210.64; EIMS (*m/e*, relative intensity) 270 (M^+, 23), 213 (100). Anal. Calcd for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 70.89; H, 6.77; N, 10.25. This material was used directly in the next step.

Preparation of (6*S*,10*S*)-5,6,7,8,10,11-Hexahydro-12-(*Z*-2′-iodo-2′-butenyl)-3-methoxy-5-methyl-6,10-iminocyclooct-[*b*]indol-9-one (38). A solution of N_a-methyl, N_b-H tetracyclic ketone **36** (4.0 g, 14.8 mmol) and *Z*-1-bromo-2′-iodo-2-butene **37** (5.35 g, 20.6 mmol) was dissolved in THF (200 mL), and K_2CO_3 (13.3 g) was added. The mixture was heated to 60 °C for 24 h. Analysis by TLC (silica gel, $CHCl_3/C_2H_5OH$ = 4:1) indicated the absence of tetracyclic ketone **36**. 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 flash chromatography (silica gel, EtOAc/hexanes = 1:9) to provide N_b-Z-2′-iodo-2′-butenyl tetracyclic ketone **38** (5.66 g, 85%): FTIR ($CHCl_3$) 1710, 1618 cm^{-1}; $[\alpha]_D = -81.96$ (*c* 1.36, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.83 (d, $J = 6.36$ Hz, 3 H), 1.96−2.18 (m, 2 H), 2.48−2.59 (m, 2 H), 2.68 (d, $J = 16.9$ Hz, 1 H), 3.12 (dd, $J = 16.9$. 6.9 Hz, 1 H), 3.37 (bs, 2 H), 3.60 (s, 3 H), 3.70 (d, $J = 6.5$ Hz, 1 H), 3.91 (s, 3 H), 4.09 (bs, 1 H), 5.85 (q, $J = 6.3$ Hz, 1 H), 6.80 (m, 2 H), 7.37 (d, $J = 9.2$ Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.54, 21.71, 29.36, 29.75, 34.27, 48.75, 55.82, 63.52, 63.93, 93.17, 105.82, 108.59, 118.68, 120.79, 132.00, 132.65, 137.83, 139.28, 156.32, 209.97; EIMS (*m/e*, relative intensity) 450 (M^+, 20), 393 (89), 213 (100), 212 (69). Anal. Calcd for $C_{20}H_{23}N_2O_2I$: C, 53.34; H, 5.15; N, 6.22. Found: C, 53.66; H, 5.29; N, 6.03. This material was used directly in the next step.

Preparation of 11-Methoxy-1-methyl-17-norsarpagan-16-one (39). A mixture of N_b-*Z*-2′-iodo-2′-butenyl tetracyclic ketone **38** (2 g, 4.44 mmol), $Pd(OAc)_2$ (50 mg, 0.22 mmol), Bu_4NBr (1.45 g, 4.44 mmol), PPh_3 (250 mg, 0.95 mmol), and K_2CO_3 (2.47 g, 17.76 mmol) in a solution of DMF−H_2O (9:1, 200 mL) was degassed under reduced pressure at rt with argon. The mixture was then heated to 70 °C (oil bath temperature) under an atmosphere of argon for 24 h. The mixture was cooled to rt, diluted with EtOAc (1000 mL), washed with H_2O (5 × 100 mL), and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the oil which resulted was chromatographed (silica gel, EtOAc/hexanes = 3:7) to provide pentacyclic ketone **39** (1.18 g, 82%): ^1H NMR (300 MHz, $CDCl_3$) δ 1.68 (d, $J = 6.9$ Hz, 3 H), 2.16 (dt, $J = 12.6$, 3.3 Hz, 1 H), 2.52 (t, $J = 11.7$ Hz, 1 H), 2.97 (dd, $J = 15.6$, 6.2 Hz, 1 H), 3.28 (d, $J = 15.5$ Hz, 1 H), 3.40 (bs, 1 H), 3.56 (s, 3 H), 3.58 (m, 1 H), 3.84 (m, 2 H), 3.89 (s, 3 H), 4.34 (d, $J = 9.3$ Hz, 1 H), 5.54 (q, $J = 6.9$ Hz, 1 H), 6.77 (m, 2 H), 7.38 (d, $J = 8.2$ Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.58, 22.50, 29.28, 36.01, 44.34, 49.66, 55.50, 55.73, 64.09, 93.09, 104.43, 108.29, 119.02, 120.87, 121.00, 132.40, 136.44, 138.18, 156.13, 217.29; CIMS (*m/e*, relative intensity) 323 ($M^+ + 1$, 100); HRMS calcd for

$C_{20}H_{22}N_2O_2$ 322.1681, found 322.1681. This material was employed directly in the next step.

Preparation of (+)-11-Methoxy-1-methylsarpagan-17-al (40). A mixture of anhydrous potassium *tert*-butoxide (6.73 g, 0.06 mol) and methoxymethyl triphenylphosphonium chloride (17.1 g, 0.05 mol) in dry benzene (500 mL) was allowed to stir at rt for 1 h. The pentacyclic ketone **39** (2.0 g, 6.9 mmol) in THF (160 mL) was then added into the above orange solution dropwise at rt. The mixture which resulted was stirred at rt for 24 h (the reaction progress was monitored by ^{1}H 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 rapid wash column on 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 which resulted was stirred at 55 °C (oil bath temperature) under an atmosphere of argon for 6 h (the reaction progress was monitored by ^{1}H 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), brine (100 mL) and dried (K_2CO_3). The solvent was removed under reduced pressure to provide N_a-methyl-16-*epi*-gardneral **40** (1.88 g, 90%): FTIR ($CHCl_3$) 1710, 1618, 1484 cm^{-1}; $[\alpha]_D$ = +30.93 (*c* 1.05, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.62 (d, J = 6.9 Hz, 3 H), 1.78 (ddd, J = 12.4, 3.7, 2.6 Hz, 1 H), 2.13 (ddd, J = 12.2, 9.8, 1.8 Hz, 1 H), 2.52 (d, J = 7.6 Hz, 1 H), 2.57 (d, J = 15.6 Hz, 1 H), 3.13 (dd, J = 15.5, 5.2 Hz, 1 H), 3.22 (m, 1 H), 3.59 (s, 3 H), 3.61−3.66 (m, 3 H), 3.89 (s, 3 H), 4.25 (d, J = 8.4 Hz, 1 H), 5.38 (q, J = 6.7 Hz, 1 H), 6.77 (m, 2 H), 7.35 (d, J = 7.8 Hz, 1 H), 9.65 (s, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.57, 26.48, 27.17, 29.33, 32.29, 49.33, 50.47, 54.75, 55.76, 56.06, 93.18, 102.92, 108.17, 116.90, 118.68, 121.53, 134.23, 137.88, 138.05, 155.95, 202.71; EIMS (70 eV, *m/e*, relative intensity) 336 (M^+, 95), 307 (100), 277 (97), 213 (50). This material was employed directly in the next step without further purification.

Preparation of (6*S*,7*R*,9*E*,10*S*,11a*S*)-9-Ethylidene-5,8,9,-10,11a,12-hexahydro-3-methoxy-5-methyl-6,10-methanoindolo[3,2-*b*]quinolizine-11,11(6*H*)-dimethanol (41). To a solution of aldehyde **40** (336 mg, 1.0 mmol) in MeOH (10 mL) were added formaldehyde [(25 equiv, 25 mmol) 1.9 mL of a 37% w/w solution in water] and 85% KOH (10 equiv, 659 mg, 10 mmol) in MeOH (10 mL). The reaction mixture which resulted was stirred at rt for 10 h, diluted with brine, and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue that resulted was purified by column chromatography (MeOH/$CHCl_3$ = 1:12) to afford **41** (320 mg, 87%): FTIR 3329, 2931, 1625, 1491 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.67 (d, J = 6.8 Hz, 3 H), 1.84−2.00 (m, 2 H), 2.66 (m, 1 H), 3.01 (m, 3 H), 3.46 (d, J = 10.9 Hz, 1 H), 3.54 (s, 3 H), 3.60 (d, J = 10.9 Hz, 1 H), 3.71 (m, 4 H), 3.90 (s, 3 H), 4.25 (d, J = 9.2 Hz, 1 H), 5.41 (q, J = 6.4 Hz, 1 H), 6.77 (m, 2 H), 7.33 (dd, J = 7.2, 1.9 Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.8, 22.2, 27.5, 28.3, 29.2, 48.2, 48.9, 55.7, 55.9, 56.8, 63.6, 70.2, 93.1, 104.8, 108.3, 117.0, 118.8, 120.2, 135.3, 135.8, 138.1, 156.1; EIMS (*m/e*, relative intensity) 368 (M^+, 100), 351 (23), 337 (57), 293 (23), 213 (69); HRMS calcd for $C_{22}H_{28}N_2O_3$ 368.2100, found 368.2087. This material was employed directly in the next step.

Preparation of (6*S*,7*R*,9*E*,10*S*,11a*S*)-9-Ethylidene-5,6,-8,9,10,11,11a,12-octahydro-11-hydromethyl-3-methoxy-5-methyl-6,10-methanoindolo[3,2-*b*]quinolizine-11-carboxaldehyde (42). The TPAP (12.3 mg, 0.034 mmol) was added to a mixture of **41** (250 mg, 0.68 mmol), 4 Å MS (340 mg, 500 mg/mmol), and NMO (123.1 mg, 1.02 mmol) in CH_2Cl_2 (50 mL) under a N_2 atmosphere. The reaction mixture which resulted was stirred at rt for 12 h, at which time it was passed through a pad of Celite and washed with CH_2Cl_2 (50 mL). The filtrate was washed with brine (2 × 50 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue that resulted was purified by preparative TLC on silica gel ($CHCl_3$/MeOH = 9:1) to provide **42** and its C-16 epimer in >8:1 ratio (186 mg, 77%). **42**: FTIR 2923, 1700, 1625, 1489 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.63 (d, J = 8.0 Hz, 3 H), 1.96 (m, 1 H), 2.10 (dt, J = 13.2, 3.4 Hz, 1H), 2.91 (d, J = 15.6 Hz, 1 H), 3.02 (d, J = 4.8 Hz, 1 H), 3.06 (m, 1 H), 3.10 (d, J = 5.0 Hz, 1 H), 3.55 (s, 3 H), 3.56 (m, 1 H), 3.64 (m, 2 H), 3.72 (m, 1 H), 3.89 (s, 3 H), 4.25 (dd, J = 9.8, 1.8 Hz, 1 H), 5.42 (q, J = 6.8 Hz, 1 H), 6.76 (m, 2 H), 7.31 (d, J = 11.0 Hz, 1 H), 9.18 (s, 1 H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 12.8, 24.0, 27.2, 27.6, 29.2, 49.2, 53.8, 55.7, 55.8, 61.3, 66.7, 93.2, 104.3, 108.2, 117.1, 118.7, 120.1, 135.8, 137.3, 138.4, 156.2, 203.8; EIMS (*m/e*, relative intensity) 366 (M^+, 53), 337 (64), 293 (34), 213 (100), 198 (29), 79 (36). This material was employed directly in the next step.

Preparation of (2α,17*S*,19*E*)-17-Aceto-16-[(acetyloxy)-methyl]-19,20-didehydro-11-methoxyajmalan-2,17-diol (43). The TFA (3 mL) was added to a solution of aldehyde **42** (100 mg, 0.27 mmol) in Ac_2O (3 mL). The reaction mixture was stirred in a sealed vessel at rt for 8 h, at which time it was concentrated under reduced pressure. The residue was diluted with CH_2Cl_2 (20 mL), and a cold solution of an aq 10% NH_4OH was added to bring the pH to 8. The organic layer was diluted with CH_2Cl_2 (20 mL), washed with brine (2 × 20 mL), dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residue that resulted was purified by preparative TLC on silica gel ($CHCl_3$/MeOH = 9:1) to provide **43** (108.7 mg, 85%): FTIR 2938, 1741, 1624, 1239 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.56 (m, 1 H), 1.60 (d, J = 6.8 Hz, 3 H), 1.78 (s, 3 H), 2.02 (s, 3 H), 2.04 (m, 1 H), 2.53 (d, J = 12.4 Hz, 1 H), 2.72 (s, 3 H), 2.76 (d, J = 4.6 Hz, 1 H), 2.88 (d, J = 4.0 Hz, 1 H), 2.97 (dd, J = 13.5, 4.7 Hz, 1 H), 3.52 (m, 2 H), 3.64 (d, J = 10.2 Hz, 1 H), 3.78 (s, 3 H), 3.92 (m, 2 H), 5.35 (s, 1 H), 5.43 (q, J = 6.7 Hz, 1 H), 6.15 (d, J = 2.1 Hz, 1 H), 6.29 (dd, J = 8.1, 2.2 Hz, 1 H), 6.96 (d, J = 8.0 Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.8, 20.6, 20.7, 22.7, 28.3, 29.4, 30.0, 43.8, 55.3, 55.6, 58.1, 58.8, 62.0, 67.8, 77.1, 81.9, 95.9, 97.8, 102.4, 116.7, 119.2, 123.3, 137.2, 153.6, 160.8, 169.4, 171.0; EIMS (*m/e*, relative intensity) 468 (M^+, 5), 452 982), 349 (5), 283 (100), 224 (94), 212 (32). This material was employed directly in the next step.

Preparation of (2α,17R,19*E*)-17-Aceto-16-[(acetyloxy)-methyl]-19,20-didehydro-11-methoxyajmalan-2,17-diol (44). The TFA (5 mL) and Et_3SiH (5 mL) were added at rt to a solution of **43** (50 mg, 0.106 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was stirred in a sealed vessel at rt for 3 d, at which time it was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (10 mL), and cold 10% aq NH_4-OH was added to bring the pH to 8. The organic layer was diluted with CH_2Cl_2 (20 mL), washed with brine (2 × 20 mL), dried (Na_2SO_4), and filtered and the solvent removed under reduced pressure. The residue that resulted was purified by preparative TLC on silica gel ($CHCl_3$/MeOH = 15:1) to provide **44** (41 mg, 85%): FTIR 2944, 1742, 1232 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.53 (dd, J = 13.7, 10.4 Hz, 1 H), 1.60 (d, J = 6.8 Hz, 3 H), 1.80 (s, 3 H), 1.82 (m, 1 H), 2.03 (s, 3 H), 2.27 (dd, J = 12.0, 4.6 Hz, 1 H), 2.65 (s, 3 H), 2.73 (d, J = 4.5 Hz, 1 H), 2.81 (d, J = 3.4 Hz, 1H), 2.98 (dd, J = 13.4, 4.8 Hz, 1 H), 3.36 (d, J = 4.6 Hz, 1 H), 3.54 (m, 2 H), 3.72 (dd, J = 9.6, 4.5 Hz, 1 H), 3.82 (s, 3 H), 3.93 (m, 2 H), 5.31 (s, 1 H), 5.39 (q, J = 6.8 Hz, 1 H), 6.21 (d, J = 2.2 Hz, 1 H), 6.32 (dd, J = 8.1, 2.2 Hz, 1 H), 6.98 (d, J = 8.1 Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.8, 20.8, 22.2, 28.8, 29.6, 34.7, 36.4, 45.0, 52.7, 54.0, 55.3, 55.6, 61.8, 68.0, 77.1, 82.6, 96.5, 103.0, 116.4, 121.4, 122.8, 137.6, 156.3, 160.6, 169.5, 171.0; EIMS (*m/e*, relative intensity) 452 (M^+, 100), 409 (6), 393 (22). This material was used directly in the next step.

Preparation of (+)-(2α,17*R*,19*E*)-19,20-Didehydro-17-hydroxy-11-methoxyajmalan-16-methanol (45). The 20% aq K_2CO_3 (5 mL) was added to a solution of **44** (30 mg, 0.066 mmol) in MeOH (5 mL) at rt. The mixture was stirred at rt for 6 h and concentrated under reduced pressure to remove the MeOH. It was then diluted with CH_2Cl_2 (20 mL) and separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residue that resulted was purified by preparative TLC on silica gel ($CHCl_3$/MeOH = 9:1) to provide **45** (21.6 mg, 90%): $[\alpha]_D$ = +24.8 (*c* 1.75, MeOH); FTIR 3372, 2915, 1618, 1489, 1459, 1262, 1227, 1077 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.53 (m, 1 H), 1.67 (d, *J* = 6.8 Hz, 3 H), 1.75 (d, *J* = 11.9 Hz, 1H), 2.18 (dd, *J* = 11.9, 4.5 Hz, 1 H), 2.65 (s, 3 H), 2.81 (d, *J* = 4.2 Hz, 1 H), 2.93 (m, 2 H), 3.42 (d, *J* = 6.7 Hz, 1 H), 3.44 (m, 1 H), 3.54 (m, 1 H), 3.57 (t, *J* = 2.2 Hz, 1 H), 3.63 (d, *J* = 10.2 Hz, 1 H), 3.74 (dd, *J* = 9.7, 5.1 Hz, 1 H), 3.82 (s, 3 H), 4.07 (s, 1 H), 5.37 (q, *J* = 6.8 Hz, 1 H), 6.32 (d, *J* = 2.1 Hz, 1 H), 6.40 (dd, *J* = 8.0, 2.2 Hz, 1 H), 7.01 (d, *J* = 8.0 Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.0, 22.6, 28.1, 34.7, 35.8, 47.3, 53.2, 54.6, 55.4, 55.5, 62.1, 67.1, 76.2, 85.8, 97.2, 104.2, 116.3, 122.0, 122.7, 137.5, 156.1, 160.7; EIMS (*m*/*e*, relative intensity) 368 (M^+, 72), 351(8), 187 (100), 174 (78). This material was used in a later step.

Preparation of N_a-Boc-vellosimine (47). To a solution of vellosimine **46** (100 mg, 0.34 mmol) and Boc_2O (100 mg, 0.47 mmol) in dry CH_3CN (1 mL) was added DMAP (5 mg). The mixture which resulted was allowed to stir at rt for 4 h. The solvent was removed under reduced pressure and the oil was chromatographed (silica gel, EtOAc/hexanes = 2:3) to provide **47** (113 mg, 85%): FTIR (NaCl) 1726, 1369 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.58 (d, *J* = 6.82 Hz, 3 H), 1.66 (s, 9 H), 1.78 (dt, *J* = 12.9, 3.1 Hz, 1 H), 2.22 (m, 1 H), 2.39 (d, *J* = 7.5 Hz, 1 H), 2.53 (dd, *J* = 16.1, 1.0 Hz, 1 H), 3.08 (ddd, *J* = 16.1, 5.4, 1.2 Hz, 1 H), 3.16 (t, *J* = 1.9 Hz, 1 H), 3.53−3.65 (m, 3 H), 4.71 (d, *J* = 7.4 Hz, 1 H), 5.32 (q, *J* = 6.9 Hz, 1 H), 7.17−7.28 (m, 2 H), 7.38 (d, *J* = 7.0 Hz, 1 H), 8.08 (d, *J* = 7.6 Hz, 1 H), 9.62 (s, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.6, 26.7, 27.2, 28.2, 33.4, 49.4, 51.3, 55.3, 56.0, 84.0, 110.7, 115.8, 116.8, 118.0, 122.7, 124.0, 129.4, 134.4, 136.0, 138.7, 150.1, 202.8; EIMS (*m*/*e*, relative intensity) 392 (M^+, 21), 336 (25), 321 (14), 307 (100), 293 (22), 263 (18), 213 (26), 169 (38); HRMS calcd for $C_{24}H_{28}N_2O_3$ 392.2100, found 392.2079. This material was used directly in the next step.

Preparation of N_a-Boc-17-hydroxysarpagan-16-methanol (48). To a solution of aldehyde **47** (392 mg, 1.0 mmol) in MeOH (10 mL) were added formaldehyde [(25 equiv, 25 mmol) 1.9 mL of a 37% w/w solution in water] and 85% KOH (10 equiv, 659 mg, 10 mmol) in MeOH (10 mL). The reaction mixture was stirred at rt for 10 h, diluted with brine, and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue that resulted was purified by column chromatography (MeOH/$CHCl_3$ = 1:12) to afford diol **48** (390 mg, 92%): FTIR 3070, 2923, 1726 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.60 (d, *J* = 6.7 Hz, 3 H), 1.68 (s, 9 H), 1.81 (dt, *J* = 13.6, 3.3 Hz, 1 H), 2.01 (td, *J* = 10.5, 2.2 Hz, 1 H), 2.81 (m, 4 H), 3.43 (d, *J* = 10.7 Hz, 1 H), 3.54 (m, 4 H), 3.70 (d, *J* = 10.7 Hz, 1 H), 4.61 (dd, *J* = 10.3, 3.4 Hz, 1 H), 5.30 (q, *J* = 6.6 Hz, 1 H), 7.29 (m, 3 H), 8.12 (d, *J* = 7.9 Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.7, 22.3, 27.9, 28.1, 28.1, 28.1, 29.2, 42.5, 50.6, 55.4, 55.9, 64.4, 70.6, 83.9, 112.6, 115.6, 115.9, 117.9, 122.6, 123.9, 128.4, 135.8, 136.9, 137.5, 149.9; EIMS (*m*/*e*, relative intensity) 424 (M^+, 100), 368 (94), 351 (49), 337 (92), 323 (30), 293 (51), 213 (52), 169 (78); HRMS calcd for $C_{25}H_{32}N_2O_4$ 424.2362, found 424.2356. This material was used directly in the next step.

Preparation of (6*S*,7*R*,9*E*,10*S*,11*S*,11a*S*)-9-Ethylidene-5,6,8,9,10,11,11a,12-octahydro-11-(hydroxymethyl)-5*H*-6,10-methanoindolo[3,2-*b*]quinolizine-11-carboxaldehyde (50). The TPAP (6.9 mg, 0.019 mmol) was added to a mixture of **48** (161 mg, 0.38 mmol), 4 Å MS (190 mg, 500 mg/mmol), and NMO (69 mg, 0.57 mmol) in CH_2Cl_2 (30 mL) under a N_2 atmosphere. The reaction mixture which resulted was stirred at rt for 12 h, at which time it was passed through a pad of Celite and washed with CH_2Cl_2 (30 mL). The filtrate was washed with brine (2 × 30 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue that resulted was purified by preparative TLC on silica gel ($CHCl_3$/MeOH = 9:1) to provide **49** and its C-16 epimer in >8:1 ratio (120 mg, 75%). The TFA (2 mL) was added to a solution of pure **49** prepared above (120 mg, 0.28 mmol) in CH_2Cl_2 (5 mL) at rt. The reaction mixture was stirred at rt for 3 h. After removal of the solvent under reduced pressure, the residue was brought to pH 9 with a cold solution of 10% aq NaOH. The mixture which resulted was extracted with CH_2Cl_2 (2 × 20 mL), the combined organic extracts were washed with brine (2 × 20 mL), dried (Na_2SO_4), and filtered, and the solvent was removed under reduced pressure. The residue that resulted was purified by column chromatography on silica gel ($CHCl_3$/MeOH = 20:1) to afford aldehyde **50** (76 mg, 84%): FTIR 3374, 2906, 1680, 1452 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.57 (d, *J* = 6.7 Hz, 3 H), 1.69 (t, *J* = 11.4 Hz, 1 H), 1.96 (m, 1 H), 2.82 (dd, *J* = 15.6, 4.6 Hz, 1 H), 2.90 (d, *J* = 3.0 Hz, 1 H), 3.02 (d, *J* = 3.7 Hz, 1 H), 3.16 (d, *J* = 5.4 Hz, 1 H), 3.38 (dd, *J* = 10.2, 4.6 Hz, 1 H), 3.47 (dd, *J* = 7.9, 1.7 Hz, 1 H), 3.65 (dd, *J* = 10.4, 4.9 Hz, 1 H), 4.11 (d, *J* = 10.2 Hz, 1 H), 4.79 (t, *J* = 4.6 Hz, 1 H), 5.32 (q, *J* = 6.7 Hz, 1 H), 6.94 (t, *J* = 7.8 Hz, 1 H), 7.02 (td, *J* = 8.8, 1.2 Hz, 1 H), 7.25 (d, *J* = 8.0 Hz, 1 H), 7.36 (d, *J* = 7.5 Hz, 1 H), 8.99 (s, 1 H), 10.87 (s, 1 H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 13.0, 23.6, 26.9, 28.1, 50.0, 53.1, 55.6, 58.4, 66.2, 104.2, 111.4, 115.3, 117.9, 118.6, 121.0, 126.1, 136.8, 138.7, 139.0, 202.2; EIMS (*m*/*e*, relative intensity) 322 (M^+, 195), 293 (72), 263 (44), 249 (53), 169 (100); HRMS calcd for $C_{20}H_{22}N_2O_2$ 322.1681, found 322.1670. This material was used directly in the next step.

Preparation of (2α,17*S*,19*E*)-17-Aceto-16-[(acetyloxy)-methyl]-19,20-didehydro-1-demethylajmalan-17-ol (52). The Ac_2O (3 mL) which was presaturated with HCl (g) was added to a solution of **50** (92 mg, 0.28 mmol). The reaction mixture was heated at 55 °C in a sealed vessel for 5 d. After cooling, the solvent was removed under reduced pressure. The residue was diluted with CH_2Cl_2 (20 mL), and cold 10% aq NH_4OH was added to bring the pH to 8. The organic layer was diluted with CH_2Cl_2 (20 mL), washed with brine (2 × 20 mL), dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residue that resulted was purified by preparative TLC on silica gel ($CHCl_3$/MeOH = 9:1) to provide a mixture of **51** and its C-17 epimer in >2:1 ratio (90 mg, 78%). To a solution of **51** prepared above (81 mg, 0.20 mmol) in AcOH (2 mL) was added $NaBH_3CN$ (20 mg, 0.30 mmol) at rt. The reaction mixture was stirred at rt for 1 h and then cooled in an ice bath. The 10% aq NH_4OH was added to bring the pH to 8 and the mixture was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with brine (2 × 20 mL), dried (Na_2SO_4), and filtered, and the solvent was removed under reduced pressure. The residue that resulted was purified by preparative TLC on silica gel ($CHCl_3$/MeOH = 9:1) to provide **52** (49 mg, 60%) and its C-17 epimer (24 mg, 30%). **52**: FTIR 3423, 1642, 1243 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.52 (m, 1 H), 1.58 (d, *J* = 6.6 Hz, 3 H), 1.77 (d, *J* = 11.7 Hz, 1 H), 1.87 (s, 3 H), 2.00 (s, 3 H), 2.45 (dd, *J* = 11.7, 4.7 Hz, 1 H), 2.71 (m, 2 H), 3.10 (d, *J* = 4.2 Hz, 1 H), 3.46 (t, *J* = 1.8 Hz, 1 H), 3.56 (dd, *J* = 9.4, 4.0 Hz, 1 H), 3.86 (m, 2 H), 3.92 (d, *J* = 10.9 Hz, 1 H), 4.11 (d, *J* = 10.9 Hz, 1 H), 5.38 (q, *J* = 6.4 Hz, 1 H), 5.63 (s, 1 H), 6.76 (m, 2 H), 7.08 (m, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.7, 20.6, 20.7, 21.6, 28.5, 36.2, 49.8, 55.1, 55.4, 57.1, 62.3, 64.3, 68.4, 74.7, 110.9, 117.2, 119.1, 123.8, 128.3, 128.8, 137.4, 151.5, 168.7, 170.9; EIMS (*m*/*e*, relative intensity) 408 (M^+, 100), 349 (71), 278 (19), 218 (27), 176 (57), 130 (94); HRMS calcd for $C_{24}H_{28}N_2O_4$ 408.2049, found 408.2049. This material was used directly in the next step.

Preparation of (+)-(2α,17*S*,19*E*)-19,20-Didehydro-17-hydroxy-1-demethylajmalan-16-methanol (53). A 20% aq solution of K_2CO_3 (2 mL) was added to a solution of **52** (8.2 mg, 0.02 mmol) in methanol (2 mL) at rt. The mixture which resulted was stirred at rt for 24 h and concentrated under reduced pressure to remove MeOH, diluted with CH_2Cl_2 (10 mL), and separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and filtered, and the solvent was removed under reduced pressure. The residue that resulted was purified by preparative TLC on silica gel ($CHCl_3$/MeOH = 9:1) to provide diol **53** as a pale yellow powder (5.5 mg, 85%): $[\alpha]_D$ = +59.2 (*c* 0.24, MOH); FTIR: 3395, 2925, 1632, 1462 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.52 (dd, *J* = 9.9, 4.1 Hz, 1 H), 1.71 (d, *J* = 6.8 Hz, 3 H), 1.75 (m, 1 H), 2.48 (m, 1 H), 2.52 (d, *J* = 7.0 Hz, 1 H), 2.74 (d, *J* = 4.6 Hz, 1 H), 3.00 (d, *J* = 4.8 Hz, 1 H), 3.46 (m, 2 H), 3.55 (m, 1 H), 3.67 (m, 2 H), 3.92 (d, *J* = 5.1 Hz, 1 H), 4.30 (s, 1 H), 5.42 (q, *J* = 6.8 Hz, 1 H), 6.82 (m, 2 H), 7.15 (m, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.9, 21.8, 28.5, 35.2, 51.5, 55.1, 55.4, 58.1, 62.7, 64.4, 68.2, 75.1, 111.1, 117.3, 119.7, 123.9, 128.5, 129.3, 137.0, 151.7; EIMS (*m/e*, relative intensity) 324 (M$^+$, 66), 307 (10), 194 (100), 176 (29), 130 (87); HRMS calcd for $C_{20}H_{24}N_2O_2$ 324.1838, found 324.1835. This material was identical to that obtained from an authentic sample of quebrachidine (**3**) described below.

Preparation of (+)-(2α,17*S*,19*E*)-19,20-Didehydro-17-hydroxy-1-demethylajmalan-16-methanol (53) from the Reduction of Natural (+)-Quebrachidine (3). The $LiAlH_4$ (4 equiv, 2.6 mg, 0.064 mmol) was added to a solution of natural (+)-quebrachidine (5.6 mg, 0.016 mmol) in THF (2 mL) at 0 °C. After the mixture was stirred for 10 min at 0 °C, the reaction was warmed to rt and stirred for an additional 4 h. it was then cooled in an ice bath. Water (0.5 mL) was slowly added to this mixture, and the mixture was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residue that resulted was purified by preparative TLC on silica gel ($CHCl_3$/MeOH = 9:1) to provide authentic diol **53** as a pale yellow powder (4.2 mg, 82%): $[\alpha]_D$ = +60.6 (*c* 0.165, MeOH); FTIR 3326, 2922, 1608, 1456 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.53 (dd, *J* = 9.9, 4.1 Hz, 1 H), 1.71 (d, *J* = 6.8 Hz, 3 H), 1.75 (m, 1 H), 2.48 (m, 1 H), 2.53 (d, *J* = 7.0 Hz, 1 H), 2.74 (d, *J* = 4.6 Hz, 1 H), 3.01 (d, *J* = 4.7 Hz, 1 H), 3.46 (m, 2 H), 3.55 (m, 1 H), 3.67 (m, 2 H), 3.92 (d, *J* = 5.0 Hz, 1 H), 4.30 (s, 1 H), 5.41 (q, *J* = 6.8 Hz, 1 H), 6.83 (m, 2 H), 7.16 (m, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.9, 21.9, 28.6, 35.2, 51.5, 55.2, 55.5, 58.2, 62.7, 64.3, 68.3, 75.2, 111.1, 117.3, 119.7, 123.9, 128.5, 129.3, 137.3, 151.7; EIMS (*m/e*, relative intensity) 324 (M$^+$, 85), 307 (6), 194 (100), 176 (28), 130 (89); HRMS calcd for $C_{20}H_{24}N_2O_2$ 324.2838, found 324.1837.

Preparation of (2α,17*R*,19*E*)-17-Aceto-16-[(acetyloxy)-methyl]-19,20-didehydroajmalan-2,17-diol (54). Aldehyde **23** (80 mg, 0.23 mmol) was dissolved in Ac_2O (5 mL) which was presaturated with HCl gas. The reaction mixture was stirred in a sealed vessel at rt for 3 d, at which time it was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (20 mL), and cold 10% aq NH_4OH was added to bring the pH to 8. The organic layer was diluted with CH_2Cl_2 (20 mL), washed with brine (2 × 20 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue that resulted was purified by preparative TLC on silica gel ($CHCl_3$/MeOH = 12:1) to provide **54** (60 mg, 60%) and its C-17 epimer (18 mg, 18%). **54**: FTIR 2950, 1743, 1477 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.59 (d, *J* = 6.8 Hz, 3 H), 1.68 (dd, *J* = 14.3, 3.7 Hz, 1 H), 1.87 (s, 3 H), 2.00 (s, 3 H), 2.24 (dd, *J* = 12.6, 4.5 Hz, 1 H), 2.57 (d, *J* = 12.6 Hz, 1 H), 2.67 (dd, *J* = 15.0, 5.0 Hz, 1 H), 2.74 (s, 3 H), 2.78 (d, *J* = 4.6 Hz, 1 H), 3.12 (d, *J* = 4.6 Hz, 1 H), 3.20 (d, *J* = 4.7 Hz, 1 H), 3.53 (m, 2 H), 3.73 (d, *J* = 10.1 Hz, 1 H), 3.90 (d, *J* = 10.9 Hz, 1 H), 4.10 (d, *J* = 10.9 Hz, 1 H), 5.49 (q, *J* = 6.8 Hz, 1 H), 5.62 (d, *J* = 1.5 Hz, 1 H), 6.62 (d, *J* = 7.8 Hz, 1 H), 6.75 (td, *J* = 7.9, 0.7 Hz, 1 H), 7.02 (dd, *J* = 7.2, 0.9 Hz, 1 H), 7.17 (td, *J* = 7.7, 1.3 Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) 12.7, 20.6, 21.6, 28.6, 29.9, 30.1, 48.9, 55.2, 58.8, 62.1, 62.7, 63.9, 75.3, 96.6, 108.7, 118.3, 118.7, 123.9, 127.0, 128.7, 135.5, 151.5, 168.6, 170.7; EIMS (*m/e*, relative intensity) 438 (M$^+$, 100), 422 (76), 379 (34), 319 (22), 289 (12), 182 (28); HRMS calcd for $C_{25}H_{30}N_2O_5$ 438.2154, found 438.2148. This material was used directly in the next step.

Preparation of *O*,*O*-Diacetylvincamajinol (55). TFA (3 mL) and Et_3SiH (3 mL) were added to a solution of **54** (66 mg, 0.15 mmol) in CH_2Cl_2 (4 mL). The reaction mixture which resulted was stirred in a sealed vessel at rt for 2 d, at which time the solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (10 mL) and brought to pH 7 with cold 10% aq NH_4OH. The organic layer was diluted with CH_2Cl_2 (20 mL), washed with brine (2 × 20 mL), and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue that resulted was purified by preparative TLC on silica gel ($CHCl_3$/MeOH = 15:1) to provide diacetate **55** (57.6 mg, 91%): FTIR 2950, 1744, 1477, 1244 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.52 (m, 1 H), 1.56 (d, *J* = 6.7 Hz, 3 H), 1.75 (d, *J* = 11.8 Hz, 1 H), 1.85 (s, 3 H), 1.98 (s, 3 H), 2.41 (dd, *J* = 6.9, 3.9 Hz, 1 H), 2.53 (dd, *J* = 14.3, 5.0 Hz, 1 H), 2.65 (s, 3 H), 2.68 (d, *J* = 4.7 Hz, 1 H), 3.08 (d, *J* = 4.6 Hz, 1 H), 3.20 (d, *J* = 4.9 Hz, 1 H), 3.43 (m, 1 H), 3.45 (t, *J* = 2.1 Hz, 1 H), 3.57 (dd, *J* = 10.0, 4.9 Hz, 1 H), 3.90 (d, *J* = 10.9 Hz, 1 H), 4.09 (d, *J* = 10.9 Hz, 1 H), 5.39 (q, *J* = 6.8 Hz, 1 H), 5.58 (d, *J* = 0.9 Hz, 1 H), 6.65 (dd, *J* = 7.4, 3.6 Hz, 1 H), 6.73 (td, *J* = 7.5, 0.6 Hz, 1 H), 7.01 (dd, *J* = 7.2, 0.8 Hz, 1 H), 7.15 (td, *J* = 7.7, 1.2 Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) 12.7, 20.5, 20.6, 21.1, 28.3, 34.0, 35.9, 49.8, 53.6, 55.4, 56.3, 62.3, 64.2, 74.6, 75.1, 109.1, 117.3, 118.6, 123.3, 128.4, 129.2, 137.1, 154.2, 169.5, 170.9; EIMS (*m/e*, relative intensity) 422 (M$^+$, 100), 379 (12), 363 (39), 319 (7); HRMS calcd for $C_{25}H_{30}N_2O_4$ 422.2206, found 422.2181. This material was used directly in the next step.

Preparation of (+)-(2α,17*S*,19*E*)-19,20-Didehydro-17-hydroxyajmalan-16-methanol (56). The 20% aq solution of K_2CO_3 (2 mL) was added to a solution of diacetate **55** (21 mg, 0.05 mmol) in methanol (2 mL) at rt. The mixture which resulted was stirred at rt for 2 d and concentrated under reduced pressure to remove MeOH, after which it was diluted with CH_2Cl_2 (15 mL), and separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and filtered, and the solvent was removed under reduced pressure. The residue that resulted was purified by preparative TLC on silica gel ($CHCl_3$/MeOH = 9:1) to provide diol **56** as a pale yellow oil (15 mg, 88%): $[\alpha]_D$ = +10.5 (*c* 0.51, MeOH); FTIR 2943, 1607, 1476 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50 (dd, *J* = 13.8, 9.8 Hz, 1 H), 1.61 (m, 1 H), 1.67 (d, *J* = 6.7 Hz, 3 H), 2.34 (dd, *J* = 14.0, 5.0 Hz, 1 H), 2.48 (dd, *J* = 11.8, 4.8 Hz, 1 H), 2.65 (s, 3 H), 2.71 (d, *J* = 5.8 Hz, 1 H), 2.94 (d, *J* = 4.7 Hz, 1 H), 3.23 (d, *J* = 4.9 Hz, 1 H), 3.42 (m, 2 H), 3.52 (m, 1 H), 3.69 (m, 2 H), 4.24 (s, 1 H), 5.39 (q, *J* = 6.7 Hz, 1 H), 6.67 (d, *J* = 7.8 Hz, 1 H), 6.83 (td, *J* = 7.5, 0.6 Hz, 1 H), 7.15 (dd, *J* = 7.2, 0.7 Hz, 1 H), 7.20 (td, *J* = 7.8, 1.2 Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) 12.9, 21.5, 28.4, 34.1, 35.2, 51.5, 54.0, 55.3, 57.4, 62.7, 64.5, 74.6, 75.5, 109.2, 117.0, 119.0, 123.6, 128.5, 130.0, 137.3, 154.5; EIMS (*m/e*, relative intensity) 338 (M$^+$, 100), 321 (10), 194 (67), 157 (71), 144 (88); HRMS calcd for $C_{21}H_{26}N_2O_2$ 338.1994, found 338.1990. This material was identical to that obtained from an authentic sample of (−)-vincamajine (**4**) described below.

Preparation of (+)-(2α,17*S*,19*E*)-19,20-Didehydro-17-hydroxyajmalan-16-methanol (56) from the Reduction of Natural (−)-Vincamajine (4). To a solution of natural (−)-vincamajine (4.4 mg, 0.012 mmol) in THF (2 mL) at 0 °C was added $LiAlH_4$ (4 equiv, 2.6 mg, 0.064 mmol). After the mixture was stirred for 10 min at 0 °C, the reaction solution was allowed to warm to rt and stirred for an additional 1 h. The reaction mixture was then quenched by slow addition of water (0.5 mL). The mixture was extracted with CH_2Cl_2 (2 × 15 mL),

washed with brine, and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue that resulted was purified by preparative TLC on silica gel ($CHCl_3$/MeOH = 9:1) to provide authentic diol **56** as a pale yellow oil (3.9 mg, 87%): $[\alpha]_D = +10.6$ (*c* 0.17, MeOH); FTIR 2943, 1607, 1476 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.53 (dd, J = 13.9, 9.9 Hz, 1 H), 1.61 (m, 1 H), 1.68 (d, J = 6.7 Hz, 3 H), 2.36 (dd, J = 13.9, 4.9 Hz, 1 H), 2.49 (dd, J = 11.8, 4.8 Hz, 1 H), 2.67 (s. 3 H), 2.71 (d, J = 5.8 Hz, 1 H), 2.99 (d, J = 4.7 Hz, 1 H), 3.27 (d, J = 4.9 Hz, 1 H), 3.47 (m, 2 H), 3.64 (m, 3 H), 4.28 (s, 1 H), 5.40 (q, J = 6.7 Hz, 1 H), 6.69 (d, J = 7.4 Hz, 1 H), 6.83 (t, J = 7.5 Hz, 1 H), 7.15 (d, J = 7.1 Hz, 1 H), 7.23 (td, J = 1.0, 7.8 Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) 12.9, 21.6, 28.4, 34.1, 35.2, 51.5, 53.9, 55.4, 57.5, 62.7, 64.4, 74.8, 75.7, 109.3, 116.9, 119.1, 123.3, 128.6, 129.9, 137.8, 154.5; EIMS (*m/e*, relative intensity) 338 (M^+, 61), 321 (5), 194 (80), 157 (100), 144 (97); HRMS calcd for $C_{21}H_{26}N_2O_2$ 338.1994, found 338.1994.

Preparation of (17*R*,19*E*)-17-Aceto-16-[(acetyloxy)methyl]-1,2,19,20-tetradehydro-1-demethylajmalan-17-ol (57). The TFA (5 mL) was added to a solution of **50** (161 mg, 0.50 mmol) in Ac_2O (5 mL). The reaction mixture was stirred in a sealed vessel at rt for 8 h, at which time the solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (40 mL), and a cold solution of 10% aq NH_4OH was added to bring the pH to 8. The organic layer was diluted with CH_2Cl_2 (40 mL), washed with brine (2 × 30 mL), dried (Na_2SO_4), and filtered and the solvent removed under reduced pressure. The residue that resulted was purified by preparative TLC on silica gel ($CHCl_3$/MeOH = 9:1) to provide diacetate **57** (184 mg, 80%): FTIR 3421, 2938, 1737, 1332 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.63 (d, J = 7.0 Hz, 3 H), 1.68 (s, 1 H), 1.82 (s, 3 H), 2.05 (m, 2 H), 2.09 (s, 3 H), 2.15 (d, J = 13.5 Hz, 1 H), 2.43 (m, 2 H), 2.86 (d, J = 4.8 Hz, 1 H), 2.93 (d, J = 4.4 Hz, 1 H), 3.62 (m, 2 H), 4.14 (m, 2 H), 4.37 (d, J = 9.4 Hz, 1 H), 5.45 (q, J = 6.7 Hz, 1 H), 6.01 (s, 1 H), 7.28 (td, J = 6.6, 0.8 Hz, 1 H), 7.37 (td, J = 7.7, 1.2 Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.7, 20.7, 20.7, 27.4, 29.3, 35.9, 46.3, 54.1, 56.3, 61.1, 64.7, 67.9, 77.8, 117.2, 120.6, 122.5, 125.4, 128.5, 134.9, 136.7, 156.4, 169.4, 170.8, 183.9; EIMS (*m/e*, relative intensity) 406 (M^+, 100), 363 (39), 347 (87), 333 (44), 303 (25), 182 (30), 169 (40); HRMS calcd for $C_{24}H_{26}N_2O_4$ 406.1893, found 406.1879. This material was used directly in the next step.

Preparation of (2α,17*R*,19*E*)-17-Aceto-16-[(acetyloxy)-methyl]-19,20-didehydro-1-demethylajmalan-17-ol (58). The TFA (3 mL) and Et_3SiH (3 mL) were added to a solution of **57** (61 mg, 0.15 mmol) in CH_2Cl_2 (4 mL) at rt. The reaction mixture which resulted was stirred in a sealed vessel at rt for 2 d, at which time the solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (10 mL) and brought to pH 7 with 10% aq NH_4OH. The organic layer was diluted with CH_2Cl_2 (20 mL), washed with brine (2 × 20 mL), and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue that resulted was purified by preparative TLC on silica gel ($CHCl_3$/MeOH = 15:1) to provide diacetate **58** (55 mg, 90%): FTIR 3345, 2920, 1736, 1236 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.52 (dd, J = 13.3, 10.2 Hz, 1 H), 1.59 (d, J = 6.7 Hz, 3 H), 1.79 (s, 3 H), 1.85 (d, J = 9.5 Hz, 1 H), 2.02 (s, 3 H), 2.30 (dd, J = 11.8, 4.7 Hz, 1 H), 2.73 (d, J = 4.6 Hz, 1 H), 2.77 (d, J = 4.4 Hz, 1 H), 3.09 (dd, J = 13.5, 4.9 Hz, 1 H), 3.50 (m, 2 H), 3.66 (m, 1 H), 3.93 (d, J = 4.7 Hz, 2 H), 4.01 (d, J = 4.8 Hz, 1 H), 5.32 (s, 1 H), 5.37 (q, J = 6.7 Hz, 1 H), 6.74 (d, J = 7.6 Hz, 1 H), 6.82 (t, J = 7.4 Hz, 1 H), 7.09 (m, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.8, 20.6, 20.8, 22.7, 29.0, 36.5, 45.2, 54.1, 55.6, 61.9, 68.0, 69.4, 83.0, 110.8, 116.3, 119.8, 123.0, 128.2, 128.6, 137.8, 152.0, 169.4, 171.0; EIMS (*m/e*, relative intensity) 408 (M^+, 94), 349 (60), 278 (15), 218 (25), 176 (62), 130 (100); HRMS calcd for $C_{24}H_{28}N_2O_4$ 408.2049, found 408.2045. This material was used directly in the next step.

Preparation of (2α,17*R*,19*E*)-19,20-Didehydro-17-hydroxy-1-demethylajmalan-16-methanol (59): The solution of 20% aq K_2CO_3 (4 mL) was added to a solution of **58** (41 mg, 0.10 mmol) in methanol (4 mL) at rt. The mixture which resulted was stirred at rt for 2 d and concentrated under reduced pressure to remove MeOH. It was then diluted with CH_2Cl_2 (30 mL) and separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and filtered, and the solvent was removed under reduced pressure. The residue that resulted was purified by preparative TLC on silica gel ($CHCl_3$/MeOH = 9:1) to provide diol **59** as a pale yellow solid (28 mg, 87%): $[\alpha]_D = +66.7$ (*c* 0.21, MeOH); FTIR 3402, 2922, 1638 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.52 (dd, J = 13.4, 9.9 Hz, 1 H), 1.66 (d, J = 6.7 Hz, 3 H), 1.78 (d, J = 11.9 Hz, 1 H), 2.18 (m, 1 H), 2.22 (d, J = 4.6 Hz, 1 H), 2.79 (d, J = 4.3 Hz, 1 H), 2.91 (d, J = 4.8 Hz, 1 H), 3.06 (dd, J = 13.5, 5.0 Hz, 1 H), 3.41 (d, J = 10.2 Hz, 1 H), 3.52 (dt, J = 9.7, 2.0 Hz, 1 H), 3.60 (d, J = 10.2 Hz, 1 H), 3.72 (m, 1 H), 4.08 (d, J = 6.3 Hz, 1 H), 4.10 (s, 1 H), 5.35 (q, J = 6.7 Hz, 1 H), 6.86 (m, 2 H), 7.14 (m, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.9, 23.0, 28.3, 35.9, 47.5, 54.5, 55.4, 56.1, 62.1, 67.0, 69.6, 85.9, 111.6, 116.2, 120.3, 122.1, 128.2, 130.2, 137.6, 151.9; EIMS (*m/e*, relative intensity) 324 (M^+, 64), 307 (10), 194 (100), 176 (29), 143 (55), 130 (100); HRMS calcd for $C_{20}H_{24}N_2O_2$ 324.1838, found 324.1839.

Preparation of (2α,19*E*)-19,20-Didehydro-16-hydroxymethylajmalan-17-one (60). The Dess−Martin periodinane (7.76 mg, 0.018 mmol) reagent was added to a solution of **25** (5.0 mg, 0.015 mmol) in CH_2Cl_2 (3 mL) at 0 °C, and the mixture was stirred at rt for 1 h. Solutions of saturated aq $NaHCO_3$ (1 mL) and saturated aq $Na_2S_2O_3$ (1 mL) were added to the mixture, and this was followed by the addition of CH_2Cl_2 (10 mL). The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and filtered, and the solvent was removed under reduced pressure to give a residue which was purified by preparative TLC on silica gel ($CHCl_3$/MeOH = 9:1) to provide ketone **60** (4.3 mg, 87%): FTIR 3560, 2945, 1735 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.68 (dd, J = 3.6, 1.8 Hz, 1 H), 1.70 (d, J = 6.8 Hz, 3 H), 2.05 (d, J = 4.4 Hz, 1 H), 2.12 (d, J = 11.7 Hz, 1 H), 2.45 (dd, J = 12.0, 4.6 Hz, 1 H), 2.65 (s, 3 H), 2.98 (d, J = 4.1 Hz, 1 H), 3.04 (d, J = 4.9 Hz, 1 H), 3.44 (d, J = 4.5 Hz, 1 H), 3.60 (m, 2 H), 3.63 (d, J = 11.4 Hz, 1 H), 3.77 (d, J = 11.0 Hz, 1 H), 3.78 (m, 1 H), 5.47 (q, J = 6.8 Hz, 1 H), 6.72 (d, J = 7.9 Hz, 1 H), 6.91 (t, J = 6.7 Hz, 1 H), 7.20 (d, J = 6.3 Hz, 1 H), 7.24 (d, J = 6.4 Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.92, 23.41, 27.32, 34.02, 35.61, 54.38, 54.96, 56.12, 59.03, 61.23, 63.73, 76.66, 109.23, 118.21, 119.58, 123.36, 127.02, 128.82, 135.54, 154.39, 218.13; EIMS (*m/e*, relative intensity) 336 (M^+, 25), 308 (20), 291 (6), 277 (5), 144 (100); HRMS calcd for $C_{21}H_{24}N_2O_2$ 336.1838, found 336.1834. This material was used directly in the next step.

Preparation of (2α,19*E*)-19,20-Didehydro-17-oxoajmalan-16-carboxaldehyde (61). To a solution of keto alcohol **60** (6.0 mg, 0.018 mmol) in CH_2Cl_2 (3 mL) was added Dess−Martin periodinane (11.8 mg, 0.027 mmol) at rt, and the mixture was stirred at rt for 30 min. Solutions of saturated aq $NaHCO_3$ (1 mL) and saturated aq $Na_2S_2O_3$ (1 mL) were then added to the mixture, and this was followed by the addition of CH_2Cl_2 (10 mL). The organic layer was separated, and the aqueous phase was further extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo to give a residue which was purified by preparative TLC on silica gel ($CHCl_3$/MeOH = 9:1) to provide **61** (5.4 mg, 90%): FTIR 3414, 2940, 1735 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.59 (d, J = 6.8 Hz, 3 H), 1.60 (m, 1 H), 2.19 (m, 1 H), 2.28 (m, 1 H), 2.66 (s, 3 H), 3.42 (m, 2 H), 3.60 (m, 3 H), 3.73 (d, J = 4.2 Hz, 1 H), 3.82 (m, 1 H), 5.41 (q, J = 6.8 Hz, 1 H), 6.73 (d, J = 7.9 Hz, 1 H), 6.88 (m, 1 H), 6.98 (d, J = 6.8 Hz, 1 H), 7.25 (m, 1 H), 9.74 (s, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.6, 23.2, 29.0, 34.1, 35.0, 54.1, 55.3, 55.4, 61.1, 66.8, 75.6, 109.4, 118.8, 119.8, 123.3, 126.2, 129.1, 132.8, 154.4, 196.4, 208.8. EIMS (*m/e*, relative intensity) 334 (M^+, 20), 306 (36), 277 (11), 183

(24), 157 (32), 144 (100); HRMS calcd for $C_{21}H_{22}N_2O_2$ 334.1681, found 334.1687. This material was used directly in the next step.

Preparation of (2α,19*E*)-19,20-Didehydro-17-oxoajmalan-16-carboxylic Acid Methyl Ester (62). Aldehydoketone **61** (8.0 mg, 0.024 mmol) was dissolved in anhydrous MeOH (1 mL), and a solution of 85% KOH (2.6 equiv, 4.1 mg, 0.062 mmol) and iodine (1.3 equiv, 7.8 mg, 0.031 mmol) in anhydrous MeOH (each 0.25 mL) was successively added at 0 °C. The mixture which resulted was stirred at rt for 1 h, and glacial acetic acid was then added dropwise to bring the pH to 8. The solution was diluted with CH_2Cl_2 (10 mL), the organic layer was washed with 10% $Na_2S_2O_3$ (10 mL) and brine (2 × 10 mL), dried (Na_2SO_4), and filtered, and the solvent was removed under reduced pressure. The residue that resulted was purified by preparative TLC on silica gel ($CHCl_3$/MeOH = 12:1) to provide **62** (7.8 mg, 92%): FTIR 2949, 2358, 1752, 1718, 1239 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.68 (dd, J = 10.9, 9.8 Hz, 1 H), 1.71 (dt, J = 6.8, 1.7 Hz, 3 H), 2.17 (m, 2 H), 2.64 (s, 3 H), 2.73 (dd, J = 12.1, 4.6 Hz, 1 H), 3.42 (d, J = 4.5 Hz, 1 H), 3.56 (d, J = 4.1 Hz, 1 H), 3.61 (m, 2 H), 3.69 (m, 2 H), 3.75 (s, 3 H), 5.35 (q, J = 6.7 Hz, 1 H), 6.71 (d, J = 7.9 Hz, 1 H), 6.89 (td, J = 7.5, 0.8 Hz, 1 H), 7.03 (dd, J = 7.4, 0.8 Hz, 1 H), 7.25 (td, J = 7.8, 1.3 Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.1, 23.7, 29.2, 34.0, 35.7, 52.4, 53.8, 55.9, 59.2, 60.5, 61.6, 76.6, 109.3, 118.2, 119.7, 123.4, 126.9, 128.9, 134.4, 154.5, 169.0, 207.4. EIMS (*m/e*, relative intensity) 364 (M^+, 19), 336 (37), 144 (100); HRMS calcd for $C_{22}H_{24}N_2O_3$ 364.1787, found 364.1779. This material was used directly in the next step.

Preparation of (−)-Vincamajinine (7). To a solution of **62** (7 mg, 0.019 mmol) in EtOH (1 mL) at 0 °C was added $NaBH_4$ (1.1 mg, 0.029 mmol). The reaction mixture was stirred at rt for 1 h. To this mixture, water (0.1 mL) was added slowly. The solution which resulted was diluted with CH_2Cl_2 (5 mL), the organic layer was washed with brine (2 × 10 mL), dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure. The residue that resulted was purified by preparative TLC on silica gel ($CHCl_3$/MeOH = 9:1) to provide **7** as a pale yellow solid (6.4 mg, 90%): $[\alpha]_D = -4.00$ (*c* 0.30, $CHCl_3$); FTIR 2919, 1726, 1453, 1255 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.50 (dd, J = 13.7, 10.2 Hz, 1 H), 1.56 (dt, J = 6.8, 1.6 Hz, 3 H), 1.74 (d, J = 11.9 Hz, 1 H), 2.54 (dd, J = 11.9, 4.7 Hz, 1 H), 2.63 (s, 3 H), 2.90 (dd, J = 13.4, 4.9 Hz, 1 H), 3.37 (d, J = 4.9 Hz, 1 H), 3.41 (d, J = 4.7 Hz, 1 H), 3.48 (m, 3 H), 3.63 (dd, J = 9.2, 4.9 Hz, 1 H), 3.68 (s, 3 H), 3.98 (s, 1 H), 5.23 (q, J = 6.7 Hz, 1 H), 6.76 (d, J = 7.9 Hz, 1 H), 6.83 (td, J = 7.4, 0.8 Hz, 1 H), 7.04 (dd, J = 7.4, 0.8 Hz, 1 H), 7.18 (td, J = 7.7, 1.3 Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.9, 23.1, 29.9, 34.9, 36.1, 51.9, 53.6, 53.8, 54.1, 55.6, 61.7, 76.2, 86.3, 109.8, 115.9, 120.1, 121.6, 128.6, 130.3, 136.7, 154.7, 175.3; EIMS (*m/e*, relative intensity) 366 (M^+, 76), 222 (9), 190 (83), 157 (100), 144 (78); HRMS calcd for $C_{22}H_{26}N_2O_3$ 366.1943, found 366.1928

Preparation of (2α,19*E*)-19,20-Didehydro-11-methoxy-17-oxoajmalan-16-carboxaldehyde (63). To a solution of diol **45** (15.0 mg, 0.041 mmol) in CH_2Cl_2 (5 mL) was added Dess−Martin periodinane (44.6 mg, 0.10 mmol) at 0 °C, and the mixture was stirred at 0 °C for 1 h. Solutions of saturated aq $NaHCO_3$ (1 mL) and saturated aq $Na_2S_2O_3$ (1 mL) were then added to the mixture, and this was followed by the addition of CH_2Cl_2 (10 mL). The organic layer was separated, and the aqueous phase was further extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and filtered, and the solvent was removed in vacuo to give a residue which was purified by preparative TLC on silica gel ($CHCl_3$/MeOH = 9:1) to provide **63** (9.6 mg, 65%): FTIR 2927, 1738, 1710, 1622, 1462, 1230 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.62 (m, 1 H), 1.70 (d, J = 4.0 Hz, 3 H), 2.15 (m, 1 H), 2.24 (m, 1 H), 2.62 (s, 3 H), 3.40 (m, 2 H), 3.60 (m, 3 H), 3.68 (d, J = 2.5 Hz, 1 H), 3.80 (s, 3 H), 3.81 (m, 1 H), 5.38 (q, J = 6.1 Hz, 1 H), 6.29 (d, J = 2.2 Hz, 1 H), 6.41 (dd, J = 8.1, 2.2 Hz, 1 H), 6.92 (d, J = 8.1 Hz, 1 H), 9.67 (s, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.1, 23.3, 29.0, 33.8, 35.4, 54.0, 54.2, 55.3, 55.8, 59.2, 66.8, 76.6, 97.0, 103.9, 118.2, 118.5, 124.0, 133.3, 155.7, 161.0, 196.8, 209.1; EIMS (*m/e*, relative intensity) 364 (M^+, 9), 336 (42), 307 (14), 213 (18), 187 (37), 174 (100). This material was employed directly in the next step.

Preparation of (2α,19*E*)-19,20-Didehydro-11-methoxy-17-oxoajmalan-16-carboxylic Acid Methyl Ester (64). The 11-methoxyaldehydoketone **63** (5.0 mg, 0.0137 mmol) was dissolved in anhydrous MeOH (1 mL), and a solution of 85% KOH (2.6 equiv, 2.35 mg, 0.0356 mmol) and iodine (1.3 equiv, 4.5 mg, 0.0178 mmol) in anhydrous MeOH (each 0.5 mL) was successively added at 0 °C. The mixture was stirred at rt for 1 h, and glacial acetic acid was added dropwise to bring the pH to 8. The solution which resulted was diluted with CH_2Cl_2 (10 mL), the organic layer was washed with 10% $Na_2S_2O_3$ (10 mL) and brine (2 × 10 mL), dried (Na_2SO_4), and filtered, and the solvent was removed under reduced pressure. The residue that resulted was purified by preparative TLC on silica gel ($CHCl_3$/MeOH = 12:1) to provide **64** (4.9 mg, 91%): FTIR 2916, 1750, 1727, 1614, 1458, 1229; ^1H NMR (300 MHz, $CDCl_3$) δ 1.60 (dd, J = 12.1, 11.7 Hz, 1 H), 1.70 (d, J = 6.7 Hz, 3 H), 2.17 (m, 2 H), 2.64 (s, 3 H), 2.69 (dd, J = 8.5, 4.7 Hz, 1 H), 3.47 (m, 2 H), 3.58 (d, J = 4.1 Hz, 1 H), 3.65 (m, 2 H), 3.70 (m, 1 H), 3.75 (s, 3 H), 3.82 (s, 3 H), 5.38 (q, J = 6.5 Hz, 1 H), 6.29 (d, J = 2.2 Hz, 1 H), 6.41 (dd, J = 8.1, 2.2 Hz, 1 H), 6.92 (d, J = 8.1 Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.1, 23.4, 29.1, 34.0, 35.4, 52.6, 53.8, 55.3, 55.7, 56.2, 59.2, 61.3, 76.5, 97.0, 104.1, 118.7, 123.8, 124.9, 137.9, 155.8, 160.0, 168.7, 207.1; EIMS (*m/e*, relative intensity) 394 (M^+, 10), 366 (55), 174 (100). This material was employed directly in the next step.

Preparation of (−)-11-Methoxy-17-epivincamajine (9). The $NaBH_4$ (1.0 mg, 0.026 mmol) was added to a solution of **64** (4 mg, 0.010 mmol) in EtOH (1 mL) at 0 °C. The reaction mixture was stirred at rt for 1 h. Water (0.1 mL) was added slowly to this solution. The mixture which resulted was diluted with CH_2Cl_2 (5 mL), washed with brine (2 × 10 mL), dried (Na_2SO_4), and filtered and the solvent removed under reduced pressure. The residue that resulted was purified by preparative TLC on silica gel ($CHCl_3$/MeOH = 9:1) to provide **9** as a pale yellow foam (3.5 mg, 93%): $[\alpha]_D = -10.5$ (*c* 0.15, $CHCl_3$) [lit.[9b] $[\alpha]_D = -12$ (*c* 0.5, $CHCl_3$)]; FTIR 3300, 2918, 1720, 1612, 1461, 787 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.52 (dd, J = 14.1, 10.0 Hz, 1 H), 1.62 (d, J = 6.8 Hz, 3 H), 1.73 (m, 1 H), 2.27 (dd, J = 12.1, 4.5 Hz, 1 H), 2.68 (s, 3 H), 2.99 (dd, J = 13.2, 5.2 Hz, 1 H), 3.41 (d, J = 4.7 Hz, 1 H), 3.44 (d, J = 4.6 Hz, 1 H), 3.47 (m, 2 H), 3.48 (d, J = 4.8 Hz, 1 H), 3.60 (m, 1 H), 3.72 (s, 3 H), 3.82 (s, 3 H), 4.00 (s, 1 H), 5.29 (q, J = 6.8 Hz, 1 H), 6.33 (d, J = 2.2 Hz, 1 H), 6.40 (dd, J = 8.1, 2.2 Hz, 1 H), 6.97 (d, J = 8.0 Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.9, 22.7, 29.6, 34.9, 35.8, 52.1, 53.3, 53.7, 54.1, 55.4, 56.0, 61.7, 76.5, 85.9, 97.4, 104.5, 116.4, 122.0, 122.8, 136.6, 156.4, 160.7, 175.0; EIMS (*m/e*, relative intensity) 396 (M^+, 100), 365 (17), 222 (87), 190 (83), 187 (64), 174 (29). The spectral data of **9** were in excellent agreement with the literature values.[9b]

Acknowledgment. We thank NIMH for support (in part) of this work. We also thank Dr. Tohru Fukuyama (The University of Tokyo) for helpful discussions as well as Professor Toh-Seok Kam (University of Malaya) and Professor Monique Zeches-Hanrot (University of Reims) for generous gifts of authentic (+)-quebrachidine and (−)-vincamajine, respectively.

Supporting Information Available: ^1H and ^{13}C NMR comparison of natural (−)-11-methoxy-17-epivincamajine (**9**) as well as diols **53** and **56**, derived from natural materials, with synthetic **9**, **53**, and **56**, respectively. This material is available free of charge via the Internet at http://pubs.acs.org.

JO040282B