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The first enantiospecific total synthesis of a C-quaternary voachalotine alkaloid, (+)-dehydrovoachalotine

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Abstract—The first enantiospecific total synthesis of the indole alkaloid (+)-dehydrovoachalotine (**1**) has been achieved from D-(+)-tryptophan methyl ester in 28% overall yield. The formation of the prochiral quaternary carbon center at C-16 in the key intermediate (**12**) was realized via a Tollens reaction from N_a-methylvellosimine (**13**) in 95% yield. This approach could also be applied to the synthesis of many other indole alkaloids that contain a quaternary carbon center at C(16).

The sarpagine-related indole alkaloids comprise one of the largest groups of structurally related indole natural products. Interest in these indole alkaloids derives from both the structural diversity and complexity of its members and the important medicinal properties of some of these natural bases.[1] Recently, a number of structurally similar sarpagine-related indole alkaloids have been synthesized in an enantiospecific fashion via a route developed in this laboratory, including (+)-vellosimine, (+)-N_a-methylvellosimine, (+)-panarine, (−)-alkaloid Q_3, (+)-N_a-methyl-16-epipericyclivine, (+)-normacusine B, (+)-10-methoxyaffinisine, (+)-N_a-methylsarpagine, (−)-(*E*)-16-epiaffinisine, (+)-(*E*)-16-epinormacusine B, and (+)-dehydro-16-epiaffinisine.[2] As part of ongoing efforts, interest has arisen in the series of bases, which contained a quaternary carbon center at C(16), examples of which are illustrated in Figure 1.[1c,d] No total synthesis of these indole alkaloids has appeared to date. (+)-Dehydrovoachalotine (**1**) was isolated both from the root bark of *Voacanga chalotiana*[3] and the leaves of *Alstonia undulata*.[4] The structure of **1** was unambiguously established by analysis of ^1H and ^{13}C NMR,[3,5] mass spectra[3] as well as nuclear Overhauser effects (NOE).[6] In addition to the interesting structural features including the asymmetric centers at C-3(*S*), C-5(*R*), C-6(*R*), C-15(*S*), C-16(*R*), the *E*-configuration at C(19)–C(20), and the cyclic ether at C(6) depicted in Figure 1, the existence of the quaternary carbon center at C-16 attracted our attention. Execution of the enantiospecific total synthesis of **1** forms the basis of this letter.

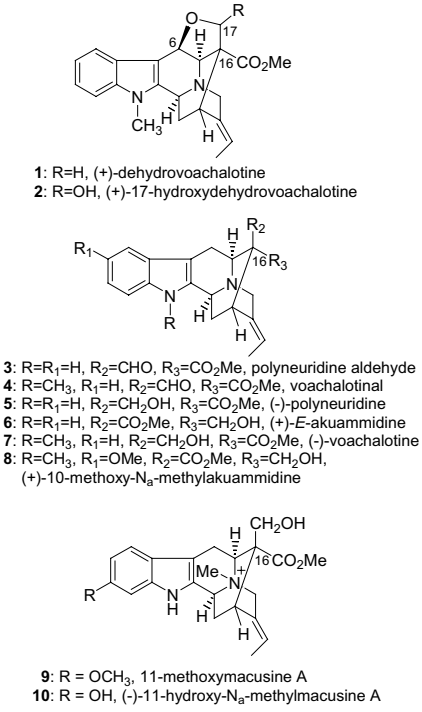

Figure 1. Structures of sarpagine-related indole alkaloids containing a quaternary center at C-16.

Keywords: Indole alkaloid; Enantiospecific total synthesis; Quaternary carbon center; Tollens reaction; DDQ oxidation; Dehydrovoachalotine.

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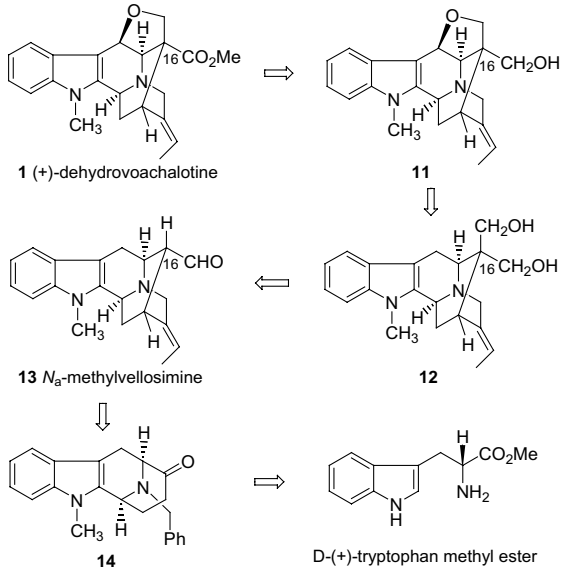
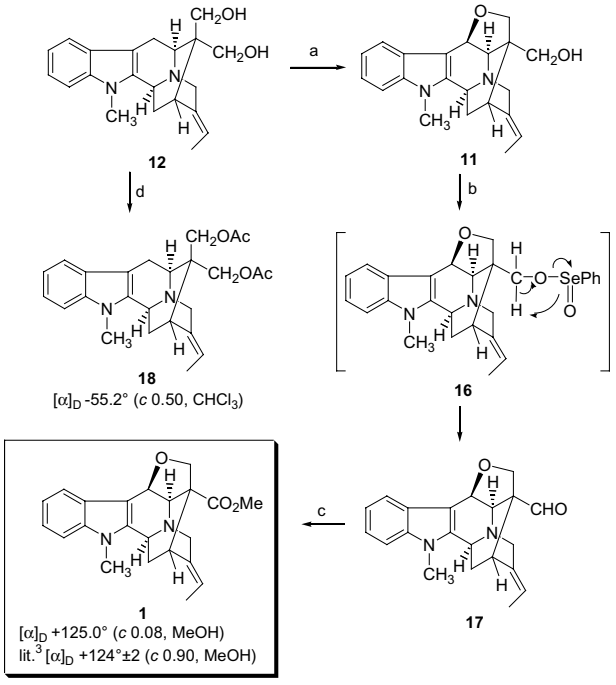
In a retrosynthetic sense (Scheme 1), (+)-dehydrovoachalotine (**1**) was envisaged to arise from alcohol **12** via a DDQ-mediated oxidative cyclization, the latter of which might be accessed by the Tollens reaction of N_a-methylvellosimine (**13**) with formaldehyde. The synthesis of **13** had been achieved recently from D-(+)-tryptophan methyl ester in eight reaction vessels in 39% overall yield via a combination of the asymmetric Pictet–Spengler reaction, Dieckmann cyclization, and a stereocontrolled intramolecular enolate driven palladium-mediated cross-coupling process.[2d,e,7] With gram quantities of **13** 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.[8] Gratifyingly, it was found that the aldehydic group at C-16 in aldehyde **13** could be converted into diol **12** in 85% yield via the Tollens reaction by using 37% aq formaldehyde (5 equiv) and 2 N KOH (10 equiv) in methanol, as shown in Table 1 (Table 1, entry 1). The prochiral quaternary carbon center at C-16 that contained the structurally hindered diol in **12** was constructed in one step. More importantly, because of the symmetry of the two diol moieties at C-16 (Scheme 2), generation of a new chiral center was avoided. Encouraged by this result, attention turned toward decreasing the reaction time for the Tollens process. The amount of 37% aq formaldehyde was, therefore, increased to facilitate the formation of **12** from intermediate **15**. This increase in the concentration of formaldehyde, tremendously 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 cases.[9,10] Examination of these new conditions

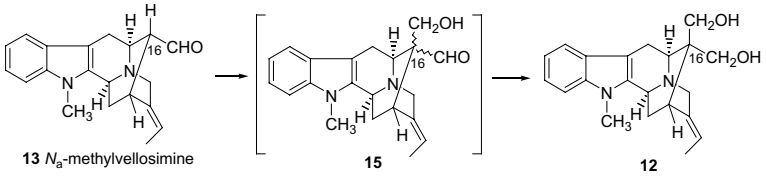


Scheme 1. Retrosynthetic analysis.



Scheme 2. Synthesis of (+)-dehydrovoachalotine: Reagents and conditions: (a) DDQ, THF, reflux, 2 h, 95%; (b) $(PhSeO)_2O$, chlorobenzene, reflux, 30 min, 92%; (c) KOH, I_2, MeOH, rt, 2 h, 90%; (d) Ac_2O, DMAP, CH_2Cl_2, 95%.

Table 1. Reaction conditions for the formation of diol **12** 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[9]	37% aq HCHO (123 equiv), Na_2CO_3 (3 equiv), MeOH/CH_2Cl_2 (2:1), rt	60	No reaction
5[10]	$(HCHO)_n$ (8 equiv), K_2CO_3 (8 equiv), MeOH, reflux	60	No reaction

(employing similar weak bases, Na_2CO_3,[9] and K_2CO_3[10]; Table 1, entries 4 and 5), unfortunately, resulted in no reaction in this system (see **13**).

Once the synthesis of diol **12** was completed as described above, further oxidative cyclization of **12** effected by DDQ in THF afforded **11** in 95% yield. The use of DDQ to form 6-oxygen substituted tetrahydro β-carbolines was developed in our laboratory several years ago,[11,12] following the earlier work of Oikawa and Yonemitsu.[13] The remaining hydroxyl moiety of cyclic ether **11** was somewhat resistant to oxidation by a variety of reagents under various reaction conditions (i.e., TEMPO/BAIB/CH_2Cl_2,[14] PDC/CH_2Cl_2,[15] SO_3·pyr/DMSO/Et_3N,[16] TPAP/NMO/4 Å MS/CH_2Cl_2,[17] $(COCl)_2$/DMSO/Et_3N/−78 °C,[18] and Dess–Martin/pyr/CH_2Cl_2,[19]); however, intramolecular oxidation of the hydroxymethyl group of **11** was successfully achieved with $(PhSeO)_2O$/PhCl/115 °C/30 min via the intermediate **16** in 92% yield.[20] The basicity of the N_b-nitrogen atom[8e,22a] certainly was responsible, in part, for the limited success in these oxidations. The aldehyde so formed was further oxidized with KOH/I_2/MeOH by the method of Yamada et al. [21] to deliver the methyl ester **1** in 90% yield. The optical rotation ($[\alpha]_D$ +125.0, lit.[3] +124 ± 2) and spectroscopic properties of synthetic (+)-**1** were in excellent agreement with those of natural (+)-dehydrovoachalotine (see Table 2).[3–5,23] The stereochemistry of the chiral centers in **1** was confirmed by 2D NOESY experiments; the asymmetric centers were present in the correct configuration, as depicted in Figure 2. Thus, a concise and efficient route for the synthesis of (+)-dehydrovoachalotine (**1**) was developed. Furthermore, the same diol **12** was converted into voachalotinol diacetate (**18**) (Scheme 2) whose ^{13}C NMR was reported by Mustich et al. The signals in the ^{13}C NMR spectrum of synthetic **18** were in excellent agreement with the reported values.[5]

Table 2. ^{13}C NMR of (+)-dehydrovoachalotine (**1**)

Carbon	Natural **1**	Synthetic **1**
2	143.6	143.3
3	47.0	47.1
5	61.5	61.4
6	72.6	72.6
7	103.5	103.4
8	126.5	126.4
9	119.1	119.2
10	120.1	120.1
11	121.7	121.8
12	109.2	109.1
13	137.7	137.7
14	29.0	29.3
15	31.0	31.0
16	53.9	53.9
17	68.3	68.3
18	12.7	12.6
19	116.5	116.5
20	135.9	135.7
21	55.4	55.4
N_a-Me	29.0	29.1
22	175.9	175.9
23	52.1	52.2

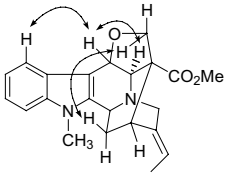
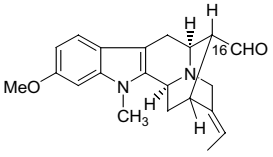
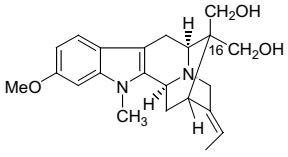
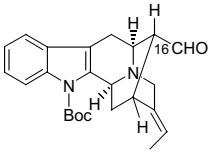
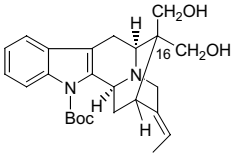
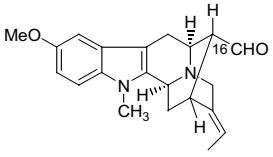
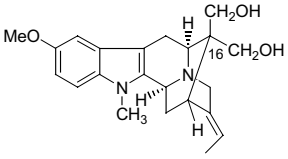
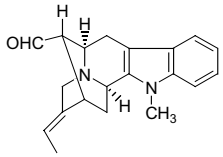
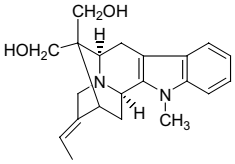


Figure 2. Selected NOESY's of (+)-dehydrovoachalotine (**1**).

Once the optimized conditions (Table 1, entry 3) had been developed, the Tollens reaction was further studied with other substrates in the presence and/or absence of a methoxyl substituent on the indole A-ring (Table 3). Treatment of 11-methoxyvellosimine (**19a**)[22] with 37% aq formaldehyde and 2 N KOH in MeOH resulted in the isolation of diol **19b** in 87% yield. Similarly, N_a-Boc protected vellosimine (**20a**), 10-methoxyvellosimine (**21a**),[2g] and the *ent*-N_a-methylvellosimine (*ent*-**13**)[22] were conveniently converted into their corresponding diols **20b**, **21b**, and *ent*-**12** in high yield via the Tollens process; the process is certainly general. These prochiral C(16) substituted indole intermediates can now be employed for the synthesis of other sarpagine-related indole alkaloids, as well as their enantiomers.

Table 3. Application of the Tollens reaction to various substrates[a]

Substrate	Product (isolated yield)
 **19a**	 **19b** (87%)
 **20a**	 **20b** (92%)
 **21a**	 **21b** (88%)
 *ent*-**13**	 *ent*-**12** (90%)

[a] All reactions were carried out by using 37% aq HCHO (25 equiv), KOH (2 N, 10 equiv), and MeOH at room temperature for 10 h.

In conclusion, the first total synthesis of (+)-dehydrovoachalotine has been realized via a simple and convergent route from D-(+)-tryptophan methyl ester in 28% overall yield. The correct configuration of the *E*-ethylidene moiety of **1** was accomplished stereospecifically by the enolate-mediated palladium catalyzed cross coupling process, while the C-16 prochiral hydroxymethyl moiety was installed in high yield by a Tollens reaction. The DDQ oxidation to provide ether **11** was also executed in stereospecific fashion and permitted discrimination between the two C(16) hydroxymethyl groups. Extension of this method to a wide variety of indole alkaloids, which contain a C-16 quaternary center, is now possible.

Acknowledgements

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23. $[\alpha]_D$ +125.0 (*c* 0.08, MeOH); lit.[3] $[\alpha]_D$ +124 ± 2 (*c* 0.90, MeOH); IR: 1736, 1467, 1238 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.60 (3H, d, $J = 7.9$ Hz), 2.03 (2H, m), 2.29 (1H, t, $J = 2.9$ Hz), 3.65 (3 H, s), 3.72 (3 H, s), 3.71–3.76 (3H, m), 3.94 (1H, d, $J = 10.1$ Hz), 4.07 (1H, dd, $J = 4.2$, 9.4 Hz), 4.52 (1H, d, $J = 7.7$ Hz), 5.36 (1H, q, $J = 7.6$ Hz), 5.78 (1H, d, $J = 7.7$ Hz), 7.14–7.33 (3H, m), 7.70 (1H, d, $J = 7.5$ Hz); ^{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 calculated for $C_{22}H_{24}N_2O_3$: 364.1786, found: 364.1765.