SYNTHESES OF (±)-Z-GEISSOSCHIZOL, (±)-3-EPI-Z-GEISSOSCHIZOL, (±)-CORYNANTHEIDOL, (±)-DIHYDROCORYNANTHEOL, (±)-3-EPI-DIHYDRO-CORYNANTHEOL AND THE CORRESPONDING CORYNAN-17-OIC ACID METHYL ESTERS

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Abstract - The utility of the Claisen rearrangement using carefully separated, diastereoisomeric allylic alcohols (1a) and (1b) in the preparation of (±)-Z-geissoschizol (4a), (±)-3-epi-Z-geissoschizol (4b), (±)-corynantheidol (7a), (±)-dihydrocorynantheol (8a), (±)-3-epi-dihydrocorynantheol (8b) and the corresponding corynan-17-oic acid methyl esters (3a, 3b, 5a, 6a and 6b) is shown. Special attention is paid to the stereochemical outcome of catalytic (PtO_2) hydrogenation of the C(20) Z-ethylidene side chain.

INTRODUCTION

Continuing our efforts on stereoselective preparation of indole alkaloids of corynantheine-type[1,2] we turned to the Claisen rearrangement, known to be highly stereoselective,[3-5] utilizing allylic alcohols (1a) and (1b)[6] together with dimethylacetamide dimethylacetal.[7] The formation, at will, of compounds possessing the C(3)H-C(15)H cis or trans relationship# combined with the

#The biogenetic numbering of Le Men and Taylor[8] is used.

presence of a C(20) Z-ethylidene side chain, catalytically easily reducible, could be expected to provide a short route to compounds possessing the allo-(3α, 15α, 20α), normal-(3α, 15α, 20β), epiallo-(3β, 15α, 20α) and pseudo-(3β, 15α, 20β) configurations.

Ziegler and Sweeny[9] have earlier synthesized dihydrocorynantheol (8a) and 3-epi-dihydrocorynantheol (8b) employing the diastereomeric mixtures of allylic alcohols (1a) and (1b) in Claisen rearrangement with dimethylacetamide dimethylacetal followed by hydrolysis, esterification, $LiAlH_4$ reduction and catalytic hydrogenation. The fact, that Ziegler and Sweeny used in their synthesis the diastereomeric mixtures of compounds (1a) and (1b), does not permit in their case the experimental verification of the expected stereoselectivity of the Claisen rearrangement. Several expected compounds [i.e. Z-geissoschizol (4a) and deformyl-Z-geissoschizine (3a)] were not detected or identified in their reaction mixtures. Moreover, many questions remain concerning the stereochemical outcome of the catalytic hydrogenation of the Z-ethylidene side chain of the formed products.

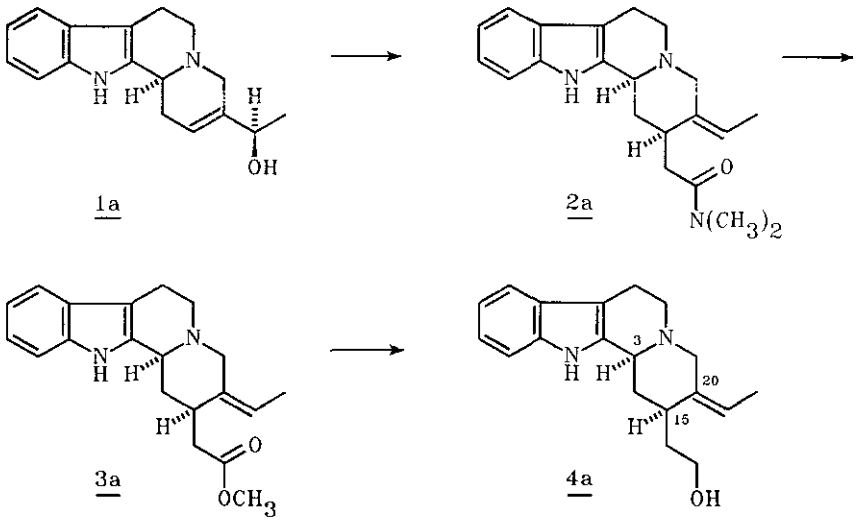
Thus, it seemed to us necessary to execute a careful re-examination of the whole reaction path and put the identification of the formed products on a solid basis. Furthermore, we deemed it interesting to find out if the intermediate corynan-17-oic acid methyl esters [deformyl-Z-geissoschizine (3a) and deformyl-3-epi-Z-geissoschizine (3b)] could be prepared directly using trimethyl orthoacetate[10] instead of dimethylacetamide dimethylacetal in the Claisen rearrangement. The present paper describes our results.

RESULTS AND DISCUSSION

Our first task, in order to take full advantage of the expected high stereoselectivity of the Claisen rearrangement, was to divide carefully our earlier described[11,12] allylic alcohol mixture[6] into its diastereoisomeric

components (1a) and (1b). This was done by successive fractional crystallizations in EtOH (cf. Experimental).

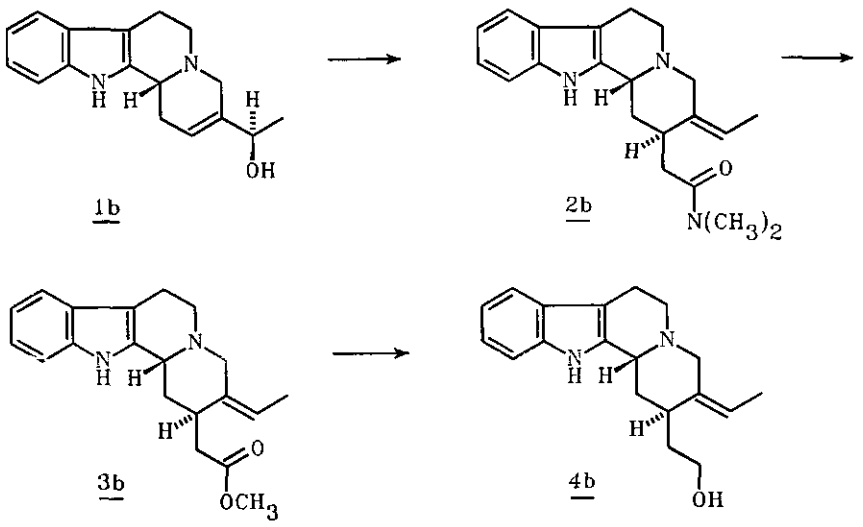
Heating compound (1a) with dimethylacetamide dimethylacetal in dioxane produced the amide (2a) with high stereoselectivity. Alkaline hydrolysis of amide (2a), followed by esterification, yielded unsaturated ester [deformyl-Z-geissoschizine (3a)][#], which was transformed by $LiAlH_4$ reduction to the corresponding alcohol [Z-geissoschizol (4a)] (Scheme 1).



Scheme 1

Similarly, treatment of compound (1b) with dimethylacetamide dimethylacetal yielded amide (2b) with high stereoselectivity. Alkaline hydrolysis and esterification of amide (2b), followed by $LiAlH_4$ reduction of the methyl ester (3b), gave the corresponding alcohol [3-epi-Z-geissoschizol (4b)] (Scheme 2).

[#]Ziegler and Sweeny[9] did not detect ester (3a) in their reaction mixture.



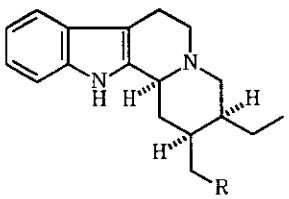
Scheme 2

Thus, the expected high stereoselectivity of the Claisen rearrangement using dimethylacetamide dimethylacetal in the preparation of Z-geissoschizol (4a) and 3-epi-Z-geissoschizol (4b) was experimentally proven.

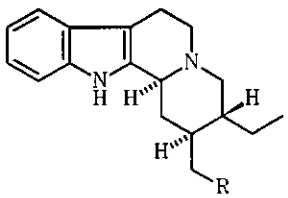
We then turned our attention to the direct transformation of allylic alcohols (1a) and (1b) to the unsaturated esters [deformyl-Z-geissoschizine (3a) and deformyl-3-epi-Z-geissoschizine (3b)], respectively, using trimethyl orthoacetate in the Claisen rearrangement.[10] In both cases the desired unsaturated esters (3a) and (3b) were obtained stereoselectively in high yield. As above, $LiAlH_4$ treatment of the formed unsaturated esters afforded Z-geissoschizols (4a) and (4b).

Catalytic reduction of the ethylidene side chain[13] of the unsaturated esters (3a) and (3b) seemed to be ideally suited for a short and easy preparation of the corresponding saturated esters [(5a) (allo) and (6a) (normal)] and [(5b) (epiallo) and (6b) (pseudo)], respectively. Similarly, reduction of the

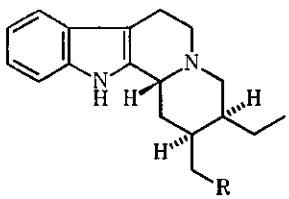
ethylidene side chain of the Z-geissoschizols (4a) and (4b) would at least theoretically give direct access to corynantheidol (7a) (allo) and dihydrocorynantheol (8a) (normal), and 3-epicorynantheidol (7b) (epiallo) and 3-epidihydrocorynantheol (8b) (pseudo), respectively. In analogy with earlier results,[13-15] however, strong stereochemical preferences in the reduction of the ethylidene side chains could be predicted. Moreover, in certain cases epimerizations at C(3) were expected (vide infra).



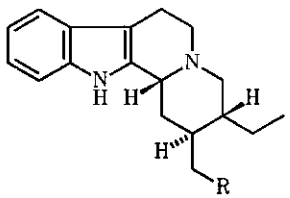
5a R=$COOCH_3$
7a R=CH_2OH



6a R=$COOCH_3$
8a R=CH_2OH



5b R=$COOCH_3$
7b R=CH_2OH



6b R=$COOCH_3$
8b R=CH_2OH

To obtain a clear insight into the outcome of the catalytic reduction of the above compounds (3a, 3b, 4a and 4b), strictly standardized reduction conditions were applied in all cases [H_2 (1 atm.), PtO_2, MeOH, room temperature]. Three different reaction times were used: 1 h, 3 h and 24 h. The results obtained are presented in Tables 1 - 4. The yield percentages given in the Tables are relative (For the absolute yields, see Experimental).

Table 1.

Deformyl-Z-geissoschizine (3a)

Reaction time: 1 h

5a	(allo)	ca. 40%
6a	(normal)	ca. 60%
5b	(epiallo)	traces
6b	(pseudo)	traces

Reaction time: 3 h

5a	(allo)	ca. 35%
6a	(normal)	ca. 65%
5b	(epiallo)	traces
6b	(pseudo)	traces

Reaction time: 24 h

5a	(allo)	ca. 35%
6a	(normal)	ca. 65%
5b	(epiallo)	traces
6b	(pseudo)	traces

Table 2.

Deformyl-3-epi-Z-geissoschizine (3b)

Reaction time: 1 h

7a	(allo)	traces
8a	(normal)	ca. 10%
7b	(epiallo)	traces
8b	(pseudo)	ca. 90%

Reaction time: 3 h

7a	(allo)	traces
8a	(normal)	ca. 25%
7b	(epiallo)	traces
8b	(pseudo)	ca. 75%

Reaction time: 24 h

7a	(allo)	traces
8a	(normal)	ca. 50%
7b	(epiallo)	traces
8b	(pseudo)	ca. 50%

Table 3.

Z-Geissoschizol (4a)

Reaction time: 1 h

7a	(allo)	ca. 45%
8a	(normal)	ca. 55%
7b	(epiallo)	traces
8b	(pseudo)	traces

Table 4.

3-Epi-Z-geissoschizol (4b)

Reaction time: 1 h

7a	(allo)	traces
8a	(normal)	ca. 10%
7b	(epiallo)	traces
8b	(pseudo)	ca. 90%

Table 3 (continued).

Z-Geissoschizol (4a)

Reaction time: 3 h

7a	(allo)	ca. 45%
8a	(normal)	ca. 55%
7b	(epiallo)	traces
8b	(pseudo)	traces

Reaction time: 24 h

7a	(allo)	ca. 40%
8a	(normal)	ca.. 60%
7b	(epiallo)	traces
8b	(pseudo)	traces

Table 4 (continued).

3-Epi-Z-geissoschizol (4b)

Reaction time: 3 h

7a	(allo)	traces
8a	(normal)	ca. 30%
7b	(epiallo)	traces
8b	(pseudo)	ca. 70%

Reaction time: 24 h

7a	(allo)	traces
8a	(normal)	ca. 50%
7b	(epiallo)	traces
8b	(pseudo)	ca. 50%

The results (Tables 1 - 4) clearly indicate that for deformyl-Z-geissoschizine (3a) and Z-geissoschizol (4a) [C(3)H-C(15)H cis relationship] the approach of the hydrogen is nearly equally favourable from both sides of the ethylidene side chain (leading to allo and normal series), whereas for deformyl-3-epi-Z-geissoschizine (3b) and 3-epi-Z-geissoschizol (4b) [C(3)H-C(15)H trans relationship] the reaction leads nearly exclusively to the pseudo structure, which then easily isomerizes to the normal structure. As a further confirmation of this isomerization, carefully purified 3-epi-dihydrocorynantheol (8b) (pseudo) was subjected to the above described catalytic hydrogenation conditions for 48 h. An approximately 60/40 mixture of dihydrocorynantheol (8a) (normal) and 3-epi-dihydrocorynantheol (8b) (pseudo) was obtained.

The ^{13}C nmr data of compounds (1a, 1b, 2a, 2b, 3a, 3b, 4a, 4b, 5a, 6a, 6b, 7a, 8a, and 8b) are given in Figure 1. Comparison of the chemical shifts

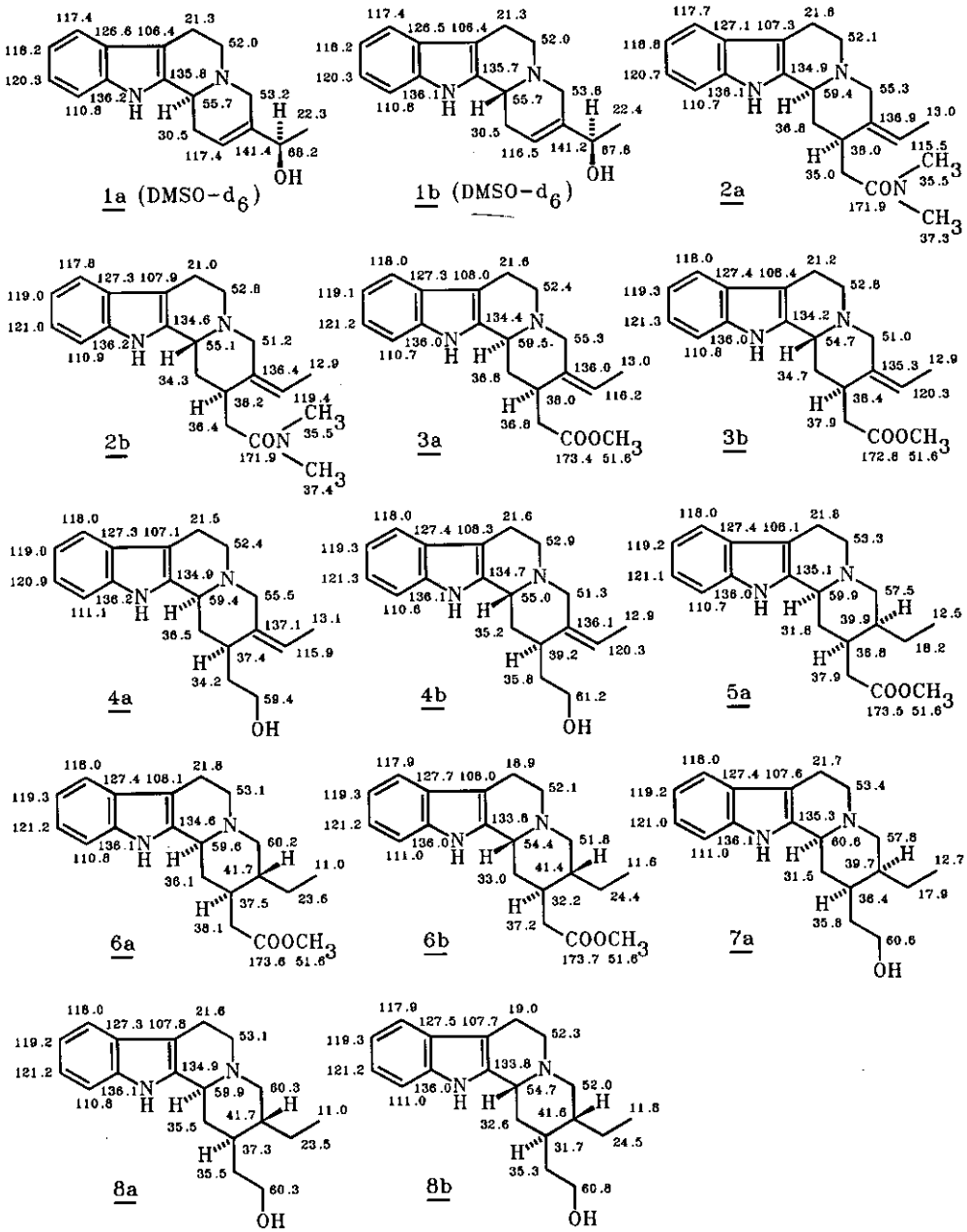


Figure 1

found, taking into account the conformational considerations relevant for indolo[2,3-a]quinolizidines, provides clear evidence of the stereostructures depicted in the formulae. It is hoped that our present and earlier[1,2] ^{13}C nmr data will be useful in resolving future stereochemical problems in the corynantheine series.

CONCLUSIONS

The Claisen rearrangement of allylic alcohols (1a) and (1b) (followed by some mundane transformations) clearly allows an efficient preparation of esters [dehydroxymethyldihydrositsirikine analogues] (5a) (allo), (6a) (normal) and (6b) (pseudo). Similarly, it permits an efficient stereoselective preparation of corynantheidol (7a) (allo), dihydrocorynantheol (8a) (normal) and 3-epi-dihydrocorynantheol (8b) (pseudo). It does not, however, permit the direct preparation of compounds in the epiallo series (compounds 5b and 7b) in any appreciable quantities. We have recently presented an alternative route to 3-epi-corynantheidol (7b).[2]

EXPERIMENTAL

Ir spectra were recorded with a Perkin-Elmer 700 spectrophotometer in $CHCl_3$, if not otherwise stated. Ir absorption bands are expressed in reciprocal centimetres (cm^{-1}). ^1H and ^{13}C nmr spectra were measured with either a Jeol JNM-FX 60 spectrometer working at 59.80 MHz (^1H nmr) and 15.04 MHz (^{13}C nmr) or a Varian Gemini-200 spectrometer working at 199.975 MHz (^1H nmr) and 50.289 MHz (^{13}C nmr). The spectra were recorded in $CDCl_3$, if not otherwise stated. Chemical shift data are given in ppm by reference to TMS (^1H nmr; δ_H = 0.0 ppm) and $CDCl_3$ (^{13}C nmr; δ_C = 77.0 ppm) or DMSO-d_6 (^{13}C nmr; δ_C = 39.5 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 on a Jeol DX 303/DA 5000

instrument.

Separation of the alcohols (1a) and (1b):

The mixture of allylic alcohols (1a) and (1b),[6] prepared according to our earlier described method,[11] was divided into its diastereoisomeric components (1a) and (1b) through successive fractional crystallizations in EtOH. The correct stereochemical choice between alcohols (1a) and (1b) (vide supra) was confirmed by their TLC (silica gel) behaviour. Alcohol (1a) was less polar than alcohol (1b), in good agreement with the results presented by Winterfeldt.[15]

Alcohol (1a): mp 228-229°C (EtOH). Ir (KBr): 3360 (br, NH and OH). ^{1}H Nmr (200 MHz)(DMSO-d_6): 1.19 (3H, d, J=6.4 Hz, -CHC$\underline{H}_3$), 4.12 (1H, q, J=6.4, -C$\underline{H}$CH$_3$), 5.69 (1H, m, -C$\underline{H}$=C), 6.96 (1H, t, J=7.4 Hz, arom. H), 7.04 (1H, t, J=7.4 Hz, arom. H), 7.31 (1H, d, J=7.4 Hz, arom. H), 7.39 (1H, d, J=7.4 Hz, arom. H), 10.78 (1H, br s, NH). Ms: 268 (M^+), 267, 170 (100%), 169; HRms found: 268.1581. Calcd for $C_{17}H_{20}N_2O$: 268.1576.

Alcohol (1b): mp 249-252°C (EtOH). Ir (KBr): 3400 (br, NH and OH). ^{1}H Nmr (200 MHz)(DMSO-d_6): 1.17 (3H, d, J=6.4 Hz, -CHC$\underline{H}_3$), 4.08 (1H, q, J=6.4 Hz, -C$\underline{H}$CH$_3$), 5.67 (1H, m, -C$\underline{H}$=C), 6.93 (1H, t, J=7.4 Hz, arom. H), 7.01 (1H, t, J=7.4 Hz, arom. H), 7.28 (1H, d, J=7.4 Hz, arom. H), 7.36 (1H, d, J=7.4 Hz, arom. H), 10.76 (1H, br s, NH). Ms: 268 (M^+), 267, 170 (100%), 169; HRms found: 268.1579. Calcd for $C_{17}H_{20}N_2O$: 268.1576.

Preparation of amide (2a):

A solution of alcohol (1a) (357 mg, 1.33 mmol) and dimethylacetamide dimethylacetal (0.38 g, 2.86 mmol) in 1,4-dioxane (40 ml) was refluxed for 24 h. Evaporation and purification by flash chromatography (silica gel,

CH_2Cl_2/MeOH:98/2) gave amide (2a) [280 mg (83%)]. mp 209-211°C (toluene) (lit.,[9] 210-213°C). Ir: 3300 (NH), 2830, 2780 (Bohlmann bands), 1630 (C=O). ^{1}H Nmr (60 MHz): 1.70 (3H, d, J=7 Hz, =CHC$\underline{H}_3$), 3.01 (6H, s, -CON(CH_3)$_2$), 5.24 (1H, m, =C$\underline{H}$CH$_3$), 7.02-7.50 (4H, m, arom. H), 8.63 (1H, br s, NH). Ms: 337 (M^+), 265, 252 (100%), 221; HRms found: 337.2178. Calcd for $C_{21}H_{27}N_3O$: 377.2154.

Preparation of amide (2b):

A solution of alcohol (1b) (173 mg, 0.65 mmol) and dimethylacetamide dimethylacetal (0.19 g, 1.43 mmol) in 1,4-dioxane (20 ml) was refluxed for 24 h. Evaporation and purification as described for amide 2a (vide supra), gave amide (2b) [156 mg (72%)]. mp 235-237°C (toluene) (lit.,[9] 234-238°C). Ir: 3300 (NH), 2830, 2780 (Bohlmann bands), 1630 (C=O). ^{1}H Nmr: 1.68 (3H, d, J=7 Hz, =CHC$\underline{H}_3$), 3.00 and 3.06 (2x3H, s, -CON(CH_3)$_2$), 3.81 (1H, br d, J=7.5 Hz, H-3), 5.36 (1H, q, J=7 Hz, =C$\underline{H}$CH$_3$), 7.02-7.50 (4H, m, arom. H), 8.74 (1H, br s, NH). Ms: 337 (M^+), 265, 251 (100%), 221; HRms found: 337.2163. Calcd for $C_{21}H_{27}N_3O$: 377.2154.

Preparation of deformyl-Z-geissoschizine (3a):

A solution of amide (2a) (214 mg, 0.64 mmol) and KOH (10 g, 178.6 mmol) in EtOH (94%, 40 ml) was refluxed for 17 h (Ar atm). The reaction mixture was evaporated in vacuum, and acetyl chloride (20 ml) in MeOH (400 ml) premixed at 0°C during 0.5 h and stirred at 0°C for 0.5 h was carefully added during 20 min at 0°C. The mixture was stirred at rt for 3 d (Ar atm), after which it was neutralized by pouring into a suspension of solid $NaHCO_3$ in CH_2Cl_2. The inorganic salts were filtered off and the filtrate was evaporated. The residue was dissolved in CH_2Cl_2, washed with a saturated $NaHCO_3$ solution and H_2O and dried (Na_2SO_4). Purification by column chromatography (alumina, CH_2Cl_2/MeOH:98/2) yielded deformyl-Z-geissoschizine (3a)[16] [133 mg (65%)]. Amorphous material (lit. 67-68.5°C dec.[17], oil[18]). Ir: 3430 (NH), 2830, 2780

(Bohlmann bands), 1730 (C=O). ^{1}H Nmr (60 MHz): 1.70 (3H, d, J=7 Hz, =CHC<u>H</u>$_3$), 3.77 (3H, s, -CO_2CH_3), 5.23 (1H, q, J=7 Hz, =C<u>H</u>CH_3). 7.09-7.50 (4H, m, arom. H), 8.25 (1H, br s, NH). Ms: 324 (M^+, 100%), 323, 309, 293, 265, 251, 237, 223, 170, 169, 156; HRms found: 324.1838. Calcd for $C_{20}H_{24}N_2O_2$: 324.1838.

<u>Preparation of deformyl-3-epi-Z-geissoschizine (3b):</u>

A solution of amide (<u>2b</u>) (108 mg, 0.32 mmol) with KOH (5 g, 89.3 mmol) in EtOH (94%, 20 ml) was refluxed for 17 h (Ar atm). The reaction mixture was evaporated in vacuum, and acetyl chloride (10 ml) in MeOH (200 ml) premixed at 0°C during 0.5 h and stirred at 0°C for 0.5 h was carefully added during 20 min at 0°C. The mixture was stirred at room temperature for 3 d (Ar atm) and worked-up and purified as described for deformyl-<u>Z</u>-geissoschizine (<u>3a</u>) (<u>vide supra</u>), to yield deformyl-3-epi-<u>Z</u>-geissoschizine (<u>3b</u>)[16] [64 mg (62%)]. Amorphous material (lit.,[18] oil). Ir 3410 (NH), 2830, 2770 (Bohlmann bands), 1730 (C=O). ^{1}H Nmr (60 MHz): 1.70 (3H, d, J=7 Hz, =CHC<u>H</u>$_3$), 3.72 (3H, s, -CO_2CH_3), 5.41 (1H, q, J=7 Hz, =C<u>H</u>CH_3), 7.10-7.50 (4H, m, arom. H), 8.28 (1H, br s, NH). Ms: 324 (M^+, 100%), 323, 309, 293, 265, 251, 237, 223, 170, 169, 156; HRms found: 324.1865. Calcd for $C_{20}H_{24}N_2O_2$: 324.1838.

<u>Preparation of Z-geissoschizol (4a):</u>

A solution of ester (<u>3a</u>) (83 mg, 0.26 mmol) in dry THF (4 ml) was added to a suspension of $LiAlH_4$ (30 mg, 0.79 mmol) in dry THF (5 ml) during 5 min at 0°C (Ar atm). After 2.5 h at room temperature H_2O was added and the mixture was extracted with CH_2Cl_2. The combined organic layers were washed with H_2O and dried (Na_2SO_4). Purification by column chromatography (alumina, CH_2Cl_2/MeOH:98/2) yielded <u>Z</u>-geissoschizol (<u>4a</u>) [67 mg (88%)]. mp 180-182°C ($CHCl_3$). Ir: 3440 (NH), 3300 (OH), 2830, 2780 (Bohlmann bands). ^{1}H Nmr (60 MHz): 1.65 (3H, d, J=6.5 Hz, =CHC<u>H</u>$_3$), 3.56 (2H, m, -CH_2OH), 5.21 (1H, m, =C<u>H</u>CH_3), 7.06-7.52 (4H, m, arom. H), 8.70 (1H, br s, NH). Ms: 296 (M^+, 100%),

295, 265, 251, 170, 169, 156; HRms found: 296.1916. Calcd for $C_{19}H_{24}N_2O$: 296.1890.

Preparation of 3-epi-Z-geissoschizol (4b):

A solution of ester (3b) (72 mg, 0.22 mmol) in dry THF (4 ml) was added to a suspension of $LiAlH_4$ (26 mg, 0.68 mmol) in dry THF during 5 min at 0°C (Ar atm). After 1.5 h at room temperature the mixture was worked-up and purified as described for Z-geissoschizol (4a) (vide supra), to yield 3-epi-Z-geissoschizol (4b) [55 mg (85%)]. mp 191-193°C ($CHCl_3$) (lit.,[9] 193-195°C). Ir: 3400 (br, NH and OH), 2820, 2770 (Bohlmann bands). ^{1}H Nmr (60 MHz): 1.61 (3H, d, J=6.5 Hz, =CHC$\underline{H}_3$), 3.55 (2H, m, -C$\underline{H}_2$OH), 5.28 (1H, m, =C$\underline{H}$CH$_3$), 7.14-7.50 (4H, m, arom. H), 8.34 (1H, br s, NH). Ms: 296 (M^+), 295 (100%), 265, 251, 170, 169; HRms found: 296.1916. Calcd for $C_{19}H_{24}N_2O$: 296.1890.

Catalytic hydrogenation of Z-geissoschizol (4a):

A. Hydrogenation (MeOH, PtO_2, 1 h) of Z-geissoschizol (4a) (50 mg, 0.17 mmol), followed by purification by flash chromatography (silica gel; hexane/EtOAc/MeOH:5/3/0.6, increasing the amount of MeOH during the elution), afforded corynantheidol (7a) (18 mg, 36%), dihydrocorynantheol (8a) (24 mg, 48%), 3-epi-corynantheidol (7b) (traces) and 3-epi-dihydrocorynantheol (8b) (traces).

B. Hydrogenation (MeOH, PtO_2, 3 h) of Z-geissoschizol (4a) (50 mg, 0.17 mmol), followed by purification as above, afforded corynantheidol (7a) (18 mg, 36%), dihydrocorynantheol (8a) (24 mg, 48%), 3-epi-corynantheidol (7b) (traces) and 3-epi-dihydrocorynantheol (8b) (traces).

C. Hydrogenation (MeOH, PtO_2, 24 h) of Z-geissoschizol (4a) (48 mg, 0.16 mmol), followed by purification as above, afforded corynantheidol (7a) (16

mg, 34%) and dihydrocorynantheol (8a) (24 mg, 50%), 3-epi-corynantheidol (7b) (traces) and 3-epi-dihydrocorynantheol (8b) (traces).

Dihydrocorynantheol (8a): mp 178-180°C (CH_2Cl_2) (lit. 178-180.5°C,[9] 181-183°C,[19] 178-181°C,[20] 179-179.5°C[21]). Ir (KBr): 3420 (NH), 3260 (OH). ^{1}H Nmr (60 MHz): 0.88 (3H, t, J=7 Hz, $-CH_2\underline{CH_3}$), 3.68 (2H, t, J=6 Hz, $-\underline{CH_2}OH$), 7.02-7.54 (4H, m, arom. H), 8.52 (1H, br s, NH). Ms: 298 (M^+), 297 (100%), 225, 184, 170, 169, 156; HRms found: 298.2035. Calcd for $C_{19}H_{26}N_2O$: 298.2045.

Corynantheidol (7a): mp 163-165°C (CH_2Cl_2)(lit. 163-165°C,[2] 158-162°C,[22] 158-160°C,[23] 157-159°C,[24] 160-161°C,[25] 162-164°C[26]). Ir: 3400 (br, NH and OH), 2830, 2780 (Bohlmann bands).^{1}H Nmr (60 MHz): 0.91 (3H, t, J=7 Hz, $-CH_2\underline{CH_3}$), 3.72 (2H, t, J=6 Hz, $-\underline{CH_2}OH$), 7.04-7.50 (4H, m, arom. H), 8.10 (1H, br s, NH). Ms: 298 (M^+), 297 (100%), 225, 184, 170, 169, 156; HRms found: 298.2038. Calcd for $C_{19}H_{26}N_2O$: 298.2045.

Catalytic hydrogenation of 3-epi-Z-geissoschizol (4b):

A. Hydrogenation (MeOH, PtO_2, 1 h) of 3-epi-Z-geissoschizol (4b) (56 mg, 0.19 mmol), followed by purification as described for Z-geissoschizol (4a) (vide supra), afforded corynantheidol (7a) (traces), dihydrocorynantheol (8a) (4 mg, 7%), 3-epi-corynantheidol (7b) (traces) and 3-epi-dihydrocorynantheol (8b) (40 mg, 71%).

B. Hydrogenation (MeOH, PtO_2, 3 h) of 3-epi-Z-geissoschizol (4b) (50 mg, 0.17 mmol), followed by purification as above, afforded corynantheidol (7a) (traces), dihydrocorynantheol (8a) (12 mg, 24%), 3-epi-corynantheidol (7b) (traces) and 3-epi-dihydrocorynantheol (8b) (27 mg, 54%).

C. Hydrogenation (MeOH, PtO_2, 24 h) of 3-epi-Z-geissoschizol (4b) (55 mg, 0.19 mmol), followed by purification as above, afforded corynantheidol (7a)

(traces), dihydrocorynantheol (8a) (22 mg, 40%), 3-epi-corynantheidol (7b) (traces) and 3-epi-dihydrocorynantheol (8b) (21 mg, 38%).

3-Epi-dihydrocorynantheol (8b): Amorphous material (lit. mp 84-87°C,[9] amorphous material[25]). Ir: 3300 (br, NH and OH). ^{1}H Nmr (60 MHz): 0.86 (3H, t, J=7 Hz, $-CH_2CH_3$), 3.78 (2H, t, J=6 Hz, $-CH_2OH$), 4.06 (1H, m, H-3), 7.10-7.50 (4H, m, arom. H), 8.15 (1H, br s, NH). Ms: 298 (M^+), 297 (100%), 225, 170, 169, 156; HRms found: 298.2041. Calcd for $C_{19}H_{26}N_2O$: 298.2045.

Epimerization of 3-epi-dihydrocorynantheol (8b) to dihydrocorynantheol (8a):

A mixture of 3-epi-dihydrocorynantheol (8b) (52 mg, 0.17 mmol) and PtO_2 (45 mg) in MeOH (20 ml) was stirred under 1 atm of hydrogen at rt for 48 h. Removal of the catalyst by filtration and evaporation, followed by purification by flash chromatography (silica gel; hexane/EtOAc/MeOH:5/3/0.8, increasing the amount of MeOH during the elution), afforded dihydrocorynantheol (8a)[24 mg (46%)] and 3-epi-dihydrocorynantheol (8b)[16 mg (31%)].

Alternative preparation of deformyl-Z-geissoschizine (3a):

Alcohol (1a) (313 mg, 1.17 mmol) was dissolved in a mixture of trimethyl orthoacetate (1000 mg, 8.33 mmol, freshly distilled), acetic acid (5 μl) and 1,4-dioxane (15 ml, Na dried and distilled). The solution was stirred for 72 h at ca. 95°C and the MeOH that formed was distilled off during the reaction. Dioxane was evaporated, saturated $NaHCO_3$ solution was added and the mixture was extracted several times with CH_2Cl_2. The crude product (341 mg) was purified by column chromatography (alumina, CH_2Cl_2/MeOH:98/2) to give deformyl-Z-geissoschizine (3a) [291 mg (77%)].

Alternative preparation of deformyl-3-epi-Z-geissoschizine (3b):

Alcohol (1b) (115 mg, 0.43 mmol) was dissolved in a mixture of trimethyl orthoacetate (360 mg, 3.00 mmol, freshly distilled), acetic acid (2 µl) and 1,4-dioxane (6 ml, Na dried and distilled). The reaction mixture was treated and worked-up as described for deformyl-Z-geissoschizine (3a) (vide supra). The crude product (121 mg) was purified by column chromatography (alumina, CH_2Cl_2/MeOH:98/2) to give deformyl-3-epi-Z-geissoschizine (3b) [106 mg (76%)].

Catalytic hydrogenation of deformyl-Z-geissoschizine (3a):

A. Hydrogenation (MeOH, PtO_2, 1 h) of deformyl-Z-geissoschizine (3a) (105 mg, 0.32 mmol), followed by purification and fractionation by column chromatography (alumina, CH_2Cl_2/MeOH:99/1), afforded ester (5a) (32 mg, 30%), ester (6a) (47 mg, 44%), ester (5b) (traces) and ester (6b) (traces).

B. Hydrogenation (MeOH, PtO_2, 3 h) of deformyl-Z-geissoschizine (3a) (115 mg, 0.35 mmol), followed by purification and fractionation as above, afforded ester (5a) (32 mg, 28%), ester (6a) (56 mg, 48%), ester (5b) (traces) and ester (6b) (traces).

C. Hydrogenation (MeOH, PtO_2, 24 h) of deformyl-Z-geissoschizine (3a) (123 mg, 0.38 mmol), followed by purification and fractionation as above, afforded ester (5a) (33 mg, 26%), ester (6a) (61 mg, 49%), ester (5b) (traces) and ester (6b) (traces).

Ester (5a): Amorphous material. Ir: 3480 (NH), 2830, 2760 (Bohlmann bands), 1735 (C=O). ^{1}H Nmr (200 MHz): 0.92 (3H, t, J=7.4 Hz, $-CH_2CH_3$, 3.73 (3H, s, $-CO_2CH_3$), 7.09 (1H, t, J=7.4 Hz, arom. H), 7.16 (1H, t, J=7.4 Hz, arom. H), 7.30 (1H, d, J=7.4 Hz, arom. H), 7.47 (1H, d, J=7.4 Hz, arom. H), 7.92 (1H, br s, NH). Ms: 326 (M^+), 325 (100%), 253, 225, 170, 169. HRms found: 326.2013.

Calcd for $C_{20}H_{26}N_2O_2$: 326.1993.

Ester (6a): Amorphous material. Ir: 3320 (NH), 2830, 2770 (Bohlmann bands), 1730 (C=O). ^{1}H Nmr (200 MHz): 0.94 (3H, t, J=7.4 Hz, $-CH_2\underline{CH_3}$), 3.74 (3H, s, $-CO_2\underline{CH_3}$), 7.10 (1H, t, J=7.4 Hz, arom. H), 7.17 (1H, t, J=7.4 Hz, arom. H), 7.31 (1H, d, J=7.4 Hz, arom. H), 7.47 (1H, d, J=7.4 Hz, arom. H), 7.92 (1H, br s, NH). Ms: 326 (M^+), 325 (100 %), 253, 225, 170, 169. HRms found: 326.1983. Calcd for $C_{20}H_{26}N_2O_2$: 326.1993.

Catalytic hydrogenation of deformyl-3-epi-Z-geissoschizine (3b):

A. Hydrogenation (MeOH, PtO_2, 1 h) of deformyl-3-epi-Z-geissoschizine (3b) (120 mg, 0.37 mmol), followed by purification and fractionation as described for deformyl-Z-geissoschizine (3a) (vide supra), afforded ester (5a) (traces), ester (6a) (10 mg, 8%), ester (5b) (traces) and ester (6b) (92 mg, 76%).

B. Hydrogenation (MeOH, PtO_2, 3 h) of deformyl-3-epi-Z-geissoschizine (3b) (106 mg, 0.33 mmol), followed by purification and fractionation as above, afforded ester (5a) (traces), ester (6a) (25 mg, 23%), ester (5b) (traces) and ester (6b) (60 mg, 56%).

C. Hydrogenation (MeOH, PtO_2, 24 h) of deformyl-3-epi-Z-geissoschizine (3b) (122 mg, 0.38 mmol), followed by purification and fractionation as above, afforded ester (5a) (traces), ester (6a) (51 mg, 42%), ester (5b) (traces) and ester (6b) (49 mg, 40%).

Ester (6b): Amorphous material. Ir: 3400 (NH), 1730 (C=O). ^{1}H Nmr (200 MHz): 0.84 (3H, t, J=7.4 Hz, $-CH_2\underline{CH_3}$), 3.73 (3H, s, $-CO_2\underline{CH_3}$), 4.09 (1H, m, H-3), 7.11 (1H, t, J=7.4 Hz, arom. H), 7.19 (1H, t, J=7.4 Hz, arom. H), 7.40 (1H, d, J=7.4 Hz, arom. H), 7.49 (1H, d, J=7.4 Hz, arom. H), 7.94 (1H, br s, NH).

Ms: 326 (M^+), 325 (100%), 253, 225, 170, 169. HRms found: 326.1974. Calcd for $C_{20}H_{26}N_2O_2$: 326.1993.

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