Enantioefficient Synthesis of α-Ergocryptine: First Direct Synthesis of (+)-Lysergic Acid

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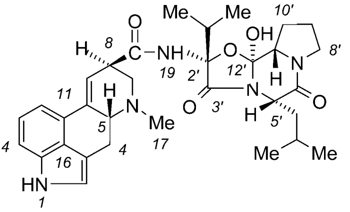
The first direct synthesis of (+)-lysergic acid (**2a**) suitable for scale-up has been achieved by the following reaction sequence. Bromoketones **4d** or **4g** were allowed to react with amine **5** followed by deprotection, and the resulting diketone **6c** was transformed into the unsaturated ketone (±)-**7** by the LiBr/Et_3N system. Resolution afforded (+)-**7**, which was further transformed by Schöllkopf's method into the mixture of esters **2e** and **2f**. Upon hydrolysis the latter mixture afforded (+)-**2a**. The peptide part of α-ergocryptine (**1**) was prepared according to the Sandoz method; the stereoefficiency, however, has been significantly improved by applying a new resolution method and recycling the undesired enantiomer. Coupling the peptide part with lysergic acid afforded **1**. Having synthetic (+)-**7** in hand, we can claim the total synthesis of all the alkaloids which were prepared earlier from (+)-**7** that had been obtained through degradation of natural lysergic acid.

Introduction

"*Ergot* alkaloids, of which lysergic acid is representative, are particularly important as they possess the widest spectrum of biological activity found in any family of natural products".[1] One of the biologically most important ergot alkaloids is α-ergocryptine (**1**). Its semisynthetic derivative, the so-called bromocryptine, is one of the most widely used drugs in this family (e.g., as a prolactin inhibitor, or an anti-Parkinsonian).[2] Great efforts have been devoted to the synthesis of ergot alkaloids during the second half of the last century. Conceptually, retrosynthetic cleavage of the central amide bond devides the problem into two parts, the synthesis of the lysergic acid and of the peptide dilactam moiety.

SCHEME 1



1 (α-ergocryptine)

The first synthesis of racemic lysergic acid was effected by Woodward and Kornfeld in 1956.[3,16] One of their main problems was to prepare ring C from the otherwise easily accessible 3-indolepropionic acid (**3**), since the ring closure of the corresponding acid chloride occurred at the more reactive pyrrole ring instead of the benzene ring. Thus the Woodward group reduced the pyrrole ring, the amine was protected by benzoylation, and thereafter the ring closure took place regioselevtively as desired. The drawback of this approach is that sooner or later the pyrroline moiety must be reoxidized to a pyrrole ring. It is difficult to perform an enantioefficient synthesis as well, since the method involves introduction of an unnecessary chiral center by the reduction. The earlier described resolution of racemic compound needs further and rather inconvenient steps.[4] So far the total synthesis of (±)-**2a** has been achieved by nine groups, but the number of publications dealing with the synthetic efforts is much higher. Among these approaches one can find about a dozen methods trying to construct the ergoline ring, some of which were successful; others remained at the level of attempt.[5] Seven of the nine successful

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(1) Bur, S. C.; Padwa, A. *Org. Lett.* **2002**, *4*, 4135−4137.

(2) *The Merck Index*, 12th ed.; Merck and Co. Inc.: Whitehouse Station, New York, 1996; p 231.

(3) (a) Somei, M.; Yokoyama, Y.; Murakami, Y.; Ninomiya, I.; Kiguchi, T.; Naito, T. *Recent Synthetic Studies on the Ergot Alkaloids and Related Compounds*; The Alkaloids, Vol. 54; Cordell, G. A., Ed.; Academic Press: San Diego, CA, 2000; pp 191−257. (b) Ninomiya, I.; Kiguchi, T. *Ergot Alkaloids*; The Alkaloids, Vol. 38; Brossi, A., Ed.; Acadenic Press: San Diego, CA, 1990; pp 1−156 and citations therein.

(4) Stoll, A.; Hofmann, A. *Helv. Chim. Acta* **1943**, *26*, 922−928.

(5) E.g.: (a) Marino, J. P., Jr.; Osterhout, M. H.; Padwa, A. *J. Org. Chem.* **1995**, *60*, 2704−2713. (b) Ralbovsky, J. L.; Scola, P. M.; Sugino, E.; Burgos-Garcia, C.; Weinreb, S. M. *Heterocycles* **1996**, *43*, 1497−1512. (c) Sader-Bakaouni, L.; Charton, O.; Kunesch, N.; Tillequin, F. *Tetrahedron* **1998**, *54*, 1773−1782. (d) Liras, A.; Lynch, C. L.; Fryer, A. M.; Vu, B. T.; Martin, S. F. *J. Am. Chem. Soc.* **2001**, *123*, 5918−5924. (e) Lee, K. L.; Goh, J. B.; Martin, S. F. *Tetrahedron Lett.* **2001**, *42*, 1635−1638.

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syntheses used the reduced indoline derivative as the starting compound. Oppolzer et al.[3] performed the first total synthesis avoiding the reduction step, but their procedure again cannot be scaled up. A second approach to the racemic acid was published recently.[6]

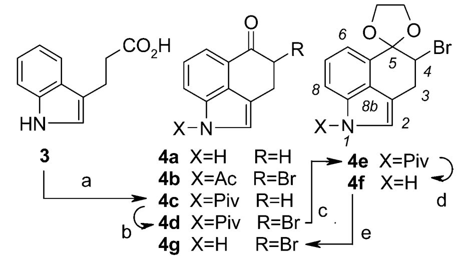
We decided to construct the ergoline skeleton starting from indole, thus avoiding the reoxidation problem, and at the same time making an enantioefficient synthesis possible.[7]

An ideal starting material was the so-called Uhle's ketone (**4a**) having the intact indole ring, although the original synthesis of **4a** is rather tedious. Uhle commenced with acetylation and subsequent bromination, and he claimed that the derived bromo-derivative **4b** could be subjected successfully to a substitution reaction with various amines.[9] Early in the seventies Bowman and co-workers reinvestigated a few results of Uhle's synthesis and established that one of the key steps, alkylation of several types of amines with **4b**, always failed.[10] The approach starting from **4a** by Stoll used the Stobbe condensation as a key step, but the reaction sequence could not be carried out,[11] thus the synthesis of lysergic acid starting from Uhle's ketone remained a challenge.

Results and Discussion

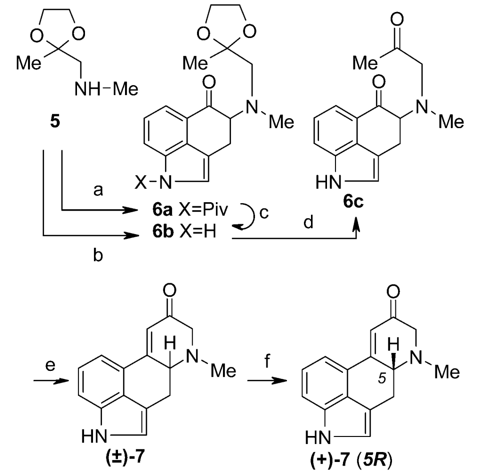
(1) Synthesis of (+)-Lysergic Acid. In 1994 the *N*-pivaloyl derivative of Uhle's ketone (**4c**) became easily accessible from 3-indolepropionic acid by Goto's method.[12] In connection with our attempt to find a reasonable total synthesis of ergoline skeleton we wished to reinvestigate the cyclization of ring D. We had 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.[13] As a second approach, ring D of the tetracyclic skeleton was formed by an intramolecular Dieckmann condensation of a diester, obtained in a modified Reformatsky reaction of a properly substituted derivative of **4c**, followed by elimination of water.[14] Neither of these methods, however, could be further elaborated to achieve (+)-lysergic acid.

SCHEME 2. Synthesis of 4-Bromo-Uhle's Ketone (4g) from 3[a]



[a] Reagents and conditions: (a) (1) powdered KOH + Piv-Cl, CH_2Cl_2 + THF, (2) $SOCl_2$, (3) $AlCl_3$ + $ClCH_2COCl$, CH_2Cl_2 (43%, overall); (b) ref 15 (85%); (c) $HO(CH_2)_2OH$, *p*-TSA, benzene, reflux, 6 h (81%); (d) $MeNH_2$, $CHCl_3$, 10−15 °C, 3−4 h (88%); (e) aq HCl (1 M), acetone, rt, 3 h (97%).

SCHEME 3. Synthesis of Tetracyclic Ketone [(+)-7][a]



[a] Reagents and conditions: (a) **5** + **4d**, toluene, 48 h, rt (35%); (b) **5** + **4g**, THF, 24 h, rt (56%); (c) $MeNH_2$, benzene, 10−15 °C, 1 h (80%); (d) aq HCl (6 M), 35−40 °C, 1 h then (e) **6c** in $CHCl_3$, LiBr + TEA, 0−5 °C, 12 h (60%, 2 steps); (f) (−)-dibenzoyl-L-tartaric acid, CH_3CN + H_2O (1:1) (38%).

To our pleasant surprise we found that bromoketone **4d**,[15] contrary to the literature,[10] can be subjected to a substitution reaction with amine **5** providing us with the so far unknown, but much sought-after, even mistakenly claimed[9] product (**6a**), if one has the patience to allow the reaction to proceed at ambient temperature in toluene. The amine component (**5**) was already known and could easily be prepared.[16] After a simple deacylation with methylamine and subsequent deprotection of the ketone the desired compound **6c** was for the first time in our hands. The yield was even better if we allowed amine **5** to react with the *N*-unprotected bromoketone **4g**, which had been prepared via ketalization of **4d**, *N*-deacetylation, and a deketalization step in high yields. This sequence yielding **6b** and leading from here to **6c** proved to be a real shortcut.

The ring closure of **6c** leading to the unsaturated ketone **7**[17] by intramolecular aldol condensation seems

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(6) Hendrickson, J. B.; Wang, J. *Org. Lett.* **2004**, *6*, 3−5.

(7) It is worth mentioning that one of our abandoned earlier routes was later developed for the synthesis of racemic LSD.[8] Galambos, G.; Szántay, Cs., Jr.; Tamás, J.; Szántay, Cs. *Heterocycles* **1993**, *36*, 2241−2245.

(8) Saá, C.; Crotts, D. D.; Hsu, G.; Vollhardt, K. P. C. *Synlett* **1994**, 487−489.

(9) Uhle, F. C. *J. Am. Chem. Soc.* **1951**, *73*, 2402−2403.

(10) Bowman, R. E.; Evans, D. D.; Guyett, J.; Weale, J.; White, A. C. *J. Chem. Soc., Perkin Trans. 1* **1973**, 760−766.

(11) (a) Stoll, A.; Rutschmann, J.; Petrzilka, T. *Helv. Chim. Acta* **1950**, *33*, 2257−2261. (b) Stoll, A.; Rutschmann, J. *Helv. Chim. Acta* **1952**, *35*, 141−147.

(12) (a) Teranishi, K.; Hayashi, S.; Nakatsuka, S.; Goto T. *Tetrahedron Lett.* **1994**, *35*, 8173−8176. (b) Although Goto's method has given a really short route to tetracyclic **4a** and **4c**, the application of the expensive and dangerous *n*-BuLi at −78 °C can interfere with their scale-up preparation. In our modification powdered KOH was applied for deprotonation of **3** at 0 °C. After acylation at room temperature, the obtained crude product was transformed directly to **4c** in 43−46% overall yield.

(13) (a) Moldvai, I.; Temesvári-Major, E.; Gács-Baitz, E.; Egyed, O.; Gömöry, Á.; Nyulászi, L.; Szántay, Cs. *Heterocycles* **1999**, *51*, 2321−2333. (b) Moldvai, I.; Temesvári-Major E.; Gács-Baitz, E.; Egyed, O.; Nyulászi L.; Szántay, Cs. *Hetrocycles* **2000**, *53*, 759.

(14) Incze, M.; Moldvai, I.; Temesvári-Major, E.; Dörnyei, G.; Kajtár-Peredy, M.; Szántay, Cs. *Tetrahedron* **2003**, *59*, 4281−4286.

(15) Moldvai, I.; Temesvári-Major, E.; Balázs, M.; Gács-Baitz, E.; Egyed, O.; Szántay, Cs. *J. Chem. Res. (S)* **1999**, 687; *J. Chem. Res. (M)* **1999**, 3018−3029.

(16) Kornfeld, E. C.; Fornefeld, E. J.; Kline, G. B.; Morrison, D. E.; Jones, G.; Woodward, R. B. *J. Am. Chem. Soc.* **1956**, *78*, 3087−3114.

to be an easy task, but with a great number of well-established agents (from potassium *tert*-butoxide through super bases to LHMDS) not even a trace of the desired teracyclic compound could be detected. It is worth noting, and not easy to explain, that in the dihydro-indole series this ring closure had been carried out;[16] however, similar intramolecular ring closure of compounds with a sulfone group instead of indole nitrogen also failed. An analogous compound of **6c** having an indole *N*-tosyl group and an acetyl group on the second nitrogen in place of the methyl group could be closed by KF, but simultaneously isomerization into a naphthalene derivative also occurred.[18] We became successful in performing the reaction by using a LiBr + triethylamine system, which was first used for condensation by Eschenmoser in the case of a different, sulfur-containing compound.[19] LiBr or triethylamine alone were totally ineffective. Likely the LiBr leads to a complementary activation of the two carbonyl groups in the presence of basic amine, since lithium ions have a higher affinity toward oxygen than nitrogen. The function of the amine is purely to abstract the proton in the α-position with respect to the *O*-complexed ketone carbonyl. An especially good result was achieved by performing the two consecutive steps (deprotection and ring closure; **6b** → **6c** → **7**) without isolation of the intermediate **6c** to give a 60% combined yield of crystalline unsaturated ketone **7**.

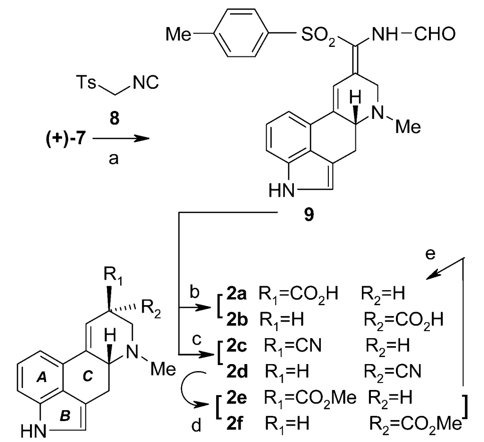
The resolution of **7** was performed with dibenzoyltartaric acid. At the same time the optically active ketone was also prepared by degradation of natural lysergic acid,[20] and by comparison the absolute configuration of our synthetic compounds was established.

To proceed, we allowed the optically active **7** to react with the isonitrile derivative **8** in the presence of base[21] to yield the formamide derivative **9**, followed by acidic hydrolysis. A mixture of lysergic acid (**2a**) and its epimer (**2b**) was obtained; after treatment with base almost pure (+)-lysergic acid was isolated as a result of epimerization, although in poor yield.

A much better result was achieved by treating intermediate **9** with base affording a mixture of nitriles (**2c**:**2d**, 1:1, 70%) and converting the mixture by Pinner reaction into lysergic acid ester diastereomers (a 3:2 mixture of **2e**:**2f**, 72%). There is no need to separate the two nitriles or esters, since the basic hydrolysis of the mixture of **2e**:**2f** results in pure (+)-lysergic acid (**2a**) through concurrent hydrolysis and epimerization.[22]

(2) Improving the Efficiency of the Peptide Part Synthesis. Above we described the synthesis of the (+)-lysergic acid component of α-ergocryptine (**1**). The synthesis of the peptide part has already been described[23] by a research group from the Sandoz Pharmaceutical Co. Our task was to improve the efficiency, especially the stereoefficiency of the reaction sequence, and to make a scale-up procedure possible.

SCHEME 4. Synthesis of (+)-Lysergic Acid (2a) from (+)-7[a]



[a] Reagents and conditions: (a) (+)-**7** + **8**, *t*-BuOK, THF + *t*-BuOH, 0 °C, 20 min then + H_2O, −5 °C (77%); (b) aq HCl (2 M), reflux, 30 min (13%); (c) NaOMe, MeOH, 70−75 °C, 30 min (70%); (d) HCl/MeOH (6.7 M), 75−80 °C, 45 min (72%); (e) aq NaOH (5 M), MeOH, 70−80 °C, 2.5 h then aq HCl (6 M) to pH 6.5 (54%).

At the outset isopropyl malonic ester was oxidized by benzoyl peroxide. According to the original procedure the excess of the benzoyl peroxide was to be eliminated by charcoal, but following this route we observed explosions in about 20% of the cases. To avoid this danger, $Na_2S_2O_3$ or $NaHSO_3$ was successfully used instead of charcoal. The resulting compound was debenzoylated, and the hydroxyl group was protected as the benzyl ether. Partial hydrolysis of diester **10** gave rise to the half ester (±)-**11**. In Sandoz's original reaction sequence this acid was resolved by the consecutive application of (−)- and (+)-pseudoephedrine, which process proved to be rather inconvenient and the yield low. Instead of pseudoephedrines we used (+)-1*S*,2*S*-2-amino-1-(4-nitrophenyl)propan-1,3-diol (**12**) for resolution. Compound **12** is the unwanted and thus discarded enantiomer formed during the manufacturing procedure of the antibiotic chloramphenicol.[24] The desired salt of the *R*-(+)-isomer [(+)-**11**)] crystallized from the solution in excellent yield. Isolation of (+)-**11** has been accomplished by acidic treatment. By this method both (−)-**11** and **12** were recovered easily.

To make the process even more economic, the unwanted *S*-enantiomer [(−)-**11**] was esterified with diethyl sulfate to **10**. Through this procedure we obtained the original, achiral diester, which we can recycle into the reaction sequence. We may call this manipulation *dechiralization*.

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[17] The first synthesis of racemic **7** has been performed via oxidation of the corresponding alcohol with the 2,3-dihydroindole ring. Only one characterization datum (mp 145−148 °C) of (±)-**7** has been described. See: Bach, N. J.; Hall, D. A.; Kornfeld, E. J. *J. Med. Chem.* **1974**, *17*, 312−314.

[18] (a) Craig, J. C.; Hurt, S. D. *J. Org. Chem.* **1979**, *44*, 1113−1117. (b) Moldvai, I.; Gács-Baitz, E.; Temesvári-Major, E.; Incze, M.; Poppe, L.; Szántay, Cs. *Heterocycles*. In press.

[19] (a) Roth, M.; Dubs, P.; Götschi, E.; Eschenmoser, A. *Helv. Chim. Acta* **1971**, *54*, 710−734. (b) Waldvogel, E.; Engeli, P.; Küsters, E. *Helv. Chim. Acta* **1997**, *80*, 2084−2099.

[20] (a) Bernardi, L.; Gandini, E.; Temperilli, A. *Tetrahedron* **1974**, *30*, 3447−3450. A few characterization data of (+)-**7** [mp 164−166 °C, $[\alpha]_D$ +703 (*c* 1, MeOH), UV spectrum] have been described. (b) Bach, N. J.; Kornfeld, E. C. *Tetrahedron Lett.* **1974**, 3225−3227.

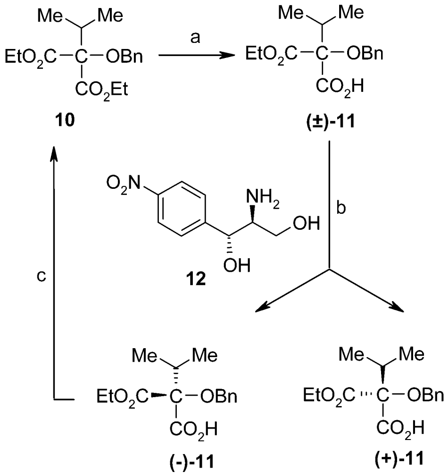
[21] (a) Schöllkopf, U.; Schröder, R.; Blume, E. *Justus Liebigs Ann. Chem.* **1972**, *766*, 130−141. (b) Schöllkopf, U.; Schröder, R. *Angew. Chem.* **1973**, *85*, 402−403.

[22] It is worth mentioning that Rapoport and co-workers published a method for synthesizing an advanced intermediate of the *Ergot* alkaloids, an optically active amino derivative of Uhle's ketone, following an entirely different route. Hurt, C. R.; Lin, R.; Rapoport, H. *J. Org. Chem.* **1999**, *64*, 225−233.

[23] Stadler, P. A.; Guttmann, S.; Hauth, H.; Huguenin, R. L.; Sandrin, E.; Wersin, G.; Willems, H.; Hofmann, A. *Helv. Chim. Acta* **1969**, *52*, 1549−1564.

[24] Kollonitsch, J.; Hajós, A.; Kraut, M.; Gábor V. *Acta Chim. Hung.* **1955**, *6*, 381−395; *Chem. Abstr.* **1955**, *49*, 6872h.

SCHEME 5. Modified Resolution of (±)-11[a]



[a] Reagents and conditions: (a) ref 23; (b) (±)-**11** + **12**, EtOH, rt, 12 h [(+)-**11**, 38%; (−)-**11**, 39%]; (c) $(EtO)_2SO_2$, acetone, refl., 3 h (90%).

The so-called aminocyclol hydrochloride (**14**), the partner needed for coupling with (+)-lysergic acid, was prepared from Z-protected proline. The proline derivative was treated with L-leucine methyl ester *p*-tolyl sulfonate salt using the mixed anhydride (chloroformic acid ester) method. After deprotection by hydrogenolysis followed by heating, the L-prolyl-L-leucyl lactam (**13**) was isolated in good yield.

The malonic acid derivative [(+)-**11**] was transformed to the acid chloride and allowed to react with lactam **13**, then deprotected by hydrogenolysis, and the resulting cyclolester hydrolyzed to the so-called cyclolcarboxylic acid. After several steps **14** was obtained.[23]

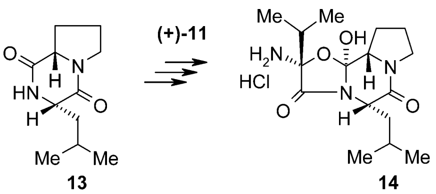
Several methods were tried for coupling lysergic acid (**2a**) with the peptide part (**14**). The most practical route was found by using lysergic acid trifluoroacetate, which was allowed to react with PCl_5. The reaction conditions (temperature, the excess of reagent) are critical. The approximate amount (80%) of acyl chloride in the obtained reaction mixture was estimated by IR spectra. By reacting the suspension of the aminocyclol hydrochloride in methylene chloride with lysergic acid chloride hydrochloride[25] at −12 °C in the presence of pyridine, α-ergocryptine (**1**) was isolated in 41% yield (as its phosphate salt).[26] In addition to its diastereomer α-ergocryptinine (**15**) was obtained (31%) after chromatographic workup.[23]

Since a thermodynamic equilibrium exists between the two stereoisomers in favor of **1** to **15** (3:1) in boiling methanol or in other solvents,[27] in principle there is a possibility to transform **15** into **1** in preparative scale. This aspect, however, was not closely investigated.

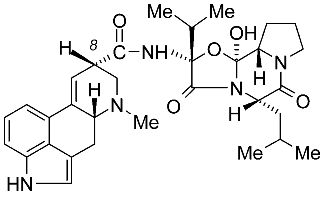
Conclusion

We have shown that a practical, direct synthesis of (+)-lysergic acid is possible while maintaining the indole ring intact throughout the synthesis, thus avoiding the necessity of introducing a needless chiral center by reduction. Furthermore we could perform the resolution of an earlier intermediate, thus avoiding the rather tedious and uneconomic resolution of the end product. Since several natural alkaloids [(+)-isosetoclavine,[20a] (+)-lysergene,[28] (−)-agroclavine[28]] have been synthesized via a semisynthesis from (+)-**7** obtained by degradation of natural (+)-lysergic acid,[20] the above approaches from now on can be regarded as the total syntheses of said alkaloids.

SCHEME 6



SCHEME 7



15 (α-ergocryptinine)

By using our modified approach, the peptide part of the alkaloid was synthesized without any side product having the undesired enantiomeric structure, i.e., (-)-**11**, since the latter was successfully recycled.

Upon coupling the two parts, we have completed an efficient total synthesis of α-ergocryptine and α-ergocryptinine.

Experimental Section

***N*-Piv-Uhle's ketone (4c; modified procedure).** To a cold (0−5 °C) solution of **3** (25.0 g, 132.0 mmol) in a mixture of dry CH_2Cl_2 (1.32 L) and THF (63 mL) were added tetrabutylammonium hydrogen sulfate (5.25 g, 15.4 mmol) and powdered KOH (25.0 g, 446.2 mmol). After the mixture was stirred for 15 min at the above temperature, pivaloyl chloride (67.5 mL, 0.54 mol) in CH_2Cl_2 (125 mL) was added dropwise. The mixture was stirred for 2 h at room temperature, then cooled again and poured into a mixture of cold water (0.8 L), aq HCl solution (1 M, 75 mL), and $CHCl_3$ (625 mL). The aqueous phase was extracted with $CHCl_3$ (0.5 L), and the combined organic phase was washed with cold water (2 × 0.75 L) and dried. The solvent was evaporated and the residue purified by vacuum distillation (100 °C, 1 mmHg) to remove excess reagent. The obtained crude product (28 g) was dissolved in thionyl chloride (37.0 mL, 309 mmol) with stirring for 15 min at room temperature, then evaporated under reduced pressure. The residue was dissolved in dry CH_2Cl_2 (260 mL) and dropped (during 0.5 h) into a mixture of aluminum chloride (36.0 g, 270 mmol) and chloroacetyl chloride (32.0 mL, 0.4 mol) in dry dichloromethane (300 mL) at 0−5 °C. The mixture was stirred for 2 h at room temperature, then poured into a mixture of crushed ice (0.5 kg), $CHCl_3$ (1.5 L), and brine (1 L). After extraction, the organic phase was washed with brine (2 × 0.75 L) and cold water (0.75 L) and dried. The crude product was crystallized from ethanol (150 mL) to yield **4c** (14.5 g, 43%), in full agreement with the reported data.[8a] Mp: 167−168 °C.

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(26) Stoll, A.; Hofmann, A. *Helv. Chim. Acta* **1943**, *26*, 1570−1601.

(27) Bandula, R.; Vasilesu, M. *Rev. Roum. Chim.* **1995**, *40*,1189−1195; *Chem. Abstr.* **1996**, *125*, 114925k.

(28) Wheeler, W. J. *Tetrahedron Lett.* **1986**, *27*, 3469−3470.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.52 (9H, s, CMe_3), 2.87 (2H, t, J = 7.1 Hz, H-4), 3.21 (2H, t, J = 7.1 Hz, H-4), 7.41 (1H, dd, J = 8.3, 8.0 Hz, H-7), 7.57 (1H, br s, H-2), 7.70 (1H, d, J = 8.3 Hz, H-8), 8.53 (1H, J = 8.0 Hz, H-8). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.7 (C-3), 28.8 (C*Me*$_3$), 38.6 (C-4), 41.2 (*C*Me$_3$), 116.3 (C-2a), 119.7 (C-8), 121.38 (C-2), 122.88 (C-6), 125.96 (C-5a), 126.35 (C-7), 133.7 (C-8b), 135.9 (C-8a), 177.2 (NCO), 197.3 (C-5). IR (KBr, cm^{-1}): 2976, 1694, 1671, 1603. HRMS (EI, 70 eV): $C_{16}H_{17}NO_2$ *m*/*z* calcd 255.1259, found 255.1264.

***N*-Piv-4-bromo-Uhle's ketone (4d).** Preparation of **4d** was described in our earlier publication.[15]

***N*-Piv-4-bromo-Uhle's Ketone Ethylene Ketal (4e).** Protection of bromoketone **4d** was carried out by applying a commonly used method (**4d**, 30.0 g, 89.7 mmol; ethylene glycol, 65 mL; *p*-TSA, 2.7 g; reflux in 0.6 L of benzene, 6 h, water separating device). After cooling, the mixture was diluted with EtOAc (2.5 L), crushed ice (1.5 L), and aq NH_4OH solution (25%, 110 mL). The organic phase was washed with water (2 × 0.6 L) and dried. The crude product was crystallized from ether (100 mL) to afford 27.4 g (81%) of ketal **4e** as a cream-colored solid. Mp: 153−155 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.51 (9H, s, CMe_3), 3.46 (1H, dd, J = 15.6, 6.7 Hz, H-3$_A$), 3.68 (1H, dd, J = 15.6, 4.2 Hz, H-3$_B$), 4.27 (4H, s, OCH_2CH_2O), 4.60 (1H, dd, J = 6.7, 4.2 Hz, H-4), 7.25−7.42 (2H, m, H-6 and H-7), 7.51 (1H, br s, H-2), 8.34 (1H, dd, J = 7.5, 1.7 Hz, H-8). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 28.5 (C*Me*$_3$), 30.8 (C-3), 40.9 (*C*Me$_3$), 53.0 (C-4), 66.11 and 66.39 (OCH_2CH_2O), 106.6 (C-5), 114.8 (C-2a), 118.16 (C-6), 118.51 (C-8), 120.4 (C-2), 126.1 (C-7), 127.4 (C-8b), 128.7 (C-5a), 135.0 (C-8a), 176.9 (NCO). IR (KBr, cm^{-1}): 2975, 2879, 1687, 1439. MS (EI, *m*/*z*, %): 377 (M$^+$, 43), 214 (39), 170 (20), 57 (100). HRMS (EI): $C_{18}H_{20}NO_3Br$ *m*/*z* calcd 377.0627, found 377.0622.

4-Bromo-Uhle's Ketone Ethylene Ketal (4f). Methylamine gas was introduced into a solution of **4e** (18.9 g, 49.9 mmol) in $CHCl_3$ (300 mL) at 10−15 °C for about 3−4 h. The mixture was washed with water (100 mL) and brine (100 mL) and dried. The crude product was crystallized from diethyl ether (50 mL) to yield 13.04 g (88%) of **4f** as a cream-colored solid. Mp: 120−122 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.50 (1H, dd, J = 15.8, 7.2 Hz, H-3$_A$), 3.71 (1H, dd, J = 15.8, 4.1 Hz, H-3$_B$), 4.28 (4H, s, OCH_2CH_2O), 4.65 (1H, dd, J = 7.2, 4.1 Hz, H-4), 6.93 (1H, br s, H-2), 7.17 (1H, dd, J = 7.1, 0.9 Hz, H-8), 7.22 (1H, dd, J = 7.1, 7.7 Hz, H-7), 7.31 (1H, dd, J = 7.7, 0.9 Hz, H-6), 8.0 (1H, br s, NH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 31.3 (C-3), 54.6 (C-4), 65.95 and 66.40 (OCH_2CH_2O), 107.2 (C-5), 109.4 (C-2a), 111.4 (C-8), 114.2 (C-6), 119.1 (C-2), 122.9 (C-7), 126.4 (C-8b), 129.0 (C-5a), 133.8 (C-8a). IR (KBr, cm^{-1}): 3358, 2878. MS (EI, *m*/*z*, %): 293 (M$^+$, 76), 293 (75), 214 (100), 170 (95). HRMS (EI): $C_{13}H_{12}NO_2Br$ *m*/*z* calcd 293.0051, found 293.0055.

4-Bromo-3,4-dihydro-1*H*-benzo[*c*,*d*]indol-5-one (4g; 4-Bromo-Uhle's Ketone). To a solution of **4f** (22.0 g, 74.8 mmol) in acetone (610 mL) at 10−15 °C was added aq HCl solution (1 M, 110 mL). The mixture was stirred for 3 h while the temperature was allowed to warm to room temperature. The organic solvent was evaporated under reduced pressure (water bath: 30−35 °C). The precipitated product was filtered off and washed with water (2 × 75 mL) and ether (2 × 50 mL) to afford 18.0 g (97%) of **4g** as a pale brown solid. (The product proved to be unstable at room temperature but it could be stored at −20 °C for a few months without any decomposition.) Mp: 119−122 °C. ^{1}H NMR ($CDCl_3$ + DMSO-d_6, 400 MHz): δ 3.60 (1H, dd, J = 17.5, 3.5 Hz, H-3$_A$), 3.89 (1H, dd, J = 17.5, 4.8 Hz, H-3$_B$), 4.91 (1H, dd, J = 4.8, 3.5 Hz, H-4), 7.24 (1H, br s, H-2), 7.28 (1H, dd, J = 7.4, 7.6 Hz, H-7), 7.58 (1H, d, J = 7.4 Hz, H-8), 7.64 (1H, d, J = 7.6 Hz, H-6), 10.79 (1H, br s, NH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 31.5 (C-3), 51.5 (C-4), 105.8 (C-2a), 116.87 (C-8), 117.21 (C-6), 122.19 (C-5a), 122.40 (C-7), 123.28 (C-2), 130.7 (C-8b), 134.9 (C8a), 190.2 (C5). IR (KBr, cm^{-1}): 3400, 1669, 1617, 1598. MS (EI, *m*/*z*, %): 249 (M$^+$, 64), 249 (65), 170 (100). HRMS (EI): $C_{11}H_8NOBr$ *m*/*z* calcd 248.9789, found 248.9788.

***N*-Piv-4-[*N*-methyl-*N*-acetonyl(2′,2′-ethylenedioxy)]amino-3,4-dihydro-1*H*-benzo[*c*,*d*]indol-5-one: Alkylation of 5 with 4d (6a).** To a solution of **4d** (1.12 g, 3.35 mmol) in dry toluene (35 mL) was added amine **5** (1.1 g, 8.3 mmol) in toluene (3.5 mL) at room temperature and the solution was stirred for 48 h. The precipitate formed was filtered off and washed with toluene and the combined filtrate was evaporated in vacuo. Purification by chromatography (eluent: EtOAc/hexane, 2:1) afforded **6a** (0.43 g, 35%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.37 (3H, s, CH_3), 1.53 (9H, s, CMe_3), 2.69 (3H, s, NCH_3), 2.87 (1H, d, J = 14.8 Hz, NCH_{2A}), 3.02 (1H, d, J = 14.8 Hz, NCH_{2B}), 3.28−3.33 (2H, m, H-3), 3.94 (1H, dd, J = 11.3, 6.9 Hz, H-4), 3.9−4.02 (4H, m, OCH_2CH_2O), 7.43 (1H, dd, J = 8.3, 7.6 Hz, H-7), 7.58 (1H, dd, J = 1.9, 1.0 Hz, H-2), 7.69 (1H, dd, J = 7.6, 0.7 Hz, H-8), 8.50 (1H, dd, J = 8.3, 0.7 Hz, H-6). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 22.8 (C*C*H$_3$), 26.4 (C-3), 28.7 (C*Me*$_3$), 41.02 (NCH_3), 41.17 (*C*Me$_3$), 61.5 (NCH_2), 65.1 (OCH_2CH_2O), 70.0 (C-4), 110.8 (*C*CH$_3$), 116.6 (C-2a), 119.7 (C-6), 121.46 (C-2), 122.68 (C-8), 126.55 (C-7), 126.60 (C-5a), 132.7 (C-8a), 135.7 (C-8b), 177. 2 (NCO), 198.4 (C-5). IR (oil, cm^{-1}): 2979, 2879, 1690, 1606. MS (FAB-NOBA, *m*/*z*, %): 385 (M + H$^+$, 50), 307 (18), 154 (100). HRMS (FAB, glycerine): $C_{22}H_{28}N_2O_4$ *m*/*z* calcd 384.2049, found 384.2041.

4-[*N*-Methyl-*N*-acetonyl(2′,2′-ethylenedioxy)]amino-3,4-dihydro-1*H*-benzo[*c*,*d*]indol-5-one (6b). (a) Alkylation of 5 with 4g. To a solution of **4g** (7.5 g, 30.0 mmol) in dry THF (130 mL) was added amine **5** (8.6 g, 65.1 mmol) in THF (20.0 mL) at room temperature and the solution was stirred for 24 h. The precipitate formed was filtered off and washed with THF and the solvent was evaporated in vacuo (bath: 30−35 °C). The residue was dissolved in a mixture of EtOAc (450 mL) and cold water (180 mL), and the pH was adjusted to ≈3 with aq HCl solution (1 M, 54 mL). The organic phase was extracted with aq HCl solution (0.5 M, 2 × 60 mL) and water (50 mL). The aqueous phase was mixed with $CHCl_3$ (450 mL) and the pH was adjusted to ≈8 with aq saturated Na_2CO_3 solution (≈40 mL) while the mixture was cooled with an ice bath. After the phases were separated, the aqueous phase was washed with $CHCl_3$ (2 × 100 mL). The combined organic phase was washed with brine (100 mL) and dried. Evaporation (bath: 30−35 °C) of the solvent provided a crude solid (6.83 g, 76%), which was crystallized from a mixture of EtOAc/hexane (1:1, 50 mL) to afford 4.727 g (52.4%) of **6b** as a cream-colored solid. A further crop of **6b** (0.295 g, 3.3%) was obtained by chromatography of the mother liquor (eluent: EtOAc/hexane, 1:1). Mp: 120−124 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.39 (3H, s, CCH_3), 2.70 (3H, s, NCH_3), 2.90 (1H, d, J = 14.5 Hz, NCH_{2A}), 3.03 (1H, d, J = 14.5 Hz, NCH_{2B}), 3.31 (1H, m, J = 15.4, 11.4, 1.6 Hz, H-3$_A$), 3.37 (1H, m, J = 15.4, 7.3, 0.7 Hz, H-3$_B$), 4.01 (1H, dd, J = 11.4, 7.3 Hz, H-4), 3.9−4.06 (4H, m, OCH_2CH_2O), 7.07 (1H, dd, J = 1.6, 0.7 Hz, H-2), 7.25 (1H, dd, J = 8.1, 7.3 Hz, H-7), 7.51 (1H, dd, J = 7.3, 0.6 Hz, H-8), 7.55 (1H, dd, J = 8.10, 0.6 Hz, H-6), 8.46 (1H, br s, NH). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 22.8 (C*C*H$_3$), 26.5 (C-3), 41.0 (NCH_3), 61.6 (NCH_2), 65.1 (OCH_2CH_2O), 71.1 (C-4), 110.9 (C-2a), 115.69 (C-6), 115.85 (C-8), 120.7 (C-2), 123.1 (C-7), 126.7 (C-5a), 131.6 (C-8a), 134.9 (C-8b), 199.7 (C-5). IR (KBr, cm^{-1}): 3133, 3094, 2974, 2950, 1671, 1619, 1600. MS (EI, *m*/*z*, %): 300 (M$^+$, 11), 213 (96), 185 (23), 170 (57), 87 (100). HRMS (EI): $C_{17}H_{20}N_2O_3$ *m*/*z* calcd 300.1474, found 300.1480.

(b) *N*-Deacetylation of 6a. Methylamine gas was introduced into a solution of **6a** (0.5 g, 1.3 mmol) in benzene (50 mL) at 10−15 °C for about 1 h. The mixture was washed with water and brine and dried. The isolation of **6b** (0.312 g, 80%) was carried out as described above.

(±)-9,10-Didehydro-6-methylergoline-8-one (7) via Diketone 6c. In the first step **6b** (1.6 g, 5.32 mmol) was dissolved in aq HCl solution (6 M, 100 mL) and stirred at 37 °C for 1 h, then cooled in an ice bath. The mixture was mixed with $CHCl_3$ (0.5 L), and the pH was adjusted to ≈7 with aq NaOH solution (5 M). After the phases were separated, the aqueous phase was washed with $CHCl_3$ (2 × 100 mL). The combined organic phase was washed with brine (100 mL) and dried. An aliquot part was evaporated (bath: 25−30 °C) in vacuo and the residue was crystallized (ether/hexane, 1:1) to yield **6c** as a pale brown solid. Mp: 100−105 °C dec. ^{1}H NMR (CDCl$_3$ + DMSO-d_6, 200 MHz): δ 2.19 (3H, s, CCH$_3$), 2.60 (3H, s, NCH$_3$), 3.25 (1H, m, *J* = 15.3, 11.3, 1.6 Hz, H-3$_A$), 3.46 (1H, m, *J* = 15.3, 6.9, 0.5 Hz, H-3$_B$), 3.58 (1H, d, *J* = 17.5 Hz, NCH$_{2A}$), 3.75 (1H, d, *J* = 17.5 Hz, NCH$_{2B}$), 3.96 (1H, dd, *J* = 11.3, 6.9 Hz, H-4), 7.11 (1H, dd, *J* = 1.6 + 1.5 Hz, H-2), 7.23 (1H, dd, *J* = 7.9 + 7.3 Hz, H-7), 7.50 (1H, dd, *J* = 7.3 + 0.6 Hz, H-8), 7.55 (1H, dd, *J* = 7.9, 0.6 Hz, H-6), 10.03 (1H, br s, NH). ^{13}C NMR (CDCl$_3$, 50 MHz): δ 24.8 (C-3), 26.9 (CO*C*H$_3$), 39.7 (NCH$_3$), 64.3 (NCH$_2$), 69.1 (C-4), 108.5 (C-2a), 114.75 (C-8), 115.92 (C-6), 121.08 (C-2), 122.08 (C-7), 125.5 (C-5a), 130.9 (C-8a), 134.5 (C-8b), 198.1 (C-5), 208.3 (*C*OCH$_3$). IR (KBr, cm^{-1}): 3143, 2849, 1721, 1682, 1617. MS (FAB-NOBA, *m/z*, %): 257 (M + H$^+$, 100), 213 (76), 198 (16). HRMS (FAB-NOBA, *m/z*, %): C$_{15}$H$_{16}$N$_2$O$_2$ *m/z* calcd 256.1212, found 256.1221.

As the second step, to a solution of LiBr (2.82 g, 32.5 mmml) in THF (40 mL) at 0−5 °C were added the solution of **6c** in CHCl$_3$, obtained after extraction and evaporation to about 100 mL, and TEA (2.82 g, 28 mmol) at 0−5 °C. The mixture was stirred at the above temperature for 12 h, then evaporated (bath: 30 °C). The residue was treated with *n*-hexane to remove TEA. The obtained oil was purified by chromatography (eluent: CHCl$_3$/MeOH, 10:1) to afford a semisolid product, which was crystallized (EtOAc/hexane, 1:1, 20 mL) to yield 0.758 g (60%) of **7**[29] as pale yellow crystals. Mp: 153−155 °C. ^{1}H NMR (CDCl$_3$, + DMSO-d_6, 400 MHz): δ 2.60 (3H, s, NCH$_3$), 2.85 (1H, m, *J* = 14.5, 11.5, 1.5 Hz, H-4$_\alpha$), 3.18 (1H, dd, *J* = 15.8, 2.4 Hz, H-7$_A$), 3.49 (1H, d, *J* = 15.8 Hz, H-7$_B$), 3.51 (1H, m, $\sum J$ = 22 Hz, H-5), 3.63 (1H, dd, *J* = 14.5, 6.6 Hz, H-4$_\beta$), 6.79 (1H, d, *J* = 2.0 Hz, H-9), 7.07 (1H, br s, H-2), 7.22 (1H, dd, *J* = 7.4, 8.0 Hz, H-13), 7.35 (1H, d, *J* = 7.4 Hz, H-12), 7.42 (1H, d, *J* = 8.0 Hz, H-14), 9.75 (1H, br s, NH). ^{13}C NMR (CDCl$_3$ + DMSO-d_6, 100 MHz): δ 25.7 (C-4), 41.6 (NCH$_3$), 61.7 (C-5), 63.0 (C-7), 108.4 (C-3), 112.8 (C-14), 113.9 (C-12), 118.82 (C-9), 119.85 (C-2), 122.35 (C-13), 123.99 (C-11), 126.9 (C-16), 133.6 (C-15), 156.0 (C-10), 194.8 (C-8). IR (KBr, cm^{-1}): 3248, 2946, 1647, 1592. MS (EI, *m/z*, %): 238 (M$^+$, 100), 194 (53), 167 (29), 154 (54). HRMS (EI): C$_{15}$H$_{14}$N$_2$O *m/z* calcd 238.1106, found 238.1104.

Resolution of (±)-7. To a solution of (±)-**7** (595 mg, 2.5 mmol) in a mixture of acetonitrile and water (1:1, 25 mL) at 60 °C was added (−)-dibenzoyl-L-tartaric acid (895 mg, 2.5 mmol) in the same mixture of solvents (12.5 mL). The mixture was stirred for 10−15 min at the above temperature, then cooled to room temperature while being stirred for about an additional 0.5 h. The mixture was kept in a refrigerator overnight. The precipitated crystals were filtered off and washed with the above solvent mixture (5 mL) to yield 585 mg (79%) of salt. [α]$_D$ +271 (*c* 0.265, MeOH). This salt (515 mg, 0.864 mmol) was suspended in a mixture of CHCl$_3$ (200 mL) and water (30 mL) at 0−5 °C and the pH was adjusted to ≈9 with aq NaOH solution (1 M, 2 mL). After the phases were separated, the aqueous phase was washed with CHCl$_3$ (2 × 50 mL). The combined organic phases were washed with water, dried, and evaporated. The residue was crystallized (hexane/ether, 1:1, 10 mL) to yield (+)-**7** (226 mg, 38%) as a yellow crystal. Mp: 165−169 °C. [α]$_D$ +686 (*c* 0.5, MeOH).

Isolation of (-)-7. The mother liquor of the first crystallization was evaporated in vacuo until an aqueous solution was obtained. The solution was diluted with water (50 mL) and CHCl$_3$ (300 mL) and cooled at 0−5 °C. The pH of the mixture was adjusted to ≈9 with aq NaOH solution (1 M, 3 mL). After the phases were separated, the organic phase was washed with water, dried, and evaporated. The residue was crystallized (hexane/ether, 1:1, 10 mL) to yield crude (−)-**7** (306 mg) as a solid. [α]$_D$ −359 (*c* 0.5, MeOH). This product (299 mg, 1.256 mmol) was resolved with (+)-dibenzoyl-D-tartaric acid as described above to yield 262 mg of salt (35%). [α]$_D$ −364 (*c* 0.25, MeOH). The salt was treated with aq NaOH in CHCl$_3$ as desribed above and the crude product was crystallized to afford 118 mg (20%) of (−)-**7**. Mp: 165−168 °C. [α]$_D$ −696 (*c* 0.5, MeOH).

Preparation of (+)- *E/Z*-Formamide 9. To a solution of (+)-**7** (453 mg, 1.9 mmol) in dry THF (10 mL) at room temperature were added *p*-toluenesulfonylmethyl isocyanide (374 mg, 1.9 mmol) then *t*-BuOK (426 mg, 3.8 mmol) in a mixture of THF (5 mL) and *t*-BuOH (2 mL) at 0 °C. After being stirred for 20 min, the mixture was cooled to −5 °C, diluted with water (50 mL), and extracted with CHCl$_3$ (3 × 50 mL). The combined organic phases were washed with brine and dried. The crude product was crystallized (hexane/ether, 1:1, 10 mL) to afford 637 mg (77%) of **9** as a cream-colored solid. Mp: 178−184 °C dec. [α]$_D$ +660 (*c* 0.5, MeOH). ^{1}H NMR (DMSO-d_6, 400 MHz) (*E*-isomer; 85−90%):[30] δ 2.39 (3H, s, TsCH$_3$), 2.41 (3H, s, NCH$_3$), 2.58 (1H, dd, *J* = 14.5, 12.0 Hz, H-4$_\alpha$), 2.95 (1H, d, *J* = 15.0 Hz, H-7$_A$), 3.29 (1H, m, H-5), 3.37 (1H, d, *J* = 15.0 Hz, H-7$_B$), 3.45 (1H, dd, *J* = 14.5, 6.3 Hz, H-4$_\beta$), 7.13 (1H, br s, H-2), 7.18 (1H, dd, *J* = 7.8, 7.1 Hz, H-13), 7.33 (1H, dd, *J* = 7.1, 0.7 Hz, H-14), 7.38 (1H, dd, *J* = 7.8, 0.7 Hz, H-12), 7.46 (2H, m, *o*-TsH), 7.85 (2H, m, *m*-TsH), 7.88 (1H, br s, H-9), 8.09 (1H, s, CHO), 9.88 and 10.87 (2 × 1H, br s, N*H*CHO + NH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 21.4 (TsCH$_3$), 26.4 (C-4), 42.3 (NCH$_3$), 55.5 (C-7), 62.4 (C-5), 108.8 (C-3), 112.35 (C-14), 112.82 (C-12), 114.5 (C-9), 120.8 (C-2), 122.9 (C-13), 124.5 (C-8), 126.21 (C-11), 127.58 (*o*-Ts), 130.3 (*m*-Ts), 134.3 (C-15), 138.5 (C-10), 141.04 + 144.48 + 144.64 (SO$_2$*C*NH + C-11 + C-16), 160.38 (*C*HO). IR (KBr, cm^{-1}): 3366, 1687, 1675, 1596. MS (ESI, *m/z*): 434.3 (M + H). HRMS (FAB, glycerine): C$_{24}$H$_{23}$N$_3$O$_3$S *m/z* calcd 433.1460, found 433.1455.

(+)-8-Cyano-9,10-didehydro-6-methylergoline (2c:2d). To a solution of **9** (783 mg, 1.8 mmol) in MeOH (30 mL) at 70−75 °C (bath temperature) was added NaOMe (375 mg, 6.9 mmol). The resulting mixture was refluxed for 30 min. Upon cooling to 0−5 °C, water (100 mL) was added and the precipitate filtered off and washed with water to afford 320 mg (70%) of a mixture of **2c** and **2d**, which was subjected to further transformations. [α]$_D$ +176 (*c* 0.5, pyr). IR (KBr, cm^{-1}): 3411, 3158, 3106, 3000, 2938, 2847, 2789, 2234, 1615, 1603, 1448. MS (EI, *m/z*, %): 249 (M$^+$, 100), 206 (55), 154 (42).

For structure determination of the crude product, an aliquot part was purified by column chromatography (eluent: CHCl$_3$/acetone, 10:1) to afford pure 8β-isomer[31] **2c**. Mp: 140−160 °C dec. [α]$_D$ +34 (*c* 0.44, pyr). ^{1}H NMR (CDCl$_3$ + DMSO-d_6, 400 MHz): δ 2.60 (3H, s, NCH$_3$), 2.64 (1H, m, *J* = 14.7, 11.5, 1.7 Hz, H-4$_\alpha$), 2.77 (1H, dd, *J* = 11.0, 10.4 Hz, H-7$_\beta$), 3.22 (1H, dd, *J* = 11.0, 4.8 Hz, H-7$_\alpha$), 3.24 (1H, m, H-5), 3.49 (1H, dd, *J* = 14.7, 5.6 Hz, H-4$_\beta$), 3.83 (1H, m, H-8), 6.28 (1H, dd, *J* = 2.5, 2.0 Hz, H-9), 6.93 (1H, dd, *J* = 1.7, 1.6 Hz, H-2), 7.11−7.17 (2H, m, H-13 and H-14), 7.26 (1H, dd, *J* = 6.3, 2.4 Hz, H-12), 9.71 (1H, br s, NH). ^{13}C NMR (CDCl$_3$ + DMSO-d_6, 100 MHz): δ 27.0 (C-4), 28.4 (C-8), 43.4 (NCH$_3$), 54.8 (C-7), 62.6 (C-5), 110.57 (C-3), 110.66 (C-12), 112.97 (C-14), 113.99 (C-9), 118.87 (C-2), 119.84 (CN), 123.6 (C-13), 126.5 (C-16), 127.21 (C-11), 134.1 (C-15), 138.73 (C-10). HRMS (EI): C$_{16}$H$_{15}$N$_3$ *m/z* calcd 249.1266, found 249.1273.

The chemical shifts of the 8α-isomer[32] **2d** were determined in the mixture.

^{1}H NMR (CDCl$_3$, + DMSO-d_6, 400 MHz): δ 2.59 (3H, s, NCH$_3$), 2.62 (1H, m, *J* = 14.5, 11.4, 1.7 Hz, H-4$_\alpha$), 2.82 (1H, dd, *J* = 11.3, 3.4 Hz, H-7$_\beta$), 3.17 (1H, dd, *J* = 11.3, 3.0 Hz,

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(29) The formation of ring D was confirmed by the presence of an NOE effect between H-9 and H-12 protons. The chemical shifts of C-9 and C-10 carbons (118.8 and 156.0 ppm, respectively) are also characteristic for an α,β-unsaturated ketone unit.

(30) Evidence for the given stereochemistry of the double bond in **9** was provided by NOE experiments. Irradiation of the H-7$_\beta$ proton (3.37 ppm) leads to observation of an NOE at the formyl proton (8.09 ppm), while the tosyl protons gave NOE with H-9 (7.88 ppm).

(31) The β-orientation of the nitril group at C-8 follows from the vicinal coupling constant (10.4 Hz) between H-8 and H-7$_\beta$ protons.

H-7$_\alpha$), 3.25 (1H, m, H-5), 3.45 (1H, m, H-8), 3.48 (1H, dd, J = 14.5, 5.4 Hz, H-4$_\beta$), 6.32 (1H, dd, J = 4.2, 2.2 Hz, H-9), 6.93 (1H, br s, H-2), 7.12−7.20 (2H, m, H-13 and H-14), 7.25 (1H, overlapped, m, H-12), 7.97 (1H, br s, NH). ^{13}C NMR ($CDCl_3$ + DMSO-d_6, 100 MHz): δ 27.18 (C-4), 27.87 (C-8), 43.6 (NCH_3), 54.2 (C-7), 62.9 (C-5), 110.69 (C-12), 111.01 (C-3), 112.66 (C-14), 113.57 (C-9), 118.9 (C-2), 120.5 (CN), 123.5 (C-13), 126.67 (C-16), 127.73 (C-11), 134.1 (C-15), 140.0 (C-10).

Preparation of Esters (2e:2f). Isomer mixture **2c**:**2d** (300 mg, 1.2 mmol) was dissolved in HCl/MeOH (6.7 M, 30 mL) and the solution was refluxed for 45 min. After being cooled with an ice bath, the mixture was poured into a mixture of $CHCl_3$ (100 mL) and crushed ice (150 g). The pH was adjusted to ≈7−8 with aq saturated Na_2CO_3 solution (120 mL). After the phases were separated, the aqueous phase was washed with $CHCl_3$ (20 mL). The combined organic phase was washed with water, dried, and evaporated to yield 246 mg (72%) of a mixture of isomers (**2e**:**2f**) as a semisolid material, which was subjected to further transformations. Mp: 131−139 °C. $[\alpha]_D$ +104 (c 0.5, $CHCl_3$). MS (EI, m/z, %): 282 (M^+, 100), 267 (8), 224 (38), 207 (27), 180 (19), 154 (25), 111 (19).

For structure determination of the crude product, an aliquot part was purified by crystallization from benzene to afford pure (+)-lysergic acid methyl ester[33] **2e** as a cream-colored solid, in agreement with the reported data.[6,34] Mp: 164−166 °C. $[\alpha]_D$ +80 (c 0.5, $CHCl_3$). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.46 (3H, s, NCH_3), 2.48 (1H, dd, J = 11.1, 10.5 Hz, H-7$_\beta$), 2.50 (1H, m, J = 14.5, 11.4, 1.8 Hz, H-4$_\alpha$), 3.02 (1H, m, H-5), 3.15 (1H, dd, J = 11.1, 5.2 Hz, H-7$_\alpha$), 3.45 (1H, dd, J = 14.5, 5.7 Hz, H-4$_\beta$), 3.63 (1H, m, J = 10.5, 5.2, 2.5 Hz, H-8), 3.69 (3H, s, OCH_3), 6.46 (1H, dd, J = 2.5, 1.8 Hz, H-9), 7.02−7.07 (3H, m, H-2, H-13 and H-14), 7.20 (1H, dd, J = 6.9, 1.7 Hz, H-12), 10.68 (1H, br s, NH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 27.3 (C-4), 42.2 (C-8), 43.9 (NCH_3), 52.5 (OCH_3), 55.1 (C-7), 63.2 (C-5), 109.52 (C-3), 110.68 (C-12), 111.77 (C-14), 118.3 (C-9), 120.0 (C-2), 122.9 (C-13), 126.7 (C-16), 127.8 (C-11), 134.56 (C-15), 135.81 (C-10), 172.9 (CO_2). IR (KBr, cm^{-1}): 3410, 3138, 3091, 3035, 2842, 2807, 1730, 1604, 1439. HRMS (EI): $C_{17}H_{18}N_2O_2$ m/z calcd 282.1368, found 282.1371.

The chemical shifts of the 8α-isomer[35] **2f** were determined in the mixture.

^{1}H NMR (DMSO-d_6, + C_6D_6, 400 MHz): δ 2.43 (3H, s, NCH_3), 2.5 (1H, overlapped, m, H-4$_\alpha$), 2.61 (1H, dd, J = 11.6, 4.4 Hz, H-7$_\beta$), 3.05 (1H, overlapped, m, H-5), 3.21 (1H, dd, J = 11.6, 2.7 Hz, H-7$_\alpha$), 3.32 (1H, overlapped, m, H-8), 3.39 (1H, overlapped, m, H-4$_\beta$), 3.60 (3H, s, OCH_3), 6.43 (1H, dd, J = 5.6, 1.8 Hz, H-9), 7.02−7.06 (3H, m, H-2, H-13 and H-14), 7.21 (1H, dd, J = 6.9, 1.7 Hz, H-12), 10.7 (1H, br s, NH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 27.3 (C-4), 41.2 (C-8), 43.9 (NCH_3), 52.3 (OCH_3), 54.1 (C-7), 63.1 (C-5), 109.70 (C-3), 110.61 (C-12), 111.73 (C-14), 118.3 (C-9), 120.0 (C-2), 122.9 (C-13), 126.6 (C-16), 128.4 (C-11), 134.5 (C-15), 136.7 (C-10), 173.48 (CO_2).

(+)-Lysergic Acid 2a. (a) Starting from Esters 2e:2f. Isomer mixture **2e**:**2f** (340 mg, 1.2 mmol) was dissolved in MeOH (30 mL) and an aq NaOH solution (5 M, 7 mL) was added. The mixture was then stirred at 75−80 °C for 45 min. The hot solution was treated with charcoal and filtered. The organic solvent was removed by evaporation, and the aqueous solution was diluted with water (10 mL) and cooled to 0−5 °C. The solution was acidified to pH 6.5 with aq HCl solution (6 M) and stirred for a further 1−2 h at 0−5 °C while a solid was formed. The precipitate was filtered off and washed with cold water (3 × 2 mL) and acetone (3 × 2 mL) to afford 174 mg (54%) of **2a** as a pale brown solid, in agreement with the reported data.[6,34a] Mp: 230−240 °C dec. $[\alpha]_D$ +40 (c 0.5, pyridine). ^{1}H NMR (DMSO-d_6, 400 MHz):[36] δ 2.50 (3H, s, NCH_3), 2.50 (1H, dd, J = 11.5, 10.9 Hz, H-7$_\beta$), 2.53 (1H, dd, J = 14.9, 11.4 Hz, H-4$_\alpha$), 3.05 (1H, m, H-5), 3.16 (1H, dd, J = 14.9, 5.9 Hz, H-4$_\beta$), 3.44 (1H, dd, J = 11.5, 5.3 Hz, H-7$_\alpha$), 3.52 (1H, m, J = 10.9, 5.3, 2.3 Hz, H-8), 6.45 (1H, dd, J = 3.0, 2.3 Hz, H-9), 7.01 (1H, br s, H-2), 7.02−7.05 (2H, m, H-13 and H-14), 7.16 (1H, dd, J = 6.9, 1.6 Hz, H-12), 10.71 (1H, br s, NH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 26.9 (C-4), 42.1 (C-8), 43.6 (NCH_3), 55.0 (C-7), 62.9 (C-5), 109.23 (C-3), 110.66 (C-12), 111.73 (C-14), 119.31 (C-9), 120.10 (C-2), 123.0 (C-13), 126.49 (C-16), 127.71 (C-11), 134.50 (C-15), 135.65 (C-10), 173.85 (CO_2H). IR (KBr, cm^{-1}): 3396, 1596, 1450. MS (EI, m/z, %): 268 (M^+, 98), 250 (23), 224 (100), 207 (30), 192 (48), 180 (37), 167 (23), 154 (38). HRMS (EI): $C_{16}H_{16}N_2O_2$ m/z calcd 268.1212, found 268.1217.

(b) Acidic Hydrolysis of (+)-9 and Epimerization. Formamide **9** (0.5 g, 1.1. mmol) was dissolved in aq HCl solution (2 M, 40 mL) and refluxed for 30 min. After cooling, the pH of the solution was adjusted to 6.5 with aq saturated $NaHCO_3$ solution and evaporated in vacuo to dryness. The residue (140 mg, 45%) was purified by chromatography (eluent: $CHCl_3$/MeOH/cm^3 NH_4OH solution, 5:5:0.1) to afford 50 mg (13%) of **2a**:**2b**. The NMR data of **2a** have been described above, and the chemical shifts of **2b** were determined from the mixture.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.46 (3H, s, NCH_3), 2.48 (1H, m, H-4$_\alpha$), 2.67 (1H, dd, J = 12.0, 4.6 Hz, H-7$_\beta$), 3.02 (1H, m, H-5), 3.20 (1H, dd, J = 12.0, 2.8 Hz, H-7$_\alpha$), 3.24 (1H, m, H-8), 3.40 (1H, m, H-4$_\beta$), 6.43 (1H, dd, J = 5.5, 1.8 Hz, H-9), 7.02−7.07 (3H, m, H-2, H-13 and H-14), 7.13 (1H, dd, J = 6.9, 1.6 Hz, H-12), 10.75 (1H, br s, NH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 26.9 (C-4), 41.2 (C-8), 43.3 (NCH_3), 54.1 (C-7), 62.9 (C-5), 109.23 (C-3), 110.66 (C-12), 111.78 (C-14), 119.42 (C-9), 120.19 (C-2), 123.0 (C-13), 126.5 (C-16), 128.0 (C-11), 134.44 (C-15), 135.90 (C-10), 174.36 (CO_2H).

In the next step 100 mg (0.37 mmol) of **2a**:**2b** was dissolved in MeOH (10 mL) at room temperature and KOH (100 mg, 1.8 mmol) was added in a mixture of MeOH (2 mL) and water (1 mL). The mixture was stirred for 48 h, then a further portion of KOH (100 mg in the same solvents) was added, and the mixture was stirred for 48 h. The solution was acidified to pH 6.5 with aq HCl solution (1 M) and evaporated in vacuo to dryness. The residue was purified by chromatography (eluent: $CHCl_3$/MeOH/cm^3 NH_4OH solution, 5:5:0.1) to afford 50 mg (50%) of **2a**.

Resolution of (±)-11. To a solution of (±)-**11** (77.2 g, 0.276 mol) in dry EtOH (0.5 L) was added **12** (58.45 g, 0.276 mol) at room temperature. The mixture was stirred for a few minutes, then kept at room temperature overnight. The precipitated crystals were filtered off, washed with cold EtOH, and recrystallized from EtOAc (1.8 L) to afford 54 g (80%) of salt. Mp: 145−147 °C. $[\alpha]_D$ +30.7 (c 2, acetone). To a suspension of the above salt (54 g) in CH_2Cl_2 (240 mL) were added crushed ice (100 g) and phosphoric acid (85%, 19.4 mL). After the solution was stirred for a few minutes, the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 200 mL). The combined organic phase was washed with aq HCl solution (2 M, 2 × 100 mL) and water and dried. The solvent was removed under reduced pressure to yield 29.2 g (38%) of (+)-isopropylbenzyloxymalonic acid monoethyl ester [(+)-**11**] as a colorless oil. $[\alpha]_D$ +8.1 (c 5, EtOH). (Compound **12** could be recovered from the aqueous phase.)

The mother liquor formed after the first crystallization and recrystallization was evaporated in vacuo to dryness. The obtained oily salt (80 g) was treated with phosphoric acid in CH_2Cl_2 as described above to afford 35.4 g (39%) of (−)-**11** as a crude product.

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[32] The configurational change at C-8 in comparison with **2c** is confirmed by the coupling constant values of H-8 with H-7$_\alpha$ and H-7$_\beta$ (3.0 and 3.4 Hz, respectively).

[33] The configuration at C-8 was determined by the NOE effect between H-8 and H-7$_\alpha$, and by the value of the coupling constant between H-8 and H-7$_\beta$ protons (10.5 Hz).

[34] (a) Smith, S.; Timmis, G. M. *J. Chem Soc.* **1936**, 1440−1444. (b) Jacobs, W. A.; Craig, L. C. *J. Biol. Chem*. **1934**, *104*, 547−549.

[35] The epimerization at C-8 is best reflected by the values of the coupling constants between H-8 and H-7$_\alpha$ and H-7$_\beta$ protons.

[36] In DMSO-d_6 solution **2a** experienced a rapid C-8 epimerization and as a result **2b** appeared in the isomer mixture.

Dechiralisation of (−)-11. To a solution of (−)-**11** (35 g, 125 mmol) in dry acetone (0.5 L) were added dry K_2CO_3 (34.5 g, 0.25 mol) and diethyl sulfate (24.6 mL, 187 mmol). The mixture was heated to reflux for 3 h, then cooled to room temperature and poured into cold water (1 L). The resulting oil was separated and the aqueous phase was extracted with ether (2 × 100 mL). The combined organic phase was washed with aqueous $NaHCO_3$ solution (5%, 2 × 100 mL) and water and dried. The solvent was removed under reduced pressure and the crude product (41.3 g) was purified by distillation (bp: 130−134 °C, 0.5 mmHg) to give 34.8 g (90%) of isopropylbenzyloxymalonic acid diethyl ester (**10**).

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for **1**, **2a**−**f**, **4c**−**g**, **6a**−**c**, (±)-**7**, **9**, **10**, (+)-**11**, **13**, and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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