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# Regiospecific, Enantiospecific Total Synthesis of the 12-Alkoxy-Substituted Indole Alkaloids, (+)-12-Methoxy-$N_a$-methylvellosimine, (+)-12-Methoxyaffinisine, and (−)-Fuchsiaefoline

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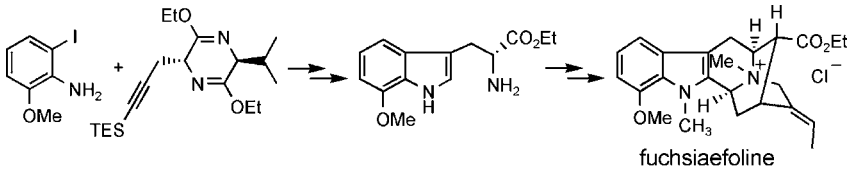
## ABSTRACT




**The enantiospecific synthesis of 7-methoxy-D-tryptophan 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 total synthesis of (+)-12-methoxy-$N_a$-methylvellosimine, (+)-12-methoxyaffinisine, and (–)-fuchsiaefoline in regiospecific, stereospecific fashion in excellent overall yield. The asymmetric Pictet–Spengler reaction and enolate-driven palladium-catalyzed cross coupling processes served as key steps.**

Sarpagine and ajmaline alkaloids have been isolated from various species of *Rauwolfia*, which are 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 position 12, for example, (+)-12-methoxy-$N_a$-methyl-vellosimine, (+)-12-methoxyaffinisine, (−)-fuchsiaefoline, and 12-methoxy-ajmaline (see Figure 1). The bases (+)-12-methoxy-$N_a$-methylvellosimine and (+)-12-methoxyaffinisine have been recently isolated from the bark of *Rauwolfia bahiensis*,[10] the structures of which were determined by detailed analysis of the $^1$H NMR, $^{13}$C NMR, and two-dimensional NMR spectra. However, the biological activity of these alkaloids has not been reported. Ajmaline has been employed in the treatment of cardiac arrhythmias for decades; however, no detailed data on 12-methoxyajmaline has appeared. In this approach, a regiospecific strategy was designed to incorporate the 12-alkoxy group into ring-A of these alkaloids early in the route. If successful, this would also provide an enantiospecific route for the synthesis of many other 12-methoxy-substituted sarpagine- and ajmaline-related indole alkaloids. On the basis of previous work on the total synthesis of indole alkaloids via the asymmetric Pictet−Spengler reaction,[11] 7-methoxy-D-tryptophan was required as the chiral transfer agent and starting material to synthesize these 12-methoxy-substituted sarpagine and ajmaline alkaloids. Herein we report the first

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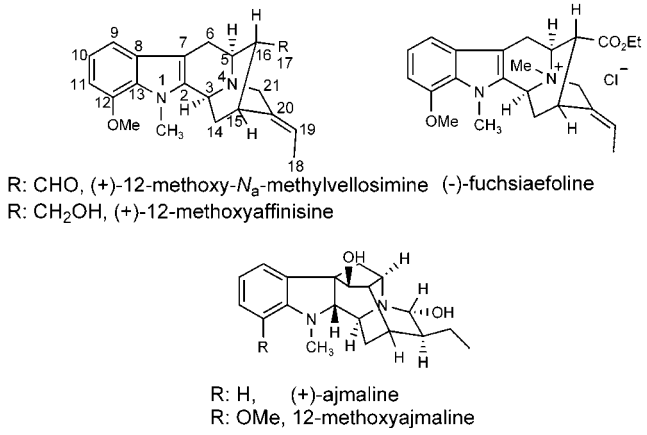


**Figure 1.**

efficient approach for the synthesis of 7-methoxytryptophans as well as the total synthesis of (+)-12-methoxy-$N_a$-methylvellosimine, (+)-12-methoxyaffinisine, and (−)-fuchsiaefoline.

The required 7-methoxy-D-tryptophan ethyl ester **6** was prepared via the Larock heteroannulation[12] process from 2-iodo-6-methoxyaniline **1**[13] and the propargyl-substituted Schöllkopf chiral auxiliary **2**[14] in the presence of Pd $(OAc)_2$, $K_2CO_3$, and LiCl in DMF at 100 °C in 75% isolated yield. The ratio of the desired indole **3** to the byproduct **4** was determined on the basis of the integration of the proton at C3 in the $^1$H NMR spectrum of the crude reaction mixture. The ratio was optimized to 15:1 (**3**:**4**) when 2% catalyst was employed rather than 5% catalyst [$Pd(OAc)_2$]. The desired indole **3** could be separated from the byproduct **4** by flash chromatography. The annulation could be readily carried out on both small (100 mg) and large scales (100 g) in good yield. Hydrolysis of the Schöllkopf chiral auxiliary accompanied by concomitant loss of the indole-2-silyl group with aqueous 2 N HCl in EtOH provided optically active 7-methoxy-D-tryptophan ethyl ester **5** in a single step in 92% yield. 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 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 with excellent regioselectivity. Since the 2-iodo-6-methoxyaniline **1**[13] and the propargyl unit **2**[14] could be readily prepared on a large scale (>100 g), this provided an efficient route to synthesize either 7-methoxy-D-tryptophan or 7-methoxy-L-tryptophan with high diastereoselectivity.

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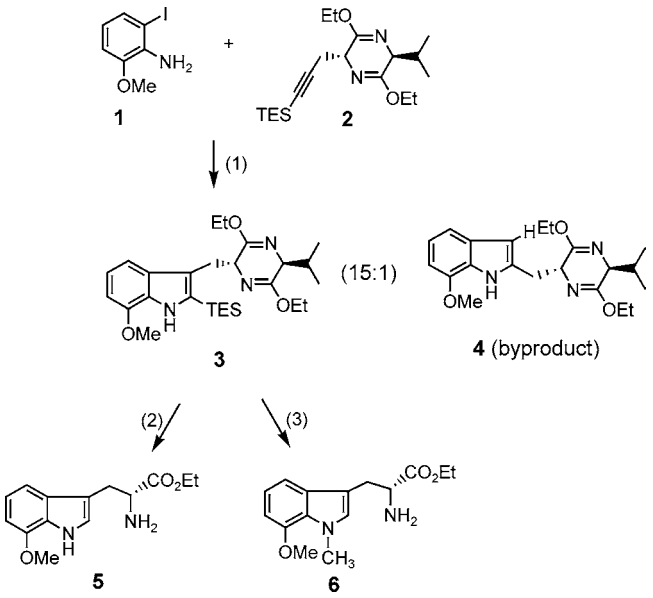
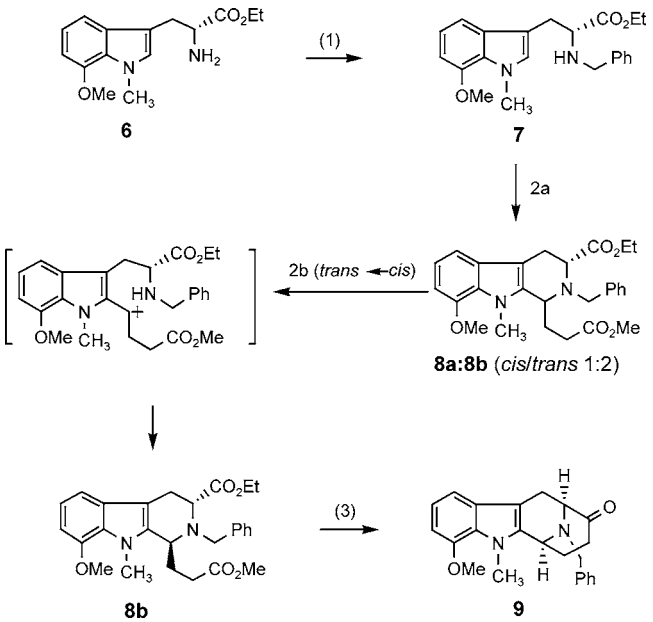
**Scheme 1**[a]




[a] Reaction conditions: (1) 2% $Pd(OAc)_2$, 2.5 equiv of $K_2CO_3$, LiCl, DMF, 100 °C, 75%. (2) 2 N aq HCl, THF, 0 °C to room temperature, 92%. (3) NaH, $CH_3I$, DMF; 2 N aq HCl, THF, 0 °C to room temperature, 90%.

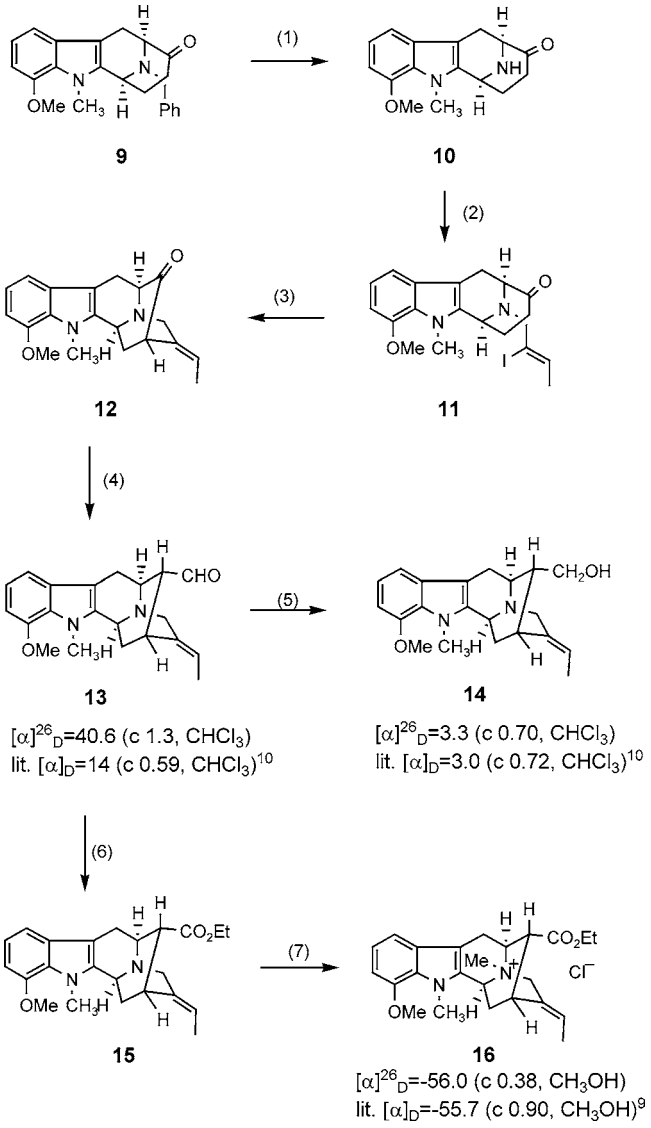
With $N_a$-methyl-7-methoxy-D-tryptophan ethyl ester **6** in hand, the 12-methoxytetracyclic ketone **9** was prepared, as shown in Scheme 2. The primary amine of **6** was converted

**Scheme 2**[a]




[a] Reaction conditions: (1) 2 equiv of PhCHO, EtOH, 5 equiv of $Na_2SO_4$, 0 °C, overnight; $NaBH_4$, −5 °C, 2 h, 90%. (2) (a) 1.5 equiv of $HCOCH_2CH_2CO_2Me$, 1 equiv of HOAc, $CH_2Cl_2$, 0 °C to room temperature, overnight; (b) 1% TFA/$CH_2Cl_2$ (~5 equiv TFA), rt, 7 days, 92%. (3) NaH (60%, 3.2 equiv), MeOH (3.5 equiv), toluene, reflux; 33% KOH, dioxane, reflux, 80%.

**Scheme 3**[a]




[a] Reaction conditions: (1) 10% Pd/C, EtOH/HCl, 7 h, 92%.. (2) 1.2 equiv of (*Z*)-1-bromo-2-iodo-2-butene, THF, 6.5 equiv of $K_2CO_3$, reflux, 24 h, 90%. (3) 5% $Pd(OAc)_2$, 20% $PPh_3$, 1 equiv of $Bu_4NBr$, 4 equiv of $K_2CO_3$, DMF/$H_2O$ (9:1), 65 °C, 12 h, 80%. (4) 8 equiv of $MeOCH_2PPh_3Cl$, 8.8 equiv of KOtBu, benzene, rt, 24 h; 2 N aq HCl/THF, 55 °C, 6 h, 90%. (5) 2 equiv of $NaBH_4$/EtOH, 0 °C to room temperature, 95%. (6) KOH, $I_2$, EtOH, 85%. (7) MeI/THF, 0 °C; AgCl, EtOH, rt, 81%.

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 *cis*-**8a** and *trans*-**8b** diesters in nearly quantitative yield in a ratio of 1:2. When 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,[15] when the Pictet−Spengler reaction was completed, 5 equiv of TFA was added to the reaction mixture to epimerize the *cis* diastereomer **8a** into the desired *trans* diastereomer **8b**. Dieckmann cyclization of the *trans* diester **8b** was followed by base-mediated hydrolysis/decarboxylation to provide optically pure ketone **9** in a one-pot process.

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**. When this ketone **11** was subjected to the conditions of the enolate-driven palladium-catalyzed intramolecular cyclization,[16−22] 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.[19] The data from the $^1$H NMR and $^{13}$C NMR spectra of **13** were identical to those reported by Kato and co-workers (see Table 1);[10] however, the optical rotation of synthetic **13** was different from the reported value. For this reason, the aldehyde **13** was reduced with $NaBH_4$ to provide 12-methoxyaffinisine **14** (95% yield), the optical

**Table 1.** $^{13}$C NMR of Indole Alkaloids **13**, **14**, and **16**

| carbon | synthetic **13** | lit. value[10] | synthetic **14** | lit. value[10] | synthetic **16** | lit. value[9] |
|---|---|---|---|---|---|---|
| 2 | 134.2 | 134.5 | 135.7 | 135.8 | 125.6 | 125.6 |
| 3 | 49.3 | 49.3 | 49.4 | 49.4 | 58.2 | 58.4 |
| 5 | 50.4 | 50.4 | 54.2 | 54.2 | 62.5 | 62.3 |
| 6 | 27.2 | 27.2 | 27.0 | 27.0 | 24.4 | 24.4 |
| 7 | 103.3 | 103.3 | 103.8 | 103.8 | 98.8 | 99.0 |
| 8 | 126.6 | 126.7 | 126.5 | 126.6 | 127.6 | 127.5 |
| 9 | 111.1 | 111.1 | 111.0 | 111.1 | 110.6 | 110.6 |
| 10 | 119.3 | 119.4 | 119.1 | 119.2 | 120.8 | 120.6 |
| 11 | 102.5 | 102.6 | 102.3 | 102.5 | 103.8 | 103.8 |
| 12 | 147.5 | 147.6 | 147.5 | 147.5 | 180.0 | 147.7 |
| 13 | 129.2 | 129.2 | 129.3 | 129.4 | 127.4 | 127.4 |
| 14 | 32.3 | 32.3 | 32.7 | 32.9 | 30.4 | 30.6 |
| 15 | 26.5 | 26.5 | 27.4 | 27.5 | 27.3 | 27.2 |
| 16 | 54.8 | 54.6 | 44.1 | 44.3 | 47.6 | 47.6 |
| 17 | 202.7 | 202.6 | 64.9 | 65.0 | 12.7 | 12.7 |
| 18 | 12.6 | 12.6 | 12.7 | 12.8 | 121.5 | 121.2 |
| 19 | 116.9 | 117.0 | 116.7 | 116.7 | 133.0 | 132.8 |
| 20 | 139.3 | 139.3 | 139.5 | 139.7 | 65.0 | 64.9 |
| 21 | 56.1 | 56.0 | 56.2 | 56.2 | 170.0 | 169.9 |
| $N_a$−$CH_3$ | 32.4 | 32.5 | 32.3 | 32.4 | 33.6 | 33.4 |
| −O−$CH_3$ | 55.3 | 55.4 | 55.3 | 55.4 | 55.5 | 55.4 |
| $N^+$−$CH_3$ | | | | | 47.0 | 46.9 |
| $CO_2\underline{C}H_2CH_3$ | | | | | 62.0 | 61.9 |
| $CO_2CH_2\underline{C}H_3$ | | | | | 14.0 | 13.9 |

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rotation of which was in excellent agreement with the reported value ($[\alpha]^{26}_D = 3.3$, lit.[10] 3.0). In addition, the signals in the $^1$H NMR and $^{13}$C NMR spectra were identical to the reported values (see Table 1).[10] 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.,[23] a process employed earlier in our laboratory to prepare sarpagine alkaloids.[24] 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.[25] 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 and Table 1).

In summary, 7-methoxy-D-tryptophan **5** was prepared via combination of the Larock heteroannulation with 2-iodo-6-methoxyaniline and the propargyl-substituted Schöllkopf chiral auxiliary in good yield. To the best of our knowledge, this is the first synthesis of an optically pure 7-alkoxy-tryptophan, although the Bartoli indole synthesis has been employed to synthesize 7-substituted indoles in moderate yield.[26] Hoveyda et al. have also reported a recent synthesis of a 7-hydroxytryptophan.[27] The strategy reported here can be employed for the synthesis of either the 7-alkoxy-D- or 7-alkoxy-L-tryptophan on a large scale.[14] The first regiospecific, enantiospecific total synthesis of (+)-12-methoxy-$N_a$-methylvellosimine in a concise manner was reported here. The synthesis of (+)-12-methoxy-$N_a$-methyl-vellosimine **13**, (+)-12-methoxy-affinisine **14**, and (−)-fuchsiaefoline **16** was accomplished (from D-tryptophan **6**) in seven, eight, and nine 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 total synthesis of 12-methoxyajmaline and other indole alkaloids (from 7-methoxytryptophan) will be reported in due course.

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