

SHORT, STEREOSELECTIVE SYNTHESIS OF N_1 -BOC-5 β -CYANO-
DEFORMYL- Σ -GEISSOSCHIZINE, A PROTOTYPE OF POTENTIAL
SYNTHONS IN THE PREPARATION OF SARPAGAN AND AJMALAN
RING SYSTEMS

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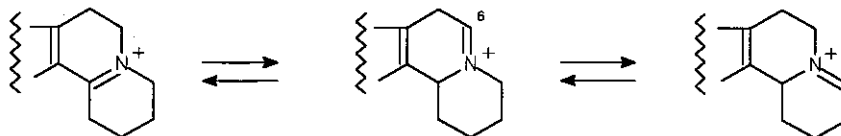
Abstract - This paper describes a short, easy synthesis of N_1 -Boc-5 β -cyano-deformyl- Σ -geissoschizine (4), a prototype of potential synthons in the preparation of sarpagan and ajmalan ring systems.

INTRODUCTION

Very few synthetic approaches have been reported for sarpagine-ajmaline type indole alkaloids.¹⁻³ One interesting approach to the preparation of sarpagan and ajmalan ring systems seems to be the formation of iminium ions (or their equivalents) at $\Delta^{5(6)}$ from appropriate indolo[2,3- α]quinolizidine derivatives.

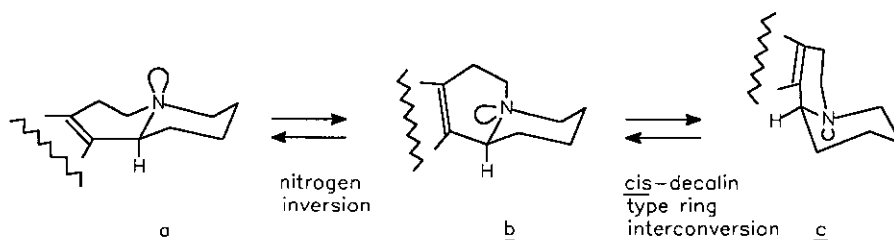
Until now, the synthetic use of $\Delta^{5(6)}$ indolo[2,3- α]quinolizidine iminium species for such purposes has been complicated by the long and tedious routes needed for their preparation,^{4,6} and by the formation of mixtures of iminium ions containing only traces of the desired $\Delta^{5(6)}$ -iminium ions. Yet a further problem is the easy

isomerization of iminium ions of this type (Scheme 1).



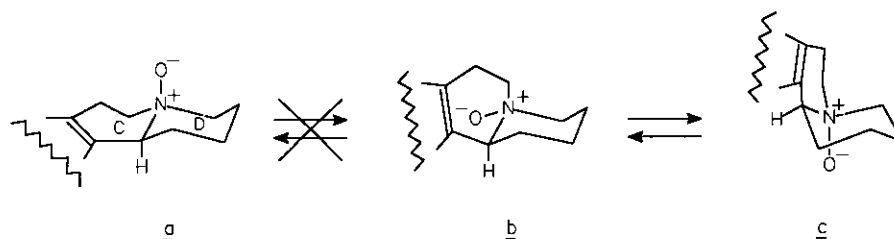
Scheme 1. Possible isomerization of the iminium ions.

An indolo[2,3-*a*]quinolizidine system can exist in three conformations, with equilibration by nitrogen inversion and *cis*-decalin type ring interconversion (Scheme 2).⁷⁻⁹



Scheme 2. Conformational equilibrium of indoloquinolizidines.

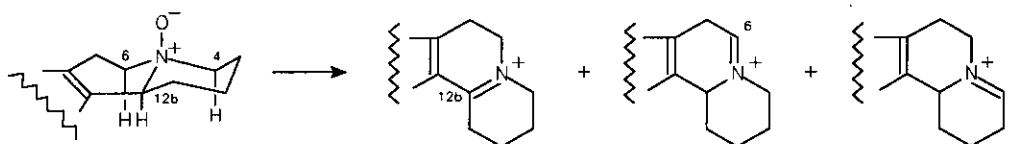
In the corresponding indoloquinolizidine *N*₆-oxides the C/D ring juncture (*trans* or *cis*) is fixed, so that there is no equilibrium between conformations (a) and (b/c) (Scheme 3). Transition between the conformations (b) and (c) continues to be possible, however.⁷⁻⁹ The contribution of conformations (b) and (c) to the conformational equilibrium is strongly influenced by the substitution pattern of the molecule in question:



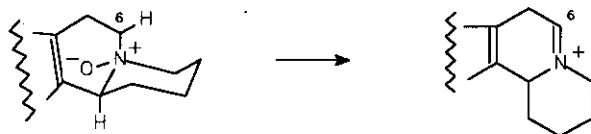
Scheme 3. Conformational equilibrium of indoloquinolizidine N_b -oxides.

The modified Polonovski reaction (Polonovski-Potier reaction)¹⁰⁻¹⁴ is widely used in the preparation of indolo[2,3-*a*]quinolizidine iminium ions from the corresponding indolo[2,3-*a*]quinolizidine N_b -oxides. It is known that the thermodynamically most stable iminium ion will be formed as the main product when stereoelectronic requirements for E2-type trans-diaxial elimination are fulfilled.^{15,16}

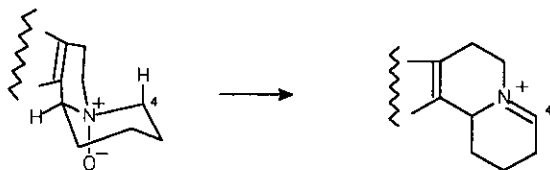
In theory, conformation (a) (C/D trans ring juncture) should lead to iminium ion formation toward C(4), C(6) and C(12b), of which C(12b) is strongly favored (Scheme 4); conformation (b) (C/D cis ring juncture), on the other hand, should lead to iminium ion formation toward C(6) (Scheme 5), and conformation (c) (C/D cis ring juncture) to iminium ion formation toward C(4) (Scheme 6). Knowledge of the exact conformation of the indolo[2,3-*a*]quinolizidine N_b -oxide in question is thus a prerequisite to predicting its behavior in iminium ion formation.



Scheme 4. Iminium ion formation from conformation (a).



Scheme 5. Iminium ion formation from conformation (b).

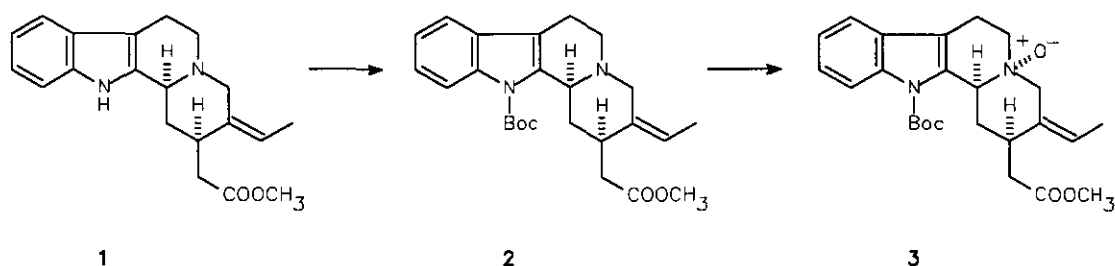


Scheme 6. Iminium ion formation from conformation (c).

We have previously shown⁷ that the *m*CPBA oxidation of *N*₄-Boc protected 2-substituted indolo[2,3-*a*]quinolizidines leads mainly, and in several cases exclusively, to *cis*-*N*₆-oxides. Where the substitution pattern permits, these exist predominantly in conformation (b). Thus the prerequisites seemed to be fulfilled for a successful preparation of *N*₄-Boc-indolo[2,3-*a*]quinolizidine $\Delta^{5(6)}$ -iminium ion (= *N*₄-Boc-deformyl-*Z*-geissoschizine $\Delta^{4(5)}$ -iminium ion)¹⁷ (6) [or its chemical equivalent (4)] from *N*₄-Boc-indolo[2,3-*a*]quinolizidine *cis*-*N*₆-oxide (= *N*₄-Boc-deformyl-*Z*-geissoschizine *cis*-*N*₆-oxide) (3) (*vide infra*).

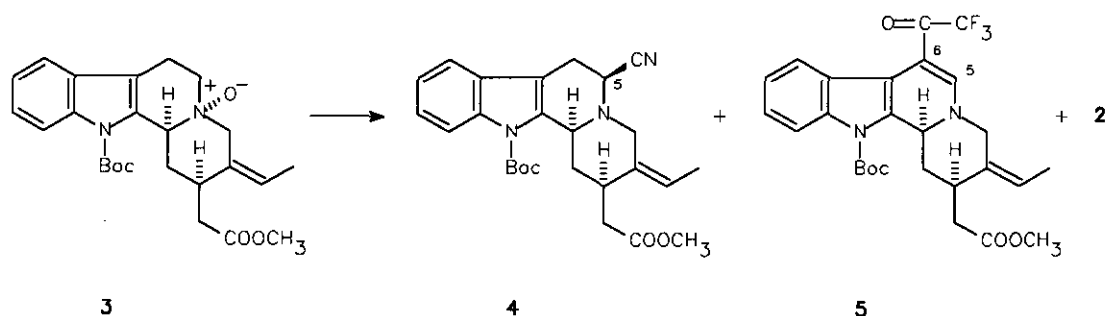
RESULTS AND DISCUSSION

Treatment of the earlier described¹⁸ deformyl-*Z*-geissoschizine (1) with di-*t*-butyl dicarbonate [(Boc)₂O] and *p*-dimethylaminopyridine (DMAP) in dry CH₂Cl₂ afforded the Boc-protected counterpart (2) in 83% yield. Oxidation of compound (2) with *m*CPBA in dry CH₂Cl₂ led exclusively to *N*₄-Boc-deformyl-*Z*-geissoschizine *cis*-*N*₆-oxide (3) in 93% yield (Scheme 7).



Scheme 7.

The easily accessible *cis*- N_6 -oxide (**3**) was dissolved in dry CH_2Cl_2 and cooled to -17°C . Trifluoroacetic anhydride (TFAA) (2.5 equiv.) was added during 5 min and stirring was continued for 3 h until the temperature rose to 0°C . Thereafter a solution of KCN (3 equiv.) in H_2O was added and the pH of the aqueous layer was adjusted to pH 5 by addition of solid NaOAc. The mixture was stirred at room temperature for 45 min, basified to pH 10 with 10% Na_2CO_3 solution and extracted with CH_2Cl_2 . After normal work-up and careful chromatographic purification the desired cyano derivative (**4**) (N_6 -Boc-5 β -cyano-deformyl-*Z*-geissoschizine) was obtained in 35% yield. Small amounts of compounds (**2**) (N_6 -Boc-deformyl-*Z*-geissoschizine) and (**5**) (N_6 -Boc-6-trifluoroacetyl-5,6-didehydro-deformyl-*Z*-geissoschizine) were isolated (Scheme 8).



Scheme 8.

The ^{13}C -Nmr data for compounds (2), (3), (4), and (5) are given in Figure 1. Comparison of the chemical shifts found, taking into account the conformational considerations relevant for indolo[2,3-*a*]quinolizidines in general¹⁹⁻²⁵, provides clear evidence of the stereostructures depicted in the formulae.

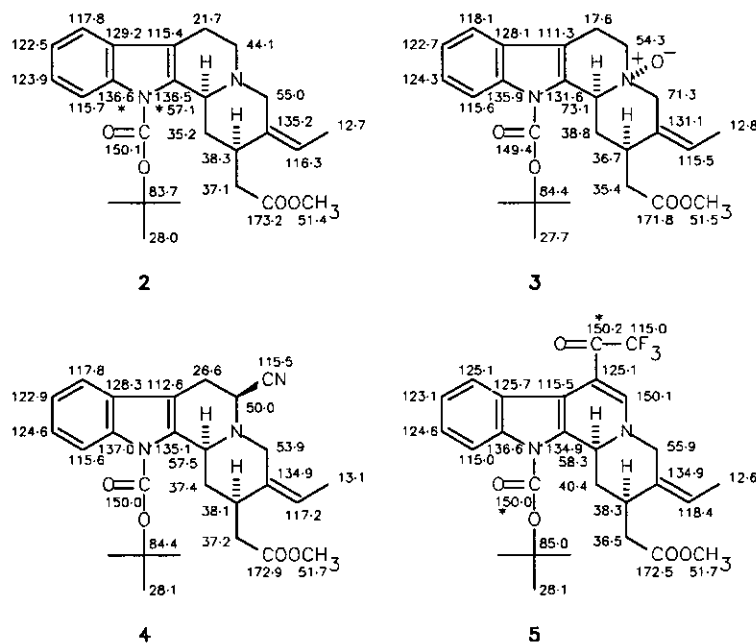


Figure 1. ^{13}C -Nmr data for compounds (2), (3), (4), and (5).

The stereostructure of compound (4) was further confirmed by complete ^1H -Nmr data (Table 1) and H, H-COSY, H,C-COSY, and NOE measurements.

The coupling constants in compound (4) between H-5 and H-6 α and between H-5 and H-6 β are 3 Hz and 5.5 Hz, respectively. Such values are only possible if H-5 is α . Further confirmation of this comes from the NOE difference measurements. Irradiation at H-14 β resulted in NOE only at H-14 α ; no NOE was observed at H-5 [conformation (b)] and thus H-5 has to be α . Irradiation of H-19 gave a 7% NOE at H-16 β (δ 2.74 ppm), which is in agreement with a chair conformation for ring D of compound (4) (Figure 2).

Table 1. ^1H -Nmr data for compound (4).

H-3	4.30	dd	H-15	2.86	m
H-5 α	4.11	dd	H-16 _A	2.27	dd
H-6 α	3.01	dd	H-16 _B	2.74	dd
H-6 β	3.25	dd	H-18	1.72	br d
H-9	7.38	dd	H-19	5.28	q
H-10	7.30	dt	H-21 α	3.24	d
H-11	7.23	dt	H-21 β	3.93	d
H-12	8.08	dd	Boc	1.69	s
H-14 α	2.48	ddd	CO ₂ CH ₃	3.69	s
H-14 β	1.23	dd			

Coupling constants:

$J_{3,14\alpha} = 2 \text{ Hz}$; $J_{3,14\beta} = 11 \text{ Hz}$; $J_{5\alpha,6\alpha} = 3 \text{ Hz}$; $J_{5\alpha,6\beta} = 5.5 \text{ Hz}$; $J_{6\alpha,6\beta} = 16 \text{ Hz}$; $J_{9,10} = 7.5 \text{ Hz}$; $J_{9,11} = 1.5 \text{ Hz}$;
 $J_{10,11} = 7.5 \text{ Hz}$; $J_{10,12} = 1.5 \text{ Hz}$; $J_{11,12} = 7.5 \text{ Hz}$; $J_{14\alpha,14\beta} = 12.5 \text{ Hz}$; $J_{14\alpha,15} = 4 \text{ Hz}$; $J_{14\beta,15} = 12 \text{ Hz}$;
 $J_{15,16A} = 8 \text{ Hz}$; $J_{15,16B} = 6.5 \text{ Hz}$; $J_{16A,16B} = 15 \text{ Hz}$; $J_{18,19} = 7 \text{ Hz}$; $J_{21\alpha,21\beta} = 13 \text{ Hz}$.

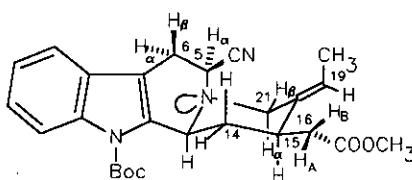
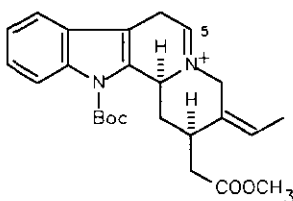


Figure 2. Predominant conformation of N -Boc-5 β -cyano-deformyl- Z -geissoschizine (4). The stereochemistry at C(16) may be inverse.

CONCLUSIONS

The present work shows that the use of N_1 -Boc-deformyl- Z -geissoschizine *cis*- N_1 -oxide (3) under the described conditions permits a stereospecific formation of N_1 -Boc-5 β -cyano-deformyl- Z -geissoschizine (4), which is the synthetic equivalent of N_1 -Boc-deformyl- Z -geissoschizine $\Delta^{4(5)}$ -iminium ion (6). The method should be useful in the preparation of compounds possessing the sarpagan or ajmalan ring system (*vide supra*). Further studies are in progress.



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Figure 3. N_1 -Boc-deformyl- Z -geissoschizine $\Delta^{4(5)}$ -iminium ion (= N_1 -Boc-indolo[2,3-*a*]quinolizidine $\Delta^{5(6)}$ -iminium ion) (6).

EXPERIMENTAL

Ir spectra were recorded with a Perkin-Elmer 700 spectrophotometer in CHCl_3 . Ir absorption bands are expressed in reciprocal centimeters (cm^{-1}). ^1H - and ^{13}C -Nmr spectra were measured with a Varian Gemini-200 spectrometer working at 199.975 MHz (^1H -Nmr) and 50.289 MHz (^{13}C -Nmr) [compounds (2), (3), and (5)] and a Varian Unity-400 NMR spectrometer working at 399.952 MHz (^1H -Nmr) and 100.577 MHz (^{13}C -Nmr) [compound (4)]. The spectra were recorded in CDCl_3 . Chemical shift data are given in ppm by reference to

TMS ($^1\text{H-Nmr}$; $\delta_{\text{H}} = 0.0$ ppm) and CDCl_3 ($^{13}\text{C-Nmr}$; $\delta_{\text{C}} = 77.0$ ppm). Abbreviations s, d, t, q, m, and br are used to designate singlet, doublet, triplet, quartet, multiplet, and broad, respectively. In ^1H measurements the spectral width was 6000 Hz, acquisition time 3.774 s, and pulse width 7.5 μs . NOE difference spectroscopy was done at 30°C. Spectra were obtained by direct subtraction using a 90° composite pulse. For the $^{13}\text{C-nmr}$ data, see Figure 1. Mass spectrometry (EIms and HRms) was done on a Jeol DX 303/DA 5000 instrument.

Preparation of deformyl-Z-geissoschizine (1):

Deformyl-Z-geissoschizine (1) was prepared according to our earlier described method.¹⁸

Preparation of N₄-Boc-deformyl-Z-geissoschizine (2):

A solution of deformyl-Z-geissoschizine (1) (210 mg, 0.65 mmol), di-*t*-butyl dicarbonate [(Boc)₂O] (170 mg, 1.2 equiv.), and *p*-dimethylaminopyridine (DMAP) (8 mg, 0.1 equiv.) in dry CH_2Cl_2 (3 ml) was stirred at room temperature for 2 h (Ar atm). Evaporation and purification by flash chromatography (silica gel, $\text{CH}_2\text{Cl}_2/\text{MeOH}$:99/1) gave compound (2).

Compound (2): Y. 230 mg (83%). Amorphous material. Ir: 1730 br (2 x C=O). $^1\text{H-Nmr}$: 1.69 [9H, s, -C(CH₃)₃], 1.70 (3H, d, $J=7$ Hz, H-18), 3.39 (1H, d, $J=14$ Hz, H-21 α), 3.68 (3H, s, -CO₂CH₃), 3.97 (1H, d, $J=14$ Hz, H-21 β), 4.63 (1H, br d, $J=10$ Hz, H-3), 5.29 (1H, q, $J=7$ Hz, H-19), 7.16-7.30 (2H, m, H-10, H-11), 7.39 (1H, d, $J=8$ Hz, H-9), 8.14 (1H, d, $J=8$ Hz, H-12). Ms: 424 (M^+), 367 (100%), 323, 295, 251, 169, 156. HRms found: 424.2349. Calcd for $\text{C}_{25}\text{H}_{32}\text{O}_4\text{N}_2$: 424.2362.

Preparation of N₄-Boc-deformyl-Z-geissoschizine cis-N₆-oxide (3):

A solution of compound (2) (130 mg, 0.31 mmol) and *m*-chloroperbenzoic acid (*m*CPBA) (58 mg, 1.1 equiv.) in dry CH_2Cl_2 (7 ml) was stirred at room temperature for 4 h (Ar atm). Normal work-up and purification by column chromatography (alumina, $\text{CH}_2\text{Cl}_2/\text{MeOH}$:98/2) yielded compound (3).

Compound (3): Y. 125 mg (93%). Amorphous material. Ir: 1730 br (2 x C=O). $^1\text{H-Nmr}$: 1.60 [9H, s, -

$C(CH_3)_3$], 1.71 (3H, d, $J=7$ Hz, H-18), 3.59 (3H, s, $-CO_2CH_3$), 3.96 (1H, d, $J=14$ Hz, H-21 α), 4.52 (1H, d, $J=14$ Hz, H-21 β), 5.05 (1H, br d, $J=13$ Hz, H-3), 5.42 (1H, q, $J=7$ Hz, H-19), 7.09-7.23 (2H, m, H-10, H-11), 7.33 (1H, d, $J=8$ Hz, H-9), 8.01 (1H, d, $J=8$ Hz, H-12). Ms: 440 (M^+), 340, 324, 251, 170, 169, 156 (100%). HRms found: 440.2303. Calcd for $C_{25}H_{32}O_5N_2$: 440.2311.

Preparation of N,-Boc-5 β -cyano-deformyl-Z-geissoschizine (4) and N,-Boc-6-trifluoroacetyl-5,6-didehydro-deformyl-Z-geissoschizine (5):

Compound (3) (602 mg, 1.37 mmol) was dissolved in dry CH_2Cl_2 (40 ml) and cooled to $-17^\circ C$. Trifluoroacetic anhydride (TFAA) (0.50 ml, 2.5 equiv.) was added with a syringe during 5 min and stirring was continued for 3 h until the temperature rose to $0^\circ C$. Then KCN (27 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 at room temperature 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 silica chromatography gave compound (5) (CH_2Cl_2 /hexane:25/75), compound (4) (CH_2Cl_2), and compound (2) (CH_2Cl_2 /MeOH:99/1).

Compound (5): Y. 71 mg (10%). Amorphous material. Ir: 1730 br (3 x C=O). 1H -Nmr: 1.72 [9H, s, $-C(CH_3)_3$], 1.79 (3H, d, $J=7$ Hz, H-18), 3.69 (3H, s, $-CO_2CH_3$), 3.72 (1H, d, $J=14$ Hz, H-21 α), 4.51 (1H, d, $J=14$ Hz, H-21 β), 5.38 (1H, q, $J=8$ Hz, H-19), 5.70 (1H, br d, $J=11$ Hz, H-3), 7.21-7.32 (2H, m, H-10, H-11), 7.52 (1H, s, H-5), 8.08 (1H, d, $J=9$ Hz, H-12), 8.47 (1H, d, $J=9$ Hz, H-9). Ms: 518 (M^+), 462, 418, 343, 264 (100%). HRms found: 518.2021. Calcd for $C_{27}H_{29}O_5N_2F_3$: 518.2028.

Compound (4): Y. 215 mg (35%). Amorphous material. Ir: 2300 (CN), 1730 br (2 x C=O). 1H -Nmr: See Table 1. Ms: 449 (M^+), 422, 392, 366 (100%), 348, 321, 293, 212, 169, 168. HRms found: 449.2328. Calcd for $C_{26}H_{31}O_4N_3$: 449.2315.

Compound (2): Y. 41 mg (7%). For analytical data, see above.

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17. Note! Two numbering systems are used. The IUPAC numbering system is used for compounds whose names are based on the word "indolo[2,3-*a*]quinolizidine", and the biogenetic numbering system of Le Men and Taylor²⁶ for compounds whose names are based on the word "geissoschizine".
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