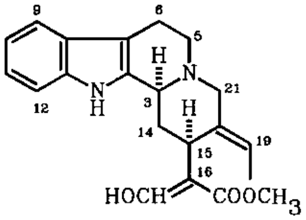
NEW, SHORT SYNTHESIS OF (±)-GEISSOSCHIZINE

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

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

Abstract - A short, easy way to prepare indole alkaloid (±)-geissoschizine (**1**) is described.

Most of the several syntheses reported[1-4] for the indole alkaloid (±)-geissoschizine (**1**)[5] are long and tedious. In this paper, we present a short and easy route.



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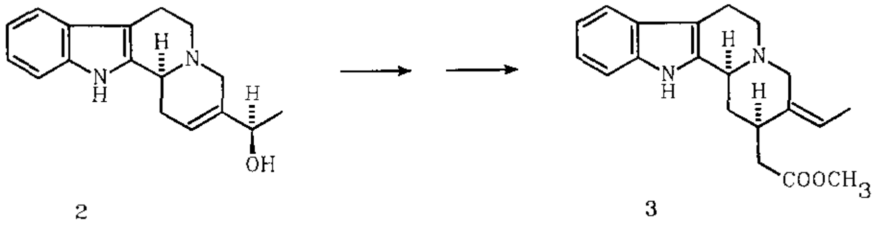
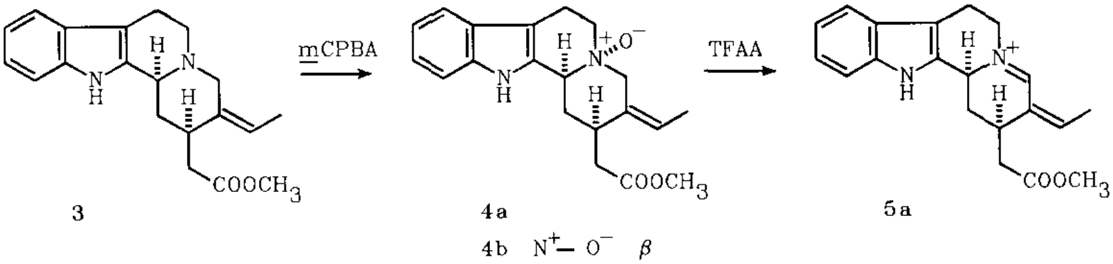
We recently described a stereoselective transformation of allylic alcohol (**2**) to deformyl-Z-geissoschizine (**3**) using dimethylacetamide dimethyl acetal or trimethyl orthoacetate in the Claisen rearrangement (Scheme 1).[6]



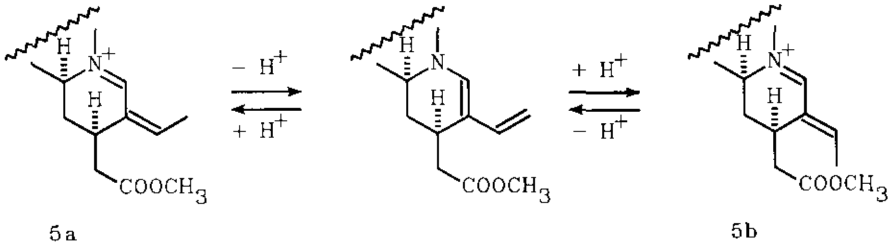
Scheme 1

Oxidation of (**3**) with *m*CPBA to the corresponding *cis*-N_b-oxide (**4a**) (together with the corresponding *trans*-N_b-oxide (**4b**), which was easily separated),[7] and TFAA treatment (modified Polonovski reaction) of this,[8] led to the iminium ion (**5a**) (Scheme 2).



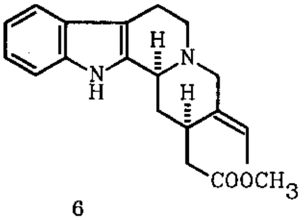
Scheme 2

Equilibration of (**5a**) gave a mixture of iminium ions (**5a**) and (**5b**) (Scheme 3).[8,9]



Scheme 3

Reduction of the iminium ion mixture with $NaBH_4$ afforded deformyl-E-geissoschizine (**6**) in 14% yield.[8] Recycling of the recovered deformyl-Z-geissoschizine (**3**) (60% yield) permitted a total Z/E side-chain isomerization in about 30% yield.



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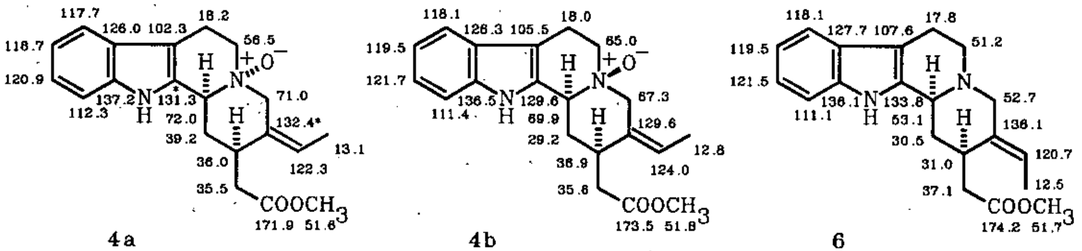
The final step, formylation of deformyl-E-geissoschizine (**6**) with methyl formate, leading to (±)-geissoschizine (**1**), has been described earlier.[10]



4a 4b 6

(+ 4 drops of CD_3OD)

Figure 1. ^{13}C Nmr data ($CDCl_3$) of compounds 4a, 4b and 6

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5. Biogenetic numbering (J. Le Men and W. Taylor, *Experientia*, 1965, **21**, 508) is used.
6. M. Lounasmaa, R. Jokela, B. Tirkkonen, J. Miettinen, and M. Halonen, *Heterocycles*, 1992, **34**, 321.
7. **Preparation of deformyl-*Z*-geissoschizine *cis*-N_b-oxide (4a) and deformyl-*Z*-geissoschizine *trans*-N_b-oxide (4b).** Deformyl-*Z*-geissoschizine (**3**) (600 mg, 1.85 mmol) was dissolved in 10 ml of dry CH_2Cl_2 and the reaction mixture was cooled to 0°C. *m*-Chloroperbenzoic acid (479 mg, 2.78 mmol, 1.5 equiv.) was added in small portions during 15 min to the stirred solution (0°C, N_2 atm.). Stirring was continued for 8 h at room temperature and the solvent was evaporated. The crude product (containing deformyl-*Z*-geissoschizine *cis*-N_b-oxide (**4a**) and deformyl-*Z*-geissoschizine *trans*-N_b-oxide (**4b**) in approx. 2:1 ratio) was fractionated by column chromatography (alumina; CH_2Cl_2/MeOH; 97/3).

   Deformyl-*Z*-geissoschizine *cis*-N_b-oxide (4a). Yield 341 mg, 54%. mp 146-149°C (CH_2Cl_2). Ir ($CHCl_3$) 1740 (s, C=O). ^{1}H Nmr ($CDCl_3$) 1.74 (3H, d, J=7 Hz, $=CHC\underline{H}_3$), 3.67 (3H, s, $-OC\underline{H}_3$), 3.92 (1H, br d, J=11 Hz, H-3), 4.41 (1H, d, J=12 Hz, H-21), 5.32 (1H, q, J=7 Hz, $=C\underline{H}CH_3$), 6.85-7.10 (3H, m, H-10, H-11, H-12), 7.43 (1H, d, J=7 Hz, H-9) 12.52 (1H, br s, NH). Ms: 340 (M^+), 324, 251, 170, 169, 156; Exact mass: 340.1792 (Calcd for $C_{20}H_{24}O_3N_2$: 340.1786).

   Deformyl-*Z*-geissoschizine *trans*-N_b-oxide (4b). Yield 163 mg, 26%. Amorphous material. Ir ($CHCl_3$) 1735 (s, C=O). ^{1}H Nmr ($CDCl_3$; 45°C) 1.62 (3H, d, J=7 Hz, $=CHC\underline{H}_3$), 3.69 (3H, s, $-OC\underline{H}_3$), 3.93 (1H, d, J=12 Hz, H-

21), 4.30 (1H, br d, J=11 Hz, H-3), 5.34 (1H, q, J=7 Hz, =C<u>H</u>CH$_3$), 6.90-7.10 (2H, m, H-10, H-11), 7.15-7.40 (2H, m, H-9, H-12), 10.17 (1H, br s, NH). Ms: 340 (M$^+$), 324, 251, 170, 169, 156; Exact mass: 340.1794 (Calcd for $C_{20}H_{24}O_3N_2$: 340.1786).

8. **Preparation of deformyl-E-geissoschizine (6).** Deformyl-Z-geissoschizine cis-N$_b$-oxide (**4a**) (80 mg, 0.24 mmol) was dissolved in dry CH_2Cl_2 (5 ml) and cooled to -17°C. Trifluoroacetic anhydride (2.5 equiv.) was added with a syringe during 5 min and the solution was stirred at room temperature for 2 h. The reaction mixture was condensed to dryness, redissolved in MeOH and stirred at room temperature for 2 h. $NaBH_4$ (6 equiv.) was added in small portions to the stirred solution during 20 min (0°C, N_2 atm.) and stirring was continued for 18 h at room temperature. Water was added, MeOH was evaporated in vacuo and the mixture was extracted with CH_2Cl_2. The organic fractions were washed with water, dried (Na_2SO_4) and evaporated. The crude product (63 mg, 83%) was fractionated by column chromatography (silica, CH_2Cl_2/MeOH; first 99/1, then 97/3).

Deformyl-E-geissoschizine (6). Yield 11 mg, 14%. Amorphous material (lit.[4] amorphous material). Ir ($CHCl_3$) 3490 (w, NH), 1725 (s, C=O). ^{1}H Nmr ($CDCl_3$) 1.64 (3H, d, J=7 Hz, =CHC<u>H</u>$_3$), 2.95 (1H, d, J=12 Hz, H-21β), 3.55 (1H, d, J=12 Hz, H-21α), 3.70 (3H, s, -OC<u>H</u>$_3$), 4.27 (1H, br s, H-3), 5.48 (1H, q, J=7 Hz, =C<u>H</u>CH$_3$), 7.10 (1H, t, J=7 Hz, H-10), 7.13 (1H, t, J=7 Hz, H-11), 7.36 (1H, d, J=7 Hz, H-12), 7.49 (1H, d, J=7 Hz, H-9), 8.60 (1H, br s, NH). Ms: 324 (M$^+$), 251, 170, 169, 151. Exact mass 324.1839 (Calcd for $C_{20}H_{24}O_2N_2$: 324.1837).

Recycling of the recovered deformyl-Z-geissoschizine (**3**) (47 mg, 60%) permitted the preparation of deformyl-E-geissoschizine (**6**) in about 30% total yield.

9. Presence of other iminium ions is also possible. See also, M. R. Uskokovic, R. L. Lewis, J. J. Partridge, C. W. Despreaux, and D. L. Pruess, J. Am. Chem. Soc., 1979, **101**, 6742.

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