145. Total Synthesis of 2,6-Dimethylergolin-8α-amines

by **Erwin Waldvogel***, **Peter Engeli**, and **Ernst Küsters**

Chemical and Analytical Development, *Pharma Novartis AG*,
Lichtstrasse 35, CH-4002 Basel

Dedicated to Professor *D. Seebach*, ETH-Zürich, on the occasion of his 60th birthday

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A stereoselective total synthesis of the racemic form of the 2,6-dimethylergolin-8α-amine derivative **III**, previously obtained semi-synthetically from lysergic acid, is described. Starting from the commercially available tricyclic lactam **1**, the 9,10-didehydroergoline skeleton containing an angular Me group in position 3 (see **18**) is built up in several steps applying a *Woodward* D-ring annelation sequence. The introduction of the 8-amino group is achieved with complete diastereoselectivity to give exclusively the 8α-derivative **22**. Subsequently, a *Wagner-Meerwein*-type migration of the angular Me group yields the 2-methylated 9,10-didehydroergoline derivative **31**. The feasibility of this key transformation was tested on the two model systems **4** and **7** prior to the evaluation of the total synthesis. A stereoselective *Birch* reduction to the *trans*-fused ergoline, and deacetylation/acylation conclude the total synthesis of the racemic target compound **34**.

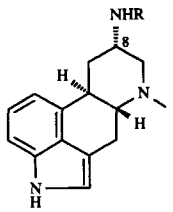
In addition, the resolution of an early intermediate (see **3**) by chromatography on a chiral stationary phase is presented which demonstrates that the described total synthesis could also be used for the preparation of the biologically active (5*R*,8*S*,10*R*)-enantiomer **III**.

1. Introduction. – Ergolin-8α-amines **I** are well-known semi-synthetic ergot derivatives [1], with interesting pharmacological activities on the central nervous system. They have been prepared from lysergic acid (**II**) by a multistep synthesis: Hydrogenation to 9,10-dihydrolysergic acid (8β-acid) [2], esterification and epimerization to the 8α-ester [3], hydrazinolysis and *Curtius* degradation to the 8α-amine [4], and finally acylation, carbamoylation, thiocarbamoylation, or aminosulfonation to the corresponding amides **Ia** [5] [6], ureas **Ib**[1]) [6], thioureas **Ic** [6], or sulfamides **Id** [6] [8].

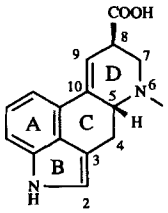
We became recently involved in the development of a manufacturing process for compound **III**, an ergolin-8α-amine derivative bearing an additional Me group in position 2 that is currently in clinical development. The amide **III** has been synthesized initially by *Häfliger* [9] using the degradation sequence described above, with introduction of the 2-methyl group in lysergic acid by dithiomethylation/desulfuration according to *Stütz* and *Stadler* [10]. A more efficient semi-synthetic route to **III** has been developed by *Mak et al.* [11] who introduced the 2-methyl group *via* 2-lithiation of di-Boc-protected-ergolin-8α-amine.

We focused our process research towards a total synthesis of **III** with the goal of finding a feasible alternative to the rather complex semi-synthetic routes described.

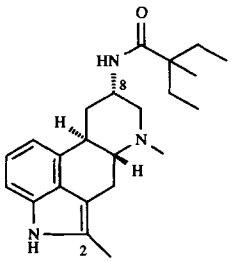
[1]) The best known derivative of this class is *N*,*N*-diethyl-*N'*-6-methylergolin-8α-yl)urea hydrogen maleate (*Terguride*®, *Leciva*, *Spofa*) used as an antipsychotic drug [7].



I a R = COR
b R = $CON(Et)_2$
c R = $CSN(Et)_2$
d R = $SO_2N(Et)_2$



II Lysergic acid



III

According to our knowledge, ergolin-8-amines as well as the corresponding 9,10-didehydro derivatives[2]) have not been the target of a total-synthesis approach. A single reference was found in *Woodward*'s [13] report on the total synthesis of lysergic acid where an ergolin-8-amine derivative was isolated as a by-product. Elements of that report have served as a basis for our synthesis approach towards **III** which is outlined in *Scheme 1*: A key feature of the approach is the introduction of the Me group in position 3 of the ring system at the beginning (**A** to **B**) and its migration to position 2 towards the end of the synthesis (**E** to **G**). This strategy has several advantages: *i*) **B** is an easily prepared and configurationally stable compound amenable to introduction of an enantiomerically pure intermediate early in the synthesis (*e.g.*, by resolution or stereoselective reaction); *ii*) the diastereoselectivity of following steps should be controlled by the angular Me group; and *iii*) the intermediate enone **D** should be stabilized towards aromatization of the C-ring, a known problem in the synthesis of the related *Woodward* intermediate **W-1** [13].

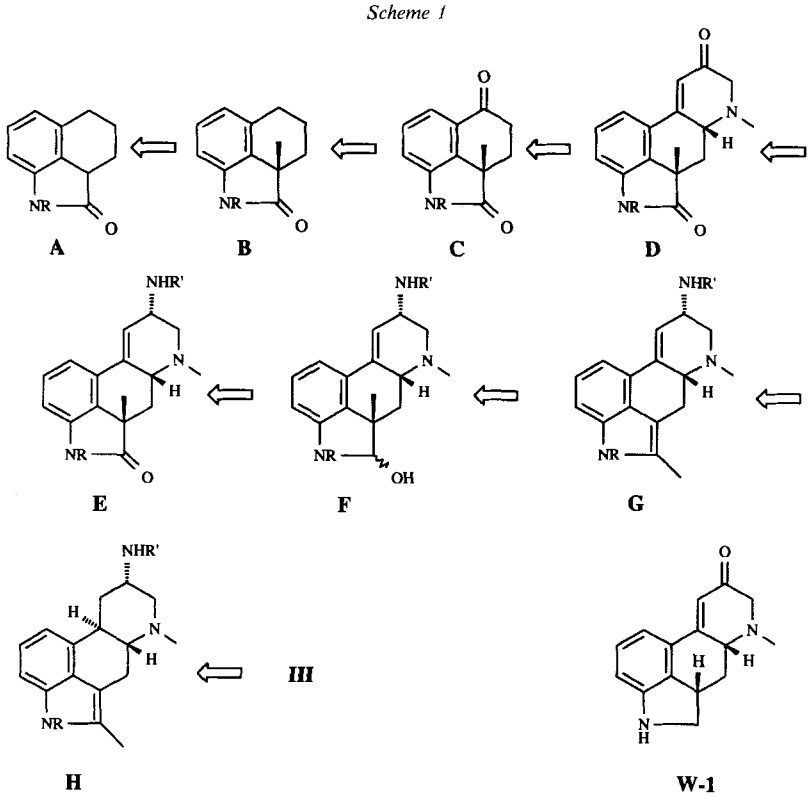
After benzylic oxidation of **B** to ketone **C**, a D-ring annelation sequence according to *Woodward* [13] is applied to obtain the enone **D**. The following amination step to **E** is achieved by ketone reduction and nucleophilic substitution. The migration of the Me group from position 3 to 2 is performed *via* the aminal **F** followed by a *Wagner-Meerwein*-type rearrangement to give **G**. The subsequent reduction of the 9,10-double bond to **H** and introduction of the proper acyl group concludes our approach towards **III**. A prerequisite for an efficient total synthesis was the achievement of complete stereochemical control thus avoiding cumbersome separations of diastereoisomers.

We now describe the total synthesis of racemic **III**, *i.e.*, of (**34**). Eventhough all chiral compounds in the following schemes are racemic, only one antipode is presented.

2. Results and Discussion. – 2.1. *Model Reactions.* Acid-catalyzed *Wagner-Meerwein*-type alkyl rearrangements of 3,3-dialkyl-2,3-dihydro-1*H*-indol-2-ols or 3,3-dialkyl-3*H*-

[2]) The best known derivative of this class is *N'*-(9,10-didehydro-6-methylergolin-8α-yl)-*N,N*-diethylurea hydrogen maleate (*Lisuride®*, *Schering*) used as an antiallergic, anti-migraine, and anti-parkinsonian drug and prolactin inhibitor [12].

Scheme 1

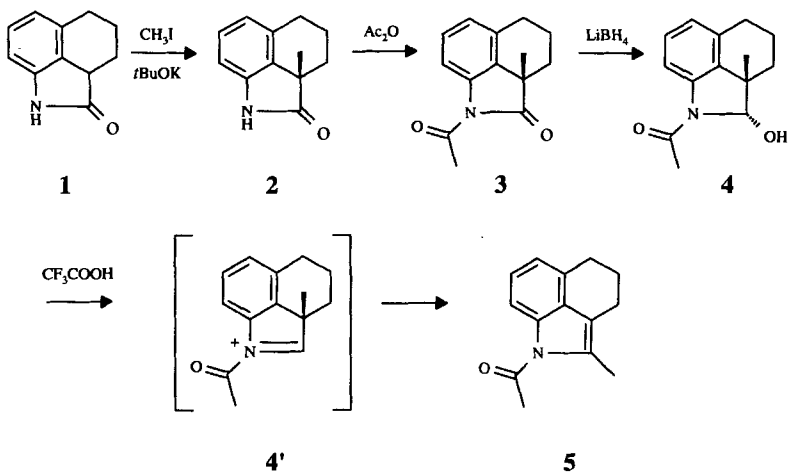


indols [14] and related 3,3-spiro systems [15] are well-known; however, the corresponding Me-migration reactions have been described only rarely [16]. Therefore, before starting our total-synthesis approach, we tested this key reaction on two model systems, the rearrangement *via* an acyl-iminium salt **4'** (*Scheme 2*) and an alkyl-iminium salt **7'** (*Scheme 3*). The precursors **4** and **7** were readily available. We were of course aware of a possibly lower reactivity of corresponding ergolines, because of their basic piperidine N-atom protonated under the reaction conditions. The positively charged N-atom could suppress the cationic rearrangement reaction occurring close by.

Methylation of the commerically available tricyclic amide **1** [17] occurred regioselectively at low temperature (−20°) using MeI and *t*-BuOK in DMF to yield **2** (*Scheme 2*). Heating of **2** with Ac_2O gave the imide **3**. The subsequent reduction to the aminal **4** required carefully controlled conditions: $LiBH_4$ or $Zn(BH_4)_2$ in THF yielded cleanly **4**, whereas $NaBH_4$ in EtOH gave a mixture of several compounds. The aminal **4** turned out to be a single diastereoisomer proven by ^{1}H-NMR NOE measurements. The subsequent rearrangement reaction to **5** was achieved in high yield by heating **4** with various acids such as Montmorillonite K 10 [18], sulfuric acid on silica gel [19], or CF_3COOH in toluene. Weak acids such as AcOH did not cause the rearrangement, but led instead to

O-acetylation of **4**, whereas strong acids in polar solvents gave undefined mixtures and decomposition products. The best conditions for our purpose appeared to be 10% CF_3COOH in toluene at 60°. To mimic the basic function of the ergoline system, Et_3N was added to the reaction mixture. In case of the Montmorillonite K 10, the rearrangement ceased completely, whereas with excess CF_3COOH the reaction rate did not change much.

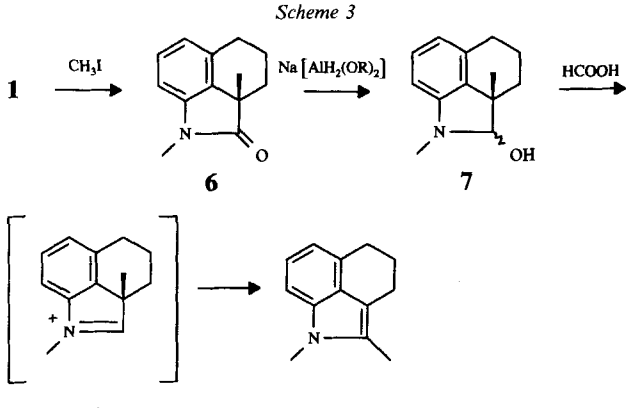
Scheme 2



1 **2** **3** **4** **4'** **5**

The precursor **7** for the second model reaction was obtained by double methylation of **1** at 20° (→ **6**) and subsequent reduction with sodium dihydro bis(2-methoxyethanolato)aluminate [20] in toluene (*Red-Al®*) (*Scheme 3*). The aminal **7** formed was a mixture of two diastereoisomers in a ratio of 2:1. The rearrangement was achieved cleanly by heating **7** in HCOOH at 85°, giving **8** in high yield. For application of this sequence to ergolines, a removable benzyl group instead of the methyl group in position 1 was envisaged.

Scheme 3

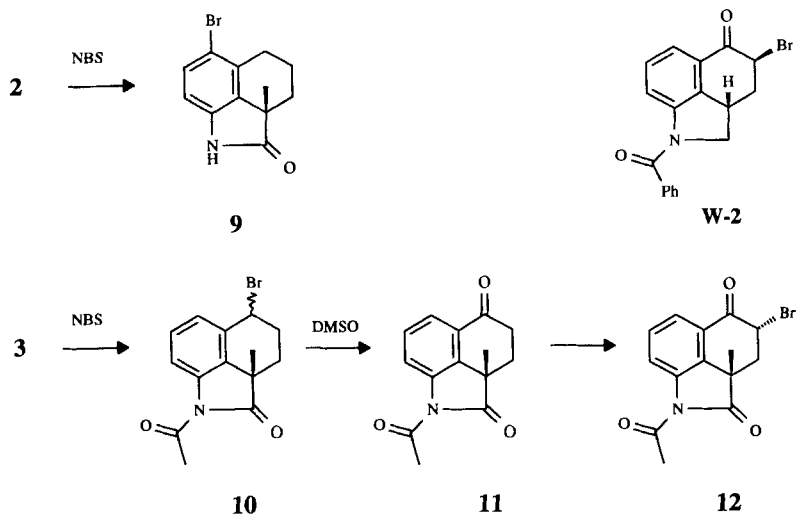


6 **7** **7'** **8**

Having two different options for the methyl-migration reaction in hand, we started our work towards the total synthesis of **III**.

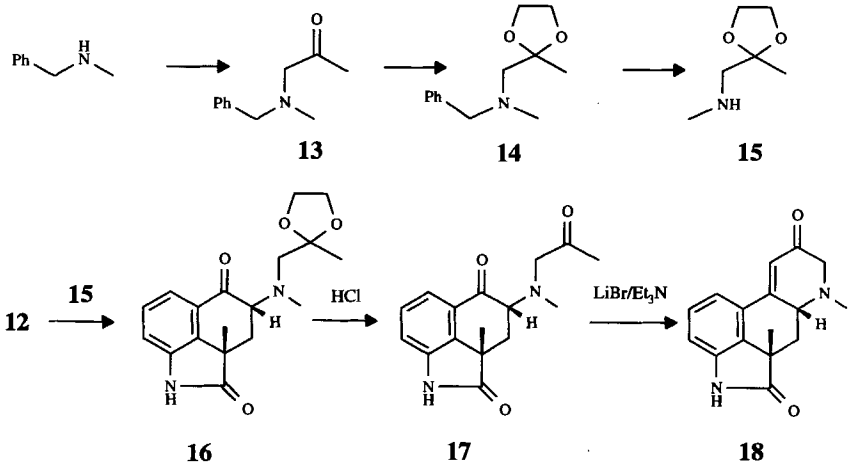
2.2. *Total Synthesis: Formation of the Ergoline System with an Angular Methyl Group.* To apply *Woodward*'s D-ring annelation methodology, the benzylic position 5 of lactam **2** had to be oxidized. For this purpose, the method described by *Gmeiner et al.* [21] *via* benzylic bromination and *Kornblum* oxidation was applied; however, radical bromination of **2** with *N*-bromosuccinimide (NBS) in refluxing CCl_4 yielded only the aromatic bromo derivative **9** (*Scheme 4*). Alternatively, imide **3** reacted, under the same conditions, to the desired benzylic bromide **10** (diastereoisomer mixture) which was converted to ketone **11** with DMSO and Et_3N in a one-pot reaction.

Scheme 4



The subsequent bromination using pyridine hydrobromide perbromide [13] gave the bromo ketone **12** in high yield. In contrast to 2-bromocyclohexanones [22] and to the related *Woodward* intermediate **W-2** [13], where the axial Br-atom is thermodynamically more stable than the equatorial one, **12** exists exclusively with the Br-atom equatorial (^{1}H-NMR), obviously for steric reasons. Therefore, we anticipated difficulties in the subsequent nucleophilic substitution reaction which requires an axially positioned Br-atom as leaving group [23]. Nevertheless, **12** reacted reasonably well with amine **15** in refluxing toluene to give the amino ketone **16** (*Scheme 5*). The reaction proceeds probably *via* the corresponding axial bromo ketone present in low concentration and provided by ketone/enol equilibration [23]. Four equiv. of **15** were needed to achieve complete conversion, and careful exlusion of O_2 and H_2O was necessary. The deacetylation step proceeded much faster than the substitution of the Br-atom. Elimination of HBr and debromination were the major side reactions detected. The method for preparing amine **15** *via* **13** and **14** described by *Benington et al.* [24] was improved substantially by changing reaction conditions.

Scheme 5

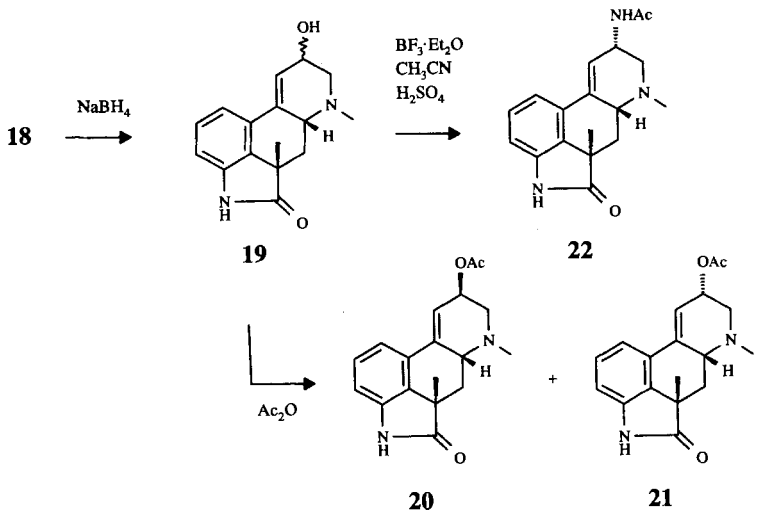


The subsequent ketal hydrolysis (**16** → **17**) was achieved with 6N HCl at 45°. The product turned out to be very unstable towards O_2, and attempts to purify it by chromatography failed, due to complete decomposition. Crude **17** was, therefore, used for the aldol condensation step. Applying *Woodward*'s conditions published for the intermediate **W-1** (NaOEt in EtOH at −20°) [13] yielded only traces of the desired enone **18**, besides products of decomposition. Many other bases and also acids were tried to increase the yield, however, without success. Finally, $LiBr/Et_3N$ in THF was found to be the proper reagent for this aldol condensation [25], and **18** was obtained in good yield. The configuration of **18** and also of the precursors **16** and **17** was established by ^{1}H-NMR, and for **18** also by NOE measurements. The enone **18** is stable under neutral conditions; however, with strong bases and air it decomposes readily. This finding did not confirm our assumption when designing the approach, namely, that the angular Me group should lead to increased stability of **18** compared to the corresponding *Woodward* system **W-1**. The instability of **18** is probably caused by facile oxidation of the D-ring.

2.3. *Total Synthesis: Stereoselective Introduction of the 8-Amino Function.* Having the enone **18** in hand, the next goal was the introduction of the 8α-amino function. We originally intended to perform this transformation *via* reduction to the 8β-alcohol [13] and an S_N2 amination reaction to give the 8α-amine. The reduction of the enone **18** with $NaBH_4$ to the allylic alcohol **19** did not proceed stereoselectively as had been hoped: a mixture of epimeric alcohols (8β/8α 7:3) was obtained (*Scheme 6*), so that no longer the S_N2 O/N-substitution was considered. For structural proof, the allylic alcohols were converted to the corresponding acetates **20** and **21** (ratio 7:3) by heating with Ac_2O in AcOH. After chromatographic separation, the configuration was assigned to **20** and **21** by ^{1}H-NMR and NOE measurements.

An alternative preparation of allylic amines from corresponding alcohols is the *Ritter* reaction [26] [13]. We treated the epimer mixture **19** with H_2SO_4 and $BF_3 \cdot Et_2O$ in MeCN and obtained the 8α-amide **22** stereoselectively in high yield (*Scheme 6*). No traces of the corresponding 8β-amide could be detected. The configuration of **22** was established by ^{1}H-NMR NOE measurements. The exclusive formation of the desired

Scheme 6

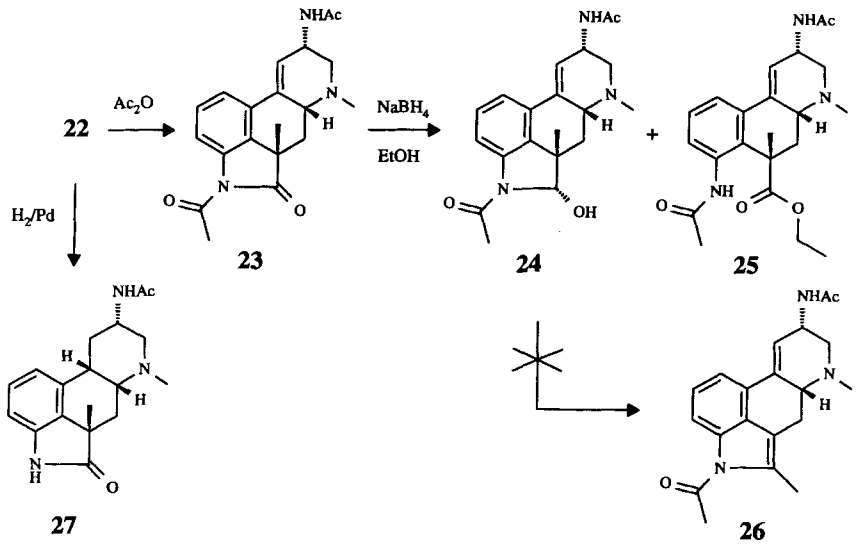


8α-diastereoisomer was surprising. In addition, a high α-selectivity was observed in the acetylation of **19** when strong acidic conditions (H_2SO_4/AcOH) were applied (ratio **21**/**20** 92:8). Thermodynamic equilibration of pure **20** or **21** in H_2SO_4/AcOH gave the same ratio of epimeric acetates. Obviously, the allylic carbenium ion formed under strongly acidic conditions is trapped by MeCN or AcOH preferentially from the α-face. The high α-selectivity may be explained by a stabilizing *gauche* effect [27] (*gauche* arrangement of N(6)–C(7)–C(8)–O or N(6)–C(7)–C(8)–N in the 8α-derivatives **21** and **22**, and *anti*-arrangement in the corresponding 8β-epimers).

2.4. *Total Synthesis:* Wagner-Meerwein-*Type Rearrangement.* The Me migration from position 3 to 2 was initially tried *via* the *N*-acetylated aminal **24** (*Scheme 7*). Acylation of the acetamide **22** using Ac_2O/NaOH in THF yielded the di-acetylated derivative **23**. The subsequent reduction to the aminal **24** required conditions different from those used for the model compound **3**. The use of $NaBH_4$ in EtOH gave the best results, whereas $LiBH_4$, which worked well in the model case, gave undefined mixtures. The aminal **24** has the same configuration at C(2)/C(3) as **4**. Besides **24**, the ring-opened by-product **25** of lactam alcoholysis was formed under the reduction conditions, indicating increased strain of the B-ring in compound **23**, as compared to the model compound **3**.

The subsequent rearrangement reaction of **24** to **26**, using the conditions optimized for model compound **4** (10% CF_3COOH in toluene, up to 85°) did not proceed at all, **24** was stable under these conditions. Although many other attempts were made, using protic acids or *Lewis* acids under various conditions, we were not able to achieve the rearrangement. Mild conditions left the starting material unchanged, and harsher conditions led to unspecified decomposition products. Whether this failure was due to the effect of the protonated piperidine N-atom mentioned above or the increased strain in ring B remains open. To release strain and increase the stability of the system, we tried to reduce the 9,10-double bond of **22** [28] before doing the rearrangement reaction.

Scheme 7



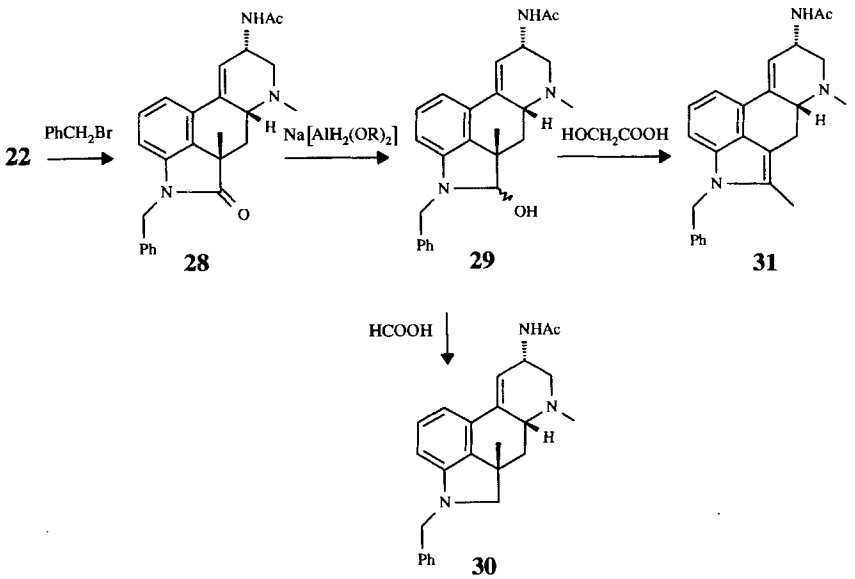
However, hydrogenation of **22** gave mainly the undesired *cis*-fused derivative **27** and only small amount of the corresponding *trans*-diastereoisomer.

Consequently, we tried to apply our second model reaction, the methyl migration *via* an alkyl-iminium salt. The precursor **29** was obtained from **22** by benzylation with BnBr/NaOH in THF to give **28**, and subsequent reduction with $Na[AlH_2(OCH_2CH_2OMe)_2]$ in THF (*Scheme 8*). As in the corresponding model compound **7**, the aminal **29** is a mixture of epimers. Using HCOOH for the rearrangement reaction of **29**, as in the model reaction, did not lead to the desired product **31**. Instead, reduction to amine **30** was observed, caused by hydride transfer from HCOOH to the intermediate iminium salt. Replacement of HCOOH by a nonreducing acid of similar acid strength and polarity such as $HOCH_2COOH$ at 80°, however, led to the desired rearranged product **31** in good yield.

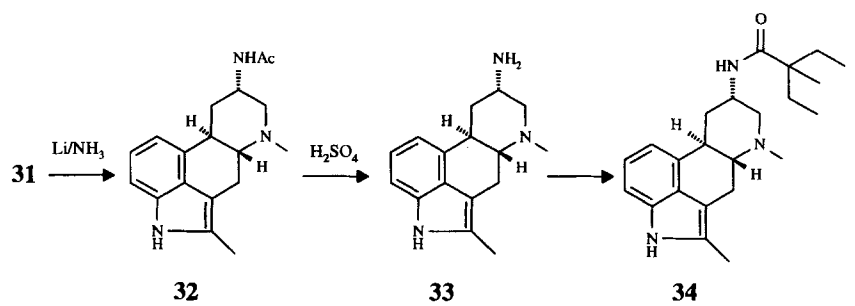
2.5. *Total Synthesis: Final Steps.* The final steps of the synthesis proceeded fairly easily. *Birch* reaction of **31** according to a procedure published by *Sauer et al.* [29] caused reduction of the 9,10-double bond as well as debenzylation [30], yielding exclusively the *trans*-fused ergoline derivative **32** (*Scheme 9*). The subsequent hydrolysis of the acetamide group in **32** was achieved by heating with 10% aqueous H_2SO_4 solution to give the amine **33** in high yield. On the other hand, basic amide cleavage with a strong base such as NaOH in ethylene glycol resulted mainly in decomposition. Final acylation [9] of **33** with 2-ethyl-2-methylbutanoyl chloride led to the racemic target compound **34**. Our racemic compounds **33** and **34** were spectroscopically and chromatographically identical with the corresponding (5*R*,8*S*,10*R*)-enantiomers obtained semi-synthetically by *Häfliger* starting from lysergic acid [9].

2.6. *Resolution of an Early Intermediate.* Having achieved the total synthesis of racemic **34**, we turned our attention to the preparation of the (5*R*,8*S*,10*R*)-enantiomer **III**. The goal was to obtain one of the early intermediates **2** or **3** in enantiomerically pure

Scheme 8



Scheme 9



form. Among various options, such as the stereoselective methylation of **1** in presence of chiral catalysts, and the resolution of **2** or **3** by enzymatic amide or imide hydrolysis or by chromatographic separation on a chiral stationary phase, we have investigated only the latter thus far. On an analytical scale, the separation of the enantiomers of **2** and **3** was achieved using the commercially available *Chiralpak-AD* as chiral stationary phase and hexane/i-PrOH/MeOH 95:2.5:2.5 as mobile phase. For a preparative resolution, lactam **2** was not suitable because of too low solubility in the mobile phase. However, imide **3** was resolved successfully on a semi-prep. column containing 20% amylose tris(3,5-dimethylphenyl carbamate) on aminopropyl-functionalized silica gel (20 μm) as chiral stationary phase[3]). Both enantiomers of **3** were obtained in > 99% e.e. Gram-quantities were prepared by repetitive injection and applying chromatography in the

[3]) This column was kindly provided by Prof. *D. Seebach* [31].

recycling mode. We have not assigned the absolute configuration of the enantiomers yet, and thus do not know the one leading to **III**.

3. Conclusions. – A stereoselective total synthesis of the racemic 2,6-dimethylergolin-8α-amine derivative **34** was developed. In addition, a method for resolving the early intermediate **3** was achieved, thus demonstrating that the approach could also be applied to the total synthesis of the biologically active (5*R*,8*S*,10*R*)-enantiomer **III**.

We thank Professor *D. Seebach* for the very helpful discussions concerning this project and many other ones over the past years.

Experimental Part

(With the collaboration of **Carole Cruz**, **Robert Schreiber**, **Bruno Heitmann**, and **Emil Schmid**)

General. Starting materials and reagents were purchased from *Aldrich* or *Fluka*. All reactions were conducted strictly under Ar to avoid oxidative degradation. The conversion was checked by TLC (*Merck F254* silica-gel plates), HPLC, or GC. Extracts were dried with Na_2SO_4. FC = flash chromatography M.p.: *Büchi-534* apparatus; not corrected. IR Spectra: *Bruker FT-IR IFS66*; KBr pellets, unless stated otherwise. ^{1}H- and ^{13}C-NMR spectra: *Bruker DPX 300*; 300 MHz; σ in ppm rel. to $SiMe_4$ (= 0 ppm), coupling constants J in Hz; $CDCl_3$ as solvent, unless stated otherwise; ^{13}C multiplicities from DEPT experiments; COSY and HETCOR spectra were measured of most compounds (not listed), as well as NOEs (not described in detail). GC/MS: *HP 5972*. MS: Spectrometer *VG TS 250* or *MAT 212* (EI or FAB).

rac-*2a,3,4,5-Tetrahydro-2a-methylbenz[*cd*]indol-2(*1H*)-one* (**2**) [17]. To a soln. of *t*-BuOK (360 g, 3.21 mol) in DMF (1.1 l), *rac*-2a,3,4,5-tetrahydrobenz[*cd*]indol-2 (1*H*)-one (**1**; 496 g, 2.87 mol) in DMF (2.4 l) was added at −20° within 90 min. After stirring for 30 min at −20°, MeI (458 g, 3.23 mol) was added at −15 to −20° within 90 min. After stirring for 90 min at −15 to −20°, H_2O (10 l) was added. The precipitated product was filtered, washed with H_2O, and dried. The crude product was crystallized from AcOEt to afford 345 g (64%) of **2** as beige crystals. M.p. 143–145°. From the mother liquor, an additional crop of 53 g (10%) of **2** was collected. IR: 3159 (br.), 1700. ^{1}H-NMR: 1.35–1.50 (*m*, 1 H); 1.42 (*s*, 3 H); 1.85–2.0 (*m*, 1 H); 2.0–2.26 (*m*, 2 H); 2.58–2.71 (*m*, 1 H); 2.82–2.97 (*m*, 1 H); 6.70 (*d*, J = 8, 1 H); 6.78 (*d*, J = 8, 1 H); 7.10 (*t*, J = 8, 1 H); 8.08 (*s*, 1 H). MS: 187 (M^+).

rac-*1-Acetyl-2a,3,4,5-tetrahydro-2a-methylbenz[*cd*]indol-2(*1H*)-one* (**3**). A mixture of **2** (100 g, 534 mmol) and Ac_2O (500 ml) was refluxed for 4 h and then evaporated. The residue was dissolved in toluene (500 ml) and washed with 10% NaOH soln. The org. phase was evaporated and the residue crystallized from EtOH (95%) to give 106 g (87%) of **3** as white crystals. M.p. 69–70°. From the mother liquor a further crop of 12.6 g (10%) of **3** was isolated. IR: 1701, 1764. ^{1}H-NMR: 1.43 (*s*, 3 H); 1.43–1.60 (*m*, 1 H); 1.84–1.97 (*m*, 1 H); 2.04–2.21 (*m*, 2 H); 2.60–2.75 (*m*, 1 H); 2.65 (*s*, 3 H); 2.82–2.96 (*m*, 1 H); 6.95 (*d*, J = 8, 1 H); 7.21 (*t*, J = 8, 1 H); 7.90 (*d*, J = 8, 1 H). MS: 229 (M^+).

*(+) and (−)-1-Acetyl-2a,3,4,5-tetrahydro-2a-methylbenz[*cd*]indol-2(*1H*)-one* (**3a** and **3b**, resp.), *by Chromatographic Resolution. Method Development:* Amylose tris(3,5-dimethylphenyl carbamate) coated on amino-functionalized silica gel turned out to exhibit excellent resolution properties for the racemate **3**. Prior to the prep. separation, the method was optimized on an anal. *Chiralpak-AD* column (purchased from *Daicel Chemical Inc.*, Tokyo, Japan). The parameters for the anal. separation, which were also used for the on-line monitoring of the prep. runs, were as follows. *Chiralpak-AD* column (4.6 × 250 mm), mobile phase hexane/i-PrOH/MeOH 95:2.5:2.5 (*v*/*v*/*v*), flow 0.5 ml/min, temp. 30°, UV detection at 220 nm, injection volume 20 µl (10 mg/20 ml), t_2 11.01 min, k'_2 = 0.84 min, α = 1.29, and R_s = 1.37. The dead time (t_0) was estimated by injection of 1,3,5-tri(*tert*-butyl)benzene. Capacity factors k' were calculated according to the equation $k' = (t_R - t_0)t_0$, the enantioselectivity α according to $\alpha = k'_2/k'_1$, and the resolution factors R_s according to $R_s = 1.18 \cdot (t_2 - t_1)/w_{1/2}(1) + w_{1/2}(2)$, where t_1 and t_2 refer to the retention time of the first- and second-eluted enantioner, and $w_{1/2}(1)$ and $w_{1/2}(2)$ represent the peak widths of the corresponding peak at half height.

Preparative Separation: Prep. chromatography was performed on a semi-prep. column (4 × 21 cm) containing 192 g of chiral stationary phase. The latter consisted of 20% amylose tris(3,5-dimethylphenyl carbamate) coated onto the surface of aminopropyl-functionalized silica gel (20 µm)[3]). In a typical-batch elution run, 100 mg of racemate **3** (dissolved in 5 ml of mobile phase) were processed at 25° with a flow rate of 20 ml/min in less than

30 min. Valley fractionation provided an enantiomeric purity of 99% e.e. for the first eluting enantiomer and only 60% e.e. for the second one (for which tailing was observed). Both enriched enantiomers were rechromatographed to obtain highly purified enantiomers. The purity of the reprocessed enantiomers was ≥ 99% e.e. Less polar enantiomer **3b**: m.p. 75–76°, $[\alpha]_D^{25} = -108.6$ ($c = 1.00$, MeOH); more polar enantiomer **3a**: m.p. 75–76°; $[\alpha]_D^{25} = +107.5$ ($c = 1.00$, MeOH). The isolation of g-quantities was achieved within 1 h by using repetitive injection or by applying chromatography in its recycling mode on the above mentioned column.

*(2*RS*,2a*RS*)-1-Acetyl-1,2,2a,3,4,5-hexahydro-2a-methylbenz[*cd*]indol-2-ol* (**4**). To a soln. of **3** (10 g, 43.6 mmol) in THF (250 ml), $LiBH_4$ (475 mg, 21.8 mmol) was added at 0° within 45 min. After 1 h stirring at 0°, the mixture was poured into 10% Na_2CO_3 soln. (300 ml) and the product extracted with AcOEt (300 ml). The extract was washed with H_2O (200 ml), dried, and evaporated. The residue was crystallized from toluene (30 ml) to give 4.94 g (49%) of **4**. White crystals. M.p. 141–143°. IR: 1634, 3350. ^{1}H-NMR ((D$_6$)DMSO): 1.19 (*s*, 3 H); 1.59–1.75 (*m*, 1 H); 1.83–2.20 (*m*, 3 H); 2.39 (*s*, 3 H); 2.55–2.70 (*m*, 1 H); 2.85 (*dd*, $J = 17, 6$, 1 H); 5.43 (*d*, $J = 7$, 1 H); 6.48 (*d*, $J = 7$, 1 H); 6.86 (*d*, $J = 8$, 1 H); 7.14 (*t*, $J = 8$, 1 H); 7.69 (*d*, $J = 8$, 1 H). The configuration was established by NOE. NMR ($CHCl_3$): two rotamers. ^{13}C-NMR ((D$_6$) DMSO): 18.7 (*t*), 23.2 (*q*), 24.8 (*t*), 25.2 (*q*), 26.5 (*t*), 42.7 (*s*), 93.4 (*d*), 113.3 (*d*), 122.7 (*d*), 127.4 (*d*), 134.2 (*s*), 135.0 (*s*), 139.4 (*s*), 169.5 (*s*). GC/MS: 231 (M^+). MS: 232 (MH$^+$).

*1-Acetyl-1,3,4,5-tetrahydro-2-methylbenz[*cd*]indol* (**5**). To a mixture of **4** (500 mg, 2.16 mmol) and Et_3N (2.18 g, 21.6 mmol) in toluene (180 ml) was added CF_3COOH (20 ml). The mixture was stirred at 60° for 2 h (TLC: complete conversion). Then the soln. was poured into 10% Na_2CO_3 soln. under ice cooling, the aq. phase extracted with toluene (90 ml), the org. phase dried and evaporated, and the crude product purified by FC (silica gel (30 g), toluene): 380 mg (83%) of **5**. White crystals. M.p. 87–88°. IR: 1696. ^{1}H-NMR: 2.00 (*p*, $J = 6$, 1 H); 2.54 (*s*, 3 H); 2.64–2.73 (*m*, 1 H); 2.70 (*s*, 3 H); 2.88 (*t*, $J = 6$, 1 H); 6.97 (*d*, $J = 8$, 1 H); 7.15 (*t*, $J = 8$, 1 H); 7.59 (*d*, $J = 8$, 1 H). ^{13}C-NMR: 14.6 (*q*), 21.0 (*t*), 23.6 (*t*), 27.0 (*q*), 27.3 (*t*), 112.5 (*d*), 117.5 (*s*), 120.9 (*d*), 123.7 (*d*), 128.9 (*s*), 129.9 (*s*), 131.4 (*s*), 134.1 (*s*), 170.1 (*s*). MS: 213 (M^+).

rac-*2a,3,4,5-Tetrahydro-1,2a-dimethylbenz[*cd*]indol-2(*1H*)-one* (**6**). To a suspension of *t*-BuOK (23.2 g, 0.206 mol) in DMF (30 ml), a soln. of **1** (13.8 g, 0.079 mol) in DMF (70 ml) was added at 0°. After stirring for 30 min, MeI (29.5 g, 0.208 mol) was added at 0° within 1 h. The mixture was stirred for 3 h at 20°. Then H_2O (100 ml) was added, the product extracted with toluene (200 ml), the extract washed with H_2O and evaporated, and the residue crystallized from toluene/hexane 1:5 (100 ml): 11.4 g (71%) of **6**. M.p. 104–117°. IR: 1700. ^{1}H-NMR: 1.26–1.41 (*m*, 1 H); 1.37 (*s*, 3 H); 1.83–1.98 (*m*, 1 H); 2.0–2.27 (*m*, 2 H); 2.55–2.71 (*m*, 1 H); 2.83–2.97 (*m*, 1 H); 3.18 (*s*, 3 H); 6.63 (*d*, $J = 8$, 1 H); 6.80 (*d*, $J = 8$, 1 H); 7.16 (*t*, $J = 8$, 1 H). MS: 201 (M^+).

rac-*1,2,2a,3,4,5-Hexahydro-1,2a-dimethylbenz[*cd*]indol-2-ol* (**7**). To a soln. of **6** (5 g, 24.8 mmol) in toluene (60 ml), sodium dihydrobis(2-methoxyethanalato)aluminate (20% in toluene; *Red-Al*®; 30 ml, 29.7 mmol) was added at 0° within 15 min. The mixture was stirred for 1 h. Then toluene (40 ml) and H_2O (40 ml) were added. The org. phase was washed with brine, dried, and evaporated: 4.8 g (96%) of **7** (diastereoisomer mixture 2:1). IR (CH_2Cl_2): 3570, 3600, 3690. ^{1}H-NMR (only H–C(2) signal): 4.27 (*d*, $J = 11$, 0.33 H); 4.46 (*d*, $J = 10$, 0.66 H). MS: 203 (M^+).

*1,3,4,5-Tetrahydro-1,2-dimethylbenz[*cd*]indol* (**8**). A soln. of **7** (100 mg, 0.49 mmol) and HCOOH (4 ml) was kept at 85° for 1 h (TLC: complete conversion). The mixture was poured into 10% Na_2CO_3 soln. and the product extracted with AcOEt. After drying, the soln. was evaporated: 90 mg (99%) of **8**. ^{1}H-NMR: 2.03 (*p*, $J = 6$, 2 H); 2.31 (*s*, 3 H); 2.74 (*t*, $J = 6$, 2 H); 2.90 (*t*, $J = 6$, 2 H); 3.62 (*s*, 3 H); 6.72–6.79 (*m*, 1 H); 6.97–7.08 (*m*, 2 H). ^{13}C-NMR: 10.3 (*q*), 21.4 (*t*), 24.6 (*t*), 27.7 (*t*), 29.5 (*q*), 105.7 (*d*), 109.0 (*s*), 115.2 (*d*), 121.1 (*d*), 126.9 (*s*), 128.9 (*s*), 131.2 (*s*), 134.9 (*s*). GC/MS: 185 (M^+).

rac-*6-Bromo-2a,3,4,5-tetrahydro-2a-methylbenz[*cd*]indol-2(*1H*)-one* (**9**). A suspension of **2** (1.87 g, 10 mmol), NBS (1.78 g, 10 mmol), and 2,2′-azo-bis(2-methylbutanenitrile) (100 mg) in CCl_4 (20 ml) was refluxed for 1 h. After addition of H_2O, the precipitated product was filtered and dried: 1.58 g (60%) of **9**. Beige crystals. M.p. 196–199°. ^{1}H-NMR: 1.30–1.49 (*m*, 1 H); 1.41 (*s*, 3 H); 1.95–2.27 (*m*, 3 H); 2.59–2.85 (*m*, 2 H); 6.62 (*d*, $J = 8$, 1 H); 7.32 (*d*, $J = 8$, 1 H); 8.19 (*s*, 1 H); the position of the Br-atom was established by NOE. GC/MS: 265, 267 (M^+).

rac-*1-Acetyl-1,2a,3,4-tetrahydro-2a-methylbenz[*cd*]indole-2,5-dione* (**11**). A suspension of **3** (30 g, 131 mmol), NBS (24.9 g, 140 mmol), and 2,2′-azo-bis(2-methylbutanenitrile) (1 g) in CCl_4 (300 ml) was refluxed for 2 h. The intermediate benzylic bromide **10** (2 diastereoisomers) was detected by GC/MS. After cooling to 20°, DMSO (150 ml) and then Et_3N (150 ml) were added, and the brown soln. was stirred at 20° for 1 h, then refluxed for 90 min. The mixture was cooled to 20° and treated with H_2O and AcOEt. The org. phase was washed with H_2O, dried, and evaporated. The residue was crystallized from *i*-PrOH (200 ml): 20.2 g (63%) of **11**. Beige crystals. M.p.

167–169°. IR (KBr): 1679, 1712, 1760. ^{1}H-NMR: 1.61 (*s*, 3 H); 2.12 (*dt*, *J* = 9, 4, 1 H); 2.40 (*ddd*, *J* = 9, 4, 1, 1 H); 2.69 (*s*, 3 H); 2.78 (*ddd*, *J* = 13, 4, 1, 1 H); 2.93 (*ddd*, *J* = 13, 4, 4, 1 H); 7.43 (*t*, *J* = 8, 1 H); 7.64 (*d*, *J* = 8, 1 H); 8.28 (*d*, *J* = 8, 1 H). ^{13}C-NMR: 24.05 (*q*), 25.91 (*q*), 28.46 (*t*), 34.20 (*t*), 43.23 (*s*), 121.14 (*d*), 121.59 (*d*), 128.38 (*s*), 129.16 (*d*), 137.83 (*s*), 138.41 (*s*), 170.67 (*s*), 180.33 (*s*), 195.34 (*s*). GC/MS: 243 (M^+). MS: 244 (MH^+).

*(2a*RS,*4*SR*)-1-Acetyl-4-bromo-1,2a,3,4-tetrahydro-2a-methylbenz[*cd*]indole-2,5-dione* (**12**). To a suspension of **11** (70 g, 288 mmol) in AcOH (700 ml), pyridine hydrobromide perbromide (94.5 g, 295 mmol) was added within 15 min at 20°. A soln. was formed for a short time, then the product crystallized out. After stirring for 1 h, the suspension was poured into H_2O (2.1 l), the product filtered and washed with H_2O, and the crude, wet residue crystallized from 95% EtOH (880 ml): 83.4 g (90%) of **12**. M.p. 175–178°. IR: 1697, 1705, 1760. ^{1}H-NMR: 1.64 (*s*, 3 H); 2.57 (*t*, *J* = 13, 1 H); 2.68 (*s*, 3 H); 3.02 (*dd*, *J* = 13, 6, 1 H); 5.10 (*dd*, *J* = 13, 6, 1 H); 7.47 (*t*, *J* = 8, 1 H); 7.72 (*d*, *J* = 8, 1 H); 8.32 (*d*, *J* = 8, 1 H). ^{13}C-NMR: 24.51 (*q*), 25.88 (*q*), 40.74 (*t*), 44.52 (*s*), 46.89 (*d*), 121.83 (*d*), 122.84 (*d*), 126.80 (*s*), 129.84 (*d*), 137.56 (*s*), 137.80 (*s*), 170.54 (*s*), 178.50 (*s*), 189.17 (*s*). MS: 321/323 (M^+).

1-[Benzyl(methyl)amino]propan-2-one (**13**) [24]. To a soln. of benzyl(methyl)amine (671 g, 5.54 mol) in toluene (2 l), chloroacetone (256 g, 2.77 mol) was added within 30 min at 55–65°. Benzyl(methyl)amine hydrochloride precipitated. After 3 h stirring at 50–55° and cooling to 20°, the salt was filtered off, and the mother liquor was washed with H_2O (500 ml) and 1N HCl (2 × 520 ml) to remove the unreacted benzyl(methyl)amine. The toluene phase was evaporated: 463.6 g (94% based on chloroacetone) of **13**. ^{1}H-NMR: 2.14 (*s*, 3 H); 2.29 (*s*, 3 H); 3.14 (*s*, 2 H); 3.57 (*s*, 2 H); 7.22–7.38 (*m*, 5 H).

N-*Benzyl*-N,*2-dimethyl-1,3-dioxolan-2-methanamine* (**14**) [24]. A mixture of **13** (433 g, 2.44 mol), *p*-toluenesulfonic acid hydrate (558 g, 2.93 mol), ethylene glycol (304 g, 4.88 mol), and cyclohexane (1200 ml) was refluxed for 12 h using a *Dean-Stark* separator to remove H_2O. After cooling to 20°, the mixture was poured into a mixture of Na_2CO_3 (388 g) and H_2O (2500 ml). The product was extracted with AcOEt (1.5 l). After washing with brine, the org. phase was evaporated and the residue distilled: 433 g (80%) of **14**. Yellow oil. B.p. 125–135°/5 mbar. ^{1}H-NMR: 1.38 (*s*, 3 H); 2.29 (*s*, 3 H); 2.48 (*s*, 2 H); 3.59 (*s*, 2 H); 3.93 (*s*, 4 H); 7.18–7.38 (*m*, 5 H).

N,*2-Dimethyl-1,3-dioxolan-2-methanamine* (**15**) [24]. A mixture of **14** (500 g, 2.26 mol) in EtOH (2 l) and 10% Pd/C (10 g) was hydrogenated for 4 h at 20° and 4 bar H_2 pressure. After filtration, the soln. was evaporated and the residue distilled using a 25-cm *Vigreux* distillation column: 237 g (80%) of **15**. Colourless hygroscopic oil. B.p. 160–163°. ^{1}H-NMR: 1.24 (*s*, 1 H); 1.36 (*s*, 3 H); 2.46 (*s*, 3 H); 2.70 (*s*, 2 H); 3.97 (*s*, 4 H).

*(2a*RS,*4*SR*)-1,2a,3,4-Tetrahydro-2a-methyl-4-{methyl[(2-methyl-1,3-dioxolan-2-yl)methyl]amino}benz[*cd*]indole-2,5-dione* (**16**). To a soln. of **15** (69 g, 526 mmol) in toluene (630 ml) under Ar, **12** (42.4 g, 131 mmol) was added at 20°. The mixture was then refluxed for 24 h (deacetylation much faster than substitution). After cooling to 20°, the mixture was washed with H_2O and extracted with a soln. of tartaric acid (36 g) in H_2O (570 ml). The aq. phase was washed with toluene and alkalinized with 10N NaOH. The alkaline aq. phase was extracted with toluene. After drying, the extract was evaporated: 21.7 g (50%) of **16**. Yellow foam. ^{1}H-NMR: 1.35 (*s*, 3 H); 1.61 (*s*, 3 H); 2.08 (*t*, *J* = 12, 1 H); 2.42–2.52 (*m*, 1 H); 2.46 (*s*, 3 H); 2.67 (*d*, *J* = 15, 1 H); 2.94 (*d*, *J* = 15, 1 H); 3.90–4.04 (*m*, 4 H); 4.08 (*dd*, *J* = 12, 5, 1 H); 7.04 (*d*, *J* = 8, 1 H); 7.29 (*t*, *J* = 8, 1 H); 7.45 (*d*, *J* = 8, 1 H); 8.48 (*s*, 1 H). ^{13}C-NMR: 22.0 (*q*), 23.0 (*q*), 33.0 (*t*), 39.6 (*q*), 42.9 (*s*), 61.0 (*t*), 64.2 (*t*), 66.1 (*d*), 109.8 (*s*), 113.2 (*d*), 117.0 (*d*), 128.1 (*d*), 128.9 (*s*), 139.7 (*s*), 140.1 (*s*), 182.8 (*s*), 197.3 (*s*). GC/MS: 330 (M^+).

*(2a*RS,*4*SR*)-1,2a,3,4-Tetrahydro-2a-methyl-4-[methyl(2-oxopropyl)amino]benz[*cd*]indole-2,5-dione* (**17**). A soln. of **16** (21 g, 63.6 mmol) and 6N HCl (360 ml) was stirred under Ar for 3 h at 45°. The mixture was added slowly to a suspension of $NaHCO_3$ (224 g) and AcOEt (300 ml) at 0°. The org. phase was separated, the aq. phase extracted with AcOEt (200 ml), and the combined org. phase washed with brine, dried, and evaporated: 16.7 g (92%) of **17**. Yellow foam. ^{1}H-NMR: 1.61 (*s*, 3 H); 2.06 (*t*, *J* = 13, 1 H); 2.18 (*s*, 3 H); 2.43 (*s*, 3 H); 2.65 (*dd*, *J* = 13, 5, 1 H); 3.47 (*d*, *J* = 18, 1 H); 3.67 (*d*, *J* = 18, 1 H); 3.97 (*dd*, *J* = 13, 5, 1 H); 7.08 (*d*, *J* = 7, 1 H); 7.31 (*t*, *J* = 7, 1 H); 7.44 (*d*, *J* = 7, 1 H); 8.50 (*s*, 1 H). ^{13}C-NMR: 23.6 (*q*), 27.2 (*q*), 33.1 (*t*), 39.4 (*q*), 43.4 (*s*), 65.0 (*t*), 65.7 (*d*), 114.1 (*d*), 118.2 (*d*), 129.0 (*d*), 129.2 (*s*), 139.5 (*s*), 140.4 (*s*), 183.5 (*s*), 197.1 (*s*), 207.6 (*s*).

rac-*9,10-Didehydro-3β,6-dimethylergoline-2,8(*3H*)-dione* (**18**). To a suspension of LiBr (30.6 g, 352 mmol) in THF (200 ml) under Ar, **17** (16.5 g, 57.6 mmol) in THF (60 ml) was added at 20°. Et_3N (30.6 g, 302 mmol) was added at 0–5° within 15 min. The suspension was stirred at 0–5° for 4 h. Then THF (75 ml), H_2O (110 ml), and brine (110 ml) were added, and the org. phase was separated. The aq. phase was extracted with THF (150 ml) and AcOEt (150 ml), the combined org. phase washed with brine, dried, and evaporated, and the residue purified by FC (silica gel (750 g), AcOEt, AcOEt/MeOH 95:5) 8.7 g (56%) of **18**. Yellowish crystals. M.p. > 260°. IR: 1724, 3186. ^{1}H-NMR: 1.56 (*s*, 3 H); 1.65 (*t*, *J* = 12, 1 H); 2.43 (*s*, 3 H); 2.53 (*dd*, *J* = 12, 6, 1 H); 3.29 (*dd*, *J* = 17, 2, 1 H); 3.56 (*d*, *J* = 17, 1 H); 3.77–3.88 (*m*, 1 H); 6.72 (*s*, 1 H); 6.90 (*d*, *J* = 7, 1 H); 7.25 (*t*, *J* = 7, 1 H); 7.33

(*d*, *J* = 7, 1 H); 8.37 (*s*, 1 H). ^{13}C-NMR ((D$_6$)DMSO): 24.0 (*q*), 31.6 (*t*), 40.0 (*q*), 43.1 (*s*), 58.7 (*d*), 65.1 (*t*), 110.8 (*d*), 116.8 (*d*), 119.9 (*d*), 128.2 (*s*), 128.9 (*d*), 135.7 (*s*), 140.9 (*s*), 153.1 (*s*), 182.7 (*s*), 196.2 (*s*). MS: 269 (*M*H$^+$).

rac-*9,10-Didehydro-8-hydroxy-3β,6-dimethylergolin-2(*3H*)-one* (**19**). Under Ar, **18** (7 g, 26.1 mmol) was dissolved in EtOH (700 ml) at 40°. The soln. was cooled to 20°, and NaBH$_4$ (987 mg, 26.10 mmol) was added in 15 min. The mixture was stirred for 4 h at 20° (TLC (AcOEt/MeOH/AcOH 50:50:0.5): complete conversion, two products, ratio 7:3). After addition of H$_2$O (450 ml), AcOH (1.5 ml) was added to destroy excess NaBH$_4$. Then 30% NaOH soln. (3 ml) was added (pH 11–12), the product extracted with CH$_2$Cl$_2$ (600 ml), and the extract dried and evaporated: 7.1 g (100%) of **19** as a yellowish powder. ^{1}H-NMR: **19a** (8β) **19b** (8α) 7:3. TLC: **19a** (major) less polar than **19b**. The epimers were not separated but used directly in the subsequent *Ritter* reaction. MS: 270 (*M*$^+$). For structural proof, see **20** and **21**.

rac-*9,10-Didehydro-8β-hydroxy-3β,6-dimethylergolin-2(*3H*)-one Acetate* (**20**) *and* rac-*9,10-Didehydro-8α-hydroxy-3β,6-dimethylergolin-2(*3H*)-one Acetate* (**21**). a) *By O-Acylation of* **19**. To a soln. of **19** (800 mg, 2.95 mmol) in AcOH (80 ml), Ac$_2$O (18.4 g, 180 mmol) was added. The soln. was stirred for 21 h and then poured into 10% Na$_2$CO$_3$ soln. (1000 ml). The aq. soln. was extracted with AcOEt (400 ml) and the extract dried and evaporated. The residue (780 mg; **20**/**21** 7:3), was separated by FC (silica gel (55 g), AcOEt/MeOH 95:5): 290 mg (31%) of less polar **20** and 150 mg (16%) of **21**, both as beige crystals. The assignment of the configuration of the epimers **20** and **21** was confirmed by NOE experiments.

Data of **20**: M.p. 195–198°. IR: 1699, 1737. ^{1}H-NMR: 1.46 (*t*, *J* = 12, 1 H); 1.54 (*s*, 3 H); 2.12 (*s*, 3 H); 2.40–2.48 (*m*, 1 H); 2.46 (*s*, 3 H); 2.54 (*dd*, *J* = 11, 10, 1 H); 3.37 (*dd*, *J* = 11, 7, 1 H); 3.42–3.51 (*m*, 1 H); 5.59–5.70 (*m*, 1 H); 6.38 (*s*, 1 H); 6.73 (*d*, *J* = 8, 1 H); 7.15 (*t*, *J* = 8, 1 H); 7.22 (*d*, *J* = 8, 1 H); 8.06 (*s*, 1 H). ^{13}C-NMR: 21.1 (*q*), 25.0 (*q*), 31.4 (*t*), 42.1 (*q*), 43.6 (*s*), 57.5 (*t*), 59.8 (*d*), 67.2 (*d*), 108.3 (*d*), 115.7 (*d*), 120.1 (*d*), 128.3 (*d*), 129.7 (*s*), 132.5 (*s*), 135.9 (*s*), 139.4 (*s*), 170.6 (*s*), 184.8 (*s*). MS: 313 (*M*H$^+$).

Data of **21**: M.p. 199–201°. IR: 1711, 1731. ^{1}H-NMR: 1.53 (*s*, 3 H); 1.56 (*t*, *J* = 12, 1 H); 2.09 (*s*, 3 H); 2.47 (*s*, 3 H); 2.54 (*dd*, *J* = 12, 4, 1 H); 2.76 (*dd*, *J* = 14, 4, 1 H); 3.16 (*d*, *J* = 14, 1 H); 3.16–3.25 (*m*, 1 H); 5.34–5.40 (*m*, 1 H); 6.45–6.53 (*m*, 1 H); 6.75 (*d*, *J* = 8, 1 H); 7.15 (*t*, *J* = 8, 1 H); 7.26 (*d*, *J* = 8, 1 H); 8.00 (*s*, 1 H). ^{13}C-NMR: 21.3 (*q*), 24.9 (*q*), 31.9 (*t*), 43.0 (*s*), 43.5 (*q*), 59.4 (*t*), 60.2 (*d*), 66.5 (*d*), 108.7 (*d*), 115.8 (*d*), 117.9 (*d*), 128.3 (*d*), 129.5 (*s*), 132.8 (*s*), 137.3 (*s*), 139.4 (*s*), 171.0 (*s*), 184.7 (*s*). MS: 313 (*M*H$^+$).

b) *From* **19** *by O-Alkylation of AcOH*. To a soln. of **19** (800 mg, 2.95 mmol) in AcOH (80 ml), H$_2$SO$_4$ (22.4 g, 224 mmol) was added at 20°. The soln. was kept at 20° for 21 h. Then the mixture was poured into 10% Na$_2$CO$_3$ soln. (900 ml) and AcOEt (400 ml) and the org. phase dried and evaporated. From the crude product (760 mg; **20**/**21** 8:92), the main component was isolated as described above: 500 mg (54%) of **21**.

c) *Thermodynamic Equilibration Experiments*. Pure **20** or **21** (100 mg, 0.32 mmol) was dissolved in AcOH (10 ml) containing H$_2$SO$_4$ (2.8 g, 28.6 mmol) and kept at 20°. According to TLC, the equilibrium was reached after 1 h already. After 22 h, the mixture was worked up as described above and the product ratio determined by ^{1}H-NMR. From both epimers, **20**/**21** in a ratio of 8:92 was obtained.

rac-N-*(9,10-Didehydro-2,3-dihydro-3β,6-dimethyl-2-oxoergolin-8α-yl)acetamide* (**22**). To a suspension of **19** (6.87 g, 25.4 mmol) in MeCN (90 ml), BF$_3$ · Et$_2$O (25.6 g, 180 mmol) and 96% H$_2$SO$_4$ soln. (5 g, 49 mmol) in MeCN (200 ml) were added. The suspension was stirred for 2 h at 25°. The mixture was then poured into 10% Na$_2$CO$_3$ soln. (500 ml), the aq. phase (pH 9) extracted with CH$_2$Cl$_2$ (1200 ml), and the extract evaporated after drying 6.63 g (84%) of **22**. Yellowish crystals. M.p. 228–230°. ^{1}H-NMR: 1.41 (*t*, *J* = 12, 1 H); 1.52 (*s*, 3 H); 1.96 (*s*, 3 H); 2.46 (*s*, 3 H); 2.54 (*dd*, *J* = 12, 4, 1 H); 2.67 (*dd*, *J* = 12, 4, 1 H); 2.92 (*d*, *J* = 12, 1 H); 3.12–3.20 (*m*, 1 H); 4.60–4.70 (*m*, 1 H); 6.15 (*d*, *J* = 9, 1 H); 6.40 (*d*, *J* = 5, 1 H); 6.72 (*d*, *J* = 7, 1 H); 7.14 (*t*, *J* = 7, 1 H); 7.22 (*d*, *J* = 7, 1 H); 8.05 (*s*, 1 H). ^{13}C-NMR ((D$_6$)DMSO): 22.7 (*q*), 25.3 (*q*), 31.9 (*t*), 42.9 (*s*), 43.5 (*d*), 43.6 (*q*), 60.2 (*t*), 60.2 (*d*), 107.7 (*d*), 115.0 (*d*), 122.2 (*d*), 128.3 (*d*), 130.0 (*s*), 132.4 (*s*), 134.7 (*s*), 140.6 (*s*), 168.6 (*s*), 183.4 (*s*). MS: 312 (*M*H$^+$).

rac-N-*(1-Acetyl-9,10-didehydro-2,3-dihydro-3β,6-dimethyl-2-oxoergolin-8α-yl)acetamide* (**23**). A suspension of pulverized NaOH (780 mg, 19.3 mmol) and **22** (2 g, 6.43 mmol) in THF (100 ml) was stirred at 50° for 30 min. Ac$_2$O (3.28 g, 32.2 mmol) was added and the mixture stirred at 50° for 18 h. The mixture was poured into 10% Na$_2$CO$_3$ soln. (100 ml) and toluene. The org. phase was washed with brine, dried, and evaporated: 1.49 g (66%) of **23**. Beige crystals. M.p. 177–184°. ^{1}H-NMR: 1.49 (*t*, *J* = 12, 1 H); 1.53 (*s*, 3 H); 1.97 (*s*, 3 H); 2.47 (*s*, 3 H); 2.55–2.73 (*m*, 2 H); 2.64 (*s*, 3 H); 2.94 (*d*, *J* = 12, 1 H); 3.09–3.19 (*m*, 1 H); 4.62–4.72 (*m*, 1 H); 6.05 (*d*, *J* = 9, 1 H); 6.42 (*d*, *J* = 5, 1 H); 7.25 (*t*, *J* = 8, 1 H); 7.40 (*d*, *J* = 8, 1 H); 7.95 (*d*, *J* = 8, 1 H). MS: 354 (*M*H$^+$).

rac-N-*(1-Acetyl-9,10-didehydro-2,3-dihydro-3β,6-dimethyl-2α-hydroxy-ergolin-8α-yl)acetamide* (**24**) *and Ethyl (2*RS*,4a*SR*,6*SR*)-2,7-Bis(acetylamino)-2,3,4,4a,5,6-hexahydro-4,6-dimethyl-benzo[f]quinoline-6-carboxylate* (**25**). NaBH$_4$ (29 mg, 0.766 mmol) was dissolved in 95% EtOH (45 ml) and cooled to 0°. Within 15 min, **23** (900 mg,

2.55 mmol) was added at 0–5°. The mixture was stirred at 0–5° for 1 h (TLC: two products, ratio 1:1). The reaction was quenched with acetone (20 ml) and 10% Na_2CO_3 soln. (40 ml), the mixture extracted with CH_2Cl_2 (50 ml), the org. phase evaporated and the residue purified by FC (silica gel (45 g) AcOEt/MeOH 9:1): 390 mg (38%) of less polar **25** and 230 mg (25%) of **24**.

Data of **25**: IR: 1653, 1727, 3295. ^{1}H-NMR ((D$_6$)DMSO): 1.09 (*t*, *J* = 7, 3 H); 1.52 (*s*, 3 H); 1.85 (*s*, 3 H); 1.80–2.00 (*m*, 1 H); 1.96 (*s*, 3 H); 2.12–2.24 (*m*, 1 H); 2.35 (*s*, 3 H); 2.42–2.50 (*m*, 1 H); 2.71 (*d*, *J* = 12, 1 H); 2.88 (*d*, *J* = 12, 1 H); 3.76–3.90 (*m*, 1 H); 4.08–4.10 (*m*, 1 H); 4.35–4.45 (*m*, 1 H); 6.23 (*d*, *J* = 5, 1 H); 7.07 (*d*, *J* = 8, 1 H); 7.24 (*t*, *J* = 8, 1 H); 7.57 (*d*, *J* = 8, 1 H); 7.96 (*d*, *J* = 8, 1 H); 8.63 (*s*, 1 H). ^{13}C-NMR ((D$_6$)DMSO): 14.7 (*q*), 23.3 (*q*), 23.9 (*q*), 25.2 (*q*), 41.3 (*t*), 43.6 (*q*), 44.8 (*d*), 45.9 (*s*), 58.0 (*t*), 58.2 (*d*), 61.3 (*t*), 120.2 (*d*), 124.5 (*d*), 127.8 (*d*), 131.1 (*d*), 134.5 (*s*), 136.3 (*s*), 136.9 (*s*), 138.6 (*s*), 169.4 (*s*), 170.1 (*s*), 177.0 (*s*). MS: 400 (*M*H$^+$).

Data of **24**: ^{1}H-NMR ((D$_6$)DMSO): 1.21 (*s*, 3 H); 1.73–1.84 (*m*, 1 H); 1.84 (*s*, 3 H); 2.10–2.20 (*m*, 1 H); 2.33 (*s*, 3 H); 2.39 (*s*, 3 H); 2.50–2.60 (*m*, 1 H); 2.80 (*d*, *J* = 12, 1 H); 3.06 (*d*, *J* = 11, 1 H); 4.35–4.45 (*m*, 1 H); 5.39 (*d*, *J* = 6, 1 H); 6.34 (*s*, 1 H); 6.55 (*d*, *J* = 6, 1 H); 7.14 (*t*, *J* = 8, 1 H); 7.35 (*d*, *J* = 8, 1 H); 7.69 (*d*, *J* = 8, 1 H); 7.94 (*d*, *J* = 8, 1 H). MS: 356 (*M*H$^+$).

*(5a*RS,*6a*SR,*9*RS,*10a*RS*)*-N-*(4,5,5a,6,6a,7,8,9,10,10a-Decahydro-5a,7-dimethyl-5-oxo-indolo[4,3-*fg*]-quinolin-9-yl)acetamide* (**27**). A mixture of **22** (200 mg, 0.643 mmol), H_2SO_4 (200 mg) dissolved in EtOH (40 ml) and 5% Pd/C (50 mg) was hydrogenated at 20° under 30 bar H_2 pressure. After filtration and treatment with 10% Na_2CO_3 soln. (20 ml), the product was extracted with CH_2Cl_2. The org. phase was dried and evaporated: 90 mg (45%) of **27**, containing *ca.* 10% of the (5a*RS*,6a*SR*,9*RS*,10a*SR*)-epimer. ^{1}H-NMR: 1.20–1.30 (*m*, 1 H); 1.49 (*s*, 3 H); 1.56 (*t*, *J* = 12, 1 H); 1.89 (*s*, 3 H); 1.90–2.05 (*m*, 1 H); 2.14 (*dd*, *J* = 12, 4, 1 H); 2.22 (*dd*, *J* = 11, 9, 1 H); 2.44 (*s*, 3 H); 2.71 (*dd*, *J* = 11, 4, 1 H); 3.20–3.30 (*m*, 1 H); 3.40–3.50 (*m*, 1 H); 4.07–4.21 (*m*, 1 H); 5.43 (*d*, *J* = 8, 1 H); 6.67 (*d*, *J* = 8, 1 H); 6.80 (*d*, *J* = 8, 1 H); 7.11 (*t*, *J* = 8, 1 H); 7.79 (*s*, 1 H), the *cis* relationship of H–C(6a) and H–C(10a) was proven by NOE experiments. MS: 314 (*M*H$^+$).

rac-N-*(1-Benzyl-9,10-didehydro-2,3-dihydro-3β,6-dimethyl-2-oxoergolin-8α-yl)acetamide* (**28**). To a soln. of **22** (3.65 g, 11.7 mmol) in THF (365 ml) was added pulverized NaOH (1.41 g, 35.16 mmol). The suspension was stirred at 50° for 30 min. Benzyl bromide (2.40 g, 14.0 mmol) in THF (15 ml) was added and the mixture stirred at 50° for 6 h. To destroy the excess of benzyl bromide, pentylamine (3.58, 41.0 mmol) was added and the mixture stirred for another 30 min at 50°. After cooling to 20°, the mixture was poured into H_2O (1000 ml), the aq. phase extracted with AcOEt (500 ml), the extract evaporated, and the residue purified by FC (silica gel (400 g), AcOEt MeOH 8:2): 3.49 g (74%) of **28**. Beige amorphous powder. ^{1}H-NMR: 1.43 (*t*, *J* = 12, 1 H); 1.54 (*s*, 3 H); 1.96 (*s*, 3 H); 2.47 (*s*, 3 H); 2.56–2.75 (*m*, 1 H); 2.92 (*d*, *J* = 14, 1 H); 3.12–3.25 (*m*, 1 H); 4.58 (*d*, *J* = 15, 1 H); 4.58–4.7 (*m*, 1 H); 5.11 (*d*, *J* = 15, 1 H); 5.98 (*d*, *J* = 8, 1 H); 6.38 (*d*, *J* = 4, 1 H); 6.54 (*d*, *J* = 8, 1 H); 7.09 (*t*, *J* = 8, 1 H); 7.21 (*d*, *J* = 8, 1 H); 7.25–7.40 (*m*, 5 H). ^{13}C-NMR: 23.2 (*q*), 25.5 (*q*), 32.2 (*t*), 43.0 (*s*), 43.4 (*t*), 43.6 (*d*), 44.0 (*q*), 60.1 (*t*), 60.8 (*d*), 107.3 (*d*), 115.6 (*d*), 120.9 (*d*), 127.1 (*d*), 127.5 (*d*), 128.1 (*d*), 128.5 (*d*), 129.6 (*s*), 131.5 (*s*), 135.1 (*s*), 135.9 (*s*), 141.1 (*s*), 168.9 (*s*), 181.8 (*s*). MS: 402 (*M*H$^+$).

rac-N-*(1-Benzyl-9,10-didehydro-2,3-dihydro-2-hydroxy-3β,6-dimethylergolin-8-yl)acetamide* (**29**). To a soln. of **28** (3.43 g, 8.54 mmol) in THF (85 ml) sodium dihydrobis(2-methoxyethanolato)aluminate (20% in toluene, *Red-Al*®; 17.25 g, 17.08 mmol) was added at −2 to −5° within 15 min. A gel precipitated. After stirring for 2 h at −2°, the reaction was quenched with H_2O (200 ml) and the aq. phase extracted with AcOEt (200 ml). The org. phase was washed with brine, dried, and evaporated: 3.19 g (93%) of **29**. Beige powder. ^{1}H-NMR ((D$_6$)DMSO): two epimers ratio 8:2. ^{13}C-NMR (main component): 23.2 (*q*), 23.7 (*q*), 33.3 (*t*), 43.4 (*s*), 43.5 (*d*), 43.6 (*q*), 47.7 (*t*), 59.9 (*t*), 60.9 (*d*), 97.0 (*d*), 105.5 (*d*), 111.7 (*d*), 119.1 (*d*), 127.1 (*d*), 127.3 (*d*), 128.5 (*d*), 128.6 (*s*), 129.6 (*s*), 131.7 (*s*), 135.5 (*s*), 138.2 (*s*), 146.8 (*s*), 169.2 (*s*). MS: 404 (*M*H$^+$).

rac-N-*(1-Benzyl-9,10-didehydro-2,3-dihydro-3β,6-dimethylergolin-8α-yl)acetamide* (**30**). A soln. of **29** (100 mg, 0.248 mmol) and HCOOH (4 ml) was kept for 30 min at 85°. After cooling the soln. was poured into 10% Na_2CO_3 soln. the aq. phase extracted with AcOEt, and the org. phase dried and evaporated: 90 mg (94%) of **30**. Brown oil. ^{1}H-NMR: 1.38 (*s*, 3 H); 1.51 (*t*, *J* = 12, 1 H); 1.95 (*s*, 3 H); 2.37 (*dd*, *J* = 12, 4, 1 H); 2.43 (*s*, 3 H); 2.64 (*dd*, *J* = 12, 4, 1 H); 2.85–2.95 (*m*, 2 H); 3.00–3.10 (*m*, 1 H); 3.23 (*d*, *J* = 8, 1 H); 3.93 (*d*, *J* = 15, 1 H); 4.44 (*d*, *J* = 15, 1 H); 4.55–4.67 (*m*, 1 H); 6.00 (*d*, *J* = 8, 1 H); 6.30–6.37 (*m*, 2 H); 6.90–7.10 (*m*, 2 H); 7.20–7.41 (*m*, 5 H).

rac-N-*(1-Benzyl-9,10-didehydro-2,6-dimethylergolin-8α-yl)acetamide* (**31**). Glycolic acid (40 g) was melted and heated to 80°. A soln. of **29** (2.0 g, 4.96 mmol) in CH_2Cl_2 (40 ml) was added within 4 h at 80–85° while CH_2Cl_2 distilled off. The mixture was stirred for 2 h at 85° (TLC: complete conversion). Then the mixture was treated with 10% Na_2CO_3 soln. (200 ml) and AcOEt (100 ml) at 25°. The org. phase was washed with brine, dried, and evaporated: 1.81 g (95%) of **31**. Green foam. IR: 3290 (br.), 1653 (br.). ^{1}H-NMR: 1.99 (*s*, 3 H); 2.28

(*d*, *J* = 1, 3 H); 2.55 (*s*, 3 H); 2.55–2.66 (*m*, 1 H); 2.73 (*dd*, *J* = 11, 3, 1 H); 2.91 (*d*, *J* = 11, 1 H); 3.06–3.16 (*m*, 1 H); 3.44 (*dd*, *J* = 14, 5, 1 H); 4.62–4.71 (*m*, 1 H); 5.27 (*s*, 2 H); 6.16 (*d*, *J* = 9, 1 H); 6.46 (*d*, *J* = 6, 1 H); 6.94–7.01 (*m*, 2 H); 7.04–7.16 (*m*, 3 H); 7.18–7.34 (*m*, 3 H); configuration established by NOE. ^{13}C-NMR: 10.4 (*q*), 23.3 (*q*), 26.7 (*t*), 43.8 (*d*), 43.9 (*d*), 46.7 (*t*), 58.6 (*t*), 63.1 (*d*), 106.4 (*s*), 108.0 (*d*), 112.2 (*d*), 118.9 (*d*), 121.9 (*d*), 125.9 (*s*), 126.2 (*s*), 126.3 (*s*), 127.1 (*d*), 128.5 (*d*), 130.3 (*s*), 134.8 (*s*), 137.9 (*s*), 138.2 (*s*), 169.2 (*s*). GC/MS: 385 (M^+). MS: 386 (MH^+).

rac-N-*(2,6-Dimethylergolin-8α-yl)acetamide* (**32**). *N*-Methylaniline (1.17 g, 10.89 mmol) and $LiNH_2$ (1.67 g, 72.6 mmol) were added to liq. NH_3 (150 ml) at −50°. A soln. of **31** (2.80 g, 7.26 mmol) in THF (30 ml) was added at −55° (white suspension). After 1 h stirring at −45 to −55°, Li-granulate (255 mg, 36.75 mmol) was added, and the mixture was stirred for 2 h at −40 to −50° (TLC and GC/MS: complete conversion). The mixture was quenched with NH_4Cl (6.5 g) and MeOH (10 ml) at −40°. NH_3 was evaporated and the residue dissolved in H_2O (250 ml) and AcOEt (250 ml). The org. phase was dried and evaporated. Only **32** and some *N*-methylaniline but no isomer of **32** were detected in the crude product (GC/MS, ^{1}H-NMR). The residue was purified by FC (silica gel (130 g), AcOEt/MeOH 8:2): 1.64 g (76%) of **32**. Beige crystals. M.p. 220–222°. ^{1}H-NMR: 1.62 (*dt*, *J* = 13, 3, 1 H); 2.03 (*s*, 3 H); 2.16 (*dt*, *J* = 10, 4, 1 H); 2.37 (*s*, 3 H); 2.43 (*s*, 3 H); 2.44–2.62 (*m*, 2 H); 2.75 (*d*, *J* = 13, 1 H); 2.84 (*d*, *J* = 12, 1 H); 2.92–3.06 (*m*, 1 H); 3.25 (*dd*, *J* = 15, 4, 1 H); 4.28–4.39 (*m*, 1 H); 6.52 (*d*, *J* = 7, 1 H); 6.80 (*d*, *J* = 6, 1 H); 7.00–7.10 (*m*, 2 H); 7.73 (*s*, 1 H). ^{13}C-NMR: 11.4 (*q*), 23.3 (*q*), 25.9 (*t*), 31.8 (*t*), 36.0 (*d*), 43.1 (*q*), 44.1 (*d*), 60.9 (*t*), 67.3 (*d*), 106.9 (*s*), 107.8 (*d*), 112.7 (*d*), 121.6 (*d*), 127.0 (*s*), 127.8 (*s*), 131.4 (*s*), 132.6 (*s*), 169.4 (*s*). GC/MS: 297 (M^+). MS: 297 (M^+).

rac-*2,6-Dimethylergolin-8α-amine* (**33**). A suspension of **32** (1.27 g, 4.27 mmol) and 10% H_2SO_4 soln. (25 ml) was stirred at 100° for 8 h under careful exclusion of light and air-O_2 (TLC: complete conversion). After cooling to 25°, the suspension was treated with 10% Na_2CO_3 soln. (100 ml) and the product extracted with CH_2Cl_2 (500 ml). The extract was dried and evaporated: 1.03 g (94%) of **33**. The racemic **33** was identical with the corresponding antipode obtained by partial synthesis from lysergic acid [9] (by ^{1}H- and ^{13}C-NMR, MS, and TLC). Beige crystals. M.p. > 200°. ^{1}H-NMR ((D_6)DMSO): 1.40 (*dt*, *J* = 13, 3, 1 H); 1.64 (*s*, 2 H); 1.82 (*dt*, *J* = 11, 4, 1 H); 2.15–2.40 (*m*, 2 H); 2.23 (*s*, 3 H); 2.25 (*s*, 3 H); 2.68 (*d*, *J* = 11, 1 H); 2.90–3.03 (*m*, 2 H); 3.13 (*dd*, J_1 = 14, 4, 1 H); 3.26 (*m*, 1 H); 6.59 (*d*, *J* = 7, 1 H); 6.83 (*t*, *J* = 7, 1 H); 6.93 (*d*, *J* = 7, 1 H); 10.39 (*s*, 1 H). ^{13}C-NMR ((D_6)DMSO): 11.5 (*q*), 25.9 (*t*), 34.9 (*d*), 35.8 (*t*), 43.4 (*q*), 45.6 (*d*), 64.0 (*t*), 67.9 (*d*), 106.6 (*s*), 107.8 (*d*), 111.9 (*d*), 121.0 (*d*), 127.2 (*s*), 128.1 (*s*), 132.4 (*s*), 132.7 (*s*). MS: 255 (M^+).

rac-N-*(2,6-Dimethylergolin-8α-yl)-2-ethyl-2-methylbutanamide* (**34**). To a mixture of **33** (0.8 g, 3.13 mmol), $NaHCO_3$ (263 mg, 3.13 mmol), Na_2CO_3 (338 mg, 3.13 mmol), H_2O (20 ml), and isopropyl acetate (40 ml), 2-ethyl-2-methylbutanoyl chloride (604 mg, 4.06 mmol) in toluene (10 ml) was added at 40° within 15 min. The mixture was stirred for 3 h at 40° (TLC: complete conversion). Then the mixture was diluted with isopropyl acetate (100 ml) and the org. phase washed with H_2O, dried, and evaporated: 1.14 g (99%) of **34**. The racemic **34** was identical with the corresponding antipode **III** obtained by partial synthesis from lysergic acid [9] (by IR (CH_2Cl_2), ^{1}H- and ^{13}C-NMR, MS, TLC, and GC). Beige crystals. M.p. 199–202°. IR (CH_2Cl_2): 3462, 1647. ^{1}H-NMR: 0.83 (*t*, *J* = 7, 3 H); 0.84 (*t*, *J* = 7, 3 H); 1.12 (*s*, 3 H); 1.34–1.51 (*m*, 2 H); 1.54–1.77 (*m*, 3 H); 2.15 (*dt*, J_1 = 11, 4, 1 H); 2.37 (*s*, 3 H); 2.43 (*s*, 3 H); 2.44–2.60 (*m*, 2 H); 2.70–2.84 (*m*, 2 H); 2.90–3.03 (*m*, 1 H); 3.25 (*dd*, J_1 = 14, 4, 1 H); 4.30–4.40 (*m*, 1 H); 6.72 (*d*, *J* = 8, 1 H); 6.77–6.83 (*m*, 1 H); 7.00–7.11 (*m*, 2 H); 7.74 (*s*, 1 H). ^{13}C-NMR: 8.9 (*q*), 11.5 (*q*), 19.8 (*q*), 26.2 (*t*), 32.1 (*t*), 32.2 (*t*), 32.4 (*t*), 36.5 (*d*), 43.4 (*q*), 44.0 (*d*), 46.1 (*s*), 61.4 (*t*), 67.5 (*d*), 107.3 (*s*), 107.8 (*d*), 112.7 (*d*), 121.8 (*d*), 125.8 (*d*), 127.1 (*s*), 127.9 (*s*), 131.9 (*s*), 132.7 (*s*), 176.1 (*s*). GC/MS: 367 (M^+). MS: 367 (M^+).

REFERENCES

[1] J. Rutschmann, P. A. Stadler, 'Ergot Alkaloids and Related Compounds', Eds. B. Berde and H. O. Schild, Springer, Berlin, 1978, pp. 29–85.

[2] A. Stoll, A. Hofmann, *Helv. Chim. Acta* **1943**, *26*, 2070; A. Cerny, M. Semonsky, *Pharmazie* **1971**, *26*, 740.

[3] Z. Brich, H. Mühle, to *Sandoz*, EP 48695, 1982.

[4] A. Hofmann, *Helv. Chim. Acta* **1947**, *30*, 44.

[5] D. M. Coward, A. K. Dixon, S. Urwyler, T. G. White, A. Enz, M. Karobath, G. Shearman, *J. Pharmacol. Exp. Ther.* **1990**, *252*, 279.

[6] P. L. Stütz, P. Stadler, J. M. Vigouret, A. Jaton, *Eur. J. Med. Chem. Chim. Ther.* **1982**, *17*, 537.

[7] V. Zikan, M. Semonsky, K. Rezabek, M. Auskova, M. Seda, *Collect. Czech. Chem. Commun.* **1972**, *37*, 2600; V. Zikan, M. Semonsky, K. Rscheschabek, M. Seda, M. Auschkowa, to *Spofa*, Ger. Offen. DE 2238540,

1973; G. Sauer, to *Schering*, Ger. Offen. DE 3001752, 1981; H. Wachtel, *J. Pharm. Pharmacol.* **1983**, *35*, 440; M. Husak, B. Kratochvil, P. Sedmera, J. Stuchlik, A. Jegorov, *Collect. Czech. Chem. Commun.* **1993**, *58*, 2944.

[8] T. Fehr, P. Stadler, P. Stütz, to *Sandoz*, Ger. Offen. DE 2657770, 1977; E. Flückiger, U. Briner, H. R. Bürki, P. Marbach, H. R. Wagner, W. Doepfner, *Experientia* **1979**, *35*, 1677.

[9] W. Häfliger, to *Sandoz*, Ger. Offen. DE 3500251, 1985; W. Häfliger, to *Sandoz*, Ger. Offen. DE 3820159, 1989.

[10] P. Stütz, P. A. Stadler, *Helv. Chim. Acta* **1972**, *55*, 75.

[11] M. Bänziger, C. P. Mak, H. Mühle, F. Nobs, W. Prikoszovich, J. L. Reber, U. Sunay, *Org. Process Res. Develop.* **1997**, in press.

[12] V. Zikan, M. Semonsky, *Collect. Czech. Chem. Commun.* **1960**, *25*, 1922; *ibid.* **1963**, *28*, 1080; *Pharmazie* **1968**, *23*, 147.

[13] E. C. Kornfeld, E. J. Fornefeld, G. B. Kline, M. J. Mann, D. E. Morrison, R. G. Jones, R. B. Woodward, *J. Am. Chem. Soc.* **1956**, *78*, 3087.

[14] J. Bergmann, N. Eklund, *Tetrahedron* **1980**, *36*, 1445; A. H. Jackson, P. P. Lynch, *J. Chem. Soc., Perkin Trans. 2*, **1987**, *9*, 1215.

[15] A. H. Jackson, P. Smith, *Tetrahedron* **1968**, *24*, 2227; T. S. T. Wang, *Tetrahedron Lett.* **1975**, *19*, 1637; G. Rodriguez, Y. Benito, F. Temprano, *Chem. Lett.* **1985**, 427.

[16] K. Brunner, *Monatsh. Chem.* **1896**, *17*, 253; T. Kitamura, T. Koga, T. Taguchi, K. Harano, *Heterocycles* **1984**, *22*, 1315.

[17] A. Walser, T. Flynn, C. Mason, H. Crowley, C. Maresca, B. Yaremko, M. O'Donnell, *J. Med. Chem.* **1991**, *34*, 1209.

[18] P. Laszlo, *Science*, **1987**, *235*, 1473.

[19] F. Chavez, S. Suarez, M. A. Diaz, *Synth. Commun.* **1994**, *24*, 2325.

[20] X. F. Pei, S. Bi, *Heterocycles* **1994**, *39*, 357.

[21] P. Gmeiner, B. Bollinger, J. Mierau, G. Höfner, *Arch. Pharm. (Weinheim)* **1995**, *328*, 609.

[22] E. J. Corey, *J. Am. Chem. Soc.* **1953**, *75*, 2301; G. Bellucci, G. Ingrosso, E. Mastrorilli, *Tetrahedron* **1978**, *34*, 387.

[23] M. Numazawa, M. Ogata, K. Abiko, M. Nagaoka, *Steroids* **1985**, *45*, 403.

[24] F. Benington, R. D. Morin, *Org. Prep. Proced. Int.* **1973**, *5*, 281.

[25] A. Eschenmoser, *Quart. Rev.* **1970**, *24*, 366; M. Roth, P. Dubs, E. Götschi, A. Eschenmoser, *Helv. Chim. Acta* **1971**, *54*, 710.

[26] L. I. Krimen, D. J. Cota, 'Organic Reactions', John Wiley & Sons, Inc., New York, 1969, Vol. 17, pp. 213–325.

[27] E. Juaristi, 'Introduction to Stereochemistry and Conformational Analysis', John Wiley & Sons, Inc., New York, 1991, pp. 299–311.

[28] V. Zikan, M. Semonsky, K. Rezabek, M. Auskova, M. Seda, *Collect. Czech. Chem. Commun.* **1972**, *37*, 2600.

[29] G. Sauer, G. Haffer, H. Wachtel, *Synthesis* **1986**, 1007.

[30] W. A. Remers, R. H. Roth, G. J. Gibs, M. J. Weiss, *J. Org. Chem.* **1971**, *36*, 1232.

[31] M. Hoffmann, St. Blank, D. Seebach, E. Küsters, E. Schmid, *Chirality* **1997**, in press.