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A new rearrangement of *N*-trifluoroacetoxyammonium salt under Polonovski–Potier reaction conditions: aziridinium versus iminium formation

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Abstract—The original hexahydro–indolizino[8,7-*b*]indole skeleton **10** has been obtained from the alkaloid ajmalicine **3** according to an original D-ring contraction under oxidative conditions.

In connection with our research programme aimed at the partial synthesis of camptothecin **1** analogues from heteroyohimbane alkaloids, we have recently published[1] our results for tetrahydroalstonine **2** (Fig. 1). In this letter we report our preliminary results with the epimeric alkaloid ajmalicine **3** which appeared to have a different chemical reactivity.

The first step of our project was the facile biomimetic oxidation of the indole nucleus of **2** or **3** to camptothecin-like skeleton **4** (Winterfeldt reaction). However, the pyridone D-ring could not be attained from **4** as its reactions led systematically to the C-5 instead of C-21 required lactam, the activated C-5 position of compound **4** allowing no hopes of a possible C-21 oxidation. Thus it appeared necessary to consider at first regioselective oxidation at the C-21 position of the tertiary amine of heteroyohimbanes **2** or **3** and then, in a second step, the indole oxidation.

The Polonovksi–Potier reaction should be an efficient approach for oxidation of the cyclic tertiary amine into the desired lactam. Indeed, treatment of amine oxides with trifluoroacetic anhydride (TFAA) followed by potassium cyanide (KCN) trapping of the intermediate iminium ion leads to an α-aminonitrile.[2] The anion of the later can be oxidised to a lactam with O_2.[3] Moreover this reaction offers certain advantages in regioselectivity which is determinated by a preferential loss of one of the three hydrogens α to the nitrogen according to an E2 elimination.

As far as the C-21 position is concerned a $\Delta^{19(20)}$ double bond will increase the H-21 acidity and direct the oxidation towards the formation of the thermodynamically more stable conjugated iminium ion $\Delta^{4(21)}$. KCN trapping should lead to the stable allylic α-aminonitrile.[4]

Lactol **5** obtained from ajmalicine **3** by hydrolysis, decarboxylation and lactol rearrangement[5] led to the required enol ether **6** by dehydration with *p*-toluenesulfonic acid (PTSA) in refluxing dioxane in 77% overall yield. It is noteworthy that the same reaction sequence

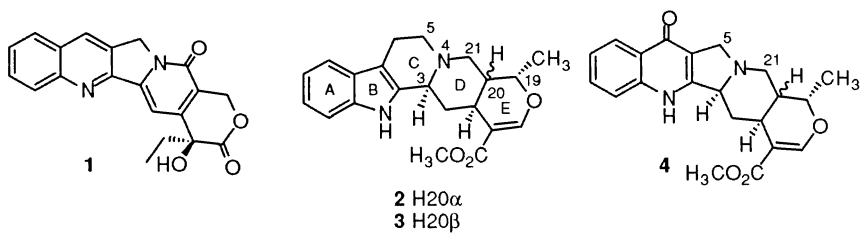

Figure 1.

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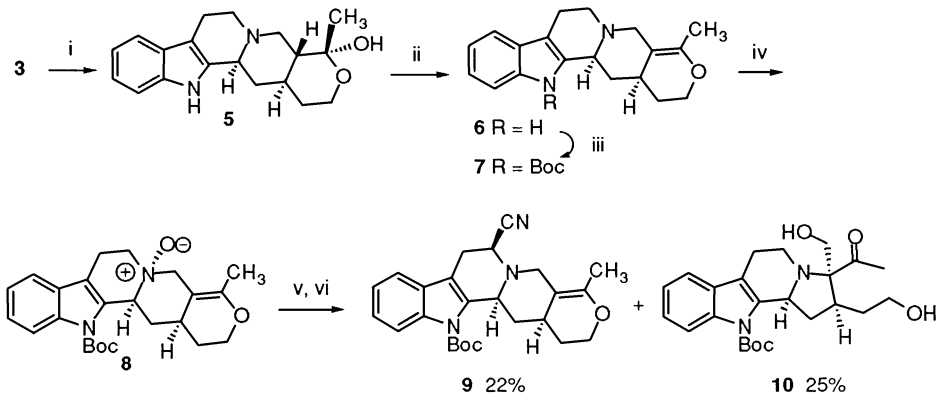


Scheme 1. (i) HCl 2N, reflux, 24 h; (ii) PTSA 1.1 equiv., 3 Å MS, dioxane, reflux, 45 min, 77% from **3**; (iii) Boc_2O, DMAP cat., CH_2Cl_2, rt, 4 h, 84%; (iv) MCPBA, 1.3 equiv., CH_2Cl_2, 0°C, 1 h, 94%; (v) TFAA, CH_2Cl_2, rt, 3 h; (vi) KCN/H_2O, pH 4, 0°C, 30 min then rt 3 h.

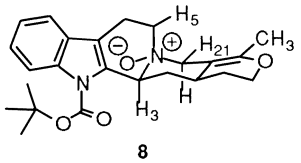


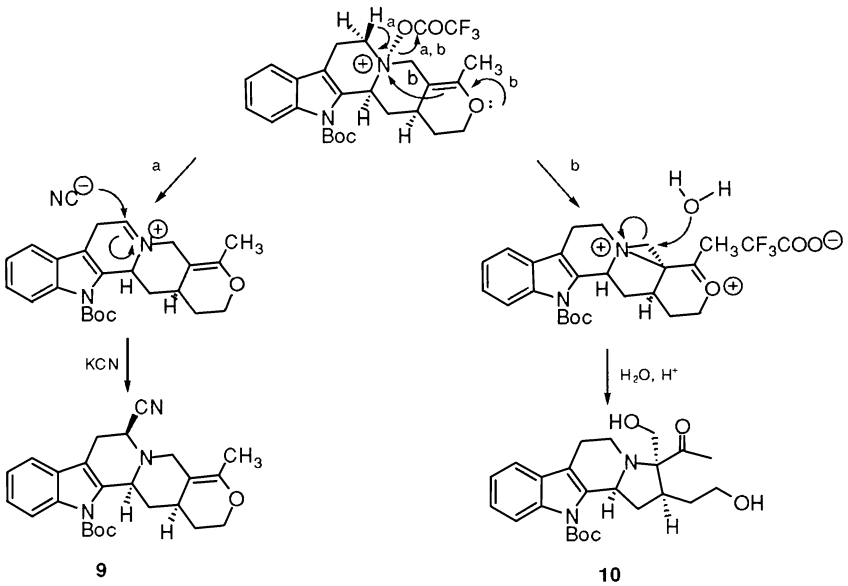
Figure 2.

conducted with tetrahydroalstonine **2** did not lead to enol ether **6**.

N-Boc protection of **6** was essential since nitrogen *N*(a) was susceptible to *m*-chloroperoxybenzoic acid (MCPBA) oxidation leading to indole oxidation products.[6] Moreover *N*(a)-Boc protection would prevent Grob type fragmentation of the tryptamine moiety, the only known alternative pathway of the modified Polonovski reaction.[7] The *cis*-quinolizidine *N*(b)-oxide **8**[8] was easily obtained by MCPBA oxidation in 94% yield. Stirring with TFAA for five hours at room temperature before adding the buffered KCN solution was necessary to achieve complete transformation of the starting material. From the complex reaction mixture two compounds **9** and **10** could be isolated in 22 and 25% yield, respectively (Scheme 1).

As shown in Fig. 2, the configuration of *cis*-*N*(b)-oxide **8** i.e. axial in relationship of the C-ring allows formation of the thermodynamically disfavoured $\Delta^{4(5)}$ iminium ion.

α-Aminonitrile **9** results from axial cyanide attack under stereoselective control on the parent iminium. The unusual hexahydro–indolizino[8,7-*b*]indole structure **10** is reminiscent of the classical piperidine ring contraction via an aziridinium ion, formed by an intramolecular S_N2 reaction at the C-3 position of the piperidine ring.[9] In the case of **10**, the formation of an aziridinium intermediate is an unexpected reaction. Its formation can be explained by an orbital overlap in D/E rings allowing nucleophilic substitution by anchimeric effect of the oxygen lone pair through homoallylic conjugation of the $\Delta^{19(20)}$ double bond.[10] The resulting aziridinium ion was subsequently opened at the less hindered position by attack of a water



Scheme 2.

molecule to give, after hydrolysis and opening of the lactol in acidic reaction conditions, diol **10**[11] (Scheme 2).

The structure of **10** was inferred from ^{1}H and ^{13}C NMR spectra analysis and confirmed by obtaining the di-*O*-acetyl derivative. The C-20 configuration as deduced by NOE effects is in agreement with antiperiplanar substitution to the N–O bond.

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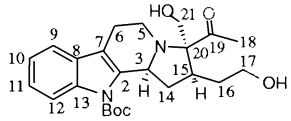
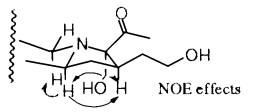
11. Analytical data of compound **10**: 1D NMR studies ^{1}H, ^{13}C confirmed by 2D NMR, COSY, HETCOR, NOESY.





^{1}H NMR (300 MHz, $CDCl_3$): 1.32–1.42 (2H, m, H_{14b} and H_{16b}), 1.62 (9H, s, *t*Bu), 1.63 (1H, m, H_{16a}), 2.16 (3H, s, H_{18}), 2.48 (1H, m, H_{15}), 2.58 (1H, dd, $J_{6a\text{-}6b}=12$ Hz, $J_{6a\text{-}5b}=6$ Hz, H_{6a}), 2.72 (2H, m, H_{14a} and H_{6b}), 2.88 (1H, ddd, $J_{5b\text{-}5a}=11.5$ Hz, $J_{5b\text{-}6a}=6$Hz, $J_{5b\text{-}6b}=1.5$ Hz, H_{5b}), 3.08 (1H, dd, $J_{5a\text{-}5b}=11.5$ Hz, $J_{5a\text{-}6b}=6$ Hz, H_{5a}), 3.45–3.55 (2H, m, H_{17a} and H_{17b}), 3.52 (1H, d, $J_{21b\text{-}21a}=12.5$ Hz, H_{21b}), 3.86 (1H, d, $J_{21a\text{-}21b}=12.5$ Hz, H_{21a}), 4.32 (1H, br d, $J_{3\text{-}14b}=11.5$ Hz, H_3), 7.08 (1H, t, $J_{11\text{-}12}=7$ Hz, H_{11}), 7.12 (1H, t, $J_{10\text{-}9}=7$ Hz, H_{10}), 7.30 (1H, d, $J_{9\text{-}10}=7$ Hz, H_9), 7.93 (1H, d, $J_{12\text{-}11}=7$ Hz, H_{12}).

^{13}C NMR (75 MHz, $CDCl_3$): 214.3 (C19), 150.3 (CO, Boc), 136.6 (C13), 135.9 (C2), 129.4 (C8), 124.0 (C11), 122.7 (C10), 118.1 (C9), 116.0 (C7), 115.4 (C12), 83.9 (tBu), 75.1 (C20), 64.5 (C21), 61.11 (C17), 58.2 (C3), 42.1 (C5), 42.0 (C15), 37.6 (C14), 34.0 (C16), 29.0 (C18), 28.3 (CH_3 Boc), 23.3 (C6).

MS (CI, NH_3): 429 (m/z, $M+H^+$), 401 (M–28), 329 (M–100).