Total Syntheses of 10-Methoxydihydrocorynantheol and 10-Methoxycorynantheidol

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Abstract

10-Methoxydihydrocorynantheol and 10-methoxycorynantheidol were synthesized from 5-methoxytryptophol and 3-acetylpyridine. ^{13}C-NMR data of the prepared compounds and their synthetic intermediates are given.

Key words

10-Methoxydihydrocorynantheol, 10-methoxycorynantheidol, indole alkaloid, total synthesis, ^{13}C-NMR data.

Introduction

10-Methoxydihydrocorynantheol (**10**) is an indole alkaloid which has been isolated from several apocynaceous plants, including *Aspidosperma marcgravianum, Ochrosia moorei*, and *Neisosperma kilneri* (1). Despite its relatively widespread occurrence in the plant kingdom, so far as we know it has never been synthesized, except for the transformation from quinine (2). The isomeric compound 10-methoxycorynantheidol (**11**) has not yet been found in nature, but its demethoxy derivative is known to be present in *Mitragyna parvifolia* (3).

In connection with our syntheses of indole alkaloids of the corynantheine type, we became interested in applying the synthetic methods developed in our laboratory (4, 5, 6) to the preparation of 10-methoxycorynantheidol (**11**) and especially to the naturally occurring 10-methoxydihydrocorynantheol (**10**). The present paper reports our results. We have earlier synthesized compound **11** by an alternative method (7).

Materials and Methods

Spectroscopic techniques

IR spectra were recorded with a Perkin-Elmer 700 IR spectrophotometer. IR absorption bands are expressed in reciprocal centimetres (cm^{-1}). ^{1}H- and ^{13}C-NMR spectra were measured with a Varian Gemini-200 spectrometer working at 199.975 MHz (^{1}H-NMR) and 50.289 (^{13}C-NMR) with $CDCl_3$ used as solvent. Chemical shifts are given in ppm with reference to TMS (^{1}H-NMR; δ_H = 0.00 ppm) and $CDCl_3$ (^{13}C-NMR; δ_C = 77.00 ppm). Signal assignments were confirmed by APT and/or DEPT experiments. Abbreviations s, d, t, q, m, def, and br are used to designate singlet, doublet, triplet, quartet, multiplet, deformed, and broad, respectively. Mass spectrometry (EI-MS and HR-MS) was done on a Jeol DX 303/DA 5000 instrument.

Synthetic studies

Preparation of 5-methoxytryptophyl bromide (**2**): 5-Methoxytryptophol (**1**; Sigma, Compound M-4126; 2.288 g, 11.97 mmol) was dissolved in dry Et_2O (50 ml). The solution was cooled to 0 °C and 1.080 g (3.99 mmol) of PBr_3 in 70 ml of Et_2O were added during 30 min. The reaction mixture was stirred for 18 h at room temperature under nitrogen. The mixture was washed first with 10 % Na_2CO_3 and then with water. The ether layer was dried over Na_2SO_4, filtered and evaporated to furnish compound **2**. Yield: 2.189 g (72 %). Amorphous material. IR ($CHCl_3$): ν = 3450 (NH), 1625, 1590 (C=C). ^{1}H-NMR: δ = 3.28 (2H, t, J = 7.5 Hz, =C-*CH*$_2$-CH$_2$-), 3.61 (2H, t, J = 7.5 Hz, -CH$_2$-*CH*$_2$-Br), 3.86 (3H, s, -OCH$_3$), 6.87 (1H, d, J_1 = 9 Hz, J_2 = 2 Hz, H-6), 7.00 (1H, d, $J \approx$ 2 Hz, H-2), 7.01 (1H, d, J = 2 Hz, H-4), 7.23 (1H, d, J = 9 Hz, H-7), 7.93 (1H, br s, NH). For the ^{13}C-NMR data, see Figure **1**. MS: *m/e* = 255 (M^+, ^{81}Br), 253 (M^+, ^{79}Br), 174, 160 (100 %), 145. HR-MS: Found: 253.0126. Calcd for $C_{11}H_{11}NO^{79}Br$: 253.0102.

Preparation of pyridinium bromide **3**: Compound **2** (1.674 g, 6.59 mmol) and 3-acetylpyridine (Fluka, Compound 01440) (798 mg, 6.59 mmol) were dissolved in 20 ml of CH_2Cl_2. The mixture was heated to 70 °C and CH_2Cl_2 was evaporated under a stream of nitrogen. Then the temperature was raised to 100 °C for 1.5 h (under N_2). The formed bromide salt **3** was triturated with dry Et_2O. Yield: 2.314 g (94 %). Mp. 191–192 °C (MeOH). IR (KBr): ν = 3195 (NH), 1700 (C=O).

Preparation of dihydropyridine **4**: Bromide salt **3** (2.172 g, 5.79 mmol) and $NaHCO_3$ (7.975 g, 94.93 mmol) were dissolved in 210 ml of aqueous MeOH (MeOH : H_2O, 2 : 1). Sodium dithionite (6.044 g, 34.71 mmol) was added in small portions during 1 h at room temperature under nitrogen and the mixture was stirred overnight. The mixture was filtered and MeOH evaporated. The filtrate was extracted several times with CH_2Cl_2, and the extracts were washed with water and dried over Na_2SO_4. Evaporation of the solvent gave compound **4**. Yield: 1.567 g (91 %). Amorphous material. IR ($CHCl_3$): ν = 3350 (NH), 1650, 1628, 1590 (C=O and C=C). ^{1}H-NMR: δ = 1.80 (3H, s, -COCH$_3$), 2.95 (2H, m, -*CH*$_2$-CH$_2$-N<), 3.03 (2H, m, H-4'), 3.41 (2H, m, -CH$_2$-*CH*$_2$-N<), 3.85 (3H, s, -OCH$_3$), 4.88 (1H, m, H-5'), 5.71 (1H, d, J = 8 Hz, H-6'), 6.52 (1H, s, H-2'), 6.83 (1H, dd, J_1 = 8 Hz, J_2 = 2 Hz, H-6), 6.97 (1H, d, $J \approx$ 2 Hz, H-2), 7.01 (1H, d, J = 2 Hz, H-4), 7.23 (1H, d, J = 8 Hz, H-7), 9.25 (1H, br s, NH). For the ^{13}C-NMR data, see Figure **1**. MS: *m/e* = 296 (M^+), 281, 253, 186, 174 (100 %), 160. HR-MS: Found: 296.1508. Calcd for $C_{18}H_{20}N_2O_2$: 296.1525.

Preparation of indoloquinolizidine **5**: Freshly distilled acetyl chloride (10 ml) was added to MeOH (200 ml) during 10 min (0 °C, nitrogen atmosphere) and the solution was stirred for 30 min at 0 °C. The solution was then added to com-

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pound **4** (1.547 g, 5.23 mmol) and the mixture was stirred for 18 h at room temperature under nitrogen. After addition of CH_2Cl_2, the mixture was neutralized with $NaHCO_3$ and filtered, and MeOH was evaporated. The residue was extracted with CH_2Cl_2 and the organic layers were washed with water and dried over Na_2SO_4. Evaporation of the solvent gave compound **5**. Yield: 1.535 g (99 %). Mp. 175–178 °C (toluene). IR ($CHCl_3$): ν = 3230 (NH), 1630 (C=O). ^{1}H-NMR: δ = 2.22 (3H, s, -$COCH_3$), 3.86 (3H, s, -OCH_3), 4.46 (1H, d, J = 10 Hz, H-12b), 6.83 (1H, d, J_1 = 8.5 Hz, J_2 = 2.5 Hz, H-10), 6.95 (1H, d, J = 2.5 Hz, H-8), 7.25 (1H, d, J = 8.5 Hz, H-11), 9.26 (1H, br s, NH). For the ^{13}C-NMR data, see Figure **1**. MS: m/e = 296 (M^+, 100 %), 295, 281, 253, 186. HR-MS: Found: 296.1531. Calcd for $C_{18}H_{20}N_2O_2$: 296.1525.

Preparation of indoloquinolizidium perchlorate **6**: For two days 1.376 mg of compound **5** (4.65 mmol), 1.36 g of maleic acid, 0.58 g of Pd/C (10 %), and 75 ml of water were refluxed under nitrogen. Pd/C was filtered off from the hot mixture and washed with MeOH. The filtrate was evaporated nearly to dryness, 3.5 ml of saturated aqueous $NaClO_4$ were added and the mixture was shaken for 5 min. After 1 h the mixture was filtered, and the perchlorate salt **6** was washed several times with cold water and Et_2O. Yield: 1.424 g (78 %). Mp. 275.5–278.5 °C (dec., MeOH). IR: ν = (KBr) 3350 (NH), 1700 (C=O), 1630 and 1620 (s, C=C).

Preparation of allylic indoloquinolizidine alcohols **7 a** *and* **7 b**: Sodium borohydride (1.588 g, 41.98 mmol) was added in small portions to the solution of perchlorate salt **6** (402 mg, 1.02 mmol) in aqueous MeOH (MeOH : H_2O, 5 : 2) (0 °C, nitrogen atmosphere) during 30 min. Stirring was continued for 3.5 h at room temperature, after which water was added and MeOH evaporated. The residue was extracted with CH_2Cl_2 and the organic layers were washed with water, dried over Na_2SO_4, filtered and evaporated to yield 241 mg of a mixture of compounds **5**, **7 a**, and **7 b**. The crude product was fractionated by column chromatography (silica, CH_2Cl_2 : MeOH, 95 : 5) to yield compound **5**, alcohol **7 a**, and a mixture of alcohols **7 a** and **7 b**.

Compound **5**: Yield: 118 mg (39 %). For the analytical data, see above.

Compound **7 a**: Yield: 43 mg (14 %). Mp. 198 – 200 °C (EtOH/toluene). IR (KBr): ν = 3350 (NH and OH). ^{1}H-NMR ($CDCl_3$ + 5 drops of MeOH-d_4): δ = 1.21 (3H, d, J = 6.5 Hz, -CHCH_3), 2.98 (1H, br d, J = 16 Hz, H-4α), 3.49 (1H, d, J = 16 Hz, H-4β), 3.78 (3H, c, -OCH_3), 4.22 (1H, q, J = 6.5 Hz, -$CH$$CH_3$), 5.67 (1H, m, -$CH_2$-$CH$=C-), 6.73 (1H, dd, J_1 = 8.5 Hz, J_2 = 2.5 Hz, H-10), 6.88 (1H, d, J = 2.5 Hz, H-8), 7.14 (1H, d, J = 8.5 Hz, H-11), 8.16 (1H, br s, NH). For the ^{13}C-NMR data, see Figure **1**. MS: m/e = 298 (M^+), 297, 200 (100 %), 199. HR-MS: Found: 298.1687. Calcd for $C_{18}H_{22}N_2O_2$: 298.1681.

Compound **7 b** (slightly contaminated with compound **7 a**): Yield: 55 mg (18 %). Amorphous material. IR (KBr): ν = 3350 (NH and OH). ^{1}H-NMR ($CDCl_3$ + 5 drops of MeOH-d_4): δ = 1.29 (3H, d, J = 6.5 Hz, -CHCH_3), 3.01 (1H, br d, J = 16 Hz, H-4α), 3.41 (1H, d, J = 16 Hz, H-4β), 3.82 (3H, s, -OCH_3), 4.16 (1H, q, J = 6.5 Hz, -$CH$$CH_3$), 5.75 (1H, m, -$CH_2$-$CH$=C-), 6.77 (1H, dd, J_1 = 8.5 Hz, J_2 = 2.5 Hz, H-10), 6.91 (1H, d, J = 2.5 Hz, H-8), 7.18 (1H, d, J = 8.5 Hz, H-11), 8.46 (1H, br s, NH). For the ^{13}C-NMR data, see Figure **1**. MS: m/e: 298 (M^+), 297, 200 (100 %), 199. HR-MS: Found: 298.1670. Calcd for $C_{18}H_{22}N_2O_2$: 298.1681.

Preparation of 10-methoxy-16-deformyl-Z-geissoschizine (**8**): Alcohol **7 a** (82 mg, 0.275 mmol), trimethyl orthoacetate (Aldrich, Compound 23, 787-6; 234 mg, 1.95 mmol), acetic acid (2 μl), and 1,4-dioxane (6 ml, Na dried and distilled) were stirred for 72 h at ca. 95 °C and the MeOH that formed was distilled off during the reaction. Dioxane was evaporated, 10 % Na_2CO_3 was added, and the mixture was extracted with CH_2Cl_2. The extracts were washed with water, dried over Na_2SO_4, filtered, and evaporated. The crude product (84 mg) was purified by column chromatography (alumina, CH_2Cl_2 : MeOH, 99.5 : 0.5) to furnish compound **8**. Yield: 63 mg (65 %). Amorphous material. IR ($CHCl_3$): ν = 3390 (NH), 2820, 2760 (Bohlmann bands), 1725 (C=O). ^{1}H-NMR: δ = 1.71 (3H, d, J = 6.5 Hz, =CHCH_3), 3.72 (3H, s, -$COOCH_3$), 3.84 (3H, s, -OCH_3), 5.21 (1H, q, J = 6.5 Hz, =$CH$$CH_3$), 6.78 (1H, dd, J_1 = 8.5 Hz, J_2 = 2.5 Hz, H-11), 6.91 (1H, d, J = 2.5 Hz, H-9), 7.16 (1H, d, J = 8.5 Hz, H-12), 7.84 (1H, br s, NH). For the ^{13}C-NMR data, see Figure **1**. MS: m/e = 354 (M^+, 100 %), 353, 200, 339, 325, 323, 295, 281, 267, 253, 200, 199, 186. HR-MS: Found: 354.1963. Calcd for $C_{21}H_{26}N_2O_3$: 354.1943.

Preparation of 10-methoxy-16-deformyl-Z-geissoschizol (**9**): THF (5 ml, Na dried) was refluxed for 30 min with $LiAlH_4$ (38 mg, 1.00 mmol) and then cooled to 0 °C. A solution of compound **8** (19 mg, 0.053 mmol) in dry THF (3 ml) was added to this suspension during 30 min (0 °C, nitrogen atmosphere). Stirring was continued for 3.5 h at room temperature. Water was

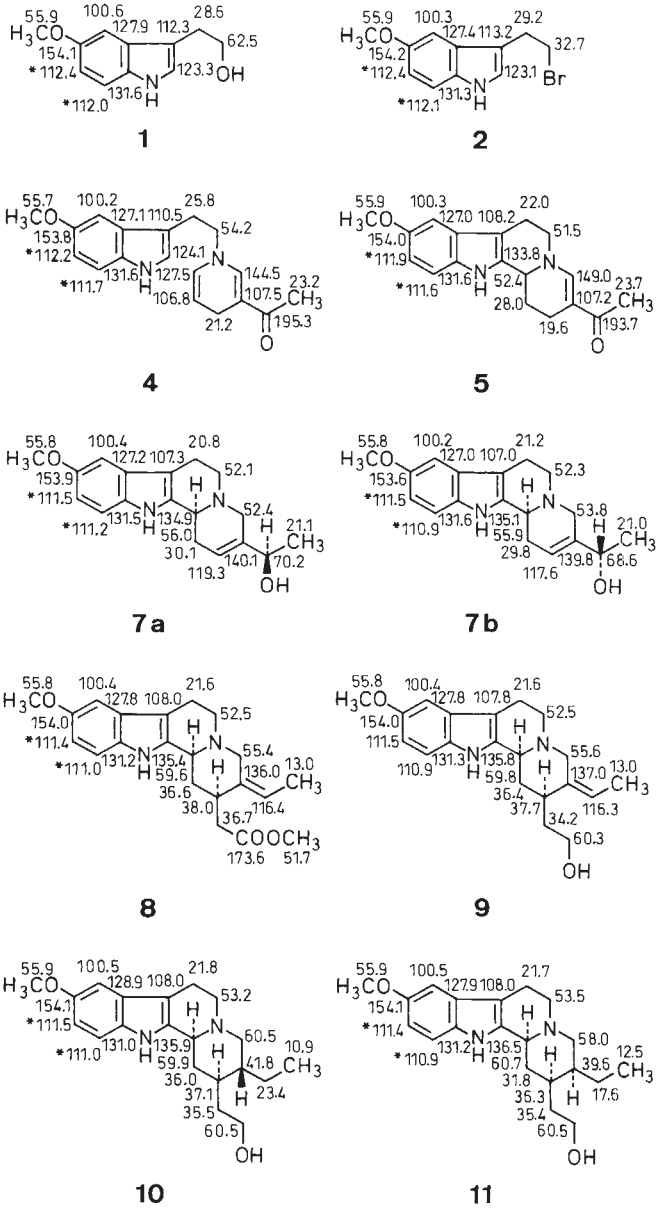
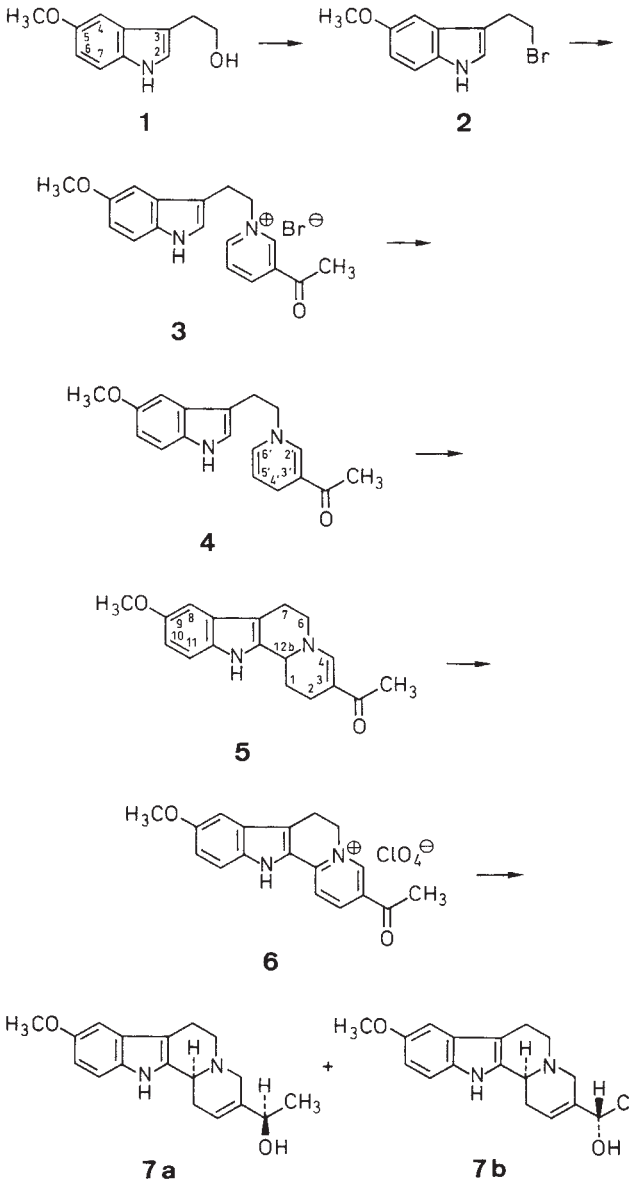


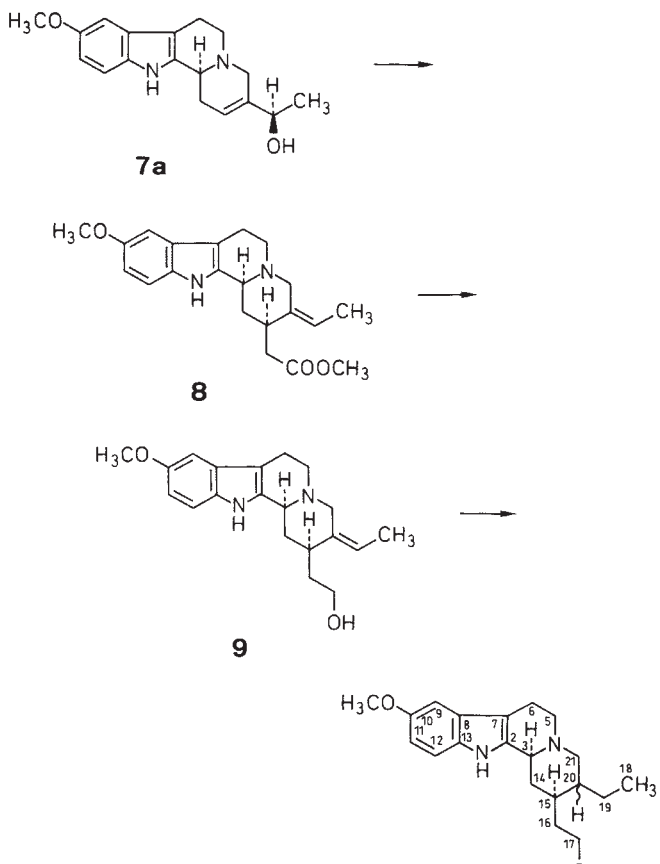
Fig. 1 ^{13}C-NMR Data of compounds **1**, **2**, **4**, **5**, **7 a**, **7 b**, **8**, **9**, **10**, and **11**. Signals marked by an asterisk (*) may be interchanged.

added and the mixture extracted with CH_2Cl_2. The extracts were washed with water, dried over Na_2SO_4, and evaporated. The crude product (22 mg) was purified by column chromatography (alumina, CH_2Cl_2 : MeOH, 98 : 2) to furnish compound **9**. Yield: 16.5 mg (95 %). Amorphous material. IR ($CHCl_3$): ν = 3300 (NH and OH), 2780, 2720 (Bohlmann bands). ^{1}H-NMR: δ = 1.69 (3H, d, J = 6.5 Hz, =CH*CH$_3$*), 3.83 (3H, s, -OCH$_3$), 5.31 (1H, q, J = 6.5 Hz, =*CH*CH$_3$), 6.78 (1H, dd, J_1 = 8.5 Hz, J_2 = 2 Hz, H-11), 6.89 (1H, d, J = 2 Hz, H-9), 7.18 (1H, d, J = 8.5 Hz, H-12), 8.06 (1H, br s, NH). For the ^{13}C-NMR data, see Figure **1**. MS: *m/e* = 326 (M$^+$, 100 %), 325, 281, 270, 255, 199. HR-MS: Found: 326.1982. Calcd for $C_{20}H_{26}N_2O_2$: 326.1994.

Preparation of 10-methoxydihydrocorynantheol (**10**) *and 10-methoxycorynantheidol* (**11**): Compound **9** (28.3 mg, 0.087 mmol) was dissolved in MeOH (5 ml) and 24 mg of $PtO_2 \cdot H_2O$ were added. After 3 h hydrogenation the mixture was filtered and evaporated. The crude product (21.5 mg) was purified by column chromatography (alumina, CH_2Cl_2 : MeOH, 98 : 2) to yield a mixture of alcohols **10** and **11** (15.9 mg, 56 %, ≈ 1 : 1). The mixture was further fractionated by repeated PLC (silica, CH_2Cl_2 : MeOH, 85 : 15).



Scheme 1 Formation of compounds **7 a** and **7 b**.



Scheme 2 Formation of compounds **10** and **11**.

Compound **10** (slightly contaminated with compound **11**). Yield: 2.9 mg (10 %). Amorphous material. ^{1}H-NMR: δ = 0.86 (3H, t, J = 7 Hz, -CH$_2$*CH$_3$*), 3.80 (3H, s, -OCH$_3$), 6.70–6.95 (2H, m, H-9, H-11), 7.22 (1H, d, J = 8.5 Hz, H-12). For the ^{13}C-NMR data, see Figure **1**. MS: *m/e* = 328 (M$^+$, 100 %), 327, 299, 283, 269, 255, 200. HR-MS: Found: 328.2142. Calcd for $C_{20}H_{28}N_2O_2$: 328.2151.

Compound **11** (slightly contaminated with compound **10**). Yield: 2.5 mg (9 %). Amorphous material [lit. (7) amorphous material]. ^{1}H-NMR: δ = 0.90 (3H, t, J = 7 Hz, -CH$_2$*CH$_3$*), 3.82 (3H, s, -OCH$_3$), 6.70–6.95 (2H, m, H-9, H-11), 7.26 (1H, d, J = 8.5 Hz, H-12). For the ^{13}C-NMR data, see Figure **1**. MS: *m/e* = 328 (M$^+$, 100 %), 327, 299, 283, 269, 255, 200. HR-MS: Found: 328.2140. Calcd for $C_{20}H_{28}N_2O_2$: 328.2151.

Results and Discussion

Our starting material, 5-methoxytryptophol (**1**), was transformed by PBr_3 treatment to 5-methoxytryptophyl bromide (**2**). Alkylation of 3-acetylpyridine with compound **2** afforded pyridinium salt **3**, which was transformed to 1,4-dihydropyridine derivative **4** by dithionite reduction. Acid-induced cyclization to indoloquinolizidine **5**, followed by oxidation, afforded indoloquinolizidine salt **6**, which by $NaBH_4$ reduction was transformed to the allylic indoloquinolizidine alcohols **7 a** and **7 b** (Scheme **1**).

Heating of compound **7a** in 1,4-dioxane with trimethyl orthoacetate afforded 10-methoxy-16-deformyl-*Z*-geissoschizine [**8**; biogenetic numbering (8)]. $LiAlH_4$ reduction of this yielded 10-methoxy-*Z*-geissoschizol (**9**), which by catalytic reduction (H_2/PtO_2) led to 10-methoxydihydrocorynantheol (**10**) and 10-methoxycorynantheidol (**11**; Scheme **2**). Comparison of the ^{13}C-NMR data for compounds **7a**, **7b**, **8**, **9**, **10**, and **11** (Figure **1**) with those of earlier experiments (9, 10) taking into account conformational considerations, provided clear evidence of the stereostructures depicted in the formulae.

The results described show that the synthetic methods developed in our laboratory (4, 5, 6) can be applied in the preparation of 10-methoxydihydrocorynantheol (**10**) and 10-methoxycorynantheidol (**11**). Except for the transformation of quinine to compound **10** (2), our synthesis of **10** appears to represent the first total synthesis of this indole alkaloid. It is hoped that the furnished ^{13}C-NMR data will be useful in the future identification of compounds of this type.

References

1 Lounasmaa, M., Tolvanen, A. (1994) in: The Monoterpenoid Indole Alkaloids, (Saxton, J. E., ed.), John Wiley & Sons Ltd, New York, pp. 57–159.

2 Sawa, Y. K., Matsumura, H. (1969) Tetrahedron 25, 5329–5337.

3 Shellard, E. J., Houghton, P. J. (1973) Planta Med. 24, 13–17.

4 Lounasmaa, M., Jokela, R., Tirkkonen, B., Miettinen, J., Halonen, M. (1992) Heterocycles 34, 321–339.
See also, Ziegler, F. E., Sweeny, J. G. (1969) Tetrahedron Lett. 1097–1100.

5 Tirkkonen, B., Miettinen, J., Salo, J., Jokela, R., Lounasmaa, M. (1994) Tetrahedron 50, 3537–3556.
See also, Rackur, G., Stahl, M., Walkowiak, M., Winterfeldt, E. (1976) Chem. Ber. 109, 3817–3824.

6 Hanhinen, P., Nurminen, T., Jokela, R., Lounasmaa, M. (1994) Heterocycles 38, 2027–2044 and references cited therein.

7 Lounasmaa, M., Jokela, R., Tiainen, L.-P. (1990) Tetrahedron 46, 7873–7884.

8 Le Men, J., Taylor, W. I. (1965) Experientia 21, 508–510.

9 Lounasmaa, M., Jokela, R., Hanhinen, P., Miettinen, J., Salo, J. (1994) Tetrahedron 50, 9207–9222.

10 Lounasmaa, M., Jokela, R. (1989) Tetrahedron 45, 3975–3992.