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New routes to clavine-type ergot alkaloids. Part 2: Synthesis of the last, so far not yet synthesized member of the clavine alkaloid family, (±)-cycloclavine☆

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Abstract

Starting from 4-bromo-Uhle's ketone (**2**), an alkylation step using ethyl 3-methylamino-propionate followed by intramolecular aldol condensation in two steps, transformation of the ester group into a methyl group, and finally cyclopropanation of the 8,9 double bond, resulted in a six-step total synthesis of (±)-cycloclavine (**1**).

Keywords: Clavine alkaloids; (±)-Cycloclavine; Total synthesis from 4-bromo-Uhle's ketone; Modified intramolecular Reformatsky-type cyclization; Cyclopropanation with diazomethane

1. Introduction

Isolation of cycloclavine from the seeds of *Ipomea hildebrandtii* was published as early as 1969 by the Sandoz research group.[2] Structure elucidation, including relative and absolute configurations of the stereogenic carbon atoms was also carried out by X-ray analysis of its methobromide derivative. The absolute configuration of the molecule was, however, incorrectly published as 5*R*,8*R*,10*R* instead of the proper one (5*R*,8*S*,10*S*), which corresponds to the structure given by the Sandoz group. Later, other research groups[3] found cycloclavine among other ergot alkaloids in different *Aspergillus* and *Argyreia* fungi. Up to now, all clavine-type alkaloids have already been prepared[4] by total synthesis except cycloclavine. Although no significant biological activities have been found among clavine-type alkaloids so far, the total synthesis of this characteristic ring system, in which the ergoline skeletal carbon atoms 8, 9, and 10 form a cyclopropane ring in place of the 9,10 double bond, presents a considerable challenge.

In our previous paper[1] we reported the first enantioselective total synthesis of several clavine-type alkaloids (three setoclavine derivatives). An efficient and common synthetic route of four other clavine alkaloids has recently been published by Somei et al.[5] There remained only one member of this family that has not been synthesized so far. In this paper we now report the total synthesis of (±)-cycloclavine according to a modificated procedure developed recently by us for the total synthesis of (+)-lysergic acid.[6]

2. Results and discussion

In the present synthesis, 4-bromo-Uhle's ketone (**2**), prepared according to the procedure developed by us,[6,7] again proved to be a well-suited starting material. Alkylation of 3-methylamino-propionic acid derivatives with **2** was the first step. Tertiary

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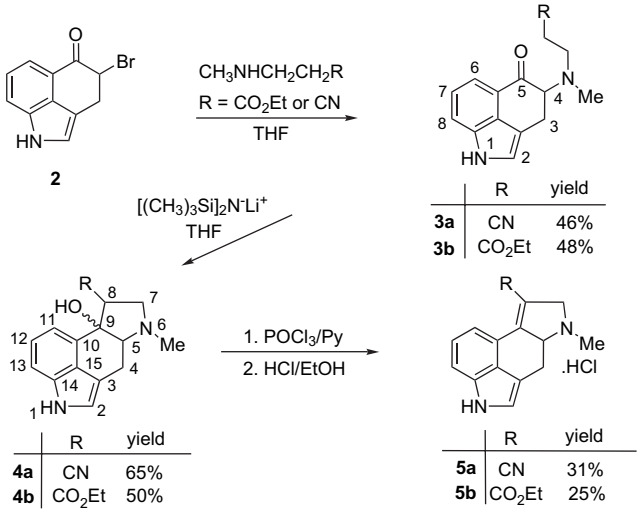
amines **3a**,**b**, obtained after the total consumption of **2**, could be isolated only in about 45–50% yield after purification via chromatography because of the facile elimination of the tertiary amine side chain. Isolation and characterization of these compounds, therefore, was performed only with aliquot quantities by transforming them into the corresponding HCl salt. Because of this sensitivity, the alkylated compounds **3a**,**b** were subjected to immediate intramolecular aldol-type cyclization.

Finding the proper method and the appropriate base required considerable experimentation. Finally, the use of excess lithium bis[trimethylsilyl]amide in THF at −70 °C proved to be successful in accomplishing this modified intramolecular Reformatsky reaction,[8] and possible diastereomers of 9-hydroxy-D-norergolene derivatives (**4a**,**b**) were prepared[9] and characterized after isolation. The next step, elimination of water, did not require the separation of the diastereomers, and was performed with $Py/POCl_3$ reagent in moderate (31 and 25%, respectively) yield (Scheme 1).

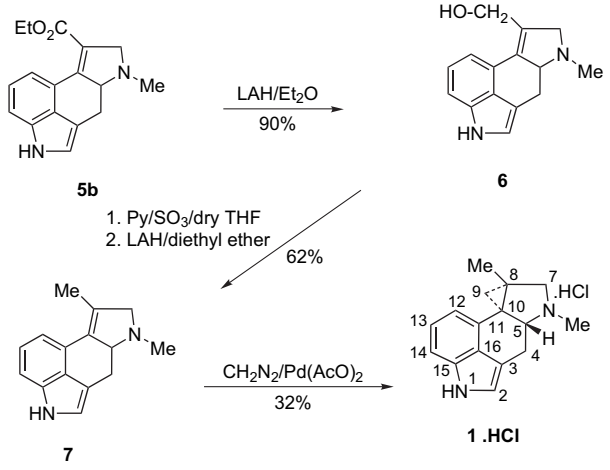


Scheme 1. Synthesis of D-nor-ergolene skeleton from 4-bromo-Uhle's ketone. Structures of compounds **2**–**5**.

Subsequent transformations toward the target molecule were carried out with ethyl ester **5b**. Reduction of the ester function to methyl group was accomplished in two steps. LAH reduction gave hydroxymethyl derivative **6** (90%), which was treated with Py/SO_3 and a second LAH reduction resulted in 8-methyl-D-norergolene derivative **7**.

The final step, cyclopropanation of the double bond of this important intermediate, caused the greatest challenge in the whole synthesis. Although the procedure aiming at inserting a carbene on a C=C double bond is a rather thoroughly investigated problem,[10] in our case most of the published methods failed. Finally, after many unsuccessful trials, application of diazomethane in the presence of palladium acetate catalyst[11] resulted in the desired alkaloid **1** as a HCl salt in racemic form (Scheme 2). It is worth mentioning that no reaction occurred without catalyst.

Elucidation of the relative configuration of the three stereogenic centers of the molecule was accomplished by NOE measurements. Upon selective inversion of the H5 proton at



Scheme 2. Conclusion of the synthesis from **5b**.

3.75 ppm, enhancements of the signals H4a (3.27 ppm), H7a (3.08 ppm), and N^+-CH_3 (2.86 ppm) were observed, while no interaction was detected with any of the H9 (cyclopropane-methylene), H4b, H7b or N^+-H protons. On the other hand, the selective inversion of H9a (2.48 ppm) resulted in an increase in the H4b (3.39 ppm), H7b (3.94 ppm), and NH^+ (12.0 ppm) proton signals. These NOE experiments distinguish between the protons situated above and below the five-membered C5–N6–C7–C8–C10 ring. The results confirm that protons of the cyclopropyl moiety (H9a, H9b) and H5 are located on opposite faces of the molecule. These findings prove unambiguously that our synthetic racemate (**1·HCl**) possesses the proper relative configurations at C5, C8, and C10 (*RS*, *SR*, and *SR*, respectively), exactly as it was elucidated in the case of the natural compound. The measurement demonstrates at the same time that in solution the N6 stereogenic center has definite and stable relative configuration (*RS*). The molecular geometry optimized with the HyperChem package, using semiempirical AM1 method, is shown in Figure 1.

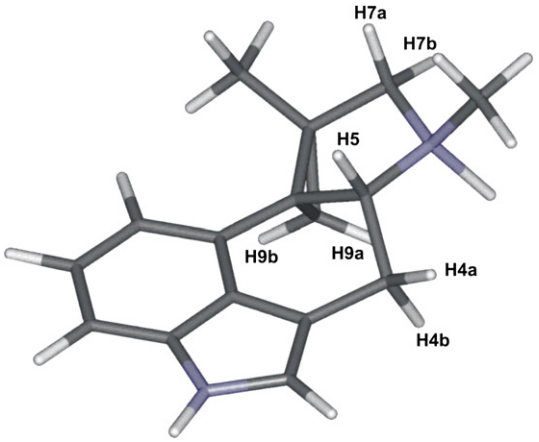


Figure 1. Steric arrangement of (±)-cycloclavine HCl salt (**1·HCl**).

Aliquot of the salt was transformed into the racemic base; its ^1H NMR behavior proved to be identical with that of the

isolated compound.[3b] As the earlier spectrum was measured only on a 60 MHz instrument, and no ^{13}C data were published up to now, a thorough evaluation is published hereby.

3. Conclusion

The above-described method provided the last, so far not yet synthesized member of the clavine alkaloid family.

4. Experimental part

4.1. General methods

Melting points are uncorrected. Elemental analyses (C, H, N) were carried out by Vario EL III (Elementar Analysen System Gmbh) automatic microanalyzer and chloride content via titration. MS spectra were run on an AEI-MS-902 (70 eV; direct insertion) and on a Kratos-MS-902 mass spectrometer. IR spectra were taken on a Nicolet 7795 FT-IR spectrophotometer. NMR measurements were performed on Varian INOVA-400 spectrometer equipped with a 5 mm inverse detection z-gradient probe. ^1H and ^{13}C NMR spectra were measured at rt (25 °C) using $CDCl_3$ and DMSO-d_6 as solvent. ^1H and ^{13}C chemical shifts are referenced to residual solvent signals. ^1H and ^{13}C NMR spectra were acquired with standard conditions. The complete signal assignment was performed by running gHSQC and gHMQC measurements. The pulse programs were taken from the Varian software library. 1D NOESY experiments were acquired with a mixing time of 600 ms, a recycle delay of 2 s and 256 transients. For TLC analyses Polygram Sil G/UV_{254} pre-coated plastic sheets (Macherey-Nagel) were used. Preparative separations were performed by column chromatography on Merck Kieselgel 60 (0.063–0.200).

4.2. Alkylation of 4-bromo-Uhle's ketone. (±)-4-(N-3-Cyanoethyl-N-methyl)amino-5-oxo-1,3,4,5-tetrahydrobenz[c,d]indole (**3a**) and (±)-4-(N-3-ethoxycarbonylethyl-N-methyl)-amino-5-oxo-1,3,4,5-tetrahydrobenz[c,d]indole (**3b**)

To the solution of 4-bromo-Uhle's ketone (**2**; 1.0 g; 4 mmol) in dry THF (20 ml) a solution of 3-methylaminopropionic acid derivative (12 mmol) in dry THF (10 ml) was mixed, and the mixture was stirred under argon protection at rt for 24 h.

Compound ***3a***: After stirring the reaction mixture, the THF solution of **3a** was decanted from a gummy insoluble material, evaporated in vacuum, and the residue was treated with a mixture of EtOAc (50 ml), water (25 ml), and 1 N HCl (10 ml). The organic phase was washed with 0.5 M HCl (2×10 ml) and water (10 ml). To the combined acidic water phase chloroform (100 ml) was mixed and the pH of the aqueous phase was set to 8 by adding satd Na_2CO_3 solution while cooling in an ice bad. After separating the phases the aqueous phase was extracted with chloroform (2×30 ml), the combined organic part washed with water (30 ml), dried, and evaporated. The residue was purified on silica (hexane–EtOAc 3:1) to provide **3a** as pale brownish oil. Yield: 0.46 g (46%). An aliquot of compound **3a** was isolated and characterized after chromatography and transformation into the HCl salt. Mp: 189–192 °C. ^1H NMR (HCl salt, $CDCl_3$+DMSO) δ (ppm): 11.4 (1H, s, NH); 10.8 (1H, br s, NH^+); 7.71 (1H, d, J=7.5 Hz, H8); 7.52 (1H, d, J=8.1 Hz, H6); 7.40 (1H, s, H2); 7.31 (1H, dd, J=8.1+7.5 Hz, H7); 5.02 (1H, dd, J=12.5+7.6 Hz, H4); 3.80 (1H, dd, J=14.6+7.6 Hz, $H3_A$); 3.72 (2H, m, N–CH_2); 3.54 (1H, dd, J=14.6+12.5 Hz, $H3_B$); 3.25 (2H, m, CH_2–CN); 3.02 (3H, s, N–CH_3). ^{13}C NMR (HCl salt, $CDCl_3$+DMSO) δ (ppm): 14.5 ($\underline{C}H_2$–CN); 22.0 (C3); 38.9 (N–CH_3); 50.2 (N–CH_2); 69.3 ($\underline{C}$4); 105.2 (C2a); 116.2 (C6); 117.9 (CN); 118.6 (C8); 122.7 (C7); 123.5 (C5a); 124.1 (C2); 131.5 (C8b); 135.5(C8a); 191.1 (C5). IR (HCl salt, KBr, cm^{-1}): 1685 (C=O ketone), 2250 (CN), 3200 (NH and N^+H). MS (EI, *m/z*, %): 253 (M^+; 73), 224 (16), 213 (19), 198 (5), 183 (29), 171 (100), 155 (16), 130 (71), 115 (32), 103 (7), 92 (9), 85 (6), 77 (10), 63 (6), 57 (8), 51 (5), 42 (19), 38 (6), 36 (16). Anal. Calcd for $C_{15}H_{15}N_3O$: C, 71.13; H, 5.97; N, 16.59. Found: C, 71.02; H, 6.05; N, 16.42.

Compound ***3b***: This was directly used for the next cyclization step without isolating the title compound. An aliquot of compound **3b**, the first intermediate in the present synthetic pathway, was isolated and characterized after chromatography and transformation into the HCl salt. Tan microcrystalline salt was thus obtained. Yield: 48%. Mp: 126–128 °C. ^1H NMR (HCl salt, DMSO-d_6) δ (ppm): 11.5 (1H, s, NH); 11.05+10.45 (1H, s, NH^+); 7.71 (1H, dd, J=8.1+1.5 Hz, H8); 7.48 (1H, dd, J=7.7+1.5 Hz, H6); 7.47 (1H, s, H2); 7.27 (1H, dd, J=8.1+7.7 Hz, H7); 5.0 (1H, m, H4); 4.1 (2H, q, J=7.1 Hz; O–CH_2); 3.71 (1H, m, $H3_A$); 3.58 (2H, m, N^+–CH_2); 3.51 (1H, m, $H3_B$); 3.03+2.9 (2H, m, CO–CH_2); 2.96 (3H, s, N^+CH_3); 1.2 (3H, t, J=7.1 Hz, CH_3). ^{13}C NMR (DMSO-d_6) δ (ppm): 14.7 ($\underline{C}H_3$); 21.1 (C3); 29.9 (CO–$\underline{C}H_2$); 39.0 (N^+–CH_3); 50.1 ($\overline{N^+}$–CH_2); 61.2 (O–CH_2); 68.1 ($\overline{C}$4); 105.8 (C2a); 116.2 (C6); 118.6 (C8); 122.9 (C7); 123.6 (C5a), 124.4 (C2); 131.6 (C8b); 135.3 (C8a); 170.8 ($\underline{C}O_2CH_2$); 191.6 (C5). IR (KBr, cm^{-1}): 1685 (C=O ketone), 1735 (C=O ester), 3240+3400 (NH+N^+H). MS (EI, *m/z*, %): 300 (M^+; 68), 271 (20), 257 (4), 243 (4), 213 (55), 199 (15), 185 (18), 171 (96), 155 (13), 144 (25), 130 (100), 115 (24), 106 (8), 92 (8), 85 (4), 70 (7), 56 (5), 44 (7). Anal. Calcd for $C_{17}H_{21}ClN_2O_3$: C, 60.62; H, 6.28; N, 8.32; Cl, 10.53. Found: C, 60.44; H, 6.10; N, 8.09; Cl, 10.71.

4.3. Cyclization of compounds ***3a*** and ***3b*** into diastereomeric mixtures of D-nor-ergolines ***4a*** and ***4b***

4.3.1. (±)-8-Cyano-9-hydroxy-6-methyl-4,5,6,7,8,9-hexahydro-1H-indolo[4,3-ef]indole (***4a***)

A solution of **3a** (1.16 g; 4.6 mmol) in dry THF (100 ml) was cooled to −70 °C under argon protection, and a 1 M solution of lithium bis[trimethylsilyl]amide in THF (10 ml; 10 mmol) was added through septum by syringe. After stirring the mixture at −70 °C for 45 min another portion of base (5 ml; 5 mmol) was added and stirred again for 45 min. This mixture was decomposed by adding acetic acid (10 ml) still maintaining the temperature at −70 °C, then let to warm up to ambient

temperature (about 10–15 min), finally the solvent was removed in vacuum (bath temp max 30 °C). The residue was extracted in a mixture of $CHCl_3$ (300 ml), water (100 ml) and cc. NH_4OH (10 ml). After separating the layers the aqueous phase was washed with $CHCl_3$ (50 ml). The combined organic phase was washed with water (2×100 ml), dried, and evaporated. Purification with chromatography ($CHCl_3$–MeOH 20:1) gave **4a** as pale yellow oil. Yield: 0.76 g (65%). Mixture of diastereomers. ^{1}H NMR ($CDCl_3$) δ (ppm): 8.10 (1H, s, NH); 7.18–7.48 (3H, m, H11+H12+H13); 6.94–6.87 (1H, m, H2); 3.56–3.45 (1H, dd, J=8.9+4.5, 8.9+5.8, 9.1+7 Hz, H8); 3.23–2.83 (1H, m, H5); 3.32–3.24 (1H, m, $H7_A$); 3.14–3.01 (1H, m, $H7_B$); 2.97–2.88 (1H, m, $H4_A$); 3.06–2.84 (1H, m, $H4_B$); 2.54–2.46 (3H, s, N–CH_3). ^{13}C NMR ($CDCl_3$) δ (ppm): 19.4+20.2 (C4); 35.4+39.4+41.1 (C8), 38.4+38.6+39.6 (N–CH_3); 54.9+55.9 (C7); 70.5+70.7+71.2 (C5); 78.7+81.0 (C9); 108.5+108.9 (C3); 111.0+111.7 (C13); 114.6+115.0+115.7 (C11); 119.3+119.4 (CN); 119.0+119.5+119.6 (C2); 122.9+123.3+123.5 (C12); 124.9+126.1 (C15); 128.6+130.5 (C10); 133.8+134.0 (C14). IR (KBr, cm^{-1}): 2245 (CN), 3437 (NH+OH). MS (EI, *m/z*, %): 253 (M^+; 69), 236 (8), 209 (6), 197 (20), 183 (6), 170 (100), 154 (15), 140 (6), 130 (39), 115 (22), 102 (7), 77 (9), 63 (6), 57 (28), 51 (5), 42 (22). Anal. Calcd for $C_{15}H_{15}N_3O$: C, 71.13; H, 5.97; N, 16.59. Found: C, 70.92; H, 6.10; N, 16.32.

*4.3.2. (±)-8-Ethoxycarbonyl-9-hydroxy-6-methyl-4,5,6,7,-8,9-hexahydro-1H-indolo[4,3-ef]indole (**4b**)*

The THF solution, obtained in the previous example, and containing about 2 mmol alkylated compound **3b** was cooled to −70 °C under argon protection, and a 1 M solution of lithium bis[trimethylsilyl]amide in THF (12 ml; 12 mmol) was added through septum by syringe. After stirring the mixture at −70 °C for 3–4 h the mixture was decomposed and neutralized by adding 20% HCl solution still maintaining the temperature at −70 °C (pH 7). Then the mixture was let to warm up to ambient temperature and the solvent THF was removed in vacuum (bath temp max 30 °C). The residue was extracted in a mixture of $CHCl_3$ (100 ml) and water (50 ml), while rendering the pH of the aqueous phase to 8 by adding satd Na_2CO_3 solution. The organic phase was dried and evaporated. Purification with chromatography ($CHCl_3$–MeOH 50:1) gave **4b** as pale yellow oil. Yield: 0.30 g (~50%), which according to ^{1}H NMR measurement proved to be a ~65:35 mixture of two diastereomers. An aliquot amount of base has been transformed into HCl salt (EtOH–diethyl ether). Mp: 165–170 °C (decomp.). The major component has an equatorial H5, the minor one (values in italics) an axial H5 proton. ^{1}H NMR (base, $CDCl_3$) δ (ppm): *8.1 (1H, s, NH)*; 8.0 (1H, s, NH); 7.54 (1H, dd, J=7+1 Hz, H11); 7.14–7.30 (2H+*3H*, m, H12+H13+*H11+H12+H13*); *6.89 (1H, dd, J=1.2+1 Hz, H2)*; 6.88 (1H, dd, J=1.5+1 Hz, H2); 4.24–4.36 (2H+*2H*, m, COO–CH_2+*COO–CH_2*); *3.81 (1H, dd, J=9.5+4 Hz, $H7_A$)*; *3.59 (1H, dd, J=9.6+4 Hz, H8)*; 3.57 (1H, dd, J=9+7 Hz, H8); 3.2 (1H+*1H*, br s, OH); 3.16 (1H, dd, J=10+9 Hz, $H7_A$); 3.12 (1H, dd, J=5.5+5 Hz, H5); 3.07 (1H, dd, J=10+7 Hz, $H7_B$); 3.04 (1H, ddd, J=15+5+1.5 Hz, $H4_A$); *3.0 (1H, ddd, J=12.5+5+1 Hz, $H4_A$)*; 2.98 (1H, ddd, J=15+5.5+1 Hz, $H4_B$); *2.90 (1H, ddd, J=12.5+11+1.2 Hz, $H4_B$)*; *2.48 (1H, dd, J=9.6+9.5 Hz, $H7_B$)*; 2.45 (3H, s, N–CH_3); *2.44 (1H, dd, J=11+5 Hz, H5)*; *2.42 (3H, s, N6–CH_3)*; 2.2–2.8 (1H+*1H*, OH+*OH*); 1.36 (3H+*3H*, m, CH_2–C$\underline{H}_3$+CH_2–C$\underline{H}_3$). ^{13}C NMR (base, $CDCl_3$) δ (ppm): 14.3, *14.2* (CH_2–$\underline{C}H_3$); 19.6, *21.6* (C4); 39.8, *39.3* (N–CH_3); 51.9, *48.7* (C8); 55.8, *57.6* (C7); 61.2, *61.0* ($\underline{C}H_2$–CH_3); 71.0, *74.0* (C5); 79.8, *79.2* (C9); 109.0, *108.8* (C3); 110.3, *111.0* (C13); 115.5, *115.4* (C11); 119.2, *119.0* (C2); 123.3, *122.7* (C12); 125.2, *127.4* (C15); 132.8, *132.5* (C10); 134.2, *134.1* (C14); 172.8, *172.3* (CO). IR (HCl salt, KBr, cm^{-1}): 1730 (C=O), 3230, 3440 (N^+H+NH+OH). MS (EI, *m/z*, %): 300 (M^+; 42), 282 (16), 255 (6), 209 (58), 170 (100), 154 (27), 140 (6), 130 (29), 115 (25), 105 (6), 77 (7), 55 (18). Anal. Calcd for $C_{17}H_{21}ClN_2O_3$: C, 60.62; H, 6.28; N, 8.32; Cl, 10.53. Found: C, 60.55; H, 6.36; N, 8.21; Cl, 10.41.

*4.4. Water elimination from compounds **4a** and **4b**. D-Norergolenes **5a** and **5b***

Solution of 9-hydroxy derivative **4a** or **4b** (3.0 mmol) in a mixture of dry pyridine (10 ml) and $POCl_3$ (0.5 ml; 6 mmol) was heated in a 120 °C oil bath for 45 min. Having cooled, the mixture was poured onto crushed ice (100 g) containing 25% NH_4OH (2 ml) and extracted with $CHCl_3$ (5×50 ml). The combined organic phase was washed with brine (70 ml), dried, and evaporated in vacuum.

*4.4.1. (±)-8-Cyano-6-methyl-4,5,6,7-tetrahydro-1H-indolo-[4,3-ef]indole hydrochloride (**5a**)*

The raw material (440 mg) was purified by chromatography ($CHCl_3$) to afford **5a** as pale yellow oil. Crystallization from diethyl ether gave pale yellow crystals. Yield: 224 mg (31%). Mp: 185–190 °C. An aliquot was transformed into the HCl salt in EtOAc–acetone–MeOH (5:5:1) mixture by treating with HCl–dioxane (pH 2). Mp: 211–214 °C. ^{1}H NMR (base, $CDCl_3$+DMSO-d_6) δ (ppm): 10.3 (1H, s, NH); 7.78 (1H, d, J=7.3 Hz, H11); 7.41 (1H, d, J=8.1 Hz, H13); 7.22 (1H, dd, J=8.1+7.3 Hz, H12); 7.03 (1H, s, H2); 4.12 (1H, dd, J=12.8+3.8 Hz, $H7_A$); 3.80 (1H, m, H5); 3.62 (1H, dd, J=12.8+6.2 Hz, $H7_B$); 3.42 (1H, dd, J=14.5+6.8 Hz, $H4_A$); 2.99 (3H, s, N–CH_3); 2.70 (1H, dd, J=14.5+10.9 Hz, $H4_B$). ^{13}C NMR ($CDCl_3$+DMSO) δ (ppm): 28.2 (C4); 62.9 (C7); 71.5 (C5); 99.2 (C8); 109.4 (C3); 113.9 (C11); 115.4 (C13); 116.7 (CN); 121.1 (C10); 121.2 (C2); 122.7 (C12); 128.4 (C15); 134.5 (C14); 154.1 (C9). IR (base, KBr, cm^{-1}): 1620 (C=C), 2207 (conj. CN), 3400 (NH). MS (EI, *m/z*, %): 235 (M^+; 100), 218 (5), 207 (14), 193 (10), 179 (4), 165 (7), 154 (9), 139 (4), 127 (3), 117 (6), 104 (5), 75 (3). Anal. Calcd for $C_{15}H_{14}ClN_3$: C, 66.30; H, 5.19; N, 15.46; Cl, 13.05. Found: C, 66.21; H, 5.33; N, 15.33; Cl, 13.28.

*4.4.2. (±)-8-Ethoxycarbonyl-6-methyl-4,5,6,7-tetrahydro-1H-indolo[4,3-ef]indole hydrochloride (**5b**)*

The raw material (400 mg) obtained starting from **4b** (901 mg; 3 mmol) was purified on silica ($CHCl_3$–MeOH 20:1)

to afford **5b** as base, which was converted into the HCl salt (EtOH+EtOH/HCl). Yield: 240 mg (25%). Mp: above 190 °C decomposes.

For spectral analysis aliquot part of the base has been recrystallized from EtOAc. Mp: 164–166 °C. ^{1}H NMR ($CDCl_3$) δ (ppm): 8.25 (1H, d, J=7.8 Hz, H11); 8.17 (1H, s, NH); 7.32 (1H, d, J=8.2 Hz, H13); 7.23 (1H, dd, J=8.2+7.8 Hz, H12); 6.96 (1H, dd, J=1.6+1 Hz, H2); 4.26–4.38 (3H, m, $H7_A$+C$\underline{H_2}$–CH_3); 3.83 (1H, m, H5); 3.68 (1H, dd, J=13.5+5.2 Hz, $H7_B$); 3.36 (1H, ddd, J=14.5+6.0+1.0 Hz, $H4_A$); 2.83 (1H, ddd, J=14.5+11.0+1.6 Hz, $H4_B$); 2.58 (3H, s, N–CH_3); 1.34 (3H, t, J=7 Hz, CH_2–C$\underline{H_3}$). ^{13}C NMR ($CDCl_3$) δ (ppm): 14.3 (CH_2–$\underline{C}H_3$); 28.7 (C4); 40.2 (N–CH_3); 60.3 ($\underline{C}H_2$–CH_3); 63.6 (C7); 73.7 (C5); 111.1 (C3); 112.5 (C13); 119.2 (C2); 119.9 (C11); 122.7 (C8); 122.9 (C12); 123.1 (C10); 128.7 (C15); 134.1 (C14); 147.2 (C9); 164.7 ($\underline{C}$=O). IR (base, KBr, cm^{-1}): 1605 (C=C), 1710 (conj. C=O). MS (EI, *m/z*, %): 282 (M^+; 34), 237 (6), 209 (100), 193 (8), 182 (4), 167 (5), 139 (5), 104 (10), 98 (4). Anal. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.19; H, 6.40; N, 9.83.

*4.5. Reductive transformation of the ester function into methyl (**5b**→**6**→**7**)*

*4.5.1. (±)-8-Hydroxymethyl-6-methyl-4,5,6,7-tetrahydro-1H-indolo[4,3-ef]indole (**6**)*

A solution of unsaturated ester **5b** (565 mg; 2 mmol) in a mixture of dry Et_2O (10 ml) and dry THF (10 ml) was cooled in an ice-water bath and while stirred under argon protection 1 M $LiAlH_4$ in Et_2O (7 ml; 7 mmol) was added, and the mixture was stirred for 40–50 min at ambient temperature, then cooled (ice-water bath) and decomposed with water (7 ml), 15% NaOH (7 ml), and water (20 ml) added carefully and successively. The precipitate was filtered off, washed with $CHCl_3$ (4–5×10 ml) and MeOH (10 ml), the combined organic phase was dried and evaporated. The residue was purified with chromatography ($CHCl_3$–MeOH 9:1) to afford alcohol **6** as pale yellow oil. Yield: 432 mg (90%). Recrystallization of an aliquot amount gave tan microcrystals of mp 158–160 °C. ^{1}H NMR ($CDCl_3$+DMSO) δ (ppm): 10.4 (1H, s, NH); 7.20 (1H, dd, J=7.5+1.2 Hz, H13); 7.08 (1H, dd, J=7.7+7.5 Hz, H12); 7.06 (1H, dd, J=7.7+1.2 Hz, H11); 6.92 (1H, dd, J=1.7+1 Hz, H2); 4.54–4.62 (2H, m, C$\underline{H_2}$OH); 4.13 (1H, dd, J=13.8+3 Hz, $H7_A$); 3.68 (1H, m, H5); 3.6 (1H, br s, OH); 3.59 (1H, dd, J=13.8+4 Hz, $H7_B$), 3.33 (1H, ddd, J=14.5+6.2+1 Hz, $H4_A$); 2.63 (1H, ddd, J=14.5+11+1.7 Hz, $H4_B$); 2.56 (3H, s, N–CH_3). ^{13}C NMR ($CDCl_3$+DMSO) δ (ppm): 29.2 (C4); 40.3 (N–CH_3); 57.6 (CH_2OH); 64.3 (C7); 72.3 (C5); 110.2 (C13); 110.3 (C3); 115.0 (C2); 119.1(C11); 122.2 (C12); 124.3 (C15); 127.4 (C10); 131.3 (C8); 134.1 (C9); 134.7 (C14). IR (KBr, cm^{-1}): 3240+3250 (NH+OH). MS (EI, *m/z*, %): 240 (M^+; 62), 221 (18), 209 (100), 193 (14), 181 (8), 167 (12), 154 (8), 139 (8), 127 (4), 104 (5), 97 (3). Anal. Calcd for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.66. Found: C, 74.90; H, 6.81; N, 11.57.

*4.5.2. (±)-6,8-Dimethyl-4,5,6,7-tetrahydro-1H-indolo[4,3-ef]-indole (**7**)*

A solution of unsaturated alcohol **6** (240 mg; 1 mmol) in dry THF (16 ml) was cooled in ice-water bath and while stirred under argon protection, SO_3Py complex (320 mg; 2 mmol) was added. The solution was kept in a cooler (0–3 °C) for 2–3 days; the conversion was checked by TLC ($CHCl_3$–MeOH 4:1). When all the starting materials disappeared, 1 M $LiAlH_4$ in Et_2O (10 ml; 10 mmol) was added, and the mixture was stirred for 1 h at 0 °C then 5 h at rt. The complex was decomposed with water (0.5 ml), 15% NaOH (0.5 ml) and water (1.5 ml) added carefully and successively. The precipitate was filtered off, washed with $CHCl_3$ (4–5×10 ml), the combined organic phase was dried and evaporated. The residue was purified with chromatography ($CHCl_3$–MeOH 4:1) to afford **7** as pale brown oil. Yield: 80 mg (36%). Upon chromatography some starting material (140 mg) could be recovered. Repeating the two-step reduction from this recovered starting material another 58 mg (26%) **7** could be prepared. Combined yield: 138 mg (62%). An aliquot amount was transformed into the HCl salt (CH_2Cl_2–Et_2O+HCl/dioxane) for analytical purpose. Mp: decomposes over 204 °C. ^{1}H NMR (base, $CDCl_3$) δ (ppm): 8.0 (1H, s, NH); 7.25 (1H, dd, J=7.6+7.2 Hz, H12); 7.18–7.21 (2H, m, H11+H13); 6.91 (1H, s, H2); 3.94 (1H, dd, J=14+3.8 Hz, $H7_A$); 3.71 (1H, m, H5); 3.52 (1H, dd, J=14+4.1 Hz, $H7_B$); 3.34 (1H, dd, J=14.5+6 Hz, $H4_A$); 2.72 (1H, dd, J=15+14.5 Hz, $H4_B$); 2.60 (3H, s, N–CH_3); 2.14 (3H, s, C8–CH_3). ^{13}C NMR ($CDCl_3$) δ (ppm): 13.6 (C8–$\underline{C}H_3$); 29.3 (C4); 40.6 (N–CH_3); 68.3 (C7), 72.5 (C5), 109.3 (C13); 112.2 (C3); 114.8 (C11); 118.3 (C2); 123.1 (C12); 125.9 (C9); 127.4 (C15); 130.2 (C8); 130.6 (C10); 134.1 (C14). IR (KBr, cm^{-1}): 3350 (NH). MS (EI, *m/z*, %): 224 (M^+; 98), 209 (100), 193 (10), 181 (8), 167 (11), 154 (18), 139 (4), 127 (5), 104 (15), 97 (8). Anal. Calcd for the HCl salt $C_{15}H_{17}ClN_2$: C, 69.09; H, 6.57; N, 10.74; Cl, 13.60. Found: C, 68.96; H, 6.63; N, 10.66; Cl, 13.49.

*4.5.3. (±)-Cycloclavine HCl (**1**·**HCl**)*

Solution of dimethyl derivative **7** (224 mg; 1 mmol) in CH_2Cl_2 (10 ml) was cooled in an ice-water bath, $Pd(OAc)_2$ (15 mg; 0.068 mmol) was added, and while stirred under argon protection, 0.3 M CH_2N_2–CH_2Cl_2 solution (35 ml; ~10 mmol) was added into the mixture. The mixture was stirred at 0–5 °C. Progress of the reaction could be checked by TLC ($CHCl_3$–MeOH 9:1; R_f **1**>R_f **7**). After 1 h reaction time another portion of CH_2N_2–CH_2Cl_2 solution (35 ml; ~10 mmol) and $Pd(OAc)_2$ (15 mg; 0.068 mmol) was added and after another 3 h one more portion of CH_2N_2–CH_2Cl_2 solution (25 ml; ~8.2 mmol). The conversion, however, stopped, so the mixture was filtered, the solution dried, and evaporated. The residue was purified by chromatography to yield starting material (**7**; 70 mg) and (±)-cycloclavine (**1**), which was isolated as the HCl salt (CH_2Cl_2–Et_2O+HCl/dioxane). Yield: 60.5 mg (32%, calculated upon the unrecovered starting material **7**). Mp: 165–172 °C. ^{1}H NMR (HCl salt, $CDCl_3$) δ (ppm): 12.0 (1H, s, N^+H); 8.66 (1H, s, NH); 7.22

(1H, d, J=7.8 Hz, H14), 7.08 (1H, dd, J=7.8+7.3 Hz, H13); 6.94 (1H, dd, J=1.7+1.5 Hz, H2), 6.80 (1H, d, J=7.3 Hz, H12), 3.94 (1H, dd, J=10.5+4.6 Hz, $H7_A$); 3.75 (1H, ddd, J=12+9.4+4.5 Hz, H5); 3.39 (1H, ddd, J=14+12+1.7 Hz, $H4_A$); 3.27 (1H, ddd, J=14+4.5+1.5 Hz, $H4_B$); 3.08 (1H, ddd, J=10.5+8.5+1.2 Hz, $H7_B$); 2.87 (3H, d, J=4.6 Hz, N^+-CH_3); 2.48 (1H, d, J=6.6 Hz, $H9_A$); 1.75 (3H, s, C8–CH_3); 0.78 (1H, d, J=6.6 Hz, $H9_B$). ^{13}C NMR (HCl salt, $CDCl_3$) δ (ppm): 15.4 (C8–$\underline{C}H_3$); 22.8 (C9); 23.6 (C4); 26.6 (C10); 33.5 (C8); 39.5 (N^+-CH_3); 63.4 (C7); 71.2 (C5); 109.4 (C3); 109.5 (C14); 110.8 (C12); 119.4 (C2); 123.2 (C13); 128.2 (C16); 130.8 (C11); 133.8 (C15). IR (KBr, cm^{-1}): 2500 (br for ammonium salt); 3250 and 3400 (indole NH and N^+H). MS (EI, *m/z*, %): 238 (M^+; 100), 223 (18), 206 (10), 194 (12), 180 (16), 167 (51), 154 (38), 142 (11), 127 (16), 115 (13), 97 (4). HRMS (EI): $C_{16}H_{18}N_2$ *m/z* calcd 328.1470, found 328.1461. Anal. Calcd for the HCl salt $C_{16}H_{19}ClN_2$: C, 69.93; H, 6.97; N, 10.19; Cl, 12.90. Found: C, 70.03; H, 6.94; N, 10.27; Cl, 12.77.

Aliquot amount (20 mg) HCl salt was transformed into the corresponding base, and NMR investigation was performed as well. ^{1}H NMR (base, $CDCl_3$) δ (ppm): 7.95 (1H, s, NH); 7.15–7.00 (2H, m, H13+H14), 6.87 (1H, d, J=2 Hz, H2), 6.80 (1H, d, J=7 Hz, H12), 3.14 (1H, d, J=9 Hz, $H7_A$); 3.12 (1H, dd, J=13.2+4.3 Hz, $H4_A$); 2.76 (1H, dd, J=11.6+4.3 Hz, H5); 2.58 (1H, ddd, J=13.2+11.6+2 Hz, $H4_B$); 2.38 (1H, d, J=9 Hz, $H7_B$); 2.34 (3H, s, N–CH_3); 1.68 (3H, s, C8–CH_3); 1.58 (1H, d, J=3.6 Hz, $H9_A$); 0.44 (1H, d, J=3.6 Hz, $H9_B$). ^{13}C NMR (base, $CDCl_3$) δ (ppm): 16.7 (C8–$\underline{C}H_3$); 24.4 (C9); 25.1 (C4); 28.0 (C10); 29.9 (C8); 40.1 (N–$\underline{C}H_3$); 65.8 (C7); 69.9 (C5); 108.1 (C14); 110.6 (C12); 113.5 (C3); 118.3 (C2); 123.1 (C13); 129.0 (C16); 133.8 (C15); 135.6 (C11).

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