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Unusual biomimetic oxidations of indoles: synthesis of suaveoline and an alkaloid G analogue

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Abstract

The one-pot conversion of ajmaline **1** into the nitrile **4** (X-ray structure) and suaveoline **2a** is reported; both reactions utilise hydroxylamine hydrochloride in a refluxing alcohol, and involve unusual multi-step mechanisms in which the product ratio can be controlled by the choice of the alcohol. In an additional unusual oxidation, the synthetic intermediate **14** used in a synthesis of suaveoline can be oxidatively cyclized to **16**. © 1999 Elsevier Science Ltd. All rights reserved.

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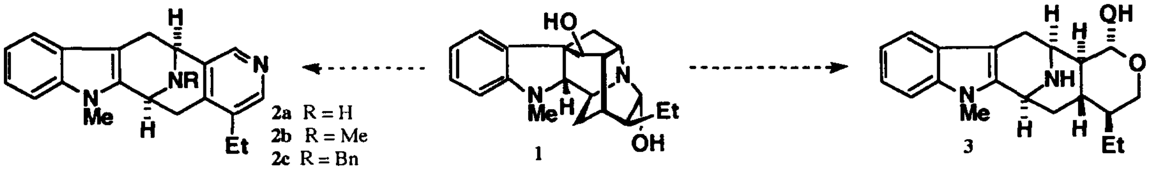
The interconversion of natural products remains an important aspect of synthetic work on biologically active compounds. It can not only provide a rapid route to advanced intermediates for the semi-synthesis of natural products or analogues thereof, but can also sometimes shed light on biosynthetic pathways. Since its discovery in 1972,[1] the biosynthetic origin of suaveoline **2a** has been investigated by several groups, and it has been shown that ajmaline **1** (which is also found in the same plants) is converted into suaveoline **2a**, *N*-methylsuaveoline **2b** and raumacline **3** in vivo (Scheme 1).[2]



Scheme 1. Known biotransformations from ajmaline **1**

We have been interested in the indole alkaloids of this family for some time, not only because of their biological activity and potential, but also because of the synthetic challenge posed by their common 1,3-disubstituted tetrahydro-β-carboline ring system. Initial mechanistic studies[3] led us to develop a simple

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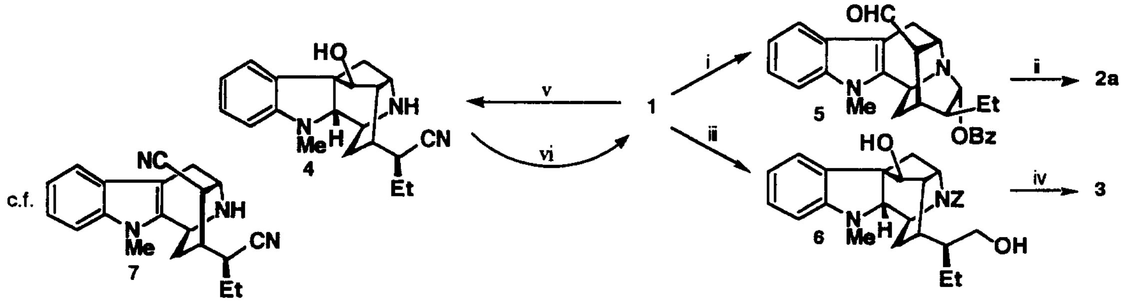
stereoselective method of gaining access to such tricyclic systems,[4] and we have subsequently applied this methodology to a number of total syntheses.[5]

In ongoing synthetic work, we wished to obtain advanced intermediates for work on ajmaline, suaveoline, and related alkaloids. Some of the published degradation/inter-conversion procedures on ajmaline are summarized in Scheme 2. We were anxious to obtain the cyano-alcohol **4**, because it can be re-converted into ajmaline,[6,7] and is very similar to an advanced synthetic intermediate **7** that we already had in hand;[5a] we also wanted to prepare a sample of suaveoline (which is not readily available) for comparison with our synthetic material.[5a]



Scheme 2. Reagents and conditions: (i) BzCl, PhH, then $Pb(OAc)_4$; (ii) reflux in MeI, then NH_3 (aq);[1] (iii) $NaBH_4$, H_2O–MeOH, rt, then ZCl, 1 M NaOH–DCM, 0°C; (iv) $Pb(OAc)_4$, then H_2, Pd–C, MeOH;[2] (v) $NH_2OH \cdot HCl$, reflux in H_2O, then AcOH, Ac_2O, HCl, then KOH, MeOH; (vi) $LiAlH_4$, Et_2O, rt[6]

To our surprise, treatment of ajmaline **1** with hydroxylamine hydrochloride in refluxing ethanol yielded the cyano-alcohol **4** directly in 89% yield, whose structure was confirmed by single crystal X-ray structure determination (Fig. 1).[8] This reaction presumably proceeded via the oxime **8**, and the unexpectedly facile dehydration might have involved intramolecular proton abstraction, as suggested in Scheme 3.

We were further surprised to discover that this reaction was acutely solvent dependent, as indicated in Table 1. The most useful and unexpected result was the direct conversion of ajmaline **1** into suaveoline **2a** (30% yield) on refluxing the former in *n*-butanol with hydroxylamine hydrochloride. As this is an oxidation reaction, we speculated that oxygen was the oxidant, and this was supported by the suppression of suaveoline formation when the reaction was conducted under argon. Further insight into the mechanism was gained by the observation that ammonium chloride/air did not effect the conversion of **1**→**2a** in refluxing butanol, strongly implicating an oxidized form of hydroxylamine as the actual

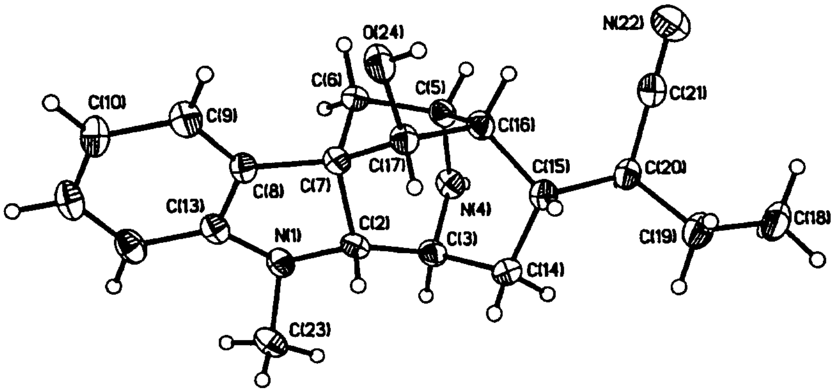
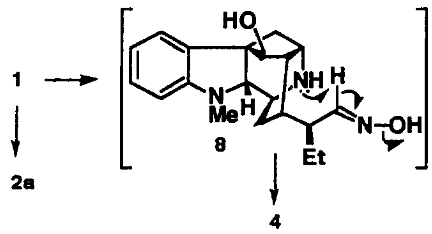


Figure 1. X-Ray crystal structure of **4**

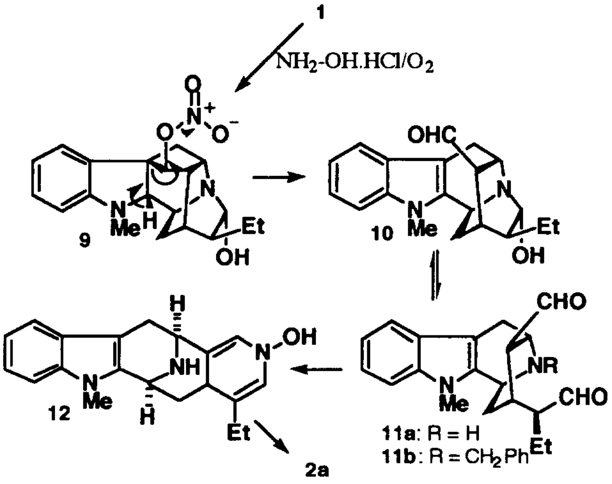


Scheme 3. Reagents and conditions: see Table 1

Table 1
Conditions for the conversion of ajmaline **1** into **2** or **4**

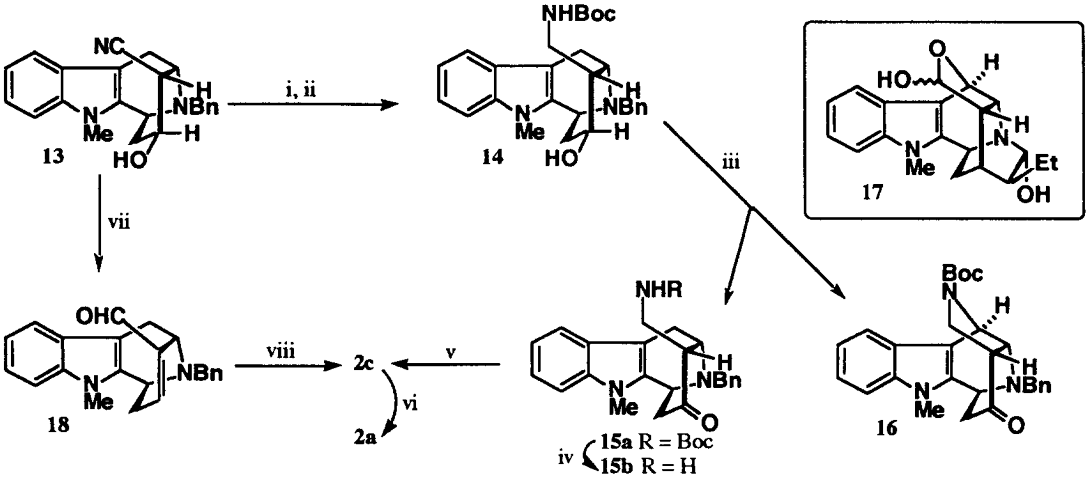
Entry	Conditions	Product(s)
1	**1**, NH_2-OH.HCl, reflux in EtOH, air	**4** (89%)
2	**1**, NH_2-OH.HCl, reflux in *n*-PrOH, air	**2a** (<5%) + **4** (31%)
3	**1**, NH_2-OH.HCl, reflux in *n*-BuOH, air	**2a** (30%)
4	**1**, NH_2-OH.HCl, reflux in PhMe, air	essentially no reaction
5	**1**, NH_2-OH.HCl, reflux in *n*-BuOH, Ar	**2a** (<5%) + mixture
6	**1**, NH_4Cl, reflux in *n*-BuOH, air	**1** (65%) (no **2a** or **4**)

oxidizing agent. In further support of this, the diimine of the protected di-aldehyde **11b** does cyclize to a pyridine derivative under similar conditions;[5a] we are therefore confident that, had NH_4Cl/air/butanol reflux generated any of the dialdehyde **11a**, then we would have observed the formation of suaveoline **2a**. On the basis of these results, it would appear that the hydroxylamine is involved in the oxidative mechanism, perhaps forming $[NO]^+$ which is trapped as the nitrite, and further oxidized to the nitrate, as indicated in Scheme 4.



Scheme 4. Proposed mechanism for conversion of **1** into **2a**

With a sample of suaveoline in hand, we attempted to complete a synthesis of this alkaloid from the advanced intermediate **13** that we had prepared earlier from L-tryptophan in nine steps.[5b] To achieve this (see Scheme 5), we reduced the nitrile **13** to the amine with $LiAlH_4$, and protected the amine with the Boc group to give **14**, prior to oxidation of the secondary alcohol. Surprisingly, both TPAP and Swern oxidation conditions led to virtually no reaction, but oxidation with PCC generated a major and minor product, both possessing a ketone functionality. The major product (31%) was identified from extensive NMR analysis as the bridged polycycle **16**,[9] whilst the desired ketone **15a** was formed in only 16% yield.



Scheme 5. Reagents and conditions: (i) $LiAlH_4$, THF, rt, O/N; (ii) Boc_2O, $NaHCO_3$, CH_2Cl_2, 30 min (64% from **13**); (iii) PCC, Florisil® (1:1), CH_2Cl_2, O/N (47%); (iv) TFA (100%); (v) *n*-PrCHO, O_2, CH_2Cl_2, MS, reflux; (vi) H_2, $Pd(OH)_2$–C (96%);[5a] (vii) $POCl_3$/py then DIBAL–H (−78°C) (86%);[5] (viii) see Fu and Cook[10]

The polycycle **16** is of interest because of the existence of indole alkaloids cyclized at this position such as Alkaloid G **17**.[11] As far as we are aware, this is the first example of transition metal oxidation leading to derivatization at this position, with DDQ being the usual reagent of choice;[12] presumably, one-electron oxidation processes operate in both cases, offering two alternative reagents for accessing compounds of this type.

Deprotection of the Boc-derivative **15a** gave an unstable amino-ketone **15b**, which was refluxed with butanal in the presence of molecular oxygen; from the product mixture, *N*-benzylsuaveoline **2c** could be detected in small amounts by comparison (TLC and mass spectrometry) with authentic material. This constitutes a new total synthesis of suaveoline **2a**, although we have already published a more efficient route from **13** to **2a**.[5b]

In summary, we have used ajmaline **1** as an advanced yet cheap indolic building block for the construction of the nitrile **4**, for use in the semi-synthesis of other targets in this family, and we have effected a one step conversion of ajmaline **1** into suaveoline **2a**. We have also identified an unexpected and useful cyclization procedure at the 3′-indole position using PCC.

Acknowledgements

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8. Crystal data for **4**: yellow crystal (0.6×0.4×0.25 mm) from $CHCl_3$/methanol mounted in epoxy resin glue in a thin-walled glass capillary, $C_{20}H_{25}N_3O$, M=323.43, orthorhombic, space group $P2_12_12_1$, a=6.8037(4) b=11.4296(8), c=22.018(3) Å, V=1712.2(2) Å^3, Z=4, D_c=1.255 g cm^{-3}, m=0.079 mm^{-1}, 2183 reflections were measured on a Siemens P4 diffractometer with Mo Ka radiation, l=0.71073 Å, w mode, q range 1.85 to 24.99° at 293 K. The structure was refined to R_1=0.0457, wR_2=0.1217 and goodness of fit 1.053 for 1855 unique observed [$I>2\sigma(I)$] data and 219 parameters with maximum and minimum residual electron density peaks of 0.32 and –0.32 eÅ^3, respectively. The Flack x parameter was refined to 1(3) i.e. absolute structure cannot be determined from X-ray data. Data collection and reduction were performed using the program XSCANS [Siemens Analytical Instruments, Inc., Madison, Wisconsin, USA, 1994]. Direct methods solution and refinements (full-matrix least squares on F^2) were performed using SHELXTL/PC version 5.03 [G. M. Sheldrick, 1994, SHELXTL/PC. Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA]. Atomic coordinates, displacement parameters and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre (CCDC).
9. Selected key data for **16**: δ_C (50 MHz, $CDCl_3$) 28.5(q), 28.7(q), 43.3(t), 44.8(t), 48.7(d), 49.5(d), 50.1(d), 57.7(t), 60.5(d), 79.5(s), 107.2(s), 108.6(d), 119.9(d), 121.5(d), 121.9(d), 126.2(s), 127.6(d), 128.6(d), 134.5(s), 137.9(2×s), 155.0(s), 206.7(s); M^+ 457.2359, calcd for $C_{28}H_{31}N_3O_3$: 457.2365.
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