SYNTHESIS OF N_a-BOC-5β-CYANO-DEFORMYL-E-GEISSOSCHIZINE: A POTENTIAL SYNTHON IN THE PREPARATION OF SARPAGAN AND AJMALAN RING SYSTEMS

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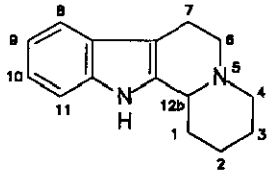
Abstract - The paper describes a short, synthetic route to N_a-Boc-5β-cyano-deformyl-E-geissoschizine (**8**), a prototype of potential synthons in the preparation of sarpagan and ajmalan ring systems.

INTRODUCTION

In the course of efforts to find feasible synthetic approaches to sarpagin ajmalin-type indole alkaloids,[1,2] it became evident to us that an easy method that would permit a regioselective formation of $\Delta^{5(6)}$-iminium ions (or their equivalents) from appropriate indolo[2,3-a]quinolizidine (**1**) derivatives was a prerequisite for a successful accomplishment of our goal.



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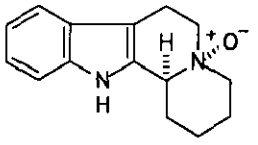

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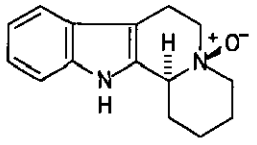

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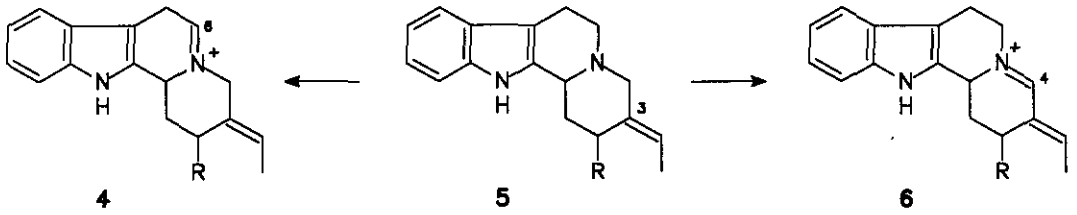
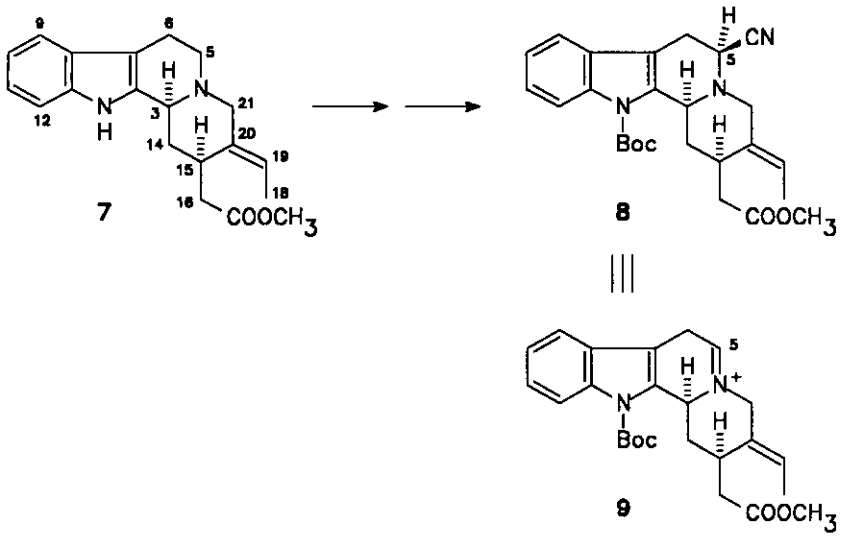
We have previously shown[3] that the formation of particular indolo[2,3-a]quinolizidine iminium ions by the modified Polonovski reaction[4-8] strongly depends on whether the intermediate indolo[2,3-a]quinolizidine N_b-oxide is cis (**2**) or trans (**3**). Thermodynamically the most stable iminium ion will be formed as the main product when stereoelectronic requirements for E2-type trans-diaxial elimination are fulfilled. As a consequence, cis-N_b-oxides should be more favourable than trans-N_b-oxides to the formation of $\Delta^{5(6)}$-iminium ions. Recently we developed a procedure that permits the oxidation of indolo[2,3-a]quinolizidines to cis- or trans-N_b-oxides to be directed at will.[9]

Thus, the time appeared ripe for a more detailed study of the preparation of indolo[2,3-a]quinolizidine $\Delta^{5(6)}$-iminium ions (**4**) (IUPAC numbering[10]) (or their equivalents), in particular from indolo[2,3-a]quinolizidine derivative possessing an E-ethylidene side-chain at C-3 (compound **5**), as do many of the indole alkaloids. Significantly, the C-3 E-ethylidene side-chain (in biogenetic numbering,[10] C-20 E-ethylidene side-chain) usually strongly favours the $\Delta^{4(5)}$-iminium ion (**6**) (IUPAC numbering) (in biogenetic numbering, $\Delta^{4(21)}$-iminium ion) formation (Scheme 1).



Scheme 1. Formation of indolo[2,3-a]quinolizidine $\Delta^{5(6)}$-iminium ion (**4**) and indolo[2,3-a]quinolizidine $\Delta^{4(5)}$-iminium ion (**6**).

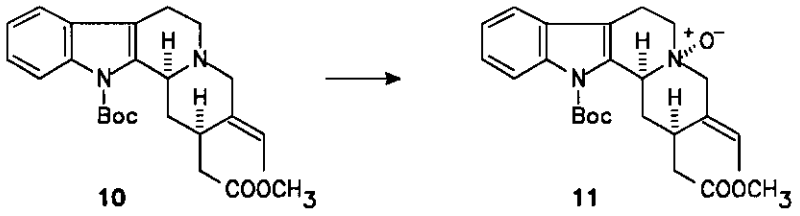
In the present paper we describe the transformation of deformyl-E-geissoschizine (**7**) (an indolo[2,3-a]-quinolizidine derivative possessing an E-ethylidene side chain at C-3; IUPAC numbering) to N_a-Boc-5β-cyano-deformyl-E-geissoschizine (**8**), which is the synthetic equivalent of N_a-Boc-deformyl-E-geissoschizine $\Delta^{4(5)}$-iminium ion (**9**) (biogenetic numbering) (Scheme 2).



Scheme 2. Formation of $\underline{N_a}$-Boc-5β-cyano-deformyl-$\underline{E}$-geissoschizine (**8**).

RESULTS AND DISCUSSION

Oxidation of our earlier described $\underline{N_a}$-Boc-deformyl-$\underline{E}$-geissoschizine (**10**)[11] with $\underline{m}$-chloroperbenzoic acid ($\underline{m}$-CPBA) led exclusively to $\underline{N_a}$-Boc-deformyl-$\underline{E}$-geissoschizine $\underline{cis}$-$\underline{N_b}$-oxide (**11**) (Scheme 3).

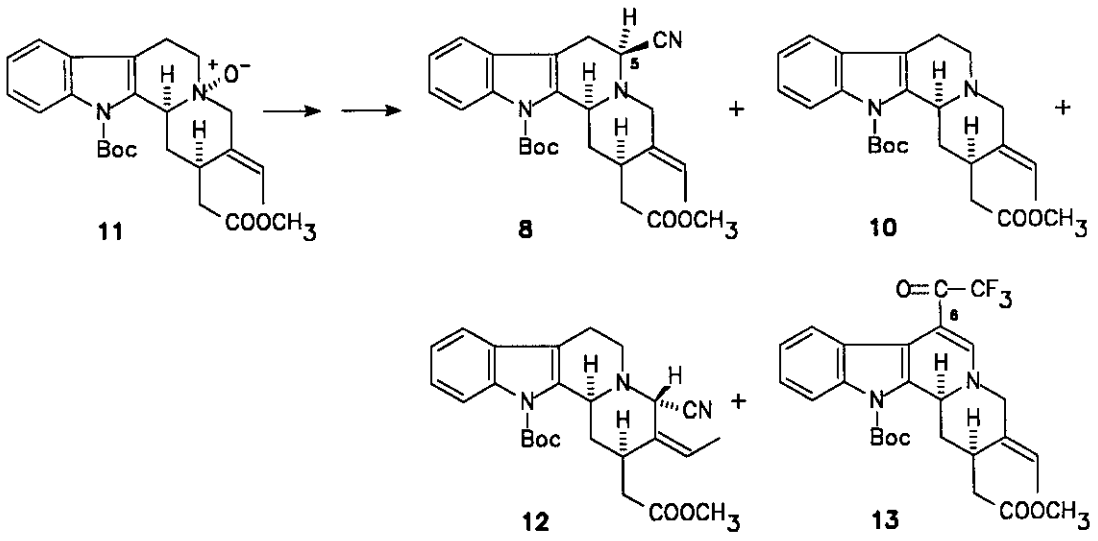


Scheme 3. Oxidation of $\underline{N_a}$-Boc-deformyl-$\underline{E}$-geissoschizine (**10**) to the corresponding $\underline{N_b}$-oxide (**11**).

We have shown earlier[1,9,11] that, when the substitution pattern permits, $\underline{N_a}$-Boc protected indolo[2,3-$\underline{a}$]quinolizidine $\underline{cis}$-$\underline{N_b}$-oxides exist predominantly in conformation $\underline{b}$ (for definition of conformation $\underline{b}$, see Ref. 11). This should favour the successful preparation of $\Delta^{5(6)}$-iminium ions (in biogenetic numbering, $\Delta^{4(5)}$-iminium ions) (Scheme 4).

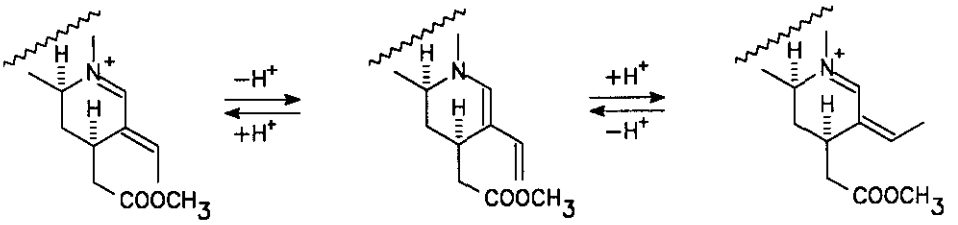
Scheme 4. Formation of an indolo[2,3-a]quinolizidine $\Delta^{5(6)}$-iminium ion from an indolo[2,3-a]quinolizidine cis-N_b-oxide in conformation b.

Treatment of the cis-N_b-oxide (**11**) with trifluoroacetic anhydride (TFAA) (modified Polonovski reaction) at -17°C and KCN (cyano trapping[12,13]) yielded N_a-Boc-5β-cyano-deformyl-E-geissoschizine (**8**) in 30% yield. Small amounts of other compounds, among them N_a-Boc-deformyl-E-geissoschizine (**10**), N_a-Boc-21α-cyano-deformyl-Z-geissoschizine (**12**), and N_a-Boc-6-trifluoroacetyl-5,6-didehydro-deformyl-E-geissoschizine (**13**), were isolated (Scheme 5).



Scheme 5. Formation of compounds (**8**), (**10**), (**12**), and (**13**).

The formation of compound (12) (Z-ethylidene side-chain) can be explained by a Z-favoured E/Z side-chain equilibrium between the intermediate iminium ions (Scheme 6).



Scheme 6. E/Z side-chain equilibrium between the intermediate iminium ions.

The ^{13}C-Nmr data for compounds (8), (11), (12), and (13) are given Figure 1. Comparison of the measured chemical shifts, taking into account the conformational considerations relevant for indolo[2,3-a]quinolizidines in general,[11,14,15] provides clear evidence of the stereostructures depicted in the formulae.

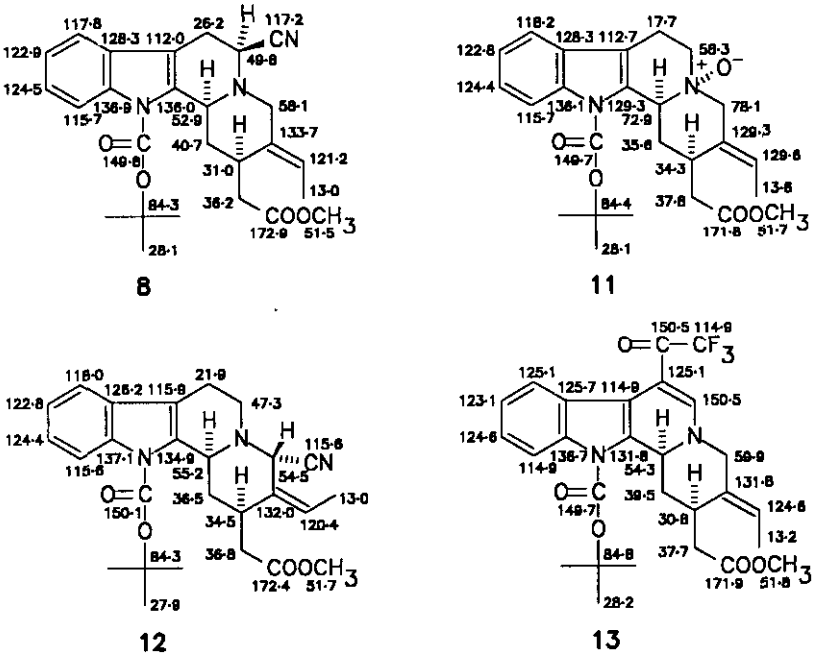
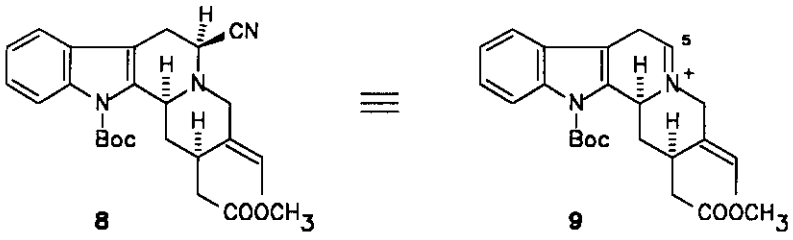


Figure 1. The ^{13}C-nmr data for compounds (8), (11), (12), and (13).

The stereochemistry of compound (**8**) (predominantly in conformation b[9]) at C-5 was confirmed by the coupling constants of H-5: 5.5 Hz and 2.5 Hz. This indicated equatorial orientation for H-5 (H-5α) and as a consequence axial orientation for the C-5 cyano-group.

CONCLUSIONS

The present results confirm that, in iminium ion formation (modified Polonovski reaction) and cyano-trapping, N_a-Boc-deformyl-E-geissoschizine cis-N_b-oxide (**11**) yields N_a-Boc-5β-cyano-deformyl-E-geissoschizine (**8**), which is the synthetic equivalent of N_a-Boc-deformyl-E-geissoschizine $\Delta^{4(5)}$-iminium ion (**9**).



The results would be useful in the preparation of compounds possessing the sarpagan or ajmalan ring system.[1,16,17] Further studies are in progress.

EXPERIMENTAL

Ir spectra were recorded with a Perkin-Elmer 700 spectrophotometer in $CHCl_3$. Ir absorption bands are given in reciprocal centimetres (cm^{-1}). ^{1}H- and ^{13}C-nmr spectra were measured in $CDCl_3$ either with a Varian Gemini-200 spectrometer working at 199.975 MHz (^{1}H-Nmr) and 50.289 MHz (^{13}C-Nmr) or a Varian Unity-400 NMR spectrometer working at 399.952 MHz (^{1}H-Nmr) and 100.577 MHz (^{13}C-Nmr). Chemical shifts are given in ppm by reference to TMS (^{1}H-Nmr; δ_H=0.0 ppm) and $CDCl_3$ (^{13}C-Nmr; δ_C=77.0 ppm). Abbreviations s, d, t, q, m, and br are used to designate singlet, doublet, triplet, quartet, multiplet, and broad, respectively. For the ^{13}C-nmr data, see Figure 1. Mass spectrometry (EIms and HRms) was done on a Jeol DX 303/DA 5000 instrument.

Preparation of N_a-Boc-deformyl-E-geissoschizine cis-N_b-oxide (11):

A solution of N_a-Boc-deformyl-E-geissoschizine (**10**)[11] (114 mg, 0.27 mmol) and m-chloroperbenzoic acid (m-CPBA) (60 mg, 1.3 equiv.) in dry CH_2Cl_2 (5 ml) was stirred at room temperature for 3 h (Ar atm). Normal work-up and purification by column chromatography (alumina, CH_2Cl_2/MeOH:98/2) yielded compound (**11**).

Compound (**11**): Y. 83 mg (70%). Amorphous material. Ir: 1725 br (2 x C=O). ^{1}H-Nmr: 1.68 [9H, s,-$C(CH_3)_3$], 1.80 (3H, d, J=7 Hz, =CHC$\underline{H}_3$), 3.68 (3H, s, -OCH_3), 4.03 (1H, d, J=13 Hz, H-21α), 4.15 (1H, d, J=13 Hz, H-21β), 4.85 (1H, br d, J=12 Hz, H-3), 5.89 (1H, q, J=7 Hz, =C$\underline{H}CH_3$), 7.23-7.29 (2H, m, H-10, H-11), 7.44 (1H, d, J=8 Hz, H-9), 8.04 (1H, d, J=8 Hz, H-12). Ms: 440 (M^+), 383, 340, 323, 295, 170, 169, 156 (100%). HRms found: 440.2304. Calcd for $C_{25}H_{32}N_2O_5$: 440.2311.

Preparation of N_a-Boc-5β-cyano-deformyl-E-geissoschizine (8):

The cis-N_b-oxide (**11**) (80 mg, 0.18 mmol) was dissolved in dry CH_2Cl_2 (6 ml) and the mixture was cooled to -17°C with an ice/salt bath. Trifluoroacetic anhydride (TFAA) (0.07 ml, 2.5 equiv.) was added with a syringe during 5 min and stirring was continued for 2 h, with the temperature kept at -17°C with an ice/salt bath. During one further hour the temperature of the reaction mixture was allowed to rise to -5°C, whereafter the bath was taken away. The temperature of the reaction mixture was allowed to rise to 20°C, KCN (36 mg, 3 equiv.) in H_2O (2 ml) was added, and the pH of the aqueous layer was adjusted to pH 5 by addition of solid NaOAc. The mixture was stirred for 45 min, basified to pH 10 with 10% Na_2CO_3, and extracted with CH_2Cl_2. Normal work-up and purification by flash chromatography (silica, CH_2Cl_2) followed by plc (silica, CH_2Cl_2/MeOH:98/2) gave compound (**8**) together with compounds (**10**), (**12**), and (**13**).

Compound (**8**): Y. 24 mg (30%). Amorphous material. Ir: 2350 m (CN), 1730 br (2 x C=O). ^{1}H-Nmr: 1.66 [9H, s, -$C(CH)_3)_3$], 1.68 (3H, d, J=7 Hz, =CHC$\underline{H}_3$), 3.64 (3H, s, -OCH_3), 4.04 (1H, dd, J_1=5.5 Hz, J_2=2.5 Hz, H-5α), 4.16 (1H, br d, J=10 Hz, H-3), 5.52 (1H, q, J=7 Hz, =C$\underline{H}CH_3$), 7.20-7.34 (2H, m, H-10, H-11), 7.42 (1H, d, J=8 Hz, H-9), 8.08 (1H, d, J=8 Hz, H-12). Ms: 449 (M^+), 422, 392 (100%), 366, 348, 321, 293, 212, 169, 168. HRms found: 449.2289. Calcd for $C_{26}H_{31}N_3O_4$: 449.2315.

Compound (**10**): Y. 8 mg (10%). Amorphous material. For the analytical data, see Ref. 11.

Compound (**12**): Y. 10 mg (12%). Amorphous material. Ir: 2300 m (CN), 1725 br (2 x C=O). ^{1}H-Nmr: 1.66 [9H, s, -$C(CH_3)_3$], 1.72 (3H, d, J=7 Hz, =CHC$\underline{H}_3$), 3.70 (3H, s, -OCH_3), 4.68 (1H, br d, J=10 Hz, H-3), 4.91 (1H, s, H-21β), 5.44 (1H, q, J=7 Hz, =C$\underline{H}CH_3$), 7.20-7.30 (2H, m, H-10, H-11), 7.39 (1H, d, J=8 Hz, H-9), 8.11 (1H, d, J=8 Hz, H-12). Ms: 449 (M^+), 422, 392, 366, 293 (100%). HRms found: 449.2302. Calcd for $C_{26}H_{31}N_3O_4$ 449.2315.

Compound (**13**): Y. 7 mg (8%). Amorphous material. Ir: 1730 br (3 x C=O). ^{1}H-Nmr: 1.68 [9H, s, -$C(CH_3)_3$], 1.74 (3H, d, J=7 Hz, =CHC$\underline{H}_3$), 3.66 (3H, s, -OCH_3), 4.23 (1H, d, J=15 Hz, H-21α), 4.32

(1H, d, J=15 Hz, H-21β), 5.49 (1H, dd, J_1=11 Hz, J_2=4 Hz, H-3), 5.63 (1H, q, J=7 Hz, =C<u>H</u>CH$_3$), 7.22-7.30 (2H, m, H-10, H-11), 7.58 (1H, s, H-5), 8.09 (1H, d, J=8 Hz, H-12), 8.46 (1H, d, J=8 Hz, H-9). Ms: 518 (M^+), 462, 418, 417, 343, 264 (100%), 195, 167. HRms found: 518.1999. Calcd for $C_{27}H_{29}F_3N_2O_5$: 518.2028.

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