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Studies on oxidation of ergot alkaloids: oxidation and desaturation of dihydrolysergol—stereochemical requirements

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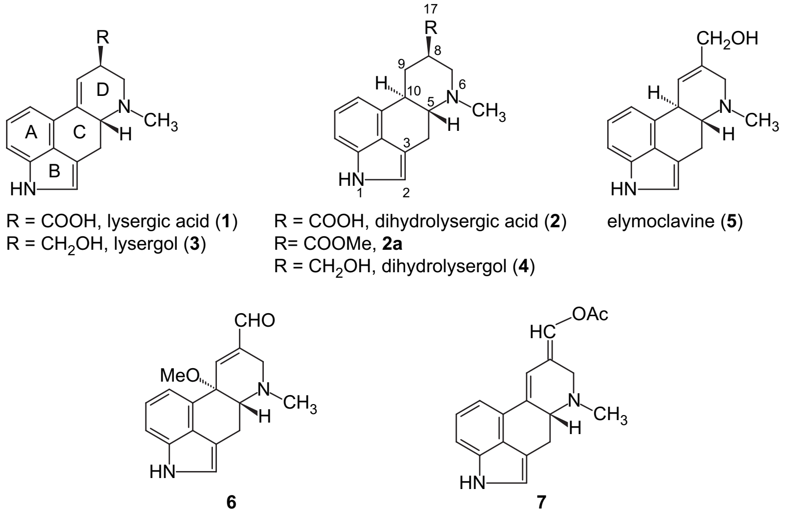
Abstract A new method for the oxidation of ergoline alcohols to aldehydes was found (TFFA DMSO, 78 °C, then DIPEA). Structural features of ergolines required for successful C7 C8 double bond introduction via Polonovski Potier reaction of respective 6 *N* oxides were defined and experimentally confirmed: (i) the presence of electron withdrawing group at C 8; (ii) trans diaxial orientation of N6 O and C7 H bonds (both requirements are fulfilled for dihydrolyserg 17 al and its 2,4 dinitrophenyl hydrazone prepared in this work).

1. Introduction

Ergot alkaloids (EA) cover a broad range of therapeutic uses as the drugs of high potency in the treatment of various disorders, such as, e.g., uterine atonia, postpartum bleeding, migraine, orthostatic circulatory disturbances, senile cerebral insufficiency, hypertension, hyperprolactinemia, acromegaly, and parkinsonism.[1] Many therapeutically used EA belong to the peptide alkaloids, but a significant number is semisynthetically prepared whose production is based on few basic precursors (Fig. 1), e.g., lysergic acid (**1**) and 9,10-dihydrolysergic acid (**2**), lysergol (**3**), 9,10-dihydrolysergol (**4**) (available from the seeds of some *Ipomoea* species[2]), and elymoclavine (**5**) produced in good yields by the submerged cultivation of some *Claviceps* strains (e.g., *C. fusiformis*).[3] The conformation



R = COOH, lysergic acid (**1**)
R = CH_2OH, lysergol (**3**)

R = COOH, dihydrolysergic acid (**2**)
R= COOMe, **2a**
R = CH_2OH, dihydrolysergol (**4**)

elymoclavine (**5**)

6

7

Figure 1. Natural ergolines, ergolenes, and their semisynthetic oxidation derivatives.

Keywords: Ergot alkaloids; Lysergol; Oxidation; Desaturation, Polonovski Potier reaction.
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of the D-ring of ergot alkaloids substantially influences binding to the different receptor class[4] as nicely demonstrated by the different biological activities displayed by the pairs **1** versus **2** and **3** versus **4**. Thus, the desaturation of D-ring at positions C5 C10 and C7 C8 could lead to new classes of ergot alkaloid derivatives with unprecedented biological activities. The new compounds could also became valuable intermediates for further modifications, as shown by the stereoselective addition of MeOH to the 9,10 double bond of lysergol to form the pharmaceutically valuable 10-α-methoxylysergol (or lumilysergol). Furthermore, changes in electronic densities of the piperidine ring and possible conjugations with the indole system could also lead to change of reactivity at the neighboring positions e.g., at C-4 that still remains a challenge for any substitution. So far a single ergolene containing the C5 C10 double bond has been reported in the literature 5,10-dehydroelymoclavine as a metabolite from the roots of African plant *Securidaca longipedunculata* Fres.[5] However, the compound was never isolated as a pure substance and its structure was suggested only on the basis of mass spectroscopic considerations.

First, and so far the only one documented introduction of a double bond into the position 7,8 of an ergoline was accomplished by Stütz and Stadler[6] by means of the Polonovski Potier reaction performed on the 6-*N*-oxide of **2a**. The same authors[6] suggested that electron withdrawing character of carboxymethyl group at C-8, which causes acidity of H-8 and thus facilitates the stabilization of the intermediate imminium salt, is crucial in the mechanism of Polonovski Potier reaction in this case. Although 6-*N*-oxide preparations of ergolines were extensively studied,[7] except the single report,[6] their use for a desaturation of the D-ring was never reported.

To corroborate the assumption given in the above paper,[6] it is necessary to prepare ergoline derivatives, containing electron-withdrawing group. Aldehyde derived from alcohol **4** (or its protected derivatives) appears to be suitable for this task.

However, the oxidation of these alcohols into their respective aldehydes and acids remains a challenge so far, although it may seem, at the first sight, quite surprising since the substrates are relatively simple and bear a primary alcoholic group.

The only ergot aldehyde obtained in good yield is chanoclavine-I-aldehyde (Fig. 2) that can be produced by chemical oxidation of chanoclavine-I (Fig. 2; MnO_2/acetone, reflux).[8]

Oxidation of 'activated' allylic alcohol group of elymoclavine (**5**) using manganese dioxide oxidation in MeOH (the reaction in acetone does not proceed)[9] yields an aldehyde **6** (Fig. 1) and the oxidation of **5** with dimethyl sulfoxide acetic anhydride provided the enol acetate **7** (Fig. 1) in 15% yield.[10] Attempts to oxidize elymoclavine following the Oppenauer protocol led only to traces of the required product.[11]

Mantegani et al.[12] reported a successful oxidation of 9,10-dihydrolysergol (**4**) by modified Parikh Doering oxidation[13] employing $SO_3 \cdot Et_3N$ complex instead of an original $SO_3 \cdot Py$ for DMSO activation (according to our experiments, $SO_3 \cdot Py$ DMSO is ineffective in this type of oxidation). However, this method failed with ergolenes as well.

Many other oxidation methods led to decomposition of ergoline skeleton, starting often at the C-2 position (most of the chromate-based oxidation procedures) or introduced new OH group into C-8 position (penniclavine, isopenniclavine).[14]

In addition, numerous oxidative biotransformations using isolated enzymes or whole cells were tested, but they afforded various products[15] and the respective aldehyde or acid were never obtained.

Therefore, we decided to investigate if modern oxidation methods are applicable for the transformation of ergoline alcohols to aldehydes (or acids) and whether the resulting aldehyde (or its protected derivative) could consecutively be tested in the Polonovski Potier reaction for the desaturation of ring D.

2. Results and discussion

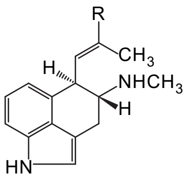
2.1. N-1 protected derivates of ergolines and ergolenes

Ergolines and ergolenes are usually poorly soluble in non-polar organic solvents such as CH_2Cl_2. This fact is inconvenient for many organic reactions, e.g., for oxidation reactions mostly requiring dichloromethane as a solvent.

Their solubility might be improved by substitution of the polar functionalities of the ergoline skeleton, e.g., alkylation or acylation/sulfonylation at N-1 position.

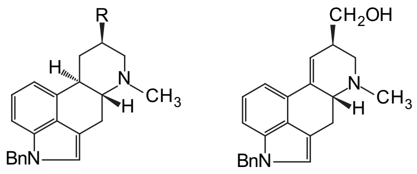
Dihydrolysergol (**4**) was selectively benzylated at N-1 to yield **8** by the action of BnBr in DMSO after deprotonization of indole nitrogen by KOH. The same procedure was used also for N-1 benzylation of lysergol to yielded **9** (Fig. 3).

Acetylation of **4** carried out in DMF using NaH and acetyl chloride (Scheme 1) gave a mixture of the acetyl derivatives **12**, **12a**, and **12b** from which the desired 1-*N*-acetyl-9,10-



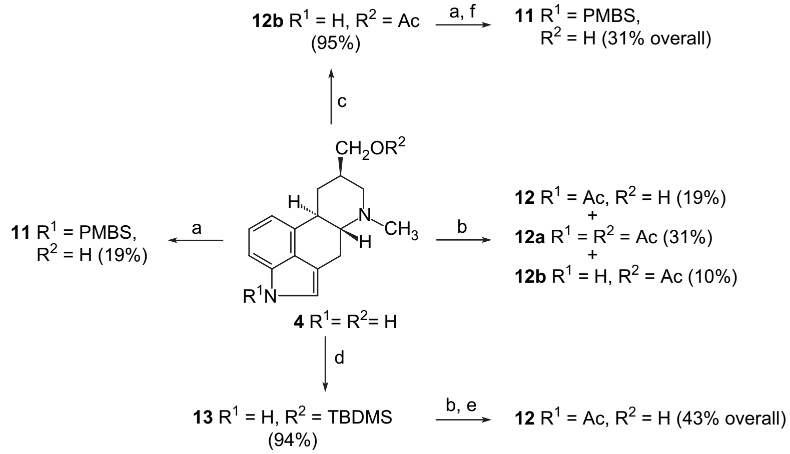
R = CH_2OH: chanoclavine I
R = CHO: chanoclavine I aldehyde

Figure 2.



8 R = CH_2OH
16 R = CHO
9

Figure 3.



Scheme 1. Reagents and conditions: (a) 4 (MeO)PhSO$_2$Cl(PMBSCl), NaH, 30 min at 0 °C, 12 h at rt; (b) AcCl, NaH, DMF, 30 min at 0 °C, 2.5 h at rt; (c) Py, Ac$_2$O, 12 h at rt; (d) TBDMSCl, imidazole, DMF, 4 h, rt; (e) BF$_3$·Et$_2$O, CH$_2$Cl$_2$, 3 h, rt; and (f) K$_2$CO$_3$, MeOH/H$_2$O (9:1), 1.5 h.

dihydrolysergol (**12**) could be isolated in 19% yield only. A better yield of **12** (43%) could be obtained by protecting the primary hydroxyl as TBDMS ether first, followed by acetylation and deprotection. Similarly, 1-*N*-(4-methoxybenzenesulfonyl)-9,10-dihydrolysergol (**11**) was obtained in poor yield by direct sulfonylation of **4** with PBMSCl and NaH, but more satisfactorily, by selectively acetylating the 17-OH group first with Py/Ac$_2$O to give **12b**.

Although the benzenesulfonyl group attached to an amine is usually rather resistant to hydrolysis, it was reported that this group can be removed from indole nitrogen under very mild conditions (Mg/MeOH).[16] Unfortunately, the method failed in the case of compound **11**, which, therefore, was not used in the following oxidative step.

2.2. Oxidation of ergolines and ergolenes to (the corresponding) aldehydes and acids

1-N-protected derivatives **8** and **9** were first used as a starting material for oxidation experiments because of their sufficient solubility in organic solvents. Oxidations were carried out with modern, mild, and selective oxidation methods; nevertheless, all the experiments were unsuccessful (Table 1) leaving the starting materials unaffected, or giving complete or partial decomposition with traces of oxidative products. Only in the case of Swern oxidation of **8** (using TFAA for DMSO activation), a low yield of the aldehyde **16** was obtained.

2.2.1. Swern oxidation (DMSO–oxalyl chloride) of dihydrolysergol silyl-ether 15. The failure of the Swern DMSO oxalyl chloride procedure to perform the oxidation of the primary alcohol function in ergoline was confirmed by the behavior of the 17-TES-ether of dihydrolysergol. In fact the conversion of the primary alcoholic group to the corresponding TES-ether represents another possibility of improving the low solubility of the studied compounds in various organic solvents. The advantage of this strategy consists of the fact that these groups could be oxidatively removed by DMSO oxalyl chloride procedure affording respective aldehyde.[20] Unfortunately, the use of this method led to the complete decomposition of the 17-*O*-TES-dihydrolysergol. Not a trace of aldehyde was formed according to a negative reaction with Ehrlich's reagent.

2.2.2. Swern oxidation (DMSO/TFAA). In contrast to oxalyl chloride, trifluoroacetic anhydride proved to be an effective activator in the Swern oxidation of ergolines but the original procedure[21] afforded rather low yield of the respective aldehyde. 1-*N*-Benzyl-dihydrolysergol (**8**) was chosen as a starting 'model' compound for the optimization of reaction conditions due to its good solubility in dichloromethane (even at low temperatures required for this method). The optimization is summarized in Table 2. The best conditions for oxidation to the aldehyde **16** are as follows: an excess of DMSO (6.0 equiv) and trifluoroacetic anhydride (4.5 equiv) at −78 °C with subsequent addition of DIPEA

Table 1. Overview of the tested oxidation experiments of the ergoline derivatives

Starting compound	Method	Result of reaction
1 *N* Benzyl dihydrolysergol (**8**)	TEMPO/NaOCl[17]	No reaction
1 *N* Benzyl dihydrolysergol (**8**)	TEMPO/laccase[18]	No reaction
1 *N* Benzyl dihydrolysergol (**8**)	Bu$_4$NCrO$_3$[19]	Partial decomposition
1 *N* Benzyl dihydrolysergol (**8**)	Swern (DMSO/oxalyl chloride)[20]	Decomposition
1 *N* Benzyl dihydrolysergol (**8**)	Swern (DMSO/TFAA)[21]	**16** (15%)
1 *N* Benzyl lysergol (**9**)	Dess Martin[22]	Decomposition
1 *N* Benzyl lysergol (**9**)	Dess Martin, Py (1.5 equiv)[23]	Traces of oxidative product
1 *N* Benzyl lysergol (**9**)	TEMPO/NaOCl[17]	No reaction
1 *N* Benzyl lysergol (**9**)	Swern (DMSO/TFAA)[21]	Decomposition
1 *N* Benzyl lysergol (**9**)	CrO$_3$/H$_5$IO$_6$, wet MeCN[24]	Total decomposition
Dihydrolysergol (**4**)	Bu$_4$NMnO$_4$[25]	No reaction
Elymoclavine (**5**)	BaMnO$_4$, DMF[26]	Partial decomposition
Elymoclavine (**5**)	Swern (DMSO/TFAA)[21]	Decomposition

Table 2. Optimization of reaction conditions for Swern oxidation[21] (DMSO/TFAA) of 1 *N* benzyl dihydrolysergol (**8**) to aldehyde **16**

	DMSO[a] (equiv)	TFAA[a] (equiv)	Reaction time after base addition (h)	Conversion[b] (%)	Yield of aldehyde[b] (%)
1.[c]	2.0	1.5	0.25	Not estimated	15
2.	3.0	2.2	0.5	50	26
3.	6.0	4.4	2.0	89	37
4.	6.0	4.5	12	82	43
5.[d]	6.0	4.5	12	82	58

All reactions were accomplished by DMSO/trifluoroacetic anhydride (TFAA) oxidation at 78 °C. The reaction was terminated by using *N* ethyl diisopropylamine (7 10 equiv).

[a] For 1 equiv of 1 *N* benzyl dihydrolysergol.

[b] Isolated yields.

[c] Et_3N (2.2 equiv) was used to terminate the reaction.

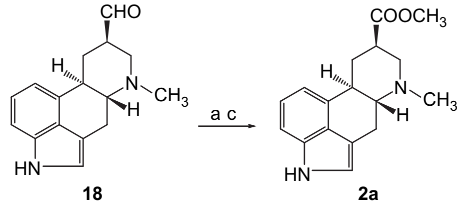
[d] Reaction was carried out in the dark.

as a base. The application of Et_3N instead of DIPEA increases side product formation. An excess of reagents is essential for a satisfactory yield of 1-*N*-benzyl-dihydrolysergal (**16**) due to the presence of tertiary amine group in the starting compound, which can presumably decompose the activated complex of DMSO TFAA. A further decrease in the side product formation was achieved when the reaction was performed in dark, allowing the isolation of **16** in fairly good yield (58%).

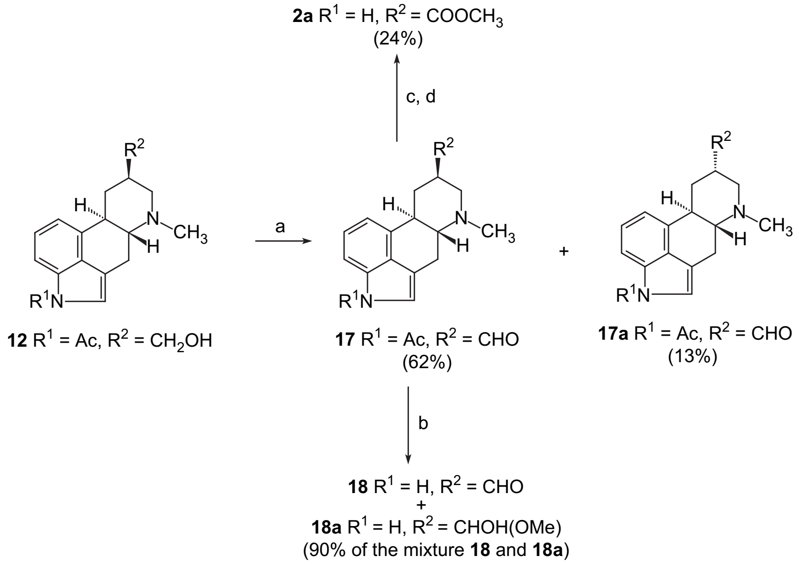
However, the hydrogenolytic deprotection (Pd/C H_2, MeOH) of 1-*N*-benzyl-dihydrolysergal (**16**) to dihydrolysergal (**18**) led to the reduction of the carbonyl group, while the benzyl group remained untouched. This highlights once again the peculiar reactivity of the ergoline moiety toward the common chemical reagents and force us to use an alternative protection strategy at N-1. The acetylation of the N-1 position in **4** overcame the problem since rather mild conditions (K_2CO_3, $MeOH/H_2O$) could be used for deprotection after primary alcoholic group oxidation.

Thus oxidation of **12** to the corresponding aldehyde **17** was achieved according to optimized conditions developed for the 1-*N*-benzyl derivative **8** (Scheme 2); however, the addition of DMSO to the dichloromethane solution of **12** was necessary for its complete dissolution. Nevertheless, it has to be noted that during this oxidation reaction partial isomerization of **17** to isodihydrolysergal-derivative **17a** occurred via the enol form of aldehyde (Scheme 2). The formation of similar side products (with 8*S* absolute configuration) was observed (according to our experiments) also in the reaction reported by Mantegani et al.[12] and in the Swern oxidation of **8** (giving the isodihydrolysergal-derivative **16a**). Hydrolysis of **17** with $K_2CO_3/MeOH/H_2O$ afforded a mixture of dihydrolysergal (**18**) accompanied by its hemiacetal **18a** and by traces of the presumed 8-*epi* analogues.

2.2.3. Oxidation of ergolines to carboxylic acids. The oxidation of **17** to dihydrolysergic acid (**2**) was accomplished by Ag_2O/NaOH in MeOH (Scheme 2). The advantage of this method consists in a simultaneous deprotection of N-1 position during oxidation. The respective acid was transformed into its methyl ester **2a** for its an easier purification. The yield of this reaction was rather low (24%) but alternative and widely used method exploiting $NaClO_2$ as an oxidation reagent (with resorcinol as a scavenger of chlorine species forming during this reaction) did not lead to the corresponding acid and considerable decomposition of the starting aldehyde occurred. TEMPO/NaOCl procedure in the presence of Bu_4NBr failed as well.[17]



Scheme 3. Reagents and conditions: (a) MCPBA, DMF, 0 °C, 1 h; (b) H_2 Pd/C, MeOH, 12 h, rt; (c) H_2SO_4 (cat.), MeOH (dry), 12 h, rt, ca. 80% (after a c).



Scheme 2. Reagents and conditions: (a) DMSO/TFAA, CH_2Cl_2, 78 °C, 45 min, then DIPEA, rt, 4 h; (b) K_2CO_3, $MeOH/H_2O$ (9:1, v/v), 2 3 h, rt; (c) Ag_2O, THF/MeOH/aqueous NaOH (10% w/w), 45 min; and (d) H_2SO_4 (cat.), MeOH (dry), 12 h, rt.

An alternative, very efficient method for the oxidation of dihydrolysergal (**18**) to dihydrolysergic acid (**2**) was developed in this work using excess of MCPBA (Scheme 3).

A drawback of this oxidation method consists in the necessity of the intermediate *N*-oxide reduction; however, rather high yield and low side products formation are unquestionable advantages in comparison with other methods tested.

2.3. Desaturation of the D-ring of ergolines—Polonovski–Potier reaction

Introduction of new double bond into the position 7,8 of 9,10-dihydroergoline derivatives was accomplished by the Polonovski Potier reaction,[6] starting from the corresponding 6-*N*-oxides. In principle, the double bond could also be introduced between position 5 and 10, but steric and electronic factors suggest that formation of the C7 C8 double bond should be strongly favored.

Ergoline/ergine N-oxidations usually employ H_2O_2 or *m*-chloroperbenzoic acid (MCPBA).[7] Bulkier MCPBA is more selective than H_2O_2 and often produces only single *N*-oxide diastereomer.[7a] This fact is very important for the course of Polonovski Potier reaction, because the reaction outcome is dictated by the configuration of the starting *N*-oxide.

17-*O*-Acetyl-lysergol 6-*N*-oxide (**21**; both possible stereoisomers in the ratio α/β ca. 4:1), 17-*O*-acetyl-dihydrolysergol 6-*N*-oxide (**22**; single stereoisomer with α-configuration), methyl dihydrolysergate 6-*N*-oxide (**23**; single stereoisomer with α-configuration), and methyl lysergate 6-*N*-oxide (**24**; both possible stereoisomers in the ratio α/β ca. 4:1) were prepared according to the described methods[7a] (Fig. 4).

Polonovski reaction (Ac_2O/Et_3N) of the 6-*N*-oxides **21** and **22** did not lead to the C7 C8 double bond formation and only complete decomposition of starting *N*-oxides was observed, in accordance with the fact that they do not exhibit any acidity at the C-8 position.

To confirm the role of the acidity of H-8, we tried to introduce C7 C8 double bond into the molecule of dihydrolysergal (**18**); however, these attempts failed due to the side reaction mentioned above (direct N-oxidation of aldehyde by MCPBA led simultaneously to oxidation of its carbonyl group to a carboxyl). Protection of the carbonyl group of **18** as 2,4-dinitrophenyl hydrazone gave, after 6-N-oxidation and Polonovski Potier reaction (Scheme 4), a comparable yield of 7,8-ergolene as was reported[6] for compound **23** despite that DMF was used instead of 'traditional' CH_2Cl_2 (for solubility reasons). Thus, although the acidity of the α-position of hydrazones is rather low, the course of this reaction is very similar to the reaction of the ester **23**.

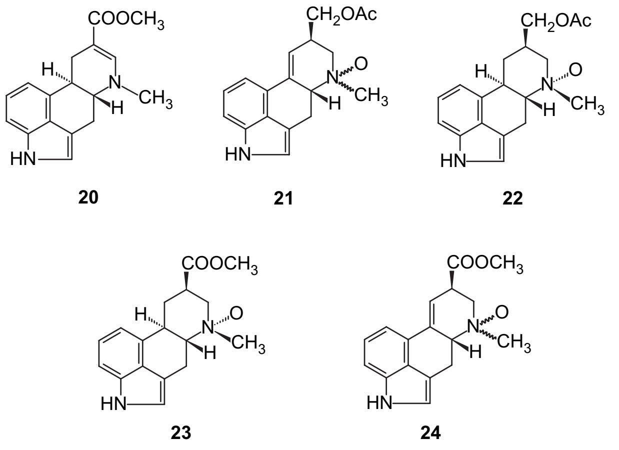
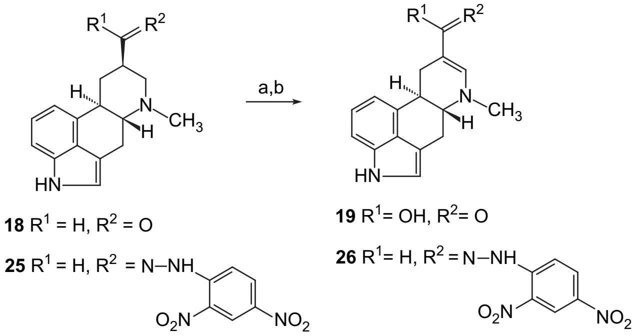


Figure 4. 6 *N* Oxides used for Polonovski Potier reaction. Compound **20** represents a single product with $\Delta^{7,8}$ described so far.



Scheme 4. Reagents and conditions: (a) MCPBA, DMF, 0 °C, 0.5 h and (b) Ac_2O, Et_3N, DMF, 0 °C, 1 h.

However, the acidity of H-8 in ergolines and ergolenes is not the only requirement for a successful Polonovski reaction since the introduction of C7 C8 double bond to the methyl lysergate via its 6-*N*-oxide **24** failed as well.

Moreover, MCPBA oxidation of **20** (product described in Ref. 6) gave mixture of two 6-*N*-oxides (in the ratio ca. 1:1), which led after attempted Polonovski Potier reaction to the partial decomposition of these intermediates (without C7 C8 double bond formation).

These experiments indicate two important requirements for successful course of the Polonovski Potier reaction in the ergoline D-ring:

1. The hydrogen at the position C-8 of the D-ring should posses an acidic character, which probably facilitates the stabilization of intermediate imminium salt (Fig. 5). The role of H-8 on the course of Polonovski Potier reaction was suggested previously[6] but without comparison with another related compounds (alcohol or its ester and aldehyde derived from the dihydrolysergic acid (**2**)).
2. Trans-diaxial relationship of *N*-oxide bond and one of the H-7 bonds must occur. This is the case of compound **23** but not the case of compound **24** (Fig. 6) where the presence of the C9 C10 double bond limits the possibility to satisfy this stereochemical requirement and therefore the reaction failed to give the desired product.

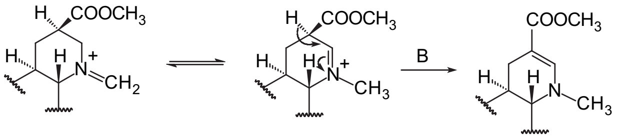


Figure 5. The role of acidic hydrogen at C 8 on the intermediate salt stabi lization.

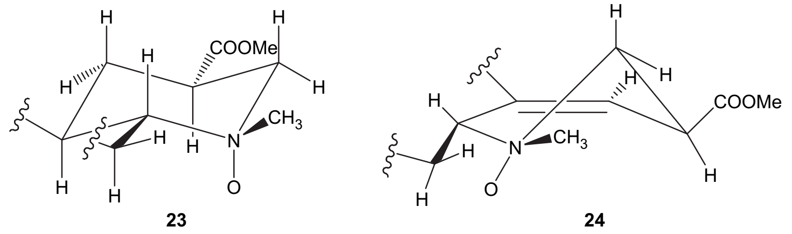


Figure 6. Conformations of the D ring in dihydrolysergate **23** and lysergate **24** 6 *N* oxides (according to the Ref. 7a).

To assess the influence of acylating reagent on the course of reaction, we also applied TFAA instead of acetic anhydride (without base addition). However, this modification in all the cases led to the decomposition of starting 6-*N*-oxides (products with C7 C8 double bond were not formed).

3. Conclusions

A further demonstration of the peculiar reactivity of ergolines and ergolenes has been given. In fact the versatile methodologies that found general application in the preparative organic chemistry failed or highlighted highly demanding requisites. Three different tasks have been faced in this study: (1) the solubility improvement of the studied compounds; (2) the oxidation of CH_2OH to aldehyde or to carboxylic acid; and (3) the desaturation of D-ring. A particular success was achieved for the oxidation of 9,10-dihydrolysergol to an aldehyde by DMSO/TFAA and the subsequent treatment with DIPEA. The experimental evidence has been given to the supposed necessary trans-diaxial disposition of H-7 and N O bonds. The relevance of the biological and pharmacological activities of these compounds justifies the efforts and stresses the importance of even small advances in this field.

4. Experimental section

4.1. General

NMR spectra were recorded on a Varian INOVA-400 spectrometer (399.89 MHz for ^{1}H, 100.55 MHz for ^{13}C) in $CDCl_3$ or DMSO-d_6 at 30 °C. Chemical shifts were referenced to the residual solvent signal (δ_H 7.265, δ_C 77.00; δ_H 2.50, δ_C 39.60). Digital resolution used justified reporting the proton and carbon chemical shifts to three and two decimal places, respectively. Coupling constants [*J*] are given in Hz. All 2D NMR experiments (HOM2DJ, gCOSY, TOCSY, HMQC, and HMBC) were performed using standard manufacturers' software. The sequence for 1D-TOCSY experiments was obtained through Varian User Library; the employed sequence gHMQC was obtained from Varian Application Laboratory in Darmstadt (DE).

Positive-ion electrospray ionization (ESI) mass spectra were recorded on a double-focusing instrument Finnigan MAT 95 (Finnigan MAT, Bremen, DE) with BE geometry. Samples dissolved in methanol/water (2:1, v/v) were continuously infused through a stainless capillary held at 3.3 kV into Finnigan ESI source via a linear syringe pump at a flow rate of 40 μL/min.

High resolution mass spectrometric experiment was performed on a commercial APEX-Qe FTMS instrument equipped with a 9.4 T superconducting magnet and a Combi ESI/MALDI ion source (Bruker Daltonics, Billerica MA) using electrospray ionization. One milligram of each sample (**8**, **9**, **11**, **12**, **13**, **25**, and **26**) was dissolved in 1 mL of MeOH and one microliter of stock solution was diluted in 1 mL of 0.1% formic acid and 80% MeCN afterward. One milligram of **16** and **17** was dissolved in 1 mL of MeCN and one microliter of stock solution was diluted in 1 mL of MeCN afterward. The flow rate was 1 μL/min and the temperature of dry gas (nitrogen) was set to 230 °C. The Q front-end consists of a quadrupole mass filter followed by a hexapole collision cell. By switching the potentials on the exit lenses appropriately under the control of the data acquisition computer, ions could be accumulated either in the hexapole of the Combi ESI source, or in the hexapole collision cell of the Q front-end, prior to transfer to the FTMS analyzer cell. Mass spectra were obtained by accumulating ions in the collision hexapole and running the quadrupole mass filter in nonmass-selective (RF-only) mode so that ions of a broad *m*/*z* range (200 2500) were passed to the FTMS analyzer cell. The accumulation time in collision cell was set at 0.5 s, the cell was opened for 4500 μs, 16 experiments were collected for one spectrum. The instrument was externally calibrated using quadruple-, triple- and double- charged ions of angiotensin I, quintuple- and quadruple- charged ions of insulin. It results in typical mass accuracy below 1 ppm. After the analysis the spectra were apodized using sin apodization with one zero fill.

4.1.1. 1-*N*-Benzyl-9,10-dihydrolysergol (8).

9,10-Dihydrolysergol (**4**, 0.5 g, 1.953 mmol) was dissolved in DMSO (6.25 mL) and powdered KOH (0.334 g, 5.964 mmol) was added. The mixture was stirred at room temperature for 10 min benzyl bromide (0.3 mL, 2.53 mmol) was added and the mixture was stirred at room temperature in the dark under argon. After 3 h, the mixture was diluted with water (50 mL) and extracted with CH_2Cl_2 (2×25 mL). Organic layers were combined, washed with saturated aqueous solution of NaCl, and dried over anhydrous Na_2SO_4. Flash chromatography ($CHCl_3$/MeOH/NH_4OH 95:5:1) afforded **8** (0.414 g, 61%) as a white amorphous solid.

^{1}H NMR ($CDCl_3$): 1.181 (1H, ddd, *J*=12.5, 12.3, 12.3, H-9a), 2.018 (1H, dd, *J*=11.3, 11.3, H-7a), 2.202 (1H, ddd, *J*=11.1, 9.7, 4.3, H-5), 2.206 (1H, m, H-8), 2.498 (3H, s, NMe), 2.718 (1H, m, H-9e), 2.737 (1H, ddd, *J*=14.7, 11.1, 1.7, H-4a), 3.025 (1H, m, H-10), 3.179 (1H, ddd, *J*=11.3, 3.6, 1.9, H-7e), 3.406 (1H, dd, *J*=14.7, 4.3, H-4e), 3.584 (1H, dd, *J*=10.7, 6.9, H-17u), 3.675 (1H, dd, *J*=10.7, 5.8, H-17d), 5.260 (2H, s, CH_2), 6.800 (1H, d, *J*=1.7, H-2), 6.930 (1H, ddd, J=7.1, 1.3, 0.8, H-12), 7.081 (1H, ddd, J=8.2, 0.8, 0.8, H-14), 7.149 (1H, dd, J=8.2, 7.1, H-13), 7.163 (2H, m, 2×H-*ortho*), 7.276 (1H, m, H-*para*), 7.306 (2H, m, 2×H-*meta*); ^{13}C NMR (CDCl$_3$): 26.19 (C-4), 30.78 (C-9), 38.68 (C-8), 40.33 (C-10), 43.28 (NMe), 50.18 (CH$_2$), 60.69 (C-7), 66.32 (C-17), 67.41 (C-5), 107.19 (C-14), 111.35 (C-3), 112.90 (C-12), 121.77 (C-2), 122.82 (C-13), 126.73 (C-16), 126.95 (2×C-*ortho*), 127.52 (C-*para*), 128.68 (2×C-*meta*), 133.54 (C-11), 134.103 (C-15), 137.92 (C-*ipso*). Positive ESIMS (*m/z*): 347 [M+H]$^+$; HRMS (ESI FTMS) calcd for $C_{23}H_{27}N_2O$ 347.2118, found for [M+H$^+$] 347.2116.

According to COSY, the molecule of **8** contains an ergoline skeleton substituted by benzyl, *N*-methyl, and CH$_2$O groups. The N-benzylation is evident from the absence of indole NH and its coupling to H-2 in the ^{1}H NMR spectrum and the heteronuclear couplings of the benzylic CH$_2$ to C-2 and C-15 (Fig. 7). The coupling $J_{5,10}$=9.7 Hz means a trans-C/D ring junction. The long-range couplings of H-10 to H-12 and H-14 further support the dihydro derivative character of the compound. Large values of $J_{8,9a}$ and $J_{7a,8}$ indicate an axial position of H-8, i.e., an 8β-CH$_2$OH orientation.

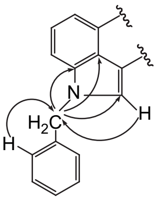


Figure 7. Some diagnostic HMBC contacts observable in compounds **8** and **9**.

4.1.2. 1-*N*-Benzyl-lysergol (9).

Powdered KOH (0.167 g, 2.982 mmol) was added to a stirred solution of **3** (0.250 g, 0.984 mmol) in DMSO (3 mL). After 10 min of stirring at room temperature, benzyl bromide (0.150 mL, 1.26 mmol) was added and the mixture was stirred at room temperature in the dark under argon. After 3 h, the mixture was diluted with water (50 mL) and extracted with CH$_2$Cl$_2$ (2×25 mL). Organic layers were combined, washed with brine, and dried over Na$_2$SO$_4$. Flash chromatography (CHCl$_3$/MeOH/NH$_4$OH 95:5:1) afforded **9** (0.214 g, 63%) as a white amorphous solid.

^{1}H NMR (CDCl$_3$): 2.425 (1H, dd, J=11.2, 8.6, H-7a), 2.581 (3H, s, NMe), 2.764 (1H, ddd, J=14.4, 11.4, 1.8, H-4a), 2.850 (1H, m, H-8), 3.126 (1H, dd, J=11.2, 4.9, H-7e), 3.305 (1H, dddd, J=11.4, 5.4, 3.1, 2.1, H-5), 3.455 (1H, dd, J=14.4, 5.4, H-4e), 3.704 (1H, dd, J=10.4, 6.2, H-17u), 3.793 (1H, dd, J=10.4, 5.2, H-17d), 5.264 (2H, s, CH$_2$), 6.386 (1H, dd, J=3.0, 2.0, H-9), 6.815 (1H, d, J=1.8, H-2), 7.095 (1H, m, H-14), 7.139 (2H, m, 2×*ortho*-Ph), 7.153 (1H, m, H-13), 7.170 (1H, m, H-12), 7.275 (1H, m, *para*-Ph), 7.302 (2H, m, 2×*meta*-Ph); ^{13}C NMR (CDCl$_3$): 25.85 (C-4), 38.38 (C-8), 43.15 (NMe), 50.22 (CH$_2$), 55.76 (C-7), 62.57 (C-5), 65.51 (C-17), 108.19 (C-14), 110.19 (C-3), 111.84 (C-12), 121.69 (C-9), 122.44 (C-2), 123.06 (C-13), 126.62 (C-16), 126.88 (2×C-*ortho*), 127.56 (C-*para*), 128.70 (2×C-*meta*), 128.76 (C-11), 134.73 (C-15), 135.05 (C-10), 137.82 (C-*ipso*). Positive ESIMS (*m/z*): 345 [M+H]$^+$; HRMS (ESI FTMS) calcd for $C_{23}H_{25}N_2O$ 345.1961, found for [M+H$^+$] 345.1958.

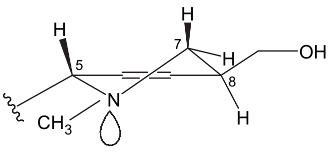


Figure 8. Flap up conformation of the D ring.

According to COSY, the molecule of **9** contains a 9-ergolene skeleton substituted by benzyl, *N*-methyl, and CH$_2$OH groups. The benzylation at N-1 is evident from the absence of indole NH and its coupling to H-2 in the ^{1}H NMR spectrum and the heteronuclear couplings of the benzylic CH$_2$ to C-2, C-15, and C-16 (Fig. 7). The chemical shift of H-5 (3.305 ppm) indicates that H-5 and the N-6 lone electron pair are antiperiplanar.[27] Couplings $J_{7a,8}$=8.6 Hz and $J_{8,9}$=3.0 Hz require a pseudoaxial H-8. Therefore, the ergolene D-ring adopts a flap-up conformation[14c,28] (Fig. 8) with pseudoequatorial (i.e., 8β) CH$_2$OH group.

4.1.3. Preparation of 1-*N*-(4-methoxybenzenesulfonyl)-9,10-dihydrolysergol (11).

4.1.3.1. Method I.

9,10-Dihydrolysergol (**4**, 200 mg, 0.781 mmol) and NaH (30 mg, 1.015 mmol, 80% w/w dispersion in min. oil) were dissolved under cooling to 0 °C in 5 mL DMF (not dissolved completely) and stirred at 0 °C under argon for 10 min. 4-Methoxybenzenesulfonic chloride (194 mg, 0.939 mmol) was then added and the reaction mixture was stirred at 0 °C for 30 min and then overnight at room temperature. The reaction mixture was then diluted with saturated aqueous solution of NaHCO$_3$ (30 mL) and extracted with ethyl acetate (2×15 mL). Organic layers were combined, washed with brine, and dried over anhydrous Na$_2$SO$_4$. Flash chromatography (CH$_2$Cl$_2$/MeOH/NH$_4$OH 89:10:1) yielded title compound **11** (63 mg, 19%) as a white amorphous solid.

^{1}H NMR (DMSO): 0.882 (1H, ddd, J=12.4, 12.2, 12.2, H-9a), 1.884 (1H, dd, J=11.1, 10.7, H-7a), 1.908 (2H, m, H-5, H-8), 2.322 (3H, s, NMe), 2.437 (1H, ddd, J=14.7, 11.5, 1.8, H-4a), 2.538 (1H, m, H-9e), 2.728 (1H, m, H-10), 2.994 (1H, m, H-9e), 3.287 (1H, dd, J=14.7, 4.2, H-4e), 3.288 (1H, m, H-17u), 3.267 (1H, m, H-17d), 3.768 (3H, s, OCH$_3$), 4.540 (1H, br s, 17-OH), 7.044 (2H, AA′BB′, ΣJ=9.0, 2×H-*ortho*), 7.066 (1H, d, J-7.4, H-12), 7.282 (1H, dd, J=8.2, 7.4, H-13), 7.402 (1H, d, J=1.8, H-2), 7.657 (1H, d, J=8.2, H-14), 7.881 (2H, AA′BB′, ΣJ=9.0, 2×H-*meta*); ^{13}C NMR (DMSO): 25.89 (C-4), 30.48 (C-9), 37.98 (C-8), 39.42 (C-10), 43.75 (NMe), 55.84 (OCH$_3$), 60.35 (C-7), 64.36 (C-17), 66.20 (C-5), 110.85 (C-14), 114.97 (2×C-*ortho*), 117.71 (C-12), 118.47 (C-3), 119.80 (C-2), 125.72 (C-13), 128.31 (C-16), 128.96 (C-*ipso*), 128.99 (2×C-*meta*), 132.20 (C-15), 134.43 (C-11), 163.62 (C-*para*). Positive ESIMS (*m/z*): 427 [M+H]$^+$; HRMS (ESI FTMS) calcd for $C_{23}H_{27}N_2O_4S$ 427.1686, found for [M+H$^+$] 427.1685.

According to COSY and HSQC, the molecule contains an ergoline substructure. The shape of the H-10 multiplet indicates a large (axial axial) coupling to H-5 which means a trans-C/D ring junction. The couplings $J_{7a,8}$ and $J_{8,9a}$ are also large so that H-8 is axial. The OH signal at 4.540 ppm, coupled to both H-17 protons is an evidence for a CH_2OH group that should have an 8β-configuration. The absence of NH signal in the ^1H NMR spectrum could be explained by $CH_3OC_6H_4SO_2$ substitution at N-1.

4.1.3.2. Method II (via acetylation of primary hydroxyl group).

*(a) Preparation of 17-O-acetyl-9,10-dihydrolysergol (**12b**)*: 9,10-dihydrolysergol (**4**, 0.350 g, 1.367 mmol) was dissolved in 4 mL of dry pyridine and 1.5 mL of acetic anhydride and the reaction mixture was stirred at room temperature for 12 h. The mixture was treated with ice-cold water solution of saturated $NaHCO_3$ (30 mL), stirred for 30 min and then extracted three times with 20 mL of the mixture CH_2Cl_2/MeOH (9:1, v/v). The combined extracts were dried over anhydrous Na_2SO_4. The residual pyridine was removed by co-evaporation with toluene. After the evaporation, the sufficiently pure title compound **12b** (0.40 g, 95%) was obtained.

*(b) 1-N-(4-Methoxybenzenesulfonyl)-9,10-dihydrolysergol (**11**) from 17-O-acetyl-9,10-dihydrolysergol (**12b**)*: 9,10-dihydrolysergol acetate (**12b**, 400 mg, 1.342 mmol) and NaH (60 mg, 2.030 mmol, 80% w/w dispersion in min. oil) were dissolved under cooling to 0 °C in DMF (5 mL) and stirred at 0 °C under argon for 10 min. 4-Methoxybenzenesulfonic chloride (361 mg, 1.747 mmol) was then added and the reaction mixture was stirred at 0 °C for 30 min and then overnight at room temperature. The reaction mixture was then diluted with saturated aqueous solution of $NaHCO_3$ (50 mL) and extracted two times with 20 mL of CH_2Cl_2. Organic layers were combined, washed with saturated aqueous solution of NaCl, and dried over anhydrous Na_2SO_4.

The crude 1-*N*-(4-methoxybenzensulfonyl)-9,10-dihydrolysergol acetate was dissolved in the mixture of MeOH/H_2O (11 mL, 10:1, v/v) and K_2CO_3 (200 mg, 1.449 mmol) was then added. The resulting mixture was stirred at room temperature for 1.5 h. The solvent was then evaporated and the mixture was directly transferred to a silica gel chromatography column (CH_2Cl_2/MeOH/NH_4OH 89:10:1). Pure **11** (178 mg, 31%) was obtained as a white amorphous solid. For MS and NMR data see above.

4.1.4. 1-*N*-Acetyl-9,10-dihydrolysergol (12).

4.1.4.1. Method I.

9,10-Dihydrolysergol (**4**, 500 mg, 1.953 mmol) and NaH (96 mg, 2.400 mmol, 60% w/w dispersion in min. oil) were dissolved under cooling to 0 °C in dry DMF (5 mL) and stirred at 0 °C under argon for 30 min. Acetyl chloride (0.190 mL, 2.676 mmol) was then added and the reaction mixture was stirred at 0 °C for 30 min and then for 2 h at room temperature. The reaction mixture was then diluted with saturated aqueous solution of $NaHCO_3$ (50 mL) and extracted with ethyl acetate (2×30 mL). Organic layers were combined, washed with brine, and dried over anhydrous Na_2SO_4.

Flash chromatography ($CHCl_3$/MeOH/NH_4OH 95:5:1) yielded 1-*N*-acetyl-dihydrolysergol (**12**, 170 mg, 19%) as a white amorphous solid.

^1H NMR (DMSO): 0.915 (1H, ddd, J=12.3, 12.3, 11.4, H-9a), 1.799 (1H, dd, J=11.3, 11.0, H-7a), 1.909 (1H, ddd, J=11.4, 9.5, 4.2, H-5), 1.929 (1H, m, H-8), 2.330 (3H, s, NMe), 2.462 (1H, ddd, J=15.3, 11.4, 2.2, H-4a), 2.577 (1H, ddd, J=12.3, 3.8, 1.8, H-9e), 2.589 (3H, s, Ac), 2.753 (1H, m, H-10), 3.000 (1H, ddd, J=11.0, 3.5, 1.8, H-7e), 3.285 (1H, J=15.3, 4.2, H-4e), 3.287 (1H, ddd, J=10.5, 5.2, 1.6, H-17u), 3.396 (1H, ddd, J=10.5, 5.3, 5.2, H-17d), 4.534 (1H, dd, J=5.3, 5.2, 17-OH), 7.088 (1H, dd, J=7.5, 0.8, H-12), 7.220 (1H, dd, J=8.1, 7.5, H-13), 7.471 (1H, d, J=2.2, H-2), 7.919 (1H, dd, J=8.1, 0.8, H-14); ^{13}C NMR (DMSO): 23.64 (Ac), 26.16 (C-4), 30.73 (C-9), 38.17 (C-8), 39.67 (C-10), 42.95 (NMe), 60.58 (C-7), 64.50 (C-17), 66.71 (C-5), 113.57 (C-14), 117.57 (C-3), 117.80 (C-12), 119.99 (C-2), 125.64 (C-13), 128.18 (C-16), 132.61 (C-15), 133.78 (C-11), 169.18 (C O). Positive ESIMS (*m/z*): 299 $[M+H]^+$; HRMS (ESI FTMS) calcd for $C_{18}H_{23}N_2O_2$ 299.1754, found for $[M+H^+]$ 299.1752.

According to COSY and HSQC, the molecule of **12** contains an ergoline skeleton substituted by a CH_2OH group at C-8, by an *N*-methyl, and one acetyl. The ample evidence for an unsubstituted primary alcoholic group is the triplet at 4.534 ppm giving no crosspeaks in gHSQC but coupled to both H-17 protons. The acetyl is easily located at N-1 as seen from the ^4J coupling of acetyl protons to C-2. A trans-C/D ring junction was confirmed by large $J_{5,10}$=9.5 Hz. The CH_2OH substituent has an 8β-configuration since $J_{7a,8}$=11.3 Hz and $J_{8,9}$=12.3 Hz.

4.1.4.2. Method II.

*17-O-(tert-Butyldimethylsilyl)-9,10-dihydrolysergol (**13**)*: 9,10-dihydrolysergol (**4**, 640 mg, 2.500 mmol), TBDMSCl (490 mg, 3.251 mmol), and imidazole (400 mg, 5.882 mmol) were dissolved in dry DMF (6 mL) and the reaction mixture was stirred under argon at room temperature. The reaction was quenched after 4 h with saturated aqueous solution of $NaHCO_3$ (50 mL), the precipitate was filtered off, washed with water, and dried to afford the pure title compound **13** (870 mg, 94%) as a slightly pink amorphous solid.

^1H NMR ($CDCl_3$): 0.092 (3H, s, SiMe), 0.097 (3H, s, SiMe), 0.932 (9H, s, CMe_3), 1.175 (1H, ddd, J=12.5, 12.3, 12.3, H-9a), 2.006 (1H, dd, J=11.2, 11.2, H-7a), 2.177 (1H, ddd, J=11.3, 11.0, 4.4, H-5), 2.182 (1H, m, H-8), 2.513 (3H, s, NMe), 2.655 (1H, dddd, J=12.5, 3.9, 3.9, 1.9, H-9e), 2.752 (1H, ddd, J=14.7, 11.0, 1.8, H-4a), 3.015 (1H, m, H-10), 3.158 (1H, ddd, J=11.2, 3.6, 1.9, H-7e), 3.428 (1H, dd, J=14.7, 4.4, H-4e), 3.543 (1H, dd, J=10.1, 6.9, H-17u), 3.645 (1H, dd, J=10.1, 5.3, H-17d), 6.887 (1H, dd, J=1.8, 1.8, H-2), 6.937 (1H, m, H-12), 7.142 (1H, m, H-13), 7.189 (1H, m, H-14), 8.026 (1H, br s, NH); ^{13}C NMR ($CDCl_3$): −5.37 (SiMe), −5.32 (SiMe), 18.34 (SiC), 25.96 (CMe_3), 26.96 (C-4), 30.70 (C-9), 38.55 (C-8), 40.41 (C-10), 43.33 (NMe), 60.93 (C-7), 65.50 (C-17), 67.42 (C-5), 108.45 (C-14), 112.03 (C-3), 113.18 (C-12), 117.67 (C-2), 123.09 (C-13), 126.24 (C-16), 133.35 (C-15), 132.56 (C-11). Positive ESIMS (*m/z*): 371 $[M+H]^+$; HRMS (ESI FTMS) calcd for $C_{22}H_{35}N_2OSi$ 371.2513, found for $[M+H^+]$ 371.2511.

According to COSY, the molecule of **13** contains an ergoline skeleton substituted by *N*-methyl and TBDMS groups. The preserved indole ring is evident from the observed indole NH and its coupling to H-2 in the ^{1}H NMR spectrum. Although there is no direct evidence available, the TBDMS group has to be attached to C-17 OH. The upfield shift of both H-17 protons with respect to the parent compound is a supporting argument. Large $J_{5,10}$=11.0 Hz indicates a trans-C/D ring junction. The configuration 8βresults from the magnitude of vicinal coupling constants $J_{7a,8}$=11.2 Hz and $J_{8,9a}$=12.3 Hz (ring D adopting a chair form).

1-N-Acetyl-9,10-dihydrolysergol (12): 17-*O*-(*tert*-butyldimethylsilyl)-9,10-dihydrolysergol (**13**, 600 mg, 1.621 mmol) and NaH (71 mg, 1.775 mmol, 60% w/w dispersion in min. oil) were dissolved under cooling to 0 °C in dry DMF (6 mL) and stirred at 0 °C under argon for 30 min. Acetyl chloride (0.140 mL, 1.972 mmol) was then added and the reaction mixture was stirred at 0 °C for 30 min and then for 2 h at room temperature. The reaction mixture was then diluted with saturated aqueous solution of $NaHCO_3$ (50 mL) and extracted with dichloromethane (2×30 mL). Organic layers were combined, dried over anhydrous Na_2SO_4, and evaporated. The crude mixture from acetylation was dissolved in dry CH_2Cl_2 (25 mL), $BF_3 \cdot Et_2O$ (2.0 mL, 50% solution) was added and the mixture was stirred for 3 h at room temperature. The mixture was then poured into the saturated aqueous solution of $NaHCO_3$ (40 mL) and shortly stirred. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (2×20 mL). Organic layers were combined and dried over anhydrous Na_2SO_4. Flash chromatography ($CHCl_3$/MeOH/NH_4OH 95:5:1) afforded 1-*N*-acetyl-9,10-dihydrolysergol (**12**, 210 mg, 43%) as a white amorphous solid. For MS and NMR data see above.

4.1.5. 1-*N*-Benzyl-9,10-dihydrolysergal (16) (according to optimized conditions).

Trifluoroacetic anhydride (0.330 mL, 2.371 mmol) in dichloromethane (0.450 mL) was added dropwise to a solution of dichloromethane (0.600 mL) and dimethyl sulfoxide (0.228 mL, 3.055 mmol) under argon at −78 °C. The solution was stirred for 10 min at −78 °C and then a solution of 1-*N*-benzyl-9,10-dihydrolysergol (**8**, 0.186 mg, 0.537 mmol) in CH_2Cl_2 (1 mL) was added dropwise. The mixture was stirred for another 30 min at −78 °C and then at the same temperature it was treated with *N*-ethyldiisopropylamine (1.2 mL, 6.902 mmol). The mixture was stirred for 10 min, allowed to warm up to room temperature and stirred in dark (under argon) for another 12 h. The mixture was diluted with brine (30 mL) and extracted with CH_2Cl_2 (3×25 mL). The combined organic layers were washed with brine (3×50 mL) and dried over anhydrous Na_2SO_4. Flash chromatography ($CHCl_3$/MeOH/NH_4OH 95:5:1) yielded 1-*N*-benzyl-9,10-dihydrolysergal (**16**, 108 mg, 58%) as a white amorphous solid and 33 mg of the starting material (18%) was recovered.

^{1}H NMR ($CDCl_3$), major component: 1.456 (1H, ddd, *J*=12.2, 12.1, 12.1, H-9a), 2.218 (1H, ddd, *J*=11.1, 9.5, 4.2, H-5), 2.269 (1H, *J*=11.8, 11.5, H-7a), 2.530 (3H, NMe), 2.731 (1H, ddd, *J*=14.7, 11.1, 1.5, H-4a), 2.934 (1H, m, H-8), 2.988 (1H, m, H-9e), 3.044 (1H, m, H-10), 3.314 (1H, ddd, *J*=11.5, 3.4, 2.2, H-7e), 3.408 (1H, dd, *J*=14.7, 4.3, H-4e), 5.269 (2H, s, CH_2), 6.816 (1H, d, *J*=1.3, H-2), 7.070 (1H, ddd, *J*=7.1, 2.1, 0.9, H-12), 7.104 (1H, ddd, *J*=8.2, 1.8, 0.9, H-14), 7.160 (1H, m, H-13), 7.165 (2H, m, 2×H-*ortho*), 7.286 (1H, m, H-*para*), 7.310 (2H, m, 2×H-*meta*), 9.786 (1H, dd, *J*=1.0, 1.0, H-17); minor component: 1.657 (1H, ddddd, *J*=12.6, 12.6, 4.8, 1.1, 1.1, H-9a), 2.465 (3H, s, NMe), 2.647 (1H, m, H-4a), 2.903 (1H, m, H-10), 3.152 (1H, m, H-9e), 3.378 (1H, dd, *J*=14.7, 4.2, H-4e), 3.475 (1H, m, H-7e), 5.257 (2H, s, CH_2), 6.779 (1H, d, *J*=1.3, H-2), 9.944 (1H, dd, *J*=1.2, 1.1, H-17); ^{13}C NMR ($CDCl_3$), major component: 26.86 (C-4), 27.84 (C-9), 40.03 (C-10), 43.14 (NMe), 48.67 (C-8), 50.24 (CH_2), 56.45 (C-7), 66.98 (C-5), 107.51 (C-14), 111.05 (C-3), 112.91 (C-12), 121.94 (C-2), 122.90 (C-13), 126.64 (C-16), 126.96 (2×C-*ortho*), 127.57 (C-*para*), 128.72 (2×C-*meta*), 132.66 (C-11), 134.13 (C-15), 137.84 (C-*ipso*), 202.51 (C-17); minor component: 26.62 (C-4), 27.74 (C-9), 37.52 (C-10, 43.49 (NMe), 46.18 (C-8), 50.19 (CH_2), 56.88 (C-7), 67.30 (C-5), 107.25 (C-14), 111.22 (C-3), 112.95 (C-12), 121.76 (C-2), 122.84 (C-13), 126.64 (C-16), 126.96 (2×C-*ortho*), 127.53 (C-*para*), 128.69 (2×C-*meta*), 133.48 (C-11), 133.76 (C-15), 137.84 (C-*ipso*), 204.64 (C-17). Positive ESIMS (*m/z*): 345 $[M+H]^+$; HRMS (ESI FTMS) calcd for $C_{23}H_{25}N_2O$ 345.1961, found for $[M+H^+]$ 345.1958.

Some signals in the ^{1}H NMR spectrum occur twice: e.g., CH O, H-2, CH_2, NMe. Therefore, the sample is a mixture of two compounds in the ratio 83:17 (~4:1). All spectral properties extracted by COSY and gHSQC correspond to an ergoline skeleton carrying an aldehyde group at C-8 and a benzyl group. No signal of indole NH was observed. The benzylic methylene is coupled to C-2 and C-15 so that N-1 is benzylated. Both $J_{7a,8}$ and $J_{8,9a}$ in the major component are large, so that the configuration at C-8 is 8β. The magnitude of $J_{5,10}$=9.5 Hz confirms a trans-C/D ring junction. Therefore, the prevailing component is **16**.

The minor component shares most of the structural features with the major one. Its C-13 chemical shifts are slightly different as well as the multiplicity of H-9a (one large coupling is replaced by a medium one (4.8 Hz)). Thus, this compound is the 8α-epimer **16a**.

4.1.6. 1-*N*-Acetyl-9,10-dihydrolysergal (17).

Trifluoroacetic anhydride (0.6 mL, 4.311 mmol) in 1.0 mL of dichloromethane was added dropwise to a solution of dichloromethane (1.0 mL) and dimethyl sulfoxide (0.4 mL, 5.360 mmol) under argon at −78 °C. The solution was stirred for 10 min at −78 °C and then a solution of **12** (0.280 g, 0.940 mmol) in the mixture of CH_2Cl_2 (2 mL) and DMSO (1 mL) was added dropwise. The mixture was stirred for another 30 min at −78 °C and then at the same temperature it was treated with *N*-ethyldiisopropylamine (2.0 mL, 11.504 mmol). The mixture was stirred for 10 min, allowed to warm up to room temperature and stirred in dark (under argon) for another 4 h. The mixture was diluted with brine (40 mL) and extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. Flash chromatography ($CHCl_3$/MeOH/Et_3N 95:5:0.5) yielded 1-*N*-acetyl-dihydrolysergal (**17**, 200 mg, 62%) as a white amorphous solid and 30 mg of the starting material (10%) was recovered.

^{1}H NMR (DMSO): 1.214 (1H, ddd, *J*=12.6, 12.6, 11.9, H-9a), 2.005 (1H, m, H-5), 2.100 (1H, dd, *J*=11.6, 11.5, H-7a), 2.395 (3H, s, NMe), 2.496 (1H, ddd, *J*=15.4, 11.4, 2.2, H-4a), 2.594 (3H, s, Ac), 2.849 (1H, m, H-8), 2.868 (1H, m, H-10), 2.881 (1H, ddd, J=12.6, 3.8, 1.9, H-9e), 3.194 (1H, m, H-7e), 3.259 (1H, dd, J=15.4, 4.2, H-4e), 7.145 (1H, d, J=7.5, H-12), 7.283 (1H, dd, J=8.0, 7.5, H-13), 7.494 (1H, d, J=2.2, H-2), 7.950 (1H, d, J=8.0, H-14), 9.677 (1H, d, J=0.8, H-17); ^{13}C NMR (DMSO): 23.62 (Ac), 25.91 (C-4), 27.41 (C-9), 38.91 (C-10), 42.46 (NMe), 47.45 (C-8), 55.79 (C-7), 65.96 (C-5), 113.78 (C-14), 117.19 (C-3), 117.86 (C-12), 120.14 (C-2), 125.70 (C-13), 128.07 (C-16), 132.61 (C-15), 132.95 (C-11), 169.18 (C=O), 203.56 (C-17). Positive ESIMS (*m/z*): 297 [M+H]$^+$; HRMS (ESI FTMS) calcd for $C_{18}H_{21}N_2O_2$ 297.1598, found for [M+H$^+$] 297.1595.

The ^{1}H NMR spectrum of **17** exhibits features required by an ergoline skeleton. The absence of indole NH signal and its coupling to H-2 indicates a substitution at N-1. The substituent is an acetyl as its protons are coupled to C-2 (^4J). The shape of the H-10 multiplet inferred from gHSQC confirms a trans-C/D ring junction. The configuration at C-8 is 8β since both $J_{7a,8}$ and $J_{8,9a}$ are large. Characteristic signals (δ_H 9.677, δ_C 203.56) support the presence of a CH=O moiety (^1J=182.9 Hz).

4.1.7. 9,10-Dihydrolysergal (18) and its hemiacetal 18a. 1-*N*-Acetyl-9,10-dihydrolysergal (**4**) (171 mg, 0.578 mmol) and K_2CO_3 (150 mg, 1.085 mmol) were dissolved in the mixture of MeOH (15 mL), CH_2Cl_2 (5 mL), and water (1.5 mL) and stirred at room temperature for 2 h. The reaction mixture was then poured into water (50 mL) and extracted with the mixture of CH_2Cl_2/MeOH (9:1, v/v, 3×25 mL). The collected organic layers were dried over anhydrous Na_2SO_4 and evaporated in vacuo. Flash chromatography on silica gel ($CHCl_3$/MeOH/NH_4OH 90:10:1) afforded an inseparable mixture of **18** and its hemiacetal **18a** (139 mg) as a white amorphous solids.

Positive ESIMS (*m/z*): 255 and 287 [M+H]$^+$. Compound **18**: ^{1}H NMR (DMSO): 1.240 (1H, ddd, J=12.1, 11.5, 11.5, H-9a), 2.039 (1H, m, H-5), 2.114 (1H, dd, J=11.7, 11.3, H-7a), 2.407 (3H, s, NMe), 2.547 (1H, ddd, J=14.7, 11.4, 1.8, H-4a), 2.837 (1H, m, H-8), 2.865 (1H, m, H-10), 2.877 (1H, m, H-9e), 3.196 (1H, m, H-7e), 3.314 (1H, dd, J=14.7, 4.3, H-4e), 6.823 (1H, ddd, J=7.1, 1.2, 0.7, H-12), 6.982 (1H, dd, J=1.8, 1.8, H-2), 7.029 (1H, dd, J=8.1, 7.1, H-13), 7.138 (1H, ddd, J=8.1, 0.7, 0.6, H-14), 9.687 (1H, d, J=0.5, H-17), 10.638 (1H, br s, NH); ^{13}C NMR (DMSO): 26.45 (C-4), 27.56 (C-9), 39.20 (C-10), 42.62 (NMe), 47.61 (C-8), 55.97 (C-7), 66.68 (C-5), 108.88 (C-14), 109.90 (C-3), 112.10 (C-12), 118.64 (C-2), 122.10 (C-13), 125.92 (C-16), 132.10 (C-11), 132.22 (C-15), 203.75 (C-17). Compound **18a**: 25.80 (C-4), 28.84 (C-9), 40.72 (NMe), 45.65 (C-8), 53.79 (OMe), 57.97 (C-7), 99.14 (C-17), 118.75 (C-2), 122.18 (C-13), 125.81 (C-16).

This sample is evidently a mixture consisting of two main components accompanied by traces of analogues, as judged from the signals of indole NH around 10.6 ppm. The major component has an ergoline skeleton substituted by an aldehyde group at C-8 (δ_H 9.687, δ_C.203.75, $^1J_{C,H}$=183.7 Hz). The configuration is 8β since both $J_{7a,8}$ and $J_{8,9a}$ are large. Also the C/D ring junction is trans (the shape of H-10 multiplet). The other significant component is a methyl hemiacetal derived from the major component, responsible for H-17 at 4.274 ppm (dd, J=6.7 and 6.4 Hz), δ_C 99.14; CH_3O at 3.271 ppm (δ_C 53.79), and 17-OH at 6.139 ppm (d, J=6.7 Hz). This deduction was supported by coupling of the methoxyl to C-17 and H-17 to the methoxyl carbon (HMBC). The trace components might be the products of C-8 epimerization and its methyl hemiacetal.

4.1.8. Methyl 9,10-dihydrolysergate (2a).

4.1.8.1. Compound 2a via Ag_2O oxidation of 17. Aqueous solution of NaOH (0.5 mL, 10% w/w) was quickly added to a stirred solution of 1-*N*-acetyl-9,10-dihydrolysergal (**17**) (90 mg, 0.304 mmol) and Ag_2O (140 mg, 0.604 mmol) in the mixture of THF/MeOH (6 mL, 1:1, v/v). After 45 min the mixture was filtered, neutralized by the addition of concd HCl (0.5 mL, 36% w/w) and evaporated to dryness. The residue was dissolved in dry MeOH (15 mL) and concd H_2SO_4 (0.5 mL, 96% w/w) was added. The resulting mixture was stirred at room temperature for 12 h then it was diluted with ice-cold saturated $NaHCO_3$ (50 mL), stirred for 5 min and extracted with CH_2Cl_2 (3×30 mL). The collected organic layers were dried over anhydrous Na_2SO_4 and evaporated. After flash chromatography ($CHCl_3$/MeOH/NH_4OH 95:5:1), the title compound **2a** (20 mg, 24%) was obtained as a pink-red amorphous solid. Analytical data were in accordance with those reported previously.[6]

4.1.8.2. Compound 2a via MCPBA oxidation of 18. MCPBA (0.190 g, 0.771 mmol, 70% w/w) was portionwise added to a stirred and cooled (0 °C) solution of dihydrolysergal (**18**, 0.070 g, 0.273 mmol) in DMF (2 mL) and the stirring was continued for another 1 h. Reaction mixture was then diluted with ice-cold saturated $NaHCO_3$ (25 mL) and extracted with CH_2Cl_2 (3×15 mL). The collected organic layers were dried over anhydrous Na_2SO_4 and evaporated. Crude solid was dissolved in MeOH (10 mL), Pd/C (10 mg, 5% w/w) was added and the mixture was stirred under hydrogen for 12 h. The solution was filtered through the Celite pad, which was then washed by MeOH. Collected filtrates were evaporated. The residual solid was re-dissolved in dry MeOH (10 mL) and concd H_2SO_4 (0.5 mL, 96% w/w) was added. The resulting mixture was stirred at room temperature for 12 h then it was diluted with ice-cold saturated $NaHCO_3$ (50 mL), stirred for 5 min and extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated. Flash chromatography on silica gel ($CHCl_3$/MeOH/NH_4OH 9:1:0.1, then 8:2:0.1) afforded the title compound **2a** (63 mg, 80%) as a brownish amorphous solid.

6-*N*-Oxides **21**–**24** were prepared according to the described procedure.[7a]

4.1.9. 2,4-Dinitrophenyl hydrazone of 9,10-dihydrolysergal 25. 2,4-Dinitrophenyl hydrazine (0.585 g, 2.952 mmol) was portionwise added to a stirred mixture of ethanol (7 mL) and H_2SO_4 (0.5 mL, 96%, v/v) and stirred for 10 min at room temperature. The clear solution of corresponding hydrazine sulfate was dropwise added to the ethanolic solution of dihydrolysergal (**18**, 0.250 g, 0.977 mmol, in 10 mL of ethanol). Reaction mixture was stirred for 30 min at room temperature. Precipitated product was filtered off, washed with ethanol (2×5 mL), and dried. The crude product (in the form of sulfate) was re-dissolved in CH_2Cl_2/MeOH mixture (100 mL, 3:1, v/v), washed with saturated solution of $NaHCO_3$ (2×75 mL), and finally with water. The organic layer was dried over anhydrous Na_2SO_4, evaporated, and the product was crystallized from methanol. The title compound **25** (278 mg, 65%) was obtained as an orange-red needles. ^1H NMR (DMSO): 1.360 (1H, ddd, J=12.3, 12.3, 12.2, H-9a), 2.078 (1H, m, H-5), 2.205 (1H, dd, J=11.3, 11.1, H-7a), 2.426 (3H, s, NMe), 2.561 (1H, ddd, J=14.6, 11.1, 1.7, H-4a), 2.828 (1H, dm, J=12.3, H-9e), 2.908 (1H, m, H-10), 3.150 (1H, dm, J=11.3, H-7e), 3.330 (1H, dd, J=14.6, 4.3, H-4e), 6.836 (1H, dd, J=7.1, 0.4, H-12), 6.985 (1H, dd, J=2.0, 1.7, H-2), 7.030 (1H, J=8.1, 7.1, H-13), 7.137 (1H, dd, J=8.1, 0.4, H-14), 7.894 (1H, d, J=9.7, H-6′), 8.043 (1H, d, J=4.6, H-17), 8.356 (1H, dd, J=9.7, 2.7, H-5′), 8.841 (1H, d, J=2.7,H-3′), 10.623 (1H, br s, indole NH), 11.366 (1H, s, N NH); ^{13}C NMR (DMSO): 26.57 (C-4), 31.33 (C-9), 38.93 (C-8), 39.72 (C-10), 42.67 (NMe), 59.38 (C-7), 66.69 (C-5), 108.80 (C-14), 110.04 (C-3), 112.08 (C-12), 116.40 (C-6′), 118.61 (C-2), 122.08 (C-13), 123.04 (C-3’), 125.98 (C-16), 128.97 (C-1′), 129.87 (C-5′), 132.30 (C-11), 133.23 (C-15), 136.71 (C-2′), 144.84 (C-4′), 155.65 (C-17). Positive ESIMS (m/z): 435 $[M+H]^+$; HRMS (ESI FTMS) calcd for $C_{22}H_{23}N_6O_4$ 435.1775, found for $[M+H^+]$ 435.1770.

Mother liquor from crystallization of **25** was evaporated and purified by column chromatography ($CHCl_3$/toluene/MeOH/NH_4OH 85:10:5:0.5) affording **25a** (42 mg, 10%) as an orange-red solid.

^1H NMR ($CDCl_3$): 1.837 (1H, ddd, J=13.3, 12.6, 4.9, H-9a), 2.261 (1H, ddd, J=11.2, 9.6, 4.3, H-5), 2.485 (3H, s, NMe), 2.652 (1H, dd, J=11.9, 3.4, H-7a), 2.685 (1H, ddd, J=14.7, 11.2, 1.8, H-4a), 3.006 (1H, m, H-8), 3.080 (1H, m, H-9e), 3.180 (1H, ddd, J=11.9, 2.2, 2.2, H-7e), 3.219 (1H, m, H-10), 3.406 (1H, dd, J=14.7, 4.3, H-4e), 6.888 (1H, dd, J=1.9, 1.8, H-2), 6.956 (1H, m, H-12), 7.183 (2H, m, H-13, H-14), 7.887 (1H, d, J=9.6, H-6′), 7.900 (1H, d, J=4.4, H-17), 8.076 (1H, br s, NH), 8.235 (1H, dd, J=9.6, 2.6, H-5′), 9.072 (1H, d, J=2.6, H-3′), 11.074 (1H, s, N′-H); ^{13}C NMR ($CDCl_3$): 26.77 (C-4), 30.02 (C-9), 36.85 (C-10), 37.01 (C-8), 43.53 (NMe), 60.17 (C-7), 67.76 (C-5), 108.69 (C-14), 111.66 (C-3), 113.02 (C-2), 116.41 (C-6′), 117.86 (C-2), 123.16 (C-13), 123.41 (C-3′), 126.17 (C-16), 128.71 (C-2′), 129.88 (C-5′), 133.14 (C-11), 133.30 (C-15), 137.75 (C-4′), 145.05 (C-1′), 155.04 (C-17). Positive ESIMS (m/z): 435 $[M+H]^+$.

Twenty-two signals were observed in the ^{13}C NMR spectrum of **25**: one methyl, three methylenes, eleven methines (three sp^3-, eight sp^2-hybridized), and seven quaternary carbons (all of sp^2-type). Eighteen protons are attached to the carbons, the remaining two are bonded to heteroatoms. The ^1H NMR spectrum contains one-proton singlet (assigned to N H), a three-proton singlet (N CH_3), and two three-spin systems representing 1,2,3- and 1,2,4-trisubstituted aromatic rings, and a partial structure NHCH $CCH_2CHCHCH_2CH(CH$ $)CH_2$ (ergoline, from indole NH to C-7). Large couplings $J_{7a,8}$=11.3 and $J_{8,9a}$=12.3 Hz indicate an axial H-8 (D-ring in the chair form), and consequently 8β-CH N . An NOE between H-17 and hydrazone NH dictates a mutual cis-relationship. Some diagnostic ROESY and HMBC contacts of the compound **25** are highlighted in Figures 9 and 10.

There are 22 signals in the ^{13}C NMR spectrum of **25a** (Fig. 11). Their distribution one methyl, three methylenes (aliphatic), eleven methines (eight CH and three CH), and seven sp^2-hybridized quaternary carbons fulfills the requirements of a hydrazone derived from an ergine-related alkaloid **25**. Only three-spin systems an ABC one of the three vicinal aromatic protons, a 1,2,4-trisubstituted benzene, and NHCH $CCH_2CHCHCH_2CH(CH$ N $)CH_2$ were found in the ^1H NMR spectrum besides two NH signals (no crosspeaks in gHSQC) and one N-methyl. The HMBC experiment was used to prove a closure of the D-ring (through the coupling of NMe protons to C-5 and C-7), the attachment of CH to C-8, the nature of the A and B rings, and the details of the hydrazone moiety (the coupling of N″-H to C-1′, C-2′, C-6′, and C-17). Furthermore, an NOE between N″-H and H-17 indicates their mutual cis-relationship. The examination of proton proton vicinal couplings proved: (i) the trans-C/D ring junction ($J_{5,10}$=9.6 Hz) and (ii) the equatorial (8β) position of H-8 ($J_{7a,8}$=3.4 Hz, $J_{8,9a}$=4.9 Hz). This implies an axial C-8 side chain in the

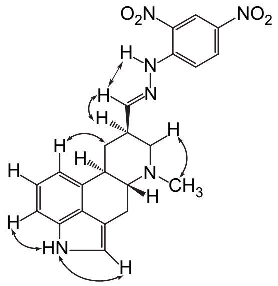


Figure 9. Diagnostic ROESY contacts of the compound **25**.

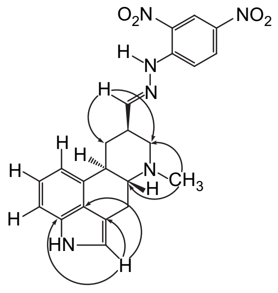


Figure 10. Selected HMBC contacts of the compound **25**.

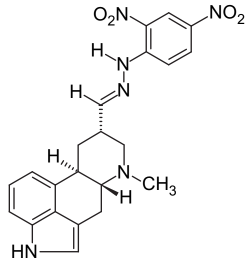


Figure 11. The structure of **25a**.

D-ring adopting a chair conformation. This deduction is consistent with a strong NOE between H-10 and H-17.

4.1.10. $\Delta^{7,8}$-Didehydrolysergal 2,4-dinitrophenylhydrazone (26).

To a solution of **25** (0.118 g, 0.272 mmol) in dry DMF (3 mL) was added MCPBA (70%, 0.100 g, 0.406 mmol) portionwise and the mixture was stirred at 0 °C for 30 min. Then Ac_2O (0.080 mL, 0.848 mmol) and Et_3N (0.565 mL, 3.968 mmol) were added and this mixture was stirred at 0 °C for an additional 1 h. The reaction mixture was poured into a saturated solution of $NaHCO_3$ (100 mL), stirred for 10 min, and the resulting suspension was filtered off. Insoluble material was washed by water, dried, and then re-dissolved in the mixture CH_2Cl_2/MeOH (100 mL, 8:2, v/v). After evaporation, flash chromatography ($CHCl_3$/toluene/MeOH/NH_4OH 85:10:5:1) afforded the title compound **26** (60 mg, 51%) as a dark-violet amorphous solid.

^{1}H NMR (DMSO): 2.247 (1H, ddd, *J*=16.1, 11.7, 1.2, H-9a), 2.776 (1H, ddd, *J*=14.4, 11.4, 1.7, H-4a), 3.109 (3H, s, NMe), 3.322 (1H, ddd, *J*=11.7, 9.6, 5.2, H-10), 3.377 (1H, ddd, *J*=11.4, 9.6, 4.4, H-5), 3.416 (1H, dd, *J*=16.1, 5.2, H-9e), 3.540 (1H, dd, *J*=14.4, 4.4, H-4e), 6.934 (1H, d, *J*=1.2, H-7), 6.995 (1H, ddd, *J*=7.1, 1.3, 0.8, H-12), 7.068 (1H, dd, *J*=1.7, 1.7, H-2), 7.115 (1H, dd, *J*=8.1, 7.1, H-13), 7.201 (1H, ddd, *J*=8.1, 0.8, 0.8, H-14), 7.968 (1H, d, *J*=9.7, H-6′), 8.133 (1H, br s, H-17), 8.272 (1H, dd, *J*=9.7, 2.7, H-5′), 8.851 (1H,d, *J*=2.7, H-3′), 10.735 (1H, d, *J*=1.7, indole NH), 11.409 (1H, s, N NH); ^{13}C NMR (DMSO), HSQC and HMBC readouts: 23.8 (C-9), 26.1 (C-4), 37.2 (C-10), 39.3 (NMe), 59,1 (C-5), 109.1 (C-3), 109.3 (C-14), 112.9 (C-12), 116.6 (C-6′), 119.2 (C-2), 122.2 (C-13), 124.0 (C-3′), 126.1 (C-16), 127.4 (C-1′), 129.7 (C-5′), 132.0 (C-11), 133.2 (C-15), 153.5 (C-17). Positive ESIMS (*m*/*z*): 433 $[M+H]^+$; HRMS (ESI FTMS) calcd for $C_{22}H_{21}N_6O_4$ 433.1619, found for $[M+H^+]$ 433.1615.

The ^{1}H NMR spectrum of **26** displays signals of two NHs and one *N*-methyl (shifted downfield with respect to the parent compound). According to COSY, the investigated molecule contains two aromatic rings, one 1,2,3- and the other 1,2,4-trisubstituted (A-ring and the dinitrophenyl moiety), a partial structure NHCH $CCH_2CHCHCH_2$, and two olefinic protons (a 1.2 Hz doublet at 6.934 and a broad singlet at 8.133 ppm). These features are consistent with a 7-ergolene structure. Both olefinic protons exhibit a homonuclear long-range coupling as well as mutual heteronuclear couplings so that they belong to a conjugated system. They were assigned to H-7 and H-17 on the basis of ROESY (Fig. 12) and HMBC (Fig. 13) experiments. A strong NOE between H-7 and H-17 means that both double bonds are trans-oriented. The chemical shift of NMe indicates a possible protonation.

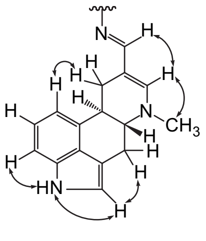


Figure 12. Diagnostic ROESY contacts of the compound **26**.

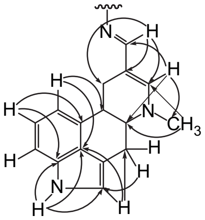


Figure 13. Selected HMBC contacts of the compound **26**.

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