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Easy Access to the Voaketone Ring System

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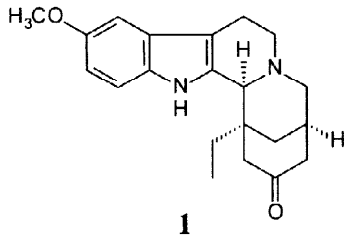
Abstract: Intramolecular aldol condensation of ketoaldehyde **8** affords three new compounds: enone **9**, hydroxyketone **10**, and enone **11**. Enone **9** possesses the ring system of (-)-voaketone (**1**), which is a skeletal rearrangement product of the indole alkaloid (-)-voacangine.

Some time ago, an interesting skeletal rearrangement of an alkaloid was observed by Schmid and co-workers.[1] The *Iboga* alkaloid (-)-voacangine was transformed in three steps to derivative **1**, which was named as (-)-voaketone. In 1962, Walls and Perez[2] succeeded in preparing the parent compound **2**, which they called 1,3-trimethylene-1,2,3,4,6,7-hexahydroindolo[2,3-*a*]quinolizine. Unfortunately, the stereochemistry of compound **2** remained unspecified. Another way to construct this skeleton was reported by Winterfeldt and coworkers,[3] who synthesized compound **3** (dehydroisoyohimbinone). This type of skeleton has not yet been found in nature and, so far, only the three methods mentioned provide access to this ring system.



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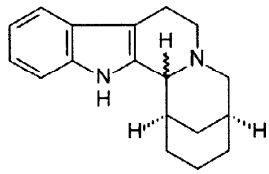

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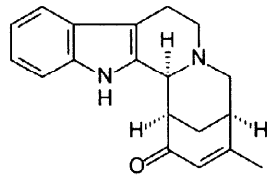

3

In connection with studies on the tacamine-type indole alkaloids we have focused our attention on the stereoselective synthesis of 1,3-disubstituted indolo[2,3-*a*]quinolizidines.[4] We now wish to report that one of our aldehyde intermediates undergoes a facile intramolecular aldol condensation providing a straightforward access to the voaketone ring system.

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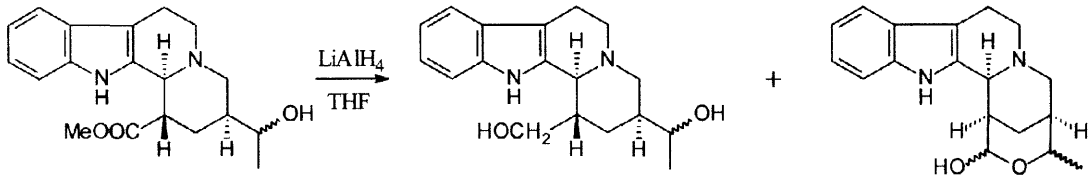
Results and Discussion

We reported recently the synthesis of hydroxy esters **4a** and **4b**.[4] With the aim of obtaining an aldehyde intermediate suitable for the synthesis of some tacamine-type alkaloids,[5] we first reduced the hydroxy esters at rt to diols **5a** and **5b** (Scheme 1). At lower temperatures, considerable amounts of lactols **6a** and **6b** were formed as a result of the epimerization and ring closure of the aldehyde intermediates.[6]



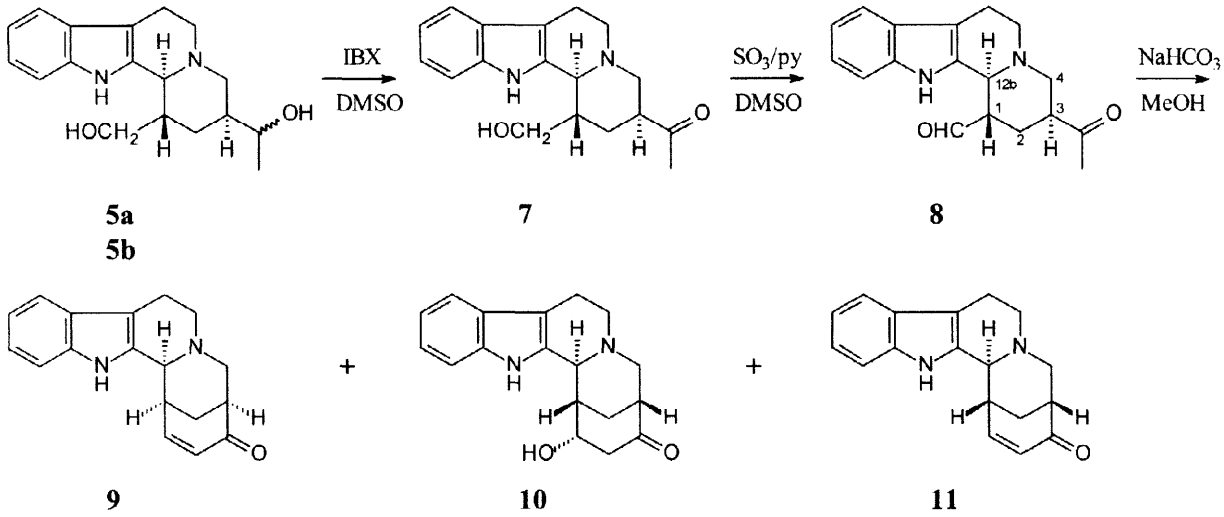
4a (β-OH)
4b (α-OH)

5a (β-OH)
5b (α-OH)

6a
6b

Scheme 1

Next the behaviour of diols **5a** and **5b** in oxidation was studied. In order to avoid epimerization and/or lactol formation at this stage, we sought for a method to oxidize only the hydroxyethyl side chain. Interestingly, when **5a** and **5b**, separately or together, were oxidized with *o*-iodoxybenzoic acid (IBX)[7] in DMSO at room temperature, the products were ketoalcohol **7** and ketoaldehyde **8**. In experiments undertaken to optimize the formation of **8** by using higher temperature or longer reaction time, ketoaldehyde **8** was obtained together with its isomers formed through its epimerization at C-12b and C-1. However, further oxidation of ketoalcohol **7** with DMSO/SO_3·pyridine gave ketoaldehyde **8** in good yield (Scheme 2).



5a
5b

7

8

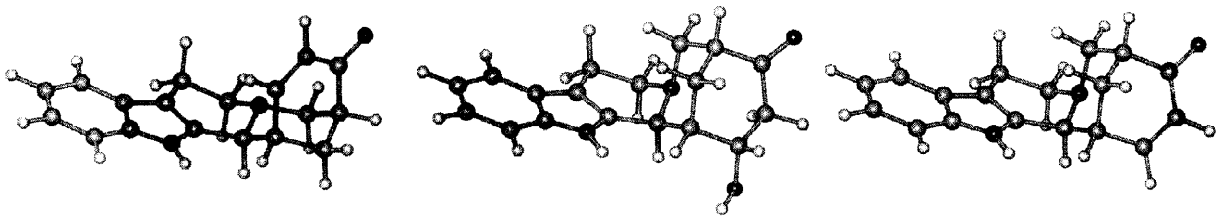
9

10

11

Scheme 2

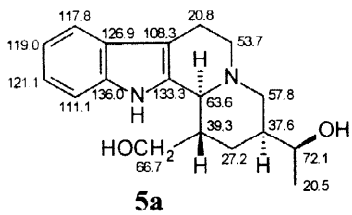
An inversion of configuration at C-1 was required to obtain a suitable intermediate for tacamine-type alkaloids. Treating ketoaldehyde **8** with $NaHCO_3$ in methanol aiming at an epimerization at C-1 gave three compounds with a three-carbon bridge: enone **9**, β-hydroxyketone **10** and enone **11** (Scheme 2). Spectral evidence showed that enone **9** contained a *trans*-fused C/D ring juncture, and thus it possessed the voaketone ring system. The other two products, **10** and **11**, were found to exist predominantly in a *cis*-fused C/D ring conformation. Formation of **9** from **8** can be explained by successive epimerization at C-1, intramolecular aldol condensation, and instantaneous water elimination. Compounds **10** and **11**, which actually contain a novel ring system, arise *via* initial epimerization at C-3. Nitrogen inversion and *cis*-decalin type ring interconversion[8] then permit the intramolecular aldol reaction to take place. NOE difference spectroscopy applied to β-hydroxyketone **10** confirmed the orientation of the hydroxyl group. The epimeric nature of enone **11** in regard to enone **9** was confirmed by its acid-catalyzed epimerization[9,10] to the voaketone compound **9**. The stereoformulas of the new products **9-11** provide a better view of the ring systems.



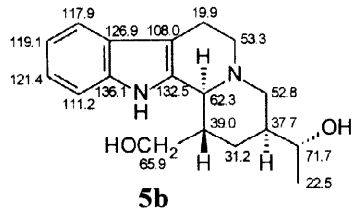
9 **10** **11**

Conclusions

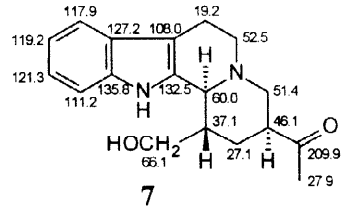
An easy way to construct the (-)-voaketone ring system (compound **9**), an important skeletal rearrangement product of the indole alkaloid (-)-voacangine, was achieved *via* an intramolecular aldol condensation of a 1,3-disubstituted indolo[2,3-a]quinolizidine derivative. Furthermore, a new ring system possessing a *cis*-fused C/D ring juncture (compounds **10** and **11**) was formed.



5a

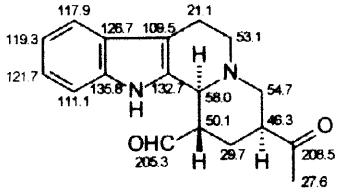


5b



7

Chart



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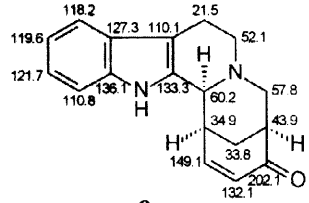
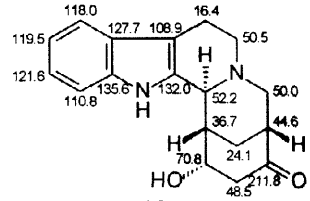


9



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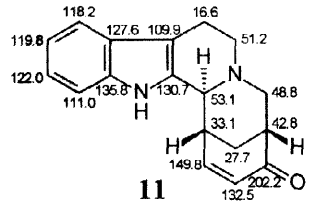


11

Chart (cont'd)

Experimental

Except where otherwise stated, all reactions were carried out under argon. Alkaline work-up comprised addition of sat. aq $NaHCO_3$, extraction with CH_2Cl_2 (3x), drying of the combined organic layers with Na_2SO_4, and evaporation of the solvent under vacuum. Melting points were determined with a Gallenkamp melting point apparatus and are uncorrected. IR spectra (cm^{-1}, in $CHCl_3$ unless otherwise noted) were recorded on a Perkin-Elmer 700 spectrophotometer. ^1H NMR (399.958 MHz, reference: TMS, δ_H = 0.0 ppm) and ^{13}C NMR (100.578 MHz, reference: $CDCl_3$, δ_C = 77.0 ppm) spectra were recorded on a Varian Unity 400 spectrometer with $CDCl_3$ used as solvent. Coupling constants (*J*) are given in Hz. Signal assignments are based on standard APT, COSY, and HETCOR experiments. For the ^{13}C NMR data of the compounds (**4a**, **4b**, and **7-11**), see Chart. EI and HR mass spectra (70 eV, *m/z*) were measured with a Jeol DX 303/DA 5000 mass spectrometer. Merck Kieselgel 60 (230-400 mesh) was used in column chromatography (CC).

Reduction of Hydroxyesters 4a and 4b. Hydroxyester **4a** (50 mg, 0.15 mmol) in dry THF (4 ml) was added *via* syringe to a suspension of $LiAlH_4$ (26.8 mg, 0.71 mmol) in dry THF (3 ml). After 1 h stirring at rt, alkaline work-up (aq NaOH) gave the crude product, which was purified by CC (CH_2Cl_2/MeOH, 92/8) to give pure diol **5a** (41 mg, 91%). Diol **5b** was prepared similarly.

Diol 5a: Mp 152-154°C (MeOH); IR: 3350 (OH); ^1H NMR: 10.05 (1H, br s, NH), 7.45-7.03 (4H, m, arom.), 5.33 (1H, br s, -OH), 4.30 (1H, br s, -OH), 3.73 (1H, dd, *J* = 11.5 and 3, -C*H*$_2$OH), 3.63 (1H, dd, *J* = 11.5 and 7, -C*H*$_2$OH), 1.11 (3H, d, *J* = 7, -CHOH*Me*); MS: 300 (M^+, 100), 299 (91), 269 (33), 255 (49), 184 (33), 171 (36), 170 (53), 169 (44); HR-MS: calcd for $C_{18}H_{24}N_2O_2$: 300.1838, found: 300.1840.

Diol 5b: Mp 201-203°C (MeOH); IR: 3330 (OH); ^1H NMR: 10.06 (1H, br s, NH), 7.43-7.03 (4H, m, arom.), 4.64 (1H, br s, -OH), 3.72 (2H, d, *J* =11, -C*H*$_2$OH), 1.11 (3H, d, *J* = 6, -CHOH*Me*); MS: 300 (M^+, 100), 299 (95), 269 (27), 255 (48), 184 (30), 171 (32), 170 (52), 169 (45); HR-MS: calcd for $C_{18}H_{24}N_2O_2$: 300.1838, found: 300.1844.

Oxidation of Diol 5a by IBX. *o*-Iodoxybenzoic acid (IBX) (52 mg, 0.18 mmol) was added to a solution of diol **5a** (25.1 mg, 0.08 mmol) in DMSO (5 ml) and the mixture was stirred for 20 h at rt. Alkaline work-up afforded the crude product, which was purified by CC (CH_2Cl_2/MeOH, 99:1) to furnish ketoalcohol **7** (8.1 mg, 34%) and ketoaldehyde **8** (3.6 mg, 15%), in addition to starting diol **5a** (6.6 mg, 27.5%).

Ketoalcohol 7: amorphous; IR: 3300 (OH), 1710 (C=O); ^{1}H NMR: 9.09 (1H, br s, NH), 7.45-7.05 (4H, m, arom.), 3.98 (1H, br s, H-12b), 3.95 (1H, dd, J = 11 and 4, -C*H*$_2$OH), 3.84 (1H, dd, J = 11 and 5.5, -C*H*$_2$OH), 2.13 (3H, s, Me); MS: 298 (M^+, 50), 281 (13), 255 (18), 240 (26), 170 (100), 169 (65); HR-MS: calcd for $C_{18}H_{22}N_2O_2$: 298.1681, found: 298.1743.

Ketoaldehyde 8: amorphous; IR: 2850-2750 (Wenkert-Bohlmann bands), 1720 (C=O), 1710 (C=O); ^{1}H NMR: 9.84 (1H, s, -CHO), 8.21 (1H, br s, NH), 7.47-7.05 (4H, m, arom.), 2.26 (3H, s, Me); MS: 296 (M^+, 53), 295 (25), 267 (8), 253 (18), 240 (30), 170 (100), 169 (60); HR-MS: calcd for $C_{18}H_{20}N_2O_2$: 296.1525, found: 296.1517.

Oxidation of Ketoalcohol 7 with DMSO/SO_3·pyridine. Sulfur trioxide pyridine complex (38.2 mg, 0.24 mmol) in DMSO (0.25 ml) was added to a mixture of ketoalcohol **7** (23.7 mg, 0.08 mmol), DMSO (5 ml), and triethylamine (0.5 ml) and the mixture was stirred for 1.5 h at rt. Alkaline work-up and CC (CH_2Cl_2/MeOH, 98:2) gave ketoaldehyde **8** (15.4 mg, 65.5%), slightly contaminated with its C-12b isomer.

Intramolecular Aldol Condensation of Ketoaldehyde 8. To a solution of ketoaldehyde **8** (25 mg, 0.08 mmol) in MeOH (5 ml) was added $NaHCO_3$ (35 mg, 0.42 mmol) and the mixture was refluxed gently for 2 h. After aqueous work-up, the residue was purified by CC (CH_2Cl_2/MeOH, 99:1) to furnish enone **9** (5.3 mg, 24%), hydroxyketone **10** (7.1 mg, 30%), and enone **11** (2.5 mg, 11%).

Enone 9: amorphous; IR: 2860-2770 (Wenkert-Bohlmann bands), 1700 (C=O), 1670 (C=C); ^{1}H NMR: 7.87 (1H, br s, NH), 7.46-7.07 (4H, m, arom.), 6.68 (1H, ddd, J = 10, 6.4 and 1.6, -C*H*=CH-CO-), 6.13 (1H, d, J = 10, -CH=C*H*-CO-), 3.62 (1H, br s, H-12b); MS: 278 (M^+, 100), 277 (98), 185 (35), 182 (52), 169 (92); HR-MS: calcd for $C_{18}H_{18}N_2O$: 278.1419, found: 278.1419.

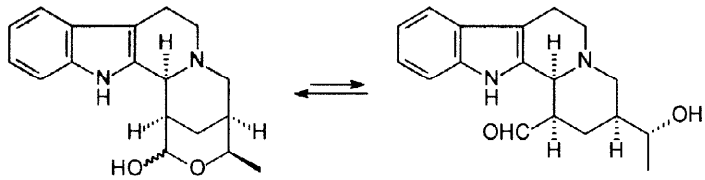
Hydroxyketone 10: amorphous; IR: 3350 (OH), 1710 (C=O); ^{1}H NMR: 7.91 (1H, br s, NH), 7.50-7.09 (4H, m, arom.), 4.84 (1H, br s, H-12b), 4.32 (1H, ddd, J = 11, 7 and 5, -C*H*OH-); MS: 296 (M^+, 53), 295 (54), 279 (54), 278 (48), 277 (53), 184 (52), 169 (100); HR-MS: calcd for $C_{18}H_{20}N_2O_2$: 296.1524, found: 296.1537.

Enone 11: amorphous; IR: 1680 (C=O), 1670 (C=C); ^{1}H NMR: 7.82 (1H, br s, NH), 7.53-7.11 (5H, m, arom. and -C*H*=CHCO-), 6.35 (1H, d, J = 10, -CH=C*H*CO-), 4.23 (1H, br s, H-12b); MS: 278 (M^+, 85), 277 (100), 184 (40), 182 (50), 169 (92); HR-MS: calcd for $C_{18}H_{18}N_2O$: 278.1419, found: 278.1414.

Acid-Catalysed Epimerization of Compound 11. Enone **11** (4.1 mg, 0.015 mmol) was dissolved in trifluoroacetic acid (TFA, 2 ml) and the solution was refluxed overnight. Evaporation of TFA, followed by alkaline work-up, gave a mixture of enones **9** and **11** (2.8 mg, 67%) in ratio 63:37 (^{1}H NMR integration).

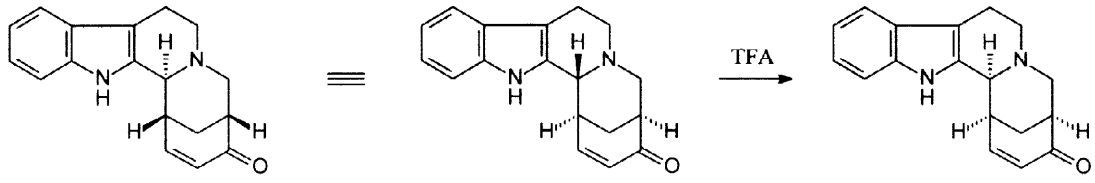
References and Notes

1. Morita, Y.; Hesse, M.; Renner, U.; Schmid, H. *Helv. Chim. Acta* **1976**, *59*, 532-551.
2. Walls, F.; Perez, G. *Bol. Inst. Quim. Univ. Nal. Auton. Mex.* **1962**, *14*, 32-47 (*Chem. Abstr.* **1963**, *59*, 2784f).
3. Rischke, H.; Wilcock, J. D.; Winterfeldt, E. *Chem. Ber.* **1973**, *106*, 3106-3118.
4. Lounasmaa, M.; Karinen, K.; Din Belle, D.; Tolvanen, A. *Heterocycles* **1997**, *45*, 361-366. Note: in this report hydroxyesters **4a** and **4b** are drawn as their mirror images.
5. Din Belle, D.; Tolvanen, A.; Lounasmaa, M. *Tetrahedron* **1996**, *52*, 11361-11378.
6. Lactols **6a** and **6b** were in equilibrium with their open counterparts, aldehydes (e.g. **6a** and **i** as shown below), and thus they could not be isolated in pure state. However, some spectral data could be obtained from the mixture. Compound **6a** (mixture of epimers): ^{1}H NMR: 9.81 (s, -CHO), 7.93 (br s, NH), 7.78 (br s, NH), 5.33 (d, J = 8, -C*H*OH-), 4.80 (s, -C*H*OH-), 4.08 (dq, J = 6.5 and 2.5, -C*H*MeO-), 3.90 (dq, J = 6.5 and 2.5, -C*H*MeO-). ^{13}C-NMR: 93.5 (-CHOH-), 71.6/67.8 (-CHMeO-). Compound **6b**: ^{1}H NMR: 9.3 (s, -CHO), 4.92 (s, -C*H*OH-), 4.28 (1H, m, -C*H*MeO-); ^{13}C-NMR: 92.1 (-CHOH-), 69.2 (-CHMeO-).



6a **i**

7. Frigerio, M.; Santagostino, M.; Sputore, S.; Palmisano, G. *J. Org. Chem.* **1995**, *60*, 7272-7276.
8. Lounasmaa, M. *Curr. Org. Chem.* **1998**, *2*, 63-90.
9. Compound **11**, which is racemic, as are all the compounds of this study, is the C-12b epimer of compound **9**, as shown below.



11 **9**

10. Lounasmaa, M.; Miikki, L.; Tolvanen, A. *Tetrahedron* **1997**, *53*, 5349-5356.