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# Short Synthetic Route to (±)-Geissoschizine

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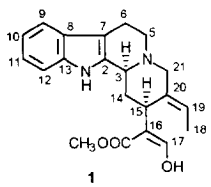
**Abstract** - A short synthetic route to (±)-geissoschizine **1** is described.


Geissoschizine **1**, a tetracyclic indole alkaloid, was first isolated by Chatterjee *et al.*[1] from *Rhazia stricta* (Decaisne) and by Janot *et al.*[2] from *Bonafousia tetrastachya* (Humboldt, Bonpland et Kunth) Markgraf [renamed *Bonafousia siphilitica* (L. f.) L. Allorge, *comb. nov.* by Allorge[3] and *Tabernaemontana siphilitica* (L. f.) Leeuwenberg, *comb. nov.* by Leeuwenberg[4]]. Later it was found in several other plants, including *Rauwolfia vomitoria* and *Melodinus phylliraeoides*.[5] Before its direct isolation from natural sources geissoschizine **1** was known as a hydrolysis product of geissospermine.[6,7]



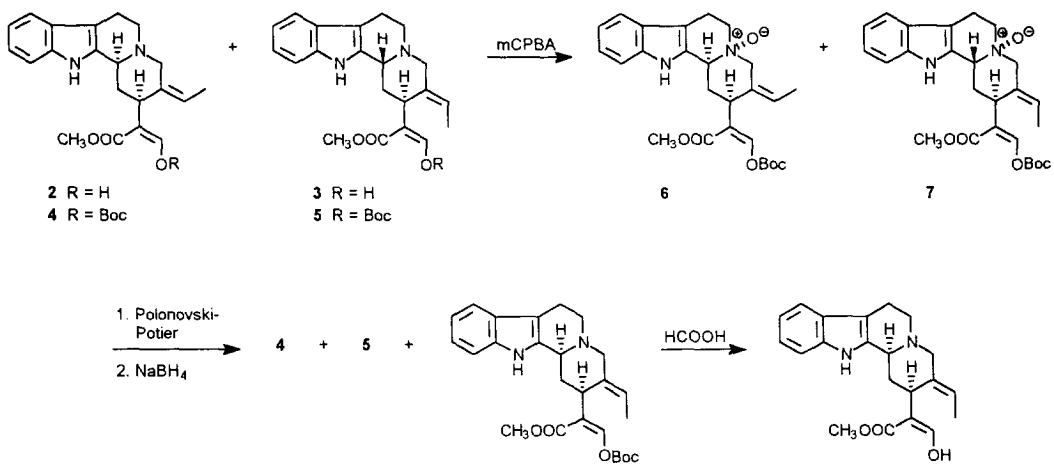

**1**

## RESULTS AND DISCUSSION

Several syntheses (total or partial) of geissoschizine **1** (biogenetic numbering[8]) have been presented,[5,9,10] but they are generally relatively long and tedious. We have developed a short synthetic route, which permits an easy access to this important indole alkaloid.

Our recently described,[11] easily accessible mixture of (±)-*Z*-geissoschizine **2** and (±)-3-epi-*E*-geissoschizine **3** [called and presented as (±)-15-epi-*E*-geissoschizine in Ref. 11] was treated with $(Boc)_2O$ (1.1 equiv.), which transformed it to a mixture of mono-Boc derivatives **4** (major) and **5** (minor). This mixture was then treated with *m*CPBA to afford a mixture of $N_b$-oxides **6** (*cis*)(major) and **7** (assumed to be *trans*)(minor) in 60%

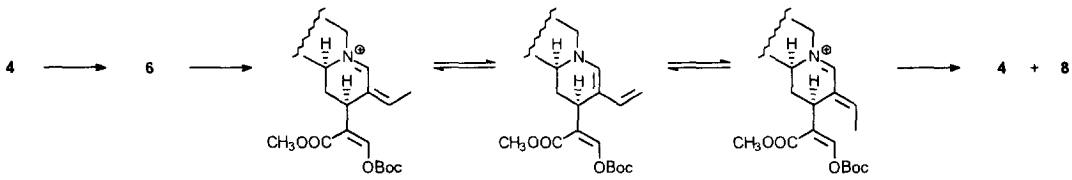
yield.[12] The Polonovski-Potier reaction[13] carried out on the mixture, followed by $NaBH_4$-treatment, gave (±)-*O*-Boc-*Z*-geissoschizine **4**, (±)-*O*-Boc-3-epi-*E*-geissoschizine **5**, and (±)-*O*-Boc-*E*-geissoschizine **8** in 85% yield. Compound **8**, obtained in about 20% yield, could be easily separated (*Cf.* Experimental). The remaining mixture of compounds **4** and **5** was recyclized twice, permitting the total yield of compound **8** to increase to about 40%. Treatment of compound **8** [containing already a small amount of (±)-*E*-geissoschizine **1**] with HCOOH afforded (±)-*E*-geissoschizine **1**[14] in nearly quantitative yield (Scheme 1).




Scheme 1.

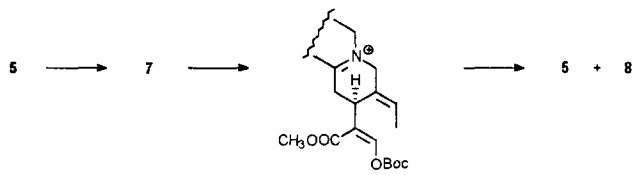
Two mechanisms, both leading to the desired (±)-O-Boc-*E*-geissoschizine **8** (and to the recyclable compounds **4** and **5**) seem to be operating:

In the case of compound **4**, the *cis*-$N_b$-oxide **6** formed from it leads in the Polonovski-Potier reaction conditions mainly to the iminium derivative **9**, which is in equilibrium *via* **10** with **11**. Treatment of the equilibrium mixture (**9** ⇄ **10** ⇄ **11**) with $NaBH_4$ affords (±)-*O*-Boc-*Z*-geissoschizine **4** and (±)-*O*-Boc-*E*-geissoschizine **8** (Scheme 2).




Scheme 2.

In the case of compound **5**, the *trans*-$N_b$-oxide **7** that forms leads in the Polonovski-Potier reaction conditions mainly to the iminium derivative **12**. Treatment of the iminium derivative **12** with $NaBH_4$ affords (±)-*O*-Boc-3-epi-*E*-geissoschizine **5** and (±)-*O*-Boc-*E*-geissoschizine **8** (Scheme 3).




12

Scheme 3.

The main part of compound **8** is formed as depicted in Scheme 2.

In order to verify simultaneously operating mechanisms that have been proposed, the mono-Boc derivatives **4** and **5** were fractionated and separately transformed to the corresponding $N_b$-oxides [**6** (*cis*); **7** (*trans*) (traces)]. The Polonovski-Potier reaction, carried out on **6** afforded, as expected, compounds **4** and **8** (Scheme 2).

The analytical data of compounds **1** and **4** - **8** (Experimental and Figure 1) are in good agreement with the proposed structures.[14]

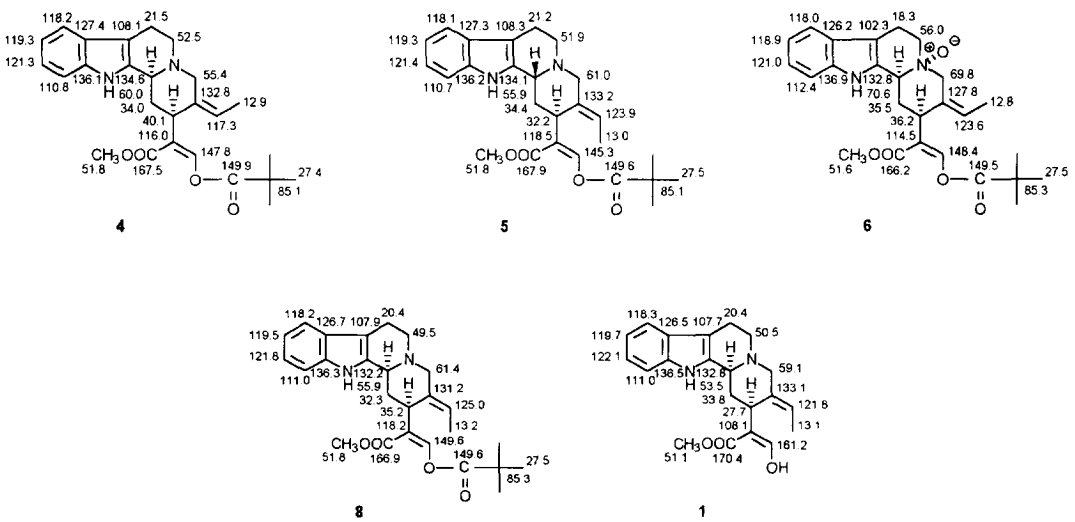



Figure 1. $^{13}$C-nmr data of compounds **4-6**, **8**, and **1** (*Cf.* Ref. 15 and Note 16).

## CONCLUSIONS

A short synthetic route, which permits an easy access to (±)-*E*-geissoschizine **1** in about 20% overall yield from readily available starting material (mixture of compounds **2** and **3**)[11], has been developed.

## EXPERIMENTAL

Ir spectra were recorded with a Perkin-Elmer 700 IR spectrophotometer using $CHCl_3$ as solvent. Ir absorption bands are expressed in reciprocal centimetres ($cm^{-1}$). $^1H$- and $^{13}C$-nmr spectra were measured with either a Varian Gemini-200 spectrometer working at 199.975 MHz ($^1H$-nmr) and 50.289 MHz ($^{13}C$-nmr) or with a Varian Unity-400 NMR spectrometer working at 399.952 MHz ($^1H$-nmr) and 100.577 MHz ($^{13}C$-nmr). $CDCl_3$ was used as solvent. Chemical shifts are given in ppm by reference to TMS ($^1H$-nmr; $\delta_H$=0.00 ppm) and $CDCl_3$ ($^{13}C$-nmr; $\delta_C$=77.00 ppm). Abbreviations s, d, t, q, m, def and br are used to designate singlet, doublet, triplet, quartet, multiplet, deformed and broad, respectively. Mass spectrometry was done on a Jeol DX 303/DA 5000 instrument.

**Preparation of *O*-Boc-*Z*-geissoschizine 4 and *O*-Boc-3-epi-*E*-geissoschizine 5:** A mixture[11] of compounds **2** and **3** (227.3 mg, 0.65 mmol), di-*tert*-butyl dicarbonate [$(Boc)_2O$] (149.8 mg, 0.69 mmol, 1.1 equiv.), and *p*-dimethylaminopyridine (DMAP) (8.4 mg, 0.07 mmol, 0.1 equiv.) in dry $CH_2Cl_2$ (10 ml) was stirred at room temperature for 3 h (Ar atm). Evaporation and purification by column chromatography (silica, $CH_2Cl_2$/MeOH, 99/1) gave a mixture of compounds **4** and **5**. Y. 261.2 mg (90%). Analytical samples were obtained by PLC (silica, $CH_2Cl_2$/MeOH, 94/6).

Compound **4**. Amorphous material. IR: 1760, 1715 (C=O). $^1H$ NMR (200 MHz, $CDCl_3$): 1.49 [9H, s, $-C(CH_3)_3$], 1.66 (3H, d, J=6 Hz, H-18), 2.02 (1H, ddd, $J_1$=12 Hz, $J_2$=2 Hz, $J_3$=2 Hz, H-14α), 2.37 (1H, ddd, $J_1$=12 Hz, $J_2$=12 Hz, $J_3$=12 Hz, H-14β), 3.72 (3H, s, $-COOCH_3$), 3.93 (1H, d, J=13 Hz, H-21β), 5.08 (1H, q, J=6 Hz, H-19), 7.04-7.20 (2H, m, H-10, H-11), 7.29 (1H, d, J=8 Hz, H-12), 7.48 (1H, d, J=8 Hz, H-9), 7.94 (1H, br s, NH), 8.25 (1H, s, H-17). $^{13}C$ NMR (50 MHz, $CDCl_3$): See Figure 1. MS (EI, *m/z*): 452 ($M^+$), 396, 395, 352, 351, 335, 323, 295, 251, 249, 237, 184, 171, 170, 169 (100%), 156. HRms: Found: 452.2305. Calcd for $C_{26}H_{32}N_2O_5$: 452.2311.

Compound **5**. Amorphous material. IR: 1760, 1720 (C=O). $^1$H NMR (200 MHz, $CDCl_3$): 1.55 [9H, s, $-C(CH_3)_3$], 1.60 (3H, d, J=6 Hz, H-18), 1.96 (1H, m, H-14$\beta$), 2.38 (1H, br d, J=12 Hz, H-14$\alpha$), 3.36 (1H, d, J=13 Hz, H-21$\alpha$), 3.76 (3H, s, $-COOCH_3$), 4.12 (1H, d, J=6.5 Hz, H-15), 5.53 (1H, q, J=6 Hz, H-19), 7.04-7.20 (2H, m, H-10, H-11), 7.26 (1H, d, J=8 Hz, H-12), 7.47 (1H, d, J=8 Hz, H-9), 7.95 (1H, br s, NH), 8.05 (1H, s, H-17). $^{13}$C NMR (50 MHz, $CDCl_3$): See Figure 1. MS (EI, *m/z*): 452 ($M^+$), 396, 395, 352, 351, 335, 323, 295, 251 (100%), 249, 237, 184, 171, 170, 169, 156. HRms: Found: 452.2291. Calcd for $C_{26}H_{32}N_2O_5$: 452.2311.

**Preparation of *O*-Boc-*Z*-geissoschizine *cis*-$N_b$-oxide 6 and *O*-Boc-3-epi-*E*-geissoschizine *trans*-$N_b$-oxide 7:**

A mixture of compounds **4** and **5** (196.2 mg, 0.43 mmol) and *m*-chloroperbenzoic acid (*m*-CPBA, 25% $H_2O$) (167.7 mg, 0.97 mmol, 2.2 equiv.; dried with $Na_2SO_4$) in dry $CH_2Cl_2$ (10 ml) was stirred at room temperature for 3 h (Ar atm). Normal work-up and purification by column chromatography (silica, $CH_2Cl_2$/MeOH, 98/2) gave a mixture of compounds **6** and **7**. Y. 120.7 mg (60%). Analytical samples were obtained by PLC (silica, $CH_2Cl_2$/MeOH, 90/10).

Compound **6**. Amorphous material. IR: 1765, 1715 (C=O). $^1$H NMR (200 MHz, $CDCl_3$): 1.56 [9H, s, $-C(CH_3)_3$], 1.65 (3H, d, J=6 Hz, H-18), 3.64 (3H, s, $-COOCH_3$), 3.90 (1H, m, H-3), 4.33 (1H, d, J=13 Hz, H-21$\beta$), 5.16 (1H, q, J=6 Hz, H-19), 6.98-7.08 (2H, m, H-10, H-11), 7.14 (1H, m, H-12), 7.54 (1H, m, H-9), 8.17 (1H, s, H-17), 11.79 (1H, br s, NH). $^{13}$C NMR (50 MHz, $CDCl_3$): See Figure 1. MS (EI, *m/z*): 468 ($M^+$, <2%), 452, 395, 368, 367, 352, 330, 329, 295, 293, 292, 271, 251, 249, 247, 170, 169 (100%), 156.

Compound **7**. Amorphous material (not very stable). $^1$H NMR (200 MHz, $CDCl_3$): 1.56 [9H, s, $-C(CH_3)_3$], 1.64 (2H, d, J=6 Hz, H-18), 3.79 (3H,s, $-COOCH_3$), 4.05 (1H, d, J=13 Hz, H-21$\alpha$), 4.82 (1H, d, J=12 Hz, H-3), 5.73 (1H, q, J=6 Hz, H-19), 7.0-7.2 (3H, m, H-10, H-11, H-12), 7.53 (1H, d, J=8 Hz, H-9), 7.90 (1H, s, H-17). MS (EI, *m/z*): 468 ($M^+$, <2%), 452, 395, 368, 367, 352, 330, 295, 293, 251, 249, 247, 170, 169 (100%), 156.

**Preparation of *O*-Boc-*Z*-geissoschizine 4 *O*-Boc-3-epi-*E*-geissoschizine 5 and *O*-Boc-*E*-geissoschizine 8:**

A mixture of compounds **6** and **7** (116.3 mg, 0.25 mmol) in dry $CH_2Cl_2$ (5 ml) was cooled to -16°C and trifluoroacetic anhydride (TFAA) (90 $\mu$l, 0.64 mmol, 2.5 equiv.) was added in portions during 5 min (Ar atm). The reaction mixture

was stirred for 2 h, with the temperature kept at 0°C. The solvent was evaporated and the residue dissolved in MeOH (2 ml). The mixture was stirred for 2 h at room temperature. $NaBH_4$ (58.2 mg, 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. $H_2O$ (10 ml) was added, MeOH evaporated, and the mixture extracted with $CH_2Cl_2$. The crude product was fractionated by PLC (silica, $CH_2Cl_2$/MeOH, 95/5) to yield a mixture of compounds **4** and **5** [Y. 73.5 mg (65%)], and compound **8** (containing traces of compound **1**)[ Y. 22.6 mg (20%)].

Compounds **4** and **5**. For the analytical data, see above.

Compound **8**. Amorphous material. IR: 1740, 1700 (C=O). $^1$H NMR (200 MHz, $CDCl_3$): 1.51 (3H, d, J=6 Hz, H-18), 1.55 [9H, s, $-C(CH_3)_3$], 2.03 (1H, br d, J=12 Hz, H-14$\beta$), 2.36 (1H, ddd, $J_1$=12 Hz, $J_2$=12 Hz, $J_3$=12 Hz, H-14$\alpha$), ≈3.7 (partly masked)(1H, d, J≈13 Hz, H-21$\beta$), 3.72 (3H, s, $-COOCH_3$), 3.99 (1H, d, J=12 Hz, H-3), 5.54 (1H, q, J=6 Hz, H-19), 7.07 (1H, t, J=8 Hz, H-10), 7.13 (1H, t, J=8 Hz, H-11), 7.29 (1H, d, J=8 Hz, H-12), 7.44 (1H, d, J=8 Hz, H-9), 8.10 (1H, s, H-17). $^{13}$C NMR (50 MHz, $CDCl_3$): See Figure 1. MS (EI, *m/z*): 452 ($M^+$), 396, 352, 351, 323, 251 (100%), 249, 237, 184, 171, 170, 169, 156. HRms: Found: 452.2299. Calcd for $C_{26}H_{32}N_2O_5$: 452.2311.

**Preparation of *E*-geissoschizine 1:**

A solution of compound **8** (containing traces of compound **1**) (7.9 mg, 0.02 mmol) in HCOOH (1 ml) was stirred at room temperature for 2 h (Ar atm). The mixture was evaporated and dissolved in $CH_2Cl_2$. Normal work-up gave compound **1**. Y. 7.4 mg (≈100%).

Compound **1**. Mp. 188-189°C (EtOH) (lit. mp. 187-189°C[17], 186-188°C[18], 189-190°C[19]). IR: 1700 (C=O). $^1$H NMR (400 MHz, $CDCl_3$): 1.82 (3H, d, J=7 Hz, H-18), 2.11 (1H, ddd, $J_1$=13.5 Hz, $J_2$=11.5 Hz, $J_3$=1.5 Hz, H-14$\beta$), 2.64 (1H, ddd, $J_1$=13.5 Hz, $J_2$=11.5 Hz, $J_3$=6 Hz, H-14$\alpha$), 2.72 (1H, ddd, $J_1$=11.5 Hz, $J_2$=11.5 Hz, $J_3$=4 Hz, H-5$\alpha$), 2.81 (1H, br dd, $J_1$=15.5 Hz, $J_2$=4 Hz, H-6$\beta$), 3.06 (1H, dddd, $J_1$=15.5 Hz, $J_2$=11.5 Hz, $J_3$=5.5 Hz, $J_4$=2 Hz, H-6$\alpha$), 3.17 (1H, d, J=13.5 Hz, H-21$\alpha$), 3.21 (1H, dd, $J_1$=11.5 Hz, $J_2$=5.5 Hz, H-5$\beta$), 3.67 (3H, s, $-COOCH_3$), 3.84 (1H, br dd, $J_1$=11.5 Hz, $J_2$=6 Hz, H-3), 3.95 (1H, ddd, $J_1$=13.5 Hz, $J_2$=2.5 Hz, $J_3$=2.5 Hz, H-21$\beta$), 4.48 (1H, dd, $J_1$=11.5 Hz, $J_2$=1.5 Hz, H-15), 5.40 (1H, q, J=6 Hz, H-19), 7.10 (1H, t, J=8 Hz, H-10), 7.16 (1H, t, J=8 Hz, H-11), 7.32 (1H, d, J=8 Hz, H-12), 7.47 (1H, d, J=8 Hz, H-9), 7.84 (1H, s, H-17), 7.98 (1H, br s, NH) (*Cf.* Ref. 15). $^{13}$C NMR (100 MHz, $CDCl_3$): See

Figure 1 (*Cf.* Ref. 15). MS (EI, *m/z*): 352 ($M^+$, 100%), 351, 324, 323, 251, 249, 237, 184, 171, 170, 169, 156 (*Cf.* Ref. 1). HRms: Found: 352.1790 Calcd for $C_{21}H_{24}N_2O_3$: 352.1787.

**Preparation of *O*-Boc-*Z*-geissoschizine 4 and *O*-Boc-*E*-geissoschizine 8:** A solution of compound **6** (11.6 mg, 0.025 mmol) in dry $CH_2Cl_2$ (0.5 ml) was cooled to -16°C and trifluoroacetic anhydride (TFAA) (9 µl, 0.064 mmol, 0.25 equiv.) was added in portions during 5 min (Ar atm). The reaction mixture was stirred for 2 h, with the temperature kept at 0°C. The solvent was evaporated and the residue dissolved in MeOH (0.2 ml). The mixture was stirred for 2 h at room temperature. $NaBH_4$ (5.8 mg, 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. Normal work-up gave compounds **4** and **8**, which were fractionated by PLC (silica, $CH_2Cl_2$/MeOH, 95/5).
Compound **4**. For the analytical data, see above.
Compound **8**. For the analytical data, see above.

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