

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

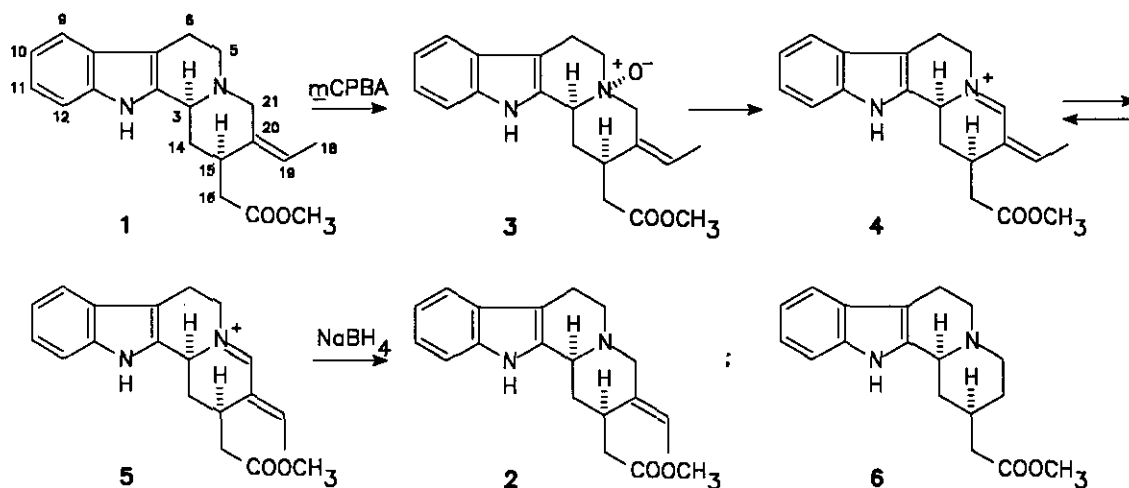
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Abstract - Cleavage of the C-20 ethylidene side-chain of deformyl-Z-geissoschizine (**1**) and deformyl-E-geissoschizine (**2**), and their N_B -Boc derivatives (**11**) and (**12**), utilizing the modified Polonovski reaction, is described. Mechanistic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

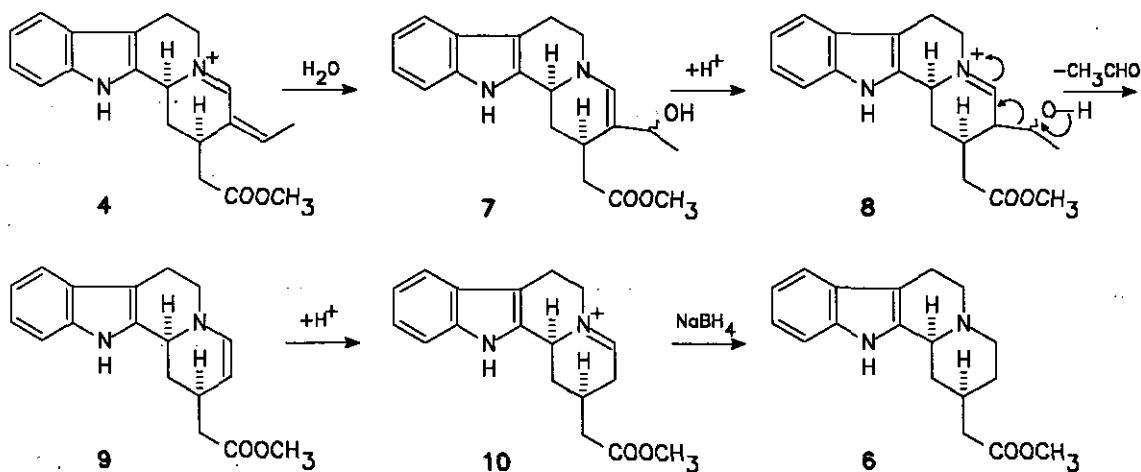
In a recent work we reported the transformation of deformyl-Z-geissoschizine (**1**) to deformyl-E-geissoschizine (**2**)¹ through oxidation of (**1**) to N_B -oxide (**3**), formation of deformyl-Z-geissoschizine $\Delta^{4(21)}$ -iminium ion (**4**) (by modified Polonovski reaction²⁻⁶), equilibration to deformyl-E-geissoschizine $\Delta^{4(21)}$ -iminium ion (**5**), and treatment with NaBH_4 (Scheme 1). The small amounts ($\sim 3\%$) 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 H₂O (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 NaBH₄ yields the desethylidene derivative (6) (Scheme 2).

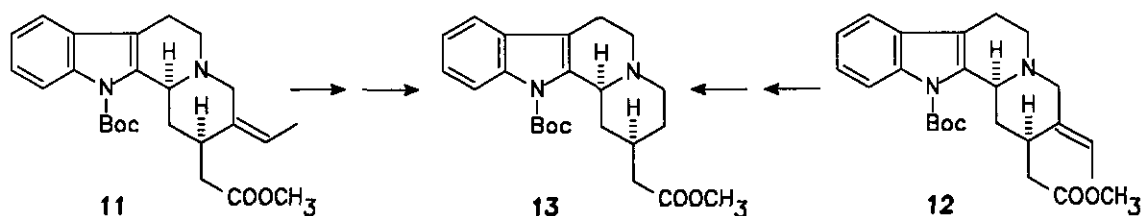


Scheme 2

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% $\rightarrow$ 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*).

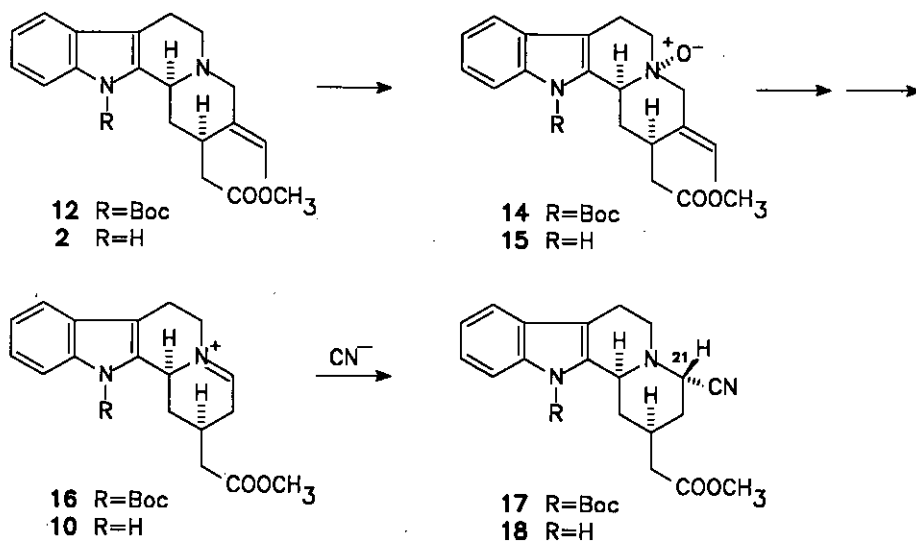
The cleavage reaction was further tested using N_L -Boc-deformyl-*Z*-geissoschizine (11)⁹ and N_L -Boc-deformyl-*E*-geissoschizine (12)¹⁰. In both cases, the same desethylidene derivative (13)¹¹ was obtained in $\sim 15\%$ yield (Scheme 3).



Scheme 3

Finally, in order to get still more evidence in support on the presented mechanism N_L -Boc-deformyl-*E*-geissoschizine (12) and deformyl-*E*-geissoschizine (2) were transformed, *via* N_L -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-derivatives²¹ is in perfect agreement with the proposed mechanism (Scheme 4).



Scheme 4

The ¹³C-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.

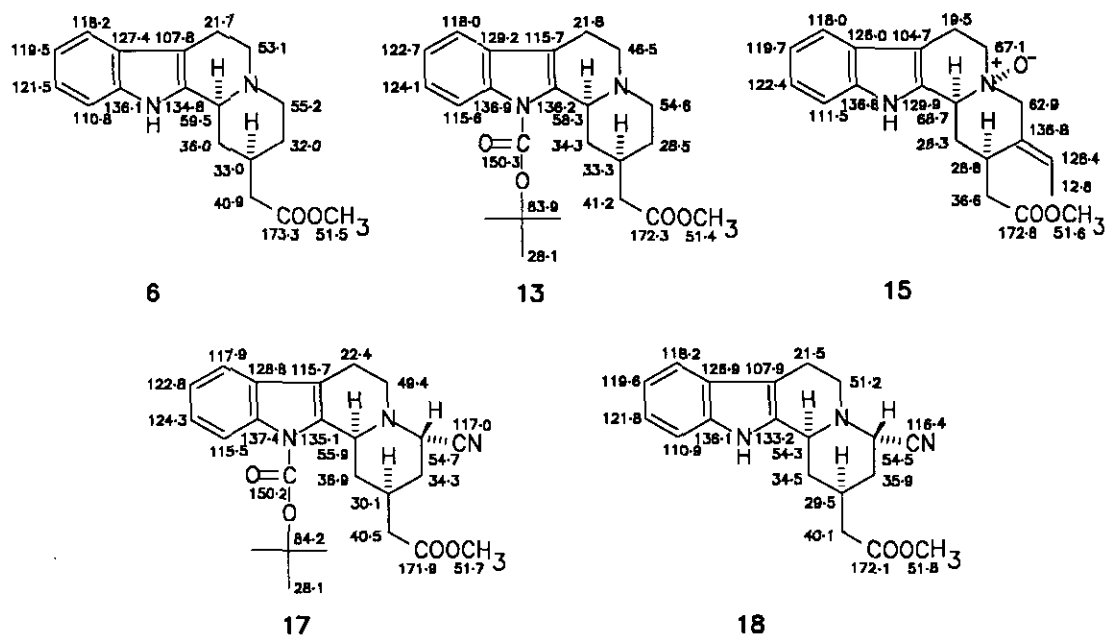
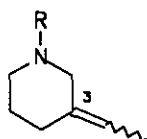


Figure 1. ^{13}C - nmr data of compounds (6), (13), (15), (17), and (18).

The stereochemistry of compound (17) at C-21 (H-21 α or β) was determined by NOE experiments. As compound (17) is an N_{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-21 β). 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-21 β). 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).



REFERENCES AND NOTES

1. M. Lounasmaa, R. Jokela, J. Miettinen, and M. Halonen, *Heterocycles*, 1992, **34**, 1497.
2. P. Potier, *Rev. Latinoamer. Quim.*, 1978, **9**, 47.
3. P. Potier, "*Stereoselective Synthesis of Natural Products*", eds. W. Bartmann and E. Winterfeldt, Excerpta Medica, Amsterdam - Oxford, 1979, pp. 19-27.
4. M. Lounasmaa and A. Koskinen, *Heterocycles*, 1984, **22**, 1591.
5. D. Grierson, "*Organic Reactions*", ed. L.A. Paquette, Vol. 39, John Wiley, New York, 1990, pp. 85-295.
6. D.S. Grierson and H.-P. Husson, "*Comprehensive Organic Synthesis*", eds. B.M. Trost and I. Fleming, Vol. 6, Pergamon Press, Oxford, 1991, pp. 909-924.
7. P. Potier, in "Indole and Biogenetically Related Alkaloids", eds. J.D. Phillipson and M.H. Zenk, Academic Press, London, 1980, pp. 157-169.
8. Compound (6). Y. 12%. Amorphous material. Ir: 3200 w (NH), 1730 br (C=O), 2740, 2830 w (Bohlmann bands). ¹H-Nmr (CDCl₃): 3.29 (1H, br d, J=11 Hz, H-3), 3.72 (3H, s, -OCH₃), 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). ¹³C-Nmr: See Figure 1. Ms: 298 (M⁺), 297 (100%), 283, 267, 225, 197, 170, 169, 156. HRms: Found: 298.1678. Calcd for C₁₈H₂₂N₂O₂: 298.1679.
9. R. Jokela, M. Halonen, and M. Lounasmaa, *Heterocycles*, 1993, **36**, 1115.

10. R. Jokela, M. Halonen, and M. Lounasmaa, *Tetrahedron*, 1993, **49**, 2567.
11. Compound (13). Y. 15%. Amorphous material. Ir: 1730 br (2 x C=O). $^1\text{H-Nmr}$ (CDCl_3): 1.68 [9H, s, $-\text{C}(\text{CH}_3)_3$], 3.68 (3H, s, $-\text{OCH}_3$), 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). $^{13}\text{C-Nmr}$: See Figure 1. Ms: 398 (M^+), 367, 341 (100%), 297, 269, 170, 169, 156. HRms: Found: 398.2220. Calcd for $\text{C}_{23}\text{H}_{30}\text{N}_2\text{O}_4$: 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). $^1\text{H-Nmr}$ (CDCl_3 + 15 drops CD_3OD): 1.69 (3H, d, $J=7$ Hz, $=\text{CHCH}_3$), 3.35 (1H, d, $J=13$ Hz, H-21 α), 3.62 (3H, s, $-\text{OCH}_3$), 4.31 (1H, d, $J=13$ Hz, H-21 β), 4.58 (1H, br, H-3), 5.66 (1H, q, $J=7$ Hz, $=\text{CHCH}_3$), 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). $^{13}\text{C-Nmr}$: See Figure 1. Ms: 340 (M^+), 324, 323, 295, 267, 251, 170, 169, 156 (100%). HRms: Found: 340.1814. Calcd for $\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}_3$: 340.1787.
14. E. M. Fry, *J. Org. Chem.*, 1964, **29**, 1647.
15. E. M. Fry and J. A. Beisler, *J. Org. Chem.*, 1970, **35**, 2809.
16. M. Lounasmaa and R. Jokela, *Tetrahedron*, 1989, **45**, 7449.
17. M. Lounasmaa, R. Jokela, B. Tirkkonen, and T. Tamminen, *Tetrahedron*, 1989, **45**, 7615.
18. M. Lounasmaa and R. Jokela, *Tetrahedron*, 1990, **46**, 615.
19. Compound (17). Y. 12%. Amorphous material. Ir: 2370 m (CN), 1730 br (2 x C=O). $^1\text{H-Nmr}$ (CDCl_3): 1.68 [9H, s, $-\text{C}(\text{CH}_3)_3$], 3.69 (3H, s, $-\text{OCH}_3$), 4.12 (1H, dd, $J_1=5$ Hz, $J_2=2.5$ Hz, H-21 β), 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). $^{13}\text{C-Nmr}$: 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 $\text{C}_{24}\text{H}_{29}\text{N}_3\text{O}_4$: 423.2158.
20. Compound (18). Y. 15%. Amorphous material. Ir: 3280 w (NH), 2350 m (CN), 1720 s (C=O). $^1\text{H-Nmr}$ (CDCl_3): 3.73 (3H, s, $-\text{OCH}_3$), 4.10 (1H, dd, $J_1=5$ Hz, $J_2=2.5$ Hz H-21 β), 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). $^{13}\text{C-Nmr}$: 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.
22. M. Lounasmaa and R. Jokela, Tetrahedron, 1989, **45**, 3975.
23. R. Jokela, T. Tamminen, and M. Lounasmaa, Heterocycles, 1985, **23**, 1707.

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