

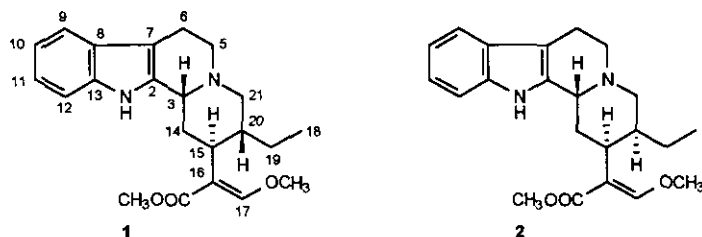
PREPARATION OF (±)-HIRSUTINE AND (±)-3-ISOCORYNANTHEIDINE

Mauri Lounasmaa*, Reija Jokela, Christiane Laine, and
Pirjo Hanhinen

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

Abstract - Preparation of indole alkaloids (±)-hirsutine (1) and (±)-3-isocorynantheidine (2) is described.

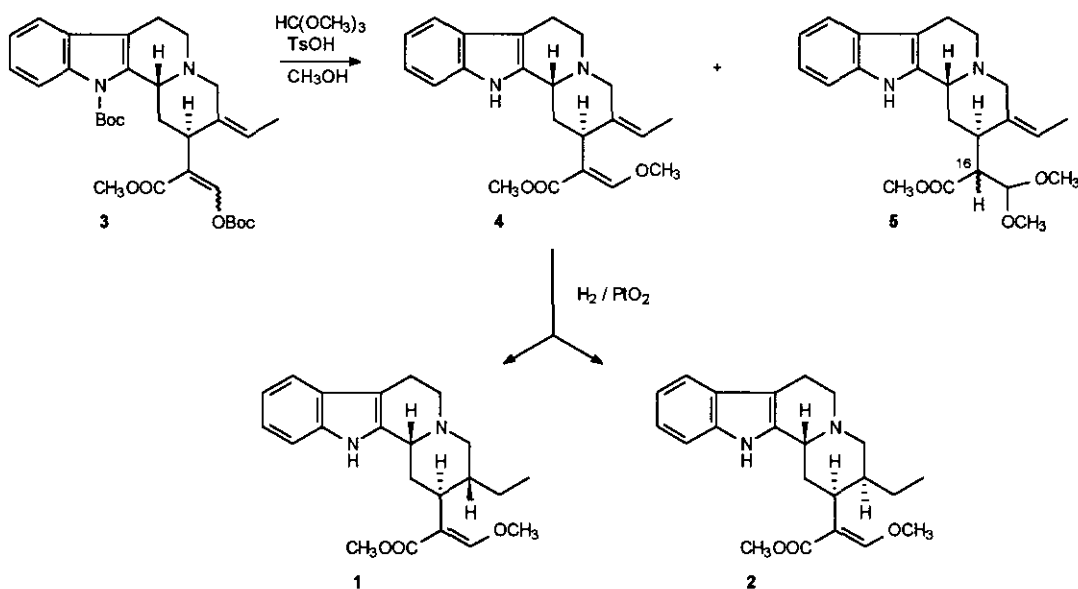
Hirsutine (1), a tetracyclic indole alkaloid, was first isolated by Shellard et al.¹ from the Asian plant, *Mitragyna hirsuta* Havil. Its 20-epimer, 3-isocorynantheidine (2), was also first isolated by Shellard et al.,² but from another Asian plant, *Mitragyna speciosa* Korth. Later, the presence of both compounds was demonstrated in several *Mitragyna* and *Uncaria* species (Rubiaceae).³⁻⁶ Various syntheses (total or partial) of hirsutine (1) and 3-isocorynantheidine (2) have been presented,⁷⁻¹² but they are generally relatively long and tedious. We recently described a short synthesis of hirsutine (1).¹³



We have now developed an easy alternative route to ($\pm$)-hirsutine (**1**), as well as a route to ($\pm$)-3-isocorynantheidine (**2**).

RESULTS AND DISCUSSION

Treatment of our recently described and easily accessible ($\pm$)- N_a , O -di-Boc-3-epi- Z -geissoschizine [($\pm$)- N_a , O -di-Boc-15-epi- Z -geissoschizine]¹⁴ (**3**) with trimethyl orthoformate and TsOH in MeOH gave a mixture of ($\pm$)-3-epi- Z -geissoschizine methyl ether (**4**)¹⁵ and ($\pm$)-3-epi- Z -geissoschizine dimethylacetal (**5**) (as a mixture of C-16 epimers), which was easily fractionated. Catalytic hydrogenation (PtO₂) of compound (**4**) led to two dihydro derivatives, ($\pm$)-hirsutine (**1**) and ($\pm$)-3-isocorynantheidine (**2**) (Scheme 1).



Scheme 1. Preparation of ($\pm$)-hirsutine (**1**) and ($\pm$)-3-isocorynantheidine (**2**) from ($\pm$)- N_a , O -di-Boc-3-epi- Z -geissoschizine (**3**).

The ¹³C-NMR data (Figure 1) are in good agreement with the proposed structures.^{13,14,16}

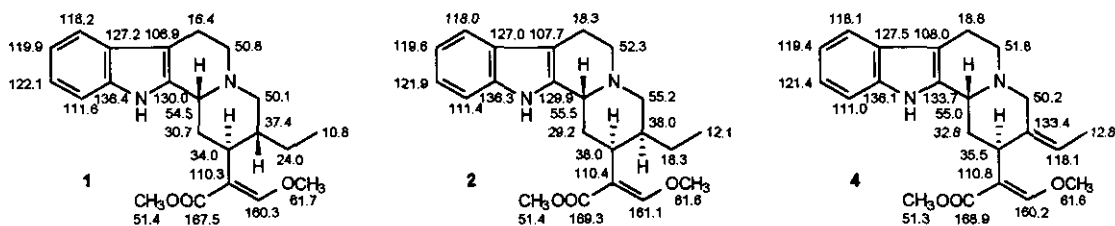


Figure 1. ^{13}C -NMR data of compounds (1, 2, and 4).

CONCLUSIONS

A new easy route is now available for the preparation of ($\pm$)-hirsutine (1) and ($\pm$)-3-isocorynantheidine (2). Complete ^1H - and ^{13}C -NMR data of compounds (1) and (2) are presented for the first time. For earlier fragmentary ^1H -NMR data, see Refs. 17-19.

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 with a JEOL DX 303/DA 5000 instrument.

Preparation of ($\pm$)-3-epi-Z-geissoschizine methyl ether (4) and ($\pm$)-3-epi-Z-geissoschizine dimethylacetal (5). ($\pm$)- N_{α} , O -Di-Boc-3-epi-Z-geissoschizine¹⁴ (3) (60 mg, 0.11 mmol) was dissolved in 3 mL of CH_3OH . After addition of $\text{CH}(\text{OCH}_3)_3$ (0.23 mL, 2.10 mmol, 19f equiv.) and TsOH (50 mg) the solvent was slowly evaporated under stirring during 90 min (oil bath, 75°C). The residue was dissolved in CH_2Cl_2 , neutralized with 10% Na_2CO_3 , washed with H_2O , dried with Na_2SO_4 , and filtered. After evaporation, the crude mixture was purified and fractionated with PLC (silica gel, $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$, 90/10) to yield compounds (4) and (5).

(±)-3-Epi-Z-geissoschizine methyl ether (4). Yield 10.0 mg (25%). Amorphous. IR: 3350 (m, N-H), 1700 (s, C=O), 1640 (m, -C=C-). ¹H-NMR: 1.63 (3H, d, J=7 Hz, H-18), 2.02 (1H, ddd, J₁=14 Hz, J₂=J₃=6 Hz, H-14β), 2.65 (1H, ddd, J₁=14 Hz, J₂=10 Hz, J₃=5 Hz, H-14α), 2.70 (1H, br d, J=13 Hz, H-6α), 3.01 (1H, ddd, J₁=12 Hz, J₂=11 Hz, J₃=4 Hz, H-5α), 3.10 (1H, m, H-6β), 3.30 (1H, ddd, J₁=12 Hz, J₂=5 Hz, J₃=1 Hz, H-5β), 3.45 (2H, def., H-21α, H-21β), 3.52 (1H, m, H-15), 3.68 (3H, s, -COOCH₃), 3.79 (3H, s, -C=C-OCH₃), 4.16 (1H, br s, H-3), 5.18 (1H, q, J=7 Hz, H-19), 7.09 (1H, t, J=7.5 Hz, H-10), 7.15 (1H, t, J=7.5 Hz, H-11), 7.33 (1H, d, J=7.5 Hz, H-12), 7.42 (1H, s, H-17), 7.48 (1H, d, J=7.5 Hz, H-9), 7.97 (1H, br s, NH). For the ¹³C-NMR data, see Figure 1. MS: 366 (M⁺, 100%), 365, 351, 335, 249, 237, 223, 184, 170, 169, 156. HRMS: Calcd for C₂₂H₂₆N₂O₃: 366.1943. Found: 366.1930. Anal. Calcd for C₂₂H₂₆N₂O₃: C, 72.11; H, 7.15; N, 7.64. Found: C, 71.84; H, 6.99; N, 7.38.

(±)-3-Epi-Z-geissoschizine dimethylacetal (5) (mixture of C-16 epimers). Yield 22.0 mg (50%). Amorphous. For the analytical data, see Ref. 16.

Preparation of (±)-hirsutine (1) and (±)-3-isocorynantheidine (2). (±)-3-Epi-Z-geissoschizine methyl ether (4) (11.0 mg, 0.030 mmol) was hydrogenated (PtO₂, 11 mg) in CH₃OH (5 ml) for 1 h. After normal work-up, the crude mixture was purified and fractionated by PLC (silica gel, CH₂Cl₂/CH₃OH; 90/10) to yield compounds (1) and (2).

(±)-Hirsutine (1). Yield 4.0 mg (36%). mp 128-130°C (EtOH/Et₂O). IR: 3400 (m, N-H), 1700 (s, C=O), 1640 (m, -C=C-). ¹H-NMR: 0.75 (3H, def. t, H-18), 3.70 (3H, s, -COOCH₃), 3.79 (3H, s, -C=C-OCH₃), 4.77 (1H, br s, H-3), 7.15 (1H, t, J=8 Hz, H-10), 7.19 (1H, t, J=8 Hz, H-11), 7.35 (1H, s, H-17), 7.44 (1H, d, J=8 Hz, H-12), 7.51 (1H, d, J=8 Hz, H-9), 8.32 (1H, br s, NH). For the ¹³C-NMR data, see Figure 1. MS: 368 (M⁺, 100%), 367, 353, 339, 337, 311, 251, 225, 197, 184, 170, 169, 156. HRMS: Calcd for C₂₂H₂₈N₂O₃: 368.2100. Found: 368.2089.

(±)-3-Isocorynantheidine (2). Yield 4.0 mg (36%). mp 216-218°C (EtOH/Et₂O). IR: 3300 (m, N-H), 1700 (s, C=O), 1635 (m, -C=C-). ¹H-NMR: 0.87 (3H, t, J=7 Hz, H-18), 3.65 (3H, s, -COOCH₃), 3.80 (3H, s, -C=C-OCH₃), 4.51 (1H, br s, H-3), 7.11 (2H, m, H-10, H-11), 7.36 (1H, d, J=8 Hz, H-12), 7.41 (1H, s, H-17), 7.43 (2H, m, H-9, NH). For the ¹³C-NMR data, see Figure 1. MS: 368 (M⁺), 367, 353, 339, 337, 251, 239, 225, 197, 184 (100%), 170, 169, 156. HRMS: Calcd for C₂₂H₂₈N₂O₃: 368.2100. Found: 368.2093.

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15. The *trans* relationship between the methoxycarbonyl and methoxyl groups in the methyl β -methoxyacrylyl moiety of compound (4) was confirmed by a comparison of the chemical shift value found for C-17-H (δ 7.42; *vide supra*) with the calculated values (*cis* δ 6.80; *trans* δ 7.37).^{20,21}
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