CLEAVAGE OF THE C-20 ETHYLIDENE SIDE-CHAIN OF DEFORMYL-Z- AND DEFORMYL-E-GEISSOSCHIZINE DERIVATIVES UTILIZING THE MODIFIED POLONOVSKI REACTION

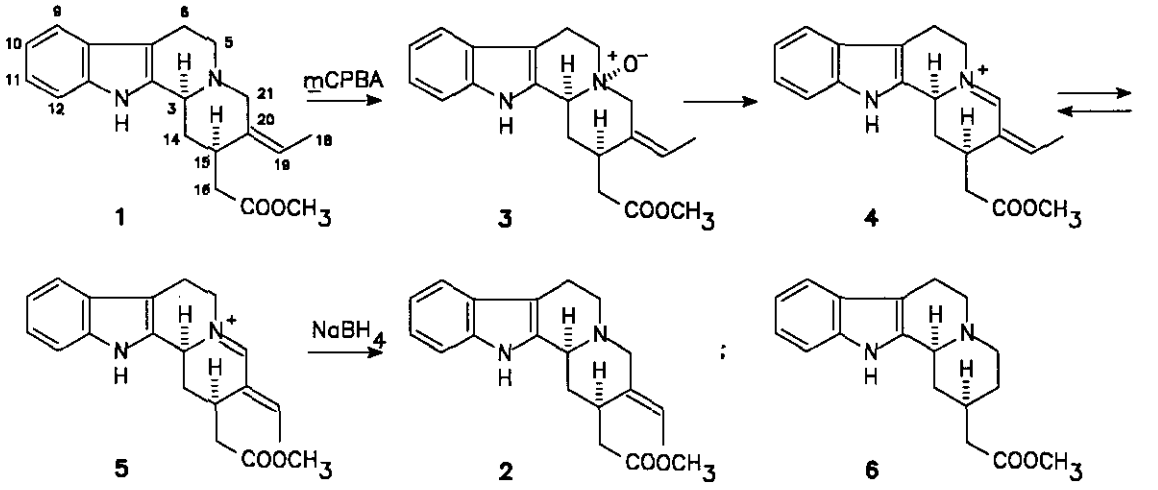
Mauri Lounasmaa*, Reija Jokela, Minna Halonen, and Jari Miettinen

Laboratory for Organic and Bioorganic Chemistry,
Technical University of Helsinki, SF-02150 Espoo, Finland

Abstract - Cleavage of the C-20 ethylidene side-chain of deformyl-Z-geissoschizine (**1**) and deformyl-E-geissoschizine (**2**), and their N_a-Boc derivatives (**11**) and (**12**), utilizing the modified Polonovski reaction, is described. Mechanistic considerations are presented.

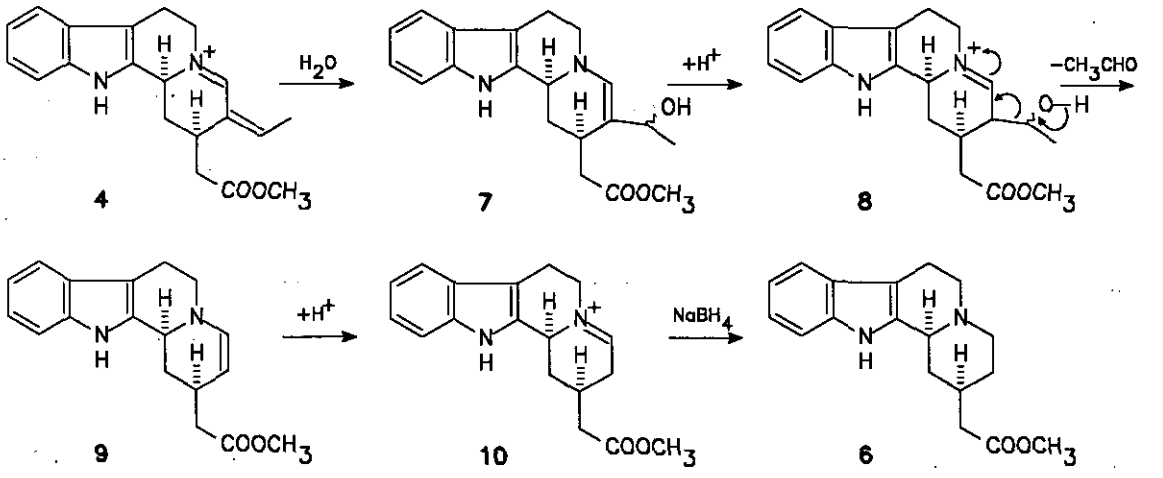
In a recent work we reported the transformation of deformyl-Z-geissoschizine (**1**) to deformyl-E-geissoschizine (**2**)[1] through oxidation of (**1**) to N_b-oxide (**3**), formation of deformyl-Z-geissoschizine $\Delta^{4(21)}$-iminium ion (**4**) (by modified Polonovski reaction[2-6]), equilibration to deformyl-E-geissoschizine $\Delta^{4(21)}$-iminium ion (**5**), and treatment with $NaBH_4$ (Scheme 1). The small amounts (~3%) of the corresponding desethylidene derivative (**6**) that were formed as well, indicated that an ethylidene side-chain cleavage had taken place.

The cleavage of the ethylidene side-chain is of particular interest because the reaction involved (modified Polonovski reaction) is considered to represent a biomimetic process.[7]



Scheme 1

The formation of desethylidene derivative (**6**) might be mechanistically postulated in the following manner: Reaction of H_2O (present in small quantities in the reaction mixture) with the conjugated iminium ion (**4**) [and/or (**5**)] leads to hydroxyenamine (**7**). This is protonated to the corresponding iminium ion (**8**). Elimination of acetaldehyde from the iminium ion (**8**) affords enamine (**9**), which is protonated to a new iminium ion (**10**). Reduction of the iminium ion (**10**) with $NaBH_4$ yields the desethylidene derivative (**6**) (Scheme 2).

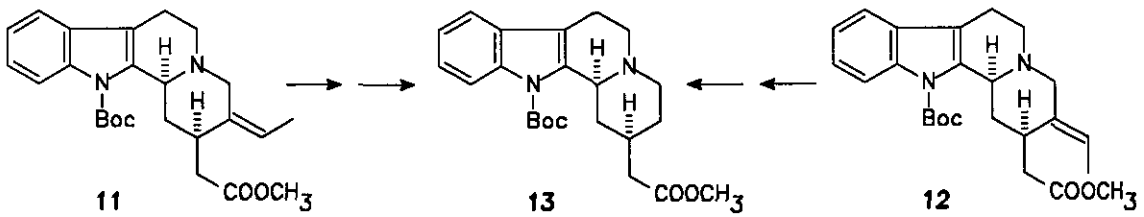


Scheme 2

To test the validity of this mechanism and to improve the yield of the desethylidene derivative (**6**), the reaction procedure (cf. ref. 1) was slightly modified. Once the iminium ion (**4**) [and/or (**5**)] was formed (~2 h), the reaction mixture was condensed to dryness, redissolved in acidic MeOH (4-5 drops of 30% HCl in MeOH), and stirred for 2 h at room temperature and then 3 h under reflux. The reaction mixture was cooled to 0°C, $NaBH_4$ (6 equiv.) was added in small portions, and stirring was continued for 18 h at room temperature. After normal work-up and chromatographic fractionation the desethylidene derivative (**6**)[8] was obtained in 12% yield.

The considerable improvement (3% → 12%) in the yield of the desethylidene derivative (**6**) under the modified conditions underlines the role of H_2O (present in 30% HCl) and supports the mechanism we propose (vide supra).

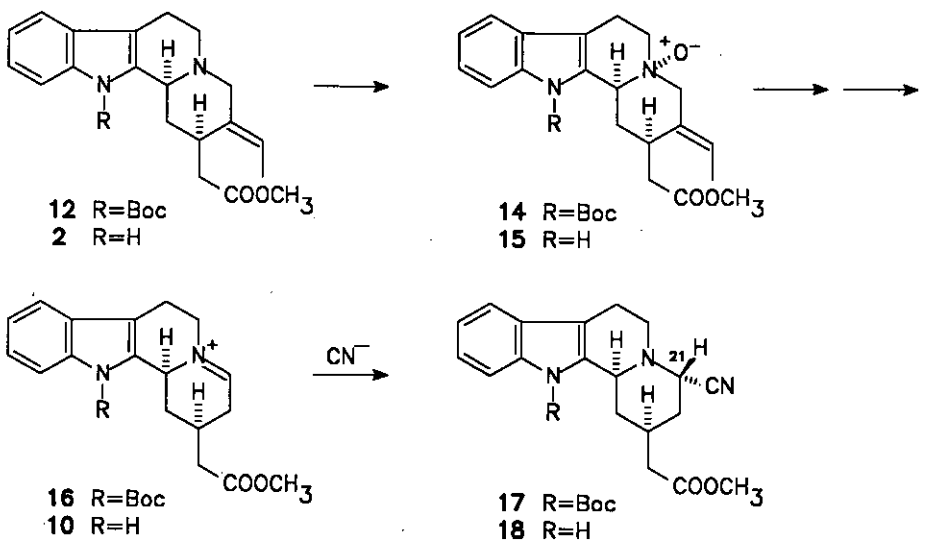
The cleavage reaction was further tested using N_a-Boc-deformyl-Z-geissoschizine (**11**)[9] and N_a-Boc-deformyl-E-geissoschizine (**12**)[10]. In both cases, the same desethylidene derivative (**13**)[11] was obtained in ~15% yield (Scheme 3).



Scheme 3

Finally, *in order to get still more evidence in support on the presented mechanism* N_a-Boc-deformyl-E-geissoschizine (**12**) and deformyl-E-geissoschizine (**2**) were transformed, via N_b-oxides (**14**)[12] and (**15**)[13] to the corresponding iminium ions (**16**) and (**10**). This time the final $NaBH_4$ reduction of the iminium ions (vide

supra) was replaced by cyano-trapping.[14-18] The formation of C-21 cyano derivatives (**17**)[19] and (**18**)[20], respectively, as the sole desethylidene cyano-derivatives[21] is in perfect agreement with the proposed mechanism (Scheme 4).



Scheme 4

The ^{13}C-nmr data for compounds (**6**), (**13**), (**15**), (**17**), and (**18**) are given in Figure 1. Comparison of the measured chemical shifts, taking into account the conformational considerations relevant for indolo[2,3-a]quinolizidines in general ,[9,12,17,22] provides clear evidence for the stereostructures depicted in the formulae.

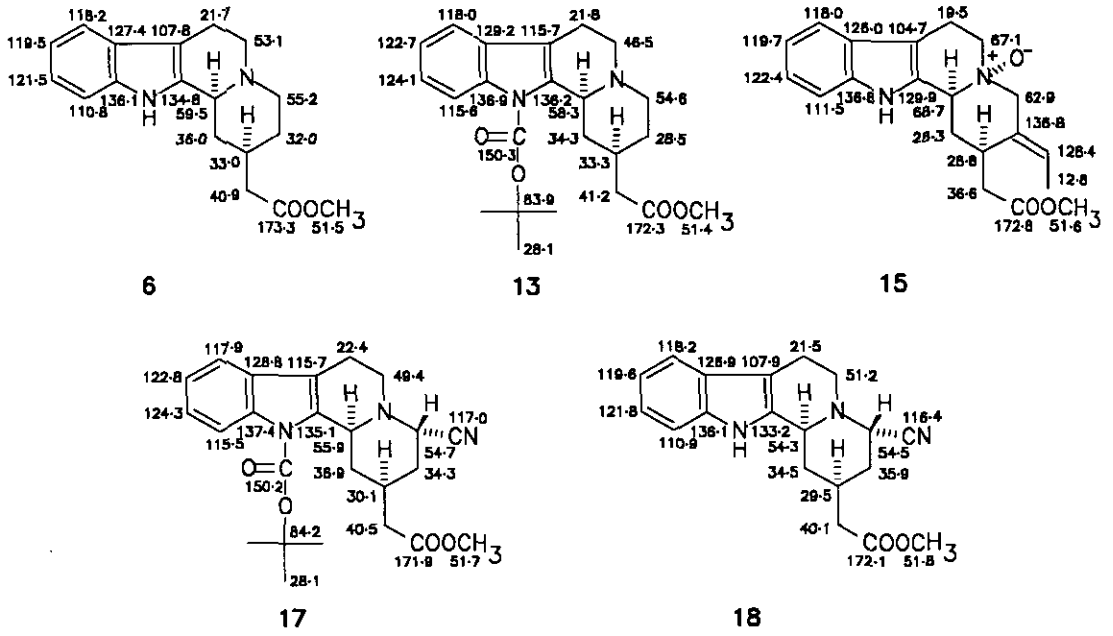
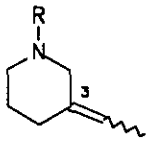


Figure 1. ^{13}C - nmr data of compounds (**6**), (**13**), (**15**), (**17**), and (**18**).

The stereochemistry of compound (**17**) at C-21 (H-21 α or β) was determined by NOE experiments. As compound (**17**) is an N$_b$-Boc derivative, the conformation b can be considered to be strongly favoured in the conformational equilibrium (cf. ref. 10). No NOE was observed at H-21 when H-3 was irradiated nor vice versa. This suggested axial orientation for the cyano-group and, as a corollary, equatorial orientation for H-21 (H-21β). The equatorial orientation of H-21 was further confirmed by its coupling constants: 5 Hz and 2.5 Hz.

The orientation of the cyano-group in compound (**18**) was mainly determined by comparison of the ^{13}C chemical shifts of C-20 in compounds (**6**) and (**18**) [δ 32.0 and 35.9, respectively; both compounds existing predominantly in conformation a (cf. ref. 10)]. The β effect found (+3.9 ppm) for the cyano group is compatible with the axial position,[23] and, as a consequence, H-21 is equatorial (H-21β). The equatorial orientation was further confirmed by the ^1H coupling constants: 5 Hz and 2.5 Hz.

Although the cleavage has so far been applied only for deformyl-geissoschizine derivatives, it seems plausible to us that it represents a general method for cleavage of C-3 ethylidene (and analogous) side-chains of appropriate piperidine derivatives (**19**).



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8. Compound (**6**). Y. 12%. Amorphous material. Ir: 3200 w (NH), 1730 br (C=O), 2740, 2830 w (Bohlmann bands). ^{1}H-Nmr ($CDCl_3$): 3.29 (1H, br d, J=11 Hz, H-3), 3.72 (3H, s, -OCH_3), 7.08-7.15 (2H, m, H-10, H-11), 7.30 (1H, d, J=8 Hz, H-9), 7.48 (1H, d, J=8 Hz, H-12), 7.77 (1H, br s, NH). ^{13}C-Nmr: See Figure 1. Ms: 298 (M^+), 297 (100%), 283, 267, 225, 197, 170, 169, 156. HRms: Found: 298.1678. Calcd for $C_{18}H_{22}N_2O_2$: 298.1679.
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11. Compound (**13**). Y. 15%. Amorphous material. Ir: 1730 br (2 x C=O). ^{1}H-Nmr ($CDCl_3$): 1.68 [9H, s, -C(CH_3)$_3$], 3.68 (3H, s, -OCH_3), 4.19 (1H, br d, J=10 Hz, H-3), 7.22-7.28 (2H, m, H-10, H-11), 7.40 (1H, d, J=8 Hz, H-9), 8.10 (1H, d, J=8 Hz, H-12). ^{13}C-Nmr: See Figure 1. Ms: 398 (M^+), 367, 341 (100%), 297, 269, 170, 169, 156. HRms: Found: 398.2220. Calcd for $C_{23}H_{30}N_2O_4$: 398.2206.

12. R. Jokela, M. Halonen, and M. Lounasmaa, unpublished results.

13. Compound (**15**). Y. 65%. Amorphous material. Ir: 3300 w (NH), 1735 s (C=O). ^{1}H-Nmr ($CDCl_3$ + 15 drops CD_3OD): 1.69 (3H, d, J=7 Hz, =CHC<u>H</u>$_3$), 3.35 (1H, d, J=13 Hz, H-21α), 3.62 (3H, s, -OCH_3), 4.31 (1H, d, J=13 Hz, H-21β), 4.58 (1H, br, H-3), 5.66 (1H, q, J=7 Hz, =C<u>H</u>CH_3), 7.09-7.24 (2H, m, H-10, H-11), 7.38 (1H, d, J=8 Hz, H-9), 7.47 (1H, d, J=8 Hz, H-12), 10.22 (1H, br s, NH). ^{13}C-Nmr: See Figure 1. Ms: 340 (M^+), 324, 323, 295, 267, 251, 170, 169, 156 (100%). HRms: Found: 340.1814. Calcd for $C_{20}H_{24}N_2O_3$: 340.1787.

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19. Compound (**17**). Y. 12%. Amorphous material. Ir: 2370 m (CN), 1730 br (2 x C=O). ^{1}H-Nmr ($CDCl_3$): 1.68 [9H, s, -C(CH_3)$_3$], 3.69 (3H, s, -OCH_3), 4.12 (1H, dd, J_1=5 Hz, J_2=2.5 Hz, H-21β), 4.26 (1H, br d, J=11 Hz, H-3), 7.20-7.30 (2H, m, H-10, H-11), 7.40 (1H, d, J=8 Hz, H-9), 8.11 (1H, d, J=8 Hz, H-12). ^{13}C-Nmr: See Figure 1. Ms: 423 (M^+), 396, 366 (100%), 340, 323, 296, 241, 223, 221, 197, 169, 168, 156. HRms: Found: 423.2162. Calcd for $C_{24}H_{29}N_3O_4$: 423.2158.

20. Compound (**18**). Y. 15%. Amorphous material. Ir: 3280 w (NH), 2350 m (CN), 1720 s (C=O). ^{1}H-Nmr ($CDCl_3$): 3.73 (3H, s, -OCH_3), 4.10 (1H, dd, J_1=5 Hz, J_2=2.5 Hz H-21β), 7.09-7.16 (2H, m, H-10, H-11), 7.32 (1H, d, J=8 Hz, H-9), 7.48 (1H, d, J=8 Hz, H-12), 7.83 (1H, br s, NH). ^{13}C-Nmr: See Figure

1. Ms: 323 (M^+), 296, 223 (100%), 221, 197, 170, 169, 156. HRms: Found: 323.1624. Calcd for $C_{19}H_{21}N_3O_2$: 323.1634.

21. For the other cyano derivatives formed, where the ethylidene side-chain cleavage had not taken place, see refs. 9 and 12.

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