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General Approach for the Synthesis of 12-Methoxy-Substituted Sarpagine Indole Alkaloids Including (−)-12-Methoxy-N_b-methylvoachalotine, (+)-12-Methoxy-N_a-methylvellosimine, (+)-12-Methoxyaffinisine, and (−)-Fuchsiaefoline

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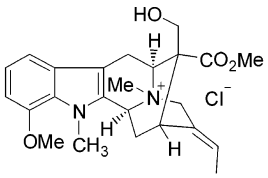
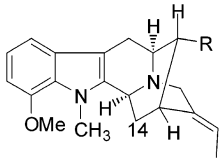
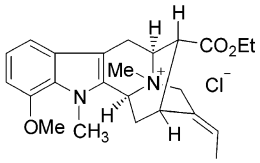
Received October 4, 2005



(-)-12-methoxy-N_b-methylvoachalotine



R=CHO, (+)-12-methoxy-N_a-methylvellosimine
R=CH_2OH, (+)-12-methoxyaffinisine



(-)-fuchsiaefoline

The enantiospecific synthesis of 7-methoxy-D-tryptophan ethyl ester was completed by combination of the Larock heteroannulation process with a Schöllkopf-based chiral auxiliary in good yield. This ester was then employed in the first regiospecific, stereospecific total synthesis of (+)-12-methoxy-N_a-methylvellosimine, (+)-12-methoxyaffinisine, (−)-fuchsiaefoline, and 12-methoxy-N_b-methylvoachalotine in excellent overall yield. The asymmetric Pictet−Spengler reaction and enolate-driven palladium-catalyzed cross-coupling processes served as key steps. The quaternary center at C(16) of 12-methoxy-N_b-methylvoachalotine was established via the Tollens reaction between (+)-12-methoxy-N_a-methylvellosimine and formaldehyde to form diol **17**. The two prochiral primary alcohols in diol **17** were differentiated by the oxidative cyclization(DDQ) of the hydroxyl group at the axial position of **17** with the benzylic postion at [C(6)] to form a cyclic ether [C(6)−O(17)]. After oxidative formation of the α-ester at C(16), the ether bond was reductively cleaved with TFA/Et_3SiH in high yield. The DDQ-mediated oxidative cyclization and TFA/Et_3SiH reductive cleavage served as protection/deprotection steps in order to provide a versatile entry into the voachalotine alkaloids.

Introduction

Sarpagine and ajmaline are biogenetically related alkaloids which have been isolated from various species of *Rauwolfia* broadly distributed throughout Asia and Africa.[1−9] These plants are widely used in traditional Chinese medicine for the treatment of neuralgia, migraine,[7] and hypertension.[3,5] Among these alkaloids some contain ring-A oxygenated functions at positions 10, 11, and 12. Examples of 12-methoxy-substituted indole alkaloids include (+)-12-methoxy-N_a-methyl-vellosimine, (+)-12-methoxyaffinisine, (−)-fuchsiaefoline, and 12-methoxy-N_b-methylvoachalotine, as shown in Figure 1. Important structural features of these natural products include the asymmetric centers at C-3(*S*), C-5(*R*), C-6(*R*), C-15(*S*), and C-16(*S*), the *E*-configuration of the olefinic bond at C(19)−C(20), as well as

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10.1021/jo052081t CCC: $33.50
Published on Web 12/08/2005

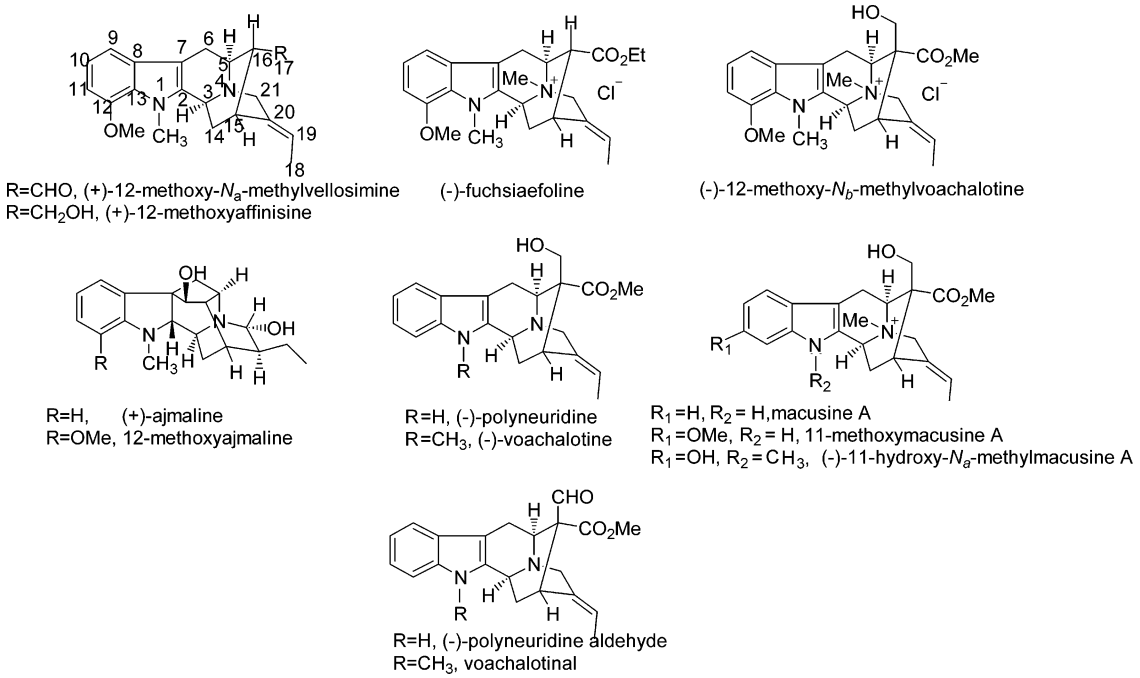

FIGURE 1. Examples of sarpagine and ajmaline indole alkaloids.

the 12-methoxy group in ring A. 12-Methoxy-N_b-methylvoachalotine is also of interest for it contains a quaternary carbon at position 16, in which the hydroxymethyl group is found at the axial position while the methyl ester function is equatorial. Such a quaternary carbon center also exists in many other indole alkaloids including (−)-polyneuridine,[10] (−)-voachalotine,[11] macusine A,[12] 11-methoxymacusine A,[13] and (−)-11-hydroxy-N_a-methylmacusine A,[14] as illustrated in Figure 1. Polyneuridine aldehyde[15] and voachalotinal[16] also contain a similar quaternary carbon center; however, in these examples, the aldehyde function is located in the axial position instead of the hydroxymethyl group. Polyneuridine aldehyde, a sarpagine alkaloid, is believed to be the biogenetic precursor[17] of the ajmaline-related alkaloid (+)-quebrachidine;[18] a subunit of the bisindole (+)-alstomacroline. (+)-Alstomacroline was isolated from the root bark of *A. macrophylla* collected in Thailand and exhibited potent activity against drug-resistant strains of malaria parasites (IC_{50} of 1.2 μM against the K1 strain of *Plasmodium falciparum*).[19] Le Quesne et al. reported a biomimetic coupling process on condensation of natural (+)-quebrachidine with macroline to furnish (+)-alstomacroline.[20] The bases (+)-12-methoxy-N_a-methylvellosimine and (+)-12-methoxyaffinisine have been recently isolated from the bark of *Rauwolfia bahiensis*,[21] the structures of which were determined by detailed analysis of the ^{1}H NMR, ^{13}C NMR, and 2D NMR spectra. However, the biological activity of these two alkaloids has not been reported. Two quaternary indoles, (−)-fuchsiaefoline and (+)-12-methoxy-N_b-methylvoachalotine were isolated from *Peschiera fuchsiaefolia* in 1987.[9] Their structures were determined by ^{1}H and ^{13}C NMR. 12-Methoxy-N_b-methylvoachalotine was reported to inhibit avian myeloblastosis virus reverse transcriptase.[22] This inhibition was dependent on the template primer used. In Brazilian folk medicine, victims of bites by poisonous animals are usually treated with plant extracts derived from the diverse national flora including *Tabernaemontana catharinensis*. 12-Methoxy-N_b-methylvoachalotine, isolated from the root bark of *T. catharinensis*, completely inhibited the lethal dose in the rat when it had been injected 20 s after 2 LD50 with South American rattlesnake venom at 1.7 mg/100 g.[23] Ajmaline has been employed in the treatment of cardiac arrhythmias for decades; however, no detailed data on 12-methoxyajmaline has appeared. Herein, we report the first enantiospecific total synthesis of 12-methoxy-N_b-methylvoachalotine, (+)-12-methoxy-N_a-methylvellosimine, (+)-12-methoxyaffinisine, and (−)-fuchsiaefoline. Bond constructions critical to the synthesis of these alkaloids include the *E*-ethylidene stereochemistry at C(19)−C(20) and the quaternary center at C(16), as mentioned.

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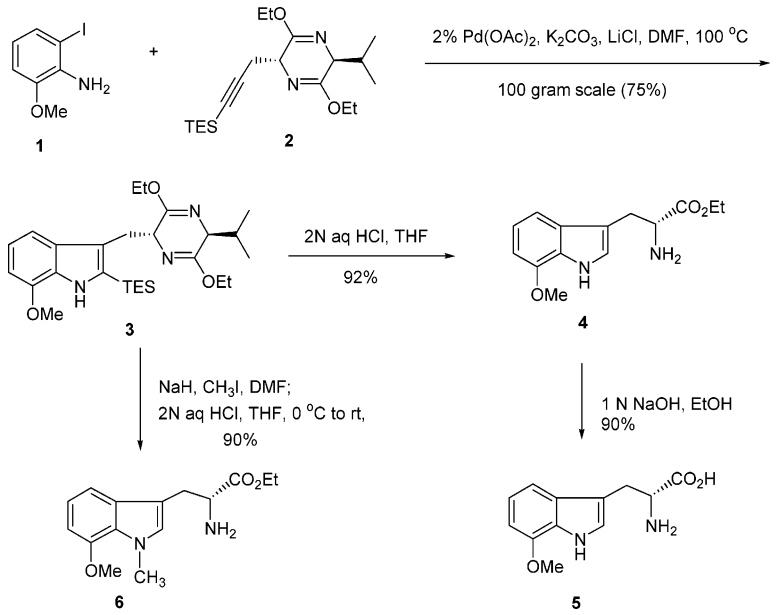
SCHEME 1. Synthesis of 7-Methoxy-D-tryptophan



In addition, regiospecific incorporation of the 12-methoxy group into the indole was of paramount importance to success.

Results and Discussion

Enantiospecific Synthesis of 7-Methoxy-D-tryptophan for Indole Alkaloid Total Synthesis. Based on previous work on the total synthesis of indole alkaloids via the asymmetric Pictet−Spengler reaction,[24] 7-methoxy-D-tryptophan was required as the chiral transfer agent and starting material to synthesize these 12-methoxy-substituted sarpagine and ajmaline alkaloids. The required 7-methoxy-D-tryptophan ethyl ester **6** was prepared via the Larock heteroannulation[25] process from 2-iodo-6-methoxyaniline **1**[26] and the propargyl-substituted Schöllkopf chiral auxiliary **2** (from L-valine)[27] in the presence of Pd $(OAc)_2$, K_2CO_3, and LiCl in DMF at 100 °C in 75% isolated yield.[28] The Larock heteroannulation was also employed successfully in the synthesis of 6-methoxy-D-tryptophan.[29] The application of this strategy to regiospecifically synthesize 4-methoxy-D-tryptophan and 5-methoxy-D-tryptophan is currently under investigation. The desired indole **3** could be easily purified by flash chromatography. The annulation could be readily carried out both on small scale (100 mg) and large scale (100 g) in good yield. Hydrolysis of the Schöllkopf chiral auxiliary with aqueous 2 N HCl in THF accompanied by concomitant loss of the indole-2-silyl group provided optically active 7-methoxy-D-tryptophan ethyl ester **4** in a single step in 92% yield. The ester **4** was then hydrolyzed to prepare 7-methoxy-D-tryptophan **5** with 1 N aq NaOH in ethanol for characterization.[30] The N_a-methyl analogue **6** was obtained by methylation of the indole N_a-H function with MeI and NaH, followed by removal of the Schöllkopf chiral auxiliary and the TES group in simple fashion (90% yield). In summary, the annulation between 2-iodo-6-methoxyaniline **1** and the propargyl-substituted Schöllkopf chiral auxiliary **2**, followed by hydrolysis provided 7-methoxy-D-tryptophan ethyl ester in good yield. Since the 2-iodo-6-methoxyaniline **1** and the propargyl unit **2** could be readily prepared on large scale (>100 g), this provided an efficient route to synthesize 7-methoxy-D-tryptophan with high diastereoselectivity; the enantiomer, 7-methoxy-L-tryptophan, could be prepared in the same fashion from the Schöllkopf chiral auxiliary from D-valine (Scheme 1).

Construction of the Tetracyclic Ketone 9. With N_a-methyl-7-methoxy-D-tryptophan ethyl ester **6** in hand, the 12-methoxy-tetracyclic ketone **9** was prepared in three reaction vessels, as shown in Scheme 2. The primary amine of tryptophan **6** was converted into the required N_b-benzyl ester **7** by reductive amination in high yield. The Pictet−Spengler condensation between the aldehyde and the N_b-benzylamine **7** was carried out in the presence of acetic acid in CH_2Cl_2 to afford a mixture (at C-1) of *trans*-**8a** and *cis*-**8b** diesters in nearly quantitative yield in a ratio of 2:1. If TFA/CH_2Cl_2 was employed in this step in place of HOAc/CH_2Cl_2, decomposition of much of the 7-methoxytryptophan **7** was observed. In keeping with the mechanistic studies on the carbocation-mediated *cis*/*trans* isomerization,[31−34] when the Pictet−Spengler reaction was completed, 5 equiv of TFA was added to the reaction mixture to epimerize the *cis* diastereomer **8b** into the desired *trans* diastereomer **8a**. It is important to note, the completion of the epimerization of the 8-methoxy N_a-methyldiester **8b** into **8a** took 7 days, which was consistent with that for the 6-methoxy N_a-methyl substituted diester. However, for the 7-methoxy N_a-methyl substituted diester, the epimerization was much faster,

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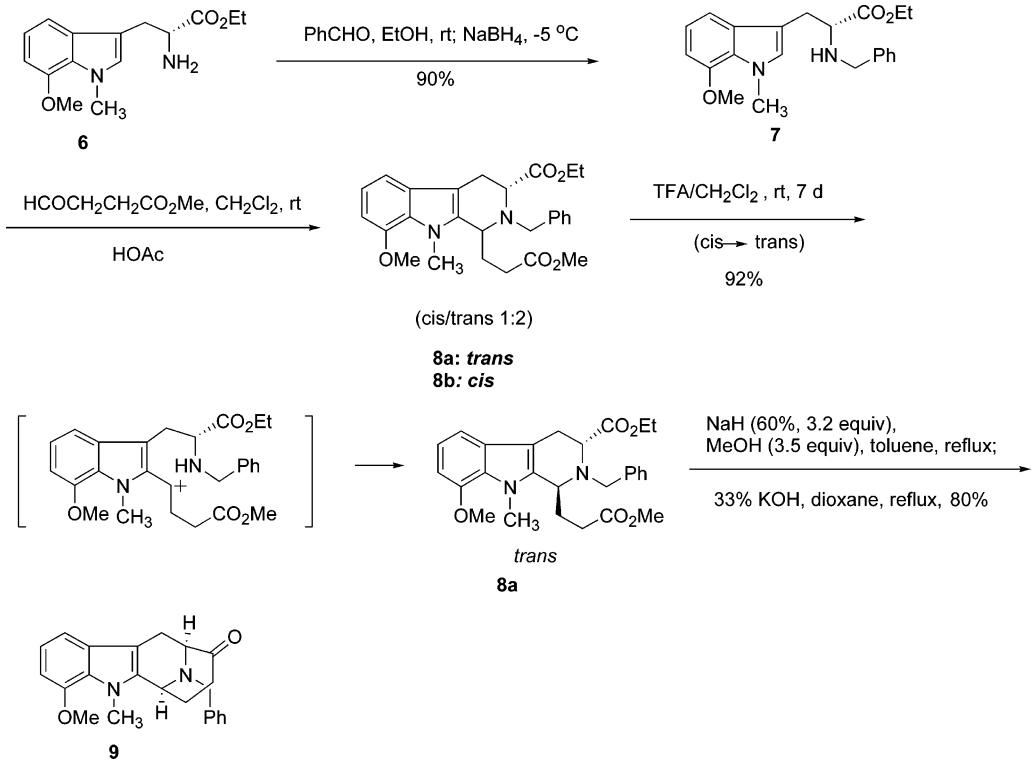
SCHEME 2. Construction of the 12-Methoxytetracyclic Ketone 9



which is in good agreement with the carbocationic intermediate (via resonance) proposed for this process.[35,36] Dieckmann cyclization of the *trans* diester **8a** was followed by base-mediated hydrolysis/decarboxylation to provide optically pure ketone **9** in a one-pot process.

Completion of the Total Synthesis of 12-Methoxy-N_a-methylvellosimine, 12-Methoxyaffinisine, and (−)-Fuchsiaefoline. The tetracyclic ketone **9** was then converted into 12-methoxy-N_a-methylvellosimine, 12-methoxyaffinisine, and fuchsiaefoline, as illustrated in Scheme 3. The N_b-benzyl group of **9** was removed via catalytic hydrogenation, and this was followed by alkylation with (*Z*)-1-bromo-2-iodo-2-butene to provide ketone **11**. This alkylation was simple to execute, for overalkylation in these azabicyclo[3.3.1] systems is very difficult. This is an advantage to this approach. When this ketone **11** was subjected to the conditions of the enolate-driven palladium-catalyzed intramolecular cyclization,[37−43] the pentacyclic ketone **12** was obtained in 80% yield. Establishment of the C(19)−C(20) *E*-ethylidene function had been achieved in stereospecific fashion. The ketone **12** was then converted into 12-methoxy-N_a-methylvellosimine **13** via a Wittig reaction followed by hydrolysis, a process developed earlier to prepare sarpagine alkaloids.[40] The ^{1}H NMR and ^{13}C NMR spectra of **13** were identical to those reported by Kato and co-workers;[21] however, the optical rotation of synthetic **13** was different from the reported value.[21] For this reason, the aldehyde **13** was reduced with $NaBH_4$ to provide 12-methoxyaffinisine **14** (95% yield), the optical rotation of which was in excellent agreement with the reported value ($[\alpha]^{26}_D = 3.3$ (lit.[21] $[\alpha]^{26}_D = 3.0$)). In addition, the signals in the ^{1}H NMR and ^{13}C NMR spectra were identical to the reported values.[21] The aldehyde function of intermediate **13** was then oxidized to the ethyl ester **15** with I_2 and KOH in EtOH, following the work of Yamada et al.,[44] a process employed earlier in our laboratory to prepare sarpagine alkaloids.[45] Subsequent quaternization of the N_b nitrogen function in ester **15** with MeI provided the N_b-methiodide salt, which was then converted into the chloride **16** on treatment with AgCl in EtOH.[46] The ^{1}H NMR spectrum, ^{13}C spectrum, and optical rotation of **16** were in good agreement with those of the reported values (see Scheme 3).

Completion of the Total Synthesis of 12-Methoxy-N_b-methylvoachalotine. Attention now turned to the establishment of the quaternary center at C(16) of 12-methoxy-N_b-methylvoachalotine. Numerous efforts (aldolizations, alkylations, and acylations of analogues of **13** devoid of methoxyl substituents on the indole A-ring) were originally attempted, but they were not successful.[47−51] However, treatment of aldehyde **13** with 37% aq formaldehyde and KOH in MeOH via the Tollens reaction provided the diol **17** in 85% yield (Scheme 4). The prochiral quaternary carbon center at C-16 that contained the

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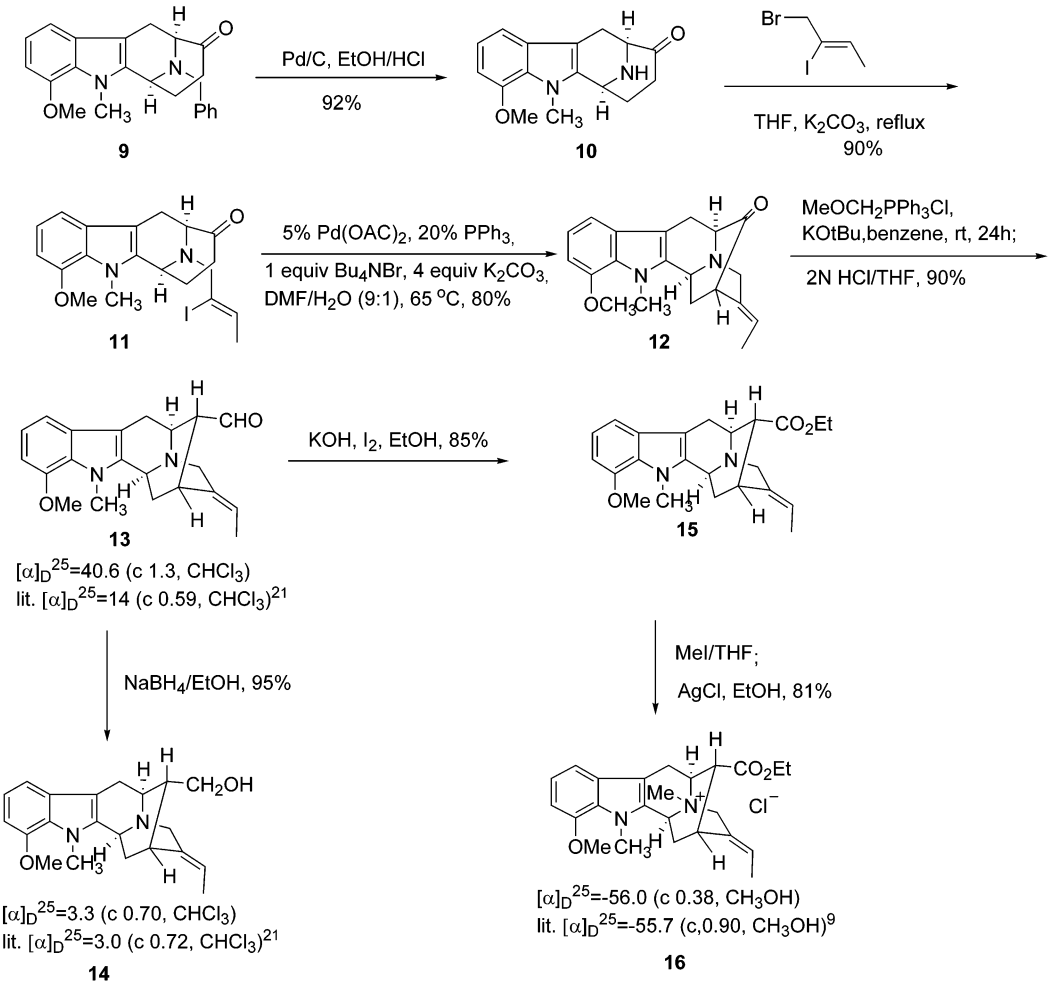
SCHEME 3. Synthesis of 12-Methoxy-N_a-methylvellosimine, 12-Methoxyaffinisine, and Fuchsiaefoline



structurally hindered diol in **17** was constructed in one step. The two prochiral hydroxymethyl groups in diol **17** must now be differentiated. This problem was solved on the basis of previous work in our laboratory[52−54] on DDQ-mediated oxidations on indoles.[52−57] Oxidative cyclization of diol **17** with DDQ in THF permitted facile bond construction between the axial-(β) hydroxymethyl function and the benzylic position at C(6). The equatorial hydroxymethyl moiety of cyclic ether **18** which remained was then oxidized intramolecularly with $(PhSeO)_2O$/PhCl at 115 °C for 30 min to furnish the aldehyde **19**,[58] which was further oxidized with KOH/I_2/MeOH to afford the methyl ester **20**. Hydrogenation of **20** with hydrogen and palladium to cleave the C(6)−O(17) bond was attempted but was unsuccessful. Because C(6) is a benzylic carbon atom in **20**, reductive cleavage of the C(6)−O(17) bond could be easily accomplished with TFA/Et_3SiH in CH_2Cl_2 in 86% yield. Subsequent quaternization of the N_b nitrogen function in ester **21** with MeI provided the N_b-methiodide salt, which was then converted into the chloride **22** on treatment with AgCl in MeOH.

It is important to note that, in the synthesis of 12-methoxy-N_b-methylvoachalotine **22**, the DDQ-mediated oxidation via a charge-transfer complex[57,59−62] permitted the selective protection of the axial hydroxymethyl group, which permitted further modification of the equatorial hydroxymethyl group to the methyl ester. TFA/Et_3SiH-mediated reduction released the hydroxymethyl function to provide alcohol **21**. This provided the first stereospecific entry into the hydroxymethyl and methyl ester groups at C(16). TFA/Et_3SiH had been earlier employed for the reduction of the carbonyl group,[63] and the olefinic bond of an α,β-unsaturated ketone.[64] Herein we demonstrated that TFA/Et_3SiH could be employed for the reductive cleavage of the ether bond. The reductive cleavage of the benzylic C(6)−O(17) bond with TFA/Et_3SiH was further studied with other

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SCHEME 4. Stereocontrolled Synthesis of 12-Methoxy-N_b-methylvoachalotine

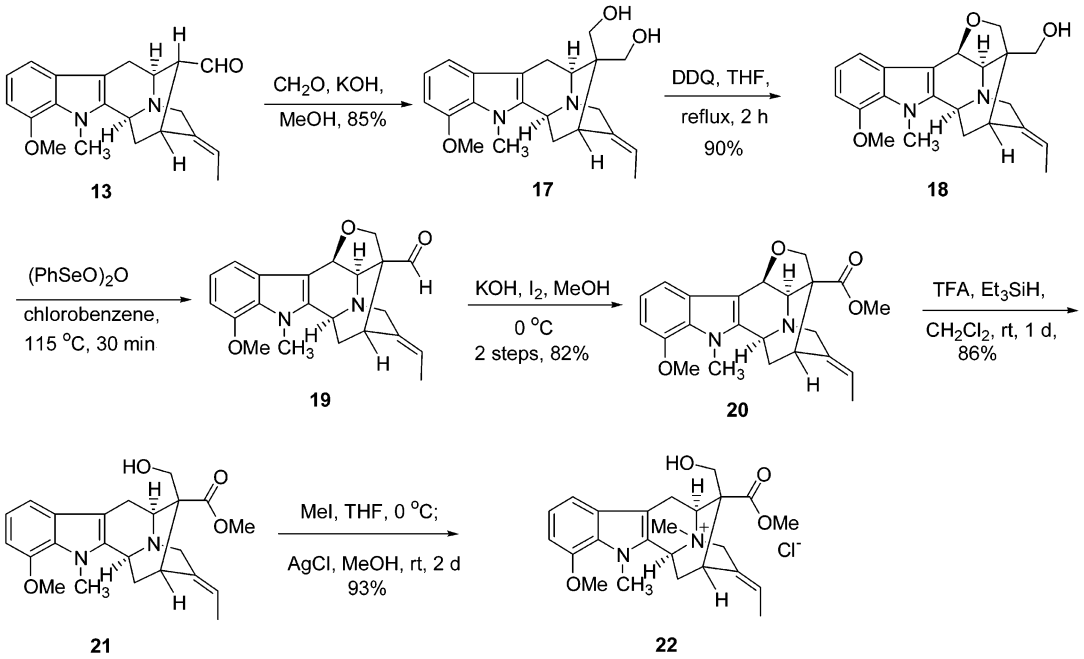
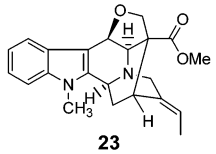
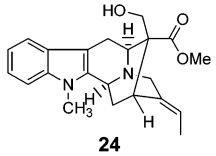
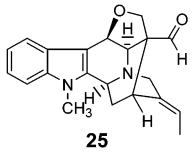
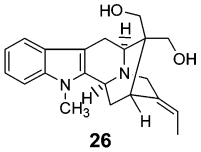
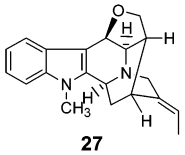
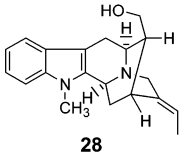
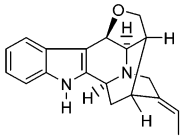
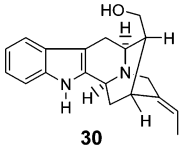
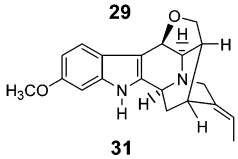
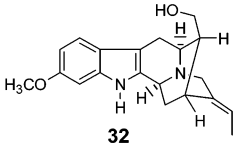


TABLE 1. Reductive Cleavage of Cyclic Ethers with Et_3SiH/TFA

entry	substrate	product	yield
1	 23	 24	88%
2	 25	 26	92%
3	 27	 28	90%
4	 29	 30	80%
5	 31	 32	85%

substrates (see Table 1). Dehydrovoachalotine **23**[65] was converted into voachalotine **24** in 88% yield after **23** was stirred with TFA/Et_3SiH in CH_2Cl_2 for 1 day at room temperature. When aldehyde **25** was treated with TFA/Et_3SiH, the cyclic ether was cleaved and the carbonyl group was again reduced to the alcohol. (−)-Epiaffinisine **28** could be prepared from (+)-dehydroepiaffinisine with TFA/Et_3SiH. This process also worked well on N_a-H-substituted substrates such as (+)-dehydro-16-epinormacusine B **29** and gardnutine **31**.

Conclusion

In summary, 7-methoxy-D-tryptophan **5** was prepared on 100 g scale via the combination of the Larock heteroannulation process with 2-iodo-6-methoxyaniline **1** and the propargyl-substituted Schöllkopf chiral auxiliary **2** in good yield. To the best of our knowledge, this is the first synthesis of an optically pure 7-alkoxytryptophan, although the Bartoli indole synthesis has been employed to synthesize 7-substituted indoles in moderate yield.[66−69] The strategy reported here can be employed for the synthesis of either 7-alkoxy-D- or 7-alkoxy-L-tryptophan on large scale. The first regiospecific, enantiospecific total synthesis of (+)-12-methoxy-N_a-methylvellosimine in a concise manner was achieved. In addition, the first synthesis of (+)-12-methoxy-N_a-methylvellosimine **13**, (+)-12-methoxyaffinisine **14**, (−)-fuchsiaefoline **16**, and 12-methoxy-N_b-methylvoachalotine **22** was accomplished (from D-tryptophan **6**) in 7 reaction vessels, 8 reaction vessels, 9 reaction vessels, and 12 reaction vessels, respectively. The asymmetric Pictet−Spengler reaction and an enolate-driven palladium-mediated cross coupling reaction are two pivotal steps employed to establish the correct stereochemistry in these natural products. The Tollens reaction, DDQ-mediated cyclization, and TFA/Et_3SiH reductive cleavage of the C−O bond were employed to install the quaternary carbon center at C(16) of 12-methoxy-N_b-methylvoachalotine and voachalotine. Since sarpagine indole alkaloids are the proposed biogenetic precursors of the ajmaline alkaloids[17] as mentioned

(65) Yu, J.; Wearing, X. Z.; Cook, J. M. *J. Org. Chem.* **2005**, *70*, 3963.

(66) Bartoli, G.; Palmieri, G.; Bosco, M.; Dalpozzo, R. *Tetrahedron Lett.* **1989**, *30*, 2129.
(67) Dobbs, A. *J. Org. Chem.* **2001**, *66*, 638.
(68) Dobson, D.; Todd, A.; Gilmore, J. *Synth. Commun.* **1991**, *21*, 611.
(69) Dobson, D.; Gilmore, J.; Long, D. A. *Synlett.* **1992**, 79.

earlier, the strategy employed here should provide a route to 12-alkoxy substituted ajmaline alkaloids. The total synthesis of 12-methoxyajmaline and other indole alkaloids (from 7-methoxytryptophan) will be reported in due course.

Experimental Section

(5*R*,2*S*)-3,6-Diethoxy-2-isopropyl-5-[7-methoxy-2-(triethylsilyl)-3-indolyl]methyl-2,5-dihydropyrazine (3). The 2-iodo-6-methoxyaniline **1** (102 g, 0.41 mol) and the Schöllkopf derivative **2** (179 g, 0.49 mol) were charged to a round-bottom flask, as well as lithium chloride (17.4 g, 0.41 mol), potassium carbonate (141.3 g, 1.02 mol), palladium(II) acetate (1.84 g, 8.2 mmol), and dry DMF (700 mL). 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 **1** had been consumed, the reaction mixture was cooled to rt and diluted with EtOAc. The mixture was washed with H_2O (5 × 20 mL) to remove DMF. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Purification by flash chromatography over silica gel (2% EtOAc/hexane) provided the desired **3** as a yellow oil (149 g, 75%): $[\alpha]^{25}_D = -23.4$ (*c* 0.77, $CHCl_3$); FTIR 2955, 1688, 1234 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.70 (t, 3H, *J* = 6.8 Hz), 0.85−1.06 (m, 18H), 1.23 (t, 3H, *J* = 7.1 Hz), 1.31 (t, 3H, *J* = 7.1 Hz), 2.29 (m, 1H), 2.85 (dd, 1H, *J* = 13.5, 10.6 Hz), 3.53 (dd, 1H, *J* = 14.1, 3.1 Hz), 3.92 (t, 1H, *J* = 3.1 Hz), 4.00 (s, 3H), 4.02−4.25 (m, 5H), 6.60 (d, 1H, *J* = 7.6 Hz), 6.98 (t, 1H, *J* = 7.8 Hz), 7.38 (d, 1H, *J* = 8.0 Hz), 8.11 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 3.6, 7.4, 14.2, 14.3, 16.6, 19.0, 31.5, 32.1, 55.1, 58.6, 60.4, 60.6, 101.4, 113.4, 118.6, 124.0, 129.1, 131.0, 131.1, 145.6, 162.6, 163.8. Anal. Calcd for $C_{27}H_{43}N_3O_3Si$: C, 66.76; H, 8.92; N, 8.65. Found: C, 66.66; H, 8.94; N, 8.59.

7-Methoxy-D-tryptophan Ethyl Ester (4). Aqueous 2 N HCl (6 mL) was added to a solution of **3** (0.34 g, 0.70 mmol) in THF (8 mL) at 0 °C. The reaction mixture was stirred at rt overnight. Ice was added to the solution, and the pH of the reaction mixture was adjusted to 8 (pH paper) with aq NH_4OH. The mixture was extracted with EtOAc (3 × 50 mL). The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the residue by flash chromatography over silica gel (gradient elution: EtOAc/hexane, 3:7, to remove L-valine ethyl ester, then EtOAc) afforded **5** (0.17 g, 92%): $[\alpha]^{25}_D = -2.2$ (*c* 1.0, $CHCl_3$); FTIR 3370, 2937, 1729, 1629, 1579, 1260 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.27 (t, 3H, *J* = 7.1 Hz), 2.45 (bs, 2H), 3.06 (dd, 1H, *J* = 14.4, 7.5 Hz), 3.30 (dd, 1H, *J* = 14.4, 4.8 Hz), 3.85 (dd, 1H, *J* = 7.5, 4.8 Hz), 3.96 (s, 3H), 4.18 (q, 2H, *J* = 7.1 Hz), 6.66 (d, 1H, *J* = 7.7 Hz), 7.05 (s, 1H), 7.05 (t, 1H, *J* = 7.8 Hz), 7.24 (d, 1H, *J* = 8.0 Hz), 8.44 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1, 30.6, 54.9, 55.2, 60.9, 101.9, 111.5, 119.8, 122.5, 126.7, 128.8, 146.1, 174.9. EIMS *m*/*e* 262 (M^+). This material was used directly in the next step.

7-Methoxy-N_a-methyl-D-tryptophan Ethyl Ester (6). Pyrazine **3** (3.3 g, 6.8 mmol) and MeI (1.45 g, 10.2 mmol) in DMF (30 mL) were cooled to 0 °C after which NaH (60%, 0.41 g, 10.2 mmol) was added portionwise. The mixture which resulted was stirred at 0 °C for 1.5 h, quenched with ice-cold water, and diluted with EtOAc (200 mL). The organic layer was washed with water (5 × 20 mL), brine, dried (Na_2SO_4), and concentrated under reduced pressure. The mixture obtained here was then dissolved in THF (80 mL) and cooled to 0 °C. A cold aqueous solution of 2 N HCl (70 mL) was slowly added to the above mixture. The mixture was allowed to warm to rt and stirred overnight. Ice was added to the solution, and the pH of the reaction mixture was adjusted to 8 (pH paper) with aq 28% NH_4OH. The mixture was extracted with EtOAc (3 × 150 mL). The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was subjected to Kugelrohr distillation at 80 °C (0.3 mmHg) to remove L-valine ethyl ester, which could be reused. Purification of the oil which remained by flash chromatography over silica gel (EtOAc) afforded **6** as a light yellow oil (1.69 g, 90%): $[\alpha]^{25}_D = -6.5$ (*c* 1.13, $CHCl_3$); FTIR 3370, 2934, 1731, 1574, 1256 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.28 (t, 3H, *J* = 7.1 Hz), 1.60 (s, 2H), 2.98 (dd, 1H, *J* = 14.3, 7.5 Hz), 3.24 (dd, 1H, *J* = 14.4, 4.8 Hz), 3.78 (dd, 1H, *J* = 7.8, 4.8 Hz), 3.93 (s, 3H), 4.02 (s, 3H), 4.19 (q, 2H, *J* = 7.1 Hz), 6.62 (d, 1H, *J* = 7.7 Hz), 6.81 (s, 1H), 7.00 (t, 1H, *J* = 7.8 Hz), 7.20 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1, 30.6, 36.2, 55.0, 55.3, 60.8, 102.3, 109.6, 111.6, 119.4, 126.6, 128.6, 130.2, 147.8, 175.3. EIMS *m*/*e* 276 (M^+); HRMS $C_{15}H_{20}N_2O_3$ calcd 276.1474, found 276.1466. This material was used directly in the next step.

N_b-Benzyl-7-methoxy-1-methyl-D-tryptophan Ethyl Ester (7). Benzaldehyde (5.58 g, 52.54 mmol) was added to a mixture of tryptophan ethyl ester **6** (7.25 g, 26.3 mmol) and Na_2SO_4 (18.7 g, 0.131 mol) in dry ethanol (150 mL) at 0 °C under nitrogen. The solution was stirred at 0 °C for 8 h, cooled to −10 °C, and treated portionwise with $NaBH_4$ (2.03 g, 52.54 mmol), during which the temperature was kept below −5 °C (about 1 h). After the mixture was allowed to stir for an additional 2 h, ice−water (0.5 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 × 100 mL). The combined organic layers were washed with brine and dried (Na_2SO_4). The mixture was concentrated under reduced pressure and purified by flash chromatography to provide the desired ester **7** (8.64 g, 90%): ^1H NMR (300 MHz, $CDCl_3$) δ 1.19 (t, 3H, *J* = 7.1 Hz), 1.74 (bs, 1H), 3.12 (m, 2H), 3.60−3.86 (m, 3H), 3.93 (s, 3H), 4.00 (s, 3H), 4.11 (q, 2H, *J* = 7.2 Hz), 6.61 (d, 1H, *J* = 7.7 Hz), 6.75 (s, 1H), 6.97 (t, 1H, *J* = 7.8 Hz), 7.15 (d, 1H, *J* = 8.0 Hz), 7.20−7.32 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1, 29.1, 36.2, 52.0, 55.3, 60.5, 61.2, 102.2, 109.6, 111.7, 119.2, 126.8, 127.6, 128.1, 128.4, 130.3, 139.7, 143.7, 147.4, 174.8; EIMS *m*/*z* 366 (M^+). Anal. Calcd for $C_{22}H_{26}N_2O_3$: C, 72.11; H, 7.15; N, 7.64. Found: C, 71.95; H, 7.09; N, 7.52. This material was used directly in the next step.

3-(2-Benzyl-8-methoxy-9-methyl-3-propionyloxy-2,3,4,9-tetrahydro-1*H*-*β*-carbolin-1-yl)propionic Acid Methyl Ester (8a). The 4-oxobutyric acid methyl ester (4.12 g, 35.49 mmol) and HOAc (1.25 g, 20.88 mmol) were added to a round-bottom flask (250 mL) which contained a solution of optically active N_a-methyl-N_b-benzyl-D-tryptophan ethyl ester **7** (7.6 g, 20.88 mmol) in dry CH_2Cl_2 (50 mL) at 0 °C. The reaction mixture which resulted was stirred at rt overnight. TFA (11.86 g, 0.104 mol) in CH_2Cl_2 (200 mL) was then added at 0 °C. The reaction mixture which resulted was stirred at rt for 7 d and then cooled in an ice bath after which it was brought to pH 8 with an aqueous solution of 28% NH_4OH. The aqeous layer was separated and extracted with CH_2Cl_2 (3 × 100 mL). After the combined organic layers were washed with brine and dried (K_2CO_3), the solvent was removed under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc/hexane = 1:4) to provide pure *trans*-**8a** (8.9 g, 92%): $[\alpha]^{25}_D = -32.9$ (*c* 0.31, $CHCl_3$); FTIR 3440, 2947, 2840, 1733, 1574, 1456, 1255 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.39 (t, 3H, *J* = 7.1 Hz), 1.81−2.07 (m, 2H), 2.38−2.65 (m, 2H), 2.98−3.17 (m, 2H), 3.38 (d, 1H, *J* = 13.2 Hz), 3.51 (s, 3H), 3.76 (dd, 1H, *J* = 10.9, 3.1 Hz), 3.83 (d, 1H, *J* = 13.2 Hz), 3.89 (s, 3H), 3.95 (s, 3H), 4.06 (dd, 1H, *J* = 10.5, 5.4 Hz), 4.24−4.38 (m, 2H), 6.66 (d, 1H, *J* = 7.6 Hz), 7.03 (t, 1H, *J* = 7.9 Hz), 7.18 (d, 1H, *J* = 7.8 Hz), 7.26−7.38 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.3, 20.2, 27.7, 29.7, 32.8, 51.3, 52.6, 53.2, 55.4, 55.9, 60.8, 102.7, 106.5, 111.0, 119.5, 126.9, 128.1, 128.6, 129.2, 136.0, 139.3, 147.6, 172.9, 173.9; EIMS *m*/*e* 464 (M^+, 5.6), 378 (25.2), 377 (100.0), 213 (34.8). Anal. Calcd for $C_{27}H_{32}N_2O_5$: C, 69.81; H, 6.94; N, 6.03. Found: C, 69.60; H, 6.99; N, 5.97.

(+)-12-Methoxyaffinisine (14). (+)-12-Methoxy-N_a-methylvellosimine **13** (50 mg, 0.149 mmol) was dissolved in EtOH (10 mL), after which $NaBH_4$ (11.5 mg, 0.298 mmol) was added to the

above solution in one portion at 0 °C. The mixture was then stirred at rt for 4 h. The reaction mixture was diluted with CH_2Cl_2 (80 mL) and poured into cold water (20 mL). The aqueous layer was extracted with additional CH_2Cl_2 (3 × 20 mL), and the combined organic layers were washed with brine (20 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford the crude product which was purified by chromatography to provide (+)-12-methoxyaffinisine **14** (48 mg, 95%): $[\alpha]^{25}_D = 3.3$ (c = 0.70, $CHCl_3$) {lit.[21] $[\alpha]_D = 3.0$ (c = 0.72, $CHCl_3$)}; FTIR 3351, 2912, 1571 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.64 (d, 3H, J = 6.8 Hz), 1.71−1.90 (m, 3H), 2.08 (m, 1H), 2.61 (d, 1H, J = 15.3 Hz), 2.81 (m, 2H), 3.05 (dd, 1H, J = 15.3, 5.2 Hz), 3.46−3.54 (m, 2H), 3.54−3.64 (m, 2H), 3.92 (s, 3H), 3.94 (s, 3H), 4.19 (dd, 1H, J = 10.0, 2.2 Hz), 5.41 (q, 1H, J = 6.8 Hz), 6.62 (d, 1H, J = 7.5 Hz), 6.97 (t, 1H, J = 7.7 Hz), 7.05 (d, 1H, J = 7.8 Hz); ^{13}C NMR (75.7 MHz, $CDCl_3$) δ 12.7, 27.0, 27.4, 32.3, 32.7, 44.1, 49.4, 54.2, 55.3, 56.2, 64.9, 102.3, 103.8, 111.0, 116.7, 119.1, 126.5, 129.3, 135.7, 139.5, 147.5. EIMS *m*/*e* 338 (M^+, 100), 337 (88), 307 (44), 213 (91.3), 212 (100), 198 (29.3), 197 (85). The spectral data for **14** were identical to those reported for **14** in the literature.[21]

(−)-Fuchsiaefoline (16). Ester **15** (35 mg, 0.09 mmol) was dissolved in THF (4 mL) and cooled to 0 °C. The MeI (65 mg, 0.46 mmol) was added to the above solution dropwise. The reaction mixture was stirred at 0 °C for 8 h. The solvent was removed under reduced pressure, and the residue was purified by chromatography over silica gel (CH_2Cl_2/MeOH 10/1) to provide the iodomethylated salt. This salt was then dissolved in EtOH (3 mL), followed by the addition of AgCl (41 mg). The mixture which resulted was stirred at rt for 2 days. The excess AgCl and AgI which formed were removed by filtration and washed with EtOH (10 mL). After removal of the solvent under reduced pressure, the residue was purified by flash chromatography over silica gel (CH_2Cl_2/MeOH 10/1) to afford fuchsiaefoline (32 mg, 81%): $[\alpha]^{25}_D = -56.0$ (c = 0.38, MeOH) {lit.[9] $[\alpha]_D = -55.7$ (c = 0.90, MeOH)}; FTIR 3420, 1730 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27 (t, 3H, J = 7.1 Hz), 1.64 (d, 3H, J = 6.8 Hz), 2.04 (dd, 1H, J = 13.0, 4.3 Hz), 2.86−2.94 (m, 3H), 3.32 (dd, 1H, J = 17.3, 5.0 Hz), 3.41 (s, 3H), 3.50 (bs, 1H), 3.92 (d, 1H, J = 18.0 Hz), 3.95 (s, 3H), 4.05 (s, 3H), 4.11−4.28 (m, 3H), 5.52 (q, 1H, J = 6.9 Hz), 5.72 (d, 1H, J = 15.5 Hz), 6.69−6.72 (m, 2H), 7.02−7.09 (m, 2H); ^{13}C NMR (75.7 MHz, $CDCl_3$) δ 12.7, 14.0, 24.4, 27.3, 30.4, 33.6, 47.0, 47.6, 55.5, 58.2, 62.0, 62.5, 65.0, 98.8, 103.8, 110.6, 120.8, 121.5, 125.6, 127.4, 127.6, 133.0, 148.0, 170.0. EIMS *m*/*z* (rel int) 394 ((M − 1)$^+$, 3), 381 (25), 380 (100), 379 (60), 366 (5), 365 (14), 351 (21), 335 (9), 307 (34), 293 (12), 280 (4), 279 (6), 212 (55), 197 (18). The spectral data for **16** were identical to those reported for **16** in the literature.[9]

Ether (18). The DDQ (231 mg, 1.016 mmol) was added to a solution of diol **17** (187 mg, 0.508 mmol) in THF (10 mL). The black mixture which resulted was heated to reflux for 2 h. The mixture was then diluted with CH_2Cl_2 (80 mL), washed with a saturated solution of aq $NaHSO_3$ (10 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, CH_2Cl_2/MeOH 10/1) to provide the cyclic ether **18** (167 mg, 90%): FTIR 3380, 2920, 1571, 1457, 1256, 1007 cm^{-1}; ^{1}H NMR (300 MHz, CDCl3) δ 1.68 (dt, 3H, J = 6.8, 3.0 Hz), 1.95 (dd, 2H, J = 8.7, 3.0 Hz), 2.24 (bs, 1H), 2.98 (t, 1H, J = 2.9 Hz), 3.14 (d, 1H, J = 7.5 Hz), 3.47−3.60 (m, 4H), 3.71 (d, 1H, J = 9.5 Hz), 3.75 (dt, 1H, J = 17.0, 1.9 Hz), 3.92 (s, 3H), 3.94 (s, 3H), 4.06 (dd, 1H, J = 8.6, 5.1 Hz), 5.44 (q, 1H, J = 6.8 hz), 5.64 (d, 1H, J = 7.5 Hz), 6.65 (d, 1H, J = 7.7 Hz), 7.03 (t, 1H, J = 7.8 Hz), 7.28 (d, 1H, J = 7.7 Hz); ^{13}C NMR (75.7 MHz, $CDCl_3$) δ 12.8, 28.7, 29.0, 32.2, 45.9, 47.3, 55.3, 55.4, 62.9, 66.7, 68.2, 72.1, 102.8, 103.5, 111.6, 116.1, 120.1, 126.6, 128.2, 136.5, 143.3, 147.5. EIMS *m*/*e* 366 (M^+). Anal. Calcd for $C_{22}H_{26}N_2O_3$: C, 72.11; H, 7.15; N, 7.64. Found: C, 72.43; H, 7.05; N, 7.40.

Methyl Ester (20). The benzeneseleninic anhydride (70%, 54 mg, 0.106 mmol) was added to a solution of dry chlorobenzene (5 mL) and cyclic ether **18** (78 mg, 0.212 mmol). The mixture was heated to 115 °C (oil bath temperature) for 30 min. The solution which resulted was cooled to rt, and the solvent was removed under reduced pressure. The oil which resulted was washed with hexane (6 × 5 mL). The residue was dissolved in anhydrous MeOH (2 mL), and a solution of 85% KOH (37 mg, 0.551 mmol) and iodine (70 mg, 0.276 mmol) in anhydrous MeOH (2 mL) were successively added at 0 °C. After 1 h, the reaction mixture was diluted with CH_2Cl_2 (80 mL), washed with a 10% aqueous solution of $NaHSO_3$ (20 mL), water (20 mL), and brine (20 mL), and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue which resulted was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH: 20/1) to provide methyl ester **20** (71 mg, 85%): FTIR 2945, 1730, 1571, 1458, 1256, 1114, 1017 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.61 (d, 3H, J = 6.8 Hz), 1.98−2.12 (m, 2H), 3.29 (t, 1H, J = 5.6 Hz), 3.69−3.75 (m, 3H), 3.72 (s, 3H), 3.92−3.95 (m, 2H), 3.92 (s, 3H), 3.94 (s, 3H), 4.50 (d, 1H, J = 7.7 Hz), 5.36 (q, 1H, J = 6.8 Hz), 5.75 (d, 1H, J = 7.7 Hz), 6.65 (d, 1H, J = 7.8 Hz), 7.03 (t, 1H, J = 7.8 Hz), 7.28 (d, 1H, J = 7.9 Hz); ^{13}C NMR (75.7 MHz, $CDCl_3$) δ 12.6, 28.8, 30.7, 32.2, 46.6, 52.1, 53.6, 55.2, 55.3, 61.1, 68.1, 72.4, 102.9, 103.3, 106.9, 111.7, 116.5, 120.2, 126.6, 128.2, 135.2, 143.4, 147.5; EIMS *m*/*e* 394 (M^+). Anal. Calcd for $C_{23}H_{26}N_2O_4$: C, 70.03; H, 6.64; N, 7.10. Found: C, 70.33; H, 6.49; N, 7.32.

12-Methoxyvoachalotine (21). The TFA (0.4 mL) and Et_3SiH (0.6 mL) were added to a solution of **20** (20 mg, 0.051 mmol) in CH_2Cl_2 (2 mL). The reaction mixture which resulted was stirred in a sealed vessel at rt for 1 d, after which the solution was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (80 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), and evaporated under reduced pressure. The residue that resulted was purified by preparative TLC on silica gel (CH_2Cl_2/MeOH: 15/1) to provide **21** (17 mg, 86%): FTIR 3337, 2948, 1731, 1572, 1456, 1257, 1117 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.62 (d, 3H, J = 6.8 Hz), 1.82 (dt, 1H, J = 13.2, 3.4 Hz), 1.99 (bs, 1H), 2.00 (td, 1H, J = 11.8, 2.2 Hz), 2.92 (d, 1H, J = 16.5 Hz), 3.12 (dd, 1H, J = 16.5, 6.4 Hz), 3.24 (t, 1H, J = 3.0 Hz), 3.60 (d, 1H, J = 11.3 Hz), 3.68−3.72 (m, 3H), 3.75 (s, 3H), 3.91 (s, 3H), 3.94 (s, 3H), 4.16 (dd, 1H, J = 10.4, 3.4 Hz), 4.30 (d, 1H, J = 6.1 Hz), 5.32 (q, 1H, J = 6.8 Hz), 6.63 (d, 1H, J = 7.6 Hz), 6.98 (t, 1H, J = 7.8 Hz), 7.08 (d, 1H, J = 7.8 Hz); ^{13}C NMR (75.7 MHz, $CDCl_3$) δ 12.7, 22.3, 28.1, 30.2, 32.2, 47.8, 52.1, 53.2, 53.6, 55.3, 55.8, 63.0, 102.5, 105.1, 111.3, 116.2, 119.2, 126.5, 128.0, 135.8, 138.2, 147.4, 176.2; EIMS *m*/*e* 396 (M^+). This material was employed directly in the next step.

12-Methoxy-N_b-methylvoachalotine (22). The synthesis of **22** from **21** was carried out analogous to the preparation of fuchsiaefoline **16** from **15** in 93% yield: $[\alpha]^{25}_D = -102.7$ (c = 0.22, MeOH) {lit.[9] $[\alpha]_D = -106.2$ (c = 1, MeOH)}; FTIR 3330, 1733 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.62 (d, 3H, J = 6.8 Hz), 1.77 (dt, 1H, J = 12.9, 3.3 Hz), 2.64 (bt, 1H, J = 12.3 Hz), 3.11−3.19 (m, 2H), 3.31 (s, 3H), 3.63 (d, 1H, J = 10.7 Hz), 3.70 (d, 1H, J = 10.1 Hz), 3.72 (s, 1H), 3.77−3.93 (m, 1H), 3.80 (s, 3H), 3.96 (s, 3H), 4.01 (s, 3H), 4.75 (d, 1H, J = 6.2 Hz), 5.43 (q, 1H, J = 6.8 Hz), 5.53 (d, 1H, J = 16.0 Hz), 6.53 (d, 1H, J = 9.9 Hz), 6.69−6.72 (m, 1H), 7.05−7.06 (m, 2H); ^{13}C NMR (75.7 MHz, $CDCl_3$) δ 12.4, 19.3, 27.9, 29.6, 33.2, 49.1, 53.1, 55.2, 55.5, 56.8, 62.9, 63.8, 64.4, 100.7, 103.8, 111.1, 120.0, 120.7, 126.2, 126.5, 127.5, 132.7, 148.0, 172.8; EIMS *m*/*e* 410 ((M − 1)$^+$). The spectra data for **22** were in agreement with the literature values.[9]

Voachalotine (24). The synthesis of voachalotine **24** from dehydrovoachalotine **23** was carried out analogous to the preparation of **21** from **20** in 88% yield: $[\alpha]^{25}_D = -2.6$ (c = 0.8, $CHCl_3$) [lit.[11] −2.8 (c = 6, $CHCl_3$)]; FTIR 3370, 2921, 1732 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.63 (d, 3H, J = 6.8 Hz), 1.81 (dt, 1H, J = 13.1, 3.5 Hz), 2.00 (ddd, 1H, J = 13.0, 10.4, 2.4 Hz), 2.96 (d, 1H, J = 16.3 Hz), 3.14 (dd, 1H, J = 16.4, 6.3 Hz), 3.24 (t, 1H, J = 2.8 Hz), 3.57−3.72 (m, 4H), 3.63 (s, 3H), 3.75 (s, 3H), 4.18 (dd, 1H,

J = 10.3, 3.3 Hz), 4.30 (d, 1H, J = 6.2 Hz), 5.32 (q, 1H, J = 6.8 Hz), 7.11 (t, 1H, J = 7.4 Hz), 7.21 (t, 1H, J = 7.5 Hz), 7.30 (d, 1H, J = 7.8 Hz), 7.50 (d, 1H, J = 7.7 Hz); ^{13}C NMR (75.7 MHz, $CDCl_3$) δ 12.7, 22.3, 28.2, 29.1, 30.2, 47.8, 52.1, 53.2, 53.5, 55.8, 63.0, 104.9, 108.7, 116.0, 118.3, 118.8, 121.0, 126.0, 136.2, 137.2, 138.3, 176.3; EIMS *m*/*e* 366 (M^+). The spectra data of **24** were in excellent agreement with the literature values.[9,70]

(70) Jokela, R.; Lounasmaa, M. *Heterocycles* **1996**, *43*, 1015.

Acknowledgment. We thank the NIMH (in part) and the graduate school (UWM) for support of this work.

Supporting Information Available: Experimental details and full characterization for compounds **9**−**13**, **15**, and **17** and ^{1}H and ^{13}C NMR spectra of compounds **6**, **12**, **15**, **17**, and **21**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO052081T