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Synthesis of the Racemates of the β-Carboline Alkaloid Chrysotricine and its Diastereomer[a]

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Summary. The racemates of the rubiacea alkaloid Chrysotricine (**1**) and its diastereomer are synthesized from the isomeric mixture of linalyl oxides **3** and tryptamine in six steps, followed by separation of the diastereomers.

Keywords. Alkaloids; β-Carboline; Chrysotricine; Hydroborations.

Introduction

The β-carboline alkaloid (+)-chrysotricine (**1**) has been isolated from the rubiacea species *Hedyotis chrysotricha*. Its structure has been eludicated, and it proved to inhibit the growth of HL-60 cells *in vitro* [1]. Along with its structure as determined by X-ray crystallography, ^{1}H and ^{13}C NMR analyses indicated the existence of tautomeric forms, with **1** dominating in apolar and **2** in polar media [1].

Stereochemically, the structure of (+)-chrysotricine is related to one (2*R*, 5*R*) of the two naturally occurring linalyl oxides **3** which should be the precursor in its biosynthesis [1].

Results and Discussion

The commercially available optically active diastereomeric mixture of **3**, derived from (−)-(3*R*)-linalool (**4**) [2], is the starting material of the presented synthesis of **1**. The diastereomers of **3** cannot be separated on a preparative scale, but their acetyl derivatives **5** could be separated by rectification over a large column [3]. Distillation proved to yield the desired compounds (2*R*, 5*R*)-**5a** and (2*R*, 5*S*)-**5b** in sufficient diastereomeric purity (96.4% and 98.8%, resp. by GC). The diastereomeric enantiomerically pure compounds **5a** and **5b** were transformed to aldehydes **6** by hydroboration with disiamylborane, being the reagent of choice because of its excellent anti-*Markovnikov* selectivity and inertness against ester groups [4], and subsequent oxidative workup with pyridinium chlorochromate in dichloromethane [5] (Scheme 1).

[a] Dedicated to Prof. *W. Wiegrebe* on the occasion of his 68th birthday
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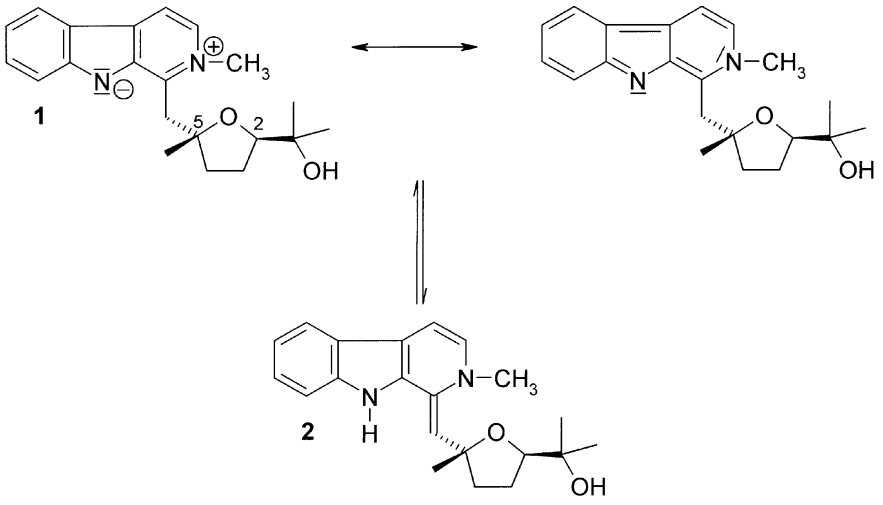
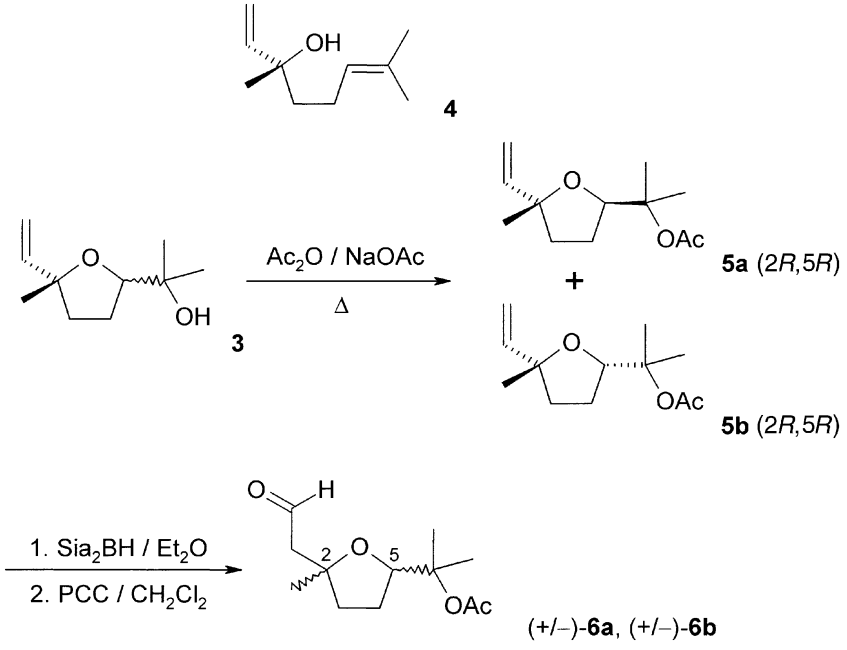
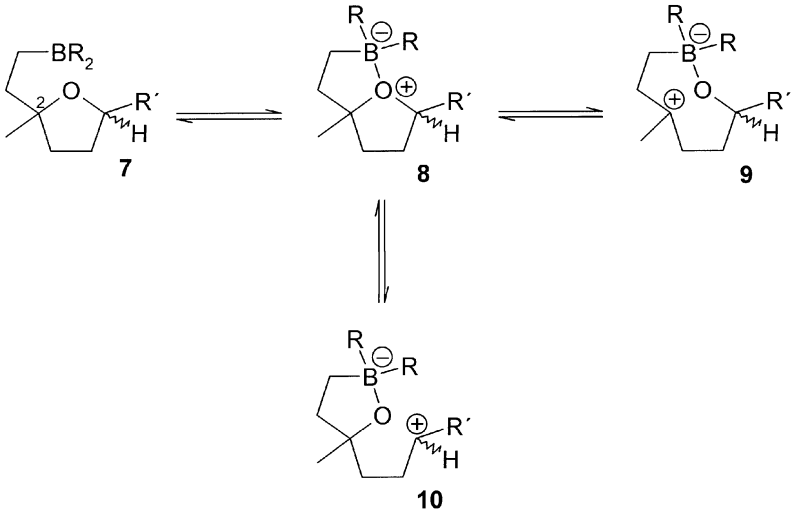


Fig. 1. Structure of chrysotricine; numbering and nomenclature according to IUPAC (cf. Scheme 3 and Experimental)



Scheme 1. Numbering according to IUPAC (cf. Scheme 3 and Experimental)

Surprisingly, the ^{1}H NMR spectra of both products **6a** and **6b** indicated mixtures of diastereomers in ratios roughly about 3:1. Moreover, **6a** and **6b** are racemates. The ratio of diastereomers in **6a**,**b** depends on the stereochemistry of the starting materials **5a** and **5b**, resp.: **5a** $(2R, 5R)$ *e.g.* leads to the dominant diastereomeric racemate **6a** $(2R^*, 5R^*)$ and *vice versa*. We assume that the intermediately formed borane **7** is configurationally unstable at C-2 and C-5 due to



R = $CH(CH_3)CH(CH_3)_2$, R' = $C(CH_3)_2OAc$

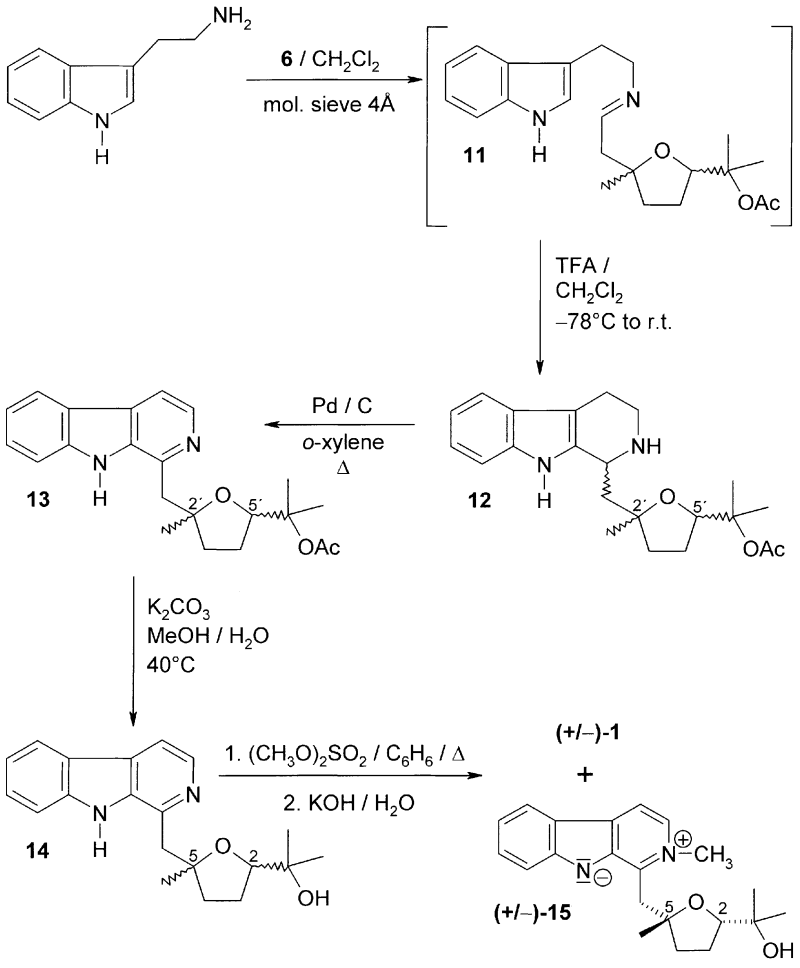
Scheme 2

ring opening of the boroxolane adduct **8**, affording the tertiary carbenium ion **9** or the secondary carbenium ion **10**, resp. (Scheme 2).

Due to fast discoloration and solidification of compounds **6** when exposed to air, we did not attempt to separate the diastereomers at this stage, but used the diastereomeric mixture of racemates **6** for a *Pictet-Spengler* reaction with tryptamine adopting a modified procedure (no isolation of the intermediate imines **11**) with *TFA* in dichloromethane from −78°C to ambient temperature [6] producing the 1-substituted 1,2,3,4-tetrahydro-β-carbolines **12** as mixtures of, at these stages, four diastereomeric racemates **12a–d** (^{1}H NMR) in high yield (Fig. 2). Within the pairs **12a,c** and **12b,d**, resp., we could not differentiate by NOE measurements.

Compounds **12** were easily dehydrogenated to the β-carbolines **13** by Pd/C adopting the protocol of *McNulty et al.* [7]. Deacetylation of **13** gave the hydroxy derivatives **14**. During these steps, the ratio of diastereomers proved to be more or less maintained (^{1}H NMR). Quaternization of **14** with dimethyl sulfate [9] and treatment of the β-carbolinium methosulfates of (+/−)-**1** and (+/−)-**15** with aequous KOH [10] led to the 2*H*-β-carbolines (+/−)-**1** and (+/−)-**15** (Scheme 3). In contrast to the precursors **12–14** – only compounds **12** showed slightly separated spots in TLC – the diastereomeric racemates (+/−)-**1** and (+/−)-**15** could be separated preparatively starting either from **5a** or **5b** by column chromatography.

IR, UV, ^{1}H, ^{13}C NMR ($CDCl_3$), and mass spectra of (+/−)-**1** obtained either from **5a** or **5b** are in accordance with the data of (+)-**1** isolated from plant material [1]; the melting point of (+/−)-**1** (210–213°C) is by far higher than that of (+)-**1** (160–161°C[1]). The diastereomer (+/−)-**15** (from **5a** or **5b**) shows ^{1}H NMR spectra remarkably different to those of (+/−)-**1**. The structures can be assigned by NOESY experiments to be ($2R^*, 5R^*$)-(**1**) and its ($2R^*, 5S^*$)-diastereomer (**15**).



Scheme 3. Numbering according to IUPAC (cf. Experimental; configurations at 2 and 5 interchange); (+/−)-**15**: only one enantiomer shown

Finally, X-ray structure analysis proved the racemic character of a crystalline sample of (+/−)-**1** (Fig. 3).

These results showed that the configurations at C-2 as well as the C-5 of **5** are not stable during the presented synthetic pathways, yielding only racemic chrysotricine (+/−)-**1**.

Experimental

General

Melting points were determined on a Büchi 512 apparatus or a Reichert Thermovar 400019 heating microscope and are uncorrected. Refractive indices were measured on a Zeiss (Jena) 801240 refractomer, polarimetry was performed on a Perkin-Elmer 241 MC instrument. FTIR spectra were recorded on a Nicolet 510 FTIR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC250 (250 MHz) or Bruker ARX400 (400 MHz) spectrometer. Mass spectra were obtained with

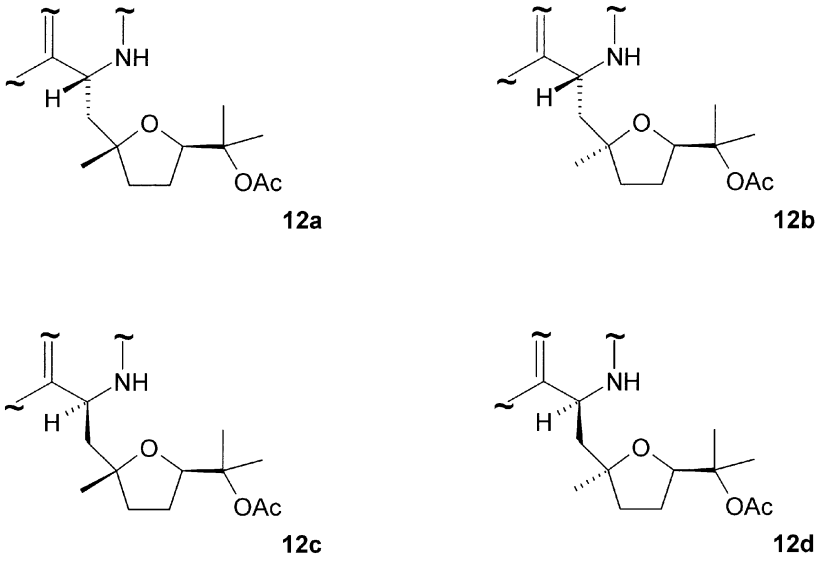


Fig. 2. Diastereomeric racemates of **12**; only one enantiomer of each is shown (ratio **12a**:**12b**:**12c**:**12d** $\approx$ 3:1:3:1 from **5a**, $\approx$ 1:1:1:1 from **5b**); the ratios determine the assignments of stereochemistry in **12a**,**c** and **12b**,**d** resp. within the mixture

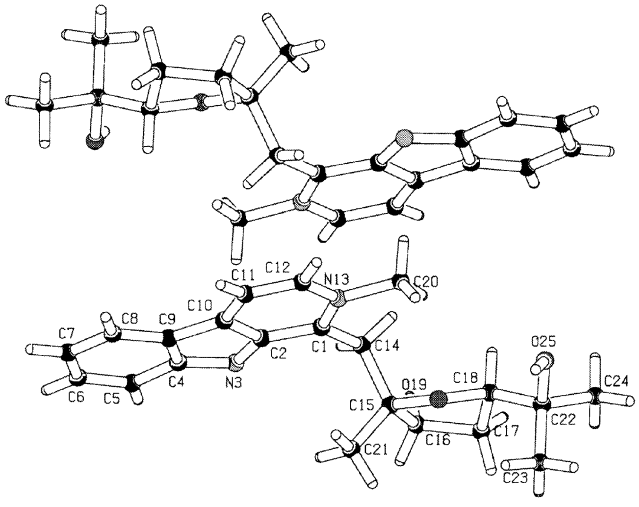


Fig. 3. Structure of (+/−)-**1** (PLATON [11] plot, both enantiomers are shown as part of the unit cell)

Varian MAT 311 A (EI, 70 eV) and Varian MAT 95 (FAB, FD) spectrometers. Elemental analyses were carried out at the Microanalytical Laboratory of the University of Regensburg. Experimental and calculated values agree within experimental error. Thin layer chromatography (TLC) was performed on aluminum sheets coated with 60 F_{254} silica or 60 F_{254} neutral alumina. Compounds were detected using UV light ($\lambda = 254$ nm), iodine fumes, a spray of 0.1% w/v 2,4-dinitrophenylhydrazine in 60% aqueous ethanol followed by 1% w/v $K_3[Fe(CN)_6]$ in 1 *N* HCl, or 3% w/v vanillin in 96% ethanol followed by 5% w/v H_2SO_4 in 96% ethanol. Column chromatography (CC) was carried out using Merck 60 (70–230 mesh ASTM) silica or ICN alumin B Super I Lot 28 (adjusted to

activity grade II with 4% H_2O). GC analyses were performed according to Ref. [3] (cf. Acknowledgements). Solvents indicated as dry were prepared according to standard procedures. All reactions were performed under nitrogen which had been dried over self-indicating silica gel, concentrated H_2SO_4, and KOH.

(2R,5R)-5-(1-Acetoxy-1-methylethyl)-2-ethenyl-2-methyl-perhydrofurane and *(2R,5S)-5-(1-Acetoxy-1-methylethyl)-2-ethenyl-2-methyl-perhydrofurane* (**5a**, **5b**; $C_{12}H_{20}O_3$)

21.41 g (125.73 mmol) of linalyl oxide **3** (mixture of stereoisomeres) and 1.54 g (18.86 mmol) anhydrous sodium acetate were heated under reflux for 3 h with 17.79 cm^3 (188.60 mmol) of dry acetic acid anhydride. The slurry resulting on cooling to room temperature was liquified with 80 cm^3 of H_2O, followed by addition of 120 cm^3 of saturated aqueous Na_2CO_3. When the evolution of CO_2 ceased after several minutes of vigorous stirring, the mixture was extracted with 3 × 200 cm^3 of ether, the combined extracts were washed with 100 cm^3 of saturated aqueous Na_2CO_3, 100 cm^3 of saturated aqueous NaCl, and dried over $MgSO_4$. The oil resulting after evaporation was predistilled to yield 24.95 g (117.53 mmol, 87%) of a colourless liquid, b.p. 47 – 53°C/70 Pa, $n_D{}^{20}$ = 1.4486; this crude product was redistilled.

(2*R*,5*R*)-**5a**: n_D^{20} = 1.4467 (Ref. [3]: 1.4448); $[\alpha]_D^{20} = -5.0°$ (neat; *de* (NMR) > 90%; Ref. [3]: −11.3°, no comment concerning conditions); IR (neat): $\tilde{\nu}$ = 3090–2880 (CH), 1735 (C = O), 1645 (C = C) cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.33 (s, 3H, 2-CH_3), 1.48 (s, 6H, C(OAc)(CH_3)$_2$), 1.64–1.95 (m, 4H, -CH_2-CH_2-), 1.99 (s, 3H, $COCH_3$), 4.07 (t, J = 6.3 Hz; 1H, 5-H), 5.00 (dd, J = 10.6, 1.5 Hz, 1H, =C*H*H (*cis*)), 5.18 (dd, J = 17.2, 1.5 Hz; 1H, =CH*H*(*trans*)), 5.87 (dd, J = 17.2, 10.6 Hz, 1H, =CH-) ppm.

(2*R*,5*S*)-**5b**: n_D^{20} = 1.4488 (Ref. [3]: 1.4485); $[\alpha]_D^{20} = -0.3°$ (neat; *de* (NMR) > 95%; Ref. [3]: −0.2°, no comment concerning conditions); IR (neat): $\tilde{\nu}$ = 3090 – 2875 (CH), 1735 (C = O), 1645 (C = C) cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.31 (s, 3H, 2-CH_3), 1.48 (s, 3H, C(OAc)(C*H*$_3$)(CH_3)), 1.49 (s, 3H, C(OAc)(CH_3)(C*H*$_3$)), 1.62 – 1.96 (m, 4H, -CH_2-CH_2-), 1.98 (s, 3H, $COCH_3$), 4.10 (dt, J_t = 6.5 Hz, J_d = 3.0 Hz, 1H, 5-H), 4.98 (dd, J = 10.8, 1.5 Hz, 1H, =C*H*H(*cis*)), 5.22 (dd, J = 17.4, 1.5 Hz, 1H, =CH*H*(*trans*)), 5.97 (dd, J = 17.4, 10.7 Hz, 1H, =CH-) ppm.

(5-(1-Acetoxy-1-methylethyl)-2-methyl-perhydro-2-furanyl)acetaldehyde (**6a** and **6b**; $C_{12}H_{20}O_4$)

At −12°C, 5.18 cm^3 (58.54 mmol) of 2-methyl-2-butene were added carefully under stirring to 2.38 cm^3 (23.37 mmol) of neat borane-dimethylsulfide complex. After 15 min, the mixture was allowed to warm to 0°C and was stirred for 1.5 h at this temperature. After addition of 4 cm^3 of dry ether, stirring at 0°C was continued for 1 h. Then, this solution was added dropwise to 4.58 g (21.57 mmol) of neat (2*R*, 5*R*)-**5a** or (2*R*,5*S*)-**5b**, resp., at 0°C with stirring. After stirring for 2 h at this temperature, ether and dimethyl sulfide were removed *in vacuo*, and the residue was dissolved in 10 cm^3 of dry dichloromethane. Under vigorous stirring, this mixture was added drop by drop to a suspension of 38.80 g (180 mmol) of *PCC* in 145 cm^3 of dry CH_2Cl_2. When the highly exothermic reaction had ceased, the mixture was heated under reflux for 2 h. After cooling to room temperature, the mixture was diluted with 75 cm^3 of ether and filter through 75 g of silica gel, followed by washing the reaction flask and the silica pad with 3×35 cm^3 of ether. Concentration of the combined solutions *in vacuo* and distillation led to a nearly colourless liquid.

Yield: 1.01 g (4.42 mmol, 20%); b.p.: 92°C/70 Pa, $[\alpha]_D^{20} = 0°$ (MeOH, c = 0.05) for **6a** and 1.43 g (6.26 mmol, 29%), b.p.: 93–95°C/70 Pa, $[\alpha]_D^{20} = 0°$ (MeOH, c = 0.38) for **6b**; IR (neat): $\tilde{\nu}$ = 2980–2740 (CH), 1730 (C = O), 1370 (CH_3) cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz): the ratio of $(2R^*, 5R^*)$-**6**/$(2R^*, 5S^*)$-**6** is *ca.* 4:1 for **6a** and *ca.* 1:2 for **6b**; data for $(2R^*, 5R^*)$-diastereomer: δ = 1.34 (s, 3H, 2-CH_3, both diastereomers), 1.46 (s, 3H, C(OAc)C*H*$_3$)(CH_3)), 1.48 (s, 3H, C(OAc)(CH_3)(C*H*$_3$)), 1.80–2.01 (m, 4H, -CH_2-CH_2-, both diastereomers), 1.99 (s, 3H, $COCH_3$),

2.51–2.67 (m, 2H, -CH_2-CHO, both diastereomers), 3.99–4.11 (m, 1H, 5-H, both diastereomers), 9.81 (t, J = 2.8 Hz; 1H, CHO) ppm; data for ($2R^*, 5S^*$)-diastereomer: $\delta = 1.34$ (s, 3H, 2-CH_3, both diastereomers), 1.45 (s, 3H, C(OAc)(CH_3)(CH_3)), 1.50 (s, 3H, C(OAc)(CH_3)(CH_3)), 1.80–2.01 (m, 4H, -CH_2-CH_2-, both diastereomers), 1.98 (s, 3H, $COCH_3$), 2.51–2.67 (m, 2H, -CH_2-CHO, both diastereomers), 3.99 – 4.11 (m, 1H, 5-H, both diastereomers), 9.85 (t, J = 2.8 Hz, 1H, CHO) ppm; EI-MS: no [$M^{+\bullet}$], m/z (%) = 213 (0.2) [M − $^{\bullet}CH_3$]$^+$, 200 (0.79), 185 (1) [M −$^{\bullet}CH_2CHO$]$^+$, 127 (3) [M −$^{\bullet}C(CH_3)_2$-OAc]$^+$.

1-(5-(1-Acetoxy-1-methylethyl)-2-methyl-perhydro-2-furanyl)-methyl-1,2,3,4-tetrahydro-9H-β-carboline (**12**; $C_{22}H_{30}N_2O_3$)

With stirring, 1.01 g (4.42 mmol) of **6a** or **6b**, resp., and 0.71 g (4.45 mmol) of tryptamine were dissolved in 75 cm^3 of dry CH_2Cl_2 and 0.73 g of dried molecular sieve (4 Å) were added. After stirring for 1 h, the molecular sieve was removed by filtration and washed with 25 cm^3 of dry CH_2Cl_2. The filtrate was cooled to −78°C, and 1.07 cm^3 (13.88 mmol) of trifluoroacetic acid in 3 cm^3 of dry CH_2Cl_2 were added during 35 min with stirring. The mixture was allowed to warm to room temperature overnight and was then poured onto 100 cm^3 of ice/H_2O. After adjusting to $pH = 9$ with saturated aqueous Na_2CO_3, the organic layer was separated, washed with 25 cm^3 of H_2O and 25 cm^3 of saturated aqueous NaCl solution, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by CC (column: 2 × 33 cm silica gel, CH_2Cl_2/ethyl acetate/MeOH = 5:3:2) to yield products **12** as colourless foam.

Yield: 1.34 g (3.62 mmol, 82%), m.p.: 47–51°C from **6a**, 1.36 g (3.67 mmol), 83%), m.p.: 45–50°C from **6b**; IR (KBr): $\tilde{\nu} = 3330$ (NH), 3055–2845 (CH), 1735 (CO), 1655, 1625, 1590 (C = C) cm^{-1}; ^{1}H NMR (*DMSO*-d_6, 250 MHz): the ratio of the pairs **12a**, **c** and **12b**, **d**, resp., are ≈3:1 when originating from **6a** and ≈1:1 when originating from **6b**; data for **12a**, **c**: $\delta = 1.32$, 1.34 (2 × s, 3H, 2′-CH_3), 1.40 (s, 3H, C(OAc)(CH_3)(CH_3)), 1.43 (s, 3H, C(OAc)(CH_3)(CH_3), four diastereomers), 1.73–2.15 (m, 7H (1H exch.), 3′-H, 4′-H, NH-CH-CH_2 + 2-NH), 1.94, 1.99 (2 × s, 3H, $COCH_3$), 2.56–2.66 (m, 2H, CH_2-CH_2-NH), 2.77–2.89 (m, 1H, C*H*H-CH_2-NH), 3.10–3.18 (m, 1H, CH*H*-CH_2-NH), 4.01–4.22 (m, 2H, 1-H + 5′-H), 6.88–7.03 (m, 2H aromat.), 7.23–7.35 (m, 2H aromat.), 10.57 (s, 1H (exch.), NH indole) ppm; data for **12b**, **d**: $\delta = 1.27$, 1.29 (2 × s, 1H, 2′-CH_3), 1.39 (s, 3H, C(OAc)(CH_3)(CH_3)), 1.43 (s, 3H, C(OAc)(CH_3)(CH_3), four diastereomers), 1.73–2.15 (m, 7H (1H exch.), 1.89, 1.90 (2 × s, 3H, $COCH_3$), 2.56–2.66 (m, 2H, CH_2-CH_2-NH), 2.77–2.89 (m, 1H, C*H*H-CH_2-NH), 3.10–3.18 (m, 1H, CH*H*-CH_2-NH), 4.01–4.22 (m, 2H, 1-H + 5′-H), 6.88–7.03 (m, 2H aromat.), 7.23–7.35 (m, 2H aromat.), 10.59 (2 × s, 1H (exch.), NH indole) ppm; FAB-MS: m/z = 741 [2M+H]$^+$, 371 [MH]$^+$, 370 [$M^{+\bullet}$], 311 [MH − HOAc]$^+$, 185, 171.

1-(5-(1-Acetoxy-1-methylethyl)-2-methyl-perhydro-2-furanyl)-methyl-9H-β-carboline (**13**; $C_{22}H_{26}H_2O_3$)

1.34 g (3.62 mmol) of **12** (mainly **12a** and **12c**, originating from **5a**, or mainly **12b** and **12d**, originating from **5b**, resp.) and 0.75 g of 10% Pd/C were heated under reflux in 125 cm^3 of *o*-xylene for 2 h. After cooling to room temperature, the catalyst was removed by filtration through Celite, followed by washing with warm ethanol. Concentration *in vacuo* and CC (column: 2 × 23 cm silica gel, CH_2Cl_2/ethyl acetate/MeOH = 4:4:1) afforded products **13** as a pale yellow wax.

Yield: 1.18 g (3.22 mmol, 89%) originating from **5a**, 1.23 g (3.37 mmol, 93%) originating from **5b**; IR (paraffin): $\tilde{\nu} = 3375$ (NH), 1735 (C = 0) cm^{-1}; ^{1}H NMR (*DMSO*-d_6, 250 MHz): the ratio of ($2'R^*, 5'R^*$)-**13**/($2'R^*, 5'S^*$)-**13** is ≈4:1 originating from **5a** and ≈1:2 originating from **5b**; data for ($2'R^*, 5'R^*$)-diastereomer: $\delta = 1.28$ (s, 3H, C(OAc)(CH_3)(CH_3)), 1.29 (s, 3H, 2′-CH_3), 1.33 (s, 3H, C(OAc)(CH_3)(CH_3)), 1.55–2.39 (m, 4H, -CH_2-CH_2-), 1.83 (s, 3H, $COCH_3$), 3.26–3.38 (m, 4H, N = C-CH_2-, both diastereomers), 3.79 (dd, J = 7.5, 7.2 Hz, 1H, 5′-H), 7.21 (dd, J_0 = 7.3 Hz, J_m =

1.1 Hz, 1H aromat.), 7.48–7.60 (m, 2H aromat.), 7.94, 8.25 (AB-system, $J_{AB} = 5.2$ Hz, 2H, 4-H, 3-H), 8.19 (br d, $J = 7.9$ Hz, 1H, 5-H), 11.33 (s, 1H (exch.), NH indole) ppm; data for $(2'R^*, 5'S^*)$-diastereomer: $\delta = 1.12$ (s, 3H, C(OAc)(CH_3)(CH$_3$)), 1.18 (s, 3H, 2′-CH$_3$), 1.22 (s, 3H, C(OAc)(CH$_3$)(CH_3)), 1.55–2.39 (m, 4H, -CH$_2$-CH$_2$-), 1.78 (s, 3H, COCH$_3$), 3.26–3.38 (m, 4H, N = C-CH$_2$-, both diastereomers), 4.02 (t, $J = 7.1$ Hz, 1H, 5′-H), 7.21 (dd, $J_0 = 7.3$ Hz, $J_m = 1.1$ Hz, 1H aromat.), 7.48–7.60 (m, 2H aromat.), 7.93, 8.24 (AB-system, $J_{AB} = 5.2$ Hz, 2H, 4-H, 3-H), 8.19 (br d, $J = 7.9$ Hz, 1H, 5-H), 11.36 (s, 1H (exch.), NH indole) ppm; FD-MS: $m/z = 366$ [M$^{+\bullet}$].

1-(5-(9H-β-Carbolin-1-ylmethyl)-5-methyl-perhydro-2-furanyl)-1-methylethyl alcohol (**14**; $C_{20}H_{24}N_2O_2$)

1.18 g (3.22 mmol) of **13** (originating from **5a** or **5b**, resp.) were dissolved in 80 cm^3 of methanol with stirring. 80 cm^3 of 3 *M* aqueous K_2CO_3 were added, and the mixture was stirred for 20 h at 40°C. Methanol was removed *in vacuo*, and the residue was extracted with 3 × 100 cm^3 of CH_2Cl_2. After washing with 75 cm^3 of H_2O and drying over Na_2SO_4 the solvent was distilled off. Purification by CC (column: 2 × 25 cm silica gel, CH_2Cl_2/ethyl acetate/MeOH = 4:4:1) afforded diastereomeric racemates **14** as a colourless foam

Yield: 0.90 g (2.77 mmol, 86%), melting range: 55–75°C, originating from **5a**, and 0.91 g (2.80 mmol; 87%), melting range: 60–85°C, originating from **5b**; IR (KBr): $\tilde{\nu} = 3390$ (NH), 3230 (OH), 3065–2870 (CH), 1630, 1570, 1500 (C = C) cm^{-1}; ^{1}H NMR (*DMSO*, 250 MHz): the ratio of $(2R^*, 5R^*)$-**14**/$(2R^*, 5S^*)$-**14** is ≈4:1 originating from **5a** and ≈1:2 originating from **5b**; data for $(2R^*, 5R^*)$-diastereomer: $\delta = 0.99$ (s, 3H, C(OH)(CH_3)(CH$_3$)), 1.00 (s, 3H, C(OH)(CH$_3$)(CH_3)), 1.23 (s, 3H, 5-CH$_3$), 1.54–2.14 (m, 2H, -CH$_2$-CH$_2$-),1.73 (dd, $J = 7.2$, 14.8 Hz, 1H, -CH$_2$-CH$_2$-), 2.19 (ddd, $J = 8.1$, 8.1, 11.7 Hz, 1H, -CH$_2$-CH$_2$-), 3.31 (s, 2H, N = C-CH$_2$-), 3.53 (dd, $J = 7.3$, 7.3 Hz, 1H, 2-H), 4.11 (s, 1H (exch.), OH), 7.18–7.24 (m, 1H aromat.), 7.48–7.63 (m, 2H aromat.), 7.94, 8.25 (AB-system, $J_{AB} = 5.2$ Hz, 2H, 4′-H, 3′-H), 8.17–8.20 (m, 1H + 0.25H, 5′-H), 11.22 (s, 1H (exch.), NH indole) ppm; data for $(2R^*, 5S^*)$-diastereomer: $\delta = 1.05$ (s, 3H, C(OH)(CH_3)(CH$_3$)), 1.07 (s, 3×0.25H, C(OH)(CH$_3$)(CH_3)), 1.15 (s, 3H, 5-CH$_3$), 1.54–2.14 (m, 4H, -CH$_2$-CH$_2$-), 3.17, 3.34 (AB-system, $J_{AB} = 12.9$ Hz, 2H, N = C-CH$_2$-), 3.73–3.79 (m, 1H, 2-H), 5.84 (s, 1H (exch.), OH), 7.18–7.24 (m, 1H aromat.), 7.48–7.63 (m, 2H aromat.), 7.95, 8.21 (AB-system, $J_{AB} = 5.3$ Hz, 2×0.25H, 4′-H, 3′-H), 8.17–8.20 (m, 1H, 5′-H), 11.69 (s, 1H (exch.), NH indole) ppm; FD-MS: $m/z = 324$ [M$^{+\bullet}$].

(2R,5R*)-1-Methyl-1-(5-(2-methyl-2H-β-carbolin-1-ylmethyl)-5-methyl-perhydro-2-furanyl) ethyl alcohol* ((+/−)-**1**; $C_{21}H_{26}N_2O_2$)

0.90 g (2.77 mmol) of **14** were dissolved in 100 cm^3 of dry benzene with stirring. 0.53 cm^3 (5.54 mmol) of dimethyl sulfate were added, and the mixture was heated under reflux for 1 h. After cooling to room temperature, the liquid was decanted from the solid which was dried *in vacuo* after washing with 10 cm^3 of dry benzene. The methosulfate thus obtained was dissolved in 50 cm^3 of H_2O at 60°C, the solution was cooled to ambient temperature, and 1.39 cm^3 (2.77 mmol) of 2 *N* KOH were added dropwise with stirring. The mixture was extracted with 3 × 100 cm^{-3} of CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, and the solvent was removed *in vacuo*. Purification of crude (+/−)-**1** by CC (column: 5 × 55 cm basic alumina (II), CH_2Cl_2/ethyl acetate/MeOH (NH_3) = 8:1:1) yielded 255 mg (0.75 mmol, 27%) of (+/−)-**1** as yellow crystals.

M.p.: 213°C (acetone); $[\alpha]_D^{20} \approx -2°$ (MeOH, $c = 0.05$); this value is within the instrumental error), $[\alpha]_D^{20} = 0°$ (MeOH, $c = 0.5$); (+)-**1** [1]: +16°); IR (KBr): $\tilde{\nu} = 3395$, 3115 (OH), 3045–2835 (CH), 1620, 1590, 1475 (C = C), 1340, 1275, 1155, 1060, 765, 750 cm^{-1}; UV (MeOH): λ_{max} (ε) = 374 (3000), 308 (18800), 254 (26000), 207 (19800) nm; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 0.99$ (s, 3H, C(OH)(CH_3)(CH$_3$)), 1.10 (s, 3H, C(OH)(CH$_3$(CH_3)), 1.39 (dd, $J = 13.5$, 6.0 Hz, 1H, 3-H), 1.41 (s, 3H, 5-CH$_3$), 1.69 (dddd, $J = 12.1$, 11.7, 10.2, 7.8 Hz, 1H, 3-H), 1.97 (s, 1H (exch.), OH), 2.00

(ddd, $J = 13.0$, 7.8, 2.0 Hz, 1H, 4-H), 2.40 (ddd, $J = 12.8$, 11.8, 7.6 Hz, 1H, 4-H), 3.04 (dd, $J = 9.7$, 4.5 Hz, 1H, 2-H), 3.75, 4.18 (AB-system, $J_{AB} = 14.0$ Hz, 2H, N = C-CH_2-), 4.33 (s, 3H, N-CH_3), 7.14 (ddd, $J = 8.1$, 6.8, 0.9 Hz, 1H, 6′-H), 7.45, 8.02 (AB-system, $J_{AB} = 6.3$ Hz, 2H, 4′-H, 3′-H), 7.54 (ddd, $J = 8.5$, 6.8, 1.3 Hz, 1H, 7′-H), 7.96 (dt, $J = 8.6$, 0.9 Hz, 1H, 8′-H), 8.17 (ddd, $J = 8.1$, 1.2, 1.0 Hz, 1H, 5′-H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 24.0$ (C(OH)(*C*H_3)(CH_3)), 25.9 (C-3), 27.6 (C(OH)(CH_3)(*C*H_3)), 29.2 (5-CH_3), 36.9 (C-4), 39.1 (-CH_2-), 44.7 (N-CH_3), 70.1 (*C*(OH)(CH_3)(CH_3)), 85.3 (C-5), 87.0 (C-2), 114.0 (C-4′), 117.5 (C-8′), 119.5 (C-6′), 121.9 (C-5′), 124.5 (C-3′), 128.2 (C-7′), 130.9 (C-4a′, C-4b′), 141.6 (C-1a′), 147.1 (C-8a′), 157.9 (C-1′) ppm; EI-MS: *m/z* (%) = 338 (6) [$M^{+\bullet}$], 323 (2) [$M - {}^{\bullet}CH_3$]$^+$, 320 (3) [$M - H_2O$]$^{+\bullet}$, 279 (10) [$M - {}^{\bullet}C(CH_3)_2OH$]$^+$, 249 (3) [$M - HO{}^{\bullet}CHC(CH_3)_2OH$]$^+$, 237 (47) [$C_{16}H_{17}N_2$]$^+$, 196 (100) [$C_{13}H_{12}N_2$]$^{+\bullet}$, 195 (11) [$C_{13}H_{11}N_2$]$^+$, 181 (5) [$C_{12}H_9N_2$]$^{+\bullet}$, 143 (2) [$C_8H_{15}O_2$]$^+$, 101 (0.4) [$C_5H_9O_2$]$^+$, 89 (0.2) [$HOCHC(CH_3)_2OH$]$^+$, 59 (5) [$C(CH_3)_2OH$]$^+$.

(2R,5S*)-1-Methyl-1-(5-(2-methyl-2H-β-carbolin-1-ylmethyl)-5-methyl-perhydro-2-furanyl) ethyl alcohol* (**15**; $C_{21}H_{26}N_2O_2$)

15 was obtained by CC as a byproduct of (+/−)-**1**. Yield: 143 mg (0.42 mmol, 15%) of pale yellow crystals; m.p.: 89–92°C (CH_2Cl_2/diethyl ether/hexane); $[\alpha]_D^{20} = 0°$ (MeOH, $c = 0.5$); IR (KBr): $\tilde{\nu} = 3410$ (OH), 3045–2865 (CH), 1620, 1590, 1475 (C = C), 1340, 1225, 1180, 1030, 755, 740 cm^{-1}; UV (MeOH): λ_{max} (ε) = 379 (5020), 310 (18300), 255 (26100), 207 (19500) nm; ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 1.04$ (s, 3H, C(OH)(C*H*$_3$)(CH_3)), 1.10 (s, 3H, C(OH)(CH_3)(C*H*$_3$)), 1.22 (s, 3H, 5-CH_3), 1.83–1.98 (m, 2H, 3-H + 4-H), 2.04 (s, 1H (exch.), OH), 2.07–2.21 (m, 2H, 3-H + 4-H), 3.10, 4.25 (AB-system, $J_{AB} = 14.1$ Hz, 2H, N = C-CH_2-), 3.83 (dd, $J = 8.8$, 6.2 Hz, 1H, 2-H), 4.07 (s, 3H, N-CH_3), 7.12 (ddd, $J = 8.0$, 6.8, 1.0 Hz, 1H, 6′-H), 7.33, 7.89 (AB-system, $J_{AB} = 6.4$ Hz, 2H, 4′-H, 3′-H), 7.52 (ddd, $J = 8.5$, 6.8, 1.3 Hz, 1H, 7′-H), 7.96 (dt, $J = 8.5$, 0.9 Hz, 1H, 8′-H), 8.09 (ddd, J = 8.1, 1.2, 0.9 Hz, 1H, 5′-H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 25.7$ (C(OH)(*C*H_3)(CH_3)), 26.0 (C-3), 26.9 (5-CH_3), 27.5 (C(OH)(CH_3)(*C*H_3)), 39.5 (-CH_2-), 39.7 (C-4), 44.4 (N-CH_3), 70.0 (*C*(OH)(CH_3(CH_3)), 84.1 (C-5), 87.7 (C-2), 114.0 (C-4′), 117.7 (C-8′), 119.0 (C-6′), 121.8 (C-5′), 125.1 (C-3′), 128.3 (C-7′), 130.9 (C-4a′, C-4b′), 141.7 (C-1a′), 145.4 (C-8a′), 156.4 (C-1′) ppm; EI-MS: *m/z* (%) = 338 (7) [$M^{+\bullet}$], 323 (2) [$M - {}^{\bullet}CH_3$]$^+$, 320 (3) [$M - H_2O$]$^{+\bullet}$, 279 (11) [$M - {}^{\bullet}C(CH_3)_2OH$]$^+$, 249 (2) [$M - HO{}^{\bullet}CHC(CH_3)_2OH$]$^+$, 237 (41) [$C_{16}H_{17}N_2$]$^+$, 196 (100) [$C_{13}H_{12}N_2$]$^{+\bullet}$, 195 (10) [$C_{13}H_{11}N_2$]$^+$, 143 (2) [$C_8H_{15}O_2$]$^+$, 101 (0.4) [$C_5H_9O_2$]$^+$, 89 (0.2) [$HOCHC(CH_3)_2OH$]$^+$, 59 (5) [$C(CH_3)_2OH$]$^+$.

X-ray stucture determination of (2R,5R*)-1-methyl-1-(5-(2-methyl-2H-β-carbolin-1-ylmethyl)-5-methyl-perhydro-2-furanyl)ethyl alcohol* ((+/−)-**1**)

A yellow crystal needle (0.032 × 0.064 × 0.256 mm) of (+/−)-**1** ($C_{21}H_{26}N_2O_2$), $Fw = 338.44$, monoclinic, space group $P2_1/c$, lattice parameters (calculated from 25 reflections with $10° < \Theta < 21°$): $a = 8.204(6)$, $b = 22.475(4)$, $c = 10.521$ (8) Å, $\beta = 111.33(3)°$, $V = 1807(2)$ Å^3, $Z = 4$, d (calcd.) = 1.244 g · cm^{-3}, $T = 293$ K was used for data collection with a CAD4 (Enraf-Nonius) diffractometer (Cu-K_α radiation, graphite monochromator, $\omega/2\Theta$ scan type, scan width 0.8 + 0.15 tanΘ and 25% left and right for underground determination; $1.5° \leq \Theta \leq 74.0°, -10 \leq h \leq 0$, $-28 \leq k \leq 0, -12 \leq l \leq 13$, 4035 reflections measured, 3695 reflections independent, $R_{int} = 0.2124$, 845($|F|/\sigma(F) > 4.0$) reflections observed, *Lorentz* and polarization correction, deviation of intensity of the check reflections (5%) corrected with cubic spline function). The structure was solved with direct methods using the program SIR92 [12] and was refined with the program SHELXL-97 [13] (full matrix refinement, 239 refined parameters, weighting scheme: $w = 1/(\sigma^2(F_0^2) + (0.078P)^2)$ with $P = (\mathrm{Max}(F_0^2, 0) + 2F_c^2)/3)$ using anisotropic displacement factors for non-hydrogen atoms. Hydrogen atoms are at geometric calculated positions and partially

isotropically refined. *R*-values: $wR_2 = 0.2975 (R_1 = 0.1044$ for observed and 0.4117 for all reflections). Goodness of fit: $S = 0.917$, maximum deviation of the parameters: 0.000* e.s.d., maximum peak height in difference *Fourier* synthesis: 0.27, –0.30 eÅ^3. Additional material to the structure determination may be ordered from Cambridge Crystallographic Data Centre (CCDC) referring to the deposition number CCDC 137392, the names of the authors, and citation of the present paper.

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Note added in proof: In the meantime we have found that *G. X. Wang*, *S. F. Chen*, and *X. T. Liang* have synthesized (+/−)-chrysotricine *via* a different route: Wang GX, Chen SF, Liang XT (1998) Chin Chem Lett **9**: 357, Chem Abstr (1999) **131**: 286628u

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