

SYNTHESIS OF N₄-BOC-5 β -CYANO-DEFORMYL-E-GEISSOSCHIZINE: A POTENTIAL SYNTHON IN THE PREPARATION OF SARPAGAN AND AJMALAN RING SYSTEMS

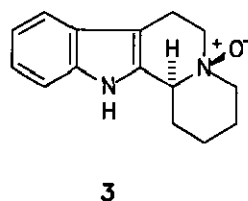
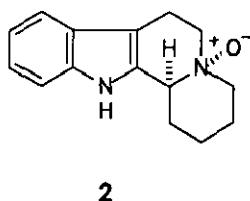
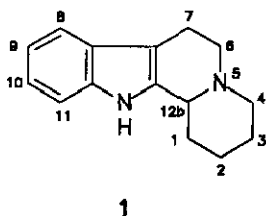
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Abstract - The paper describes a short, synthetic route to N₄-Boc-5 β -cyano-deformyl-E-geissoschizine (**8**), a prototype of potential synthons in the preparation of sarpagan and ajmalan ring systems.

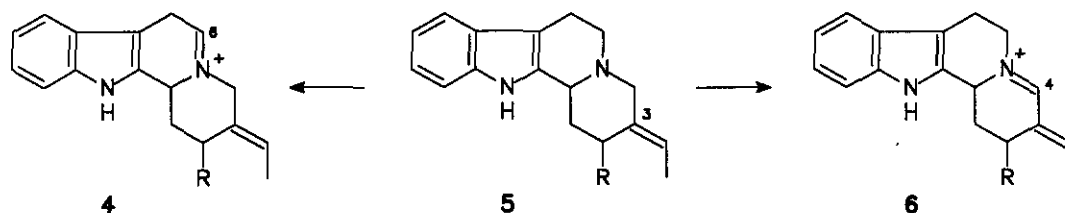
INTRODUCTION

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.



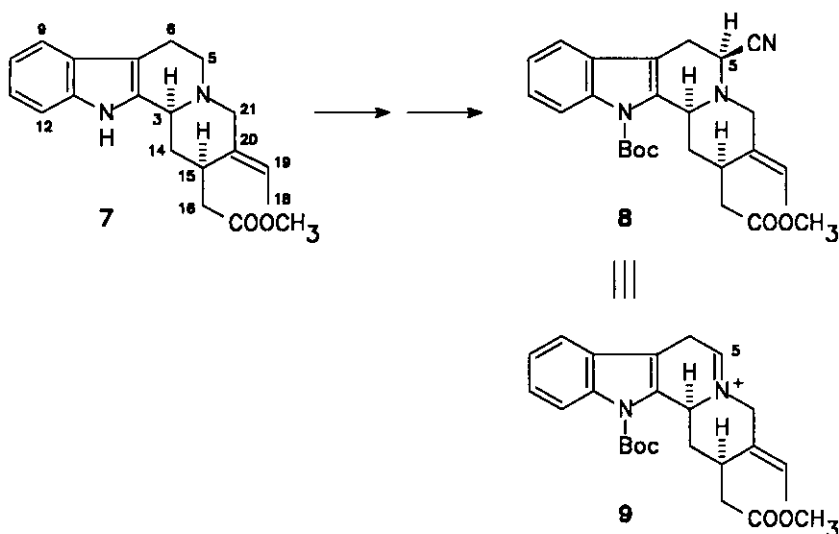
We have previously shown³ that the formation of particular indolo[2,3-*a*]quinolizidine iminium ions by the modified Polonovski reaction^{4,8} strongly depends on whether the intermediate indolo[2,3-*a*]quinolizidine *N*₅-oxide is *cis* (2) or *trans* (3). Thermodynamically the most stable iminium ion will be formed as the main product when stereoelectronic requirements for E2-type *trans*-diaxial elimination are fulfilled. As a consequence, *cis*-*N*₅-oxides should be more favourable than *trans*-*N*₅-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*₅-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 numbering¹⁰) (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).

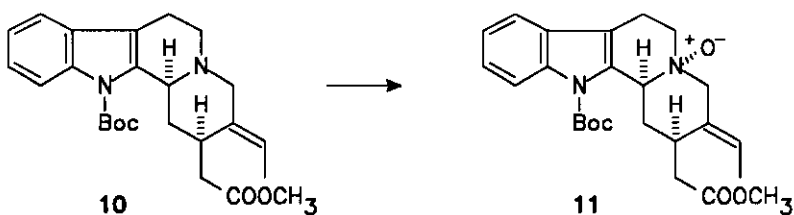
In the present paper we describe the transformation of deformyl-*E*-geissoschizine (7) (an indolo[2,3-*a*]quinolizidine derivative possessing an *E*-ethylidene side chain at C-3; IUPAC numbering) to *N*₅-Boc-5 β -cyano-deformyl-*E*-geissoschizine (8), which is the synthetic equivalent of *N*₅-Boc-deformyl-*E*-geissoschizine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



Scheme 2. Formation of N_A -Boc-5 β -cyano-deformyl-E-geissoschizine (**8**).

RESULTS AND DISCUSSION

Oxidation of our earlier described N_A -Boc-deformyl-E-geissoschizine (**10**)¹¹ with *m*-chloroperbenzoic acid (*m*-CPBA) led exclusively to N_A -Boc-deformyl-E-geissoschizine *cis*- N_B -oxide (**11**) (Scheme 3).



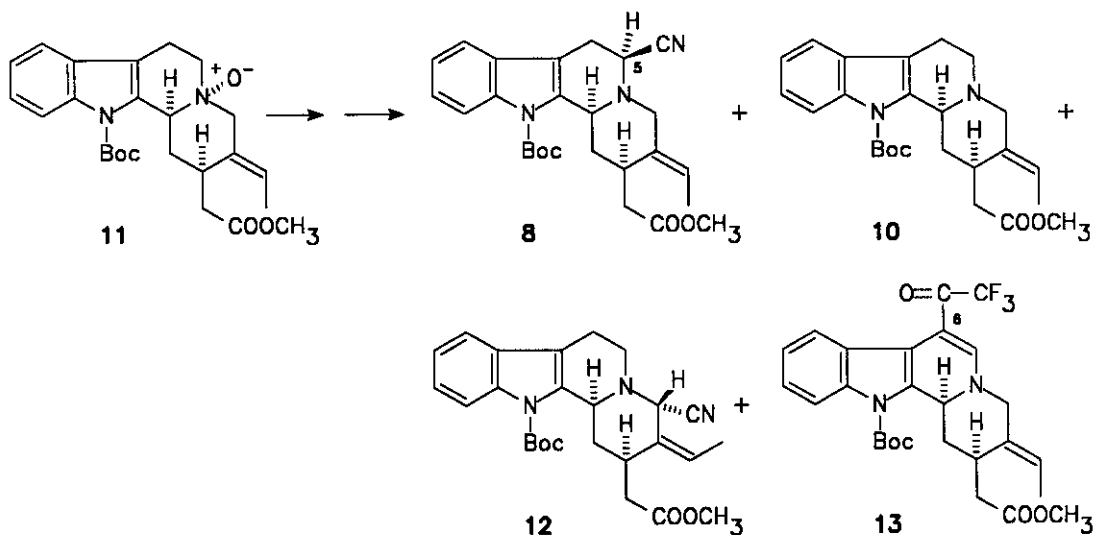
Scheme 3. Oxidation of N_A -Boc-deformyl-E-geissoschizine (**10**) to the corresponding N_B -oxide (**11**).

We have shown earlier^{1,9,11} that, when the substitution pattern permits, N_A -Boc protected indolo[2,3-*a*]quinolizidine *cis*- N_B -oxides exist predominantly in conformation **b** (for definition of conformation **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).



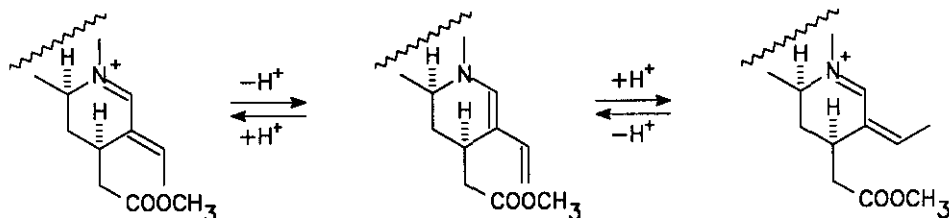
Scheme 4. Formation of an indolo[2,3-a]quinolizidine $\Delta^{5(6)}$ -iminium ion from an indolo[2,3-a]quinolizidine cis-N₆-oxide in conformation b.

Treatment of the cis-N₆-oxide (11) with trifluoroacetic anhydride (TFAA) (modified Polonovski reaction) at -17°C and KCN (cyano trapping^{12,13}) yielded N₄-Boc-5 β -cyano-deformyl-E-geissoschizine (8) in 30% yield. Small amounts of other compounds, among them N₄-Boc-deformyl-E-geissoschizine (10), N₄-Boc-21 α -cyano-deformyl-Z-geissoschizine (12), and N₄-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.

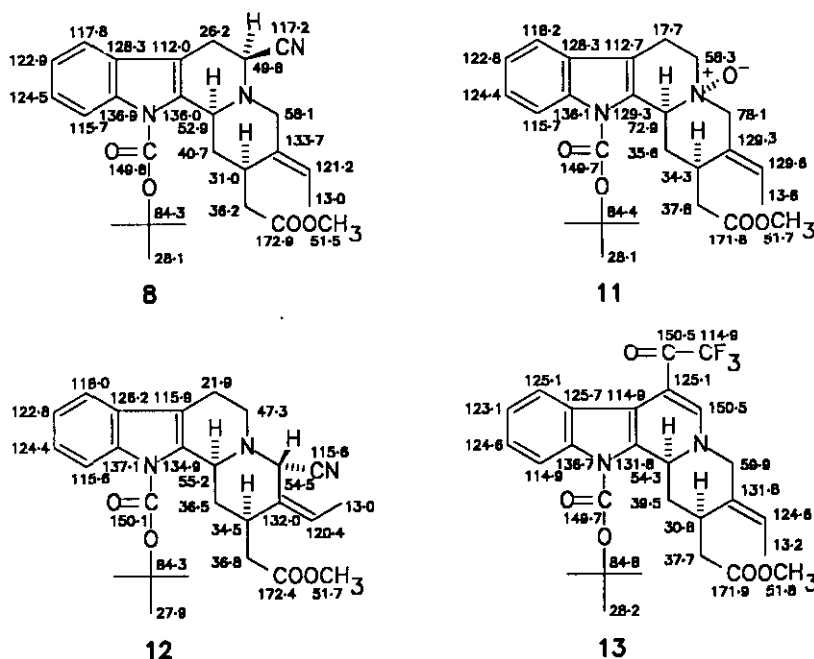
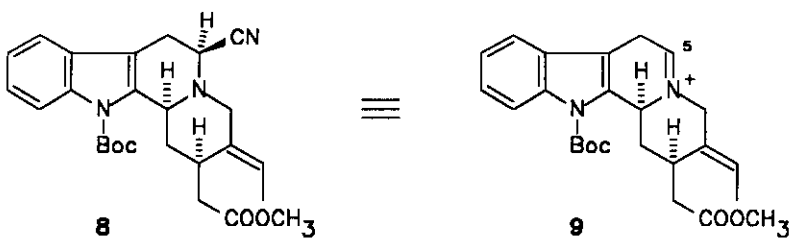


Figure 1. The ^{13}C -nmr data for compounds (8), (11), (12), and (13).

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-5 α) 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*₁-Boc-deformyl-*E*-geissoschizine *cis*-*N*₁-oxide (**11**) yields *N*₁-Boc-5 β -cyano-deformyl-*E*-geissoschizine (**8**), which is the synthetic equivalent of *N*₁-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}). ^1H - and ^{13}C -nmr spectra were measured in CDCl_3 either with a Varian Gemini-200 spectrometer working at 199.975 MHz (^1H -Nmr) and 50.289 MHz (^{13}C -Nmr) or a Varian Unity-400 NMR spectrometer working at 399.952 MHz (^1H -Nmr) and 100.577 MHz (^{13}C -Nmr). Chemical shifts are given in ppm by reference to TMS (^1H -Nmr; $\delta_{\text{H}}=0.0$ ppm) and CDCl_3 (^{13}C -Nmr; $\delta_{\text{C}}=77.0$ 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 N₄-Boc-deformyl-E-geissoschizine cis-N₆-oxide (11):

A solution of N₄-Boc-deformyl-E-geissoschizine (10)¹¹ (114 mg, 0.27 mmol) and *m*-chloroperbenzoic acid (*m*-CPBA) (60 mg, 1.3 equiv.) in dry CH₂Cl₂ (5 ml) was stirred at room temperature for 3 h (Ar atm). Normal work-up and purification by column chromatography (alumina, CH₂Cl₂/MeOH:98/2) yielded compound (11).

Compound (11): Y. 83 mg (70%). Amorphous material. Ir: 1725 br (2 x C=O). ¹H-Nmr: 1.68 [9H, s, -C(CH₃)₃], 1.80 (3H, d, J=7 Hz, =CHCH₃), 3.68 (3H, s, -OCH₃), 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, =CHCH₃), 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 C₂₅H₃₂N₂O₅: 440.2311.

Preparation of N₄-Boc-5β-cyano-deformyl-E-geissoschizine (8):

The cis-N₆-oxide (11) (80 mg, 0.18 mmol) was dissolved in dry CH₂Cl₂ (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 H₂O (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% Na₂CO₃, and extracted with CH₂Cl₂. Normal work-up and purification by flash chromatography (silica, CH₂Cl₂) followed by plc (silica, CH₂Cl₂/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). ¹H-Nmr: 1.66 [9H, s, -C(CH₃)₃], 1.68 (3H, d, J=7 Hz, =CHCH₃), 3.64 (3H, s, -OCH₃), 4.04 (1H, dd, J₁=5.5 Hz, J₂=2.5 Hz, H-5α), 4.16 (1H, br d, J=10 Hz, H-3), 5.52 (1H, q, J=7 Hz, =CHCH₃), 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 C₂₆H₃₁N₃O₄: 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). ¹H-Nmr: 1.66 [9H, s, -C(CH₃)₃], 1.72 (3H, d, J=7 Hz, =CHCH₃), 3.70 (3H, s, -OCH₃), 4.68 (1H, br d, J=10 Hz, H-3), 4.91 (1H, s, H-21β), 5.44 (1H, q, J=7 Hz, =CHCH₃), 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 C₂₆H₃₁N₃O₄: 449.2315.

Compound (13): Y. 7 mg (8%). Amorphous material. Ir: 1730 br (3 x C=O). ¹H-Nmr: 1.68 [9H, s, -C(CH₃)₃], 1.74 (3H, d, J=7 Hz, =CHCH₃), 3.66 (3H, s, -OCH₃), 4.23 (1H, d, J=15 Hz, H-21α), 4.32

(1H, d, $J=15$ Hz, H-21 β), 5.49 (1H, dd, $J_1=11$ Hz, $J_2=4$ Hz, H-3), 5.63 (1H, q, $J=7$ Hz, =CHCH₃), 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 C₂₇H₂₉F₃N₂O₅: 518.2028.

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Received, 21st September, 1993