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Chemistry of indoles carrying a basic function. Part 8: A new approach to the ergoline skeleton☆

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Abstract—Starting from *N*-pivaloyl-Uhle's ketone a new synthetic approach to the ergoline skeleton has been elaborated. Ring D of the tetracyclic skeleton was formed by an intramolecular Dieckmann-condensation of a diester, obtained in a Reformatsky reaction of a properly substituted derivative of *N*-pivaloyl Uhle's ketone followed by elimination of water.

The striking physiological properties of compounds having an ergoline skeleton directed the attention of several chemists to the total synthesis[2] of such compounds. The vast majority of the successful approaches used indoline intermediates, and the indole ring was introduced at the end of the reaction sequence by a reoxidation step.

The so-called Uhle's ketone (**1a**) seemed to be an ideal starting material, because no reduction and reoxidation in a later stage is required. Several researchers tried, but failed to achieve this goal.[3] We reported the first successful reaction sequence to this end by applying an unprecedented intramolecular Stobbe-condensation taking advantage of a lithium complex formed as an intermediate.[4]

Now we report another approach to the required skeleton starting from the *N*-pivaloyl derivative of Uhle's ketone (**1b**), obtained in three steps from indole-3-propionic acid according to the method of Goto et al.[5] Transformation of **1b** into the α-amino ketone **1e** via bromination (**1c**) and bromine→azide exchange (**1d**) was described by us earlier.[6] Direct alkylation of this amine with bromoacetic acid esters was unsuccessful because of their susceptibility to very easy oxidation and rearrangement into a naphthalene derivative. Having protected the carbonyl group of the azide intermediate **1d** as a ketal (**2**), however, the alkylation of the α-amino-ketal **3**, obtained after catalytic reduction of **2**, was performed smoothly. Methylation of ketal-ester **4** using formaldehyde and sodium cyanoborohydride supplied the tertiary amine **5**, which after deprotection with sulphuric acid resulted in the required dialkylated intermediate **6** as a stable hydrochloride salt (Scheme 1).

Following the envisaged reaction sequence in order to build up the D ring of the ergoline skeleton, Wittig–Horner and Knoevenagel-type reactions were attempted to form a C=C bond in place of the carbonyl function at position 5. Though Wittig–Horner reaction of unsubstituted Uhle's ketone with triethyl phosphonoacetate[7] or Knoevenagel–Doebner-type condensation of Uhle's ketone[7] or 4-acetamino Uhle's ketone[8] with malononitrile or ethyl cyanoacetate could be performed in reasonably good yield, similar processes with our dialkylated intermediate **6** failed. However, using methyl or ethyl acetate lithiated with bis(trimethylsilyl)-amide at −78°C[9] we were at last successful in achieving our goal and preparing hydroxy-diester **7** from the freshly prepared base of HCl salt **6**. In our earlier attempts we were unable to eliminate water from a related derivative already possessing the ergoline skeleton,[4] but in this case the $POCl_3$/pyridine system worked, and a mixture of geometric isomers of unsaturated esters **8** and **9** was obtained in reasonably good yield. In the reaction, about 40% of naphthalene derivative **10** was also formed by endocyclic water elimination or double bond migration. This mixture, in which the *Z* isomer (**8**) dominated, could be separated by column chromatography. The structures of the geometric isomers **8** and **9** as well as that of the naphthalene derivative **10** were elucidated by ^{1}H NMR spectroscopy and NOE measurements. The presence or absence of the olefinic proton as well as the lack of one aromatic proton (H2) in the endocyclic by-product **10** is diagnostic in differentiating the exocyclic geometric isomers (**8** and **9**) from the naphthalene derivative **10**. A strong NOE interaction measured between

☆ See Ref. 1.

Keywords: alkaloids; ergolines; modified Reformatsky reaction; cyclisation; Dieckmann condensation.

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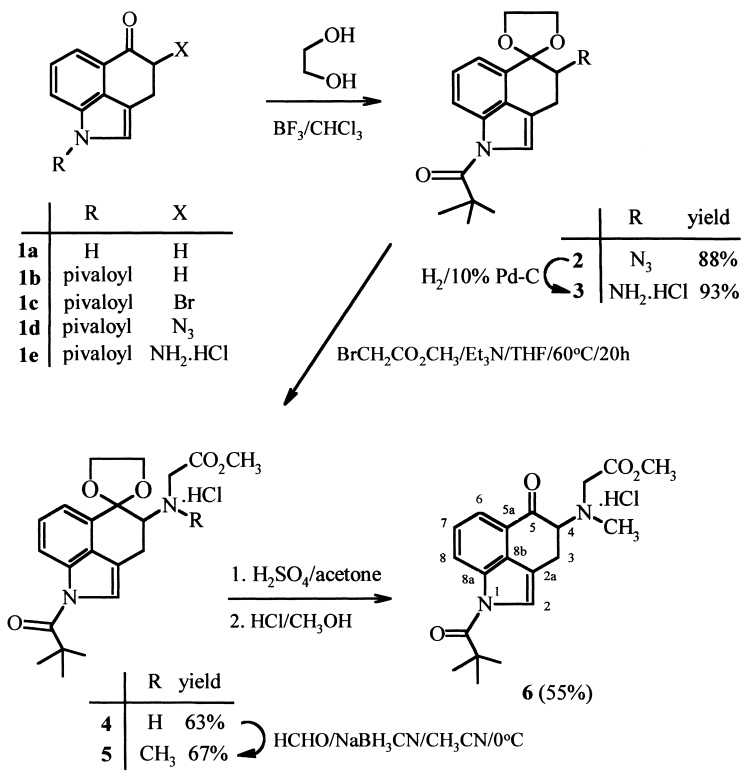
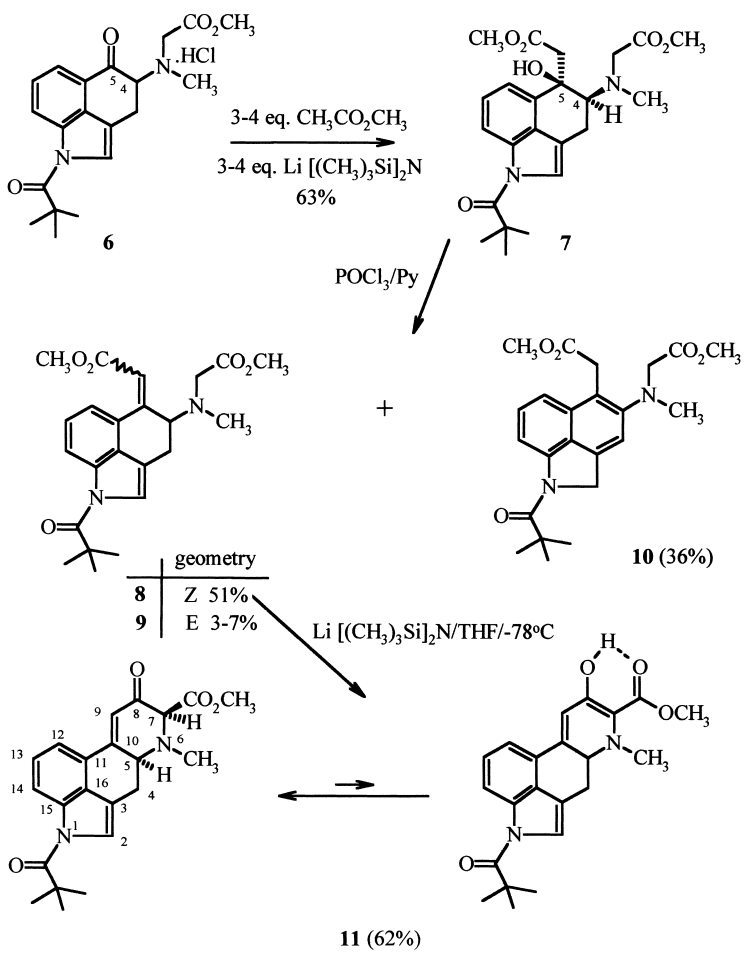
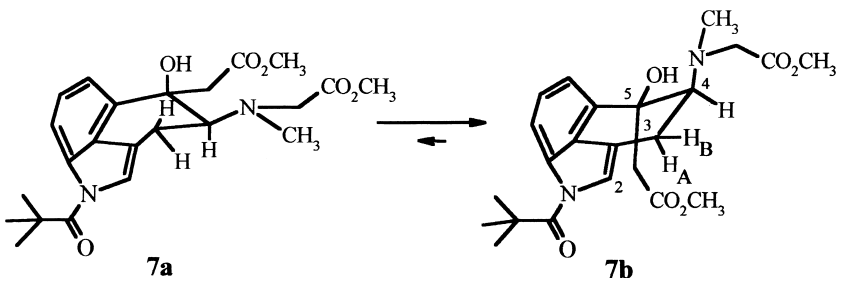


Scheme 1.



Scheme 2.



Scheme 3.

the olefinic proton in *Z* isomer **8** and the aromatic proton (H6) makes possible the assignment of stereochemistry in **8** and **9** (Scheme 2).

The reaction sequence concluded with a Dieckmann cyclisation of the *Z* isomer **8** yielding compound **11**. In the reaction lithium bis(trimethylsilyl)amide proved to be the best base.

It is worth mentioning that the stereochemistry of hydroxy-ester **7** contradicts the expectation. The NMR study unambiguously proved that H4 is quasi equatorial (from $J_{3,4}$=5.2, 5.0 Hz) and the two bulky substituents at C4 and C5 occupy *trans* diaxial relationship (NOE measurements, see Section 1), i.e. **7b** proved to be the most stable conformation (Scheme 3).[10]

According to evidence provided by ^{1}H NMR as well as IR spectroscopy, derivative **11** exists both in the crystalline form and in chloroform solution mainly (85%) in the keto form, as the thermodynamically more stable diastereomer. The orientation of the ester group is quasi-equatorial with a *cis* arrangement between the hydrogens at C5 and C7, unambiguously proven by NOE measurements (see Section 1).

Using the above described reaction sequence a new route leading to ergot derivatives has been elaborated. Further transformation of keto-ester **11** into other useful derivatives is in progress and will be reported in due course.

1. Experimental

1.1. General

Melting points are uncorrected. Mass spectra were run on an AEI-MS-902 (70 eV; direct insertion) mass spectrometer. IR spectra were taken on a Nicolet 205 and Nicolet 7795 FT-IR spectrophotometers. NMR spectroscopy measurements were carried out on a Varian Unity Inova (400 MHz) instrument. Chemical shifts are given relative to TMS=0.00 ppm. Peaks with identical signs are interchangeable. Elemental analyses (C, H, N) were carried out by Vario EL III (Elementar Analysen Systeme GmbH) automatic microanalyzer, ionic halide content was measured by titration with mercuric perchlorate. For TLC analyses MN Polygram SIL G/UV$_{254}$ sheets were used. Preparative separations were performed by column chromatography on Merck Kieselgel 60 (0.063–0.200).

Glassware was flame dried before use. Solvents were carefully dried and purified by appropriate methods. The majority of the reactions were carried out under argon.

1.1.1. (±)-4-Azido-5,5-ethylenedioxy-1-pivaloyl-1,3,4,5-tetrahydrobenz[*c*,*d*]indole (2). Protection of the oxo function was accomplished similarly to Bowmann's method[8] as follows.

To the solution of 4-azido-Uhle ketone (5.93 g; 20 mmol) in dry $CHCl_3$ (250 mL) borontrifluoride–diethyl etherate (25 mL; 28 g; 0.2 mol) and ethylene glycol (25 mL; 27.8 g; 0.45 mol) were added. The solution was stirred at rt under argon for 28 h, then poured into excess saturated aq. $NaHCO_3$ solution (ca. 500 mL). After shaking the organic phase was separated, washed with water, dried (Na_2SO_4) and evaporated. The red oil (6.6 g; 97%) could be used without further purification in the next step.

For analytical purposes the oil was purified by column chromatography (eluent: hexane/$CHCl_3$/ethyl acetate 20:1:1) followed by crystallization in a diethyl ether/hexane 1:1 mixture to give the colourless crystals (88%) of the protected azide **2**. Mp 100–101°C. [Found C, 63.7; H, 6.0; N, 16.3. $C_{18}H_{20}N_4O_3$ requires C, 63.5; H, 5.9; N, 16.5%]; ν_{max} (KBr) 2830 (CH_2O), 2106 (azide), 1685 cm^{-1} (CO amide); δ_H (400 MHz, $CDCl_3$) 8.32 (1H, dd, J=8.1, 0.9 Hz, 8-*H*), 7.49 (1H, dd, J=1.5, 1.3 Hz, 2-*H*),7.38 (1H, dd, J=8.1, 7.4 Hz, 7-*H*), 7.32 (1H, dd, J=7.4, 0.9 Hz, 6-*H*), 4.20–4.40 (4H, m, OCH_2CH_2O), 4.02 (1H, dd, J=8.0, 4.5 Hz, 4-*H*), 3.14+3.26 (2×1H, 2×ddd, J=15.8, 8.0, 4.5, 1.3 Hz, 3-H_AH_B), 1.50 [9H, s, $C(CH_3)_3$]; δ_C (100.6 MHz, $CDCl_3$) 176.9 (NCO), 135.1 (C8a), 129.3° (C5a), 127.8° (C8b), 126.2 (C7), 120.5* (C2), 118.4* (C8), 118.2* (C6), 114.2 (C2a), 107.7 (C5), 65.8+66.4 (OCH_2CH_2O), 63.0 (C4), 40.9 (CMe_3), 28.6 [$C(CH_3)_3$], 25.7 (C3); *m/z* (EI) 340 (M^+, 1), 312 (2), 285 (41), 200 (100), 173 (6), 156 (17), 128 (25), 101 (8), 41 (18%).

1.1.2. (±)-4-Amino-5,5-ethylenedioxy-1-pivaloyl-1,3,4,5-tetrahydrobenz[*c*,*d*]indole hydrochloride (3). The crude azide **2** (6.8 g; 20 mmol) was dissolved in acetic acid (200 mL) and hydrogenated in the presence of 10% Pd–C catalyst (3.0 g) at rt and normal pressure. (In the course of the reaction no gas consumption can be observed, as during the reduction nitrogen gas is liberated. Because of this fact ventilation with hydrogen gas is recommended.) The reaction was completed after 1–1.5 h (TLC, eluent $CHCl_3$–MeOH 10:1, R_f amine<R_f azide.) Then the mixture is filtered, and the solution was admixed with 3.6N HCl/MeOH (5.6 mL; 20 mmol). The oily syrup obtained after

evaporation was treated with diethyl ether. After filtration pale tan crystals of amine HCl (**3**) (6.5 g; 93%) were obtained. Mp 186–188°C. [Found C, 61.5; H, 6.7; Cl, 10.0; N, 8.0. $C_{18}H_{23}ClN_2O_3$ requires C, 61.6; H, 6.6; Cl, 10.1; N, 8.0%]; ν_{max} (KBr) 3430 (NH_3^+), 1700 cm^{-1} (CO amide).

For spectroscopic characterisation the free base was prepared and investigated. The pale tan crystals melt at 158–160°C (diethyl ether). [Found C, 68.7; H, 7.1; N, 8.9. $C_{18}H_{22}N_2O_3$ requires C, 68.8; H, 7.0; N, 8.9%]; ν_{max} (KBr) 3400 (NH_2), 2860 (CH_2O), 1680 cm^{-1} (CO amide); δ_H (400 MHz, $CDCl_3$) 8.31 (1H, dd, *J*=8.1, 0.9 Hz, 8-*H*), 7.47 (1H, dd, *J*=2×1.5 Hz, 2-*H*), 7.36 (1H, dd, *J*=8.1, 7.2 Hz, 7-*H*), 7.28 (1H, dd, *J*=7.2, 0.9 Hz, 6-*H*), 4.13–4.36 (4H, m, OCH_2CH_2O), 3.38 (1H, dd, *J*=7.8, 4.6 Hz, 4-*H*), 2.93+3.23 (2×1H, 2×ddd, *J*=15.8, 7.8, 1.5+15.8, 4.6, 1.5 Hz, 3-H_2), 1.51 [9H, s, $C(CH_3)_3$]; δ_C (100.6 MHz, $CDCl_3$) 177.0 (NCO), 135.2 (C8a), 130.1° (C5a), 128.0° (C8b), 126.0 (C7), 120.4* (C2), 118.8* (C8), 117.8* (C6), 115.7 (C2a), 108.2 (C5), 65.0+66.5 (OCH_2CH_2O), 54.3 (C4), 40.9 (CMe_3), 28.5 [$C(CH_3)_3$], 27.6 (C3); *m/z* (EI) 314 (M^+, 58), 286 (7), 229 (7), 202 (22), 184 (18), 174 (4), 157 (8), 130 (23), 115 (5), 85 (6), 57 (100), 41 (18%).

1.1.3. (±)-5,5-Ethylenedioxy-4-(*N*-methoxycarbonylmethyl)amino-1-pivaloyl-1,3,4,5-tetrahydrobenz[*c*,*d*]indole hydrochloride (4). To the stirred suspension of amine hydrochloride **3** (7.02 g; 20 mmol) in dry THF (50 mL) the solution of methyl bromoacetate (1.9 mL; 3.06 g; 20 mmol) in dry THF (50 mL) was added. The suspension was heated to 60°C and a solution of triethylamine (5.6 mL; 4.04 g; 40 mmol) in dry THF (50 mL) was admixed dropwise. The mixture was stirred at 60°C for 20 h. Progress of the alkylation can be followed by TLC (hexane/ethyl acetate 1:1). The insoluble inorganics were filtered off, the solution was evaporated in vacuo. The residue was purified by column chromatography (eluent: hexane/ethyl acetate 1:1). After evaporation the oily residue was dissolved in MeOH (15 mL) and the pH of the solution was adjusted to acidic (pH 3) by addition of 3.6N HCl/MeOH (ca. 5 mL). Colourless crystals of **4** HCl, obtained after addition of diethyl ether, were filtered. Yield: 5.33 g (63%), mp 182–186°C. [Found C, 59.5; H, 6.4; Cl, 8.3; N, 6.6. $C_{21}H_{27}ClN_2O_5$ requires C, 59.6; H, 6.4; Cl, 8.4; N, 6.6%]; ν_{max} (KBr) 3400 (NH_2^+), 1750 (CO ester), 1690 cm^{-1} (CO amide); δ_H (400 MHz, $CDCl_3$+DMSO-d_6) 9.20+10.1 (2×1H, 2×br, $^+NH_2$), 8.28 (1H, dd, *J*=8.1, 1.0 Hz, 8-*H*), 7.70 (1H, brs, 2-*H*), 7.38 (1H, dd, *J*=8.1, 7.6 Hz, 7-*H*), 7.29 (1H, dd, *J*=7.6, 1.0 Hz, 6-*H*), 4.18+4.37–4.47 (1H+3H, 2×m, OCH_2CH_2O), 4.08+4.12 (2×1H, 2×d, *J*=17.0 Hz, NCH_2COOMe), 4.05 (1H, dd, *J*=9.6, 4.8 Hz, 4-*H*), 3.81 (3H, s, OCH_3), 3.42+3.57 (2×1H, 2×ddd, *J*=15.6, 9.6, 1.5+15.6, 4.8, ~1 Hz, 3-H_2), 1.51 [9H, s, $C(CH_3)_3$]; δ_C (100.6 MHz, $CDCl_3$+DMSO-d_6) 176.8 (NCO), 167.0 (CO_2Me), 134.8 (C8a), 128.0° (C5a), 127.4° (C8b), 125.9 (C7), 121.5* (C2), 118.4* (C8), 118.2* (C6), 112.5 (C2a), 105.8 (C5), 64.4+66.7 (OCH_2CH_2O), 58.6 (C4), 52.7 (OMe), 46.6 (NCH_2CO), 40.8 (CMe_3), 28.4 [$C(CH_3)_3$], 23.4 (C3); *m/z* (EI) 386 (M^+, 44), 358 (12), 327 (7), 314 (3), 301 (8), 273 (19), 255 (7), 230 (6), 197 (8), 184 (3), 169 (12), 156 (6), 142 (4), 130 (15), 85 (8), 57 (100), 43 (23%).

1.1.4. (±)-5,5-Ethylenedioxy-4-(*N*-methoxycarbonylmethyl-*N*-methyl)amino-1-pivaloyl-1,3,4,5-tetrahydrobenz[*c*,*d*]indole hydrochloride (5). To the stirred and cooled (0°C) suspension of the hydrochloride salt of methyl glycinate **4** (4.23 g; 10 mmol) in a mixture of dry acetonitrile (100 mL) and acetic acid (20 mL), 40% formaldehyde solution (30 mL; ~0.4 mol) and sodium cyanoborohydride (1.26 g; 20 mmol) were added. Progress of the reductive methylation can be followed by TLC (hexane/ethyl acetate 1:1; R_f product>R_f starting material). The reaction is complete after 30 min. Then the solution was diluted with distilled water (100 mL) and the pH was adjusted to 7–7.5 by addition of 10% aq. Na_2CO_3 solution. The slurry was extracted with chloroform. The dried (Na_2SO_4) organic phase was evaporated, the residue purified by column chromatography (eluent: hexane/ethyl acetate 1:1). After evaporation the oily base (3.8 g; 95%) was dissolved in MeOH (5 mL) and the pH was adjusted to acidic (pH 2–3) by addition of 3.6N HCl/MeOH (ca. 2.5 mL). Colourless crystals of hydrochloride salt of **5**, obtained after addition of diethyl ether, were filtered. Yield: 3.80 g (67%), mp 125–127°C. [Found C, 60.4; H, 6.8; Cl, 8.0; N, 6.3. $C_{22}H_{29}ClN_2O_5$ requires C, 60.5; H, 6.7; Cl, 8.1; N, 6.4%]; ν_{max} (KBr) 3400 (NH^+), 2906 (OCH_2), 1754 (CO ester), 1685 cm^{-1} (CO amide); δ_H (400 MHz, base formed in the tube by addition of solid K_2CO_3, $CDCl_3$) 8.26 (1H, dd, *J*=8.1, 0.8 Hz, 8-*H*), 7.43 (1H, dd, *J*=1.7, 1.1 Hz, 2-*H*), 7.33 (1H, dd, *J*=8.1, 7.4 Hz, 7-*H*), 7.25 (1H, dd, *J*=7.4, 0.8 Hz, 6-*H*), 4.0–4.35 (4H, m, OCH_2CH_2O), 3.71 (3H, s, OCH_3), 3.56+3.78 (2×1H, 2×d, *J*=17.2 Hz, NCH_2CO_2-Me), 3.37 (1H, dd, *J*=10.3, 5.0 Hz, 4-*H*), 3.21+3.27 (2×1H, 2×ddd, *J*=15.7, 10.3, 1.7+15.7, 5.0, 1.1 Hz, 3-H_2), 2.63 (3H, s, N*Me*), 1.50 [9H, s, $C(CH_3)_3$]; δ_C (100.6 MHz, HCl salt, DMSO-d_6) 177.1 (NCO), 166.8 (CO_2Me), 134.4 (C8a), 129.4° (C8b), 127.3° (C5a), 125.9 (C7), 122.2* (C2), 118.1* (C8), 117.8* (C6), 113.3 (C2a), 105.8 (C5), 64.2+66.6 (OCH_2CH_2O), 63.3 (C4), 55.4 ($^+NCH_2CO$), 52.7 (OCH_3), 40.8 (CMe_3), 28.1 [$C(CH_3)_3$], 20.2 (C3), $^+NCH_3$ (covered by the signals of DMSO); *m/z* (EI) 400 (M^+, 71), 341 (10), 327 (12), 315 (20), 287 (21), 269 (19), 255 (12), 243 (35), 183 (17), 169 (10), 156 (13), 130 (14), 115 (10), 85 (18), 69 (6), 57 (100), 41 (20%).

1.1.5. (±)-4-(*N*-Methoxycarbonylmethyl-*N*-methyl)-amino-5-oxo-1-pivaloyl-1,3,4,5-tetrahydrobenz[*c*,*d*]indole hydrochloride (6). The oily methyl glycinate base **5** (4.0 g; 10 mmol) was dissolved in a mixture of acetone (200 mL) and 2N aq. H_2SO_4 (50 mL) solution. The mixture was refluxed on an 80°C oil bath. Progress of the deprotection can be followed by TLC (hexane/ethyl acetate 1:1 after treating the sheet with NH_3 vapour; R_f ketone<R_f ketal). The reaction is complete after 9–10 h then the solution was evaporated in vacuo, while yellow crystal mass precipitated. The suspension was diluted with chloroform (200 mL) and distilled water (50 mL), the pH of the aqueous phase was adjusted to 7–7.5 by addition of saturated aq. $NaHCO_3$ solution. The slurry was separated, the aqueous phase extracted with chloroform (3×60 mL). The combined organic phase was acidified immediately with HCl/MeOH and evaporated. The residue was crystallised in CH_2Cl_2–diethyl ether to obtain pale yellow crystals of deprotected ketone HCl **6** (2.16 g; 55%); mp 128–130°C (decomp.). [Found C, 61.0; H, 6.3; Cl, 9.1; N, 7.2. $C_{20}H_{25}ClN_2O_4$

requires C, 61.1; H, 6.4; Cl, 9.0; N, 7.1%]; ν_{max} (KBr) 3400 (NH^+), 1751 (CO ester), 1693 cm^{-1} (CO ketone and amide); δ_H (400 MHz, $CDCl_3$+DMSO-d_6) 8.57 (1H, dd, J=8.1, 0.8 Hz, 8-*H*), 7.97 (1H, brs, 2-*H*), 7.73 (1H, dd, J=7.5, 0.8 Hz, 6-*H*), 7.48 (1H, dd, J=8.1, 7.5 Hz, 7-*H*), 6.1 ($^+$NH together/in change with H_2O content of the solvent), 4.94 (1H, dd, J=12.6, 6.5 Hz, 4-*H*), 4.39+4.52 (2×1H, 2×d, J=17.0 Hz, $^+NCH_2CO_2Me$), 4.02 (1H, brdd, J=15.0, 6.5 Hz, 3-H_{eq}), 3.85 (3H, s, OCH_3), 3.55 (1H, brdd, J=15.0, 12.6 Hz, 3-H_{ax}), 3.22 (3H, s, $^+CH_3$), 1.53 [9H, s, $C(CH_3)_3$]; δ_C (100.6 MHz, DMSO-d_6) 190.7 (C5), 177.2 (NCO), 167.4 (CO_2Me), 134.9 (C8a), 132.3 (C8b), 126.5 (C7), 124.5* (C8), 123.9 (C5a), 123.2* (C2), 119.9* (C6), 112.7 (C2a), 67.8 (C4), 54.2 ($^+NCH_2CO$), 52.9 (OMe),), 40.9 (CMe_3), 28.0 [$C(CH_3)_3$], 21.5 (C3), $^+NCH_3$ (covered by the signals of DMSO); *m/z* (EI) 356 (M^+,12), 297 (32), 271 (100), 255 (87), 243 (11), 213 (4), 183 (16), 170 (24), 155 (5), 142 (6), 130 (10), 115 (16), 85 (4), 72 (7), 57 (82), 36 (15%).

1.1.6. Methyl (±)-5-hydroxy-4-(*N*-methoxycarbonylmethyl-*N*-methyl)amino-1-pivaloyl-1,3,4,5-tetrahydrobenz[*c*,*d*]indole-5-acetate (7). A well dried 3-neck-flask was immersed in an acetone/dry CO_2 cooling bath (−78°C) and under argon protection 1N lithium bis(trimethylsilyl)-amid/THF solution (6 mL; 6 mmol) and methyl acetate (0.48 mL; 0.45 g; 6 mmol) were admixed. The solution was stirred for 15 min at −78°C. Then a solution of ketone base **6** in dry THF (40 mL), obtained from the suspension of the HCl salt (0.785 g; 2 mmol) by having treated with Hünig base (diisopropyl–ethylamine (0.34 mL, 0.26 g; 2 mmol), was admixed and washed into the reaction mixture with additional amounts of dry THF (2×10 mL). Progress of the addition can be followed by TLC (hexane/ethyl acetate 2:1; R_f diester>R_f ketone). If necessary, the reaction mixture was added to another stirred and cold (−78°C) lithiated methyl acetate (2 mmol) prepared as above. The reaction usually is complete after 15–30 min. At this temperature 20% aq. HCl (2 mL) was added to the mixture, which was left to warm up to rt. The pH of the mixture should be 7, if not, adjustment is required by additional amount of 20% aq. HCl. After distilling off the THF in vacuo, the residue was dissolved in a mixture of chloroform (50 mL) and water (30 mL). The organic phase was dried (Na_2SO_4), evaporated, the residue purified by column chromatography (eluent: hexane/ethyl acetate 2:1). After evaporation to dryness hydroxy-diester **7** was obtained as an oily base (0.54 g; 63%), which was used in the next step immediately. ν_{max} (KBr) 3410 (OH), 1738 (CO ester), 1688 cm^{-1} (CO amide); δ_H (400 MHz, $CDCl_3$) 8.22 (1H, dd, J=7.4, 1.5 Hz, 8-*H*), 7.43 (1H, brdd, J=1.7, 1.5 Hz, 2-*H*), 7.37 (1H, dd, J=7.0, 1.5 Hz, 6-*H*), 7.34 (1H, dd, J=7.4, 7.0 Hz, 7-*H*), 5.0 (1H, brs, 5-O*H*), 3.64+3.71 (2×3H, 2×s, 2×OCH_3), 3.52 (1H, dd, J=5.2, 5.0 Hz, 4-*H*), 3.22+3.40 (2×1H, 2×d, J=16.8 Hz, NCH_2CO_2Me), 3.31 (1H, 2×ddd, J=16.8, 5.0, 1.5 Hz, 3-H_B), 3.20 (1H, ddd, J=16.8, 5.2, 1.7 Hz, 3-H_A), 2.80+2.97 (2×1H, 2×d, J=14.4 Hz, 5-CH_2CO), 2.28 (3H, s, NCH_3), 1.51 [9H, s, $C(CH_3)_3$]; NOE 2.28 (NCH_3)→3.52 (4-*H*), 3.22+3.40 (NCH_2), 3.31 (3-H_B), no interaction with 3.20 (3-H_A) and 2.80+2.97 (5-CH_2); 2.80 (5-CH_A)→2.97 (5-CH_B), 3.20 (3-H_A), 3.52 (4-*H*); 3.52 (4-*H*)→2.28 (NCH_3), 3.22+3.40 (NCH_2), 2.80+2.97 (5-CH_2), 3.20 (3-H_A), 3.31 (3-H_B), 5.0 (O*H*); δ_C (100.6 MHz, $CDCl_3$) 177.0 (NCO), 172.0+172.1 (2×CO_2Me), 134.9 (C5a+C8a), 126.9 (C8b), 126.6 (C7), 119.2* (C2), 118.8* (C8), 116.7* (C6), 116.4 (C2a), 72.5 (C5), 64.9 (C4), 57.0 (NCH_2CO), 51.6+51.7 (2×OCH_3), 44.1 (5-CH_2CO), 40.9 (CMe_3), 40.1 (NCH_3), 28.6 [$C(CH_3)_3$], 19.0 (C3); *m/z* (EI) 430 (M^+, 47), 399 (4), 371 (11), 354 (5), 345 (28), 211 (9), 182 (7), 170 (10), 154 (8), 116 (100), 88 (5), 70 (6), 57 (53), 41 (11%).

1.1.7. *Z*/*E* Methyl (±)-4-(*N*-methoxycarbonylmethyl-*N*-methyl)amino-1-pivaloyl-1,3,4,5-tetrahydrobenz[*c*,*d*]indole-5-acrylate (8 and 9) and methyl (±)-4-(*N*-methoxycarbonylmethyl-*N*-methyl)amino-1-pivaloyl-1,2-dihydrobenz[*c*,*d*]indole-5-acetate (10). To the solution of the oily hydroxy-diester **7** (0.43 g; 1 mmol) in pyridine (30 mL) $POCl_3$ (0.6 mL) was added, and the mixture was refluxed on an 120°C oil bath. Progress of the water elimination can be followed by TLC (chloroform/acetonitrile 9:1; R_f products>R_f hydroxy-diester). The conversion usually is complete after 1.5 h. The mixture was evaporated in vacuo, the residue was dissolved in a mixture of chloroform (50 mL) and water (20 mL), while the pH of the water phase was adjusted to a value of 7–7.5. The organic phase was dried (Na_2SO_4), evaporated, the residue purified by column chromatography (eluent: chloroform/acetonitrile 20:1).

Oily base of compound with highest R_f value proved to be a naphthalene derivative (**10**). Yield: 160 mg (36%). [Found C, 67.1; H, 6.7; N, 6.7. $C_{23}H_{28}N_2O_5$ requires C, 67.0; H, 6.8; N, 6.8%]; ν_{max} (KBr) 1740 (CO esters) 1671 cm^{-1} (CO amide); δ_H (400 MHz, $CDCl_3$) 7.99 (1H, dd, J=7.5, 0.7 Hz, 8-*H*), 7.45 (1H, dd, J=8.4, 7.5 Hz, 7-*H*), 7.37 (1H, t, J=1.5 Hz, 3-*H*), 7.34 (1H, dd, J=8.4, 0.7 Hz, 6-*H*), 5.48 (2H, d, J=1.5 Hz, 2-H_2), 4.24 (2H, s, 5-CH_2CO), 3.83 (2H, s, NCH_2CO_2Me), 3.66+3.68 (2×3H, 2×s, 2×OCH_3), 2.91 (3H, s, NCH_3), 1.45 [9H, s, $C(CH_3)_3$]; NOE 2.91 (NCH_3)→7.37 (3-*H*), 3.83 (NCH_2CO), 4.24 (5-CH_2CO); 4.24 (5-CH_2CO)→7.34 (6-*H*), 3.83 (NCH_2CO), 2.91 (NCH_3); 5.48 (2-H_2)→1.45 [$C(CH_3)_3$], 7.37 (3-*H*); δ_C (100.6 MHz, $CDCl_3$) 176.7 (NCO), 171.0+172.5 (2×CO_2Me), 150.7 (C4), 145.7 (C8a), 131.5+135.7 (C5+C5a), 130.2 (C7), 127.3 (C8b), 123.1 (C2a), 116.4 (C8), 112.3 (C6), 111.0 (C3), 59.0 (NCH_2CO), 55.1 (C2), 51.2+51.4 (2×OCH_3), 42.6 (NCH_3), 40.5 (CMe_3), 33.2 (5-CH_2CO), 27.8 [$C(CH_3)_3$].

Z isomer **8** (R_f<R_f **10**) is the main product, isolated as an oil as well. Yield: 170–210 mg (41–51%). [Found C, 66.9; H, 6.8; N, 6.7. $C_{23}H_{28}N_2O_5$ requires C, 67.0; H, 6.8; N, 6.8%]; ν_{max} (KBr) 1747 (CO ester), 1715 (CO conj. ester), 1689 cm^{-1} (CO amide); δ_H (400 MHz, $CDCl_3$) 8.32 (1H, dd, J=7.9, 0.9 Hz, 8-*H*), 7.47 (1H, brd, J=2.2, <1 Hz, 2-*H*), 7.40 (1H, dd, J=7.5, 0.9 Hz, 6-*H*), 7.35 (1H, dd, J=7.9, 7.5 Hz, 7-*H*), 6.49 (1H, s, =C*H*CO), 5.48 (1H, dd, J=4.2, 2.5 Hz, 4-*H*), 3.66+3.79 (2×3H, 2×s, 2×OCH_3), 3.31+3.34 (2×1H, 2×d, J=17.0 Hz, NCH_2CO_2Me), 2.99+3.34 (2×1H, 2×ddd, J=17.0, 4.2, 2.2+17.0, 2.5, <1 Hz, 3-H_2), 2.38 (3H, s, NCH_3), 1.51 [9H, s, $C(CH_3)_3$]; NOE 6.49 (=C*H*CO)→7.40 (6-*H*); δ_C (100.6 MHz, $CDCl_3$) 176.9 (NCO), 171.9 (CH_2CO_2Me), 166.5 (=$CHCO_2Me$), 151.5 (C5), 135.3 (C8a), 129.2° (C5a), 128.1° (C8b), 126.6 (C7), 120.3* (C2), 119.1* (C8), 118.0* (C6), 117.5* (=*C*HCO), 116.2 (C2a), 55.2 (NCH_2CO), 54.9 (C4), 51.2+51.4

(2×OCH_3), 40.9 (CMe_3), 39.8 (NCH_3), 28.6 [$C(CH_3)_3$], 26.1 (C3); *m/z* (EI) 412 (M^+, 59), 381 (4), 353 (38), 339 (13), 327 (6), 310 (8), 280 (10), 267 (7), 209 (8), 194 (30), 167 (19), 154 (12), 127 (5), 57 (100), 41 (21%).

E isomer **9** has the lowest R_f among the new derivatives and was isolated as oil. Yield: 10–30 mg (2.5–7%). ν_{max} (KBr) 1745 (CO ester), 1718 (CO conj. ester), 1689 cm^{-1} (CO amide); δ_H (400 MHz, $CDCl_3$) 8.31 (1H, dd, *J*=8.0, 0.8 Hz, 8-*H*), 7.69 (1H, dd, *J*=7.6, 0.8 Hz, 6-*H*), 7.47 (1H, brd, *J*=2.0, ~1 Hz, 2-*H*), 7.32 (1H, dd, *J*=8.0, 7.6 Hz, 7-*H*), 6.19 (1H, s, =C*H*CO), 4.00 (1H, dd, *J*=4.1, 3.5 Hz, 4-*H*), 3.68+3.77 (2×3H, 2×s, 2×OCH_3), 3.33 (2H, covered, NCH_2CO_2Me), 3.08+3.22 (2×1H, 2×ddd, *J*=16.5, 4.1, 2.0+16.5, 3.5, ~1 Hz, 3-H_2), 2.48 (3H, s, NCH_3), 1.50 [9H, s, $C(CH_3)_3$]; NOE 6.19 (=C*H*CO)→4.00 (4-*H*); *m/z* (EI): 412 (M^+, 63), 381 (5), 353 (34), 339 (11), 327 (7), 310 (8), 280 (11), 267 (7), 209 (10), 194 (32), 167 (20), 154 (11), 127 (4), 57 (100), 41 (20%).

1.1.8. (±)-7-Methoxycarbonyl-8-oxo-ergolene (11). To the stirred solution of pure *Z* geometric isomer **8** (412 mg; 1 mmol) in dry THF (60 mL) 1N lithium bis(trimethylsilyl)-amide/THF solution (4 mL; 4 mmol) was added at −78°C. Progress of the Dieckmann condensation could be followed by TLC (hexane/ethyl acetate 2:1; R_f ergolene<R_f *Z* diester). If necessary, further amount of 1N lithium bis(trimethylsilyl)amide/THF (4 mL; 4 mmol) was added to the stirred mixture. The reaction usually is complete after 24 h. At this temperature 20% aq. HCl (1 or 2 mL, depending on the amount of base applied) was added to the mixture, which was left to warm up to rt. The pH of the mixture should be 7, if not adjustment is required by additional amount of 20% aq. HCl. After distilling off the THF in vacuo the residue was dissolved in a mixture of chloroform (50 mL) and water (20 mL). The organic phase was dried (Na_2SO_4), evaporated, the residue purified by column chromatography (eluent: hexane/ethyl acetate 2:1). After evaporation an oily base (285 mg; 75%) was isolated, which was crystallised from diethyl ether to supply yellow crystals of ergolene **11**. Yield: 236 mg (62%), mp 155–157°C. [Found C, 69.5; H, 6.4; N, 7.4. $C_{22}H_{24}N_2O_4$ requires C, 69.5; H, 6.4; N, 7.4%]; ν_{max} (KBr) 1730 (CO ester), 1690 (CO ketone), 1669 cm^{-1} (CO amide); δ_H (400 MHz, $CDCl_3$) 8.38 (1H, brd, *J*=8.1 Hz, 14-*H*), 7.57 (1H, brd, *J*=2.2, <1 Hz, 2-*H*), 7.50 (1H, brd, *J*=7.6 Hz, 12-*H*), 7.41 (1H, dd, *J*=8.1, 7.6 Hz, 13-*H*), 6.73 (1H, brd, *J*=2.2 Hz, 9-*H*), 4.40 (1H, ddd, *J*=11.8, 6.5, 2.2 Hz, 5-*H*), 4.24 (1H, s, 7-*H*), 3.71 (3H, s, OCH_3), 3.62 (1H, ddd, *J*=15.0, 6.5, <1 Hz, 4-H_{eq}), 2.76 (3H, s, NCH_3), 2.73 (1H, ddd, *J*=15.0, 11.8, 2.2 Hz, 4-H_{ax}), 1.53 [9H, s, $C(CH_3)_3$]; NOE 4.40 (5-*H*)→4.24 (7-*H*); δ_C (100.6 MHz, $CDCl_3$) 189.5 (C8), 177.0 (NCO), 168.4 (CO_2Me), 156.3 (C10), 135.2 (C15), 128.6° (C16), 126.7 (C13), 125.1° (C11), 120.9* (C2), 120.2* (C9), 119.3* (C12), 119.1* (C14), 115.6 (C3), 72.7 (C7), 57.0 (C5), 52.1 (OCH_3), 41.0 (CMe_3), 39.3 (NCH_3), 28.6 [$C(CH_3)_3$], 26.6 (C4); *m/z* (EI): 380 (M^+, 82), 321 (78), 295 (9), 279 ((49), 263 (4), 237 (37), 221 (12), 207 (23), 194 (30), 180 (6), 166 (18), 154 (13), 139 (18), 102 (2), 85 (5), 69 2), 57 (100), 41 (25%).

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