SHORT SYNTHESIS OF 14,15-DIDEHYDRO-*E*-DEPLANCHEINE, PRESUMED BIOSYNTHETIC INTERMEDIATE IN THE FORMATION FROM GEISSOSCHIZINE, OF *CORYNANTHÉ* ALKALOIDS MISSING THE THREE-CARBON UNIT AT C-15

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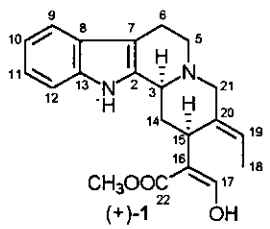
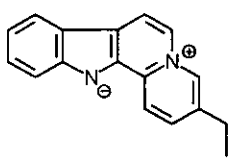
Abstract- A short synthesis of 14,15-didehydro-*E*-deplancheine (**4**) and its *Z*-analogue (**5**) is described.

The carbon skeleton of the indole alkaloids of the *Corynanthé* group, *e.g.* (+)-geissoschizine [(+)-**1**] (biogenetic numbering[1]) usually bears a three-carbon unit (C-16, C-17, and C-22) at the C-15 position. However, in some of these alkaloids {*e.g.* flavopereirine (**2**), (+)-deplancheine [(+)-**3**]} the three-carbon unit is missing.[2]



(+)-**1**



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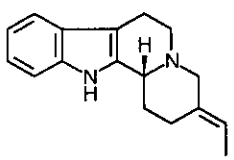
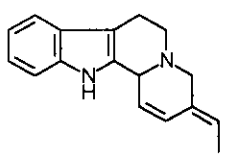


(+)-**3**

In the present paper we describe a short route to 14,15-didehydro-*E*-deplancheine (**4**) and 14,15-didehydro-*Z*-deplancheine (**5**). The former is presumed to be the biosynthetic intermediate in the formation from geissochizine (**1**), of *Corynanthé* alkaloids missing the three-carbon unit at C-15.[3,4]



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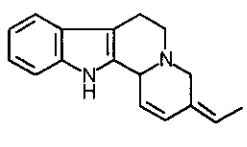
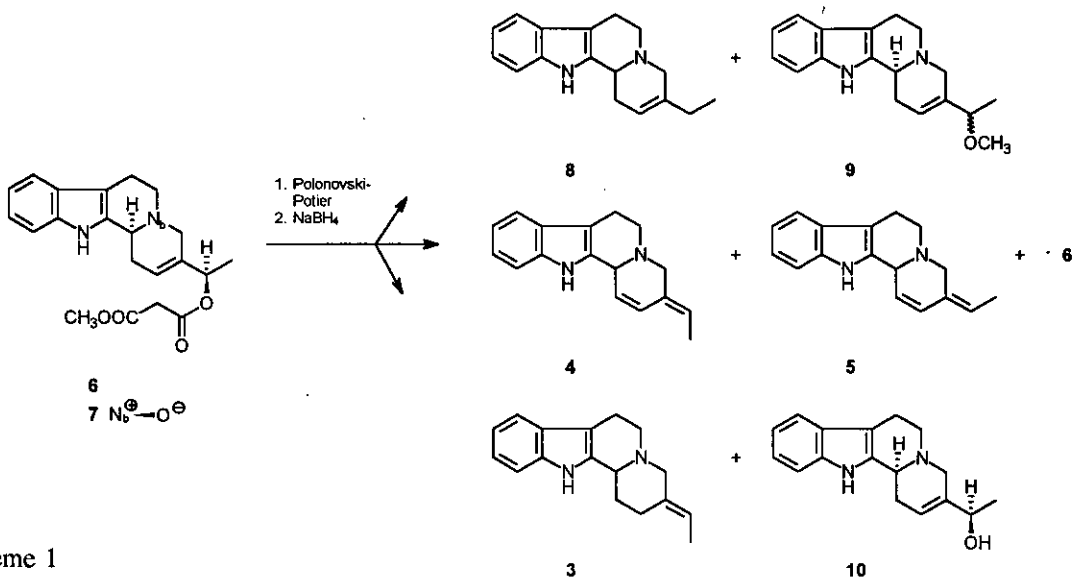


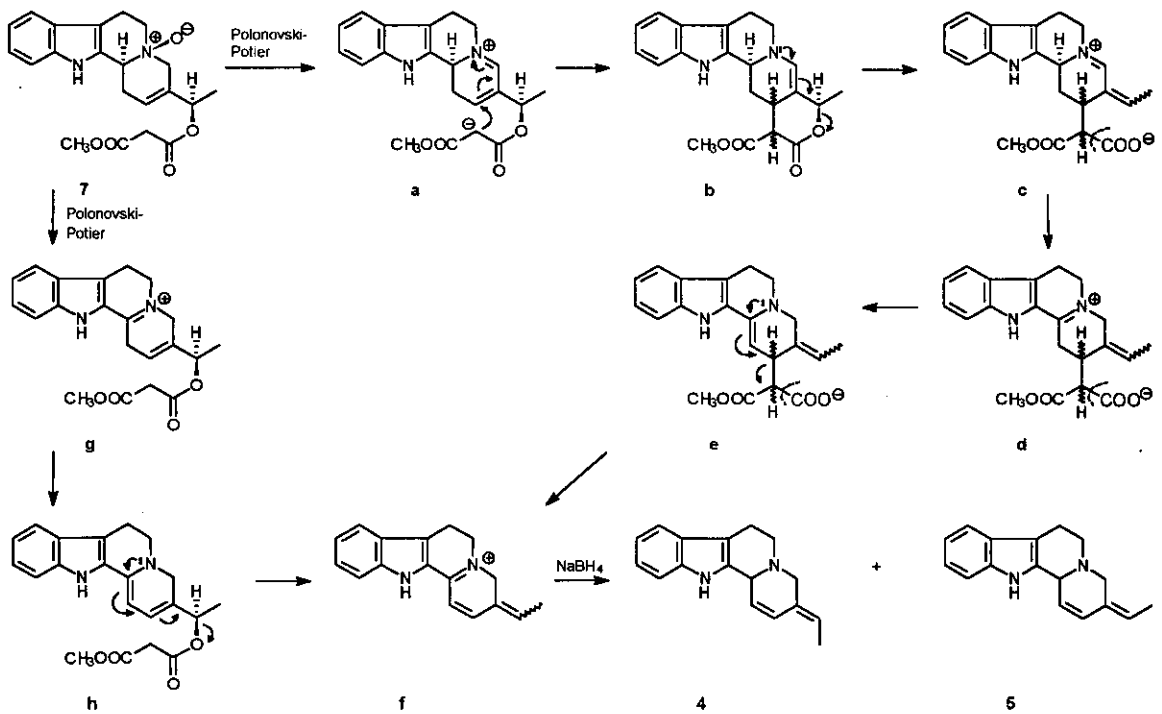
5

N_b-Oxide (**7**),[5] prepared with *m*-CPBA from our recently described monomalonate of allylic alcohol (**6**),[6] was allowed to react with TFAA under Polonovski-Potier conditions. The mixture obtained was treated with $NaBH_4$. After normal work-up, compounds (**4**, **5**), [(**6**) (deoxygenated starting material)], (**8**, **9**), [(**3**) (traces)], and (**10**) were isolated and purified by tlc (Scheme 1).[7]



Scheme 1

The formation of the major compounds (**4**) and (**5**) can be presented in two manners: The Polonovski-Potier reaction of N_b-oxide (**7**) leads to the conjugated iminium ion (**a**). An intramolecular nucleophilic attack takes place and affords the pentacycle (**b**). A *retro*-Mannich reaction follows and yields the iminium ion (**c**). Isomerization of the iminium ion (**c**) to the new iminium ion (**d**),[8] followed by proton

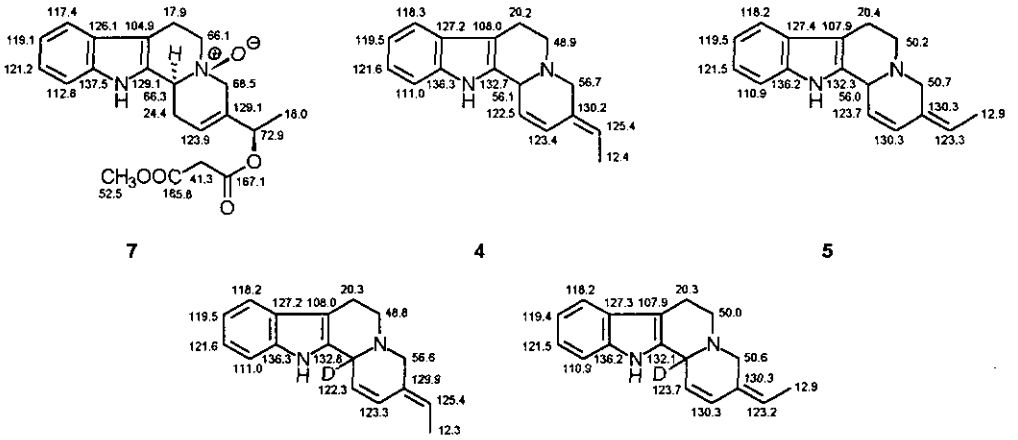


Scheme 2

cleavage, leads to the enamine (**e**), from which a second *retro*-Mannich reaction affords the conjugated iminium ion (**f**). Alternatively, and more likely, the direct formation of the iminium ion (**g**) from N_b-oxide (**7**), followed by proton cleavage, leads to the enamine (**h**), from which a conjugated *retro*-Mannich reaction affords the iminium ion (**f**). $NaBH_4$ reduction completes the formation of compounds (**4**) and (**5**) (Scheme 2).

When the same reaction was carried out using $NaBD_4$ instead of $NaBH_4$, deuterium was exclusively found in the C-3 position of compounds (**4**) and (**5**) (compounds **4**-3-d_1 and **5**-3-d_1), in agreement with the proposed mechanisms.

The spectral data (*cf.* References and Notes, and Figure 1) and earlier results[9] are in full accord with the proposed structures.

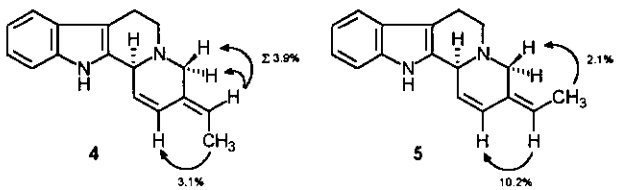


7 **4** **5**

4-3-d_1 **5**-3-d_1

Figure 1

The choice between the C-20 ethylene side chain configurations (*E- versus Z-*) of compounds (**4**) and (**5**) was confirmed by NOE measurements, which gave the following results (Figure 2).



4 **5**

Figure 2.

REFERENCES AND NOTES

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2. M. Lounasmaa and A. Tolvanen, *"The Monoterpenoid Indole Alkaloids"*, ed. by J.E. Saxton, 2nd Edition, Wiley, New York, 1994, pp. 57-159.
3. A.I. Scott, *Bioorg. Chem.*, 1974, **3**, 398. See also, C. Kan-Fan and H.-P. Husson, *Tetrahedron Lett.*, 1980, **21**, 4265.
4. Although naturally occurring (+)-geissoschizine [(+)-**1**] and (+)-deplancheine [(+)-**3**] have turned out to have opposite configurations at C-3,[10] the mechanism proposed by Scott[3] is still applicable for the formation of deplancheine from geissoschizine.

5. **Preparation of the *trans*-N_b-oxide (7).** A solution of compound (**6**)[6] (215.7 mg, 0.59 mmol) and *m*-CPBA (110.7 mg, 0.64 mmol, 1.1 equiv.) in dry CH_2Cl_2 (20 ml) was stirred for 4 h at room temperature (Ar atm). The solvent was evaporated and the crude product was purified by column chromatography (alumina, CH_2Cl_2/MeOH; 99/1, CH_2Cl_2/MeOH; 98/2) to give compound (**7**). Yield: 118.2 mg (53%) (amorphous material). Ir: 1730 cm^{-1} (C=O). ^{1}H-Nmr: δ 1.25 (3H, d, J=6 Hz, -OCH*CH*$_3$), 3.35 (2H, s, OC*H*$_2$CO), 3.73 (3H, s, -O*CH*$_3$), 5.32 (1H, q, J=6 Hz, -O*CH*CH$_3$), 6.80 (1H, br, H-15), 7.0-7.1 (2H, m, H-10, H-11), 7.44 (2H, d, J=8 Hz, H-9, H-12), 11.20 (1H, s, NH). For the ^{13}C-nmr data, see Figure 1. Ms: 384 (M^+), 368, 268, 251, 170 (100%). Anal. Calcd for $C_{21}H_{24}N_2O_5$: C, 65.61; H, 6.29; N, 7.29. Found C, 65.42; H, 6.10; N, 7.14.
6. M. Lounasmaa, P. Hanhinen, and R. Jokela, *Tetrahedron*, 1995, **51**, 8623.
7. **Behaviour of compound (7) in the Polonovski-Potier reaction conditions and in $NaBH_4$ treatment.** A solution of *trans*-*N*-oxide (**7**) (79.7 mg, 0.21 mmol) in dry CH_2Cl_2 (7.0 ml) was cooled to -15 °C and trifluoroacetic anhydride (TFAA) (80 μl, 2.5 equiv.) was added in portions (Ar atm). The reaction mixture was stirred for 2 h at room temperature. The solvent was evaporated and the residue dissolved in MeOH/HCl_{aq} [7.0 ml MeOH + 10 μl HCl (16%)]. The mixture was stirred for 2 h at room temperature. $NaBH_4$ (47.5 mg, 1.25 mmol, 6 equiv.) was added to the mixture in small portions at -2 °C during 15 min (Ar atm). The mixture was stirred at room temperature overnight. H_2O (12 ml) was added, MeOH evaporated, and the mixture extracted with CH_2Cl_2. The crude product (68.7 mg) was fractionated by plc (silica gel, CH_2Cl_2/MeOH; 95/5).
   Compound (**6**). Yield: 2.0 mg (3%). For analytical data, see ref. 6.
   Compound (**8**). Yield: 5.1 mg (10%). For analytical data, see ref. 9.
   Compound (**9**). Yield: 4.4 mg (8%). For analytical data, see ref. 9.
   Compound (**5**). Yield: 14.8 mg (29%) (amorphous material). ^{1}H-Nmr: δ 1.71 (3H, d, J=7 Hz, =CH*CH*$_3$), 3.43 (1H, d, J=14 Hz, H-21α), 3.76 (1H, d, J=14 Hz, H-21β), 4.51 (1H, br s, H-3), 5.47 (1H, q, J=7 Hz, =*CH*CH$_3$), 5.82 (1H, br d, J=10 Hz, H-14), 6.21 (1H, dd, J_1=10, J_2=1 Hz, H-15), 7.09 (1H, t, J=7 Hz, H-10), 7.12 (1H, t, J=7 Hz, H-11), 7.30 (1H, d, J=7 Hz, H-12), 7.47 (1H, d, J=7 Hz, H-9), 8.07 (1H, br s, NH). For the ^{13}C-nmr data, see Figure 1. Ms: 250 (M^+, 100%), 249, 235, 170, 169. Anal. Calcd for $C_{17}H_{18}N_2$: C, 81.56; H, 7.25; N, 11.19. Found C, 81.32; H, 7.18; N, 11.02.
   Compound (**4**). Yield: 6.5 mg (13%) (amorphous material). ^{1}H-Nmr: δ 1.72 (3H, d, J=7 Hz, =CH*CH*$_3$), 3.49 (2H, def., H-21α, H-21β), 4.65 (1H, br s, H-3), 5.37 (1H, q, J=7 Hz, =*CH*CH$_3$), 5.92 (1H, br d, J=10 Hz, H-14), 6.58 (1H, dd, J_1=10 Hz, J_2=1 Hz, H-15), 7.06 (1H, t, J=7 Hz, H-10), 7.10 (1H, t, J=7 Hz, H-11), 7.30 (1H, d, J=7 Hz, H-12), 7.45 (1H, d, J=7 Hz, H-9), 8.17 (1H, br s, NH). For the ^{13}C-nmr data, see Figure 1. Ms: 250 (M^+, 100%), 249, 235, 170, 169. Anal. Calcd for $C_{17}H_{18}N_2$: C, 81.56; H, 7.25; N, 11.19. Found C, 81.34; H, 7.12; N, 10.98.
   Compound (**3**). Yield: Traces. For analytical data, see ref. 9.
   Compound (**10**). Yield: 3.9 mg (7%). For analytical data, see ref. 9.
   Replacement of $NaBH_4$ with $NaBD_4$ in the above procedure:
   Compound (**5**-3-d_1). Yield: 14.1 mg (28%) (amorphous material). ^{1}H-Nmr: As for compound (**5**) (δ 4.51 was absent). For the ^{13}C-nmr data, see Figure 1. Ms: 251 (M^+, 100%), 250, 249, 236, 235, 171, 170, 169. HRms: Found: 251.1527. Calcd for $C_{17}H_{17}DN_2$: 251.1532.
   Compound (**4**-3-d_1). Yield: 7.0 mg (14%) (amorphous material). ^{1}H-Nmr: As for compound (**4**) (δ 4.65 was absent). For the ^{13}C-nmr data, see Figure 1. Ms: 251 (M^+, 100%), 250, 249, 236, 235, 171, 170, 169. HRms: Found: 251.1537. Calcd for $C_{17}H_{17}DN_2$: 251.1532.
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10. A.I. Meyers, T. Sohda, and M.F. Loewe, *J. Org. Chem.*, 1986, **51**, 3108.

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